5-Cis-substituierte Prolinamine

–

Modulare Synthese und Anwendung in der enantioselektiven Katalyse

DISSERTATION

zur Erlangung des akademischen Grades eines

Doktors der Naturwissenschaften (Dr. rer. nat.)

im Fach Chemie

an der Fakultät für Biologie, Chemie und Geowissenschaften

der Universität Bayreuth

vorgelegt von

Felix Prause

aus Coburg

Bayreuth 2017

Die vorliegende Arbeit wurde in der Zeit von Oktober 2012 bis Dezember 2016 in Bayreuth am Lehrstuhl Organische Chemie I/2 unter Betreuung von Herrn Professor Dr. Matthias Breuning angefertigt.

Vollständiger Abdruck der von der Fakultät für Biologie, Chemie und Geowissenschaften der Universität Bayreuth genehmigten Dissertation zur Erlangung des akademischen Grades eines Doktors der Naturwissenschaften (Dr. rer. nat.).

Dissertation eingereicht am: 21.02.2017

Zulassung durch die Promotionskommission: 22.03.2017

Wissenschaftliches Kolloquium: 21.06.2017

Amtierender Dekan: Prof. Dr. Stefan Schuster

Prüfungsausschuss:

Prof. Dr. Matthias Breuning	(Erstgutachter)
Prof. Dr. Rainer Schobert	(Zweitgutachter)
Prof. Dr. Peter Strohriegl	(Vorsitz)
Prof. Dr. Birgit Weber	

Meiner Familie

What I cannot create, I do not understand

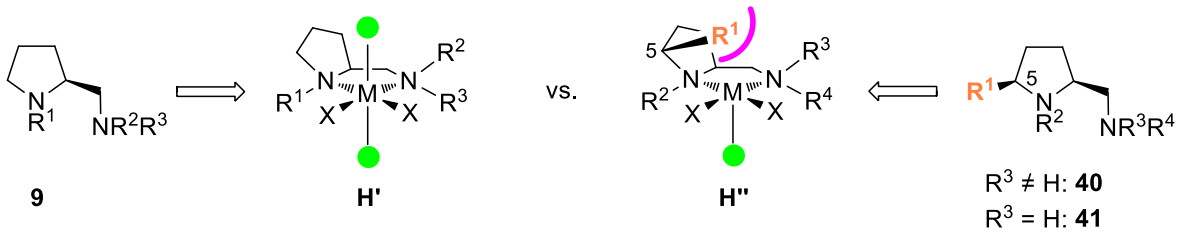
Richard Feynman

INHALTSVERZEICHNIS

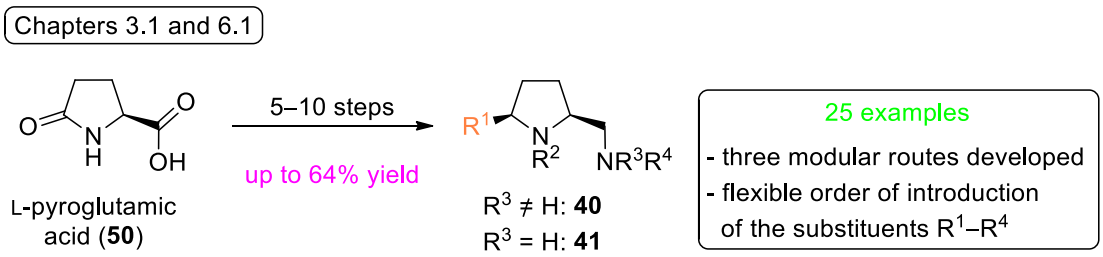
SUMMARY

Focus of this thesis was the modular synthesis of 5-*cis*-substituted prolinamines **40** and **41** and their application in asymmetric catalysis.

Enantiopure compounds are often prepared by utilizing catalytic amounts of chirally modified transition metal complexes. Some of the ligands used for this purpose are considered to be privileged, such as the proline-derived amines **9**. In the past, the pyrrolidines **9** have mainly been optimized by varying the nitrogen substituents; no attention, however, has been paid to a 5-*cis* substituent R^1. This is astonishing since the additional group R^1 in **40** and **41** should shield the "upper" hemisphere of a metal catalyst, which might permit enhanced levels of chirality transfer (**H'** vs. **H''**). Primary objective of the present dissertation was the verification of this hypothesis.

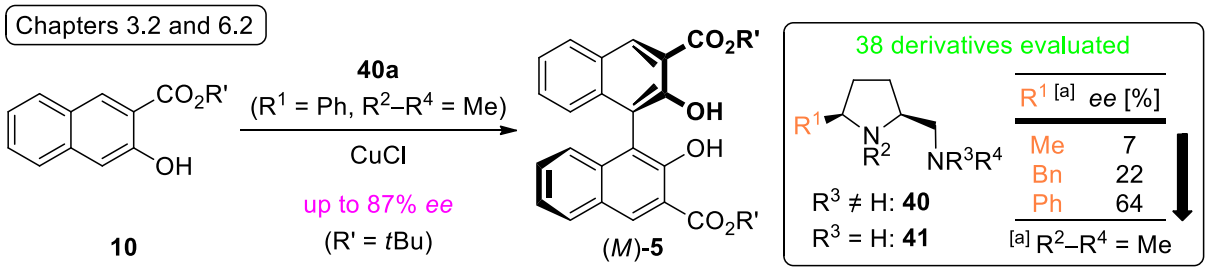


Synthesis of the 5-cis prolinamines **40** *and* **41**: Starting from L-pyroglutamic acid (**50**), three stereoselective routes toward the targeted 5-*cis*-substituted prolinamines **40** and **41** were developed and established. They permit a flexible introduction of the substituents R^1–R^4, which minimizes the requisite synthetic effort. To demonstrate the efficiency of these modular approaches, 25 derivatives **40** and **41** with varying substitution patterns were prepared (partly via several routes) in 5–10 steps and up to 64% overall yield (see chapters 3.1 and 6.1).

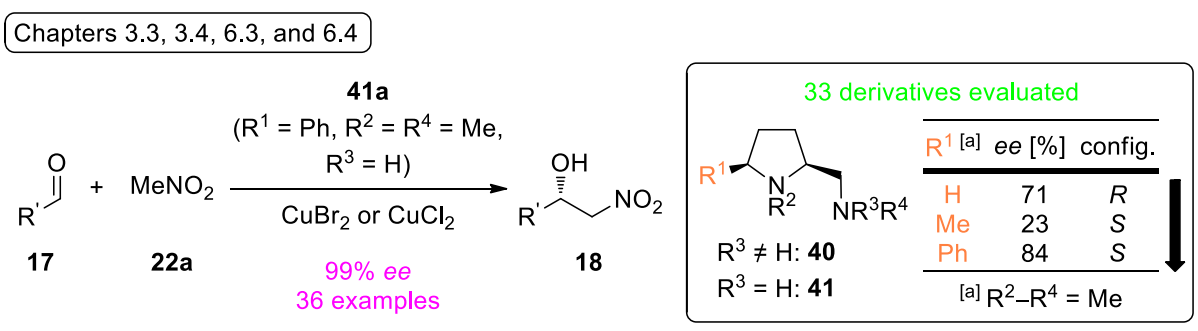


Application in catalysis: Using the diamines **40** and **41**, in-depth structure-selectivity investigations were conducted on three model reactions, in which the substituents R^1–R^4 were systematically varied. The substrate scope of the most potent ligand was then explored under optimized conditions. In total, more than 50 different pyrrolidines **40** and **41** were examined within these studies.

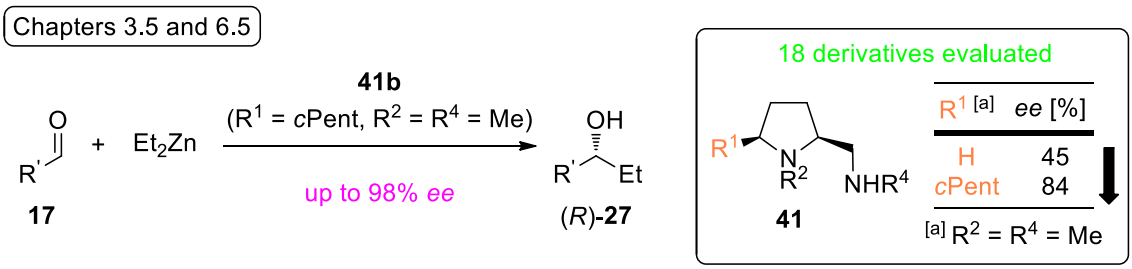
In *copper-catalyzed oxidative biaryl couplings*, 38 5-*cis* prolinamines **40** and **41** were evaluated. It became apparent that the 5-*cis* substituent R^1 has a significant influence on the chirality transfer. By gradually increasing the steric bulk at this position, the enantiomeric excess of the product (*M*)-**5** could be raised step-by-step. The prime diamine **40a** (R^1 = Ph, R^2–R^4 = Me) delivered the binaphthol **5i**, which is equipped with two sterically demanding *t*Bu-esters, with excellent 87% *ee* – the best value for this substrate so far. Based on the structure-selectivity investigations, a mechanism was proposed, that rationally explains all findings (among others the levels of stereoselection and the reversal of the sense of the asymmetric induction with some ligands; see chapters 3.2 and 6.2).



In the second model reaction, the *addition of nitromethane* (**22a**) *to aldehydes*, the 5-*cis* substituent R^1 had an even greater impact on the stereochemical steering. While the copper complex of the 5-*cis*-unsubstituted derivative **9u** (R^1 = H, R^2–R^4 = Me) provided the (*R*)-enantiomer of **18c** (R' = Ph) in 71% *ee*, the enantio-complementary product (*S*)-**18c** (23% *ee*) was isolated in presence of the analogous 5-*cis* methyl-substituted diamine **40b** (R^1–R^4 = Me). Systematic variation of the substituents R^1–R^4 (33 derivatives evaluated) revealed **41a** (R^1 = Ph, R^2 = R^4 = Me, R^3 = H) as the ligand of choice. By using $CuBr_2$•**41a** (or $CuCl_2$•**41a**) as the catalyst, 36 different (aromatic, heteroaromatic, aliphatic, and vinylic) substrates were converted into the corresponding products **18** with superb enantiocontrol (99% *ee* in each case). These extraordinary levels of enantiomeric excess are unique for Cu•diamine-catalyzed Henry reactions. The catalytic system was also well suited for gram-scale nitroaldol additions and for diastereo- and enantioselective transformations. Preliminary mechanistic studies indicated that the chirality transfer occurs in the C,C-coupling step and that the secondary prolinamines **41** are more reactive than the tertiary derivatives **40** (see chapters 3.3, 3.4, 6.3, and 6.4).



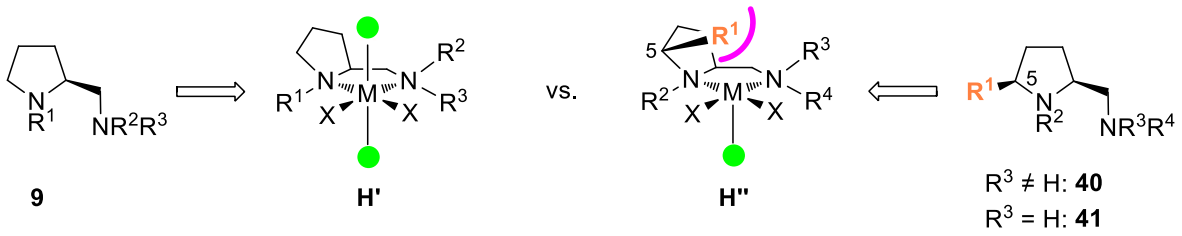
The *enantioselective addition of Et_2Zn to aldehydes* was selected as the final model reaction. Here, 18 prolinamines **41** containing a protic NH function were evaluated. The most simple, 5-*cis*-unsubstituted derivative **9v** (R^1 = H, R^2 = R^4 = Me) provided (*R*)-**27b** (R' = Ph) in 45% *ee*; by utilizing 5-*cis*-substituted pyrrolidines, this value could be increased to 84% (**41b**, R^1 = *c*Pent, R^2 = R^4 = Me), which again highlights the impact of the additional R^1 substituent. The diamines **41**, which carry an exocyclic sulfonamide group, surprisingly delivered the enantiomeric product (*S*)-**27**. This outcome was illustrated by discussing the different transition states. In the conversion of various aldehydes, the most powerful derivative **41b** yielded up to 98% *ee*, which makes it one of the best, solely amino-functionalized ligands for this reaction (see chapters 3.5 and 6.5).



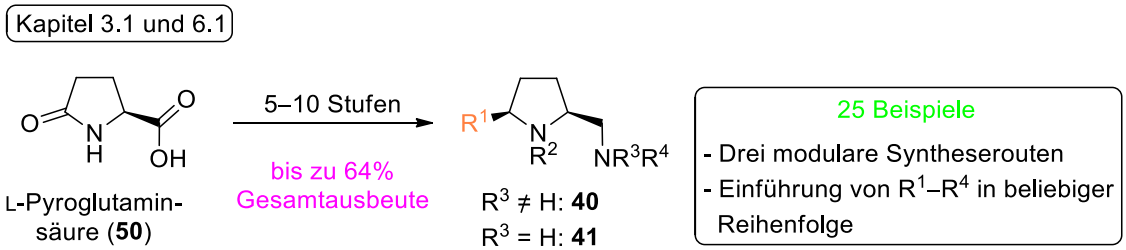
ZUSAMMENFASSUNG

Im Fokus dieser Dissertation stand die modulare Synthese von 5-*cis*-substituierten Prolinaminen **40** und **41** und deren Anwendung in der asymmetrischen Katalyse.

Enantiomerenreine Moleküle werden häufig durch den Einsatz katalytischer Mengen chiral modifizierter Übergangsmetallkomplexe gewonnen. Unter den hierfür genutzten Liganden gelten einige als privilegiert, so auch die Prolin-abgeleiteten Amine **9**. Deren Optimierung erfolgte bis dato zumeist durch Variation der Substituenten an den Stickstoffatomen; einem 5-*cis*-Substituenten R^1 wurde hingegen keine Aufmerksamkeit gewidmet. Dieser Umstand ist erstaunlich, da der zusätzliche Rest R^1 in **40** und **41** die „obere" Hemisphäre der Metallkatalysatoren blockieren sollte, was einen besseren Stereotransfer ermöglichen könnte (**H'** vs. **H''**). Hauptziel der vorliegenden Arbeit war die Überprüfung dieser These.

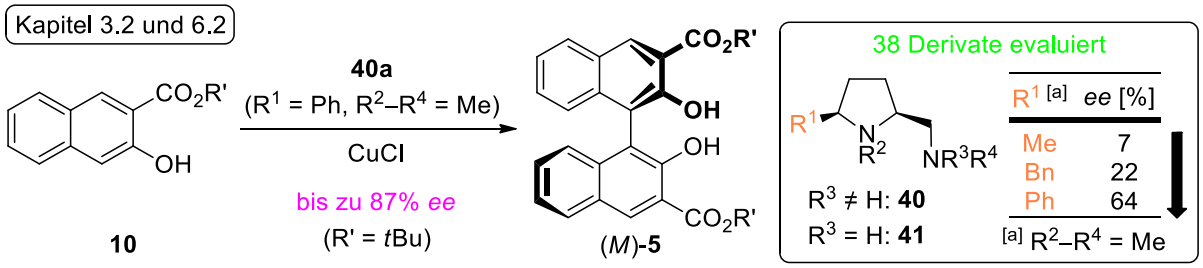


Synthese der 5-cis-Prolinamine **40** *und* **41**: Ausgehend von L-Pyroglutaminsäure (**50**) wurden zuerst drei stereoselektive Synthesesequenzen hin zu den gewünschten 5-*cis*-substituierten Prolinaminen **40** und **41** entwickelt und etabliert. Diese erlauben eine modulare Einführung der Reste R^1–R^4 in beliebiger Reihenfolge, was den erforderlichen Syntheseaufwand minimiert. Die Darstellung 25 unterschiedlicher Derivate **40** und **41** (z. T. über mehrere Wege) über 5–10 Stufen mit bis zu 64% Gesamtausbeute beweist die Leistungsfähigkeit der Routen (s. Kapitel 3.1 und 6.1).

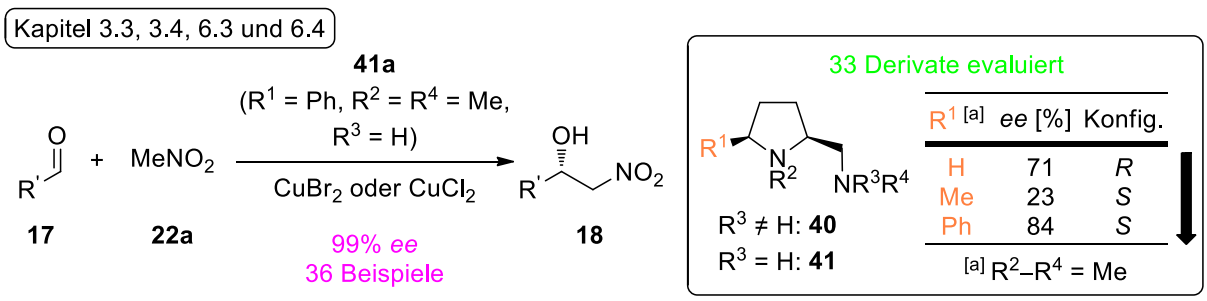


Anwendung in der Katalyse: Mit den Diaminen **40** und **41** wurden an drei Modellreaktionen detaillierte Struktur-Selektivitäts-Studien durchgeführt, in denen die Reste R^1–R^4 systematisch variiert wurden. Unter optimierten Reaktionsbedingungen wurde dann die Substratbreite des jeweils besten Liganden bestimmt. Insgesamt kamen in diesen Untersuchungen mehr als 50 verschiedene Pyrrolidine **40** und **41** zum Einsatz.

In *Kupfer-katalysierten oxidativen Biarylkupplungen* wurden 38 5-*cis*-Prolinamine **40** und **41** evaluiert. Dabei zeigte sich, dass der 5-*cis*-Substituent R^1 einen signifikanten Einfluss auf den Stereotransfer hat. Durch sukzessives Vergrößern des sterischen Blocks an dieser Position ließ sich der Enantiomerenüberschuss im Produkt (*M*)-**5** schrittweise steigern. Das leistungsfähigste Diamin **40a** (R^1 = Ph, R^2–R^4 = Me) ergab das Binaphthol **5i**, welches zwei sterisch anspruchsvolle *t*Bu-Ester trägt, in sehr guten 87% *ee* – der bisher beste erreichte Wert für dieses Substrat. Aufbauend auf den Struktur-Selektivitäts-Untersuchungen wurde ein Mechanismus postuliert, mit dem sich alle Befunde (u. a. die Höhe des Stereotransfers und die Umkehr der Richtung der asymmetrischen Induktion bei einigen Liganden) rational erklären lassen (s. Kapitel 3.2 und 6.2).

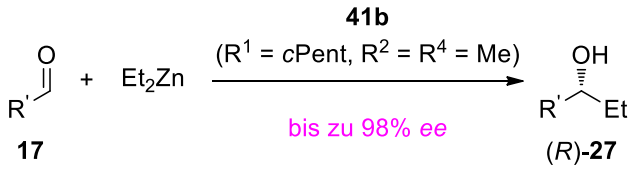


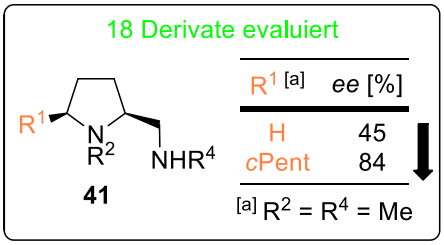
In der zweiten Modellreaktion, der *Addition von Nitromethan* (**22a**) *an Aldehyde*, hatte der neue 5-*cis*-Substituent R^1 eine noch größere Auswirkung auf den Stereotransfer. Während der Kupfer-Komplex des 5-*cis*-unsubstituierten Derivats **9u** (R^1 = H, R^2–R^4 = Me) das (*R*)-Enantiomer von **18c** (R' = Ph) mit 71% *ee* lieferte, wurde mit dem analogen 5-*cis*-Methyl-substituierten Diamin **40b** (R^1–R^4 = Me) das enantiokomplementäre Produkt (*S*)-**18c** (23% *ee*) isoliert. Systematische Variation aller Reste (33 Derivate evaluiert) führte zu **41a** (R^1 = Ph, R^2 = R^4 = Me, R^3 = H) als besten Liganden. Unter Verwendung von $CuBr_2$•**41a** bzw. $CuCl_2$•**41a** als Katalysator wurden bei der Umsetzung 36 verschiedener (aromatischer, heteroaromatischer, aliphatischer und vinylischer) Substrate die entsprechenden Produkte **18** mit jeweils hervorragenden 99% *ee* erhalten. Diese exzellenten Enantiomerenüberschüsse sind einmalig auf dem Gebiet der Cu•Diamin-katalysierten Henry-Reaktion. Das katalytische System war ebenfalls gut geeignet für Nitroaldol-Additionen im großen Maßstab und für diastereo- und enantioselektive Varianten. Erste mechanistische Untersuchungen zeigten, dass der Stereotransfer im C-C-Knüpfungsschritt stattfindet und dass die sekundären Prolinamine **41** in dieser Umsetzung reaktiver sind als die tertiären Derivate **40** (s. Kapitel 3.3, 3.4, 6.3 und 6.4).



Als finale Modellreaktion im Rahmen dieser Doktorarbeit wurde die *enantioselektive Addition von Et_2Zn an Aldehyde* gewählt. Hier wurden 18 Prolinamine **41** mit protischer NH-Funktion evaluiert. Das einfachste, 5-*cis*-unsubstituierte Derivat **9v** (R^1 = H, R^2 = R^4 = Me) lieferte (*R*)-**27b** (R' = Ph) mit 45% *ee*; dieser Wert konnte durch Verwendung 5-*cis*-substituierter Pyrrolidine auf 84% gesteigert werden (**41b**, R^1 = *c*Pent, R^2 = R^4 = Me), was den Einfluss des zusätzlichen Restes R^1 erneut hervorhebt. Die Diamine **41**, die eine exocyclische Sulfonamid-Gruppe (R^4 = SO_2R") tragen, ergaben überraschenderweise das enantiomere Produkt (*S*)-**27**. Dieser Befund ließ sich anhand verschiedener Übergangszustände erklären. Mit dem leistungsfähigsten Derivat **41b** wurden bei der Umsetzung verschiedener Aldehyde bis zu 98% *ee* erhalten, was **41b** zu einem der besten, ausschließlich Amino-funktionalisierten Liganden für diese Reaktion macht (s. Kapitel 3.5 und 6.5).

Kapitel 3.5 und 6.5





ABKÜRZUNGSVERZEICHNIS

In den Formelbildern und im Text werden folgende Abkürzungen verwendet:

Boc	*tert*-Butyloxycarbonyl
Bz	Benzoyl
CBS	Corey-Bakshi-Shibata
Cy	Cyclohexyl
de	Diastereomerenüberschuss
DABCO	1,4-Diazabicyclo[2.2.2]octan
DAIB	(2*S*)-3-*exo*-(Dimethylamino)isoborneol
DBNE	*N*,*N*-Dibutylnorephedrin
DIPEA	*N*,*N*-Diisopropylethylamin
DPMPM	α,α-Diphenyl-*N*-methyl-2-pyrrolidinmethanol
ee	Enantiomerenüberschuss
FDA	U.S. Food and Drug Administration
Konfig.	Konfiguration
MS	Molsieb
Ms	Mesyl
Naph	Naphthyl
NLE	nichtlinearer Effekt
Piv	Pivaloyl
Py	Pyridin
QSAR	quantitative Struktur-Wirkungs-Beziehung
RAMP	(*R*)-(+)-1-Amino-2-methoxymethylpyrrolidin
RT	Raumtemperatur
SAMP	(*S*)-(–)-1-Amino-2-methoxymethylpyrrolidin
TES	Triethylsilyl
TFA	Trifluoressigsäure
TIPS	Triisopropylsilyl
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylendiamin
Ts	*p*-Toluolsulfonyl
ÜN	über Nacht
Δ	Erhitzen auf Siedetemperatur

1 EINLEITUNG

Die fortwährende Isolierung immer neuer bioaktiver Substanzen aus der Natur generiert der Pharmaforschung einen nahezu unerschöpflichen Vorrat an Leitstrukturen. Um einen kleinen Einblick in die Vielfalt der hierbei entdeckten Molekülgerüste zu geben, sind in Abbildung 1 verschiedene, pharmakologisch höchst interessante Naturstoffe gezeigt.

Littoralison (**1**) ist ein sehr stark modifiziertes Iridoid[1] mit insgesamt sechs miteinander verknüpften Ringen, wovon der vierfach-substituierte Cyclobutanring sowie das oxygenierte η-Lacton am ungewöhnlichsten sind. Es wurde im Jahr 2001 von Ohizumi *et al.* aus dem Kraut *Verbena littoralis* isoliert und verstärkt das Nervenwachstum.[2] Das Alkaloid[3] Vinblastin (**2**),[4] als Chemotherapeutikum unter dem Namen Velbe® vertrieben, erinnert an eine Art Hantel, bei der zwei äußerst komplexe Hälften durch eine einzige Bindung miteinander verknüpft sind. Tatsächlich ist die südliche Hemisphäre des Moleküls ebenfalls ein eigener Naturstoff, der – wie **2** – im Madagaskar-Immergrün (*Vinca rosea*) gefunden wurde.[5] Im Gegensatz zu den beiden vorherigen Verbindungen besitzt das 1990 im Schwamm *Discodermia dissoluta* entdeckte Immunsuppressivum Discodermolid (**3**, es wirkt außerdem anti-karzinogen) nur einen Heterocyclus.[6] Dominierendes Merkmal des Polyketids[7] **3** ist eine hochsubstituierte Tetralkenylkette.

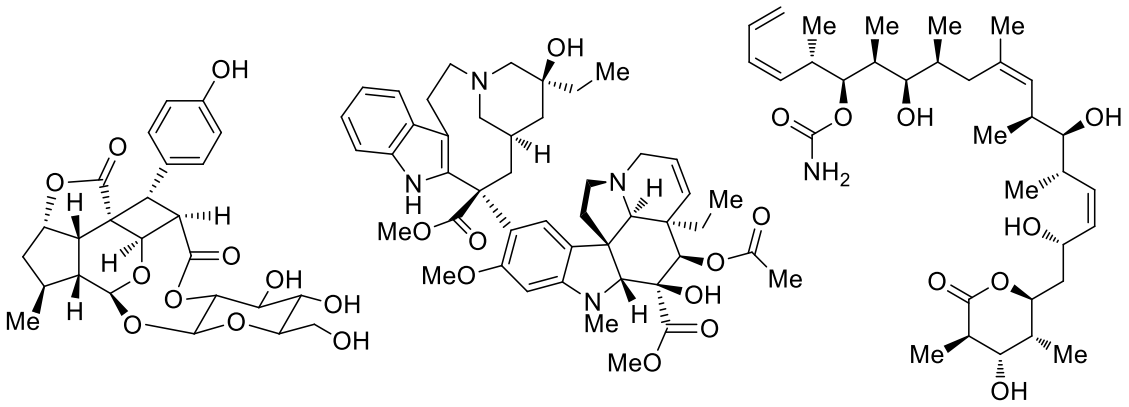


Abb. 1. Littoralison (**1**), Vinblastin (**2**) und Discodermolid (**3**) als Beispiele für hochkomplexe, bioaktive Naturstoffe.[2,4,6]

Alle drei vorgestellten Naturstoffe **1**–**3** lassen sich mit ihrem Spiegelbild nicht zur Deckung bringen; sie sind also chiral und werden in der Natur in enantiomerenreiner Form erzeugt. Ebenfalls chiral sind Enzyme, welche häufig die Targets bioaktiver Moleküle darstellen. Gemäß dem Schlüssel-Schloss-Prinzip (bzw. der erweiterten Induced-Fit-Theorie) reagieren diese nur mit einem passenden Substrat, was impliziert, dass die beiden Enantiomere eines Wirkstoffs in einem Lebewesen unterschiedliche Reaktionen auslösen können (Abbildung 2).[8] Äußerst deutlich wurde dies bei dem Schlaf- und Beruhigungsmittel Contergan®, das als bioaktive Substanz racemisches Thalidomid (*rac*-**4**) enthielt. Während das (*R*)-Enantiomer

von **4** die gewünschte sedative Wirkung hervorrief, führte (*S*)-**4** zu Missbildungen bei tausenden neugeborenen Kindern.[9] Diese Tragödie verdeutlicht mit Nachdruck die Notwendigkeit des Einsatzes enantiomerenreiner Pharmaka[10] in Medikamenten, was sich auch in einer Grundsatzerklärung der FDA wiederspiegelt.[11]

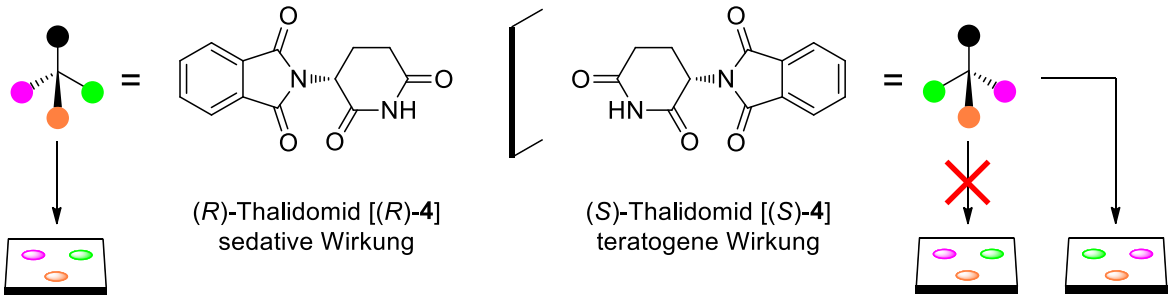


Abb. 2. Erläuterung des Schlüssel-Schloss-Prinzips[8] am Beispiel von Thalidomid (**4**). Mit (*R*)-**4** (links) ist die gewünschte Wechselwirkung mit dem Target möglich, während mit (*S*)-**4** (rechts) nur eine ungewünschte eintreten kann.

Eine nicht asymmetrische Synthese des Wirkstoffs Discodermolid (**3**, Abbildung 1) wäre völlig wertlos, da der Naturstoff insgesamt 16 stereogene Zentren enthält und somit bei dessen Darstellung bis zu 2^{16} verschiedene Konfigurationsisomere entstehen könnten. Folglich würde das gewünschte immunsuppressiv und anti-kanzerogen wirkende Stereoisomer in maximal 0.002% Ausbeute erhalten werden. Diese Zahl steht im starken Kontrast zu den – das Potenzial einer asymmetrischen Synthese unter Beweis stellenden – 11% Gesamtausbeute, die Paterson *et al.* in ihrer („third-generation“) Totalsynthese von **3** erzielten.[12] Da Discodermolid (**3**) in der Natur nur in geringen Mengen gebildet wird, entschloss sich zur Jahrtausendwende die Novartis AG, die für die klinischen Studien benötigten Mengen an **3** totalsynthetisch darzustellen.[13] Dieses Projekt lieferte mehr als 100 g enantiomerenreines Material in einer Ausbeute von 1% über alle Stufen.

Der Ausbeuteunterschied beider Totalsynthesen, einmal im akademischen und einmal im industriellen Maßstab, verdeutlicht die Notwendigkeit der Forschung nach neuen, skalierbaren Umsetzungen, aktiveren Katalysatoren und selektiveren, chiralen Liganden – mit dem Ziel, leistungsfähigere Methoden zur asymmetrischen Synthese chiraler Verbindungen zu entwickeln. Dadurch wird sichergestellt, dass dem Synthese-Chemiker der Zukunft ein breites Repertoire an Werkzeugen zur Darstellung enantiomerenreiner Zielmoleküle (z. B. Derivate von bekannten Wirkstoffen für QSAR-Studien oder wie im obigen Beispiel den aktiven Naturstoff selbst) zur Verfügung steht.

1.1 Methoden zur Darstellung enantiomerenreiner Zielmoleküle

Es existieren verschiedene Methoden, die zur Darstellung enantiomerenreiner Zielmoleküle geeignet sind (Abbildung 3).[14]

Bei der einfachsten handelt es sich um die Racematspaltung, also der Auftrennung eines zuvor synthetisieren Racemats. Diese Methode erfordert wenig Aufwand, besitzt aber den Nachteil, dass maximal 50% Ausbeute erreicht werden können, da das ungewollte Enantiomer verworfen werden muss. Eine Ausnahme hierzu bilden dynamisch kinetische Racemat-spaltungen, bei denen sich beide Edukt-Enantiomere *in situ* ineinander umwandeln, wovon eines dem Gleichgewicht entzogen wird.[15]

Bei der Ex-Chiral-Pool-Synthese wird ein enantiomerenreines Edukt aus der Natur entnommen und in die Synthesesequenz integriert.[14,16] Vorteilig ist der (meist) sehr hohe *ee* des Naturstoffs, nachteilig jedoch dessen oftmals notwendige, mehrstufige Anpassung an das jeweilige Zielmolekül.

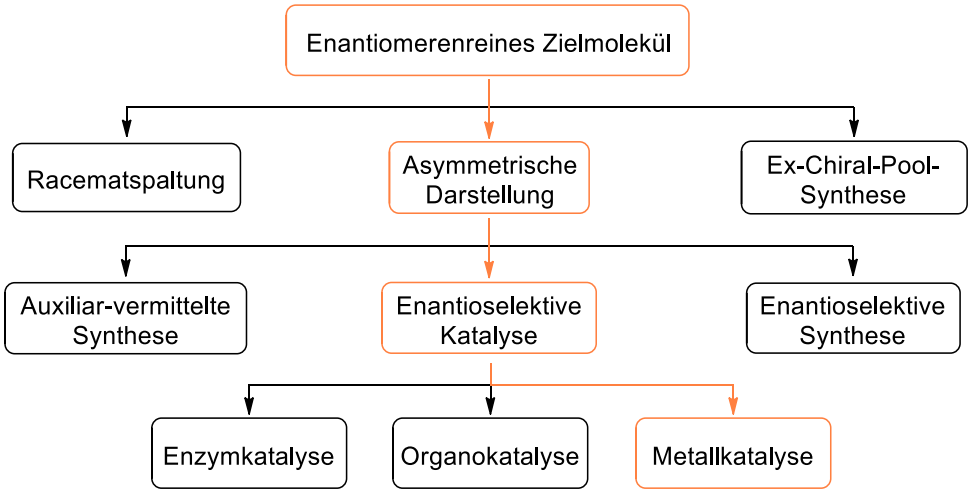


Abb. 3. Übersicht über die Methoden zur Darstellung enantiomerenreiner Zielmoleküle.[14]

Interessanter ist die gezielte asymmetrische *de novo* Synthese von Stereoelementen, da dadurch Chiralität generiert wird. Hier kann zwischen diastereoselektiv und enantioselektiv verlaufenden Reaktionen unterschieden werden. Bei ersteren werden kovalent an das Edukt gebundene chirale Auxiliare[17] (wie zum Beispiel Evans Oxazolidinone und Enders Hydrazine SAMP und RAMP)[18] für die Übertragung der Stereoinformation verwendet. Deren Anbringung und Entfernung erfordert jedoch zusätzliche Schritte.

Bei der enantioselektiven Synthese wird für den Stereotransfer die chirale Umgebung eines nicht kovalent gebundenen, enantiomerenreinen Reagenzes genutzt.[19] Setzt man dieses nur in unterstöchiometrischen Mengen ein, spricht man von enantioselektiver Katalyse. Dies ist die attraktivste Variante, da hier im Vergleich zu den beiden anderen *de novo* Methoden die größte Vervielfältigung von Chiralität erreicht wird und die Aufreinigung der gewünschten Produkte aufgrund der kleineren Menge an verwendeten Reagenzien einfacher ist. Dieser

Bereich gliedert sich in die Enzymkatalyse, Organokatalyse und Metallkatalyse auf. Enzyme als Katalysatoren[20] können oftmals das gewünschte Produkt mit ausgezeichnetem *ee* und unter milden Bedingungen ergeben, besitzen jedoch, gerade wenn es sich um Wildtypen handelt, häufig eine eingeschränkte Substratbreite. Des Weiteren sind sie anfällig gegenüber Hitze, Kälte und organischen Solvenzien; Hauptnachteil ist jedoch, das mit einem Enzym nur ein Enantiomer zugänglich ist, während die anderen katalytischen Methoden – mit den verfügbaren spiegelbildlichen Katalysatoren – beide liefern können. Als Organokatalysator werden kleine organische Moleküle bezeichnet, welche metallfrei sind und meist unter nicht-inerten Bedingungen eine Umsetzung beschleunigen.[21] Nachteil der Organokatalyse ist, dass häufig sehr lange Reaktionszeiten und hohe Katalysatorbeladungen benötigt werden. Die letzte Methode zur Darstellung enantiomerenreiner Zielmoleküle ist die Metallkatalyse, bei der die gewünschten Produkte meist mit ausgezeichneten Enantiomerenüberschüssen bei geringer Beladung erhalten werden. Ihre eminente Wichtigkeit für die Industrie und ihre Leistungsfähigkeit spiegeln sich nicht zuletzt in den 2001 an W. S. Knowles und R. Noyori „für ihre Arbeiten über chiral katalysierte Hydrierungen“ und K. B. Sharpless „für seine Arbeiten über chiral katalysierte Oxidationen“ verliehenen Nobelpreisen wieder.[22] An der Weiter- und Neuentwicklung chiraler Liganden mittels Struktur-Selektivitäts-Studien besteht besonderes Interesse, da sich hier eine große Chance bietet, das Potential (Reaktivität, Stereotransfer, etc.) eines Übergangsmetallkatalysators zu steigern.

1.2 Privilegierte chirale Liganden

Molekülgerüste chiraler Liganden bezeichnet man als privilegiert, wenn auf ihnen basierende Metallkomplexe bei verschiedenen asymmetrischen Transformationen und einer Vielzahl von Substraten hervorragende Enantioselektivitäten liefern.[23]

Ein solches privilegiertes Gerüst ist beispielsweise der axialchirale (*vide infra*) Grundkörper von 2,2'-substituierten 1,1'-Binaphthylen (**5**, Abbildung 4). Die beiden bekanntesten davon abgeleiteten Liganden sind BINAP (**5a**), welches z. B. in Noyoris Hydrierungen Anwendung findet (bis zu 100% *ee*),[24b] und BINOL (**5b**), das bis zu 98% *ee* in CN-Additionen an Aldehyde ergibt.[24a] Die auf dem Bisoxazolin-Gerüst **6** basierenden BOX-Liganden wurden ebenfalls mit großem Erfolg eingesetzt. Mit diesen konnten u. a. die jeweiligen Produkte Cu•**6**-katalysierter Mannich-,[25a] Diels-Alder-[25b] und Cyclopropanierungs-Reaktionen[25c] mit hervorragenden Enantiomerenüberschüssen von bis zu 99% erhalten werden. Komplexe mit chiralen Varianten des Bis(salicyliden)ethylendiamin-Liganden (SALEN-Liganden) **7** gehören gleichermaßen zu den leistungsfähigsten asymmetrischen Katalysatoren. So gelang der Gruppe um Katsuki die **7a**•Ru(CO)-katalysierte Aziridinierung von Vinylketonen mit bis zu 99% Ausbeute und 99% *ee*.[26a] Jacobsen *et al.* nutzen den Liganden **7b** erfolgreich in enantioselektiven, Chrom-katalysierten Epoxid-Öffnungen[26b] sowie in Mangan-katalysierten Epoxidierungen,[26c] bei denen sie jeweils bis zu 98% *ee* erzielten.

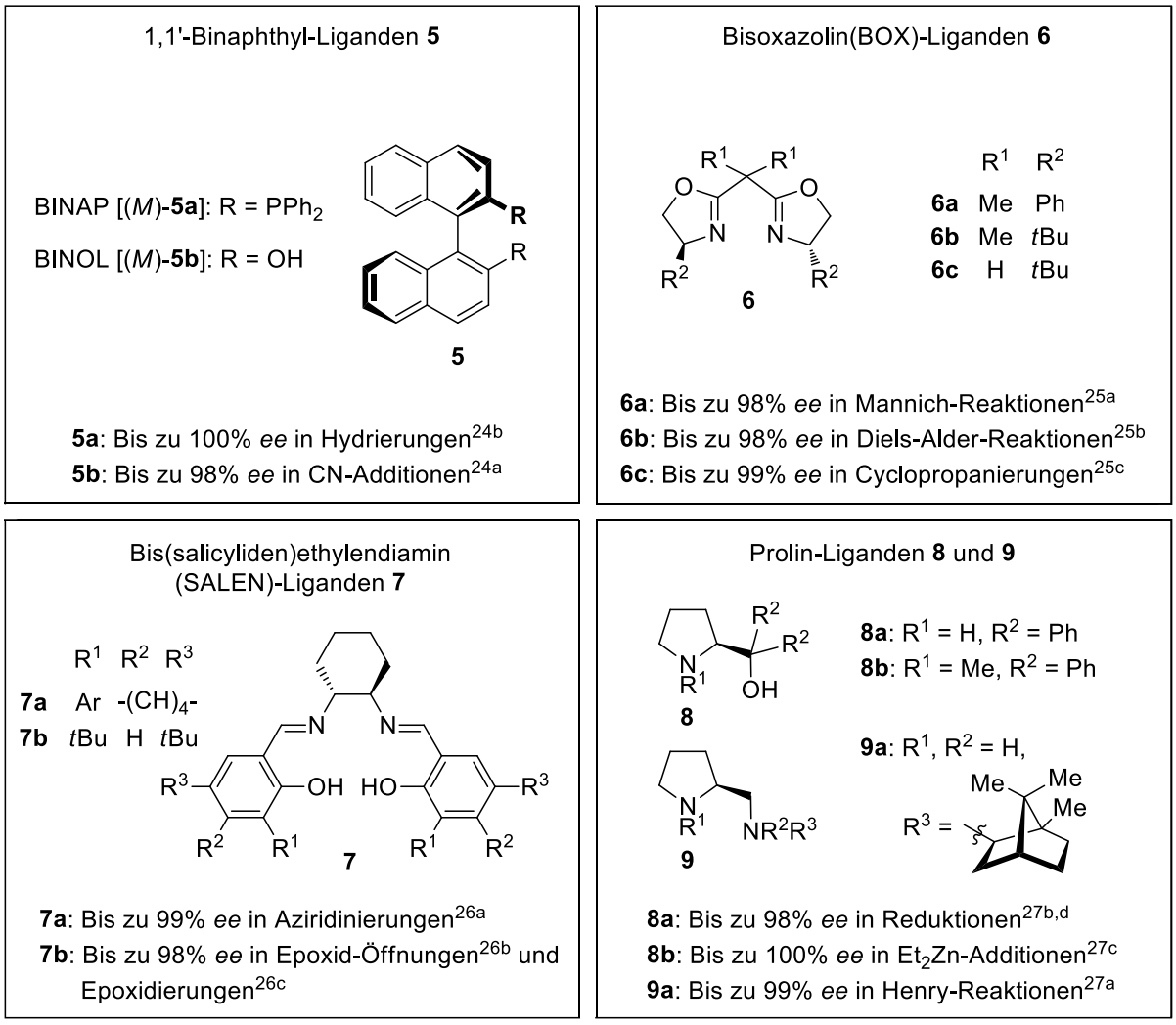


Abb. 4. Ein kleiner Auszug privilegierter chiraler Liganden **5**–**9** und Beispiele für ihre erfolgreiche Anwendung in der asymmetrischen Katalyse.[24–27] Ar = (*M*)-2-(3,5-Dichloro-4-(trimethylsilyl)phenyl)-naphthalen-1-yl.

Alle drei bisher vorgestellten Molekülgerüste **5**–**7** sind C_2-symmetrisch, was die Anzahl an möglichen Übergangszuständen senkt und damit (meist) den Stereotransfer verbessert. Eine Sonderstellung innerhalb der privilegierten Liganden nehmen die Prolin-abgeleiteten Pyrrolidine **8** und **9** ein, da diese trotz C_1-Symmetrie in der Lage sind, hervorragende Enantiomerenüberschüsse zu liefern. Bei dem bekannten CBS-Katalysator handelt es sich beispielsweise um ein Boronsäure-Derivat des Prolinols **8a**, mit dem bis zu 98% *ee* in enantioselektiven Reduktionen erreicht werden.[27b,d] Des Weiteren berichteten 1987 Soai und Mitarbeiter, dass **8b** ein hochselektiver (bis zu 100% *ee*) Ligand für Et_2Zn-Additionen an Aldehyde ist.[27c] Setzt man Kupfer-Komplexe von Gongs Prolinamin **9a** als Katalysator in asymmetrischen Henry-Reaktionen ein, werden die entsprechenden *β*-Nitroalkohole mit bis zu 99% *ee* erhalten.[27a]

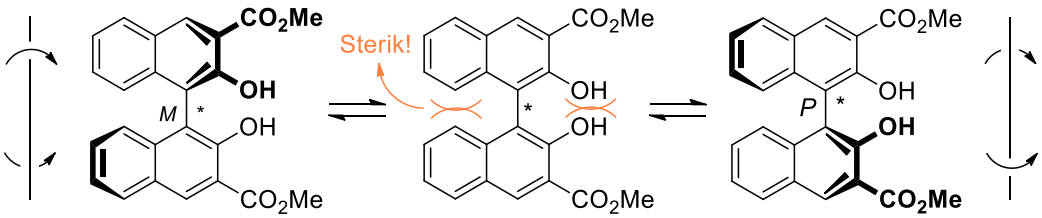
1.3 Prolinamine als chirale Liganden in der asymmetrischen Metallkatalyse

Betrachtet man die Liganden **8** und **9** (s. Abbildung 4, Kapitel 1.2) genauer, so fällt auf, dass bei den Prolinaminen **9** im Vergleich zu Prolinolen **8** aufgrund des zusätzlichen Restes an der exocyclischen Aminofunktion ein weiterer sterischer Block eingeführt werden kann. Dadurch bieten diese in Struktur-Selektivitäts-Untersuchungen – mit dem Ziel potentere Katalysatoren zu finden – eine größere Variabilität. Sie sind damit ein besonders attraktives Studienobjekt innerhalb dieser C_1-symmetrischen und hochinteressanten Ligandenklasse.

Im Folgenden sollen sowohl die Leistungsfähigkeit als auch das in den Prolinaminen **9** vorhandene Potential als chirale Liganden anhand von den in drei unterschiedlichen Modellreaktionen erzielten Ergebnissen verdeutlicht werden.

1.3.1 Cu•Diamin-katalysierte enantioselektive oxidative Biarylkupplungen

Biarylachsen sind chiral, sofern diese unsymmetrische Aryl-Gruppen verbinden und rotationsgehindert sind. Man spricht von Atropisomerie (griech. a = nicht, tropos = drehen), sobald bei einer gegebenen Temperatur eine Isolierung beider Rotamere zumindest potentiell möglich wäre und diese eine Halbwertszeit von mindestens 1000 s besitzen.[28] Die hierfür zu überwindende Rotationsbarriere ist abhängig von Größe und Anzahl der *ortho*-Substituenten, da diese, wie am Modellsubstrat **5c** in Abbildung 5 verdeutlicht, im Übergangszustand aneinander vorbeigleiten müssen. Dieser sterische Block kann bei einfach *ortho*-substituierten Biarylen sehr leicht überwunden werden (→ konfigurativ labil oder semistabil), wohingegen Verbindungen mit zwei sehr großen *ortho*-Substituenten oder dreifach- bzw. vierfach-substituierte Derivate in der Regel konfigurativ stabile Atropisomere bilden.[29e]



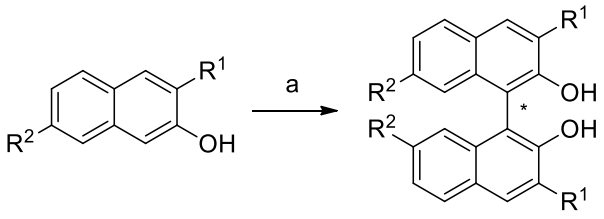
(*M*)-**5c** **5c** (*P*)-**5c**

Abb. 5. Gehinderte Atropisomerisierung axialchiraler Biaryle am Beispiel des Modellsubstrates **5c.**

Zur Synthese enantiomerenreiner, axialchiraler Biaryle stehen verschiedene Methoden zur Verfügung, u. a. die enantioselektive Kupplung zweier Arylbausteine.[29] Hierbei sticht die milde, biomimetische,[30] Cu•Diamin-vermittelte oxidative[31] Kupplung von Naphtholen **10** (Tabelle 1) als elegante, umweltfreundliche Herangehensweise hervor. Eine effiziente kata-

lytische, allerdings noch nicht stereoselektive Variante dieser Umsetzung publizierte erstmals 1994 die Gruppe um Nakajima.[32,33] Unter Verwendung von 1 Mol-% CuCl(OH)•TMEDA als Katalysator und Luftsauerstoff als Oxidationsmittel wurden verschieden substituierte Binaphthole *rac*-**5** in Ausbeuten ≥ 95% erhalten.

Tabelle 1. Nicht stereoselektive, CuCl(OH)•TMEDA-katalysierte oxidative Biarylkupplungen.[32]
Reagenzien und Bedingungen: (a) CuCl(OH)•TMEDA (1 Mol-%), Luftsauerstoff, CH_2Cl_2.



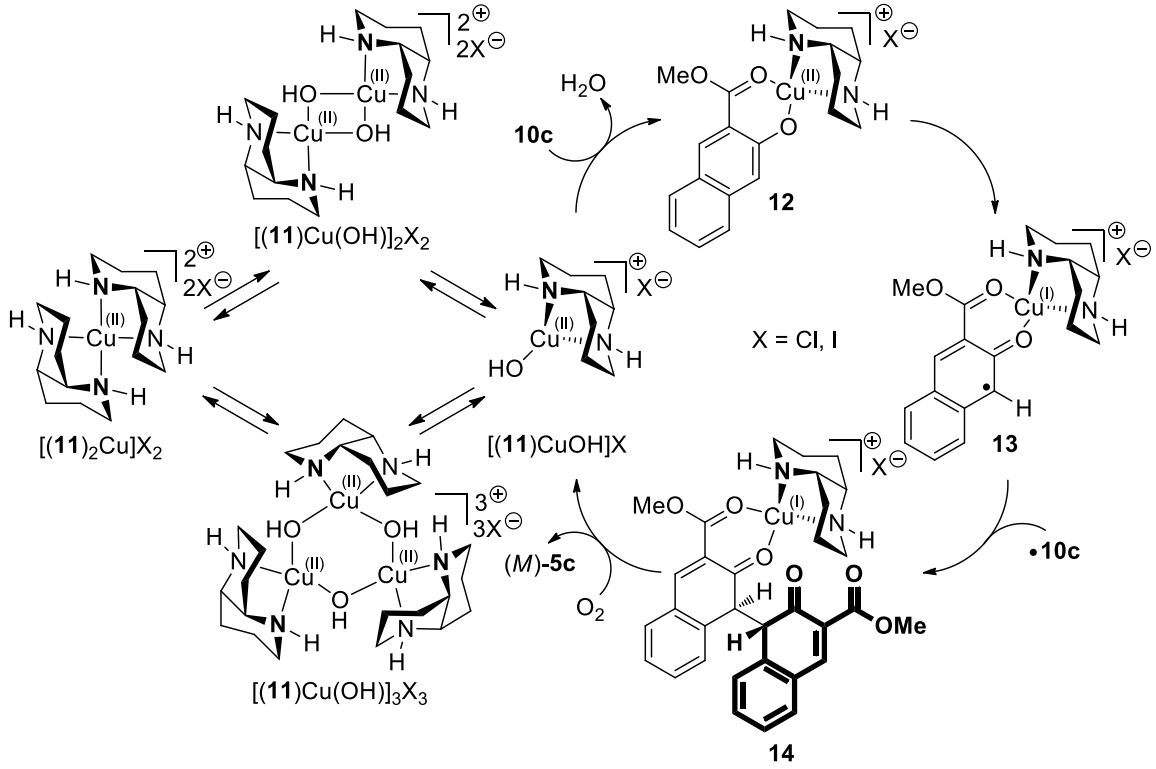
10 *rac*-**5**

Eintrag	Naphthol (**10**)	Binaphthol (**5**)	R^1	R^2	Temperatur [°C]	Laufzeit [h]	Ausbeute [%]
1	**10b**	**5b**	H	H	0	20	96
2[a]	**10c**	**5c**	CO_2Me	H	Δ	144	99
3	**10d**	**5d**	Me	H	RT	1	96
4	**10e**	**5e**	H	OMe	RT	2	95

[a] Solvens: MeOH

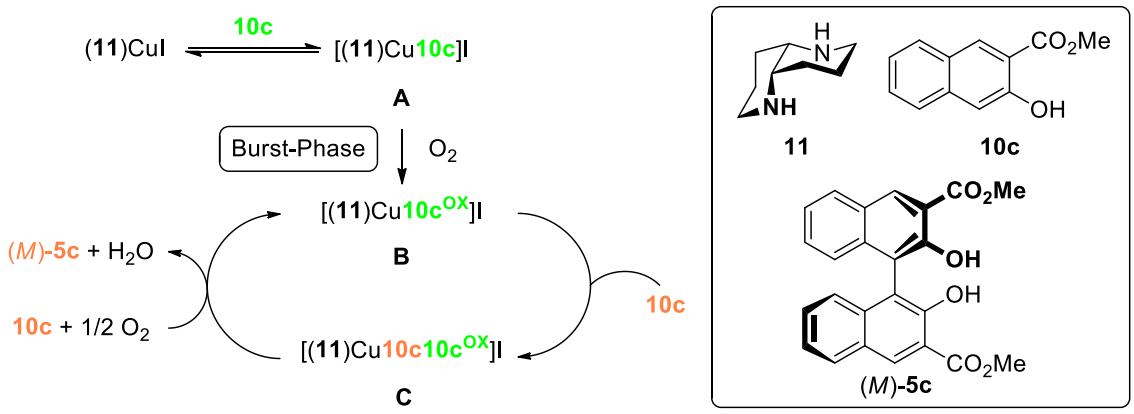
1.3.1.1 Mechanistische Untersuchungen

Der Mechanismus der asymmetrischen, Cu•Diamin-katalysierten oxidativen Biarylkupplung[34] wurde von der Gruppe um Kozlowski anhand ihres Liganden **11** (Schema 1) intensiv untersucht.[35] Der Kupfer-Ligand-Komplex liegt in Lösung als Dimer bzw. Oligomer vor {vgl. $[(\mathbf{11})_2Cu]X_2$, $[(\mathbf{11})Cu(OH)]_2X_2$ und $[(\mathbf{11})Cu(OH)]_3X_3$, X = Cl oder I}, womit sie den von ihnen gefunden NLE[36] erklärten; katalytisch aktiv ist jedoch ein kationisches Monomer wie [(**11**)CuOH)]X. Durch Ligandenaustausch (→ **12**, das Substrat muss für einen guten Stereotransfer zweibindig sein, *vide infra*) und Oxidation bildet sich das Intermediat **13**, aus dem **14** durch enantioselektive Kupplung[37] mit einem weiteren Radikal[38,39] generiert wird. Vervollständigt wird der Katalysezyklus durch einen Zentro- zu Axialchiralität-Transfer während der Rearomatisierung,[40] anschließende Produktabspaltung und der geschwindigkeitsbestimmenden[35a] Reoxidation des Kupfers.



Schema 1. Erster postulierter Katalysezyklus der **11**•Cu-katalysierten oxidativen Biarylkupplung.[35b–d]

In neueren kinetischen Untersuchungen[35a] fanden Kozlowski *et al.* eine Abhängigkeit erster Ordnung bezüglich Sauerstoff und Katalysator. Außerdem detektierten sie eine „Burst"-Phase (**A** → **B**) am Anfang der Reaktion, bei der O_2 und **10c** verbraucht werden, jedoch nur sehr wenig Produkt **5c** gebildet wird. Die Gruppe vermutete deshalb, dass der im Gleichgewicht hauptsächlich vorliegende Katalysator **C** ein oxidiertes, Chinon-artiges Naphthol **10c**^{ox} enthält. Sie postulierten, dass dieser Cofaktor die beobachtete, geschwindigkeitsbestimmende Oxidoreduktase-Aktivität von **C** kontrolliert und erweiterten ihren Mechanismus hin zu dem in Schema 2 gezeigten.

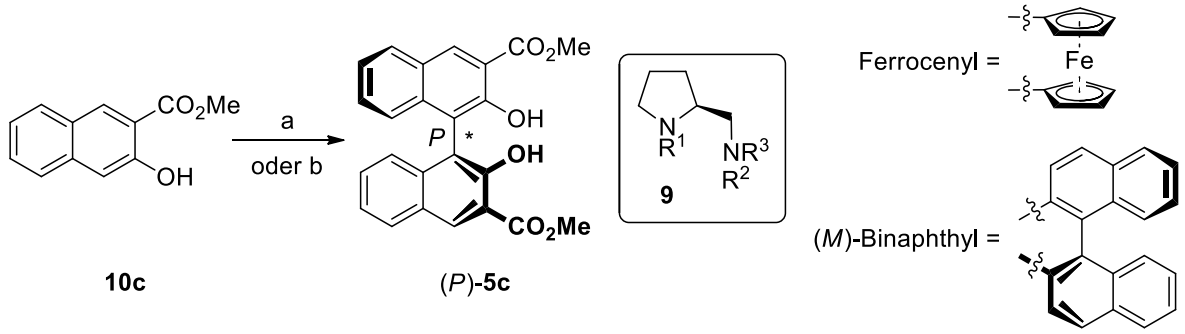


Schema 2. Erweiterter Mechanismus der oxidativen Biarylkupplung gemäß Kozlowski *et al.*[35a]

1.3.1.2 Auf Prolinaminen 9 basierende Katalysatoren

Aufbauend auf ihren Vorarbeiten[32] (s. Kapitel 1.3.1) untersuchten Nakajima *et al.* verschiedene chirale Prolinamin-Derivate **9** auf ihr Potential in der asymmetrischen oxidativen Biarylkupplung von **10c** (Tabelle 2).[41] Sie fanden, dass ein sekundäres Stickstoffatom im Pyrrolidinring (R^1 = H, Eintrag 1 vs. 2) sowie eine tertiäre, exocyclische Aminofunktion (Eintrag 2 vs. 3) den besten Chiralitätstransfer erlauben. Als optimaler Rest R^2 erwies sich eine Phenylgruppe. Bei Vergrößerung oder Verkleinerung des sterischen Anspruchs an dieser Position sank der *ee* (Eintrag 3 vs. 4 vs. 5), ebenso bei zu großem R^3 (Eintrag 3 vs. 7). Der beste in diesem Screening evaluierte Ligand war das *N*-Ethylanilin-Derivat **9g** (R^1 = H, R^2 = Ph, R^3 = Et), das (*P*)-**5c** in 78% Ausbeute und mit 70% *ee* lieferte (Eintrag 6). In späteren Arbeiten[42] fanden Cui *et al.* durch weitere Variation von R^2 und R^3 die beiden potenten Liganden **9i** und **9j** [Eintrag 8 und 9, R^1 = H, R^2, R^3 = (*M*)-Binaphthyl bzw. Ferrocenyl]; mit letzterem konnten in der Modellreaktion hervorragende 92% *ee* bei 79% Ausbeute erzielt werden.[43]

Tabelle 2. Ausgewählte Ergebnisse der Evaluierung verschiedener Prolinamine **9** in der enantioselektiven Biarylkupplung von **10c**.[41a,43]
Reagenzien und Bedingungen: (a) **9** (11 Mol-%), CuCl (10 Mol-%), O_2, CH_2Cl_2, Δ, 24 h. (b) **9** (10 Mol-%), CuCl (10 Mol-%), Luftsauerstoff, CH_3CN, 15 °C, 4 d.

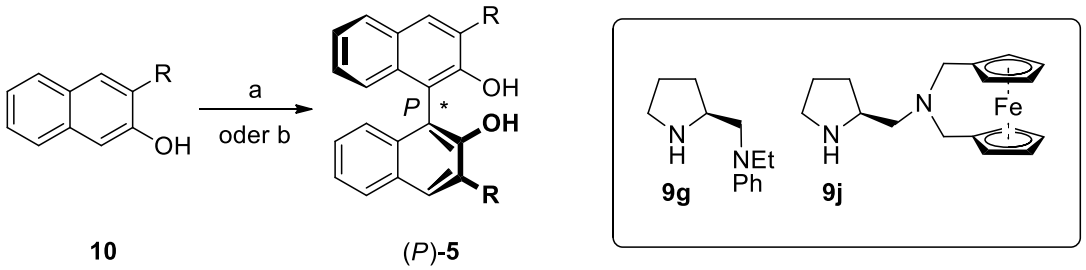


10c (*P*)-**5c**

Eintrag	Ref.	Diamin **9**	R^1	R^2	R^3	Bedingungen	Ausbeute [%]	*ee* [%]
1	41a	**9b**	Me	Ph	H	a	77	4
2	41a	**9c**	H	Ph	H	a	74	30
3	41a	**9d**	H	Ph	Me	a	76	59
4	41a	**9e**	H	1-Naph	Me	a	25	34
5	41a	**9f**	H	$-(CH_2)_4-$		a	82	31
6	41a	**9g**	H	Ph	Et	a	78	70
7	41a	**9h**	H	Ph	Ph	a	66	12
8	43	**9i**	H	$-CH_2$-(*M*)-Binaphthyl-CH_2-		b	74	80
9	43	**9j**	H	$-CH_2$-Ferrocenyl-CH_2-		b	79	92

Bei Untersuchungen zur Substratbreite ihres besten Katalysators **9g**•CuCl fanden Nakajima *et al.*, dass für einen befriedigenden Stereotransfer neben dem Alkohol eine zweite, koordinierende Gruppe im Edukt **10** zwingend notwendig ist (Tabelle 3, Einträge 1 und 2 vs. 3–7).[41a,44] Am besten geeignet hierfür war eine Methylester-Funktion (Einträge 3 und 4 vs. 5). Vergrößerte man an dieser Stelle den sterischen Anspruch, sanken sowohl Ausbeute als auch *ee* (**5c**: R = CO_2Me, 85% Ausbeute, 78% *ee* vs. **5h**: R = CO_2Et, 77% Ausbeute, 73% *ee* vs. **5i**: R = CO_2tBu, 69% Ausbeute, 58% *ee*, Eintrag 5 vs. 6 vs. 7). Der gleiche Trend wurde bei Verwendung des chiralen Liganden **9j** gefunden (Einträge 8–10).[43]

Tabelle 3. Substratbreite der Prolinamin-Katalysatoren **9g**•CuCl und **9j**•CuCl.[41a,43]
Reagenzien und Bedingungen: (a) **9g**•CuCl (10 Mol-%), O_2, CH_2Cl_2, RT, 24 h. (b) **9j** (10 Mol-%), CuCl (10 Mol-%), Luftsauerstoff, CH_3CN, 15 °C, 4 d.



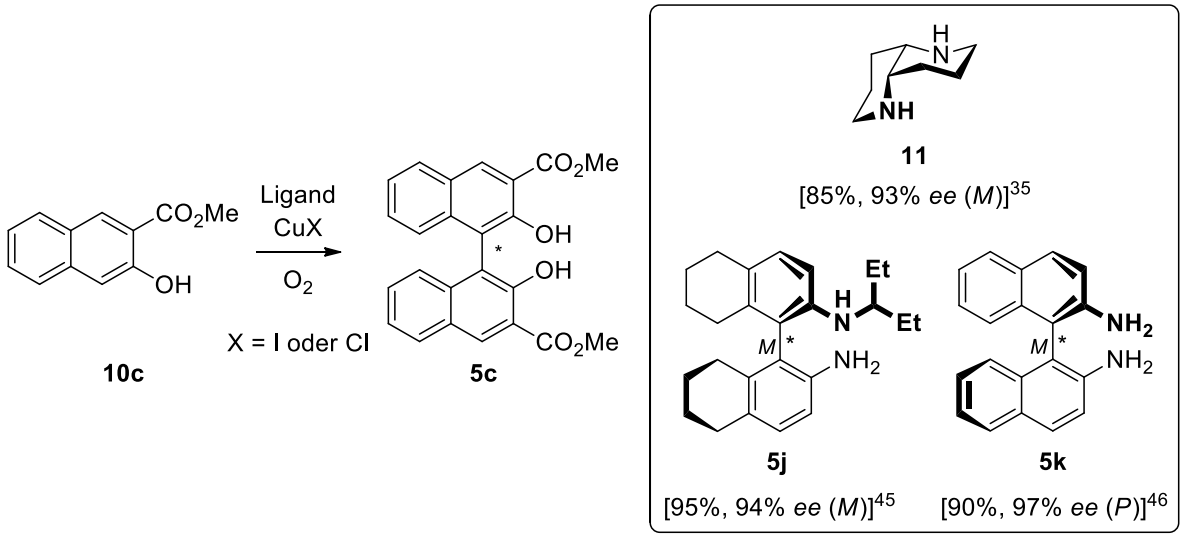
10 (*P*)-**5**

Eintrag	Ref.	Diamin	**10**	(*P*)-**5**	R	Bedingungen	Ausbeute [%]	*ee* [%]
1	41a	**9g**	**10b**	**5b**	H	a	89	17
2	41a	**9g**	**10d**	**5d**	Me	a	93	12
3	41a	**9g**	**10f**	**5f**	COMe	a	71	37
4	41a	**9g**	**10g**	**5g**	CONHBn	a	65	24
5	41a	**9g**	**10c**	**5c**	CO_2Me	a	85	78
6	41a	**9g**	**10h**	**5h**	CO_2Et	a	77	73
7	41a	**9g**	**10i**	**5i**	CO_2tBu	a	69	58
8	43	**9j**	**10c**	**5c**	CO_2Me	b	79	92
9	43	**9j**	**10h**	**5h**	CO_2Et	b	73	50
10	43	**9j**	**10i**	**5i**	CO_2tBu	b	Spuren	–

1.3.1.3 Nicht-Prolin-basierte Benchmark-Diamin-Liganden

Neben dem Ferrocenyl-Prolinamin **9j** (*vide supra*) sind nur ein paar wenige andere Diamine bekannt, die in der Cu-katalysierten Modellreaktion **10c** → **5c** über 90% *ee* liefern (Schema 3). Eines davon ist 1,5-Diaza-*cis*-decalin (**11**), mit dessen Kupfer-Komplex ein Enantiomerenüberschuss von 93% erhalten wird.[35] Einen nahezu identischen Chiralitätstransfer (94% *ee*) induziert der auf dem privilegierten Binaphthyl-Gerüst basierende Ligand **5j**.[45] Das bisher potenteste untersuchte Amin, welches **5c** mit hervorragenden 97% *ee* ergibt, ist jedoch BINAM (**5k**) selbst.[46] Mit den Liganden **11** und **5k** wurde ebenfalls der Einfluss der Größe

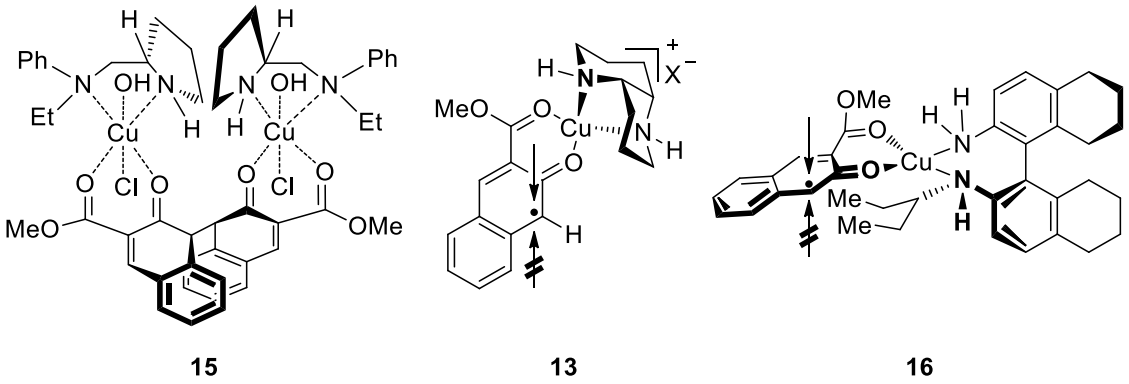
des Ester-Substituenten im Edukt **10** untersucht, wobei der von Nakajima und Cui gefundene Trend (Tabelle 3) bestätigt wurde: je sterisch anspruchsvoller diese funktionelle Gruppe ist, desto schlechter ist der Chiralitätstransfer.[47]



Schema 3. Benchmark-Diamin-Liganden für die Modellreaktion **10c** → **5c**.[35,45,46]

1.3.1.4 Postulierte Übergangszustände

Bei den hier vorgestellten Liganden wurde nur für die Diamine **9g**, **11** und **5j** eine Erklärung für die beobachtete stereochemische Induktion geliefert. Nakajima *et al.* postulierten, dass der nach der Kupplung entstehende, oktaedrische Kupfer-Ligand-Diketon-Komplex **15** (Abbildung 6) eine entscheidende Rolle für den Stereotransfer spielt.[41a] Die Anordnung der beiden Pyrrolidine **9g** in diesem Dimer minimiert destruktive Wechselwirkungen zwischen deren Substituenten. Kozlowski[35] und Ha[45] schlugen hingegen tetraedrische Übergangszustände vor (**13** für **11** und **16** für **5j**), in denen der jeweilige chirale Ligand eine der beiden möglichen Angriffs-Trajektorien auf das Radikal blockiert.

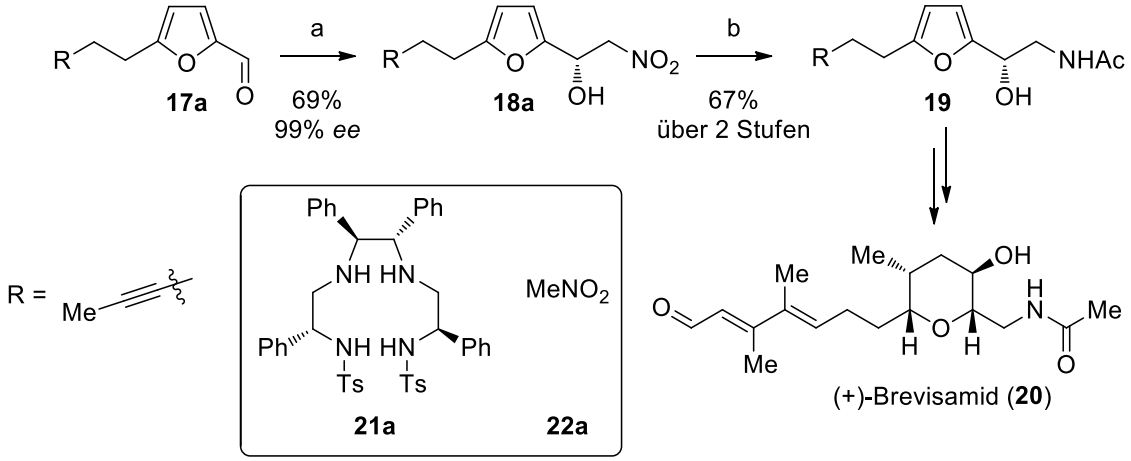


15 13 16

Abb. 6. Die stereochemisch entscheidenden Intermediate der Cu•Diamin-katalysierten oxidativen Biarylkupplung gemäß Nakajima,[41a] Kozlowski[35] und Ha.[45]

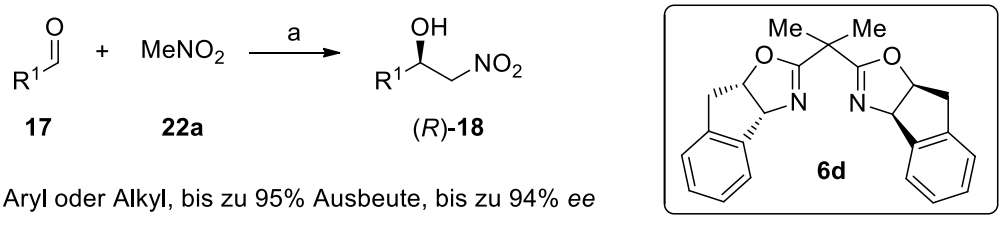
1.3.2 Cu•Diamin-katalysierte asymmetrische Henry-Reaktionen

Die Henry (oder auch Nitroaldol)-Reaktion[48] ist eine bedeutende Methode zur C-C-Verknüpfung und eine Standardreaktion[49] zur Evaluierung neuer chiraler Katalysatoren.[50] Die hierbei erhaltenen (skalemischen) *β*-Nitroalkohole **18** (Schema 4) sind wertvolle Syntheseintermediate und können auf vielfältige Weise weiter umgesetzt werden, u. a. hin zu *α*-Hydroxysäuren oder *β*-Aminoalkoholen. Letztere Modifikation (**18a** → **19**) nutzten beispielsweise Zakarian *et al.* in ihrer asymmetrischen Totalsynthese des aus dem Dinoflagellaten *Karenia brevis* isolierten[51] cyclischen Ethers (+)-Brevisamid (**20**).[52] Der stereochemisch entscheidende Schritt ihrer Synthesesequenz war die enantioselektive Henry-Reaktion von **17a** zu **18a** in Gegenwart des chiralen Katalysators $Cu(OAc)_2$•**21a**, die das gewünschte Produkt mit 69% Ausbeute und mit hervorragenden 99% *ee* lieferte.



Schema 4. Stereochemisch entscheidende Henry-Reaktion in der Totalsynthese von (+)-Brevisamid (**20**).[52] *Reagenzien und Bedingungen*: (a) **22a**, **21a** (5 Mol-%), $Cu(OAc)_2$•H_2O (2.5 Mol-%), EtOH, RT, 40 h. (b) I. $LiAlH_4$, THF, –15 °C → Δ, 2.5 h. II. Ac_2O, EtOAc, MeOH, RT, 12 h.

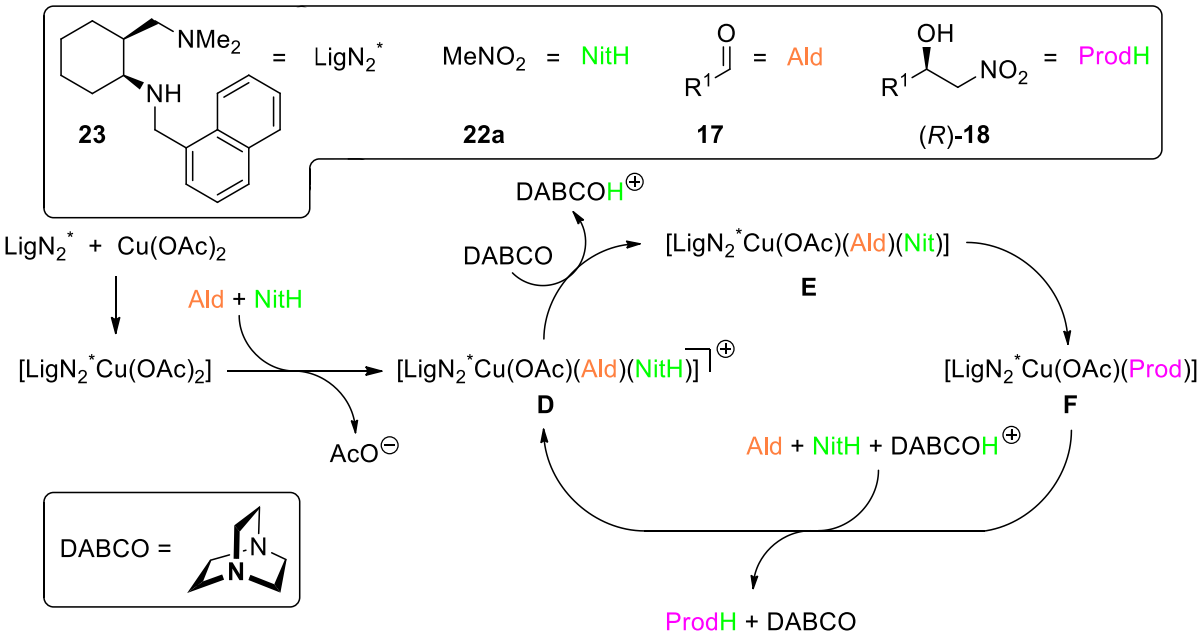
Chirale Kupfer-Stickstoff-Komplexe wie **21a**•$Cu(OAc)_2$ gehören zu den leistungsfähigsten Katalysatoren für die enantioselektive Henry-Reaktion.[53–57] Seit der wegweisenden Arbeit von Evans *et al.*, in der **6d**•$Cu(OAc)_2$-katalysiert verschiedene *β*-Nitroalkohole (*R*)-**18** in Ausbeuten von bis zu 95% und Enantiomerenüberschüssen von bis zu 94% erhalten werden konnten,[58,59] wurde eine Vielzahl weiterer stickstoffhaltiger Liganden (u. a. Box-, Iminoalkohol-, Aminoalkohol-basierte etc.) anhand der in Schema 5 gezeigten Modellreaktion evaluiert. Besonders erfolgreich waren dabei Diamine (*vide infra*).[53j–q]



Schema 5. Erste hochenantioselektive, Cu•Box-katalysierte Addition von $MeNO_2$ (**22a**) an Aldehyde.[58] *Reagenzien und Bedingungen*: (a) **6d** (5.5 Mol-%), $Cu(OAc)_2$•H_2O (5 Mol-%), EtOH, RT.

1.3.2.1 Postulierter Mechanismus

Für Henry-Reaktionen in Gegenwart von Kupferkomplexen, die mit einem über zwei Stickstoffatome gebundenen Liganden chiral modifiziert sind,[60] existieren in der Literatur eine Vielzahl an postulierten Katalysezyklen.[61] Je nach Oxidationsstufe des eingesetzten Kupfers,[62] der Art[63] und Bindigkeit[64] des Liganden oder den gewählten Reaktionsbedingungen[65] unterscheiden sich diese im Detail. Exemplarisch ist in Schema 6 der 2011 von Hirose *et al.* für den Katalysator **23**•$Cu(OAc)_2$ vorgeschlagene Reaktionsmechanismus gezeigt:[61g] Der Ligand **23** bildet hier mit $Cu(OAc)_2$ einen Komplex an den sich, unter Verdrängung eines Acetats, **22a** und der Aldehyd **17** anlagern. Das an der resultierenden, kationischen Spezies **D** gebundene und somit aktivierte Nitromethan (NitH, **22a**) wird durch die Hilfsbase DABCO deprotoniert (→ **E**) und es kommt zur C-C-Bindungsknüpfung (→ **F**). Vervollständigt wird der Katalysezyklus via Abspaltung des durch $DABCOH^+$ protonierten Produkts (*R*)-**18** und erneute Anlagerung von **22a** und **17**, was wieder zu **D** führt.



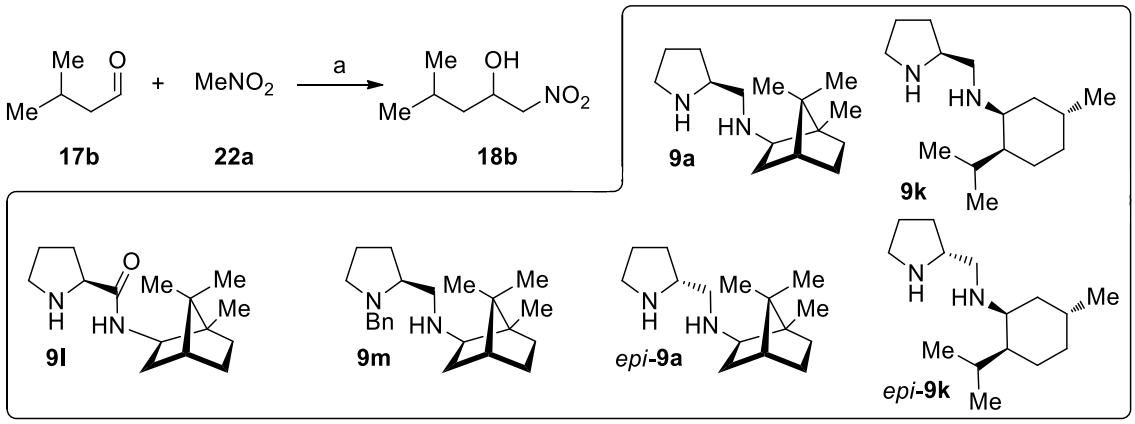
Schema 6. Mechanismus der **23**•$Cu(OAc)_2$-katalysierten Henry-Reaktion nach Hirose *et al.*[61g]

1.3.2.2 Gongs Prolinamin 9a

Gong *et al.* untersuchten diverse Prolin-abgeleitete, C_1-symmetrische Diamine[66] **9** in der Kupfer-katalysierten Addition von Nitromethan (**22a**) an Isovaleraldehyd (**17b**). Dabei identifizierten sie den Kupfer-Komplex des Liganden **9a** (s. auch Kapitel 1.2) als einen vielversprechenden Katalysator (Tabelle 4, Eintrag 1).[27a,67] In diesen Versuchen konnten sie sowohl die Überlegenheit von einem Campher- gegenüber einem Menthon-abgeleiteten Substituenten (Eintrag 1 vs. 2) als auch von einem Amin gegenüber einem Amid (Eintrag 1 vs. 3) am exocyclischen Stickstoff zeigen. Am Pyrrolidin erwies sich eine NH-Funktion als optimal (Eintrag 1 vs. 4). Des Weiteren bestimmte die Konfiguration des Prolin-Gerüsts zum Großteil die

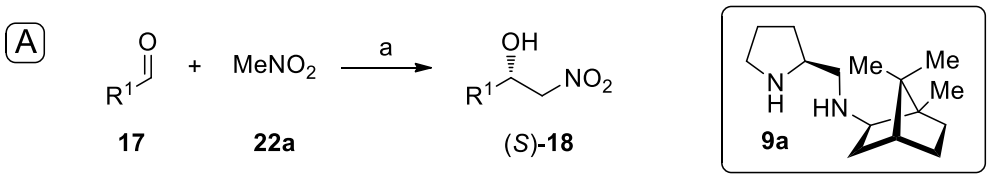
erhaltene Stereoinduktion [Einträge 1 und 2, **9a** und **9k**, 91% bzw. 76% *ee* (*S*) vs. Einträge 5 und 6, *epi*-**9a** und *epi*-**9k**, 37% bzw. 60% *ee* (*R*)].

Tabelle 4. Von Gong *et al.* in der Henry-Reaktion evaluierte Prolinamine **9** (Auswahl).[27a]
Reagenzien und Bedingungen: (a) **9** (5 Mol-%), $Cu(OAc)_2 \cdot H_2O$ (5 Mol-%), DIPEA, EtOH, 4 °C.

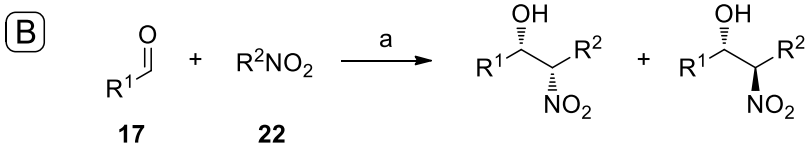


Eintrag	Prolinamin **9**	Ausbeute [%]	*ee* [%]	Konfig.
1	**9a**	65	91	*S*
2	**9k**	61	76	*S*
3	**9l**	49	11	*S*
4	**9m**	63	61	*S*
5	*epi*-**9a**	56	37	*R*
6	*epi*-**9k**	66	60	*R*

Nach Optimierung der Reaktionsbedingungen wurden in Gegenwart von **9a**•$CuCl_2$ 19 verschiedene Aldehyde **17**, darunter Substrate mit aromatischen, aliphatischen und heteroaromatischen Resten, zu den entsprechenden *β*-Nitroalkoholen (*S*)-**18** umgesetzt (Schema 7 A).



R^1 = Aryl, Heteroaryl oder Alkyl, 19 Beispiele, ≥ 90% Ausbeute, ≥ 95% *ee*



R^1 = Aryl, Heteroaryl oder Alkyl,
R^2 = Et (**22b**), *n*Pr (**22c**), CH_2CH_2Ph (**22d**),
11 Beispiele, ≥ 80% Ausbeute, *syn*:*anti* 55:45 bis zu 90:10, *ee*(*syn*) ≥ 93%, *ee*(*anti*) ≥ 60%

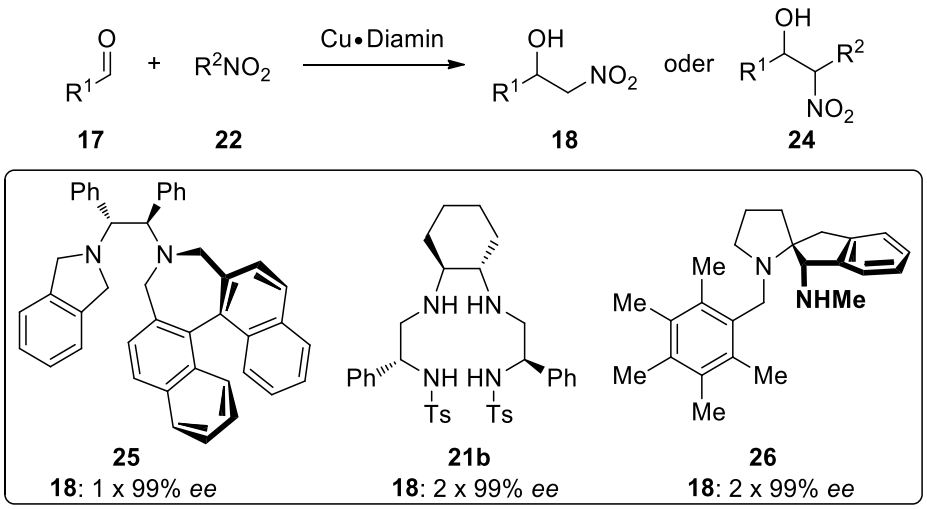
Schema 7. Diastereo- und enantioselektive **9a**•$CuCl_2$-katalysierte Henry-Reaktionen.[27a]
Reagenzien und Bedingungen: (a) **9a** (2.5 Mol-%), $CuCl_2 \cdot 2H_2O$ (2.5 Mol-%), DIPEA, THF, –20 °C oder 4 °C.

Sie erhielten hierbei sehr gute Ausbeuten von ≥ 90% und hervorragende Enantiomerenüberschüsse von ≥ 95%. Der Katalysator war ebenfalls geeignet für diastereoselektive Henry-Reaktionen (Schema 7 B). Hier lieferte **9a** bei der Addition von Nitroethan (**22b**), Nitropropan (**22c**) bzw. Phenylnitroethan (**22d**) an diverse Edukte **17** (in Summe 11 Beispiele) gute Ausbeuten (80–95%), moderate bis akzeptable Diastereomerenüberschüsse (10–80% *de*) und ausgezeichnete Enantiomerenüberschüsse (*syn*–**24**: 93–98% *ee*).[27a]

In späteren Arbeiten der Gruppe konnte die Leistungsfähigkeit von **9a** bestätigt werden,[68] was dessen Cu-Komplex zu einem der potentesten verfügbaren Katalysatoren für asymmetrische Henry-Reaktionen macht (in Summe konnten drei verschiedene *β*-Nitroalkohole **18** mit ausgezeichneten 99% *ee* dargestellt werden).[53]

1.3.2.3 Weitere erfolgreich evaluierte Diamine

Eines der wenigen weiteren Diamine, das in Nitroaldol-Additionen ähnlich hervorragende Ergebnisse wie **9a** liefert (s. Kapitel 1.3.2.2),[53j–q] ist z. B. Arais axialchiraler Ligand **25** (Schema 8). Mit dem entsprechenden Kupfer-Komplex wurden *β*-Nitroalkohole (*S*)-**18** mit Ausbeuten ≥ 92% und Enantiomerenüberschüssen ≥ 91% (in einem Beispiel 99%) erhalten.[53o] Minimal bessere Ergebnisse [zweimal (*R*)-**18** mit 99% *ee*] konnten mit dem Diamin-Disulfonamid **21b** erzielt werden.[53l] Beide Liganden waren ebenfalls für diastereoselektive Henry-Reaktionen geeignet und ergaben bevorzugt *syn*-**24** mit moderater bis ausgezeichneter Selektivität (*syn*: *anti* = 2:1 bis zu 32:1) und akzeptablen bis hervorragenden *ee* (72–99%). Mit Kałużas Spiro-Ligand **26** wurde ausschließlich Nitromethan (**22a**) als Nukleophil genutzt; hier konnte ebenfalls zweimal (*R*)**-18** mit 99% *ee* isoliert werden.[53j]



25: R^2 = Me, ≥ 92% Ausbeute, ≥ 91% *ee* (*S*). R^2 ≠ Me, ≥ 70% Ausbeute, *syn*:*anti* ≥ 3:1, ≥ 96% *ee* (*S*,*S*)
21b: R^2 = Me, ≥ 70% Ausbeute, ≥ 92% *ee* (*R*). R^2 ≠ Me, ≥ 57% Ausbeute, *syn*:*anti* ≥ 2:1, ≥ 72% *ee* (*R*,*R*)
26: R^2 = Me, ≥ 58% Ausbeute, ≥ 76% *ee* (*R*).

Schema 8. Weitere erfolgreich in diastereo- und enantioselektiven Henry-Reaktionen getestete Diamine.[53j,l,o]

1.3.2.4 Modell des Übergangszustandes

Zur Erklärung der in den Cu•Diamin-katalysierten, asymmetrischen Henry-Reaktionen beobachteten stereochemischen Induktion nutzen viele Arbeitsgruppen das Modell von Evans *et al.*,[58] in dem die Bildung eines Jahn-Teller-entarteten oktaedrischen Cu(II)-Komplexes **G** postuliert wird (Abbildung 7 A). Dieser besitzt äquatorial vier stark Lewis-saure (orange markiert) und axial zwei weniger stark Lewis-saure Koordinationsstellen (grün markiert).

An erstgenannte Stellen erfolgt die Anlagerung des zweibindigen Liganden sowie der Gegenionen X, wodurch sich der in Abbildung 7 B gezeigte quadratisch planare Komplex **H** bildet (vgl. auch Schema 6, Kapitel 1.3.2.1).

Der Aldehyd verdrängt im Katalysezyklus ein Gegenion und lagert sich in der Ebene des Liganden an, wo er die größtmögliche Aktivierung erfährt, während das Nitronat senkrecht zu dieser an den Komplex koordiniert und damit kleinstmöglich deaktiviert ist (Abbildung 7 C). Das exakte Aussehen der sich hieraus ergebenden reaktivsten Übergangszustände ist von den sterischen und elektronischen Eigenschaften des Liganden abhängig; Evans zieht beispielsweise sowohl einen sesselartigen wie **I** als auch einen bootartigen wie **J** in Betracht.

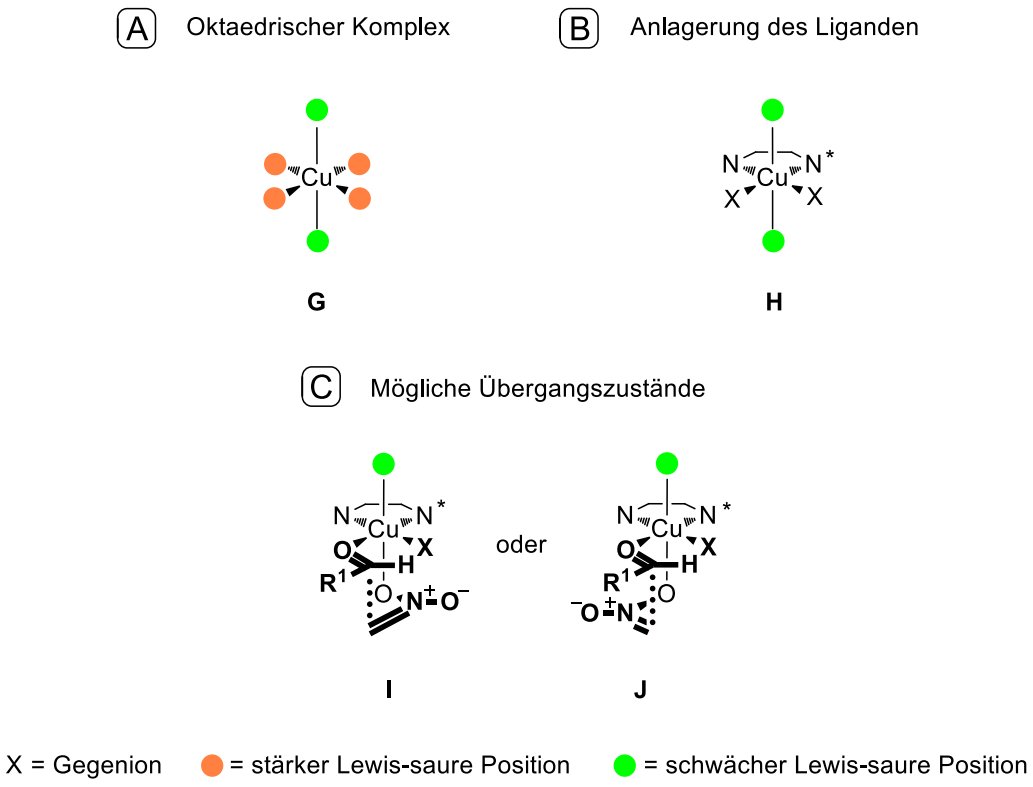
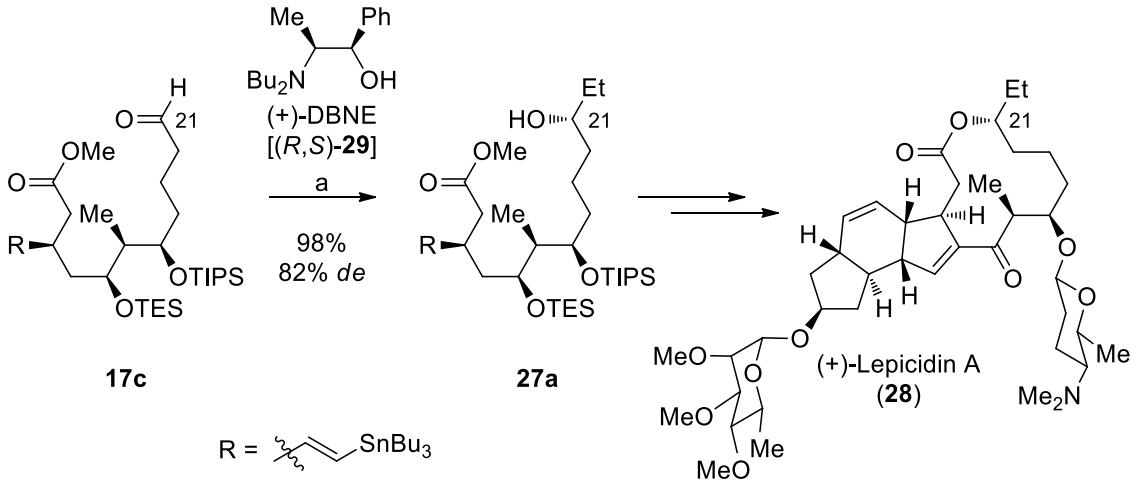


Abb. 7. Evans Modell zur Erklärung der stereochemischen Induktion in Cu•Diamin-katalysierten Henry-Reaktionen.[58]

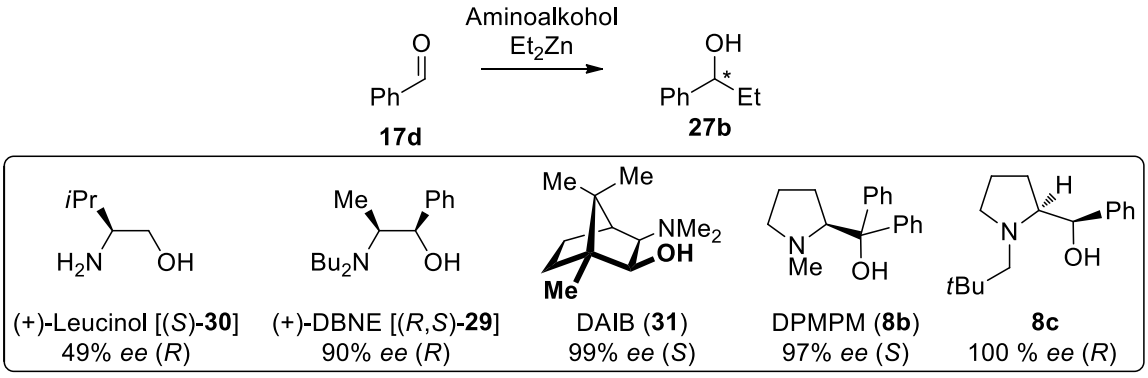
1.3.3 Zn•Diamin-katalysierte asymmetrische Et_2Zn-Additionen an Aldehyde

Die enantioselektive Et_2Zn-Addition an Aldehyde[69] ist ebenfalls – wie die Henry-Reaktion – eine bedeutende C-C-Knüpfungsmethode und wurde beispielsweise in der Totalsynthese des Insektizids[70] (+)-Lepicidin A (**28**, Schema 9) verwendet.[71] Im Detail nutzten Evans und Black in ihrer Route diese, hier (+)-DBNE [(*R*,*S*)-**29**]-katalysierte, Umsetzung (**17c** → **27a**), um das Chiralitätszentrum an C21 des Naturstoffs **28** stereoselektiv aufzubauen.



Schema 9. Asymmetrische Et_2Zn-Addition (**17c** → **27a**) in der Synthese von (+)-Lepicidin A (**28**).[71]
Reagenzien und Bedingungen: (a) **29** (5 Mol-%), Et_2Zn, Hexan, 0 °C, 45 min, dann **17c**, Hexan, 0 °C, 20 h.

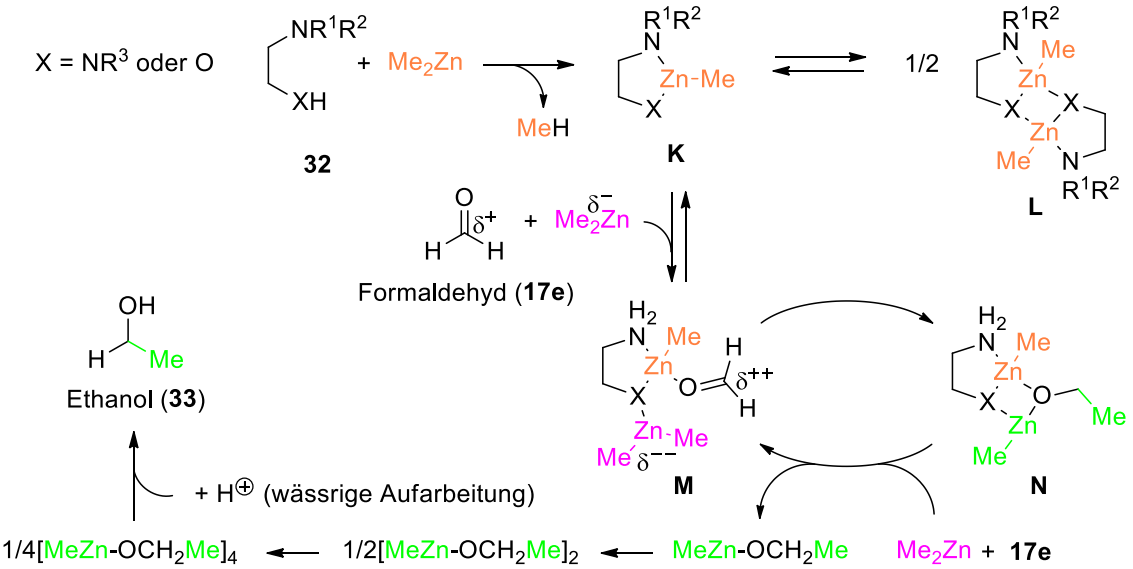
Seit dem Bericht von Oguni und Omi,[72] dass chirale Aminoalkohole die enantioselektive Et_2Zn-Addition an Aldehyde katalysieren, ist diese auch eine Standardreaktion zur Evaluierung neuer Liganden.[73] Während der 1984 erzielte Enantiomerenüberschuss bei der Umsetzung von Benzaldehyd (**17d**, Schema 10) mit Diethylzink noch moderat war {(+)-Leucinol [(*S*)-**30**]: 49% *ee*},[72] wurden kurz darauf Aminoalkohole gefunden, die hervorragende Ergebnisse lieferten, allen voran die kommerziell erhältlichen[74] DBNE (**29**, 90% *ee*),[75] DAIB (**31**, 99% *ee*)[76] und DPMPM (**8b**, 97% *ee*),[27c] sowie **8c** (100% *ee*).[27c]



Schema 10. Chirale Aminoalkohol-Liganden für die Addition von Et_2Zn an Benzaldehyd (**17d**).[27c,72,75,76]

1.3.3.1 Mechanismus der Dialkylzink-Addition

Ein Grund, weshalb die Et_2Zn-Addition gerne[73] als Testreaktion für neue Liganden genutzt wird, ist, dass unter den Reaktionsbedingungen keine achirale, den *ee* des Produkts senkende Hintergrundreaktion stattfindet.[69] Wie Rechnungen von Yamakawa und Noyori am Modellsystem Formaldehyd (**17e**, Schema 11) und Me_2Zn zeigten, wird diese eigentlich exotherme Umsetzung durch die zu große Aktivierungsbarriere unterbunden.[77] Führt man die Addition in Gegenwart katalytischer Mengen an Aminoalkoholen bzw. Diaminen mit acider NH-Funktion durch, verläuft sie über den in Schema 11 am Modellsystem gezeigten und heute allgemein akzeptierten[69] Katalysezyklus.[77] Der Ligand **32** (in den Rechnung waren R^1 und R^2 = H, X = O) reagiert unter Abspaltung von Methan mit einem Äquivalent Me_2Zn und es kommt zur Bildung der katalytisch aktiven Spezies **K**. Diese steht im Gleichgewicht mit dem Dimer **L** – dessen Diastereomere können beim Einsatz skalemischer Liganden unterschiedliche Stabilitäten aufweisen, was den in DAIB-katalysierten (**31**, s. Schema 10)[76] Umsetzungen gefundenen großen NLE[36] erklärt[78,79] – und dem Komplex **M**, welcher sich nach schrittweiser Anlagerung von **17e** und Me_2Zn bildet. Durch die duale Lewis-saure und -basische Aktivierung der beiden Reaktanden an **M** wird die geschwindigkeitsbestimmende C-C-Bindungsknüpfung ermöglicht (→ **N**); dabei wird eine Methyl-Gruppe des neu angelagerten Me_2Zn übertragen. Das so entstandene Ethanolzinkalkoxid wird durch erneute Anlagerung von **17e** und Me_2Zn aus dem Komplex verdrängt und bildet stabile Tetramere, welche eine Produktinhibierung verhindern. Aus diesen wird durch die wässrig-saure Aufarbeitung nach vollständiger Umsetzung das Produkt Ethanol (**33**) freigesetzt.

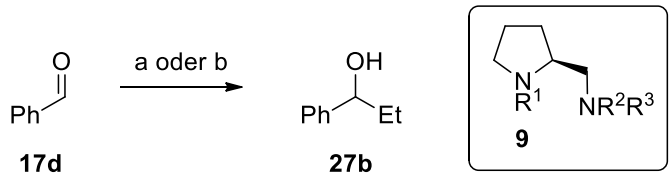


Schema 11. Berechneter Mechanismus der **32**-katalysierten Dimethylzink-Addition an Formaldehyd (**17e**).[77]

1.3.3.2 Prolinamin-Liganden 9 in der enantioselektiven Et_2Zn-Addition

Während bei Soais Prolinol-Liganden[27c] **8b** und **8c** (s. Schema 10, Kapitel 1.3.3) die Phenyl-Substituenten in α-Stellung entscheidend für gute Enantiomerenüberschüsse waren,[80] kann bei den Prolinaminen **9** (Tabelle 5) auf diese verzichtet werden. In einer ersten Arbeit, in der sie die Addition von Et_2Zn an Benzaldehyd (**17d**) als Modellreaktion nutzten, fanden Asami *et al.*, dass für einen guten Stereotransfer das Prolinamin **9** mindestens eine sekundäre Aminofunktion enthalten muss (**9n**, R^1 = Me: 7% *ee* vs. **9f**, R^1 = H: 80 % *ee*, Eintrag 1 vs. Eintrag 2, *vide supra*).[81b,82] Daraufhin untersuchten sie, bei gegebenen R^1 = H, den Einfluss verschiedener exocyclischer Substituenten R^2 und R^3 auf den Chiralitätstransfer und identifizierten das Pyrrolidinyl-Pyrrolidin **9f** als potenten Liganden (80% Ausbeute, 80% *ee*, Eintrag 2 vs. Eintrag 3 und 4).[83,84] Später evaluierte die Gruppe Diamine **9** mit sekundären 2-(Arylamino)-methyl-Substituenten (R^2 = Aryl, R^3 = H, Einträge 5–9), da sie sich durch die gesteigerte Acidität der NH-Funktion einen besseren Stereotransfer versprachen.[81a] An dieser Position wurden mit einer Phenyl-Gruppe als Aryl die besten Ergebnisse erhalten. Ebenfalls getestete, sterisch anspruchsvollere Aromaten wie 2-MePh lieferten durchweg einen geringeren *ee* (Eintrag 5 vs. Eintrag 6). Bei der anschließenden schrittweisen Vergrößerung von R^1 konnte zuerst eine Verbesserung des Chiralitätstransfers festgestellt werden (Eintrag 5 vs. 7 vs. 8), bevor dieser bei zu großem Substituenten wieder sank (Eintrag 8 vs. 9). Als optimal erwies sich eine Benzyl-Funktion wie in **9s** (R^2 = Ph, R^3 = H, 86% Ausbeute, 84% *ee*).

Tabelle 5. Ausgewählte Ergebnisse der Evaluierung verschiedener Prolinamine **9** in der enantioselektiven Et_2Zn-Addition an Benzaldehyd (**17d**) gemäß Asami *et al.*[81]
Reagenzien und Bedingungen: (a) **9** (15 Mol-%), Et_2Zn, Hexan, Cyclohexan, RT, 15 h. (b) **9** (5 Mol-%), Et_2Zn, Hexan, Cyclohexan, RT, 18 h.

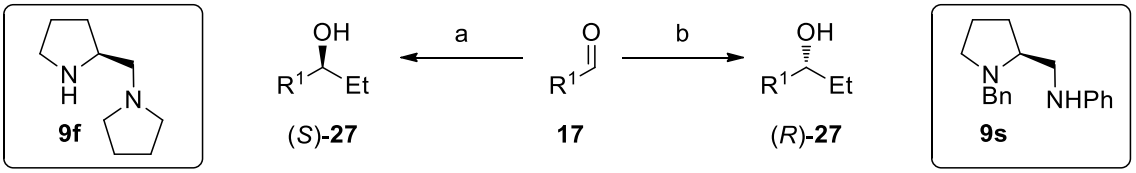


17d **27b** **9**

Eintrag	Ref.	Diamin **9**	R^1	R^2	R^3	Bedingungen	Ausbeute [%]	*ee* [%]	Konfig.
1	81b	**9n**	Me	–$(CH_2)_4$–		a	71	7	*S*
2	81b	**9f**	H	–$(CH_2)_4$–		a	80	80	*S*
3	81b	**9o**	H	Et	Et	a	82	67	*S*
4	81b	**9p**	H	–$(CH_2)_5$–		a	81	45	*S*
5	81a	**9b**	Me	Ph	H	b	91	67	*R*
6	81a	**9q**	Me	2-MePh	H	b	78	50	*R*
7	81a	**9r**	*i*Bu	Ph	H	b	89	81	*R*
8	81a	**9s**	Bn	Ph	H	b	86	84	*R*
9	81a	**9t**	$CHPh_2$	Ph	H	b	54	34	*R*

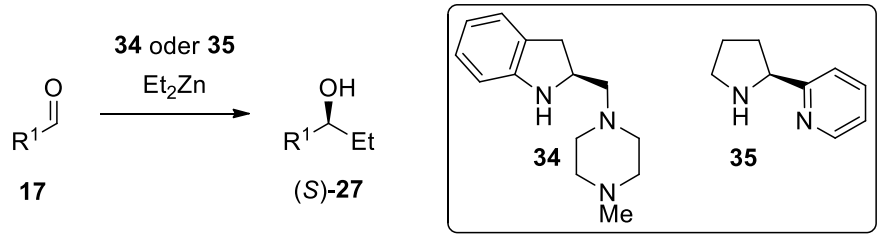
Unter optimierten Bedingungen untersuchten Asami *et al.* ebenfalls die Substratbreite ihrer beiden besten Prolinamine **9f** und **9s** (Tabelle 6).[81] Beide lieferten bei der Reaktion von aromatischen Aldehyden (**17d**, **f–i**), egal ob elektronenarm oder elektronenreich, mit Diethylzink gute bis sehr gute Enantiomerenüberschüsse (**9f**: bis zu 87% *ee*, Eintrag 3; **9s**: bis zu 94% *ee*, Eintrag 5). Für die Umsetzung vinylischer bzw. gesättigter Edukte **17j–l** waren die Liganden hingegen nur unzureichend geeignet (max. 66% Ausbeute, max. 46% *ee*, Einträge 6–8). Die unter Verwendung der Substrate **17k** und **17l** erzielten geringen Ausbeuten begründete die Gruppe durch deren Enolisierung am Katalysator.[81b]

Tabelle 6. Substratbreite der Prolinamine **9f** und **9s**.[81]
Reagenzien und Bedingungen: (a) **9f** (15 Mol-%), Et_2Zn, Hexan, Cyclohexan, RT, 15 h. (b) **9s** (15 Mol-%), Et_2Zn, Hexan, Cyclohexan, 0 °C, 18 h.



				Bedingungen a: **9f**		Bedingungen b: **9s**	
Eintrag	Edukt	Produkt	R^1	Ausbeute [%]	*ee* [%]	Ausbeute [%]	*ee* [%]
1	**17d**	**27b**	Ph	80	80	94	92
2	**17f**	**27c**	4-MeOPh	75	76	95	90
3	**17g**	**27d**	4-ClPh	86	87	–	–
4	**17h**	**27e**	2-BrPh	–	–	86	81
5	**17i**	**27f**	1-Naph	–	–	79	94
6	**17j**	**27g**	(*E*)-PhCH=CH	66	5	65	27
7	**17k**	**27h**	$PhCH_2CH_2$	22	35	57	18
8	**17l**	**27i**	Cy	25	46	65	14

Die auf dem Prolinamin-Skelett basierenden Liganden **34**[85] und **35**[86] (Schema 12) wurden ebenfalls in der Et_2Zn-Addition an Aldehyde evaluiert und erwiesen sich als noch potenter als die bereits vorgestellten **9f** und **9s** (*vide supra*). Beide lieferten bei der Umsetzung Aryl-substituierter Edukte **17** hervorragende Ergebnisse (**34**: ≥ 71% Ausbeute, bis auf eine Ausnahme ≥ 91% *ee*; **35**: ≥ 77% Umsatz, ≥ 92% *ee*). Wurde auf den Aromaten im Substrat **17** verzichtet, sank jedoch, wie auch schon mit **9f** und **9s**, der erhaltene *ee* (**34**: max. 66% *ee*; **35**: max. 67% *ee*, für eine Erklärung s. Kapitel 1.3.3.4.). Eine Ausnahme hiervon bildete bei beiden Liganden Cyclohexancarbaldehyd (**17l**, Tabelle 6), dessen Additionsprodukt **27i** mit dem Liganden **34** in 70% Ausbeute und 97% *ee* und mit **35** bei 77% Umsatz mit 90% *ee* erhalten wurde. Mit dem Pyridinyl-Pyrrolidin **35** konnte außerdem noch Zimtaldehyd (**17j**) mit guten *ee* (91%) umgesetzt werden.[87]

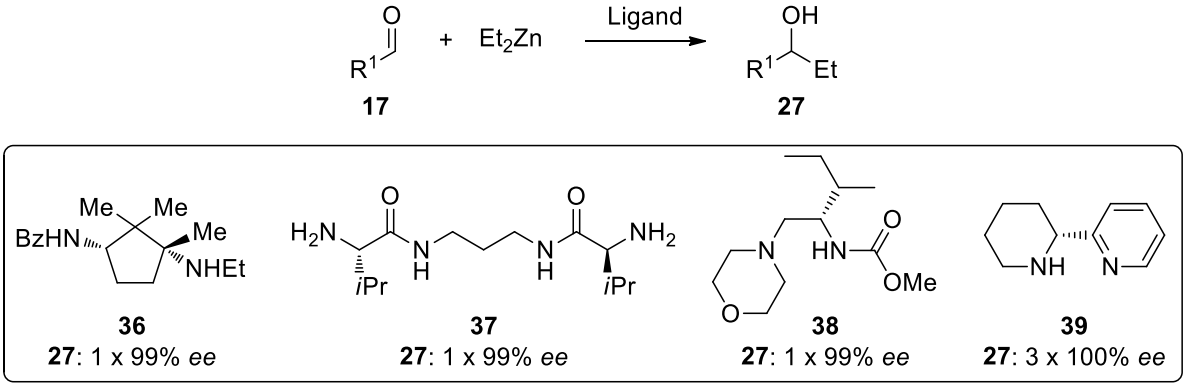


34: R^1 = Aryl, Vinyl oder Alkyl, 8 Beispiele, ≥ 67% Ausbeute, ≥ 59% *ee*, 4 x > 90% *ee*
35: R^1 = Aryl, Heteroaryl, Vinyl, Alkinyl oder Alkyl, 12 Beispiele, ≥ 50% Umsatz, ≥ 24% *ee*, 3 x 100% *ee*

Schema 12. Weitere potente, auf dem Prolinamin-Skelett basierende Liganden für die enantioselektive Addition von Et_2Zn an Aldehyde.[85,86]

1.3.3.3 Weitere erfolgreiche, über Stickstoffatome koordinierende Liganden

Für die enantioselektive Addition von Et_2Zn an Aldehyde (Schema 13) wurden hauptsächlich[88] Aminoalkohol-Komplexe als Katalysatoren evaluiert.[27c,72,75,76,89] Über Liganden ohne Hydroxyfunktion, die ähnlich hervorragende Enantiomerenüberschüsse ergeben, ist nur wenig bekannt. Die potentesten Distickstoff-haltigen unter ihnen besitzen meist noch (mindestens) ein zusätzliches Heteroatom[90] (wie auch **34**)[85] oder einen Pyridinring[91] wie **35**[86] (*vide supra*), was Asamis Prolinamin **9s** (s. Tabelle 6, Kapitel 1.3.3.2)[81a] umso mehr hervorhebt.[92,93] Beispiele für Liganden, die zusätzlich zu den beiden Stickstoff- auch Sauerstoffatome enthalten, sind Murtinhos *cis*-1,3-Cyclopentanaminamid **36**[90b], das lineare Diamindiamid **37**[90c] von Luis sowie Setos Carbamat **38**,[90d] die alle drei bei der Umsetzung eines Aldehyds **17** mit Et_2Zn 99% *ee* liefern können (Schema 13). Unverkennbar ist die Ähnlichkeit des Pyridinyl-Amins **39**[91a] zum Prolinamin-abgeleiteten Liganden **35** (s. Schema 12) und so überrascht es nur wenig, dass dieser ebenso hochselektiv ist (**27**: drei mal 100% *ee*).



36: 10 Beispiele, ≥ 70% Umsatz, ≥ 72% *ee* (*S*) ||| **37**: 4 Beispiele, ≥ 68% Ausbeute, ≥ 82% *ee* (*S*)
38: 7 Beispiele, ≥ 66% Ausbeute, ≥ 58% *ee* (*S*) ||| **39**: 12 Beispiele, ≥ 87% Ausbeute, ≥ 40% *ee* (*R*)

Schema 13. Hochselektive über zwei Stickstoffatome koordinierende Liganden für die Et_2Zn-Addition an Aldehyde.[90b–d,91a]

1.3.3.4 Übergangszustände für Liganden mit aciden H-Atom

Zur Erklärung des teilweise exzellenten Stereotransfers in der Et_2Zn-Addition an Aldehyde müssen für protische Liganden in Summe acht mögliche Übergangszustände beachtet werden.[94] Diese sind in Abbildung 8 anhand des Katalysators Zn•**9s** (s. Tabelle 6, Kapitel 1.3.3.2) dargestellt und unterschieden sich zum einem darin, ob der Aldehyd **17** mit dem freien Elektronenpaar *cis* oder *trans* zu R^1 koordiniert (orange markiert in **O**) und zum anderen bezüglich der Orientierung (*syn* oder *anti*, grün markiert) der äußeren beiden Ringe am vorrübergehend gebildeten inneren Vierring. Des Weiteren kann die Anlagerung der Substrate oberhalb des N-Zn-N-Heterocyclus (in diesem Fall also *endo* zum Pyrrolidinring) oder unterhalb (*exo*, violett markiert) erfolgen, je nachdem, welche Seite des Katalysators bevorzugt ist.

Rechnungen[94] mit Aminoalkoholen zeigten, dass unter diesen Anordnungen die *syn-cis*- (**P'** und **R'**) sowie für Prolin-abgeleitete Liganden auch die *endo-syn-trans*-Konfiguration (**R**) aufgrund von sterischer Abstoßung energetisch sehr ungünstig sind. Am günstigsten sind *anti-trans*-Übergangszustände (**O** und **Q**) und das Hauptenantiomer wird über denjenigen der beiden gebildet, der auf der sterisch weniger gehinderten Katalysatorseite liegt. Für das Diamin **9s** ist das die südliche Hemisphäre – in der nördlichen stört der anellierte Pyrrolidinring –, weshalb ein Großteil der Umsetzungen über **O** verläuft.[81a]

Der für die Bildung des Minderenantiomers ursächliche Übergangszustand ist stark vom Liganden abhängig, da sowohl die auf der bevorzugten (bei **9s**: *exo*) Seite des Katalysators liegenden *syn-trans*- (**P**) und *anti-cis*-Anordnungen (für **9s**: **O'**, vor allem bei gesättigten Aldehyden) als auch die *anti-trans*-Konfiguration in der gehinderten Hemisphäre (für **9s**: **Q**) auf ähnlichen Energieniveaus liegen können. Von diesen diskutieren Asami *et al.* **O'**, um den mit **9s** erhaltenen hohen Enantiomerenüberschuss zu erklären.[81a]

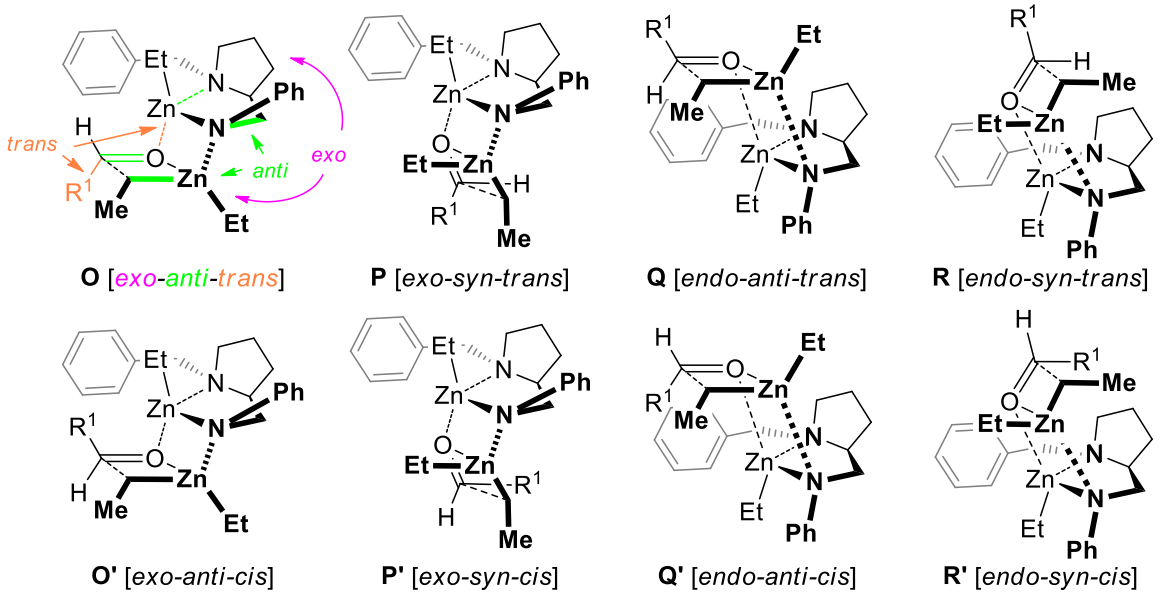


Abb. 8. **O**, **O'**: Von Asami *et al.* für den Liganden **9s** postulierte Übergangszustände;[81a] **P**–**R**, **P'**–**R'**: weitere energetisch relevante Anordnungen, dargestellt an Zn•**9s**.[94]

1.4 5-*Cis*-substituierte Prolinamine 40 und 41 sowie Prolinole 44

Wie Kapitel 1.3 zu entnehmen ist, wurden auf der Suche nach leistungsstärkeren Prolin-abgeleiteten Liganden **9** hauptsächlich die Aminofunktionen variiert. Keinerlei Aufmerksamkeit[95] erhielten bislang 5-*cis*-substituierte[96] Prolinamine der allgemeinen Struktur **40** und **41** (Abbildung 9). Dies ist bemerkenswert, da der zusätzliche Substituent R^1 einen weiteren Quadranten der sich intermediär bildenden, rigiden, bicyclischen Komplexe blockieren sollte (**H'** vs. **H''**; vergleiche hierzu z. B. Evans Modell des Übergangszustandes für Cu•Diamin-katalysierte, asymmetrische Henry-Reaktionen, s. Kapitel 1.3.2.4) und durch die verkleinerte Anzahl an Übergangszuständen einen besseren Stereotransfer ermöglichen könnte.

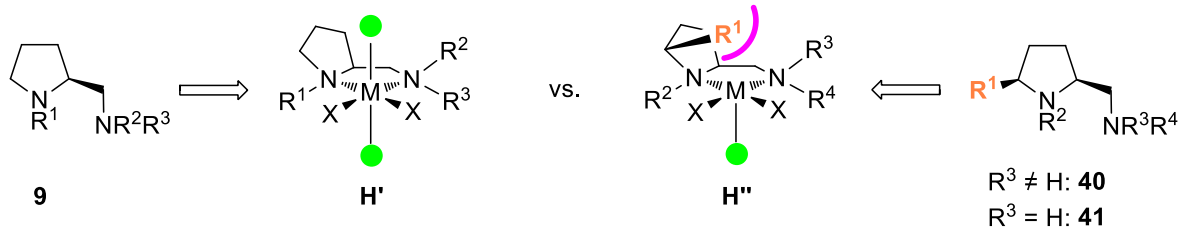
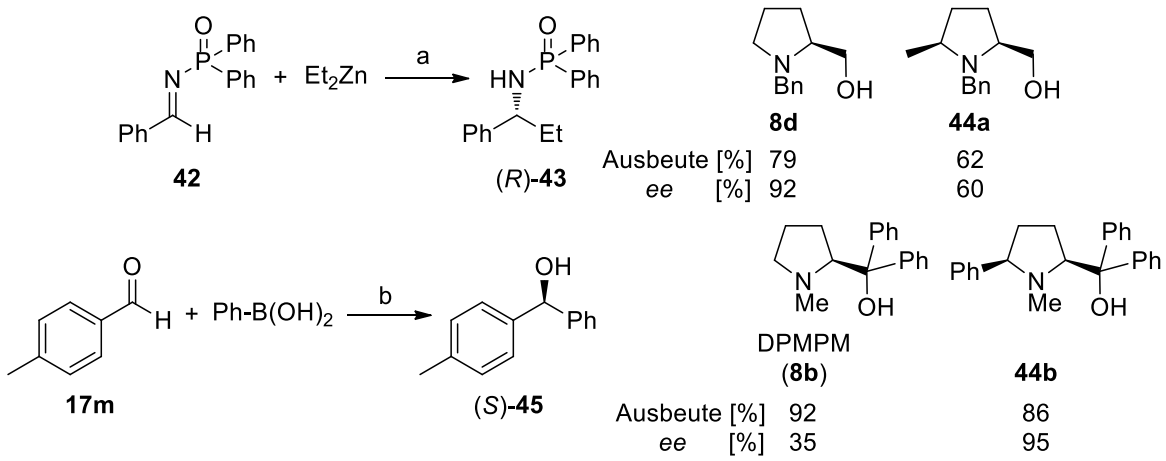


Abb. 9. Zusätzliche sterische Abschottung in rigiden bicyclischen Metallkomplexen **H'** und **H''** durch 5-*cis*-substituierte Prolinamine **40** und **41**.[97]

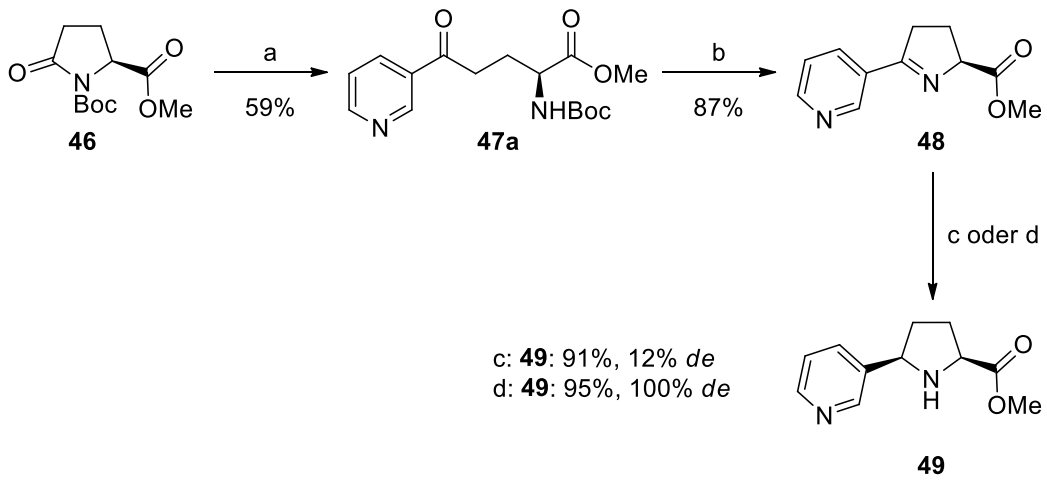
Wird die Suche nach 5-*cis*-substituierten Liganden auf Prolinole **44** (Schema 14) erweitert, werden ebenfalls nur wenige Beispiele[98] in der Literatur gefunden. Im Falle der Addition von Et_2Zn an das Imin **42** sank beispielsweise bei Verwendung des 5-Methyl-Prolinols **44a** als chiralen Liganden – verglichen mit dem unsubstituierten Derivat **8d** – der *ee* des Produkts (*R*)-**43** um 32%.[98d] Lüdtke *et al.* fanden bei der Umsetzung des Aldehyds **17m** mit Phenylboronsäure den entgegengesetzten Trend; hier konnte der Enantiomerenüberschuss **44b**-katalysiert um beeindruckende 60% [(*S*)-**45**: 95% *ee*] gegenüber DPMPM (**8b**) gesteigert werden.[98b]



Schema 14. Einfluss des 5-*cis*-Substituenten auf den Chiralitätstransfer anhand zweier Beispielreaktionen.[98b,d] *Reagenzien und Bedingungen*: (a) **8d** oder **44a** (50-Mol-%), Toluol, RT. (b) Ph-B(OH)$_2$, Et_2Zn, Toluol, 60 °C, 12 h, dann **8b** oder **44b** (10 Mol-%), Toluol, RT, 15 min, dann **17m**, 0 °C, 6 h.

Aus den genannten Beispielen, wie auch aus exploratorischen Versuchen[99] im Arbeitskreis Breuning, lässt sich der enorme Einfluss des zusätzlichen 5-*cis*-Substituenten auf den Chiralitätstransfer ableiten.

Für die stereoselektive Synthese des **40** und **41** zugrunde liegenden 2,5-*cis*-disubstituierten Pyrrolidin-Gerüsts (s. Abbildung 9) sind in der Literatur eine Vielzahl an Methoden bekannt.[100,101] Oftmals wird als Edukt ein geschütztes Pyroglutaminsäure-Derivat wie **46** genutzt, wie in Schema 15 anhand der Darstellung des 5-*cis*-Pyrrolidinesters **49** gezeigt.[100e] Im ersten Schritt wird der neue Substituent über Addition eines Metallorganyls chemoselektiv eingeführt (**46** → **47a**, 59% Ausbeute) und anschließend die *N*-Schutzgruppe entfernt, wodurch es zu einer Recyclisierung hin zu einem Imin (**48**, 87% Ausbeute) kommt. Dieses wird zum Abschluss diastereoselektiv – meist unter Verwendung eines modifizierten Borhydrids oder einer Übergangsmetall-katalysierten Hydrierung – reduziert, wodurch die gewünschten Produkte wie **49** erhalten werden. Rapoport *et al.* evaluierten in der gezeigten Synthesesequenz beide Methoden. Während **49** mit $NaCNBH_3$ in sehr guten 91% Ausbeute, jedoch nur mit moderaten 12% *de* isoliert werden konnte, gelang dessen Darstellung mit H_2 als Reduktans diastereomerenrein (95% Ausbeute, 100% *de*).



Schema 15. Stereoselektive Darstellung des 5-*cis*-Pyrrolidins **49**.[100e]
Reagenzien und Bedingungen: (a) 3-PyLi, THF, Et_2O, –78 °C, 80 min. (b) HCl, EtOAc, RT, ÜN. (c) $NaCNBH_3$, AcOH, NaOAc, MeOH, H_2O, RT, ÜN. (d) Pd/C, H_2, *i*PrOH, RT, ÜN.

2 ZIELSETZUNG

Prolinamine **9** (Abbildung 10) gehören zu den privilegierten chiralen Liganden, jedoch sind die mit ihnen erzielten Ergebnisse durchaus optimierbar (s. Kapitel 1). So wurden zum Beispiel in Cu•**9**-katalysierten, asymmetrischen oxidativen Biarylkupplungen maximal 78% *ee* erreicht[41a,102] und in Henry-Reaktionen bei nur drei Substraten[27a,53k] 99% *ee*. Mit dem potentesten Prolinamin **9s** (s. Tabelle 6, Kapitel 1.3.3.2) konnten in enantioselektiven Et_2Zn-Additionen an Aldehyde bestenfalls 94% *ee* erzielt werden.[81a]

Die Literatur[98b] und Vorarbeiten[99] im Arbeitskreis Breuning lieferten Hinweise darauf, dass durch Einführung eines zusätzlichen 5-*cis*-Substituenten (**9** → **40**/**41**) die Leistungsfähigkeit dieser Ligandenklasse gesteigert werden könnte (s. auch Kapitel 1.4, Abbildung 9). Hieraus ergab sich das Ziel dieser Doktorarbeit: Die Untersuchung von 5-*cis*-substituierten Prolinaminen **40** und **41** als neue chirale Liganden in der enantioselektiven Katalyse (Abbildung 10).

Zuerst war die Darstellung einer Bibliothek mit möglichst vielen Derivaten **40** und **41** geplant. Aufbauend auf vorhandenen Erkenntnissen[99,100] sollten hierfür verschiedene effiziente Syntheserouten entwickelt und etabliert werden, die eine effektive, modulare Einführung der Reste R^1–R^4 erlauben.

Das Potential dieser Ligandenklasse sollte anschließend anhand von Struktur-Selektivitäts-Studien evaluiert werden. Als Modellreaktionen wurden die oben erwähnten Umsetzungen gewählt, da a) bei ihnen Verbesserungspotential vorhanden ist, b) dadurch ein Vergleich hinsichtlich der Selektivität mit bereits bekannten chiralen Liganden ermöglicht wird und c) in den Reaktionen unterschiedliche Metalle, Oxidationsstufen und Nukleophile zum Einsatz kommen, wodurch die Vielseitigkeit der 5-*cis*-Prolinamine **40** und **41** belegt werden könnte. Primäres Ziel war hierbei zum einen, den Einfluss des neuen 5-*cis*-Substituenten auf den Chiralitätstransfer zu ermitteln und zum anderen, einen möglichst leistungsfähigen Katalysator zu finden. Dessen Substratbreite sollte danach unter optimierten Bedingungen untersucht werden. Sekundäres Ziel waren gegebenenfalls mechanistische Untersuchungen.

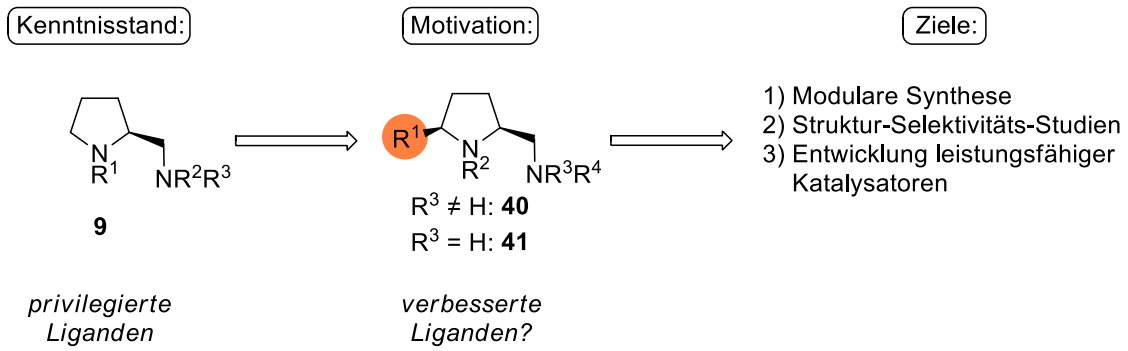


Abb. 10. Motivation und Ziele der vorliegenden Dissertation.

3 SYNOPSIS

Die vorliegende kumulative Dissertation enthält vier Publikationen sowie ein Manuskript, welche in Kapitel 6 zu finden sind.

Ziel dieser Arbeiten war die modulare Synthese von 5-*cis*-substituierten Prolinaminen **40** und **41** sowie die Anwendung dieser neuen Ligandenklasse in der enantioselektiven Katalyse (Schema 16). Es wurde durch Struktur-Selektivitäts-Studien anhand dreier ausgewählter Modellreaktionen – der oxidativen Biarylkupplung, der Henry-Reaktion und der Addition von Et_2Zn an Aldehyde – zum einem der Einfluss des neuen 5-*cis*-Substituenten R^1 auf den Chiralitätstransfer untersucht und zum anderen, durch systematische Variation aller Reste R^1–R^4, der jeweils leistungsfähigste Ligand ermittelt. Um dessen Potential zu belegen wurde im Anschluss daran unter optimierten Bedingungen die jeweilige Substratbreite bestimmt.

Im ersten Teil dieser Dissertation werden die zur Darstellung der Pyrrolidine **40** und **41** genutzten Routen anhand 25 verschiedener Derivate vorgestellt (Schema 16). Aufbauend auf die Literatur[100] und Vorarbeiten[99] im Arbeitskreis Breuning wurden drei effiziente Zugangswege, ausgehend von kommerziell erhältlicher L-Pyroglutaminsäure (**50**), entwickelt und etabliert. Diese erlauben eine modulare Einführung der Reste R^1–R^4 und ermöglichen damit eine maßgeschneiderte Synthese der gewünschten Zielmoleküle (Kapitel 6.1). Weitere neue 5-*cis*-Prolinamine **40** und **41** sind ebenfalls in den Kapiteln 6.2–6.5 zu finden.

Im zweiten Teil dieser Arbeit steht die Anwendung der Liganden **40** und **41** in der asymmetrischen Katalyse im Mittelpunkt (Schema 16). Hierbei zeigte sich in allen untersuchten Modellreaktionen, dass der neue 5-*cis*-Substituent R^1 einen entscheidenden positiven Einfluss auf den Stereotransfer hat.

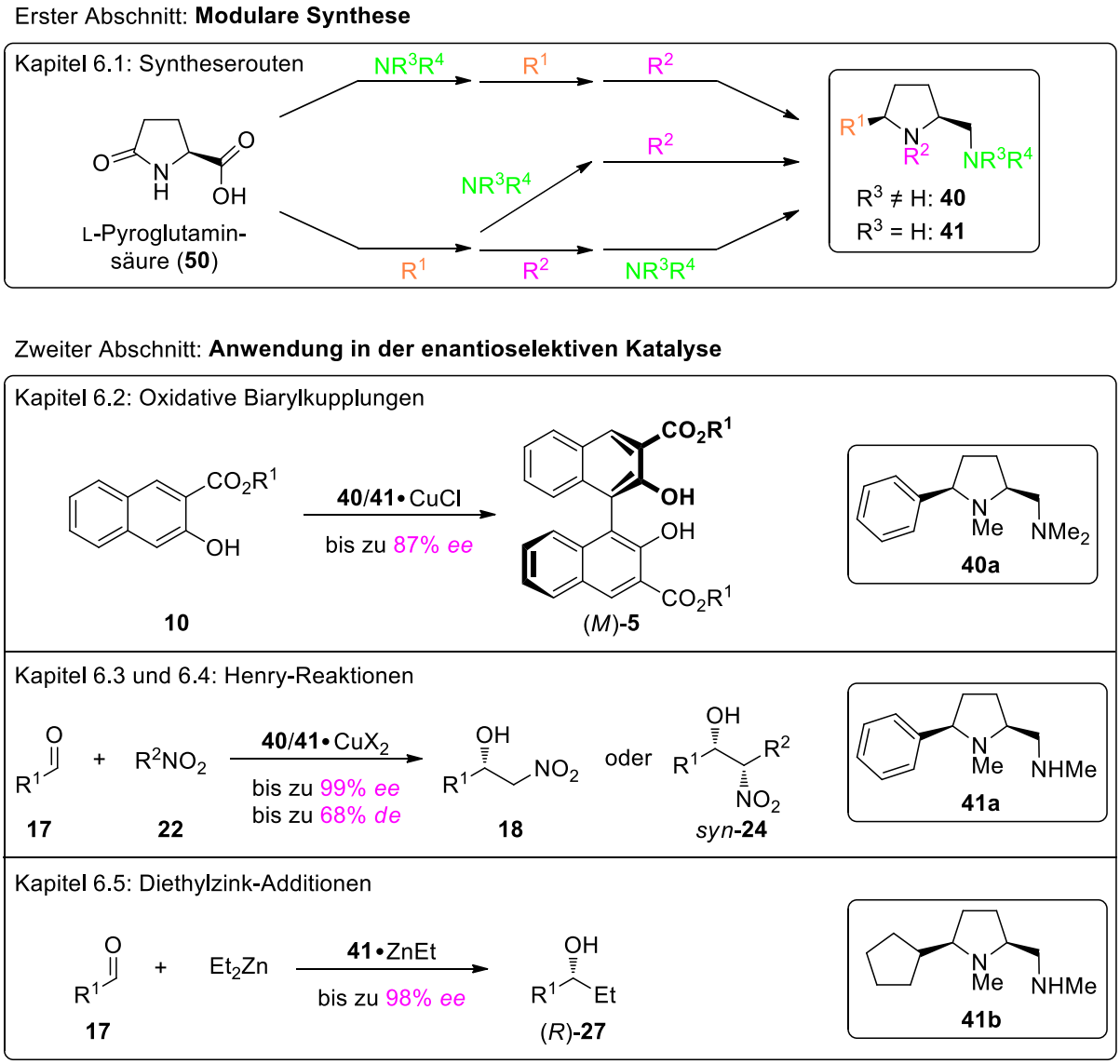
Struktur-Selektivitäts-Studien lieferten das Diamin **40a** als optimierten Liganden für oxidative Biarylkupplungen sowie, zusammen mit mechanistischen Untersuchungen, Hinweise darauf, dass – im Gegensatz zu den bisher publizierten Ergebnissen[35,41,43,46,47] – mit einem sterisch anspruchsvolleren Edukt **10** ein besserer Stereotransfer erhalten werden könnte. Diese Vermutung wurde durch die Darstellung von **5i** (R^1 = *t*Bu) mit einem Enantiomerenüberschuss von 87% bestätigt (der bisher beste erreichte Wert für dieses Substrat, Kapitel 6.2).

Bei der **41a**•$CuCl_2$/$CuBr_2$-katalysierten Addition von Nitromethan (**22a**, R^2 = Me) an Aldehyde konnten hervorragende Ergebnisse erzielt werden. An 36 verschiedenen Beispielen wurden *β*-Nitroalkohole **18** mit einem *ee* von 99% isoliert, was diesen Komplex zum leistungsfähigsten bekannten Cu-abgeleiteten[53] Katalysator macht (Kapitel 6.3).

Die Entwicklung dieses Katalysatoren-Systems ist in Kapitel 6.4 dargestellt. Bei Variation der Reste R^1–R^4 zeigte sich, dass eine sekundäre exocyclische Aminofunktion für einen guten Stereotransfer essentiell ist. Die Anwendungsbreite des Komplexes **41a**•$CuCl_2$/$CuBr_2$ wurde außerdem auf diastereoselektive Reaktionen und Umsetzungen im großen Maßstab erweitert.

Erste mechanistische Untersuchungen zeigten, dass der Stereotransfer im C-C-Kupplungsschritt stattfindet und dass die sekundären Derivate **41** deutlich reaktiver als die tertiären Diamine **40** sind.

In Kapitel 6.5 wurden sowohl 5-*cis*-Prolinamine **41** als auch 5-*cis*-Prolinole (**44**, s. Schema 14, Kapitel 1.4) in der Addition von Et_2Zn an Aldehyde evaluiert. Mit dem Zink-Komplex des Pyrrolidins **41b** wurde ebenfalls ein neuer, äußerst potenter Katalysator (vgl. Kapitel 1.3.3.2 und 1.3.3.3) gefunden, der die gewünschten Alkohole **27** in bis zu 98% *ee* liefert. Zur Erklärung der hier beobachteten Stereoinduktionen wurden aufbauend auf Rechnungen[94] verschiedene Übergangszustände vorgeschlagen.

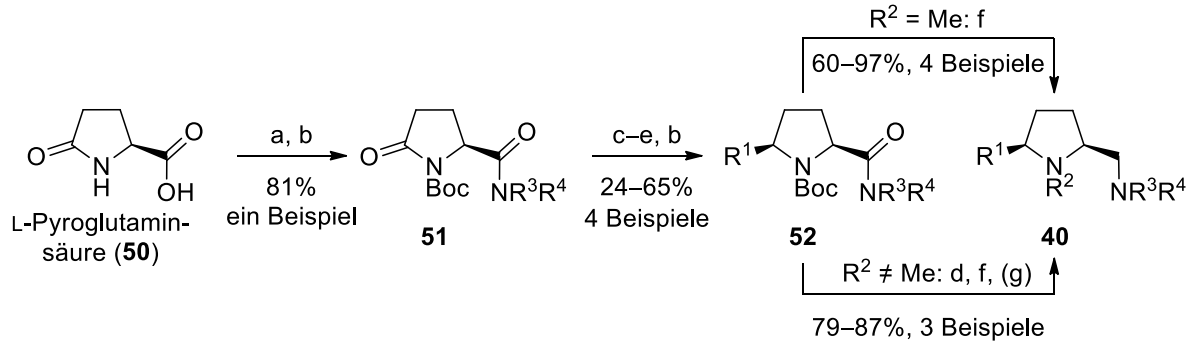


Schema 16. Schematische Darstellung der Inhalte dieser Doktorarbeit.

3.1 Flexible und modulare Synthese der enantiomerenreinen, 5-*cis*-substituierten Prolinamine 40 und 41 ausgehend von L-Pyroglutaminsäure (50)*

Um Struktur-Selektivitäts-Untersuchungen (*vide infra*) an den 5-*cis*-substituierten Prolinaminen **40** und **41** (Schema 18) als chirale Liganden in der enantioselektiven Katalyse durchführen zu können, wurden für deren Darstellung effiziente Zugangswege benötigt. Aus diesem Grund erfolgte die Entwicklung bzw. Etablierung dreier – auf Literaturprotokollen[100] und Vorarbeiten[99] im Arbeitskreis Breuning basierenden – Routen, welche billige L-Pyroglutaminsäure (**50**) als Startmaterial nutzen und sich in der Reihenfolge der Einführung der Reste R^1–R^4 unterscheiden. Dieser modulare Aufbau erlaubt eine gezielte Änderung eines Substituenten bei möglichst geringem synthetischem Aufwand, eine essentielle Grundvoraussetzung für die geplanten Arbeiten.

In Route I (Schema 17) wurde zunächst NR^3R^4 per Amidierung eingeführt (→ **51**). Erst im zweiten Schritt erfolgte die Addition einer Grignard-Verbindung R^1MgX, weshalb sich diese Route am besten zur Variation des 5-*cis*-Substituenten R^1 eignet. Die Recyclisierung der hier entstandenen Ketone hin zum 5-*cis*-Amid **52** gelang über eine dreistufige Entschützungs-Reduktions-Schützungssequenz, die ohne Isolierung der Intermediate in einem Kolben durchgeführt wurde. Ebenfalls evaluiert, jedoch aufgrund der geringeren Flexibilität verworfen, wurde eine durch Martins Einstufen-Recyclisierung[100j,k] um zwei Stufen verkürzte Sequenz. Im Fall von R^2 = Me lieferte eine globale $LiAlH_4$-Reduktion von **52** die gewünschten Produkte **40**; für $R^2 \neq$ Me wurde zuvor die Boc-Gruppe entfernt und R^2 via reduktiver Aminierung im letzten Schritt angebracht.

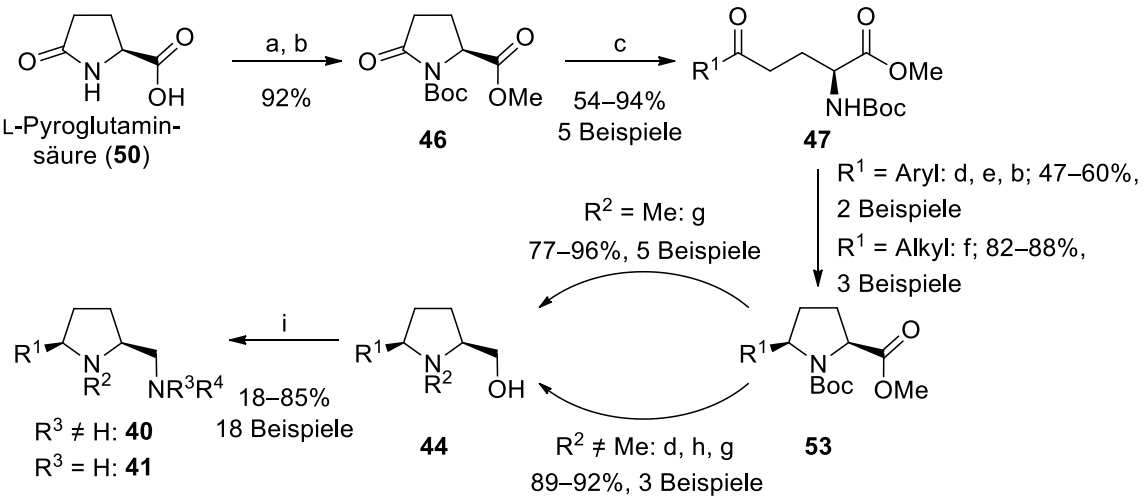


Schema 17. Route I: Einführung von 1. NR^3R^4, 2. R^1 und 3. R^2.
Reagenzien: (a) MeOH, H^+, dann HNR^3R^4. (b) Boc_2O. (c) R^1MgX. (d) TFA. (e) $NaBH_4$. (f) $LiAlH_4$. Für R^1 = 3,5-$(CF_3)_2$Ph: 1. TFA. 2. MeI. 3. BH_3. (g) AcOH, $NaBH_4$ oder PhCHO, $NaBH(OAc)_3$.

In Route II wurde als erstes R^1 via Grignard-Addition an **46** (Schema 18) eingeführt. Die nachfolgende reduktive Recyclisierung der Ester-Ketone **47** gelang für aliphatische Reste R^1 in einer Stufe, während für aromatische auf die schon in Route I genutzte Dreistufen-Sequenz

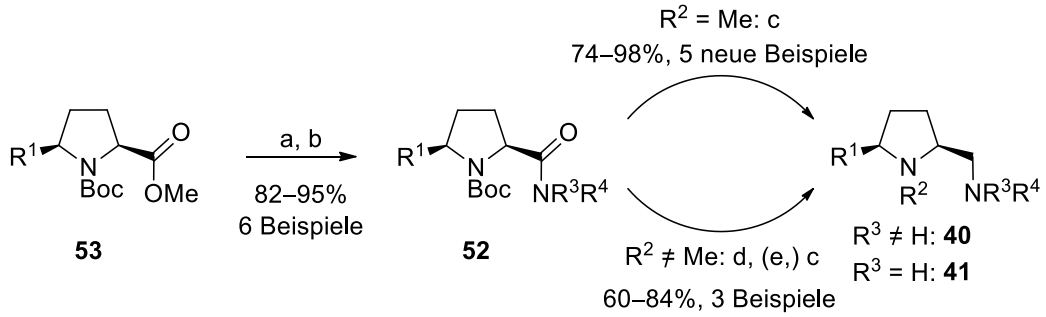
* Dieser Abschnitt der Dissertation wurde veröffentlicht in *Synthesis* **2015**, *47*, 575–586. Siehe Kapitel 6.1.

zurückgegriffen werden musste (→ **53**). R^2 wurde vor der Reduktion zum Alkohol **44** gegebenenfalls durch Entschützung und reduktive Aminierung abgewandelt. Die Einführung der Reste R^3R^4 erfolgte auf letzter Stufe durch Hydroxy-Amin-Austausch via S_N2-Reaktion, womit sich Route II besonders zur Variation an der exocyclischen Aminofunktion eignet.



Schema 18. Route II: Einführung von 1. R^1, 2. R^2 und 3. NR^3R^4.
Reagenzien: (a) MeOH, H^+. (b) Boc_2O. (c) R^1MgX. (d) TFA. (e) $NaBH_4$. (f) TFA, $NaBH(OAc)_3$. (g) $LiAlH_4$. (h) AcOH, $NaBH_4$ oder PhCHO/Aceton, $NaBH(OAc)_3$. (i) MsCl, dann HNR^3R^4.

Oftmals war bei der vorherigen Sequenz die Aufreinigung der polaren, manchmal flüchtigen Endprodukte **40** und **41** äußerst arbeitsaufwendig, u. a. wegen des im Überschuss eingesetzten Amins. Route III umgeht dieses Problem durch die Verwendung einer $LiAlH_4$-Reduktion im letzten Schritt. Ausgehend vom 5-*cis*-substituierten Ester **53** wurden hier die Reste NR^3R^4 via Verseifung und Amidierung eingeführt (→ **52**) und R^2 wurde, im Gegensatz zu Route I, vor der finalen Umsetzung variiert. Hierdurch war außerdem ein mit Route II inkompatibles Prolinamin **41** zugänglich.



Schema 19. Route III: Einführung von 1. R^1, 2. NR^3R^4 und 3. R^2.
Reagenzien: (a) LiOH. (b) PivCl, dann HNR^3R^4. (c) $LiAlH_4$. (d) TFA. (e) AcOH, $NaBH_4$ oder PhCHO, $NaBH(OAc)_3$.

Die Synthese 25 verschiedener, neuer 5-*cis*-Prolinamine **40** und **41** (z. T. über mehrere Wege) über 5–10 Stufen mit bis zu 64% Gesamtausbeute stellt die Leistungsfähigkeit der drei Routen unter Beweis. Insgesamt wurden gemäß diesen Sequenzen mehr als 50 neue Derivate präpariert (s. auch Kapitel 6.2–6.5).

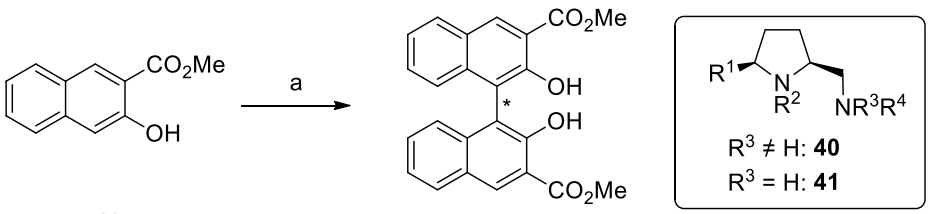
3.2 Detaillierte Struktur-Selektivitäts-Untersuchungen zu asymmetrischen, Kupfer-katalysierten oxidativen Biarylkupplungen in Gegenwart der 5-*cis*-substituierten Prolinamine 40 und 41*

Um den Einfluss des neuen 5-*cis*-Substituenten der Prolinamine **40** und **41** auf den Stereotransfer zu ermitteln, wurden umfangreiche Struktur-Selektivitäts-Studien durchgeführt. Die erste hierfür ausgewählte Modellreaktion war die enantioselektive, Kupfer-katalysierte oxidative Biarylkupplung.

Aufbauend auf die Literatur[35,41] wurde als Testsubstrat 3-Hydroxy-2-naphthoesäuremethylester (**10c**, Tabelle 7) gewählt, da dieses den besten Chiralitätstransfer versprach. Überraschenderweise gestaltete sich die Analyse des Enantiomerenüberschusses des Produkts **5c** als schwierig, da es eine hohe Tendenz aufwies, als Feststoff Konglomerate mit unterschiedlicher optischer Reinheit zu bilden. Daher wurde zuerst eine verlässliche Enantiomerenanalytik entwickelt.

Anschließend erfolgte unter den zuvor optimierten Bedingungen die Evaluierung 25 bekannter und 13 neuer Prolinamine **40** und **41** als chirale Liganden (Tabelle 7).

Tabelle 7. Evaluierung der 5-*cis*-Prolinamine **40** und **41** in der Modellreaktion **10c** → **5c** (Auswahl). *Reagenzien und Bedingungen*: (a) **40** oder **41** (10 Mol-%), CuCl (9 Mol-%), O_2 (1 bar) , MS 4 Å, CH_2Cl_2, 20 °C, 3 d.



10c **5c**

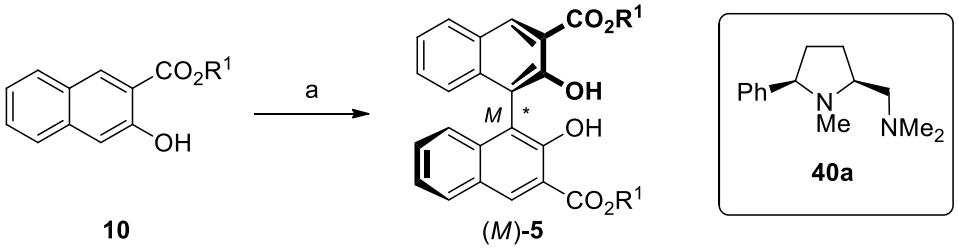
Eintrag	**40/41**	R^1	R^2	R^3	R^4	Ausbeute [%]	*ee* [%]	Konfig.
1	**40b**	Me	Me	Me	Me	95	7	*M*
2	**40c**	Bn	Me	Me	Me	95	22	*M*
3	**40a**	Ph	Me	Me	Me	91	64	*M*
4	**40d**	1-Naph	Me	Me	Me	59	25	*M*
5	**40e**	Ph	H	Me	Me	64	15	*M*
6	**40f**	Ph	Et	Me	Me	81	28	*M*
7	**40g**	Ph	Me	Et	Et	73	6	*M*
8	**41a**	Ph	Me	H	Me	96	19	*P*
9	**41c**	Ph	Me	H	H	85	36	*P*

* Dieser Abschnitt der Dissertation wurde veröffentlicht in *Catal. Sci. Technol.* **2015**, *5*, 2215–2226. Siehe Kapitel 6.2.

Zu Beginn wurde der 5-*cis*-Substituent R^1 an den tertiären Aminen **40** variiert (mit R^2–R^4 = Me). Wie erhofft, verbesserte sich der Stereotransfer durch Vergrößerung des sterischen Anspruchs an dieser Position (Tabelle 7, Einträge 1–3), bevor er bei zu groß gewählten R^1 wieder sank (**40a**, R^1 = Ph, 64% *ee* vs. **40d**, R^1 = 1-Naph, 25% *ee*, Eintrag 3 vs. 4). Optimaler Rest R^2 war eine Methyl-Funktion wie in **40a**, da jeder andere Substituent am Pyrrolidin-Stickstoff einen geringeren Enantiomerenüberschuss im Produkt (*M*)-**5c** zur Folge hatte (Eintrag 3 vs. 5 und 6). Als entscheidend für die stereochemische Steuerung erwiesen sich die exocyclischen Amin-Substituenten R^3 und R^4. Während bei den tertiären Diaminen **40** jede größere Gruppe als Methyl zu einem Induktionsverlust führte (R^1 = Ph, R^2 = Me, Eintrag 3 vs. 7), lieferte bei den sekundären Derivaten das kleinstmögliche **41a** (R^3 = H, R^4 = Me, Eintrag 8) bemerkenswerterweise das enantiokomplementäre Produkt (*P*)-**5c** mit 19% *ee*. Als noch *P*-selektiver erwies sich das primäre Prolinamin **41c** (Eintrag 9), mit dem 36% *ee* erzielt werden konnten. Versuche, die Bildung von (*P*)-**5c** durch Variation von R^1 und R^2 (der Liganden **41**) noch stärker zu forcieren, blieben erfolglos.

Von allen untersuchten Diaminen ergab letzten Endes **40a** den besten Enantiomerenüberschuss (64% *ee*, Eintrag 1, Tabelle 8). Basierend auf diesen Ergebnissen, der Literatur[35] sowie auf durchgeführten mechanistischen Untersuchungen wurde ein Katalysezyklus sowie ein Übergangszustand vorgeschlagen. Aus letzteren kann gefolgert werden, dass einzig die Anlagerung des Naphthols **10** an den Katalysator über den Stereotransfer entscheidet. Konsequenterweise ließ sich dieser durch Vergrößerung des Esters im Edukt **10** steigern (Tabelle 8). Andere Publikationen berichten bisher nur vom entgegengesetzten Trend und die 87% *ee*, die bei der CuCl•**40a**-katalysierten Umsetzung von **10i** (Eintrag 4, R^1 = *t*Bu) erzielt wurden, sind der bisher beste mit diesem Substrat erreichte Wert.[35,41,43] Dies sowie die Tatsache, dass **40a** im Gegensatz zu anderen potenten Liganden (s. Kapitel 1.3.1.2 und 1.3.1.3) keine NH-Funktion enthält, stellt eine Besonderheit der 5-*cis*-Prolinamine **40** und **41** dar.

Tabelle 8. CuCl•**40a**-katalysierte oxidative Biarylkupplungen sterisch anspruchsvoller Ester **10**.
Reagenzien und Bedingungen: (a) **40a** (10 Mol-%), CuCl (9 Mol-%), O_2 (1 bar) , MS 4 Å, CH_2Cl_2.



10 (*M*)-**5** **40a**

Eintrag	Edukt **10**	Produkt **5**	R^1	Temperatur [°C]	Laufzeit [d]	Ausbeute [%]	*ee* [%]
1	**10c**	**5c**	Me	20	3	91	64
2	**10j**	**5l**	*i*Pr	20	3	94	69
3	**10i**	**5i**	*t*Bu	20	6	99	78
4	**10i**	**5i**	*t*Bu	0	8	96	87

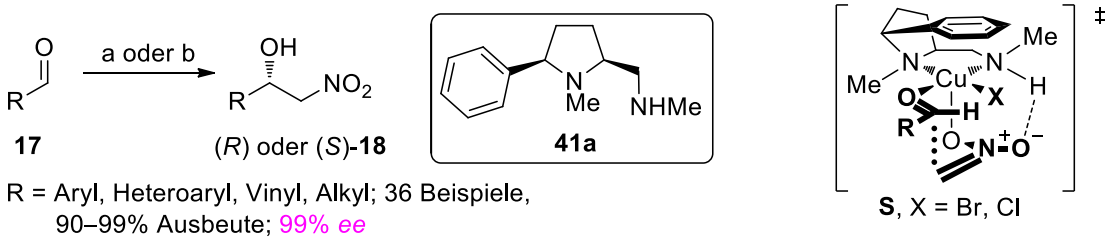
3.3 (2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidin (41a), ein chiraler Diamin-Ligand für Kupfer(II)-katalysierte Henry-Reaktionen mit herausragender Enantiokontrolle*

Das Diamin (2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidin (**41a**, Schema 20) ist der bisher leistungsstärkste[53] chirale Ligand für Kupfer-katalysierte enantioselektive Henry-Reaktionen, was das Potential 5-*cis*-substituierter Prolinamine **40** und **41** eindrucksvoll unterstreicht. Die Struktur-Selektivitäts-Studien, die zu dessen Entdeckung führten, sind in Kapitel 3.4 und 6.4 zu finden. Hier (bzw. in Kapitel 6.3) werden ausschließlich die herausragenden Ergebnisse – 99% *ee* als Regelfall und nicht aus Ausnahme – betrachtet, die bei der Addition von Nitromethan (**22a**) an Aldehyde erzielt werden konnten.

Der Komplex **41a**•$CuBr_2$ lieferte bei der Umsetzung aromatischer (21 Beispiele, evaluiert wurden elektronenreiche, elektronenarme und elektronisch neutrale Arylaldehyde mit *ortho*-, *meta*- und *para*-Substituenten) sowie heteroaromatischer (6 Beispiele, verschiedene Heterocyclen wurden getestet) Aldehyde mit **22a** ausgezeichnete 90–99% Ausbeute und 99% *ee*. Derselbe hervorragende Stereotransfer wurde bei Verwendung *α*,*β*-ungesättigter Edukte **17** erhalten (2 Beispiele, 90 bzw. 97% Ausbeute, 99% *ee*).

Für aliphatische Substrate war ein Wechsel des Kupfersalzes ($CuBr_2$ → $CuCl_2$) sowie eine Erhöhung der Katalysatorbeladung und Temperatur notwendig. Unter diesen modifizierten Bedingungen gelang auch hier die Darstellung der entsprechenden Produkte **18**, egal ob linear oder *α*-verzweigt, mit ≥ 95% Ausbeute und 99% *ee* (7 Beispiele).

Um den äußerst selektiven *Re*-Seitenangriff zu erklären, wurde ein auf dem Evans Modell[58] (s. Kapitel 1.3.2.4) basierender Übergangszustand **S** vorgeschlagen. In diesem blockiert die 5-*cis*-Phenylgruppe die nördliche Hemisphäre des Kupferkomplexes und die Substrate lagern sich wie in Schema 20 gezeigt an, wobei das Nitronat durch eine Wasserstoffbrückenbindung zusätzlich fixiert sein könnte.



Schema 20. Enantioselektive, **41a**•CuX_2-katalysierte Henry-Reaktionen und der postulierte Übergangszustand **S**. Gegensätzliche Stereodeskriptoren in **18** sind der IUPAC-Nomenklatur geschuldet.
Reagenzien und Bedingungen: Für R^1 = Aryl, Heteroaryl, Vinyl: (a) **41a** (2.2 Mol-%), $CuBr_2$ (2 Mol-%), NEt_3 (1.5 Mol-%), $MeNO_2$ (**22a**), THF, –25 °C. Für R^1 = Alkyl: (b) **41a** (8.8 Mol-%), $CuCl_2$ (8 Mol-%), NEt_3 (6 Mol-%), $MeNO_2$ (**22a**), THF, –20 °C.

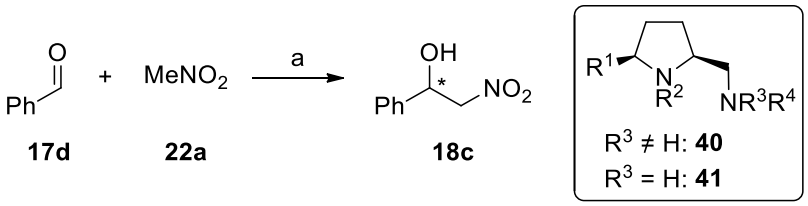
* Dieser Abschnitt der Dissertation wurde veröffentlicht in *Chem. Commun.* **2014**, *50*, 6623–6625. Siehe Kapitel 6.3.

3.4 Evaluierung der 5-*cis*-substituierten Prolinamine 40 und 41 als Liganden in enantioselektiven, Kupfer-katalysierten Henry-Reaktionen*

Aufgrund der mit Cu•Diamin-Katalysatoren erzielten sehr guten Ergebnisse (s. Kapitel 1.3.2) wurde, wie bereits in Kapitel 3.3 erwähnt, zur Evaluierung des Potentials der neuen, 5-*cis*-substituierten Prolinamine **40** und **41** die Henry-Reaktion gewählt.

In diesem Projekt wurden in Summe 11 neue und 22 bekannte Liganden **40** und **41** anhand der in Tabelle 9 gezeigten Umsetzung von Benzaldehyd (**17d**) mit Nitromethan (**22a**) untersucht und dabei deren Reste R^1–R^4 systematisch variiert.

Tabelle 9. Ausgewählte Ergebnisse der Evaluierung der 5-*cis*-Prolinamine **40** und **41** in der Kupfer-katalysierten Addition von Nitromethan (**22a**) an Benzaldehyd (**17d**).
Reagenzien und Bedingungen: (a) **9**, **40** oder **41** (4.4 Mol-%), $CuCl_2$ (4 Mol-%), NEt_3 (3 Mol-%), MeOH, –20 °C, 18–113 h.



17d **22a** **18c**

Eintrag	Prolinamin	R^1	R^2	R^3	R^4	Ausbeute [%]	*ee* [%]	Konfig.
1	**9u**	H	Me	Me	Me	99	71	*R*
2	**40b**	Me	Me	Me	Me	93	23	*S*
3	**40h**	Cy	Me	Me	Me	93	88	*S*
4	**40a**	Ph	Me	Me	Me	95	84	*S*
5	**40i**	3,5-Me_2Ph	Me	Me	Me	92	90	*S*
6	**40j**	Ph	Me	*t*Bu	Me	0	–	–
7	**41a**	Ph	Me	H	Me	99	98	*S*
8	**41d**	Ph	Me	H	*i*Pr	50	85	*S*
9	**41c**	Ph	Me	H	H	28	93	*S*
10	**41e**	Ph	H	H	Me	23	77	*S*
11	**41f**	Ph	Bn	H	Me	32	90	*S*

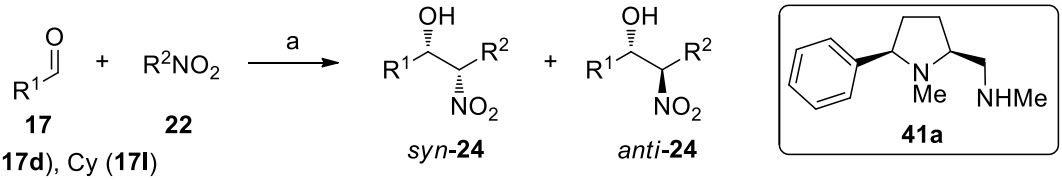
Begonnen wurde mit der Untersuchung des 5-*cis*-Substituenten R^1 in den tertiären Prolinaminen **40** (mit R^2–R^4 = Me), welcher in diesen Reaktionen einen noch größeren Einfluss auf den Stereotransfer als in der oxidativen Biarylkupplung (Kapitel 3.2) hatte. Während das unsubstituierte Derivat **9u** das (*R*)-Produkt in 71% *ee* lieferte, bildete sich bereits mit einem

* Dieser Abschnitt der Dissertation wurde veröffentlicht in *ChemCatChem* **2016**, *8*, 1846–1856. Siehe Kapitel 6.4.

Methyl-Rest R^1 vorzugsweise (*S*)-**18c** mit einem Enantiomerenüberschuss von 23% (**40b**, Tabelle 9, Eintrag 1 vs. 2). Dieser Wert konnte unter Verwendung eines sterisch anspruchsvollen Alkyl- oder eines Aryl-Substituenten auf ein Plateau von 84–90% *ee* angehoben werden (Einträge 3–5). Das Screening von NR^3R^4 erfolgte mit R^1 = Ph und R^2 = Me, da diese Derivate am leichtesten zugänglich waren. Als optimal an dieser Position erwies sich eine NHMe-Funktion wie im Pyrrolidin **41a**, mit der hervorragende 98% *ee* erhalten wurden (Eintrag 7 vs. 6 vs. 8 und 9). Dieser Wert konnte durch Verkleinerung oder Vergrößerung des R^2-Substituenten nicht weiter verbessert werden (Eintrag 7 vs. 10 und 11).

Anhand von **41a** wurden anschließend die Reaktionsparameter (d. h. Kupferquelle, Solvens, Temperatur, Konzentration, Base, Stöchiometrien, Katalysatorbeladung etc.), teilweise an mehreren Testsubstraten, für aliphatische und aromatische Aldehyde optimiert, was zu dem in Kapitel 3.3 vorgestellten hochenantioselektiven katalytischen System führte. Unter den neuen Bedingungen wurde außerdem R^1 erneut evaluiert, da im ersten Screening auch andere Reste als Phenyl gute Ergebnisse ergaben. Es konnte dabei jedoch kein leistungsfähigeres Derivat als **41a** gefunden werden.

Nächstes Ziel war die Vergrößerung der Anwendungsbreite des Komplexes $CuBr_2$•**41a**. Hier wurde gezeigt, dass dieser ebenfalls im großen Maßstab (> 1 g Aldehyd **17**) bei geringer Beladung hervorragende Enantiomerenüberschüsse erbringt (2 Beispiele, 1-Mol % **41a**, 94% Ausbeute, 99% *ee*) und auch für diastereo- und enantioselektive Henry-Reaktionen sehr gut geeignet ist [≥ 84% Ausbeute, *syn*:*anti* bis zu 84:16, *ee*(*syn*) ≥ 98%, *ee*(*anti*) ≥ 82%, Schema 21].



17 **22** *syn*-**24** *anti*-**24** **41a**

R^1 = Ph (**17d**), Cy (**17l**)
R^2 = Et (**22b**), *n*Pr (**22c**), CH_2CH_2OTBS (**22e**),
4 Beispiele, ≥ 84% Ausbeute, *syn*:*anti* 60:40 bis zu 84:16, *ee*(*syn*) ≥ 98%, *ee*(*anti*) ≥ 82%

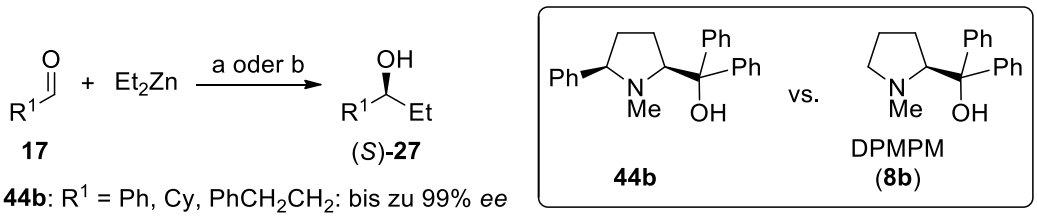
Schema 21. Diastereo- und enantioselektive $CuBr_2$•**41a**-katalysierte Henry-Reaktionen.
Reagenzien und Bedingungen: (a) **41a** (8.8 Mol-%), $CuBr_2$ (8 Mol-%), NEt_3 (6 Mol-%), THF, –20 °C.

Erste mechanistische Untersuchungen zeigten, dass der Stereotransfer während der C-C-Bindungsknüpfung stattfindet. In diesem Zusammenhang wurden außerdem die relativen Reaktionsgeschwindigkeiten der CuX_2-Komplexe des tertiären Diamins **40a** (R^1 = Ph, R^2–R^4 = Me) und des Enantiomers des besten Liganden *ent*-**41a** mittels Konkurrenzreaktionen miteinander verglichen. Das sekundäre Derivat *ent*-**41a** reagierte hierbei, je nach Solvens, deutlich schneller [($k_{ent\text{-}\mathbf{41a}}/k_{\mathbf{40a}}$) = 2.73–7.32], was zum einen direkte Wechselwirkungen zwischen dem Katalysator und den Solvensmolekülen impliziert. Zum anderen muss die im Übergangszustand **S** (s. Kapitel 3.3, Schema 20) postulierte Wasserstoffbrückenbindung in Frage gestellt werden, da diese das Nitronat deaktivieren und somit die Reaktion mit *ent*-**41a** im Vergleich zu **40a** verlangsamen sollte.

3.5 Enantioselektive Et_2Zn-Addition an Aldehyde katalysiert durch die 5-*cis*-substituierten Prolinderivate 41 und 44*

Um das Potential der 5-*cis*-Prolinamine **41** (auf tertiäre Derivate **40** wurde hier verzichtet, da ein protisches Wasserstoffatom im Liganden meist essentiell ist) mit einem anderem Metall als Kupfer zu untersuchen, wurde als letzte Modellreaktion die Addition von Diethylzink an Aldehyde gewählt (Schema 22). Aufbauend auf den in Kapitel 1.3.3 vorgestellten Literaturergebnissen erfolgte außerdem eine Evaluierung der 5-*cis*-substituierten Prolinole **44**.

Zuerst sollte der Nachweis erfolgen, dass der 5-*cis*-Substituent R^1 in dieser Umsetzung einen positiven Einfluss auf den Stereotransfer hat. Zu diesem Zweck wurde das bekannte Prolinol **44b**[98b] als chiraler Ligand eingesetzt und die erzielten Ergebnisse mit den publizierten Werten von Soais DPMPM (**8b**)[27c] verglichen (Schema 22). Der Aminoalkohol **44b** lieferte, wie erhofft, mit zwei von drei Substraten bessere Enantiomerenüberschüsse.



44b: R^1 = Ph, Cy, $PhCH_2CH_2$: bis zu 99% *ee*
8b : R^1 = Ph, Cy, $PhCH_2CH_2$: bis zu 97% *ee* (Ergebnisse entnommen aus Lit.[27c])

Schema 22. Untersuchung des Einflusses des 5-*cis*-Substituenten bei Prolinolen (**44b** vs. **8b**).[27c]
Reagenzien und Bedingungen: (a) **44b** (10 Mol-%), Hexan, RT. (b) **8b** (2 Mol-%), (Cyclohexan), Hexan, 0 °C.

Als nächstes wurden die Prolinamine **41** auf ihre Leistungsfähigkeit hin untersucht und die Reste R^1, R^2 und R^4 (R^3 = H) systematisch variiert. Insgesamt wurden in diesem Projekt 13 bekannte und 5 neue Derivate von **41** evaluiert.

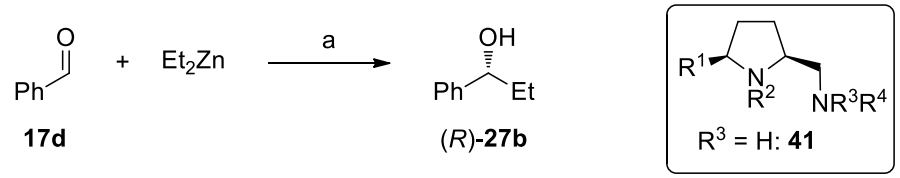
Der erste getestete Ligand war das Diamin **41a** – der Paradeligand in der Henry-Reaktion – welches in der Umsetzung von Benzaldehyd (**17d**) mit Et_2Zn 71% *ee* ergab (Tabelle 10, Eintrag 1). Durch Variation von R^2 und R^4 konnten keine besseren Substituenten als die bereits vorhandenen Methyl-Gruppen gefunden werden (Eintrag 1 vs. 2–5). Der positive Einfluss des 5-*cis*-Substituenten R^1 war erneut vorhanden (Eintrag 6 vs. 1, 7 und 8), jedoch nicht so ausgeprägt wie in den vorherigen Reaktionen (s. Kapitel 3.2 und 3.4). Der beste Wert (84% *ee*) wurde mit dem 5-Cyclopentyl-substituierten Derivat **41b** erhalten und konnte durch Optimierung der Reaktionsbedingungen auf 90% *ee* gesteigert werden.

Beim Screening der Substratbreite des Liganden **41b** anhand 12 verschiedener Aldehyde wurden die Produkte (*R*)-**27** mit moderaten bis sehr guten Enantiomerenüberschüssen erhalten. Hervorzuheben ist, dass **41b** bei Verwendung aliphatischer Edukte deutlich leistungsfähiger als Asamis bester Ligand **9s** war (**41b**: bis zu 98% *ee*, **9s**: bis zu 18% *ee*, s. Tabelle 6,

* Dieser Abschnitt der Dissertation ist als Manuskript fertig zur Einreichung. Siehe Kapitel 6.5.

Kapitel 1.3.3.2),[81a] was den Komplex Zn•**41b** zu einem der potentesten, nur Amino-funktionalisierten Katalysatoren für diese Reaktion macht.[81,85,92]

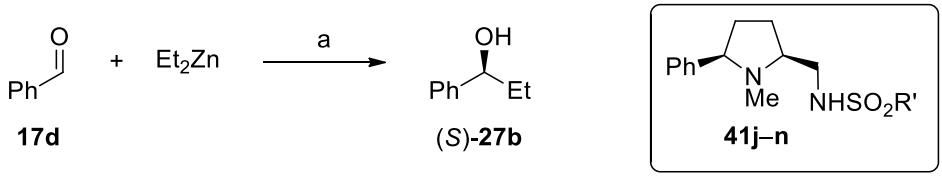
Tabelle 10. Ausgewählte Ergebnisse der Evaluierung der 5-*cis*-Prolinamine **41** in der Et_2Zn-Addition an Benzaldehyd (**17d**).
Reagenzien und Bedingungen: (a) **41** (10 Mol-%), Hexan, RT, 18 h.



17d (*R*)-**27b**

Eintrag	Prolinamin	R^1	R^2	R^4	Ausbeute [%]	*ee* [%]
1	**41a**	Ph	Me	Me	81	71
2	**41c**	Ph	Me	H	69	12
3	**41g**	Ph	Me	Et	91	4
4	**41e**	Ph	H	Me	63	11
5	**41h**	Ph	Et	Me	59	12
6	**9v**	H	Me	Me	68	45
7	**41i**	3,5-Me_2Ph	Me	Me	76	61
8	**41b**	*c*Pent	Me	Me	88	84

Um Asamis These, dass eine hohe Acidität der NH-Funktion wichtig für einen guten Stereotransfer ist, zu untersuchen,[81a,85] wurden ebenfalls die 5-*cis*-Prolinamine **41j–n** mit einer exocyclischen Sulfonamid-Gruppe in der Modellreaktion evaluiert (Schema 23). Diese lieferten überraschenderweise, genauso wie das Prolinol **44b**, die (*S*)-Enantiomere von **27b** – ganz im Gegensatz zu den mit **41b** erhaltenen (*R*)-Produkten – mit bis zu 78% *ee* (**41k**, R' = CF_3).



17d (*S*)-**27b** **41j–n**

41j: R' = Me: 95%, 68% *ee*. **41k**: R' = CF_3: 84%, 78% *ee*. **41l**: R' = 4-MePh: 90%, 64% *ee*.
41m: R' = Bn: 63%, 72% *ee*. **41n**: R' = 2,4,6-Me_3Ph: 87%, 17% *ee*.

Schema 23. 5-*cis*-Prolinsulfonamide **41j–n** als chirale Liganden in der Et_2Zn-Addition an Benzaldehyd (**17d**).
Reagenzien und Bedingungen: (a) **41** (10 Mol-%), Toluol, Hexan, RT, 18 h.

Zur Erklärung der höchst unterschiedlichen Stereoinduktionen, welche die leistungsfähigsten 5-*cis*-substituierten Liganden **44b** (99% *ee*, *S*), **41b** (90% *ee*, *R*) und **41k** (78% *ee*, *S*) bei der Addition von Et_2Zn an Benzaldehyd (**17d**) ergaben, wurden aufbauend auf die Literatur[94] (s. auch Kapitel 1.3.3.4) verschiedene Übergangszustände diskutiert.

4 LITERATURVERZEICHNIS

1 Ausgewählte Übersichtsartikel: (a) „Synthetic Aspects of Iridoid Chemistry“: H. Franzyk in *Progress in the Chemistry of Organic Natural Products*, Vol. 79 (Hrsg.: H. Herz, H. Falk, G. W. Kirby, R. E. Moore), Springer, Wien, **2000**, S. 1–114. (b) L.-F. Tietze, „Secologanin, a Biogenetic Key Compound – Synthesis and Biogenesis of the Iridoid and Secoiridoid Glycosides“, *Angew. Chem.* **1983**, *95*, 840–853; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 828–841.

2 Y.-S. Li, K. Matsunaga, M. Ishibashi, Y. Ohizumi, „Littoralisone, a Novel Neuritogenic Iridolactone Having an Unprecedented Heptacyclic Skeleton Including Four- and Nine-Membered Rings Consisting of Glucose from *Verbena littoralis*“, *J. Org. Chem.* **2001**, *66*, 2165–2167.

3 Ausgewählte Bücher: (a) G. Habermehl, P. E. Hammann, H. C. Krebs, W. Ternes, Naturstoffchemie: Eine Einführung, Springer, Berlin, Heidelberg, **2008**. (b) E. Breitmaier, Alkaloide: Betäubungsmittel, Halluzinogene und andere Wirkstoffe, Leitstrukturen aus der Natur, Vieweg+Teubner, Wiesbaden, **2008**.

4 (a) Isolierung: R. L. Noble, C. T. Beer, J. H. Cutts, „Role Of Chance Observations in Chemotherapy: *Vinca Rosea*“, *Ann. N. Y. Acad. Sci*. **1958**, *76*, 882–894. (b) Abschließende Strukturaufklärung: J. W. Moncrief, W. N. Lipscomb, „Structures of Leurocristine (Vincristine) and Vincaleukoblastine. X-Ray Analysis of Leurocristine Methiodide“, *J. Am. Chem. Soc*. **1965**, *87*, 4963–4964.

5 (a) Isolierung: V. N. Karmat, J. de Sa, A. Vaz, F. Fernandes, S. S. Bhatnagar, „Isolation and Characterization of Chemical Constituents from *Vinca rosea*“, *Indian J. Med. Res*. **1958**, *46*, 588–597. (b) Abschließende Strukturaufklärung: M. Gorman, N. Neuss, K. Biemann, „Vinca Alkaloids. X. The Structure of Vindoline“, *J. Am. Chem. Soc*. **1962**, *84*, 1058–1059.

6 S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, „Discodermolide: A New Bioactive Polyhydroxylated Lactone from the Marine Sponge *Discodermia dissoluta*“, *J. Org. Chem.* **1990**, *55*, 4912–4915. Für eine Korrektur der im Artikel gezeichneten Strukturformel von *ent*-**3** siehe: S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, „Discodermolide: A New Bioactive Polyhydroxylated Lactone from the Marine Sponge *Discodermia dissoluta*“, *J. Org. Chem.* **1991**, *56*, 1346.

7 Ausgewählte Übersichtsartikel: (a) C. Hertweck, „The Biosynthetic Logic of Polyketide Diversity“, *Angew. Chem.* **2009**, *121*, 4782–4811; *Angew. Chem. Int. Ed.* **2009**, *48*, 4688–4716. (b) S. Smith, S.-C. Tsai, „The type I fatty acid and polyketide synthases: a tale of two megasynthases“, *Nat. Prod. Rep*. **2007**, *24*, 1041–1072.

8 (a) E. Fischer, „Einfluss der Configuration auf die Wirkung der Enzyme“, *Ber. Dtsch. Chem. Ges*. **1894**, *27*, 2985–2993. (b) D. E. Koshland Jr., „Application of a Theory of Enzyme Specificity to Protein Synthesis“, *Proc. Natl. Acad. Sci.* **1958**, *44*, 98–104. (c) D. E. Koshland Jr., „The Key–Lock Theory and the Induced Fit Theory“, *Angew. Chem.* **1994**, *106*, 2468–2472; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 2375–2378.

9 Dieser Fall ist wohl das bekannteste Beispiel vom „guten“ und „bösen“ Enantiomer. Für eine Zusammenfassung dieser Tragödie sei auf K. Roth, „Eine unendliche chemische Geschichte“, *Chem. Unserer Zeit* **2005**, *39*, 212–217 und die darin zitierte Literatur verwiesen.

10 Bzw. der Kenntnis der Pharmakokinetik beider Enantiomere, falls ein Racemat eingesetzt wird.

11 „FDA’s Policy Statement for the Development of New Stereoisomeric Drugs“, *Chirality* **1992**, *4*, 338–340.

12 I. Paterson, I. Lyothier, „Total Synthesis of (+)-Discodermolide: An Improved Endgame Exploiting a Still−Gennari-Type Olefination with a C1−C8 β-Ketophosphonate Fragment“, *Org. Lett.* **2004**, *6*, 4933–4936.

13 (a) S. J. Mickel, G. H. Sedelmeier, D. Niederer, R. Daeffler, A. Osmani, K. Schreiner, M. Seeger-Weibel, B. Bérod, K. Schaer, R. Gamboni, S. Chen, W. Chen, C. T. Jagoe, F. R. Kinder Jr., M. Loo, K. Prasad, O. Repič, W.-C. Shieh, R.-M. Wang, L. Waykole, D. D. Xu, S. Xue, „Large-Scale Synthesis of the

Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 1: Synthetic Strategy and Preparation of a Common Precursor“, *Org. Process Res. Dev*. **2004**, *8*, 92−100. (b) S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, D. Grimler, G. Koch, R. Daeffler, A. Osmani, A. Hirni, K. Schaer, R. Gamboni, A. Bach, A. Chaudhary, S. Chen, W. Chen, B. Hu, C. T. Jagoe, H.-Y. Kim, F. R. Kinder Jr., Y. Liu, Y. Lu, J. McKenna, M. Prashad, T. M. Ramsey, O. Repič, L. Rogers, W.-C. Shieh, R.-M. Wang, L. Waykole, „Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 2: Synthesis of Fragments $C_{1–6}$ and $C_{9–14}$“, *Org. Process Res. Dev*. **2004**, *8*, 101−106. (c) S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, G. Koch, E. Kuesters, R. Daeffler, A. Osmani, M. Seeger-Weibel, E. Schmid, A. Hirni, K. Schaer, R. Gamboni, A. Bach, S. Chen, W. Chen, P. Geng, C. T. Jagoe, F. R. Kinder Jr., G. T. Lee, J. McKenna, T. M. Ramsey, O. Repič, L. Rogers, W.-C. Shieh, R.-M. Wang, L. Waykole, „Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 3: Synthesis of Fragment $C_{15–21}$“, *Org. Process Res. Dev*. **2004**, *8*, 107−112. (d) S. J. Mickel, G. H. Sedelmeier, D. Niederer, F. Schuerch, M. Seger, K. Schreiner, R. Daeffler, A. Osmani, D. Bixel, O. Loiseleur, J. Cercus, H. Stettler, K. Schaer, R. Gamboni, A. Bach, G.-P. Chen, W. Chen, P. Geng, G. T. Lee, E. Loeser, J. McKenna, F. R. Kinder Jr., K. Konigsberger, K. Prasad, T. M. Ramsey, N. Reel, O. Repič, L. Rogers, W.-C. Shieh, R.-M. Wang, L. Waykole, S. Xue, G. Florence, I. Paterson, „Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 4: Preparation of Fragment $C_{7–24}$“, *Org. Process Res. Dev*. **2004**, *8*, 113−121. (e) S. J. Mickel, D. Niederer, R. Daeffler, A. Osmani, E. Kuesters, E. Schmid, K. Schaer, R. Gamboni, W. Chen, E. Loeser, F. R. Kinder Jr., K. Konigsberger, K. Prasad, T. M. Ramsey, O. Repič, R.-M. Wang, G. Florence, I. Lyothier, I. Paterson, „Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 5: Linkage of Fragments $C_{1–6}$ and $C_{7–24}$ and Finale“, *Org. Process Res. Dev*. **2004**, *8*, 122−130. (f) K. C. Nicolaou, J. S. Chen, Classics in Total Synthesis III: Further Targets, Strategies, Methods, Wiley-VCH, Weinheim, **2011**.

14 S. Hanessian, S. Giroux, B. L. Merner, Design and Strategy in Organic Synthesis: From the *Chiron Approach* to Catalysis, Wiley-VCH, Weinheim, **2013**.

15 Ausgewählte Übersichtsartikel: (a) „Catalytic Kinetic Resolution“: H. Pellissier in *Separation Of Enantiomers: Synthetic Methods* (Hrsg.: M. Todd), Wiley-VCH, Weinheim, **2014**, S. 75–122. (b) H. Pellissier, „Recent developments in dynamic kinetic resolution“, *Tetrahedron* **2011**, *67*, 3769–3802. (c) H. Pellissier, „Dynamic kinetic resolution“, *Tetrahedron* **2003**, *59*, 8291–8327. (d) R. S. Ward, „Dynamic kinetic resolution“, *Tetrahedron: Asymmetry* **1995**, *6*, 1475–1490.

16 *Comprehensive Chirality Volume 2: Synthetic Methods I – Chiral Pool and Diastereselective Methods* (Hrsg.: E. M. Carreira, H. Yamamoto, J. Mulzer), Elsevier, Amsterdam, **2012**, S. 1–8 und 122–345.

17 *Comprehensive Chirality Volume 3: Synthetic Methods II – Chiral Auxiliaries* (Hrsg.: E. M. Carreira, H. Yamamoto, R. K. Boeckman Jr.), Elsevier, Amsterdam, **2012**.

18 Für einen Überblick siehe: L. Kürti, B. Czakó, Strategic Applications of Named Reactions in Organic Synthesis, Elsevier, Burlington, **2005** und die darin zitierte Literatur.

19 Realisiert wurde dies zum Beispiel in asymmetrischen Deprotonierungs- und Abfangreaktionen cyclischer Amine: E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, „Direct α-Functionalization of Saturated Cyclic Amines“, *Chem. Eur. J.* **2012**, *18*, 10092–10142 oder in asymmetrische Aldol-Reaktionen mit chiralen Organo-Bor-Verbindungen: C. J. Cowden, I. Paterson, „Asymmetric Aldol Reactions Using Boron Enolates“, *Org. React.* **1997**, *51*, 1–200 (Übersichtsartikel).

20 (a) *Enzyme Catalysis in Organic Synthesis* (Hrsg.: K. Drauz, H. Gröger, O. May), Wiley-VCH, Weinheim, **2012**. (b) C.-H. Wong, „Enzymatic Catalysts in Organic Synthesis“, *Science* **1989**, *244*, 1145–1152.

21 (a) *Enantioselective Organocatalysis* (Hrsg.: P. I. Dalko), Wiley-VCH, Weinheim, **2007**. (b) A. Berkessel, H. Gröger, Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis, Wiley-VCH, Weinheim, **2005**.

22 Nobelprize.org, The Nobel Prize in Chemistry 2001, Nobel Media AB **2014**, zu finden unter: www.nobelprize.org/nobel_prizes/chemistry/laureates/2001.

23 (a) *Privileged Chiral Ligands and Catalysts* (Hrsg.: Q.-L. Zhou), Wiley-VCH, Weinheim, **2011**. (b) T. P. Yoon, E. N. Jacobsen, „Privileged Chiral Catalysts“, *Science* **2003**, *299*, 1691–1693.

24 (a) M. Hatano, T. Ikeno, T. Miyamoto, K. Ishihara, „Chiral Lithium Binaphtholate Aqua Complex as a Highly Effective Asymmetric Catalyst for Cyanohydrin Synthesis“, *J. Am. Chem. Soc.* **2005**, *127*, 10776–10777. (b) R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, „Asymmetric Synthesis of Isoquinoline Alkaloids by Homogeneous Catalysis“, *J. Am. Chem. Soc.* **1986**, *108*, 7117–7119.

25 (a) K. Juhl, N. Gathergood, K. A. Jørgensen, „Catalytic Asymmetric Direct Mannich Reactions of Carbonyl Compounds with *α*-Imino Esters“, *Angew. Chem.* **2001**, *113*, 3083–3085; *Angew. Chem. Int. Ed.* **2001**, *40*, 2995–2997. (b) D. A. Evans, S. J. Miller, T. Lectka, „Bis(oxazoline)copper(II) Complexes as Chiral Catalysts for the Enantioselective Diels–Alder Reaction“, *J. Am. Chem. Soc.* **1993**, *115*, 6460–6461. (c) R. E. Lowenthal, A. Abiko, S. Masamune, „Asymmetric Catalytic Cyclopropanation of Olefins: Bis-Oxazoline Copper Complexes“, *Tetrahedron Lett.* **1990**, *31*, 6005–6008.

26 (a) Y. Fukunaga, T. Uchida, Y. Ito, K. Matsumoto, T. Katsuki, „Ru(CO)-salen-Catalyzed Synthesis of Enantiopure Aziridinyl Ketones and Formal Asymmetric Synthesis of (+)-PD 128907“, *Org. Lett.* **2012**, *14*, 4658–4661. (b) L. E. Martínez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, „Highly Enantioselective Ring Opening of Epoxides Catalyzed by (salen)Cr(III) Complexes“, *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898. (c) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, „Highly Enantioselective Epoxidation Catalysts Derived from 1,2-Diaminocyclohexane“, *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064.

27 (a) Y. Zhou, J. Dong, F. Zhang, Y. Gong, „Synthesis of C_1-Symmetric Chiral Secondary Diamines and Their Applications in the Asymmetric Copper(II)-Catalyzed Henry (Nitroaldol) Reactions“, *J. Org. Chem.* **2011**, *76*, 588–600. (b) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, „A Stable and Easily Prepared Catalyst for the Enantioselective Reduction of Ketones. Applications to Multistep Syntheses“, *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926. (c) K. Soai, A. Ookawa, T. Kaba, K. Ogawa, „Catalytic Asymmetric Induction. Highly Enantioselective Addition of Dialkylzincs to Aldehydes Using Chiral Pyrrolidinylmethanols and Their Metal Salts“, *J. Am. Chem. Soc.* **1987**, *109*, 7111–7115. (d) E. J. Corey, R. K. Bakshi, S. Shibata, „Highly Enantioselective Borane Reduction of Ketones Catalyzed by Chiral Oxazaborolidines. Mechanism and Synthetic Implications“, *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.

28 Diese willkürlich gewählte, aber zweckmäßige Definition stammt von M. Õki, siehe: „Recent Advances in Atropisomerism“: M. Õki in *Topics in Stereochemistry*, Vol. 14 (Hrsg.: N. L. Allinger, E. L. Eliel, S. H. Wilen), John Wiley & Sons, New York, **1983**, S. 1–81.

29 Übersichtsartikel: (a) P. Loxq, E. Manoury, R. Poli, E. Deydier, A. Labande, „Synthesis of axially chiral biaryl compounds by asymmetric catalytic reactions with transition metals“, *Coord. Chem. Rev.* **2016**, *308*, 131–190. (b) J. Wencel-Delord, A. Panossian, F. R. Leroux, F. Colobert, „Recent advances and new concepts for the synthesis of axially stereoenriched biaryls“, *Chem. Soc. Rev.* **2015**, *44*, 3418–3430. (c) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, „Atropselective Total Synthesis of Axially Chiral Biaryl Natural Products“, *Chem. Rev.* **2011**, *111*, 563–639. (d) M. C. Kozlowski, B. J. Morgan, E. C. Linton, „Total synthesis of chiral biaryl natural products by asymmetric biaryl coupling“, *Chem. Soc. Rev.* **2009**, *38*, 3193–3207. (e) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, „Atroposelective Synthesis of Axially Chiral Biaryl Compounds“, *Angew. Chem.* **2005**, *117*, 5518–5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427.

30 (a) T. Pal, A. Pal, „Oxidative phenol coupling: A key step for the biomimetic synthesis of many important natural Products“, *Curr. Sci.* **1996**, *71*, 106–108. (b) B. Feringa, H. Wynberg, „Biomimetic Asymmetric Oxidative Coupling of Phenols“, *Bioorg. Chem.* **1978**, *7*, 397–408.

31 Übersichtsartikel: S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, „Aerobic Copper-Catalyzed Organic Reactions“, *Chem. Rev.* **2013**, *113*, 6234–6458.

32 M. Noji, M. Nakajima, K. Koga, „A New Catalytic System of Aerobic Oxidative Coupling of 2-Naphthol Derivatives by the use of CuCl-Amine Complex: A Practical Synthesis of Binaphthol Derivatives“, *Tetrahedron Lett.* **1994**, *35*, 7983–7984.

33 Die erste asymmetrische, Cu•Diamin-katalysierte oxidative Biarylkupplung (41% Ausbeute, 32% *ee*) gelang 1993 Smrčina *et al.*, siehe: M. Scmrčina, J. Poláková, Š. Vyskočil, P. Kočovský, „Synthesis of Enantiomerically Pure Binaphthyl Derivatives. Mechanism of the Enantioselective, Oxidative Coupling of Naphthols and Designing a Catalytic Cycle“, *J. Org. Chem.* **1993**, *58*, 4534–4538.

34 Übersichtsartikel: (a) „Asymmetric Oxidative Biaryl Coupling Reactions“: C. Zheng, S.-L. You in *Asymmetric Functionalization of C-H Bonds* (Hrsg.: S.-L. You), The Royal Society of Chemistry, Cambridge, **2015**, S. 92–125. (b) H. Wang, „Recent Advances in Asymmetric Oxidative Coupling of 2-Naphthol and its Derivatives“, *Chirality* **2010**, *22*, 827–837.

35 (a) J. B. Hewgley, S. S. Stahl, M. C. Kozlowski, „Mechanistic Study of Asymmetric Oxidative Biaryl Coupling: Evidence for Self-Processing of the Copper Catalyst to Achieve Control of Oxidase vs Oxygenase Activity“, *J. Am. Chem. Soc.* **2008**, *130*, 12232–12233. (b) X. Li, J. B. Hewgley, C. A. Mulrooney, J. Yang, M. C. Kozlowski, „Enantioselective Oxidative Biaryl Coupling Reactions Catalyzed by 1,5-Diazadecalin Metal Complexes: Efficient Formation of Chiral Functionalized BINOL Derivatives“, *J. Org. Chem.* **2003**, *68*, 5500–5511. (c) M. C. Kozlowski, X. Li, P. J. Carroll, Z. Xu, „Copper(II) Complexes of Novel 1,5-Diaza-*cis*-decalin Diamine Ligands: An Investigation of Structure and Reactivity“, *Organometallics* **2002**, *21*, 4513–4522. (d) X. Li, J. Yang, M. C. Kozlowski „Enantioselective Oxidative Biaryl Coupling Reactions Catalyzed by 1,5-Diazadecalin Metal Complexes“, *Org. Lett.* **2001**, *3*, 1137–1140.

36 Übersichtsartikel: (a) T. Satyanarayana, S. Abraham, H. B. Kagan, „Nonlinear Effects in Asymmetric Catalysis“, *Angew. Chem.* **2009**, *121*, 464–503; *Angew. Chem. Int. Ed.* **2009**, *48*, 456–494. (b) H. B. Kagan, „Nonlinear Effects in Asymmetric Catalysis: A Personal Account“, *Synlett* **2001**, 888–899. (c) D. G. Blackmond, „Kinetic Aspects of Nonlinear Effects in Asymmetric Catalysis“, *Acc. Chem. Res.* **2000**, *33*, 402–411. (d) C. Girard, H. B. Kagan, „Nonlinear Effects in Asymmetric Synthesis and Stereoselective Reactions: Ten Years of Investigation“, *Angew. Chem.* **1998**, *110*, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959.

37 Siehe Ref.[35d] In früheren Arbeiten mit (über)stöchiometrischen Mengen an Cu•Diamin-Komplex wurden zwei weitere, substratabhängige Mechanismen zum Stereotransfer gefunden, die nicht auf einer asymmetrischen Kupplung beruhen. 1) Eine diastereoselektive Kristallisation eines Cu•Diamin•Produkt-Komplexes aus dem Produktgemisch, der 2) ein Racemat-Gleichgewicht vorgeschaltet sein kann. Siehe: (a) M. Scmrčina, M. Lorenc, V. Hanuš, P. Sedmera, P. Kočovský, „Synthesis of Enantiomerically Pure 2,2'-Dihydroxy-1,1'-binaphthyl, 2,2'-Diamino-1,1'-binaphthyl, and 2-Amino-2'-hydroxy-1,1'-binaphthyl. Comparison of Processes Operating as Diastereoselective Crystallization and as Second-Order Asymmetric Transformation“, *J. Org. Chem.* **1992**, *57*, 1917–1920. (b) J. Brussee, J. L. G. Groenendijk, J. M. te Koppele, A. C. A. Jansen, „On the Mechanism of the Formation of *S*(–)-[1,1'-Binaphthalene]-2,2'-diol via Copper(II)amine Complexes“, *Tetrahedron* **1985**, *41*, 3313–3319. (c) J. Brussee, A. C. A. Jansen, „A Highly Stereoselective Synthesis of *S*(–)-[1,1'-Binaphthalene]-2,2'-diol“, *Tetrahedron Lett.* **1983**, *24*, 3261–3262. (d) Ref.[33]

38 Gefolgert wurde dies über die Produktverteilung in Konkurenzexperimenten.[35b,d] Bei überstöchiometrischen Mengen an Cu•Diamin-Komplex scheint hingegen eine Radikal-Anion-Kupplung abzulaufen, siehe: (a) M. Smrčina, Š. Vyskočil, B. Máca, M. Polášek, T. A. Claxton, A. P. Abbott, P. Kočovský, „Selective Cross-Coupling of 2-Naphthol and 2-Naphthylamine Derivatives. A Facile Synthesis of 2,2',3-Trisubstituted and 2,2',3,3'-Tetrasubstituted 1,l'-Binaphthyls“, *J. Org. Chem.* **1994**, *59*, 2156–2163. (b) M. Hovorka, J. Günterová, J. Závada, „Highly Selective Oxidative Cross-Coupling of Substituted 2-Naphthols: A Convenient Approach to Unsymmetrical 1,1'-Binaphthalene-2,2'-Diols“, *Tetrahedron Lett.* **1990**, *31*, 413–416.

39 Die genaue Identität des zweiten Radikals ist unbekannt.

40 Die erforderliche Rotation erfolgt vorbei an den sterisch weniger anspruchsvollen Carbonylfunktionen.[35b] (a) A. I. Meyers, D. G. Wettlaufer, „Complete Intramolecular Transfer of a Central Chiral Element to an Axial Chiral Element. Oxidation of (*S*)-4-Naphthyldihydroquinolines to (*S*)-4-Naphthylquinolines“, *J. Am. Chem. Soc*. **1984**, *106*, 1135–1136. (b) A. I. Meyers, K. A. Lutomski, „Enantioselective Synthesis of Binaphthyls via Nucleophilic Aromatic Substitution on Chiral Oxazolines“, *J. Am. Chem. Soc*. **1982**, *104*, 879–881.

41 (a) M. Nakajima, I. Miyoshi, K. Kanayama, S. Hashimoto, M. Noji, K. Koga, „Enantioselective Synthesis of Binaphthol Derivates by Oxidative Coupling of Naphthol Derivates Catalyzed by Chiral Diamine·Copper Complexes“, *J. Org. Chem.* **1999**, *64*, 2264–2271. (b) M. Nakajima, K. Kanayama, I. Miyoshi, S. Hashimoto, „Catalytic Asymmetric Synthesis of Binaphthol Derivatives by Aerobic Oxidative Coupling of 3-Hydroxy-2-naphthoates with Chiral Diamine-Copper Complex“, *Tetrahedron Lett.* **1995**, *36*, 9519–9520.

42 Die erzielten Ergebnisse wurden zeitgleich mit unseren eigenen Arbeiten publiziert.

43 Q. Zhang, X. Cui, L. Chen, H. Liu, Y. Wu, „Syntheses of Chiral Ferrocenophanes and Their Application to Asymmetric Catalysis“, *Eur. J. Org. Chem.* **2014**, 7823–7829.

44 Dies wurde von Kozlowski für zweibindige Diamin-Liganden später bestätigt.[35b] Bei sechsbindigen Chelatliganden kann hingegen auf die zweite Koordinationsstelle im Edukt verzichtet werden, siehe: J. Gao, J. H. Reibenspies, A. E. Martell, „Structurally Defined Catalysts for Enantioselective Oxidative Coupling Reactions“, *Angew. Chem.* **2003**, *115*, 6190–6194; *Angew. Chem. Int. Ed.* **2003**, *42*, 6008–6012.

45 K. H. Kim, D.-W. Lee, Y.-S. Lee, D.-H. Ko, D.-C. Ha, „Enantioselective oxidative coupling of methyl 3-hydroxy-2-naphthoate using mono-*N*-alkylated octahydrobinapththyl-2,2'-diamine ligand“, *Tetrahedron* **2004**, *60*, 9037–9042.

46 S. K. Alamsetti, E. Poonguzhali, D. Ganapathy, G. Sekar, „Enantioselective Oxidative Coupling of 2-Naphthol Derivatives by Copper-(*R*)-1,1'-Binaphthyl-2,2'-diamine-TEMPO Catalyst“, *Adv. Synth. Catal*. **2013**, *355*, 2803–2808.

47 Den gleichen Trend fanden außerdem Sisti *et al*., siehe: A. Caselli, G. B. Giovenzana, G. Palmisano, M. Sisti, T. Pilati, „Synthesis of C_2-symmetrical diamine based on (1*R*)-(+)-camphor and application to oxidative aryl coupling of naphthols“, *Tetrahedron: Asymmetry* **2003**, *14*, 1451–1454.

48 Übersichtsartikel: (a) „The Henry (Nitroaldol) Reaction“: H. Sasai in *Comprehensive Organic Synthesis (2nd Edition)*, Vol. 2 (Hrsg.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, S. 543–570. (b) F. A. Luzzio, „The Henry reaction: recent examples“, *Tetrahedron* **2001**, *57*, 915–945. (c) N. Ono, „The Nitro Group in Organic Synthesis“, Wiley-VCH, New York, **2001**. (d) Ref.[18]

49 Eine SciFinder® Suche nach den Schlagworten „enantioselective Henry reaction“ liefert beispielweise über 50 Publikationen, die im Zeitraum November 2015 bis November 2016 erschienen sind.

50 Übersichtsartikel: (a) G. Murugavel, P. Sadhu, T. Punniyamurthy, „Copper(II)-Catalyzed Nitroaldol (Henry) Reactions: Recent Developments“, *Chem. Rec*. **2016**, *16*, 1906–1917. (b) P. Drabina, L. Harmand, M. Sedlak, „Enantioselective Henry Reaction Catalyzed By Supported Transition Metal Complexes“, *Curr. Org. Synth*. **2014**, *11*, 879–888. (c) „Stereoselective Addition of Nitromethane“: R. Ballini, M. Petrini in *Science of Synthesis C-1 Building Blocks in Organic Synthesis 1* (Hrsg.: P. W. N. M. van Leeuwen), Thieme, Stuttgart, **2014**, S. 507–524. (d) N. Ananthi, S. Velmathi, „Asymmetric Henry reaction catalysed by transition metal complexes: A short review“, *Indian J. Chem.* **2013**, *52B*, 87–108. (e) C. Palomo, M. Oiarbide, A. Laso, „Recent Advances in the Catalytic Asymmetric Nitroaldol (Henry) Reaction“, *Eur. J. Org. Chem.* **2007**, 2561–2574. (f) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, „Catalytic asymmetric Henry reaction“, *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326.

51 M. Satake, A. J. Bourdelais, R. M. Van Wagoner, D. G. Baden, J. L. C. Wright, „Brevisamide: An Unprecedented Monocyclic Ether Alkaloid from the Dinoflagellate *Karenia brevis* That Provides a Potential Model for Ladder-Frame Initiation“, *Org. Lett*. **2008**, *10*, 3465–3468.

52 A. T. Herrmann, S. R. Martinez, A. Zakarian, „A Concise Asymmetric Total Synthesis of (+)-Brevisamide“, *Org. Lett.* **2011**, *13*, 3636–3639.

53 Chirale Kupfer-Katalysatoren, die bei der Addition von $MeNO_2$ (**22a**, Schema 5) an einen beliebigen Aldehyd **17** mindestens einmal ein Produkt **18** mit 99% *ee* liefern:

I. Komplexe mit Box-Liganden: (a) H. Cruz, G. Aguirre, D. Madrigal, D. Chávez, R. Somanathan, „Enantioselective nitromethane addition to brominated and fluorinated benzaldehydes (Henry reaction) catalyzed by chiral bisoxazoline–copper(II) complexes“, *Tetrahedron: Asymmetry* **2016**, *27*, 1217–1221. (b) T. Deng, C. Cai, „Fluorous chiral bis(oxazolines): Synthesis and application in asymmetric Henry reaction“, *J. Fluorine Chem.* **2013**, *156*, 183–186. (c) B. V. S. Reddy, J. George, „Enantioselective Henry reaction catalyzed by a copper(II) *gluco*BOX complex“, *Tetrahedron: Asymmetry* **2011**, *22*, 1169–1175.

II. Komplexe mit Salen-Liganden: (d) A. Das, R. I. Kureshy, K. J. Prathap, M. K. Choudhary, G. V. S. Rao, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, „Chiral recyclable Cu(II)-catalysts in nitroaldol reaction of aldehydes with various nitroalkanes and its application in the synthesis of a valuable drug (*R*)-isoproterenol“, *Appl. Catal., A* **2013**, *459*, 97–105. (e) R. I. Kureshy, A. Das, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, „Cu(II)-Macrocylic [H_4]Salen Catalyzed Asymmetric Nitroaldol Reaction and Its Application in the Synthesis of α1-Adrenergic Receptor Agonist (*R*)-Phenylephrine“, *ACS Catal.* **2011**, *1*, 1529–1535.

III. Komplexe mit Aminoalkohol-Liganden: (f) D.-D. Qin, W.-H. Lai, D. Hu, Z. Chen, A.-A. Wu, Y.-P. Ruan, Z.-H. Zhou, H.-B. Chen, „Highly Enantioselective Henry Reactions of Aromatic Aldehydes Catalyzed by an Amino Alcohol–Copper(II) Complex“, *Chem. Eur. J.* **2012**, *18*, 10515–10518. (g) G. Lai, F. Guo, Y. Zheng, Y. Fang, H. Song, K. Xu, S. Wang, Z. Zha, Z. Wang, „Highly Enantioselective Henry Reactions in Water Catalyzed by a Copper Tertiary Amine Complex and Applied in the Synthesis of (*S*)-*N-trans*-Feruloyl Octopamine“, *Chem. Eur. J.* **2011**, *17*, 1114–1117.

IV. Komplexe mit Iminoalkohol-Liganden: (h) L. Yao, Y. Wei, P. Wang, W. He, S. Zhang, „Promotion of Henry reactions using $Cu(OTf)_2$ and a sterically hindered Schiff base: access to enantioenriched β-hydroxynitroalkanes“, *Tetrahedron* **2012**, *68*, 9119–9124. (i) Y. Wei, L. Yao, B. Zhang, W. He, S. Zhang, „Novel Schiff base ligands derived from *Cinchona* alkaloids for Cu(II)-catalyzed asymmetric Henry reaction“, *Tetrahedron* **2011**, *67*, 8552–8558.

V. Komplexe mit Diamin-Liganden: (j) R. Ćwiek, P. Niedziejko, Z. Kałuża, „Synthesis of Tunable Diamine Ligands with Spiro Indane-2,2′-pyrrolidine Backbone and Their Applications in Enantioselective Henry Reaction“, *J. Org. Chem.* **2014**, *79*, 1222–1234. (k) Y. Zhou, Y. Zhu, S. Yan, Y. Gong, „Copper-Catalyzed Enantioselective Henry Reaction of Enals and Subsequent Iodocyclization: Stereoselective Construction of Chiral Azatricyclic Frameworks“, *Angew. Chem.* **2013**, *125*, 10455–10459; *Angew. Chem. Int. Ed.* **2013**, *52*, 10265–10269. (l) W. Jin, X. Li, B. Wan, „A Highly Diastereo- and Enantioselective Copper(I)-Catalyzed Henry Reaction Using a Bis(sulfonamide)-Diamine Ligand“, *J. Org. Chem.* **2011**, *76*, 484–491. (m) W. Jin, X. Li, Y. Huang, F. Wu, B. Wan, „A Highly Effective Bis(sulfonamide)–Diamine Ligand: A Unique Chiral Skeleton for the Enantioselective Cu-Catalyzed Henry Reaction“, *Chem. Eur. J.* **2010**, *16*, 8259–8261. (n) G. Zhang, E. Yashima, W.-D. Woggon, „Versatile Supramolecular Copper(II) Complexes for Henry and Aza-Henry Reactions“, *Adv. Synth. Catal.* **2009**, *351*, 1255–1262. (o) T. Arai, M. Watanabe, A. Yanagisawa, „Practical Asymmetric Henry Reaction Catalyzed by a Chiral Diamine-$Cu(OAc)_2$ Complex“, *Org. Lett.* **2007**, *9*, 3595–3597. (p) M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi, C. Ventrici, „Highly enantioselective nitroaldol reaction catalyzed by new chiral copper complexes“, *Chem. Commun.* **2007**, 616–618. (q) Ref.[27a,52]

54 Enzymkatalysatoren, die bei der Addition von $MeNO_2$ (**22a**, Schema 5) an einen beliebigen Aldehyd **17** mindestens einmal ein Produkt **18** mit 99% *ee* liefern: (a) M. Bekerle-Bogner, M. Gruber-Khadjawi, H. Wiltsche, R. Wiedner, H. Schwab, K. Steiner, „(*R*)-Selective Nitroaldol Reaction Catalyzed by Metal-Dependent Bacterial Hydroxynitrile Lyases“, *ChemCatChem* **2016**, *8*, 2214–2216. (b) X. Yu, B. Pérez, Z. Zhang, R. Gao, Z. Guo, „Mining catalytic promiscuity from *Thermophilic archaea*: an acyl-peptide releasing enzyme from *Sulfolobus tokodaii* (ST0779) for nitroaldol reactions“, *Green Chem.* **2016**, *18*,

2753–2761. (c) M. Gruber-Khadjawi, T. Purkarthofer, W. Skranc, H. Griengl, „Hydroxynitrile Lyase-Catalyzed Enzymatic Nitroaldol (Henry) Reaction“, *Adv. Synth. Catal*. **2007**, *349*, 1445–1450.

55 Organokatalysatoren, die bei der Addition von $MeNO_2$ (**22a**, Schema 5) an einen beliebigen Aldehyd **17** mindestens einmal ein Produkt **18** mit 99% *ee* liefern: (a) V. Ashokkumar, K. Duraimurugan, A. Siva, „A new series of bipyridine based chiral organocatalysts for enantioselective Henry reaction“, *New J. Chem*. **2016**, *40*, 7148–7156. (b) P. K. Vijaya, S. Murugesan, A. Siva, „Highly enantioselective asymmetric Henry reaction catalyzed by novel chiral phase transfer catalysts derived from cinchona alkaloids“, *Org. Biomol. Chem*. **2016**, *14*, 10101–10109.

56 Metallkatalysatoren (außer Kupfer-basierte), die bei der Addition von $MeNO_2$ (**22a**, Schema 5) an einen beliebigen Aldehyd **17** mindestens einmal ein Produkt **18** mit ≥ 97% *ee* liefern: (a) J. Dimroth, M. Weck, „Co–salen complexes as catalysts for the asymmetric Henry reaction – reversed enantioselectivity through simple ligand modification“, *RSC Adv.* **2015**, *5*, 29108–29113. (b) Y.-L. Wei, K.-F. Yang, F. Li, Z.-J. Zheng, Z. Xu, L.-W. Xu, „Probing the evolution of an Ar-BINMOL-derived salen–Co(III) complex for asymmetric Henry reactions of aromatic aldehydes: salan–Cu(II) *versus* salen–Co(III) catalysis“, *RSC Adv.* **2014**, *4*, 37859–37867. (c) S. Wu, J. Tang, J. Han, D. Mao, X. Liu, X. Gao, J. Yu, L. Wang, „Design of C2-symmetric salen ligands and their Co(II)- or Yb(III)-complexes, and their role in the reversal of enantioselectivity in the asymmetric Henry reaction“, *Tetrahedron* **2014**, *70*, 5986–5992. (d) K. Lang, J. Park, S. Hong, „Urea/Transition-Metal Cooperative Catalyst for *anti*-Selective Asymmetric Nitroaldol Reactions“, *Angew. Chem.* **2012**, *124*, 1652–1656; *Angew. Chem. Int. Ed.* **2012**, *51*, 1620–1624. (e) C. Palomo, M. Oiarbide, A. Laso, „Enantioselective Henry Reactions under Dual Lewis Acid/Amine Catalysis Using Chiral Amino Alcohol Ligands“, *Angew. Chem.* **2005**, *117*, 3949–3952; *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884.

57 Heterobimetallkatalysatoren, die bei der Addition eines Nitroalkans **22** (Schema 7) an einen beliebigen Aldehyd **17** mindestens einmal ein Produkt **24** mit ≥ 98% *ee* liefern: (a) A. Nonoyama, K. Hashimoto, A. Saito, N. Kumagai, M. Shibasaki, „Preparation of Nd/Na heterogeneous catalyst from bench-stable and inexpensive Nd salt for an *anti*-selective catalytic asymmetric nitroaldol reaction“, *Tetrahedron Lett*. **2016**, *57*, 1815–1819. (b) Y. Li, P. Deng, Y. Zeng, Y. Xiong, H. Zhou, „*anti*-Selective Asymmetric Henry Reaction Catalyzed by a Heterobimetallic Cu−Sm−Aminophenol Sulfonamide Complex“, *Org. Lett*. **2016**, *18*, 1578–1581. (c) D. Sureshkumar, K. Hashimoto, N. Kumagai, M. Shibasaki, „A Modified Preparation Procedure for Carbon Nanotube-Confined Nd/Na Heterobimetallic Catalyst for *anti*-Selective Catalytic Asymmetric Nitroaldol Reactions“, *J. Org. Chem.* **2013**, *78*, 11494–11500. (d) T. Ogawa, N. Kumagai, M. Shibasaki, „Self-Assembling Neodymium/Sodium Heterobimetallic Asymmetric Catalyst Confined in a Carbon Nanotube Network“, *Angew. Chem.* **2013**, *125*, 6316–6321; *Angew. Chem. Int. Ed.* **2013**, *52*, 6196–6201. (e) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai, M. Shibasaki, „*anti*-Selective Catalytic Asymmetric Nitroaldol Reaction via a Heterobimetallic Heterogeneous Catalyst“, *J. Am. Chem. Soc.* **2009**, *131*, 13860–13869.

58 D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, „A New Copper Acetate-Bis(oxazoline)-Catalyzed, Enantioselective Henry Reaction“, *J. Am. Chem. Soc*. **2003**, *125*, 12692–12693.

59 Für ähnliche Studien zur gleichen Zeit siehe: T. Risgaard, K. V. Gothelf, K. A. Jørgensen, „Catalytic asymmetric Henry reactions of silyl nitronates with aldehydes“, *Org. Biomol. Chem*. **2003**, *1*, 153–156.

60 Für Katalysezyklen mit Mono-Stickstoff-Liganden, die zusätzlich (mindestens) eine Hydroxy-Funktion enthalten, siehe z. B.: (a) G. Lu, F. Zheng, L. Wang, Y. Guo, X. Li, X. Cao, C. Wang, H. Chi, Y. Dong, Z. Zhang, „Asymmetric Henry reaction catalyzed by Cu(II)-based chiral amino alcohol complexes with C_2-symmetry“, *Tetrahedron: Asymmetry* **2016**, *27*, 732–739. (b) A. Das, R. I. Kureshy, P. S. Subramanian, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, „Synthesis and characterization of chiral recyclable dimeric copper(II)–salen complexes and their catalytic application in asymmetric nitroaldol (Henry) reaction“, *Catal. Sci. Technol.* **2014**, *4*, 411–418. (c) G.-R. Qiang, T.-H. Shen, X.-C. Zhou, X.-X. An, Q.-B. Song, „Synthesis of Novel Chiral Tridentate Schiff-Base Ligands and Their Applications in Catalytic Asym-

metric Henry Reaction“, *Chirality* **2014**, *26*, 780–783. (d) T. Shen, Q. Qin, H. Ni, T. Xia, X. Zhou, F. Cui, J. Li, D. Ran, Q. Song, „Asymmetric Henry reaction catalyzed by Cu(I)-based chiral amino alcohol complex“, *Turk. J. Chem.* **2013**, *37*, 966–977. (e) K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen, Z. Wang, „A Highly *anti*-Selective Asymmetric Henry Reaction Catalyzed by a Chiral Copper Complex: Applications to the Syntheses of (+)-Spisulosine and a Pyrroloisoquinoline Derivative“, *Chem. Eur. J.* **2012**, *18*, 12357–12362. (f) R. Boobalan, G.-H. Lee, C. Chen, „Copper Complex of Aminoisoborneol Schiff Base Cu_2(SBAIB-d)$_2$: An Efficient Catalyst for Direct Catalytic Asymmetric Nitroaldol (Henry) Reaction“, *Adv. Synth. Catal.* **2012**, *354*, 2511–2520. (g) S. Jammi, P. Saha, S. Sanyashi, S. Sakthivel, T. Punniyamurthy, „Chiral binuclear copper(II) catalyzed nitroaldol reaction: scope and mechanism“, *Tetrahedron* **2008**, *64*, 11724–11731.

61 (a) E. Wolińska, Z. Karczmarzyk, W. Wysocki, „Structural characterization of copper complexes with chiral 1,2,4-triazine-oxazoline ligands“, *Heterocycl. Commun.* **2016**, *22*, 265–274. (b) E. Chinnaraja, R. Arunachalam, M. K. Choudhary, R. I. Kureshy, P. S. Subramanian, „Binuclear Cu(II) chiral complexes: synthesis, characterization and application in enantioselective nitroaldol (Henry) reaction“, *Appl. Organomet. Chem.* **2016**, *30*, 95–101. (c) A. Das, M. K. Choudhary, R. I. Kureshy, K. Jana, S. Verma, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, B. Ganguly, „Asymmetric Henry reaction of trifluoromethyl ketone and aldehyde using Cu(II)-complex: computational study offers the origin of enantioselectivity with varied size of catalysts“, *Tetrahedron* **2015**, *71*, 5229–5237. (d) M. Kannan, T. Punniyamurthy, „Effect of ligand N,N-substituents on the reactivity of chiral copper(II) salalen, salan, and salalan complexes toward asymmetric nitroaldol reactions“, *Tetrahedron: Asymmetry* **2014**, *25*, 1331–1339. (e) S. E. Song, Q. T. Nguyen, J. J. Yu, H.-I. Lee, J. H. Jeong, „Synthesis and characterisation of Cu(II) complexes bearing N,N'-di(methoxybenzyl)-(*R*,*R*)-1,2-diaminocyclohexane as catalysts for the asymmetric nitroaldol reaction“, *Polyhedron* **2014**, *67*, 264–269. (f) J. D. White, S. Shaw, „A New Catalyst for the Asymmetric Henry Reaction: Synthesis of *β*-Nitroethanols in High Enantiomeric Excess“, *Org. Lett.* **2012**, *14*, 6270–6273. (g) K. Kodama, K. Sugawara, T. Hirose, „Synthesis of Chiral 1,3-Diamines Derived from *cis*-2-Benzamidocyclohexanecarboxylic Acid and Their Application in the Cu-Catalyzed Enantioselective Henry Reaction“, *Chem. Eur. J.* **2011**, *17*, 13584–13592. (h) Q. J. Yao, Z. M. A. Judeh, „1,1'-Methylene-bis(1,1',2,2',3,3',4,4'-octahydroisoquinoline): synthesis, reaction, resolution, and application in catalytic enantioselective transformations“, *Tetrahedron* **2011**, *67*, 4086–4092. (i) A. Noole, K. Lippur, A. Metsala, M. Lopp, T. Kanger, „Enantioselective Henry Reaction Catalyzed by Cu^{II} Salt and Bipiperidine“, *J. Org. Chem.* **2010**, *75*, 1313–1316. (j) G. Blay, V. Hernández-Olmos, J. R. Pedro, „Enantioselective addition of nitromethane to *α*-keto esters catalyzed by copper(II)–iminopyridine complexes“, *Org. Biomol. Chem.* **2008**, *6*, 468–476. (k) Y. Xiong, F. Wang, X. Huang, Y. Wen, X. Feng, „A New Copper(I)–Tetrahydrosalen-Catalyzed Asymmetric Henry Reaction and Its Extension to the Synthesis of (*S*)-Norphenylephrine“, *Chem. Eur. J.* **2007**, *13*, 829–833. (l) C. Christensen, K. Juhl, R. G. Hazell, K. A. Jørgensen, „Copper-Catalyzed Enantioselective Henry Reactions of *α*-Keto Esters: An Easy Entry to Optically Active *β*-Nitro-*α*-hydroxy Esters and *β*-Amino-*α*-hydroxy Esters“, *J. Org. Chem.* **2002**, *67*, 4875–4881. (m) Ref.[53e,58]

62 Cu(I): Ref.[61a,f,h,k] Cu(II): Ref.[53e,58,61b–e,g,i,j,l]

63 Diamin-basierte Liganden: Ref.[53e,61c–i,k]; Diimin-basierte Liganden: Ref.[58,61a,b,j,l]

64 Zweibindige Liganden: Ref.[58,61a,e,g–j,l]; mehrbindige Liganden: Ref.[53e,61b–d,f,k]

65 Einsatz einer Hilfsbase: Ref.[61b,c,e,g,i,j,l]; keine Hilfsbase: Ref.[53e,58,61a,d,f,h,k]

66 Für Prolin-abgeleitete, nicht-Diamin-Liganden, deren Cu-Komplexe als Katalysator in der Addition von $MeNO_2$ (**22a**, Schema 7) an Aldehyde evaluiert wurden, siehe z. B.: (a) S. Pellegrino, G. Facchetti, A. Contini, M. L. Gelmi, E. Erba, R. Gandolfi, I. Rimoldi, „Ctr-1 Mets7 motif inspiring new peptide ligands for Cu(I)-catalyzed asymmetric Henry reactions under green conditions“, *RSC Adv.* **2016**, *6*, 71529–71533. (b) C. Ao, J. Men, Y. Wang, T. Shao, Y. Huang, J. Huo, G. Gao, „The development of new amine–amide ligands for application in Cu(II)-catalyzed enantioselective Henry reactions“, *Tetrahedron: Asymmetry* **2016**, *27*, 589–595. (c) V. V. Veselovsky, A. V. Stepanov, „Novel catalysts for the enantio-

selective Henry reaction“, *Russ. Chem. Bull., Int. Ed*. **2014**, *63*, 422–425. (d) H. A. Sema, G. Bez, S. Karmakar, „Asymmetric Henry reaction catalysed by L-proline derivatives in the presence of $Cu(OAc)_2$: isolation and characterization of an *in situ* formed Cu(II) complex“, *Appl. Organomet. Chem*. **2014**, *28*, 290–297. (e) B. Ni, J. He, „Highly asymmetric Henry reaction catalyzed by chiral copper(II) complexes“, *Tetrahedron Lett*. **2013**, *54*, 462–465. (f) B. V. S. Reddy, S. M. Reddy, S. Manisha, C. Madan, „Asymmetric Henry reaction catalyzed by a chiral Cu(II) complex: a facile enantioselective synthesis of (*S*)-2-nitro-1-arylethanols“, *Tetrahedron: Asymmetry* **2011**, *22*, 530–535. (g) Ref.[53g]

67 Nach Veröffentlichung unserer eigenen Arbeiten evaluierte die Gruppe um Kałuża weitere Prolindiamine **9** als chirale Liganden in Cu-katalysierten Henry-Reaktionen, siehe: P. Niedziejko, M. Szewczyk, P. Kalicki, Z. Kałuża, „L-Proline derived arylmethanamine ligands and their application in the copper-catalyzed asymmetric Henry reaction: a rare example of a Cu-complex with a dicopper tetraacetate core“, *Tetrahedron: Asymmetry* **2015**, *26*, 1083–1094.

68 (a) Y. Zhou, Q. Yang, J. Shen, X. Chen, Y. Peng, Y. Gong, „Merging Asymmetric Henry Reaction with Organocatalytic Cascade Reaction for the Construction of a Chiral Indolizidine Alkaloid Skeleton“, *J. Org. Chem*. **2015**, *80*, 1446–1456. (b) H. Yuan, J. Hu, Y. Gong, „Asymmetric synthesis of 1,2,3-trisubstituted indanes via an enantioselective copper(II)-catalyzed asymmetric nitroaldol reaction followed by an intramolecular Michael cyclization“, *Tetrahedron: Asymmetry* **2013**, *24*, 699–705. (c) D. Lu, Y. Zhou, Y. Li, S. Yan, Y. Gong, „Copper(II)-Catalyzed Asymmetric Henry Reaction of *o*-Alkynylbenzaldehydes Followed by Gold(I)-Mediated Cycloisomerization: An Enantioselective Route to Chiral 1*H*-Isochromenes and 1,3-Dihydroisobenzofurans“, *J. Org. Chem*. **2011**, *76*, 8869−8878. (d) Ref.[53k]

69 Übersichtsartikel: (a) L. Pu, „Asymmetric Functional Organozinc Additions to Aldehydes Catalyzed by 1,1'-Bi-2-naphthols (BINOLs)“, *Acc. Chem. Res*. **2014**, *47*, 1523−1535. (b) „Recent Advances in Organozinc Reagents“: T. Hirose, K. Kodama in *Comprehensive Organic Synthesis (2nd Edition)*, Vol. 1 (Hrsg.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, S. 204–266. (c) C. M. Binder, B. Singaram, „Asymmetric Addition of Diorganozinc Reagents to Aldehydes and Ketones“, *Org. Prep. Proced. Int*. **2011**, *43*, 139–208. (d) L. Pu, H.-B. Yu, „Catalytic Asymmetric Organozinc Additions to Carbonyl Compounds“, *Chem. Rev*. **2001**, *101*, 757–824. (e) K. Soai, S. Niwa, „Enantioselective Addition of Organozinc Reagents to Aldehydes“, *Chem. Rev*. **1992**, *92*, 833–856. (f) R. Noyori, M. Kitamura, „Enantioselective Addition of Organometallic Reagents to Carbonyl Compounds: Chirality Transfer, Multiplication, and Amplification“, *Angew. Chem*. **1991**, *103*, 34–55; *Angew. Chem. Int. Ed. Engl*. **1991**, *30*, 49–69.

70 L. D. Boeck, H. Chio, T. E. Eaton, O. W. Godfrey Jr., K. H. Michel, W. M. Nakatsukasa, R. C.-F. Yao, „Macrolide Compounds“, *Eur. Pat. Appl*., EP 0 375 316 A1, **1990**.

71 D. A. Evans, W. C. Black, „Total Synthesis of (+)-A83543A [(+)-Lepicidin A]“, *J. Am. Chem. Soc*. **1993**, *115*, 4497–4513.

72 N. Oguni, T. Omi, „Enantioselective Addition of Diethylzinc to Benzaldehyde Catalyzed by a Small Amount of Chiral 2-Amino-1-alcohols“, *Tetrahedron Lett*. **1984**, *25*, 2823–2824.

73 Sucht man im SciFinder® nach den Schlagworten „enantioselective diethylzinc“, „asymmetric diethylzinc“ etc. findet man in dem Zeitraum 2014–2016 ca. 50 neue Publikationen, in denen diese Modellreaktion (**17** → **27**, Schema 10) zur Evaluierung neuer Katalysatoren genutzt wird.

74 (+)-DBNE: Sigma-Aldrich, Artikelnummer 407135-1G; DAIB: Toronto Research Chemicals, Artikelnummer D471070; DPMPM: Alfa Aesar, Artikelnummer L19399.

75 K. Soai, S. Yokoyama, K. Ebihara, T. Hayasaka, „A New Chiral Catalyst for the Highly Enantioselective Addition of Dialkylzinc Reagents to Aliphatic Aldehydes“, *J. Chem. Soc., Chem. Commun*. **1987**, 1690–1691.

76 M. Kitamura, S. Suga, K. Kawai, R. Noyori, „Catalytic Asymmetric Induction. Highly Enantioselective Addition of Dialkylzincs to Aldehydes“, *J. Am. Chem. Soc*. **1986**, *108*, 6071–6072.

77 M. Yamakawa, R. Noyori, „An Ab *Initio* Molecular Orbital Study on the Amino Alcohol-Promoted Reaction of Dialkylzincs and Aldehydes“, *J. Am. Chem. Soc*. **1995**, *117*, 6327–6335.

78 (a) M. Kitamura, S. Suga, H. Oka, R. Noyori, „Quantitative Analysis of the Chiral Amplification in the Amino Alcohol-Promoted Asymmetric Alkylation of Aldehydes with Dialkylzincs“, *J. Am. Chem. Soc*. **1998**, *120*, 9800–9809. (b) M. Kitamura, S. Suga, M. Niwa, R. Noyori, „Self and Nonself Recognition of Asymmetric Catalysts. Nonlinear Effects in the Amino Alcohol-Promoted Enantioselective Addition of Dialkylzincs to Aldehydes“, *J. Am. Chem. Soc*. **1995**, *117*, 4832–4842. (c) M. Kitamura, S. Okada, S. Suga, R. Noyori, „Enantioselective Addition of Dialkylzincs to Aldehydes Promoted by Chiral Amino Alcohols. Mechanism and Nonlinear Effect“, *J. Am. Chem. Soc*. **1989**, *111*, 4028–4036.

79 1988 berichteten Oguni *et al*. erstmals von der Beobachtung eines NLE bei Et_2Zn-Additionen, siehe: N. Oguni, Y. Matsuda, T. Kaneko, „Asymmetric Amplifying Phenomena in Enantioselective Addition of Diethylzinc to Benzaldehyde“, *J. Am. Chem. Soc*. **1988**, *110*, 7877–7878.

80 (*S*)-(1-Methylpyrrolidin-2-yl)methanol ohne α-Substituenten induzierte bei der Umsetzung von Benzaldehyd (**17d**, Tabelle 5) mit Et_2Zn keinerlei Stereotransfer (0% *ee*), siehe Ref.[27c]

81 (a) N. Hosoda, H. Ito, T. Takimoto, M. Asami, „Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by (*S*)-1-Alkyl-2-(arylamino)methylpyrrolidine“, *Bull. Chem. Soc. Jpn*. **2012**, *85*, 1014–1022. (b) M. Asami, S. Inoue, „Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by (*S*)-2-(*N*,*N*-Disubstituted aminomethyl)pyrrolidine“, *Bull. Chem. Soc. Jpn*. **1997**, *70*, 1687–1690.

82 Dieser Umstand wurde für Prolinamin **9**-abgeleitete Liganden öfters beobachtet und mit der Ausbildung einer Zn-N Bindung, wie sie in Schema 11, Kapitel 1.3.3.1 gezeigt ist, begründet, siehe z. B. Ref.[85,86] Um gute Ergebnisse mit nicht-Prolinamin **9**-abgeleiteten, über zwei Stickstoffatome koordinierenden Liganden zu erzielen, ist diese NH-Funktion nicht zwingend nötig, siehe z. B. Ref.[90e,92] Es lassen sich jedoch auch hier Beispiele finden, wo sie für einen guten Stereotransfer essentiell ist.[91a]

83 Martens *et al*. evaluierten das Lithiumsalz eines weiteren Prolinamins **9** – mit NH-Funktion im Pyrrolidinring und tertiärem exocyclischen Amin – als Katalysator für die Addition von Et_2Zn an Benzaldehyd (**17d**, Tabelle 5). Sie erzielten hierbei moderate 45% *ee*, siehe: J. Eilers, J. Wilken, J. Martens, „Syntheses of New Chiral 1,2-Diamines and δ-Amino-Alcohols and their Application in Catalytic Enantioselective C-C Bond Formations at an Elevated Temperature of up to 110 °C“, *Tetrahedron: Asymmetry* **1996**, *7*, 2343–2357.

84 Leider wurden in diesem Screening keine Liganden mit sekundären exocyclischen Aminofunktionen evaluiert.

85 M. Asami, H. Watanabe, K. Honda, S. Inoue, „Enantioselective addition of dialkylzinc to aldehydes catalyzed by (*S*)-2-(*N*,*N*-disubstituted aminomethyl)indoline“, *Tetrahedron: Asymmetry* **1998**, *9*, 4165–4173.

86 G. Chelucci, S. Conti, M. Falorni, G. Giacomelli, „Chiral Ligands Containing Heteroatoms. 8.1 2-[(2S)-2-Pyrrolidinyl]pyridine as a Novel Catalyst in the Enantioselective Addition of Diethylzinc to Aldehydes“, *Tetrahedron* **1991**, *47*, 8251–8258.

87 Überraschenderweise wurde hier, im Gegensatz zu allen anderen Substraten, das (*R*)-Enantiomer isoliert.

88 Ausgewählte neuere Liganden (außer Aminoalkole und Distickstoff-haltige), die bei der Addition von Et_2Zn an einen beliebigen Aldehyd **17** mindestens einmal das Produkt **27** mit 99% *ee* liefern (Schema 13): (a) M. E. S. Serra, D. Costa, D. Murtinho, N. C. T. Tavares, T. M. V. D. Pinho e Melo, „D-Penicillamine and L-cysteine derived thiazolidine catalysts: an efficient approach to both enantiomers of secondary alcohols“, *Tetrahedron* **2016**, *72*, 5923–5927. (b) H.-L. Wu, P.-Y. Wu, Y.-N. Cheng, B.-J. Uang, „Enantioselective addition of organozinc reagents to carbonyl compounds catalyzed by a camphor derived chiral γ-amino thiol ligand“, *Tetrahedron* **2016**, *72*, 2656–2665. (c) Y. Gök, L. Kekeç, „Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by C_2-symmetric chiral diols“, *Tetrahedron Lett*. **2014**, *55*, 2727–2729.

89 Neuere Aminoalkohol-Liganden, die bei der Addition von Et_2Zn an einen beliebigen Aldehyd **17** mindestens einmal ein Produkt **27** mit ≥ 98% *ee* liefern (Schema 13): (a) Z. Szakonyi, Á. Csőr, A. Csámpai, F. Fülöp, „Stereoselective Synthesis and Modelling-Driven Optimisation of Carane-Based Aminodiols and 1,3-Oxazines as Catalysts for the Enantioselective Addition of Diethylzinc to Benzaldehyde“, *Chem. Eur. J*. **2016**, *22*, 7163–7173. (b) M. Asami, A. Hasome, N. Yachi, N. Hosoda, Y. Yamaguchi, S. Ito, „Enantioselective addition of diethylzinc to aldehydes catalyzed by *o*-xylylene-type chiral 1,4-amino alcohols with an aminal structure“, *Tetrahedron: Asymmetry* **2016**, *27*, 322–329. (c) W.-X. Zhao, N. Liu, G.-W. Li, D.-L. Chen, A.-A. Zhang, M.-C. Wang, L. Liu, „Synthesis of dendrimer-supported ferrocenylmethyl aziridino alcohol ligands and their application in asymmetric catalysis“, *Green Chem*. **2015**, *17*, 2924–2930. (d) X. Wan, W. Zhao, G. Li, G. Liu, J. Wang, M. Wang, L. Liu, „Enantioselective addition of diethylzinc to aldehydes catalyzed by aziridine carbinols“, *Tetrahedron: Asymmetry* **2015**, *26*, 815–820. (e) M. Asami, A. Nagai, Y. Sasahara, K. Ichikawa, S. Ito, N. Hosoda, „Enantioselective Addition of Diethylzinc to Aldehydes Catalyzed by Diastereomeric 1,4-Amino Alcohols with *o*-Xylylene Skeleton“, *Chem. Lett*. **2015**, *44*, 345–347. (f) M. A. Aga, B. Kumar, A. Rouf, B. A. Shah, S. C. Taneja, „Vasicine as tridentate ligand for enantioselective addition of diethylzinc to aldehydes“, *Tetrahedron Lett*. **2014**, *55*, 2639–2641.

90 Liganden, die zwei Stickstoffatome und keine Hydroxyfunktion enthalten, die bei der Addition von Et_2Zn an einen beliebigen Aldehyd **17** mindestens einmal ein Produkt **27** mit 99% *ee* liefern (Ausnahme: Pyridinamin-Liganden, siehe Ref.[91], Schema 13): (a) F. Li, H. Huang, H. Zong, G. Bian, L. Song, „Investigation on the asymmetric addition reactions between varied nonaromatic aldehydes and diethylzinc catalyzed by chiral phosphoramide and thiophosphorodiamide ligands“, *Tetrahedron Lett*. **2015**, *56*, 2071–2076. (b) D. Murtinho, M. E. S. Serra, A. M. d'A. R. Gonsalves, „Enantioselective ethylation of aldehydes with 1,3-*N*-donor ligands derived from (+)-camphoric acid“, *Tetrahedron: Asymmetry* **2010**, *21*, 62–68. (c) M. I. Burguete, J. Escorihuela, S. V. Luis, A. Lledós, G. Ujaque, „New chiral tetraaza ligands for the efficient enantioselective addition of dialkylzinc to aromatic aldehydes“, *Tetrahedron* **2008**, *64*, 9717–9724. (d) M. L. Richmond, C. T. Seto, „Modular Ligands Derived from Amino Acids for the Enantioselective Addition of Organozinc Reagents to Aldehydes“, *J. Org. Chem*. **2003**, *68*, 7505–7508. (e) C. L. Gibson, „Enantioselective addition of diethylzinc to aldehydes catalysed by a β-amino disulfide derived from L-proline“, *Chem. Commun*. **1996**, 645–646.

91 Pyridinamin-Liganden, die bei der Addition von Et_2Zn an einen beliebigen Aldehyd **17** mindestens einmal ein Produkt **27** mit ≥ 98% *ee* liefern (Schema 13): (a) Y.-Q. Cheng, Z. Bian, C.-Q. Kang, H.-Q. Guo, L.-X. Gao, „Chiral ligand 2-(2'-piperidinyl)pyridine: synthesis, resolution and application in asymmetric diethylzinc addition to aldehydes“, *Tetrahedron: Asymmetry* **2008**, *19*, 1572–1575. (b) S. Conti, M. Falorni, G. Giacomelli, F. Soccolini, „Chiral Ligands Containing Heteroatoms. 10.1 1-(2-Pyridyl)alkylamines as Chiral Catalysts in the Addition of Diethylzinc to Aldehydes: Temperature Dependence on the Enantioselectivity.“, *Tetrahedron* **1992**, *48*, 8993–9000. (c) Ref.[86]

92 Für ein weiteres Beispiel eines > 90% *ee* liefernden reinen Diamin-Liganden, siehe: R. Melgar-Fernández, R. González-Olvera, J. L. Olivares-Romero, V. González-López, L. Romero-Ponce, M. del Refugio Ramírez-Zárate, P. Demare, I. Regla, E. Juaristi, „Synthesis of Novel Derivatives of (1*S*,4*S*)-2,5-Diazabicyclo[2.2.1]heptane and Their Evaluation as Potential Ligands in Asymmetric Catalysis“, *Eur. J. Org. Chem*. **2008**, 655–672.

93 Teilweise wurden mit lithiierten Diaminen hervorragende Ergebnisse bei der Addition von Et_2Zn an Aldehyde (Schema 13) erzielt, siehe z. B.: (a) S. Niwa, K. Soai, „Asymmetric Synthesis Using Chiral Piperazines. Part 3. Enantioselective Addition of Dialkylzincs to Aryl Aldehydes Catalysed by Chiral Piperazines“, *J. Chem. Soc., Perkin Trans. 1* **1991**, 2717–2720. (b) K. Soai, S. Niwa, Y. Yamada, H. Inoue, „Chiral Piperazine as a New Chiral Catalyst for the Enantioselective Addition of Dialkyl Zincs to Aryl Aldehydes“, *Tetrahedron Lett*. **1987**, *28*, 4841–4842. (c) Ref.[83] Die Verwendung des Lithium-Salzes von **34** (Schema 12) brachte jedoch keinen verbesserten Chiralitätstransfer.[85] Wurden Li•**35** (Schema

12) und Li•**9f** (Tabelle 6) als Katalysatoren eingesetzt, konnten nur noch nahezu racemische Produkte detektiert werden.[81b,86]

94 Siehe z. B.: (a) T. Rasmussen, P.-O. Norrby, „Modeling the Stereoselectivity of the *β*-Amino Alcohol-Promoted Addition of Dialkylzinc to Aldehydes“, *J. Am. Chem. Soc*. **2003**, *125*, 5130–5138. (b) M. Panda, P.-W. Phuan, M. C. Kozlowski, „Theoretical and Experimental Studies of Asymmetric Organozinc Additions to Benzaldehyde Catalyzed by Flexible and Constrained γ-Amino Alcohols“, *J. Org. Chem*. **2003**, *68*, 564–571. (c) T. Rasmussen, P.-O. Norrby, „Characterization of New Six-Membered Transition States of the Amino-Alcohol Promoted Addition of Dialkyl Zinc to Aldehydes“, *J. Am. Chem. Soc*. **2001**, *123,* 2464–2465. (d) M. Yamakawa, R. Noyori, „Asymmetric Addition of Dimethylzinc to Benzaldehyde Catalyzed by (2*S*)-3-*exo*-(Dimethylamino)isobornenol. A Theoretical Study on the Origin of Enantioselection“, *Organometallics* **1999**, *18*, 128–133. (e) B. Goldfuss, K. N. Houk, „Origin of Enantioselectivities in Chiral *β*-Amino Alcohol Catalyzed Asymmetric Additions of Organozinc Reagents to Benzaldehyde: PM3 Transition State Modeling“, *J. Org. Chem*. **1998**, *63*, 8998–9006. (f) Ref.[77,89a]

95 Zu Beginn unserer Arbeiten waren in der Literatur unseres Wissens nach nur zwei andere, keine weiteren Heteroatome enthaltenden, 5-*cis*-Prolinamine bekannt, siehe: (a) A. C. Castro, K. M. Depew, M. J. Grogan, E. B. Holson, B. T. Hopkins, C. W. Johannes, G. F. Keaney, N. O. Koney, T. Liu, D. A. Mann, M. Nevalainen, S. Peluso, L. B. Perez, D. A. Snyder, T. T. Tibbitts, „Compounds and Methods for Inhibiting the Interaction of BCL Proteins with Binding Partners“, WO 2008 024337 A2, **2008**. (b) A. Hutchison, J. Peterson, D. Doller, L. E. Gustavson, T. Caldwell, T. Yoon, W. Pringle, R. Bakthavatchalam, Y. Shen, C. Steenstra, H. Yin, R. De Simone, X. He, „Melanin Concentrating Hormone Receptor Ligands: Substituted 1-Benzyl-4-aryl Piperazine Analogues“, WO 2002 094799 A2, **2002**.

96 Bis einschließlich Kapitel 3 wird innerhalb dieser Arbeit zur Vereinfachung die Position des neu eingeführten Substituenten als 5 bezeichnet, selbst wenn diese nach IUPAC-Nomenklatur 2 wäre.

97 Möglich wäre auch eine (nicht abgebildete) äquatoriale Stellung des 5-*cis*-Substituenten weg vom Reaktionszentrum. Durch diese Konformation würde die C2-C3-Bindung in eine axiale Position gezwungen werden, wodurch die H-Atome an C3 für die sterische Abschirmung der in diesem Fall nördlichen Hemisphäre des Komplexes **H''** (Abbildung 9) sorgen würden.

98 (a) B. M. Trost, F. Miege, „Development of ProPhenol Ligands for the Diastereo- and Enantioselective Synthesis of *β*-Hydroxy-*α*-amino Esters“, *J. Am. Chem. Soc*. **2014**, *136*, 3016–3019. (b) A. V. Moro, E. R. T. Tiekink, J. Zukerman-Schpector, D. S. Lüdtke, C. R. D. Correia, „Chiral Triphenylprolinol Ligands for the Efficient Catalytic Asymmetric Arylation of Aldehydes“, *Eur. J. Org. Chem*. **2010**, 3696–3703. (c) R. Almansa, D. Guijarro, M. Yus, „Microwave-accelerated enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines catalysed by β-aminoalcohols with the prolinol skeleton“, *Tetrahedron: Asymmetry* **2008**, *19*, 1376–1380. (d) R. Almansa, D. Guijarro, M. Yus „Enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines catalysed by β-aminoalcohols with the prolinol skeleton“, *Tetrahedron: Asymmetry* **2007**, *18*, 2828–2840. (e) E. J. Corey, P.-W. Yuen, F. J. Hannon, D. A. Wierda, „Polyfunctional, Structurally Defined Catalysts for the Enantioselective Addition of Dialkylzinc Reagents to Aldehydes“, *J. Org. Chem*. **1990**, *55*, 784–786.

99 Abschlussarbeiten: (a) F. Prause, „(2*S*,5*R*)-2-(Aminomethyl)-5-arylpyrrolidine als chirale Liganden in Cu-katalysierten atropenantioselektiven Biarylkupplungen“, *Masterarbeit* **2012**, Würzburg. (b) F. Sedlag, „Synthese 2,5-*cis*-disubstituierter Pyrrolidin-basierter Diamin-Liganden“, *Bachelorarbeit* **2012**, Würzburg. (c) B. Arensmeyer, „Synthese 2,5-disubstituierter Pyrrolidin-basierter Diamin-Liganden zur späteren Untersuchung in Kupfer-katalysierten enantioselektiven oxidativen Biarylkupplungen“, *Bachelorarbeit* **2011**, Würzburg. (d) B. Fröhlich, „Synthese Pyrrolidin-basierter Diamin-Liganden und deren Evaluierung in enantioselektiven oxidativen Biarylkupplungen“, *Diplomarbeit* **2011**, Würzburg. (e) F. Prause, „Synthese und Evaluierung neuer Diamine als chirale Liganden für atropenantioselektive Kupfer-katalysierte oxidative Biarylkupplungen“, *Bachelorarbeit* **2010**, Würzburg.

100 Ausgewählte Beispiele ausgehend von Pyroglutaminsäure-Derivaten wie **46** (Schema 15):

I. Mit Entfernung der *N*-Schutzgruppe: (a) V. A. Verma, D. G. M. Shore, H. Chen, J. Chen, S. Do, D. H. Hackos, A. Kolesnikov, J. P. Lyssikatos, S. Tay, L. Wang, A. A. Estrada, „*α*-Aryl pyrrolidine sulfonamides as TRPA1 antagonists“, *Bioorg. Med. Chem. Lett*. **2016**, *26*, 495–498. (b) Y. Sang, J. Zhao, X. Jia, H. Zhai, „Asymmetric Synthesis of (+)-Pyrido[3,4-*b*]homotropane“, *J. Org. Chem*. **2008**, *73*, 3589–3592. (c) Z. Pei, X. Li, K. Longenecker, T. W. von Geldern, P. E. Wiedeman, T. H. Lubben, B. A. Zinker, K. Stewart, S. J. Ballaron, M. A. Stashko, A. K. Mika, D. W. A. Beno, M. Long, H. Wells, A. J. Kempf-Grote, D. J. Madar, T. S. McDermott, L. Bhagavatula, M. G. Fickes, D. Pireh. L. R. Solomon, M. R. Lake, R. Edalji, E. H. Fry, H. L. Sham, J. M. Trevillyan, „Discovery, Structure–Activity Relationship, and Pharmacological Evaluation of (5-Substituted-pyrrolidinyl-2-carbonyl)-2-cyano–pyrrolidines as Potent Dipeptidyl Peptidase IV Inhibitors“, *J. Med. Chem.* **2006**, *49*, 3520–3535. (d) S. C. Turner, H. Zhai, H. Rapoport, „Enantiospecific Synthesis of Annulated Nicotine Analogues from D- and L-Glutamic Acid. Pyridotropanes“, *J. Org. Chem*. **2000**, *65*, 861–870. (e) Y. Xu, J. Choi, M. I. Calaza, S. Turner, H. Rapoport, „Conformationally Constrained Nicotines. 1-Pyridinyl-7-azabicyclo[2.2.1]heptane and 1-Pyridinyl-8-azabicyclo[3.2.1]octane Analogues“, *J. Org. Chem*. **1999**, *64*, 4069–4078. (f) A. Momotake, H. Togo, M. Yokoyama, „Convenient synthesis of *C*-aza-2,3-dideoxynucleosides“, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193–1200. (g) M.-C. Fournie-Zaluski, P. Coric, V. Thery, W. Gonzalez, H. Meudal, S. Turcaud, J.-B. Michel, B. P. Roques, „Design of Orally Active Dual Inhibitors of Neutral Endopeptidase and Angiotensin-Converting Enzyme with Long Duration of Action“, *J. Med. Chem*. **1996**, *39*, 2594–2608.

II. Ohne Entfernung der *N*-Schutzgruppe: (h) G.-J. Lin, P.-Q. Huang, „A concise and fully selective synthesis of the ant venom alkaloid (3*S*,5*R*,8*S*,9*S*)-3-butyl-5-propyl-8-hydroxyindolizidine“, *Org. Biomol. Chem*. **2009**, *7*, 4491–4495. (i) T. S. McDermott, L. Bhagavatula, T. B. Borchardt, K. M. Engstrom, J. Gandarilla, B. J. Kotecki, A. W. Kruger, M. J. Rozema, A. Y. Sheikh, S. H. Wagaw, S. J. Wittenberger, „Development of a Scalable Synthesis of Dipeptidyl Peptidase-4 Inhibitor ABT-279“, *Org. Process Res. Dev*. **2009**, *13*, 1145–1155. (j) J. B. Brenneman, R. Machauer, S. F. Martin, „Enantioselective synthesis of (+)-anatoxin-a via enyne metathesis“, *Tetrahedron* **2004**, *60*, 7301–7314. (k) A. C. Rudolph, R. Machauer, S. F. Martin, „Synthesis of *cis*-2,5-disubstituted pyrrolidines via diastereoselective reduction of *N*-acyl iminium ions“, *Tetrahedron Lett*. **2004**, *45*, 4895–4898. (l) Ref.[98a]

101 Andere ausgewählte Darstellungsmethoden: (a) S. Haldar, S. K. Roy, B. Maity, D. Koley, C. K. Jana, „Regio- and Diastereoselective and Enantiospecific Metal-Free C(sp^3)–H Arylation: Facile Access to Optically Active 5-Aryl 2,5-Disubstituted Pyrrolidines“, *Chem. Eur. J*. **2015**, *21*, 15290–15298. (b) F. C. Sequeira, B. W. Turnpenny, S. R. Chemler, „Copper-Promoted and Copper-Catalyzed Intermolecular Alkene Diamination“, *Angew. Chem*. **2010**, *122*, 6509–6512; *Angew. Chem. Int. Ed*. **2010**, *49*, 6365–6368. (c) M. E. Bouillon, H. H. Meyer, „Diastereoselective total synthesis of (+)-morusimic acid B, an amino acid from *Morus alba*“, *Tetrahedron* **2007**, *63*, 2712–2723. (d) T. J. Donohoe, G. H. Churchill, K. M. P. Wheelhouse (née Gosby), P. A. Glossop, „Stereoselective Synthesis of Pyrrolidines: Catalytic Oxidative Cyclizations Mediated by Osmium“, *Angew. Chem*. **2006**, *118*, 8193–8196; *Angew. Chem. Int. Ed*. **2006**, *45*, 8025–8028. (e) J. M. Andrés, I. Herráiz, R. Pedrosa, A. Pérez-Encabo, „Diastereoselective Cyclization of γ-δ Epoxyketones with (–)-Phenylglycinol: Synthesis of Both Enantiomers of *cis*-5-Alkyl-2-hydroxymethyl Pyrrolidines“, *Synlett* **2004**, 2016–2018. (f) Q. Wang, N. A. Sasaki, C. Riche, P. Potier, „A Versatile Method for the Facile Synthesis of Enantiopure *trans*- and *cis*-2,5-Disubstituted Pyrrolidines“, *J. Org. Chem*. **1999**, *64*, 8602–8607. (g) H. Pettersson-Fasth, S. W. Riesinger, J.-E. Bäckvall, „An Enantioselective Route to *cis*- and *trans*-2-(Hydroxymethyl)-5-alkylpyrrolidines“, *J. Org. Chem*. **1995**, *60*, 6091–6096. (h) N. Ozasa, K. Tokioka, Y. Yamamoto, „Asymmetric Trans-esterification of *meso*-2,5-Dibromoadipate and Synthesis of Optically Active *cis*-2,5-Disubstituted Pyrrolidines“, *Biosci., Biotech., Biochem*. **1995**, *59*, 1905–1907. (i) Ref.[98b]

102 Dieser Wert konnte erst in einer zeitgleich mit unseren eigenen Arbeiten veröffentlichten Publikation gesteigert werden, siehe Ref.[43]

5 DARSTELLUNG DES EIGENANTEILS

Die in dieser Dissertation präsentierten Publikationen und das Manuskript wurden in Kooperation mit anderen Wissenschaftlern, allen voran Dagmar Scharnagel und Johannes Kaldun, erarbeitet. Im Folgenden wird der Beitrag aller Koautoren zu den jeweiligen Arbeiten detailliert dargestellt.

Kapitel 6.1

Diese Arbeit wurde publiziert in Synthesis (*Synthesis* **2015**, *47*, 575–586) unter dem Titel

„Flexible and Modular Syntheses of Enantiopure 5-*cis*-Substituted Prolinamines from L-Pyroglutamic Acid“

von den Autoren *Felix Prause, Johannes Kaldun, Benjamin Arensmeyer, Benedikt Wennemann, Benjamin Fröhlich, Dagmar Scharnagel und Matthias Breuning**

* Matthias.Breuning@uni-bayreuth.de

Diese Publikation ging aus der arbeitskreisinternen Kooperation mit Johannes Kaldun und Dagmar Scharnagel hervor, bei der mein Fokus auf der Bereitstellung der benötigten Liganden lag. Die Mehrheit der hier präsentierten synthetischen Arbeiten (inklusive der Charakterisierung der neuen Substanzen) wurde von mir durchgeführt, aber auch Johannes Kaldun leistete zur Etablierung der Routen wichtige Beiträge. Benjamin Arensmeyer und Benedikt Wennemann waren im Rahmen einer Bachelorarbeit und verschiedener Praktika unter der Betreuung von Prof. Dr. Matthias Breuning und mir an exploratorischen Versuchen zur Evaluierung der Routen beteiligt. Benjamin Fröhlich trug im Rahmen seiner Diplomarbeit ebenfalls dazu bei. Dagmar Scharnagel arbeitete an der Darstellung einiger Verbindungen mit.

An wissenschaftlichen Diskussionen über dieses Projekt waren Johannes Kaldun, Dagmar Scharnagel, Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Prof. Dr. Matthias Breuning und mir, mit Unterstützung von Johannes Kaldun und Dagmar Scharnagel, verfasst.

Eigenanteil: ca. 60%

Kapitel 6.2

Diese Arbeit wurde publiziert in Catalysis Science & Technology (*Catal. Sci. Technol.* **2015**, *5*, 2215–2226) unter dem Titel

„In-depth structure–selectivity investigations on asymmetric, copper-catalyzed oxidative biaryl coupling in the presence of 5-*cis*-substituted prolinamines“

von den Autoren *Felix Prause, Benjamin Arensmeyer, Benjamin Fröhlich und Matthias Breuning**

* Matthias.Breuning@uni-bayreuth.de

Die Mehrheit der hier präsentierten synthetischen Arbeiten (inklusive der Charakterisierung der neuen Substanzen) wurde von mir durchgeführt. Benjamin Arensmeyer war als wissenschaftliche Hilfskraft und im Rahmen eines Praktikums unter der Betreuung von Prof. Dr. Matthias Breuning und mir an der Synthese der evaluierten 5-*cis*-Prolinamine beteiligt. Benjamin Fröhlich leistete im Rahmen seiner Diplomarbeit exploratorische Forschungen zu diesem Projekt.

An wissenschaftlichen Diskussionen über dieses Projekt waren Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Prof. Dr. Matthias Breuning und mir verfasst.

Eigenanteil: ca. 80%

Kapitel 6.3

Diese Arbeit wurde publiziert in Chemical Communications (*Chem. Commun.* **2014**, *50*, 6623–6625) unter dem Titel

„(2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a chiral diamine ligand for copper(II)-catalysed Henry reactions with superb enantiocontrol“

von den Autoren *Dagmar Scharnagel,‡ Felix Prause,‡ Johannes Kaldun,‡ Robert G. Haase und Matthias Breuning**

‡ Autoren haben gleiche Beiträge geleistet.

* Matthias.Breuning@uni-bayreuth.de

Diese Publikation ging aus der arbeitskreisinternen Kooperation mit Johannes Kaldun und Dagmar Scharnagel hervor, bei der mein Fokus auf der Bereitstellung der benötigten Liganden lag. Ich führte erste exploratorische Versuche mit 5-*cis*-substituierten Prolinaminen als chiralen Liganden in der Henry-Reaktion durch, die Robert Haase in seiner Masterarbeit erweiterte. Weiterhin synthetisierte und charakterisierte ich den in der Publikation verwendeten chiralen Liganden. Johannes Kaldun setzte die Henry-Reaktionen an die im Anschluss von ihm, Dagmar Scharnagel und mir aufgereinigt wurden. Dagmar Scharnagel führte die Enantiomerenanalytik durch und stellte die hierfür benötigten Racemate dar.

An wissenschaftlichen Diskussionen über dieses Projekt waren Johannes Kaldun, Dagmar Scharnagel, Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Dagmar Scharnagel, Johannes Kaldun, Prof. Dr. Matthias Breuning und mir verfasst.

Eigenanteil: ca. 30%

Kapitel 6.4

Diese Arbeit wurde publiziert in ChemCatChem (*ChemCatChem* **2016**, *8*, 1846–1856) unter dem Titel

„Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions“

von den Autoren *Johannes Kaldun, Felix Prause, Dagmar Scharnagel, Frederik Freitag und Matthias Breuning**

* Matthias.Breuning@uni-bayreuth.de

Diese Publikation ging aus der arbeitskreisinternen Kooperation mit Johannes Kaldun und Dagmar Scharnagel hervor, bei der mein Fokus auf der Bereitstellung der benötigten Liganden lag. Ich synthetisierte den Großteil der hier evaluierten Liganden. Johannes Kaldun führte die Henry-Reaktionen durch und war, wie auch Frederick Freitag im Rahmen seiner Bachelorarbeit, ebenfalls an der Ligandensynthese beteiligt. Dagmar Scharnagel führte die Diastereomerenanalytik durch und stellte die hierfür benötigten Racemate dar.

An wissenschaftlichen Diskussionen über dieses Projekt waren Johannes Kaldun, Dagmar Scharnagel, Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Prof. Dr. Matthias Breuning und Johannes Kaldun, mit Unterstützung von Dagmar Scharnagel und mir, verfasst.

Eigenanteil: ca. 30%

Kapitel 6.5

Diese Arbeit ist als Manuskript fertig zur Einreichung unter dem Titel

„Enantioselective addition of diethylzinc to aldehydes catalyzed by 5-*cis*-substituted proline derivatives“

Von den Autoren *Felix Prause, Stefan Wagner und Matthias Breuning**

* Matthias.Breuning@uni-bayreuth.de

Die hier präsentierten synthetischen Arbeiten wurden von mir oder unter meiner Anleitung durchgeführt. Stefan Wagner leistete im Rahmen seiner Bachelorarbeit hierzu einige Beiträge.

An wissenschaftlichen Diskussionen über dieses Projekt waren Prof. Dr. Matthias Breuning und ich beteiligt. Die Publikation wurde von Prof. Dr. Matthias Breuning und mir verfasst.

Eigenanteil: ca. 90%

6 PUBLIKATIONEN UND MANUSKRIPTE

6.1 Flexible and Modular Syntheses of Enantiopure 5-*cis*-Substituted Prolinamines from L-Pyroglutamic Acid

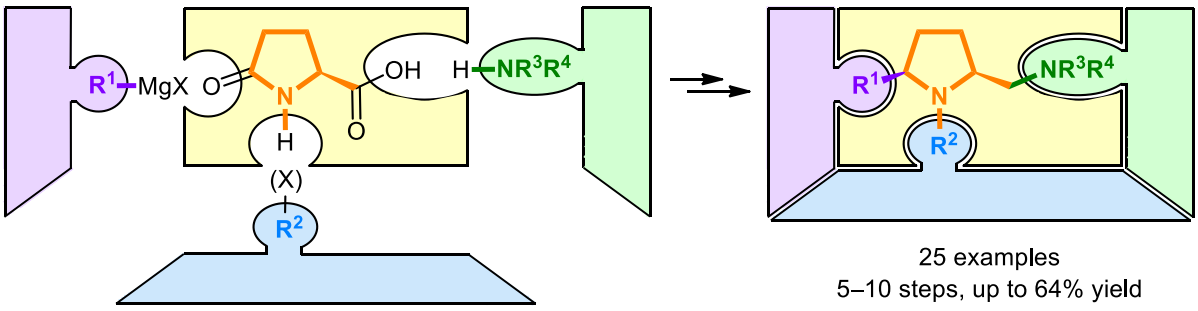
Felix Prause,[a] Johannes Kaldun,[a] Benjamin Arensmeyer,[b] Benedikt Wennemann,[c] Benjamin Fröhlich,[b] Dagmar Scharnagel[a] and Matthias Breuning*[a]

[a] Organic Chemistry Laboratory, University of Bayreuth, Universitätsstraße 30, 95447 Bayreuth, Germany.

[b] Institute of Organic Chemistry, University of Würzburg, Am Hubland, 97074 Würzburg, Germany.

[c] Institute of Inorganic Chemistry, University of Würzburg, Am Hubland, 97074 Würzburg, Germany.

* Matthias.Breuning@uni-bayreuth.de



Published in: *Synthesis* **2015**, *47*, 575–586.

https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0034-1379457

doi: 10.1055/s-0034-1379457

† Der Thieme Verlag erlaubt nicht das Einbinden des erschienen Manuskripts in eine kumulative Dissertation, sondern nur der eingereichten, angenommen Word-Version. Daher können im folgenden Abdruck geringe Änderungen gegenüber dem erschienen Manuskript vorhanden sein.

Abstract

A variety (25 examples) of 5-*cis*-substituted prolinamines was prepared in five to ten steps from cheap L-pyroglutamic acid. Three routes, differing mainly in the order of introduction of the substituents at 5-*cis* position, the pyrrolidine nitrogen atom, and the exocyclic amino function, were successfully developed.

Key words

amines, ligands, stereoselective synthesis, pyrrolidines, prolinamines

Introduction

Proline-derived amino alcohols and diamines have found manifold applications in asymmetric catalysis. Some prominent examples are Corey's bicyclic CBS-catalyst **1** (Figure 1), nowadays routinely used in enantioselective ketone reductions,[3] Jørgensen's diarylprolinol silyl ether **2**, a standard chiral organocatalyst,[4] Soai's tertiary amino alcohol **3**, one of the first chiral ligands for enantioselective additions of diorgano zinc reagents to aldehydes,[5] and Gong's isoborneol substituted diamine **4**, which permits excellent enantioselectivities in copper-catalyzed Henry reactions.[6] All these compounds gain their high stereodiscriminating abilities from the rigid bi- or oligocyclic nature of the intermediately formed reactive species, which, in return, is defined by the privileged prolinol or prolinamine skeleton. Surprisingly, no attention in asymmetric catalysis has as yet been paid to proline derivatives possessing an additional substituent in 5-*cis* position, although such a substituent might further enhance the level of chirality transfer.

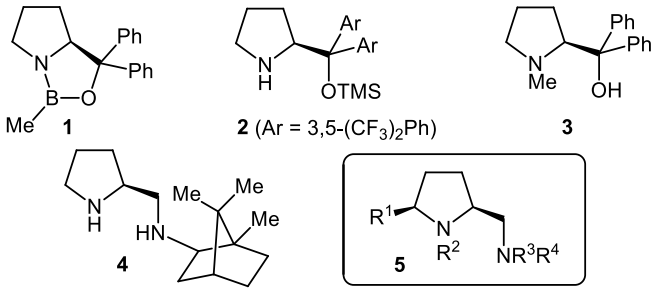
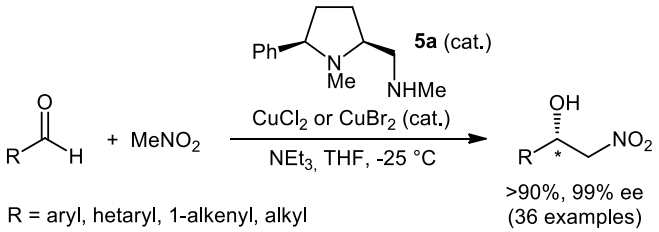


Figure 1 The privileged proline derived ligands **1–4**[3–6] and the new 5-*cis*-substituted prolinamines **5**

In the course of our studies on conformationally rigid ligands[7] we became interested in prolinamines of general structure **5** and their performance in enantioselective catalysis. Due to their close structural relationship to **4**, we tested these compounds in copper(II)-catalyzed Henry reactions.[8,9] And indeed, the simple diamine **5a**, which carries a 5-*cis*-phenyl group, proved to be an excellent chiral ligand (Scheme 1).[10] Extraordinarily high asymmetric inductions of 99% ee were obtained with a wide variety of aromatic, heteroaromatic, vinylic, and aliphatic aldehydes (36 examples), thus making diamine **5a** superior to all other chiral ligands

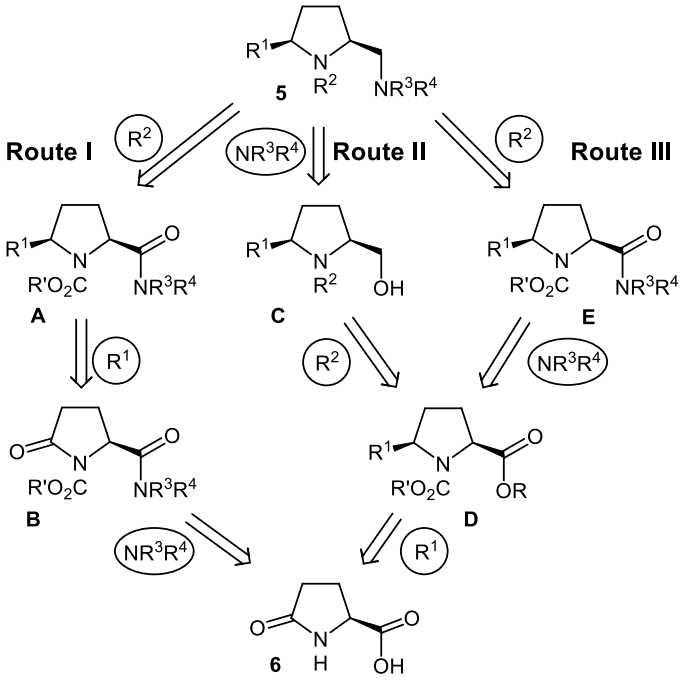
examined so far in this type of reaction. Encouraged by this success, we decided to study more intensively this interesting, but almost unknown class[11] of diamines **5**, and therefore we had to develop efficient and modular routes for their preparation.



Scheme 1 Enantioselective Henry reactions catalyzed by the prolinamine–copper(II) complexes [CuX_2·**5a**] (X = Cl, Br)[10]

Synthetic Routes

An important precondition for our planned synthesis of various prolinamines **5** was the elaboration of effective strategies (Scheme 2), which permit a flexible screening of the substituent R^1 at 5-*cis* position, R^2 at the pyrrolidine nitrogen atom, and R^3R^4 at the exocyclic amino function. Based on literature protocols on the conversion of carbamate protected pyroglutamic esters to 5-*cis*-substituted proline esters,[12,13] we focused on three major routes (I–III) that all start from cheap L-pyroglutamic acid (**6**), but differ in the order of introduction of R^1–R^4.



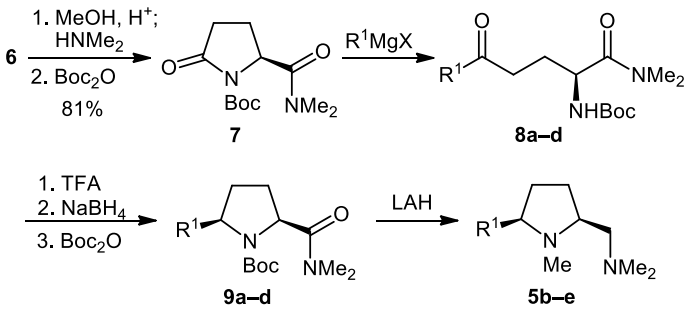
Scheme 2 Envisioned synthetic routes I–III

Route I is characterized by an early-stage installment of the NR^3R^4 group via an amide (**6** → **B**), an intermediate attachment of R^1 (**B** → **A**), and a final incorporation of R^2 (**A** → **5**). In

route II, by contrast, R^1 is introduced first (**6** → **D**), then R^2 (**D** → **C**), and NR^3R^4 last by hydroxy–amine exchange (**C** → **5**). Route III also proceeds via the ester **D**, but NR^3R^4 is installed via amidation (**D** → **E**) before R^2 (**E** → **5**). All three routes offer distinct advantages with respect to the substituent to be varied. While the synthetic work is minimized in route I for a screening of R^1 and R^2, route II seems to be well suited for a broad variation of the amino function NR^3R^4 since it can be done in the very last step. Route III provides a welcome alternative to route II, in particular if NR^3R^4 cannot be introduced last for compatibility reasons.

Route I

Our initial investigations aimed at a fast screening of the 5-*cis* substituent R^1, for which route I is predestinated, and methyl groups were chosen for R^2–R^4 in order to keep the system as simple as possible (Scheme 3 and Table 1). The required precursor, the *N*-Boc-protected dimethyl amide **7**, was prepared in two steps and good 81% yield by esterification of L-pyroglutamic acid (**6**) with methanol, in-situ amidation with $HNMe_2$, and *N*-Boc protection. Four different aryl substituents R^1 were introduced in analogy to known sequences on pyroglutamic esters.[12,13] Treatment of **7** with a slight excess of the respective Grignard reagent R^1MgX afforded the amino ketones **8a–d** in acceptable to good 43–76% yield. The following three-step cyclizations of **8a–d** (*N*-Boc deprotection with concomitant imine formation, reduction of the intermediate Δ^1-pyrrolidine, and renewed *N*-Boc protection) were accomplished in one pot without isolation of the intermediates, giving the prolinamides **9a–c**[14] in good yields (76–90%). The *cis* selectivities in the reductive cyclization step were pleasing (dr ≥ 85:15),[15] even with cheap $NaBH_4$ as the reductant.[16] Solely for the 1-naphthyl derivative **9d**, the *cis* selectivity dropped to 70:30,[15] which explains the low 56% yield isolated. The Boc group at the pyrrolidine nitrogen atom was re-attached for two reasons, because it significantly facilitates the chromatographic purification and because it serves as the precursor for an *N*-methyl group. The final reduction of **9a**,**b**,**d** with LAH at reflux delivered the desired diamines **5b**,**c**,**e** in excellent ≥85% yield. In the case of **9c**, however, partial defluorination of the arylic CF_3-groups occurred, leading to an inseparable mixture.



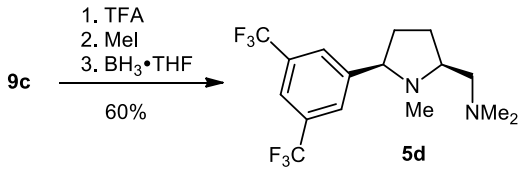
Scheme 3 Route I – three step cyclization

Table 1 Yields of **8**, **9** and **5** prepared according to Scheme 3

Entry	R^1	Yield of **8** (%)	Yield of **9** (%)[a]	Yield of **5** (%)
1	Ph	72 (**8a**)	76 (**9a**)	85 (**5b**)
2	4-$MeOC_6H_4$	55 (**8b**)	90 (**9b**)	97 (**5c**)
3	3,5-$(F_3C)_2C_6H_3$	76 (**8c**)	85 (**9c**)	--[b] (**5d**)
4	1-naphthyl	43 (**8d**)	56 (**9d**)	87 (**5e**)

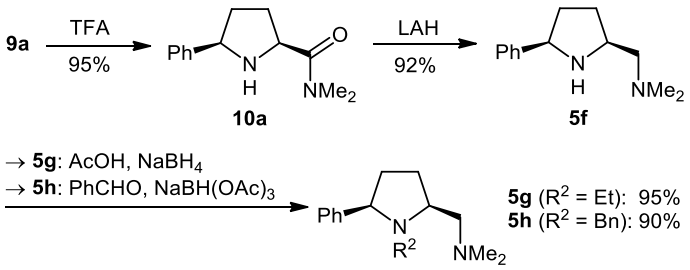
[a] Isolated yield of the pure *cis* diastereomer. [b] Inseparable mixture of **5d** and partially deflourinated derivatives.

In order to prevent the unwanted fluoride–hydride exchange, we elaborated a milder, stepwise route for the conversion of **9c** to **5d** (Scheme 4). After *N*-deprotection of **9c** with TFA and methylation of the pyrrolidine nitrogen atom, the amide function was reduced with BH_3·THF in refluxing THF. This sequence provided the diamine **5d** in overall 60% yield without the formation of any defluorinated by-products.



Scheme 4 Preparation of diamine **5d** from **9c**

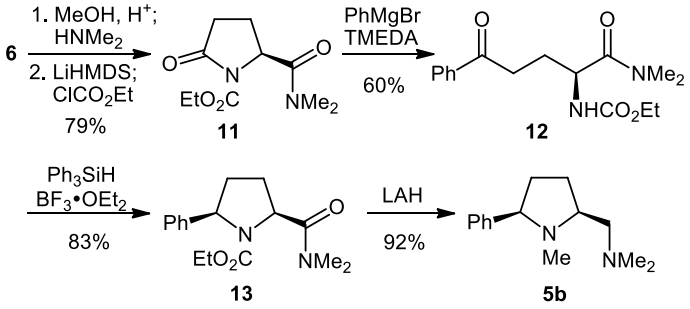
The possibility of a last-step variation of the substituent R^2 at the pyrrolidine nitrogen was demonstrated on the 5-phenyl derivative **9a** (Scheme 5). *N*-Deprotection with TFA afforded amide **10a**, which was reduced with LAH to give diamine **5f**[14] in 87% yield over two steps. Reductive amination of **5f** with PhCHO–$NaBH(OAc)_3$ provided the *N*-benzyl derivative **5h** in good 90% yield, while the analogous ethylation failed to give sufficient product formation. With the reagent combination AcOH–$NaBH_4$,[17] however, the *N*-ethylated prolinamine **5g** was obtained in high 95% yield.



Scheme 5 Route I – variation of R^2

A further shortening of this approach to diamines **5** might be possible by using a variant of Martin's procedure,[18] in which a two-step protocol is described for the introduction of 5-*cis*-substituents to *N*-ethoxycarbonyl protected pyroglutamic esters. We explored this route in the synthesis of diamine **5b** (Scheme 6). The preparation of the required amide **11** was first met with some difficulties. After conversion of L-pyroglutamic acid (**6**) into the corresponding

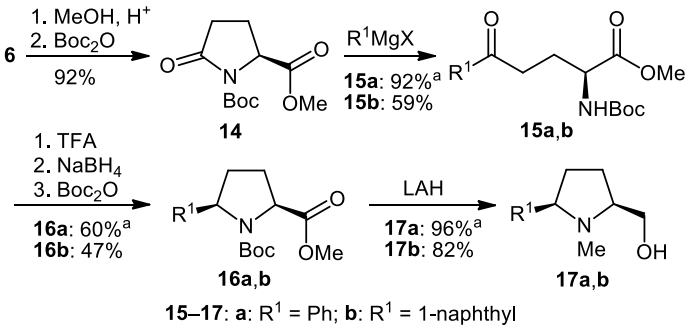
dimethyl amide, all attempts to attach the ethoxycarbonyl group to the lactam function under standard conditions (EtOCOCl, weak base such as NEt_3)[19] failed to give decent yields of **11**, due to fast decomposition of the chloroformate.[19a] This problem was overcome by quantitative deprotonation with LiHMDS and subsequent trapping with EtOCOCl, which delivered **11** in overall 79% yield from **6**. Addition of PhMgBr in the presence of TMEDA,[20] which is required to suppress a competing attack on the carbamate group,[18] afforded the ring-opened ketone **12** in 60% yield. The following reductive one-step cyclization with Ph_3SiH–$BF_3{\cdot}OEt_2$ provided the pyrrolidine amide **13** with excellent *cis* selectivity (initial dr >95:5).[15] Final global reduction with LAH delivered the desired diamine **5b** in overall just five steps and 36% yield from **6**. Compared to the synthesis of **5b** using the three-step cyclization (cf. Scheme 3 and Table 1, entry 1: seven steps, 38% overall yield), this route is shorter by two steps, but the requisite ethoxycarbonyl protective group makes the synthesis more laborious (anhydrous conditions for EtOCOCl attachment, Grignard–TMEDA adducts for addition)[20] and restricts the chemical flexibility (harsher conditions for carbamate cleavage)[21].



Scheme 6 Route I – one-step cyclization

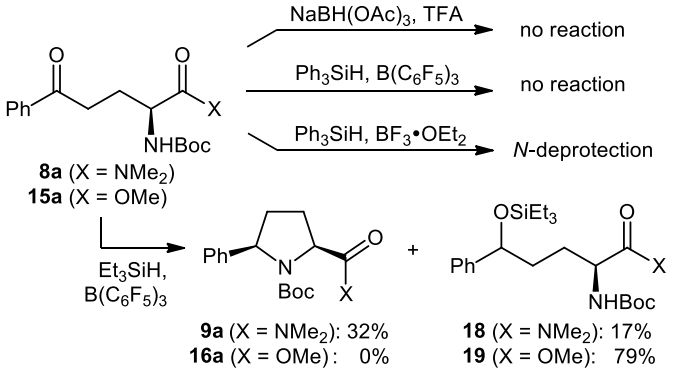
Route II

In route II, prolinols of general type **C** (see Scheme 2) are required as the precursors for the last-step variation of the exocyclic amino group NR^3R^4 by hydroxy–amine exchange. The two 5-*cis*-aryl derivatives **17a** and **17b** were prepared as outlined in Scheme 7 starting from L-pyroglutamic acid **6**, which was converted in high 92% yield into the known pyroglutamate **14**[22] by esterification and subsequent *N*-Boc protection. Applying the four-step sequence[12,13,16] that had already been successfully used in route I delivered the prolines **16a**[10] and **16b**[23] in 51% and 26% overall yield, albeit with a lower *cis* preference in the cyclization step (dr = 70:30, 50:50),[15] as compared to the analogous reaction on the corresponding dimethyl amides **7** (dr = 85:15, 70:30, cf. Scheme 3). Interestingly, a partially diastereomer-differentiating *N*-Boc protection was observed for the phenyl substituted intermediate. With just a slight excess of Boc_2O, the *cis/trans* ratio raised from 70:30 to 85:15 in **16a**, presumably since the pyrrolidine nitrogen atom in the *cis* isomer is more freely accessible than in the *trans* one. Global reduction of **16a**,**b** with LAH in refluxing THF afforded the 5-*cis*-aryl substituted prolinols **17a**,**b** in good 82–96% yield and diastereomerically pure form after purification.



Scheme 7 Route II – synthesis of the prolinol precursors **17a**,**b**[23]
[a] Data taken from ref.[10]

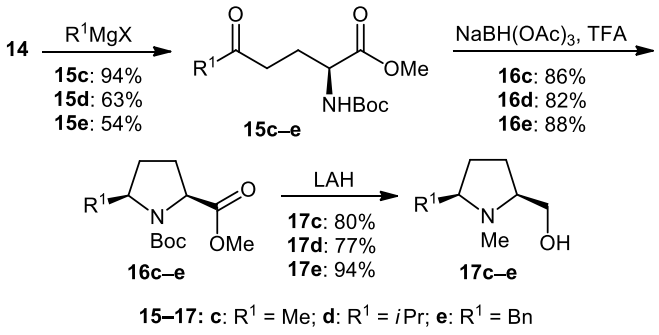
At this point we focused on an omission of the uneconomic *N*-Boc removal and re-attachment, which is a necessary part of the standard three-step cyclizations[12,13] of *N*-Boc-protected α-amino δ-oxo esters. Literature protocols describing more efficient one-step reductive cyclizations are rare; there is just a single report from McDermott et al. about a $NaBH(OAc)_3$–TFA mediated ring closure of an alkynyl derivative of **15**[24] and there are two reports about Ph_3SiH–$B(C_6F_5)_3$ induced cyclizations of alkyl derivatives of **15**.[25] We applied the two conditions to the phenyl substituted model substrates **8a** and **15a** (Scheme 8), but no reaction was observed. The reactivity of the latter phenyl ketones is apparently significantly reduced as compared to those of the alkyl and alkynyl ones. The attempted reductive cyclizations of **8a** and **15a** with Ph_3SiH in the presence of the stronger Lewis acid $BF_3{\cdot}OEt_2$ resulted, as expected, in a quantitative loss of the *N*-Boc group. Some success was achieved with the less bulky silane Et_3SiH. Treatment of the amide **8a** with Et_3SiH–$B(C_6F_5)_3$ afforded a 2:1-mixture of the desired prolinamide **9a** (32% yield) and the non-cyclized, silylated alcohol **18** (17% yield).[26] In the case of ester **15a**, however, no product **16a** was detected; only the carbonyl hydrosilylation product **19** was formed in 79% yield.[26]



Scheme 8 Studies on the one-step cyclizations of the *N*-Boc-protected γ-amino phenylketones **8a** and **15a**[26]

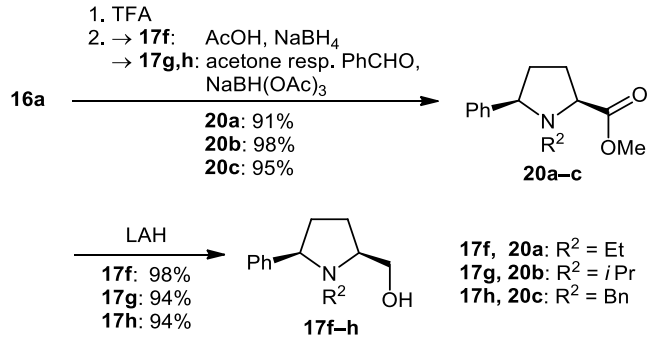
While all attempts on single-step cyclizations of aryl substituted *N*-Boc α-amino δ-oxo esters and amides failed, we were successful in developing such a procedure for aliphatic derivatives. The amino ketone precursors **15c–e** (R^1 = Me,[27] *i*Pr, Bn), which were prepared in acceptable to high yields by treatment of **14** with the respective Grignard reagents at –40 °C, readily cyclized upon treatment with $NaBH(OAc)_3$–TFA in EtOAc (McDermott conditions)[24].

The resulting *N*-Boc-protected pyrrolidines **16c–e**[23,28,29] were isolated in good 82–88% yield and with pleasing *cis* selectivities (initial dr > 85:15).[15] Thus, this reagent combination permits an efficient synthesis of 5-*cis*-alkyl prolines without the need of any *N*-deprotection–reprotection steps. Final reduction of **16c–e** delivered the prolinols **17c–e** in 77–94% yield.



Scheme 9 Route II – synthesis of the prolinol precursors **17c–e**[23]

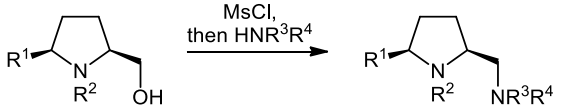
Variations of the substituent R^2 at the pyrrolidine nitrogen atom were done on the 5-phenyl substituted ester **16a** (Table 2). *N*-Deprotection with TFA followed by reductive amination with AcOH–$NaBH_4$, acetone–$NaBH(OAc)_3$, and, respectively, benzaldehyde–$NaBH(OAc)_3$ delivered the *N*-ethyl, *N*-isopopyl and *N*-benzyl pyrrolidine esters **20a–c** in excellent 91–98% yield over two steps. Reduction with LAH provided the prolinols **17f–h** in ≥94% yield.



Scheme 10 Route II – variation of the substituent R^2

The final hydroxy–amine exchange on the prolinols **17a–h** was put into practice by activation of the alcohol function as a mesylate and subsequent treatment of the crude intermediate with an excess of the respective amine (Table 2).[30] A set of 18 5-*cis*-substituted prolinamines **5** was thus prepared by amination with ammonia (→ **5i–m**), methylamine (→ **5a**,[10] **5n–p**), dimethylamine (→ **5b,e,q–s**), and other secondary amines such as diethylamine, pyrrolidine, piperidine, and methyl benzyl amine (→ **5t–w**). The product formation in this two-step sequence was generally high, irrespective of the attached substituents R^1 and R^2, but the high polarity of the products made their purification difficult, which explains the, in part, mediocre isolated yields. In the case of the 5-methyl and 5-isopropyl derivatives **5k**,**l**,**q**,**r**, additional problems arose from their high volatility.

Table 2 Route II – variation of the exocyclic amino group NR^3R^4



Entry	**17**	R^1	R^2	**5**	NR^3R^4	Yield (%)[a]
1	**a**	Ph	Me	**i**	NH_2	85
2	**b**	1-naphthyl	Me	**j**	NH_2	49
3	**c**	Me	Me	**k**	NH_2	24
4	**d**	*i*Pr	Me	**l**	NH_2	48
5	**e**	Bn	Me	**m**	NH_2	32
6	**a**	Ph	Me	**a**	NHMe	75[b]
7	**f**	Ph	Et	**n**	NHMe	84
8	**g**	Ph	*i*Pr	**o**	NHMe	77
9	**h**	Ph	Bn	**p**	NHMe	77
10	**a**	Ph	Me	**b**	NMe_2	65
11	**b**	1-naphthyl	Me	**e**	NMe_2	54
12	**c**	Me	Me	**q**	NMe_2	18
13	**d**	*i*Pr	Me	**r**	NMe_2	23
14	**e**	Bn	Me	**s**	NMe_2	44
15	**a**	Ph	Me	**t**	NEt_2	40
16	**a**	Ph	Me	**u**	pyrrolidinyl	52
17	**a**	Ph	Me	**v**	piperidinyl	51
18	**a**	Ph	Me	**w**	NMeBn	73

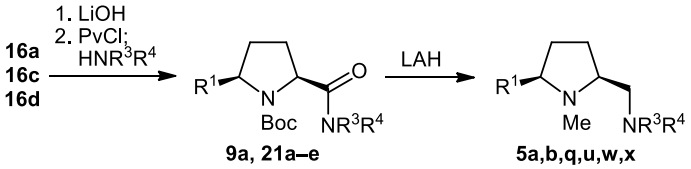
[a] Yields not optimized. [b] Data taken from ref.[10].

Route III

Route III also proceeded via the *N*-Boc-protected methyl esters **16**, but the NR^3R^4 substituents were introduced by amidation and the reductions to the amines were done as the last step (Table 3). After saponification of **16a** (R^1 = Ph), **16c** (R^1 = Me), and **16d** (R^1 = *i*Pr) with LiOH in ethanol, the resulting crude acids were activated with PvCl as unsymmetric anhydrides and in-situ trapped with the respective amines (methylamine, dimethylamine, pyrrolidine, and methyl benzylamine) to give the corresponding amides **9a** and **21a–e**[31] in high 82–95% yield. Reductions with LAH were uneventful and delivered the amines **5a**,**b**,**q**,**u**,**w**,**x** as the major products in 74–98% yield. Smaller amounts of by-products, which were formed in the reductions of the secondary amides **21a**,**b**, were easily removed by column chromatog-

raphy. This provided a distinctive advantage over route II, where the removal of the excess amine, as required for the hydroxy–amine exchange, from the polar diamines **5** was more laborious. In the cases of the prolinamines **5q** and **5u**, which were also prepared via route II from the esters **16c** and **16a** in low 14% and 50% yield (see Schemes 7 and 9 and Table 2), the overall yields could be significantly raised to 86% and 80%, respectively, by using route III.

Table 3 Route III – introduction of NR^3R^4 via amides

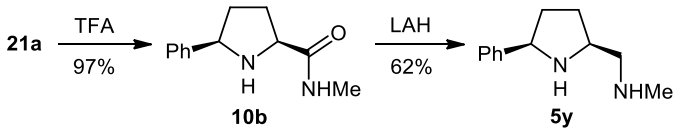


9a, 21a–e **5a,b,q,u,w,x**

Entry	**16**	R^1	NR^3R^4	Yield of **21**, **9a** (%)	Yield of **5** (%)
1	**a**	Ph	NHMe	86 (**21a**)	82 (**5a**)
2	**d**	*i*Pr	NHMe	82 (**21b**)	74 (**5x**)
3	**a**	Ph	NMe_2	92 (**9a**)	85 (**5b**)[a]
4	**c**	Me	NMe_2	88 (**21c**)	98 (**5q**)
5	**a**	Ph	pyrrolidinyl	82 (**21d**)	98 (**5u**)
6	**a**	Ph	NMeBn	95 (**21e**)	84 (**5w**)

[a] Identically to Table 1, Entry 1.

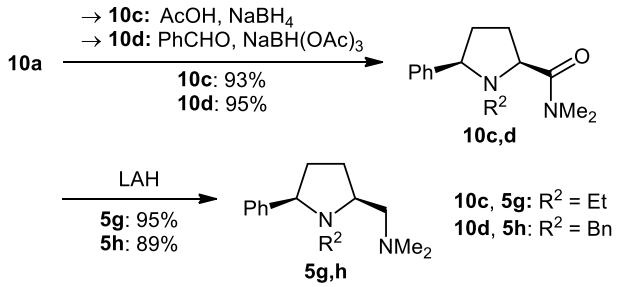
The preparation of the diamine **5y**, in which the pyrrolidine nitrogen atom is unsubstituted, is shown in Scheme 11. *N*-deprotection of the amide **21a** with TFA and reduction of **10b** with LAH afforded **5y** in 60% yield. It should be noted that this compound will presumably not be accessible via route II since the secondary NH function will prohibit the required selective mesylation of the alcohol (cp. Table 2, R^2 would be H).



10b **5y**

Scheme 11 Synthesis of the secondary diamine **5y**

Variations of the substituent R^2 were carried out on the secondary amide **10a** (Scheme 12), which was prepared from **9a** according to Scheme 5. Reductive aminations delivered the amides **10c** and **10d**, which were reduced to give the corresponding amines **5g** and **5h** in 85–88% yield over two steps. This sequence provides a welcome alternative to the one shown in Scheme 5, in which the reduction step precedes the reductive amination.



Scheme 12 Route III – variation of the substituent R^2

Conclusions

Each of the discussed approaches to 5-*cis*-substituted prolinamines of general type **5** includes three key sequences, the installment of the 5-*cis* substituent R^1 via a Grignard addition–re-cyclization protocol, the introduction of R^2 by direct reduction of the protective group (R^2 = Me) or by *N*-deprotection–reductive amination, and the attachment of the exocyclic NR^3R^4 group, either by amidation or by amination. Major difference is the order of introduction, which directly couples the usefulness of a route with the envisioned substituent pattern.

Route I (order of substituent introduction: NR^3R^4 first, then R^1, and R^2 last) is well suited for a fast screening of R^1 and R^2 under the premise of a given NR^3R^4 group. Moreover, the shortness of this approach (seven to nine steps, by using Martin's one-step cyclization just five steps) in combination with the good diastereoselectivities in the cyclization step makes this route particularly attractive for the larger scale synthesis of a given target prolinamine **5**. Route II (order of substituent introduction: R^1 first, then R^2, and NR^3R^4 last) offers the advantage of a last step variation of NR^3R^4. With the vast number of commercially available amines, this approach provides a facile access to a plethora of derivatives. In route III (order of substituent introduction: R^1 first, then NR^3R^4, and R^2 last), an amide reduction is done as the last step, which normally delivers the diamine **5** with high purity, thus avoiding the need of a time-consuming purification on the stage of the polar final products. Furthermore, due to the introduction of NR^3R^4 as an amide, this approach also permits the synthesis of derivatives that are not accessible by route II without the use of additional protective groups.

In addition, it was shown for the first time that aliphatic, *N*-Boc-protected α-amino δ-oxo esters can be directly cyclized to the corresponding 5-*cis*-alkyl prolines by using $NaBH(OAc)_3$–TFA. This redundantizes an *N*-Boc removal and re-attachment which is required under the standard cyclization conditions.

In summary, we developed three routes to the novel and interesting class of 5-*cis*-substituted prolinamines **5**. Starting from L-pyroglutamic acid (**6**), the diamines **5** were prepared in five to ten steps, depending on the route and the substitution pattern chosen, and up to 64% yield (diamine **5q**). The practicability, applicability and modularity of the approaches were demonstrated in the synthesis of 25 diamines **5**, which carry a broad variety of different substituents

R^1–R^4. The now possible, quick access to tailor-made derivatives will permit further investigations on the potential of the diamines **5** as chiral ligands in asymmetric catalysis.

Experimental Section

All reactions with moisture-sensitive reagents were carried out under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[32] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey-Nagel, particle size 40–63 µm) was used for column chromatography. Melting points were measured on a Stuart SMP10 digital or a Büchi M-565 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance 300, a Bruker Avance 400, or a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^1H and ^{13}C NMR data were made on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a Jasco FT-IR-410 or a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra on a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization).

The syntheses of **5b**, **5f**, and **5h** along route I, of **5l** and **5n** along route II, and of **5u** along route III are described here exemplarily. For the preparations of all other compounds, see Supporting Information.

(*S*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-oxopyrrolidine-1-carboxylate (7)

A solution of (*S*)-pyroglutamic acid (**6**, 15.0 g, 116 mmol) and $TsOH•H_2O$ (663 mg, 3.49 mmol) in anhydrous MeOH (150 mL) was heated under reflux for 24 h. Gaseous $HNMe_2$ was bubbled through the solution at r.t. for 6 h (volume of the solution increased by ca. 25 mL) and the stoppered flask was stirred at r.t. for 48 h. The solvent and excess $HNMe_2$ were carefully removed under reduced pressure to give the crude amide (17.4 g) as yellowish oil that solidifies upon standing. This material was dissolved in anhydrous CH_2Cl_2 (200 mL) and Boc_2O (30.3 g, 139 mmol), NEt_3 (19.3 mL, 15.3 g, 151 mmol), and DMAP (709 mg, 5.80 mmol) were added at r.t. After 24 h of stirring, the reaction mixture was quenched with sat. aq NH_4Cl (200 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, and evaporated. Flash chromatography (silica gel, CH_2Cl_2–MeOH, 100:0–95:5) delivered the product **7** (24.0 g, 93.6 mmol, 81%) as a yellowish resin, which crystallized upon standing to give a slightly yellow solid.

Mp 86−89 °C; $[\alpha]_D^{21}$ −35.8 (*c* 1.04, MeOH); R_f = 0.34 (CH_2Cl_2–MeOH, 95:5).

FT-IR (ATR): 2977, 2937, 1771, 1648, 1365, 1305, 1285, 1251, 1146, 1021, 840 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, $C(CH_3)_3$), 1.87 (m, 1 H, 3-*H*H), 2.22 (m, 1 H, 3-H*H*), 2.42 (ddd, *J* = 17.4, 9.5, 3.0 Hz, 1 H, 4-*H*H), 2.70 (ddd, *J* = 17.4, 10.3, 9.8 Hz, 1 H, 4-H*H*), 2.98 (s, 3 H, NCH_3), 3.08 (s, 3 H, NCH_3), 4.92 (dd, *J* = 9.2, 2.4 Hz, 1 H, 2-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (C-3), 28.0 ($C(CH_3)_3$), 31.4 (C-4), 36.0 (NCH_3), 36.8 (NCH_3), 56.4 (C-2), 83.1 ($C(CH_3)_3$), 149.8 (1-CO_2), 170.7 (2-CON), 173.8 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{12}H_{20}N_2O_4$: 279.1315; found: 279.1316.

(*S*)-2-(*tert*-Butoxycarbonylamino)-*N*,*N*-dimethyl-5-oxo-5-phenylpentanamide (8a)

PhMgBr (1.0 M in THF, 12.1 mL, 12.1 mmol) was added at –20 °C to a solution of the 5-oxo-pyrrolidine **7** (3.00 g, 11.7 mmol) in anhydrous THF (80 mL) and the reaction was allowed to warm to r.t. overnight. Sat. aq NH_4Cl (50 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 1:2–0:1) afforded the amino ketone **8a** (2.82 g, 8.42 mmol, 72%) as a colorless solid.

Mp 74–77 °C; $[\alpha]_D^{22}$ +0.3 (*c* 1.00, MeOH); R_f = 0.31 (Et_2O).

FT-IR (ATR): 3349, 2974, 2931, 1702, 1678, 1645, 1492, 1365, 1163, 1050, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (m, 9 H, $C(CH_3)_3$), 1.82 (m, 1 H, 3-*H*H), 2.22 (m, 1 H, 3-H*H*), 2.95 (s, 3 H, NCH_3), 2.96 (m, 1 H, 4-*H*H), 3.19 (s, 3 H, NCH_3), 3.20 (m, 1 H, 4-H*H*), 4.71 (m, 1 H, 2-H), 5.53 (d, *J* = 8.0 Hz, 1 H, NH), 7.43 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.54 (t, *J* = 7.4 Hz, 1 H, Ph-H), 7.94 (d, *J* = 7.4 Hz, 2 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4 (C-3), 28.4 ($C(CH_3)_3$), 33.8 (C-4), 35.8 (NCH_3), 37.2 (NCH_3), 49.7 (C-2), 79.6 ($C(CH_3)_3$), 128.1, 128.6, 133.1 (CH-Ph), 137.1 (C_q-Ph), 155.8 (NCO_2), 172.0 (C-1), 199.4 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{26}N_2O_4$: 357.1785; found: 357.1786.

(2*S*,5*R*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-phenylpyrrolidine-1-carboxylate (9a)

A solution of the amino ketone **8a** (1.64 g, 4.92 mmol) in anhydrous CH_2Cl_2 (50 mL) was treated at r.t. with TFA (7.50 mL, 11.1 g, 97.4 mmol) and stirred overnight. The solvent was removed under reduced pressure and the resulting orange oil was diluted five times with CH_2Cl_2 (30 mL) and evaporated again, in order to remove excess TFA. $NaBH_4$ (279 mg, 7.38 mmol) was slowly added at 0 °C to a solution of the residue in MeOH (80 mL). The solvent was removed after stirring overnight at r.t. The resulting orange oil was diluted four times

with MeOH (35 mL) and evaporated again. The residue was suspended in anhydrous CH_2Cl_2 (100 mL) and NEt_3 (1.03 mL, 747 mg, 7.38 mmol), Boc_2O (1.61 g, 7.38 mmol), and DMAP (30.1 mg, 246 µmol) were added at r.t. Sat. aq NH_4Cl (100 mL) was added after 1 d of stirring and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 2:1–1:2) afforded the pyrrolidine amide **9a**[14] (1.19 g, 3.74 mmol, 76%) as a slightly yellowish oil.

$[\alpha]_D^{21}$ +35.8 (*c* 0.60, CH_2Cl_2); R_f = 0.50 (EtOAc).

FT-IR (ATR): 2974, 1689, 1655, 1389, 1362, 1155, 729, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$):* δ = 1.10 (s, 6.4 H, $C(CH_3)_3$), 1.39 (s, 2.6 H, $C(CH_3)_3$), 1.97 (m, 1.3 H, 3-*H*H, 4-*H*H), 2.14 (m, 1.7 H, 3-*H*H, 4-H*H*), 2.28 (m, 1 H, 3-H*H*), 3.04 (s, 3 H, NCH_3), 3.12 (s, 0.9 H, NCH_3), 3.15 (s, 2.1 H, NCH_3), 4.68 (m, 1 H, 2-H, 5-H), 4.80 (m, 0.7 H, 2-H), 4.95 (m, 0.3 H, 5-H), 7.19 (t, *J* = 7.3 Hz, 1 H, Ph-H), 7.31 (t, *J* = 7.5 Hz, 2 H, Ph-H), 7.74 (d, *J* = 7.3 Hz, 2 H, Ph-H). * 70:30 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.2, 28.4 ($C(CH_3)_3$), 28.7, 28.9 (C-3), 34.8, 35.9 (C-4), 36.3, 37.2 ($N(CH_3)_2$), 58.0, 62.5 (C-5), 63.6 (C-2), 79.8 ($C(CH_3)_3$), 126.6, 127.0, 128.1, 128.4 (CH-Ph), 144.6 (C_q-Ph), 154.8 (1-CO_2), 172.6 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{26}N_2O_3$: 319.2016; found: 319.2018.

(2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-phenylpyrrolidine (5b)

LAH (2.0 M in THF, 3.84 mL, 7.69 mmol) was added at 0 °C to a solution of amide **9a** (408 mg, 1.28 mmol) in anhydrous THF (18 mL). After 1 h, the reaction mixture was heated under reflux overnight. The solution was diluted with Et_2O (25 mL) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was thoroughly washed (CH_2Cl_2–MeOH, 9:1, 300 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH, 90:10) delivered diamine **5b** (238 mg, 1.09 mmol, 85%) as a slightly yellowish oil.

$[\alpha]_D^{29}$ +20.1 (*c* 1.00, MeOH); R_f = 0.26 (CH_2Cl_2–MeOH, 9:1).

FT-IR (ATR): 2943, 2765, 1454, 1155, 1032, 850, 754, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.70 (m, 2 H, 3-*H*H, 4-*H*H), 2.04 (m, 2 H, 3-H*H*, 4-H*H*), 2.18 (s, 3 H, 1-CH_3), 2.30 (s, 6 H, $N(CH_3)_2$), 2.37 (dd, *J* = 12.0, 8.2 Hz, 1 H, 2-H), 2.52 (m, 2 H, 2-CH_2), 3.24 (m, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.30 (m, 2 H, Ph-H), 7.35 (m, 2 H, Ph-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 29.5 (C-3), 34.0 (C-4), 39.7 (1-CH_3), 46.6 ($N(CH_3)_2$), 64.7 (C-2), 65.3 (2-CH_2), 72.7 (C-5), 127.0 , 127.5, 128.4 (CH-Ph), 143.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{22}N_2$: 219.1856; found: 219.1858.

(2*S*,5*R*)-*N*,*N*-Dimethyl-5-phenylpyrrolidine-2-carboxamide (10a)

A solution of amide **9a** (1.21 g, 3.80 mmol) in CH_2Cl_2 (38 mL) was treated with TFA (5.86 mL, 8.67 g, 76.0 mmol) and stirred overnight at r.t. The solvent was removed under reduced pressure and the resulting oil was diluted five times with CH_2Cl_2 (20 mL) and evaporated again, in order to remove excess TFA. The residue was filtered through a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1) to give amide **10a** (790 mg, 3.62 mmol, 95%) as a yellowish solid.

Mp 106−109 °C; $[\alpha]_D^{22}$ –37.7 (*c* 0.50, MeOH); R_f = 0.48 (CH_2Cl_2–MeOH, 9:1).

FT-IR (ATR): 3288, 2952, 2924, 1629, 1397, 1091, 870, 760, 704 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70 (m, 1 H, 4-*H*H), 1.92 (m, 1 H, 3-*H*H), 2.20 (m, 2 H, 3-H*H*, 4-H*H*), 2.89 (br s, 1 H, NH), 3.01 (s, 3 H, NCH_3), 3.05 (s, 3 H, NCH_3), 4.10 (m, 2 H, 2-H, 5-H), 7.25 (m, 1 H, Ph-H), 7.33 (m, 2 H, Ph-H), 7.47 (m, 2 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.4 (C-3), 34.8 (C-4), 36.0, 36.6 ($N(CH_3)_2$), 58.6 (C-2), 64.5 (C-5), 127.0, 127.3, 128.6 (CH-Ph), 142.8 (C_q-Ph), 174.1 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{18}N_2O$: 219.1492; found: 219.1493.

(2*S*,5*R*)-2-(Dimethylaminomethyl)-5-phenylpyrrolidine (5f)

Amide **10a** (960 mg, 4.40 mmol) was dissolved in THF (70 mL) and LAH (1.0 M in THF, 13.2 mL, 13.2 mmol) was added at 0 °C. After 1 h, the reaction mixture was heated under reflux overnight. The solution was diluted with Et_2O (30 mL) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 300 mL). Evaporation of the solvent and filtration through a pad of basic alumina (activity I, petroleum ether–Et_2O, 1:0–0:1) provided diamine **5f**[14] (825 mg, 4.04 mmol, 92%) as a yellowish oil.

$[\alpha]_D^{21}$ +13.4 (*c* 1.00, MeOH); R_f= 0.21 (CH_2Cl_2–MeOH–NEt_3, 90:10:1.

FT-IR (ATR): 3500–3100, 2942, 2765, 1454, 1263, 1098, 1038, 845, 754, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59 (m, 1 H, 3-*H*H), 1.73 (m, 1 H, 4-*H*H), 2.02 (m, 1 H, 3-H*H*), 2.17 (m, 1 H, 4-H*H*), 2.32 (s, 6 H, $N(CH_3)_2$), 2.38 (dd, *J* = 12.1, 5.4 Hz, 1 H, 2-C*H*H), 2.47 (dd, *J* = 12.1, 8.3 Hz, 1 H, 2-CH*H*), 3.49 (m, 1 H, 2-H), 3.57 (br s, 1 H, NH), 4.25 (dd, *J* = 8.8, 7.1 Hz, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.30 (m, 2 H, Ph-H), 7.38 (m, 2 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.0 (C-3), 33.5 (C-4), 46.0 ($N(CH_3)_2$), 56.4 (C-2), 62.6 (C-5), 65.7 (2-CH_2), 126.8, 127.1, 128.5 (CH-Ph), 143.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{20}N_2$: 205.1699; found: 205.1700.

(2*S*,5*R*)-1-Benzyl-2-(dimethylaminomethyl)-5-phenylpyrrolidine (5h)

Benzaldehyde (39.8 µL, 41.8 mg, 394 µmol) and AcOH (30.0 µL, 31.6 mg, 524 µmol) were added at r.t. to a solution of the amine **5f** (53.6 mg, 262 µmol) in DCE (0.5 mL). $NaBH(OAc)_3$ (88.8 mg, 420 µmol) was added after 10 min and the solution was stirred for 4 h. The reaction mixture was quenched with sat. aq $NaHCO_3$ (4 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 3 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 190:9:1) provided diamine **5h** (69.2 mg, 235 µmol, 90%) as a colorless oil.

$[\alpha]_D^{28}$ +20.3 (*c* 1.00, MeOH); R_f = 0.15 (EtOAc).

FT-IR (ATR): 3030, 2937, 2815, 2769, 1491, 1452, 1033, 754, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.67 (m, 1 H, 4-*H*H), 1.78 (m, 1 H, 3-*H*H), 1.98 (m, 3 H, 3-H*H*, 4-H*H*, 2-C*H*H), 2.11 (s, 6 H, $N(CH_3)_2$), 2.24 (t, *J* = 11.1 Hz, 1 H, 2-CH*H*), 2.96 (m, 1 H, 2-H), 3.45 (d, *J* = 13.4 Hz, 1 H, 1-C*H*H), 3.69 (dd, *J* = 9.8, 5.6 Hz, 1 H, 5-H), 3.83 (d, *J* = 13.4 Hz, 1 H, 1-CH*H*), 7.23 (m, 6 H, Ph-H), 7.33 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.46 (d, *J* = 7.3 Hz, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.6 (C-3), 34.9 (C-4), 46.3 ($N(CH_3)_2$), 57.0 (1-CH_2), 60.8 (C-2), 65.9 (2-CH_2), 69.8 (C-5), 126.9, 127.0, 127.6, 128.0, 128.4, 129.8 (CH-Ph), 139.1, 144.4 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{20}H_{26}N_2$: 295.2169; found: 295.2170.

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-6-methyl-5-oxoheptanoate (15d)

*i*PrMgBr (2.9 M in 2Me-THF, 5.33 mL, 15.5 mmol) was added at –40 °C to a solution of the 5-oxopyrrolidine **14**[22] (2.51 g, 10.3 mmol) in anhydrous THF (30 mL). After 2 h at –40 °C, sat. aq NH_4Cl (100 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 4:1–1:1) delivered **15d** (1.86 g, 6.47 mmol, 63%) as a colorless oil.

$[\alpha]_D^{25}$ +40.4 (*c* 0.48, $CHCl_3$); R_f = 0.52 (petroleum ether–EtOAc, 4:1).

FT-IR (ATR): 3500–3250, 2973, 1744, 1707, 1389, 1364, 1200, 1161, 1025, 1013, 757 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$), 1.05 (d, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$), 1.39 (s, 9 H, $C(CH_3)_3$), 1.85 (m, 1 H, 3-*H*H), 2.06 (m, 1 H, 3-H*H*), 2.52 (m, 3 H, 4-H_2, 6-H), 3.69 (s, 3 H, OCH_3), 4.22 (m, 1 H, 2-H), 5.09 (d, *J* = 7.4 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.27, 18.29 (C-7, 6-CH_3), 26.5 (C-3), 28.3 (C(CH_3)$_3$), 36.1 (C-6), 41.0 (C-4), 52.4 (OCH_3), 53.1 (C-2), 80.0 ($C(CH_3)_3$), 155.5 (NCO_2), 173.0 (C-1), 213.5 (C-5).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{25}NO_5$: 288.1806; found: 288.1803.

(2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-isopropylpyrrolidine-1,2-dicarboxylate (16d)

$NaBH(OAc)_3$ (1.83 g, 8.64 mmol) was added at 0 °C to a solution of the amino ketone **15d** (1.90 g, 6.61 mmol) in EtOAc (35 mL). After 10 min, TFA (2.20 mL, 3.26 g, 28.6 mmol) was added dropwise over a period of 40 min. The reaction mixture was stirred for 2 h at 0 °C and overnight at r.t. Sat. aq $NaHCO_3$ (100 mL) was added and most of the organic solvent was removed under reduced pressure. CH_2Cl_2 (100 mL) was added, the layers were separated and the organic layer was washed with sat. aq $NaHCO_3$ (2 × 100 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 6:1) provided **16d** (1.47 g, 5.42 mmol, 82%) as a colorless oil.

$[\alpha]_D^{30}$ +40.4 (*c* 1.00, $CHCl_3$); R_f = 0.70 (petroleum ether–EtOAc, 4:1).

FT-IR (ATR): 2959, 2874, 1754, 1692, 1381, 1364, 1194, 1162, 1103, 929, 769 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$):* δ = 0.87 (d, *J* = 6.7 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.94 (d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$), 1.37 (br s, 5.4 H, C(CH_3)$_3$), 1.41 (br s, 3.6 H, C(CH_3)$_3$), 1.86 (m, 4 H, 3-*H*H, 4-H_2, C*H*(CH_3)$_2$), 2.14 (m, 1 H, 3-H*H*), 3.59 (m, 0.4 H, 5-H), 3.67 (m, 0.6 H, 5-H), 3.68 (s, 3 H, OCH_3), 4.17 (m, 0.6 H, 2-H), 4.28 (m, 0.4 H, 2-H). * 60:40 mixture of rotamers.

^{13}C NMR (75 MHz, $CDCl_3$):* δ = 18.2, 18.6 (CH(*C*H$_3$)$_2$), 19.9, 20.1 (CH(*C*H$_3$)$_2$), 26.5, 27.5 (C-4), 28.3 (C(*C*H$_3$)$_3$), 29.2 (C-3), 31.3, 31.4 (*C*H(CH_3)$_2$), 51.8, 52.0 (OCH_3), 60.0, 60.5 (C-2), 64.1, 64.4 (C-5), 79.8 ($C(CH_3)_3$), 154.6 (1-CO_2), 173.8, 174.0 (2-CO_2). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{14}H_{25}NO_4$: 294.1676; found: 294.1673.

(2*S*,5*S*)-2-(Hydroxymethyl)-5-isopropyl-1-methylpyrrolidine (17d)

LAH (1.23 g, 32.5 mmol) was added at 0 °C to a solution of ester **16d** (1.47 g, 5.42 mmol) in anhydrous THF (30 mL). The reaction mixture was heated under reflux for 16 h. Aq NaOH (10%, 6 mL) was added at 0 °C and the reaction mixture was stirred for 30 min at r.t. The solids formed were removed by filtration through a pad of celite® and the filter cake was rinsed with Et_2O (200 mL). Evaporation of the solvent delivered amino alcohol **17d** (654 mg, 4.16 mmol, 77%) as a slightly yellowish oil.

$[\alpha]_D^{25}$ +47.0 (*c* 2.00, $CHCl_3$); R_f = 0.70 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 80:18:2).

FT-IR (ATR): 3600–3100, 2955, 2871, 2783, 1465, 1385, 1367, 1209, 1032, 963, 755 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$), 0.83 (d, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$), 1.35–1.85 (m, 5 H, 3-H_2, 4-H_2, $CH(CH_3)_2$), 2.19 (s, 3 H, 1-CH_3), 2.30 (m, 1 H, 5-H), 2.48 (m, 1 H, 2-H), 2.94 (br s, 1 H, OH), 3.31 (dd, *J* = 10.5, 1.9 Hz, 1 H, 2-CHH), 3.58 (dd, *J* = 10.6, 3.6 Hz, 1 H, 2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3 ($CH(CH_3)_2$), 20.2 ($CH(CH_3)_2$), 23.8 (C-4), 26.0 (C-3), 29.0 ($CH(CH_3)_2$), 39.0 (1-CH_3), 61.2 (2-CH_2), 67.1 (C-2), 71.9 (C-5).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_9H_{19}NO$: 158.1539; found: 158.1542.

(2*S*,5*R*)-2-(Aminomethyl)-5-isopropyl-1-methylpyrrolidine (5l)

K_2CO_3 (100 mg, 725 μmol) was added to a solution of the alcohol **17d** (76.0 mg, 483 μmol) in CH_2Cl_2 (3 mL). The resulting suspension was treated with MsCl (46.8 μL, 69.2 mg, 604 μmol) and stirred overnight. Aq NH_3 (25%, 3 mL, 44.0 mmol) and MeOH (3 mL) were added and the reaction mixture was stirred overnight. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1) provided the prolinamine **5l** (36.0 mg, 230 μmol, 48%) as a yellowish oil.

$[\alpha]_D^{25}$ +30.6 (*c* 1.00, $CHCl_3$); R_f = 0.30 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

FT-IR (ATR): 3600–2400, 2955, 2871, 2781, 1462, 1320, 1150, 985, 766 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$), 0.84 (d, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$), 1.48 (m, 3 H, 3-*H*H, 4-H_2), 1.67 (br s, 2 H, NH_2), 1.72 (m, 2 H, 3-H*H*, $CH(CH_3)_2$), 2.19 (s, 3 H, 1-CH_3), 2.22 (m, 1 H, 5-H), 2.34 (m, 1 H, 2-H), 2.61 (dd, *J* = 12.9, 3.1 Hz, 1 H, 2-CHH), 2.71 (dd, *J* = 12.9, 5.1 Hz, 1 H, 2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.4 ($CH(CH_3)_2$), 20.3 ($CH(CH_3)_2$), 23.5 (C-4), 26.4 (C-3), 29.1 ($CH(CH_3)_2$), 39.6 (1-CH_3), 43.8 (2-CH_2), 68.2 (C-2), 72.2 (C-5).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_9H_{20}N_2$: 157.1699; found: 157.1702.

(2*S*,5*R*)-Methyl 1-ethyl-5-phenylpyrrolidin-2-carboxylate (20a)

A solution of the ester **16a**[10] (3.20 g, 10.5 mmol) in CH_2Cl_2 (120 mL) was treated with TFA (16.1 mL, 23.9 g, 210 mmol) and stirred overnight at r.t. The solvent was removed under reduced pressure and the resulting oil was diluted five times with CH_2Cl_2 (80 mL) and evaporated again, in order to remove excess TFA. The residue was filtered through a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5) to give the known[33] ester (2*S*,5*R*)-methyl 5-phenylpyrrolidine-2-carboxylate (2.13 g, 10.4 mmol, 99%) as a colorless oil; R_f = 0.39 (CH_2Cl_2–MeOH, 95:5).

$NaBH_4$ (292 mg, 7.72 mmol) was portionwise added at 0 °C to a solution of the ester prepared above (336 mg, 1.64 mmol) in AcOH (3 mL). After gas evolution had ceased, the solution was heated to 60 °C for 2 h. Sat. aq $NaHCO_3$ (4 mL) was slowly added and the reaction mixture was made basic with solid Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 10:1) afforded the ester **20a** (352 mg, 1.51 mmol, 92%) as a colorless oil.

$[\alpha]_D^{27}$ +53.0 (*c* 1.00, MeOH); R_f = 0.43 (petroleum ether–EtOAc, 9:1).

FT-IR (ATR): 2967, 2951, 1749, 1732, 1192, 1163, 1074, 756, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.85 (m, 1 H, 4-*H*H), 2.01 (m, 1 H, 3-*H*H), 2.12 (m, 2 H, 3-H*H*, 4-H*H*), 2.51 (dq, *J* = 12.9, 7.1 Hz, 1H, 1-C*H*H), 2.69 (dq, *J* = 13.0, 7.3 Hz, 1H, 1-CH*H*), 3.47 (dd, *J* = 9.1, 4.8 Hz, 1 H, 2-H), 3.71 (dd, *J* = 9.4, 5.9 Hz, 1 H, 5-H), 3.76 (s, 3 H, OCH_3), 7.23 (m, 1 H, Ph-H), 7.32 (m, 2 H, Ph-H), 7.48 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.6 (1-CH_2CH_3), 29.4 (C-3), 35.7 (C-4), 47.0 (1-CH_2CH_3), 51.9 (OCH_3), 65.0 (C-2), 69.2 (C-5), 127.1, 127.4, 128.3 (CH-Ph), 144.3 (C_q-Ph), 176.3 (2-CO_2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}NO_2$: 234.1487; found: 234.1489.

(2*S*,5*R*)-1-Ethyl-2-(hydroxymethyl)-5-phenylpyrrolidine (17f)

To a solution of ester **20a** (310 mg, 1.33 mmol) in anhydrous THF (15 mL), LAH (106 mg, 2.79 mmol) was added at 0 °C and the reaction mixture was stirred at r.t. overnight. The solution was diluted with Et_2O (15 mL) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 100 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5) provided amino alcohol **17f** (268 mg, 1.31 mmol, 98%) as a colorless oil.

$[\alpha]_D^{28}$ +70.2 (*c* 1.00, MeOH); R_f = 0.36 (CH_2Cl_2–MeOH, 95:5).

FT-IR (ATR): 3500–3100, 2963, 2873, 1452, 1193, 1028, 756, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.71 (m, 1 H, 4-*H*H), 1.88 (m, 1 H, 3-*H*H), 1.99 (m, 1 H, 3-H*H*), 2.78 (m, 1 H, 4-H*H*), 2.64 (m, 2 H, 1-CH_2), 3.00 (br s, 1 H, OH), 3.04 (m, 1 H, 2-H), 3.48 (dd, *J* = 10.5, 2.7 Hz, 1 H, 2-C*H*H), 3.70 (dd, *J* = 10.5, 4.1 Hz, 1 H, 2-CH*H*), 3.76 (dd, *J* = 9.7, 6.5 Hz, 1 H, 5-H), 7.24 (m, 1 H, Ph-H), 7.32 (m, 2 H, Ph-H), 7.36 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ =12.3 (1-CH_2CH_3), 27.9 (C-3), 35.4 (C-4), 45.9 (1-CH_2CH_3), 63.1 (C-2), 63.6 (2-CH_2), 69.2 (C-5), 127.2, 128.5 (CH-Ph), 144.3 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{19}NO$: 206.1539; found: 206.1540.

(2*S*,5*R*)-1-Ethyl-2-(methylaminomethyl)-5-phenylpyrrolidine (5n)

NEt_3 (272 µL, 197 mg, 1.95 mmol) and MsCl (102 µL, 152 mg, 1.32 mmol) were added at 0 °C to a solution of the alcohol **17f** (160 mg, 779 µmol) in CH_2Cl_2 (6 mL). After stirring overnight at r.t., aq NH_2Me (40%, 2.12 mL, 23.3 mmol), NEt_3 (108 µL, 78.8 mg, 779 µmol), and MeOH (6 mL) were added and the reaction mixture was stirred overnight. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2) provided the prolinamine **5n** (142 mg, 654 µmol, 84%) as a colorless wax.

$[\alpha]_D^{26}$ +59.7 (*c* 1.00, MeOH); R_f = 0.29 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

FT-IR (ATR): 2964, 2790, 1452, 1372, 1190, 1135, 1028, 755, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.67 (m, 1 H, 4-*H*H), 1.79 (m, 1 H, 3-*H*H), 1.95 (m, 1 H, 3-H*H*), 2.05 (m, 1 H, 4-H*H*), 2.52 (s, 3 H, NCH_3), 2.63 (m, 4 H, 1-CH_2, 2-C*H*H, NH), 2.71 (dd, *J* = 11.4, 4.5 Hz, 1 H, 2-CH*H*), 3.00 (m, 1 H, 2-H), 3.69 (dd, *J* = 9.2, 6.6 Hz, 1 H, 5-H), 7.21 (m, 1 H, Ph-H), 7.29 (m, 2 H, Ph-H), 7.37 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4 (1-CH_2CH_3), 28.9 (C-3), 35.3 (C-4), 37.0 (NCH_3), 46.4 (1-CH_2CH_3), 57.0 (2-CH_2), 62.1 (C-2), 69.0 (C-5), 126.8, 127.2, 128.2 (CH-Ph), 145.3 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{22}N_2$: 219.1856; found: 219.1857.

(2*R*,5*S*)-*tert*-Butyl 2-phenyl-5-(pyrrolidine-1-carbonyl)pyrrolidine-1-carboxylate (21d)

$LiOH·H_2O$ (49.7 mg, 1.18 mmol) was added to a solution of the ester **16a**[10] (213 mg, 697 µmol) in EtOH (3 mL). After 16 h of stirring, HCl (1 N, 15 mL) was added and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude acid (200 mg), which was dissolved in anhydrous THF (7 mL). NEt_3 (195 µL, 142 mg, 1.40 mmol) and PvCl (135 µL, 133 mg, 1.10 mmol) were added at r.t. and the resulting suspension was stirred for 2.5 h. Pyrrolidine (165 µL, 147 mg, 2.06 mmol) was added and stirring was continued for 16 h. The reaction mixture was evaporated and sat. aq $NaHCO_3$ (50 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated. Column chromatography (silica gel, petroleum ether–EtOAc, 3:1–0:1) afforded the amide **21d** (197 mg, 572 µmol, 82%) as a colorless resin.

$[\alpha]_D^{25}$ 32.8 (*c* 1.00, MeOH); R_f = 0.34 (petroleum ether–EtOAc, 1:1).

FT-IR (ATR): 2973, 2873, 1687, 1651, 1389, 1363, 1153, 1118, 760, 733, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$):* δ = 1.08 (s, 6 H, $C(CH_3)_3$), 1.37 (s, 3 H, $C(CH_3)_3$), 1.78–2.21 (m, 7 H, 3-*H*H, 4-H_2, $N(CH_2CH_2)_2$), 2.26 (m, 1 H, 3-H*H*), 3.46 (m, 2 H, $N(CH_2CH_2)_2$), 3.62 (m, 1.34 H, $N(CH_2CH_2)_2$), 3.76 (m, 0.66 H, $N(CH_2CH_2)_2$), 4.45 (m, 0.34 H, 5-H), 4.60 (m, 0.66 H, 5-H), 4.66 (t, *J* = 7.2 Hz, 0.66 H, 2-H), 4.94 (dd, *J* = 7.9, 2.9 Hz, 0.34 H, 2-H), 7.19 (m, 1 H, Ph-H), 7.29 (m, 2 H, Ph-H), 7.75 (m, 2 H, Ph-H). * 66:34 mixture of rotamers.

^{13}C NMR (125 MHz, $CDCl_3$):* δ = 24.15, 24.24, 26.3, 26.4 ($N(CH_2CH_2)_2$), 28.1, 28.35 ($C(CH_3)_3$), 28.43, 28.7 (C-4), 34.7, 35.8 (C-3), 46.10, 46.16, 46.18, 46.3 ($N(CH_2CH_2)_2$), 59.3, 59.6 (C-5), 62.2, 63.4 (C-2), 79.7, 79.9 ($C(CH_3)_3$), 126.5, 126.6, 126.9, 128.0, 128.3 (CH-Ph), 143.6, 144.6 (C_q-Ph), 153.8, 154.6 (1-CO_2), 171.2 (5-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + 2\ H - Boc]^+$ calcd for $C_{20}H_{28}N_2O_3$: 245.1648; found: 245.1650.

(2*R*,5*S*)-1-Methyl-2-phenyl-5-(pyrrolidin-1-yl)methylpyrrolidine (5u)

LAH (95.8 mg, 2.53 mmol) was added at 0 °C to a solution of ester **21d** (145 mg, 421 µmol) in anhydrous THF (10 mL). After 1 h at 0 °C, the reaction mixture was heated under reflux for 18 h. The solution was diluted with Et_2O (20 mL) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 200 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 97:3:0–85:13.5:1.5) provided diamine **5u** (101 mg, 413 µmol, 98%) as a slightly brownish oil.

$[\alpha]_D^{21}$ 2.0 (*c* 0.5, MeOH); R_f = 0.20 (CH_2Cl_2–MeOH, 9:1).

FT-IR (ATR): 2954, 2925, 2777, 1453, 1073, 880, 755, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.73 (m, 6 H, 3-*H*H, 4-*H*H, $N(CH_2CH_2)_2$), 2.05 (m, 2 H, 3-H*H*, 4-H*H*), 2.20 (s, 3 H, 1-CH_3), 2.54 (m, 6 H, 5-H, 5-C*H*H, $N(CH_2CH_2)_2$), 2.73 (dd, *J* = 11.1, 3.1 Hz, 1 H, 5-CH*H*), 3.24 (m, 1 H, 2-H), 7.22 (m, 1 H, Ph-H), 7.32 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6 ($N(CH_2CH_2)_2$), 29.6 (C-4), 34.0 (C-3), 39.8 (1-CH_3), 55.1 ($N(CH_2CH_2)_2$), 62.0 (5-CH_2), 65.8 (C-5), 72.6 (C-2), 126.9, 127.5, 128.3 (CH-Ph), 144.0 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{24}N_2$: 245.2012; found: 245.2010.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

The financial support of the German research foundation (DFG) is gratefully acknowledged.

References

(1) New address: Institute of Organic Chemistry, University of Würzburg, Am Hubland, 97074 Würzburg, Germany.

(2) New address: Institute of Inorganic Chemistry, University of Würzburg, Am Hubland, 97074 Würzburg, Germany.

(3) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986.

(4) (a) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 4212. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

(5) (a) Soai, K.; Ookawa, A.; Ogawa, K.; Kaba, T. *J. Chem. Soc., Chem. Commun.* **1987**, 467. (b) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.

(6) (a) Zhou, Y.; Dong, J.; Zhang, F.; Gong, Y. *J. Org. Chem.* **2011**, *76*, 588. b) Zhou, Y.; Gong, Y. *Eur. J. Org. Chem.* **2011**, 6092. (c) Zhou, Y.; Zhu, Y.; Yan, S.; Gong, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 10265.

(7) (a) Breuning, M.; Steiner, M. *Synthesis* **2008**, 2841. (b) Breuning, M.; Hein, D.; Steiner, M.; Gessner, V. H.; Strohmann, C. *Chem.–Eur. J.* **2009**, *15*, 12764. (c) Breuning, M.; Steiner, M.; Mehler, C.; Paasche, A.; Hein, D. *J. Org. Chem.* **2009**, *74*, 1407. (d) Breuning, M.; Steiner, M.; Hein, D.; Hörl, C.; Maier, P. *Synlett* **2009**, 2749. (e) Breuning, M.; Hein, D. *Eur. J. Org. Chem.* **2013**, 7575.

(8) Reviews: (a) Boruwa, J. ; Gogoi, N.; Saikia, P. P.; Barua, N. C. *Tetrahedron: Asymmetry* **2006**, *17*, 3315. (b) Palomo, C.; Oiarbide, M.; Laso A. *Eur. J. Org. Chem.* **2007**, 2561. (c) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Synlett* **2011**, 1195. (d) Chelucci, G. *Coord. Chem. Rev.* **2013**, *257*, 1887. (e) Ananthi, N.; Velmathi, S. *Ind. J. Chem.* **2013**, *52B*, 87.

(9) Selected recent examples: (a) Yao, L.; Wei, Y.; Wang, P.; He, W.; Zhang, S. *Tetrahedron* **2012**, *68*, 9119. (b) Qin, D.-D.; Lai, W.-H.; Hu, D.; Chen, Z.; Wu, A.-A.; Ruan, Y.-P.; Zhou, Z.-H.; Chen, H.-B. *Chem.–Eur. J.* **2012**, *18*, 10515. (c) Xu, K.; Lai, G.; Zha, Z.; Pan, S.; Chen, H.; Wang, Z. *Chem.–Eur. J.* **2012**, *18*, 12357. (d) Leighty, M. W.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2012**, *134*, 15233. (e) White, J. D.; Shaw, S. *Org. Lett.* **2012**, *14*, 6270. (f) Dai, Q.; Rana, N. K.; Zhao, J. C.-G. *Org. Lett.* **2013**, *15*, 2922. (g) Qin, D.-D.; Yu, W.; Zhou, J.-D.; Zhang, Y.-C.; Ruan, Y.-P.; Zhou, Z.-H.; Chen, H.-B. *Chem.–Eur. J.* **2013**, *19*, 16541. (h) Das, A.; Kureshy, R. I.; Prathap, K. J.; Choudhary, M. K.; Rao, G. V. S.; Khan, N. H.; Abdi, S. H. R.; Bajaj, H. C. *Appl. Catal. A* **2013**, *459*, 97. (i) Deng, T.; Cai, C. *J. Fluorine Chem.* **2013**, *156*, 183. (j) Ćwiek, R.; Niedziejko, P.; Kałuża, Z. *J. Org. Chem.* **2014**, *79*, 1222.

(10) Scharnagel, D.; Prause, F.; Kaldun, J.; Haase, R. G.; Breuning, M. *Chem. Commun.* **2014**, *50*, 6623.

(11) Besides **5a**,[10] there are only two further diamines of type **5** known, namely **5f** and a 5-*cis*, *N'*-diaryl derivative: (a) Castro, A. C.; Depew, K. M.; Grogan, M. J.; Holson, E. B.; Hopkins, B. T.; Johannes, C. W.; Keaney, G. F.; Koney, N. O.; Liu, T.; Mann, D. A.; Nevalainen, M.; Peluso, S.; Perez, L. B.; Snyder,

D. A.; Tibbitts, T. T. PCT Int. Appl. WO 2008024337 A2, 2008. (b) Hutchison, A.; Peterson, J.; Doller, D.; Gustavson, L. E.; Caldwell, T.; Yoon, T.; Pringle, W.; Bakthavatchalam, R.; Shen, Y.; Steenstra, C.; Yin, H.; De Simone, R.; He, X.-s. PCT Int. Appl. WO 2002094799 A2, 2002.

(12) Selected examples: (a) Fournie-Zaluski, M.-C.; Coric, P.; Thery, V.; Gonzalez, W.; Meudal, H.; Turcaud, S.; Michel, J.-B.; Roques, B. P. *J. Med. Chem.* **1996**, *39*, 2594. (b) Xu, Y.; Choi, J.; Calaza, M. I.; Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069. (c) Baldwin, J. J.; McDonald, E.; Moriarty, K. J.; Sarko, C. R.; Machinaga, N.; Nakayama, A.; Chiba, J.; Shin, I.; Yoneda, Y. PCT Int. Appl. WO 2001000206 A1, 2001. (d) Pei, Z.; Li, X.; Longenecker, K.; von Geldern, T. W.; Wiedeman, P. E.; Lubben, T. H.; Zinker, B. A.; Stewart, K.; Ballaron, S. J.; Stashko, M. A.; Mika, A. K.; Beno, D. W. A.; Long, M.; Wells, H.; Kempf-Grote, A. J.; Madar, D. J.; McDermott, T. S.; Bhagavatula, L.; Fickes, M. G.; Pireh, D.; Solomon, L. R.; Lake, M. R.; Edalji, R.; Fry, E. H.; Sham, H. L.; Trevillyan, J. M.; *J. Med. Chem.* **2006**, *49*, 3520. (e) Kimura, T.; Kawano, K.; Doi, E.; Kitazawa, N.; Takaishi, M.; Ito, K.; Kaneko, T.; Sasaki, T.; Miyagawa, T.; Hagiwara, H.; Yoshida, Y. U.S. Pat. Appl. US 20070117839 A1, 2007. (f) Alvaro, G.; Bergauer, M.; Giovannini, R.; Profeta, R. PCT Int. Appl. WO 2007042239 A1, 2007. (g) Ref. 11b, 13b, 27.

(13) Selected examples: (a) Momotake, A.; Togo, H; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193. (b) Hoveyda, H.; Schils, D.; Zoute, L.; Parcq, J. PCT Int. Appl. WO 2011073376 A1, 2011.

(14) Amide **9a** and diamine **5f** are known, but not characterized compounds, see ref. 11a.

(15) The *cis/trans* ratios were judged from the ^{1}H NMR spectra of the crude reaction mixtures after reductive cyclization. The determination of the exact values was difficult for the *N*-Boc protected pyrrolidines since both diastereomers exist as mixtures of rotamers.

(16) In most literature protocols, hydrogenations[12] or modified borohydrides[13] are used for the reduction of the intermediate Δ^1-pyrrolidines. Even though these reagents often allow better *cis* selectivities, we choose cheap $NaBH_4$ for the reductions, because this permits to perform the *N*-deprotection, reductive cyclization, and *N*-re-protection sequence as a one-pot three-step procedure with comparable overall yields. To the best of our knowledge, there is just one example in which $NaBH_4$ was used, see. ref. 12e.

(17) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766.

(18) (a) Rudolph, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895. (b) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301.

(19) Such protocols work well for the corresponding esters, see: (a) Rigo, B.; Lespagnol, C.; Pauly, M. *J. Heterocycl. Chem.* **1988**, *25*, 49. (b) Jain, R. *Org. Prep. Proced. Int.* **2001**, *33*, 405.

(20) In further studies we found that Grignard reagents containing lithium salts, as formed by transmetalation of lithium organyls, are not suited for addition. The reaction of **11** with PhMgBr–LiCl–TMEDA (1.5:1.9:1.5), for example, provided **12** in just 5% yield.

(21) According to ref. 18a, the ethoxycarbonyl group can be removed with TMSI in refluxing MeCN.

(22) Pyroglutamate **14** is also commercially available. For selected procedures on the preparation of **14** from **6** or of *ent*-**14** from *ent*-**6**, see: (a) Coudert, E.; Acher, F.; Azerad, R. *Synthesis* **1997**, 863. (b) Aggarwal, V. K.; Astle, C. J.; Iding, H.; Wirz, B.; Rogers-Evans, M. Tetrahedron Lett. ***2005***, *46*, 945. (c) Reilly, M. PCT Int. Appl. WO 2007110835 A2, 2007. (d) Vaswani, R. G.; Chamberlin, A. R. *J. Org. Chem.* **2008**, 73, 1661. (e) Anelli, P. L.; Brocchetta, M.; Lattuada, L.; Manfredi, G.; Morosini, P.; Murru, M.; Palano, D.; Sipioni, M.; Visigalli, M. *Org. Process Res. Dev.* **2009**, *13*, 739. (f) Hsu, M.-C.; King, C.-H. R.; Yuan, J.; Chen, W.-C.; Chou, S.-Y.; Shi, B. PCT Int. Appl. WO 2010009014 A2, 2010.

(23) In the cases of **16b** and **16c**, the minor diastereomers could not fully be removed on this stage and the mixtures were carried on to the next step, where separation by column chromatography was successful.

(24) McDermott, T. S.; Bhagavatula, L.; Borchardt, T. B.; Engstrom, K. M.; Gandarilla, J.; Kotecki, B. J.; Kruger, A. W.; Rozema, M. J.; Sheikh, A. Y.; Wagaw, S. H.; Wittenberger, S. J. *Org. Proc. Res. Dev.* **2009**, *13*, 1145.

(25) (a) Lin, G.-J.; Huang, P.-Q. *Org. Biomol. Chem.* **2009**, *7*, 4491. (b) Aebi, J.; Binggeli, A.; Green, L.; Hartmann, G.; Maerki, H. P.; Mattei, P. U.S. Pat. Appl. Publ. US 20110082294 A1, 2011. For related cyclizations of γ-amino ketones, see: (c) Abels, F.; Lindemann, C.; Schneider, C. *Chem.–Eur. J.* **2014**, *20*, 1964.

(26) The silyl ethers **18** and **19** were isolated as single diastereomers with unknown absolute configurations.

(27) Amino ketone **15c** is a known, but not characterized compound: Ayesa, S.; Belda, O.; Björklund, C.; Nilsson, M.; Russo, F.; Sahlberg, C.; Wiktelius, D. PCT Int. Appl. WO 2013095275 A1, 2013.

(28) (a) Mohite, A. R.; Bhat, R. G. *J. Org. Chem.* **2012**, *77*, 5423. (b) Belema, M.; Hewawasam, P. U.S. Pat. Appl. Publ. US 20110237636 A1, 2011.

(29) For other approaches to **16c**, see ref. 28a and: Wei, L.; Lubell, W. D. *Can. J. Chem.* **2001**, *79*, 94.

(30) The structures of the products **5** prepared by hydroxy–amine exchange were unambiguously confirmed by 2D NMR experiments and, for **5a**[10] and **5b**, by comparison with material obtained via route III. Rearrangements of **17** to β-amino piperidines via the sequence mesylation–aziridinium formation–nucleophilic attack at C-2 under ring enlargement were not observed. It had been shown that such rearrangements do not occur under mild mesylation conditions and with amines as the nucleophiles, see: (a) Pargo, D. G.; Cossy, J. *Chem.–Eur. J.* **2014**, *20*, 4516. See also: (b) Reitsema, R. H. *J. Am. Chem. Soc.* **1949**, *71*, 2041. (c) Biel, J. H.; Hoya, W. K.; Leiser, H. A. *J. Am. Chem. Soc.* **1959**, *81*, 2527. (d) Hammer, C. F.; Heller, S. R.; Craig, J. H. *Tetrahedron* **1972**, *28*, 239.

(31) Amide **21c** is a known, but only partially characterized compound: Miyazaki, M.; Naito, H.; Sugimoto, Y.; Yoshida, K.; Kawato, H.; Okayama, T.; Shimizu, H.; Miyazaki, M.; Kitagawa, M.; Seki, T.; Fukutake, S.; Shiose, Y.; Aonuma, M.; Soga, T. *Bioorg. Med. Chem.* **2013**, *21*, 4319.

(32) *Purification of Laboratory Chemicals*, 4th ed., Armarego, W. L. F.; Perrin, D. D., Eds.; Butterworth-Heinemann: Oxford, **2000**.

(33) (a) Haddad, M.; Imogai, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680. (b) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305. (c) van Esseveldt, B. C. J; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791. (d) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.

Supporting Information

Flexible and Modular Syntheses of Enantiopure 5-*cis*-Substituted Prolinamines from L-Pyroglutamic Acid

Felix Prause, Johannes Kaldun, Benjamin Arensmeyer, Benedikt Wennemann, Benjamin Fröhlich, Dagmar Scharnagel, Matthias Breuning*

Organic Chemistry Laboratory
University of Bayreuth
Universitätsstraße 30
95447 Bayreuth, Germany
E-mail: Matthias.Breuning@uni-bayreuth.de

Table of Contents

1. General Information

For general information about apparatus and methods used, see article.

2. General Procedures

2.1. Grignard Addition to Pyroglutamic Esters and Amides (GP–1)[1]

A solution of the Grignard reagent (1.2–3.5 equiv) in anhydrous THF (0.5–3.0 M) was added to a solution of the pyroglutamate **X** (1.0 equiv) in anhydrous THF (5 mL/mmol **X**). For work up, sat. aq NH_4Cl (5 mL/mmol **X**) was added and the organic layer was removed under reduced pressure. The remaining aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL/mmol **X**), and the combined organic layers were washed with brine (5 mL/mmol **X**) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography afforded amino ketone **8** or **15**.

2.2. Three-Step Cyclization to 5-*cis*-substituted Pyroglutamic Esters and Amides (GP–2)[1]

A solution of the amino ketone **X** (1.0 equiv) in anhydrous CH_2Cl_2 (10 mL/mmol **X**) was treated at r.t. with TFA (20 equiv) and stirred overnight. The solvent was removed under reduced pressure and the resulting orange oil was diluted five times with CH_2Cl_2 (6 mL/mmol **X**) and evaporated again, in order to remove excess TFA. $NaBH_4$ (1.5–2.0 equiv) was slowly added at 0 °C to a solution of the residue in MeOH (16 mL/mmol **X**). The solvent was removed after stirring overnight at r.t. The resulting orange oil was diluted three times with MeOH (7 mL/mmol **X**) and evaporated again. The residue was suspended in anhydrous CH_2Cl_2 (25 mL/mmol **X**) and NEt_3 (1.5 equiv), Boc_2O (1.5 equiv), and DMAP (0.05 equiv) were added at r.t. Sat. aq NH_4Cl (20 mL/mmol **X**) was added after 1–3 d of stirring and the

(1) Selected examples of related procedures: (a) Fournie-Zaluski, M.-C.; Coric, P.; Thery, V.; Gonzalez, W.; Meudal, H.; Turcaud, S.; Michel, J.-B.; Roques, B. P. *J. Med. Chem.* **1996**, *39*, 2594. (b) Xu, Y.; Choi, J.; Calaza, M. I.; Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069. (c) Momotake, A.; Togo, H; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193. (d) Baldwin, J. J.; McDonald, E.; Moriarty, K. J.; Sarko, C. R.; Machinaga, N.; Nakayama, A.; Chiba, J.; Shin, I.; Yoneda, Y. PCT Int. Appl. WO 2001000206 A1, 2001. (e) Hutchison, A.; Peterson, J.; Doller, D.; Gustavson, L. E.; Caldwell, T.; Yoon, T.; Pringle, W.; Bakthavatchalam, R.; Shen, Y.; Steenstra, C.; Yin, H.; De Simone, R.; He, X.-s. PCT Int. Appl. WO 2002094799 A2, 2002 (f) Pei, Z.; Li, X.; Longenecker, K.; von Geldern, T. W.; Wiedeman, P. E.; Lubben, T. H.; Zinker, B. A.; Stewart, K.; Ballaron, S. J.; Stashko, M. A.; Mika, A. K.; Beno, D. W. A.; Long, M.; Wells, H.; Kempf-Grote, A. J.; Madar, D. J.; McDermott, T. S.; Bhagavatula, L.; Fickes, M. G.; Pireh, D.; Solomon, L. R.; Lake, M. R.; Edalji, R.; Fry, E. H.; Sham, H. L.; Trevillyan, J. M.; *J. Med. Chem.* **2006**, *49*, 3520. (g) Kimura, T.; Kawano, K.; Doi, E.; Kitazawa, N.; Takaishi, M.; Ito, K.; Kaneko, T.; Sasaki, T.; Miyagawa, T.; Hagiwara, H.; Yoshida, Y. U.S. Pat. Appl. US 20070117839 A1, 2007. (h) Alvaro, G.; Bergauer, M.; Giovannini, R.; Profeta, R. PCT Int. Appl. WO 2007042239 A1, 2007. (i) McDermott, T. S.; Bhagavatula, L.; Borchardt, T. B.; Engstrom, K. M.; Gandarilla, J.; Kotecki, B. J.; Kruger, A. W.; Rozema, M. J.; Sheikh, A. Y.; Wagaw, S. H.; Wittenberger, S. J. *Org. Proc. Res. Dev.* **2009**, *13*, 1145. (j) Belema, M.; Hewawasam, P. U.S. Pat. Appl. Publ. US 20110237636 A1, 2011. (k) Mohite, A. R.; Bhat, R. G. *J. Org. Chem.* **2012**, *77*, 5423.

layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL/mmol **X**) and the combined organic layers were extracted with brine (10 mL/mmol **X**) and dried over $MgSO_4$. Removal of the solvent and column chromatography afforded pyrrolidine **9** or **16**.

2.3. Reductions with LAH (GP–3)

$LiAlH_4$ (6.0 equiv in the case of the *N*-Boc derivatives, 3.0 equiv in the case of the *N*-alkyl and *N*-H derivatives) was added at 0 °C to a solution of the pyrrolidine amide or ester **X** (1.0 equiv.) in anhydrous THF (15 mL/mmol **X**). The reaction mixture was stirred for 1 h at 0 °C and then refluxed overnight. The resulting suspension was diluted with Et_2O (15 mL/mmol **X**) and treated with sat. aq Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 200 mL/mmol **X**). Evaporation of the solvent and column chromatography provided diamine **5** or amino alcohol **17**.

2.4. Reductive Amination (GP–4)

AcOH (2.0 equiv) and the aldehyde or ketone (1.5 equiv) were added at r.t. to a solution of the pyrrolidine **X** (1.0 equiv) in anhydrous DCE (2 mL/mmol **X**). After 10 min, $NaBH(OAc)_3$ (1.6 equiv) was added and stirring was continued for 2–3 h. Sat. aq. $NaHCO_3$ (10 mL/mmol **X**) and CH_2Cl_2 (10 mL/mmol **X**) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL/mmol **X**) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and column chromatography afforded the *N*-alkylated pyrrolidine.

2.5. Mesylation and Amination of Prolinols 17 (GP–5)

MsCl (1.1 equiv) and NEt_3 (1.5 equiv) were added at 0 °C to a solution of the alcohol **17** (1.0 equiv) in anhydrous CH_2Cl_2 (3–11 mL/mmol **17**). After 1 d at r.t., an excess of the amine (10–30 equiv) was added and stirring was continued for 1–4 d. Evaporation of the solvent and column chromatography provided prolinamine **5**.

2.6. Saponification and Amidation of Esters 16 (GP–6)

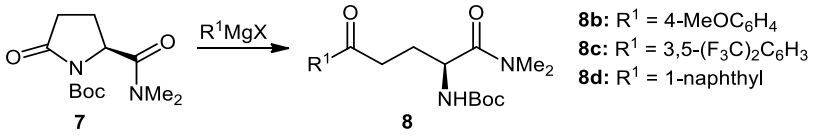
$LiOH•H_2O$ (1.7 equiv) was added at r.t. to a solution of the ester **16** (1.0 equiv) in EtOH (4 mL/mmol **16**). After stirring overnight, aq HCl (1 N, 20 mL/mmol **16**) was added and the aqueous Layer was extracted with EtOAc (4 × 15 mL/mmol **16**). The combined organic layers were dried over $MgSO_4$ and the solvent removed. The resulting crude acid was dissolved in anhydrous CH_2Cl_2 (8 mL/mmol **16**) and NEt_3 (2.0 equiv) and PvCl (1.6 equiv) were added at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and 1.5 h at r.t. The amine or the

amine hydrochloride (3.0 equiv) and NEt_3 (4.0 equiv in the case of free amine base, 7.0 equiv in the case of hydrochlorides) were added and stirring was continued overnight. Sat. aq. $NHCO_3$ (10 mL/mmol **16**) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL/mmol **16**) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and column chromatography afforded pyrrolidine amide **9a** or **21**.

3. Synthesis of Diamines 5 According to Route I

The preparation of compounds **7**, **8a**, **9a**, **10a**, **5b**, **5f**, and **5h** is described in the article.

3.1. Amino Ketones 8b–d



3.1.1. (*S*)-2-(*tert*-Butoxycarbonylamino)-5-(4-methoxyphenyl)-*N*,*N*-dimethyl-5-oxopentanamide (8b)

Pyroglutamate **7** (1.00 g, 3.90 mmol) was treated with 4-methoxyphenylmagnesium bromide (1.0 M in THF, 4.68 mL, 4.68 mmol) according to GP–1 (addition at –40 °C, then warm up to r.t. overnight) to give, after column chromatography (silica gel, petroleum ether–EtOAc, 2:1–1:1), keto amide **8b** (783 mg, 2.15 mmol, 55%) as a colorless, highly viscous oil.

$[\alpha]_D^{21}$ +4.8 (*c* 1.00, MeOH); R_f = 0.5 (EtOAc).

IR (ATR): 3450–3350, 3350–3200, 2974, 2932, 1639, 1599, 1246, 1166, 1025, 840 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (s, 9 H, $C(CH_3)_3$), 1.80 (m, 1 H, 3-*H*H), 2.20 (m, 1 H, 3-H*H*), 2.91 (m, 1 H, 4-*H*H), 2.96 (s, 3 H, NCH_3), 3.15 (m, 1 H, 4-H*H*), 3.18 (s, 3 H, NCH_3), 3.85 (s, 3 H, OCH_3), 4.69 (m, 1 H, 2-H), 5.51 (d, *J* = 7.0 Hz, 1 H, NH), 6.91 (d, *J* = 8.9 Hz, 2 H, Ar-H), 7.92 (d, *J* = 8.9 Hz, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6 (C-3), 28.4 ($C(CH_3)_3$), 33.4 (C-4), 35.8 (NCH_3), 37.2 (NCH_3), 49.8 (C-2), 55.6 (OCH_3), 79.6 ($C(CH_3)_3$), 113.8 (CH-Ar), 130.2 (C_q-Ar), 130.4 (CH-Ar), 155.8 (C_q-Ar), 163.6 (NCO_2), 172.0 (C-1), 197.9 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{19}H_{28}N_2O_5$: 387.1890; found: 387.1892.

3.1.2. (*S*)-5-(3,5-Bis(trifluoromethyl)phenyl)-2-(*tert*-butoxycarbonylamino)-*N*,*N*-dimethyl-5-oxopentanamide (8c)

The Grignard reagent (3,5-bis(trifluoromethyl)phenyl)magnesium bromide (1.2 equiv) was prepared by addition of *i*PrMgCl (2 M in THF, 3.80 mL, 7.60 mmol) at –10 °C to a solution of 1-bromo-3,5-bis(trifluoromethyl)benzene (1.31 mL, 2.22 g, 7.60 mmol) in anhydrous THF (4 mL). The resulting brownish solution was stirred at –10 °C for 1 h.

Pyroglutamate **7** (1.60 g, 6.24 mmol) was treated with the Grignard reagent prepared above according to GP–1 (addition at –15 °C, then warm up to r.t. overnight) to give, after column chromatography (silica gel, Et_2O), keto amide **8c** (2.32 g, 4.76 mmol, 76 %) as a colorless, highly viscous oil.

$[\alpha]_D^{21}$ +0.16 (*c* 0.98, MeOH); R_f = 0.40 (CH_2Cl_2–MeOH, 95:5).

IR (ATR): 3450–3370, 3370–3200, 2978, 2933, 1699, 1644, 1490, 1366, 1277, 1171, 1130, 681 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9 H, $C(CH_3)_3$), 1.77 (m, 1 H, 3-*H*H), 2.31 (m, 1 H, 3-H*H*), 2.93 (m, 1 H, 4-*H*H), 2.99 (s, 3 H, NCH_3), 3.24 (s, 3 H, NCH_3), 3.36 (m, 1 H, 4-H*H*), 4.68 (m, 1 H, 2-H), 5.63 (d, *J* = 7.6 Hz, 1 H, NH), 8.05 (s, 1 H, Ar-H), 8.38 (s, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (C-3), 28.3 ($C(CH_3)_3$), 34.1 (C-4), 35.9 (NCH_3), 37.2 (NCH_3), 49.3 (C-2), 79.9 ($C(CH_3)_3$), 123.1 (q, *J* = 272.7 Hz, CF_3), 126.3 (m, CH-Ar), 128.2 (d, *J* = 3.0 Hz, CH-Ar), 132.4 (q, *J* = 33.7 Hz, CCF_3), 138.7 (C_q-Ar), 156.1 (NCO_2), 171.7 (C-1), 196.8 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{24}F_6N_2O_4$: 493.1533; found: 493.1531.

3.1.3. (*S*)-2-(*tert*-Butoxycarbonylamino)-*N*,*N*-dimethyl-5-(naphthalen-1-yl)-5-oxopentanamide (8d)

A 0.5 M solution of the Grignard reagent 1-naphthylmagnesium bromide was prepared by reaction of 1-bromonaphthalene (1.75 mL, 2.59 g, 12.5 mmol) with Mg turnings (340 mg, 14.0 mmol, activated by some drops of 1,2-dibromoethane) in anhydrous THF (25 mL). After most of the Mg had been reacted, the reaction mixture was stirred for additional 30 min at r.t. and then heated under reflux for 2 h.

Pyroglutamate **7** (500 mg, 1.95 mmol) was treated with the Grignard reagent prepared above (0.5 M in THF, 4.70 mL, 2.35 mmol) according to GP–1 (addition at –40 °C, then warm up to r.t. overnight) to give, after column chromatography (silica gel, petroleum ether–EtOAc, 2:1–0:1), a mixture of **8d** and the corresponding 4,5-dihydropyrrole. The latter mixture was dissolved in MeOH (2 mL), and water (200 μL) and $TsOH•H_2O$ (10 mg) were added. After 48 h at r.t., the solvent was removed in vacuum and the residue was dissolved in CH_2Cl_2 (10 mL). The organic layer was washed with sat. aq $NaHCO_3$ (2 × 10 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, Et_2O) delivered keto

amide **8d** (325 mg, 845 µmol, 43%) as a colorless, highly viscous oil.

$[\alpha]_D^{21}$ –15.1 (*c* 1.00, MeOH); R_f = 0.48 (Et_2O).

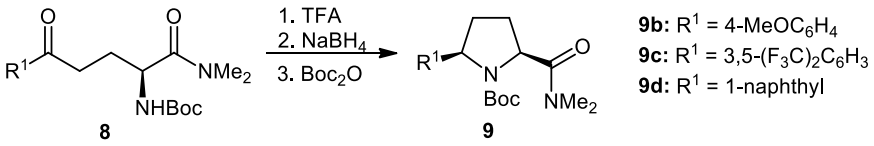
IR (ATR): 3450–3375, 3375–3200, 2975, 2931, 1702, 1638, 1490, 1165, 1049, 800, 776 cm^{-1}.

^1H NMR: (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H, $C(CH_3)_3$), 1.88 (m, 1 H, 3-*H*H), 2.29 (m, 1 H, 3-H*H*), 2.99 (s, 3 H, NCH_3), 3.05 (m, 1 H, 4-*H*H), 3.24 (s, 3 H, NCH_3), 3.29 (m, 1 H, 4-H*H*), 4.80 (td, *J* = 8.8, 3.0 Hz, 1 H, 2-H), 5.56 (d, *J* = 8.4 Hz, 1 H, NH), 7.53 (m, 3 H, Ar-H), 7.87 (m, 2 H, Ar-H), 7.97 (d, *J* = 8.3 Hz, 1 H, Ar-H), 8.55 (d, *J* = 8.6 Hz, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.7 (C-3), 28.5 ($C(CH_3)_3$), 35.9 (NCH_3), 37.3 (NCH_3), 37.5 (C-4), 49.7 (C-2), 79.7 ($C(CH_3)_3$), 124.5, 125.9, 126.5, 127.7, 127.9, 128.5 (CH-Ar), 130.2 (C_q-Ar), 132.5 (CH-Ar), 134.1, 136.3 (C_q-Ar), 155.9 (NCO_2), 172.0 (C-1), 203.7 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{28}N_2O_4$: 407.1941; found: 407.1939.

3.2. Pyrrolidine Amides 9b–d



3.2.1 (2*S*,5*R*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-(4-methoxyphenyl)pyrrolidine-1-carboxylate (9b)

According to GP–2, the keto amide **8b** (1.00 g, 2.74 mmol) was reductively cyclized to give, after column chromatography (silica gel, petroleum ether–EtOAc, 1:1–0:1), pyrrolidine amide **9b** (856 mg, 2.46 mmol, 90%) as a slightly yellowish solid.

Mp 118–121 °C; $[\alpha]_D^{21}$ +28.8 (*c* 1.00, MeOH); R_f = 0.47 (EtOAc).

IR (ATR): 2971, 2932, 1677, 1649, 1513, 1391, 1244, 1154, 1030, 820 cm^{-1}.

^1H NMR: (400 MHz, $CDCl_3$):* δ = 1.13 (s, 6.3 H, $C(CH_3)_3$), 1.38 (s, 2.7 H, $C(CH_3)_3$), 1.95 (m, 1.3 H, 3-*H*H, 4-*H*H), 2.11 (m, 1.7 H, 3-H*H*, 4-*H*H), 2.24 (m, 1 H, 4-H*H*), 3.03 (s, 3 H, NCH_3), 3.11 (s, 0.9 H, NCH_3), 3.14 (s, 2.1 H, NCH_3), 3.77 (s, 0.9 H, OCH_3), 3.79 (s, 2.1 H, OCH_3), 4.66 (m, 1 H, 2-H, 5-H), 4.78 (m, 0.7 H, 2-H), 4.90 (m, 0.3 H, 5-H), 6.86 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.66 (d, *J* = 8.5 Hz, 2 H, Ar-H). * 70:30 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.2, 28.4 ($C(CH_3)_3$), 28.7 (C-3), 34.9, 35.9 (C-4), 36.3, 37.2 (NCH_3), 55.3, 55.4 (OCH_3), 57.9 (C-2), 61.9, 63.0 (C-5), 79.8, 79.9 ($C(CH_3)_3$), 113.5 113.8, 127.7, 128.1 (CH-Ar), 135.9, 136.9 (C_q-Ar), 153.9, 154.8 (1-CO_2), 158.4 (C_q-Ar), 172.7, 172.8 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{19}H_{28}N_2O_4$: 371.1941; found: 371.1943.

3.2.2 (2*R*,5*S*)-*tert*-Butyl 2-(3,5-bis(trifluoromethyl)phenyl)-5-(dimethylcarbamoyl)pyrrolidine-1-carboxylate (9c)

According to GP–2, the keto amide **8c** (2.00 g, 4.25 mmol) was reductively cyclized to give, after column chromatography (silica gel, petroleum ether–EtOAc, 1:1–0:1), pyrrolidine amide **9c** (1.64 g, 3.62 mmol, 85%) as a colorless solid.

Mp 80−84 °C; $[\alpha]_D^{21}$ +19.4 (*c* 1.03, MeOH); R_f = 0.64 (CH_2Cl_2–MeOH, 95:5).

IR (ATR): 3032, 2986, 2938, 1694, 1651, 1376, 1367, 1274, 1163, 1124, 682 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$):* δ = 1.10 (s, 6.0 H, $C(CH_3)_3$), 1.39 (s, 3.0 H, $C(CH_3)_3$), 1.98 (m, 1.3 H, 3-*H*H, 4-*H*H), 2.19 (m, 1.7 H, 3-H*H*, 4-*H*H), 2.37 (m, 1 H, 4-H*H*), 3.04 (s, 2.0 H, NCH_3), 3.05 (s, 1.0 H, NCH_3), 3.12 (s, 1.0 H, NCH_3), 3.15 (s, 2.0 H, NCH_3), 4.73 (m, 0.3 H, 5-H), 4.79 (m, 0.7 H, 2-H), 4.87 (dd, *J* = 8.1, 2.7 Hz, 0.7 H, 5-H), 5.01 (m, 0.3 H, 2-H), 7.72 (s, 0.3 H, Ar-H), 7.75 (s, 0.7 H, Ar-H), 8.31 (s, 2 H, Ar-H). * 67:33 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.1, 28.3 ($C(CH_3)_3$), 29.0 (C-4), 34.5, 35.6 (C-3), 36.4, 37.2 (NCH_3), 57.8, 57.9 (C-5), 61.9, 62.9 (C-2), 80.5, 80.8 ($C(CH_3)_3$), 120.7 (m, CH-Ar), 123.7 (q, *J* = 272.5 Hz, CF_3), 127.2, 127.6 (CH-Ar), 131.5 (q, *J* = 33.0 Hz, CCF_3), 146.4, 147.6 (C_q-Ar), 153.8, 154.1 (1-CO_2), 172.3, 172.4 (5-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{20}H_{24}F_6N_2O_3$: 477.1583; found: 477.1586.

3.2.3 (2*S*,5*R*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-(naphthalen-1-yl)pyrrolidine-1-carboxylate (9d)

According to GP–2, the keto amide **8d** (500 mg, 1.30 mmol) was reductively cyclized to give, after column chromatography (silica gel, Et_2O), pyrrolidine amide **9d** (270 mg, 733 µmol, 56%) as a colorless solid.

Mp (decomp.) 190 °C; $[\alpha]_D^{21}$ +55.2 (*c* 1.00, MeOH); R_f = 0.24 (Et_2O).

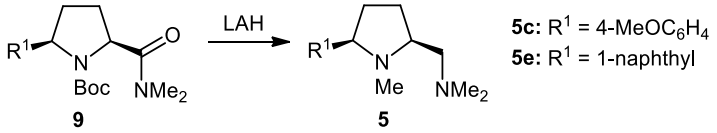
IR (ATR): 3062, 2971, 1692, 1650, 1386, 1159, 1116, 810, 784 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$):* δ = 1.04 (s, 5.0 H, $C(CH_3)_3$), 1.43 (s, 4.0 H, $C(CH_3)_3$), 1.94–2.25 (m, 3.0 H, 3-H_2, 4-*H*H), 2.50 (m, 1.0 H, 4-H*H*), 3.07 (s, 3 H, NCH_3), 3.16 (s, 1.4 H, NCH_3), 3.19 (s, 1.6 H, NCH_3), 4.71 (dd, J = 9.6, 6.5 Hz, 0.45 H, 2-H), 4.83 (t, *J* = 7.1 Hz, 0.55 H, 2-H), 5.64 (dd, *J* = 7.3, 5.3 Hz, 0.55 H, 5-H), 5.79 (d, *J* = 8.7 Hz, 0.45 H, 5-H), 7.45 (m, 2 H, Ar-H), 7.55 (m, 1 H, Ar-H), 7.72 (m, 1 H, Ar-H), 7.84 (m, 1 H, Ar-H), 7.97 (dd, *J* = 15.1, 8.3 Hz, 1 H, Ar-H), 8.68 (m, 1 H, Ar-H). * 55:45 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.1, 28.4 ($C(CH_3)_3$), 28.7 (C-3), 33.3, 34.4 (C-4), 36.37, 36.42, 37.3 (NCH_3), 58.1, 58.3 (C-2), 59.3 (C-5), 79.8, 80.2 ($C(CH_3)_3$), 122.6 123.0, 124.4, 124.6, 125.0, 125.6, 126.3, 126.8, 127.2, 129.0 (CH-Ar), 130.4, 130.6, 133.7, 134.1, 138.2, 139.4 (C_q-Ar), 154.1, 154.9 (1-CO_2), 172.4, 172.6 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{28}N_2O_3$: 391.1992; found: 391.1991.

3.3. Diamines 5c and 5e



3.3.1. (2*S*,5*R*)-2-(Dimethylaminomethyl)-5-(4-methoxyphenyl)-1-methylpyrrolidine (5c)

According to GP–3, the pyrrolidine **9b** (630 mg, 1.81 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1), prolinamine **5c** (436 mg, 1.76 mmol, 97%) as a beige solid.

Mp 25–27 °C; $[\alpha]_D^{21}$ +11.4 (*c* 0.50, MeOH); R_f = 0.15 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 2945, 2815, 1612, 1510, 1457, 1242, 1170, 1034, 827 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.69 (m, 2 H, 3-*H*H, 4-*H*H), 2.03 (m, 2 H, 3-H*H*, 4-H*H*), 2.16 (s, 3 H, 1-CH_3), 2.31 (s, 6 H, $N(CH_3)_2$), 2.38 (dd, *J* = 12.9, 9.1 Hz, 1 H, 2-H), 2.53 (m, 2 H, 2-CH_2), 3.18 (dd, *J* = 9.1, 6.2 Hz, 1 H, 5-H), 3.79 (s, 3 H, OCH_3), 6.84 (m, 2 H, Ar-H), 7.25 (m, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.4 (C-3), 33.9 (C-4), 39.6 (1-CH_3), 46.5 ($N(CH_3)_2$), 55.4 (OCH_3), 64.5 (C-2), 65.2 (2-CH_2), 72.2 (C-5), 113.8, 128.6 (CH-Ar), 135.6, 158.8 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{24}N_2O$: 249.1961; found: 249.1960.

3.3.2. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-(naphthalen-1-yl)pyrrolidine (5e)

According to GP–3, the pyrrolidine **9d** (200 mg, 543 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1), prolinamine **5e** (127 mg, 473 µmol, 87%) as a colorless oil.

$[\alpha]_D^{21}$ +61.2 (*c* 0.50, MeOH); R_f = 0.33 (CH_2Cl_2–MeOH, 9:1).

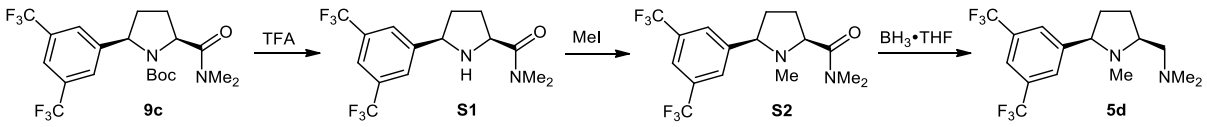
IR (ATR): 2943, 2763, 1595, 1456, 1154, 1032, 931, 853, 797, 776 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.76 (m, 2 H, 3-*H*H, 4-*H*H), 2.18 (m, 1 H, 3-H*H*), 2.30 (s, 3 H, 1-CH_3), 2.36 (m, 1 H, 4-H*H*), 2.39 (s, 6 H, $N(CH_3)_2$), 2.51 (dd, *J* = 12.1, 8.2 Hz, 1 H, 2-C*H*H), 2.67 (dd, *J* = 12.1, 3.7 Hz, 1 H, 2-CH*H*), 2.72 (m, 1 H, 2-H), 4.08 (m, 1 H, 5-H), 7.47 (m, 3 H, Ar-H), 7.75 (m, 2 H, Ar-H), 7.86 (m, 1 H, Ar-H), 8.22 (m, 1 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (C-3), 33.0 (C-4), 40.2 (1-CH_3), 46.5 ($N(CH_3)_2$), 64.6 (C-2), 65.1 (2-C), 68.8 (C-5), 123.6, 123.7, 125.3, 125.6, 126.0, 127.1, 128.9 (CH-Ar), 131.8, 134.1, 139.6 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{24}N_2$: 269.2012; found: 269.2013.

3.4. Synthesis of 5d from 9c



3.4.1. (2*S*,5*R*)-5-(3,5-Bis(trifluoromethyl)phenyl)-*N*,*N*-dimethylpyrrolidine-2-carboxamide (S1)

A solution of the amide **9c** (1.20 g, 2.64 mmol) in anhydrous CH_2Cl_2 (30 mL) was treated at r.t. with TFA (4.04 mL, 6.02 g, 52.8 mmol) and stirred overnight. The solvent was removed under reduced pressure and the residue was diluted five times with CH_2Cl_2 (30 mL) and evaporated again, in order to remove excess TFA. Filtration through a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1) afforded the *N*-deprotected pyrrolidine **S1** (874 mg, 2.47 mmol, 93%) as a colorless oil.

$[\alpha]_D^{21}$ –1.2 (*c* 1.00, MeOH); R_f = 0.51 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 3497, 3279, 2941, 1633, 1379, 1275, 1172, 1122, 898, 842, 708, 681 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (m, 1 H, 4-*H*H), 1.96 (m, 1 H, 3-*H*H), 2.22 (m, 2 H, 3-H*H*, 4-H*H*), 2.76 (s, 1 H, NH), 2.98 (s, 3 H, $N(CH_3)_2$), 3.04 (s, 3 H, $N(CH_3)_2$), 4.09 (dd, *J* = 8.8, 4.9 Hz, 1 H, 2-H), 4.21 (dd, *J* = 9.8, 5.5 Hz, 1 H, 5-H), 7.73 (s, 1 H, Ar-H), 7.91 (s, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.9 (C-3), 34.3 (C-4), 36.0, 36.6 ($N(CH_3)_2$), 58.3 (C-2), 63.3 (C-5), 121.2 (sept, *J* = 3.9 Hz, CH-Ar), 123.5 (q, *J* = 272.7 Hz, CF_3), 127.3 (d, *J* = 2.6 Hz, CH-Ar), 131.7 (q, *J* = 33.2 Hz, *C*CF_3), 145.6 (C_q-Ar), 173.5 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{16}F_6N_2O$: 355.1240; found: 355.1235.

3.4.2. (2*S*,5*R*)-5-(3,5-Bis(trifluoromethyl)phenyl)-*N*,*N*,1-trimethylpyrrolidine-2-carboxamide (S2)

Cs_2CO_3 (1.03 g, 3.16 mmol) and MeI (108 µL, 247 mg, 1.74 mmol) were added at r.t. to a solution of the pyrrolidine **S1** (560 mg, 1.58 mmol) in anhydrous CH_2Cl_2 (25 mL). After vigorous stirring for 4 d, sat. aq $NaHCO_3$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 1:0–0:1) delivered the *N*-methylated pyrrolidine **S2** (500 mg, 1.36 mmol, 86%) as a colorless oil.

$[\alpha]_D^{21}$ +19.3 (*c* 0.50, MeOH); R_f = 0.44 (EtOAc).

IR (ATR): 2948, 2785, 1651, 1276, 1167, 1122, 897, 842, 709, 682 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.77 (m, 1 H, 4-*H*H), 1.96 (m, 1 H, 3-*H*H), 2.16 (s, 3 H, 1-CH_3), 2.19 (m, 2 H, 3-H*H*, 4-H*H*), 2.98 (s, 3 H, $N(CH_3)_2$), 3.15 (s, 3 H, $N(CH_3)_2$), 3.44 (m, 2

H, 2-H, 5-H), 7.72 (s, 1 H, Ar-H), 7.88 (s, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 (C-3), 34.7 (C-4), 36.3, 36.8 ($N(CH_3)_2$), 39.6 (1-CH_3), 67.7 (C-2), 70.7 (C-5), 121.3 (sept, *J* = 3.9 Hz, CH-Ar), 123.5 (q, *J* = 272.6 Hz, CF_3), 127.8 (d, *J* = 2.6 Hz, CH-Ar), 131.8 (q, *J* = 33.2 Hz, *C*CF_3), 146.2 (C_q-Ar), 172.2 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{18}F_6N_2O$: 369.1396; found: 369.1397.

3.4.3. (2*R*,5*S*)-2-(3,5-Bis(trifluoromethyl)phenyl)-5-(dimethylaminomethyl)-1-methylpyrrolidine (5d)

BH_3•THF (1.0 M in THF, 8.91 mL, 8.91 mmol) was added at 0 °C to a solution of **S2** (547mg, 1.49 mmol) in anhydrous THF (30 mL). The reaction mixture was stirred for 1 h at 0 °C and then refluxed for 72 h. The solvent was removed under reduced pressure and the residue was diluted five times with MeOH (30 mL) and evaporated again. The residue was dissolved in CH_2Cl_2 (10 mL) and MeOH (5 mL), and TFA (910 µL, 1.35 g, 11.9 mmol) was added. After heating to 40 °C overnight, the solvent was removed and the residue was diluted three times with CH_2Cl_2 (15 mL) and evaporated again. Column chromatography (silica gel, 1. petroleum ether/EtOAc, 1:0–0:1; 2. CH_2Cl_2–MeOH, 95:5–90:10) afforded diamine **5d** (396 mg, 1.12 mmol, 75%) as a slightly yellowish oil.

$[\alpha]_D^{21}$ +30.1 (*c* 1.00, MeOH); R_f = 0.46 (CH_2Cl_2–MeOH, 9:1).

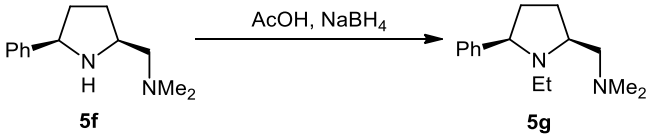
IR (ATR): 2947, 2770, 1459, 1379, 1345, 1276, 1169, 1127, 897, 708, 682 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60 (m, 1 H, 3-*H*H), 1.74 (m, 1 H, 4-*H*H), 2.09 (m, 2 H, 3-H*H*, 4-H*H*), 2.20 (s, 3 H, 1-CH_3), 2.28 (s, 6 H, $N(CH_3)_2$), 2.36 (dd, *J* = 12.2, 8.2 Hz, 1 H, 5-C*H*H), 2.49 (dd, *J* = 12.2, 4.0 Hz, 1 H, 5-CH*H*), 2.63 (m, 1 H, 5-H), 3.42 (dd, *J* = 9.0, 6.9 Hz, 1 H, 2-H), 7.73 (s, 1 H, Ar-H), 7.80 (s, 2 H, Ar-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.5 (C-4), 34.6 (C-3), 39.8 (1-CH_3), 46.6 ($N(CH_3)_2$), 64.6 (C-5), 65.3 (5-C), 71.8 (C-2), 121.1 (sept, *J* = 3.8 Hz, CH-Ar), 123.7 (q, *J* = 272.6 Hz, CF_3), 127.6 (d, *J* = 2.6 Hz, CH-Ar), 131.7 (q, *J* = 33.0 Hz, *C*CF_3), 147.4 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{20}F_6N_2$: 355.1603; found: 355.1602.

3.5. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-ethyl-5-phenylpyrrolidine (5g)



5f **5g**

$NaBH_4$ (35.6 mg, 940 µmol) was portionwise added at 0 °C to a solution of the amine **5f** (40.8 mg, 200 µmol) in AcOH (350 µL). After gas evolution had ceased, the solution was heated to 60 °C for 2 h. Sat. aq $NaHCO_3$ (4 mL) was slowly added and the reaction mixture was made basic with solid Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (4 × 4 mL) and the

combined organic layers were dried over $MgSO_4$. Evaporation of the solvent afforded the analytically pure amine **5g** (44.2 mg, 190 µmol, 95%) as a colorless oil.

$[\alpha]_D^{21}$ +14.1 (*c* 1.00, MeOH); R_f = 0.50 (CH_2Cl_2–MeOH, 8:2).

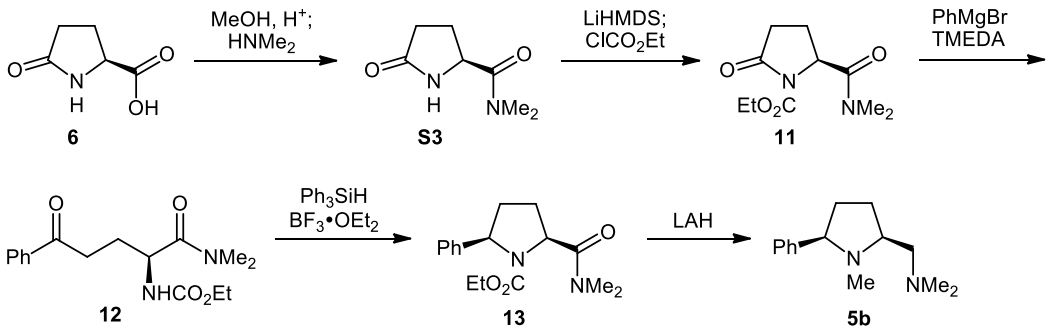
IR (ATR): 2965, 2935, 2815, 2764, 1453, 1153, 1035, 850, 756, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.66 (m, 1 H, 4-*H*H), 1.77 (m, 1 H, 3-*H*H), 2.00 (m, 2 H, 3-H*H*, 4-H*H*), 2.30 (s, 6 H, $N(CH_3)_2$), 2.38 (m, 2 H, 2-CH_2), 2.61 (m, 2 H, 1-CH_2CH_3), 2.92 (m, 1 H, 2-H), 3.66 (dd, *J* = 9.0, 6.3 Hz, 1 H, 5-H), 7.20 (m, 1 H, Ph-H), 7.29 (m, 2 H, Ph-H), 7.38 (m, 2 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9 (1-CH_2CH_3), 29.7 (C-3), 35.1 (C-4), 46.6 ($N(CH_3)_2$), 46.8 (1-CH_2CH_3), 61.1 (C-2), 66.8 (2-CH_2), 69.3 (C-5), 126.8, 127.3, 128.2 (CH-Ph), 145.5 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{24}N_2$: 233.2012; found: 233.2011.

3.6. Synthesis of Diamine 5b via One-Step Cyclisation



3.6.1. Synthesis of 11 from 6

3.6.1.1. (*S*)-*N*,*N*-Dimethyl-5-oxopyrrolidine-2-carboxamide (S3)

A solution of-pyroglutamic acid (**6**, 30.0 g, 232 mmol) and $TsOH•H_2O$ (1.33 g, 6.97 mmol) in anhydrous MeOH (300 mL) was heated under reflux for 24 h. Gaseous $HNMe_2$ was bubbled through the solution at r.t. for 6 h (volume of the solution increased by ca. 50 mL) and the stoppered flask was stirred at 40 °C for 48 h. The solvent and excess $HNMe_2$ were carefully removed under reduced pressure. Purification by flash chromatography (silica gel, CH_2Cl_2–MeOH, 98:2–95:5) and crystallization from CH_2Cl_2–Et_2O delivered the known[2] amide **S3** (33.0 g, 211 mmol, 91%) in analytically pure form as colorless needles, mp 118–120 °C {ref. 2a: Mp 115–117 °C; ref. 2b: Mp 114–115 °C}; $[\alpha]_D^{29}$ –35.6 (*c* 2.00, H_2O) {ref. 2a: $[\alpha]_D^{22}$ –37.2 (*c* 1.16, H_2O); ref. 2b: $[\alpha]_D^{23}$ –33.5 (*c* 2.00, H_2O)}.

The spectroscopic data of **16c** were consistent with those reported in literature.[2b]

(2) (a) Angier, R. B.; Smith, V. K. *J. Org. Chem.* **1956**, *21*, 1540. (b) Doyle, M. P.; Winchester, W. R.; Simonsen, S. H.; Ghosh, R. *Inorg. Chim. Acta* **1994**, *220*, 193.

3.6.1.2. (*S*)-Ethyl 2-dimethylcarbamoyl-5-oxopyrrolidine-1-carboxylate (11)

The amide **S3** (15.0 g, 96.1 mmol) was dissolved in anhydrous THF (1.1 L) and cooled to –78 °C. LiHMDS (1.0 M in THF, 106 mL, 106 mmol) was added dropwise within 20 min to the resulting beige suspension. After 30 min at –78 °C, $ClCO_2Et$ (11.0 mL, 12.5 g, 115 mmol) in anhydrous THF (100 mL) was added slowly. The reaction was warmed to 0 °C within 2 h and quenched with sat. aq NH_4Cl (800 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 800 mL), and the combined organic layers were washed with brine (800 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and crystallization (CH_2Cl_2–Et_2O–petroleum ether, 1:2:6) delivered imide **11** (19.1 g, 83.7 mmol, 87%) as colorless needles.

Mp 116–120 °C; $[\alpha]_D^{21}$–22.8 (*c* 1.00, MeOH); R_f = 0.27 (CH_2Cl_2–MeOH, 95:5).

IR (ATR): 2979, 2959, 2933, 1746, 1705, 1650, 1294, 1275, 1035, 846, 778, 608 cm^{-1}.

^1H NMR: (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.91 (ddt, *J* = 12.9, 9.7 Hz, 2.5 Hz, 1 H, 3-*H*H), 2.25 (ddt, *J* = 12.8, 10.6 Hz, 9.4 Hz, 1 H, 3-H*H*), 2.45 (ddd, *J* = 17.4, 9.5, 2.7 Hz, 1 H, 4-*H*H), 2.73 (ddd, *J* = 17.4, 10.6, 9.7 Hz, 1 H, 4-H*H*), 2.97 (s, 3 H, NCH_3), 3.09 (s, 3 H, NCH_3), 4.26 (m, 2 H, OCH_2CH_3), 4.98 (dd, *J* = 9.2, 2.2 Hz, 1 H, 2-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 21.7 (C-3), 31.3 (C-4), 36.1 (NCH_3), 36.8 (NCH_3), 56.3 (C-2), 63.0 (OCH_2CH_3), 151.7 (1-CO_2), 170.5 (2-CON), 173.3 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{10}H_{16}N_2O_4$: 251.1002; found: 251.1003.

3.6.2. (*S*)-2-(Ethoxycarbonylamino)-*N*,*N*-dimethyl-5-oxo-5-phenylpentanamide (12)

TMEDA (491 μL, 381 mg, 3.28 mmol) was added at r.t. to a solution of PhMgBr (3.0 M in Et_2O, 1.09 mL, 3.28 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred at r.t. for 30 min, cooled to –78 °C, and then added to a solution of amide **11** (500 mg, 2.19 mmol) in anhydrous THF (11 mL). After 90 min at –78 °C, sat. aq NH_4Cl (11 mL) was added and stirring was continued for 1 h at r.t. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, Et_2O) delivered keto amide **12** (400 mg, 1.31 mmol, 60%) as a colorless oil.

$[\alpha]_D^{21}$ +4.9 (*c* 1.00, MeOH); R_f = 0.45 (EtOAc).

IR: 3440–3370, 3770–3290, 2933, 1712, 1683, 1637, 1497, 1229, 1052, 743, 690 cm^{-1}.

^1H NMR: (500 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 1.85 (m, 1 H, 3-*H*H), 2.23 (m, 1 H, 3-H*H*), 2.97 (s, 3 H, NCH_3), 3.01 (m, 1 H, 4-*H*H), 3.21 (m, 1 H, 4-H*H*), 3.22 (s, 3 H, NCH_3), 4.05 (m, 2 H, OCH_2CH_3), 4.76 (td, *J* = 8.7, 3.1 Hz, 1 H, 2-H), 5.69 (d, *J* = 8.2 Hz, 1 H, NH), 7.45 (t, *J* = 7.7 Hz, 2 H, Ph-H), 7.55 (t, *J* = 7.3 Hz, 1 H, Ph-H), 7.95 (d, *J* = 7.7 Hz, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.7 ($OCH_2\mathit{C}H_3$), 27.3 (C-3), 33.7 (C-4), 35.9 (NCH_3), 37.2 (NCH_3), 50.1 (C-2), 61.1 ($O\mathit{C}H_2CH_3$), 128.1, 128.7, 133.2 (CH-Ph), 136.9 (C_q-Ph), 156.7 (NCO_2), 171.8 (C-1), 199.4 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{16}H_{22}N_2O_4$: 329.1472; found: 329.1270.

3.6.3. (2*S*,5*R*)-Ethyl 2-(dimethylcarbamoyl)-5-phenylpyrrolidine-1-carboxylate (13)

The keto amide **12** (557 mg, 1.82 mmol) and Ph_3SiH (521 mg, 2.00 mmol) were dissolved in CH_2Cl_2 (8 mL). BF_3•Et_2O (250 µL, 2.00 mmol) was added at –78 °C and the reaction mixture was allowed to slowly warm to r.t. overnight. Aq NaOH (1 N, 2 mL) was added and, after 20 min of stirring, CH_2Cl_2 (20 mL) and H_2O (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, 1. petroleum ether; 2. CH_2Cl_2–MeOH, 1:0–9:1) delivered pyrrolidine **13** (439 mg, 1.51 mmol, 83%) as a crystalline colorless solid.

Mp 73–76 °C; $[\alpha]_D^{21}$ +40.2 (*c* 1.02, MeOH); R_f = 0.35 (EtOAc).

IR (ATR): 2979, 2958, 2929, 1693, 1649, 1405, 1334, 1110, 1011, 755, 707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$):* δ = 0.90 (t, *J* = 7.0 Hz, 2.0 H, $OCH_2C\mathit{H}_3$), 1.18 (m, 1.0 H, $OCH_2C\mathit{H}_3$), 2.00 (m, 1 H, 3-*H*H), 2.12 (m, 2 H, 3-H*H*, 4-*H*H), 2.31 (m, 1 H, 4-H*H*), 3.03 (s, 3 H, NCH_3), 3.13 (s, 1 H, NCH_3), 3.16 (s, 2 H, NCH_3), 3.93 (q, *J* = 7.0 Hz, 1.3 H, $OC\mathit{H}_2CH_3$), 4.05 (m, 0.7 H, $OC\mathit{H}_2CH_3$), 4.79 (m, 1.7 H, 2-H, 5-H), 4.92 (m, 0.3 H, 5-H), 7.19 (m, 1 H, Ph-H), 7.31 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.72 (m, 2 H, Ph-H). * 67:33 mixture of rotamers.

^{13}C NMR (100 MHz, $CDCl_3$):* δ = 14.3, 14.7 ($OCH_2\mathit{C}H_3$), 28.5, 29.2 (C-4), 34.7, 35.6 (C-3), 36.3, 37.3 (NCH_3), 57.7, 58.3 (C-2), 61.2 ($O\mathit{C}H_2CH_3$), 62.9, 63.2 (C-5), 126.7, 126.8, 128.2, 128.3 (CH-Ph), 143.2, 143.9 (C_q-Ph), 154.8, 155.7 (1-CO_2), 172.3, 172.6 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{16}H_{22}N_2O_3$: 313.1523; found: 313.1521.

3.6.4. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-phenylpyrrolidine (5b)

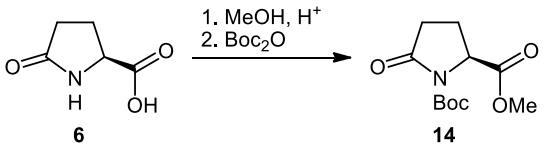
According to GP–3, the pyrrolidine **13** (39.2 mg, 135 µmol) was reduced to give, after filtration through a pad of cotton wool, prolinamine **5b** (27.0 mg, 124 µmol, 92%) as a colorless oil.

For characterization of **5b**, see article.

4. Synthesis of Diamines 5 According to Route II

The preparation of compounds **15a**, **16a**, **17a** and **5a** is described in ref. 3, the preparation of **15d**, **16d**, **17d**, **17f**, **20a**, **5l**, and **5n** is described in the article.

4.1. (*S*)-1-*tert*-Butyl 2-methyl 5-oxopyrrolidine-1,2-dicarboxylate (14)

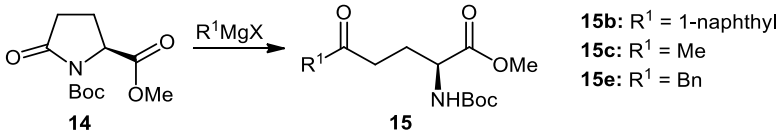


Note: Pyroglutamate **14** is commercially available, but it can conveniently be prepared in high 92% yield from **6** by the following procedure. For a selection of other procedures for the preparation of **14** from **6** (or *ent*-**14** from *ent*-**6**), see ref. 4.

A solution of L-pyroglutamic acid (**6**, 20.0 g, 155 mmol) and TsOH•H_2O (884 mg, 4.65 mmol) in anhydrous MeOH (250 mL) was heated under reflux for 24 h. The solvent was evaporated and the resulting oil was dissolved in CH_2Cl_2 (200 mL). Boc_2O (37.2 g, 170 mmol), NEt_3 (32.2 mL, 23.5 g, 232 mmol), and DMAP (1.89 g, 15.5 mmol) were added at r.t. and stirring was continued for 24 h. The reaction mixture was washed with sat. aq NH_4Cl (3 × 200 mL) and the combined aq layers were extracted with CH_2Cl_2 (200 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Flash chromatography (silica gel, petroleum ether–EtOAc, 5:1–1:1) delivered the known[4] pyroglutamate **14** (34.6 g, 142 mmol, 92%) as a colorless solid, $[\alpha]_D^{22}$ –33.7 (*c* 1.00, CH_2Cl_2) {ref. 4b: $[\alpha]_D^{21}$ –32.1 (*c* 1.00, CH_2Cl_2)}.

The spectroscopic data of **14** were consistent with those reported in literature.[4a–d]

4.2. Amino Ketones 15



(3) Scharnagel, D.; Prause, F.; Kaldun, J.; Haase, R. G.; Breuning, M. *Chem. Commun.* **2014**, *50*, 6623.

(4) (a) Coudert, E.; Acher, F.; Azerad, R. *Synthesis* **1997**, 863. (b) Aggarwal, V. K.; Astle, C. J.; Iding, H.; Wirz, B.; Rogers-Evans, M. Tetrahedron Lett. ***2005***, *46*, 945. (c) Reilly, M. PCT Int. Appl. WO 2007110835 A2, 2007. (d) Vaswani, R. G.; Chamberlin, A. R. *J. Org. Chem.* **2008**, 73, 1661. (e) Anelli, P. L.; Brocchetta, M.; Lattuada, L.; Manfredi, G.; Morosini, P.; Murru, M.; Palano, D.; Sipioni, M.; Visigalli, M. *Org. Process Res. Dev.* **2009**, *13*, 739. (f) Hsu, M.-C.; King, C.-H. R.; Yuan, J.; Chen, W.-C.; Chou, S.-Y.; Shi, B. PCT Int. Appl. WO 2010009014 A2, 2010.

4.2.1. (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-(naphthalen-1-yl)-5-oxopentanoate (15b)

Pyroglutamate **14** (4.00 g, 16.5 mmol) in anhydrous THF (20 mL) was treated with 1-naphthylMgBr (0.5 M in THF, 58.0 mL, 29.0 mmol) according to GP–1 (addition at 0 °C, then warm up to r.t. overnight) to give, after column chromatography (silica gel, petroleum ether–Et_2O, 1:0–1:1), a mixture of **15b** and the corresponding 4,5-dihydropyrrole. The latter mixture was dissolved in MeOH (50 mL), and water (5 mL) and TsOH•H_2O (100 mg) were added. After 5 d at r.t., the solvent was removed in vacuum and the residue was dissolved in CH_2Cl_2 (100 mL). The organic layer was washed with sat. aq $NaHCO_3$ (2 × 75 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–Et_2O, 1:0–1:1) delivered amino ketone **15b** (3.64 g, 9.80 mmol, 59%) as a brownish gum.

$[\alpha]_D^{28}$ –11.5 (*c* 1.00, MeOH); R_f = 0.51 (petroleum ether–Et_2O, 1:2).

IR (ATR): 3470–3230, 2978, 1707, 1683, 1507, 1365, 1160, 1051, 775, 731 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, $C(CH_3)_3$), 2.16 (m, 1 H, 3-*H*H), 2.37 (m, 1 H, 3-H*H*), 3.17 (m, 2 H, 4-H_2), 3.75 (s, 3 H, OCH_3), 4.43 (m, 1 H, 2-H), 5.22 (m, 1 H, NH), 7.53 (m, 3 H, Ar-H), 7.86 (m, 2 H, Ar-H), 7.97 (d, *J* = 8.3 Hz, 1 H, Ar-H), 8.59 (d, *J* = 8.4 Hz, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3 (C-3), 28.3 ($C(CH_3)_3$), 38.0 (C-4), 52.5 (OCH_3), 53.2 (C-2), 80.1 ($C(CH_3)_3$), 124.4, 125.8, 126.5, 127.7, 128.0, 128.5 (CH-Ar),130.2 (C_q-Ar), 132.9 (CH-Ar), 134.0, 135.7 (C_q-Ar) 155.6 (NCO_2), 173.0 (C-1), 203.0 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{21}H_{25}NO_5$: 394.1625; found: 394.1615.

4.2.2. (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-oxohexanoate (15c)

Pyroglutamate **14** (6.08 g, 25.0 mmol) was treated with MeMgBr (3.0 M in THF, 10.4 mL, 31.3 mmol) according to GP–1 (addition at –55 °C, then 2 h at –40 °C) to give, after removal of the solvent under reduced pressure, amino ketone **15c**[5] (6.11 g, 23.6 mmol, 94%) as a colorless oil.

$[\alpha]_D^{30}$ +4.8 (*c* 1.00, $CHCl_3$); R_f = 0.65 (petroleum ether–EtOAc, 1:2).

IR (ATR): 3465–3225, 2973, 2934, 1705, 1511, 1365, 1210, 1162, 1049, 1025, 753, 666 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H, $C(CH_3)_3$), 1.83 (m, 1 H, 3-*H*H), 2.06 (m, 1 H, 3-H*H*), 2.10 (s, 3 H, 6-H_3), 2.50 (m, 2 H, 4-H_2), 3.69 (s, 3 H, OCH_3), 4.22 (m, 1 H, 2-H), 5.14 (d, *J* = 7.2 Hz, 1 H, NH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5 (C-3), 28.3 ($C(CH_3)_3$), 30.0 (C-6), 39.3 (C-4), 52.4

(5) Amino ketone **15c** is a known, but not characterized compound: Ayesa, S.; Belda, O.; Björklund, C.; Nilsson, M.; Russo, F.; Sahlberg, C.; Wiktelius, D. PCT Int. Appl. WO 2013095275 A1, 2013.

(OCH_3), 52.9 (C-2), 80.0 ($C(CH_3)_3$), 155.5 (NCO_2), 172.9 (C-1), 207.5 (C-5).

HRMS–ESI: *m/z* $[M + NH_4]^+$ calcd for $C_{12}H_{21}NO_5$: 277.1758; found: 277.1758.

4.2.3. (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-oxo-6-phenylhexanoate (15e)

Pyroglutamate **14** (4.00 g, 16.5 mmol) in anhydrous THF (20 mL) was treated with BnMgBr (1.4 M in THF, 42.3 mL, 59.2 mmol) according to GP–1 (addition at –40 °C, then 4 h at –40 °C) to give, after column chromatography (silica gel, petroleum ether–Et_2O, 1:0–1:2), amino ketone **15e** (2.99 g, 8.91 mmol, 54%) as a colorless oil.

$[\alpha]_D^{25}$ –14.1 (*c* 1.00, MeOH); R_f = 0.38 (petroleum ether–Et_2O, 1:2).

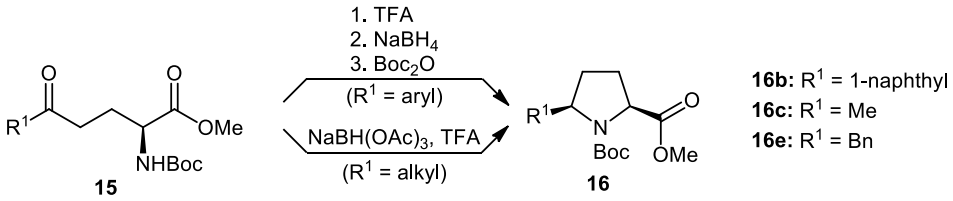
IR (ATR): 3470–3240, 2932, 1708, 1497, 1366, 1160, 1050, 1028, 736, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, $C(CH_3)_3$), 1.87 (m, 1 H, 3-*H*H), 2.11 (m, 1 H, 3-H*H*), 2.57 (m, 2 H, 4-H_2), 3.69 (m, 2 H, 6-H_2), 3.71 (s, 3 H, OCH_3), 4.26 (m, 1 H, 2-H), 5.13 (d, *J* = 7.7 Hz, 1 H, NH), 7.21 (m, 2 H, Ph-H), 7.31 (m, 3 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6 (C-3), 28.3 ($C(CH_3)_3$), 37.8 (C-4), 50.2 (C-6), 52.4 (OCH_3), 52.9 (C-2), 80.0 ($C(CH_3)_3$), 127.1, 128.8, 129.5 (CH-Ar),134.1 (C_q-Ar), 155.5 (NCO_2), 172.9 (C-1), 207.1 (C-5).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{25}NO_5$: 358.1625; found: 358.1624.

4.3. Esters 16



4.3.1. (2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-(naphthalen-1-yl)pyrrolidine-1,2-dicarboxylate (16b)

According to GP–2, the keto ester **15b** (2.85 g, 7.67 mmol) was reductively cyclized to give, after column chromatography (silica gel, petroleum ether–EtOAc, 3:1), a 90:10 mixture of pyrrolidine ester **16b** and its C5-epimer 5-*epi*-**16b**[6] (1.27 g, 3.57 mmol, 47%) as a brownish gum.

$[\alpha]_D^{28}$ +29.4 (*c* 0.5, MeOH); R_f = 0.50 (petroleum ether–EtOAc, 3:1).

IR (ATR): 3060, 2979, 1743, 1691, 1390, 1365, 1200, 1156, 1128, 911, 781, 728 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$):* δ = 1.10 (s, 4.5 H, $C(CH_3)_3$), 1.14 (s, 0.45 H, $C(CH_3)_3$), 1.45

(6) 5-*Epi*-**16b** is a known compound: Trost, B. M.; Miege, F. *J. Am. Chem. Soc.* **2014**, *136*, 3016.

(m, 4.95 H, $C(CH_3)_3$), 2.03 (m, 2.20 H, 3-*H*H, 4-*H*H), 2.24 (m, 1.10 H, 3-H*H*), 2.51 (m, 1.10 H, 4-H*H*), 3.81 (s, 0.15 H, OCH_3), 3.82 (s, 0.15 H, OCH_3), 3.85 (s, 3.00 H, OCH_3), 4.41 (dd, *J* = 9.4, 6.9 Hz, 0.50 H, 2-H), 4.52 (t, *J* = 7.2 Hz, 0.50 H, 2-H), 4.65 (d, *J* = 8.6 Hz, 0.05 H, 2-H), 4.75 (m, 0.05 H, 2-H), 5.66 (dd, *J* = 7.5, 3.2 Hz, 0.5 H, 5-H), 5.84 (m, 0.55 H, 5-H), 5.98 (d, *J* = 8.6 Hz, 0.05 H), 7.49 (m, 3.40 H, Ar-H), 7.75 (m, 1.10 H, Ar-H), 7.87 (m, 1.20 H, Ar-H), 7.96 (t, *J* = 7.0 Hz, 1 H, Ar-H), 8.23 (dd, *J* = 11.1, 7.3 Hz, 1 H, Ar-H). * 50:50 mixture of rotamers, 90:10 mixture of diastereomers.[6]

^{13}C NMR (75 MHz, $CDCl_3$):* δ = 28.1, 28.3 ($C(CH_3)_3$), 28.8, 29.2 (C-3), 33.1, 34.1 (C-4), 52.1, 52.3 (OCH_3), 59.2, 59.4 (C-5), 60.5, 61.1 (C-2), 80.2, 80.6 ($C(CH_3)_3$), 122.6, 123.0 123.2, 123.5, 125.2, 125.77, 125.81, 127.1, 127.4, 129.0 (CH-Ar), 130.3, 130.5, 133.7, 134.1, 137.9, 139.0 (C_q-Ar) 154.0, 154.7 (1-CO_2), 173.6, 173.8 (2-CO_2). * Mixture of rotamers; signals of the minor diastereomer[6] are not listed.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{21}H_{25}NO_4$: 378.1676; found: 378.1677.

4.3.2. (2*S*,5*S*)-1-*tert*-Butyl 2-methyl 5-methylpyrrolidine-1,2-dicarboxylate (16c)

$NaBH(OAc)_3$ (6.51 g, 30.7 mmol) was added at 0 °C to a solution of the ester **15c** (6.11 g, 23.6 mmol) in EtOAc (120 mL). After 10 min, TFA (7.80 mL, 11.6 g, 102 mmol) was added dropwise. The reaction mixture was allowed to come to r.t. overnight and then quenched with sat. aq $NaHCO_3$ (200 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL) and the combined organic layers were washed with brine (2 × 150 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 6:1–3:1) provided an inseparable 9:1 mixture of the known[7] pyrrolidine **16c** and its C5-epimer (4.96 g, 20.4 mmol, 86%) as a colorless oil, $[\alpha]_D^{30}$ +30.2 (*c* 1.00, $CHCl_3$) {ref. 7: $[\alpha]_D^{25}$ –28.4 (*c* 1.00, MeOH)}.

The spectroscopic data of **16c** were consistent with those reported in literature.[7]

4.3.3. (2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-benzylpyrrolidine-1,2-dicarboxylate (16e)

$NaBH(OAc)_3$ (2.05 g, 9.69 mmol) was added at 0 °C to a solution of the ester **15e** (2.50 g, 7.45 mmol) in EtOAc (25 mL). After 10 min, TFA (2.47 mL, 3.65 g, 32.0 mmol) was added dropwise. The reaction mixture was allowed to come to r.t. within 7 h, EtOAc (25 mL) was added, and then quenched with sat. aq $NaHCO_3$ (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 1:0–2:1) provided ester **16e**[8] (2.09 g, 6.54 mmol, 88%) as a colorless

(7) (a) Mohite, A. R.; Bhat, R. G. *J. Org. Chem.* **2012**, *77*, 5423. (b) Belema, M.; Hewawasam, P. U.S. Pat. Appl. Publ. US 20110237636 A1, 2011.

(8) Racemic **16e** is a known, but not characterized compound, which was prepared by hydrogenation of the corresponding pyrrole, see: Kaiser, H.-P.; Muchowski, J. M., *J. Org. Chem.* **1984**, *49*, 4203.

oil.

$[\alpha]_D^{27}$ –65.5 (*c* 1.0, MeOH); R_f = 0.48 (petroleum ether–Et_2O, 1:1).

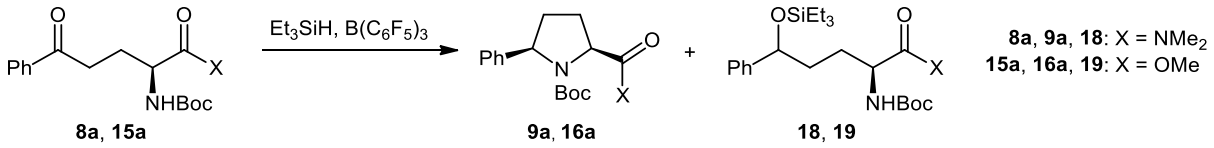
IR (ATR): 2975, 1750, 1693, 1388, 1365, 1199, 1167, 1140, 1113, 740, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$):* δ = 1.45 (m, 9.00 H, $C(CH_3)_3$), 1.77 (m, 2.00 H, 4-H_2), 2.03 (m, 1.00 H, 3-*H*H), 2.21 (m, 1.00 H, 3-H*H*), 2.60 (m, 1.00 H, 5-C*H*H), 3.28 (dd, *J* = 13.0, 4.0 Hz, 0.45 H, 5-CH*H*), 3.42 (dd, *J* = 13.2, 3.3 Hz, 0.55 H, 5-CH*H*), 3.77 (s, 3.00 H, OCH_3), 4.08 (m, 1.00 H, 5-H), 4.25 (t, *J* = 8.1 Hz, 0.55 H, 2-H), 4.37 (t, *J* = 7.8 Hz, 0.45 H, 2-H), 7.25 (m, 5 H, Ph-H). * 55:45 mixture of rotamers.

^{13}C NMR (75 MHz, $CDCl_3$):* δ = 28.3 (C-4), 28.4 ($C(CH_3)_3$), 28.8 (C-3), 29.5 (C-4), 39.8, 40.9 (5-CH_2), 52.1, 52.2 (OCH_3), 59.5, 60.0, 60.2, 60.4 (C-2, C-5), 80.1 ($C(CH_3)_3$), 126.2, 128.4, 128.5, 129.4, 129.5(CH-Ph), 139.3 (C_q-Ph) 153.6, 154.3 (1-CO_2), 173.9, 174.0 (2-CO_2). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{18}H_{25}NO_4$: 342.1676; found: 342.1673.

4.4. Attempted One-Step Cyclizations of 8a and 15a



4.4.1. Reaction of 8a with Et_3SiH–$B(C_6F_5)_3$

$B(C_6F_5)_3$ (15.3 mg, 29.9 μmol) was slowly added to a solution of Et_3SiH (115 μL, 83.4 mg, 718 μmol) in anhydrous CH_2Cl_2 (2.5 mL). The amide **8a** (200 mg, 598 μmol), dissolved in anhydrous CH_2Cl_2 (7.5 mL), was added at –78 °C. The reaction mixture was allowed to warm to r.t. and stirred for 3 d. Sat. aq $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–EtOAc, 1:0–1:1) delivered pyrrolidine **9a** (61.2 mg, 192 μmol, 32%) and diastereomerically pure, silylated amide **18** (46.1 mg, 102 μmol, 17%), both as colorless oils.

For characterization of **9a**, see article.

(2*S*)-2-(*tert*-Butoxycarbonylamino)-*N*,*N*-dimethyl-5-phenyl-5-(triethylsilyloxy)pentanamide (**18**):

$[\alpha]_D^{21}$ –7.8 (*c* 0.93, MeOH); R_f = 0.70 (petroleum ether–EtOAc 1:1).

IR (ATR): 3610–3360, 3360–3180, 2875, 1692, 1634, 1494, 1167, 1048, 1015, 848, 728, 700

cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.51 (m, 6 H, Si(C*H*$_2$CH$_3$)$_3$), 0.87 (t, *J* = 7.9 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$), 1.42 (s, 9 H, CH(C*H*$_3$)$_3$), 1.57 (m, 1 H), 1.72 (m, 3 H), 2.91 (s, 3 H, NCH$_3$), 2.98 (s, 3 H, NCH$_3$), 4.57 (m, 1 H), 4.70 (m, 1 H), 5.32 (d, *J* = 8.6 Hz, 1 H), 7.18 (m, 1 H, Ph-H), 7.26 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.81 (Si(*C*H$_2$CH$_3$)$_3$), 6.76 (Si(CH$_2$*C*H$_3$)$_3$), 28.3 (C(*C*H$_3$)$_3$), 28.5 (C-3), 35.6 (NCH$_3$), 35.9 (C-4), 37.0 (NCH$_3$), 50.1 (C-2), 74.1 (C-5), 79.4 (*C*(CH$_3$)$_3$), 125.8, 127.0, 128.0 (CH-Ph), 144.9 (C$_q$-Ph), 155.5 (NCO$_2$), 172.1 (C-1).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{24}H_{42}N_2O_4Si$: 473.2806; found: 473.2800.

4.4.2. Reaction of 15a with $Et_3SiH–B(C_6F_5)_3$

$B(C_6F_5)_3$ (15.3 mg, 29.9 μmol) was slowly added to a solution of Et_3SiH (115 μL, 83.4 mg, 718 μmol) in anhydrous CH_2Cl_2 (2.5 mL). The ester **15a** (193 mg, 598 μmol), dissolved in anhydrous CH_2Cl_2 (7.5 mL), was added at –78 °C. The reaction mixture was allowed to warm to r.t. and stirred for 3 d. Sat. aq $NaHCO_3$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, petroleum ether–Et_2O, 1:0–3:1) delivered diastereomerically pure, silylated ester **19** (206 mg, 471 μmol, 79%) as a colorless oil.

(2*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-phenyl-5-(triethylsilyloxy)pentanoate (**19**):

$[\alpha]_D^{21}$ –24.2 (*c* 1.01, MeOH); R_f = 0.65 (petroleum ether–Et_2O 1:1).

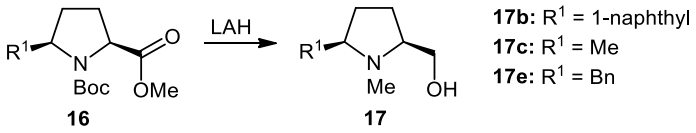
IR (ATR): 3470–3410, 3410–3190, 2953, 2876, 1743, 1714, 1165, 1003, 726, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.52 (m, 6 H, Si(C*H*$_2$CH$_3$)$_3$), 0.87 (t, *J* = 7.9 Hz, 9 H, Si(CH$_2$C*H*$_3$)$_3$), 1.43 (s, 9 H, C(CH$_3$)$_3$), 1.69 (m, 3 H), 1.85 (m, 1 H), 3.70 (s, 3 H, OCH$_3$), 4.29 (m, 1H), 4.70 (t, *J* = 5.5 Hz, 1 H), 5.05 (d, *J* = 7.6 Hz, 1 H, NH), 7.20 (m, 1 H, Ph-H), 7.28 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 4.7 (Si(*C*H$_2$CH$_3$)$_3$), 6.7 (Si(CH$_2$*C*H$_3$)$_3$), 28.3 (C(*C*H$_3$)$_3$), 28.4 (C-3), 36.2 (C-4), 52.1 (OCH$_3$), 53.1 (C-2), 73.8 (C-5), 79.7 (*C*(CH$_3$)$_3$), 125.7, 127.0, 128.0 (CH-Ph), 144.9 (C$_q$-Ph), 155.3 (NCO$_2$), 173.3 (C-1).

HRMS–ESI: *m/z* $[M + Na]^+$ calcd for $C_{23}H_{39}NO_5Si$: 460.2490; found: 460.2486.

4.5. Prolinols 17b, 17c, and 17e



4.5.1. (2*S*,5*R*)-2-(Hydroxymethyl)-1-methyl-5-(napthalen-1-yl)pyrrolidine (17b)

According to GP–3, a 9:1 mixture of the pyrrolidine ester **16b** and its C5-epimer (1.02 g, 2.87 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1), prolinol **17b** (567 mg, 2.35 mmol, 82%) as a brownish oil.

$[\alpha]_D^{29}$ +133.7 (*c* 0.50, MeOH); R_f = 0.51 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 3600–3200, 2948, 1596, 1394, 1234, 1087, 1026, 799, 777, 732 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.72 (m, 1 H, 4-*H*H), 2.05 (m, 2.00 H, 3-H_2), 2.30 (s, 3 H, 1-CH_3), 2.41 (m, 1 H, 4-H*H*), 2.78 (br s, 1 H, OH) 2.80 (tdd, *J* = 8.0, 3.4, 1.8 Hz, 1 H, 2-H), 3.61 (dd, *J* = 10.8, 1.7 Hz, 1 H, 2-C*H*H), 3.88 (dd, *J* = 10.8, 3.4 Hz, 1 H, 2-CH*H*), 4.26 (dd, *J* = 9.2, 7.5 Hz, 1 H, 5-H), 7.50 (m, 3 H, Ar-H), 7.76 (m, 2H, Ar-H), 7.89 (m, 1 H, Ar-H), 8.16 (m, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.4 (C-3), 33.4 (C-4), 39.1 (1-CH_3), 61.7 (2-CH_2), 66.7 (C-2), 68.3 (C-5), 123.0, 123.2, 125.4, 125.8, 125.9, 127.3, 129.0 (CH-Ar), 131.8, 134.1, 139.0 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{19}NO$: 242.1539; found: 242.1539.

4.5.2. (2*S*,5*S*)-2-(Hydroxymethyl)-1,5-dimethylpyrrolidine (17c)

According to GP–3, a 9:1 mixture of the pyrrolidine ester **16c** and its C5-epimer (2.25 g, 9.25 mmol) was reduced to give, after column chromatographic (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 80:18:2) removal of the minor diastereomer, prolinol **17c**[9] (956 mg, 7.40 mmol, 80%) as a colorless oil.

$[\alpha]_D^{25}$ +30.2 (*c* 2.00, $CHCl_3$); R_f = 0.26 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

IR (ATR): 3600–3000, 2961, 2870, 2786, 1458, 1378, 1204, 1049, 1025, 946, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.0 Hz, 3 H, 5-CH_3), 1.31 (m, 1 H, 4-*H*H), 1.61-1.86 (m, 3 H, 3-H_2, 4-H*H*), 2.23 (s, 3 H, 1-CH_3), 2.36 (m, 1 H, 5-H), 2.45 (m, 1 H, 2-H), 2.95 (br s, 1 H, OH), 3.38 (dd, *J* = 10.8, 2.3 Hz, 1 H, 2-C*H*H), 3.61 (dd, *J* = 10.8, 3.6 Hz, 1 H, 2-CH*H*).

(9) Racemic **17c** is a known, but not characterized compound, which was prepared by reduction of the *N*-ethoxycarbonyl protected ethyl ester, see: Mizoguchi, T.; Iijima, I. *Yakugaku Zasshi* **1965**, *85*, 641.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (5-CH_3), 25.7 (C-3), 32.5 (C-4), 38.4 (1-CH_3), 61.8 (2-CH_2), 62.8 (C-5), 67.3 (C-2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_7H_{15}NO$: 130.1226; found: 130.1227.

4.5.3. (2*R*,5*S*)-2-Benzyl-5-(hydroxymethyl)-1-methylpyrrolidine (17e)

According to GP–3, the pyrrolidine ester **16e** (551 mg, 1.73 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1), prolinol **17e** (335 mg, 1.63 mmol, 94%) as a brownish oil.

$[\alpha]_D^{26}$ +50.4 (*c* 0.10, MeOH); R_f = 0.33 (CH_2Cl_2–MeOH, 9:1).

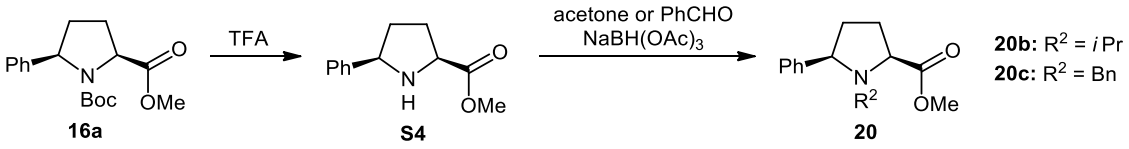
IR (ATR): 3500–3100, 2945, 2855, 2789, 1495, 1453, 1092, 1031, 744, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.62 (m, 1 H, 3-*H*H), 1.88 (m, 3 H, 3-H*H*, 4-H_2), 2.54 (s, 3 H, 1-CH_3), 2.75 (m, 3 H, 2-H, 5-H, 2-C*H*H), 3.12 (br s, 1 H, OH), 3.14 (dd, *J* = 13.0, 4.0 Hz, 1 H, 2-CH*H*), 3.55 (dd, *J* = 10.8, 2.2 Hz, 1 H, 5-C*H*H), 3.80 (dd, *J* = 10.7, 3.6 Hz, 1 H, 5-CH*H*), 7.35 (m, 3 H, Ph-H), 7.44 (m, 2 H, Ph-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.7 (C-4), 29.9 (C-3), 39.1 (1-CH_3), 40.8 (2-CH_2), 61.7 (5-CH_2), 67.3 (C-5), 68.6 (C-2), 126.1, 128.2, 129.4 (CH-Ph), 139.5 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{19}NO$: 206.1539; found: 206.1538.

4.6. Esters 20b and 20c



The preparation of the known[10] compound **S4** is described in the article (intermediate from **16a** to **20a**).

4.6.1. (2*S*,5*R*)-Methyl 1-isopropyl-5-phenylpyrrolidin-2-carboxylate (20b)

According to GP–4, pyrrolidine ester **S4** (650 mg, 3.17 mmol) was *N*-isopropylated with acetone–$NaBH(OAc)_3$ to give, after column chromatography (silica gel, petroleum ether–EtOAc, 9:1–5:1), ester **20b** (774 mg, 3.13 mmol, 99%) as a colorless oil.

$[\alpha]_D^{26}$ +48.3 (*c* 1.00, MeOH); R_f = 0.60 (CH_2Cl_2).

(10) (a) Haddad, M.; Imogai, H.; Larchevêque, M. *J. Org. Chem.* **1998**, *63*, 5680. (b) Severino, E. A.; Costenaro, E. R.; Garcia, A. L. L.; Correia, C. R. D. *Org. Lett.* **2003**, *5*, 305. (c) van Esseveldt, B. C. J; Vervoort, P. W. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2005**, *70*, 1791. (d) Stead, D.; O'Brien, P.; Sanderson, A. *Org. Lett.* **2008**, *10*, 1409.

IR (ATR): 2962, 1749, 1730, 1385, 1191, 1164, 1116, 1077, 757, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.4 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 0.97 (d, *J* = 6.8 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.85 (m, 1 H, 4-*H*H), 1.97 (m, 1 H, 3-*H*H), 2.03 (m, 1 H, 3-H*H*), 2.09 (m, 1 H, 4-H*H*), 2.91 (sept, *J* = 6.6 Hz, 1 H, 1-C*H*(CH$_3$)$_2$), 3.75 (m, 1 H, 2-H), 3.76 (s, 3 H, OCH_3), 4.01 (dd, *J* = 8.5, 6.2 Hz, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.32 (m, 2 H, Ph-H), 7.55 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.0 (1-CH(*C*H$_3$)$_2$), 21.6 (1-CH(*C*H$_3$)$_2$), 30.5 (C-3), 36.3 (C-4), 49.1 (1-*C*H(CH$_3$)$_2$), 51.9 (OCH_3), 59.8 (C-2), 65.9 (C-5), 126.8, 127.3, 128.3 (CH-Ph), 145.8 (C_q-Ph), 177.5 (1-CO_2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{21}NO_2$: 248.1645; found: 248.1647.

4.6.2. (2*S*,5*R*)-Methyl 1-benzyl-5-phenylpyrrolidin-2-carboxylate (20c)

According to GP–4, pyrrolidine ester **S4** (616 mg, 3.00 mmol) was *N*-benzylated with benzaldehyde–$NaBH(OAc)_3$ to give, after column chromatography (silica gel, petroleum ether–EtOAc, 9:1–5:1), ester **20c** (851 mg, 2.88 mmol, 96%) as a colorless oil.

$[\alpha]_D^{27}$ +7.0 (*c* 1.00, MeOH); R_f = 0.52 (petroleum ether–EtOAc, 9:1).

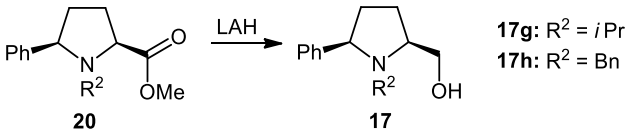
IR (ATR): 3028, 2950, 1745, 1732, 1454, 1195, 1167, 1130, 1075, 752, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.91 (m, 1 H, 4-*H*H), 2.00 (m, 1 H, 3-*H*H), 2.09 (m, 2 H, 3-H*H*, 4-H*H*), 3.47 (m, 2 H, 1-C*H*H, 2-H), 3.48 (s, 3 H, OCH_3), 3.77 (dd, *J* = 9.4, 5.8 Hz, 1 H, 5-H), 3.91 (d, *J* = 13.7 Hz, 1 H, 1-CH*H*), 7.21 (m, 3 H, Ph-H), 7.27 (m, 3 H, Ph-H), 7.38 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.59 (d, *J* = 7.2 Hz, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.1 (C-3), 35.4 (C-4), 51.6 (OCH_3), 56.5 (1-CH_2), 64.8 (C-2), 69.1 (C-5), 127.1, 127.3, 127.8, 128.0, 128.5, 129.7 (CH-Ph), 137.7, 143.4 (C_q-Ph), 175.5 (1-CO_2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{19}H_{21}NO_2$: 296.1645; found: 296.1646.

4.7. Prolinols 17g and 17h



4.7.1. (2*S*,5*R*)-2-(Hydroxymethyl)-1-isopropyl-5-phenylpyrrolidine (17g)

According to GP–3, the pyrrolidine **20b** (620 mg, 2.51 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5), prolinol **17g** (519 mg, 2.37 mmol, 94%) as a colorless oil.

$[\alpha]_D^{28}$ +69.6 (*c* 1.00, MeOH); R_f = 0.52 (petroleum ether–EtOAc, 1:1).

IR (ATR): 3500–3160, 2962, 2871, 1451, 1383, 1195, 1066, 1026, 756, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.7 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.07 (d, *J* = 6.7 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.73 (m, 1 H, 4-*H*H), 1.80 (m, 1 H, 3-*H*H), 1.91 (m, 1 H, 3-H*H*), 2.08 (m, 1 H, 4-H*H*), 2.91 (sept, *J* = 6.7 Hz, 1 H, 1-C*H*(CH$_3$)$_2$), 3.08 (br s, 1 H, OH), 3.27 (m, 1 H, 2-H), 3.44 (dd, *J* = 10.3, 4.1 Hz, 1 H, 2-C*H*H), 3.61 (dd, *J* = 10.4, 5.2 Hz, 1 H, 2-CH*H*), 4.02 (dd, *J* = 9.2, 6.6 Hz, 1 H 5-H), 7.22 (m, 1 H, Ph-H), 7.31 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.37 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.9 (1-CH(*C*H$_3$)$_2$), 20.9 (1-CH(*C*H$_3$)$_2$), 29.4 (C-3), 35.8 (C-4), 49.8 (1-*C*H(CH$_3$)$_2$), 59.1 (C-2), 65.2 (2-CH_2), 65.7 (C-5), 126.9, 128.4 (CH-Ph), 145.8 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{21}NO$: 220.1696; found: 220.1694.

4.7.2. (2*S*,5*R*)-1-Benzyl-2-(hydroxymethyl)-5-phenylpyrrolidine (17h)

According to GP–3, the pyrrolidine **20c** (800 mg, 2.71 mmol) was reduced to give, after column chromatography (silica gel, petroleum ether–EtOAc, 1:1), prolinol **17h** (681 mg, 2.55 mmol, 94%) as a colorless gum.

$[\alpha]_D^{28}$ +65.0 (*c* 1.00, MeOH); R_f = 0.39 (petroleum ether–EtOAc, 4:1).

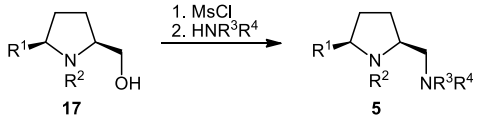
IR (ATR): 3570–3080, 2932, 2868, 1454, 1391, 1283, 1133, 1065, 1026, 746, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (m, 1 H, 4-*H*H), 1.89 (m, 1 H, 3-*H*H), 1.96 (m, 1 H, 3-H*H*), 2.04 (m, 1 H, 4-H*H*), 2.45 (s, 1 H, OH), 3.02 (m, 1 H, 2-H), 3.29 (d, *J* = 2.8 Hz, 2 H, 2-CH_2), 3.45 (d, *J* = 13.6 Hz, 1 H, 1-C*H*H), 3.75 (dd, *J* = 10.1, 6.1 Hz, 1 H, 5-H), 3.85 (d, *J* = 13.6 Hz, 1 H, 1-CH*H*), 7.16 (m, 2 H, Ph-H), 7.25 (m, 4 H, Ph-H), 7.36 (m, 2 H, Ph-H), 7.44 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8 (C-3), 35.2 (C-4), 56.2 (1-CH_2), 63.4 (2-CH_2), 63.9 (C-2), 70.0 (C-5), 127.36, 127.43, 127.6, 128.4, 128.7, 129.4 (CH-Ph), 138.4, 143.5 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}NO$: 268.1696; found: 268.1696.

4.8. Diamines 5



5	R^1	R^2	NR^3R^4
b	Ph	Me	NMe_2
e	Ar^1	Me	NMe_2
i	Ph	Me	NH_2
j	Ar^1	Me	NH_2
k	Me	Me	NH_2

5	R^1	R^2	NR^3R^4
m	Bn	Me	NH_2
o	Ph	*i*Pr	NHMe
p	Ph	Bn	NHMe
q	Me	Me	NMe_2
r	*i*Pr	Me	NMe_2

5	R^1	R^2	NR^3R^4
s	Bn	Me	NMe_2
t	Ph	Me	NEt_2
u	Ph	Me	pyrrolidinyl
v	Ph	Me	piperidinyl
w	Ph	Me	NMeBn

[1] Ar = 1-naphthyl

4.8.1. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-phenylpyrrolidine (5b)

According to GP–5, the alcohol **17a** (790 mg, 4.13 mmol) was mesylated and treated with $HNMe_2$•HCl (3.37 g, 41.3 mmol) and NEt_3 (5.76 mL, 4.18 g, 41.3 mmol) to give, after filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1) and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 98:1.8:0.2–90:9:1), prolinamine **5b** (589 mg, 2.70 mmol, 65%) as a yellowish oil.

For characterization of **5b**, see article.

4.8.2. (2*S*,5*R*)-2-(Dimethylaminomethyl)-1-methyl-5-(naphthalen-1-yl)pyrrolidine (5e)

According to GP–5, the alcohol **17b** (100 mg, 414 µmol) was mesylated and treated with $HNMe_2$•HCl (336 mg, 4.14 mmol) and NEt_3 (578 µL, 419 mg, 4.14 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 99:0.9:0.1–95:4.5:0.5) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1), prolinamine **5e** (60.1 mg, 224 µmol, 54%) as a colorless oil.

For characterization of **5e**, see 3.3.2.

4.8.3. (2*S*,5*S*)-2-(Aminomethyl)-1-methyl-5-phenylpyrrolidine (5i)

According to GP–5, the alcohol **17a** (740 mg, 3.87 mmol) was mesylated and treated with aq ammonia (25%, 29 mL, 387 mmol) and MeOH (40 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5–80:18:2), prolinamine **5i** (624 mg, 3.28 mmol, 85%) as a yellowish oil.

$[\alpha]_D^{22}$ +54.4 (*c* 0.50, MeOH); R_f = 0.35 (CH_2Cl_2–MeOH, 9:1, silica gel deactivated with NH_3).

IR (ATR): 3500–3140, 2945, 2782, 1491, 1451, 1365, 1200, 1119, 1028, 930, 911, 755, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.65 (m, 1 H, 4-*H*H), 1.78 (m, 1 H, 3-*H*H), 1.94 (m, 1 H, 3-H*H*), 2.07 (m, 1 H, 4-H*H*), 2.14 (s, 3 H, 1-CH_3), 2.35 (br s, 2 H, NH), 2.55 (m, 1 H, 2-H), 2.79 (br d, *J* = 12.9 Hz, 1 H, 2-C*H*H), 2.89 (dd, *J* = 12.9, 5.2 Hz, 1 H, 2-CH*H*), 3.31 (dd, *J* = 9.6, 6.7 Hz, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.32 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.8 (C-3), 34.5 (C-4), 39.1 (1-CH_3), 43.9 (2-CH_2), 67.2 (C-2), 72.5 (C-5), 127.1, 127.4, 128.4 (CH-Ph), 143.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{18}N_2$: 191.1543; found: 191.1542.

4.8.4. (2*S*,5*R*)-2-(Aminomethyl)-1-methyl-5-(naphthalen-1-yl)pyrrolidine (5j)

According to GP–5, the alcohol **17b** (200 mg, 829 µmol) was mesylated and treated with aq ammonia (25%, 1.2 mL, 16.0 mmol) and MeOH (3 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 99:0.9:0.1–90:9:1) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5j** (97.0 mg, 404 µmol, 49%) as a colorless oil.

$[\alpha]_D^{29}$ +137.4 (*c* 0.50, MeOH); R_f = 0.38 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 2945, 2842, 2783, 1595, 1509, 1455, 1203, 1051, 857, 798, 776 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.77 (m, 4 H, 3-*H*H, 4-*H*H, NH_2), 2.01 (m, 1 H, 3-H*H*), 2.26 (s, 3 H, 1-CH_3), 2.38 (m, 1 H, 4-H*H*), 2.65 (m, 1 H, 2-H), 2.87 (d, *J* = 12.6 Hz, 1 H, 2-C*H*H), 2.98 (dd, *J* = 12.9, 5.1 Hz, 1 H, 2-CH*H*), 4.14 (t, *J* = 8.2 Hz, 1 H, 5-H), 7.49 (m, 3 H, Ar-H), 7.75 (d, *J* = 8.1 Hz, 1 H, Ar-H), 7.80 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.88 (m, 1 H, Ar-H), 8.21 (m, 1 H, Ar-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8 (C-3), 33.0 (C-4), 39.4 (1-CH_3), 43.8 (2-CH_2), 67.5 (C-2), 68.5 (C-5), 123.39, 123.43, 125.3, 125.5, 125.9, 127.1, 128.8 (CH-Ar), 131.7, 134.0, 139.6 (C_q-Ar).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{20}N_2$: 241.1699; found: 241.1699.

4.8.5. (2*S*,5*S*)-2-(Aminomethyl)-1,5-dimethylpyrrolidine (5k)

According to GP–5, the alcohol **17c** (243 mg, 1.88 mmol) was mesylated and treated with aq ammonia (25%, 5 mL, 66.7 mmol) and MeOH (5 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5k** (58.0 mg, 452 µmol, 24%) as a yellowish oil.

$[\alpha]_D^{25}$ +5.8 (*c* 1.00, $CHCl_3$); R_f = 0.20 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

IR (ATR): 3600–3000, 2961, 2925, 2851, 1459, 1319, 1151, 985, 818, 767 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (d, *J* = 6.1 Hz, 3 H, 5-CH_3), 1.22 (m, 1 H, 4-*H*H), 1.43 (m, 1 H, 3-*H*H), 1.50 (br s, 2 H, NH_2), 1.71 (m, 2 H, 3-H*H*, 4-H*H*), 2.14 (s, 3 H, 1-CH_3), 2.16 (m, 2 H, 2-H, 5-H), 2.58 (dd, *J* = 12.7, 5.9 Hz, 1 H, 2-C*H*H), 2.65 (dd, *J* = 12.7, 3.5 Hz, 1 H, 2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (5-CH_3), 26.2 (C-3), 31.8 (C-4), 38.8 (1-CH_3), 44.4 (2-CH_2), 62.7 (C-5), 68.6 (C-2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_7H_{16}N_2$: 129.1386; found: 129.1387.

4.8.6. (2*S*,5*R*)-2-(Aminomethyl)-5-benzyl-1-methylpyrrolidine (5m)

According to GP–5, the alcohol **17e** (200 mg, 974 µmol) was mesylated and treated with aq ammonia (25%, 700 µL, 9.34 mmol) and MeOH (2 mL) to give, after column chromatography (1. silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 100:0:0–90:9:1; 2. silica gel, EtOAc–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5m** (63.1 mg, 309 µmol, 32%) as a colorless oil.

$[\alpha]_D^{29}$ +53.7 (*c* 1.00, MeOH); R_f = 0.17 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

IR (ATR): 2944, 2846, 2782, 1603, 1495, 1453, 1356, 1200, 1031, 743, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64 (m, 4 H, 3-*H*H, 4-*H*H, NH_2), 1.86 (m, 2 H, 3-H*H*, 4-H*H*), 2.53 (s, 3 H, 1-CH_3), 2.55 (m, 1 H, 2-H), 2.67 (m, 2 H, 5-H, 5-C*H*H), 2.88 (d, *J* = 3.6 Hz, 2 H, 2-CH_2), 3.16 (dd, *J* = 12.0, 2.9 Hz, 1H, 5-CH*H*), 7.35 (m, 3 H, Ph-H), 7.44 (m, 2 H, Ph-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.2 (C-3), 29.6 (C-4), 39.6 (1-CH_3), 41.0 (5-CH_2), 44.4 (2-CH_2), 68.6 (C-2), 69.0 (C-5), 126.0, 128.2, 129.4 (CH-Ph), 139.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{20}N_2$: 205.1699; found: 205.1698.

4.8.7. (2*S*,5*R*)-1-Isopropyl-2-(methylaminomethyl)-5-phenylpyrrolidine (5o)

According to GP–5, the alcohol **17g** (160 mg, 750 µmol) was mesylated and treated with aq NH_2Me (40%, 2.05 mL, 22.5 mmol), NEt_3 (105 µL, 75.9 mg, 750 µmol), and MeOH (6 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 97:2.7:0.3–90:9:1), prolinamine **5o** (134 mg, 577 µmol, 77%) as a colorless oil.

$[\alpha]_D^{24}$ +66.7 (*c* 1.00, MeOH); R_f = 0.32 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

IR (ATR): 2962, 2932, 2787, 1450, 1382, 1195, 1113, 1027, 753, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.6 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.04 (d, *J* = 6.8 Hz, 3 H, 1-CH(C*H*$_3$)$_2$), 1.67 (m, 1 H, 4-*H*H), 1.76 (m, 1 H, 3-*H*H), 1.86 (m, 1 H, 3-H*H*), 2.07 (m, 1 H, 4-H*H*), 2.54 (s, 3 H, NCH_3), 2.64 (dd, *J* = 11.5, 7.2 Hz, 1 H, 2-C*H*H), 2.69 (dd, *J* = 11.5, 4.9 Hz, 1 H, 2-CH*H*), 2.94 (sept, *J* = 6.7 Hz, 1 H, 1-C*H*(CH$_3$)$_2$), 3.27 (m, 1 H, 2-H), 3.38 (br s, 1 H, NH), 3.98 (dd, *J* = 8.7, 6.7 Hz, 1 H, 5-H), 7.19 (m, 1 H, Ph-H), 7.28 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.37 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3 (1-CH(*C*H$_3$)$_2$), 20.6 (1-CH(*C*H$_3$)$_2$), 29.9 (C-3), 35.9 (C-4), 36.7 (NCH_3), 50.2 (1-*C*H(CH$_3$)$_2$), 58.0 (C-2), 58.4 (2-CH_2), 65.1 (C-5), 126.6, 126.8, 128.2 (CH-Ph), 146.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{24}N_2$: 233.2012; found: 233.2011.

4.8.8. (2*S*,5*R*)-1-Benzyl-2-(methylaminomethyl)-5-phenylpyrrolidine (5p)

According to GP–5, the alcohol **17h** (160 mg, 598 µmol) was mesylated and treated with aq NH_2Me (40%, 1.63 mL, 17.9 mmol), NEt_3 (83.5 µL, 60.5 mg, 598 µmol), and MeOH (5 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 99:0.9:0.1–90:9:1), prolinamine **5p** (129 mg, 460 µmol, 77%) as a colorless oil.

$[\alpha]_D^{27}$ +35.4 (*c* 1.00, MeOH); R_f = 0.23 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5).

IR (ATR): 3028, 2931, 2791, 1493, 1453, 1127, 1105, 1076, 1028, 754, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.72 (m, 1 H, 4-*H*H), 1.90 (m, 2 H, 3-H_2), 2.01 (m, 1 H, 4-H*H*), 2.16 (s, 3 H, NCH_3), 2.24 (dd, *J* = 11.5, 5.6 Hz, 1 H, 2-C*H*H), 2.43 (dd, *J* = 11.5, 2.8 Hz, 1 H, 2-CH*H*), 2.98 (m, 2 H, 2-H, NH), 3.33 (d, *J* = 13.6 Hz, 1 H, 1-C*H*H), 3.64 (d, *J* = 9.9, 6.1 Hz, 1 H, 5-H), 3.83 (d, *J* = 13.5 Hz, 1 H, 1-CH*H*), 7.18 (m, 3 H, Ph-H), 7.23 (m, 3 H, Ph-H), 7.33 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.44 (d, *J* = 7.4 Hz, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.6 (C-3), 34.9 (C-4), 36.4 (NCH_3), 55.4 (2-CH_2), 57.0 (1-CH_2), 63.2 (C-2), 70.3 (C-5), 126.9, 127.1, 127.6, 128.1, 128.4, 129.1 (CH-Ph), 139.4, 144.9 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{19}H_{24}N_2$: 281.2012; found: 281.2014.

4.8.9. (2*S*,5*S*)-2-(Dimethylaminomethyl)-1,5-dimethylpyrrolidine (5q)

According to GP–5, the alcohol **17c** 242 mg, 1.87 mmol) was mesylated and treated with $HNMe_2$•HCl (1.52 g, 18.6 mmol), K_2CO_3 (2.59 g, 18.7 mmol), and CH_2Cl_2 (5 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5q** (54.0 mg, 346 µmol, 18%) as a yellowish oil.

$[\alpha]_D^{25}$–20.9 (*c* 1.00, $CHCl_3$); R_f = 0.15 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

IR (ATR): 2960, 2781, 1711, 1674, 1458, 1376, 1157, 1116, 798 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.1 Hz, 3 H, 5-CH_3), 1.35 (m, 1 H, 4-*H*H), 1.50 (m, 1 H, 3-*H*H), 1.80 (m, 1 H, 4-H*H*), 1.91 (m, 1 H, 3-H*H*), 2.21 (m, 2 H, 5-H, 2-C*H*H), 2.22 (s, 6 H, $N(CH_3)_2$), 2.29 (s, 3 H, $N(CH_3)$), 2.31 (m, 1 H, 2-H), 2.42 (dd, *J* = 11.2, 3.4 Hz, 1 H, 2-CH*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1 (5-CH_3), 28.9 (C-3), 31.8 (C-4), 39.5 (1-CH_3), 46.5 ($N(CH_3)_2$), 63.0 (C-5), 65.3 (C-2), 65.6 (2-CH_2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_9H_{20}N_2$: 157.1699; found: 157.1701.

4.8.10. (2*S*,5*R*)-2-(Dimethylaminomethyl)-5-isopropyl-1-methylpyrrolidine (5r)

According to GP–5, the alcohol **17d** (60.0 mg, 382 µmol) was mesylated and treated with $HNMe_2$•HCl (311 mg, 3.82 mmol) and K_2CO_3 (528 mg, 3.82 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5r** (16.0 mg, 86.8 µmol, 23%) as a yellowish oil.

$[\alpha]_D^{25}$ –35.6 (*c* 1.00, $CHCl_3$), R_f = 0.27 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:8:2).

IR (ATR): 2956, 2764, 1457, 1385, 1262, 1160, 1104, 1032, 847 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.79 (d, *J* = 6.8 Hz, 3 H, CH(C*H*$_3$)$_2$), 0.86 (d, *J* = 6.9 Hz, 3 H, CH(C*H*$_3$)$_2$), 1.43 (m, 2 H, 3-*H*H, 4-*H*H), 1.56 (m, 1 H, 4-H*H*), 1.77 (m, 1 H, C*H*(CH$_3$)$_2$), 1.87 (m, 1 H, 3-H*H*), 2.17 (m, 2 H, 2-H, 5-H), 2.24 (s, 6 H, N(CH$_3$)$_2$), 2.26 (s, 3 H, 1-CH$_3$), 2.39 (m, 2 H, 2-CH$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6 (CH(*C*H$_3$)$_2$), 20.4 (CH(*C*H$_3$)$_2$), 23.3 (C-4), 29.0 (*C*H(CH$_3$)$_2$), 29.5 (C-3), 40.4 (1-CH$_3$), 46.6 (N(CH$_3$)$_2$), 65.4 (2-CH$_2$), 65.5 (C-2), 72.6 (C-5).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{11}H_{24}N_2$: 185.2012; found: 185.2011.

4.8.11. (2*R*,5*S*)-2-Benzyl-5-(dimethylaminomethyl)-1-methylpyrrolidine (5s)

According to GP–5, the alcohol **17e** (200 mg, 974 µmol) was mesylated and treated with $HNMe_2$• HCl (794 mg, 9.74 mmol) and NEt_3 (1.36 mL, 986 mg, 9.74 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 100:0:0–90:9:1), prolinamine **5s** (100 mg, 430 µmol, 44%) as a colorless, highly viscous oil.

$[\alpha]_D^{29}$ +7.2 (*c* 0.50, MeOH); R_f = 0.47 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5).

IR (ATR): 2942, 2766, 1453, 1348, 1155, 1030, 850, 742, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (m, 2 H, 3-*H*H, 4-*H*H), 1.66 (m, 1 H, 3-H*H*), 1.88 (m, 1 H, 4-H*H*), 2.26 (m, 1 H, 5-C*H*H), 2.27 (s, 6 H, N(CH$_3$)$_2$), 2.46 (s, 3 H, 1-CH$_3$), 2.47 (m, 4 H, 2-H, 5-H, 2-C*H*H, 5-CH*H*), 3.08 (dd, *J* = 17.6, 8.6 Hz, 1 H, 2-CH*H*), 7.20 (m, 3 H, Ph-H), 7.28 (m, 2 H, Ph-H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.6 (C-4), 29.5 (C-3), 40.0 (1-CH$_3$), 41.0 (2-CH$_2$), 46.4 (N(CH$_3$)$_2$), 65.2 (C-5), 65.4 (5-CH$_2$), 69.4 (C-2), 126.0, 128.2, 129.2 (CH-Ph), 140.0 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{24}N_2$: 233.2012; found: 233.2013.

4.8.12. (2*S*,5*R*)-2-(Diethylaminomethyl)-1-methyl-5-phenylpyrrolidine (5t)

According to GP–5, the alcohol **17a** (100 mg, 523 µmol) was mesylated and treated with $HNEt_2$ (1.08 mL, 764 mg, 10.5 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–

MeOH, 9:1), prolinamine **5t** (51.0 mg, 207 µmol, 40%) as a brownish oil.

$[\alpha]_D^{22}$ +1.8 (*c* 1.00, MeOH); R_f = 0.18 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 2966, 2791, 1452, 1383, 1291, 1201, 1067, 1039, 754, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.1 Hz, 6 H, $N(CH_2CH_3)_2$), 1.70 (m, 2 H, 3-*H*H, 4-*H*H), 2.04 (m, 2 H, 3-H*H*, 4-H*H*), 2.19 (s, 3 H, 1-CH_3), 2.44 (dd, *J* = 12.4, 8.3 Hz, 1 H, 2-C*H*H), 2.59 (m, 6 H, 2-H, 2-CH*H*, $N(CH_2CH_3)_2$), 3.24 (m, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.33 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0 ($N(CH_2CH_3)_2$), 29.7 (C-3), 34.1 (C-4), 39.8 (1-CH_3), 48.2 ($N(CH_2CH_3)_2$), 58.6 (2-CH_2), 65.3 (C-2), 72.8 (C-5), 127.0, 127.5, 128.4 (CH-Ph), 144.1 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{16}H_{26}N_2$: 247.2169; found: 247.2168.

4.8.13. (2*R*,5*S*)-1-Methyl-2-phenyl-5-(pyrrolidin-1-ylmethyl)pyrrolidine (5u)

According to GP–5, the alcohol **17a** (180 mg, 941 µmol) was mesylated and treated with pyrrolidine (1.57 mL, 1.34 g, 18.8 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1), prolinamine **5u** (119 mg, 487 µmol, 52%) as a slightly brownish oil.

For characterization of **5u**, see article.

4.8.14. (2*R*,5*S*)-1-Methyl-2-phenyl-5-(piperidin-1-ylmethyl)pyrrolidine (5v)

According to GP–5, the alcohol **17a** (180 mg, 941 µmol) was mesylated and treated with piperidine (1.86 mL, 1.60 g, 18.8 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 1:0–9:1) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1), prolinamine **5v** (123 mg, 476 µmol, 51%) as a slightly yellowish oil.

$[\alpha]_D^{22}$ +12.7 (*c* 1.00, MeOH); R_f = 0.28 (CH_2Cl_2–MeOH, 9:1).

IR (ATR): 2932, 2772, 1452, 1154, 1119, 1057, 1038, 991, 836, 754, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (m, 2 H, 3'-H_2), 1.60 (m, 4 H, 2× 2'-H_2), 1.71 (m, 2 H, 3-*H*H, 4-*H*H), 2.05 (m, 2 H, 3-H*H*, 4-H*H*), 2.21 (s, 3 H, 1-CH_3), 2.36 (dd, *J* = 13.3, 8.6 Hz, 1 H, 5-C*H*H), 2.46 (m, 4 H, 2× 1'-H_2), 2.60 (m, 2 H, 5-H, 5-CH*H*), 3.23 (m, 1 H, 2-H), 7.23 (m, 1 H, Ph-H), 7.33 (m, 4 H, Ph-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6 (C-3'), 26.2 (C-2'), 30.0 (C-4), 34.1 (C-3), 39.8 (1-CH_3), 55.6 (C-1'), 64.2 (C-5), 65.1 (5-CH_2), 72.7 (C-2), 127.0, 127.5, 128.4 (CH-Ph), 144.1 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{17}H_{26}N_2$: 259.2169; found: 259.2168.

4.8.15. (2*S*,5*R*)-2-(Benzyl(methyl)aminomethyl)-1-methyl-5-phenylpyrrolidine (5w)

According to GP–5, the alcohol **17a** (100 mg, 523 µmol) was mesylated and treated with HNMeBn (1.35 mL, 1.27 g, 10.5 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5–90:10) and filtration over a pad of basic alumina (activity I, CH_2Cl_2–MeOH, 9:1), prolinamine **5w** (113 mg, 384 µmol, 73%) as a colorless oil.

$[\alpha]_D^{22}$ –3.3 (*c* 0.50, MeOH); R_f = 0.51 (petroleum ether–EtOAc, 3:1).

IR (ATR): 2945, 2837, 2778, 1493, 1452, 1072, 1026, 755, 737, 697 cm^{-1}.

^{1}H NMR: (400 MHz, $CDCl_3$): δ = 1.69 (m, 1 H, 4-*H*H), 1.78 (m, 1 H, 3-*H*H), 2.07 (m, 2 H, 3-H*H*, 4-H*H*), 2.23 (s, 3 H, 1-CH_3), 2.30 (s, 3 H, NCH_3), 2.50 (dd, *J* = 13.3, 8.9 Hz, 1 H, 2-C*H*H), 2.65 (m, 2 H, 2-H, 2-CH*H*), 3.27 (dd, *J* = 9.3, 6.5 Hz, 1 H, 5-H), 3.57 (d, *J* = 13.2 Hz, 1 H, NC*H*HPh), 3.63 (d, *J* = 13.2 Hz, 1 H, NCH*H*Ph), 7.23−7.41 (m, 10 H, Ph-H).

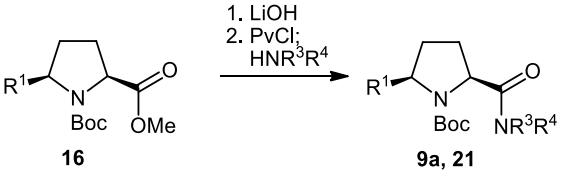
^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3 (C-3,) 34.1 (C-4), 39.8 (1-CH_3), 43.4 (NCH_3), 62.8 (2-CH_2), 63.4 (N*C*H_2Ph), 64.9 (C-2), 72.9 (C-5), 126.96, 127.00, 127.5, 128.3, 128.4, 129.1 (CH-Ph), 139.6, 144.0 (C_q-Ph).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{20}H_{26}N_2$: 295.2169; found: 295.2171.

5. Synthesis of Diamines 5 According to Route III

The preparation of compounds **21d** and **5u** is described in the article. For the reduction of **9a** to **5b**, see Route I.

5.1. Amides 9a and 21



Cmpd	R^1	NR^3R^4
9a	Ph	NMe_2
21a	Ph	NHMe
21b	*i* Pr	NHMe
21c	Me	NMe_2
21e	Ph	NMeBn

5.1.1. (2*S*,5*R*)-*tert*-Butyl 2-dimethylcarbamoyl-5-phenylpyrrolidine-1-carboxylate (9a)

According to GP–6, the ester **16a** (1.36 g, 4.46 mmol) was saponified, activated with PvCl, and treated with $HNMe_2$•HCl to give, after column chromatography (silica gel, petroleum ether–EtOAc, 3:1–0:1), pyrrolidine amide **9a** (1.30 g, 4.09 mmol, 92 %) as a slightly yellowish oil.

For characterization of **9a**, see article.

5.1.2. (2*S*,5*R*)-*tert*-Butyl 2-(methylcarbamoyl)-5-phenylpyrrolidine-1-carboxylate (21a)

According to GP–6, the ester **16a** (1.36 g, 4.46 mmol) was saponified, activated with PvCl in THF (45 mL), and treated with aq H_2NMe (40%) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 99:0.9:0.1–96:3.6:0.4), pyrrolidine amide **21a** (1.17 g, 3.84 mmol, 86%) as a colorless solid.

Mp 136–138 °C; $[\alpha]_D^{26}$ +24.5 (*c* 1.00, MeOH); R_f = 0.41 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5).

IR (ATR): 3358, 2982, 1670, 1552, 1397, 1365, 1150, 1120, 766, 741, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$):* δ = 1.15 (br s, 9 H, $C(CH_3)_3$), 1.93 (m, 2 H, 3-*H*H, 4-*H*H), 2.27 (m, 1 H, 4-H*H*), 2.51 (br s, 1 H, 3-H*H*), 2.88 (m, 3 H, NCH_3), 4.42 (br s, 1 H, 2-H), 4.63 (br s, 1 H, 5-H), 7.24 (m, 5 H, Ph-H). * Broad signals due to rotamers close to the coalescence temperature.

^{13}C NMR (125 MHz, $CDCl_3$): * δ = 26.4 (NCH_3), 27.1 (br, C-3), 28.1 ($C(CH_3)_3$), 36.1 (br, C-4), 61.5 (br, C-2), 63.8 (br, C-5), 80.8 ($C(CH_3)_3$), 126.3, 126.9, 128.4 (CH-Ph), 144.0 (br, C_q-Ph), 156.3 (br, 1-CO_2), 172.9 (2-CON). * Broad signals due to rotamers close to the coalescence temperature.

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{17}H_{24}N_2O_3$: 305.1860; found: 305.1860.

5.1.3. (2*R*,5*S*)-*tert*-Butyl 2-isopropyl-5-(methylcarbamoyl)pyrrolidine-1-carboxylate (21b)

According to GP–6, the ester **16d** (819 mg, 3.02 mmol) was saponified, activated with PvCl, and treated with aq H_2NMe (40%; MeOH (4 mL) was added as a cosolvent) to give, after column chromatography (silica gel, petroleum ether–EtOAc, 2:1–1:1), pyrrolidine amide **21b** (670 mg, 2.48 mmol, 82%) as a colorless oil.

$[\alpha]_D^{31}$ –38.0 (*c* 1.00, MeOH); R_f = 0.39 (petroleum ether–EtOAc, 1:1).

IR (ATR): 3420–3220, 2962, 1667, 1549, 1384, 1366, 1253, 1166, 1119, 931 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$):* δ = 0.77 (br d, *J* = 3.7 Hz, 3 H, $CH(CH_3)_2$), 0.87 (br d, *J* = 5.4 Hz, 3 H, $CH(CH_3)_2$), 1.45 (s, 9.0 H, $C(CH_3)_3$), 1.77 (q, *J* = 7.0 Hz, 2 H, 3-H_2), 1.89 (br s, 1 H, 4-*H*H), 1.98 (sept, *J* = 6.9 Hz, 1 H, $CH(CH_3)_2$), 2.32 (br s, 1 H, 4-H*H*), 2.79 (d, *J* = 4.9 Hz, 3 H, NCH_3), 3.67 (br d, *J* = 5.4 Hz, 1 H, 2-H), 4.27 (br s, 1 H, 5-H), 6.91 (br s, 1 H, NH). * Broad signals due to rotamers close to the coalescence temperature.

^{13}C NMR (125 MHz, $CDCl_3$):* δ = 17.2 (br, $CH(CH_3)_2$), 20.0 ($CH(CH_3)_2$), 25.7 (br, C-4, NCH_3), 26.2 (C-3), 28.5 ($C(CH_3)_3$), 30.3 (br, $CH(CH_3)_2$), 61.1 (br, C-5), 64.7 (br, C-2), 80.6 ($C(CH_3)_3$), 156.5 (br, 1-CO_2), 173.1 (5-CON). * Broad signals due to rotamers close to the coalescence temperature.

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{14}H_{26}N_2O_3$: 271.2016; found: 271.2016.

5.1.4. (2*S*,5*S*)-*tert*-Butyl 2-(dimethylcarbamoyl)-5-methylpyrrolidine-1-carboxylate (21c)

According to GP–6, a 9:1 mixture of the pyrrolidine ester **16c** and its C5-epimer (854 mg, 3.51 mmol) was saponified, activated with PvCl, and treated with $HNMe_2$•HCl to give, after column chromatography (silica gel, petroleum ether–Et_2O, 2:1–0:1), the known[11] pyrrolidine amide **21c** (792 mg, 3.09 mmol, 88%) as a colorless oil.

$[\alpha]_D^{29}$ –14.3 (*c* 1.00, MeOH); R_f = 0.24 (Et_2O).

IR (ATR): 2975, 2934, 1694, 1659, 1456, 1392, 1366, 1257, 1174, 1123, 1084 cm^{-1}.

^1H NMR: (500 MHz, $CDCl_3$):* δ = 1.34 (d, *J* = 6.2 Hz, 1.65 H, 5-CH_3), 1.35 (d, *J* = 6.4 Hz, 1.35 H, 5-CH_3), 1.39 (s, 4.0 H, $C(CH_3)_3$), 1.45 (s, 5.0 H, $C(CH_3)_3$), 1.70 (m, 1 H, 4-*H*H), 1.97 (m, 3 H, 3-H_2, 4-H*H*), 2.97 (s, 1.65 H, $N(CH_3)_2$), 2.98 (s, 1.35 H, $N(CH_3)_2$), 3.06 (s, 1.35 H, $N(CH_3)_2$), 3.10 (s, 1.65 H, $N(CH_3)_2$), 3.91 (m, 0.55 H, 5-H), 4.04 (m, 0.45 H, 5-H), 4.55 (t, *J* = 7.5 Hz, 0.45 H, 2-H), 4.69 (dd, *J* = 8.1, 5.5 Hz, 0.55 H, 2-H). * 55:45 mixture of rotamers.

^{13}C NMR (125 MHz, $CDCl_3$):* δ = 19.7, 20.6 (5-CH_3), 28.2 (C-3), 28.5 ($C(CH_3)_3$), 28.7 (C-3, $C(CH_3)_3$), 31.9, 32.6 (C-4), 36.1, 36.2, 37.1, 37.2 ($N(CH_3)_2$), 54.2, 54.4 (C-5), 57.5, 57.7 (C-2), 79.4, 79.5 ($C(CH_3)_3$), 153.5, 154.5 (1-CO_2), 172.6, 173.0 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{13}H_{24}N_2O_3$: 257.1860; found: 257.1864.

5.1.5. (2*S*,5*R*)-*tert*-Butyl 2-(benzyl(methyl)carbamoyl)-5-phenylpyrrolidine-1-carboxylate (21e)

According to GP–6, the ester **16a** (160 mg, 524 µmol) was saponified, activated with PvCl, and treated with HNMeBn to give, after column chromatography (silica gel, petroleum ether–EtOAc, 9:1–2:1), pyrrolidine amide **21e** (196 mg, 498 µmol, 95%) as a colorless oil.

$[\alpha]_D^{30}$ +25.3 (*c* 1.00, MeOH); R_f = 0.33 (petroleum ether–EtOAc, 1:1).

IR (ATR): 2973, 2934, 1691, 1659, 1454, 1391, 1365, 1157, 1125, 701 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ =* 1.12 (s, 6.4 H, $C(CH_3)_3$), 1.37 (s, 1.6 H, $C(CH_3)_3$), 1.43 (s, 1.0 H, $C(CH_3)_3$), 1.98 (m, 1.7 H, 3-H_2), 2.19 (m, 1.6 H, 3-H*H*, 4-H_2), 2.32 (m, 0.7 H, 4-H*H*), 3.02 (s, 0.6 H, NCH_3), 3.05 (s, 2.4 H, NCH_3), 4.63 (m, 2.6 H, 2-H, 5-H, NC*H*HPh), 4.92 (m, 1.4 H, 2-H, 5-H, NCH*H*Ph), 7.21 (m, 1 H, Ph-H), 7.30 (m, 6 H, Ph-H), 7.38 (m, 1 H, Ph-H), 7.75 (m, 2 H, Ph-H). * 70:20:10 mixture of rotamers.

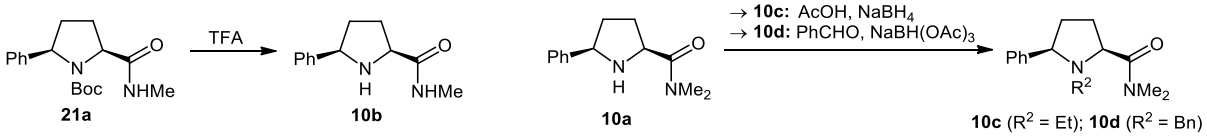
^{13}C NMR (125 MHz, $CDCl_3$):* δ = 28.1, 28.2, 28.4, 28.6 ($C(CH_3)_3$), 28.9, 29.1, 29.5, 29.7 (C-3), 34.57 (C-4), 34.64, 34.8 (NCH_3), 34.9 (C-4), 35.0 (NCH_3), 35.8, 35.9 (C-4), 51.4, 51.5, 53.4 (NCH_2Ph), 57.7, 58.0, 58.18, 58.24 (C-2), 62.6, 62.9, 63.5, 63.6 (C-5), 79.8, 79.9, 80.1, 80.4 ($C(CH_3)_3$), 126.4, 126.55, 126.57, 126.61, 126.66, 126.73, 126.9, 127.0, 127.3, 127.6, 127.7, 127.8, 128.0, 128.12, 128.14, 128.3, 128.39, 128.42, 128.8, 129.0, 129.1 (CH-Ph),

(11) Amide **21d** is a known, but only partially characterized (^1H NMR, MS) compound: Miyazaki, M.; Naito, H.; Sugimoto, Y.; Yoshida, K.; Kawato, H.; Okayama, T.; Shimizu, H.; Miyazaki, M.; Kitagawa, M.; Seki, T.; Fukutake, S.; Shiose, Y.; Aonuma, M.; Soga, T. *Bioorg. Med. Chem.* **2013**, *21*, 4319.

136.8, 137.1, 137.3, 143.5, 143.7, 144.5, 144.7 (C_q-Ph), 154.0, 154.75, 154.77 (1-CO_2), 172.9, 173.1, 173.5 (2-CON). * Mixture of rotamers.

HRMS–ESI: *m/z* $[M + 2\ H - Boc]^+$ calcd for $C_{24}H_{30}N_2O_3$: 295.1805; found: 295.1807.

5.2. Amides 10b–d



5.2.1. (2*S*,5*R*)-*N*-Methyl-5-phenylpyrrolidine-2-carboxamide (10b)

A solution of the amide **21a** (660 mg, 2.17 mmol) in anhydrous CH_2Cl_2 (20 mL) was treated at r.t. with TFA (3.34 mL, 4.94 g, 43.4 mmol) and stirred overnight. The solvent was removed under reduced pressure and the residue was diluted five times with CH_2Cl_2 (20 mL) and evaporated again, in order to remove excess TFA. Filtration through a pad of basic alumina (activity I, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1) afforded the *N*-deprotected amide **10b** (432 mg, 2.11 mmol, 97%) as a colorless oil.

$[\alpha]_D^{28}$ –31.0 (*c* 1.00, MeOH); R_f = 0.27 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5).

IR (ATR): 3390–3220, 2944, 1651, 1527, 1493, 1408, 1276, 1246, 1105, 756, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.62 (m, 1 H, 4-*H*H), 2.14 (m, 2 H, 3-*H*H, 4-H*H*), 2.30 (m, 1 H, 3-H*H*), 2.46 (br s, 1 H, NH), 2.87 (d, *J* = 5.1 Hz, 3 H, NCH_3), 3.90 (dd, *J* = 10.1, 3.6 Hz, 1 H, 2-H), 4.33 (dd, *J* = 10.2, 5.8 Hz, 1 H, 5-H), 7.27 (m, 1 H, Ph-H), 7.36 (m, 4 H, Ph-H), 7.70 (br s, 1 H, NH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.0 (NCH_3), 31.1 (C-3), 33.8 (C-4), 60.1 (C-2), 63.1 (C-5), 126.6, 127.3, 128.6 (CH-Ph), 143.9 (C_q-Ph), 176.1 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{16}N_2O$: 205.1335; found: 205.1334.

5.2.2. (2*S*,5*R*)-1-Ethyl-*N*,*N*-dimethyl-5-phenylpyrrolidine-2-carboxamide (10c)

$NaBH_4$ (81.5 mg, 2.15 mmol) was portionwise added at 0 °C to a solution of the amide **10a** (100 mg, 458 µmol) in AcOH (0.8 mL). After the gas evolution had ceased, the solution was heated to 60 °C for 2 h. CH_2Cl_2 (10 mL) and sat. aq $NaHCO_3$ (10 mL) were slowly added and the reaction mixture was made basic with solid Na_2CO_3. The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 98:1.8:0.2–90:9:1) afforded the amide **10c** (105 mg, 426 µmol, 93%) as a colorless oil.

$[\alpha]_D^{29}$ +41.4 (*c* 1.00, MeOH); R_f = 0.40 (CH_2Cl_2–MeOH, 19:1).

IR (ATR): 2965, 2932, 1654, 1636, 1492, 1454, 1397, 1136, 1062, 761, 703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.2 Hz, 3 H, 1-CH_2CH_3), 1.83 (m, 1 H, 4-*H*H), 1.91 (m, 1 H, 3-*H*H), 2.16 (m, 2 H, 3-H*H*, 4-H*H*), 2.39 (dq, *J* = 13.1, 7.1 Hz, 1 H, 1-C*H*H), 2.64 (dq, *J* = 13.0, 7.4 Hz, 1 H, 1-CH*H*), 2.99 (s, 3 H, NCH_3), 3.31 (s, 3 H, NCH_3), 3.56 (dd, *J* = 9.2, 6.4 Hz, 1 H, 5-H), 3.60 (dd, *J* = 9.0, 6.8 Hz, 1 H, 2-H), 7.24 (t, *J* = 7.3 Hz, 1 H, Ph-H), 7.32 (t, *J* = 7.5 Hz, 2 H, Ph-H), 7.46 (d, *J* = 7.5 Hz, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.3 (1-CH_2CH_3), 28.1 (C-3), 35.1 (C-4), 36.6 (NCH_3), 37.1 (NCH_3), 47.2 (1-CH_2), 66.7 (C-2), 69.5(C-5), 127.1, 127.6, 128.5 (CH-Ph), 144.0 (C_q-Ph), 174.4 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{15}H_{22}N_2O$: 247.1805; found: 247.1805.

5.2.3. (2*S*,5*R*)-1-Benzyl-*N*,*N*-dimethyl-5-phenylpyrrolidine-2-carboxamide (10d)

According to GP–4, the amide **10a** (100 mg, 458 µmol) was *N*-benzylated with benzaldehyde–$NaBH(OAc)_3$ to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 100:0:0–95:4.5:0.5), pyrrolidine amide **10d** (134 mg, 434 µmol, 95%) as a colorless oil.

$[\alpha]_D^{32}$ +27.6 (*c* 1.00, MeOH); R_f = 0.35 (EtOAc).

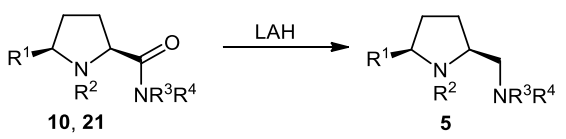
IR (ATR): 3027, 2937, 2798, 1634, 1491, 1452, 1395, 1116, 747, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.88 (m, 1 H, 3-*H*H), 1.95 (m, 1 H, 4-*H*H), 2.11 (m, 2 H, 3-H*H*, 4-H*H*), 2.68 (s, 3 H, NCH_3), 2.91 (s, 3 H, NCH_3), 3.41 (d, *J* = 13.7 Hz, 1 H, 1-C*H*H), 3.61 (m, 2 H, 2-H, 5-H), 3.86 (d, *J* = 13.7 Hz, 1 H, 1-CH*H*), 7.18 (m, 3 H, Ph-H), 7.26 (m, 3 H, Ph-H), 7.37 (t, *J* = 7.6 Hz, 2 H, Ph-H), 7.58 (m, 2 H, Ph-H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.0 (C-3), 35.0 (C-4), 36.1 (NCH_3), 36.7 (NCH_3), 56.4 (1-CH_2), 65.0 (C-2), 69.1 (C-5), 127.1, 127.3, 127.8, 127.9, 128.6, 129.7 (CH-Ph), 137.3, 143.3 (C_q-Ph), 173.7 (2-CON).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{20}H_{24}N_2O$: 309.1961; found: 309.1967.

5.3. Diamines 5



10, **21** **5**

5	R^1	R^2	NR^3R^4
a	Ph	Me	NHMe
g	Ph	Et	NMe_2
h	Ph	Bn	NMe_2
q	Me	Me	NMe_2

5	R^1	R^2	NR^3R^4
w	Ph	Me	NMeBn
x	*i*Pr	Me	NHMe
y	Ph	H	NHMe

5.3.1. (2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine (5a)

According to GP–3, the amide **21a** (100 mg, 372 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 95:4.5:0.5–85:13.5:1.5), prolinamine **5a** (54.6 mg, 267 µmol, 82%) as a yellowish oil.

For characterization of **5a**, see ref. 3.

5.3.2. (2*S*,5*R*)-2-Dimethylaminomethyl-1-ethyl-5-phenylpyrrolidine (5g)

According to GP–3, the amide **10c** (50.0 mg, 203 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5), prolinamine **5g** (44.8 mg, 193 µmol, 95%) as a colorless oil.

For characterization of **5g**, see 3.5.

5.3.3. (2*S*,5*R*)-1-Benzyl-2-dimethylaminomethyl-5-phenylpyrrolidine (5h)

According to GP–3, the amide **10d** (172 mg, 557 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1), prolinamine **5h** (146 mg, 495 µmol, 89%) as a colorless oil.

For characterization of **5h**, see article.

5.3.4. (2*S*,5*S*)-2-(Dimethylaminomethyl)-1,5-dimethylpyrrolidine (5q)

According to GP–3, the amide **21c** (250 mg, 975 µmol) was reduced to give, after column chromatography (basic alumina, activity I, CH_2Cl_2–MeOH, 100:0–98:2), prolinamine **5q** (150 mg, 962 µmol, 98%) as a yellowish oil.

For characterization of **5q**, see 4.8.9.

5.3.5. (2*S*,5*R*)-2-Benzyl(methyl)aminomethyl-1-methyl-5-phenylpyrrolidine (5w)

According to GP–3, the amide **21e** (100 mg, 253 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 190:9:1), prolinamine **5w** (62.3 mg, 212 µmol, 84%) as a colorless oil.

For characterization of **5w**, see 4.8.15.

5.3.6. (2*R*,5*S*)-2-Isopropyl-1-methyl-5-(methylaminomethyl)pyrrolidine (5x)

According to GP–3, the amide **21b** (93.0 mg, 344 µmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 93:6.3:0.7), prolinamine **5x** (43.3 mg, 254 µmol, 74%) as a yellowish oil.

$[\alpha]_D^{20}$ +0.7 (*c* 0.50, MeOH); R_f = 0.23 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

IR (ATR): 2958, 2780, 1651, 1593, 1466, 1366, 1293, 1041 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 6.8 Hz, 3 H, $CH(CH_3)_2$), 0.87 (d, *J* = 6.9 Hz, 3 H, $CH(CH_3)_2$), 1.47 (m, 1 H, 3-*H*H), 1.58 (m, 2 H, 3-H*H*, 4-*H*H), 1.79 (m, 2 H, 4-H*H*, $CH(CH_3)_2$), 2.16 (br s, 1 H, NH), 2.23 (m, 1 H, 2-H), 2.24 (s, 3 H, 1-CH_3), 2.47 (s, 3 H, $NHCH_3$), 2.49 (m, 1 H, 5-H), 2.56 (dd, *J* = 11.3, 5.6 Hz, 1 H, 5-C*H*H), 2.65 (dd, *J* = 11.4, 3.8 Hz, 1 H, 5-CH*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.6 ($CH(CH_3)_2$), 20.4 ($CH(CH_3)_2$), 23.6 (C-3), 27.7 (C-4), 29.1 ($CH(CH_3)_2$), 37.1 ($NHCH_3$), 40.2 (1-CH_3), 55.0 (5-CH_2), 66.3 (C-5), 72.4 (C-2).

HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{10}H_{22}N_2$: 171.1856; found: 171.1855.

5.3.7. (2*S*,5*R*)-2-Methylaminomethyl-5-phenylpyrrolidine (5y)

According to GP–3, the amide **10b** (250 mg, 1.22 mmol) was reduced to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1–85:13.5:1.5), prolinamine **5y** (144 mg, 757 µmol, 62%) as a colorless oil.

$[\alpha]_D^{29}$ +41.2 (*c* 1.00, MeOH); R_f = 0.16 (CH_2Cl_2–MeOH–NH_3 (aq, 25%), 90:9:1).

IR (ATR): 3600–3050, 2934, 1555, 1491, 1451, 1374, 1350, 1065, 1028, 813, 756, 700 cm^{-1}.

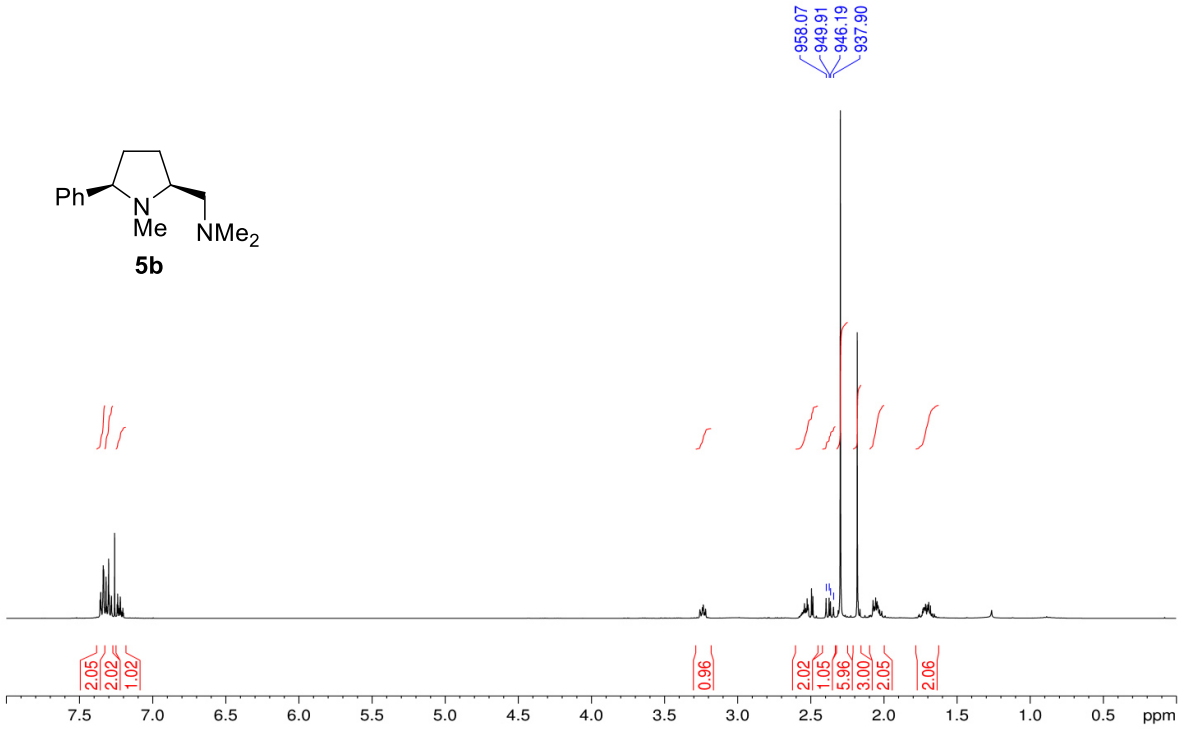
^1H NMR (500 MHz, $CDCl_3$): δ = 1.61 (m, 1 H, 3-*H*H), 1.68 (m, 1 H, 4-*H*H), 1.97 (m, 1 H, 3-H*H*), 2.03 (br s, 2 H, NH), 2.14 (m, 1 H, 4-H*H*), 2.48 (s, 3 H, NCH_3), 2.62 (dd, *J* = 11.4, 7.7 Hz, 1 H, 2-C*H*H), 2.67 (dd, *J* = 11.4, 4.8 Hz, 1 H, 2-CH*H*), 3.43 (m, 1 H, 2-H), 4.21 (dd, *J* = 8.8, 7.0 Hz, 1 H, 5-H), 7.22 (m, 1 H, Ph-H), 7.31 (m, 2 H, Ph-H), 7.38 (m, 2 H, Ph-H).

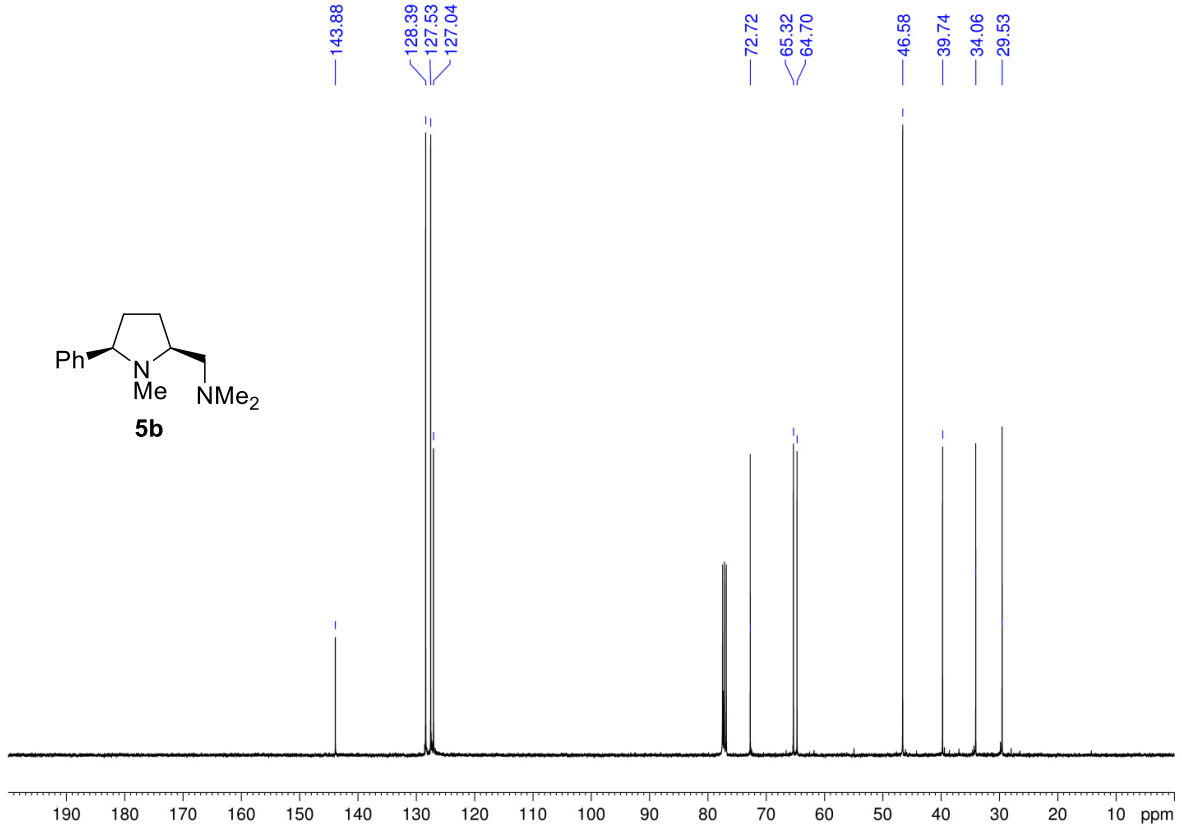
^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.7 (C-3), 34.3 (C-4), 36.9 (NCH_3), 57.9 (C-2), 58.3 (2-CH_2), 62.8 (C-5), 126.7, 126.9, 128.4 (CH-Ph), 145.0 (C_q-Ph).

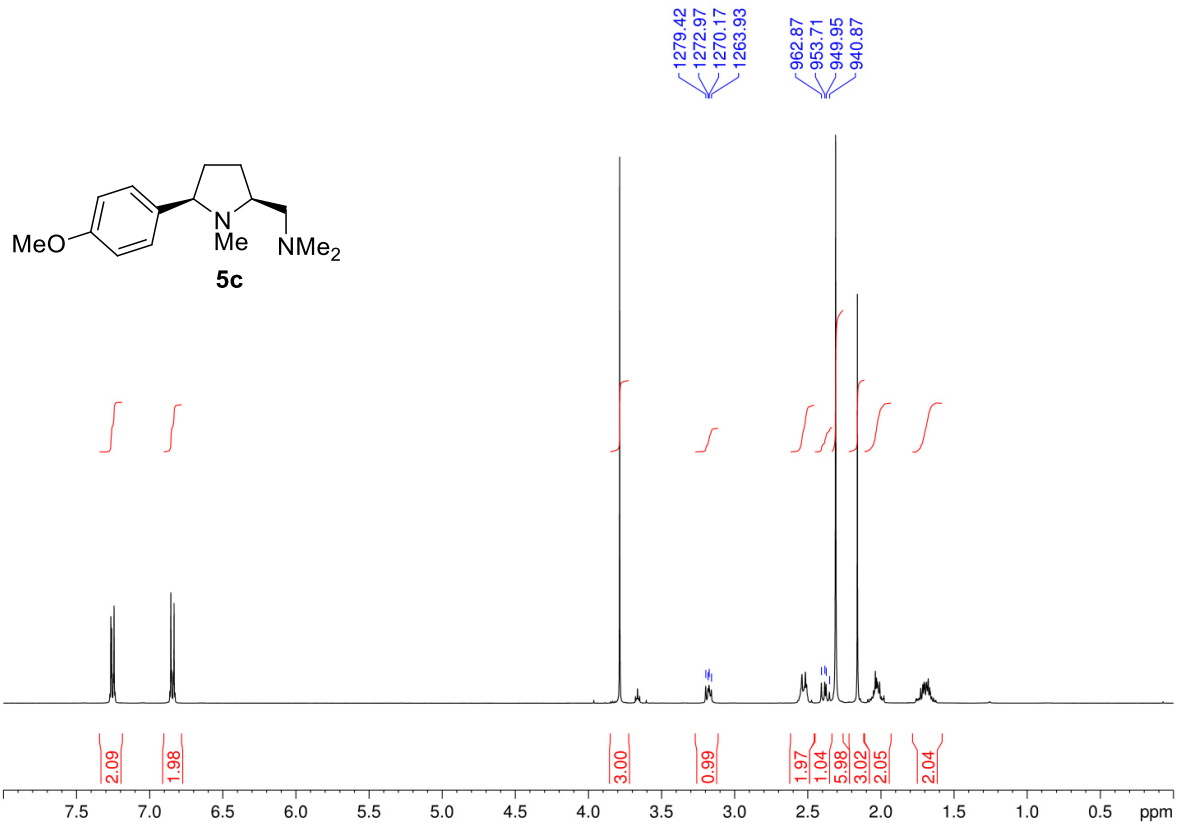
HRMS–ESI: *m/z* $[M + H]^+$ calcd for $C_{12}H_{18}N_2$: 191.1543; found: 191.1537.

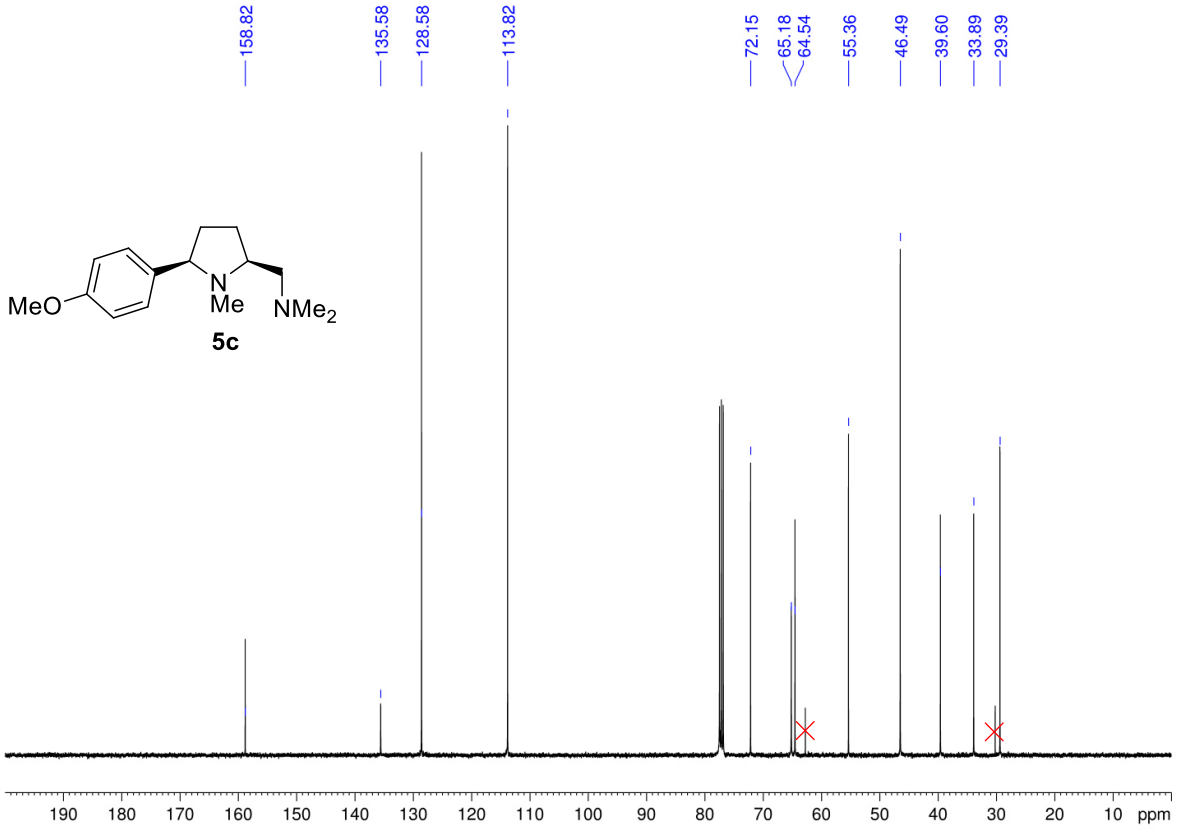
6. Copies of ^{1}H and ^{13}C NMR Spectra

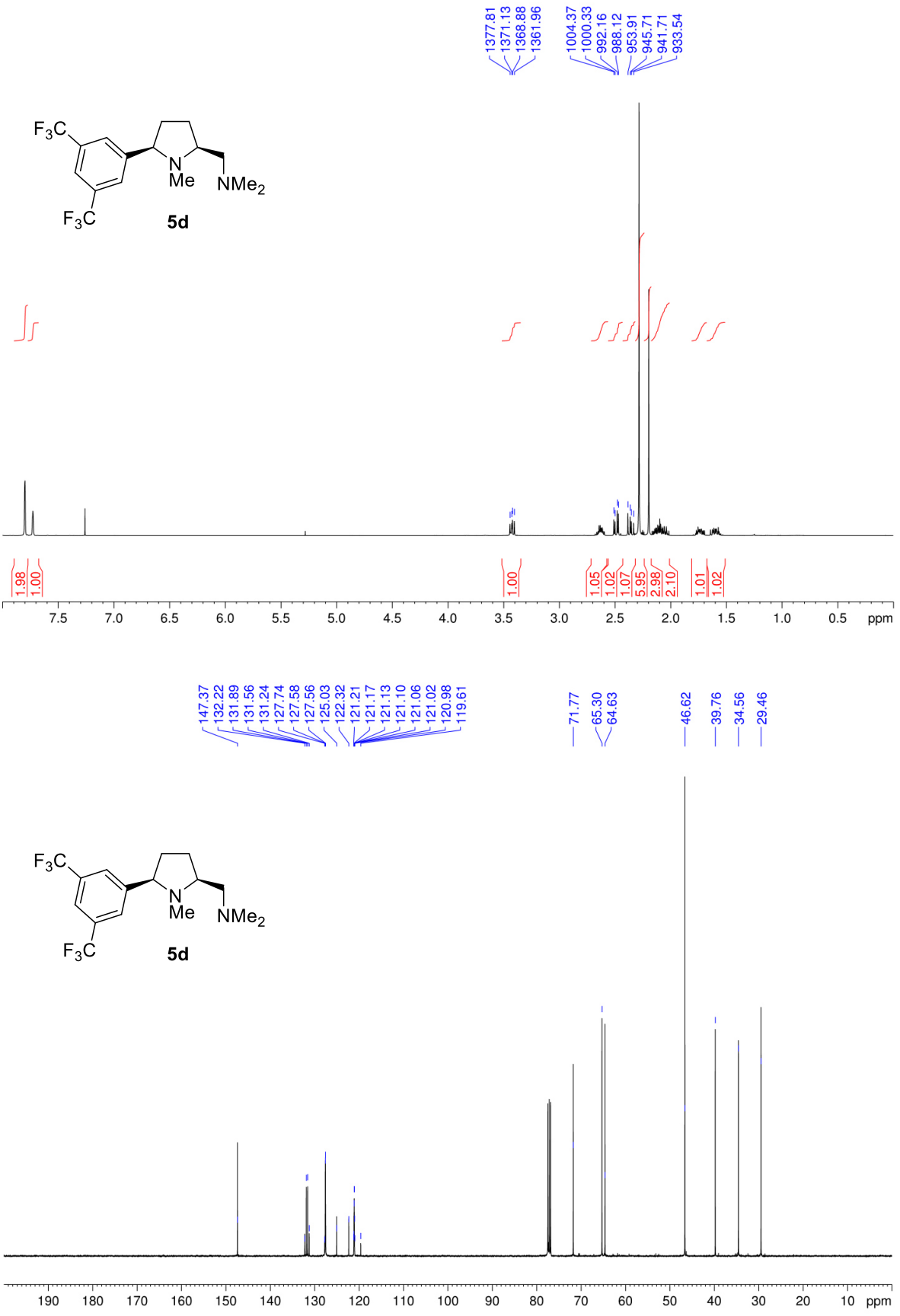
The ^{1}H and ^{13}C NMR spectra of all new compounds are listed in numerical order.

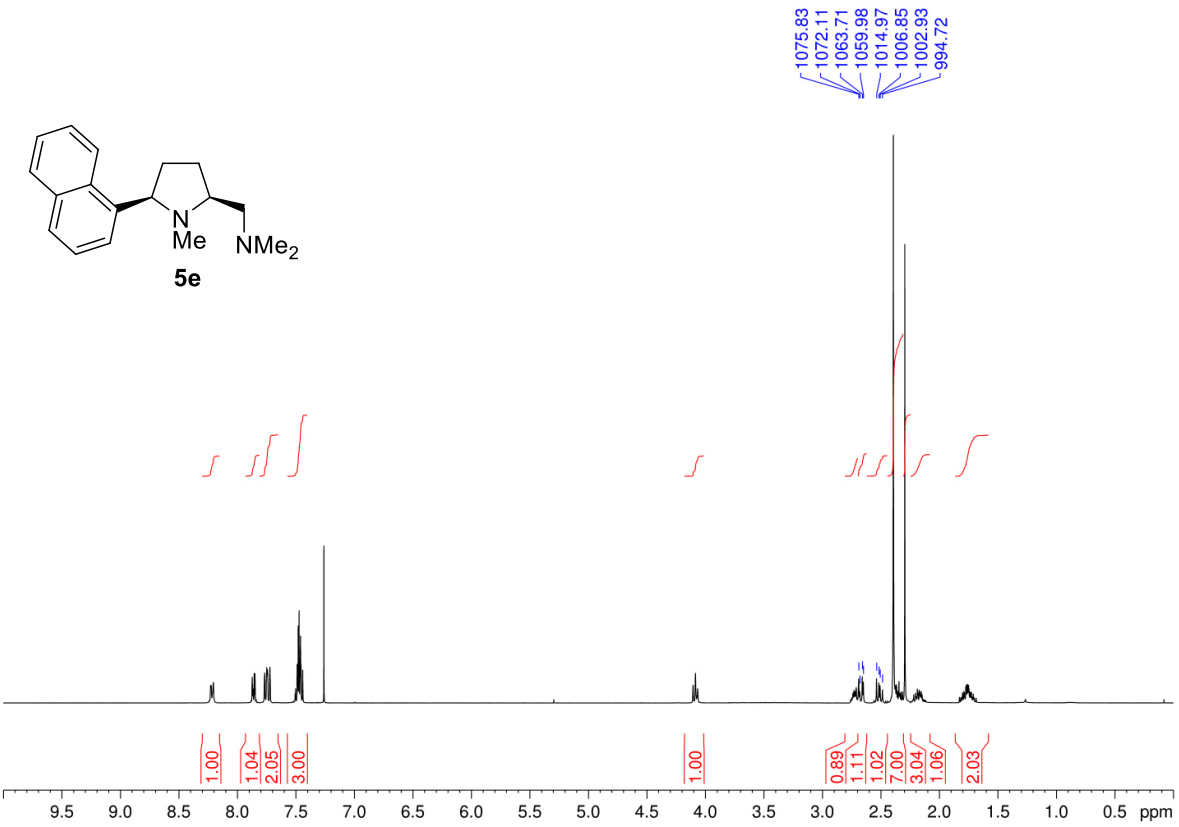


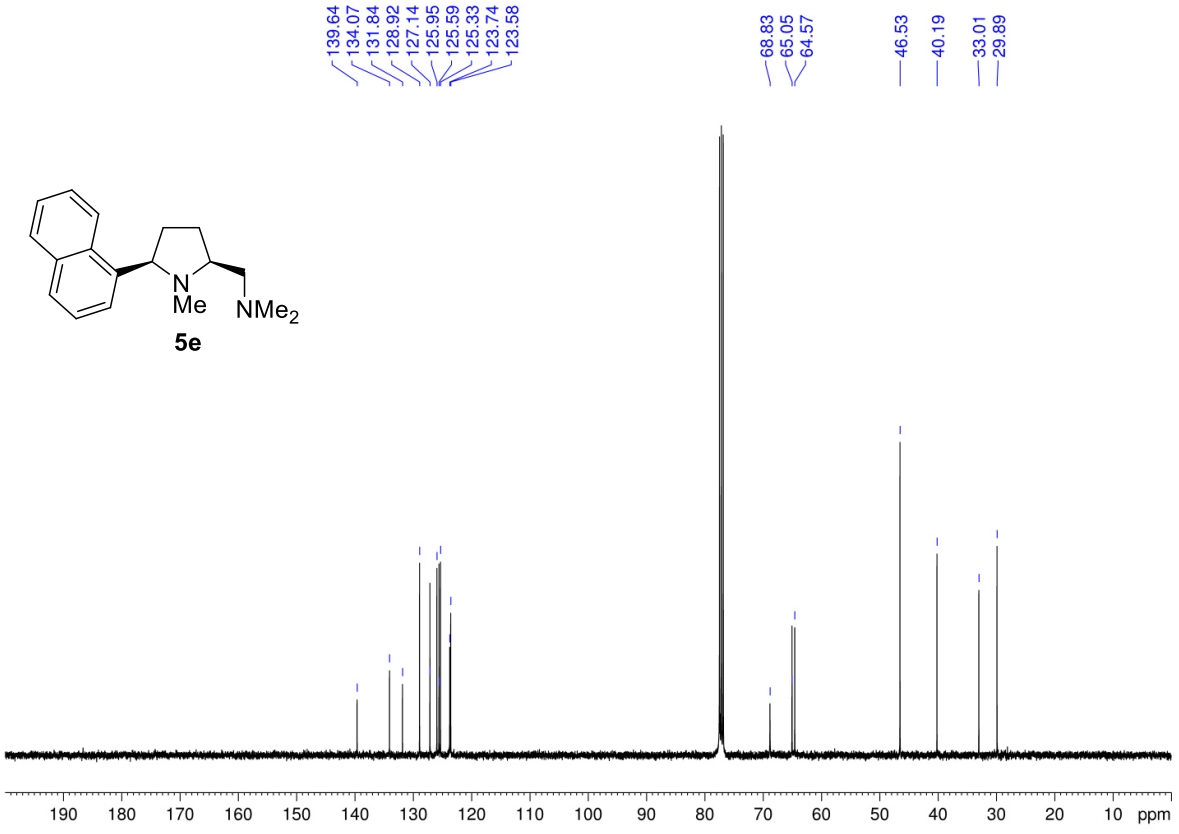


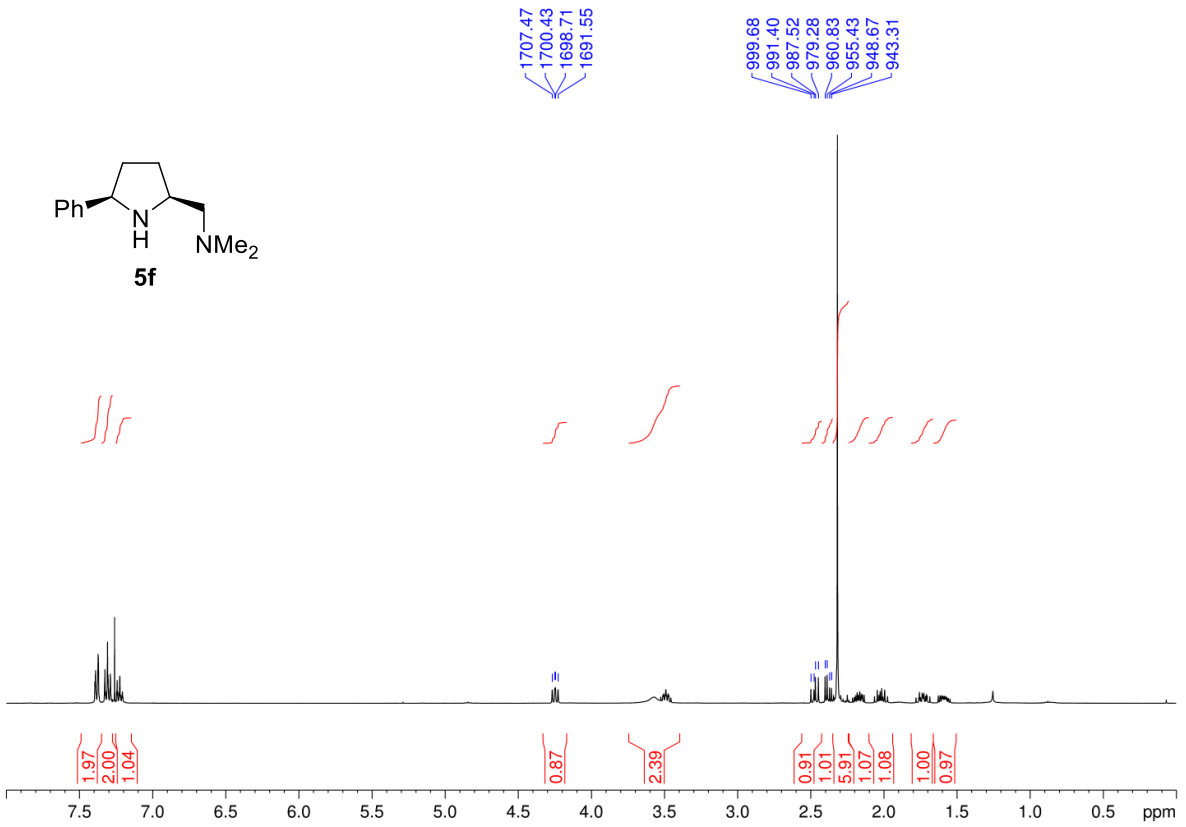

1279.42
1272.97
1270.17
1263.93
962.87
953.71
949.95
940.87
MeO
N
Me
NMe2
5c
2.09
1.98
3.00
0.99
1.97
1.04
5.98
3.02
2.05
2.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

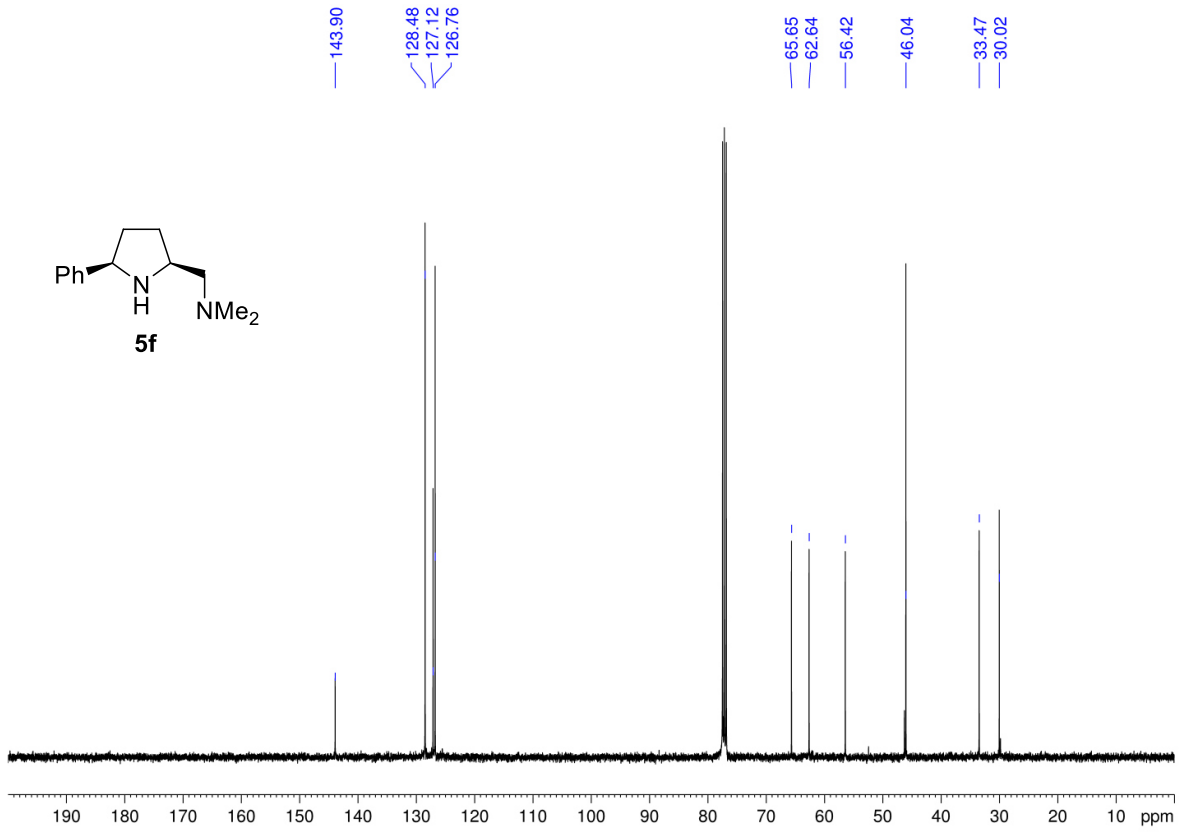

158.82
135.58
128.58
113.82
72.15
65.18
64.54
55.36
46.49
39.60
33.89
29.39
MeO
N
Me
NMe2
5c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

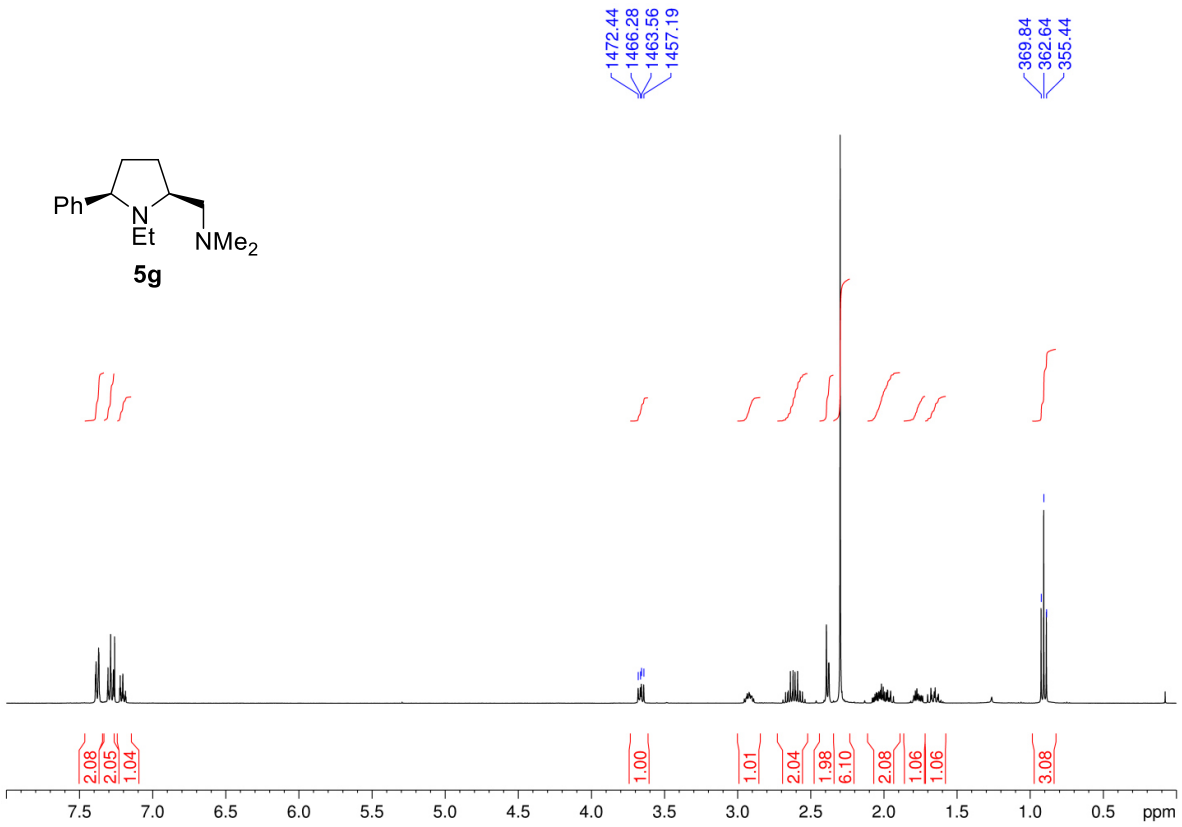

1377.81
1371.13
1368.88
1361.96
1004.37
1000.33
992.16
988.12
953.91
945.71
941.71
933.54
F3C
N
Me
NMe2
F3C
5d
1.98
1.00
1.00
1.05
1.02
1.07
5.95
2.98
2.10
1.01
1.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
147.37
132.22
131.89
131.56
131.24
127.74
127.58
127.56
125.03
122.32
121.21
121.17
121.13
121.10
121.06
121.02
120.98
119.61
71.77
65.30
64.63
46.62
39.76
34.56
29.46
F3C
N
Me
NMe2
F3C
5d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

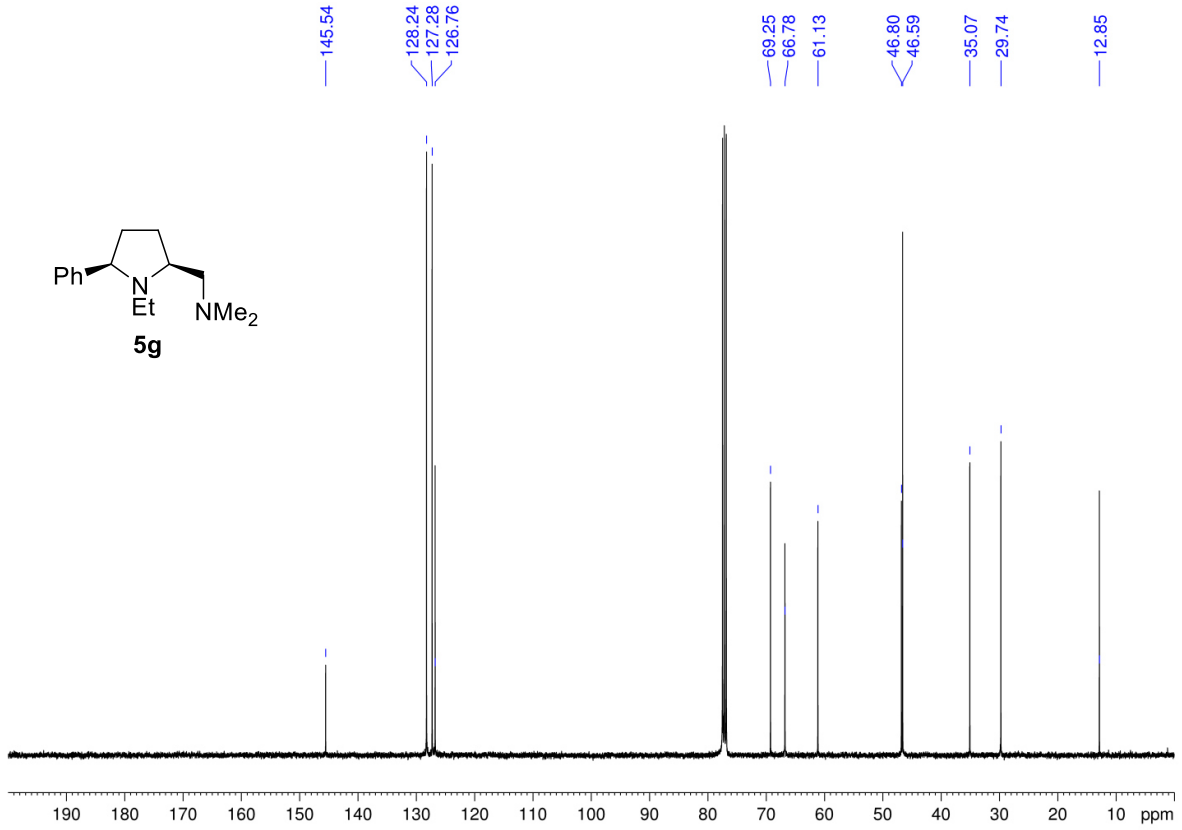

1075.83
1072.11
1063.71
1059.98
1014.97
1006.85
1002.93
994.72
N
Me
NMe2
5e
1.00
1.04
2.05
3.00
1.00
0.89
1.11
1.02
7.00
3.04
1.06
2.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

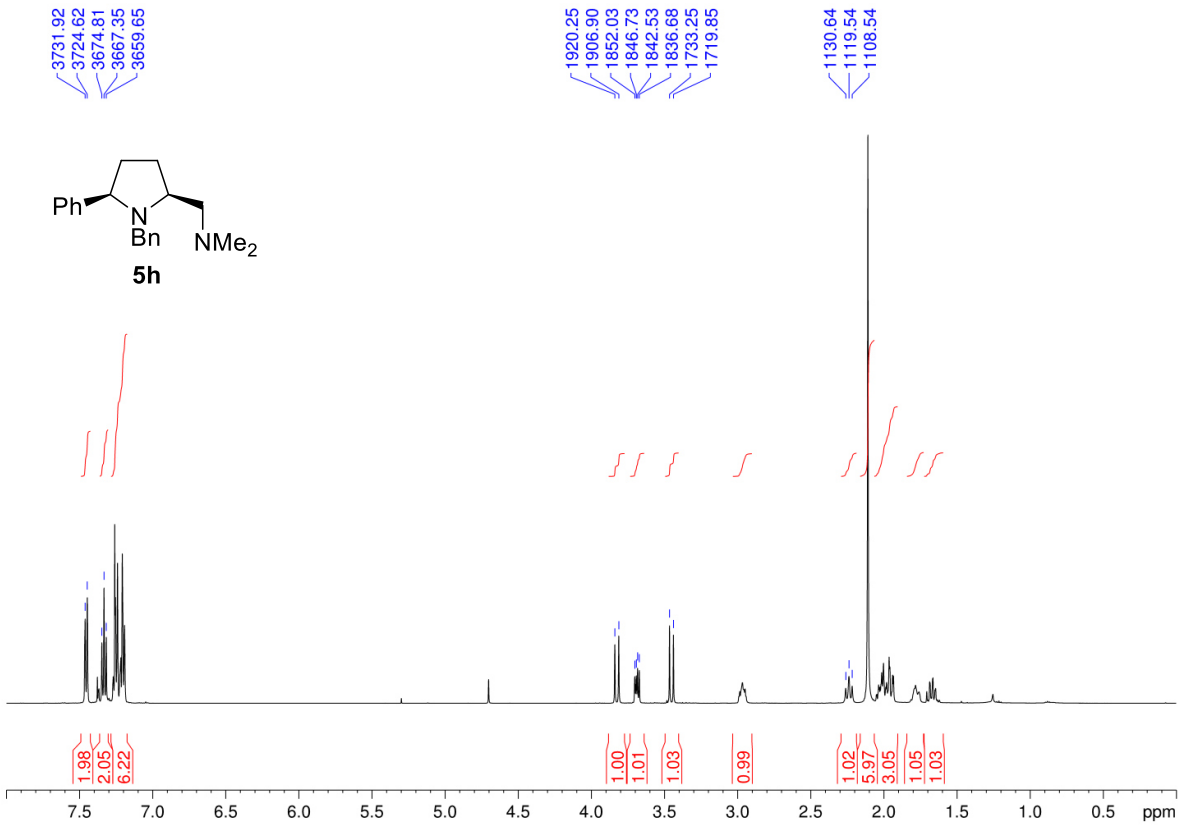

139.64
134.07
131.84
128.92
127.14
125.95
125.59
125.33
123.74
123.58
68.83
65.05
64.57
46.53
40.19
33.01
29.89
N
Me
NMe2
5e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

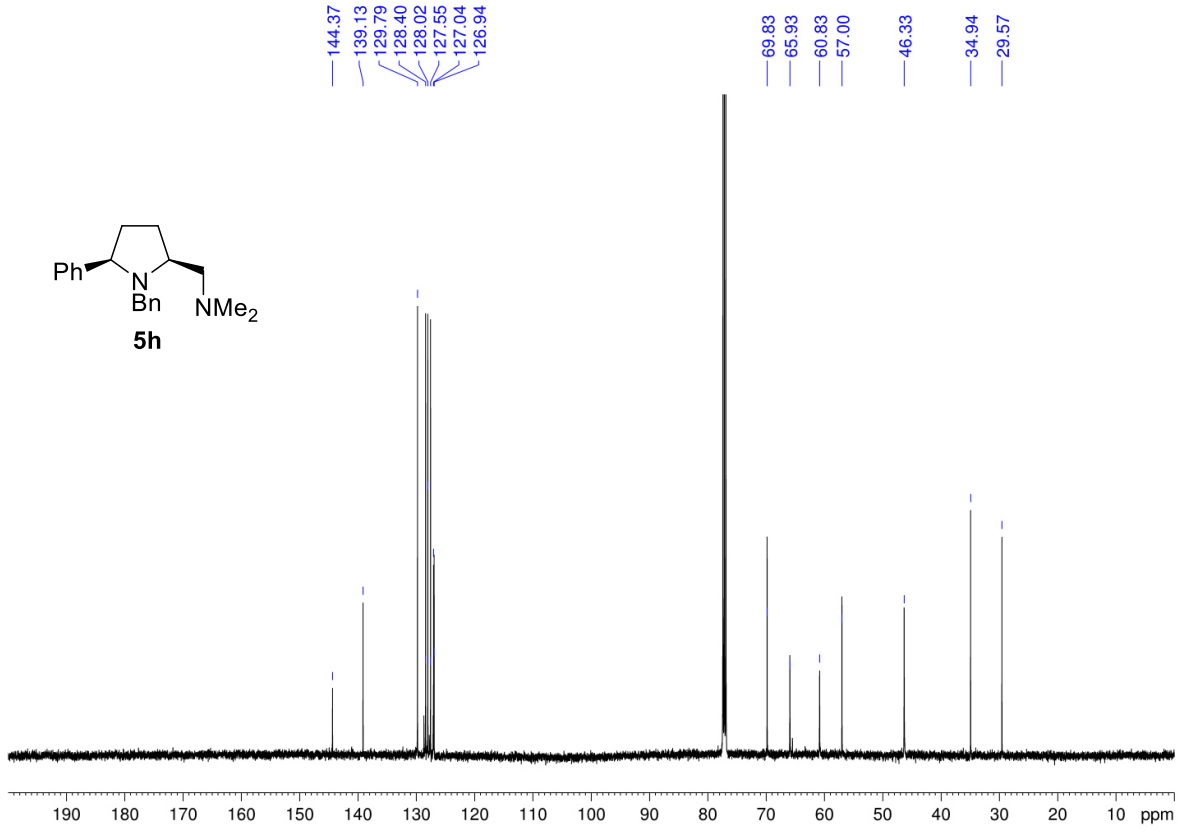

1707.47
1700.43
1698.71
1691.55
999.68
991.40
987.52
979.28
960.83
955.43
948.67
943.31
Ph
N
H
NMe2
5f
1.97
2.00
1.04
0.87
2.39
0.91
1.01
5.91
1.07
1.08
1.00
0.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

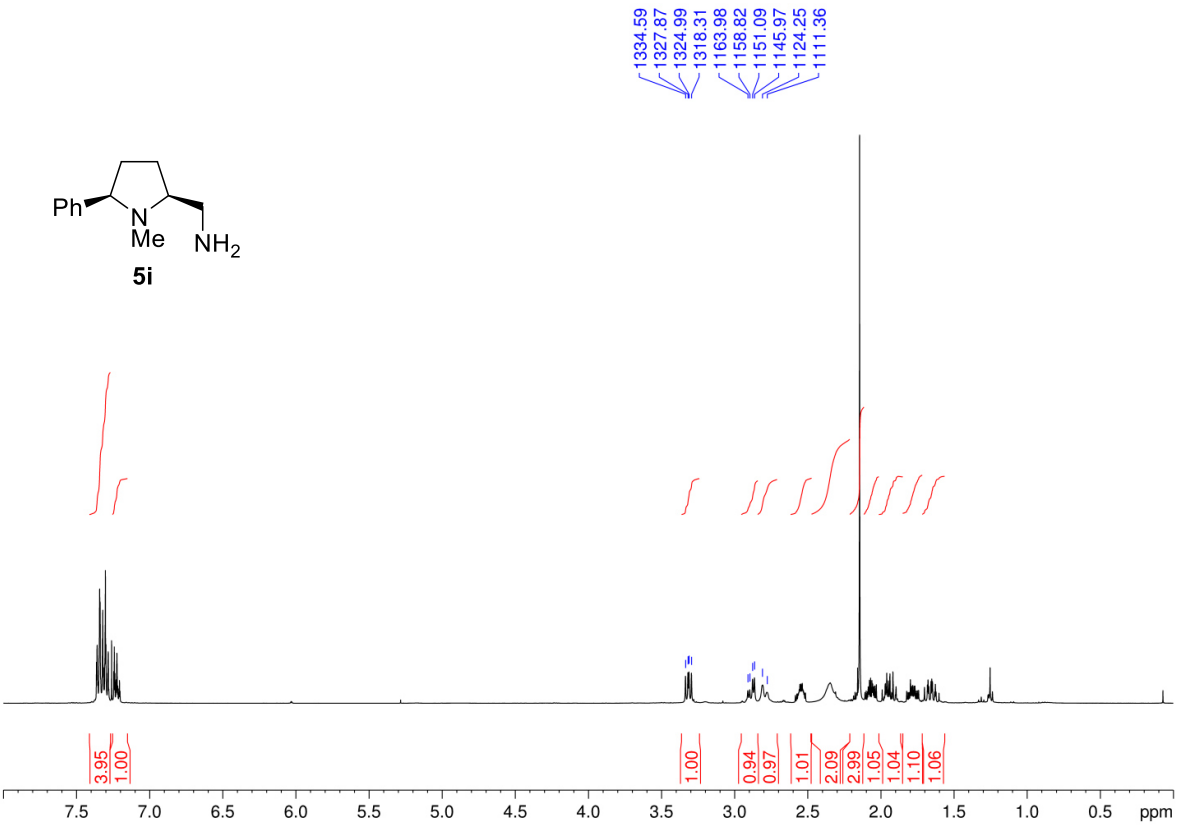

143.90
128.48
127.12
126.76
65.65
62.64
56.42
46.04
33.47
30.02
Ph
N
H
NMe2
5f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

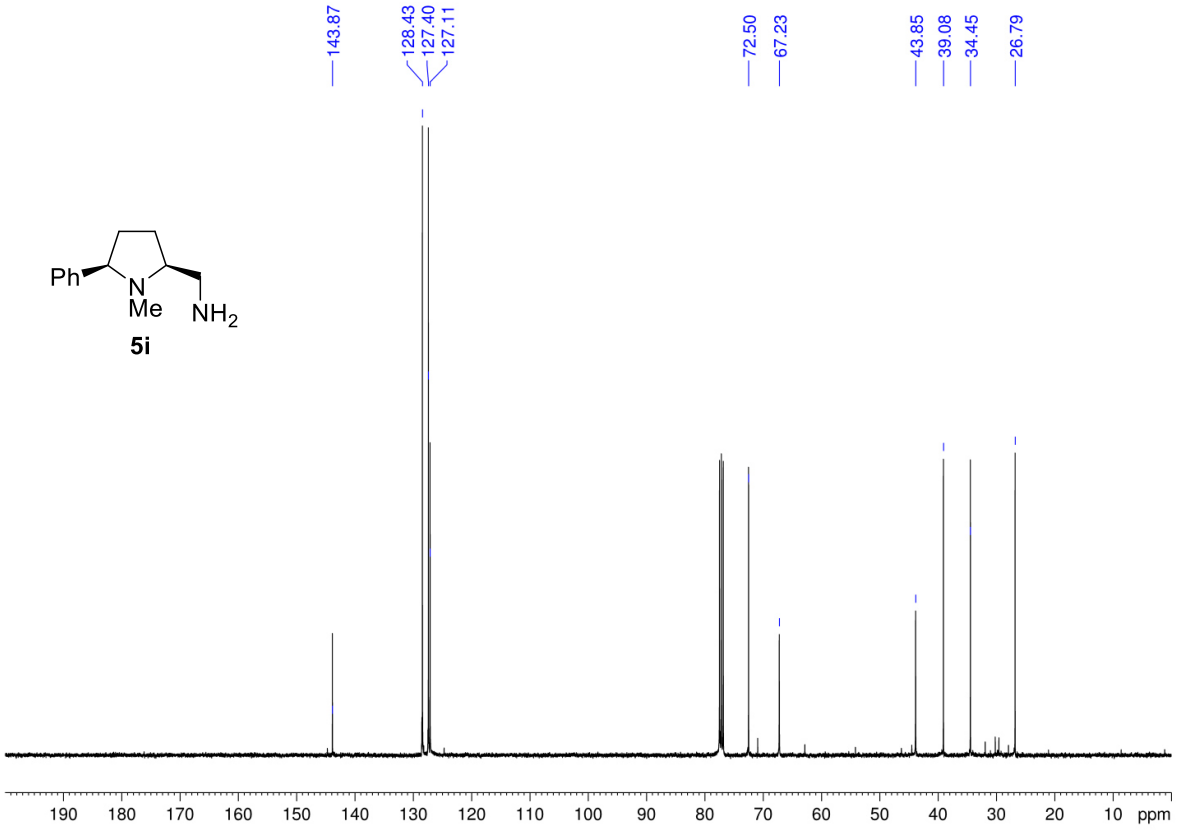

1472.44
1466.28
1463.56
1457.19
369.84
362.64
355.44
Ph
N
Et
NMe2
5g
2.08
2.05
1.04
1.00
1.01
2.04
1.98
6.10
2.08
1.06
1.06
3.08
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

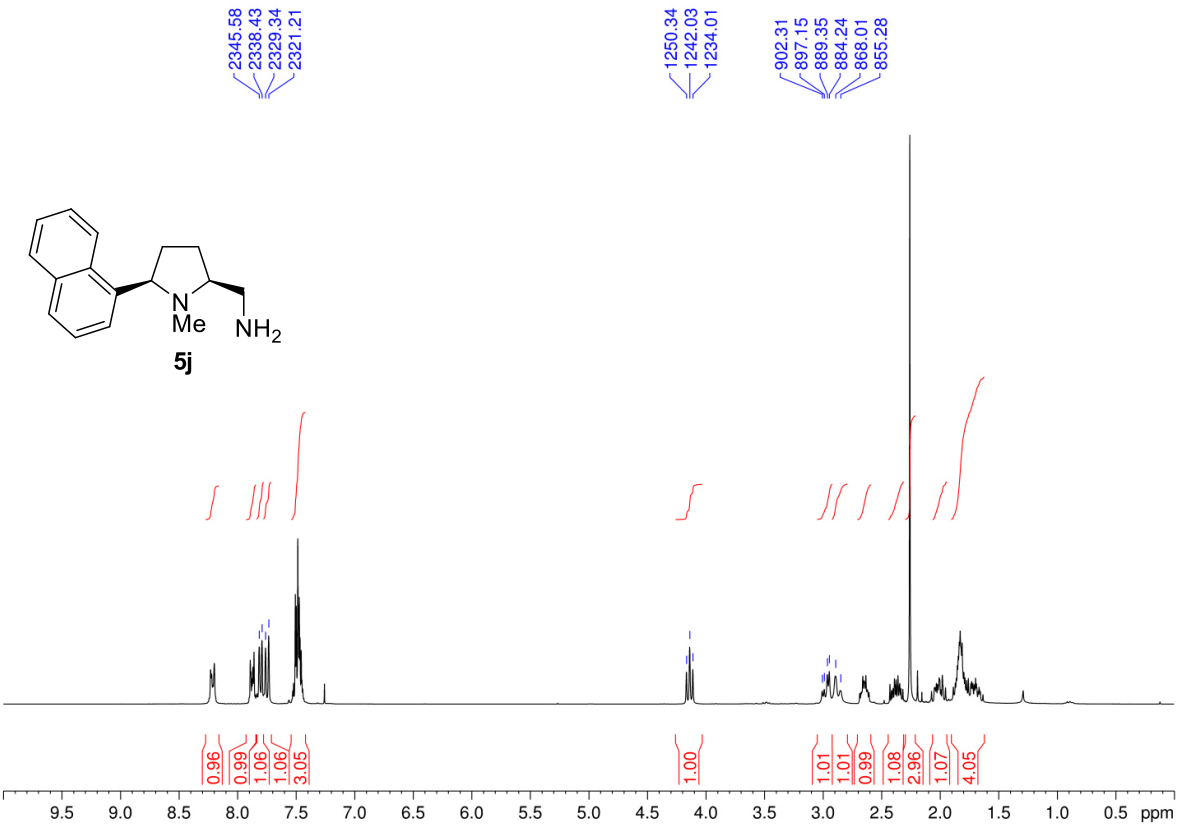

145.54
128.24
127.28
126.76
69.25
66.78
61.13
46.80
46.59
35.07
29.74
12.85
Ph
N
Et
NMe2
5g
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

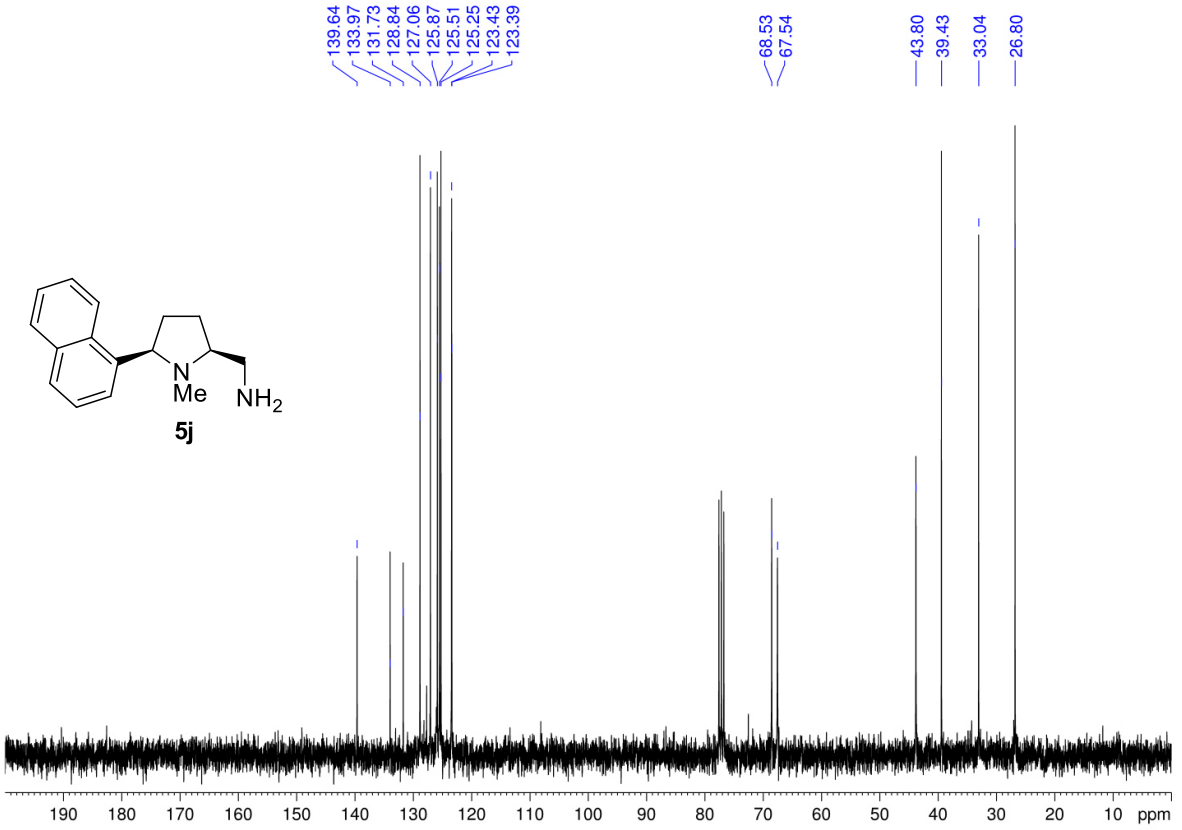

3731.92
3724.62
3674.81
3667.35
3659.65
1920.25
1906.90
1852.03
1846.73
1842.53
1836.68
1733.25
1719.85
1130.64
1119.54
1108.54
Ph
N
Bn
NMe2
5h
1.98
2.05
6.22
1.00
1.01
1.03
0.99
1.02
5.97
3.05
1.05
1.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

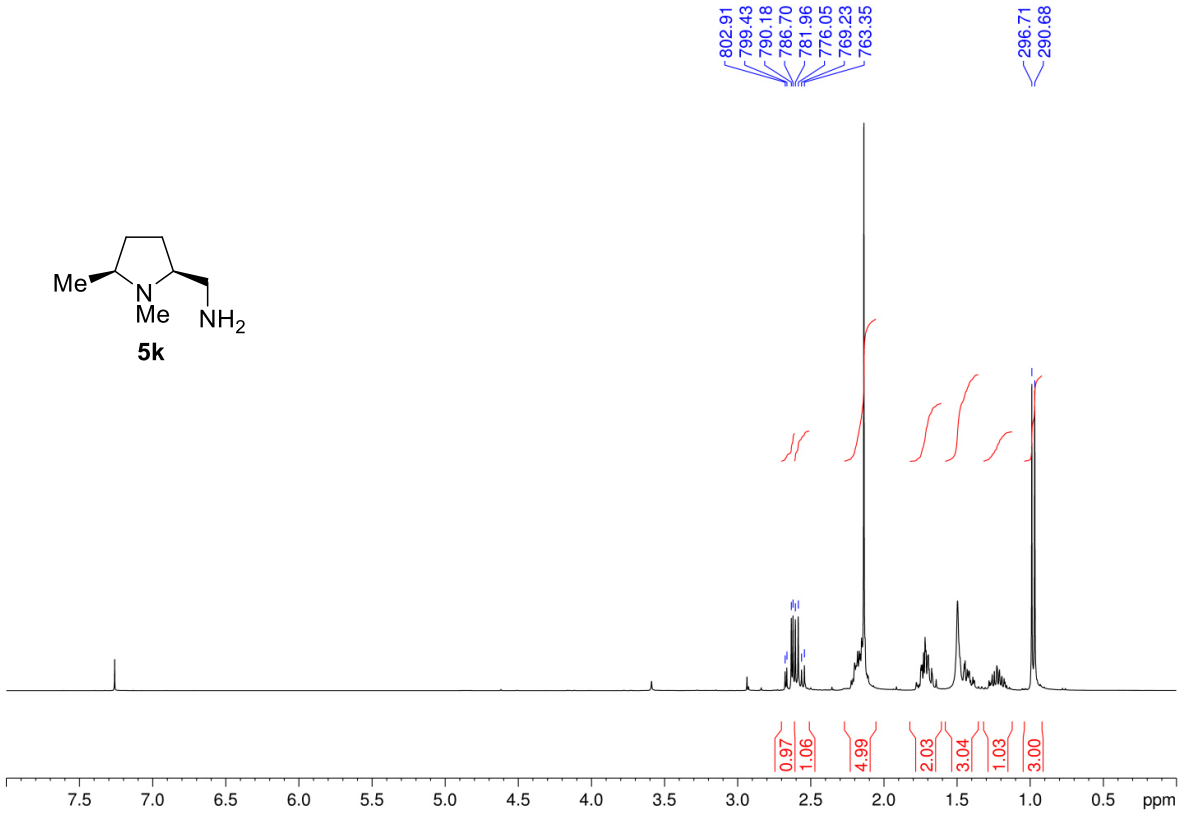

144.37
139.13
129.79
128.40
128.02
127.55
127.04
126.94
69.83
65.93
60.83
57.00
46.33
34.94
29.57
Ph
N
Bn
NMe2
5h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

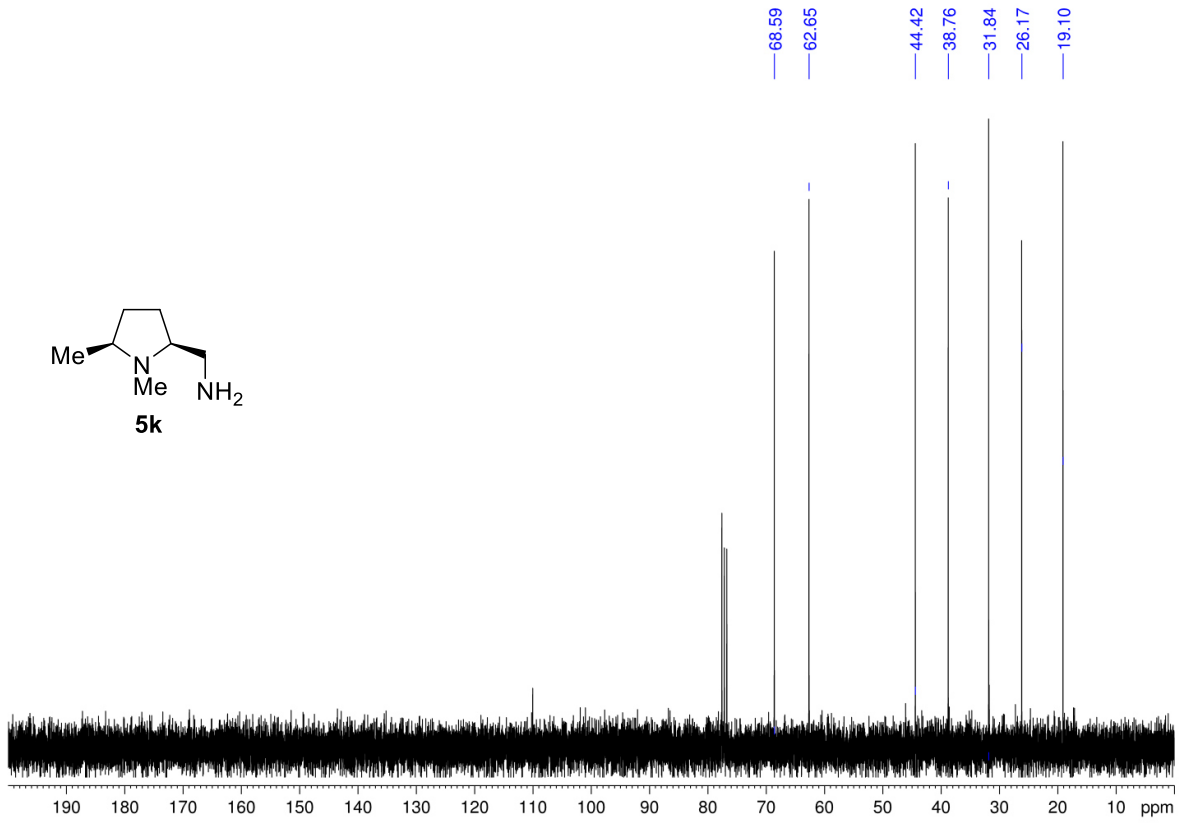

1334.59
1327.87
1324.99
1318.31
1163.98
1158.82
1151.09
1145.97
1124.25
1111.36
Ph
N
Me
NH2
5i
3.95
1.00
1.00
0.94
0.97
1.01
2.09
2.99
1.05
1.04
1.10
1.06
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

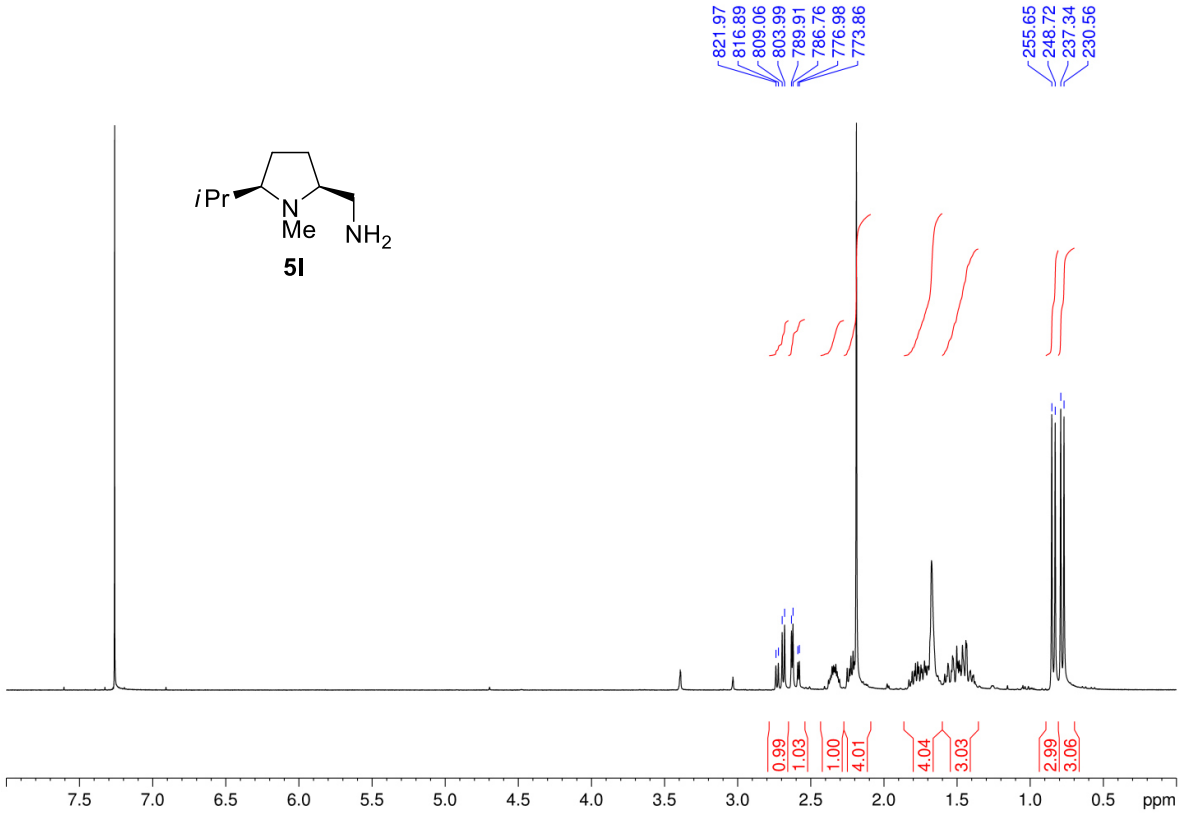

143.87
128.43
127.40
127.11
72.50
67.23
43.85
39.08
34.45
26.79
Ph
N
Me
NH2
5i
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

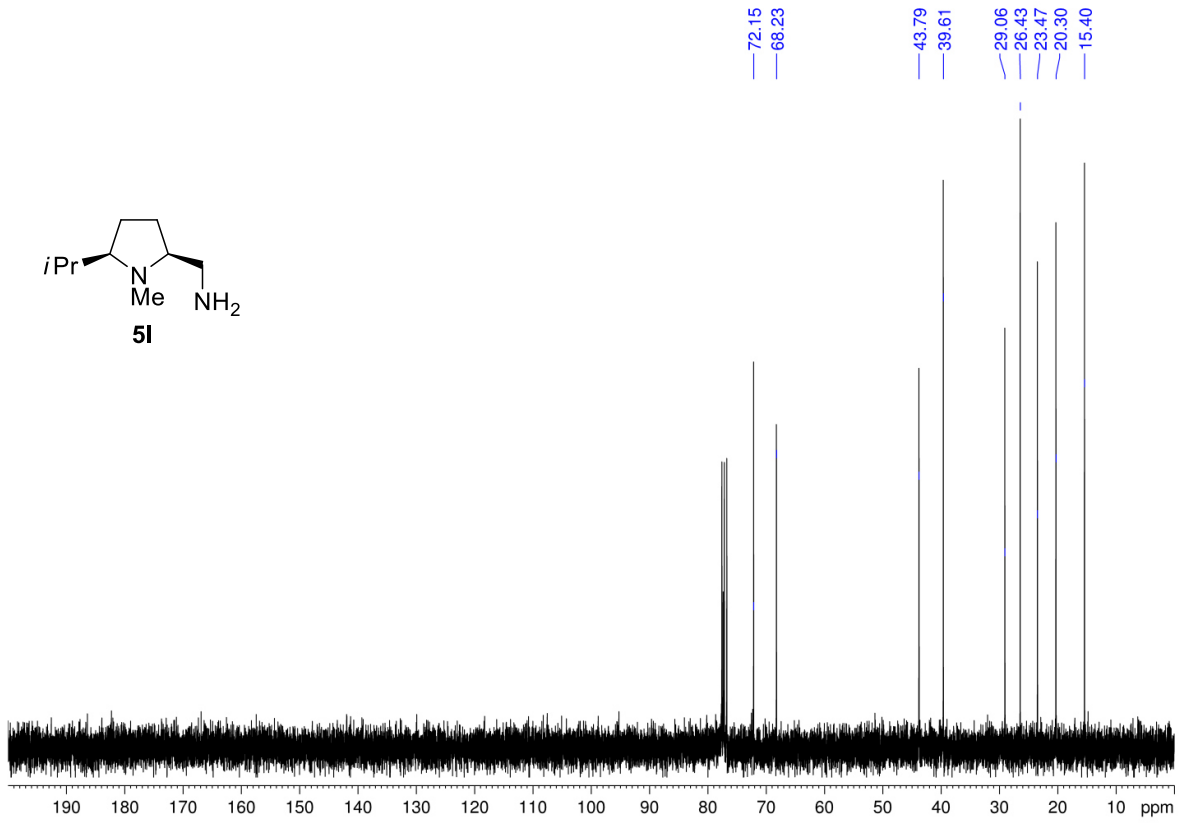

2345.58
2338.43
2329.34
2321.21
1250.34
1242.03
1234.01
902.31
897.15
889.35
884.24
868.01
855.28
N
Me
NH2
5j
0.96
0.99
1.06
1.06
3.05
1.00
1.01
1.01
0.99
1.08
2.96
1.07
4.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

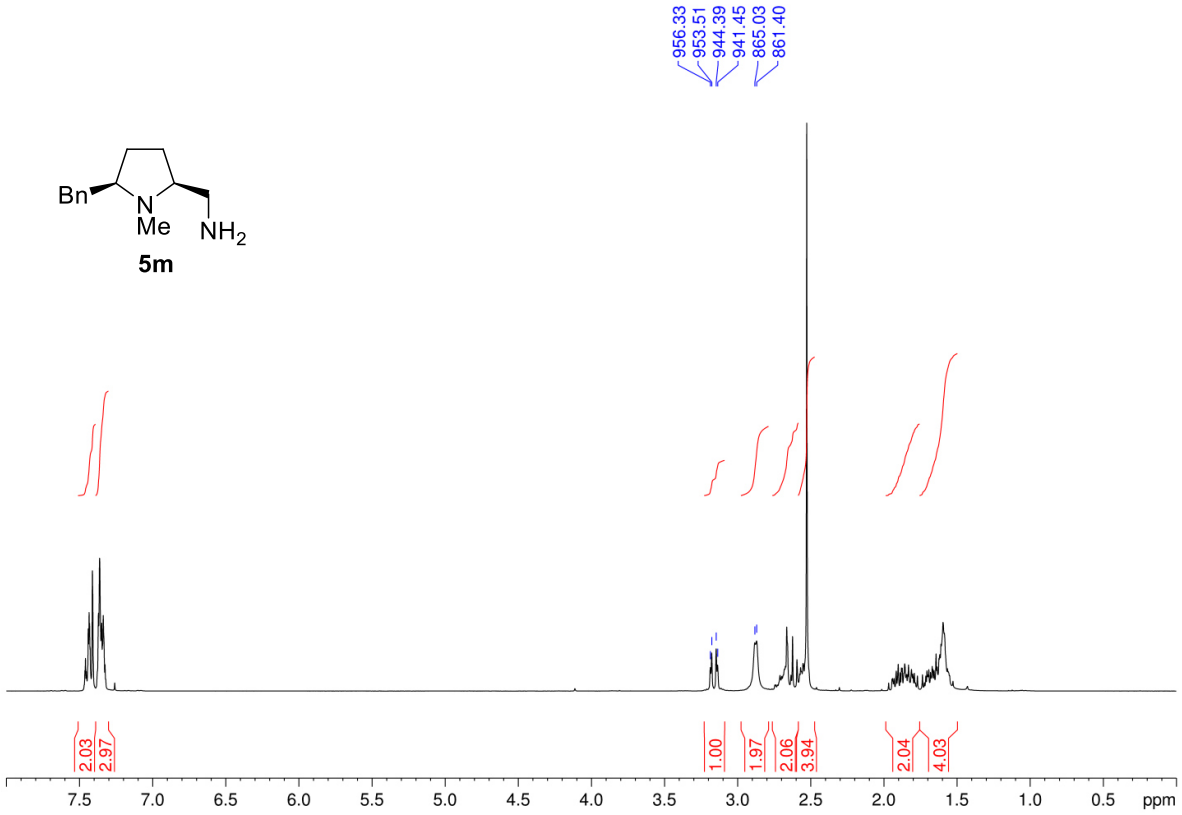

139.64
133.97
131.73
128.84
127.06
125.87
125.51
125.25
123.43
123.39
68.53
67.54
43.80
39.43
33.04
26.80
N
Me
NH2
5j
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

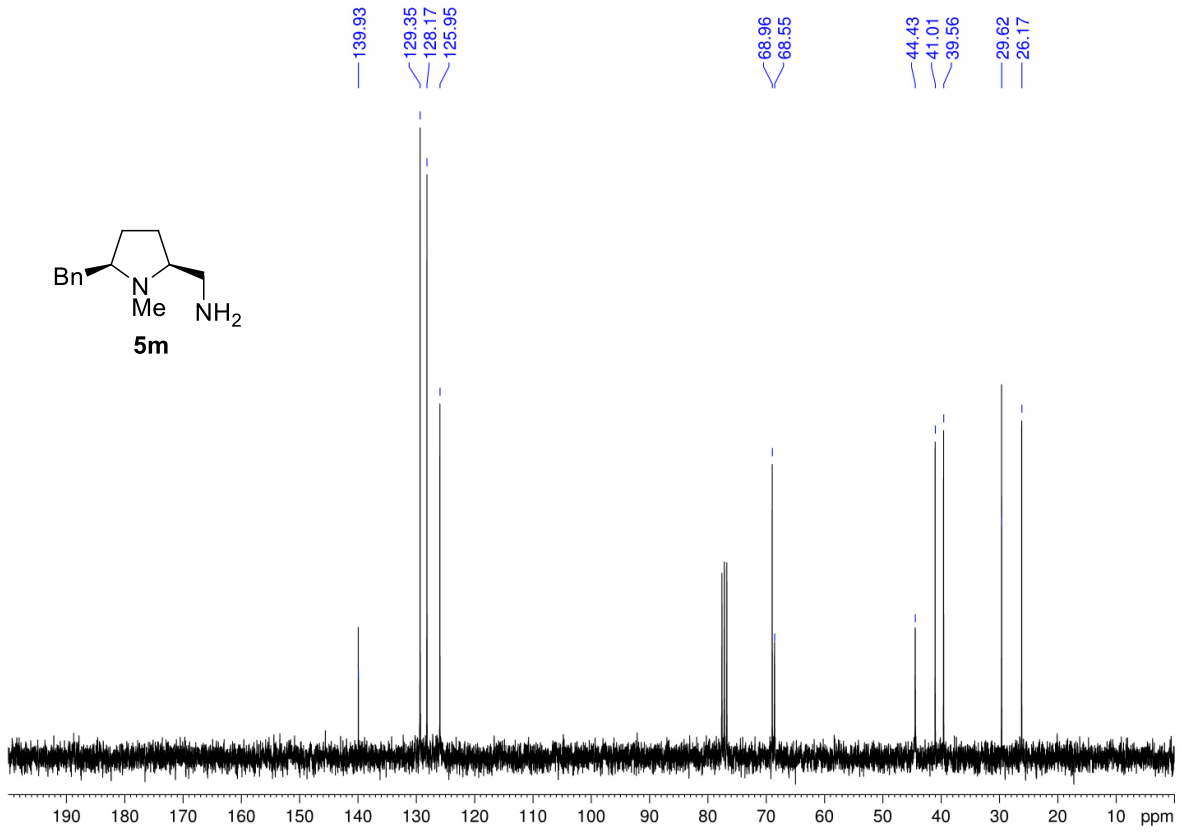

802.91
799.43
790.18
786.70
781.96
776.05
769.23
763.35
296.71
290.68
Me
N
Me
NH2
5k
0.97
1.06
4.99
2.03
3.04
1.03
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

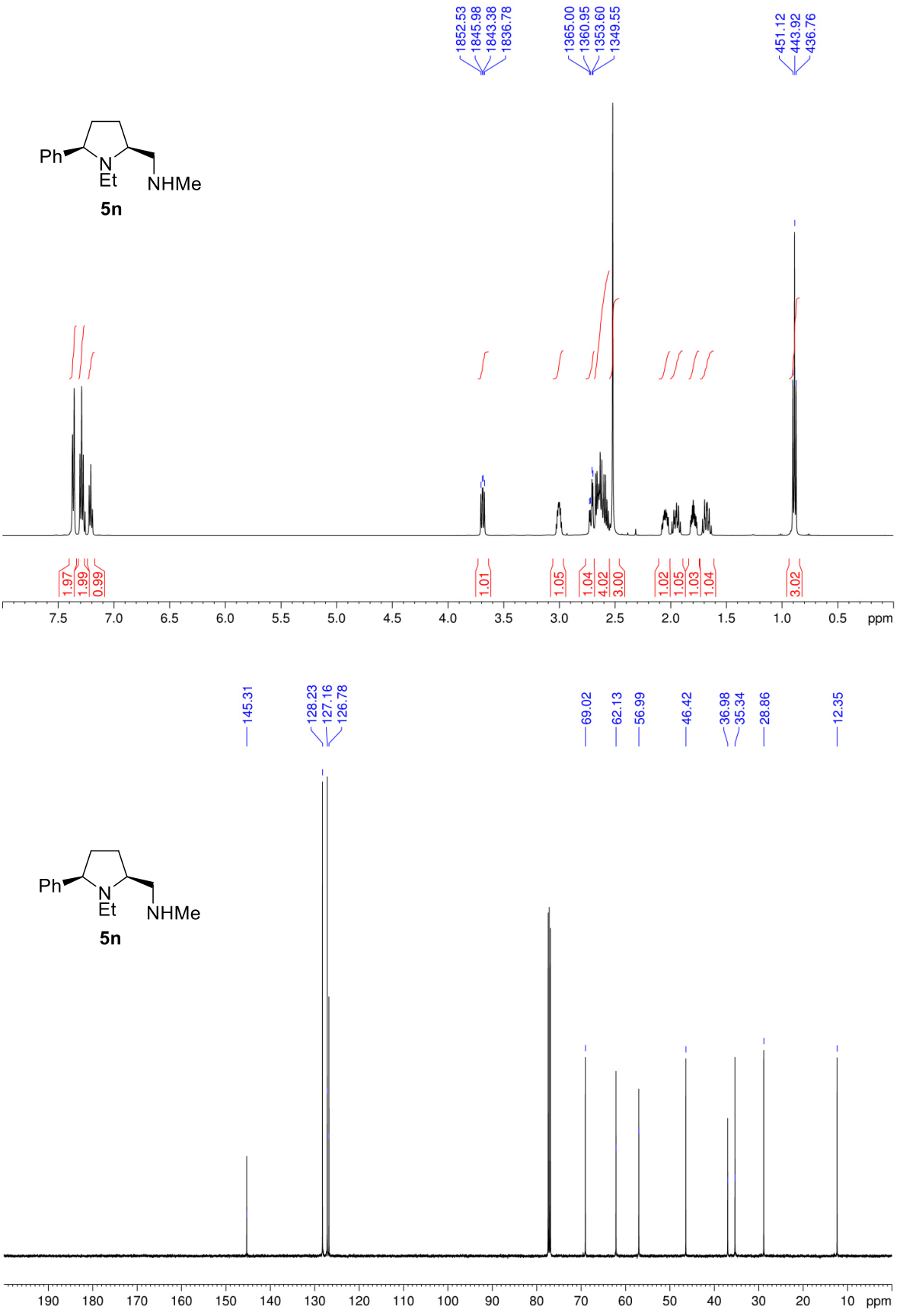

68.59
62.65
44.42
38.76
31.84
26.17
19.10
Me
N
Me
NH2
5k
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

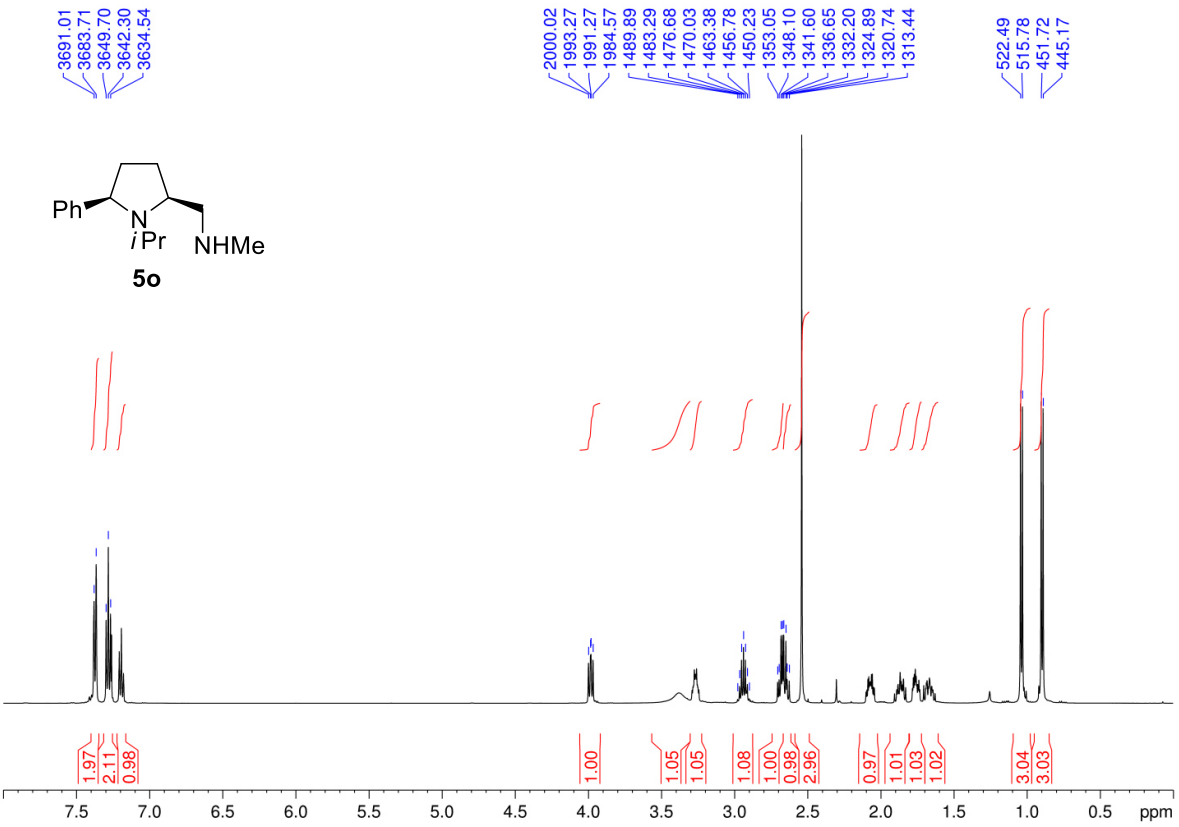

821.97
816.89
809.06
803.99
789.91
786.76
776.98
773.86
255.65
248.72
237.34
230.56
iPr
N
Me
NH2
5l
0.99
1.03
1.00
4.01
4.04
3.03
2.99
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

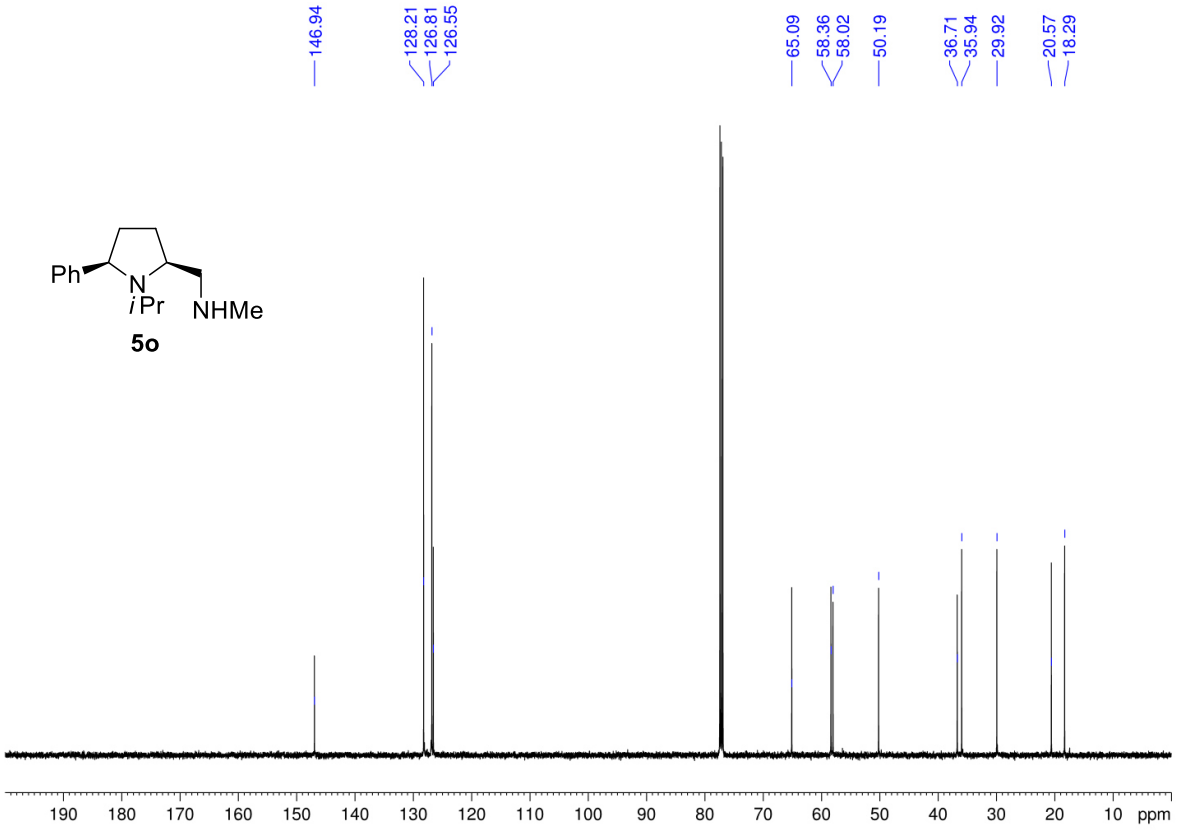

72.15
68.23
43.79
39.61
29.06
26.43
23.47
20.30
15.40
iPr
N
Me
NH2
5l
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

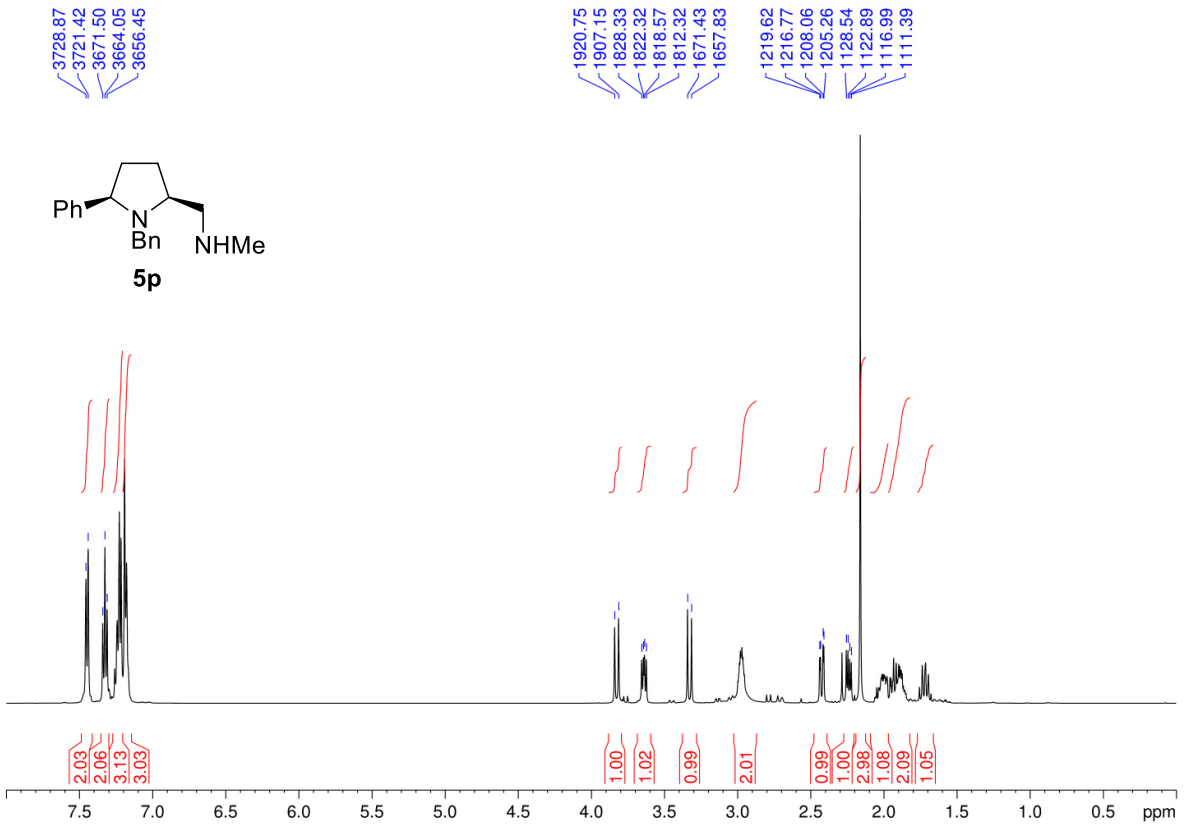

956.33
953.51
944.39
941.45
865.03
861.40
Bn
N
Me
NH2
5m
2.03
2.97
1.00
1.97
2.06
3.94
2.04
4.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

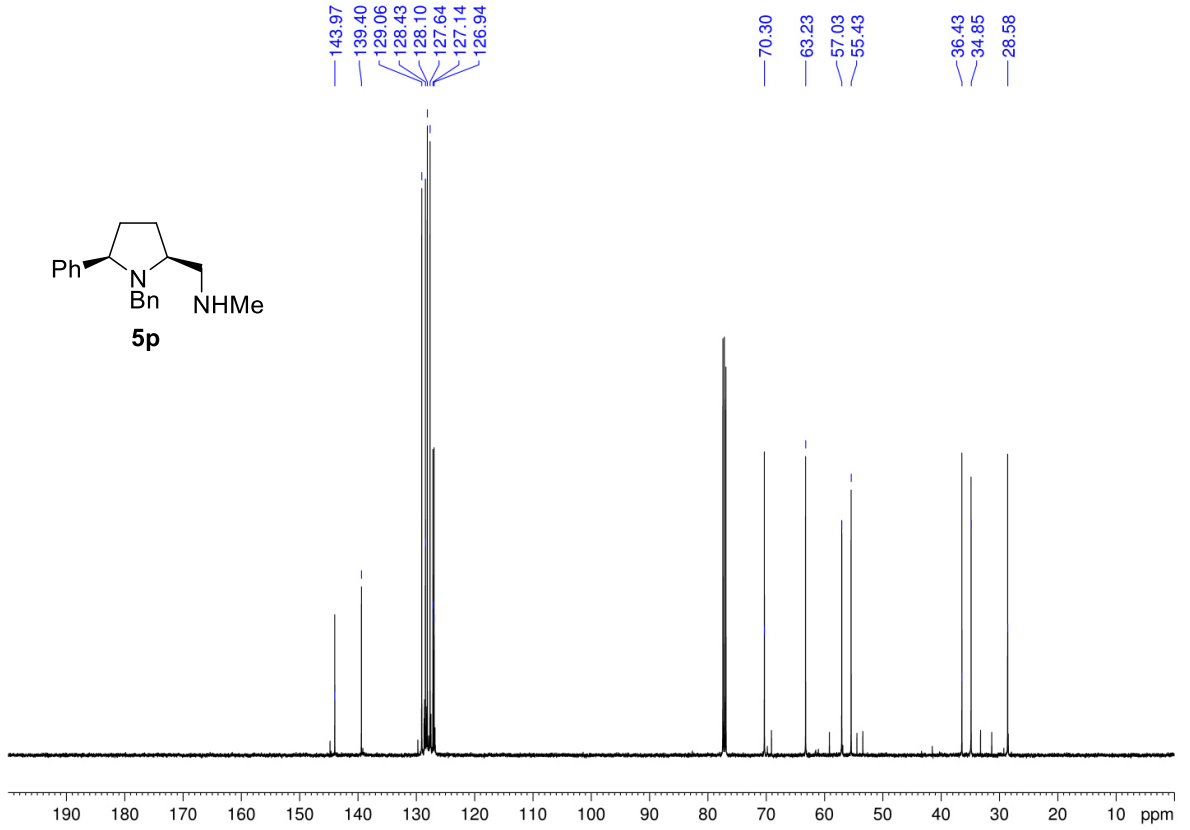

139.93
129.35
128.17
125.95
68.96
68.55
44.43
41.01
39.56
29.62
26.17
Bn
N
Me
NH2
5m
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

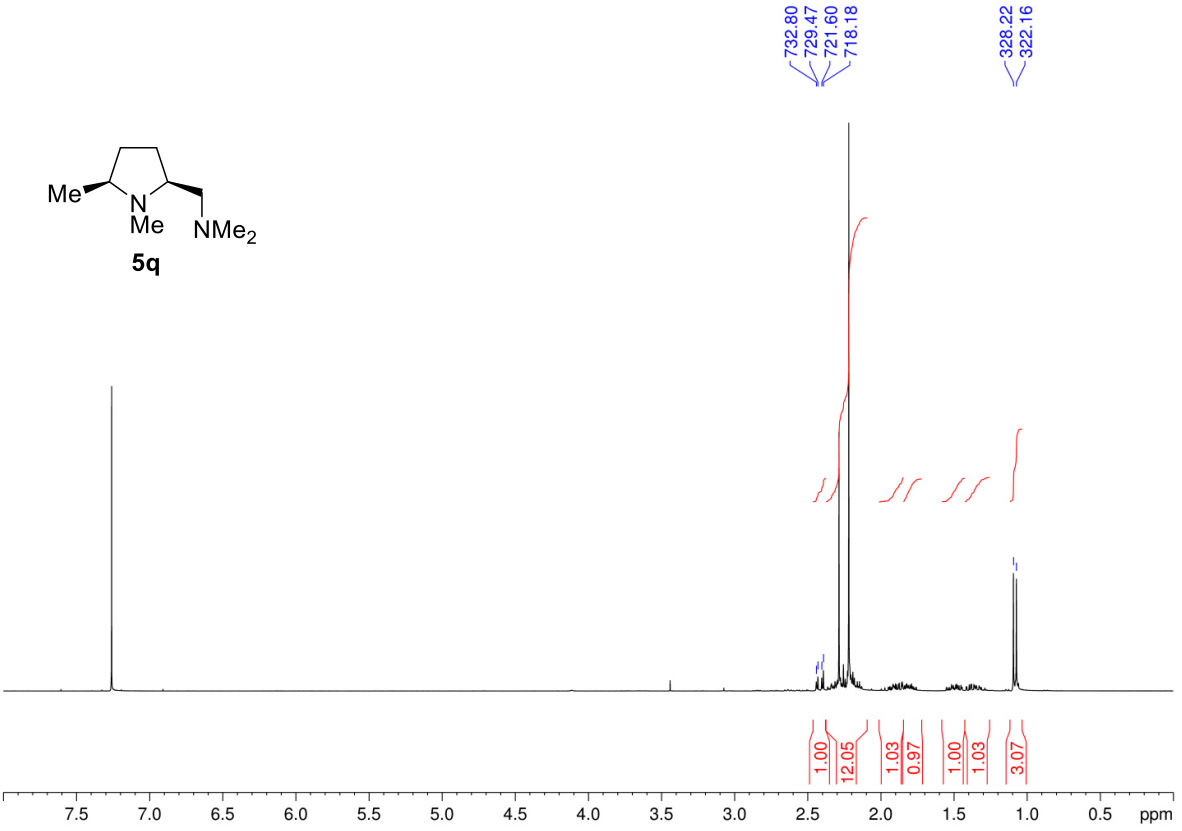

1852.53
1845.98
1843.38
1836.78
1365.00
1360.95
1353.60
1349.55
451.12
443.92
436.76
Ph
N
Et
NHMe
5n
1.97
1.99
0.99
1.01
1.05
1.04
4.02
3.00
1.02
1.05
1.03
1.04
3.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
145.31
128.23
127.16
126.78
69.02
62.13
56.99
46.42
36.98
35.34
28.86
12.35
Ph
N
Et
NHMe
5n
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

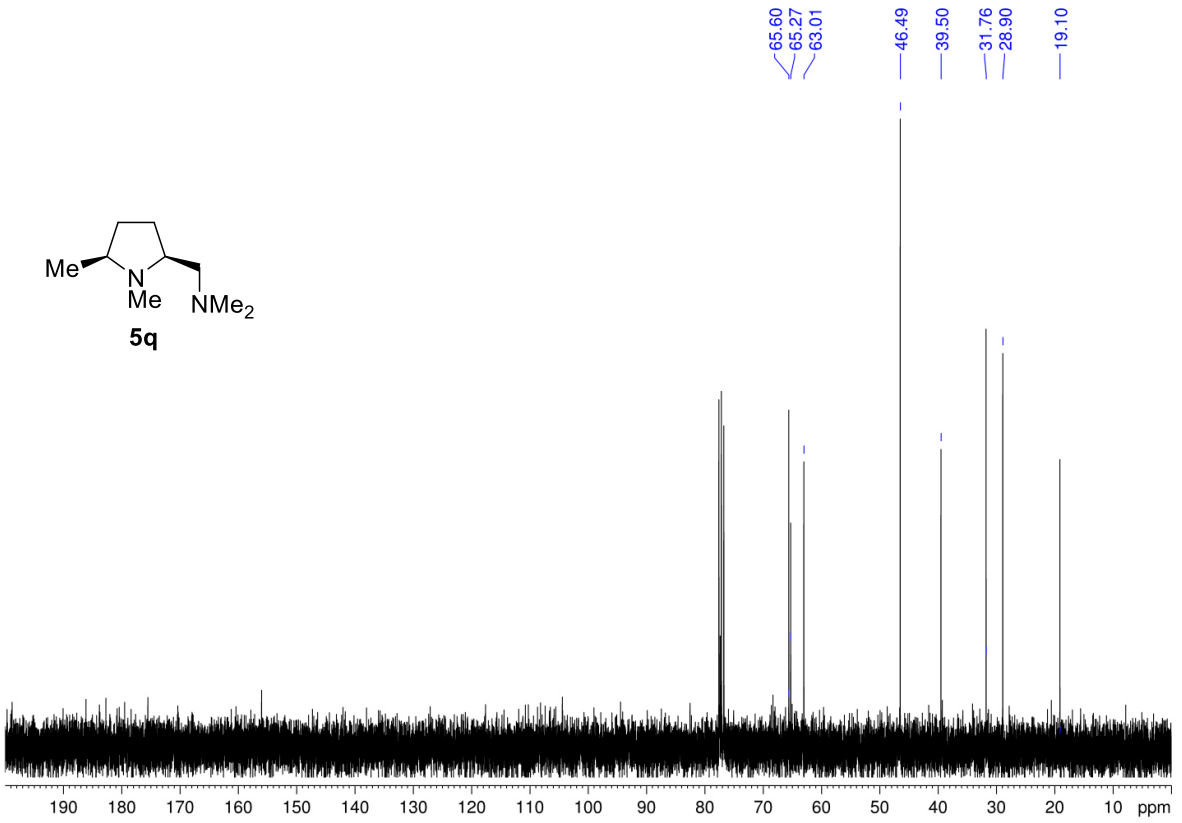

3691.01
3683.71
3649.70
3642.30
3634.54
2000.02
1993.27
1991.27
1984.57
1489.89
1483.29
1476.68
1470.03
1463.38
1456.78
1450.23
1353.05
1348.10
1341.60
1336.65
1332.20
1324.89
1320.74
1313.44
522.49
515.78
451.72
445.17
Ph
N
iPr
NHMe
5o
1.97
2.11
0.98
1.00
1.05
1.05
1.08
1.00
0.98
2.96
0.97
1.01
1.03
1.02
3.04
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

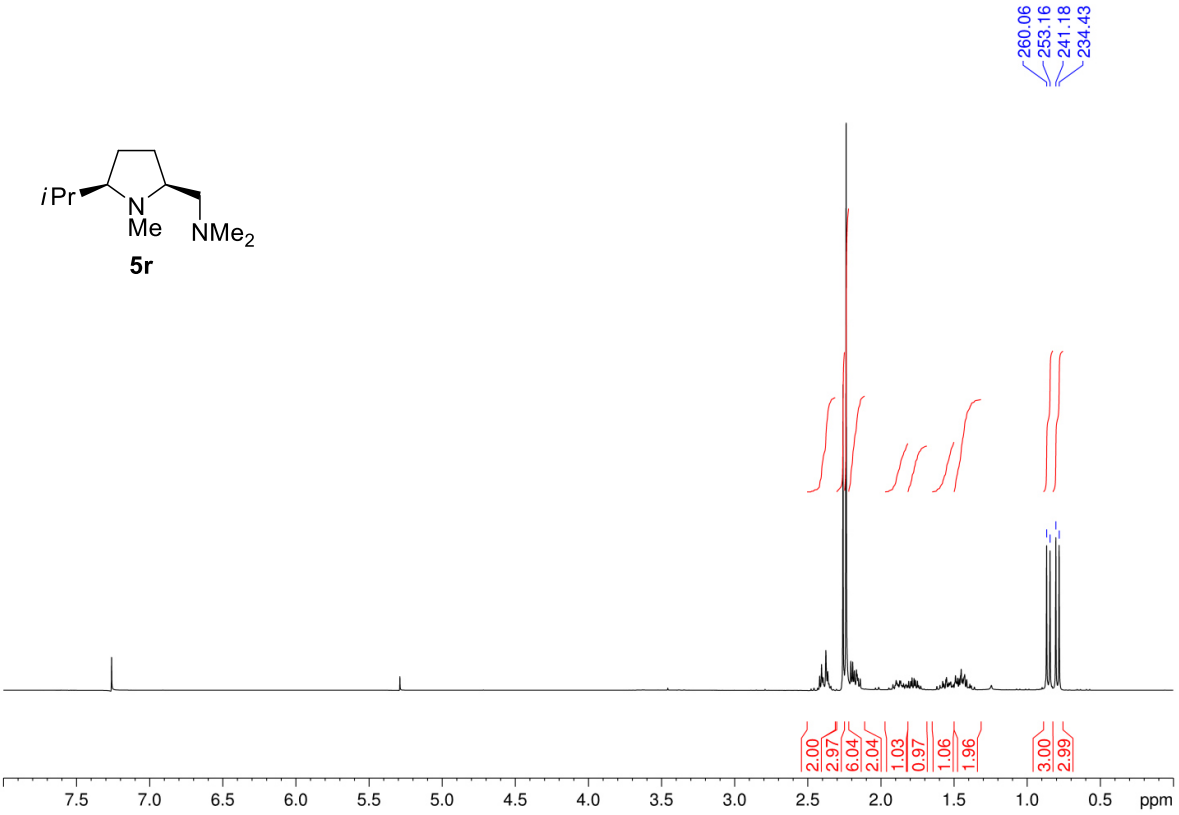

146.94
128.21
126.81
126.55
65.09
58.36
58.02
50.19
36.71
35.94
29.92
20.57
18.29
Ph
N
iPr
NHMe
5o
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

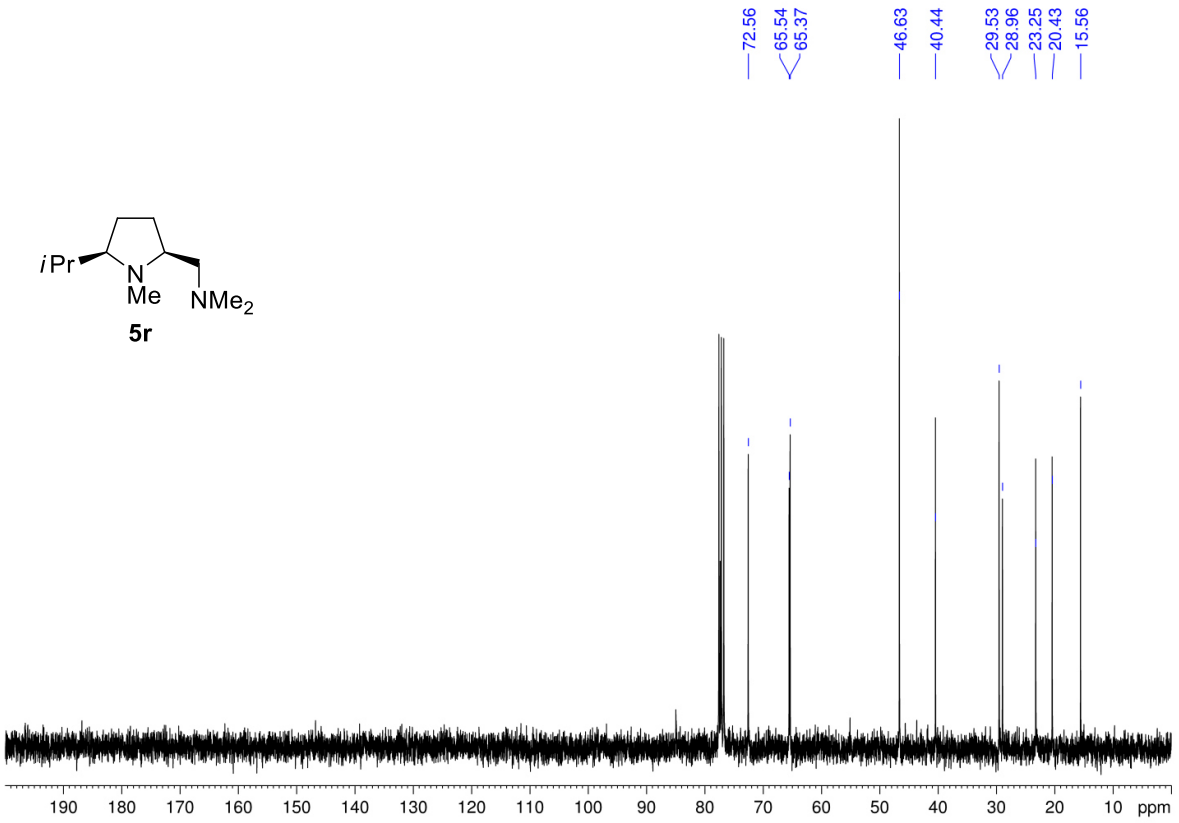

3728.87
3721.42
3671.50
3664.05
3656.45
1920.75
1907.15
1828.33
1822.32
1818.57
1812.32
1671.43
1657.83
1219.62
1216.77
1208.06
1205.26
1128.54
1122.89
1116.99
1111.39
Ph
N
Bn
NHMe
5p
2.03
2.06
3.13
3.03
1.00
1.02
0.99
2.01
0.99
1.00
2.98
1.08
2.09
1.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

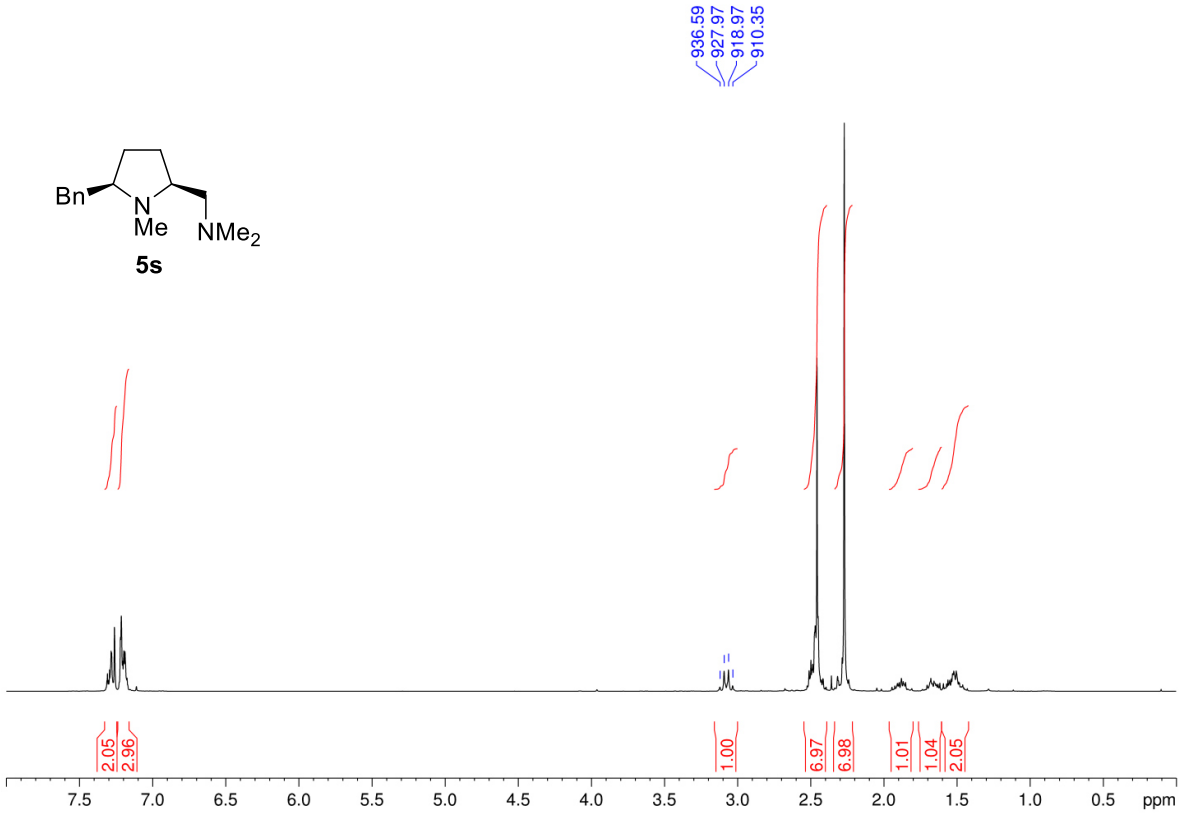

143.97
139.40
129.06
128.43
128.10
127.64
127.14
126.94
70.30
63.23
57.03
55.43
36.43
34.85
28.58
Ph
N
Bn
NHMe
5p
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

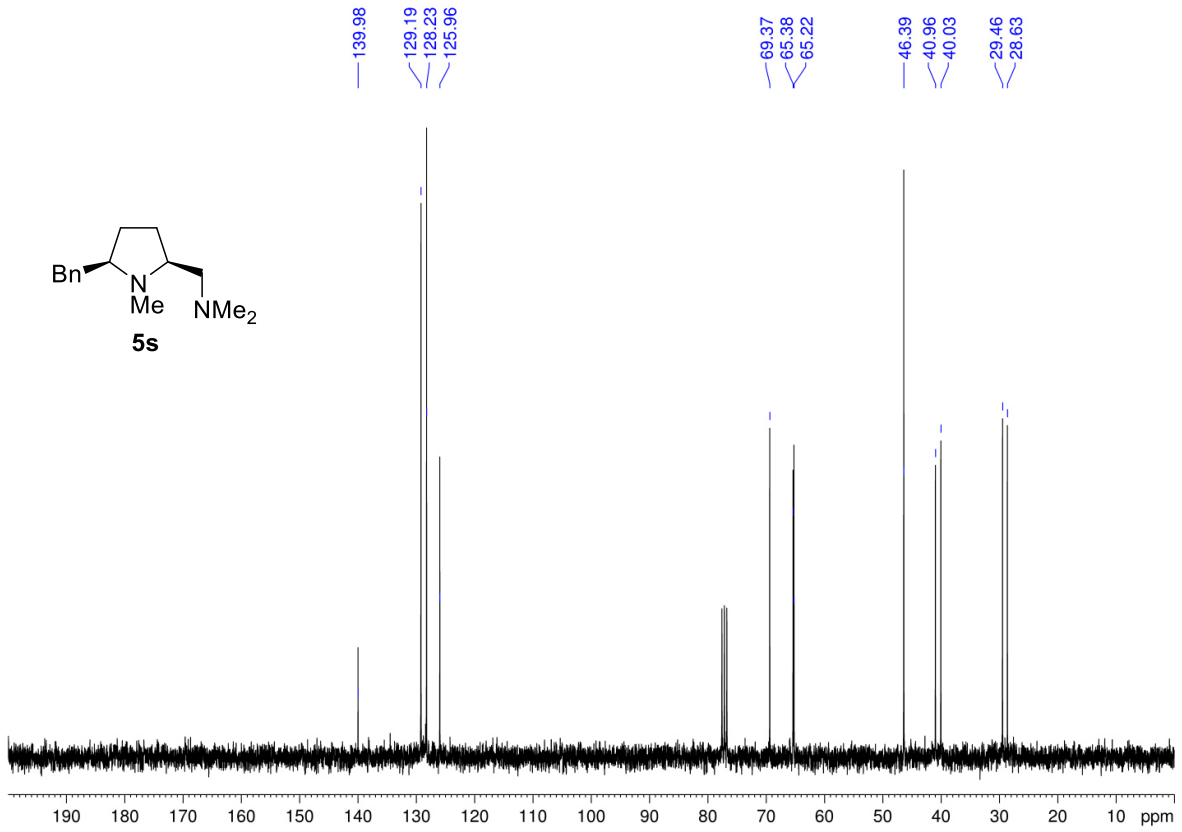

732.80
729.47
721.60
718.18
328.22
322.16
Me
N
Me
NMe2
5q
1.00
12.05
1.03
0.97
1.00
1.03
3.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

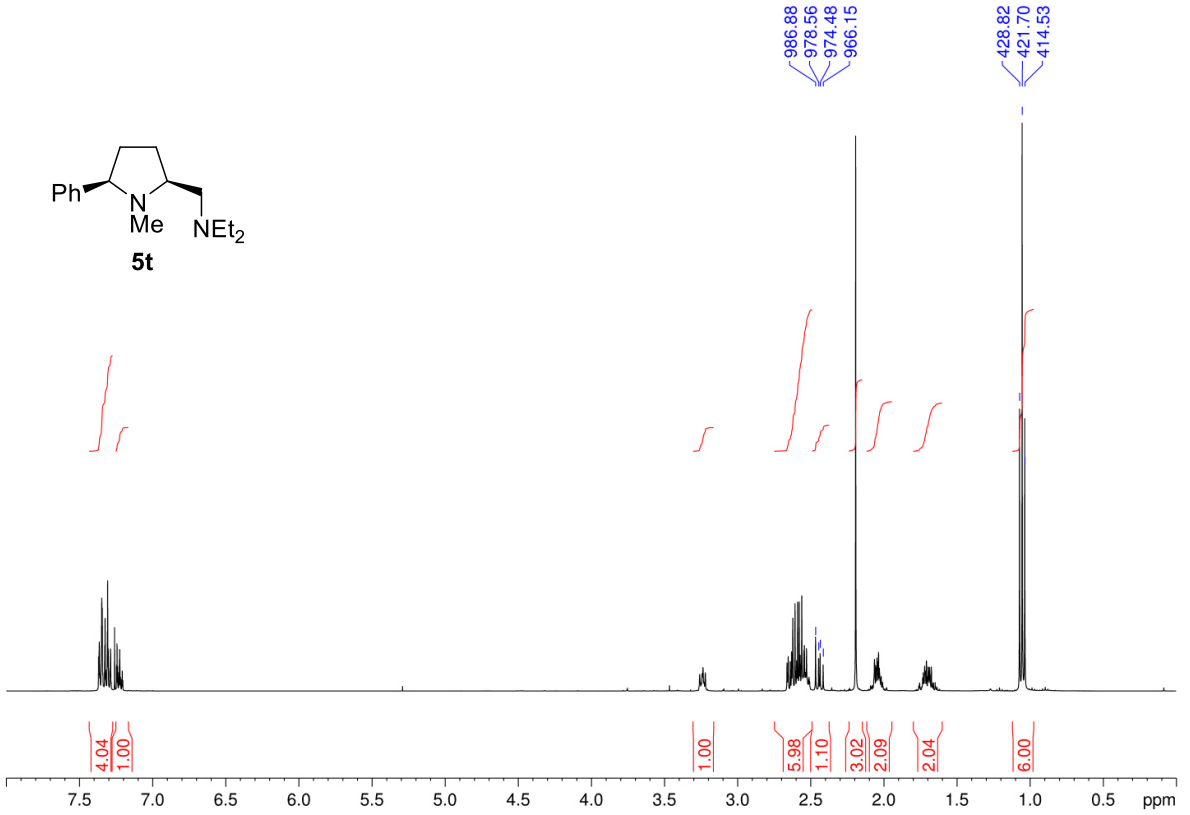

65.60
65.27
63.01
46.49
39.50
31.76
28.90
19.10
Me
N
Me
NMe2
5q
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

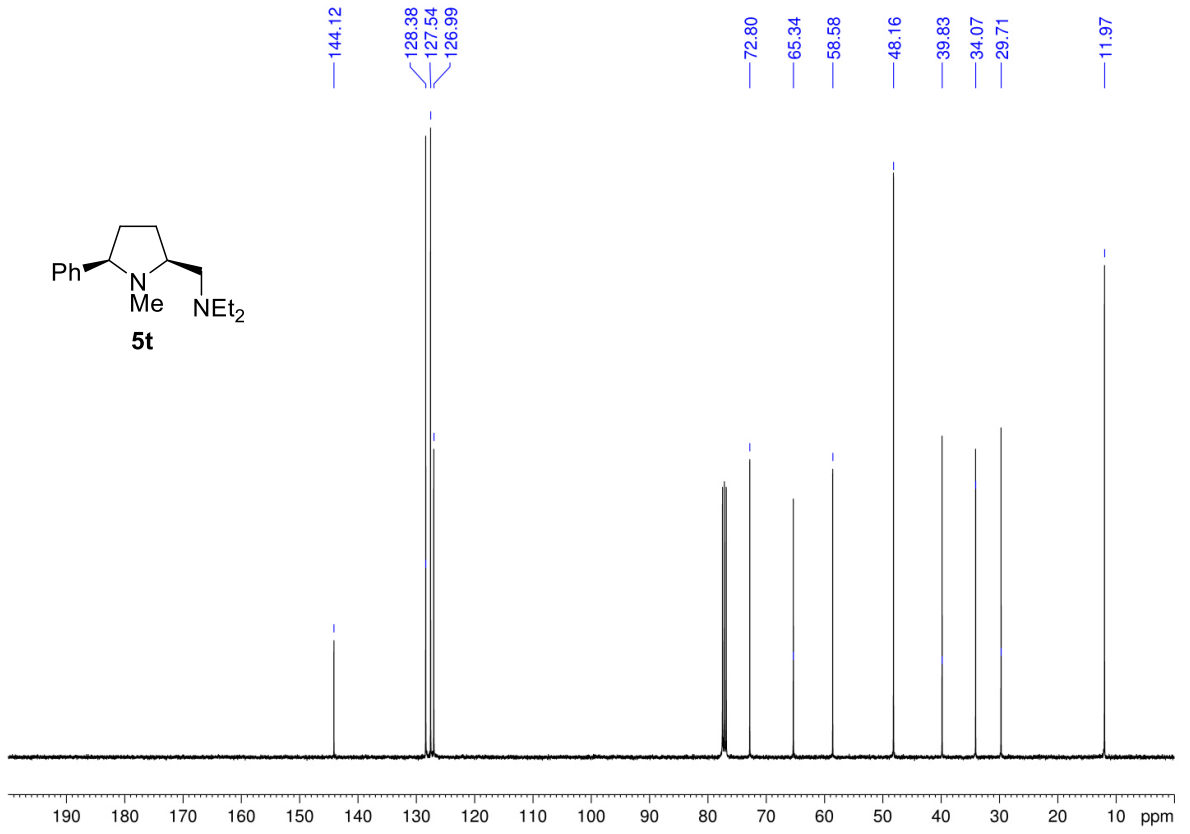

260.06
253.16
241.18
234.43
iPr
N
Me
NMe2
5r
2.00
2.97
6.04
2.04
1.03
0.97
1.06
1.96
3.00
2.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

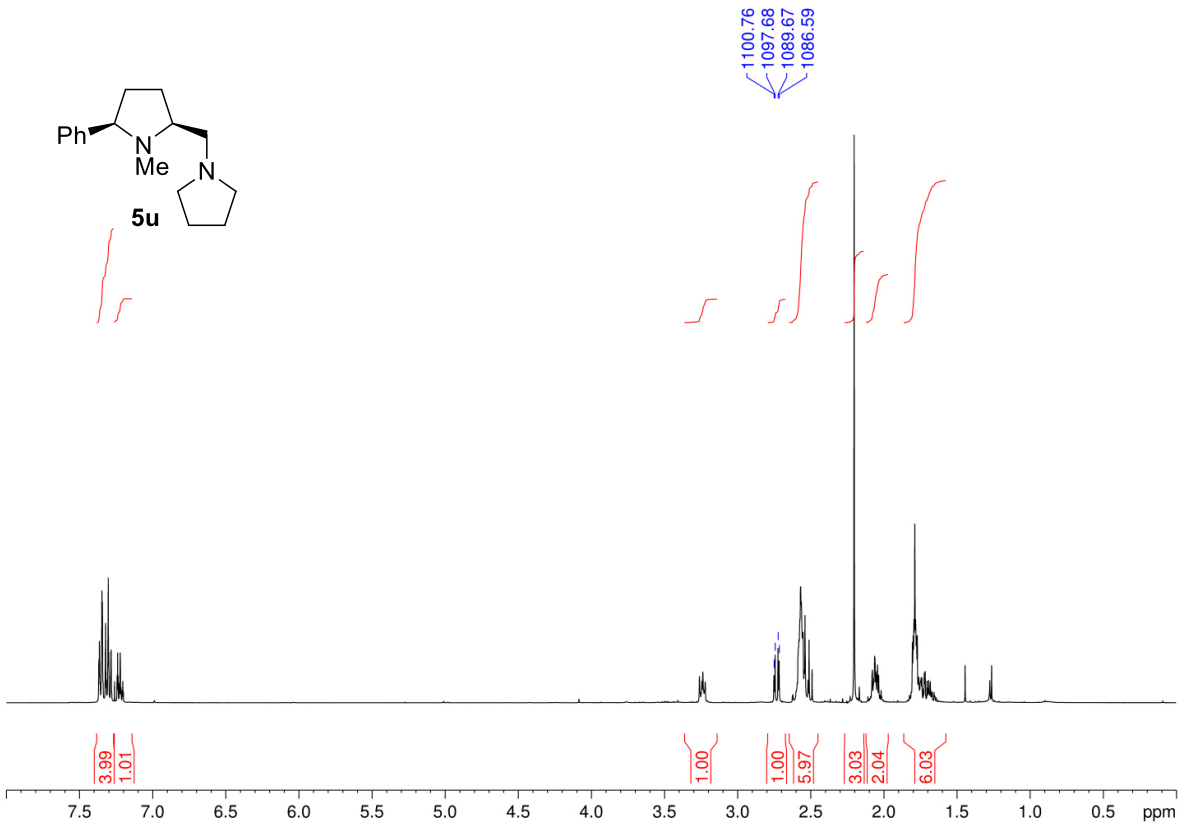

72.56
65.54
65.37
46.63
40.44
29.53
28.96
23.25
20.43
15.56
iPr
N
Me
NMe2
5r
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

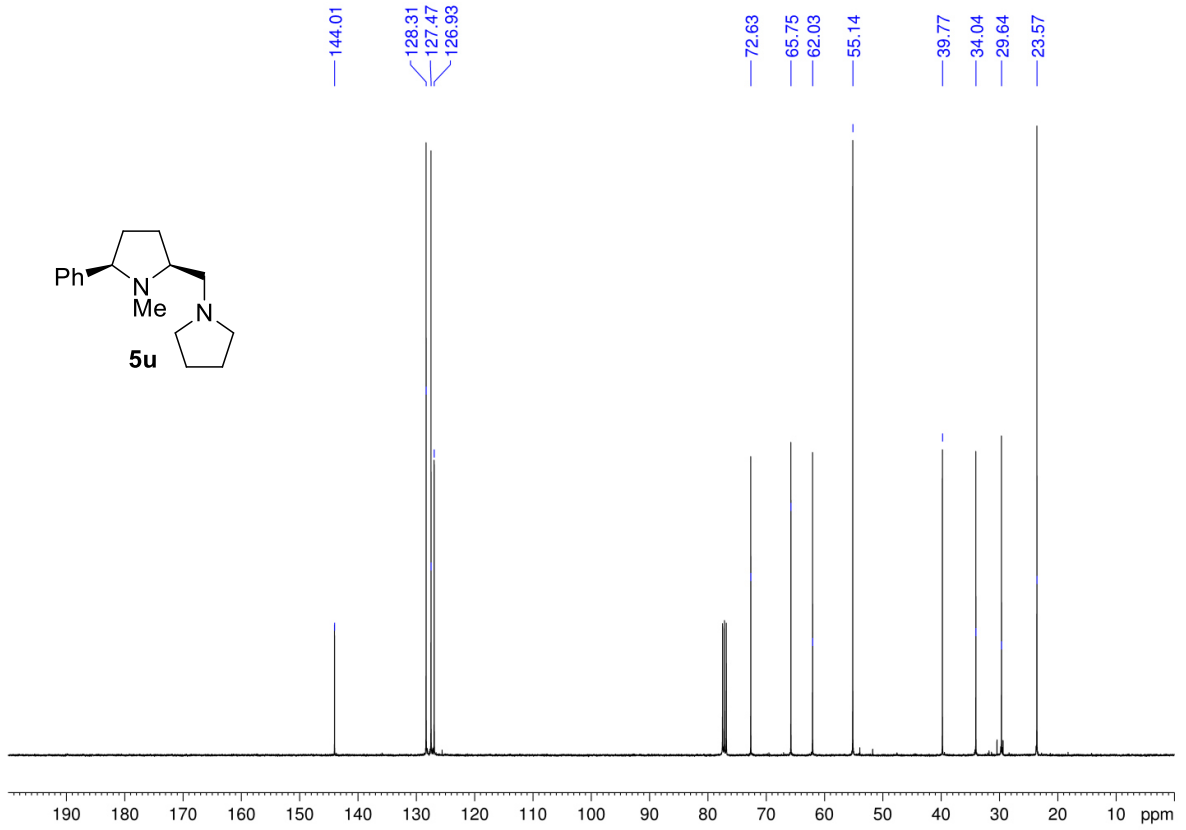

936.59
927.97
918.97
910.35
Bn
N
Me
NMe2
5s
2.05
2.96
1.00
6.97
6.98
1.01
1.04
2.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

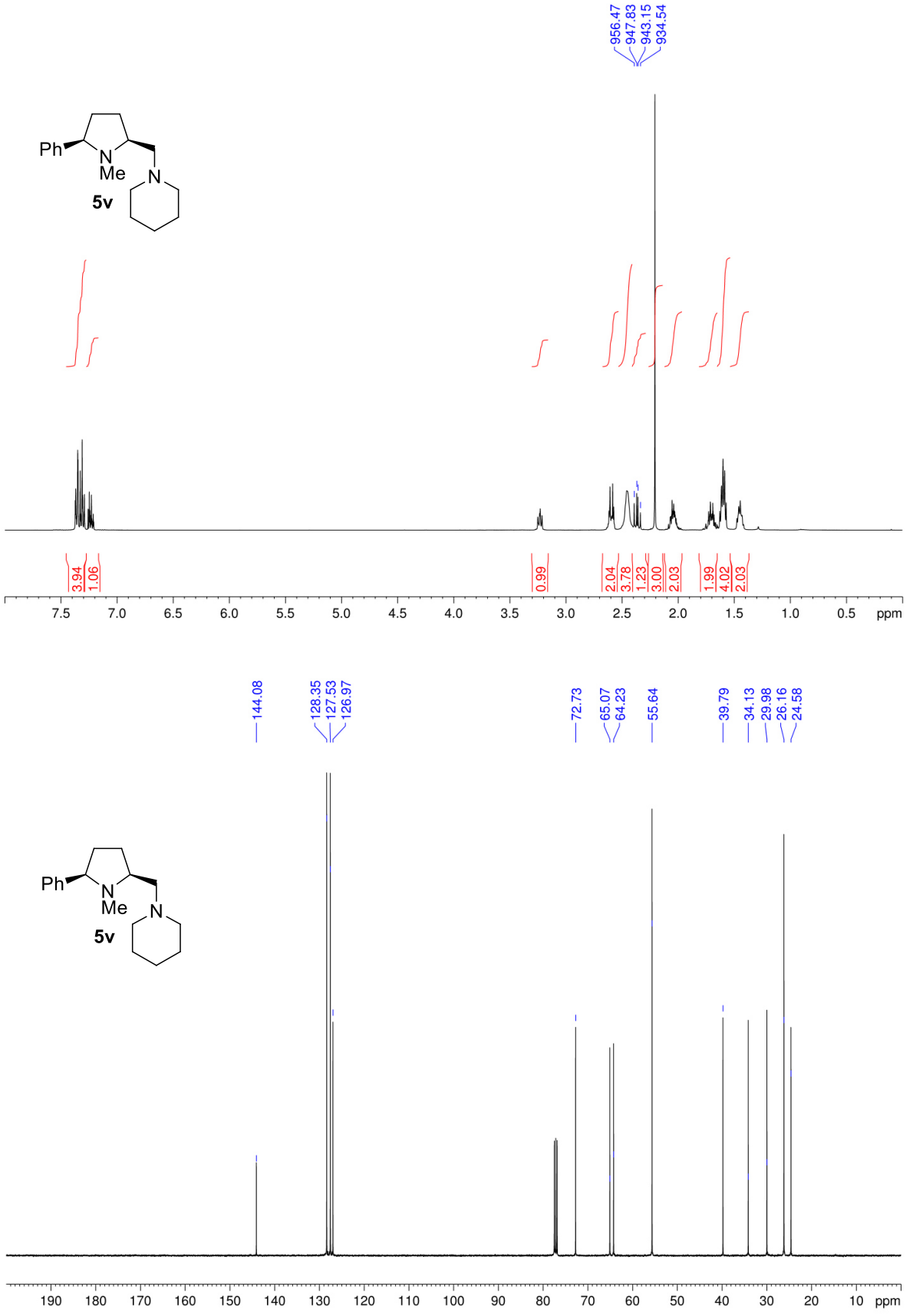

139.98
129.19
128.23
125.96
69.37
65.38
65.22
46.39
40.96
40.03
29.46
28.63
Bn
N
Me
NMe2
5s
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

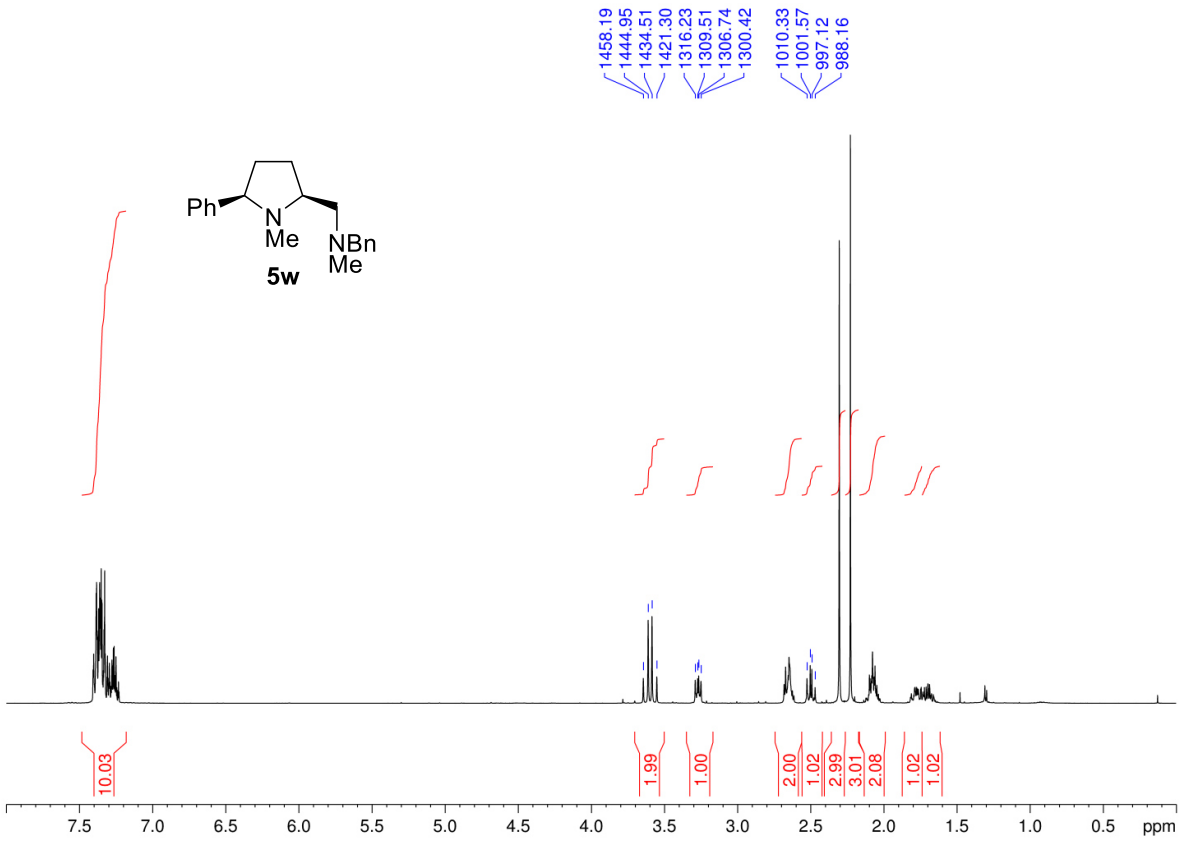

986.88
978.56
974.48
966.15
428.82
421.70
414.53
Ph
N
Me
NEt2
5t
4.04
1.00
1.00
5.98
1.10
3.02
2.09
2.04
6.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

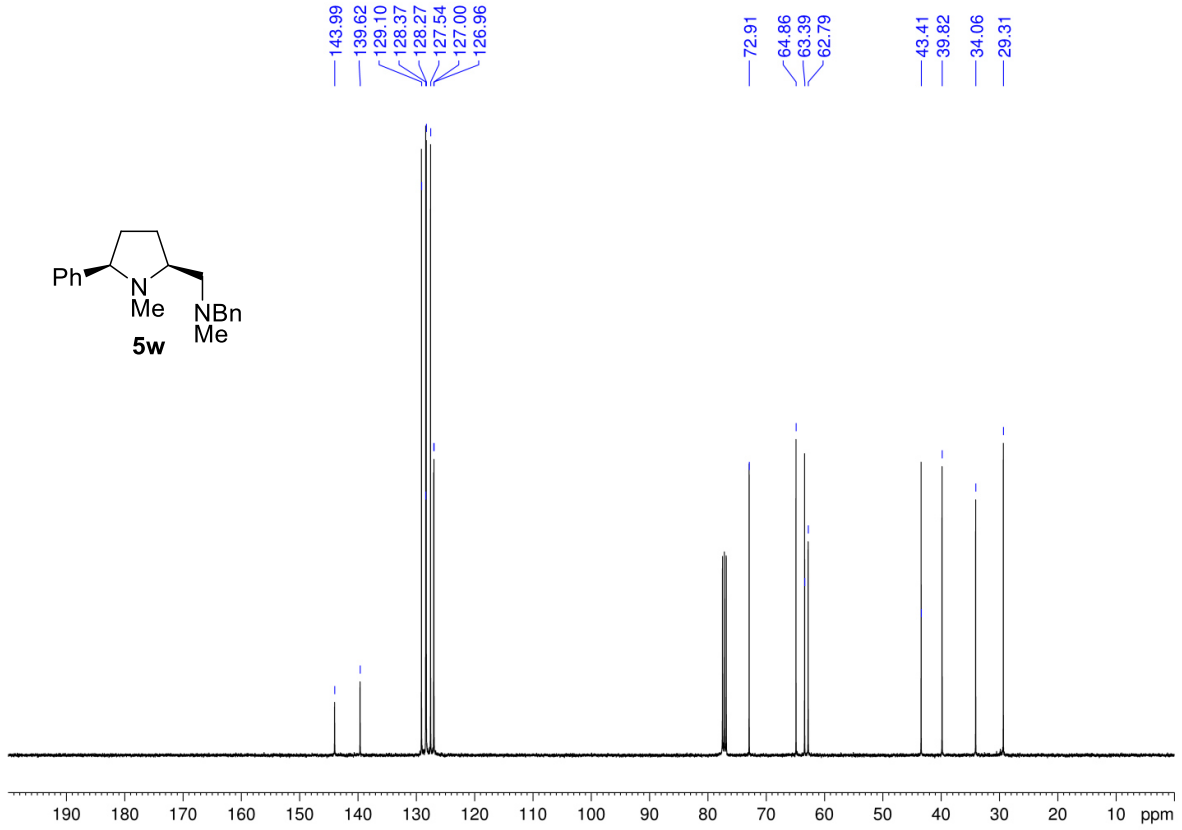

144.12
128.38
127.54
126.99
72.80
65.34
58.58
48.16
39.83
34.07
29.71
11.97
Ph
N
Me
NEt2
5t
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

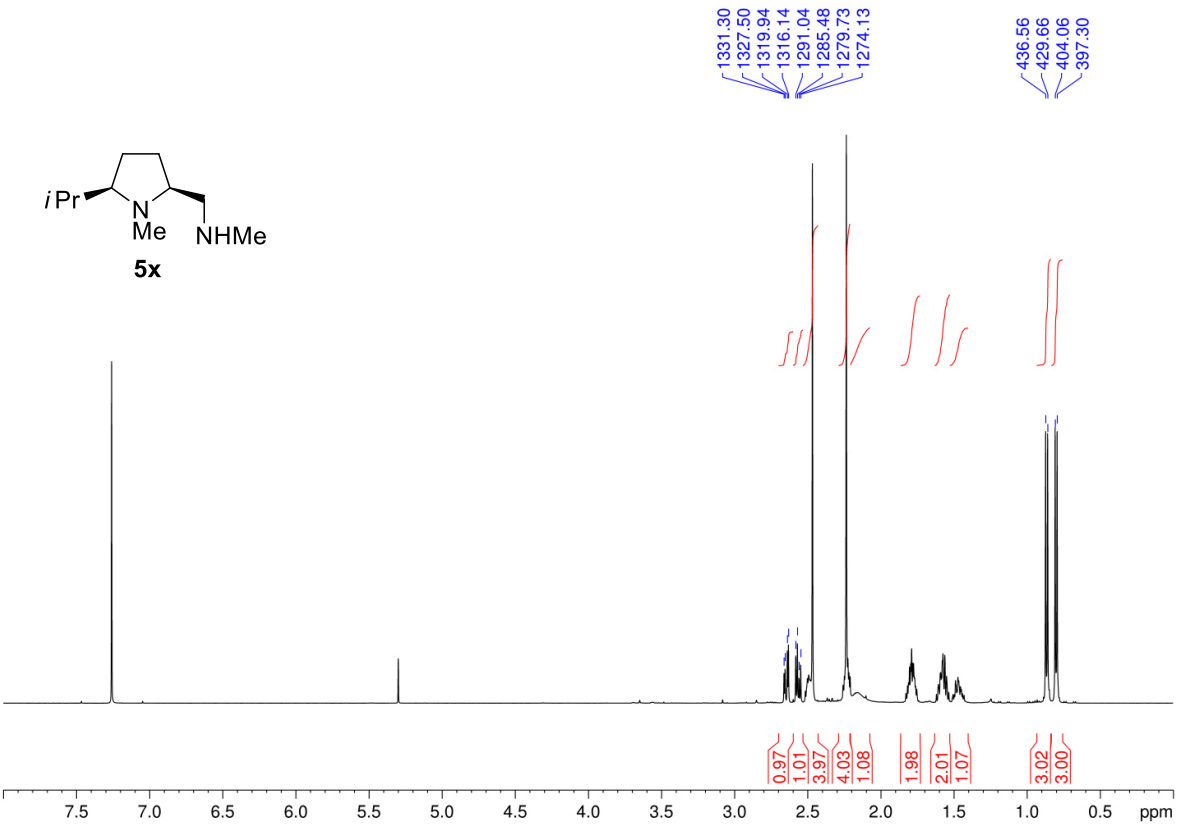

1100.76
1097.68
1089.67
1086.59
Ph
N
Me
N
5u
3.99
1.01
1.00
1.00
5.97
3.03
2.04
6.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

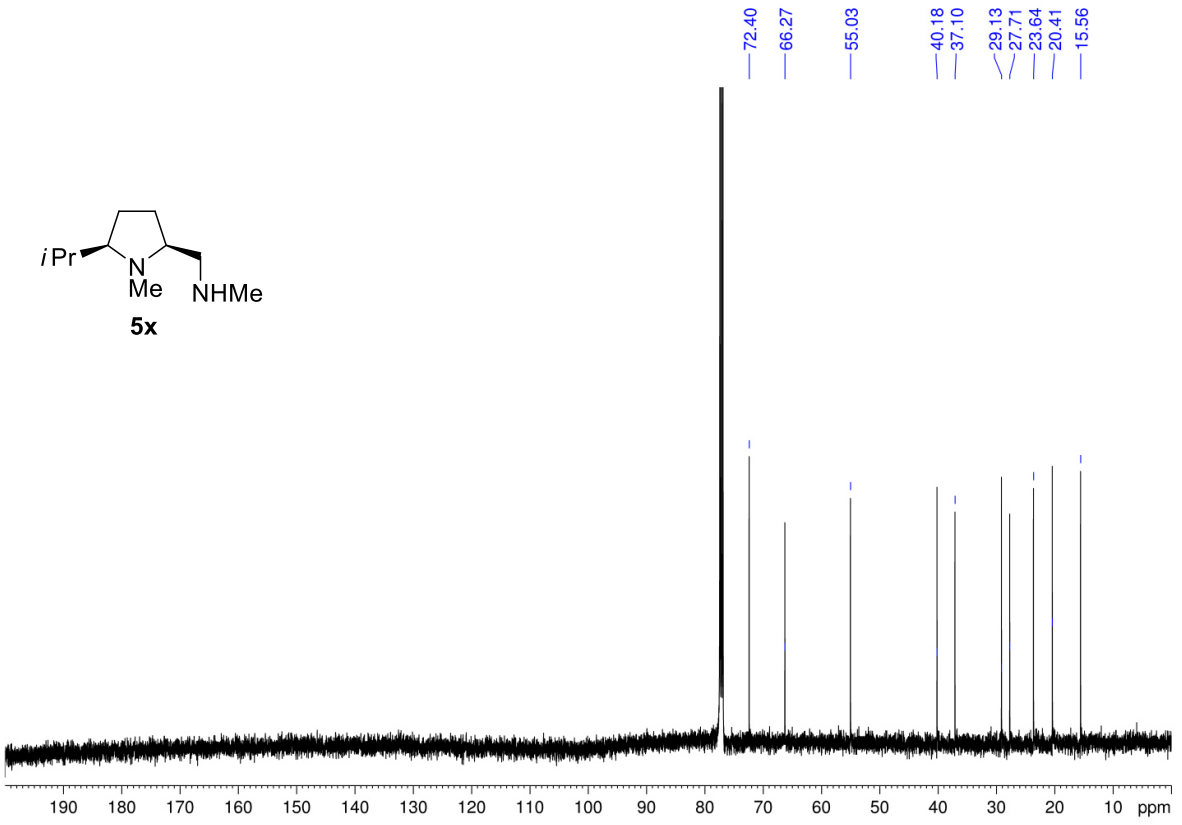

144.01
128.31
127.47
126.93
72.63
65.75
62.03
55.14
39.77
34.04
29.64
23.57
Ph
N
Me
N
5u
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

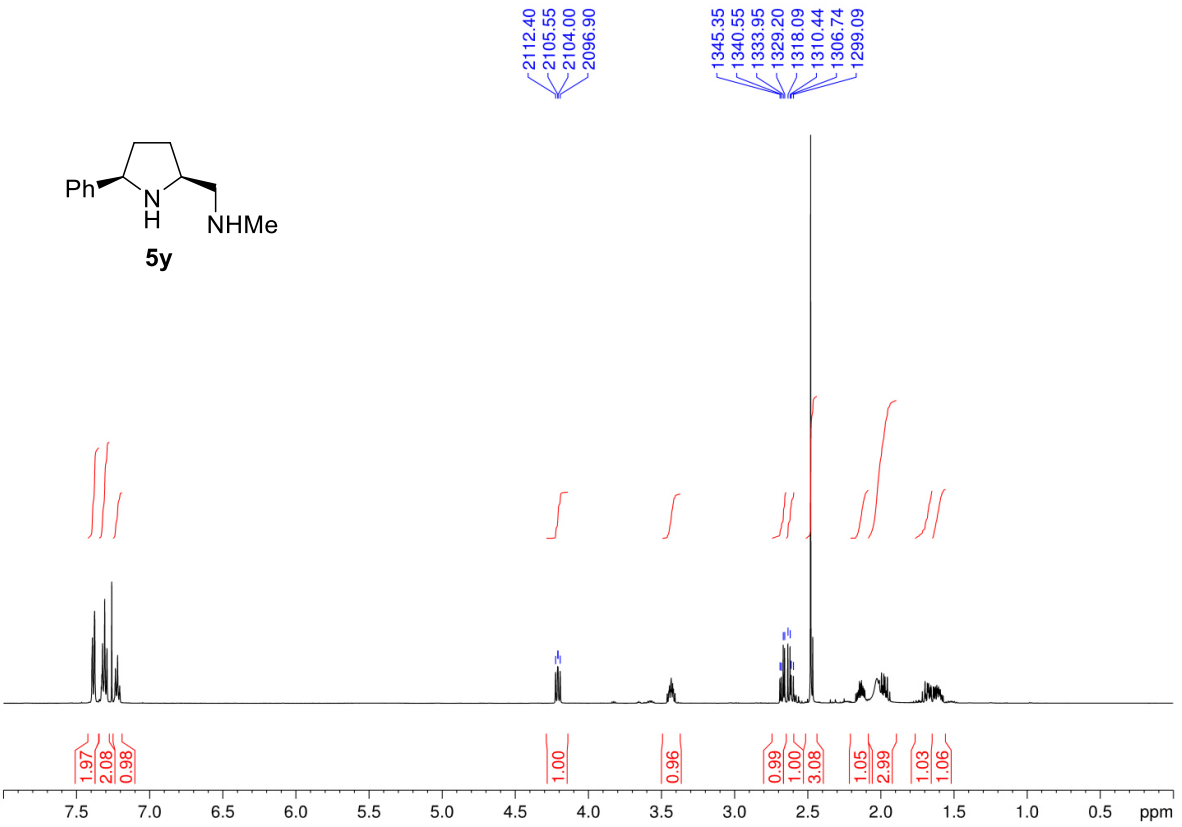

956.47
947.83
943.15
934.54
Ph
N
Me
N
5v
3.94
1.06
0.99
2.04
3.78
1.23
3.00
2.03
1.99
4.02
2.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
144.08
128.35
127.53
126.97
72.73
65.07
64.23
55.64
39.79
34.13
29.98
26.16
24.58
Ph
N
Me
N
5v
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

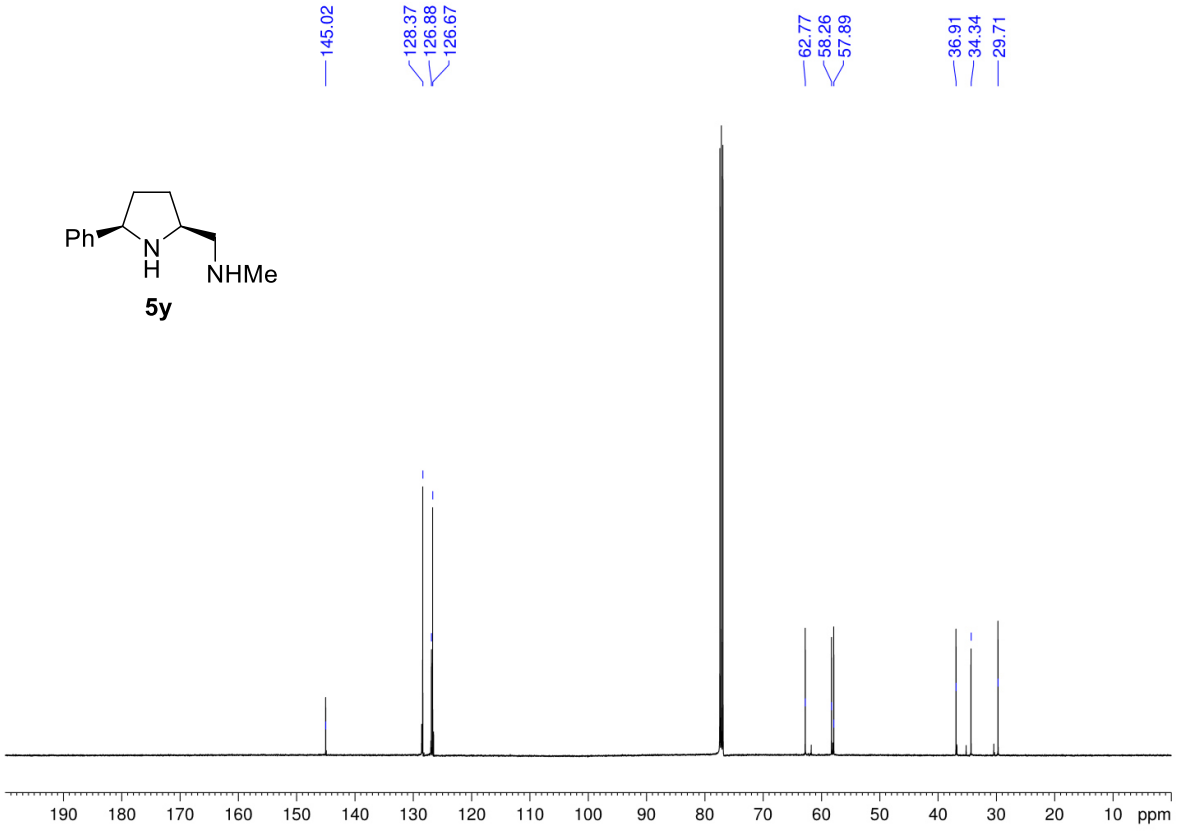

1458.19
1444.95
1434.51
1421.30
1316.23
1309.51
1306.74
1300.42
1010.33
1001.57
997.12
988.16
Ph
N
Me
NBn
Me
5w
10.03
1.99
1.00
2.00
1.02
2.99
3.01
2.08
1.02
1.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

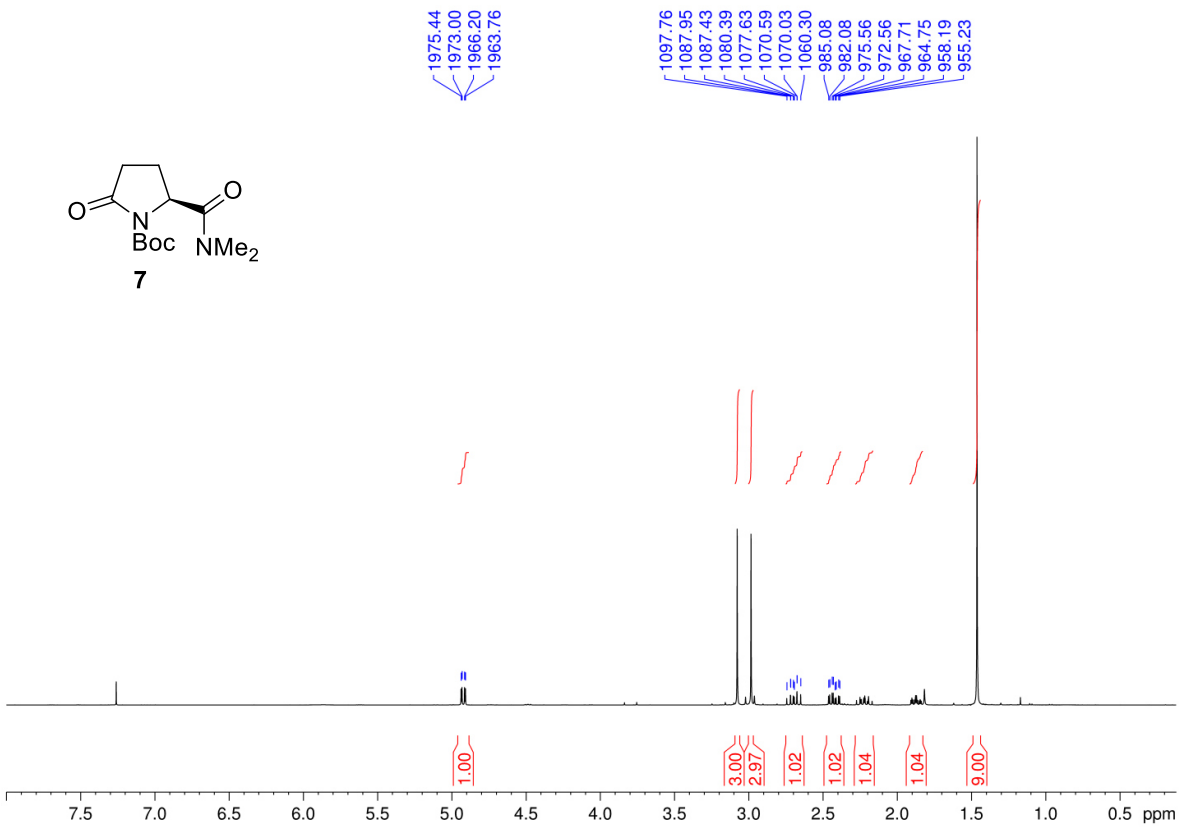

143.99
139.62
129.10
128.37
128.27
127.54
127.00
126.96
72.91
64.86
63.39
62.79
43.41
39.82
34.06
29.31
Ph
N
Me
NBn
Me
5w
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

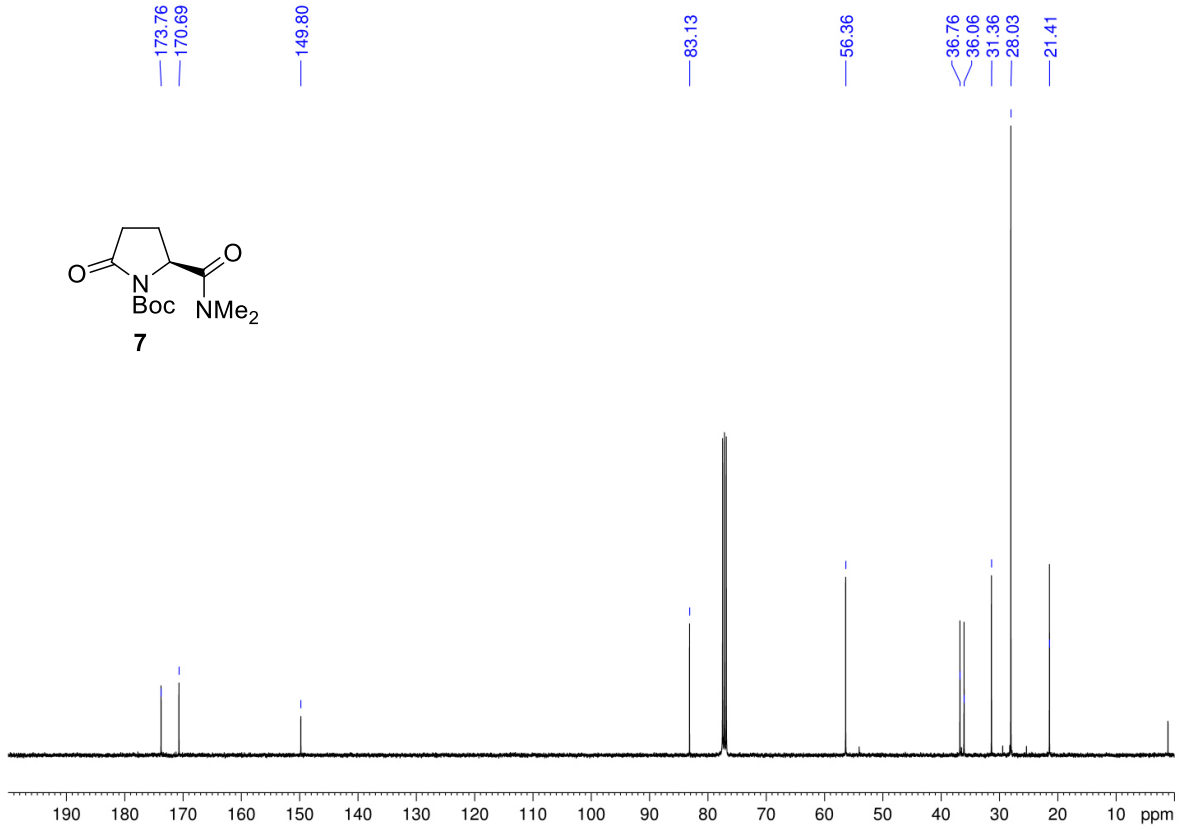

1331.30
1327.50
1319.94
1316.14
1291.04
1285.48
1279.73
1274.13
436.56
429.66
404.06
397.30
iPr
N
Me
NHMe
5x
0.97
1.01
3.97
4.03
1.08
1.98
2.01
1.07
3.02
3.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

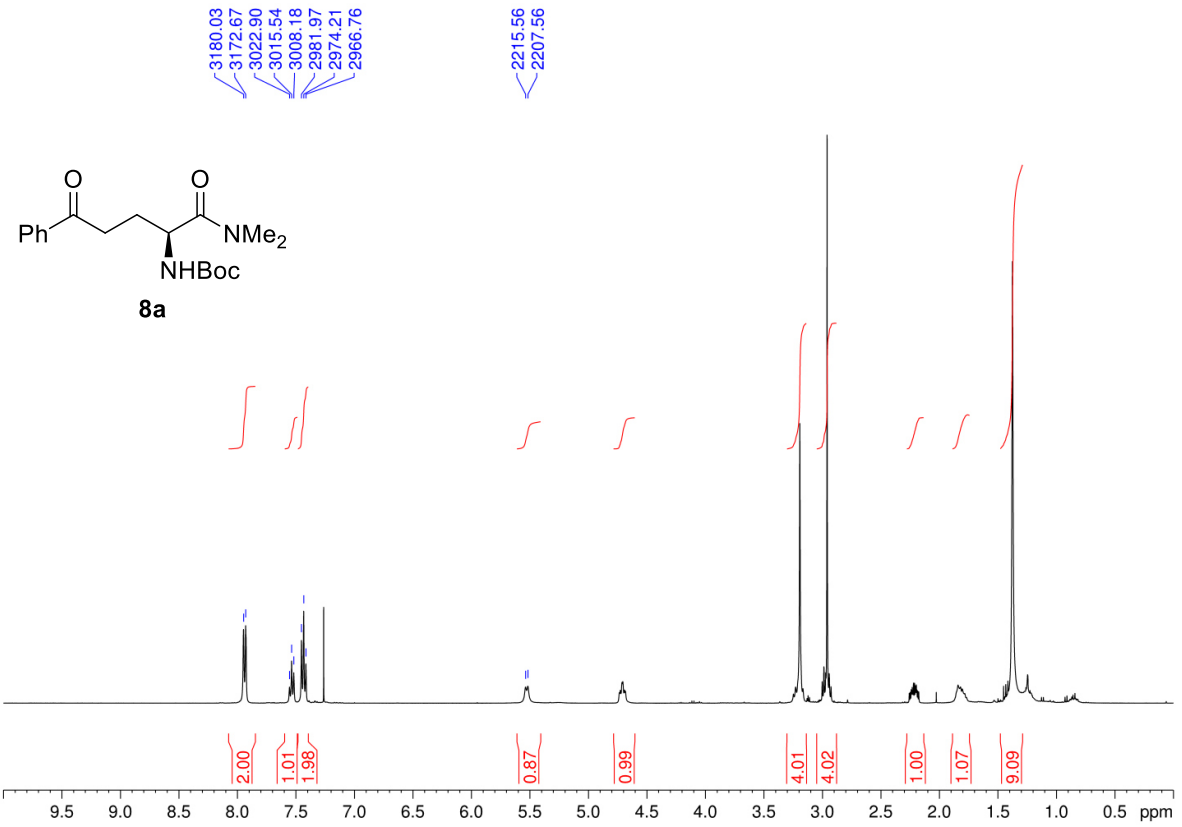

72.40
66.27
55.03
40.18
37.10
29.13
27.71
23.64
20.41
15.56
iPr
N
Me
NHMe
5x
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

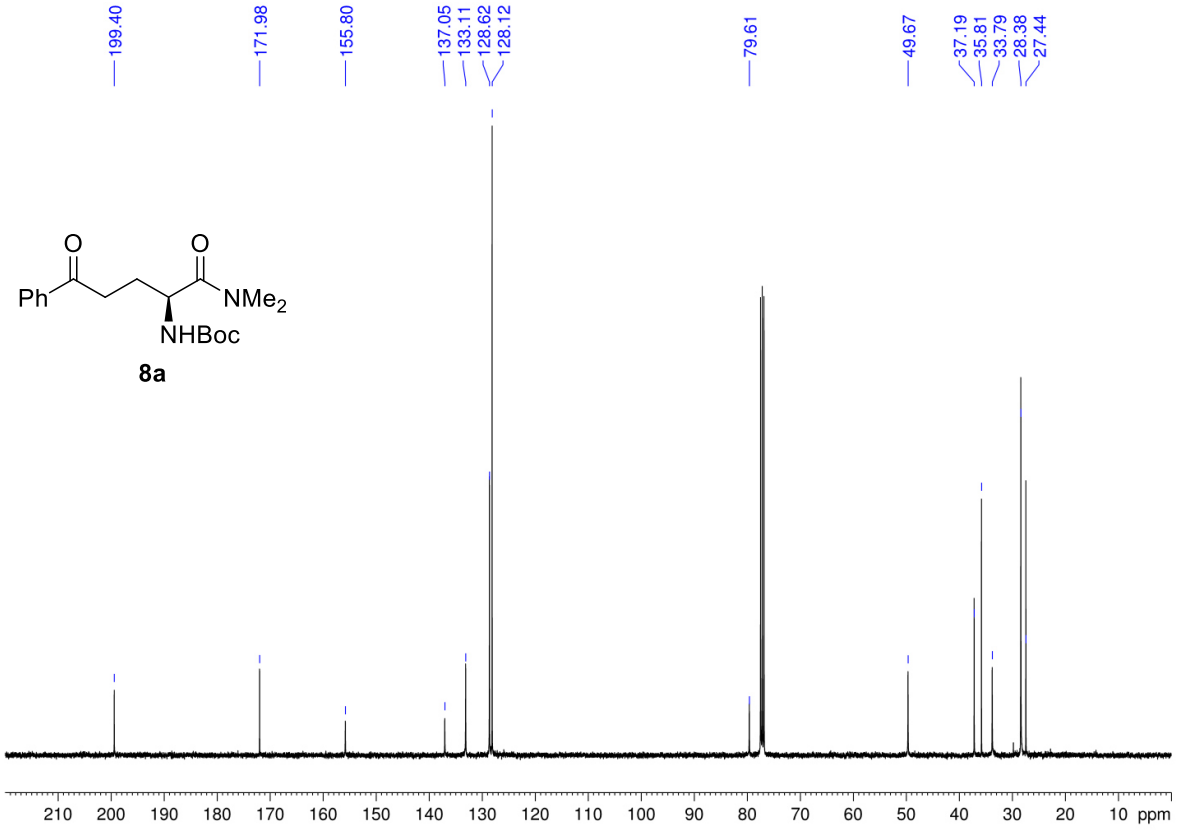

2112.40
2105.55
2104.00
2096.90
1345.35
1340.55
1333.95
1329.20
1318.09
1310.44
1306.74
1299.09
Ph
N
H
NHMe
5y
1.97
2.08
0.98
1.00
0.96
0.99
1.00
3.08
1.05
2.99
1.03
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

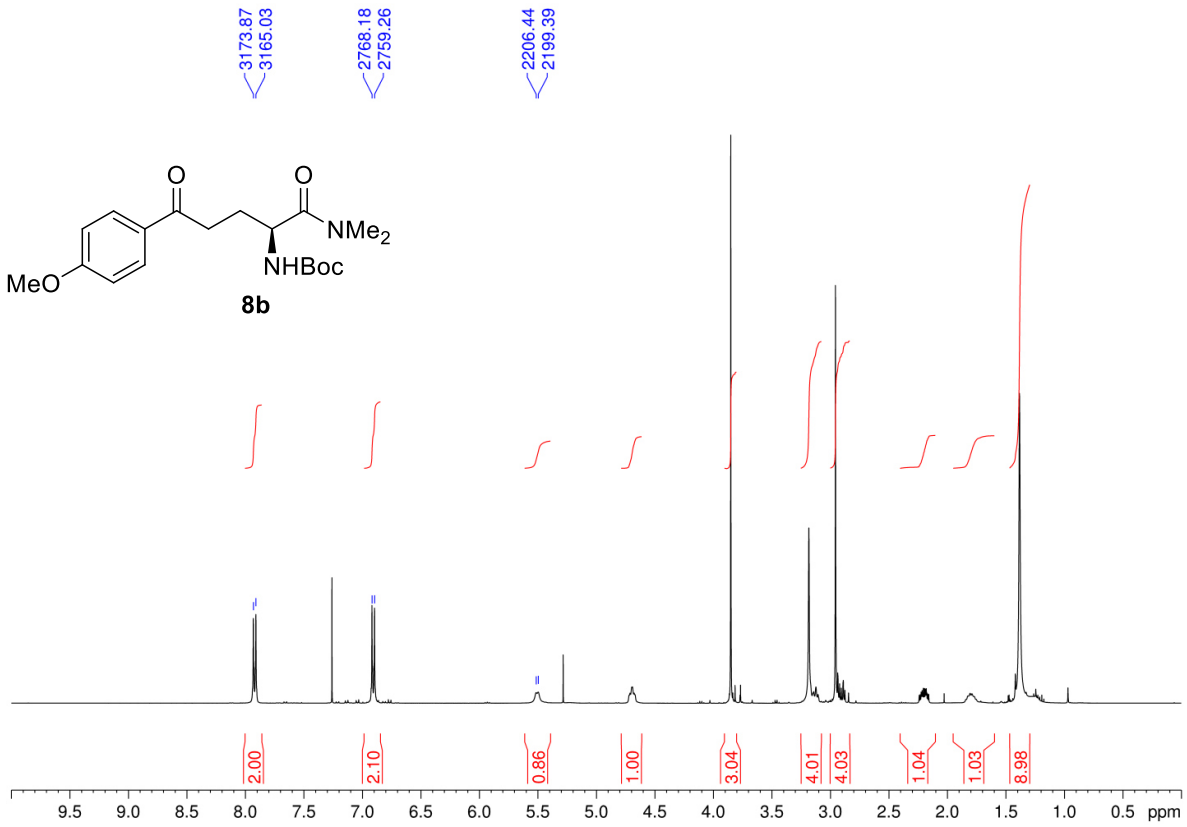

145.02
128.37
126.88
126.67
62.77
58.26
57.89
36.91
34.34
29.71
Ph
N
H
NHMe
5y
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

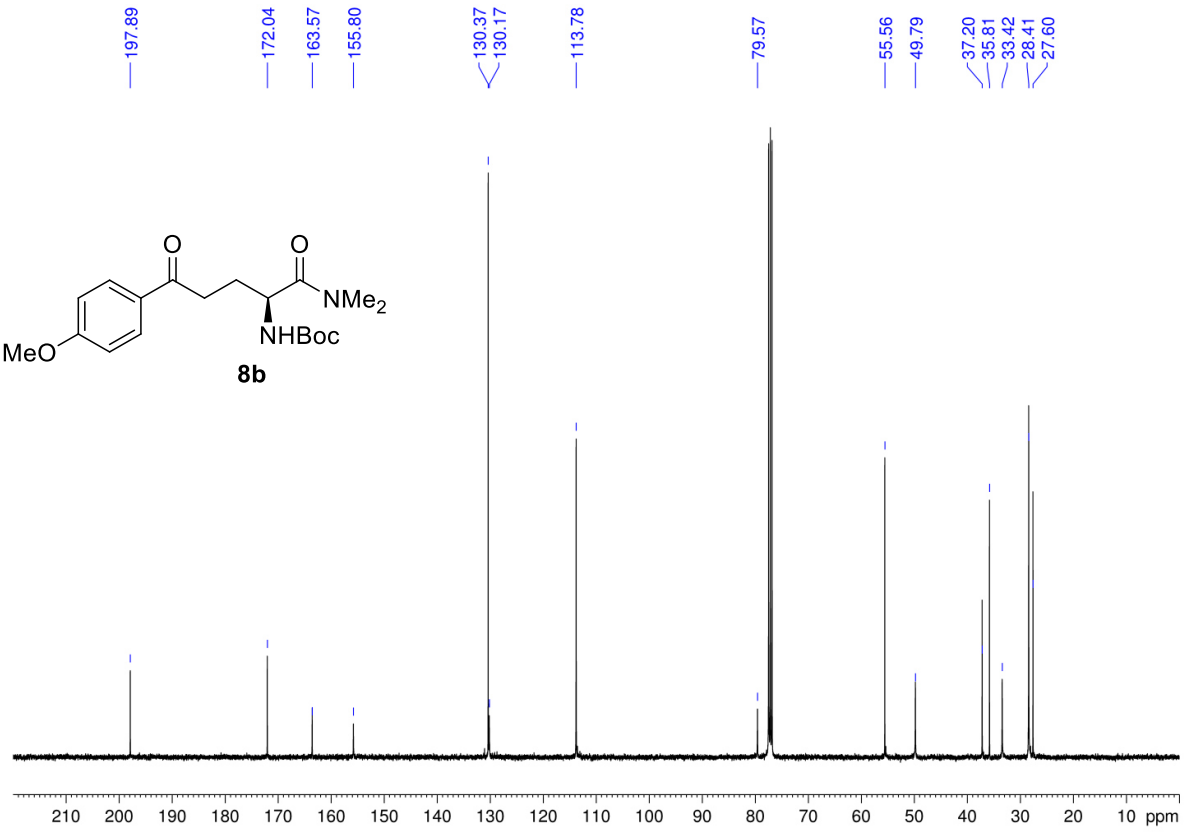

1975.44
1973.00
1966.20
1963.76
1097.76
1087.95
1087.43
1080.39
1077.63
1070.59
1070.03
1060.30
985.08
982.08
975.56
972.56
967.71
964.75
958.19
955.23
O
O
N
Boc
NMe2
7
1.00
3.00
2.97
1.02
1.02
1.04
1.04
9.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

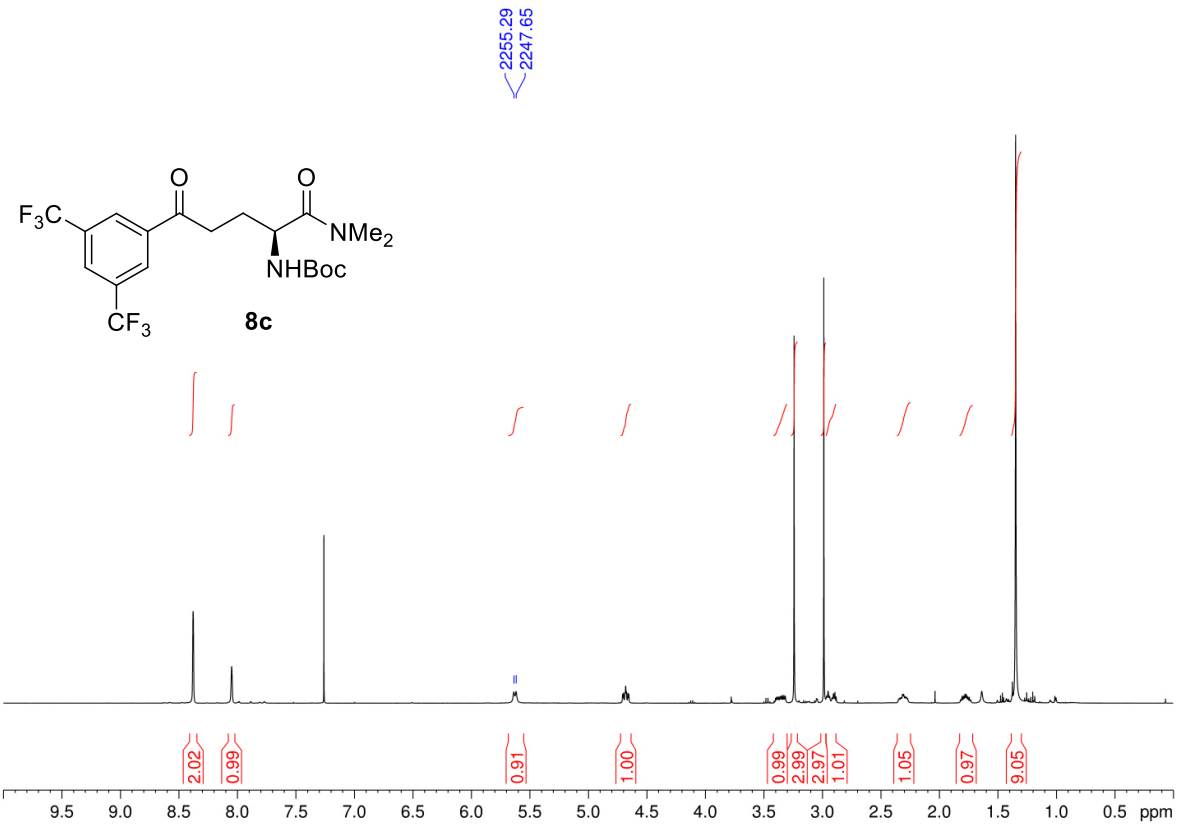

173.76
170.69
149.80
83.13
56.36
36.76
36.06
31.36
28.03
21.41
O
O
N
Boc
NMe2
7
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

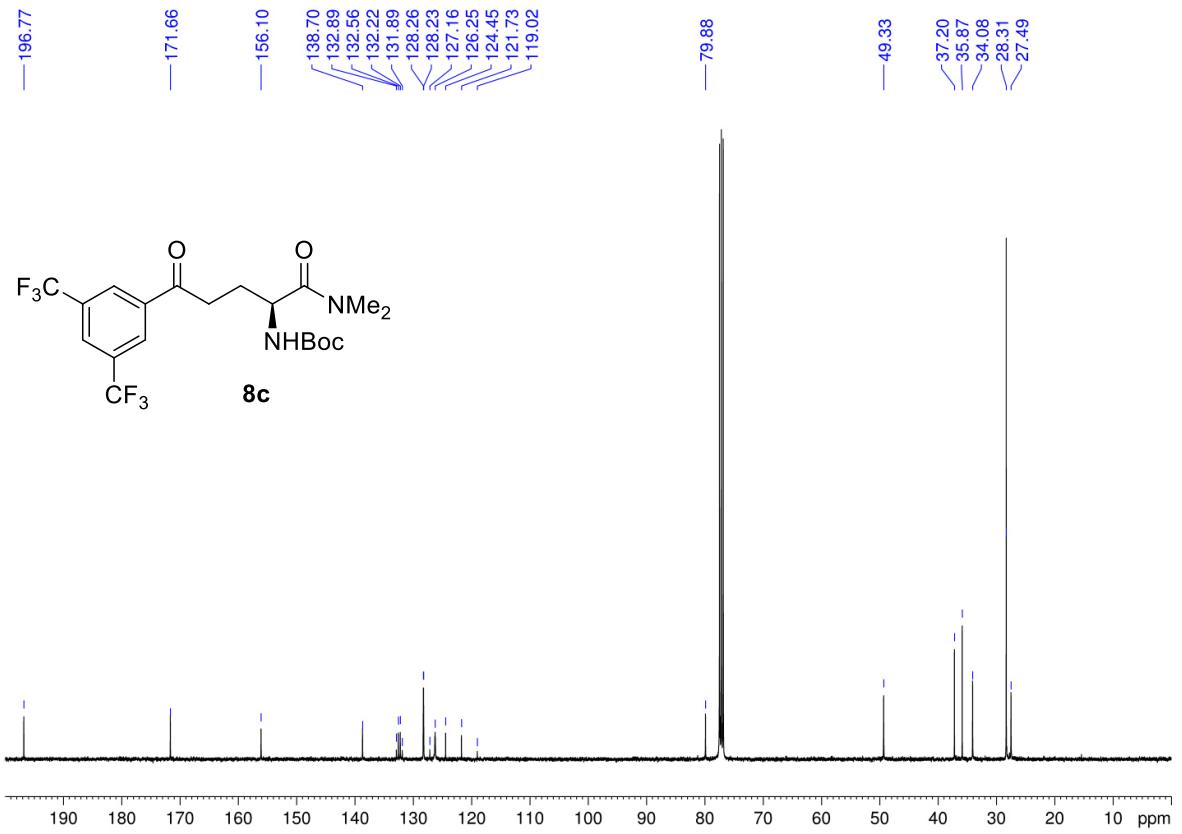

3180.03
3172.67
3022.90
3015.54
3008.18
2981.97
2974.21
2966.76
2215.56
2207.56
Ph
O
O
NMe2
NHBoc
8a
2.00
1.01
1.98
0.87
0.99
4.01
4.02
1.00
1.07
9.09
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

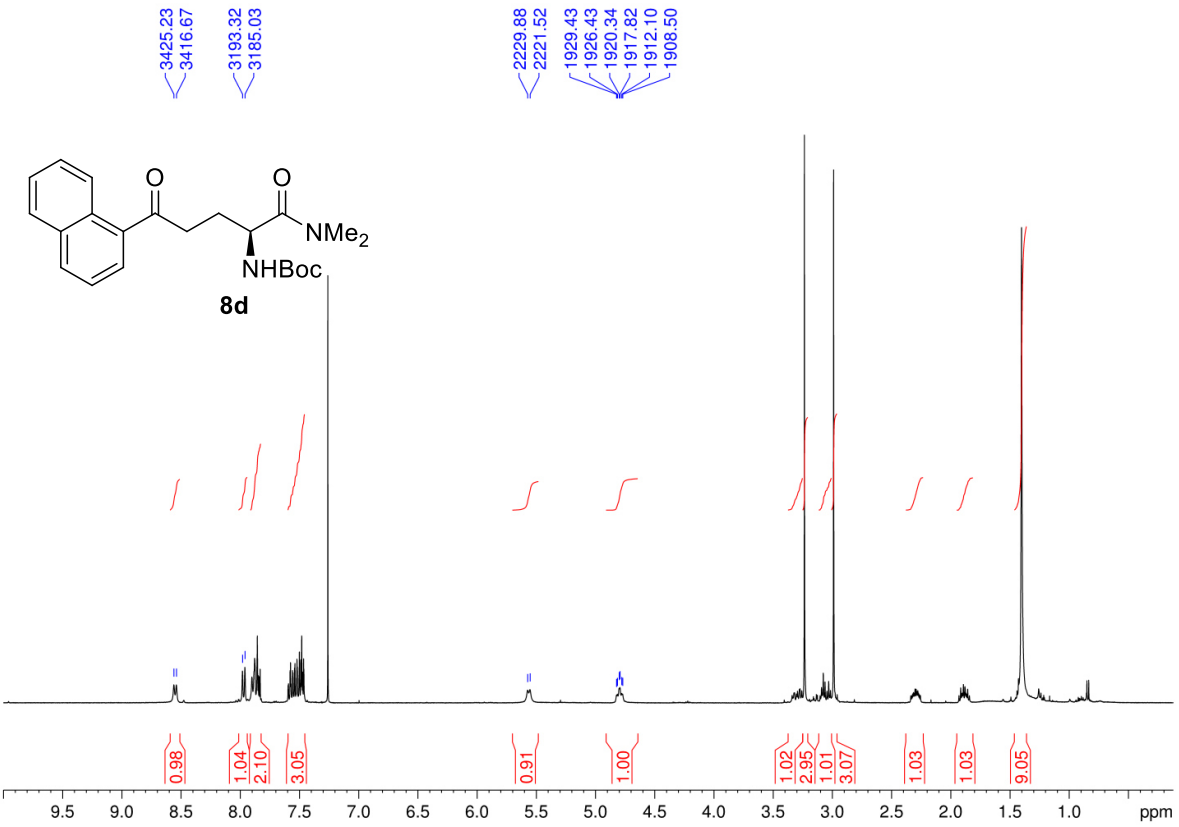

199.40
171.98
155.80
137.05
133.11
128.62
128.12
79.61
49.67
37.19
35.81
33.79
28.38
27.44
Ph
O
O
NMe2
NHBoc
8a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

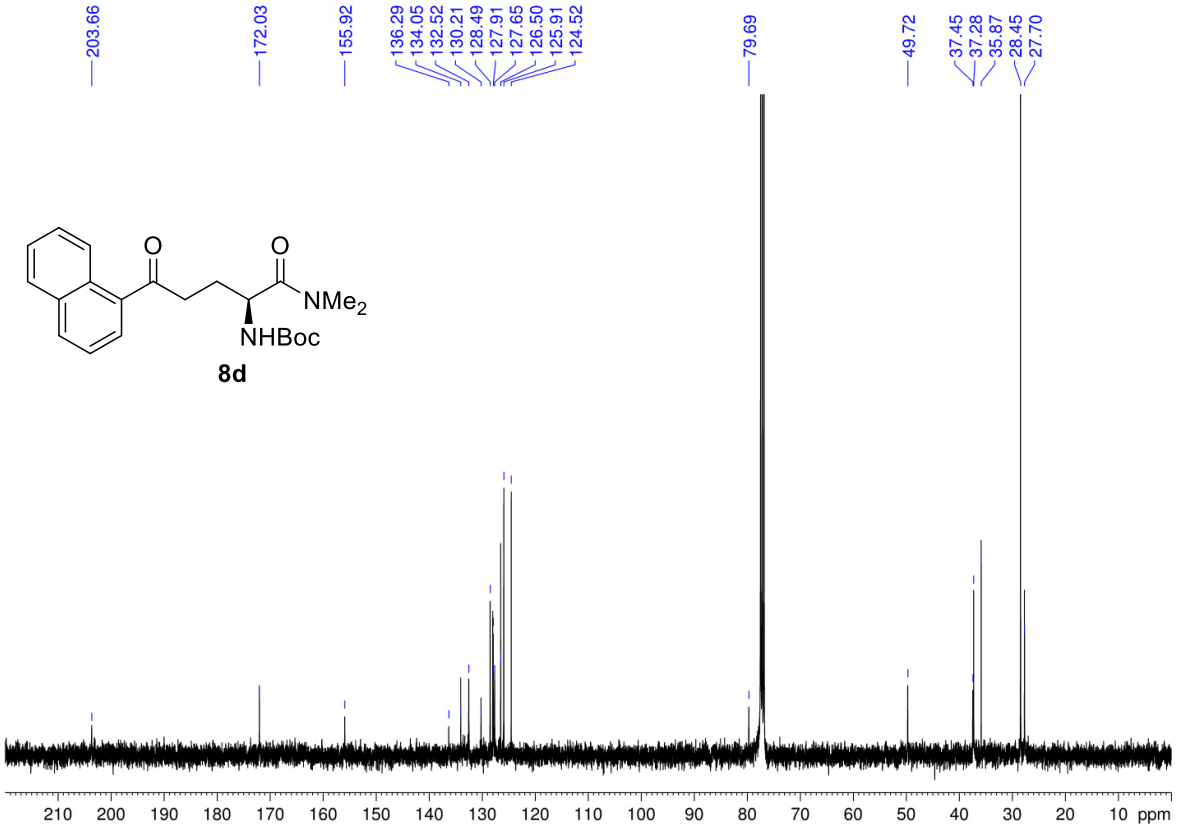

3173.87
3165.03
2768.18
2759.26
2206.44
2199.39
O
O
NMe2
NHBoc
MeO
8b
2.00
2.10
0.86
1.00
3.04
4.01
4.03
1.04
1.03
8.98
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

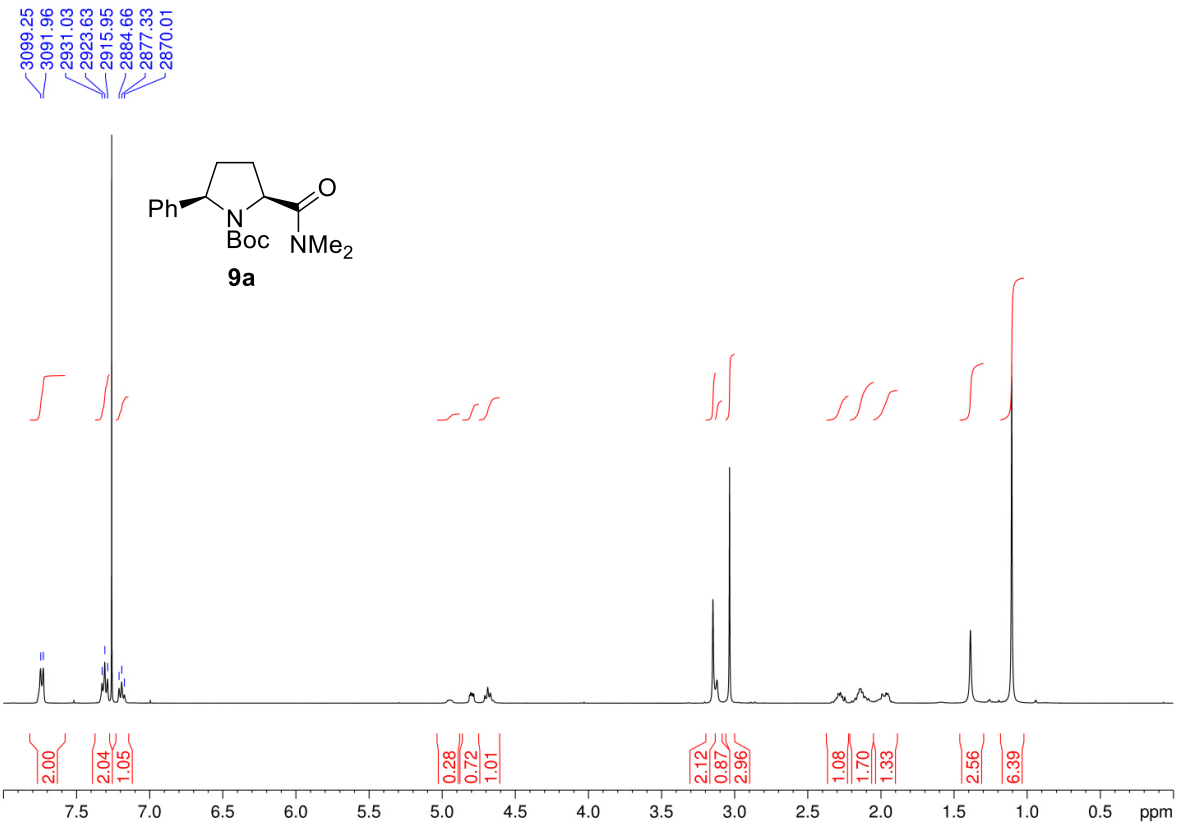

197.89
172.04
163.57
155.80
130.37
130.17
113.78
79.57
55.56
49.79
37.20
35.81
33.42
28.41
27.60
O
O
NMe2
NHBoc
MeO
8b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

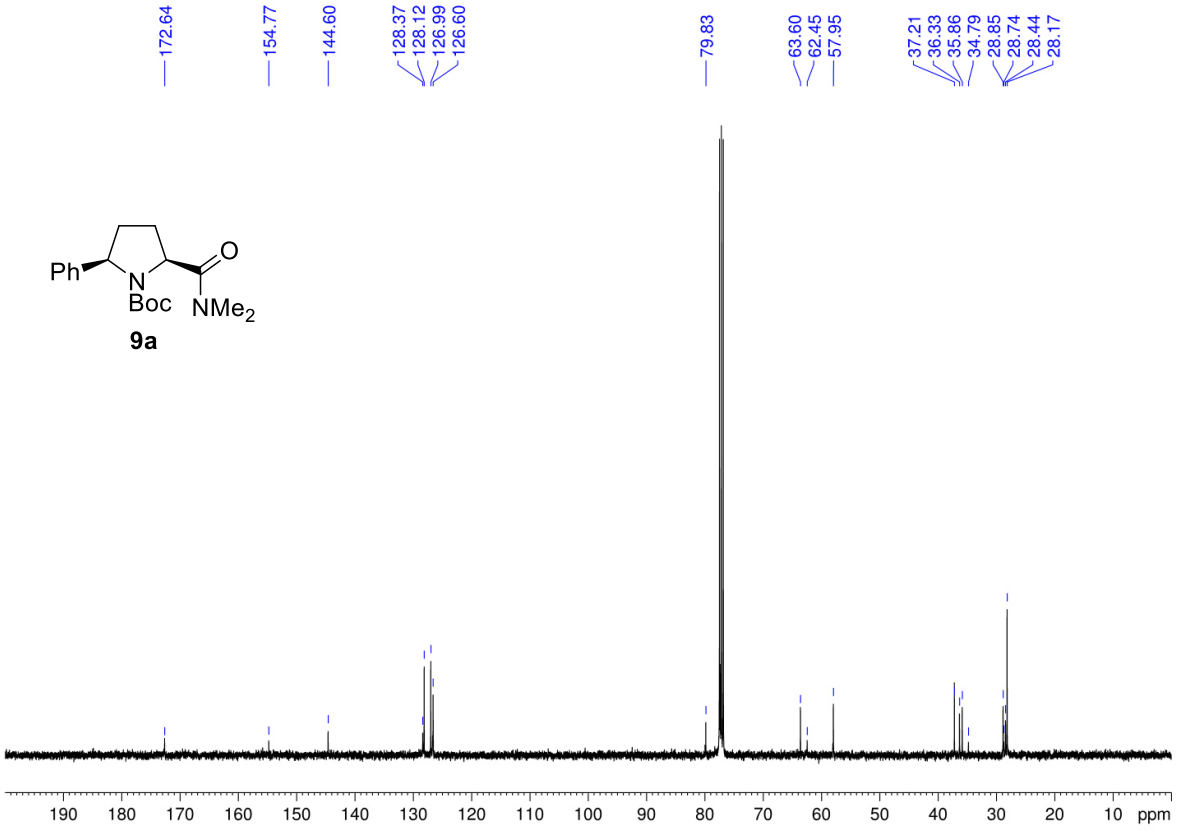

2255.29
2247.65
F3C
O
O
NMe2
NHBoc
CF3
8c
2.02
0.99
0.91
1.00
0.99
2.99
2.97
1.01
1.05
0.97
9.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

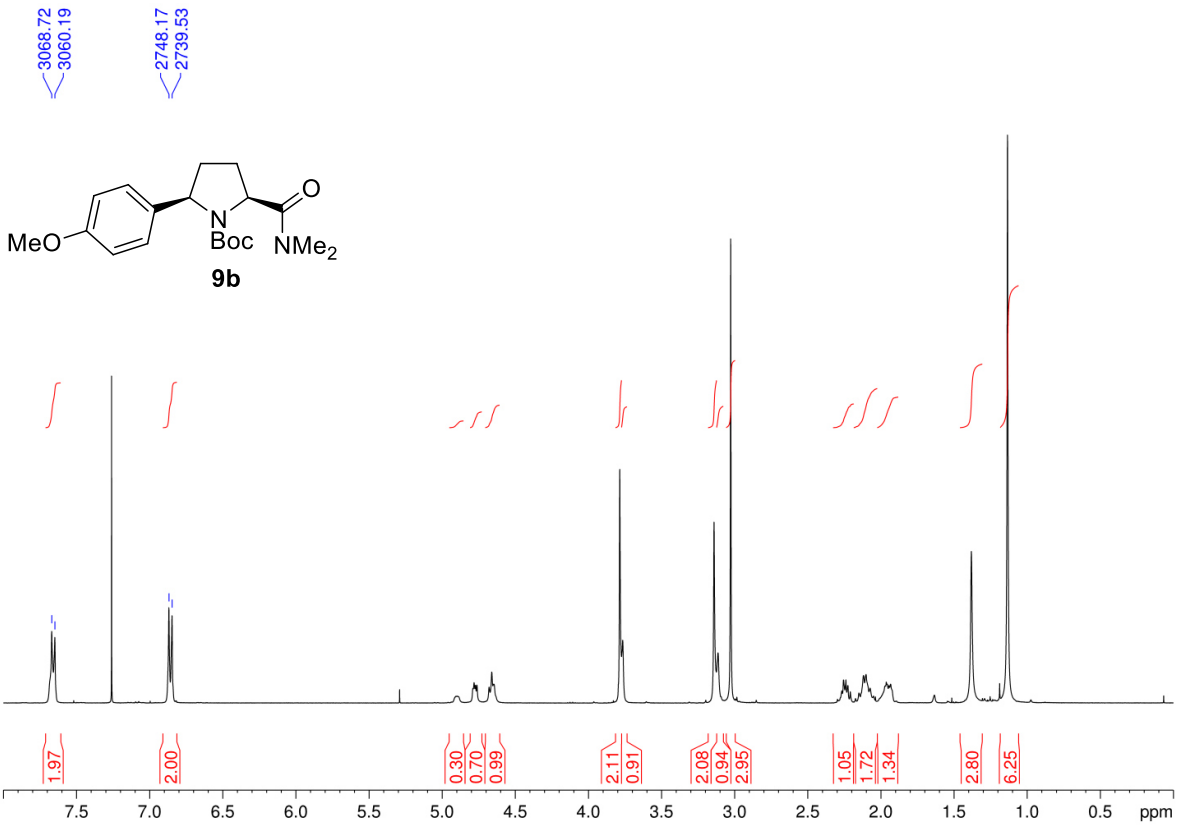

196.77
171.66
156.10
138.70
132.89
132.56
132.22
131.89
128.26
128.23
127.16
126.25
124.45
121.73
119.02
79.88
49.33
37.20
35.87
34.08
28.31
27.49
F3C
O
O
NMe2
NHBoc
CF3
8c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

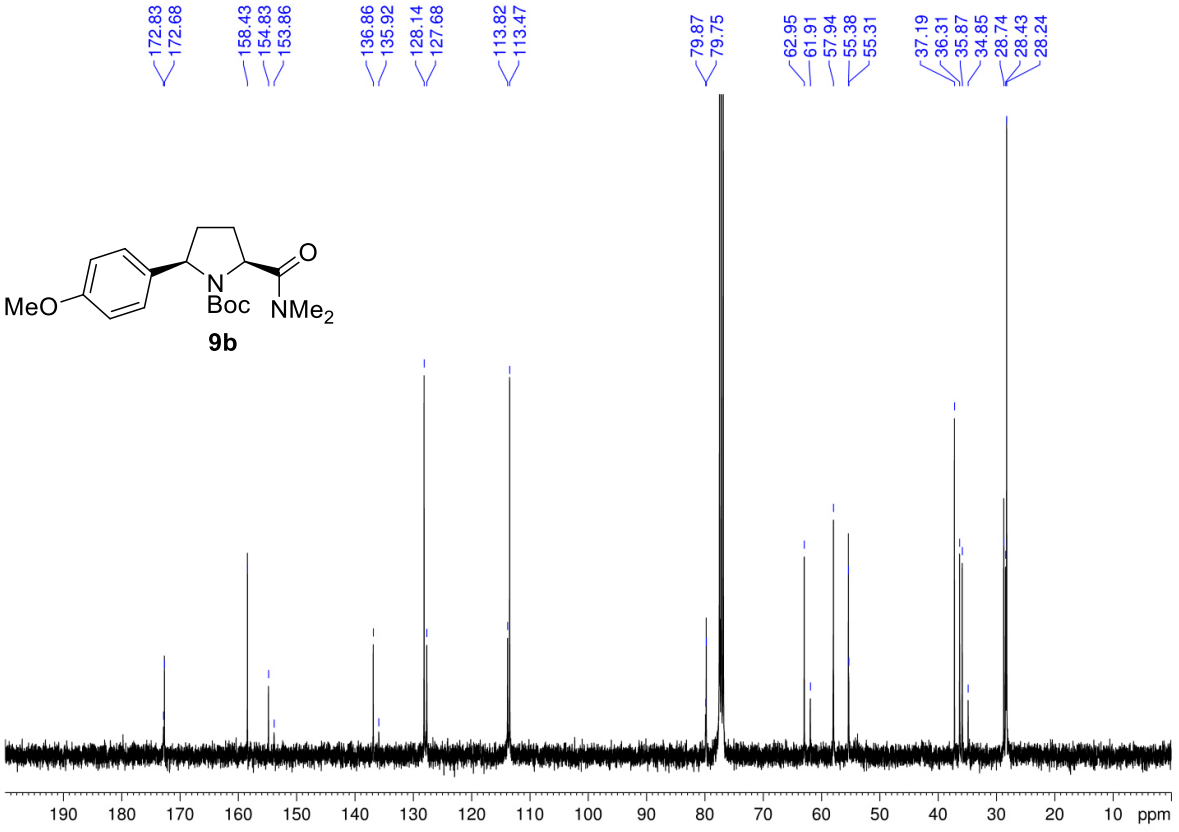

3425.23
3416.67
3193.32
3185.03
2229.88
2221.52
1929.43
1926.43
1920.34
1917.82
1912.10
1908.50
O
O
NMe2
NHBoc
8d
0.98
1.04
2.10
3.05
0.91
1.00
1.02
2.95
1.01
3.07
1.03
1.03
9.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm

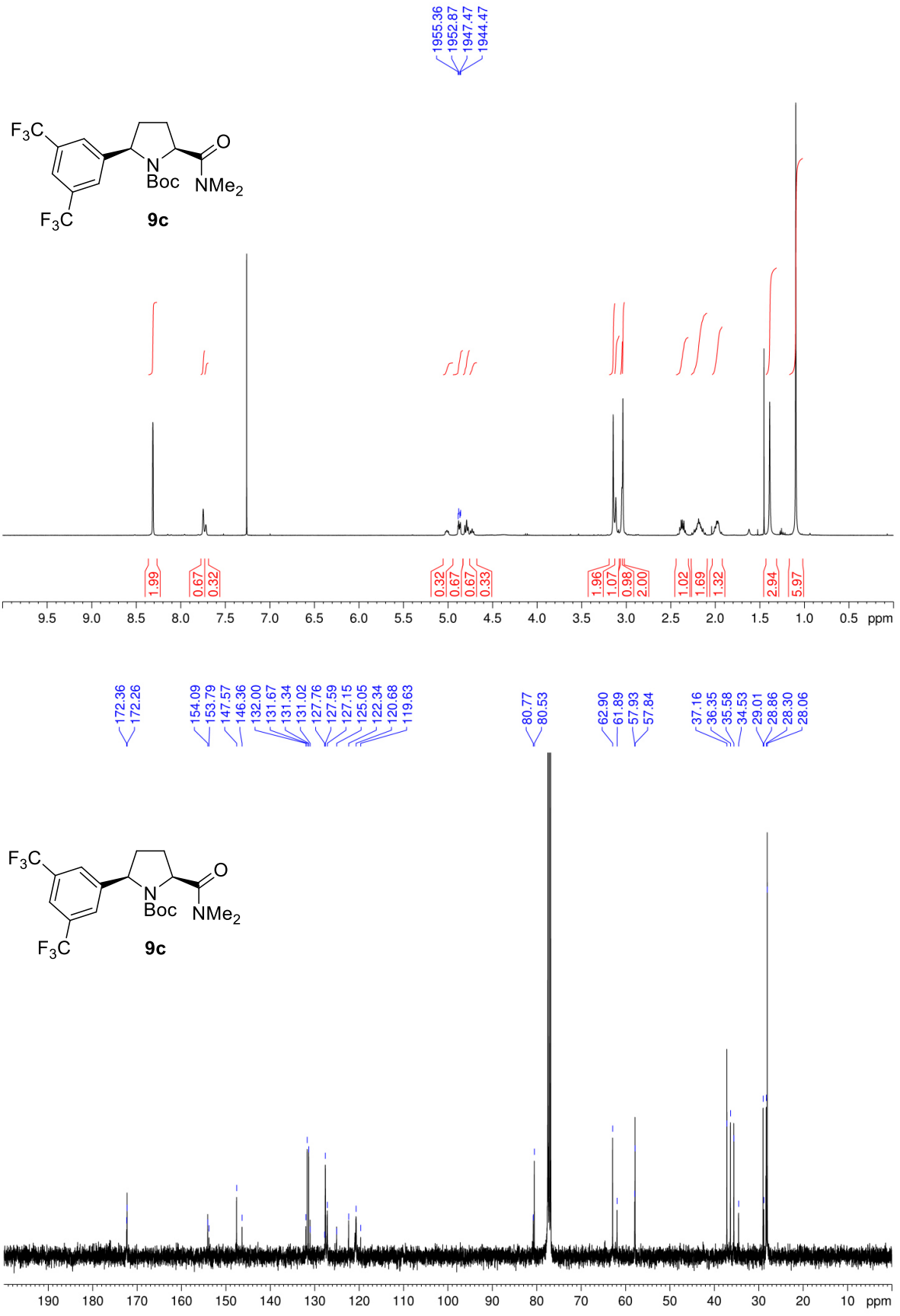

203.66
172.03
155.92
136.29
134.05
132.52
130.21
128.49
127.91
127.65
126.50
125.91
124.52
79.69
49.72
37.45
37.28
35.87
28.45
27.70
O
O
NMe2
NHBoc
8d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

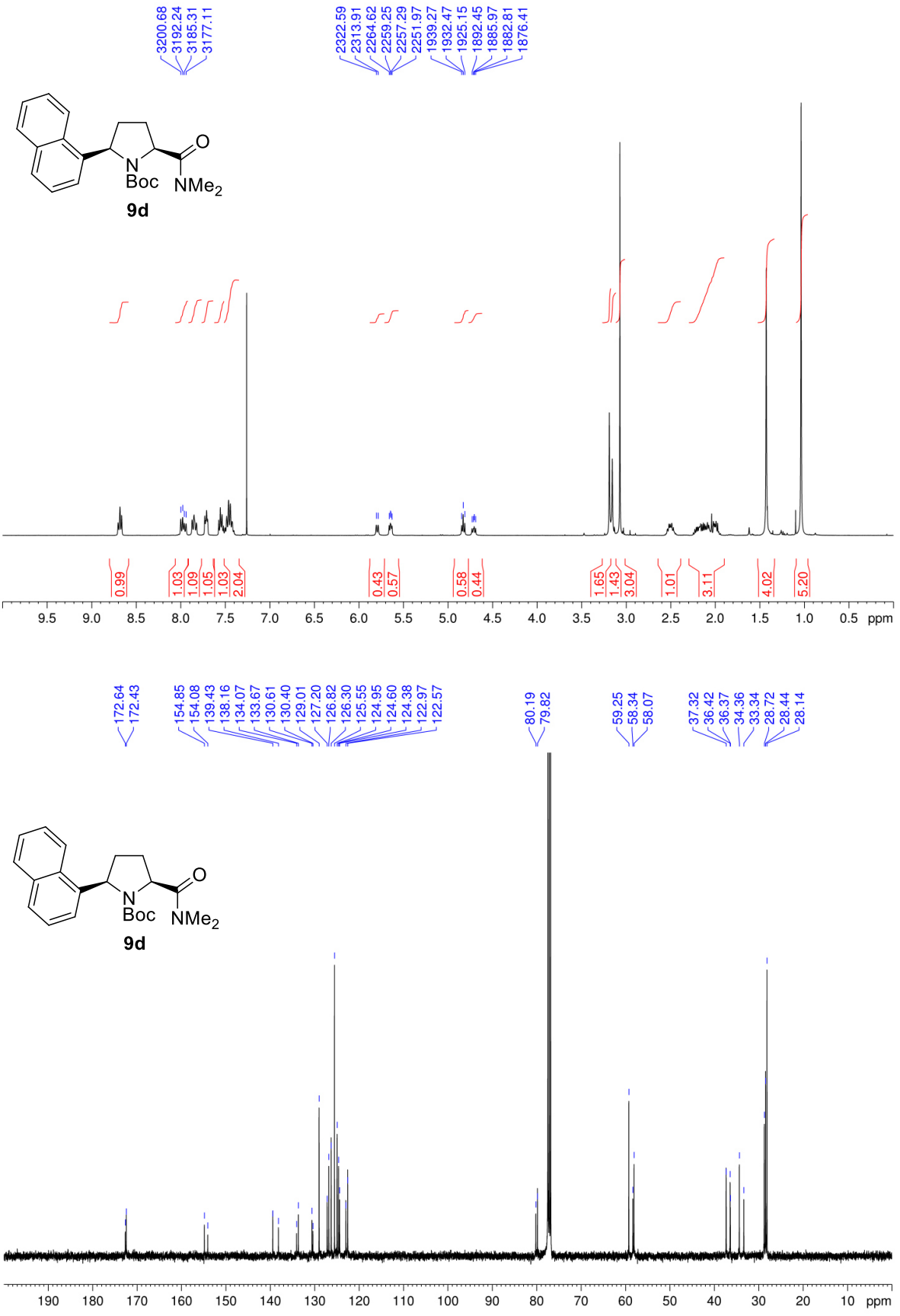

3099.25
3091.96
2931.03
2923.63
2915.95
2884.66
2877.33
2870.01
Ph
N
Boc
O
NMe2
9a
2.00
2.04
1.05
0.28
0.72
1.01
2.12
0.87
2.96
1.08
1.70
1.33
2.56
6.39
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

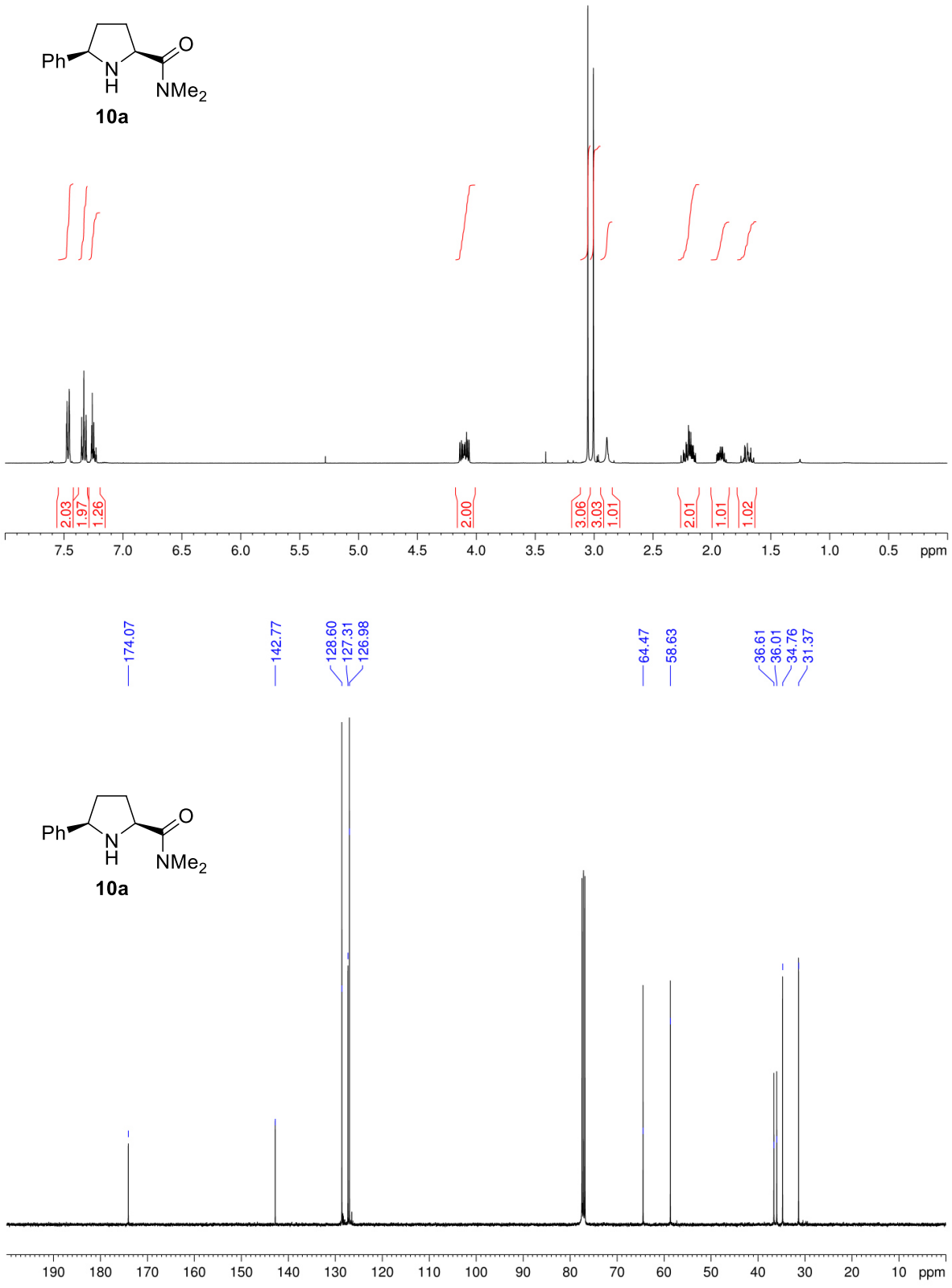

172.64
154.77
144.60
128.37
128.12
126.99
126.60
79.83
63.60
62.45
57.95
37.21
36.33
35.86
34.79
28.85
28.74
28.44
28.17
Ph
N
Boc
O
NMe2
9a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

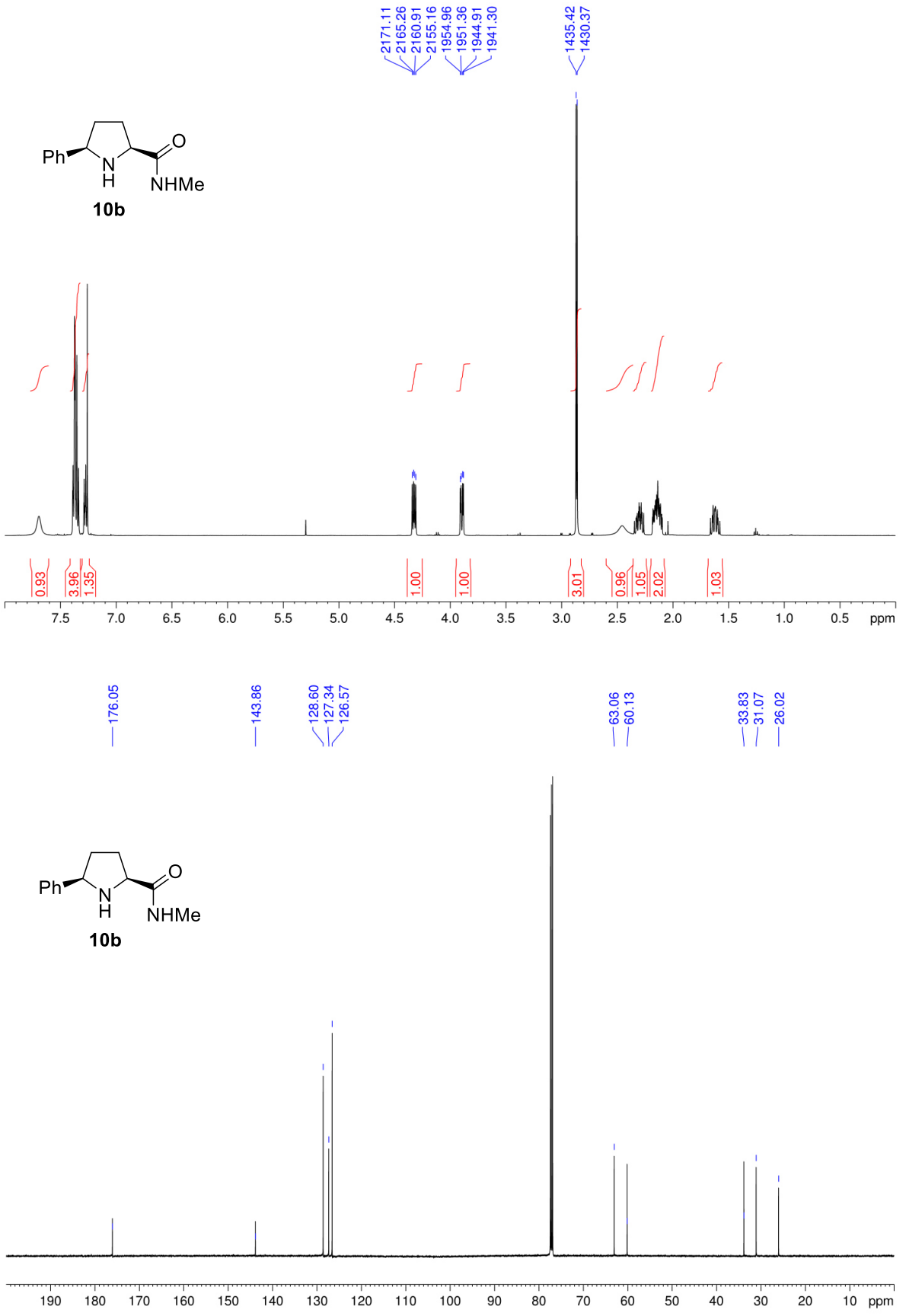

3068.72
3060.19
2748.17
2739.53
MeO
N
Boc
O
NMe2
9b
1.97
2.00
0.30
0.70
0.99
2.11
0.91
2.08
0.94
2.95
1.05
1.72
1.34
2.80
6.25
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

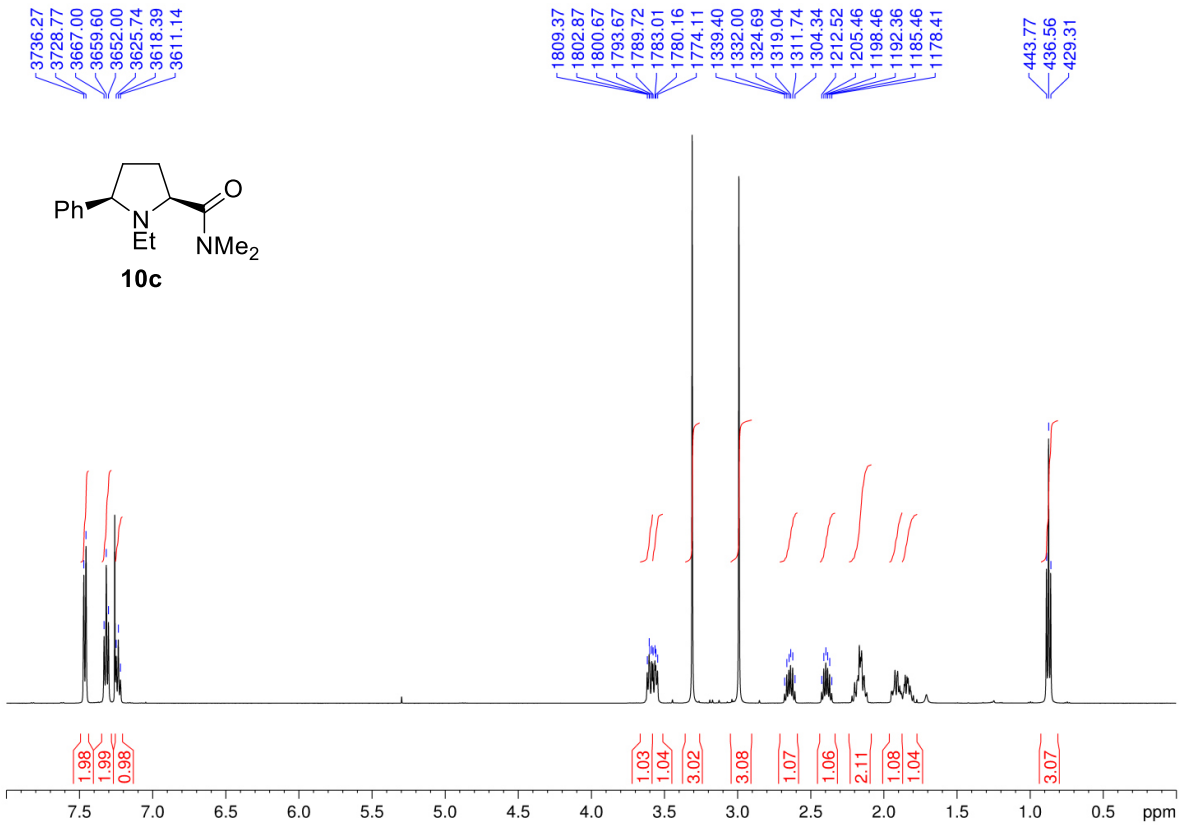

172.83
172.68
158.43
154.83
153.86
136.86
135.92
128.14
127.68
113.82
113.47
79.87
79.75
62.95
61.91
57.94
55.38
55.31
37.19
36.31
35.87
34.85
28.74
28.43
28.24
MeO
N
Boc
O
NMe2
9b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

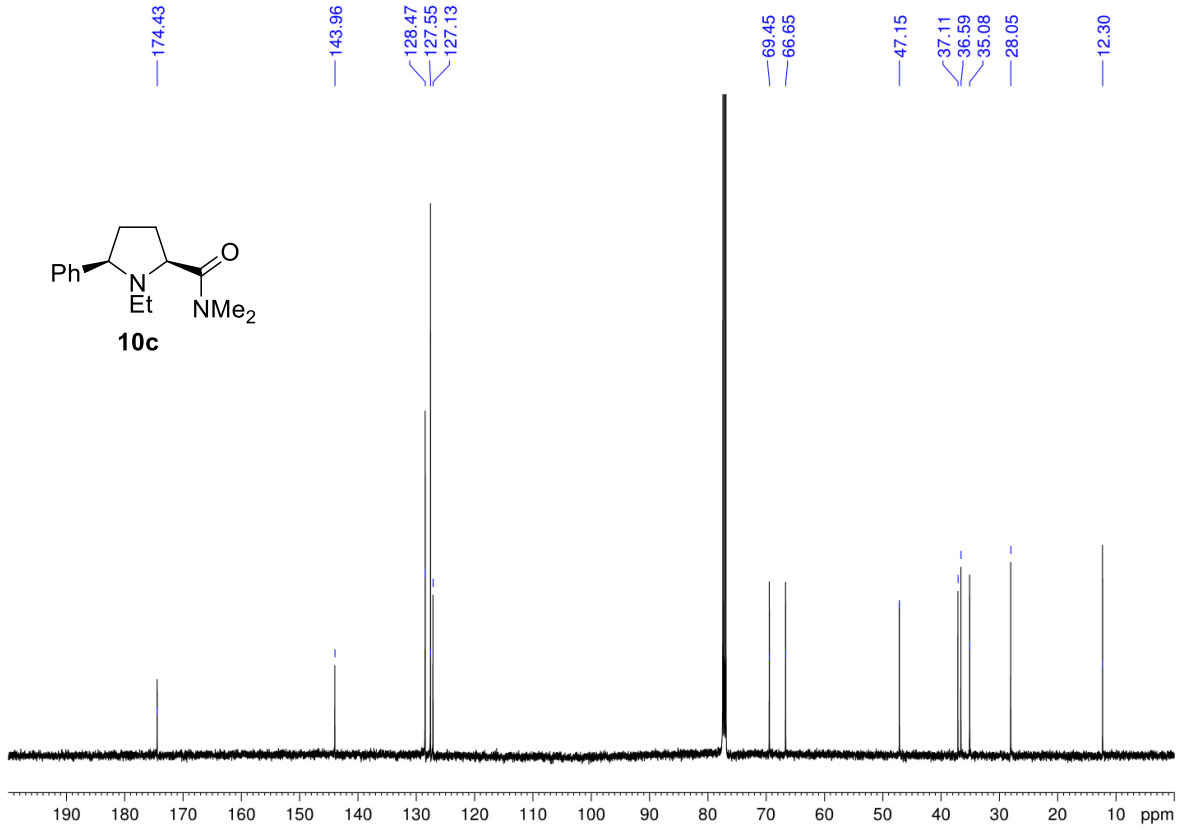

1955.36
1952.87
1947.47
1944.47
F3C
N
Boc
O
NMe2
F3C
9c
1.99
0.67
0.32
0.32
0.67
0.67
0.33
1.96
1.07
0.98
2.00
1.02
1.69
1.32
2.94
5.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
172.36
172.26
154.09
153.79
147.57
146.36
132.00
131.67
131.34
131.02
127.76
127.59
127.15
125.05
122.34
120.68
119.63
80.77
80.53
62.90
61.89
57.93
57.84
37.16
36.35
35.58
34.53
29.01
28.86
28.30
28.06
F3C
N
Boc
O
NMe2
F3C
9c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

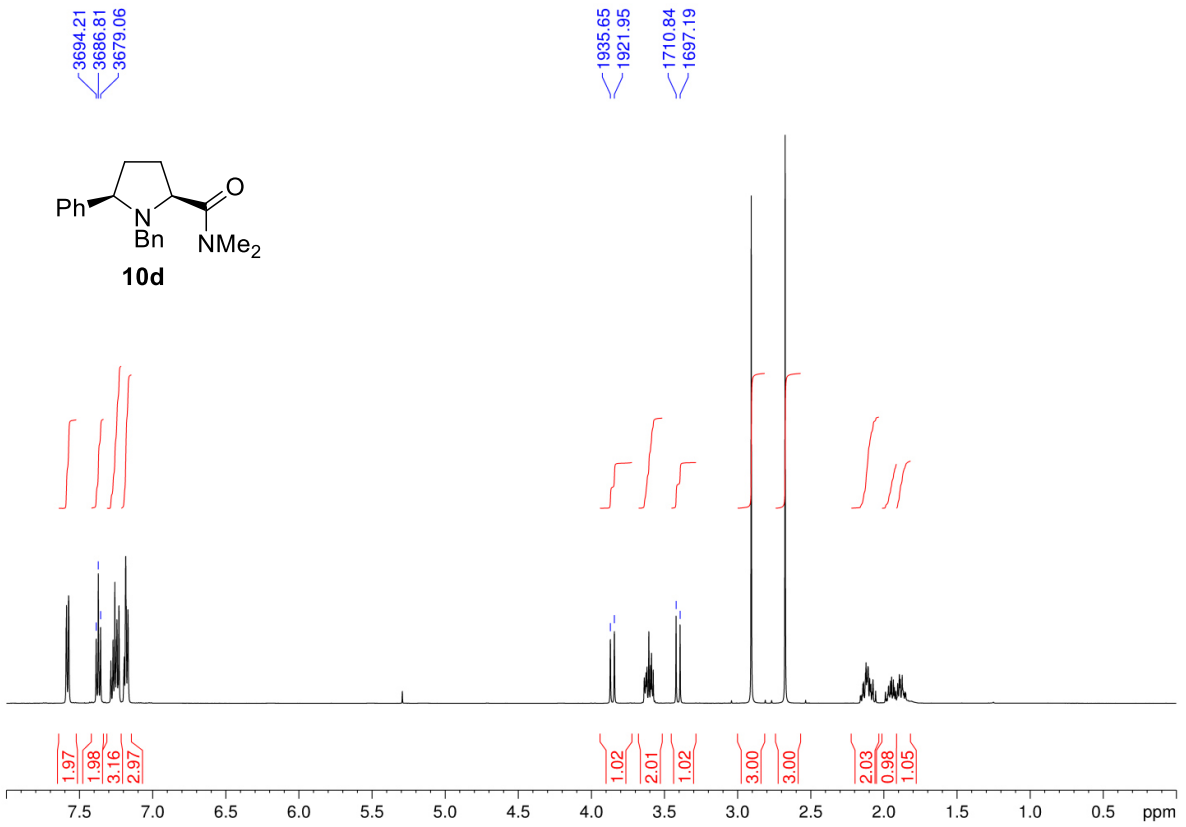

3200.68
3192.24
3185.31
3177.11
2322.59
2313.91
2264.62
2259.25
2257.29
2251.97
1939.27
1932.47
1925.15
1892.45
1885.97
1882.81
1876.41
N
Boc
O
NMe2
9d
0.99
1.03
1.09
1.05
1.03
2.04
0.43
0.57
0.58
0.44
1.65
1.43
3.04
1.01
3.11
4.02
5.20
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
172.64
172.43
154.85
154.08
139.43
138.16
134.07
133.67
130.61
130.40
129.01
127.20
126.82
126.30
125.55
124.95
124.60
124.38
122.97
122.57
80.19
79.82
59.25
58.34
58.07
37.32
36.42
36.37
34.36
33.34
28.72
28.44
28.14
N
Boc
O
NMe2
9d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

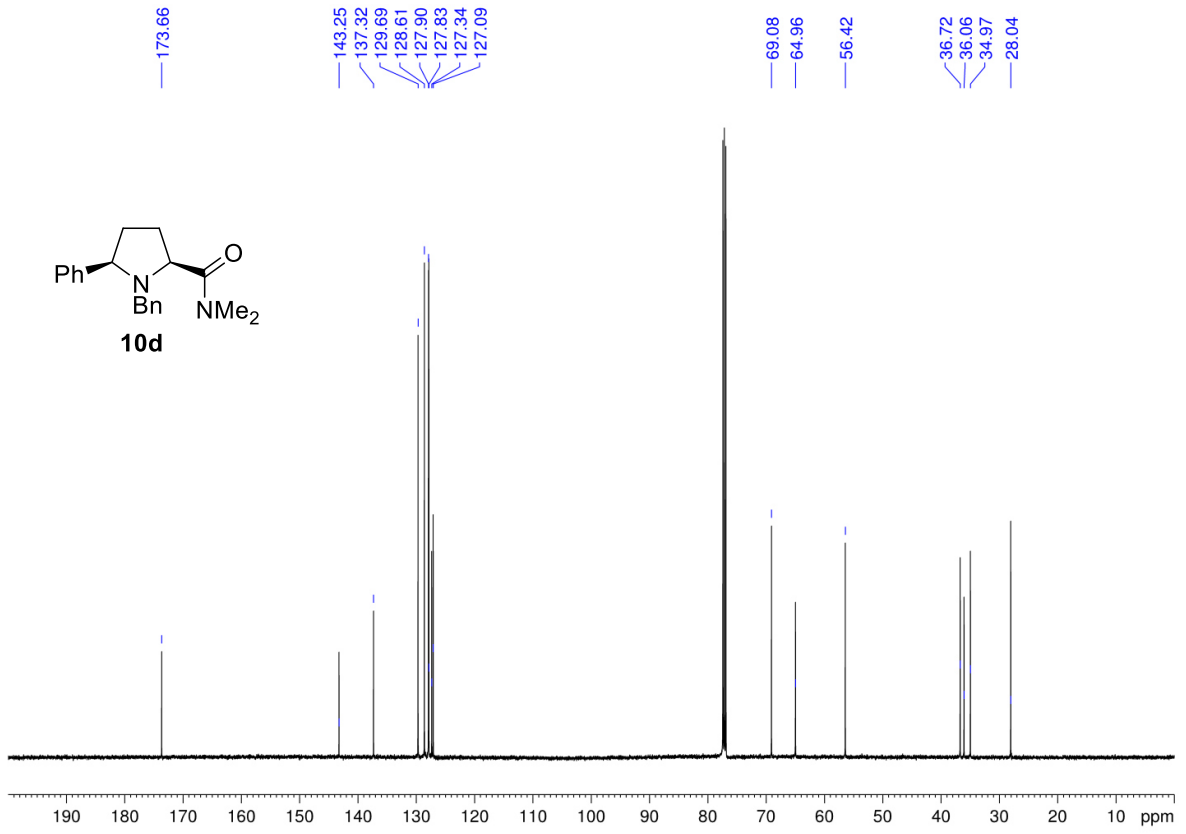

Ph
N
H
O
NMe2
10a
2.03
1.97
1.26
2.00
3.06
3.03
1.01
2.01
1.01
1.02
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
174.07
142.77
128.60
127.31
126.98
64.47
58.63
36.61
36.01
34.76
31.37
Ph
N
H
O
NMe2
10a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

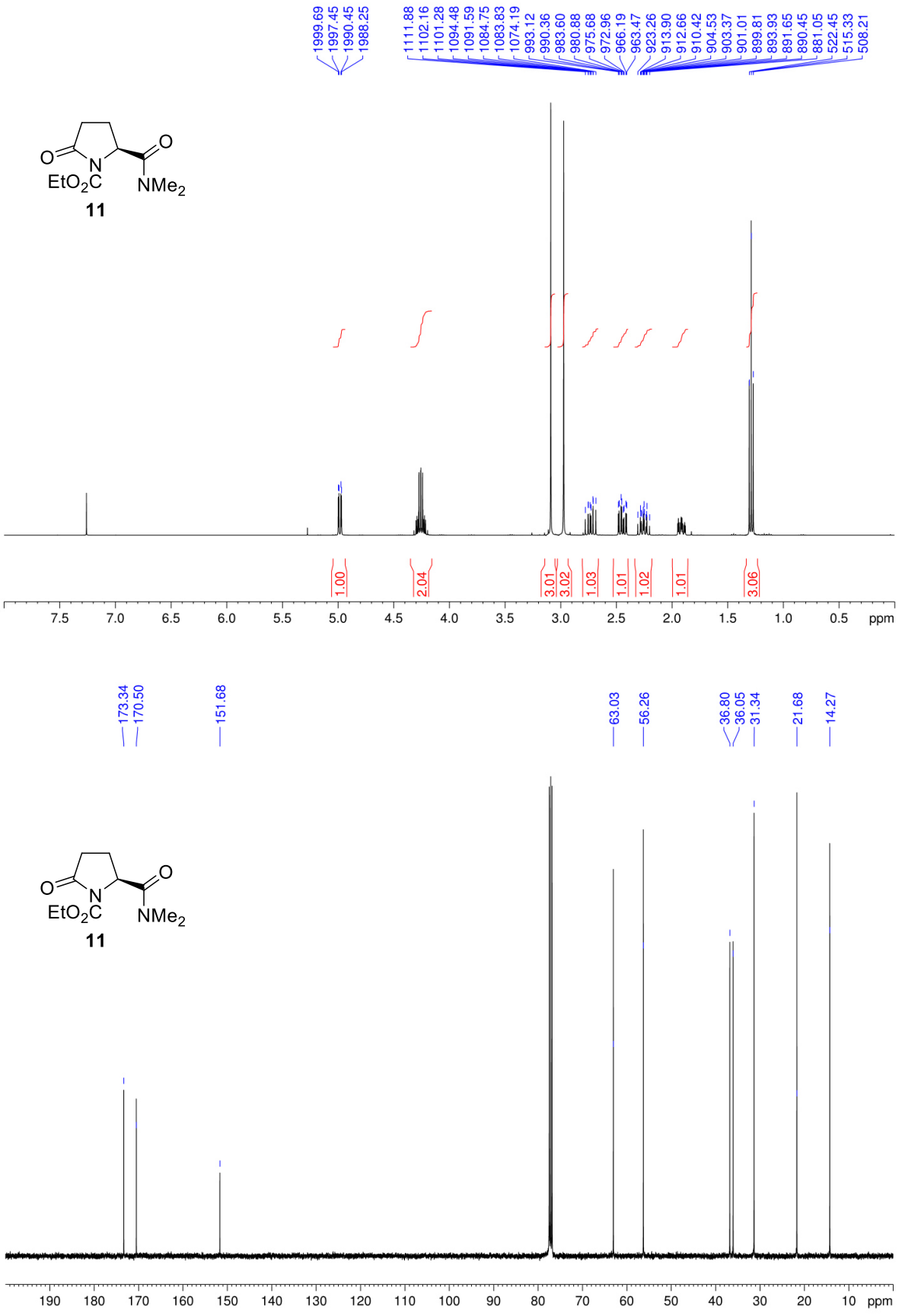

2171.11
2165.26
2160.91
2155.16
1954.96
1951.36
1944.91
1941.30
1435.42
1430.37
Ph
N
H
O
NHMe
10b
0.93
3.96
1.35
1.00
1.00
3.01
0.96
1.05
2.02
1.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
176.05
143.86
128.60
127.34
126.57
63.06
60.13
33.83
31.07
26.02
Ph
N
H
O
NHMe
10b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

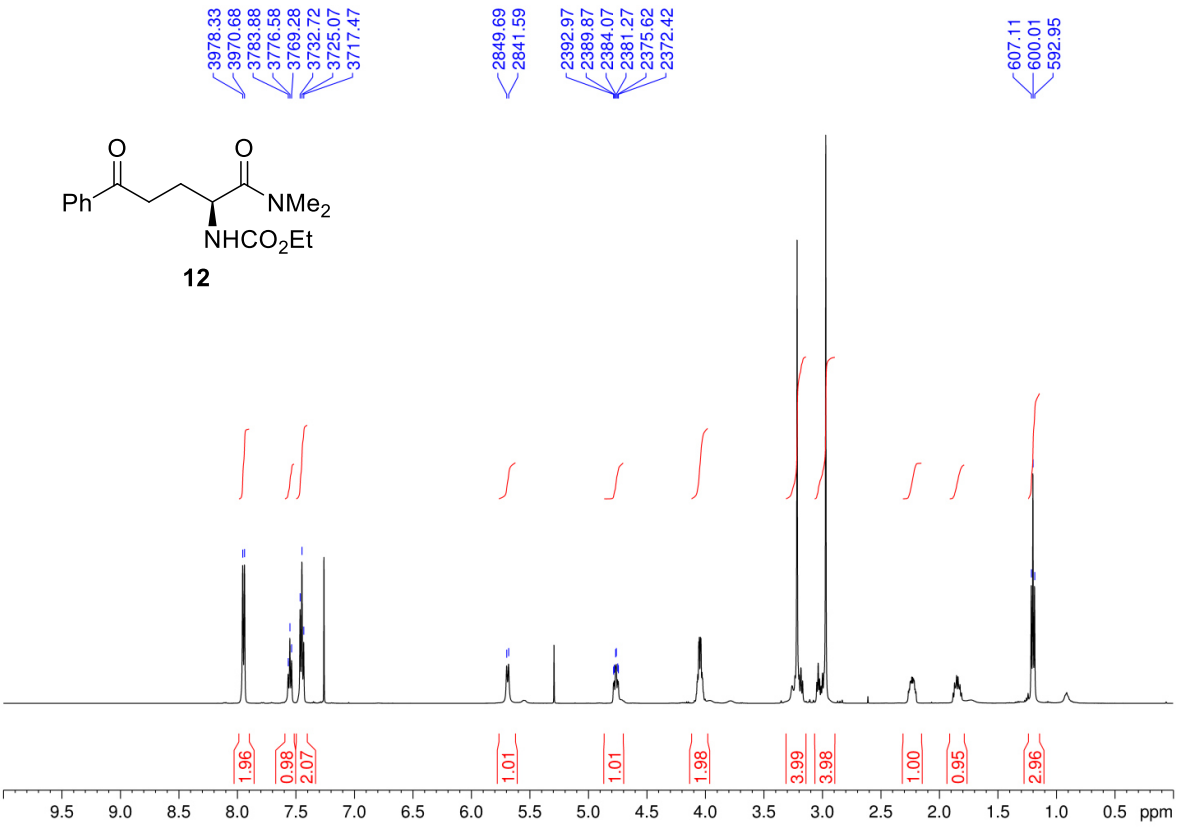

3736.27
3728.77
3667.00
3659.60
3652.00
3625.74
3618.39
3611.14
1809.37
1802.87
1800.67
1793.67
1789.72
1783.01
1780.16
1774.11
1339.40
1332.00
1324.69
1319.04
1311.74
1304.34
1212.52
1205.46
1198.46
1192.36
1185.46
1178.41
443.77
436.56
429.31
Ph
N
Et
O
NMe2
10c
1.98
1.99
0.98
1.03
1.04
3.02
3.08
1.07
1.06
2.11
1.08
1.04
3.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

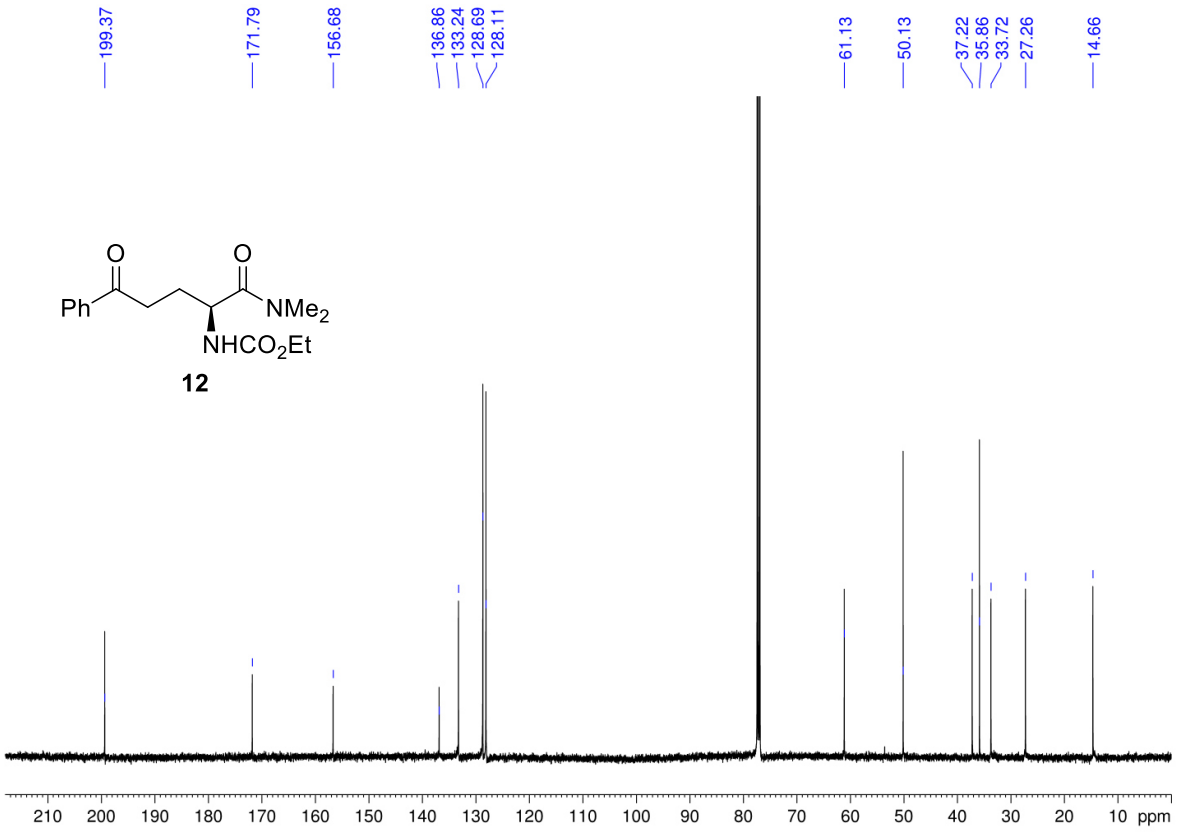

174.43
143.96
128.47
127.55
127.13
69.45
66.65
47.15
37.11
36.59
35.08
28.05
12.30
Ph
N
Et
O
NMe2
10c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

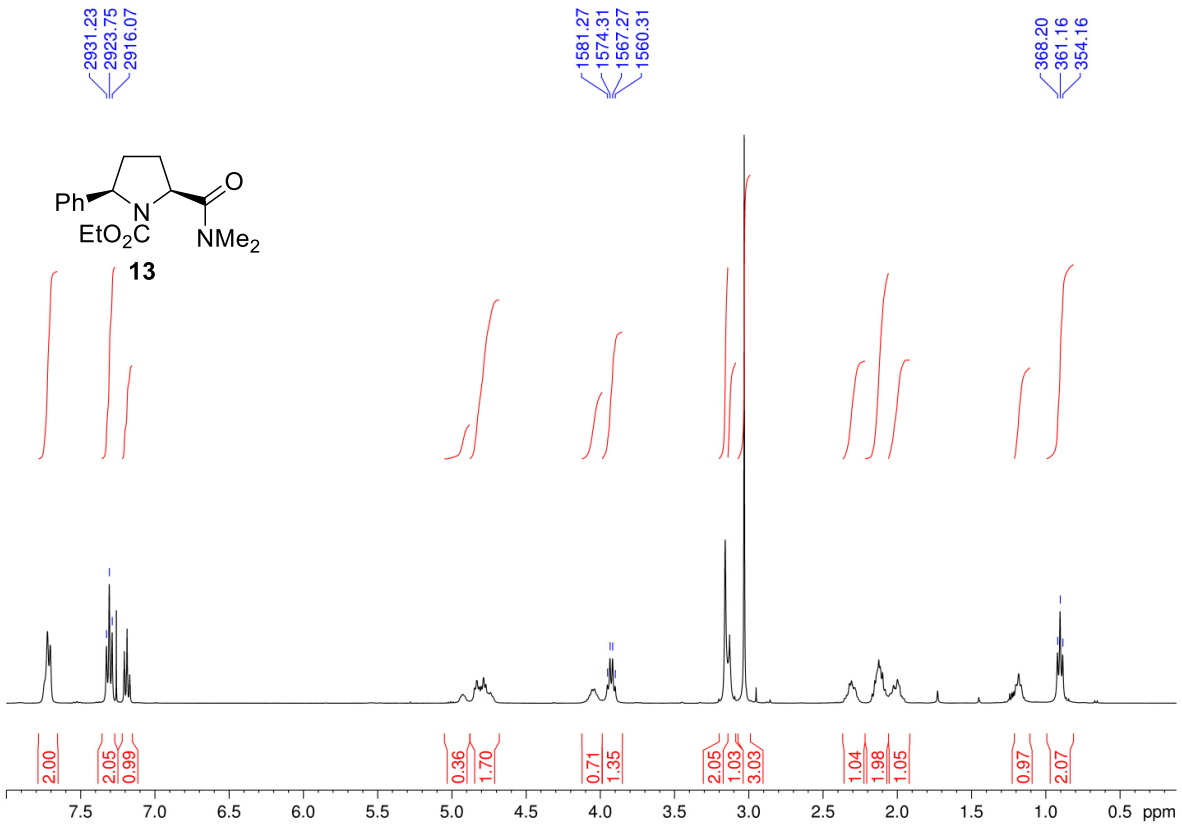

3694.21
3686.81
3679.06
1935.65
1921.95
1710.84
1697.19
Ph
N
Bn
O
NMe2
10d
1.97
1.98
3.16
2.97
1.02
2.01
1.02
3.00
3.00
2.03
0.98
1.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

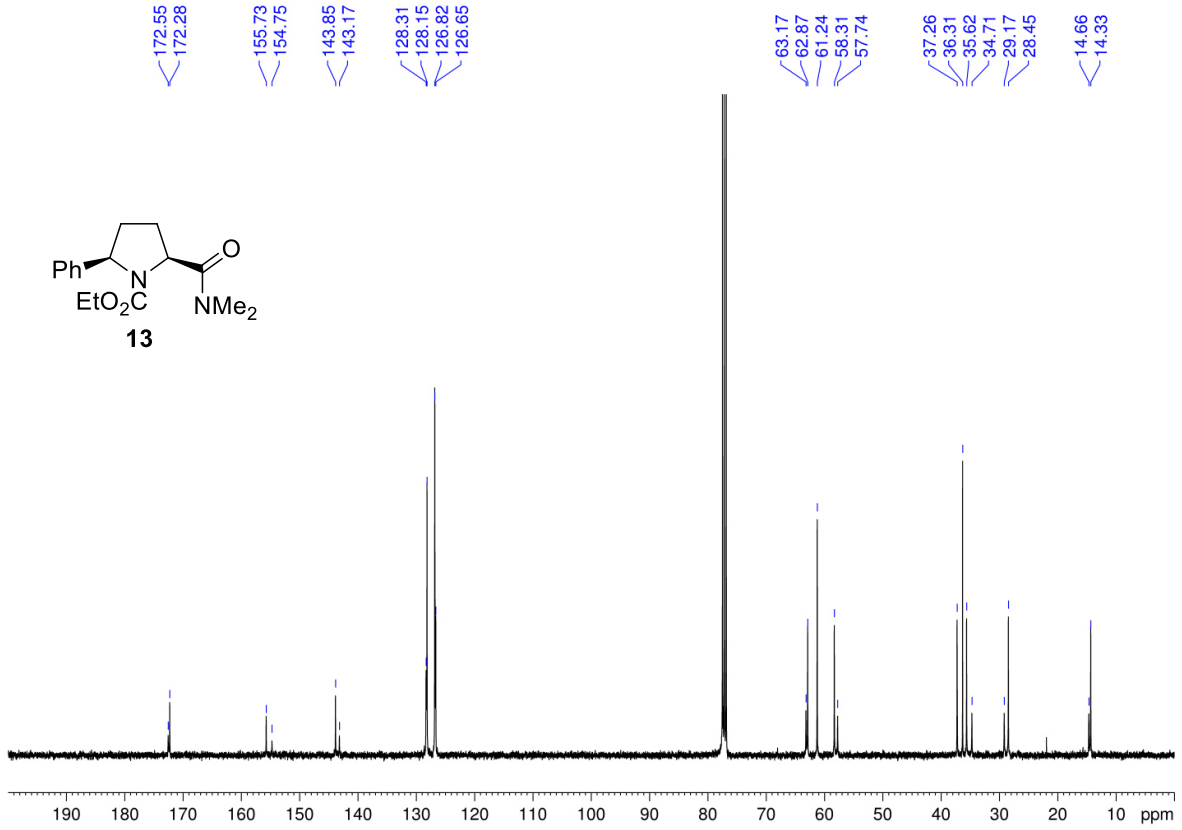

173.66
143.25
137.32
129.69
128.61
127.90
127.83
127.34
127.09
69.08
64.96
56.42
36.72
36.06
34.97
28.04
Ph
N
Bn
O
NMe2
10d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

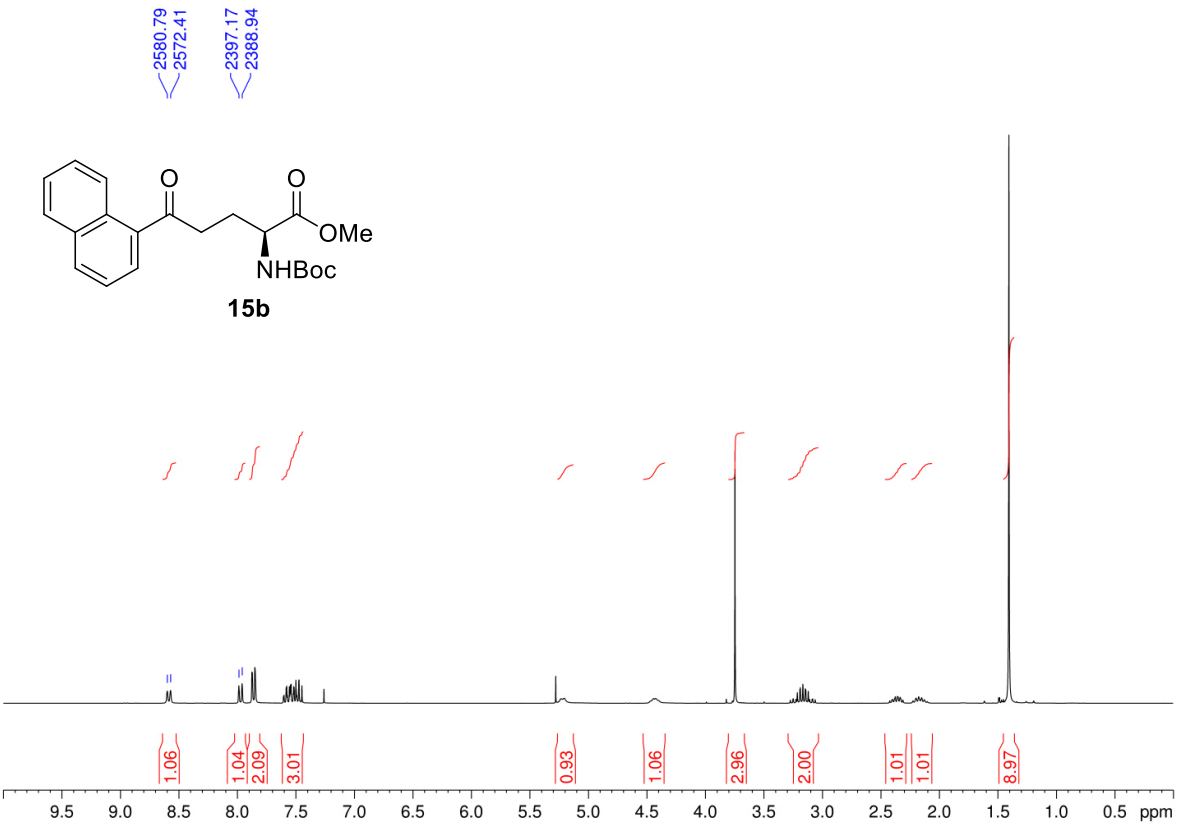

1999.69
1997.45
1990.45
1988.25
1111.88
1102.16
1101.28
1094.48
1091.59
1084.75
1083.83
1074.19
993.12
990.36
983.60
980.88
975.68
972.96
966.19
963.47
923.26
913.90
912.66
910.42
904.53
903.37
901.01
899.81
893.93
891.65
890.45
881.05
522.45
515.33
508.21
O
O
N
EtO2C
NMe2
11
1.00
2.04
3.01
3.02
1.03
1.01
1.02
1.01
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
173.34
170.50
151.68
63.03
56.26
36.80
36.05
31.34
21.68
14.27
O
O
N
EtO2C
NMe2
11
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

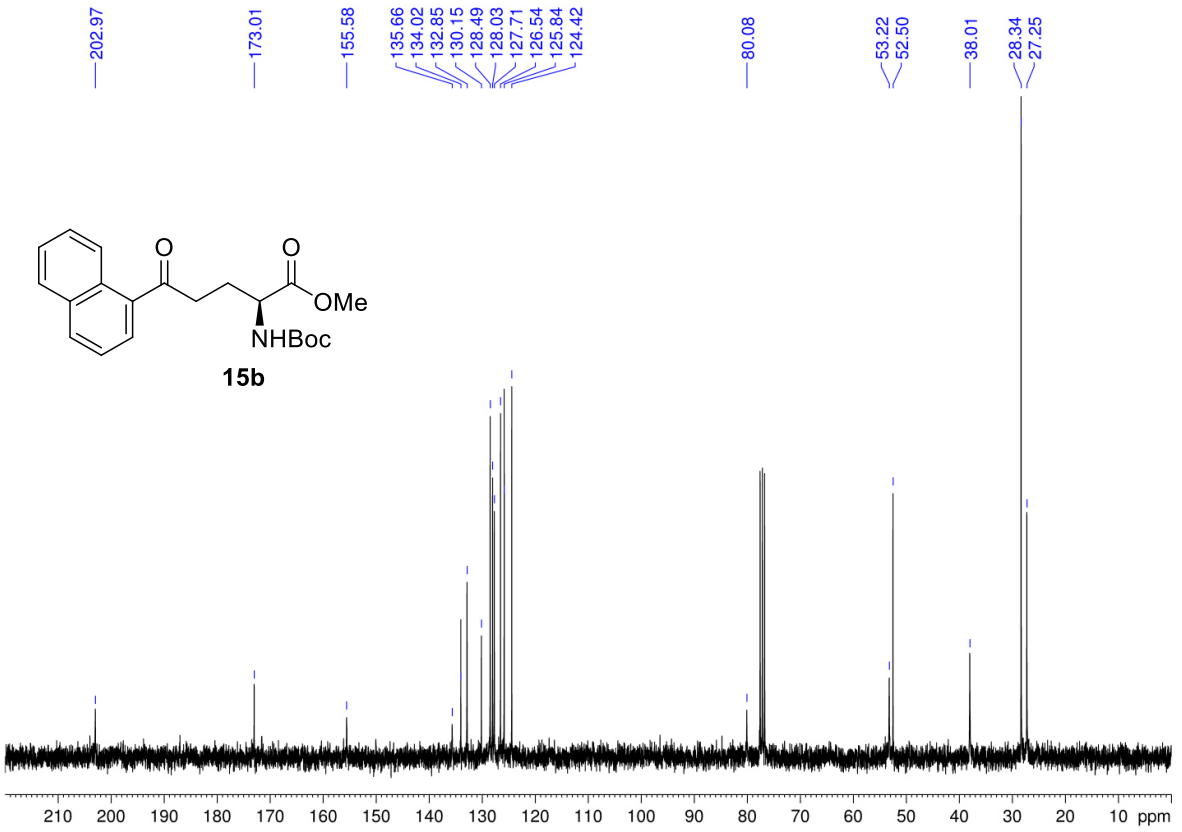

3978.33
3970.68
3783.88
3776.58
3769.28
3732.72
3725.07
3717.47
2849.69
2841.59
2392.97
2389.87
2384.07
2381.27
2375.62
2372.42
607.11
600.01
592.95
O
O
Ph
NMe2
NHCO2Et
12
1.96
0.98
2.07
1.01
1.01
1.98
3.99
3.98
1.00
0.95
2.96
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

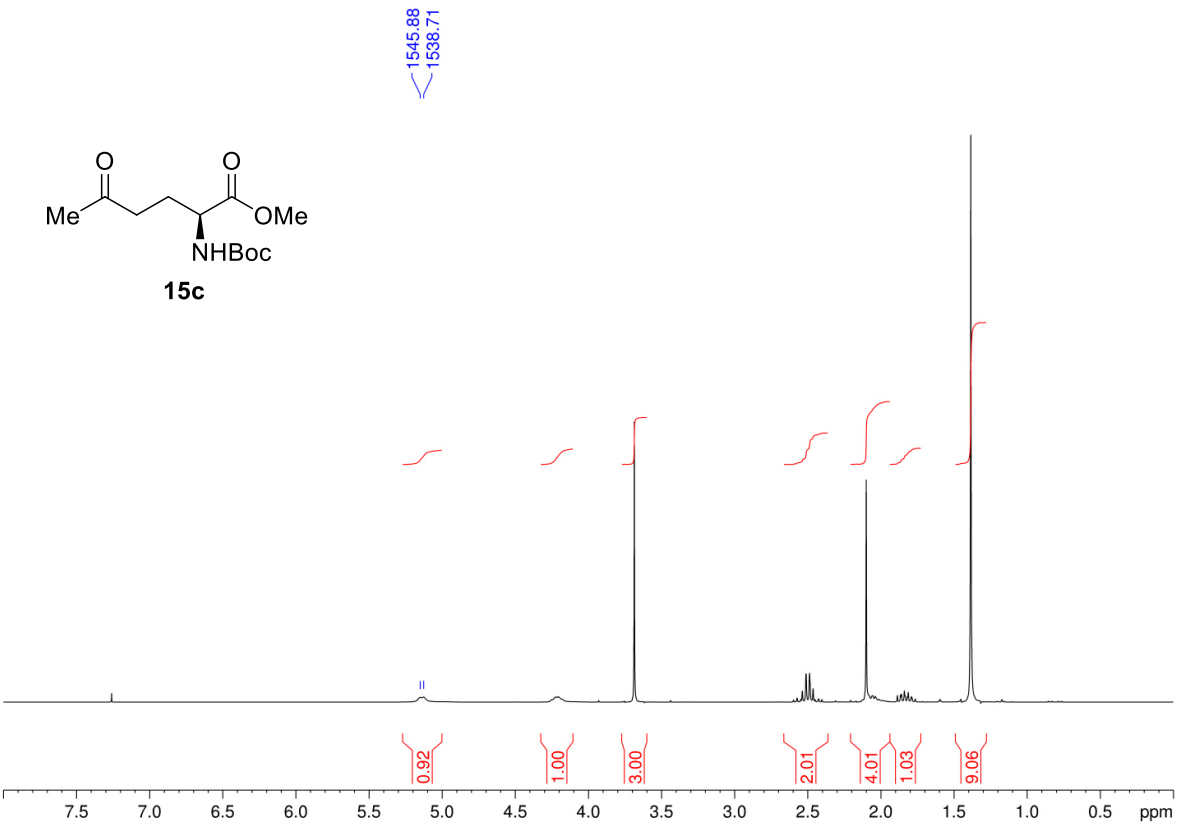

199.37
171.79
156.68
136.86
133.24
128.69
128.11
61.13
50.13
37.22
35.86
33.72
27.26
14.66
O
O
Ph
NMe2
NHCO2Et
12
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

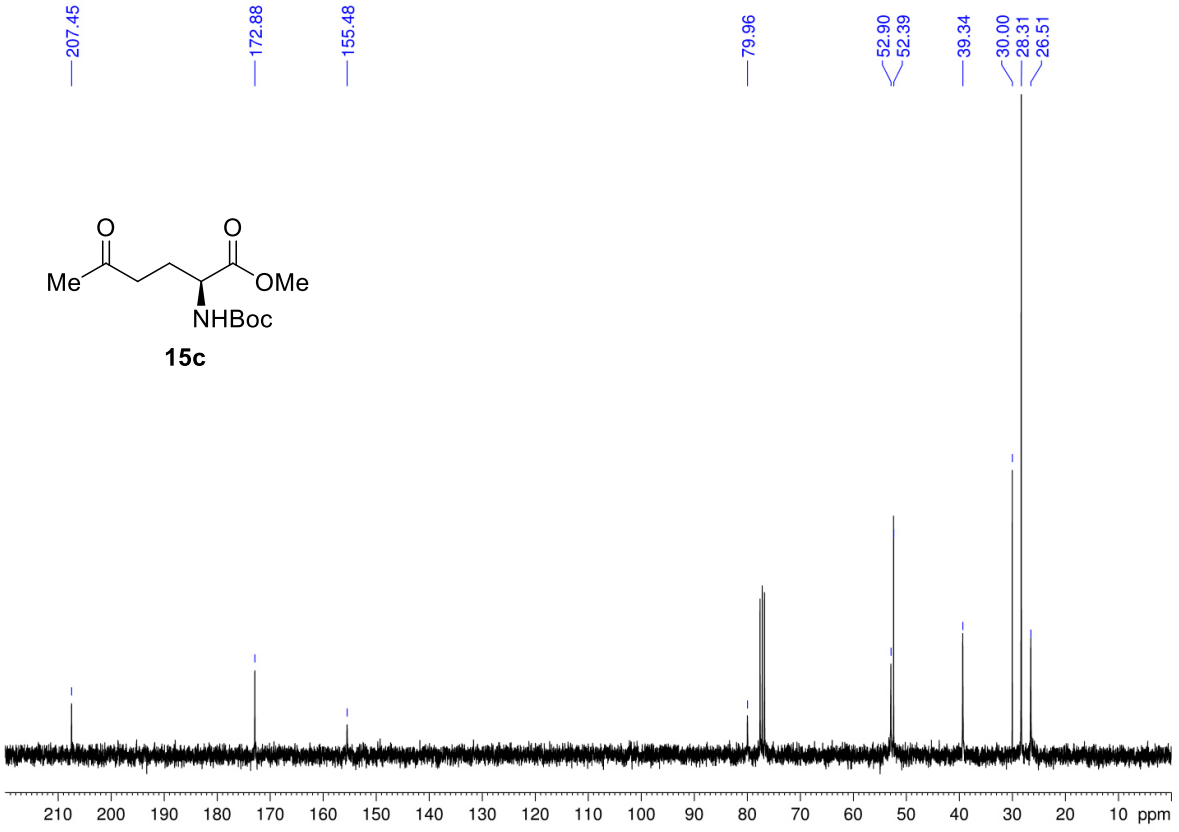

2931.23
2923.75
2916.07
1581.27
1574.31
1567.27
1560.31
368.20
361.16
354.16
Ph
N
O
EtO2C
NMe2
13
2.00
2.05
0.99
0.36
1.70
0.71
1.35
2.05
1.03
3.03
1.04
1.98
1.05
0.97
2.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

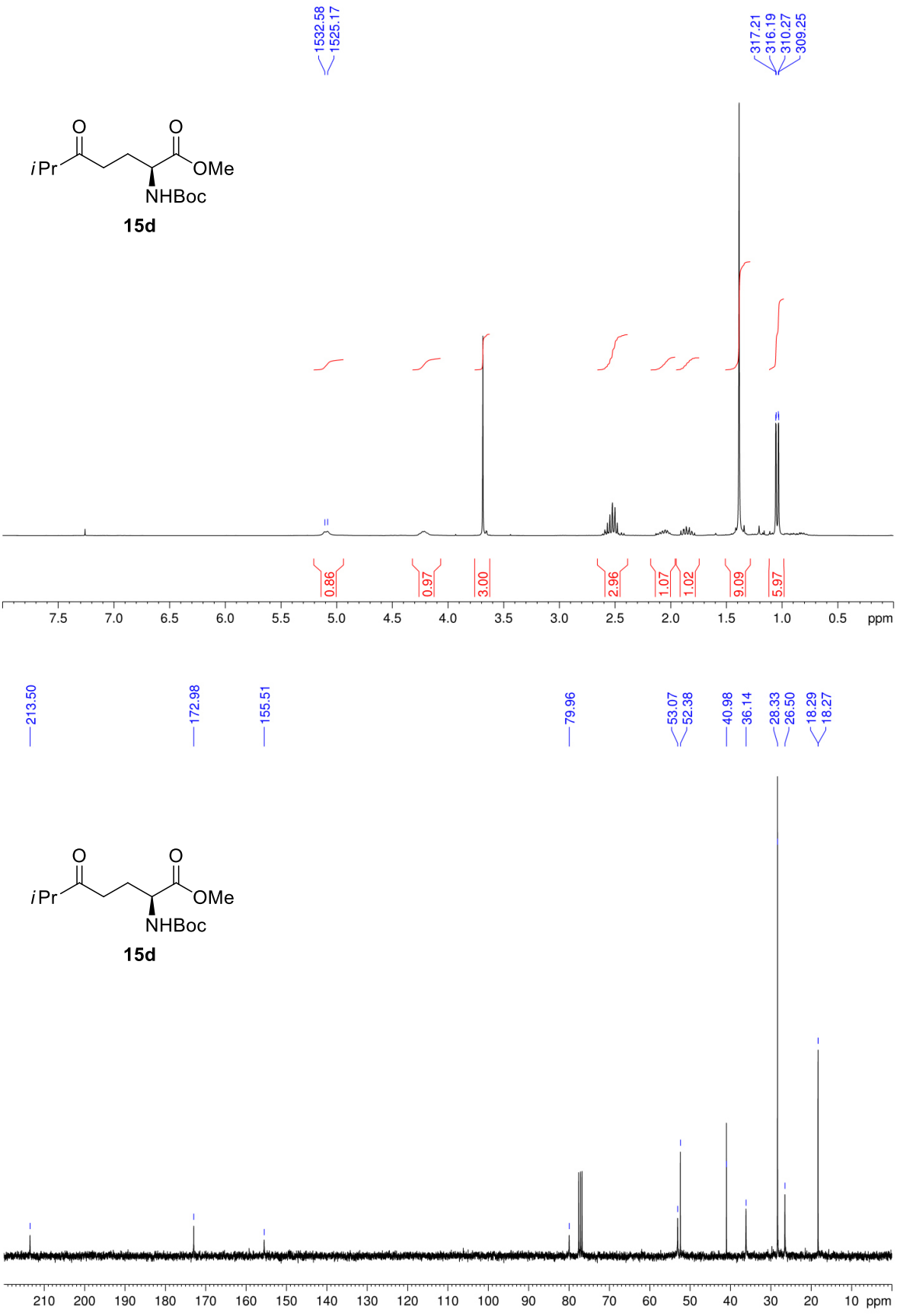

172.55
172.28
155.73
154.75
143.85
143.17
128.31
128.15
126.82
126.65
63.17
62.87
61.24
58.31
57.74
37.26
36.31
35.62
34.71
29.17
28.45
14.66
14.33
Ph
N
O
EtO2C
NMe2
13
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

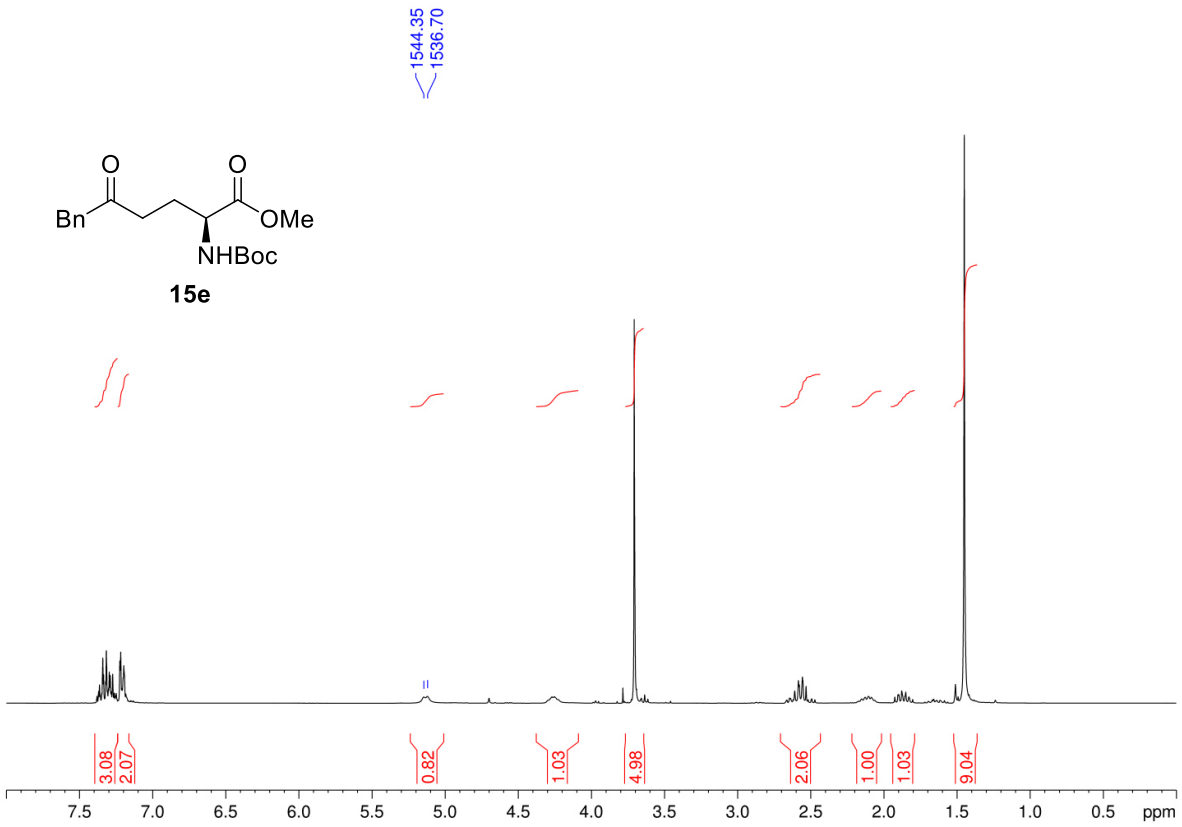

2580.79
2572.41
2397.17
2388.94
O
O
OMe
NHBoc
15b
1.06
1.04
2.09
3.01
0.93
1.06
2.96
2.00
1.01
1.01
8.97
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

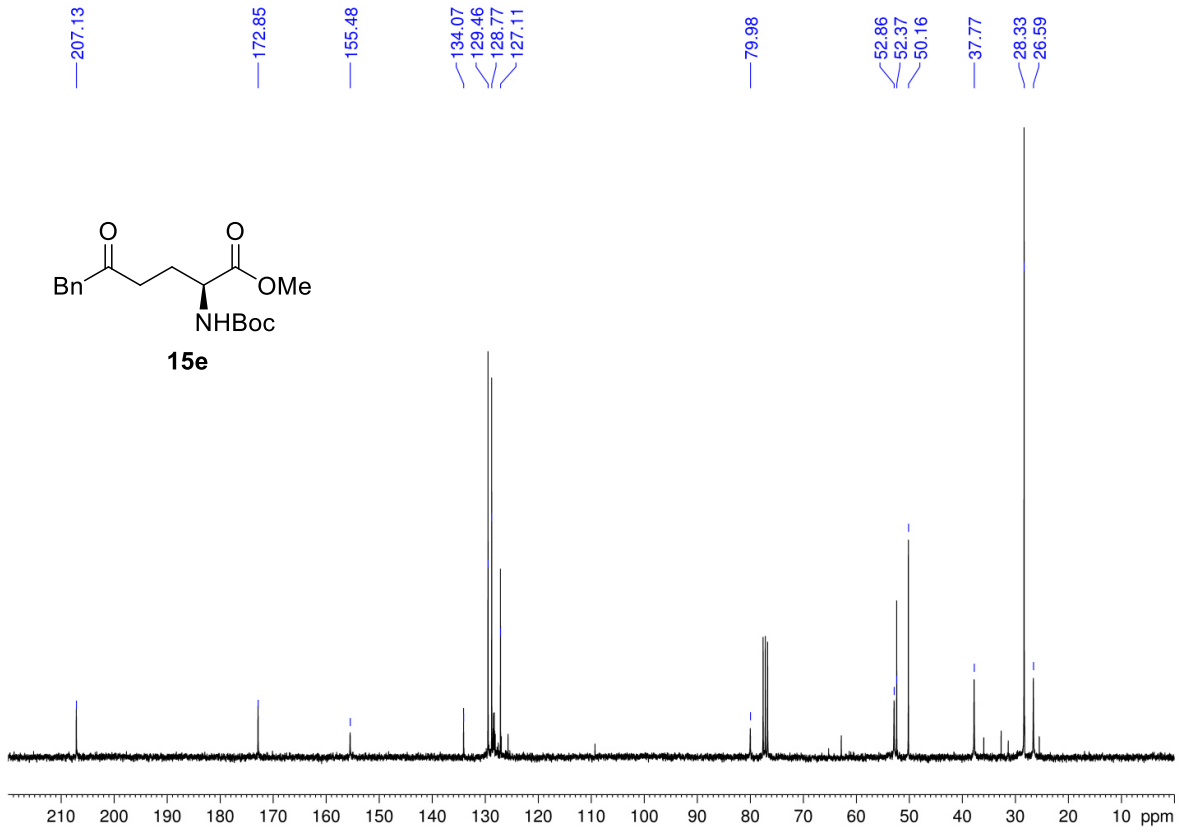

202.97
173.01
155.58
135.66
134.02
132.85
130.15
128.49
128.03
127.71
126.54
125.84
124.42
80.08
53.22
52.50
38.01
28.34
27.25
O
O
OMe
NHBoc
15b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

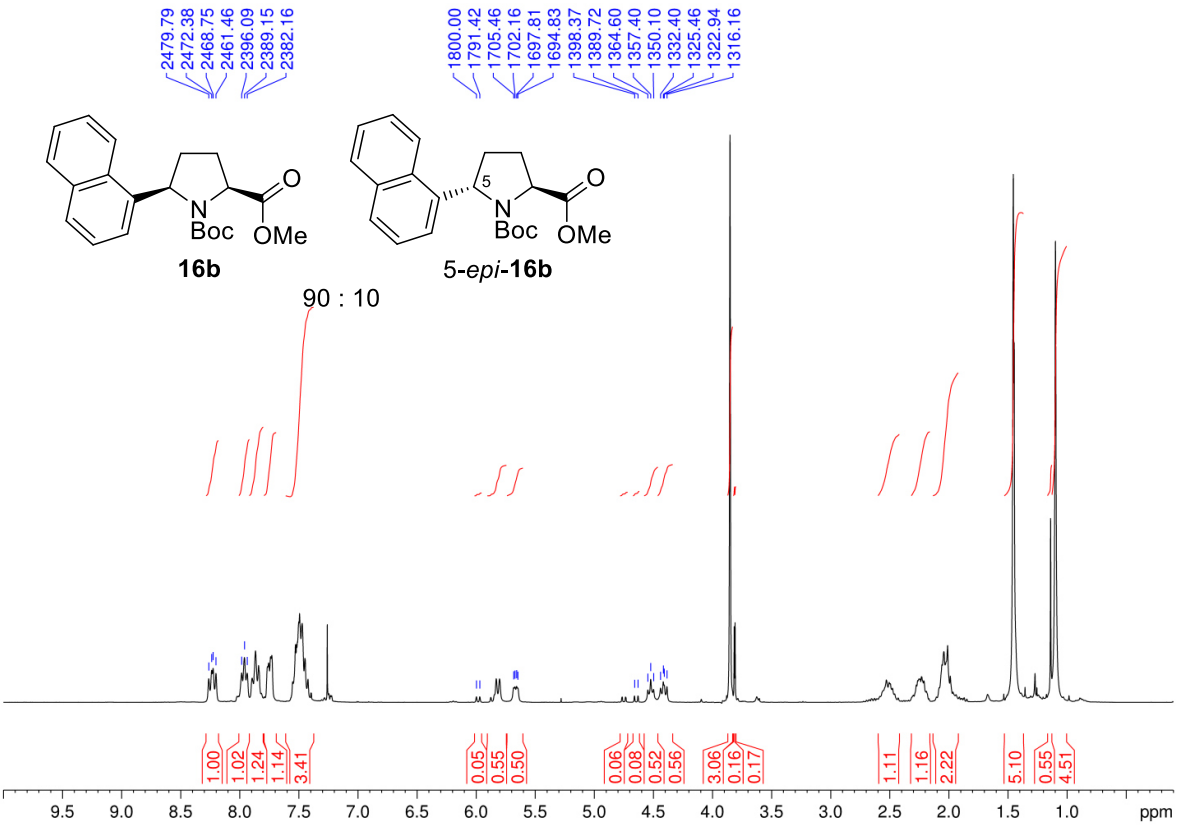

1545.88
1538.71
Me
OMe
NHBoc
15c
0.92
1.00
3.00
2.01
4.01
1.03
9.06
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

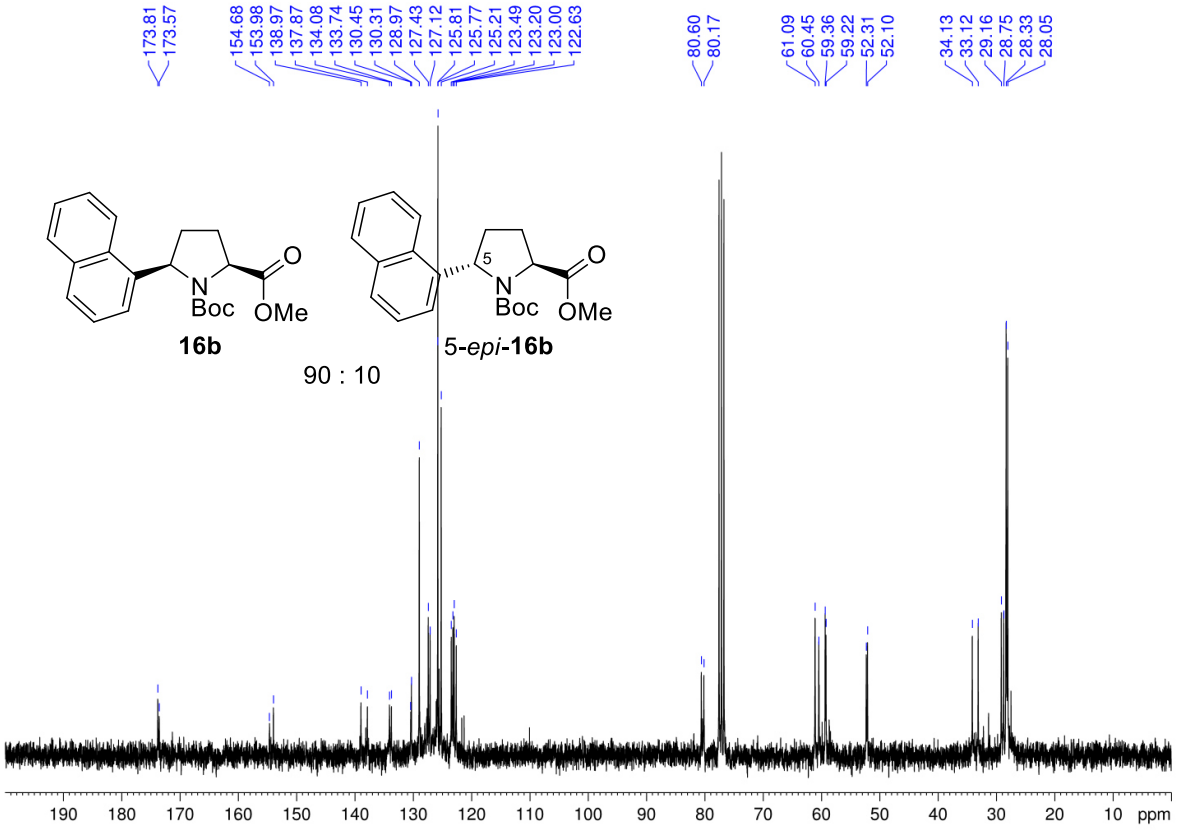

207.45
172.88
155.48
79.96
52.90
52.39
39.34
30.00
28.31
26.51
Me
OMe
NHBoc
15c
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

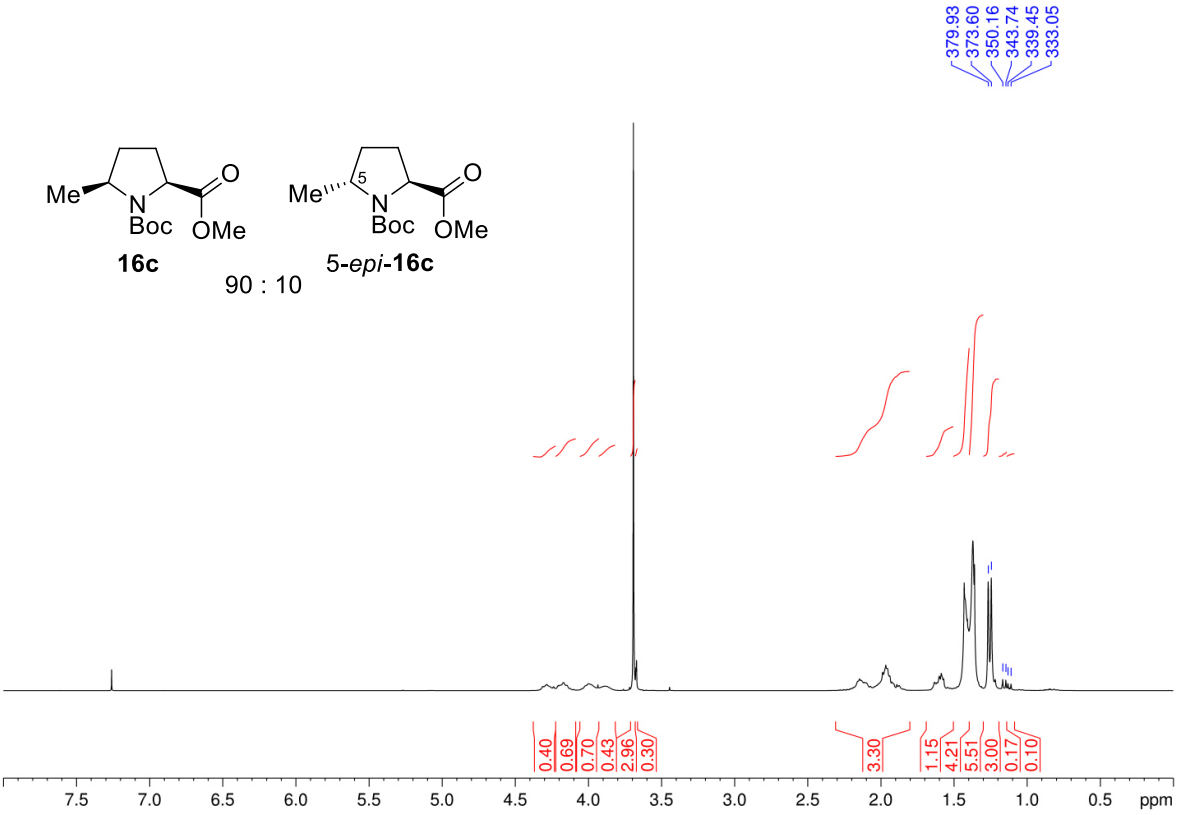

1532.58
1525.17
317.21
316.19
310.27
309.25
O
O
iPr
OMe
NHBoc
15d
0.86
0.97
3.00
2.96
1.07
1.02
9.09
5.97
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
213.50
172.98
155.51
79.96
53.07
52.38
40.98
36.14
28.33
26.50
18.29
18.27
O
O
iPr
OMe
NHBoc
15d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

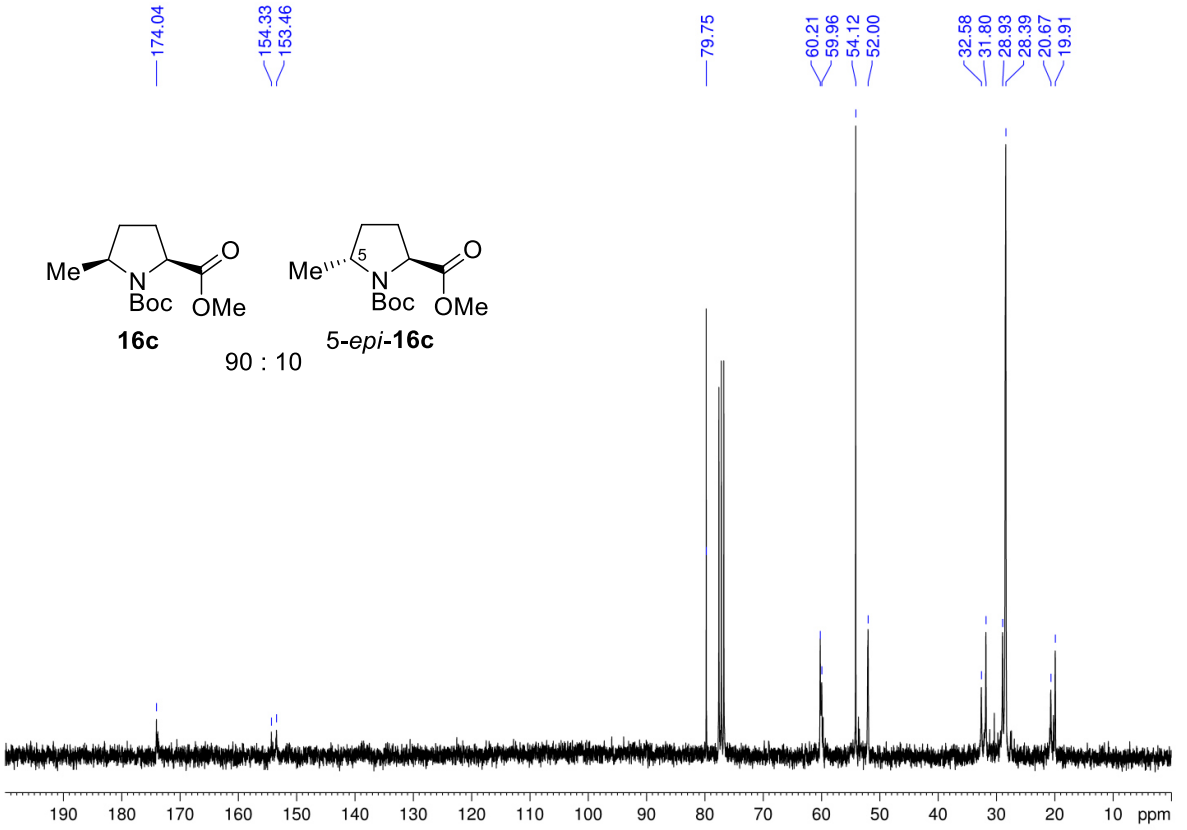

1544.35
1536.70
Bn
OMe
NHBoc
15e
3.08
2.07
0.82
1.03
4.98
2.06
1.00
1.03
9.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

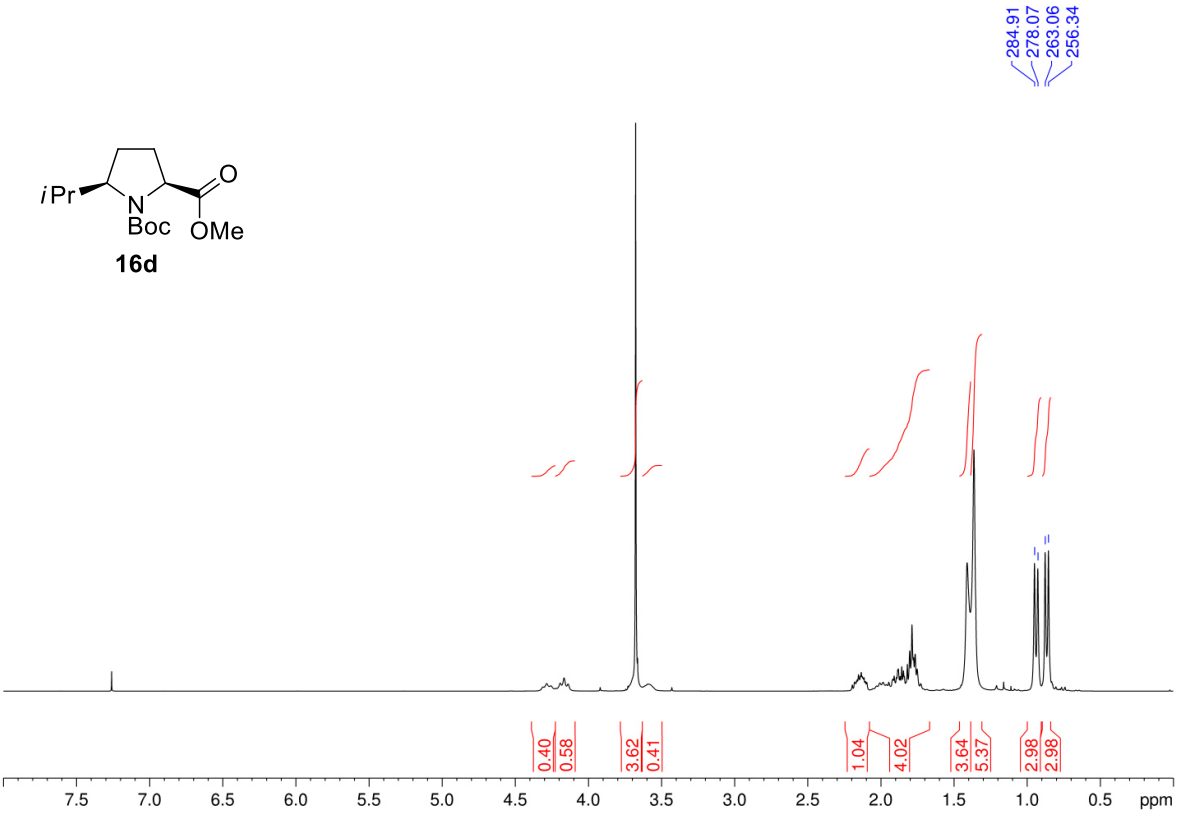

207.13
172.85
155.48
134.07
129.46
128.77
127.11
79.98
52.86
52.37
50.16
37.77
28.33
26.59
Bn
OMe
NHBoc
15e
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

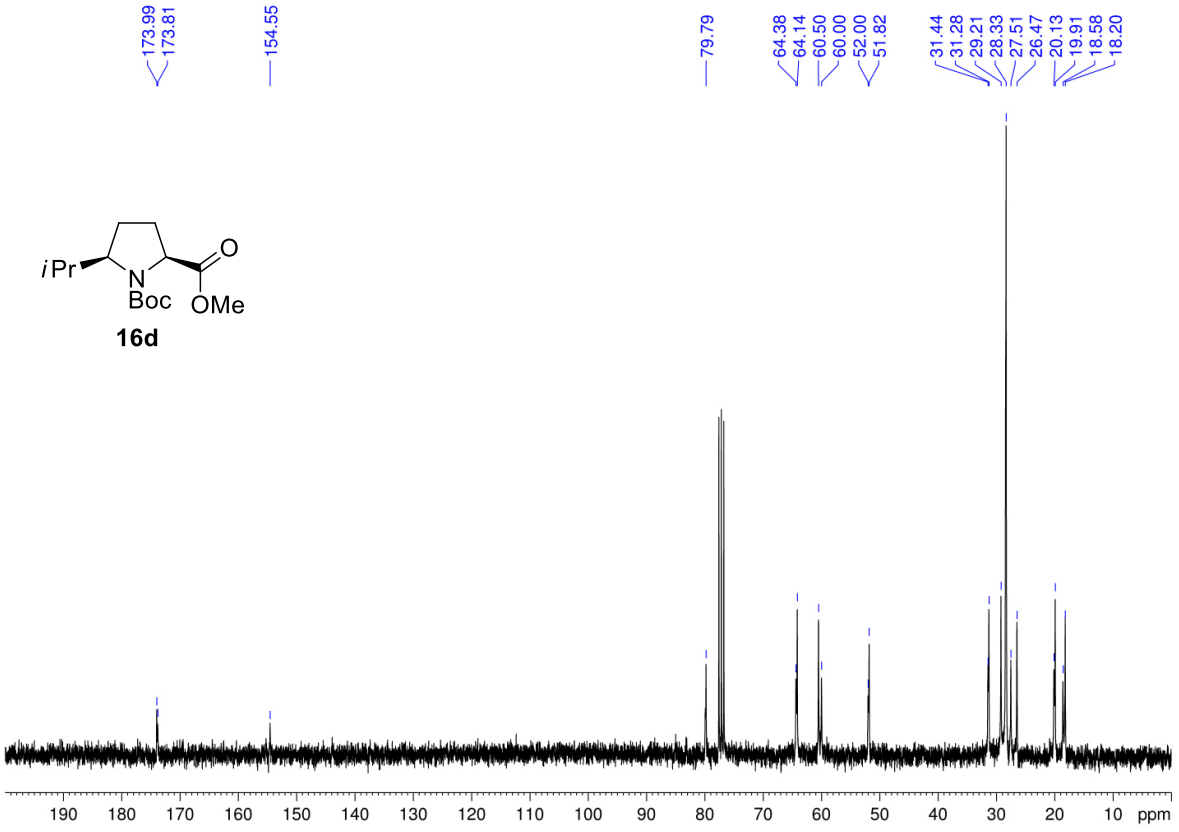

2479.79
2472.38
2468.75
2461.46
2396.09
2389.15
2382.16
1800.00
1791.42
1705.46
1702.16
1697.81
1694.83
1398.37
1389.72
1364.60
1357.40
1350.10
1332.40
1325.46
1322.94
1316.16
Boc
OMe
16b
5-epi-16b
90 : 10
1.00
1.02
1.24
1.14
3.41
0.05
0.55
0.50
0.06
0.08
0.52
0.56
3.06
0.16
0.17
1.11
1.16
2.22
5.10
0.55
4.51
ppm

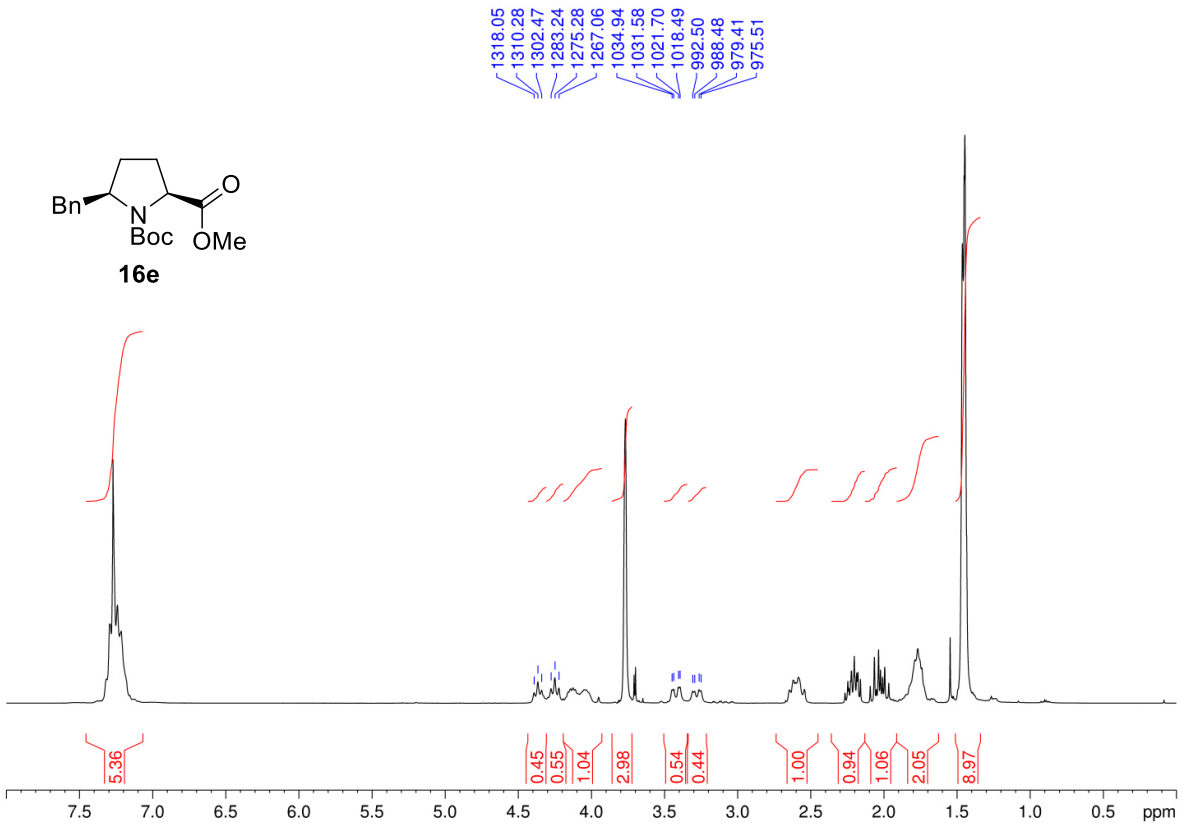

173.81
173.57
154.68
153.98
138.97
137.87
134.08
133.74
130.45
130.31
128.97
127.43
127.12
125.81
125.77
125.21
123.49
123.20
123.00
122.63
80.60
80.17
61.09
60.45
59.36
59.22
52.31
52.10
34.13
33.12
29.16
28.75
28.33
28.05
Boc
OMe
16b
5-epi-16b
90 : 10
ppm

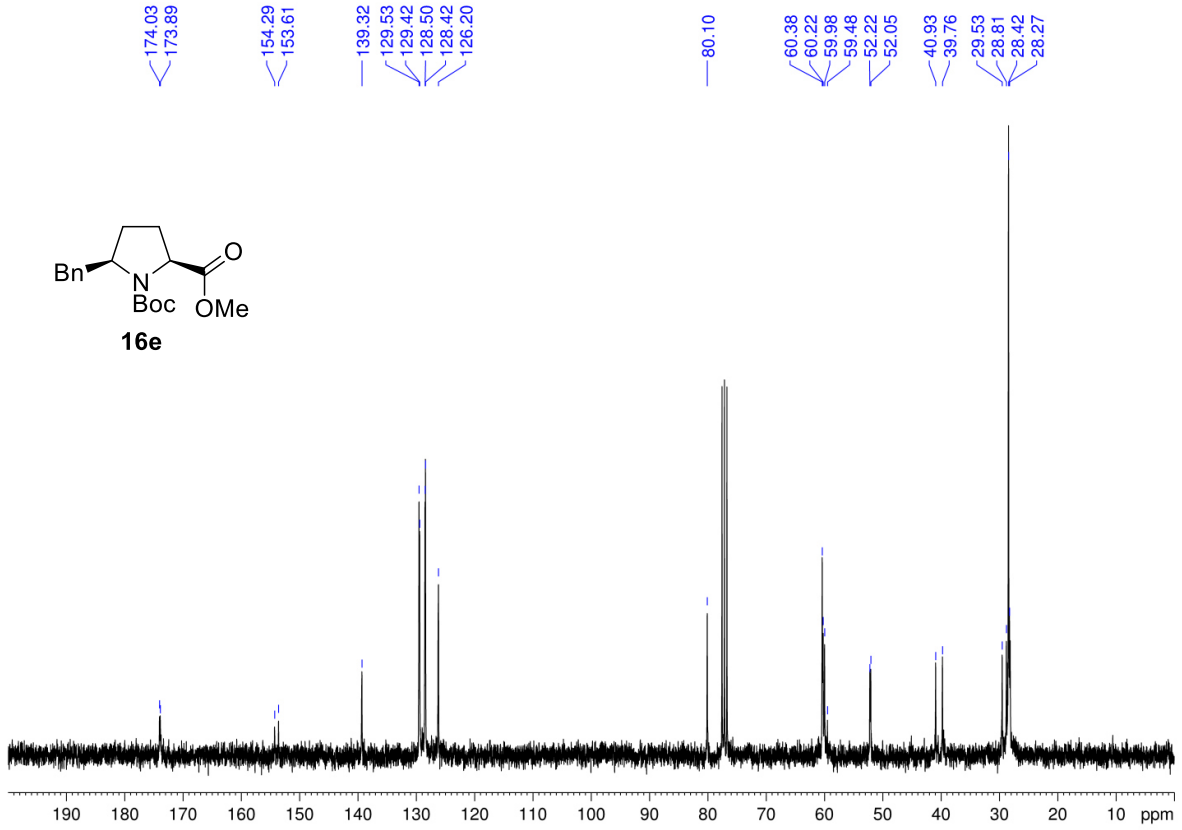

379.93
373.60
350.16
343.74
339.45
333.05
Me
N
Boc
OMe
O
16c
5-epi-16c
90 : 10
0.40
0.69
0.70
0.43
2.96
0.30
3.30
1.15
4.21
5.51
3.00
0.17
0.10
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

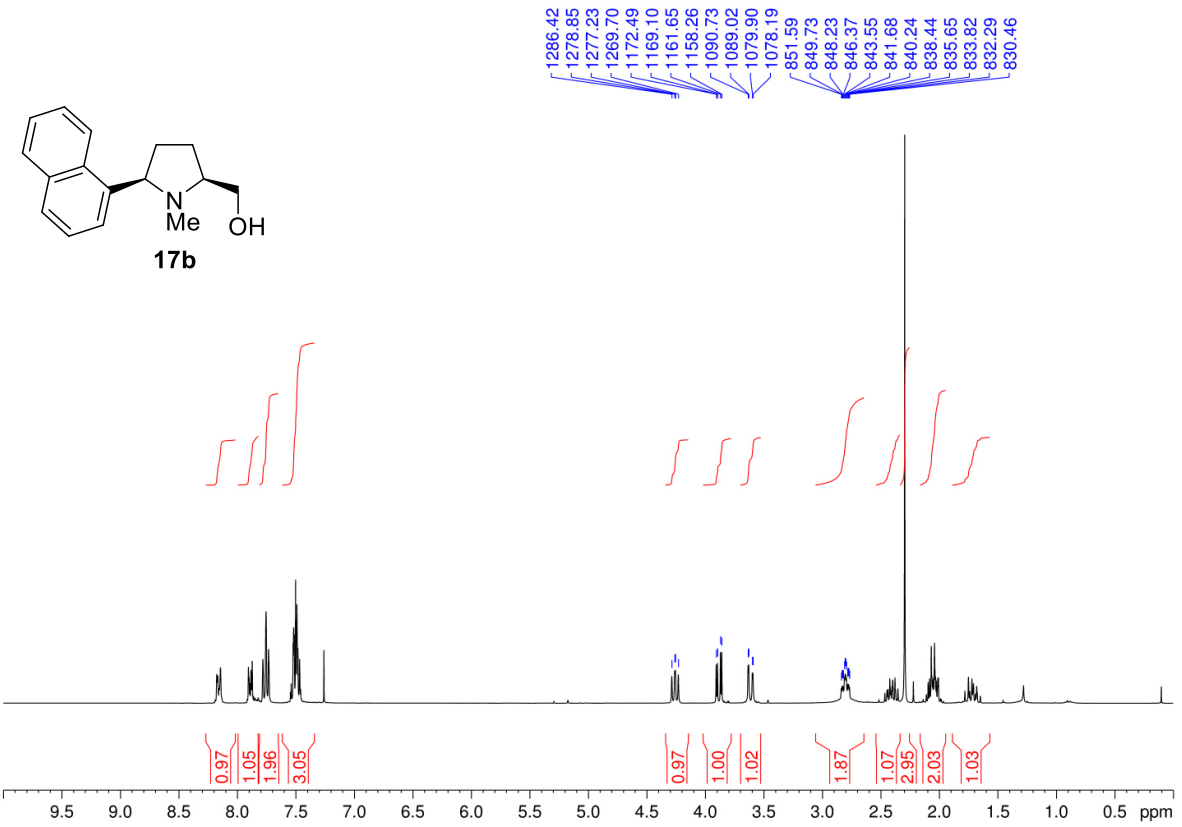

174.04
154.33
153.46
79.75
60.21
59.96
54.12
52.00
32.58
31.80
28.93
28.39
20.67
19.91
Me
N
Boc
OMe
O
16c
5-epi-16c
90 : 10
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

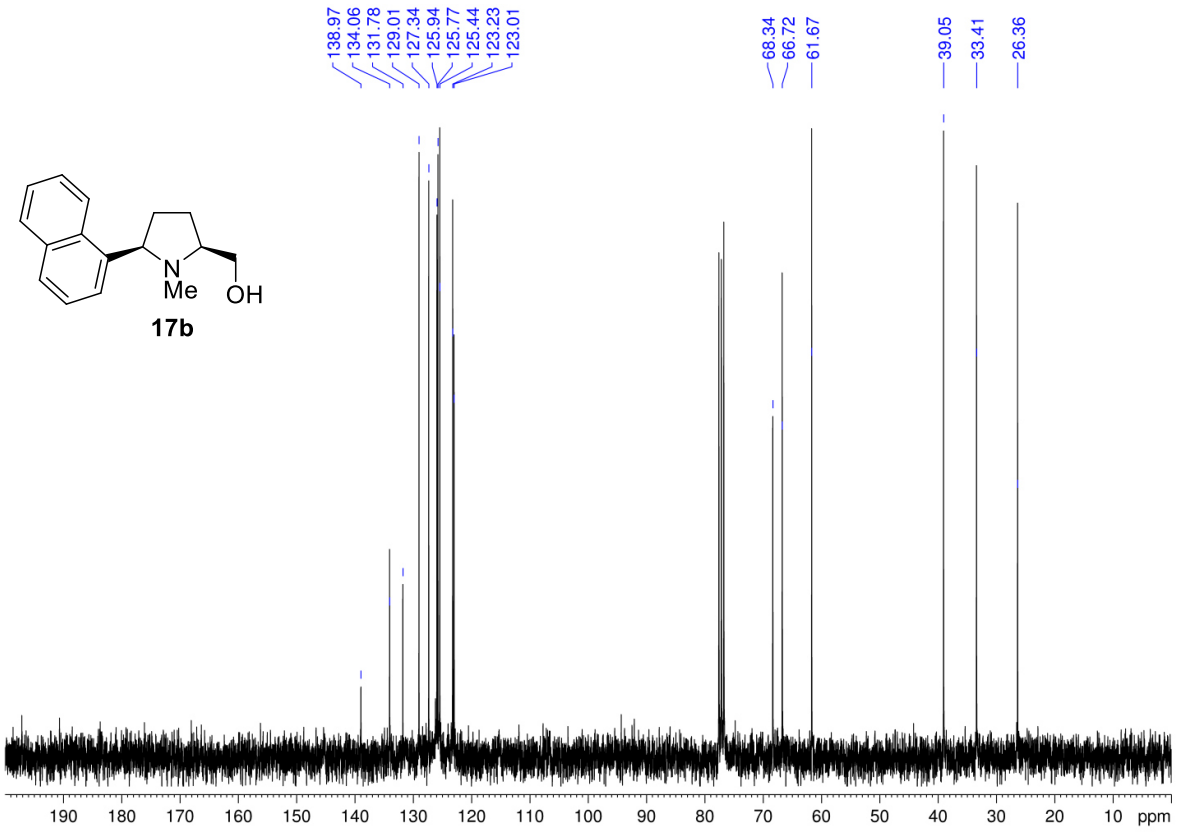

284.91
278.07
263.06
256.34
iPr
N
Boc
O
OMe
16d
0.40
0.58
3.62
0.41
1.04
4.02
3.64
5.37
2.98
2.98
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

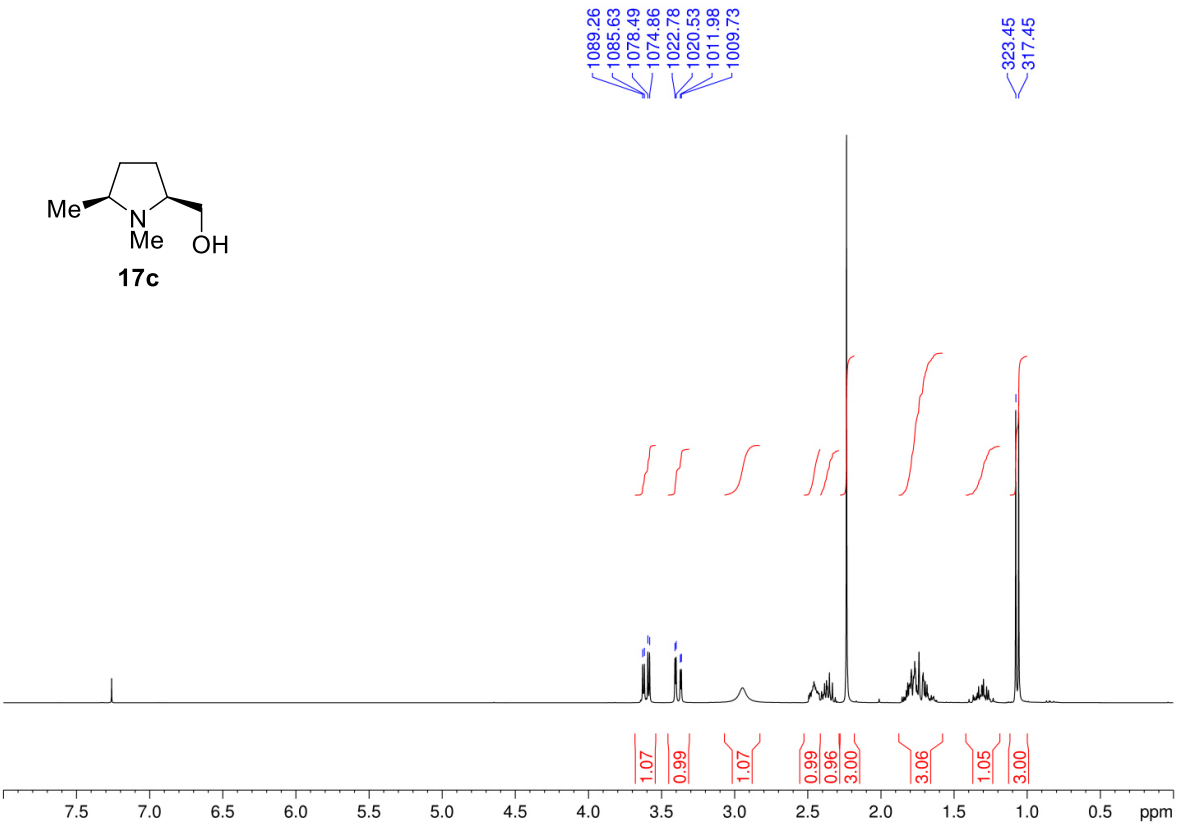

173.99
173.81
154.55
79.79
64.38
64.14
60.50
60.00
52.00
51.82
31.44
31.28
29.21
28.33
27.51
26.47
20.13
19.91
18.58
18.20
iPr
N
Boc
O
OMe
16d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

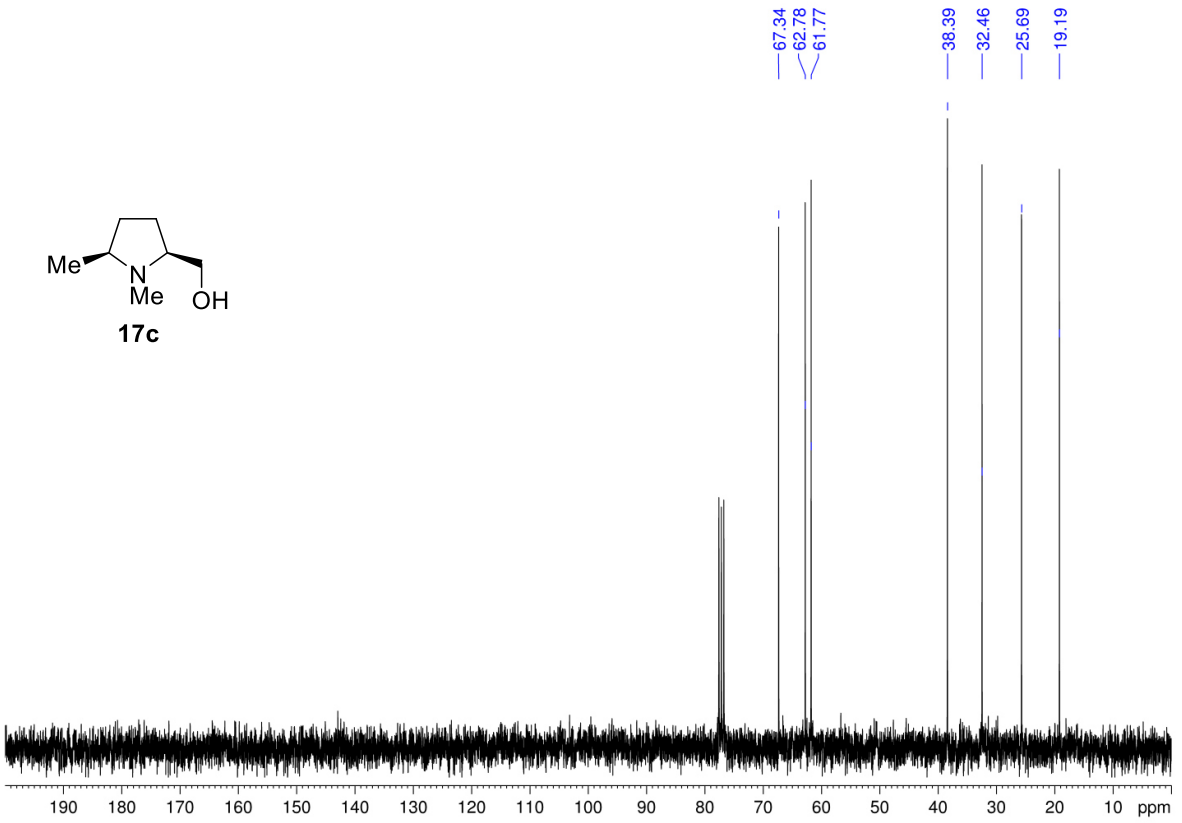

1318.05
1310.28
1302.47
1283.24
1275.28
1267.06
1034.94
1031.58
1021.70
1018.49
992.50
988.48
979.41
975.51
Bn
N
Boc
O
OMe
16e
5.36
0.45
0.55
1.04
2.98
0.54
0.44
1.00
0.94
1.06
2.05
8.97
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

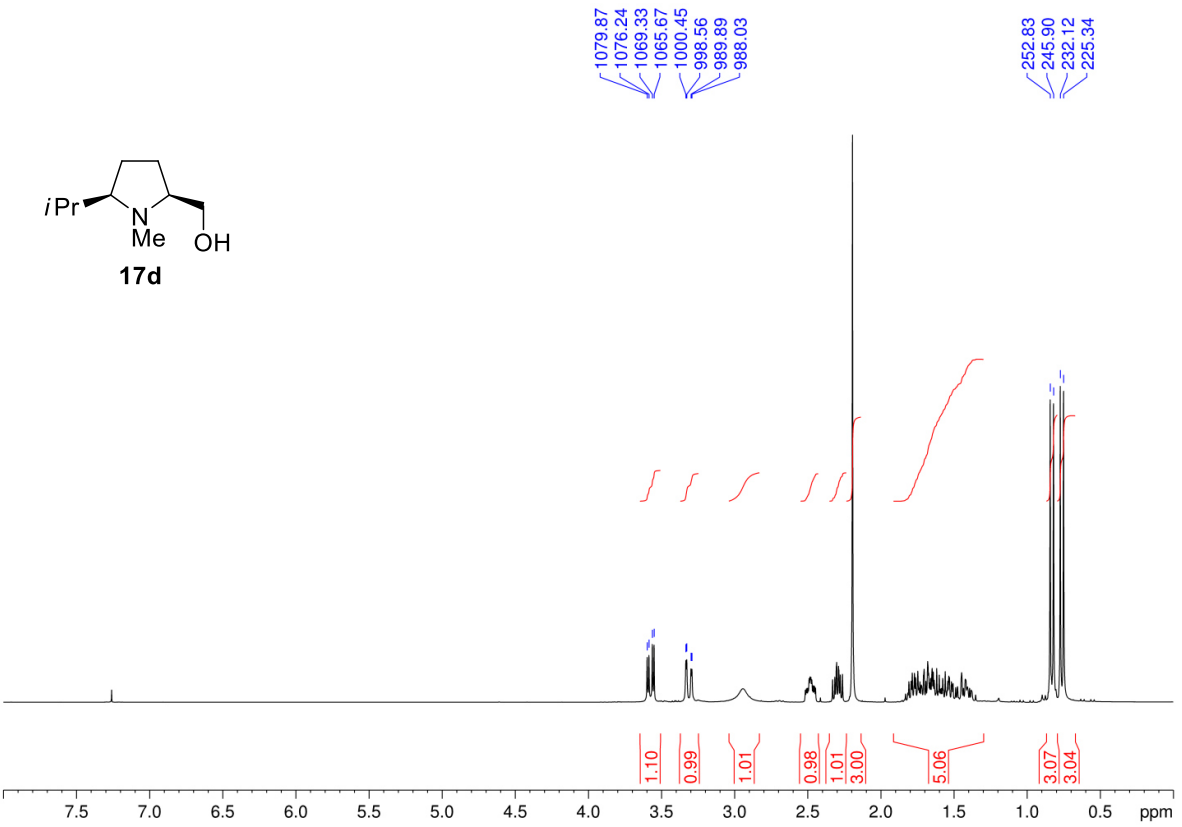

174.03
173.89
154.29
153.61
139.32
129.53
129.42
128.50
128.42
126.20
80.10
60.38
60.22
59.98
59.48
52.22
52.05
40.93
39.76
29.53
28.81
28.42
28.27
Bn
N
Boc
O
OMe
16e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

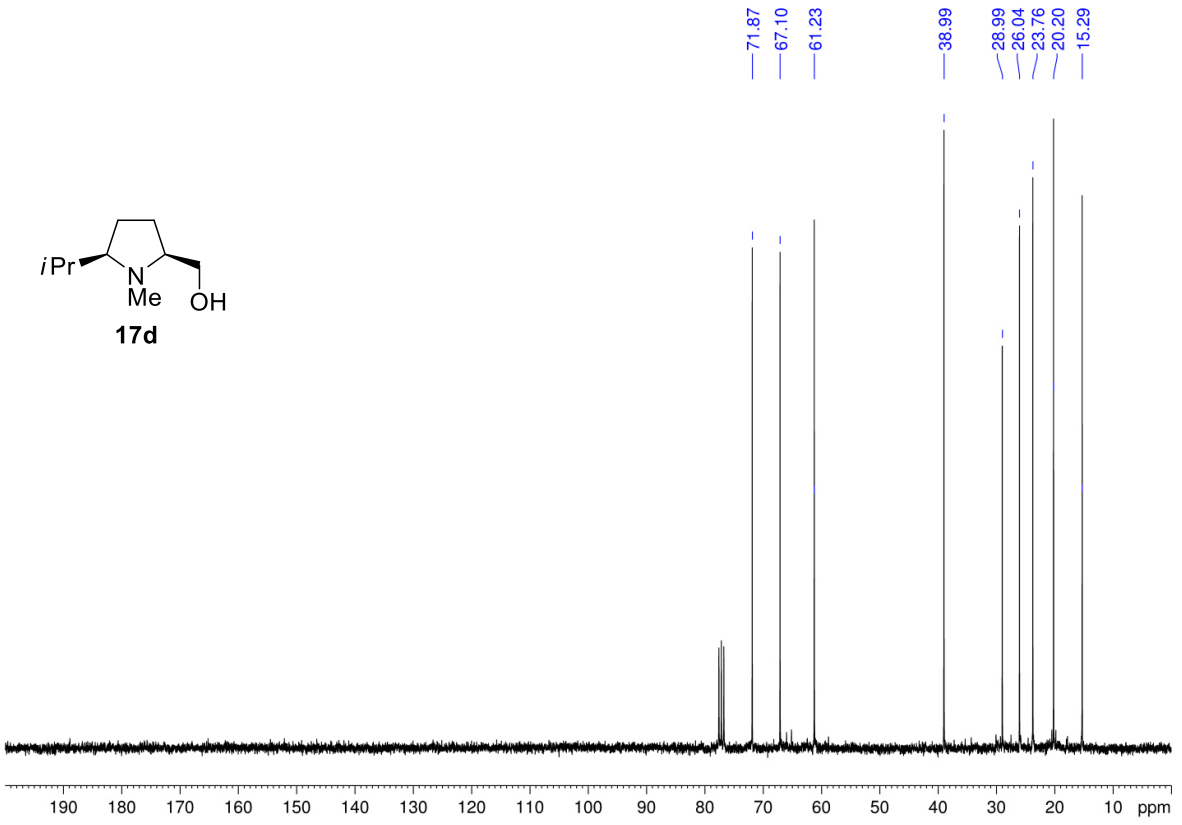

1286.42
1278.85
1277.23
1269.70
1172.49
1169.10
1161.65
1158.26
1090.73
1089.02
1079.90
1078.19
851.59
849.73
848.23
846.37
843.55
841.68
840.24
838.44
835.65
833.82
832.29
830.46
N
Me
OH
17b
0.97
1.05
1.96
3.05
0.97
1.00
1.02
1.87
1.07
2.95
2.03
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

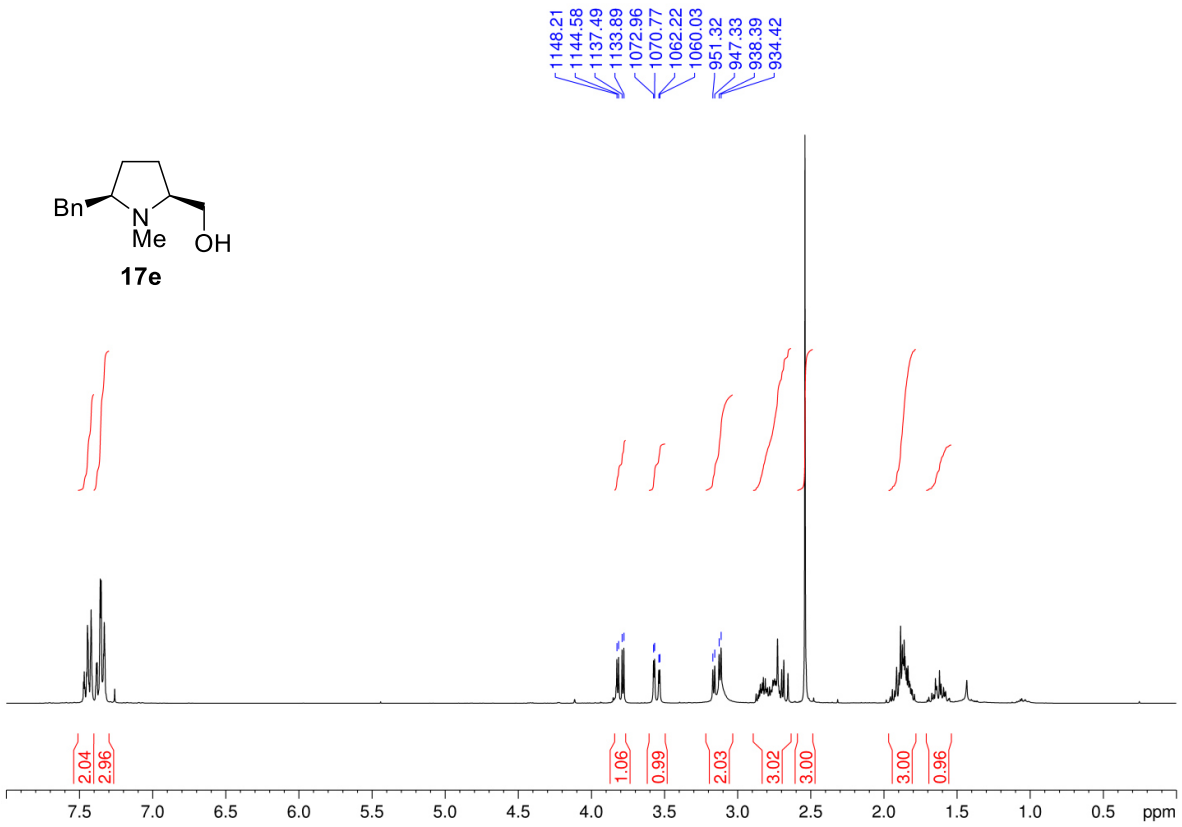

138.97
134.06
131.78
129.01
127.34
125.94
125.77
125.44
123.23
123.01
68.34
66.72
61.67
39.05
33.41
26.36
N
Me
OH
17b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

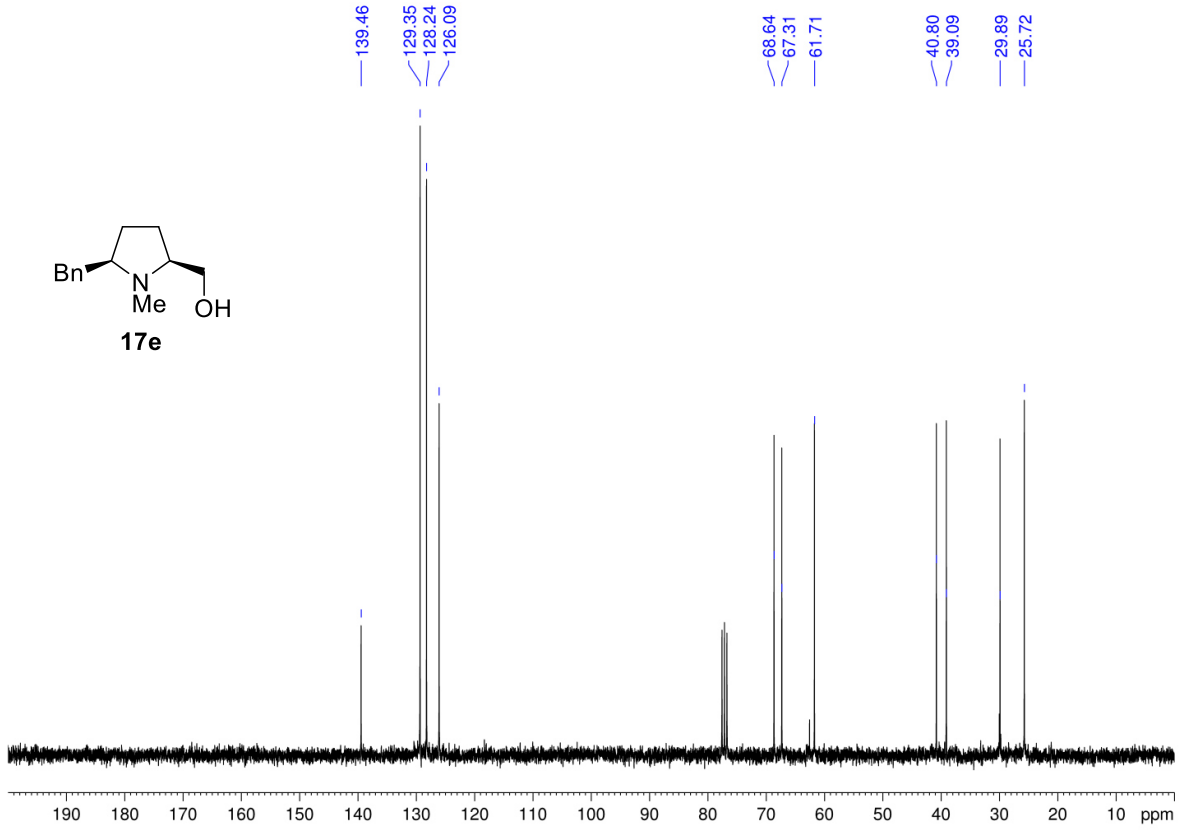

1089.26
1085.63
1078.49
1074.86
1022.78
1020.53
1011.98
1009.73
323.45
317.45
Me
N
Me
OH
17c
1.07
0.99
1.07
0.99
0.96
3.00
3.06
1.05
3.00
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

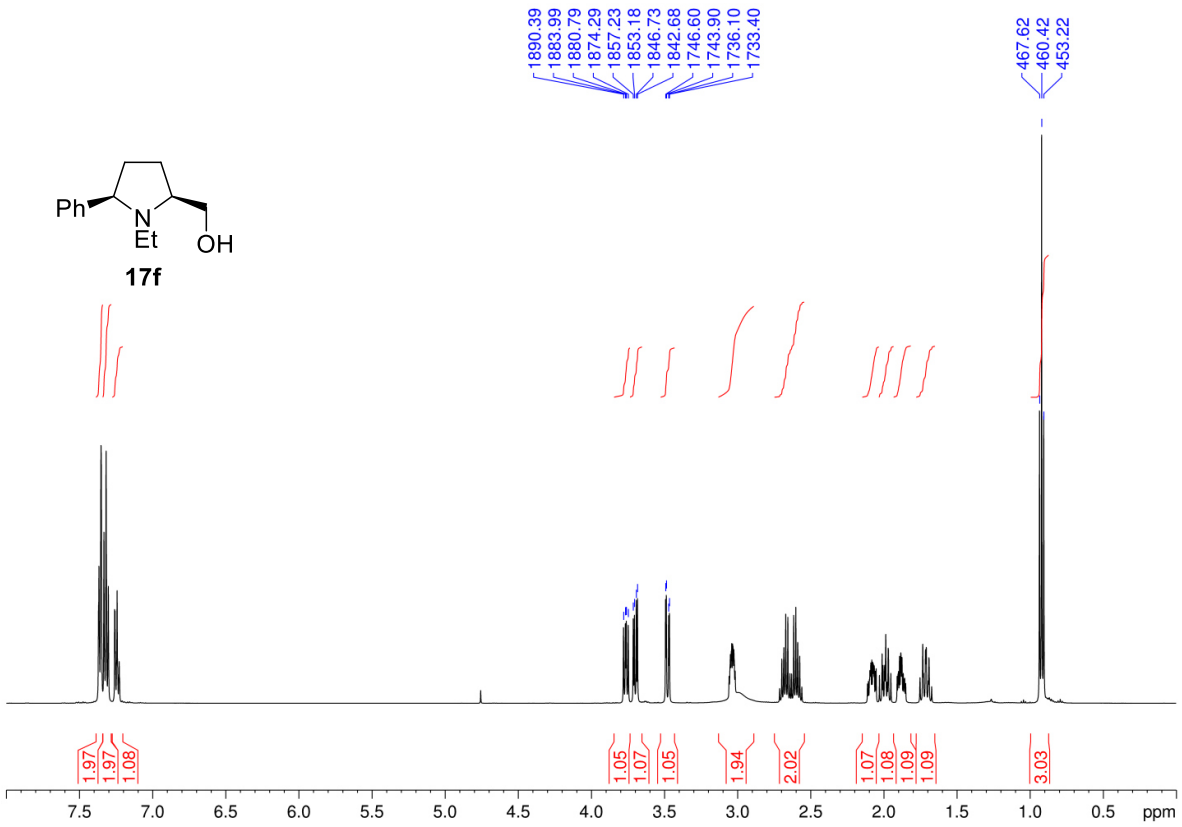

67.34
62.78
61.77
38.39
32.46
25.69
19.19
Me
N
Me
OH
17c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

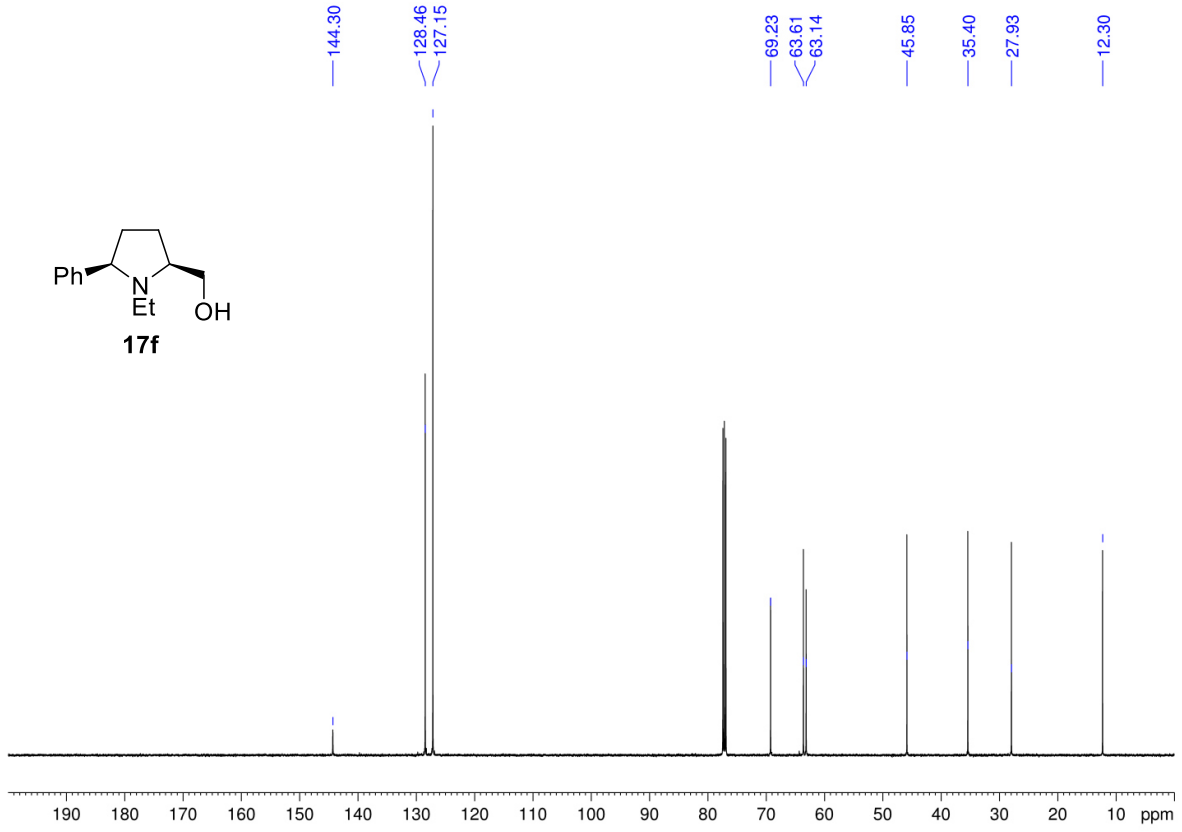

1079.87
1076.24
1069.33
1065.67
1000.45
998.56
989.89
988.03
252.83
245.90
232.12
225.34
iPr
N
Me
OH
17d
1.10
0.99
1.01
0.98
1.01
3.00
5.06
3.07
3.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

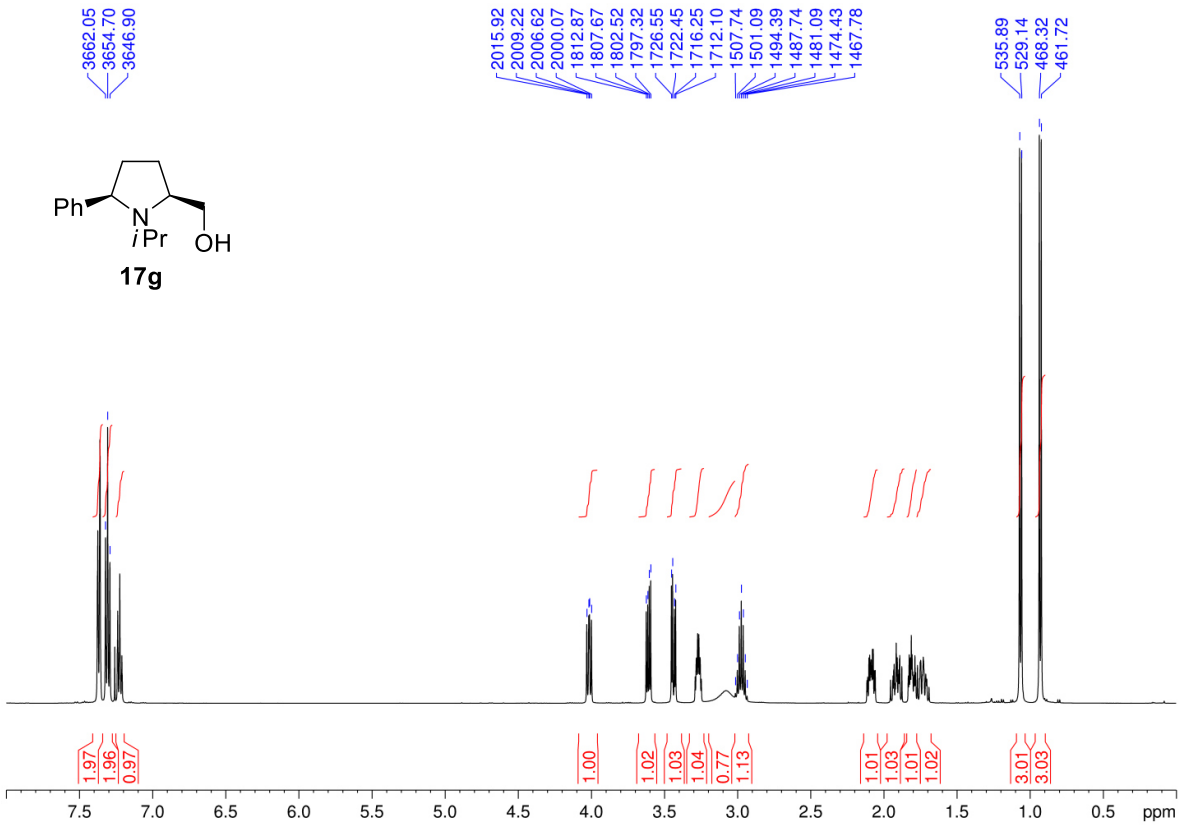

71.87
67.10
61.23
38.99
28.99
26.04
23.76
20.20
15.29
iPr
N
Me
OH
17d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

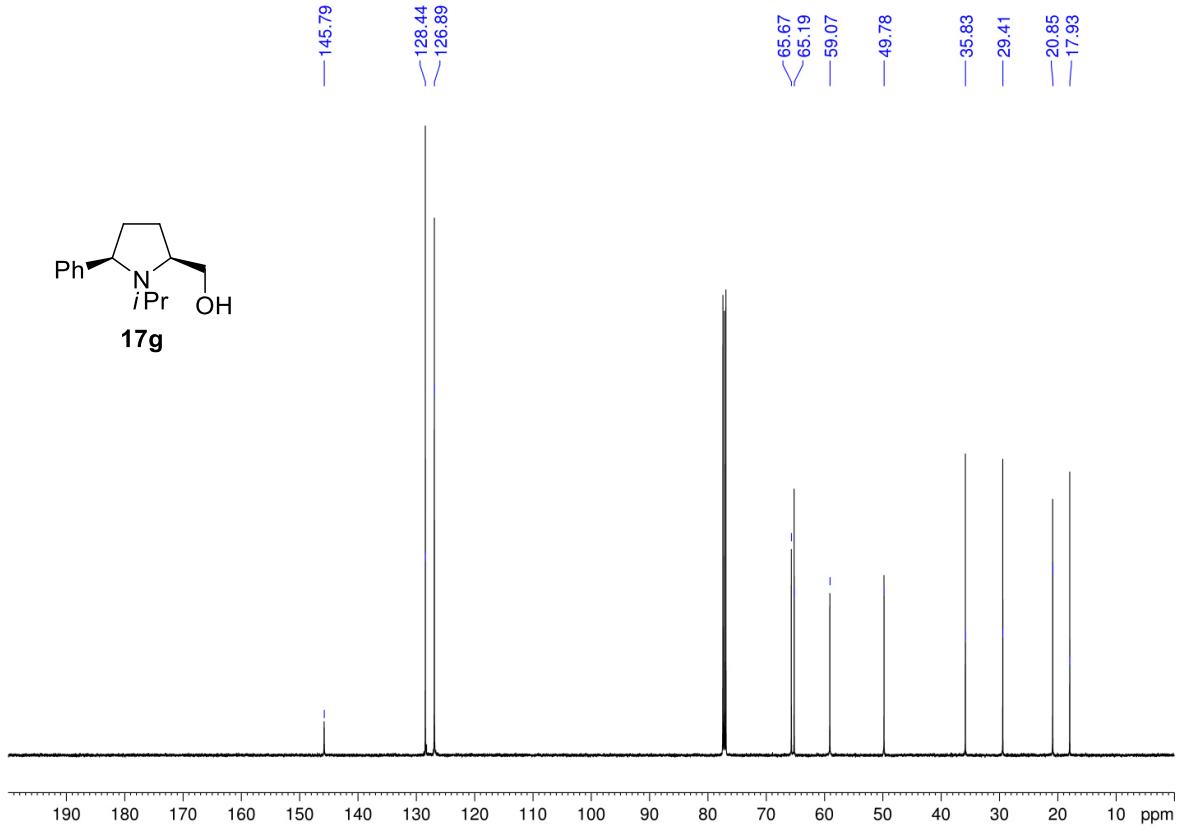

1148.21
1144.58
1137.49
1133.89
1072.96
1070.77
1062.22
1060.03
951.32
947.33
938.39
934.42
Bn
N
Me
OH
17e
2.04
2.96
1.06
0.99
2.03
3.02
3.00
3.00
0.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

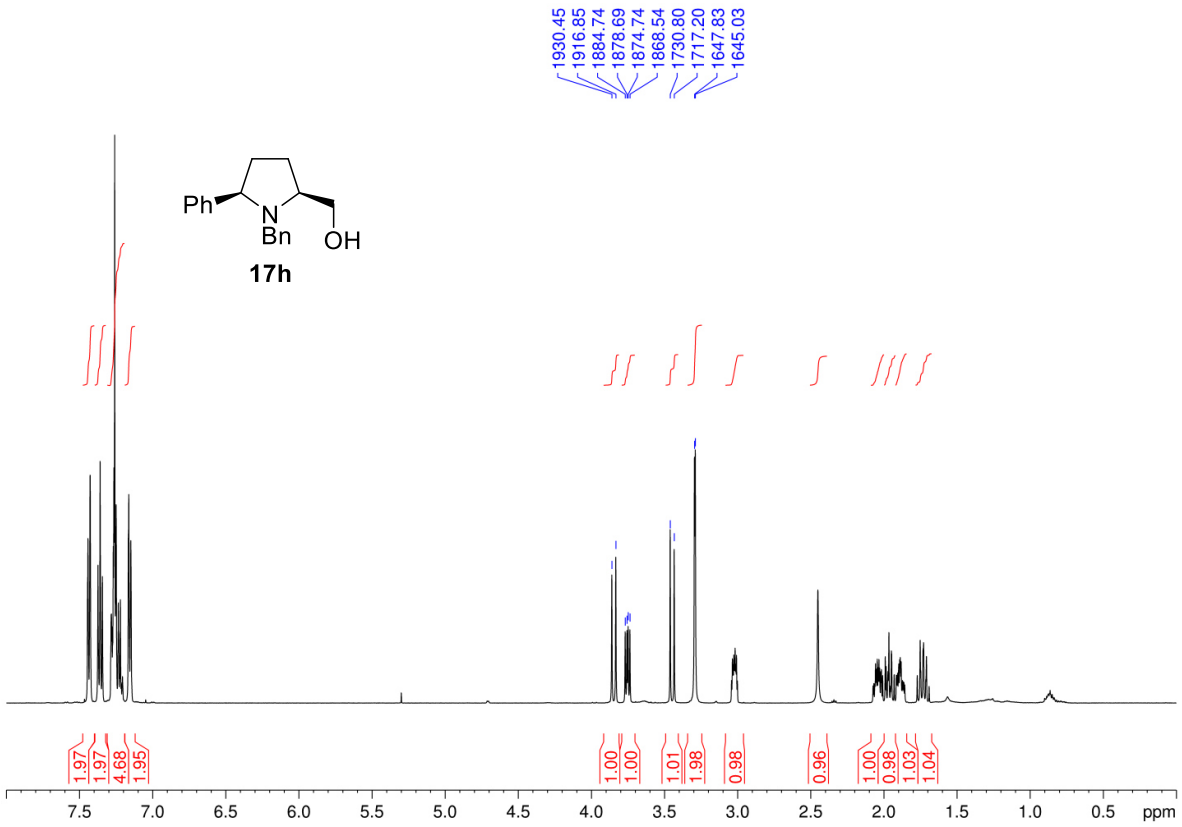

139.46
129.35
128.24
126.09
68.64
67.31
61.71
40.80
39.09
29.89
25.72
Bn
N
Me
OH
17e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

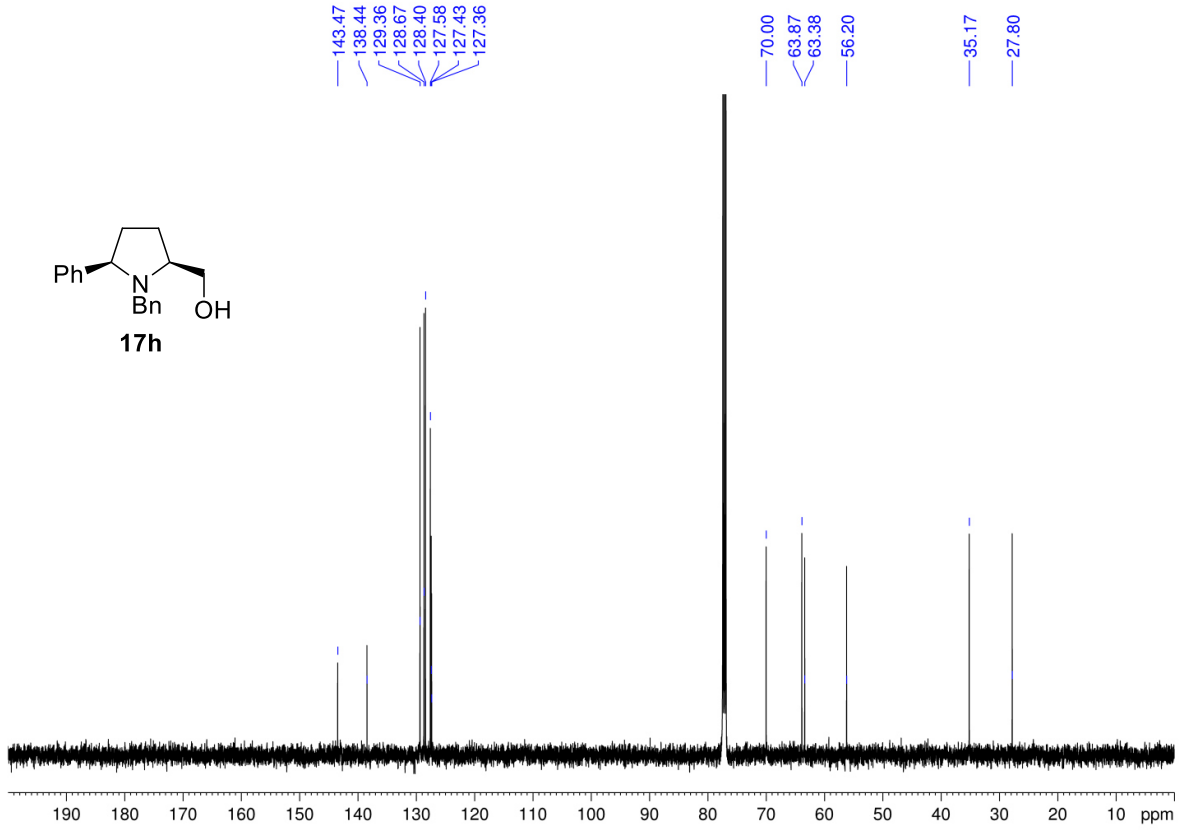

1890.39
1883.99
1880.79
1874.29
1857.23
1853.18
1846.73
1842.68
1746.60
1743.90
1736.10
1733.40
467.62
460.42
453.22
Ph
N
Et
OH
17f
1.97
1.97
1.08
1.05
1.07
1.05
1.94
2.02
1.07
1.08
1.09
1.09
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

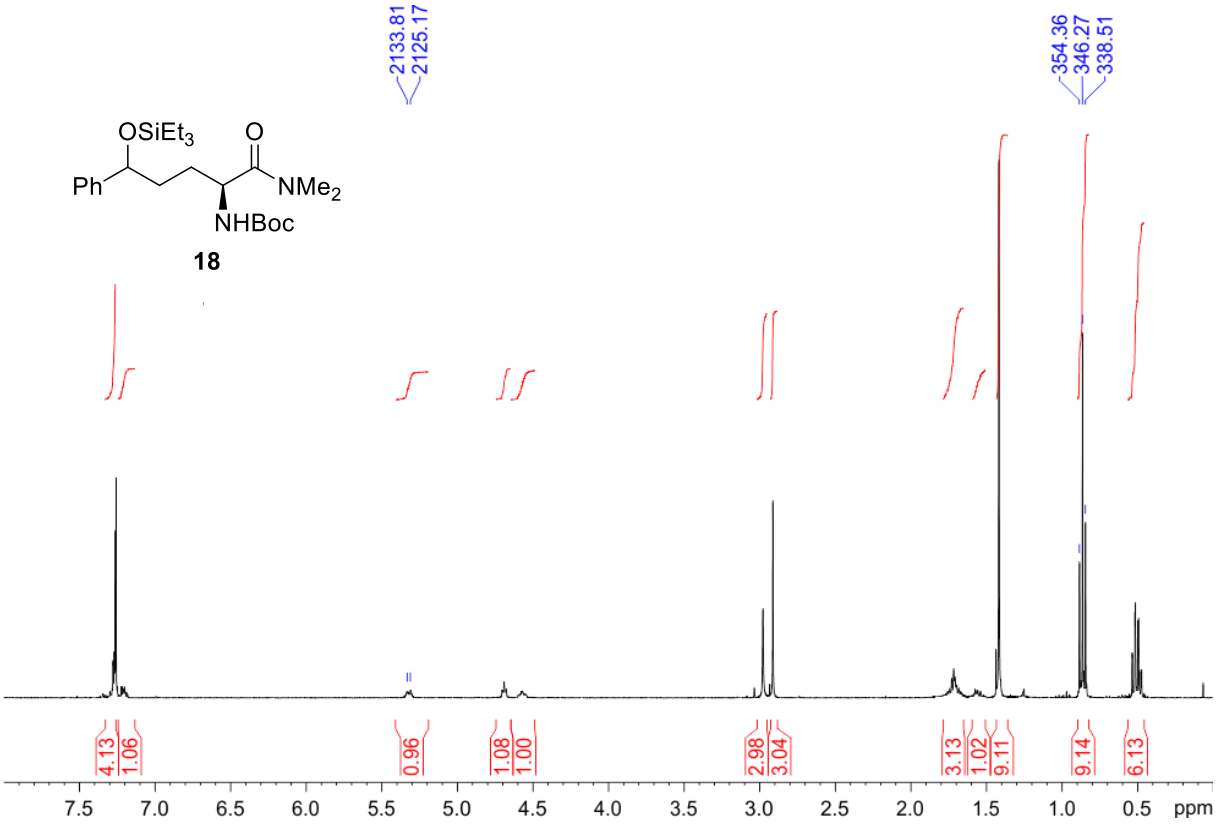

144.30
128.46
127.15
69.23
63.61
63.14
45.85
35.40
27.93
12.30
Ph
N
Et
OH
17f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

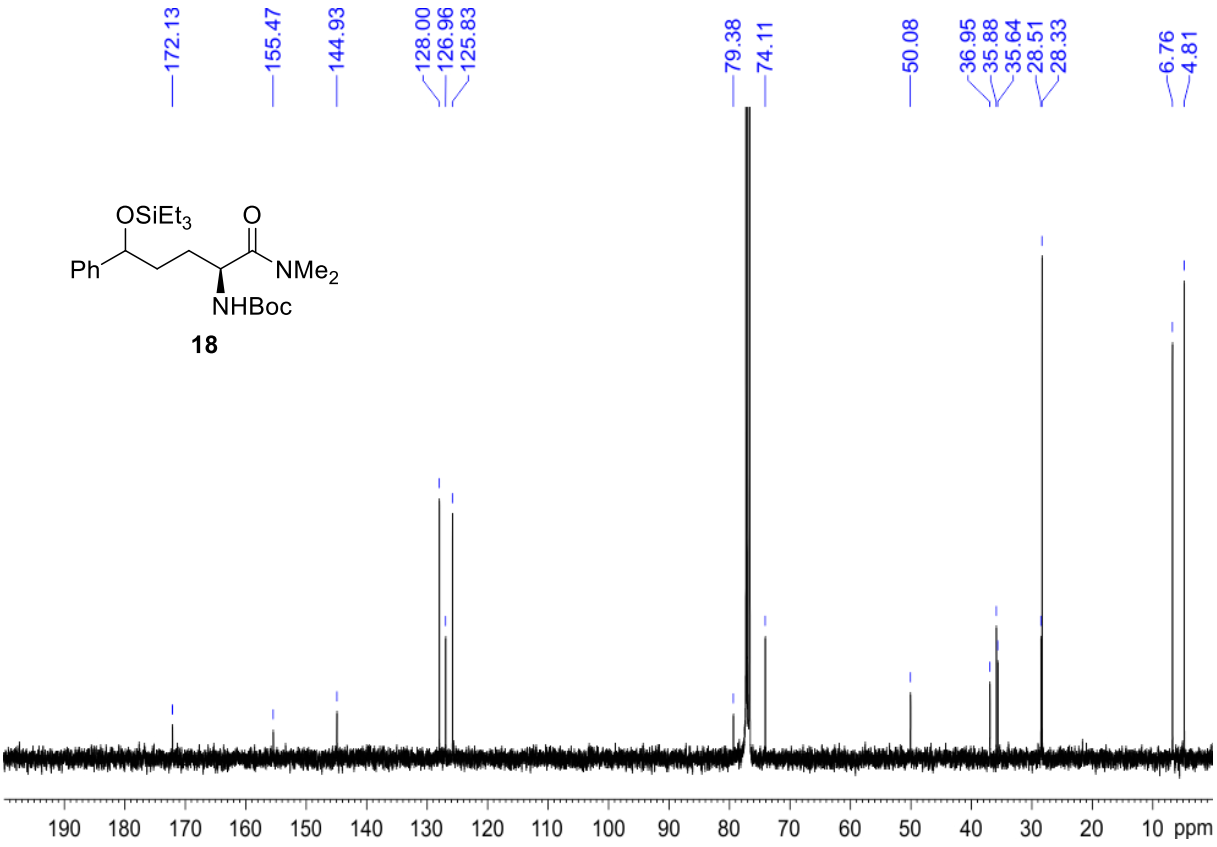

3662.05
3654.70
3646.90
2015.92
2009.22
2006.62
2000.07
1812.87
1807.67
1802.52
1797.32
1726.55
1722.45
1716.25
1712.10
1507.74
1501.09
1494.39
1487.74
1481.09
1474.43
1467.78
535.89
529.14
468.32
461.72
Ph
N
iPr
OH
17g
1.97
1.96
0.97
1.00
1.02
1.03
1.04
0.77
1.13
1.01
1.03
1.01
1.02
3.01
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

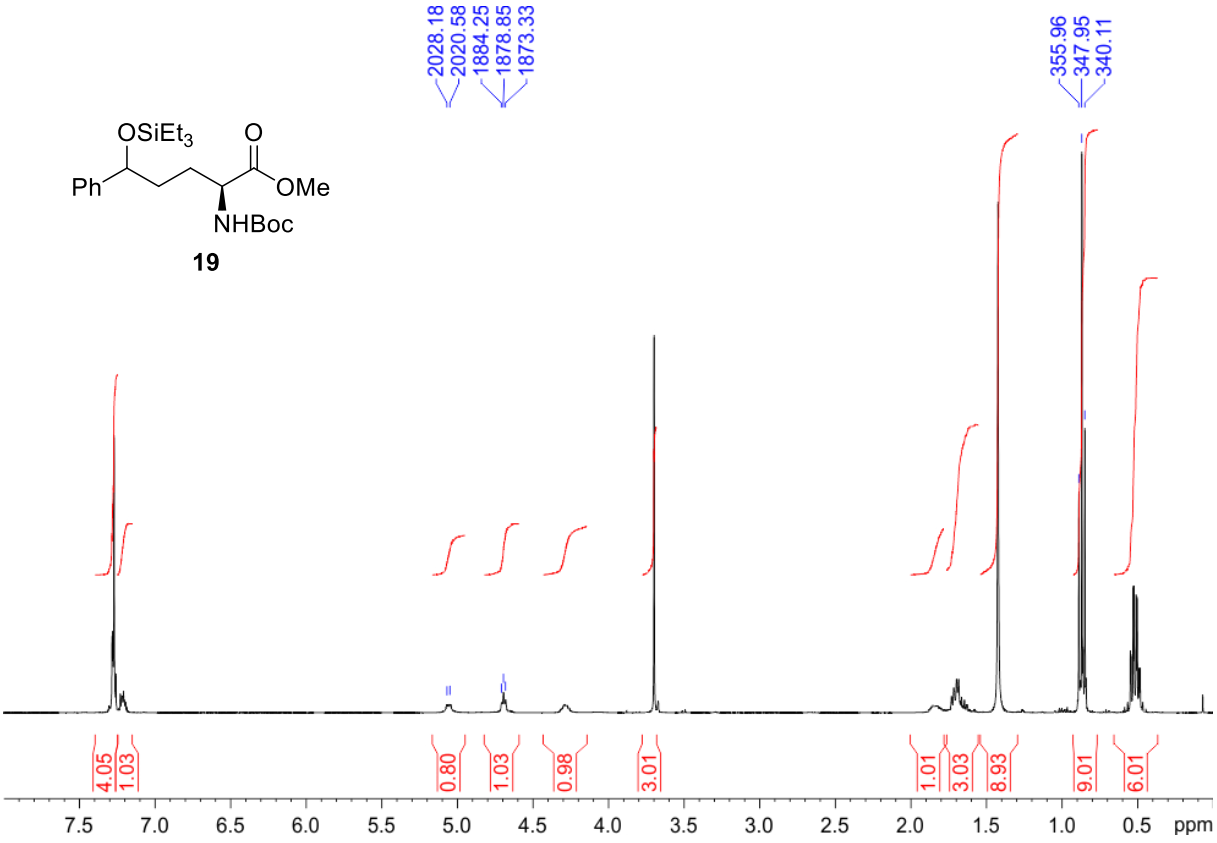

145.79
128.44
126.89
65.67
65.19
59.07
49.78
35.83
29.41
20.85
17.93
Ph
N
iPr
OH
17g
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

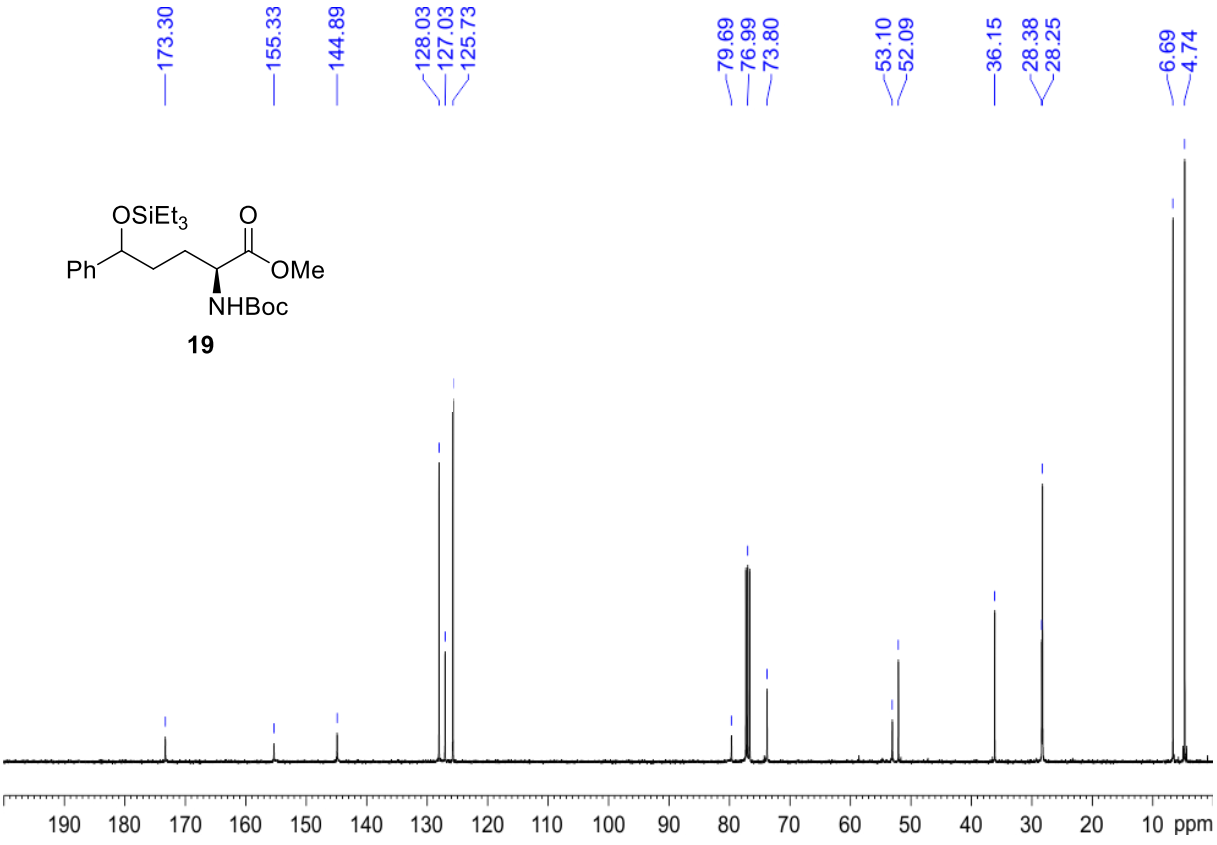

1930.45
1916.85
1884.74
1878.69
1874.74
1868.54
1730.80
1717.20
1647.83
1645.03
Ph
N
Bn
OH
17h
1.97
1.97
4.68
1.95
1.00
1.00
1.01
1.98
0.98
0.96
1.00
0.98
1.03
1.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

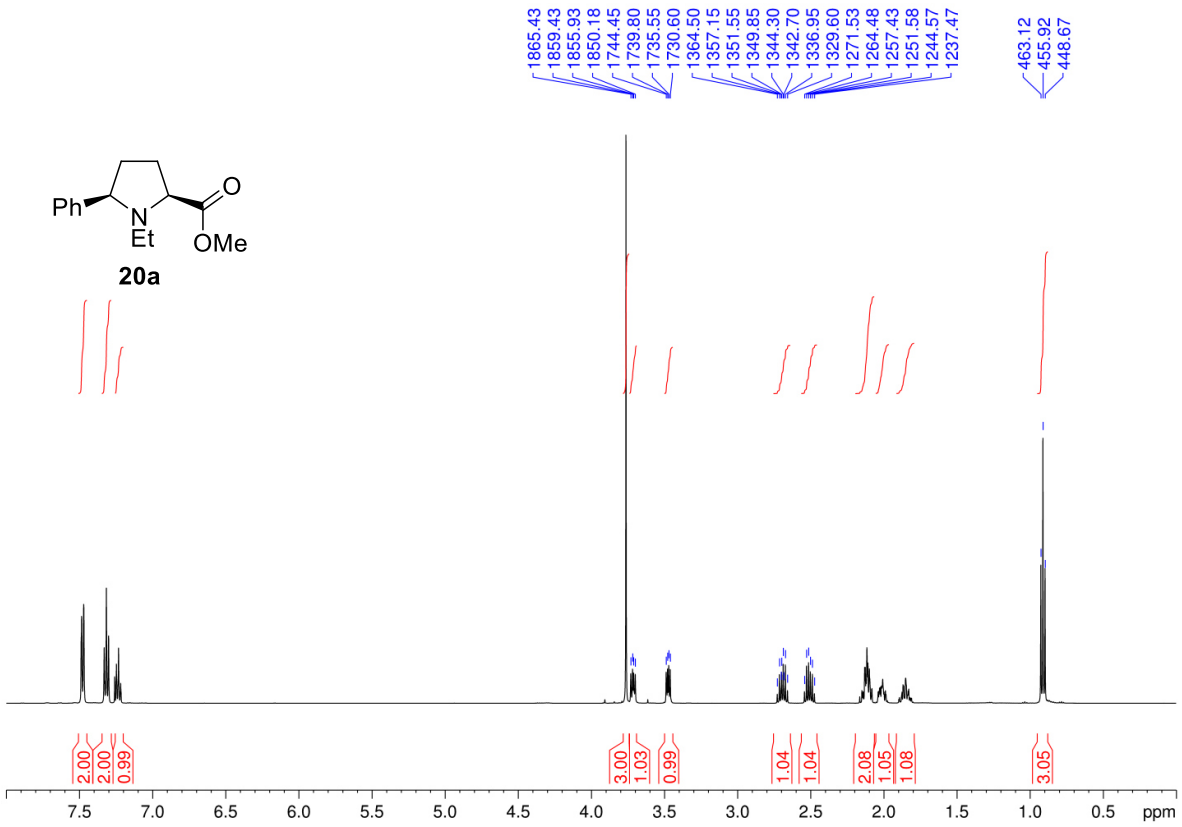

143.47
138.44
129.36
128.67
128.40
127.58
127.43
127.36
70.00
63.87
63.38
56.20
35.17
27.80
Ph
N
Bn
OH
17h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

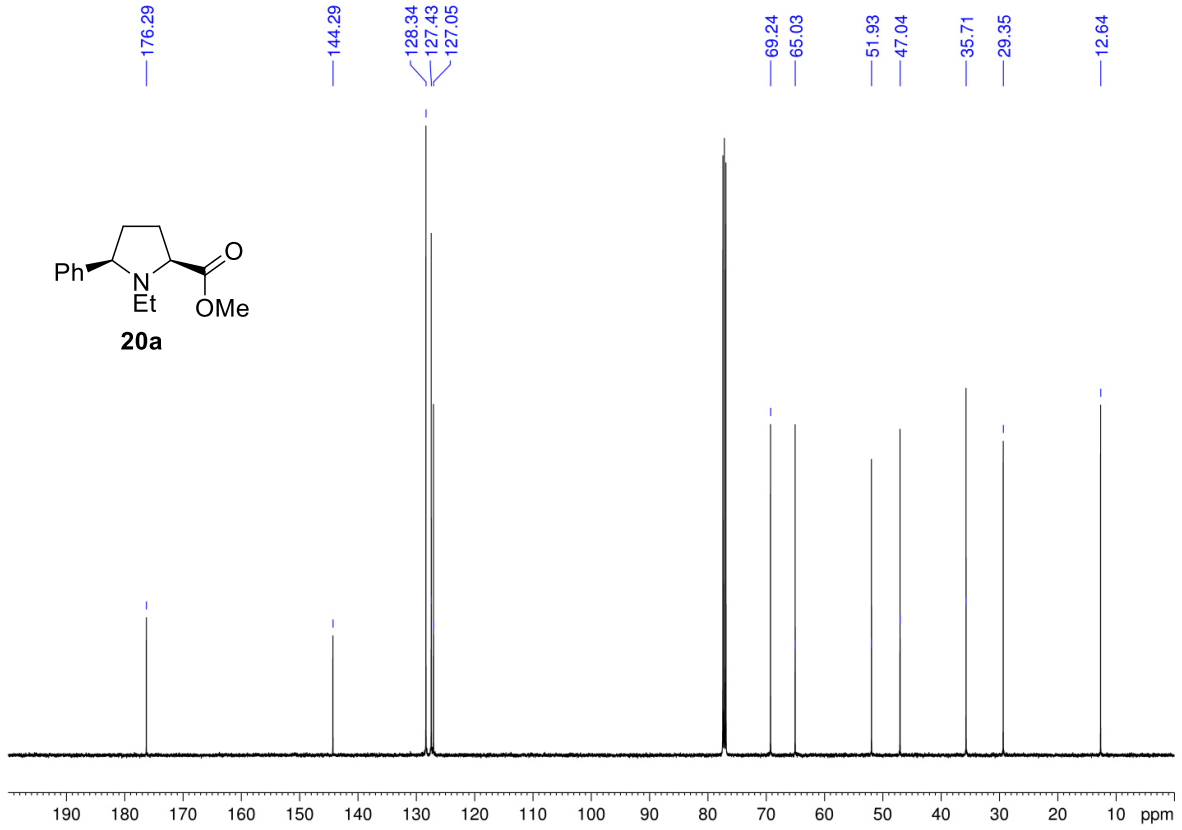

2133.81
2125.17
354.36
346.27
338.51
OSiEt3
O
Ph
NMe2
NHBoc
18
4.13
1.06
0.96
1.08
1.00
2.98
3.04
3.13
1.02
9.11
9.14
6.13
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

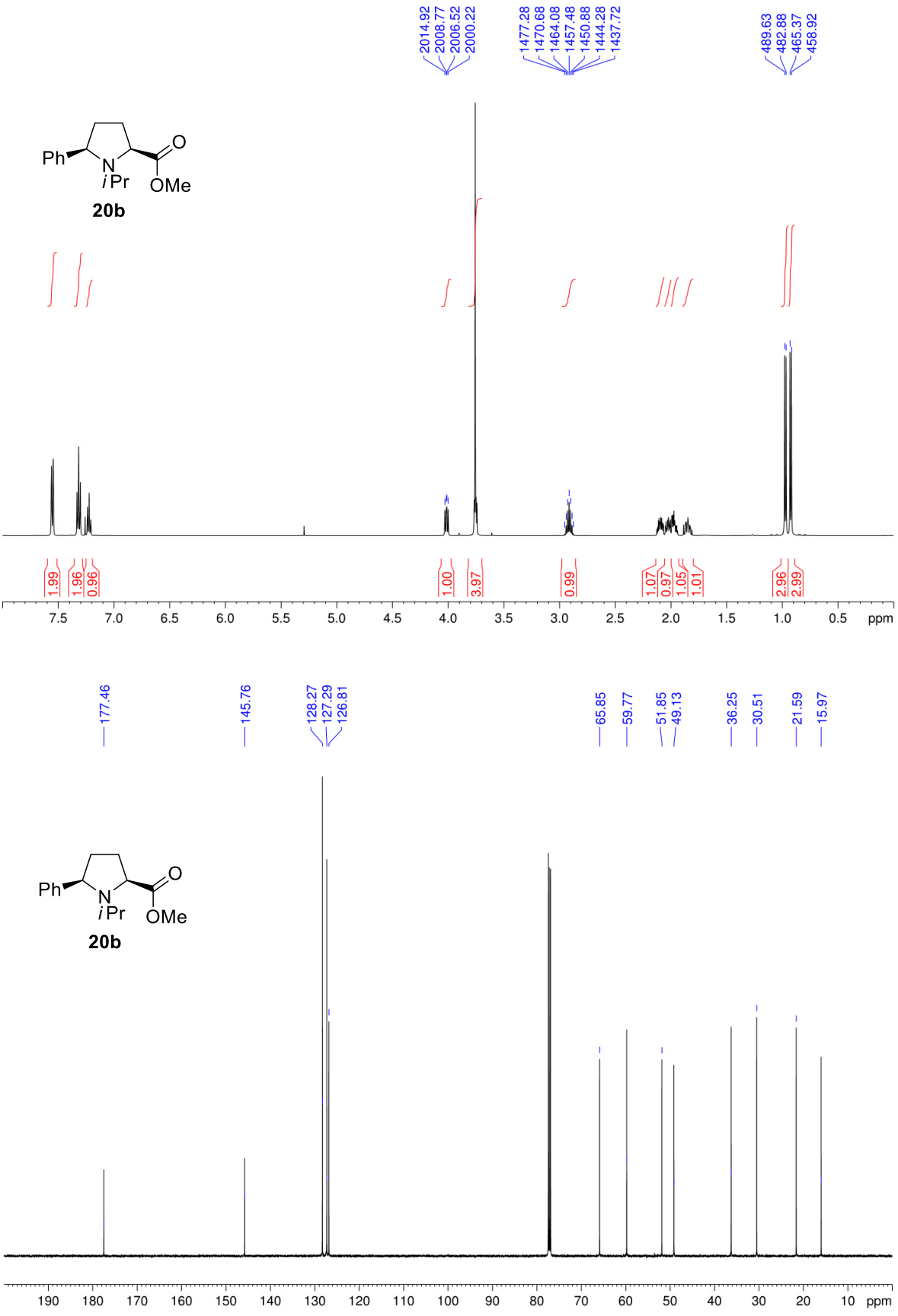

172.13
155.47
144.93
128.00
126.96
125.83
79.38
74.11
50.08
36.95
35.88
35.64
28.51
28.33
6.76
4.81
OSiEt3
O
Ph
NMe2
NHBoc
18
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

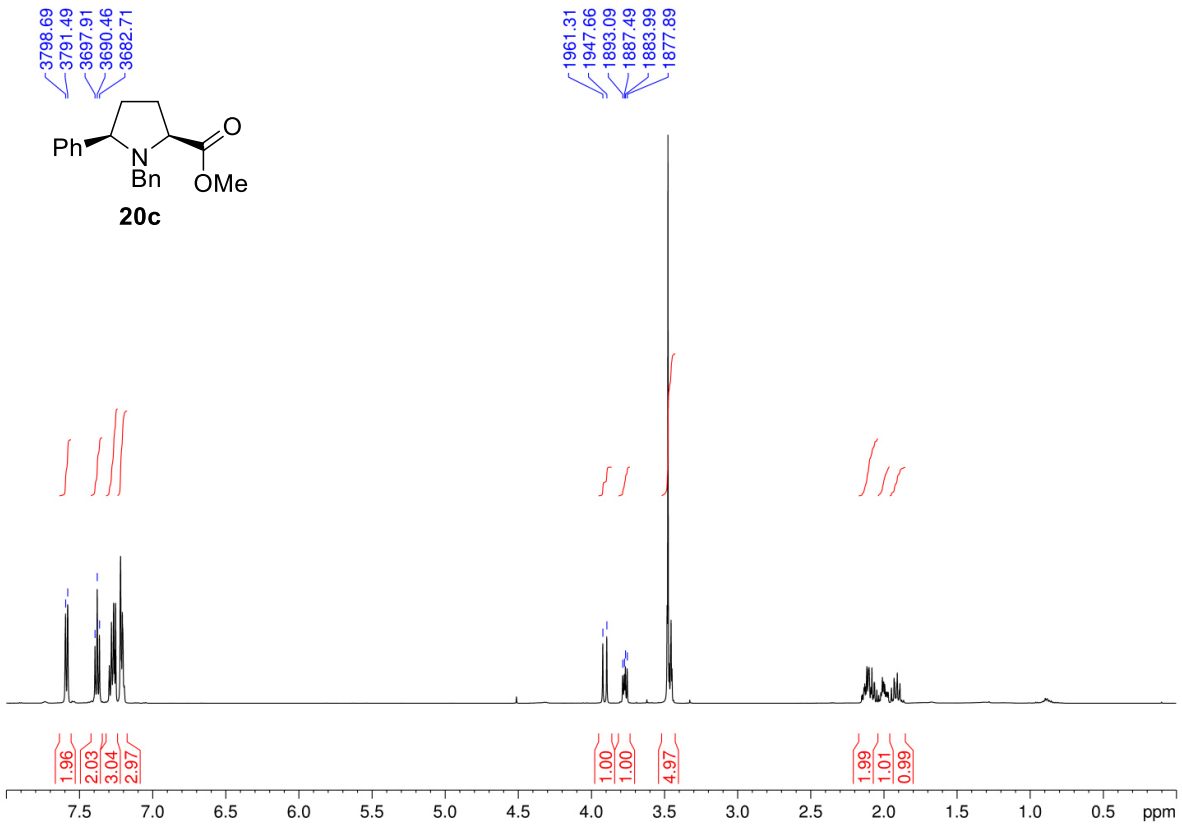

2028.18
2020.58
1884.25
1878.85
1873.33
355.96
347.95
340.11
OSiEt3
O
Ph
OMe
NHBoc
19
4.05
1.03
0.80
1.03
0.98
3.01
1.01
3.03
8.93
9.01
6.01
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

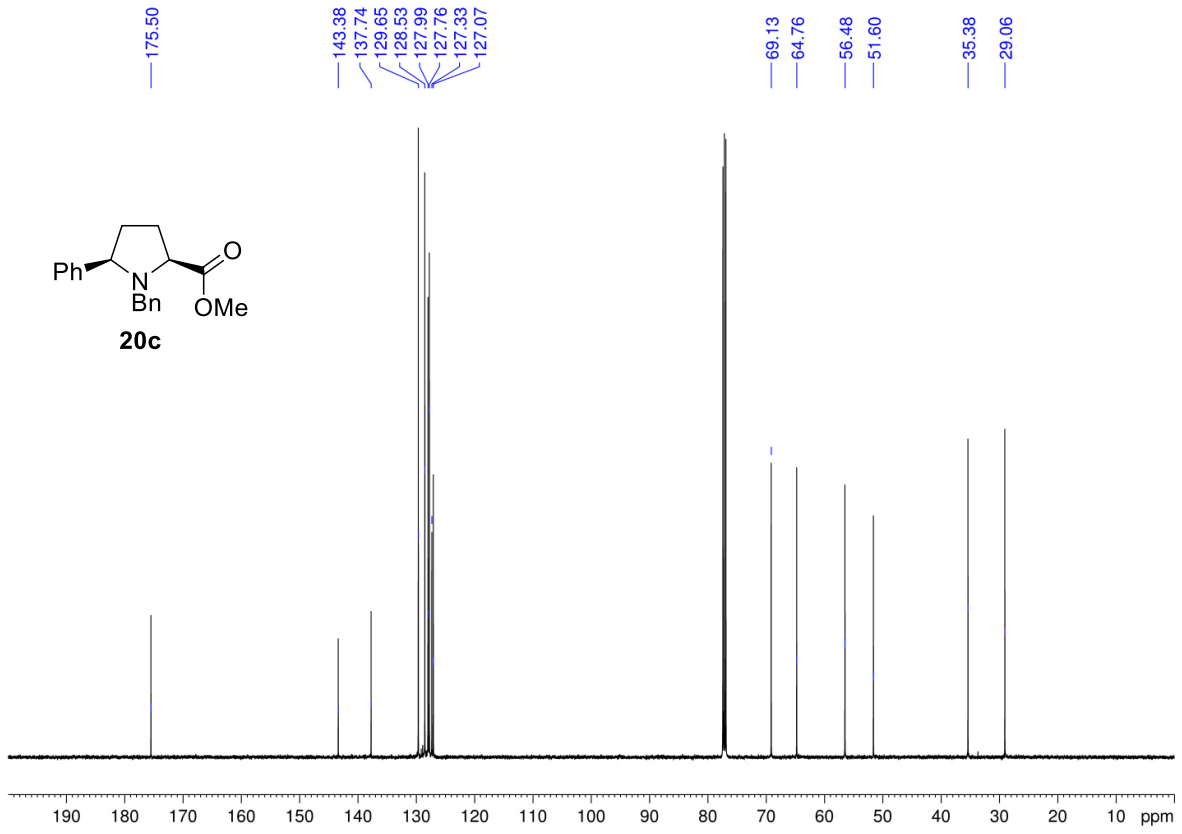

173.30
155.33
144.89
128.03
127.03
125.73
79.69
76.99
73.80
53.10
52.09
36.15
28.38
28.25
6.69
4.74
OSiEt3
O
Ph
OMe
NHBoc
19
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

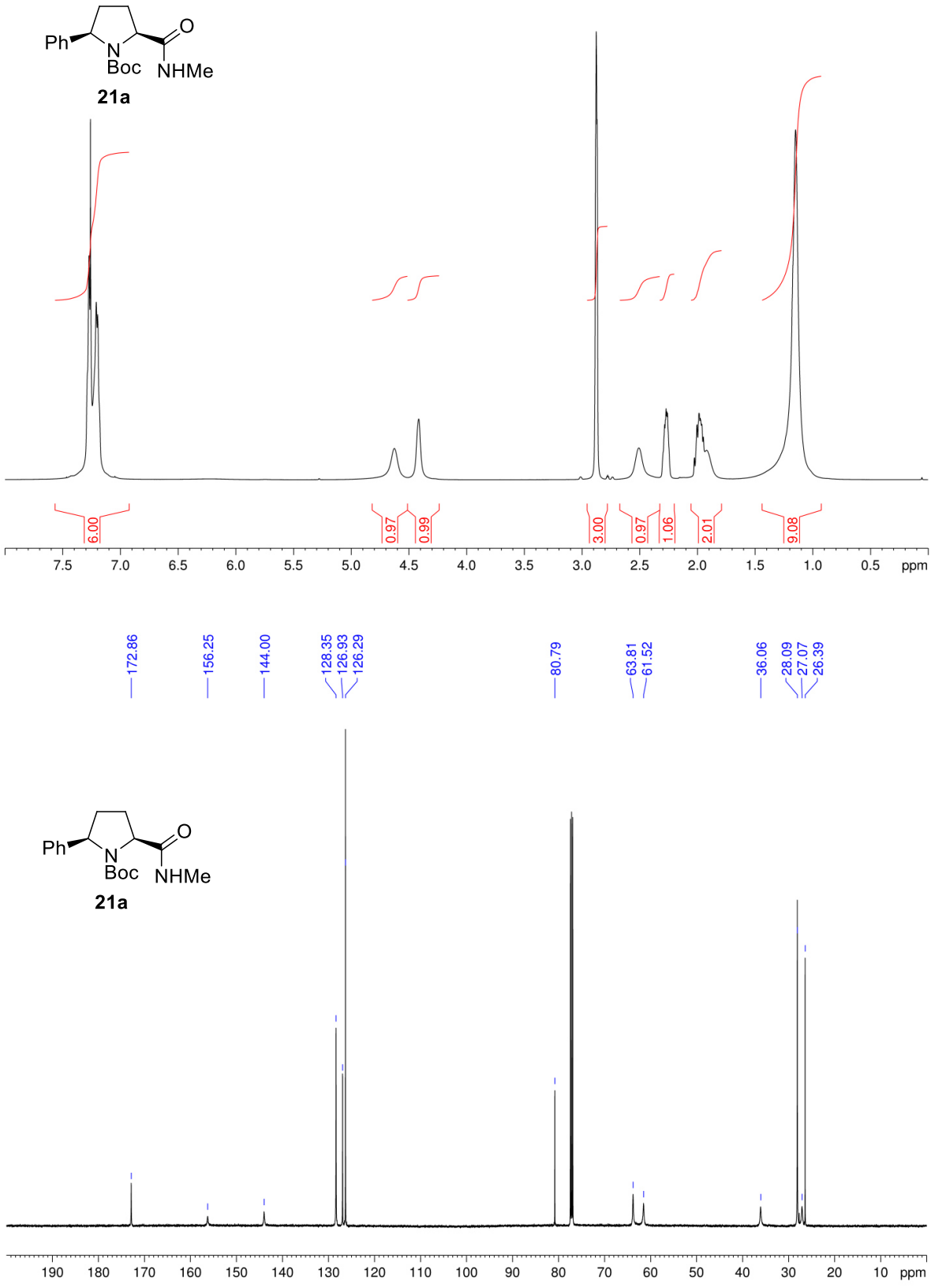

1865.43
1859.43
1855.93
1850.18
1744.45
1739.80
1735.55
1730.60
1364.50
1357.15
1351.55
1349.85
1344.30
1342.70
1336.95
1329.60
1271.53
1264.48
1257.43
1251.58
1244.57
1237.47
463.12
455.92
448.67
Ph
N
Et
O
OMe
20a
2.00
2.00
0.99
3.00
1.03
0.99
1.04
1.04
2.08
1.05
1.08
3.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

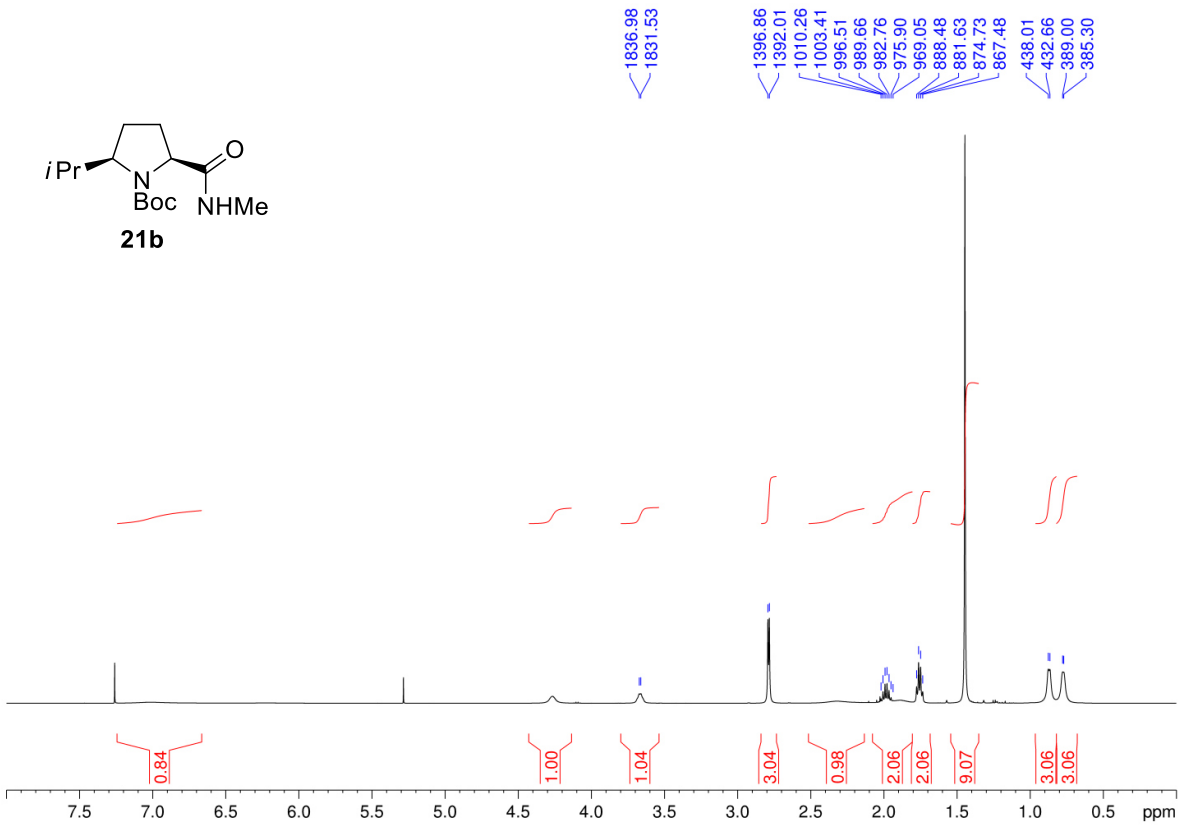

176.29
144.29
128.34
127.43
127.05
69.24
65.03
51.93
47.04
35.71
29.35
12.64
Ph
N
Et
O
OMe
20a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

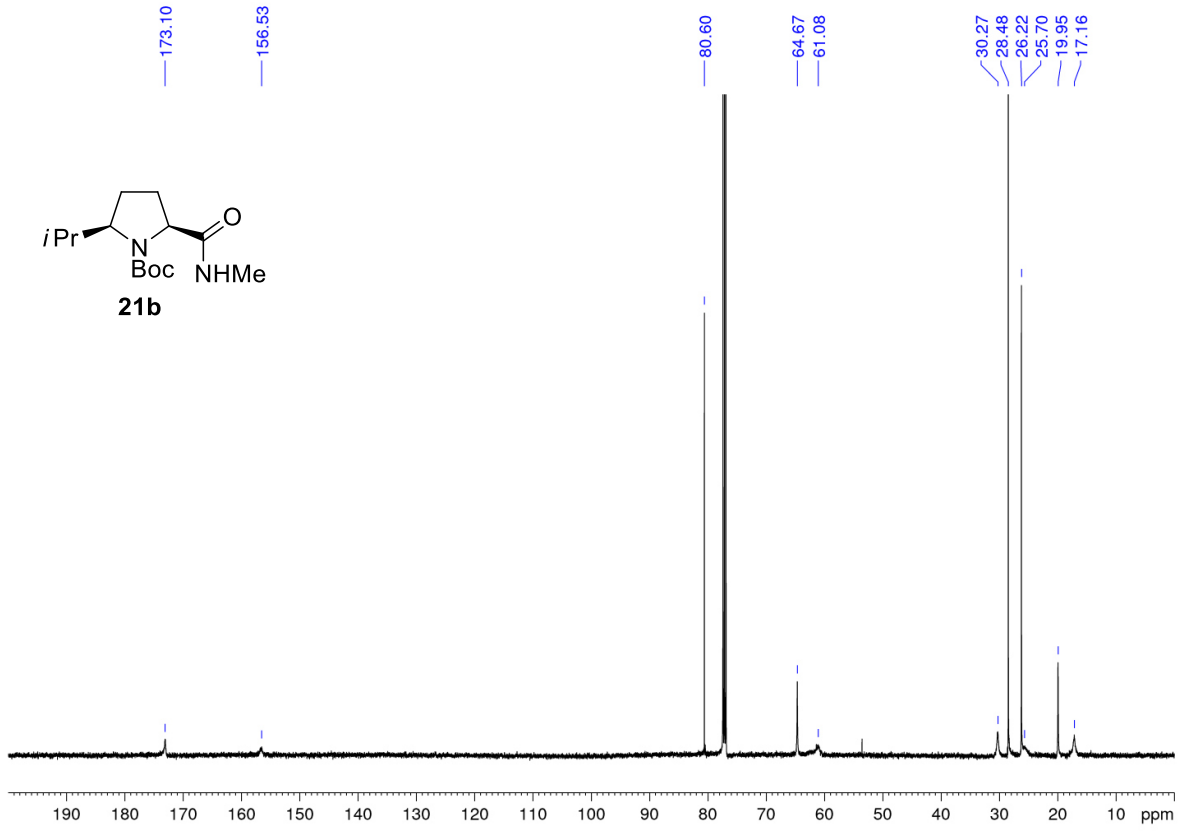

2014.92
2008.77
2006.52
2000.22
1477.28
1470.68
1464.08
1457.48
1450.88
1444.28
1437.72
489.63
482.88
465.37
458.92
Ph
N
iPr
O
OMe
20b
1.99
1.96
0.96
1.00
3.97
0.99
1.07
0.97
1.05
1.01
2.96
2.99
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
177.46
145.76
128.27
127.29
126.81
65.85
59.77
51.85
49.13
36.25
30.51
21.59
15.97
Ph
N
iPr
O
OMe
20b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

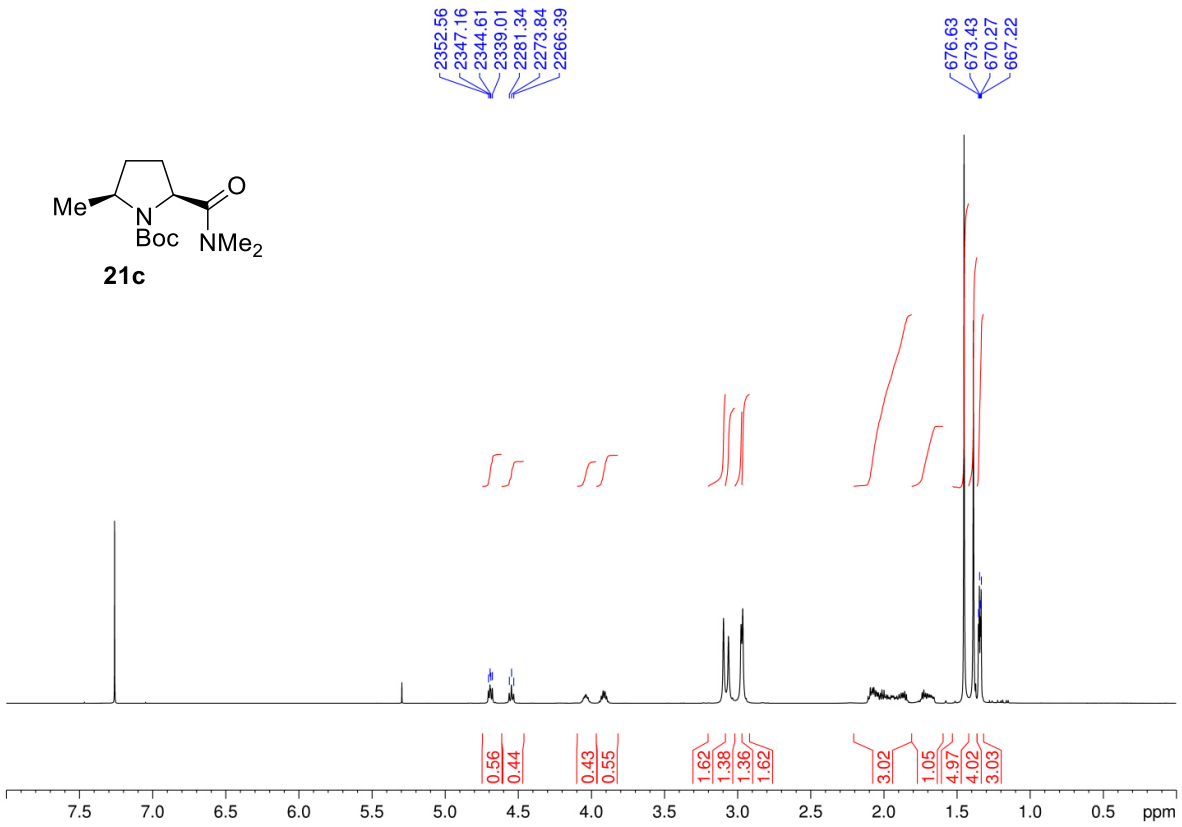

3798.69
3791.49
3697.91
3690.46
3682.71
1961.31
1947.66
1893.09
1887.49
1883.99
1877.89
Ph
N
Bn
O
OMe
20c
1.96
2.03
3.04
2.97
1.00
1.00
4.97
1.99
1.01
0.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

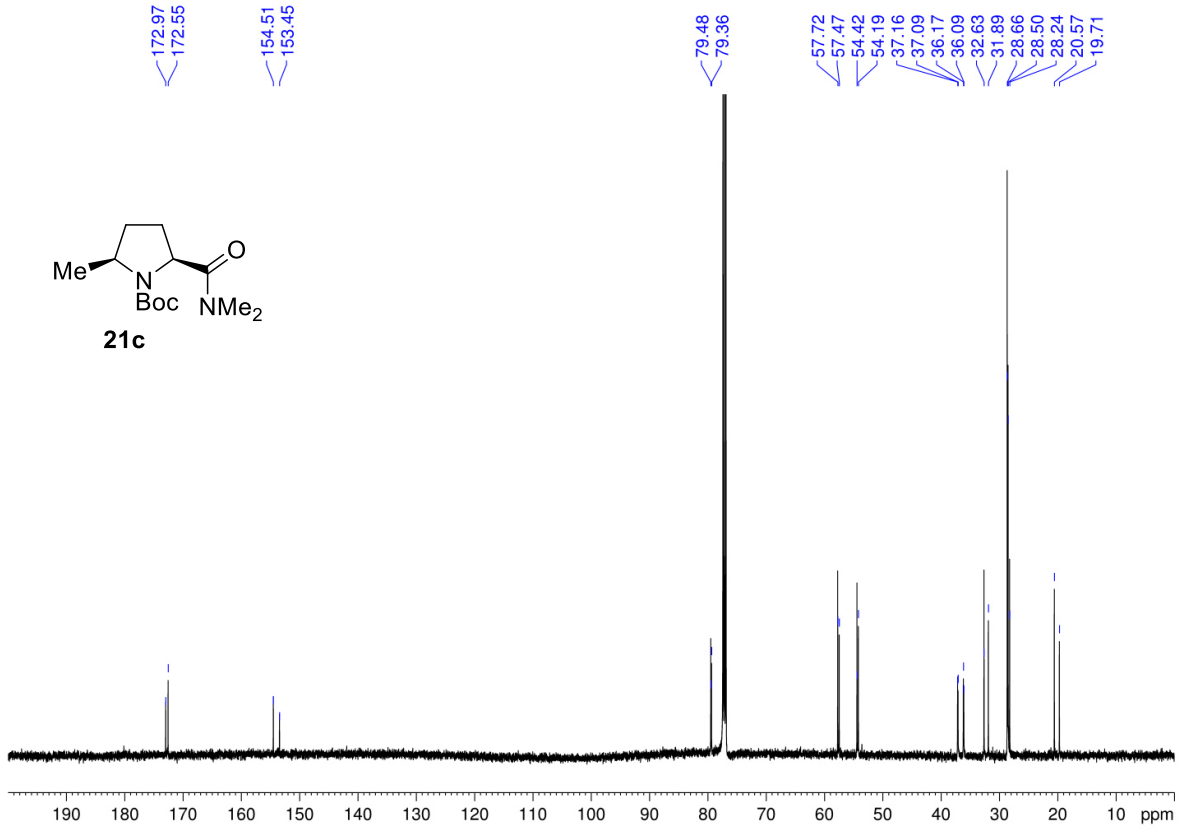

175.50
143.38
137.74
129.65
128.53
127.99
127.76
127.33
127.07
69.13
64.76
56.48
51.60
35.38
29.06
Ph
N
Bn
O
OMe
20c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

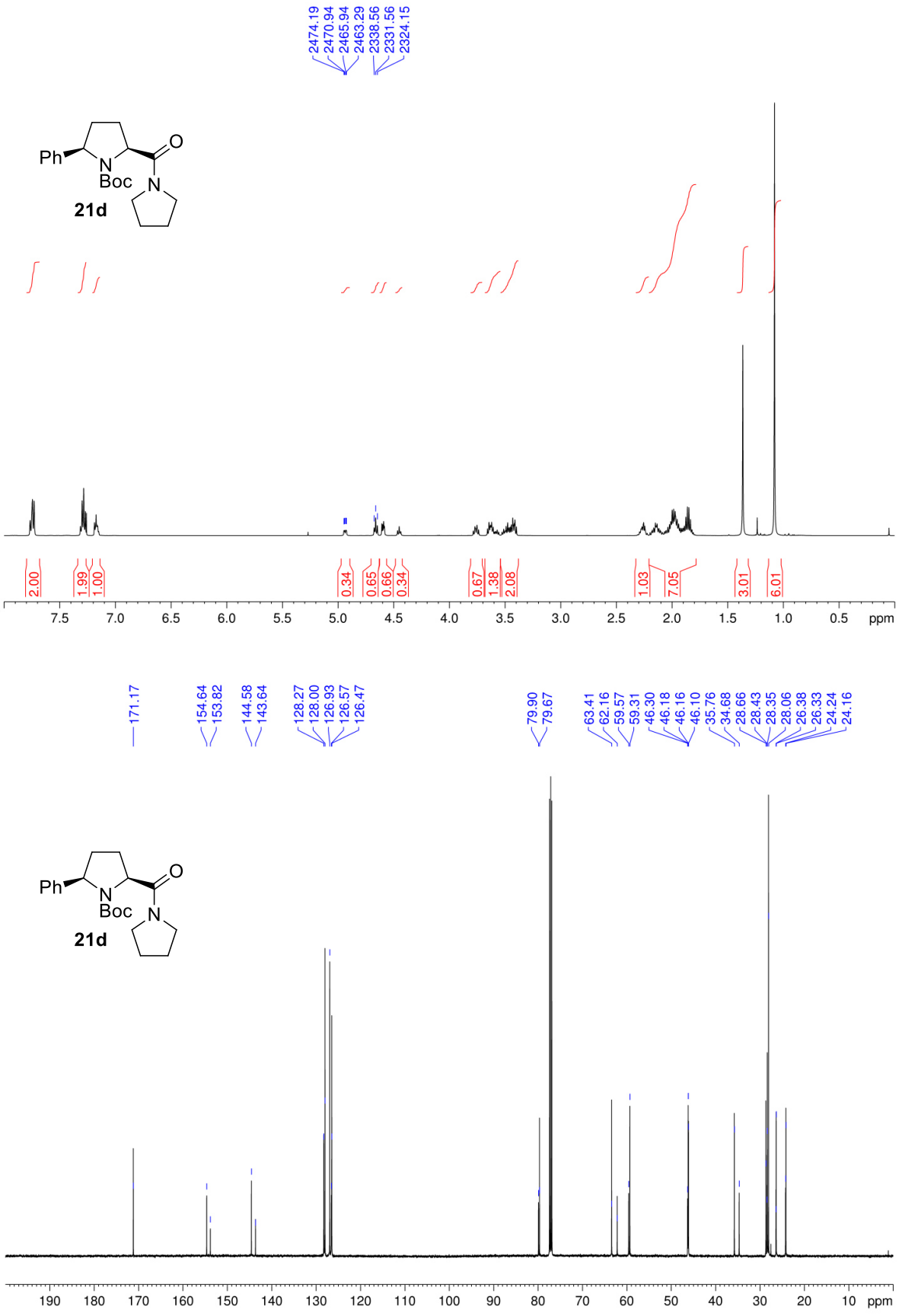

Ph
N
Boc
O
NHMe
21a
6.00
0.97
0.99
3.00
0.97
1.06
2.01
9.08
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
172.86
156.25
144.00
128.35
126.93
126.29
80.79
63.81
61.52
36.06
28.09
27.07
26.39
Ph
N
Boc
O
NHMe
21a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

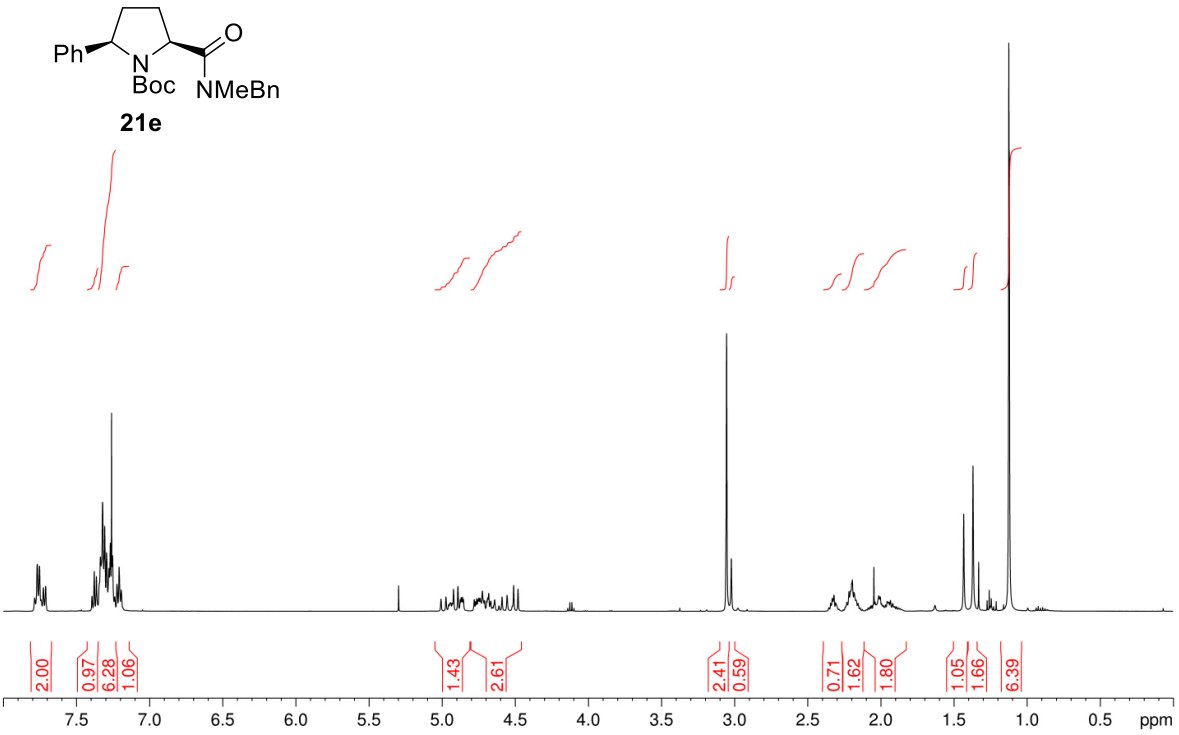

1836.98
1831.53
1396.86
1392.01
1010.26
1003.41
996.51
989.66
982.76
975.90
969.05
888.48
881.63
874.73
867.48
438.01
432.66
389.00
385.30
iPr
N
Boc
O
NHMe
21b
0.84
1.00
1.04
3.04
0.98
2.06
2.06
9.07
3.06
3.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

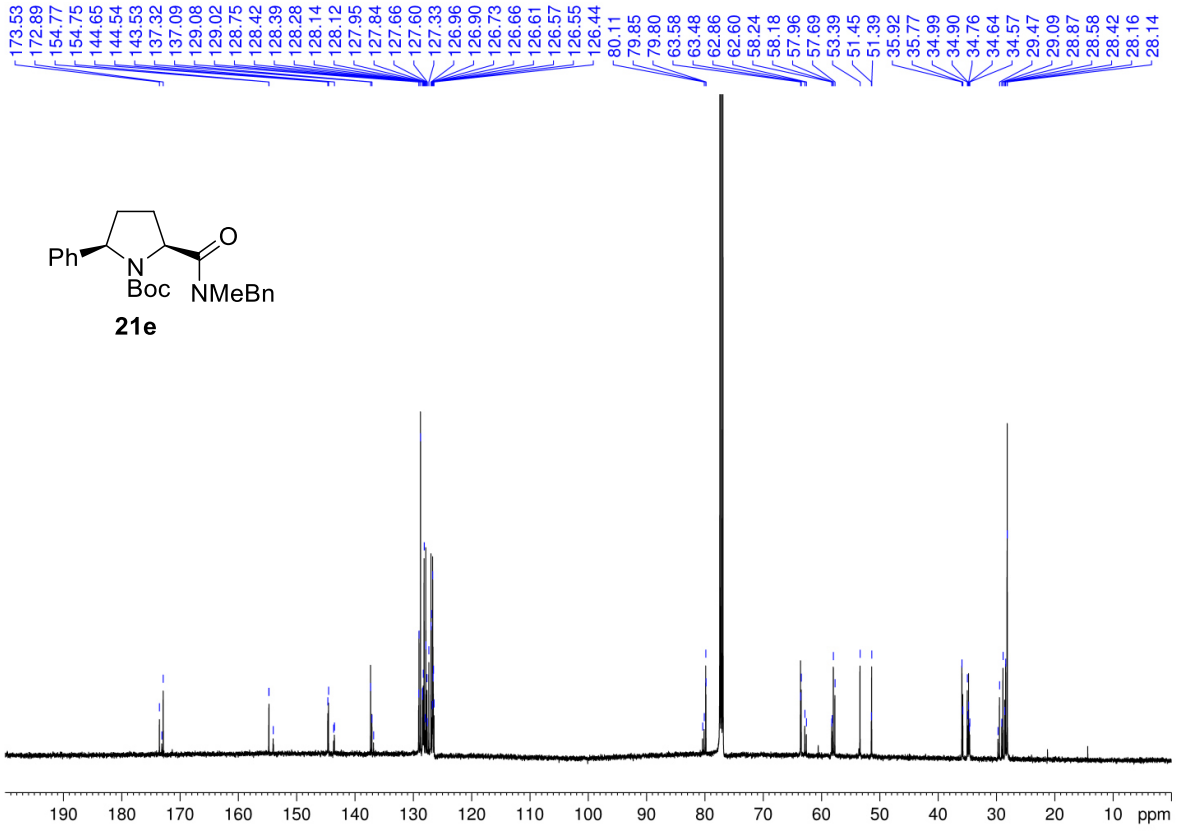

173.10
156.53
80.60
64.67
61.08
30.27
28.48
26.22
25.70
19.95
17.16
iPr
N
Boc
O
NHMe
21b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

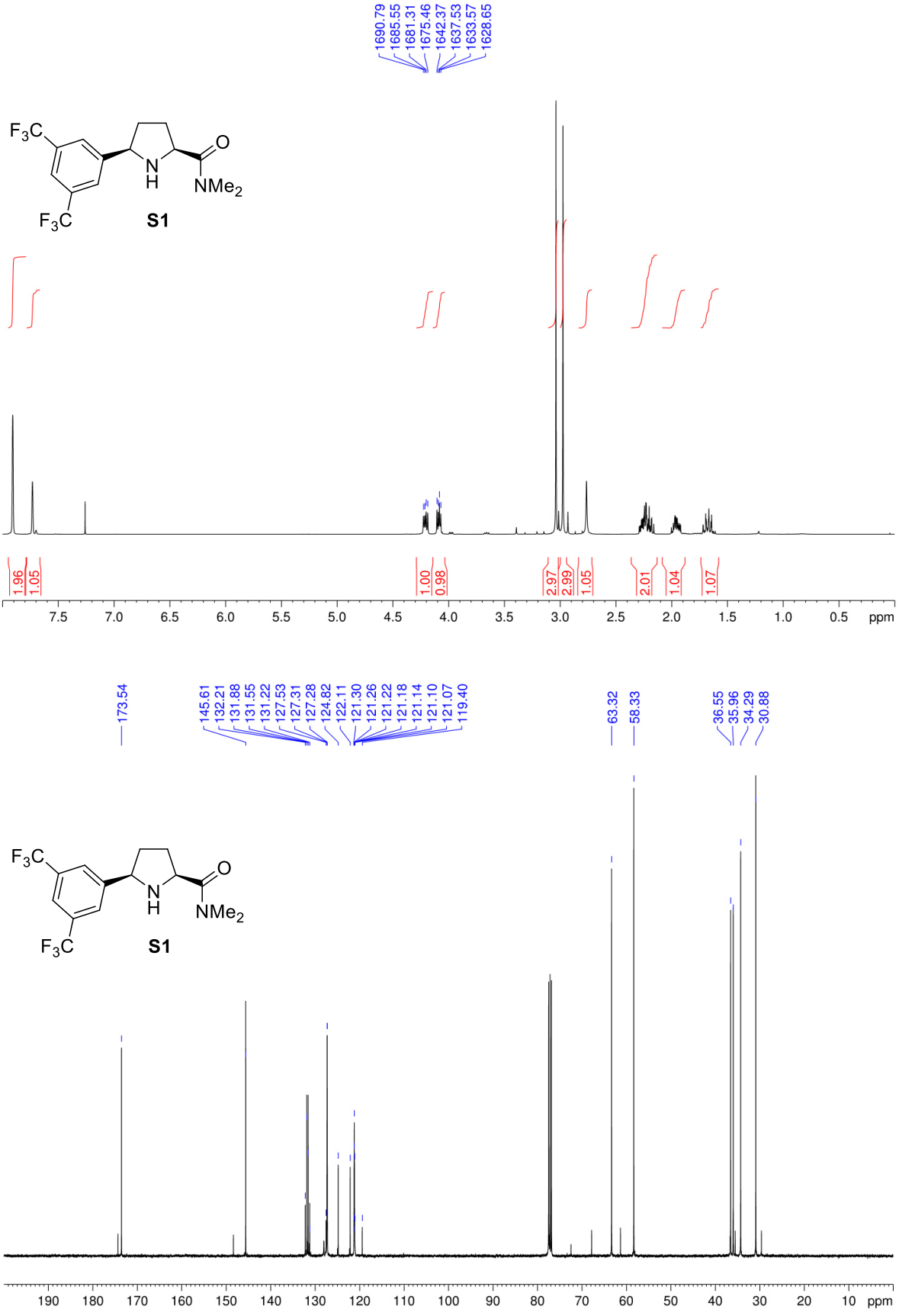

2352.56
2347.16
2344.61
2339.01
2281.34
2273.84
2266.39
676.63
673.43
670.27
667.22
Me
N
Boc
O
NMe2
21c
0.56
0.44
0.43
0.55
1.62
1.38
1.36
1.62
3.02
1.05
4.97
4.02
3.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

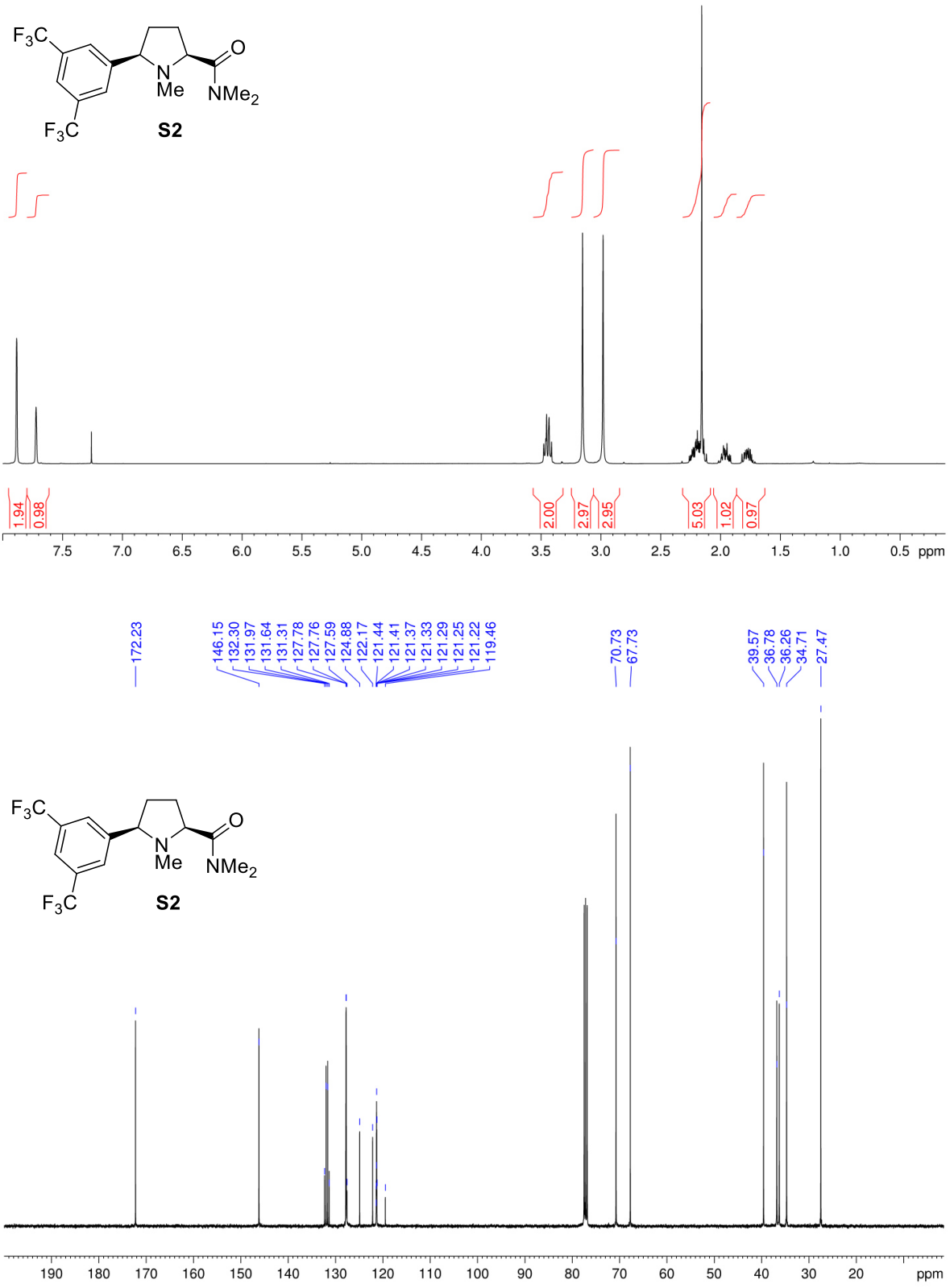

172.97
172.55
154.51
153.45
79.48
79.36
57.72
57.47
54.42
54.19
37.16
37.09
36.17
36.09
32.63
31.89
28.66
28.50
28.24
20.57
19.71
Me
N
Boc
O
NMe2
21c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

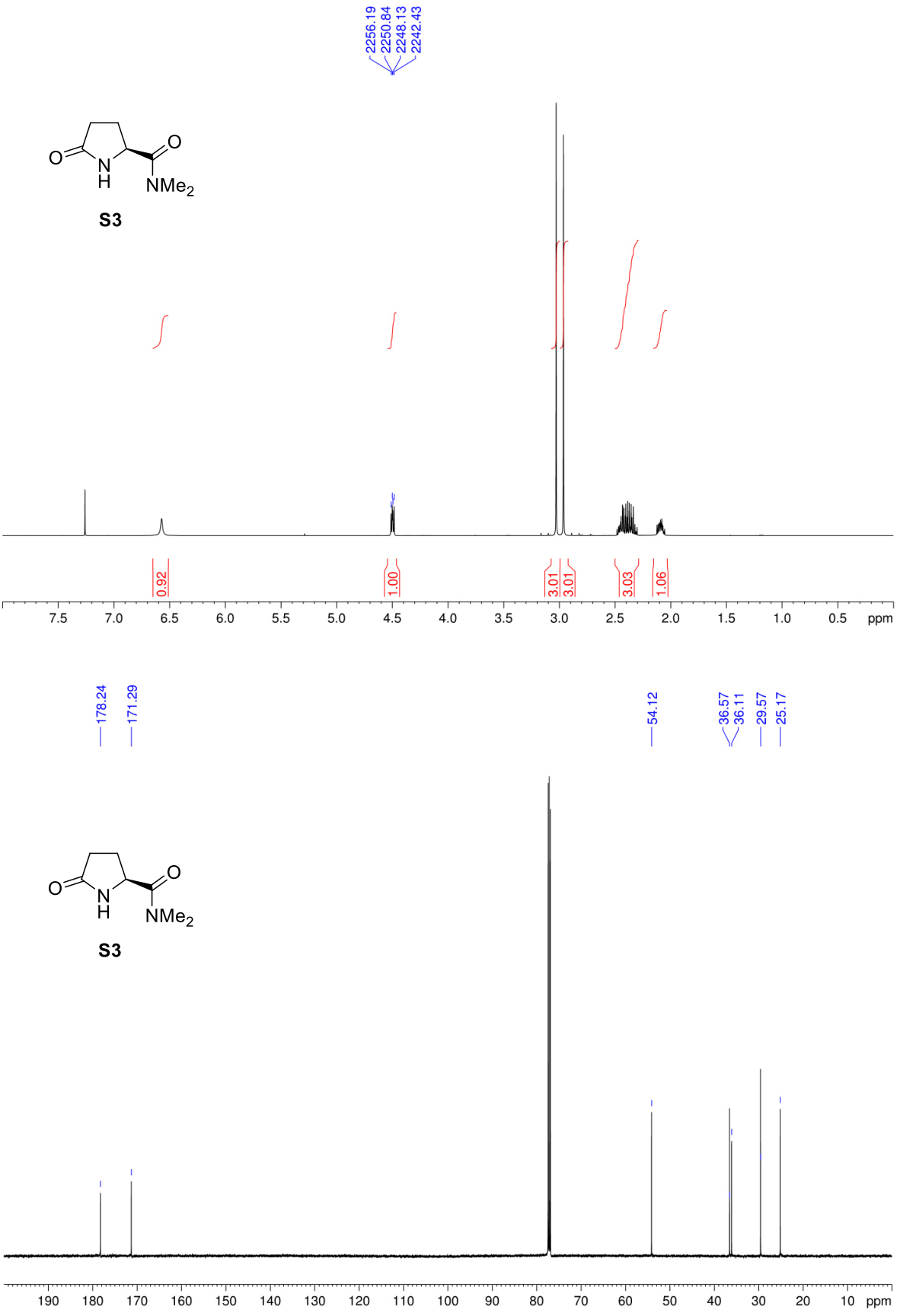

2474.19
2470.94
2465.94
2463.29
2338.56
2331.56
2324.15
Ph
N
Boc
O
N
21d
2.00
1.99
1.00
0.34
0.65
0.66
0.34
0.67
1.38
2.08
1.03
7.05
3.01
6.01
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
171.17
154.64
153.82
144.58
143.64
128.27
128.00
126.93
126.57
126.47
79.90
79.67
63.41
62.16
59.57
59.31
46.30
46.18
46.16
46.10
35.76
34.68
28.66
28.43
28.35
28.06
26.38
26.33
24.24
24.16
Ph
N
Boc
O
N
21d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


Ph
N
Boc
O
NMeBn
21e
2.00
0.97
6.28
1.06
1.43
2.61
2.41
0.59
0.71
1.62
1.80
1.05
1.66
6.39
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


173.53
172.89
154.77
154.75
144.65
144.54
143.53
137.32
137.09
129.08
129.02
128.75
128.42
128.39
128.28
128.14
128.12
127.95
127.84
127.66
127.60
127.33
126.96
126.90
126.73
126.66
126.61
126.57
126.55
126.44
80.11
79.85
79.80
63.58
63.48
62.86
62.60
58.24
58.18
57.96
57.69
53.39
51.45
51.39
35.92
35.77
34.99
34.90
34.76
34.64
34.57
29.47
29.09
28.87
28.58
28.42
28.16
28.14
Ph
N
Boc
O
NMeBn
21e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


1690.79
1685.55
1681.31
1675.46
1642.37
1637.53
1633.57
1628.65
F3C
N
H
O
NMe2
F3C
S1
1.96
1.05
1.00
0.98
2.97
2.99
1.05
2.01
1.04
1.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
173.54
145.61
132.21
131.88
131.55
131.22
127.53
127.31
127.28
124.82
122.11
121.30
121.26
121.22
121.18
121.14
121.10
121.07
119.40
63.32
58.33
36.55
35.96
34.29
30.88
F3C
N
H
O
NMe2
F3C
S1
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


F3C
N
Me
O
NMe2
F3C
S2
1.94
0.98
2.00
2.97
2.95
5.03
1.02
0.97
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
172.23
146.15
132.30
131.97
131.64
131.31
127.78
127.76
127.59
124.88
122.17
121.44
121.41
121.37
121.33
121.29
121.25
121.22
119.46
70.73
67.73
39.57
36.78
36.26
34.71
27.47
F3C
N
Me
O
NMe2
F3C
S2
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


2256.19
2250.84
2248.13
2242.43
O
N
H
O
NMe2
S3
0.92
1.00
3.01
3.01
3.03
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
178.24
171.29
54.12
36.57
36.11
29.57
25.17
O
N
H
O
NMe2
S3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

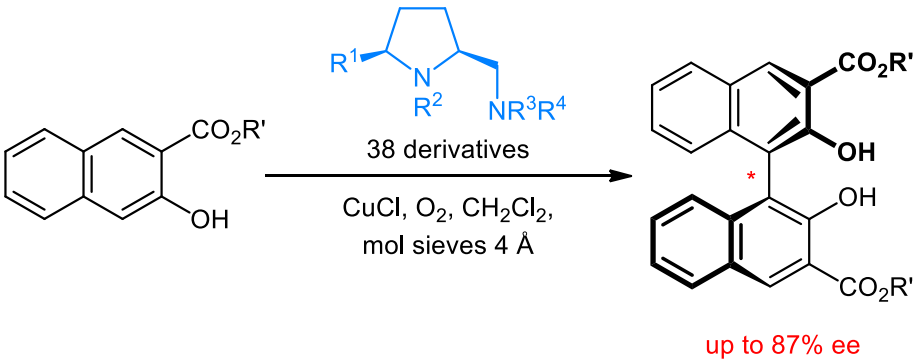
6.2 In-depth structure–selectivity investigations on asymmetric, copper-catalyzed oxidative biaryl coupling in the presence of 5-*cis*-substituted prolinamines

Felix Prause,[a] Benjamin Arensmeyer,[b] Benjamin Fröhlich[b] and Matthias Breuning*[a]

[a] Organic Chemistry Laboratory, University of Bayreuth, Universitätsstraße 30, 95447 Bayreuth, Germany.

[b] Institute of Organic Chemistry, University of Würzburg, Am Hubland, 97074 Würzburg, Germany.

* Matthias.Breuning@uni-bayreuth.de



Published in: *Catal. Sci. Technol.* **2015**, *5*, 2215–2226.

http://pubs.rsc.org/en/content/articlelanding/2015/cy/c4cy01676a#!divAbstract

doi: 10.1039/C4CY01676A

Catalysis Science & Technology

PAPER

View Article Online
View Journal | View Issue

Cite this: *Catal. Sci. Technol.*, 2015, 5, 2215

In-depth structure–selectivity investigations on asymmetric, copper-catalyzed oxidative biaryl coupling in the presence of 5-*cis*-substituted prolinamines†

Felix Prause,[a] Benjamin Arensmeyer,[b] Benjamin Fröhlich[b] and Matthias Breuning*[a]

Received 15th December 2014,
Accepted 16th January 2015

DOI: 10.1039/c4cy01676a

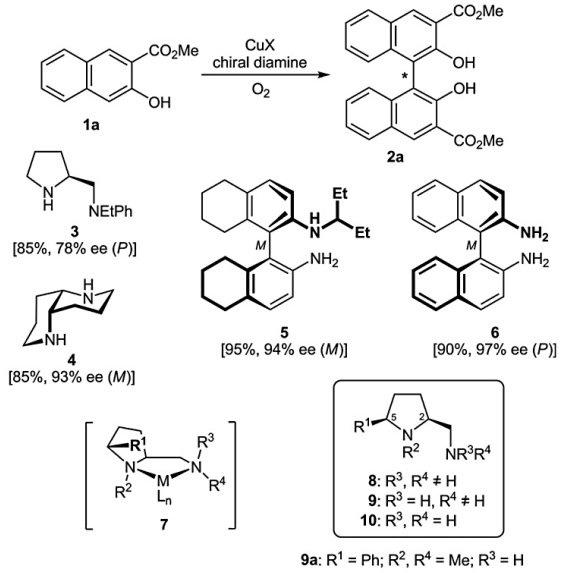
www.rsc.org/catalysis

Thirteen new and 25 known prolinamines carrying an additional 5-*cis* substituent were evaluated as the chiral ligands in asymmetric copper-catalyzed, oxidative biaryl coupling of 3-hydroxy-2-naphthoates. Comprehensive structure–selectivity investigations revealed that a phenyl group in the 5-*cis* position and a small substituent at the pyrrolidine nitrogen (*e.g.*, Me) are essential for high levels of chirality transfer. The sense of the asymmetric induction depends on the steric demand of the exocyclic amino function. In the coupling of methyl 2-hydroxy-3-naphthoate, a primary amino group permitted up to 36% ee in favor of the *P*-enantiomer, while up to 64% ee in favor of the *M*-enantiomer was reached with secondary and tertiary amino functions (*e.g.* NMe_2, (*S*)-NHCH(Me)Ph). A fully linear relationship between the enantiomeric excess of the prolinamine and the binaphthol was observed. A mechanism consistent with all stereochemical findings is proposed, indicating that 3-hydroxy-2-naphthoates with bulkier ester groups should permit better stereocontrol. Indeed, the enantiomeric excess was raised to good 87% when *tert*-butyl 3-hydroxy-2-naphthoate was used as the substrate.

Introduction

A chiral biaryl axis is the characteristic and dominating feature of a wide variety of bioactive natural products[1] and privileged ligands for enantioselective synthesis.[2] During the past three decades, many efficient and strategically diverse methods for the stereoselective construction of chiral biaryl bonds have been developed, from the desymmetrization of achiral, but rotationally hindered biaryls and the stereochemical fixation of configurationally labile ones through the atroposelective construction of aromatic rings to diastereo- and enantioselective biaryl coupling reactions.[3,4]

Among the latter approaches, oxidative coupling reactions of 2-naphthols[3c] in the presence of chirally modified copper catalysts have received particular attention,[5–7] since these reactions offer a direct access to the important class of axially chiral 1,1′-binaphthol derivatives.[2] A first breakthrough in this field was achieved by Nakajima *et al.* in 1995.[8–10] The oxidative coupling of the naphthol **1a**, catalyzed by 10 mol% of a complex generated from CuCl and the prolinamine **3**, provided the 1,1′-binaphthyl-2,2′-ol **2a** in good 85% yield and



Scheme 1 The oxidative biaryl coupling of **1a** to **2a**, a selection of successfully used chiral diamines (**3**–**6**), the metal complex **7** and the new 5-*cis*-substituted prolinamines **8**–**10**.

[a] *Organic Chemistry Laboratory, University of Bayreuth, Universitätsstraße 30, 95447 Bayreuth, Germany. E-mail: matthias.breuning@uni-bayreuth.de*
[b] *Institute of Organic Chemistry, University of Würzburg, Am Hubland, 97074 Würzburg, Germany*

† Electronic supplementary information (ESI) available: Experimental procedures, HPLC and NMR spectra. See DOI: 10.1039/c4cy01676a

78% ee (Scheme 1). As for most copper–diamine catalysts developed so far, the additional ester group at C2 (or another coordinating electron-withdrawing group allowing bidentate binding) is crucial for a high level of enantioselection.[11] Further seminal work was done by Kozlowski *et al.* introducing the C_2-symmetric 1,5-diaza-*cis*-decalin **4**.[12,13] The CuI complex of **4** proved to be a highly enantioselective catalyst, providing, for example, the model biaryl **2a** in good 85% yield and excellent 93% ee.[12] This system was successfully applied in the total synthesis of several axially chiral biaryl natural products.[13] Among all other diamines evaluated so far in the enantioselective, copper-catalyzed oxidative coupling of **1a**,[14] only the CuCl complex of Ha's C_1-symmetric BINAM (1,1′-binaphthyl-2,2′-diamine) derivative **5** was able to provide binaphthol **2a** in comparable 94% ee.[15] The highest level of asymmetric induction (97% ee) was recently reported by Sekar *et al.*, using a 2 : 1 ratio of C_2-symmetric BINAM (**6**) and CuCl in combination with the stable radical additive TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl).[16]

In the course of our investigations on conformationally rigid diamines[17] we became interested in prolinamines of general types **8**–**10**, which possess, as compared to other proline derived ligands, an additional substituent R^1 in the 5-*cis* position. Upon chelation of a metal (see complex **7**), this substituent R^1 should shield the upper left face, which might result in enhanced levels of stereocontrol in asymmetric synthesis. This assumption was recently corroborated by copper-catalyzed, enantioselective Henry reactions[18] of nitromethane with a series of aromatic, heteroaromatic, vinylic, and aliphatic aldehydes.[19] The $CuCl_2$ and $CuBr_2$ complexes of the simple prolinamine **9a** (R^1 = Ph; R^2, R^4 = Me; R^3 = H) provided the corresponding β-nitro alcohols with 99% ee in all cases (36 examples). This successful application and the structural similarity of **8**–**10** to Nakajima's diamine **3** prompted us to study the performance of **8**–**10** in the enantioselective, copper-catalyzed oxidative biaryl coupling of **1** to **2**. With the broad variety of derivatives available, in-depth investigations on structure–selectivity relationships should be possible.

Results and discussion

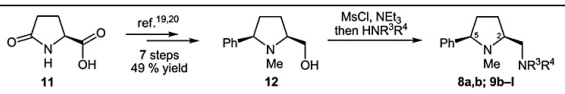
Synthesis of the prolinamines

We recently developed three tailor-made routes to prolinamines of type **8**–**10** that all start from cheap L-pyroglutamic acid (**11**), but differ in the order of introduction of the substituent at the 5-*cis* position (R^1), at the pyrrolidine nitrogen atom (R^2), and at the exocyclic aminomethyl function (R^3, R^4).[20] The high flexibility and applicability of these approaches was demonstrated in the preparation of more than 25 derivatives with widely varying substitution patterns. Some of these compounds were used in this study. The new prolinamines **8a**, **b** and **9b–l** (Table 1) were all synthesized from the amino alcohol **12**, which is available from **11** in seven steps and 49% overall yield[19,20] and possesses a 5-*cis*-phenyl substituent and an *N*-methyl group at the pyrrolidine. Activation of the hydroxy function of **12** by mesylation and subsequent treatment with an excess of the respective amine HNR^3R^4 afforded the target prolinamines in one pot operations.[21] Two bulky tertiary amines (**8a**, **b**), ten secondary amines (**9b–k**) with varying steric demand and, in part, additional stereogenic centers, and one aniline substituent (**9l**) were thus introduced in acceptable to good 47–78% yield.

Validation of the enantiomer analysis

Initially, an accurate determination of the enantiomeric excess of the stereochemically enriched binaphthyl **2a** by HPLC on chiral phase proved to be difficult.[22] Just picking a

Table 1 Preparation of the prolinamines **8a**, **b** and **9b–l** from **12**



Entry	Cmpd.	R^3	R^4	Yield[a] (%)
1	**8a**	Me	*t*Bu	72
2	**8b**	Me	Ph	66
3	**9b**	H	Et	62
4	**9c**	H	CH_2tBu	78
5	**9d**	H	iPr	53
6	**9e**	H	3-Pentyl	55
7	**9f**	H	(*S*)-CH(Me)Ph	74
8	**9g**	H	(*S*)-CH(Et)Ph	65
9	**9h**	H	(*S*)-CH(Me)*t*Bu	52
10	**9i**	H	(*R*)-CH(Me)Ph	62
11	**9j**	H	*t*Bu	65
12	**9k**	H	$C(CH_2OBn)_3$	47
13	**9l**	H	Ph	73

[a] Isolated yield.

small sample from the product, which was obtained as a slightly yellowish solid after column chromatography, and dissolving it in the HPLC solvent led to huge derivations in the ee measured. For example, the ee-values of a scalemic sample with 63% ee varied between 27% and 80%, depending on the position the material was taken from. Thus, the solid material of **2a** is not stereochemically homogeneous, but a conglomerate of areas with different enantiopurities. Furthermore, the low solubility of **2a** in typical HPLC solvents such as hexane, isopropanol, ethanol, or methanol in connection with the high tendency of **2a** to form racemic (micro)crystals[8b] bears the risk of an exaggerated enantiomeric excess in the solution to be measured.

We solved these problems by using the following procedure for sample preparation: the complete material of **2a** gathered from column chromatography was dissolved in dichloromethane (*ca.* 1 mL per 10 mg) giving a homogeneous, clear solution. A small aliquot was taken, evaporated, and dissolved in methanol (*ca.* 50 μg mL^{-1}) under ultra-sonification and warming. The resulting solution was directly injected into HPLC, providing reliably and reproducibly ee-values (Δee ≤ 1%) as checked by several control measurements.

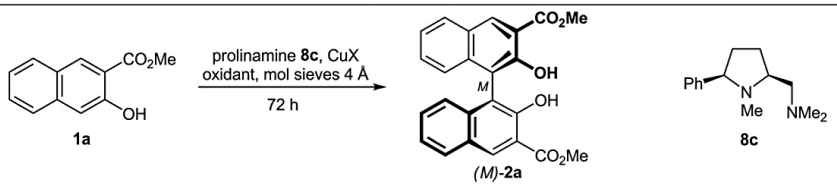
Optimization of the reaction conditions

All copper–diamine complexes were freshly prepared prior to use by stirring a solution of the copper salt and the respective 5-*cis*-substituted prolinamine **8–10** in acetonitrile–dichloromethane 0.9 : 1 for 20 min. After evaporation, the residue was dissolved in the reaction solvent, providing a clear green solution.

The reaction conditions were optimized using the simple prolinamine **8c** (R^1 = Ph, R^2–R^4 = Me) as the chiral ligand (Table 2). Because of the close structural relationship of **8c** with diamine **3**,[8b] we initially chose Nakajima's conditions (entry 1), but added mol sieves 4 Å, which is known[12a] to be beneficial to the reaction rate and yield. After 72 h at 20 °C, the oxidative coupling of naphthol **1a** afforded binaphthol **2a** in high 91% yield and acceptable 61% ee in favor of the *M*-enantiomer. In agreement with the literature,[8b] the enantiomeric excess of **2a** was easily raised by trituration with ethyl acetate, giving highly enriched (*M*)-**2a** (96% ee) in the mother liquor.

Variation of the reaction parameters showed that chlorinated hydrocarbons and mol sieves 4 Å are essential for high yields and enantioselectivities (entries 1–6). Small changes in the relative stoichiometry CuCl/**8c** (1.2 : 1–0.9 : 1) had no

Table 2 Optimization of the reaction conditions for the oxidative biaryl coupling of **1a** to **2a** in the presence of **8c**



Entry	Solvent	Conc. (M)	**8c** (mol%)	CuX (mol%)	Temp. (°C)	Oxidant	Yield[a] (%)	ee[b] (%)
1	CH_2Cl_2	0.1	10	CuCl (10)	20	O_2	91	61 (96)[c]
2	$(CH_2Cl)_2$	0.1	10	CuCl (10)	20	O_2	80	61
3	$CHCl_3$	0.1	10	CuCl (10)	20	O_2	83	62
4	MeCN	0.1	10	CuCl (10)	20	O_2	45	25
5	Et_2O[d]	0.1	10	CuCl (10)	20	O_2	22	28
6[e]	CH_2Cl_2	0.1	10	CuCl (10)	20	O_2	67	62
7	CH_2Cl_2	0.1	10	CuCl (12)	20	O_2	87	61
8	CH_2Cl_2	0.1	10	CuCl (9)	20	O_2	94	62
9	CH_2Cl_2	0.1	20	CuCl (18)	20	O_2	94	62
10	CH_2Cl_2	0.1	5	CuCl (4.5)	20	O_2	59	61
11	CH_2Cl_2	0.1	1	CuCl (0.9)	20	O_2	23	55
12	CH_2Cl_2	0.1	10	CuI (9)	20	O_2	43[f]	59
13	MeCN	0.1	10	CuI (9)	20	O_2	55[f]	19
14	CH_2Cl_2	0.1	10	$CuCl_2 \cdot H_2O$ (9)	20	O_2	81	63
15	$(CH_2Cl)_2$	0.1	10	CuCl (9)	40	O_2	78[g]	53
16	CH_2Cl_2	0.1	10	CuCl (9)	0	O_2	65	75
17	CH_2Cl_2	0.5	20	CuCl (18)	−20	O_2	56[h]	77
18	CH_2Cl_2	0.05	10	CuCl (9)	20	O_2	85	63
19	**CH_2Cl_2**	**0.5**	**10**	**CuCl (9)**	**20**	**O_2**	**91**	**64**
20	CH_2Cl_2	0.5	10	CuCl (9)	20	Air	84	63
21	CH_2Cl_2	0.5	10	CuCl (9)	20	*t*BuOOH	12	55
22	CH_2Cl_2	0.5	10	CuCl (9)	20	AgCl	77	56
23	CH_2Cl_2	0.5	10	CuCl (9)	20	DDQ	0	—

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] After trituration with ethyl acetate. [d] Suspension. [e] Without mol sieves 4 Å. [f] Side products formed. [g] Reaction time: 18 h. [h] Reaction time: 7 days.

measureable effect on the chirality transfer (entries 7 and 8). Nine mol% of the catalyst was required; lower loadings resulted in significantly reduced yields (entries 9–11). CuI was not suited as the metal salt because of the formation of side products (entries 12 and 13). $CuCl_2 \cdot 2H_2O$ (entry 14) and CuCl gave comparable results, as expected from the redox process Cu(I) ⇄ Cu(II) in the catalytic cycle, in which both oxidation states are involved. The enantioselectivity of the oxidative biaryl coupling can be enhanced to 75% ee by lowering the temperature from 20 °C to 0 °C (entry 16), albeit at the price of a reduced yield (65% within 72 h). At −20 °C, a drastic breakdown of the reaction rate was observed (56% yield after 7 days in the presence of 18 mol% catalyst), in combination with just a poor further gain in chirality control (77% ee, entry 17). The dilution had no significant effect on the chirality transfer, although the best results at 20 °C (91% yield, 64% ee) were obtained at higher concentration (c = 0.5 M, entry 19). As the oxidant, air can be used instead of oxygen, but the reaction rate slows somewhat down (entry 20). *t*BuOOH and AgCl afforded lower yields and diminished enantioselectivities, while no biaryl coupling was observed with DDQ (entries 21–23).

The optimum conditions with respect to reaction rate, yield, and stereoselectivity, which were used in the following diamine screening, are thus as follows: diamine (10 mol%), CuCl (9 mol%), O_2 (1 bar), CH_2Cl_2 (c = 0.5 M), mol sieves 4 Å, 20 °C, 72 h (entry 19).

Structure–selectivity studies

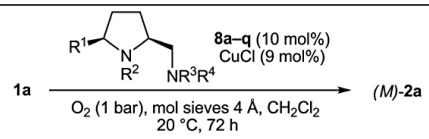
The facile and modular access to various prolinamines of type **8**–**10** permitted in-depth investigations on the structure–enantioselectivity relationship. All four substituents R^1–R^4 were separately varied and their influence on the chirality transfer was studied.

Prolinamines **8**, which are characterized by a tertiary exocyclic amino function (R^3, $R^4 \neq$ H), were screened first (Table 3). The bulkiness of the 5-*cis* substituent R^1 was found to exert a profound influence on the chirality transfer (entries 1–8). The enantiomeric excess of **2a** rose from low 4% to acceptable 62–64% by increasing the steric demand of R^1 from H (**8d**) to 4-methoxyphenyl (**8h**) and phenyl (**8c**). Larger substituents R^1 such as 3,5-(bistrifluoromethyl)phenyl in **8i** and 1-naphthyl in **8j**, however, resulted in a deterioration of the chirality transfer (48% and 25% ee, respectively).

The *N*-methyl group at the pyrrolidine nitrogen atom is essential since all variations of R^2 (**8k–m**, R^2 = H, Et, Bn) led to lower enantioselectivities (15–28% ee, entries 9–11). A similar small substituent tolerance was observed for R^3 and R^4 at the exocyclic amino function (entries 12–17). Good enantioselectivities (63–64% ee) were only reached with the model diamine **8c** (R^3, R^4 = Me) and the pyrrolidine derivative **8o**. Even a slight increase in the steric demand of one or both substituents at the NR^3R^4 group as, for example, in **8q** (NR^3R^4 = NEt_2) and **8p** (NR^3R^4 = piperidinyl) resulted in drastically reduced enantioselectivities (6–42% ee). Finally, it should be noted that the formation of the *M*-atropoenantiomer of **2a** was favored in all coupling reactions in the presence of a diamine **8**.

In the screening of the secondary prolinamines **9** (R^3 = H), we first kept the optimized substituents R^1 = Ph and R^2 = Me and varied R^4 at the exocyclic amino group (Table 4). To our surprise and in contrast to the results with all tertiary diamines **8** (see Table 3), the *P*-atropoenantiomer of **2a** was

Table 3 Oxidative biaryl coupling of **1a** in the presence of the tertiary prolinamines **8**



Entry	8	R^1	R^2	R^3	R^4	Yield[a] (%)	ee[b] (%)
1	**d**	H	Me	Me	Me	95	4
2	**e**	Me	Me	Me	Me	95	7
3	**f**	Bn	Me	Me	Me	95	22
4	**g**	iPr	Me	Me	Me	73	28
5	**h**	4-$MeOC_6H_5$	Me	Me	Me	98	62
6[c]	**c**	Ph	Me	Me	Me	91	64
7	**i**	3,5-$(CF_3)_2C_6H_3$	Me	Me	Me	74	48
8	**j**	1-Naphthyl	Me	Me	Me	59	25
9	**k**	Ph	H	Me	Me	64	15
10	**l**	Ph	Et	Me	Me	81	28
11	**m**	Ph	Bn	Me	Me	93	19
12	**n**	Ph	Me	Me	Bn	74	12
13	**a**	Ph	Me	Me	*t*Bu	46	10
14	**b**	Ph	Me	Me	Ph	20	10
15	**o**	Ph	Me	$-(CH_2)_4-$		77	63
16	**p**	Ph	Me	$-(CH_2)_5-$		54	42
17	**q**	Ph	Me	Et	Et	73	6

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] See Table 2, entry 19.

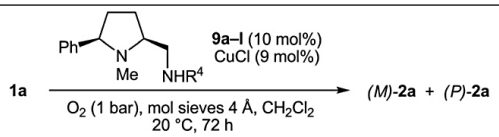
preferentially formed (19% ee) in the presence of **9a**, which possesses the sterically least hindered secondary aminomethyl function (R^4 = Me, entry 1). Even a slight increase in the bulkiness of R^4 deteriorated the *P*-preference and a racemic mixture was obtained with **9b** (R^4 = Et, entry 2). More demanding α-branched substituents R^4 tilted the sense of stereoinduction in favor of the *M*-enantiomer. A broad maximum plateau in the range of 58–61% ee was reached for R^4 = 3-pentyl, (*S*)-1-phenylethyl, (*S*)-1-phenylpropyl, and (*S*)-3,3-dimethylbutan-2-yl (**9e–h**, entries 5–8). The configuration of the stereocenter in the α-position in **9f–h** was also of importance, as seen in the reaction with **9i**, which carries, compared to **9f**, the enantiomeric (*R*)-1-phenylethyl side chain, and provided (*M*)-**2a** in lower 49% ee (entry 9). A further increase in the steric demand in R^4 was not favorable. With bulky α-tertiary substituents such as *t*Bu (**9j**) and $C(CH_2OBn)_3$ (**9k**), the stereoinduction sharply dropped to 42% and 22% ee, respectively (entries 10 and 11). The reaction rates, which roughly correspond to the isolated yields after 72 h, also decreased with the rising steric demand of R^4. The aniline derivative **9l** failed to induce a good chirality transfer (38% ee, entry 12).

Curious by the reversed stereoinduction observed with the prolinamine **9a**, we wondered whether the *P*-preference could be raised by the appropriate choice of the substituents. Since an increase in the size of R^2 at the pyrrolidine nitrogen atom had led to a loss of chirality transfer with the *M*-selective prolinamines **8l** and **8m** (see Table 3, entries 10 and 11), we anticipated that the opposite effect, an enhanced *P*-selectivity, should occur with the analogous derivatives of **9a**. However, just slightly higher 24% ee (*vs.* 19% ee for **9a**) was found for the *N*-ethyl diamine **9m**, whereas the sense of stereoinduction switched back to *M* for **9n** and **9o** carrying the larger *N*-benzyl and *N*-isopropyl groups (Table 5, entries 1–3).

An increase in *P*-selectivity might also result if the steric demand at the exocyclic NR^3R^4 group is minimized, as in the primary diamines **10a–f** (NR^3R^4 = NH_2, entries 4–9). Indeed, derivative **10e** delivered, compared to corresponding secondary amine **9a**, the binaphthol (*P*)-**2a** with an improved *P*-selectivity (36% ee *vs.* 19% ee for **9a**). Increasing the size of R^1 as in **10f** (R^1 = 1-naphthyl) as well as decreasing it as in **10b–10d** (R^1 = iPr, Bn, Me) resulted in diminished enantioselectivities, while the formation of the *M*-atropoisomer was slightly favored for the 5-*cis*-unsubstituted prolinamine **10a** (R^1 = H, 8% ee).

The structure–enantioselectivity relationships found show that there is a complex interplay between the relative and absolute steric bulk of the substituents R^1–R^4. Significant findings are: (i) the catalyst system is highly sensitive to steric overcrowding. In particular at the positions R^2 and R^3, only the small substituents (R^2 = Me and R^3 = Me, H) are tolerated. (ii) The stereoselection rises with an enhanced steric demand of R^1. This accounts for the *M*-selective prolinamines as well as for the *P*-selective ones. (iii) In the prolinamine series with R^1 = Ph and R^2 = Me (**8a–c**, **n–q**, **9a–l** and **10e**), the sense of stereoinduction can be steered by the size and degree of substitution of the exocyclic NR^3R^4 group. Tertiary diamines of type **8** generally provide the *M*-enantiomer of **2a**, but good levels of enantioselection require small substituents as in **8c** and **8o** (NR^3R^4 = NMe_2, pyrrolidinyl). Roughly the same chirality transfer is achieved with the secondary diamines **9e–h** possessing a sterically more demanding, α-branched alkyl substituent R^4. (iv) *P*-configured **2a** is preferentially formed, albeit with lower stereocontrol, if an NHMe group as in **9a** and **9m** or a primary NH_2 group as in **10b–f** is present. (v) A hydrogen bridging between the catalyst and the naphthols to be coupled can be excluded for the *M*-selective prolinamines since the best ligand, **8c**, does not possess an acidic proton; for the *P*-selective ligands **9a**, **m** and **10b–f**

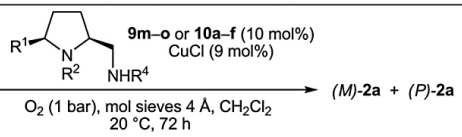
Table 4 Oxidative biaryl coupling of **1a** in the presence of the secondary prolinamines **9a–l**



Entry	9	R^4	Yield[a] (%)	ee[b] (%)	Config.
1	**a**	Me	96	19	*P*
2	**b**	Et	99	0	—
3	**c**	CH_2tBu	60	42	*M*
4	**d**	iPr	81	47	*M*
5	**e**	3-Pentyl	64	58	*M*
6	**f**	(*S*)-CH(Me)Ph	72	61	*M*
7	**g**	(*S*)-CH(Et)Ph	73	61	*M*
8	**h**	(*S*)-CH(Me)*t*Bu	77	61	*M*
9	**i**	(*R*)-CH(Me)Ph	68	49	*M*
10	**j**	*t*Bu	61	42	*M*
11	**k**	$C(CH_2OBn)_3$	38	22	*M*
12	**l**	Ph	49	38	*M*

[a] Isolated yield. [b] Determined by HPLC on chiral phase.

Table 5 Oxidative biaryl coupling of **1a** in the presence of the primary and secondary prolinamines **9m–o** and **10a–f**



Entry	Diamine	R^1	R^2	R^4	Yield[a] (%)	ee[b] (%)	Config.
1	**9m**	Ph	Et	Me	96	24	*P*
2	**9n**	Ph	Bn	Me	90	3	*M*
3	**9o**	Ph	iPr	Me	74	15	*M*
4	**10a**	H	Me	H	90	8	*M*
5	**10b**	Me	Me	H	91	19	*P*
6	**10c**	Bn	Me	H	89	29	*P*
7	**10d**	iPr	Me	H	93	33	*P*
8	**10e**	Ph	Me	H	85	36	*P*
9	**10f**	Naph[c]	Me	H	82	19	*P*

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] Naph = 1-naphthyl.

(NR^3R^4 = NH_2), however, such an additional prefixation might be possible.

Furthermore, the screening revealed that there are significant differences between our prolinamines and the known diamines **3**[8] and **4**.[12] For example, both latter ligands require at least one secondary amino function for high levels of asymmetric induction, while **8c** has just tertiary ones. In addition, the optimum reaction conditions elaborated for diamine **4** (CuI, solvent MeCN) gave only unsatisfying results with our prolinamine **8c** (see Table 2, entries 4, 12, and 13).

Mechanistic and stereochemical considerations

Kozlowski *et al.*[12] did extensive studies on the mechanism of enantioselective, oxidative biaryl coupling[23] in the presence of their catalyst CuI·**4**, finding first order dependences on the oxygen and catalyst concentrations.[12d] The rate determining step of the catalytic cycle is the reoxidation of the catalyst by O_2,[12d] which presumably involves several oxygenated dimeric or oligomeric species.[24,25] The stereochemically decisive formation of the biaryl axis is proposed to proceed in two consecutive steps, a face-selective coupling of two naphthyl radicals,[26] of which at least one is chelated to a tetrahedral diamine–Cu-complex, followed by a central-to-axial chirality transfer upon rearomatization.[12c,27] Since the counter ion has no effect on the stereoselection, it is likely that the reaction takes place at a cationic metal complex.[12b] Finally, a positive nonlinear effect[28] was observed, hinting at dimeric or oligomeric catalyst species in solution.[12b] This assumption was furthermore corroborated by VPO measurements.[12b]

Our mechanistic studies started with the proof that the 64% ee in the product (*M*)-**2a**, as achieved with the catalyst CuCl·**8c**, is based on a stereodifferentiating coupling step, and not, as observed for coupling with stoichiometric amounts of chirally modified Cu complexes,[9] on a non-stereoselective coupling followed by resolution or deracemization of the primarily formed, racemic biaryl. A mere diastereoselective crystallization of CuCl·**8c**·(*M*)-**2** can safely be excluded because the amount of (*M*)-**2** isolated was by far larger than the amount of the catalyst used. A subsequent deracemization by atropodiastereomerization of configurationally unstable copper complexes, namely CuCl·**8c**·(*M*/*P*)-**2** to CuCl·**8c**·(*M*)-**2**, can be ruled out since there was no change in the optical purity if scalemic or racemic **2a** were treated with the catalyst for several days.

A fully linear relationship between the enantiomeric excess of the prolinamine **8c** and the product **2a** was found (Fig. 1). The absence of a nonlinear effect[28] makes the existence of dimeric or oligomeric catalyst species as well as a participation of two molecules of the catalyst in the stereochemically decisive biaryl coupling step unlikely (although both possibilities cannot fully be ruled out).

Based on the aforementioned mechanistic investigations and our studies we propose the following mechanism for the oxidative biaryl coupling of **1a** in the presence of our prolinamine-derived copper catalysts (Scheme 2). For simplification of the discussion, a phenyl group in the 5-*cis* position (R^1 = Ph) and an *N*-methyl group at the pyrrolidine nitrogen atom (R^2 = Me), which are both essential for good levels of stereoselection, and a secondary or primary exocyclic amino function are set. The ligands **9e–h** (NR^3R^4 = NHR^4;

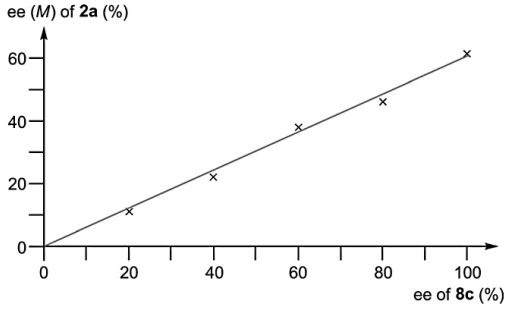
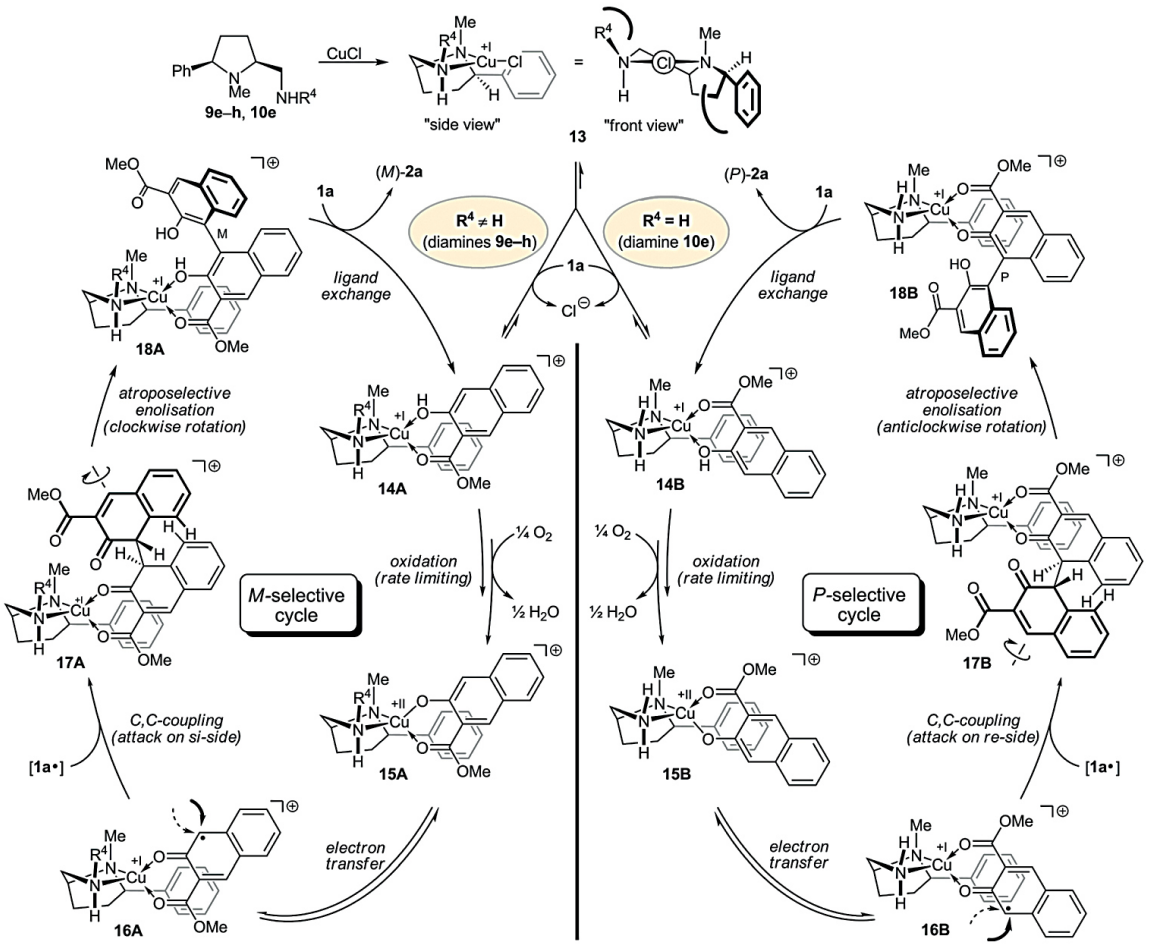


Fig. 1 Fully linear relationship between the enantiomeric excess of the prolinamine **8c** and the binaphthol **2a**.



Scheme 2 Proposed mechanism for the *M*- and *P*-selective oxidative biaryl coupling of **1a** in the presence of the prolinamines **9e–h** and **10e**.

R^4 = secondary alkyl, 58–61% ee in favor of *M*) and **10e** ($NR^3R^4 = NH_2$, 36% ee in favor of *P*) fulfill these premises. Taking the relative and absolute steric demands of the substituents R^1–R^4 into account, this mechanism can be extended to all prolinamines that provided significant levels of asymmetric induction.

Initial chelation of the chiral prolinamine to CuCl provides the bicyclic, C_1-symmetric complex **13**, to which the naphthol **1a** principally can bind in two different orientations, as illustrated in the tetrahedral[29] complexes **14A** and **14B**.[30] The preference for one or the other is controlled by steric factors. On the side of the naphthol **1a**, the methoxy group of the ester function is more demanding than the two carbon atoms C-4 and C-4a of the aryl ring. On the side of the chiral catalyst, it is reasonable that, in the energetically most favored conformation, the larger substituents at the two nitrogen atoms (R^4 and the annelated pyrrolidine) occupy opposite positions with respect to the central copper heterocycle and align pseudo-equatorially, as the phenyl group does. As a consequence of this arrangement depicted in **13**, the lower right quadrant is shielded by the phenyl group and the upper left one by R^4 (see "front view"). In the case of **10e** with R^4 = H, only the repulsion by the phenyl group exists, thus favoring the formation of **14B**, while in the cases of **9e–h** (R^4 = secondary alkyl), the higher steric demand of R^4 dominates, thus favoring the orientation shown in **14A**.

The following steps are identical for both catalytic cycles. Multistage[24] and rate-limiting[12d,25] oxidation of the copper(I) atom in **14** by O_2 affords the copper(II) complexes **15**, which can undergo electron transfer from the naphthol to the copper atom to give the naphthyl radicals **16**. In both complexes, the backside of the naphthyl radical is efficiently shielded by the phenyl group, possibly supported by some π-stacking, which directs the attack of a second naphthyl radical [**1a**•] to the front side, thus leading to **17**. It should be noted that the true nature of [**1a**•] is still unclear,[26] although the observed absence of a nonlinear effect (see Fig. 1) makes the

complexation of [**1a**$^{\bullet}$] to a second, chirally modified copper atom and, thus, a coupling between two molecules of **16**, unlikely.

During the rearomatization process *via* twofold ketoenol tautomerism, the two (pre)aromatic moieties have to rotate in order to reach the orthogonal alignment in biaryls. This rotation follows the pathway of the least steric hindrance, which means that the carbonyl groups pass each other and not the aromatic rings (repulsion of the *peri*-H).[12c,27] Consequently, the rotation is clockwise in **17A**, leading to *M*-configuration at the newly created biaryl axis in **18A**, whereas an anticlockwise rotation takes place in **17B**, creating the *P*-configured biaryl axis in **18B**. Final exchange of the binaphthol **2a** against naphthol **1a** completes the catalytic cycle. For the orientation of **1a** upon complexation, the very same steric arguments apply as in the chelation of **1a** to **13** giving **14A** and **14B**.

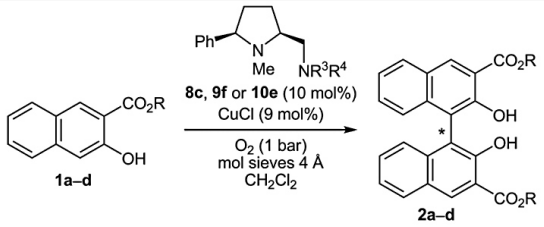
Since most of the prolinamines **8–10** used in this study favored the formation of (*M*)-**2a**, the top faces of the respective copper complexes must be more strongly shielded than the bottom faces, which forces the incoming naphthol **1a** to bind in a fashion shown in **14A**. This also means that the steric demand of the annelated, R^1-substituted pyrrolidine cannot be high, probably due to its pseudo-equatorial orientation with respect to the central copper heterocycle. The size of R^1 at this ring, however, exerts a drastic effect on the level of stereoselection. Since the same trends – decreasing the bulkiness of R^1 led to a reduced chirality transfer (see **8d–j**, Table 3, and **10a–f**, Table 5) – were observed for the *M*- and the *P*-directing prolinamines, this substituent cannot play an important role in the binding of **1a**, but must be decisive in the shielding of the backside of the complexed naphthyl radical in **16A** and **16B** (see Scheme 2), which is in good agreement with the mechanism proposed.

Consequences of the mechanism

Under the assumption that the backside-shielding in **16** and the central-to-axial chirality transfer occur with high selectivity, the resulting enantiomeric excess in the binaphthol **2a** is thus determined by the orientation of **1a** during binding to **18** (and **13** in the starting sequence). As a consequence, the enantioselection of the *M*-selective catalysts should increase if the steric differentiation in the naphthol substrate is more pronounced, which can be achieved by raising the steric bulk of the ester group at C-2. In order to consolidate this theory, we synthesized the naphthol esters **1b–d** and subjected these compounds to the coupling procedures (Table 6). Indeed, the levels of stereoselection significantly increased by using the sterically more hindered esters. The binaphthol **2d** (R = *t*Bu) was produced in good 78% and 75% ee with the prolinamines **8c** and **9f** as the chiral ligands (entries 4 and 8). This trend is in sharp contrast to the observations made in other oxidative biaryl coupling reactions in the presence of diamine–copper catalysts, in which the chirality transfer dropped when the size of the ester group was increased.[8b,12c,14a,16] By lowering the reaction temperature to 0 °C, the enantiomeric excess in the CuCl·**8c** catalyzed coupling of **1d** to **2d** was further improved to 87%, without any noticeable loss in yield (96%, entry 9). The latter result is the best asymmetric induction so far reached with the naphthyl ester **1d**.

For the *P*-selective catalyst CuCl·**10e**, the enantioselection achieved with the methyl ester **1a** and the *t*-butyl ester **1d** was virtually identical (entries 10 and 11). This result is also in

Table 6 Oxidative biaryl coupling of **1a–d** in the presence of the prolinamines **8c**, **9f** and **10e**



8c: $NR^3R^4 = NMe_2$; **9f**: NR^3R^4 = (*S*)-NHCH(Me)Ph; **10e**: $NR^3R^4 = NH_2$

Entry	Biaryl 1, 2	R	Diamine	Temp. (°C)	*t* (day)	Yield[a] (%)	ee[b] (%)	Config.
1[c]	**1a**	Me	**8c**	20	3	91	64	*M*
2	**1b**	iPr	**8c**	20	3	94	69	*M*
3	**1c**	Bn	**8c**	20	3	93	73	*M*
4	**1d**	*t*Bu	**8c**	20	6	99	78	*M*
5[d]	**2a**	Me	**9f**	20	3	72	61	*M*
6	**2b**	iPr	**9f**	20	5	94	75	*M*
7	**2c**	Bn	**9f**	20	5	99	72	*M*
8	**2d**	*t*Bu	**9f**	20	7	94	75	*M*
9	**1d**	*t*Bu	**8c**	0	8	96	87	*M*
10[e]	**1a**	Me	**10e**	20	3	85	36	*P*
11	**1d**	*t*Bu	**10e**	20	5	99	36	*P*

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] See Table 2, entry 19. [d] See Table 4, entry 6. [e] See Table 5, entry 8.

good agreement with the proposed catalytic cycle, since the interaction between the ester group and the chiral backbone is just weak (see **14B**, Scheme 2).

Conclusions

A series of 38 prolinamines **8–10**, which differ in the substituents R^1 at the 5-*cis* position, R^2 at the pyrrolidine nitrogen atom, and R^3R^4 at the exocyclic amino function, were evaluated in their performance as chiral ligands in the copper-catalyzed oxidative biaryl coupling of the naphthol **1a**. Essential for good enantioselectivities were a 5-*cis*-phenyl (R^1) and an *N*-methyl group (R^2). With these two substituents given, the level and sense of the asymmetric induction can be steered by the NR^3R^4 group. Good 58–64% ee in favor of the *M*-enantiomer of **2a** were reached with the tertiary amine **8c** (NR^3R^4 = NMe_2) and the secondary amines **9e–h** (NR^3R^4 = NHR^4, with R^4 = secondary alkyl), while the *P*-enantiomer of **2a** was preferentially formed with the primary amine **10e** (36% ee, NR^3R^4 = NH_2). A mechanism, in which the steric demand of the NR^3R^4 group of the chiral ligand determines the orientation of **1a** upon complexation to the copper atom and, thus, the sense of the chirality transfer, was proposed. The 5-*cis*-phenyl group (R^1) plays the decisive role in the face-selective *C*,*C*-coupling step by shielding one side of the complexed naphthyl radical. As a consequence of the structure–enantioselectivity investigations, we concluded that naphthols with bulkier ester groups should permit better stereocontrol. Indeed, the enantiomeric excess of the oxidative coupling of **1d** (CO_2R = CO_2tBu) was improved to up to 87% ee by using CuCl·**8c** as the chiral catalyst.

Experimental

All reactions with moisture-sensitive reagents were carried out under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[31] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey-Nagel, particle size 40–63 μm) was used for column chromatography. Melting points were measured by a Stuart SMP10 digital or a Thermo Scientific 9300 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance 300, a Bruker Avance 400, or a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^{1}H and ^{13}C NMR data were performed on the basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a Jasco FT-IR-410 or a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra on a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization). The enantiomeric excess of the binaphthols **2a–d** was determined by HPLC analysis (Waters Alliance HPLC; Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralpak AD-H).

The synthesis of **9f** and the general procedure for the oxidative biaryl coupling under optimized conditions are described here exemplary. For the preparation of all other new compounds, see the ESI.†

(2*R*,5*S*)-1-Methyl-2-phenyl-5-((((*S*)-1-phenylethyl)amino)methyl)pyrrolidine (9f)

NEt_3 (197 μL, 143 mg, 1.41 mmol) and MsCl (87.4 μL, 129 mg, 1.13 mmol) were added at 0 °C to a solution of the alcohol **12**[19] (180 mg, 941 μmol) in anhydrous CH_2Cl_2 (8 mL). After 1 day at r.t., the solution was treated with (*S*)-1-phenylethylamine (2.40 mL, 2.28 g, 18.8 mmol) and stirring was continued for 5 days. The solvent was removed under reduced pressure and the crude material was directly subjected to column chromatography (1. silica gel, CH_2Cl_2/MeOH, 100 : 0–97 : 3, 2. silica gel, EtOAc). Filtration through a pad of basic alumina (activity I, CH_2Cl_2/MeOH, 9 : 1) delivered the prolinamine **9f** (205 mg, 697 μmol, 74%) as a yellowish oil.

R_f 0.65 (EtOAc). $[\alpha]_D^{21}$ 8.2 (*c* 0.50 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2968w, 2784w, 1491w, 1450s, 1122w, 1041w, 1027w, 757s, 697vs; ^{1}H NMR δ_H (500 MHz; $CDCl_3$) 1.43 (3 H, d, *J* = 6.7 Hz, CHC*H*$_3$), 1.67 (1 H, m, 3-*H*H), 1.83 (1 H, m, 4-*H*H), 1.98 (1 H, m, 4-H*H*), 2.05 (1 H, m, 3-H*H*), 2.06 (3 H, s, 1-CH_3), 2.52 (1 H, dd, *J* = 11.1, 6.4 Hz, 5-C*H*H), 2.58 (1 H, m, 5-H), 2.75 (1 H, dd, *J* = 11.1, 3.1 Hz, 5-CH*H*), 3.27 (1 H, dd, *J* = 9.7, 6.7 Hz, 2-H), 3.82 (1 H, q, *J* = 6.7 Hz, C*H*CH_3), 7.26 (2 H, m, Ar–H), 7.33 (8 H, m, Ar–H) ppm. ^{13}C NMR δ_C (125 MHz, $CDCl_3$) 24.4 (CH*C*H_3), 28.1 (C-4), 34.3 (C-3), 39.3 (1-CH_3), 50.7 (5-CH_2), 58.8 (*C*HCH_3), 65.9 (C-5), 72.6 (C-2), 126.7, 127.0, 127.1, 127.4, 128.4, 128.6 (CH–Ar), 143.9, 145.9 (C_q-Ar) ppm. HRMS (ESI, pos.) *m*/*z* calcd for $C_{20}H_{27}N_2$ $[M + H]^+$ 295.2169, found 295.2169.

General procedure for the oxidative biaryl coupling under optimized conditions

Oxidative coupling. A solution of CuCl (4.46 mg, 45.0 μmol, 9 mol%) in MeCN (450 μL) was added to a solution of the prolinamine **8c**, **9f**, or **10e** (50.0 μmol, 10 mol%) in anhydrous CH_2Cl_2 (500 μL). After stirring for 20 min, the solvent was removed *in vacuo* and the residue was dissolved in anhydrous CH_2Cl_2 (1 mL) to give a greenish solution. The temperature was adjusted to 20 °C or 0 °C and the naphthols **1a–d** (500 μmol, 101 mg in the case of **1a**) and powdered mol sieves 4 Å (30 mg) were added. After 3–8 days under an O_2 atmosphere (1 bar), the reaction mixture was diluted with CH_2Cl_2 (5 mL) and directly subjected to column chromatography (for **2a**: silica gel, petroleum ether/EtOAc, 10 : 1–2 : 1; for **2b–d**: silica gel, petroleum ether/CH_2Cl_2, 3 : 1–1 : 9), delivering the product **2a–d**[8b] as a yellowish solid.

Enantiomer analysis. Sample preparation: the complete material of **2a–d** gathered from column chromatography was dissolved in CH_2Cl_2 (1 mL per 10 mg). A small aliquot (50 μL) was taken, evaporated, and dissolved in MeOH (10 mL) under warming and ultra-sonification. This solution was directly used for HPLC analysis on chiral phase (Daicel Chiralpak AD-H). HPLC conditions: **2a**: *n*-hexane/iPrOH 8 : 2, 1.0 mL min^{-1}, 254 nm: t_R (*P*-enantiomer) = 8.8 min; t_R (*M*-enantiomer) = 14.3 min;[8b] **2b**: *n*-hexane/iPrOH 98 : 02, 1.0 mL min^{-1}, 254 nm: t_R (*P*-enantiomer) = 7.9 min; t_R (*M*-enantiomer) = 9.5 min; the absolute configuration of **2b** was determined after transesterification of **2b** into **2a**; **2c**: *n*-hexane/iPrOH 9 : 1, 1.0 mL min^{-1}, 254 nm: t_R (*P*-enantiomer) = 14.6 min; t_R (*M*-enantiomer) = 23.1 min;[8b] **2d**: *n*-hexane/iPrOH 98 : 02, 1.0 mL min^{-1}, 254 nm: t_R (*M*-enantiomer) = 6.8 min; t_R (*P*-enantiomer) = 7.6 min.[8b]

Acknowledgements

The financial support of the German Research Foundation (DFG) is gratefully acknowledged.

Notes and references

1 Reviews: (*a*) U. Weiss, L. Merlini and G. Nasini, *Prog. Chem. Org. Nat. Prod.*, 1987, **52**, 1; (*b*) G. Bringmann, C. Günther, M. Ochse, O. Schupp and S. Tasler, *Prog. Chem. Org. Nat. Prod.*, 2001, **82**, 1; (*c*) O. Baudoin and F. Guéritte, *Stud. Nat. Prod. Chem.*, 2003, **29**(Part J), 355; (*d*) H. Aldemir, R. Richarz and T. A. M. Gulder, *Angew. Chem., Int. Ed.*, 2014, **53**, 8286.

2 Reviews: (*a*) L. Pu, *Chem. Rev.*, 1998, **98**, 2405; (*b*) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, 1994; (*c*) C. Rosini, L. Franzini, A. Raffaelli and P. Salvadori, *Synthesis*, 1992, 503; (*d*) T. Hayashi, *Acc. Chem. Res.*, 2000, **33**, 354; (*e*) J. M. Brunel, *Chem. Rev.*, 2005, **105**, 857; (*f*) M. Berthod, G. Mignani, G. Woodward and M. Lemaire, *Chem. Rev.*, 2005, **105**, 1801.

3 For reviews about the atroposelective synthesis of axially chiral biaryls (methodology and application), see: (*a*) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem., Int. Ed.*, 2005, **44**, 5384; (*b*) O. Baudoin, *Eur. J. Org. Chem.*, 2005, 4223; (*c*) M. C. Kozlowski, B. J. Morgan and E. C. Linton, *Chem. Soc. Rev.*, 2009, **38**, 3193; (*d*) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563; (*e*) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234.

4 For selected recent developments in the atroposelective synthesis of biaryls, see: (*a*) X. Shen, G. O. Jones, D. A. Watson, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 11278; (*b*) J. L. Gustafson, D. Lim and S. J. Miller, *Science*, 2010, **328**, 1251; (*c*) F. Guo, L. C. Konkol and R. J. Thomson, *J. Am. Chem. Soc.*, 2011, **133**, 18; (*d*) N. Asakura, S. Fujimoto, N. Michihata, K. Nishii, H. Imagawa and H. Yamada, *J. Org. Chem.*, 2011, **76**, 9711; (*e*) P. Wessig, C. Pick and U. Schilde, *Tetrahedron Lett.*, 2011, **52**, 4221; (*f*) S. Ogaki, Y. Shibata, K. Noguchi and K. Tanaka, *J. Org. Chem.*, 2011, **76**, 1926; (*g*) M. Leibeling and D. B. Werz, *Chem. – Eur. J.*, 2012, **18**, 6138; (*h*) A. Ros, B. Estepa, A. Bermejo, E. Álvarez, R. Fernández and J. M. Lassaletta, *J. Org. Chem.*, 2012, 77, 4740; (*i*) Y. Kasai, N. Michihata, H. Nishimura, T. Hirokane and H. Yamada, *Angew. Chem., Int. Ed.*, 2012, **51**, 8026; (*j*) Z.-H. Shan, J. Liu, L.-M. Xu, Y.-F. Tang, J.-H. Chen and Z. Yang, *Org. Lett.*, 2012, **14**, 3712; (*k*) M. Groh, D. Meidlinger, G. Bringmann and A. Speicher, *Org. Lett.*, 2012, **14**, 4548; (*l*) F. R. Leroux, A. Berthelot, L. Bonnafoux, A. Panossian and F. Colobert, *Chem. – Eur. J.*, 2012, **18**, 14232; (*m*) S. Postikova, M. Sabbah, D. Wightman, I. T. Nguyen, M. Sanselme, T. Besson, J.-F. Brière, S. Oudeyer and V. Levacher, *J. Org. Chem.*, 2013, **78**, 8191; (*n*) G.-Q. Li, H. Gao, C. Keene, M. Devonas, D. H. Ess and L. Kürti, *J. Am. Chem. Soc.*, 2013, **135**, 7414; (*o*) N. Kadoya, M. Murai, M. Ishiguro, J. Uenishi and M. Uemura, *Tetrahedron Lett.*, 2013, **54**, 512; (*p*) A. Link and C. Sparr, *Angew. Chem., Int. Ed.*, 2014, **53**, 5458; (*q*) G. Xu, W. Fu, G. Liu, C. H. Senanayake and W. Tang, *J. Am. Chem. Soc.*, 2014, **136**, 570; (*r*) Y. Zhou, X. Zhang, H. Liang, Z. Cao, X. Zhao, Y. He, S. Wang, J. Pang, Z. Zhou, Z. Ke and L. Qiu, *ACS Catal.*, 2014, **4**, 1390; (*s*) C. K. Hazra, Q. Dherbassy, J. Wencel-Delord and F. Colobert, *Angew. Chem., Int. Ed.*, 2014, **53**, 13871.

5 For selected examples of oxidative biaryl couplings catalyzed by chiral vanadium complexes, see: (*a*) S.-W. Hon, C.-H. Li, J.-H. Kuo, N. B. Barhate, Y.-H. Liu, Y. Wang and C.-T. Chen, *Org. Lett.*, 2001, **3**, 869; (*b*) C.-Y. Chu, D.-R. Hwang, S.-K. Wang and B.-J. Uang, *Chem. Commun.*, 2001, 980; (*c*) Z. Luo, Q. Liu, L. Gong, X. Cui, A. Mi and Y. Jiang, *Chem. Commun.*, 2002, 914; (*d*) N. B. Barhate and C.-T. Chen, *Org. Lett.*, 2002, **4**, 2529; (*e*) C.-Y. Chu and B.-J. Uang, *Tetrahedron: Asymmetry*, 2003, **14**, 53; (*f*) H. Somei, Y. Asano, T. Yoshida, S. Takizawa, H. Yamataka and H. Sasai, *Tetrahedron Lett.*, 2004, **45**, 1841; (*g*) M. Tada, T. Taniike, L. M. Kantam and Y. Iwasawa, *Chem. Commun.*, 2004, 2542; (*h*) M. Tada, N. Kojima, Y. Izumi, T. Taniike and Y. Iwasawa, *J. Phys. Chem. B*, 2005, **109**, 9905; (*i*) Q.-X. Guo, Z.-J. Wu, Z.-B. Luo, Q.-Z. Liu, J.-L. Ye, S.-W. Luo, L.-F. Cun and L.-Z. Gong, *J. Am. Chem. Soc.*, 2007, **129**, 13927; (*j*) S. Takizawa, T. Katayama, H. Somei, Y. Asano, T. Yoshida, C. Kameyama, D. Rajesh, K. Onitsuka, T. Suzuki, M. Mikami, H. Yamataka, D. Jayaprakash and H. Sasai, *Tetrahedron*, 2008, **64**, 3361; (*k*) S. Takizawa, J. Kodera, Y. Yoshida, M. Sako, S. Breukers, D. Enders and H. Sasai, *Tetrahedron*, 2014, **70**, 1786.

6 For oxidative biaryl couplings catalyzed by other chiral transition metal complexes, see: Ru: (*a*) T. Hamada, H. Ishida, S. Usui, Y. Watanabe, K. Tsumura and K. Ohkubo, *J. Chem. Soc., Chem. Commun.*, 1993, 909; (*b*) R. Irie, K. Masutani and T. Katsuki, *Synlett*, 2000, 1433; Fe; (*c*) H. Egami and T. Katsuki, *J. Am. Chem. Soc.*, 2009, **131**, 6082; (*d*) H. Egami, K. Matsumoto, T. Oguma, T. Kunisu and T. Katsuki, *J. Am. Chem. Soc.*, 2010, **132**, 13633.

7 For other types of enantioselective oxidative biaryl couplings, see: Electrochemically: (*a*) T. Osa, Y. Kashiwagi, Y. Yanagisawa

and J. M. Bobbitt, *J. Chem. Soc., Chem. Commun.*, 1994, 2535; enzymatic; (*b*) M. Takemoto, Y. Suzuki and K. Tanaka, *Tetrahedron Lett.*, 2002, **43**, 8499; (*c*) F. Trotta, G. Cravotto and S. Rossignoli, *J. Inclusion Phenom. Macrocyclic Chem.*, 2002, **44**, 293; (*d*) F. Trotta, G. Cravotto and G. Casile, *Environ. Sci. Pollut. Res.*, 2003, **10**, 144.

8 (*a*) M. Nakajima, K. Kanayama, I. Miyoshi and S.-I. Hashimoto, *Tetrahedron Lett.*, 1995, **36**, 9519; (*b*) M. Nakajima, I. Miyoshi, K. Kanayama, S.-I. Hashimoto, M. Noji and K. Koga, *J. Org. Chem.*, 1999, **64**, 2264.

9 The atroposelectivities observed in earlier biaryl couplings of 2-naphthols mediated by an (over)stoichiometric amount of a copper–diamine complex are not the result of an asymmetric coupling step, but of a succeeding dynamic kinetic resolution or a diastereoselective crystallization of the initially formed biaryl–copper–diamine complexes: (*a*) J. Brussee and A. C. A. Jansen, *Tetrahedron Lett.*, 1983, **24**, 3261; (*b*) J. Brussee, J. L. G. Groenendijk, J. M. te Koppele and A. C. A. Jansen, *Tetrahedron*, 1985, **41**, 3313; (*c*) M. Smrčina, M. Lorenc, V. Hanuš, P. Sedmera and P. Kočovský, *J. Org. Chem.*, 1992, **57**, 1917; (*d*) M. Smrčina, J. Poláková, Š. Vyskočil and P. Kočovský, *J. Org. Chem.*, 1993, **58**, 4534.

10 The first truly[9] asymmetric oxidative biaryl coupling was reported in 1993 by Smrčina and Kočovský *et al.*[9d] In the presence of 10 mol% of a sparteine-$CuCl_2$ complex and with AgCl as the stoichiometric oxidant, the product biaryl was obtained in low 32% ee.

11 For a copper-catalyzed, enantioselective oxidative biaryl coupling of 1-naphthol, see: J. Gao, J. H. Reibenspies and A. E. Martell, *Angew. Chem., Int. Ed.*, 2003, **42**, 6008.

12 (*a*) X. Li, J. Yang and M. C. Kozlowski, *Org. Lett.*, 2001, **3**, 1137; (*b*) M. C. Kozlowski, X. Li, P. J. Carroll and Z. Xu, *Organometallics*, 2002, **21**, 4513; (*c*) X. Li, J. B. Hewgley, C. A. Mulrooney, J. Yang and M. C. Kozlowski, *J. Org. Chem.*, 2003, **68**, 5500; (*d*) J. B. Hewgley, S. S. Stahl and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2008, **130**, 12232.

13 Applications of diamine **4** in the atroposelective synthesis of biaryl natural products: (*a*) C. A. Mulrooney, X. Li, E. S. DiVirgilio and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2003, **125**, 6856; (*b*) M. C. Kozlowski, E. C. Dugan, E. S. DiVirgilio, K. Maksimenka and G. Bringmann, *Adv. Synth. Catal.*, 2007, **349**, 583; (*c*) E. S. DiVirgilio, E. C. Dugan, C. A. Mulrooney and M. C. Kozlowski, *Org. Lett.*, 2007, **9**, 385; (*d*) E. M. O'Brien, B. J. Morgan and M. C. Kozlowski, *Angew. Chem., Int. Ed.*, 2008, **47**, 6877; (*e*) B. J. Morgan, S. Dey, S. W. Johnson and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2009, **131**, 9413; (*f*) C. A. Mulrooney, B. J. Morgan, X. Li and M. C. Kozlowski, *J. Org. Chem.*, 2010, **75**, 16; (*g*) B. J. Morgan, C. A. Mulrooney, E. M. O'Brien and M. C. Kozlowski, *J. Org. Chem.*, 2010, **75**, 30; (*h*) B. J. Morgan, C. A. Mulrooney and M. C. Kozlowski, *J. Org. Chem.*, 2010, **75**, 44; (*i*) E. M. O'Brien, B. J. Morgan, C. A. Mulrooney, P. J. Carroll and M. C. Kozlowski, *J. Org. Chem.*, 2010, **75**, 57; (*j*) E. E. Podlesny and M. C. Kozlowski, *Org. Lett.*, 2012, **14**, 1408; (*k*) E. E. Podlesny and M. C. Kozlowski, *J. Org. Chem.*, 2013, **78**, 466.

14 For the oxidative biaryl coupling of **1** catalyzed by other chiral copper–diamine complexes, see: (*a*) A. Caselli, G. B. Giovenzana, G. Palmisano, M. Sisti and T. Pilati, *Tetrahedron: Asymmetry*, 2003, **14**, 1451; (*b*) J. Illesinghe, R. Ebeling, B. Ferguson, J. Patel, E. M. Campi, W. R. Jackson and A. J. Robinson, *Aust. J. Chem.*, 2004, **57**, 167; (*c*) S. Arai, S. Takita and A. Nishida, *Eur. J. Org. Chem.*, 2005, 5262; (*d*) L. Chen, J.-b. Lan and R.-g. Xie, *Hecheng Huaxue*, 2006, **14**, 581; (*e*) P. Yan, Y. Sugiyama, Y. Takahashi, H. Kinemuchi, T. Temma and S. Habaue, *Tetrahedron*, 2008, **64**, 4325; (*f*) Y. Yusa, I. Kaito, K. Akiyama and K. Mikami, *Chirality*, 2010, **22**, 224; (*g*) S. Sabarinathan, G. Vasuki and P. S. Rao, *Eur. J. Chem.*, 2010, **1**, 360; (*h*) G. Grach, G. Pieters, A. Dinut, V. Terrasson, R. Medimagh, A. Bridoux, V. Razafimahaleo, A. Gaucher, S. Marque, J. Marrot, D. Prim, R. Gil, J. G. Planas, C. Viñas, I. Thomas, J.-P. Roblin and Y. Troin, *Organometallics*, 2011, **30**, 4074.

15 K. H. Kim, D.-W. Lee, Y.-S. Lee, D.-H. Ko and D.-C. Ha, *Tetrahedron*, 2004, **60**, 9037.

16 S. K. Alamsetti, E. Poonguzhali, D. Ganapathy and G. Sekar, *Adv. Synth. Catal.*, 2013, **355**, 2803.

17 (*a*) M. Breuning, D. Hein, M. Steiner, V. H. Gessner and C. Strohmann, *Chem. – Eur. J.*, 2009, **15**, 12764; (*b*) M. Breuning, M. Steiner, C. Mehler, A. Paasche and D. Hein, *J. Org. Chem.*, 2009, **74**, 1407; (*c*) M. Breuning, T. Häuser, C. Mehler, C. Däschlein, C. Strohmann, A. Oechsner and H. Braunschweig, *Beilstein J. Org. Chem.*, 2009, **5**(81); (*d*) M. Breuning, A. Paasche, M. Steiner, S. Dilsky, V. H. Gessner, C. Strohmann and B. Engels, *J. Mol. Struct.*, 2011, **1005**, 178; (*e*) M. Breuning and D. Hein, *Eur. J. Org. Chem.*, 2013, 7575.

18 Reviews: (*a*) J. Boruwa, N. Gogoi, P. P. Saikia and N. C. Barua, *Tetrahedron: Asymmetry*, 2006, **17**, 3315; (*b*) C. Palomo, M. Oiarbide and A. Laso, *Eur. J. Org. Chem.*, 2007, 2561; (*c*) G. Blay, V. Hernández-Olmos and J. R. Pedro, *Synlett*, 2011, 1195; (*d*) G. Chelucci, *Coord. Chem. Rev.*, 2013, **257**, 1887; (*e*) N. Ananthi and S. Velmathi, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2013, **52**, 87.

19 D. Scharnagel, F. Prause, J. Kaldun, R. G. Haase and M. Breuning, *Chem. Commun.*, 2014, **50**, 6623.

20 F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel and M. Breuning, *Synthesis*, 2015, DOI: 10.1055/s-0034-1379457.

21 The structures of the products **8** and **9** prepared by hydroxy–amine exchange were unambiguously confirmed by 2D NMR experiments. Rearrangements of **12** to β-amino piperidines *via* the sequence of mesylation–aziridinium formation–nucleophilic attack at C-2 under ring enlargement were not observed. It had been shown that such rearrangements do not occur under mild mesylation conditions and with amines as the nucleophiles, see: (*a*) D. G. Pargo and J. Cossy, *Chem. – Eur. J.*, 2014, **20**, 4516. See also: (*b*) R. H. Reitsema, *J. Am. Chem. Soc.*, 1949, **71**, 2041; (*c*) J. H. Biel, W. K. Hoya and H. A. Leiser, *J. Am. Chem. Soc.*, 1959, **81**, 2527; (*d*) C. F. Hammer, S. R. Heller and J. H. Craig, *Tetrahedron*, 1972, **28**, 239.

22 To our surprise, this problem has not yet been mentioned in any other publication[8,12,14a–d,f–h,15,16] dealing with the enantiomer analysis of **2**.

23 For proposed transition states in the presence of other chiral diamines, see ref. 8*b*,12*a–c*,14*g* and 15.

24 (*a*) Ref. 12*b*, and 14*f*; (*b*) L. M. Mirica, X. Ottenwaelder and T. D. P. Stack, *Chem. Rev.*, 2004, **104**, 1013; (*c*) V. Mahadevan, Z. Hou, A. P. Cole, D. E. Root, T. K. Lal, E. I. Solomon and T. D. P. Stack, *J. Am. Chem. Soc.*, 1997, **119**, 11996; (*d*) S. Mahapatra, J. A. Halfen and W. B. Tolman, *J. Am. Chem. Soc.*, 1996, **118**, 11575; (*e*) V. Mahadevan, M. J. Henson, E. I. Solomon and T. D. P. Stack, *J. Am. Chem. Soc.*, 2000, **122**, 10249; (*f*) S. Dong, J. Zhu and J. A. Porco Jr., *J. Am. Chem. Soc.*, 2008, **130**, 2738; (*g*) P. Kang, E. Bobyr, J. Dustman, K. O. Hodgson, B. Hedman, E. I. Solomon and T. D. P. Stack, *Inorg. Chem.*, 2010, **49**, 11030; (*h*) J. Jover, P. Spuhler, L. Zhao, C. McArdle and F. Maseras, *Catal. Sci. Technol.*, 2014, **4**, 4200.

25 Kozlowski *et al.* also observed a fast uptake of O_2 and **1a** in the beginning of the reaction, but without any product formation.[12d] On this basis they proposed that the catalytically active Cu-species contains an additional, oxidized naphthyl ligand, presumably an *ortho*-quinonic species, which functions like a cofactor in enzymes. We do not think that this is the only possible explanation for the observation made. We suppose that there is a fast ligand exchange at and oxygenation of the initially applied complex CuI·**4** ("burst phase"), leading to a catalytically inactive, oxygenated copper complex of type $[CuO_x{\cdot}\mathbf{4}{\cdot}\mathbf{1a}]_n$ (resting state; for examples of oxygenated di- and oligomeric Cu-complexes, see ref. 24), which only slowly breaks down to the oxygen-free, catalytically active Cu^{II}-species. This pathway is also fully consistent with the experimental results. We therefore did not include an oxidized naphthol ligand in our mechanistic model.

26 The product distribution in competition experiments is most consistent with a radical–radical coupling.[12a,c] In contrast, a radical–anion coupling seems to occur in the presence of a stoichiometric amount of a copper–diamine complex, see: (*a*) M. Hovorka, J. Günterová and J. Závada, *Tetrahedron Lett.*, 1990, **31**, 413; (*b*) M. Smrčina, Š. Vyskočil, B. Máca, M. Polášek, T. A. Claxton, A. P. Abbott and P. Kočovský, *J. Org. Chem.*, 1994, **59**, 2156.

27 (*a*) A. I. Meyers and K. A. Lutomski, *J. Am. Chem. Soc.*, 1982, **104**, 879; (*b*) A. I. Meyers and D. G. Wettlaufer, *J. Am. Chem. Soc.*, 1984, **106**, 1135.

28 (*a*) C. Girard and H. B. Kagan, *Angew. Chem., Int. Ed.*, 1998, **37**, 2922; (*b*) D. Heller, H.-J. Drexler, C. Fischer, H. Buschmann, W. Baumann and B. Heller, *Angew. Chem., Int. Ed.*, 2000, **39**, 495; (*c*) D. G. Blackmond, *Acc. Chem. Res.*, 2000, **33**, 402; (*d*) H. B. Kagan, *Synlett*, 2001, 888.

29 A catalytic cycle *via* octahedral copper species cannot be fully excluded, but is very unlikely. For a short discussion, see footnote 58 in ref. 12*c*.

30 An oxidation of the copper(I) atom in **13** prior to the chelation of **1a** is also possible (and stereochemically not of relevance). This sequence, however, seems to be less likely since the oxidation is slow (rate-limiting step in the catalytic cycle).[12d]

31 W. L. F. Armarego and D. D. Perrin, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, 4th edn, 2000.

Electronic Supplementary Material (ESI) for Catalysis Science & Technology.

In-depth structure–selectivity investigations on asymmetric, copper-catalyzed oxidative biaryl coupling in the presence of 5-*cis*-substituted prolinamines

Felix Prause, Benjamin Arensmeyer, Benjamin Fröhlich and Matthias Breuning*

Organic Chemistry Laboratory
University of Bayreuth
Universitätsstraße 30
95447 Bayreuth, Germany
E-mail: Matthias.Breuning@uni-bayreuth.de

Table of contents

1. Synthetic procedures

For general information about apparatus and methods used, the synthesis of **9f** and the procedure for the oxidative biaryl coupling, see article.

Biaryl **1c**,[1] prolinamines **8c**,**e**–**q**,[2] **9a**,[3] **9m**–**o**,[2] and **10b**–**f**,[2] prolinol **12**,[3] and amine $H_2NC(CH_2OBn)_3$[4] were prepared according to literature procedures. Prolinamines **8d** and **10a** are commercially available.

1.1 Prolinamines 8 and 9

1.1.1 General procedure for the mesylation and amination of prolinol 12

MsCl (1.05 equiv) and NEt_3 (1.5 equiv) were added at 0 °C to a solution of the alcohol **12** (1.0 equiv) in anhydrous CH_2Cl_2 (10 mL/mmol **12**). After 1–2 d at r.t., an excess of the amine (4–20 equiv) was added and stirring was continued for 1–4 d. Evaporation of the solvent and column chromatography provided prolinamines **8** and **9**.

1.1.2 (2*S*,5*R*)-2-((*tert*-Butyl(methyl)amino)methyl)-1-methyl-5-phenylpyrrolidine (8a)

According to the general procedure, alcohol **12** (180 mg, 941 µmol) was mesylated and treated with *tert*-butylmethylamine (900 µL, 654 mg, 7.51 mmol) to give, after column chromatography (silica gel, CH_2Cl_2/MeOH, 1:0–9:1) and filtration through a pad of basic alumina (activity I, CH_2Cl_2/MeOH, 9:1), prolinamine **8a** (177 mg, 680 µmol, 72%) as a slightly brownish oil.

R_f 0.27 (CH_2Cl_2/MeOH 9:1). $[\alpha]_D^{22}$ –6.2 (*c* 1.00 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2967w, 2777w, 1452w, 1360w, 1219w, 1190w, 1021w, 964w, 755s, 699vs. ^{1}H NMR δ_H(400 MHz; $CDCl_3$) 1.09 (9 H, s, $C(CH_3)_3$), 1.68 (2 H, m, 3-*H*H, 4-*H*H), 2.05 (2 H, m 3-H*H*, 4-H*H*), 2.21 (3 H, s, 1-CH_3), 2.27 (3 H, s, $NCH_3C(CH_3)_3$), 2.51 (3 H, m, 2-H, 2-CH_2), 3.26 (1 H, dd, *J* = 8.4, 6.6 Hz, 5-H), 7.23 (1 H, m, Ar-H), 7.34 (4 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz; $CDCl_3$) 26.2 ($C(CH_3)_3$), 29.6 (C-3), 34.1 (C-4), 36.3 ($N(CH_3)C(CH_3)_3$), 39.8 (1-CH_3), 54.2 ($C(CH_3)_3$), 56.8 (2-CH_2), 66.1 (C-2), 72.9 (C-5), 127.0, 127.5, 128.4 (CH-Ar), 144.2 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{17}H_{29}N_2$ $[M + H]^+$ 261.2325, found 261.2327.

1.1.3 (2*S*,5*R*)-1-Methyl-2-((methyl(phenyl)amino)methyl)-5-phenylpyrrolidine (8b)

According to the general procedure, the alcohol **12** (180 mg, 941 µmol) was mesylated and treated with *N*-methylaniline (2.04 mL, 2.02 g, 18.8 mmol) to give, after column chromatography (silica gel, CH_2Cl_2/MeOH, 1:0–9:1) and filtration through a pad of basic alumina (activity I, CH_2Cl_2/MeOH, 9:1), prolinamine **8b** (174 mg, 620 µmol, 66%) as a brownish oil.

R_f 0.73 (CH_2Cl_2/MeOH 9:1). $[\alpha]_D^{21}$ 25.9 (*c* 0.50 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2945w, 2871w, 2783w, 1598vs, 1504vs, 1450s, 1365s, 1191s, 1033w, 990w, 745vs, 691vs. ^{1}H NMR δ_H (400 MHz; $CDCl_3$) 1.74 (2 H, m, 3-*H*H, 4-*H*H), 2.05 (2 H, m, 3-H*H*, 4-H*H*), 2.28 (3 H, s, 1-CH_3), 2.89 (1 H, m, 2-H), 3.09 (3 H, s, N(CH_3)Ar), 3.35 (2 H, m, 5-H, 2-C*H*H), 3.67 (1 H, dd, *J* = 14.7, 5.2 Hz, 2-CH*H*), 6.73 (1 H, m, Ar-H), 6.81 (2 H, m, Ar-H), 7.28 (3 H, m, Ar-H), 7.36 (2 H, m, Ar-H), 7.41 (2 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz; $CDCl_3$) 28.7 (C-3), 34.3 (C-4), 39.6 (NCH_3Ar), 40.0 (1-CH_3), 57.8 (2-CH_2), 64.5 (C-2), 72.7 (C-5), 112.1, 116.1, 127.1, 127.4, 128.4, 129.2 (CH-Ar), 144.1, 149.9 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{19}H_{25}N_2$ $[M + H]^+$ 281.2012, found 281.2014.

1.1.4 (2*S*,5*R*)-2-((Ethylamino)methyl)-1-methyl-5-phenylpyrrolidine (9b)

According to the general procedure, alcohol **12** (150 mg, 784 µmol) was mesylated and treated with aq ethylamine (70%, 1.27 mL, 707 mg, 15.7 mmol) and MeOH (2 mL) to give, after column chromatography (1. silica gel, deactivated with 7.5% aq NH_3 (25%), CH_2Cl_2/MeOH, 1:0–9:1; 2. silica gel, deactivated with 7.5% aq NH_3 (25%), petroleum ether/Et_2O, 1:0–0:1), prolinamine **9b** (106 mg, 488 µmol, 62%) as a brownish oil.

R_f 0.27 (Et_2O, deact. SiO_2). $[\alpha]_D^{21}$ 36.7 (*c* 0.10 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2962w, 2786w, 1452w, 1138w, 1073w, 1040w, 755s, 699vs. ^{1}H NMR δ_H(400 MHz; $CDCl_3$) 1.16 (3 H, t, *J* = 7.1 Hz, NCH_2CH_3), 1.69 (2 H, m, 4-*H*H, NH), 1.82 (1 H, m, 3-*H*H), 1.97 (1 H, m, 3-H*H*), 2.06 (1 H, m, 4-H*H*), 2.16 (3 H, s, 1-CH_3), 2.61 (1 H, m, 2-H), 2.72 (3 H, m, 2-C*H*H, NCH_2CH_3), 2.81 (1 H, dd, *J* = 11.3, 3.6 Hz, 2-CH*H*), 3.28 (1 H, dd, *J* = 9.5, 6.6 Hz, 5-H), 7.23 (1 H, m, Ar-H), 7.32 (4 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz; $CDCl_3$) 15.4 (NCH_2CH_3), 28.2 (C-3), 34.3 (C-4), 39.5 (1-CH3), 44.8 (NCH_2CH_3),

1 X. Li, J. B. Hewgley, C. A. Mulrooney, J. Yang and M. C. Kozlowski, *J. Org. Chem.*, 2003, **68**, 5500.

2 F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel and M. Breuning, *Synthesis*, 2015, DOI: 10.1055/s-0034-1379457.

3 D. Scharnagel, F. Prause, J. Kaldun, R. G. Haase and M. Breuning, *Chem. Commun.*, 2014, **50**, 6623.

4 M. Segura, F. Sansone, A. Casnati and R. Ungaro, *Synthesis*, 2001, 2105.

53.1 (2-CH_2), 66.0 (C-2), 72.7 (C-5), 127.1, 127.5, 128.4 (Ar-H), 144.0 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{23}N_2$ $[M + H]^+$ 219.1856, found. 219.1854.

1.1.5 (2*S*,5*R*)-1-Methyl-2-((neopentylamino)methyl)-5-phenylpyrrolidine (9c)

According to the general procedure, alcohol **12** (150 mg, 784 µmol) was mesylated and treated with neopentylamine hydrochloride (1.77 g, 14.3 mmol) NEt_3 (2.00 mL, 1.46 g, 14.3 mmol) and MeOH (2 mL) to give, after column chromatography (silica gel, CH_2Cl_2/MeOH, 1:0–9:1) and filtration through a pad of basic alumina (activity I, CH_2Cl_2/MeOH, 9:1), prolinamine **9c** (160 mg, 614 µmol, 78%) as a colorless resin.

R_f 0.51 (CH_2Cl_2/MeOH 9:1). $[\alpha]_D^{22}$ = 38.5 (*c* 0.50 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2949s, 2866w, 2784w, 1454s, 1361w, 1139w, 1040w, 755s, 698vs. ^{1}H NMR δ_H(400 MHz; $CDCl_3$) 0.95 (9 H, s, $C(CH_3)_3$), 1.30 (1 H, br s, NH), 1.68 (1 H, m, 4-*H*H), 1.84 (1 H, m, 3-*H*H), 1.95 (1 H, m, 3-H*H*), 2.05 (1 H, m, 4-H*H*), 2.18 (3 H, s, 1-CH_3), 2.39 (1 H, d, *J* = 11.3 Hz, C*H*HC$(CH_3)_3$), 2.44 (1 H, d, *J* = 11.3 Hz, CH*H*C$(CH_3)_3$), 2.63 (1 H, m, 2-H), 2.72 (1 H, dd, *J* = 11.4, 5.6 Hz, 2-C*H*H), 2.78 (1 H, dd, *J* = 11.4, 4.0 Hz, CH*H*N), 3.30 (1 H, dd, *J* = 9.6, 6.7 Hz, 5-H), 7.23 (1 H, m, Ar-H), 7.33 (4 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz; $CDCl_3$) 28.0 (C(*C*H_3)$_3$), 28.2 (C-3), 31.9 (*C*$(CH_3)_3$), 34.6 (C-4), 39.6 (1-CH_3), 54.5 (2-CH_2), 63.2 (*C*H_2C$(CH_3)_3$), 66.2 (C-2), 72.7 (C-5), 127.0, 127.4, 128.4 (CH-Ar), 144.3 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{17}H_{29}N_2$ $[M + H]^+$ 261.2325, found 261.2326.

1.1.6 (2*S*,5*R*)-2-((Isopropylamino)methyl)-1-methyl-5-phenylpyrrolidine (9d)

According to the general procedure, alcohol **12** (150 mg, 784 µmol) was mesylated and treated with isopropylamine (1.34 mL, 926 mg, 15.7 mmol) to give, after column chromatography (1. silica gel, deactivated with 7.5% aq NH_3 (25%), CH_2Cl_2/MeOH, 1:0–9:1; 2. silica gel, deactivated with 7.5% aq NH_3 (25%), petroleum ether/Et_2O, 1:0–0:1), prolinamine **9d** (97.0 mg, 417 µmol, 53%) as a yellow oil.

R_f 0.31 (Et_2O, deact. SiO_2). $[\alpha]_D^{21}$ 15.0 (*c* 0.20 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2962w, 2783w, 1453w, 1378w, 1336w, 1173w, 1139w, 1080w, 1043w, 755s, 698vs. ^{1}H NMR δ_H(400 MHz; $CDCl_3$) 1.09 (3 H, d, *J* = 6.2 Hz, NCH(CH_3)$_2$), 1.11 (3 H, d, *J* = 6.2 Hz, NCH(CH_3)$_2$), 1.48 (1 H, br s, NH), 1.67 (1 H, m, 4-*H*H), 1.80 (1 H, m, 3-*H*H), 1.97 (1 H, m, 3-H*H*), 2.06 (1 H, m, 4-H*H*), 2.16 (3 H, s, 1-CH_3), 2.59 (1 H, m, 2-H), 2.66 (1 H, dd, *J* = 11.0, 6.4 Hz, 2-C*H*H), 2.83 (2 H, m, CH*H*N, NC*H*$(CH_3)_2$), 3.29 (1 H, dd, *J* = 9.5, 6.7 Hz, 5-H), 7.22 (1 H, m, Ar-H), 7.32 (4 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz; $CDCl_3$) 23.0 (NCH(*C*H_3)$_2$), 23.3 (NCH(*C*H_3)$_2$), 28.2 (C-3), 34.3 (C-4), 39.4 (1-CH_3), 49.5 (N*C*H$(CH_3)_2$), 51.0 (2-*C*H_2), 66.2 (C-2), 72.6 (C-5), 127.0, 127.4, 128.4 (CH-Ar), 144.1 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{15}H_{25}N_2$ $[M + H]^+$ 233.2012, found 233.2013.

1.1.7 (2*S*,5*R*)-1-Methyl-2-((pentan-3-ylamino)methyl)-5-phenylpyrrolidine (9e)

According to the general procedure, alcohol **12** (150 mg, 784 µmol) was mesylated and treated with 3-pentylamine (914 µL, 683 mg, 7.84 mmol) to give, after column chromatography (silica gel, Et_2O), prolinamine **9e** (112 mg, 430 µmol, 55%) as a colorless oil.

R_f 0.13 (Et_2O). $[\alpha]_D^{22}$ 29.0 (*c* 0.50 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2958s, 2872w, 2784w, 1453s, 1350w, 1158w, 1082w, 1043w, 754s, 698vs. ^{1}H NMR δ_H(400 MHz; $CDCl_3$) 0.92 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 0.94 (3 H, t, *J* = 7.5 Hz, CH_2CH_3), 1.46 (5 H, m, CH(C$H_2$$CH_3$)$_2$, N*H*), 1.69 (1 H, m, 4-*H*H), 1.86 (1 H, m, 3-*H*H), 1.97 (1 H, m, 3-H*H*), 2.05 (1 H, m, 4-H), 2.16 (3 H, s, 1-CH_3), 2.39 (1 H, quint, *J* = 6.0 Hz, NC*H*(C$H_2$$CH_3$)$_2$), 2.60 (1 H, m, 2-H), 2.65 (1 H, dd, *J* = 11.0, 6.1 Hz, 2-C*H*H), 2.79 (1 H, dd, *J* = 11.0, 3.2 Hz, 2-CH*H*), 3.29 (1 H, dd, *J* = 9.6, 6.7 Hz, 5-H), 7.23 (1 H, m, Ar-H), 7.33 (4 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz; $CDCl_3$) 10.1, 10.3 (CH_2CH_3), 26.2, 26.3 (*C*$H_2$$CH_3$), 28.1 (C-3), 34.4 (C-4), 39.3 (1-CH_3), 50.2 (2-CH_2), 61.1 ((N*C*H(C$H_2$$CH_3$)$_2$), 66.4 (C-2), 72.6 (C-5), 127.0, 127.4, 128.4 (CH-Ar), 144.1 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{17}H_{29}N_2$ $[M + H]^+$ 261.2325, found. 261.2325.

1.1.8 (2*R*,5*S*)-1-Methyl-2-phenyl-5-((((*S*)-1-phenylpropyl)amino)methyl)pyrrolidine (9g)

According to the general procedure, alcohol **12** (150 mg, 784 µmol) was mesylated and treated with (*S*)-1-phenylpropylamine (967 µL, 900 mg, 6.66 mmol) to give, after column chromatography (silica gel, petroleum ether/EtOAc, 1:0–1:1), prolinamine **9g** (157 mg, 509 µmol, 65%) as a colorless oil.

R_f 0.32 (CH_2Cl_2/MeOH 9:1). $[\alpha]_D^{21}$ 19.8 (*c* 0.50 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2958w, 2783w, 1491w, 1451s, 1356w, 1283w, 1193w, 1122w, 1043w, 754s, 698vs. ^{1}H NMR δ_H(400 MHz; $CDCl_3$) 0.85 (3 H, t, *J* = 7.4 Hz, CH_2CH_3), 1.66 (2 H, m, 3-*H*H, C*H*HCH_3), 1.82 (3 H, m, 4-*H*H, CH*H*CH_3, N*H*), 1.96 (1 H, m, 4-H*H*), 2.05 (1 H, m, 3-H*H*), 2.07 (3 H, s, 1-CH_3), 2.54 (2 H, m, 5-H, 5-C*H*H), 2.66 (1 H, dd, *J* = 10.8, 3.1 Hz, 5-CH*H*), 3.26 (1 H, dd, *J* = 9.6, 6.6 Hz, 2-H), 3.52 (1 H, dd, *J* = 7.8, 5.8 Hz, C*H*CH_2CH_3), 7.24 (2 H, m, Ar-H), 7.33 (8 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz; $CDCl_3$) 11.0 (CH_2CH_3), 28.2 (C-4), 31.1 (*C*$H_2$$CH_3$), 34.5 (C-3), 39.4 (1-$CH_3$), 50.8 (5-$CH_2$), 65.4 (*C*H$CH_2CH_3$), 66.2 (C-5), 72.7 (C-2), 126.9, 127.0, 127.40, 127.43, 128.36, 128.40 (CH-Ar), 144.2, 144.9 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{21}H_{29}N_2$ $[M + H]^+$ 309.2325, found 309.2327.

1.1.9 (2*S*,5*R*)-2-((((*S*)-3,3-dimethylbutan-2-yl)amino)methyl)-1-methyl-5-phenylpyrrolidine (9h)

According to the general procedure, alcohol **12** (150 mg, 784 µmol) was mesylated and treated with (*S*)-3,3-dimethyl-2-butanylamine (1.19 mL, 900 mg, 8.89 mmol) to give, after column chromatography (silica gel, CH_2Cl_2/MeOH, 100:0–97:3) and filtration through a pad of basic alumina (activity I, CH_2Cl_2/MeOH, 9:1), prolinamine **9h** (111 mg, 404 µmol, 52%) as a colorless oil.

R_f 0.4 (EtOAc). $[\alpha]_D^{21}$ 48.6 (*c* 0.50 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2952w, 2784w, 1452w, 1370w, 1335w, 1203w, 1149w, 1119w, 1041w, 754s, 698vs. ^{1}H NMR δ_H(400 MHz; $CDCl_3$) 0.93 (9 H, s, C(CH_3)$_3$), 0.99 (3 H, d, *J* = 6.4 Hz, CHC*H*$_3$), 1.38 (1 H, br s, NH), 1.66 (1 H, m, 4-*H*H), 1.92 (2 H, m, 3-H$_2$), 2.05 (1 H, m, 4-H*H*), 2.14 (3 H, s, 1-CH_3), 2.27 (1 H, q, *J* = 6.4 Hz, C*H*CH_3), 2.49 (1 H, dd, *J* = 11.0, 6.0 Hz, 2-C*H*H), 2.59 (1 H, m, 2-H), 2.96 (1 H, dd, *J* = 11.0, 2.8 Hz, CH*H*N), 3.29 (1 H, dd, *J* = 9.5, 6.9 Hz, 5-H), 7.23 (1 H, m, Ar-H), 7.32 (4 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz; $CDCl_3$) 15.3 (CH*C*H$_3$), 26.7 (C(*C*H$_3$)$_3$), 28.1 (C-3), 34.5 (C-4), 34.6 (*C*(CH$_3$)$_3$), 39.1 (1-CH_3), 52.3 (2-CH_2), 64.0 (*C*HCH$_3$), 66.5 (C-2), 72.5 (C-5), 127.0, 127.4, 128.4 (CH-Ar), 144.3 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{18}H_{31}N_2$ $[M + H]^+$ 275.2482, found 275.2481.

1.1.10 (2*R*,5*S*)-1-Methyl-2-phenyl-5-((((*R*)-1-phenylethyl)amino)methyl)pyrrolidine (9i)

According to the general procedure, alcohol **12** (180 mg, 941 µmol) was mesylated and treated with (*R*)-1-phenylethylamine (2.40 mL, 2.28 g, 18.8 mmol) to give, after column chromatography (1. silica gel, CH_2Cl_2/MeOH, 100:0–97:3, 2. silica gel, petroleum ether/EtOAc, 1:0–2:1) and filtration through a pad of basic alumina (activity I, CH_2Cl_2/MeOH, 9:1), prolinamine **9i** (173 mg, 588 µmol, 62%) as an orange solid.

R_f 0.47 (EtOAc). Mp 52–55 °C. $[\alpha]_D^{21}$ 60.5 (*c* 1.00 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2960w, 2841w, 2784w, 1490w, 1447s, 1341w, 1199s, 1128w, 1083s, 1041w, 755vs, 698vs. ^{1}H-NMR δ_H(400 MHz; $CDCl_3$) 1.43 (3 H, d, *J* = 6.6 Hz, CHC*H*$_3$), 1.74 (2 H, m, 3-*H*H, NH), 1.95 (2 H, m, 4-H$_2$), 2.08 (1 H, m, 3-H*H*), 2.16 (3 H, s, 1-CH_3), 2.59 (2 H, m, 5-C*H*H, 5-H), 2.67 (1 H, m, 5-CH*H*), 3.31 (1 H, dd, *J* = 9.8, 6.7 Hz, 2-H), 3.85 (1 H, q, *J* = 6.6 Hz, C*H*CH$_3$), 7.27 (2 H, m, Ar-H), 7.38 (8 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz, $CDCl_3$) 25.1 (CH*C*H$_3$), 27.8 (C-4), 34.6 (C-3), 39.4 (1-CH_3), 50.7 (5-CH_2), 59.0 (*C*HCH$_3$), 66.1 (C-5), 72.7 (C-2), 126.78, 126.81, 127.0, 127.4, 128.38, 128.41 (CH-Ar), 144.2, 146.4 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{20}H_{27}N_2$ $[M + H]^+$ 295.2169, found 295.2167.

1.1.11 (2*S*,5*R*)-2-((*tert*-Butylamino)methyl)-1-methyl-5-phenylpyrrolidine (9j)

According to the general procedure, alcohol **12** (150 mg, 784 µmol) was mesylated and treated with *tert*-butylamine (1.65 mL, 1.15 g, 15.7 mmol) to give, after column chromatography (silica gel, deactivated with 7.5% aq NH_3 (25%), CH_2Cl_2/MeOH, 1:0–9:1), prolinamine **9j** (125 mg, 507 µmol, 65%) as a yellow oil.

R_f 0.35 (CH_2Cl_2/MeOH 9:1). $[\alpha]_D^{21}$ 16.6 (*c* 0.20 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2961s, 2836w, 2782w, 1452w, 1360s, 1230s, 1085w, 1027w, 755s, 698vs. ^{1}H-NMR δ_H(400 MHz; $CDCl_3$) 1.15 (9 H, s, C(CH_3)$_3$), 1.25 (1 H, br s, NH), 1.69 (1 H, m, 4-*H*H), 1.78 (1 H, m, 3-*H*H), 1.98 (1 H, m, 3-H*H*), 2.06 (1 H, m, 4-H*H*), 2.17 (3 H, s, 1-CH_3), 2.57 (1 H, m, 2-H), 2.65 (1 H, dd, *J* = 10.6, 6.7 Hz, 2-C*H*H), 2.78 (1 H, dd, *J* = 10.6, 3.6 Hz, 2-CH*H*), 3.29 (1 H, dd, *J* = 9.4, 6.6 Hz, 5-H), 7.23 (1 H, m, Ar-H), 7.33 (4 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz; $CDCl_3$) 28.3 (C-3), 29.2 (C(*C*H$_3$)$_2$), 34.3 (C-4), 39.5 (1-CH_3), 46.2 (2-CH_2), 50.1 (*C*(CH$_3$)$_2$), 66.5 (C-2), 72.6 (C-5), 127.0, 127.4, 128.4 (CH-Ar), 144.1 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{16}H_{27}N_2$ $[M + H]^+$ 247.2169, found 247.2170.

1.1.12 (2*S*,5*R*)-2-(((1,3-bis(benzyloxy)-2-((benzyloxy)methyl)propan-2-yl)amino)methyl)-1-methyl-5-phenylpyrrolidine (9k)

According to the general procedure, alcohol **12** (200 mg, 1.05 mol) was mesylated and treated with 1,3-bis(benzyloxy)-2-((benzyloxy)methyl)propan-2-amine (1.64 g, 4.20 mmol) to give, after column chromatography (1. silica gel, CH_2Cl_2/MeOH, 100:0–95:5, 2. silica gel, petroleum ether/EtOAc/MeOH/NH_3 (aq, 25%), 400:600:9:1 prolinamine **9k** (279 mg, 494 µmol, 47 %) as a colorless oil.

R_f 0.66 (petroleum ether/EtOAc/MeOH/aq NH_3 (25%), 400:600:9:1). $[\alpha]_D^{28}$ 28.6 (*c* 1.0 MeOH). IR (ATR) ν_{max}/cm^{-1} 2855w, 1452w, 1363w, 1204w, 1090s, 1074s, 1027w, 733s, 695vs. ^{1}H-NMR δ_H(300 MHz; $CDCl_3$) 1.63-1.90 (2 H, m, 3-*H*H, 4-*H*H), 1.91-2.15 (3 H, m, 3-H*H*, 4-H*H*, NH), 2.18 (3 H, s, 1-CH_3), 2.63 (1 H, m, 2-H), 2.77 (1 H, dd, *J* = 10.3, 6.9 Hz, 2-C*H*H), 2.90 (1 H, dd, *J* = 10.4, 3.4 Hz, 2-CH*H*), 3.32 (1 H, dd, *J* = 9.5, 6.5 Hz, 5-H), 3.58 (3 H, d, *J* = 9.2 Hz, C(C*H*HO)$_3$), 3.62 (3 H, d, *J* = 9.2 Hz, C(CH*H*O)$_3$), 4.59 (6 H, s, CH_2Ar), 7.23-7.46 (20 H, m, Ar-H) ppm. ^{13}C NMR δ_C(75 MHz; $CDCl_3$) 28.1 (C-3), 34.4 (C-4), 39.4 (1-CH_3), 45.6 (2-CH_2), 59.4 (*C*(CH$_2$)$_3$), 66.5 (C-2), 70.3 (C(*C*H$_2$)$_3$), 72.5 (C-5), 73.4 (CH_2Ar), 126.9, 127.41, 127.44, 127.5, 128.3 (Ar-H), 138.8, 144.1 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{37}H_{45}N_2O_3$ $[M + H]^+$ 565.3425, found 565.3421.

1.1.13 (2*R*,5*S*)-1-Methyl-2-phenyl-5-((phenylamino)methyl)pyrrolidine (9l)

According to the general procedure, alcohol **12** (150 mg, 784 µmol) was mesylated and treated with aniline (1.43 mL, 1.46 g, 15.7 mmol) to give, after column chromatography (1. silica gel, deactivated with 7.5% aq NH_3 (25%), petroleum ether/EtOAc, 1:0–3:1; 2. silica gel, deactivated with 7.5% aq NH_3 (25%), petroleum ether/Et_2O, 1:0–11:1) and filtration through a pad of basic alumina (activity I, CH_2Cl_2/MeOH, 9:1), prolinamine **9l** (152 mg, 570 µmol, 73%) as a colorless oil.

R_f 0.77 (petroleum ether/EtOAc 3:1, deact. SiO_2). $[\alpha]_D^{21}$ 23.9 (*c* 0.20 in MeOH). IR (ATR) ν_{max}/cm^{-1} 3376br, 2947w, 2839w, 2788w, 1602vs, 1504vs, 1428s, 1315s, 1086w, 1045w, 938w, 746vs, 690vs. ^{1}H NMR δ_H(400 MHz; $CDCl_3$) 1.75 (1 H, m, 3-*H*H), 1.99 (2 H, m, 4-H_2), 2.14 (1 H, m, 3-H*H*), 2.20 (3 H, s, 1-CH_3), 2.82 (1 H, m, 5-H), 3.24 (1 H, dd, *J* = 11.7, 4.7 Hz, 5-C*H*H), 3.32 (1 H, dd, *J* = 11.8, 2.5 Hz, 5-CH*H*), 3.39 (1 H, dd, *J* = 9.6, 6.9 Hz, 2-H), 4.40 (1 H, br s, NH), 6.73 (3 H, m, Ar-H), 7.24 (2 H, m, Ar-H), 7.30 (1 H, m, Ar-H), 7.40 (4 H, m, Ar-H) ppm. ^{13}C NMR δ_C(100 MHz, $CDCl_3$) 26.5 (C-4), 33.3 (C-3), 37.7 (1-CH_3), 44.1 (5-CH_2), 63.9 (C-5), 71.4 (C-2), 112.0, 116.1, 126.2, 126.4, 127.5, 128.4 (CH-Ar), 142.7, 148.2 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{18}H_{23}N_2$ $[M + H]^+$ 267.1856, found 267.1855.

1.2 Naphthol esters 1

1.2.1 Isopropyl 3-hydroxy-2-naphthoate (1b)[5]

A suspension of 3-hydroxy-2-naphthoic acid (480 mg, 2.55 mmol) in anhydrous benzene (10 mL) and anhydrous DMF (20 µL) was treated dropwise with $SOCl_2$ (556 µL, 910 mg, 7.65 mmol) and stirred for 3 h at 40 °C. The solvent was removed under reduced pressure and the resulting orange solid was suspended in *i*PrOH (15 mL). The solvent was removed after 18 h at 60 °C and sat. aq Na_2CO_3 (20 mL) was slowly added. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, petroleum ether/EtOAc, 19:1) delivered the ester **1b** (438 mg, 1.90 mmol, 75%) as a yellow solid.

R_f 0.71 (petroleum ether/Et_2O 5:1). Mp 67–68 °C. IR (ATR) ν_{max}/cm^{-1} 3252br, 2974w, 1678s, 1304s, 1277vs, 1207vs, 1142vs, 1101vs, 1065vs, 788s, 739s, 689s. ^{1}H NMR δ_H(500 MHz; $CDCl_3$) 1.46 (6 H, d, *J* = 6.3 Hz, CH(C*H*$_3$)$_2$), 5.37 (1 H, sept, *J* = 6.3 Hz, C*H*(CH$_3$)$_2$), 7.32 (2 H, m, 4-H, 7-H), 7.49 (1 H, m, 6-H), 7.68 (1 H, d, *J* = 8.3 Hz, 5-H), 7.81 (1 H, d, *J* = 8.2 Hz, 8-H), 8.48 (1 H, s, 1-H), 10.65 (1 H, s, OH) ppm. ^{13}C NMR δ_C(125 MHz, $CDCl_3$) 22.0 (CH(*C*H$_3$)$_2$), 69.8 (*C*H(CH$_3$)$_2$), 111.7 (C-4), 114.8 (C-2), 124.0 (C-7), 126.4 (C-5), 127.1 (C-8a), 129.1 (C-6), 129.3 (C-8), 132.4 (C-1), 137.9 (C-4a), 156.6 (C-3), 169.6 (CO_2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{14}O_3Na$ $[M + Na]^+$ 253.0835, found 253.0828.

1.2.2 *tert*-Butyl 3-hydroxy-2-naphthoate (1d)[6]

A solution of 3-hydroxy-2-naphthoic acid (3.00 g, 15.9 mmol) and 1,1'-carbonyldiimidazole (2.58 g, 15.9 mmol) in anhydrous DMF (16 mL) was stirred at 50 °C for 1 h. DBU (2.38 mL, 2.42 g, 15.9 mmol) and *t*BuOH (2.98 mL, 2.36 g, 31.8 mmol) were added and stirring was continued for 16 h at 50 °C. Et_2O (100 mL) and sat. aq $NaHCO_3$ (100 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (100 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, petroleum ether/CH_2Cl_2, 2:1) delivered the ester **1d** (2.04 g, 11.8 mmol, 74%) as a yellow solid.
The spectroscopic data of **1d** were consistent with those reported in literature.[6]

1.3 Binaphthols 2

1.3.1 Preparation of homochiral (*M*)-2a by trituration

Scalemic (*M*)-**2a** (62% ee, 740 mg, 1.84 mmol) was suspended in EtOAc (11 mL) and ultra-sonificated for 2 min. Filtration afforded crystalline material of (*M*)-**2a** with low enantiopurity (414 mg, 1.03 mmol, 56%, 35% ee) and, from the mother liquor, highly enantioenriched material of (*M*)-**2a** (326 mg, 810 µmol, 44%, 96% ee).

1.3.2 Diisopropyl (*M*)-2,2'-dihydroxy-1,1'-binaphthyl-3,3'-dicarboxylate [(*M*)-2b (75% ee)][5]

This compound was obtained in the oxidative coupling of **1b** in the presence of CuCl•**9f** (see Table 6, entry 6).

Yellow solid. R_f 0.38 (petroleum ether/Et_2O 5:1). Mp 205–207 °C. $[\alpha]_D^{29}$ 111.5 (*c* 1.00 in CH_2Cl_2). IR (ATR) ν_{max}/cm^{-1} 3200br, 2982w, 1667s, 1338w, 1281vs, 1215s, 1104vs, 1072s, 915w, 795s, 737s. ^{1}H NMR δ_H(500 MHz; $CDCl_3$) 1.47 (6 H, d, *J* = 6.3 Hz, CH(C*H*$_3$)$_2$), 1.49 (6 H, d, *J* = 6.3 Hz, CH(C*H*$_3$)$_2$), 5.38 (2 H, sept, *J* = 6.3 Hz, C*H*(CH$_3$)$_2$), 7.15 (2 H, m, 5-H), 7.34 (4 H, m, 6-H, 7-H), 7.93 (2 H, m, 8-H), 8.67 (2 H, s, 1-H), 10.93 (2 H, s, OH) ppm. ^{13}C NMR δ_C(125 MHz, $CDCl_3$) 22.1 (CH(*C*H$_3$)$_2$), 69.9 (*C*H(CH$_3$)$_2$), 114.8 (C-2), 117.0 (C-4), 124.0 (C-7), 124.8 (C-5), 127.3 (C-8a), 129.4 (C-6), 129.9

5 Compounds **1b** and **2b** are known, but not fully characterized: (a) A. Caselli, G. B. Giovenzana, G. Palmisano, M. Sisti and T. Pilati, *Tetrahedron: Asymmetry*, 2003, **14**, 1451; (b) S. K. Alamsetti, E. Poonguzhali, D. Ganapathy and G. Sekar, *Adv. Synth. Catal.,* 2013, **355**, 2803.

6 For a different approach to **1d**, see: M. Noji, T. Ohno, K. Fuji, N. Futaba, H. Tajima and K. Ishii, *J. Org. Chem.*, 2003, **68**, 9340.

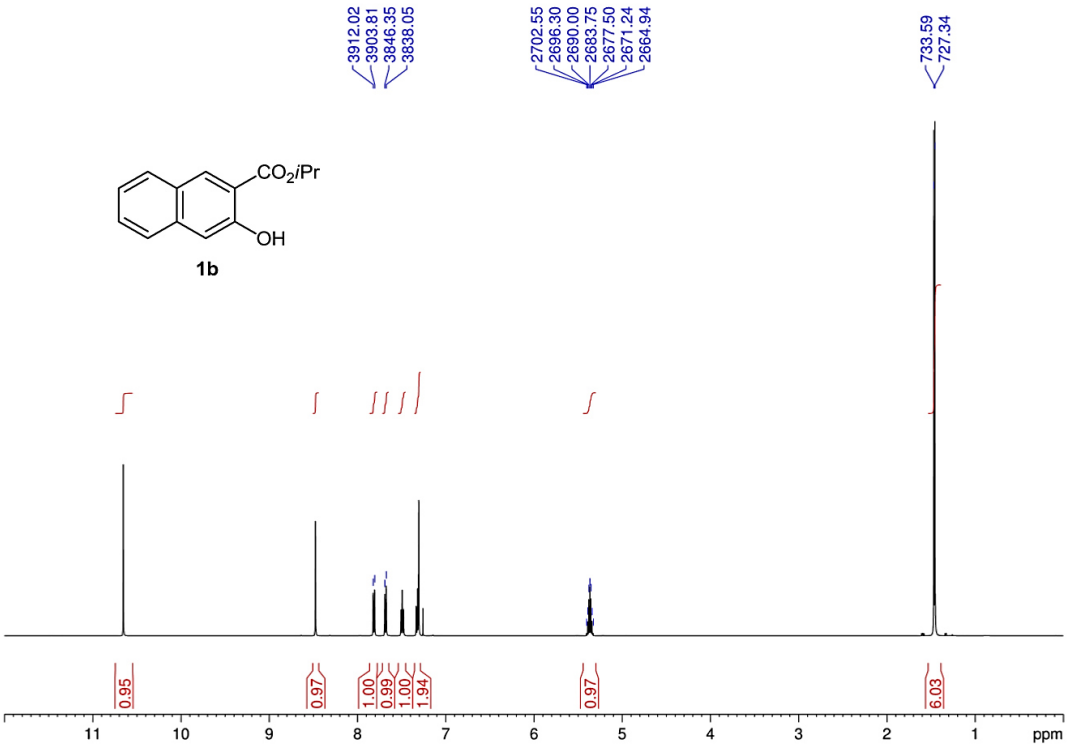
(C-8), 132.8 (C-1), 137.2 (C-4a), 154.3 (C-3), 169.8 (CO_2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{28}H_{26}O_6Na$ $[M + Na]^+$ 481.1622, found 481.1613.

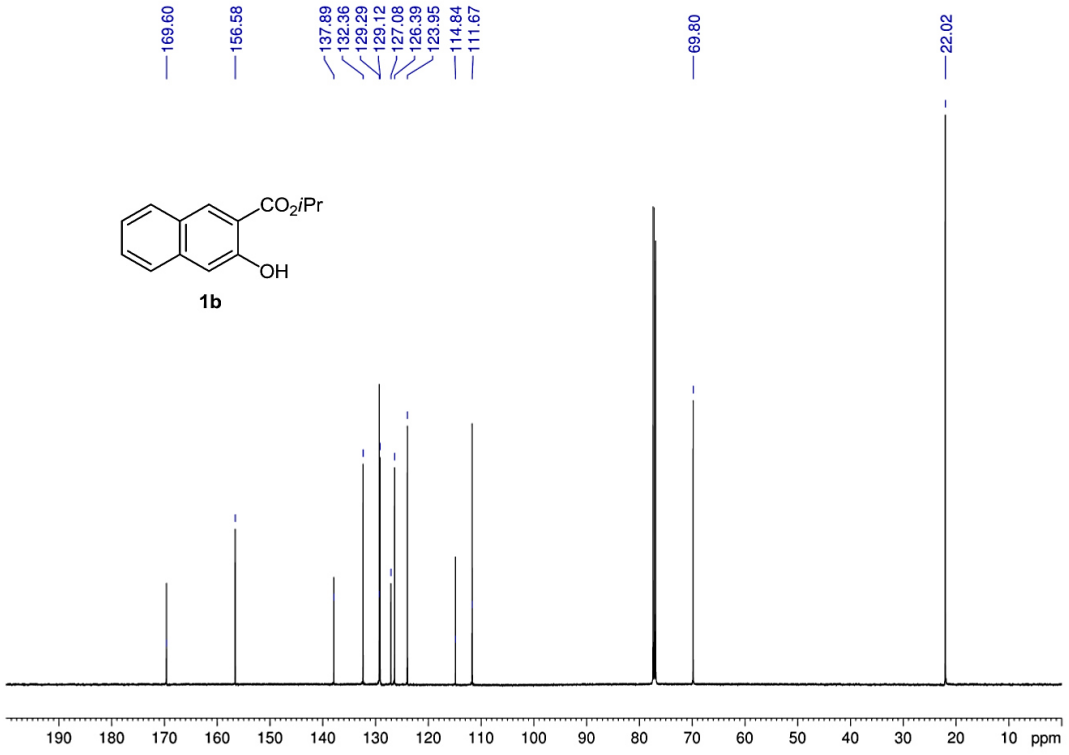
1.3.3 Transesterification of (*M*)-2b to (*M*)-2a

LiOMe (0.1 M in MeOH, 665 µL, 66.5 µmol) was added to a solution of (*M*)-**2c** (61 mg, 133 µmol, 69% ee, obtained in the oxidative coupling of **1b** in the presence of CuCl•**9c**, see Table 6, entry 2) in anhydrous MeOH (6 mL) and anhydrous CH_2Cl_2 (5 mL). LiOMe (0.1 M in MeOH, 133 µL, 13.3 µmol) was added after 2 d at r.t. and stirring was continued for 1 d. Sat. aq NH_4Cl (2 mL) was added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, petroleum ether/CH_2Cl_2, 1:2/0:1) delivered the binol (*M*)-**2a** (50 mg, 124 µmol, 93%, 68% ee) as a yellow solid.

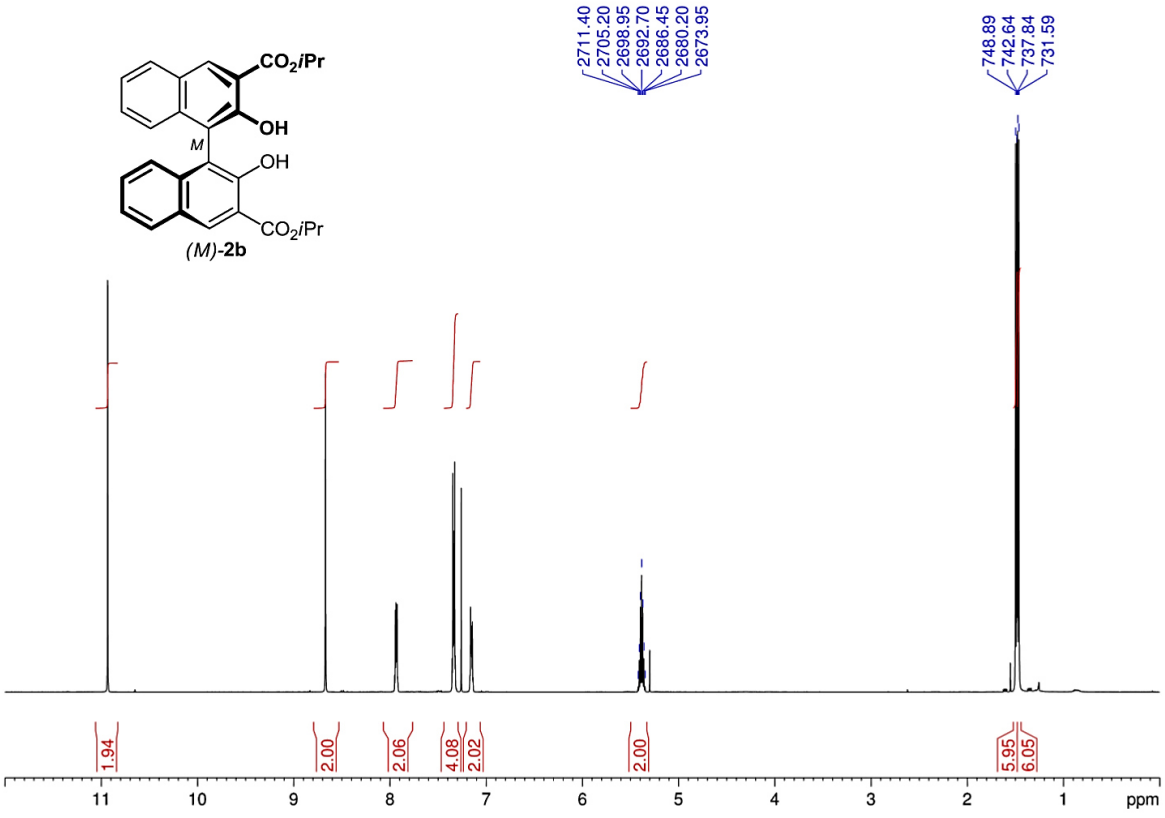
2. Copies of ^{1}H and ^{13}C NMR spectra

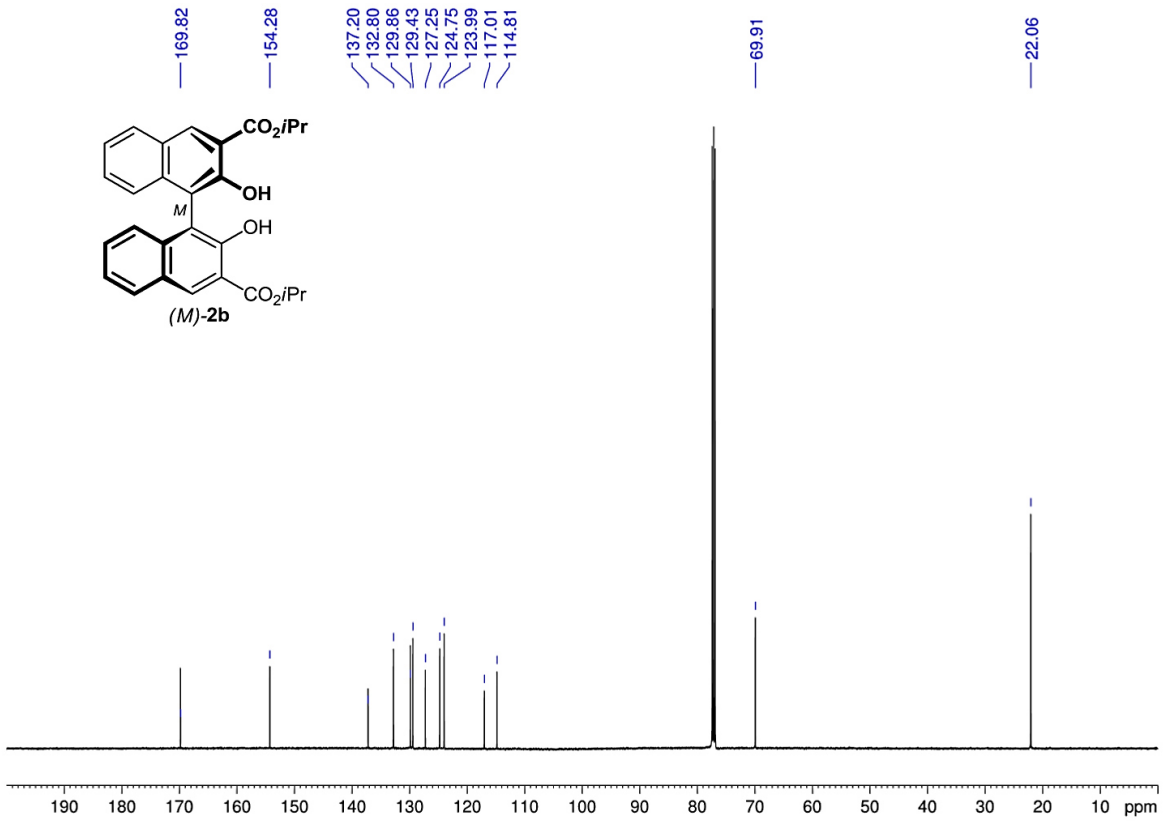
The ^{1}H and ^{13}C NMR spectra of all new compounds are listed in numerical order.



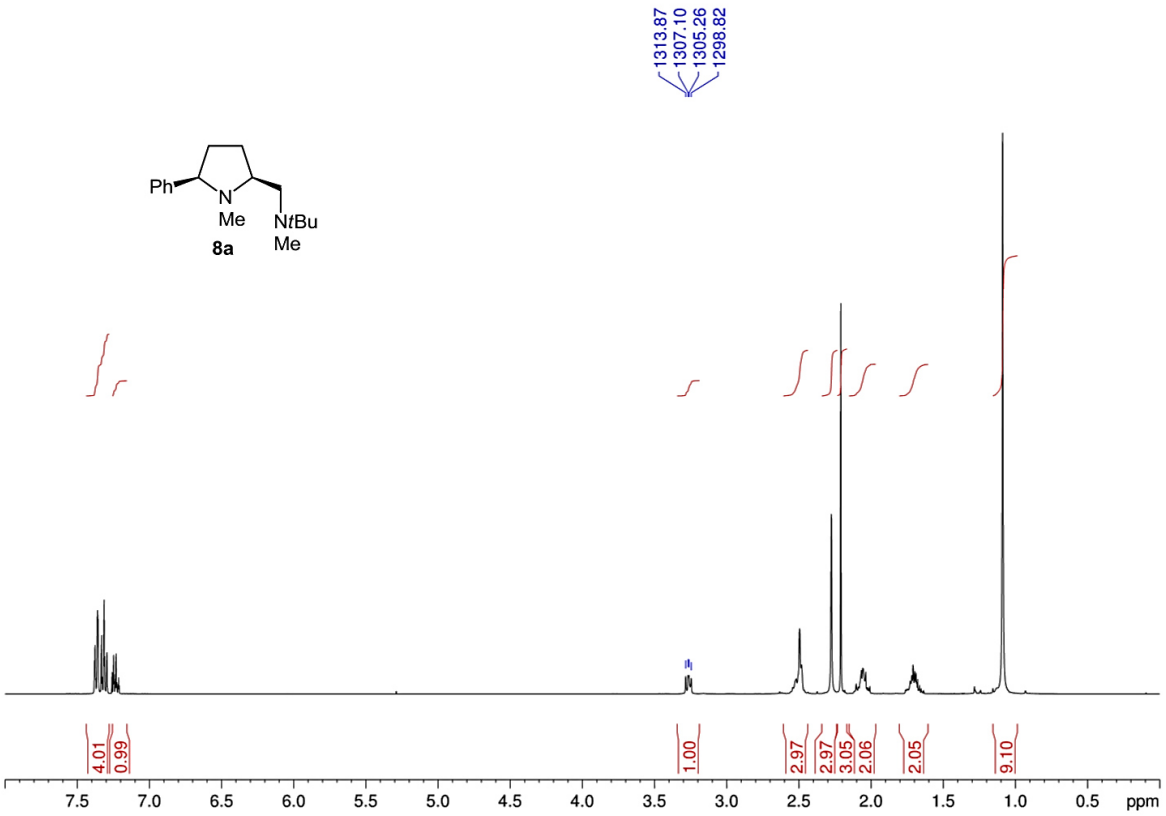


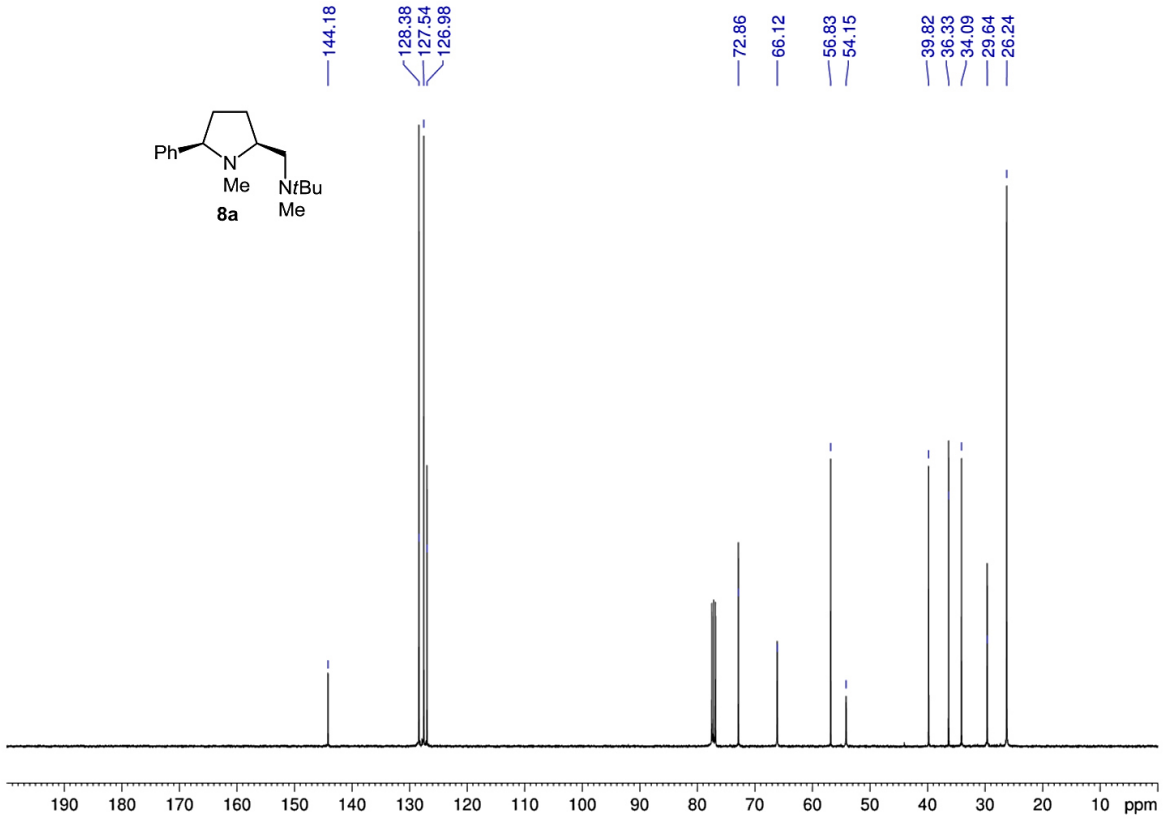
8


CO2iPr
OH
M
OH
CO2iPr
(M)-2b
2711.40
2705.20
2698.95
2692.70
2686.45
2680.20
2673.95
748.89
742.64
737.84
731.59
1.94
2.00
2.06
4.08
2.02
2.00
5.95
6.05
11
10
9
8
7
6
5
4
3
2
1
ppm

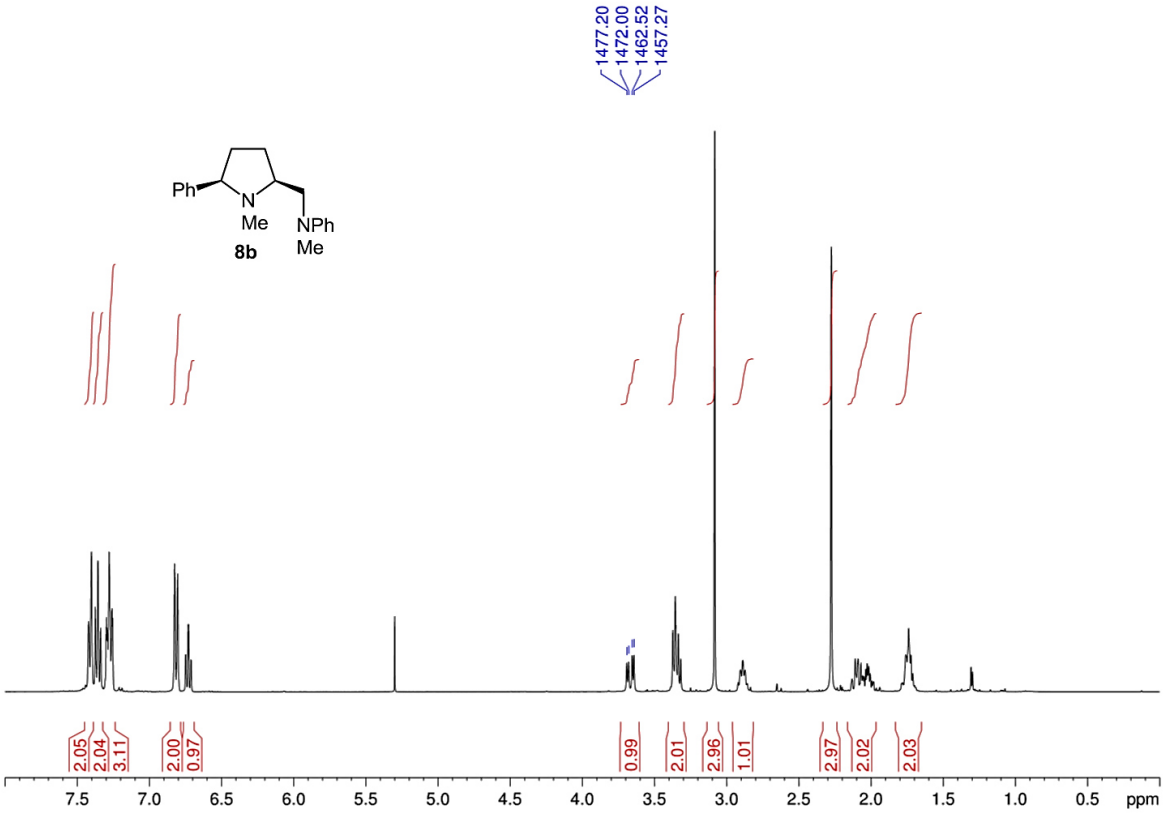

169.82
154.28
137.20
132.80
129.86
129.43
127.25
124.75
123.99
117.01
114.81
69.91
22.06
CO2iPr
OH
M
OH
CO2iPr
(M)-2b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

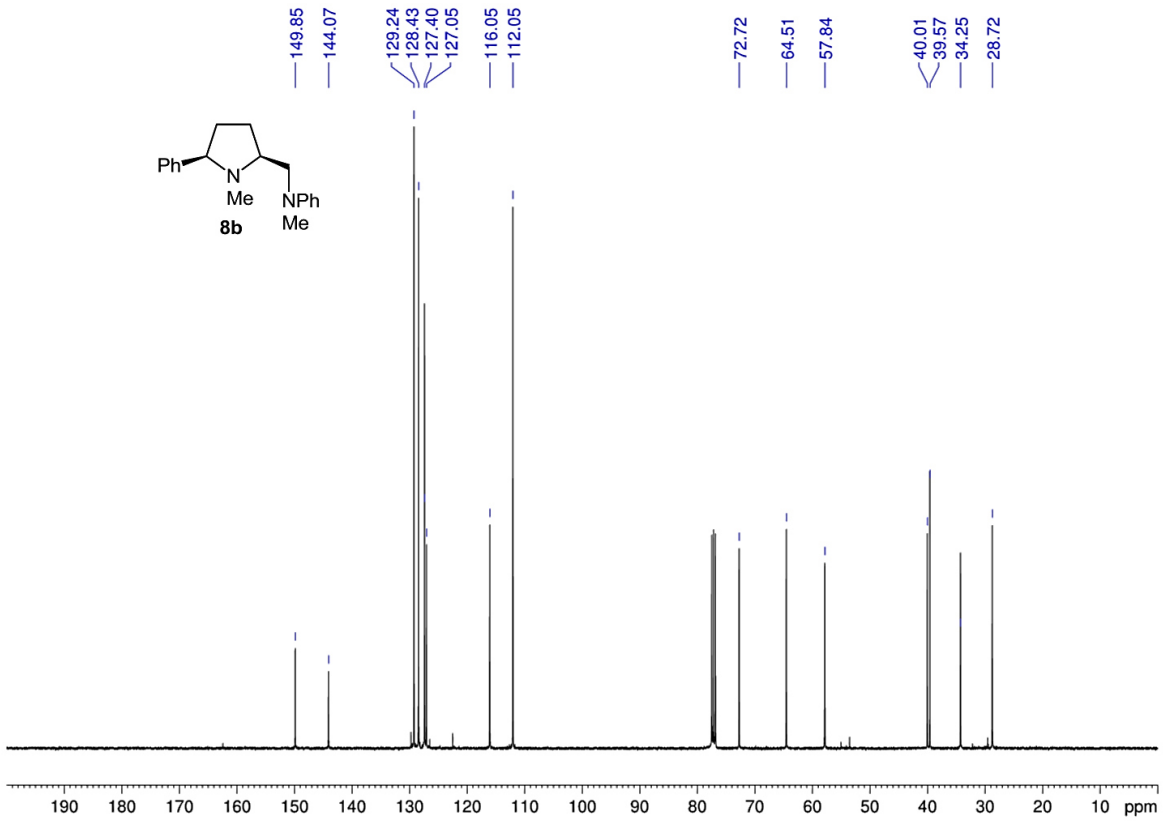
9


1313.87
1307.10
1305.26
1298.82
Ph
N
Me
NtBu
Me
8a
4.01
0.99
1.00
2.97
2.97
3.05
2.06
2.05
9.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

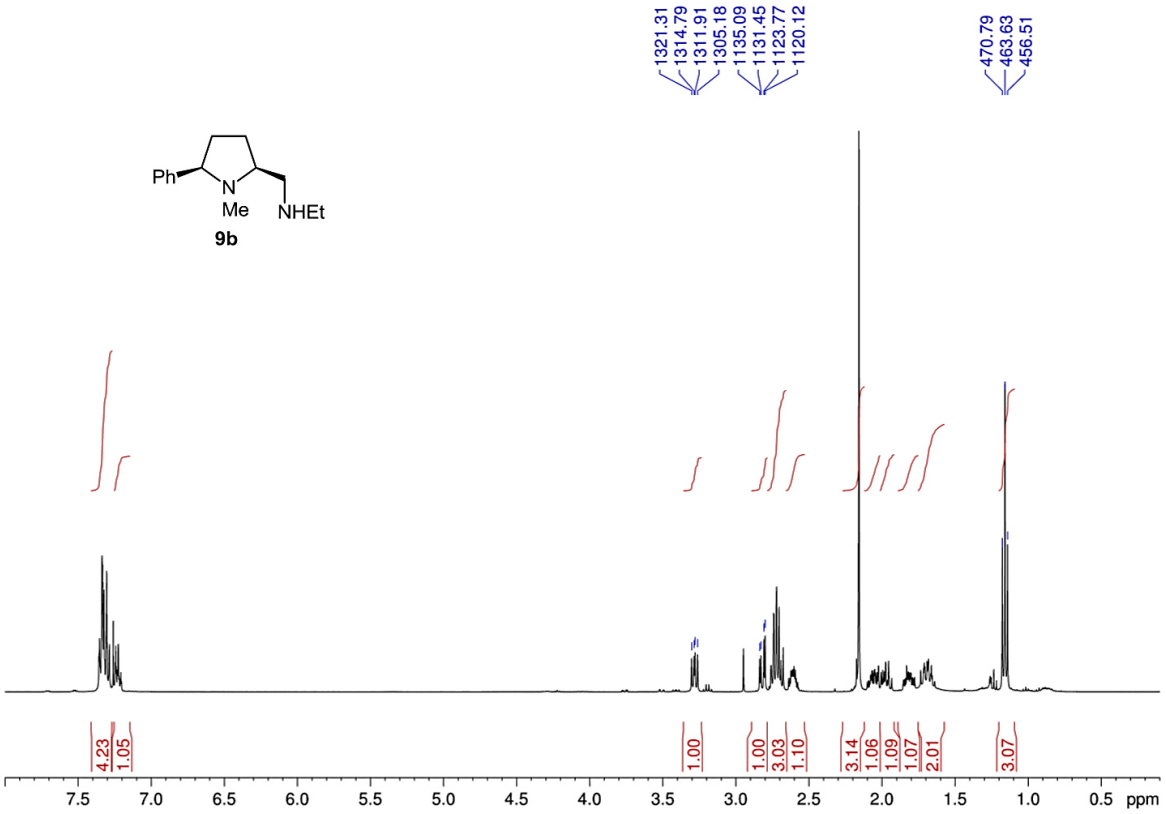

144.18
128.38
127.54
126.98
72.86
66.12
56.83
54.15
39.82
36.33
34.09
29.64
26.24
Ph
N
Me
NtBu
Me
8a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

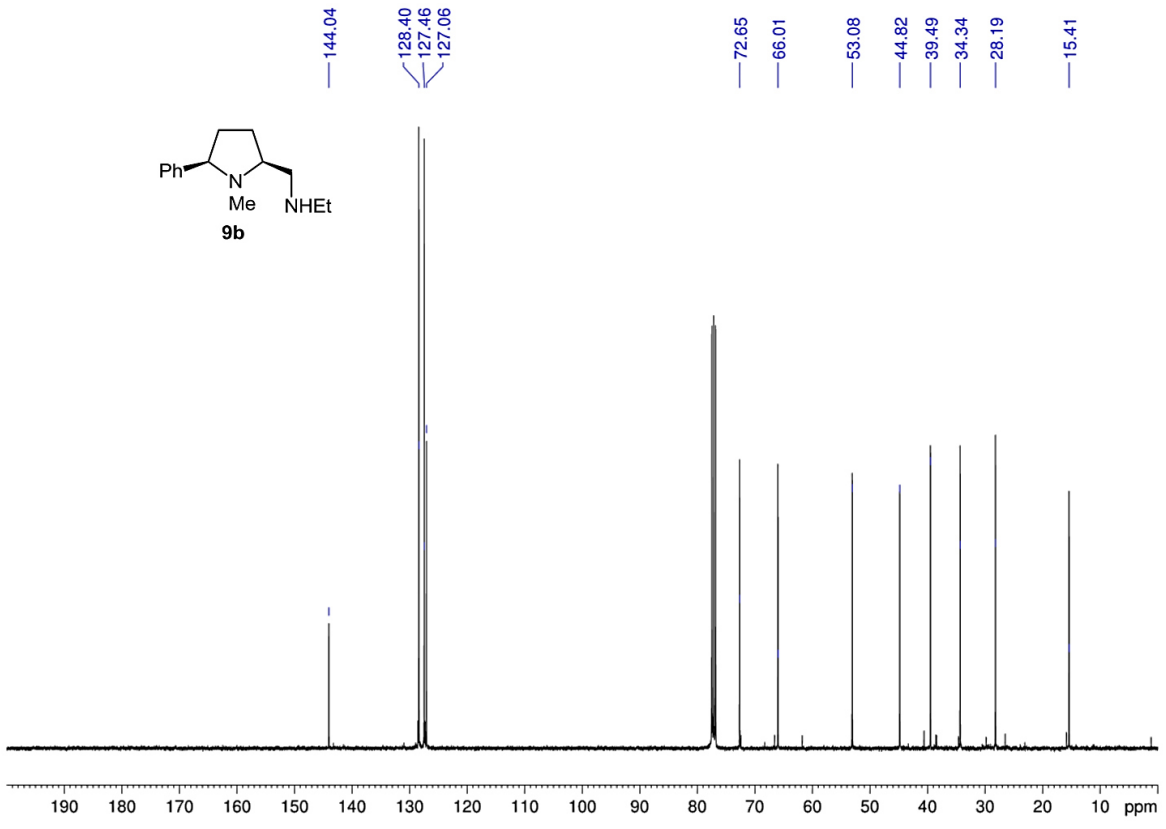
10


1477.20
1472.00
1462.52
1457.27
Ph
N
Me
NPh
Me
8b
2.05
2.04
3.11
2.00
0.97
0.99
2.01
2.96
1.01
2.97
2.02
2.03
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

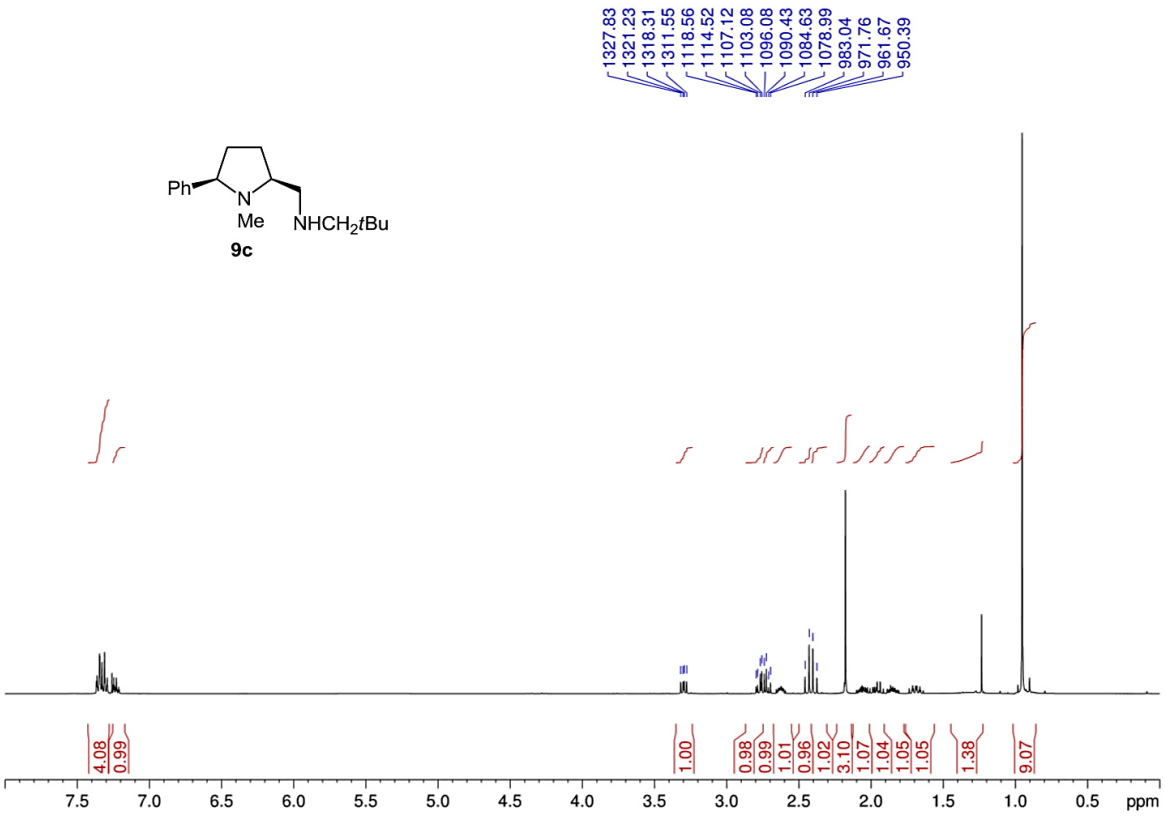

149.85
144.07
129.24
128.43
127.40
127.05
116.05
112.05
72.72
64.51
57.84
40.01
39.57
34.25
28.72
Ph
N
Me
NPh
Me
8b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

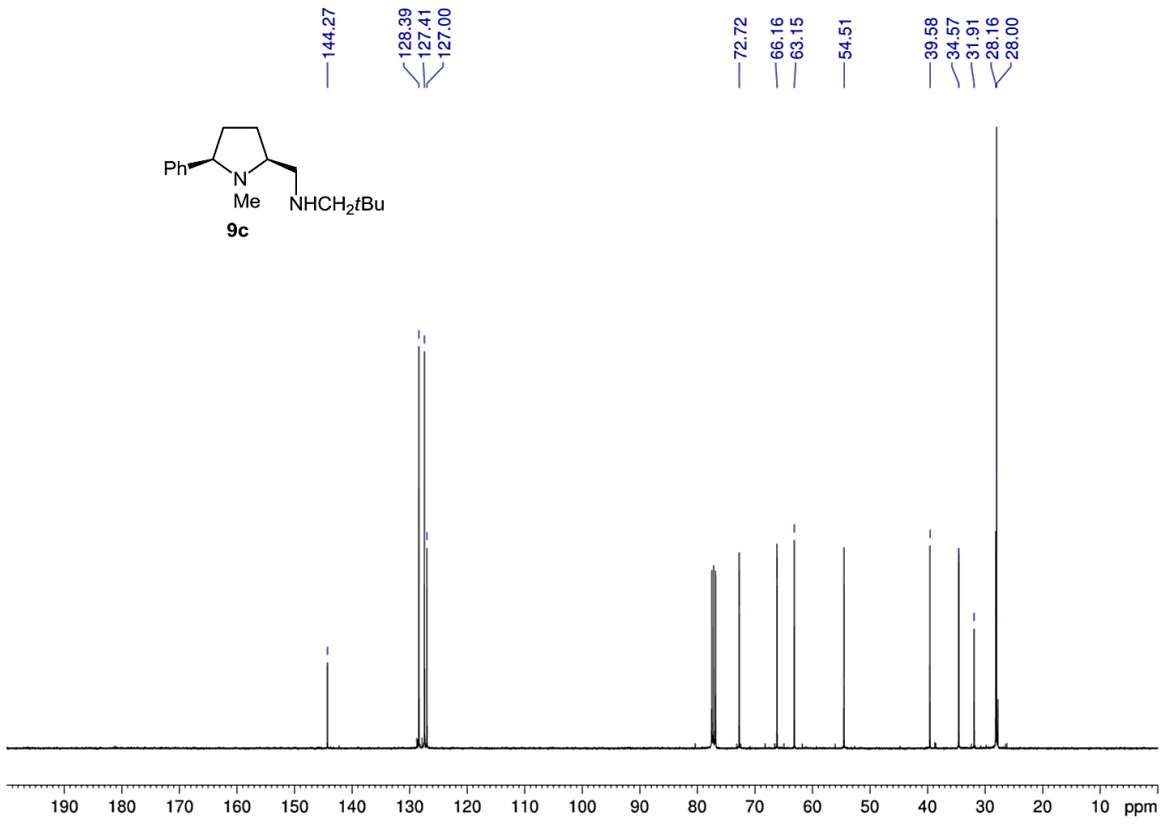
11


1321.31
1314.79
1311.91
1305.18
1135.09
1131.45
1123.77
1120.12
470.79
463.63
456.51
Ph
N
Me
NHEt
9b
4.23
1.05
1.00
1.00
3.03
1.10
3.14
1.06
1.09
1.07
2.01
3.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

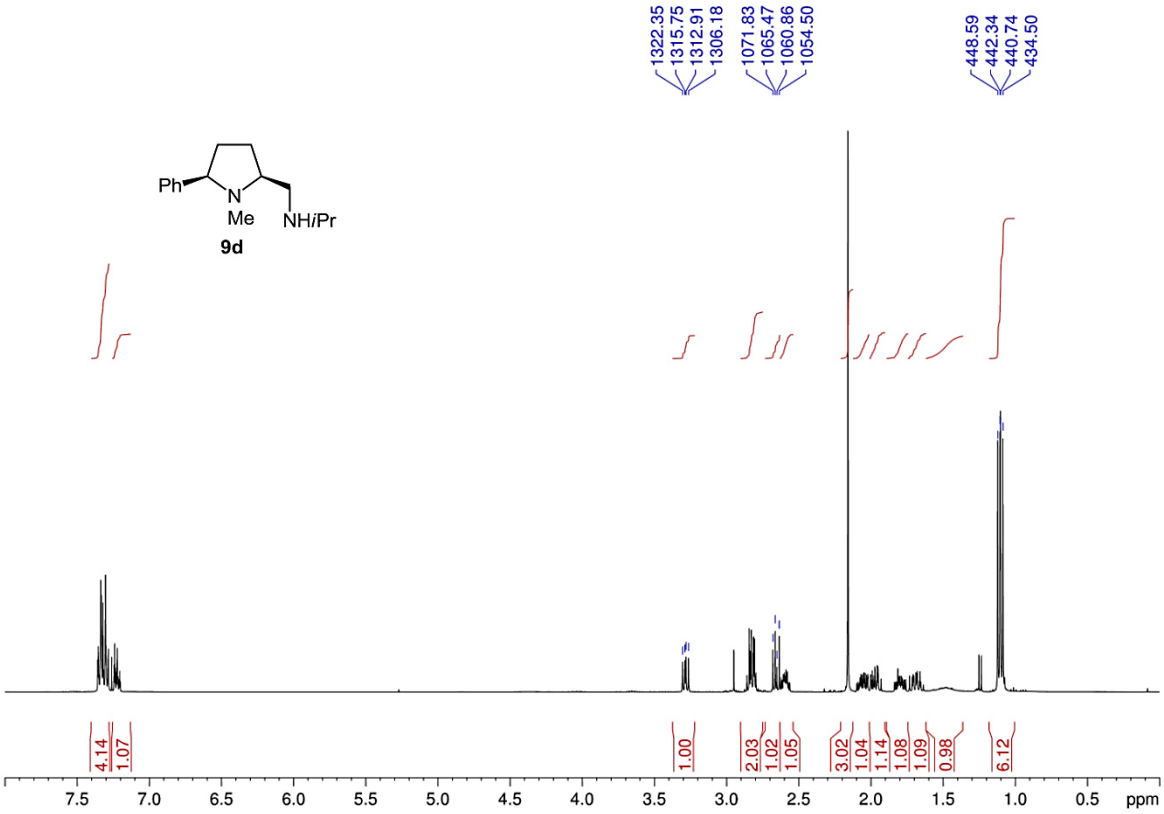

144.04
128.40
127.46
127.06
72.65
66.01
53.08
44.82
39.49
34.34
28.19
15.41
Ph
N
Me
NHEt
9b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

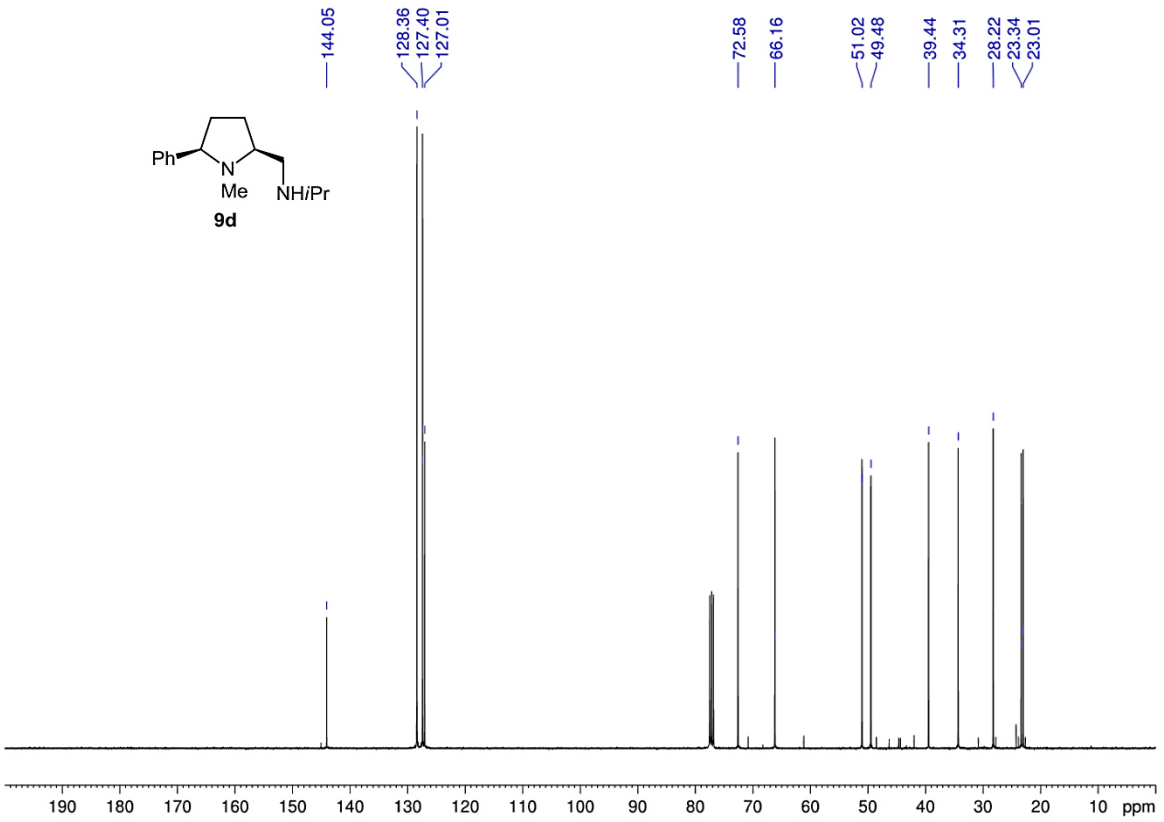
12


1327.83
1321.23
1318.31
1311.55
1118.56
1114.52
1107.12
1103.08
1096.08
1090.43
1084.63
1078.99
983.04
971.76
961.67
950.39
Ph
N
Me
NHCH2tBu
9c
4.08
0.99
1.00
0.98
0.99
1.01
0.96
1.02
3.10
1.07
1.04
1.05
1.05
1.38
9.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

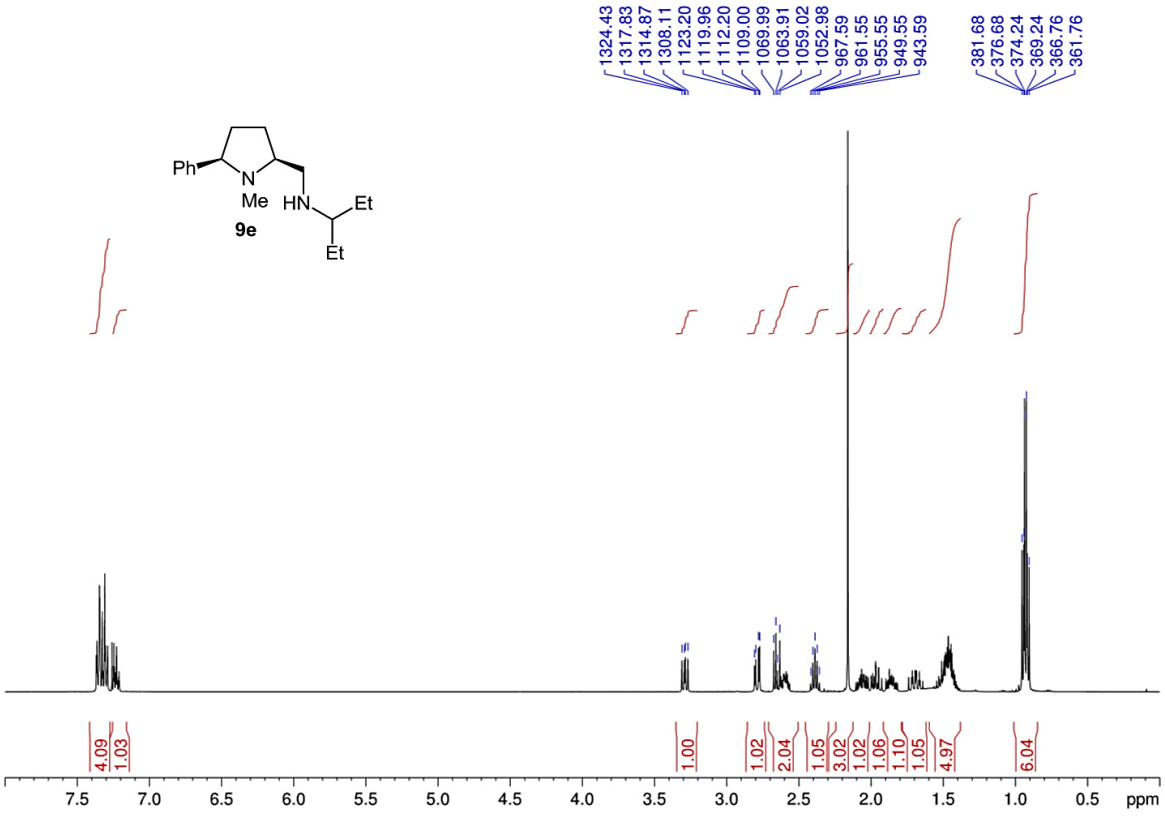

144.27
128.39
127.41
127.00
72.72
66.16
63.15
54.51
39.58
34.57
31.91
28.16
28.00
Ph
N
Me
NHCH2tBu
9c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

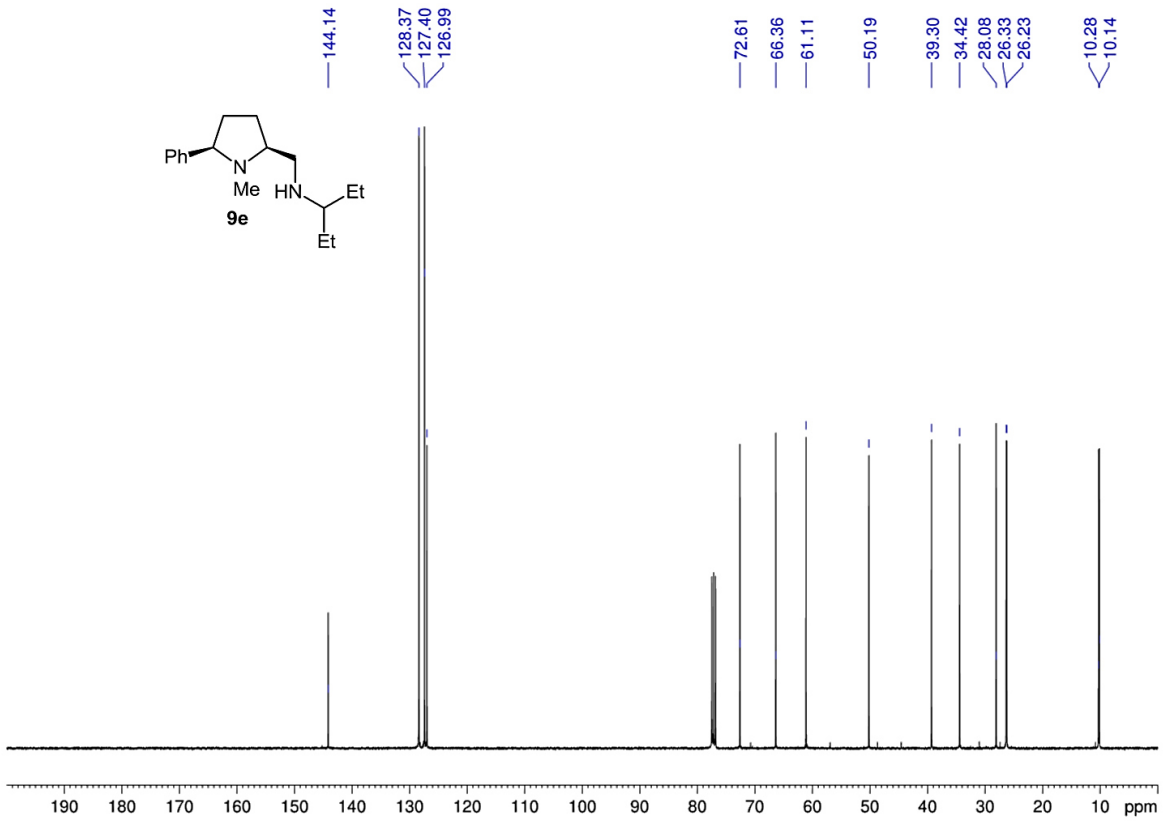
13


1322.35
1315.75
1312.91
1306.18
1071.83
1065.47
1060.86
1054.50
448.59
442.34
440.74
434.50
Ph
N
Me
NH*i*Pr
9d
4.14
1.07
1.00
2.03
1.02
1.05
3.02
1.04
1.14
1.08
1.09
0.98
6.12
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

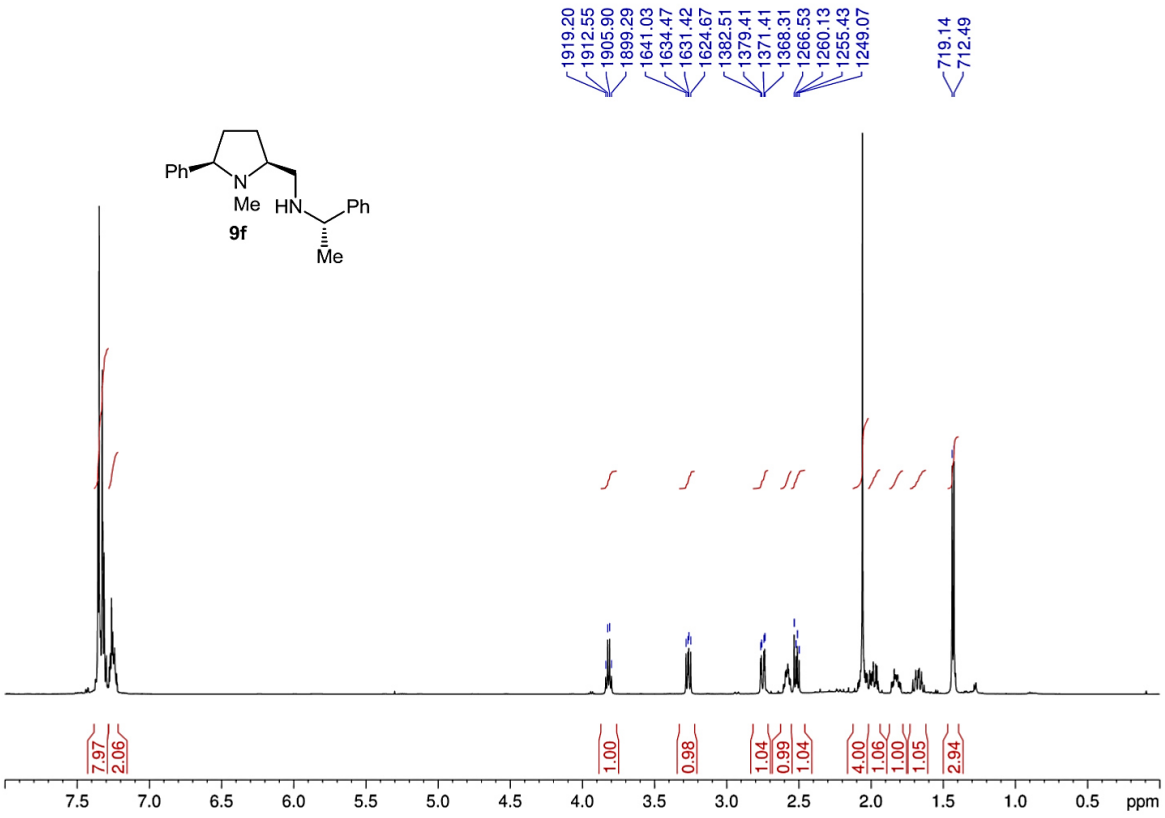

144.05
128.36
127.40
127.01
72.58
66.16
51.02
49.48
39.44
34.31
28.22
23.34
23.01
Ph
N
Me
NH*i*Pr
9d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

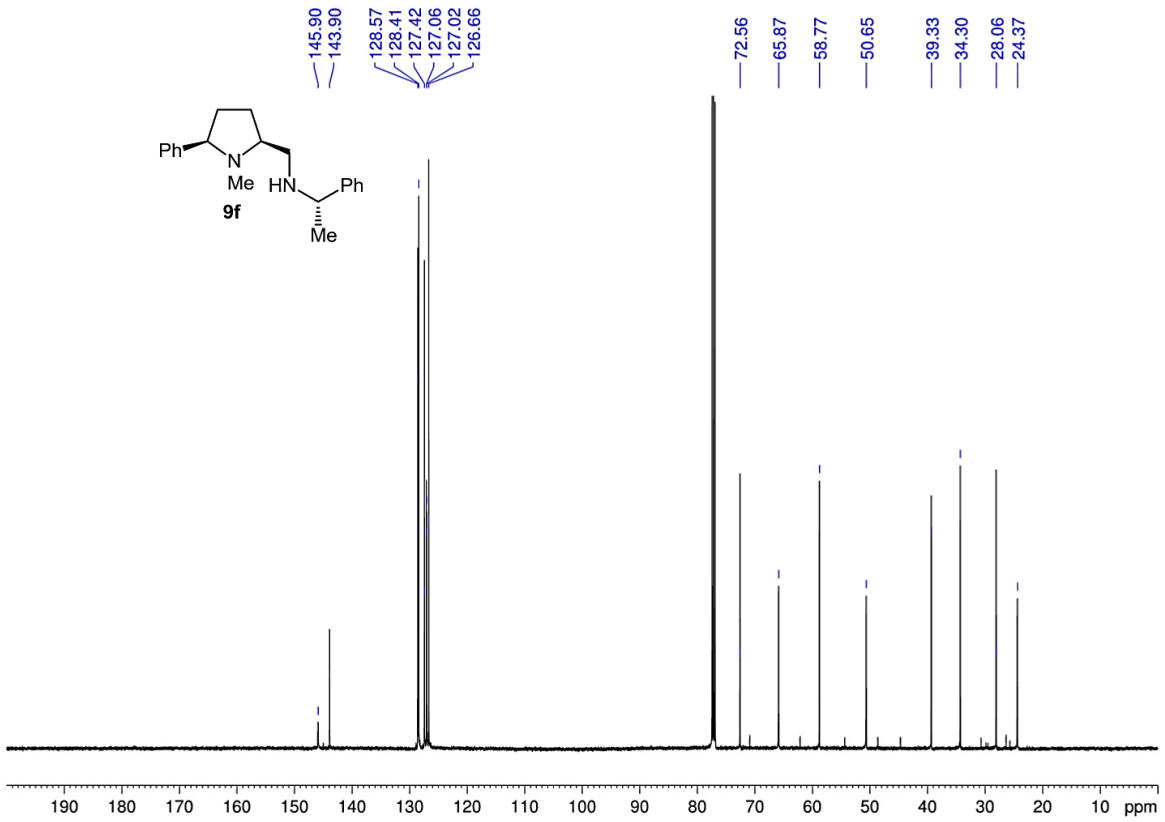
14


1324.43
1317.83
1314.87
1308.11
1123.20
1119.96
1112.20
1109.00
1069.99
1063.91
1059.02
1052.98
967.59
961.55
955.55
949.55
943.59
381.68
376.68
374.24
369.24
366.76
361.76
Ph
N
Me
HN
Et
Et
9e
4.09
1.03
1.00
1.02
2.04
1.05
3.02
1.02
1.06
1.10
1.05
4.97
6.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

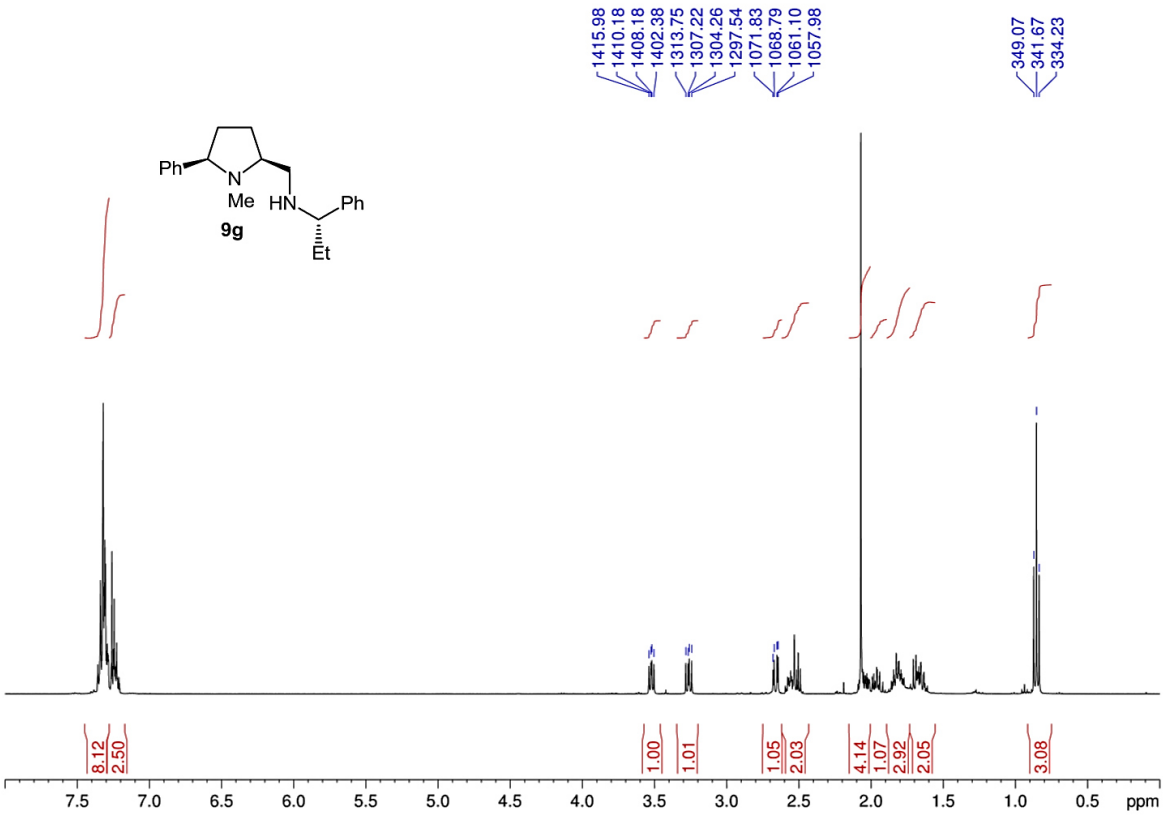

144.14
128.37
127.40
126.99
72.61
66.36
61.11
50.19
39.30
34.42
28.08
26.33
26.23
10.28
10.14
Ph
N
Me
HN
Et
Et
9e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

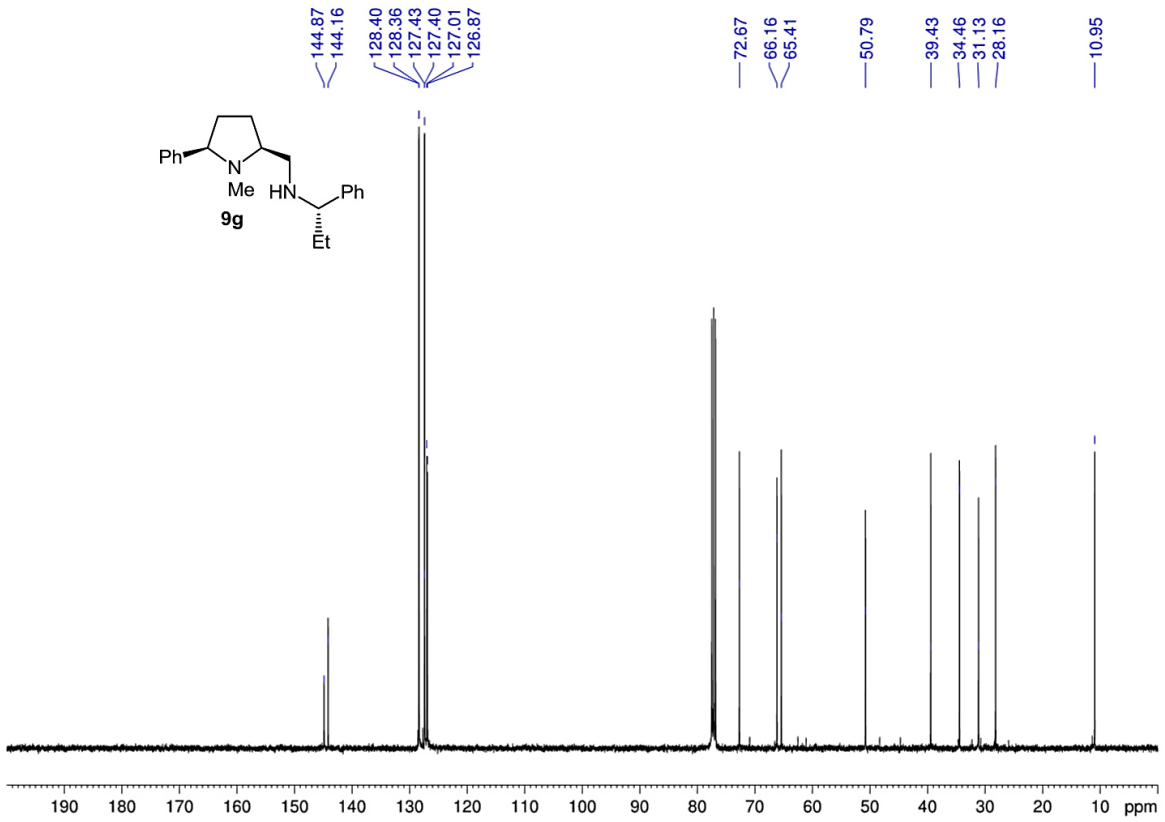
15


1919.20
1912.55
1905.90
1899.29
1641.03
1634.47
1631.42
1624.67
1382.51
1379.41
1371.41
1368.31
1266.53
1260.13
1255.43
1249.07
719.14
712.49
Ph
N
Me
HN
Ph
Me
9f
7.97
2.06
1.00
0.98
1.04
0.99
1.04
4.00
1.06
1.00
1.05
2.94
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

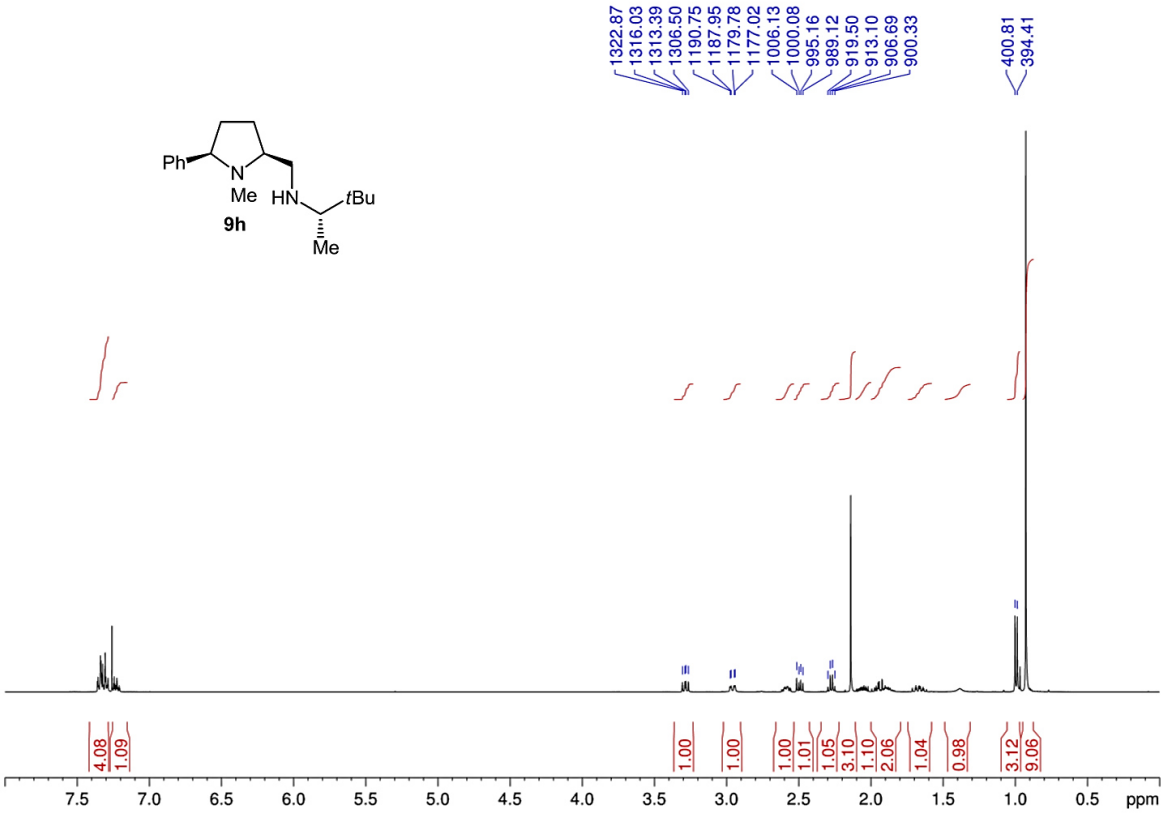

145.90
143.90
128.57
128.41
127.42
127.06
127.02
126.66
72.56
65.87
58.77
50.65
39.33
34.30
28.06
24.37
Ph
N
Me
HN
Ph
Me
9f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

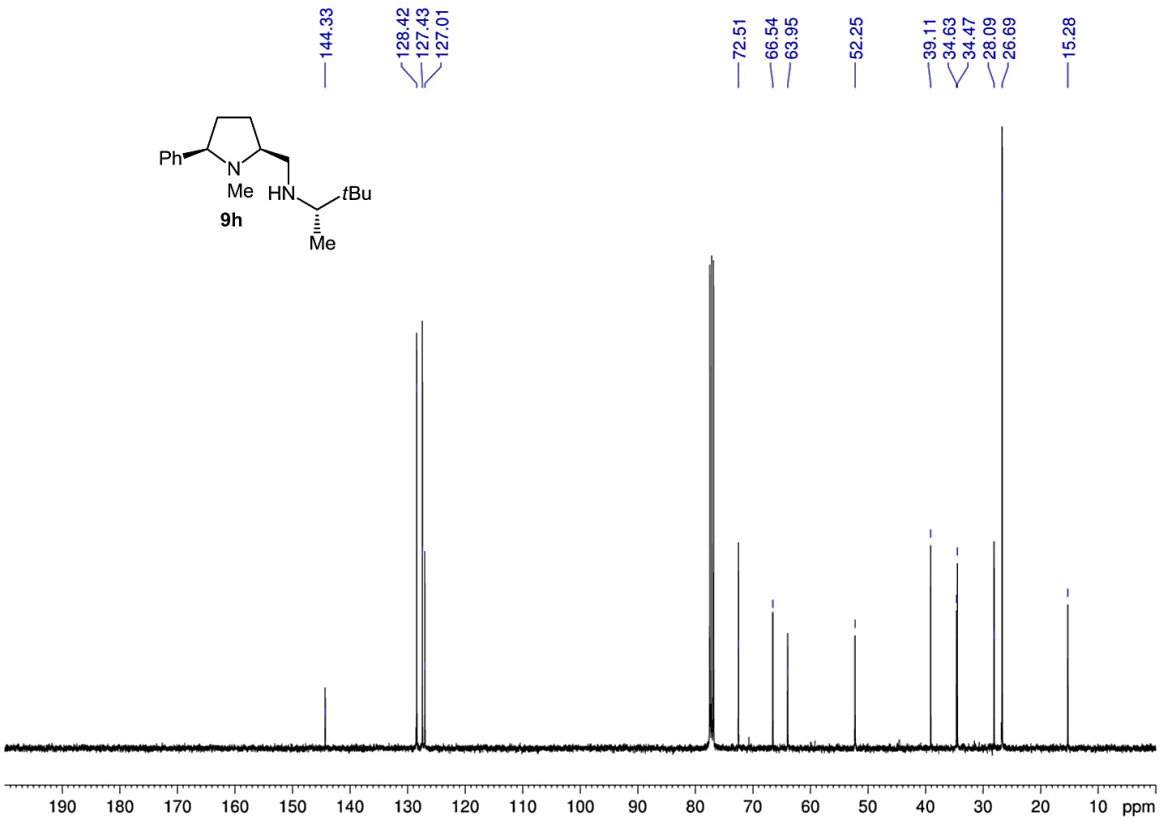
16


1415.98
1410.18
1408.18
1402.38
1313.75
1307.22
1304.26
1297.54
1071.83
1068.79
1061.10
1057.98
349.07
341.67
334.23
Ph
N
Me
HN
Ph
Et
9g
8.12
2.50
1.00
1.01
1.05
2.03
4.14
1.07
2.92
2.05
3.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

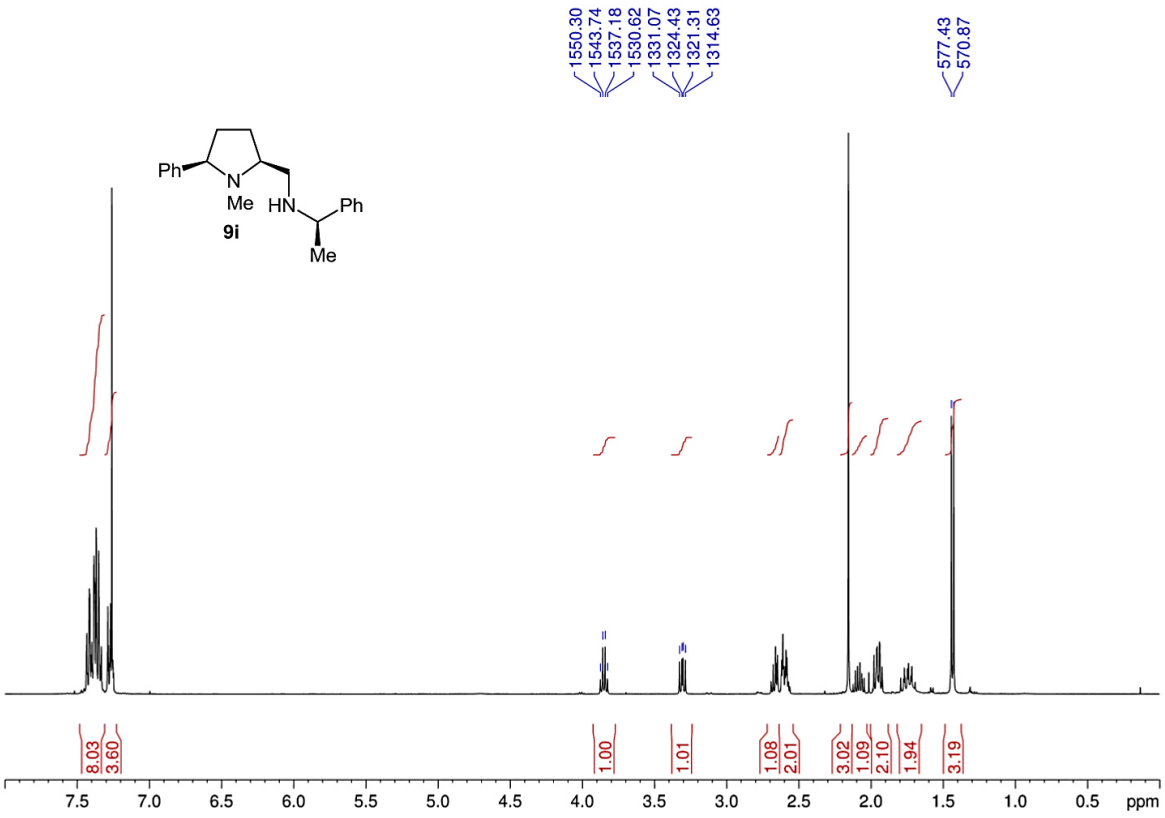

144.87
144.16
128.40
128.36
127.43
127.40
127.01
126.87
72.67
66.16
65.41
50.79
39.43
34.46
31.13
28.16
10.95
Ph
N
Me
HN
Ph
Et
9g
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

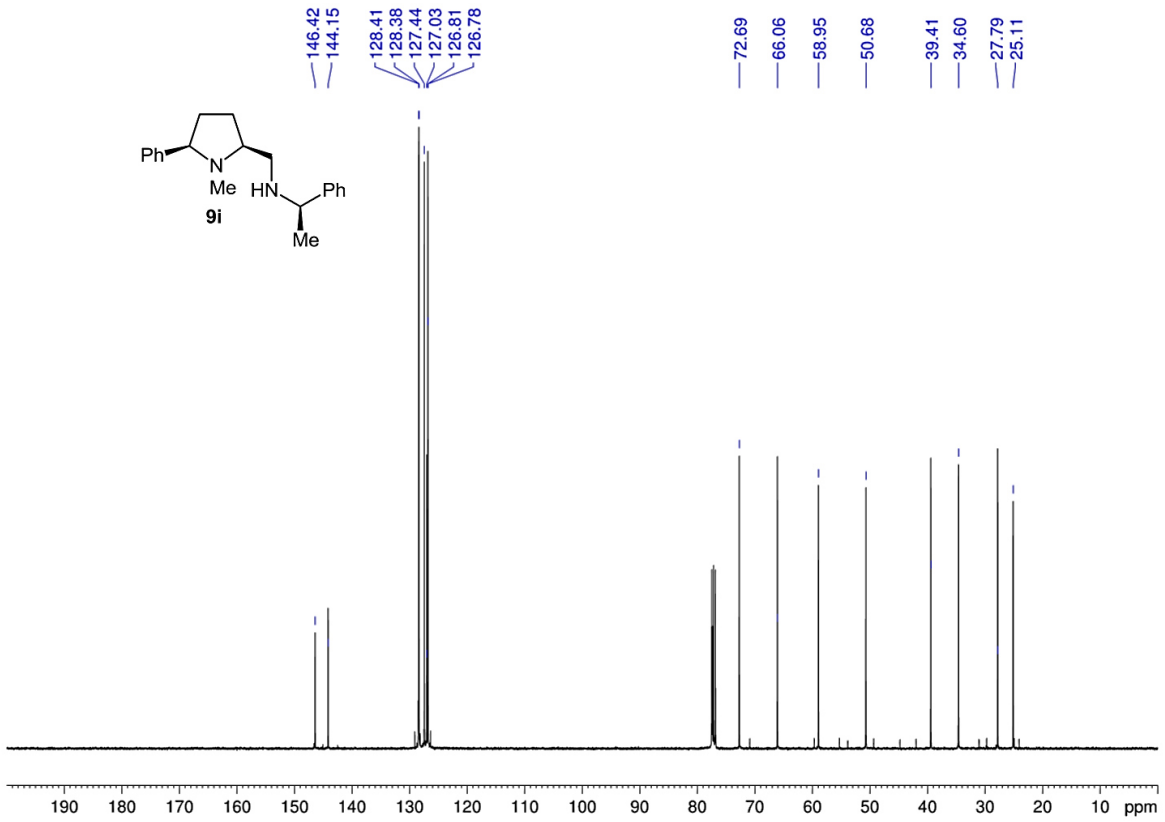
17

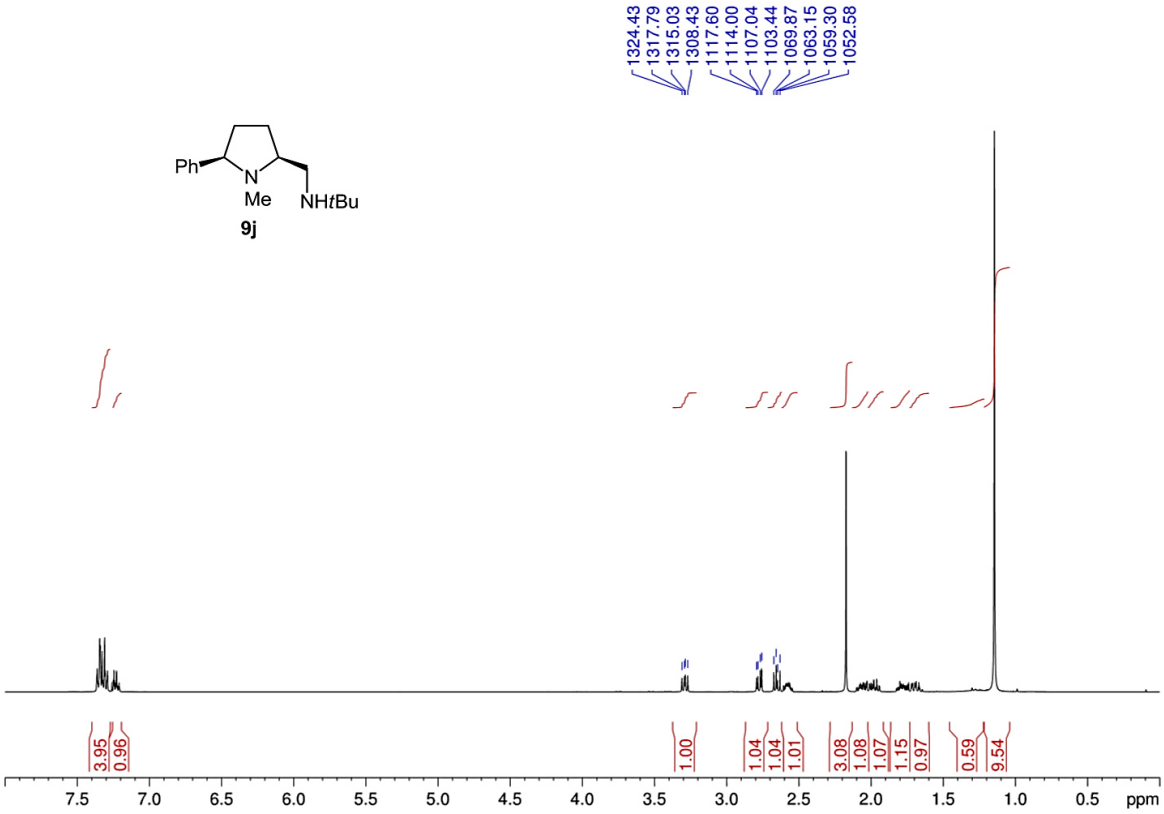

1322.87
1316.03
1313.39
1306.50
1190.75
1187.95
1179.78
1177.02
1006.13
1000.08
995.16
989.12
919.50
913.10
906.69
900.33
400.81
394.41
Ph
N
Me
HN
tBu
Me
9h
4.08
1.09
1.00
1.00
1.00
1.01
1.05
3.10
1.10
2.06
1.04
0.98
3.12
9.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

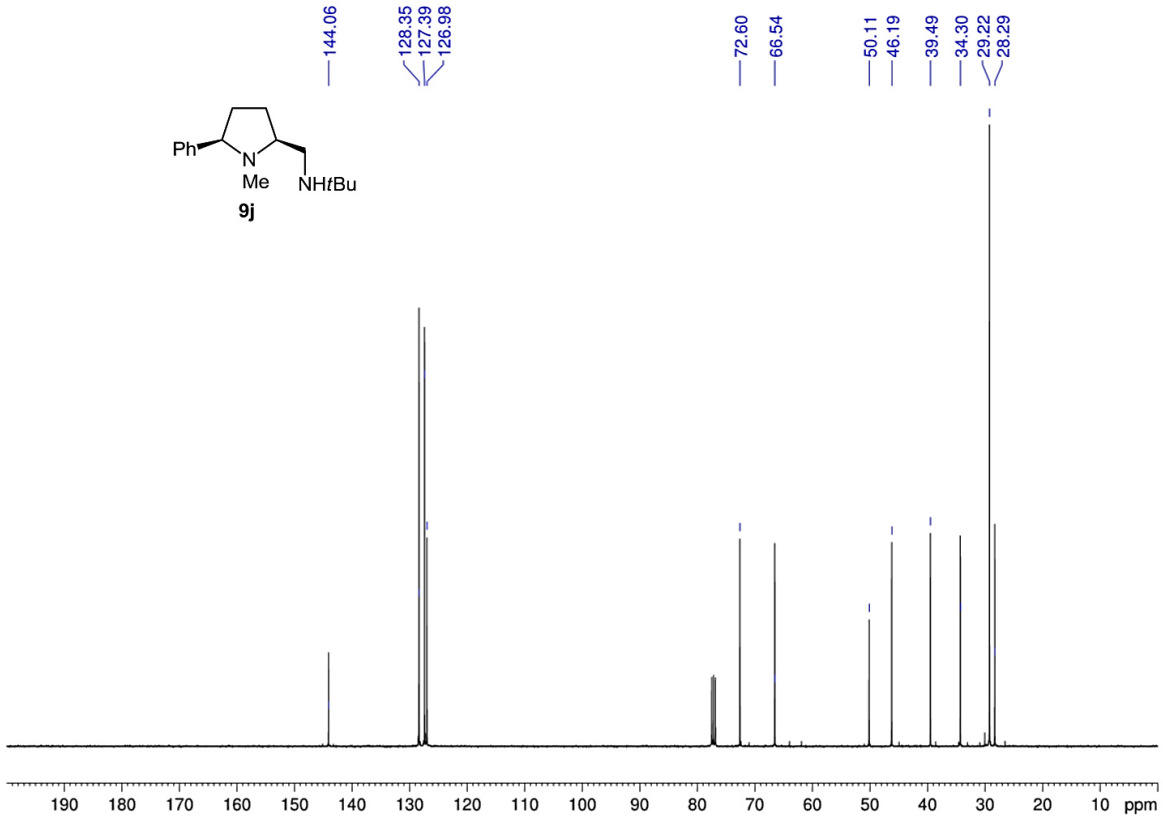

144.33
128.42
127.43
127.01
72.51
66.54
63.95
52.25
39.11
34.63
34.47
28.09
26.69
15.28
Ph
N
Me
HN
tBu
Me
9h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

18

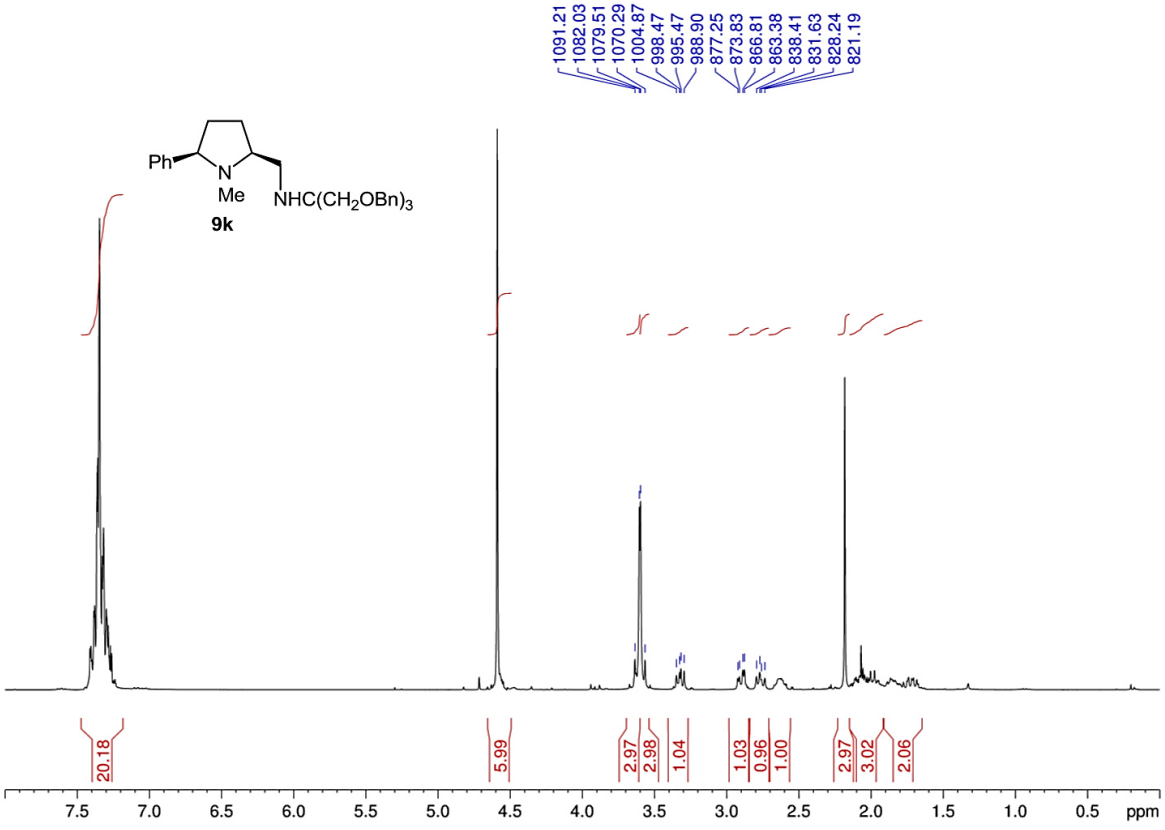

1550.30
1543.74
1537.18
1530.62
1331.07
1324.43
1321.31
1314.63
577.43
570.87
Ph
N
Me
HN
Ph
Me
9i
8.03
3.60
1.00
1.01
1.08
2.01
3.02
1.09
2.10
1.94
3.19
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

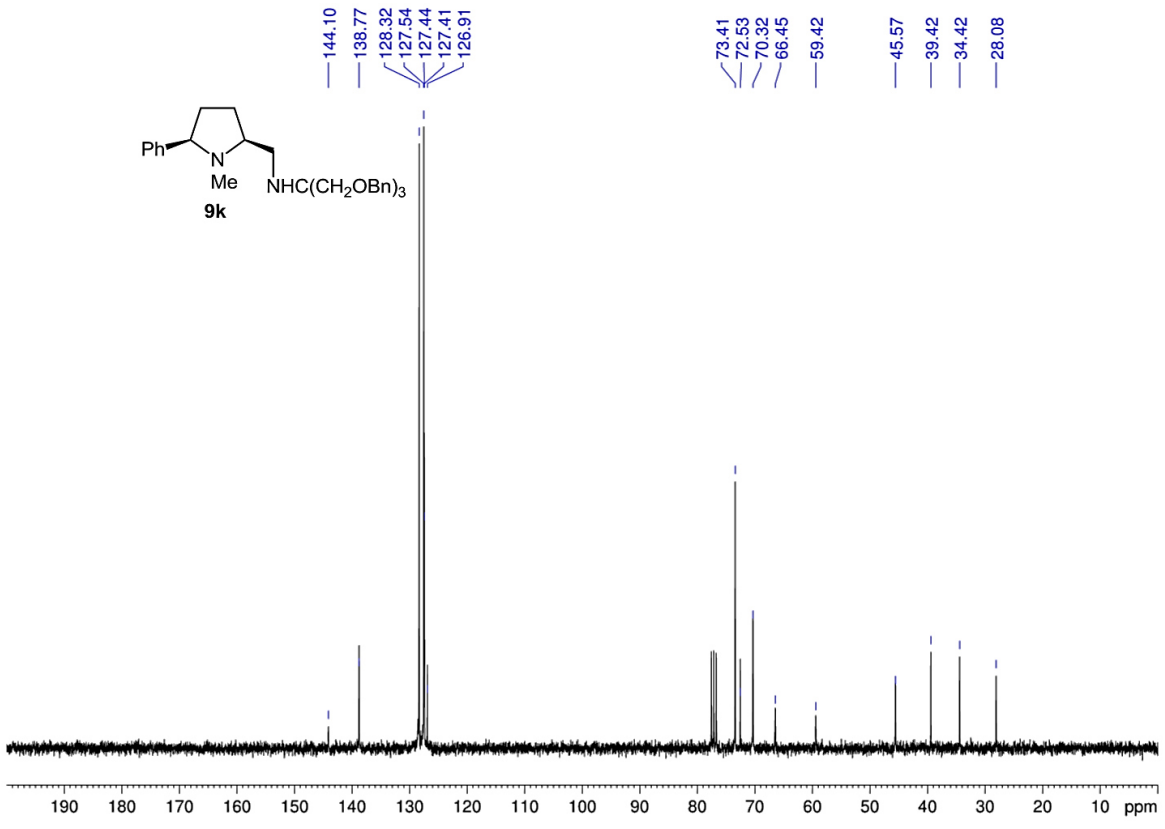

146.42
144.15
128.41
128.38
127.44
127.03
126.81
126.78
72.69
66.06
58.95
50.68
39.41
34.60
27.79
25.11
Ph
N
Me
HN
Ph
Me
9i
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


1324.43
1317.79
1315.03
1308.43
1117.60
1114.00
1107.04
1103.44
1069.87
1063.15
1059.30
1052.58
Ph
N
Me
NHtBu
9j
3.95
0.96
1.00
1.04
1.04
1.01
3.08
1.08
1.07
1.15
0.97
0.59
9.54
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

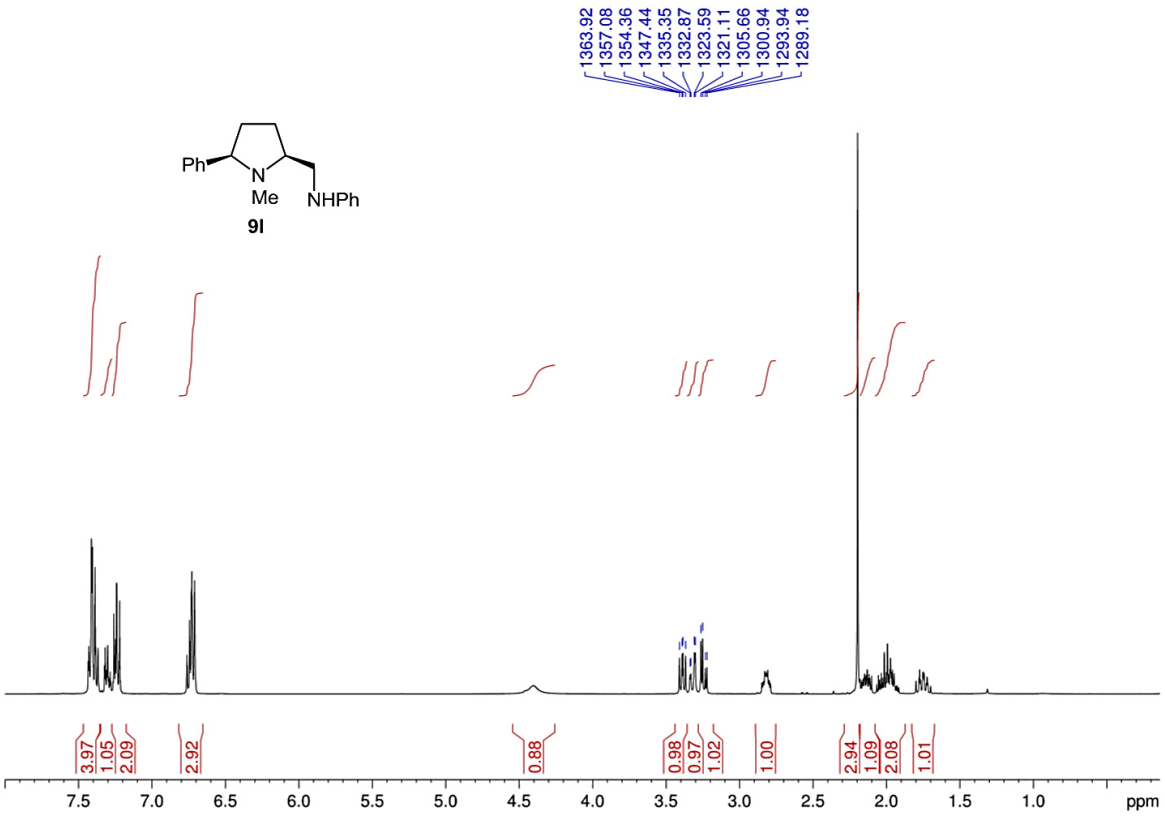

144.06
128.35
127.39
126.98
72.60
66.54
50.11
46.19
39.49
34.30
29.22
28.29
Ph
N
Me
NHtBu
9j
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

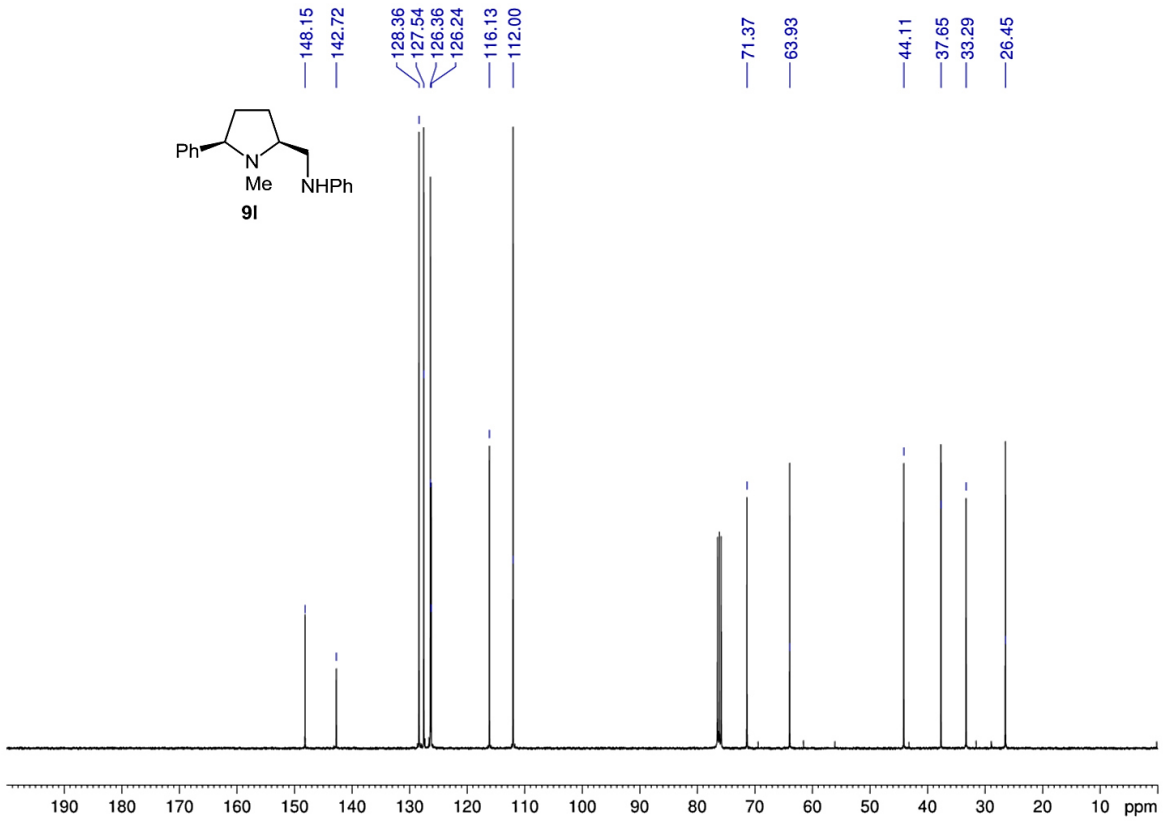
20


1091.21
1082.03
1079.51
1070.29
1004.87
998.47
995.47
988.90
877.25
873.83
866.81
863.38
838.41
831.63
828.24
821.19
Ph
N
Me
NHC(CH2OBn)3
9k
20.18
5.99
2.97
2.98
1.04
1.03
0.96
1.00
2.97
3.02
2.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


144.10
138.77
128.32
127.54
127.44
127.41
126.91
73.41
72.53
70.32
66.45
59.42
45.57
39.42
34.42
28.08
Ph
N
Me
NHC(CH2OBn)3
9k
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

21


1363.92
1357.08
1354.36
1347.44
1335.35
1332.87
1323.59
1321.11
1305.66
1300.94
1293.94
1289.18
Ph
N
Me
NHPh
9l
3.97
1.05
2.09
2.92
0.88
0.98
0.97
1.02
1.00
2.94
1.09
2.08
1.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

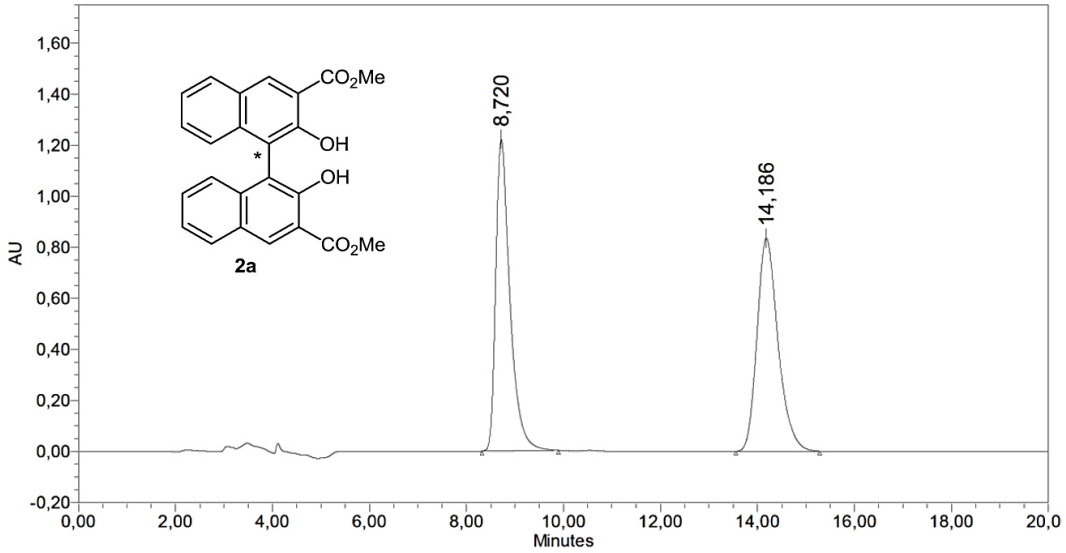

148.15
142.72
128.36
127.54
126.36
126.24
116.13
112.00
71.37
63.93
44.11
37.65
33.29
26.45
Ph
N
Me
NHPh
9l
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

3. Copies of HPLC spectra

The HPLC spectra of binaphthol esters **2a**–**2d** are listed in numerical order.

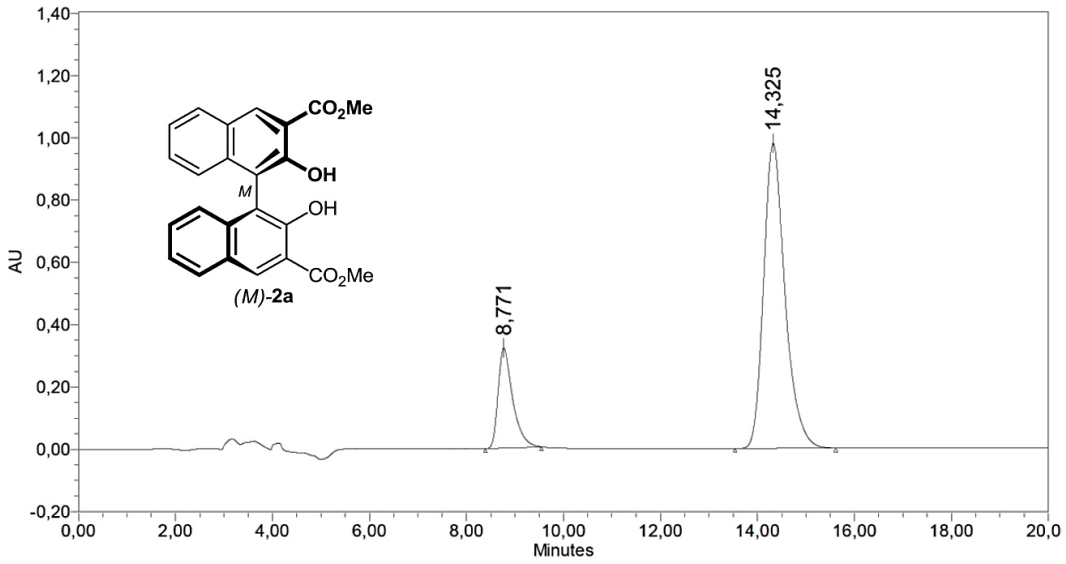
2a (racemic sample):

HPLC conditions: Chiralpak AD-H, *n*-hexane/*i*PrOH 80:20, 1.0 mL/min, 254 nm.



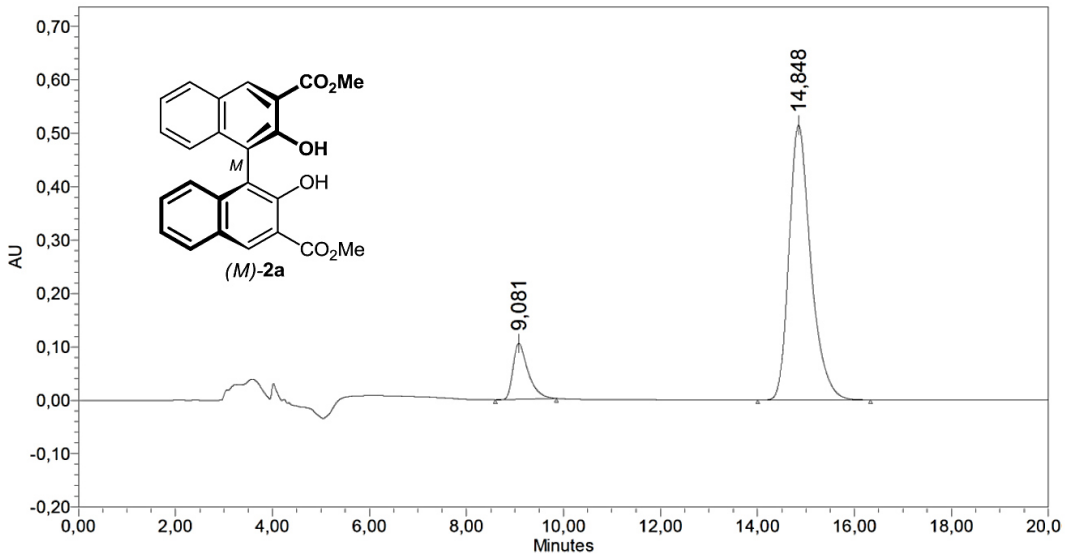
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	8,72	8,33	9,90	1222414	59,44	24738536	49,64
2	14,19	13,56	15,28	834282	40,56	25092940	50,36

(*M*)-**2a** (64% ee, see Table 2, entry 19):



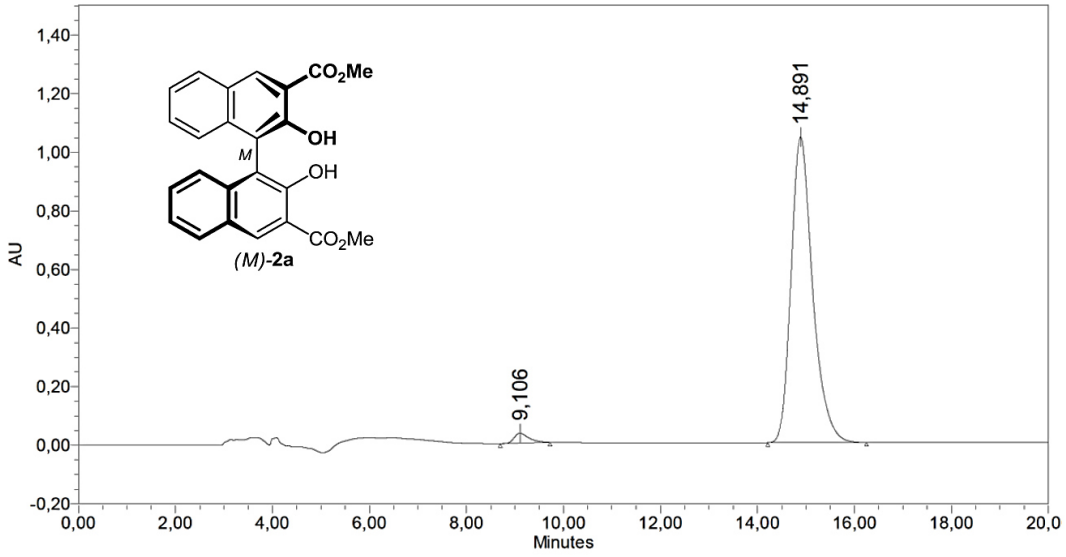
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	8,77	8,39	9,55	321613	24,72	6667356	18,20
2	14,32	13,54	15,62	979449	75,28	29975097	81,80

(*M*)-**2a** (75% ee, see Table 2, entry 16):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,08	8,60	9,86	104838	16,91	2245076	12,27
2	14,85	14,01	16,33	514984	83,09	16056029	87,73

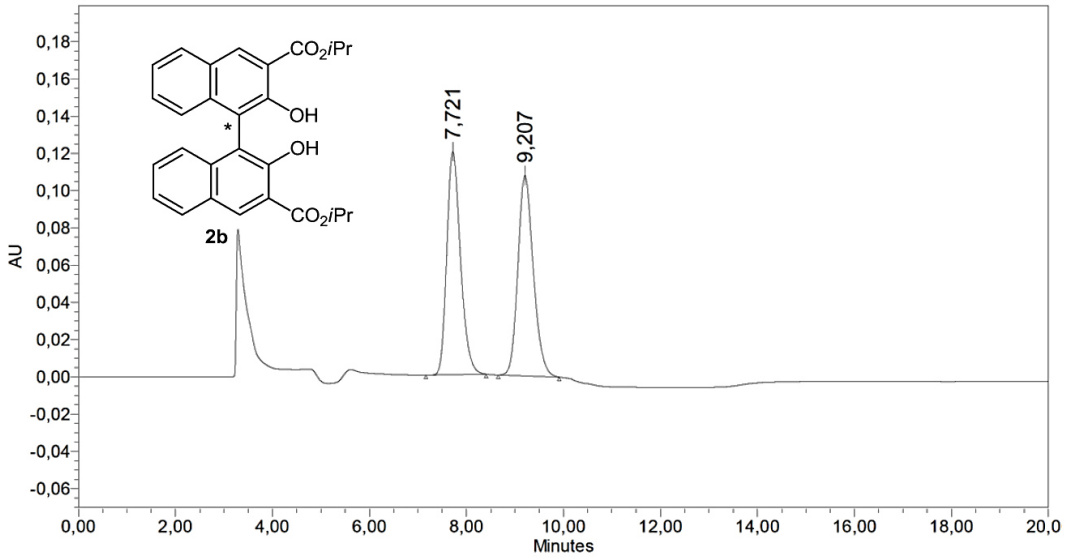
(*M*)-**2a** (96% ee, see Table 2, entry 1):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,11	8,70	9,73	34162	3,17	712273	2,16
2	14,89	14,22	16,25	1042945	96,83	32296852	97,84

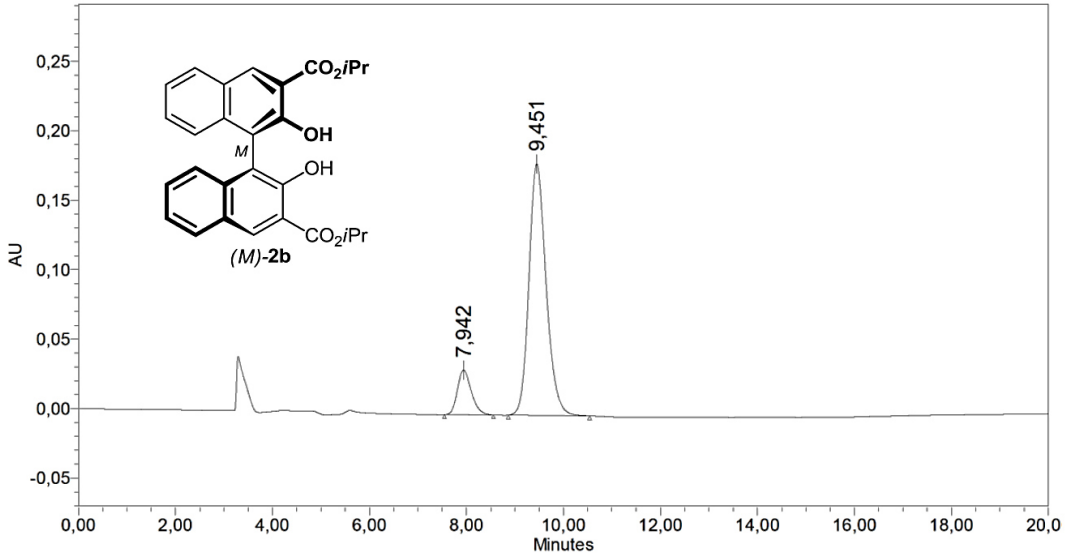
2b (racemic sample):

HPLC conditions: Chiralpak AD-H, *n*-hexane/*i*PrOH 98:02, 1.0 mL/min, 254 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	7,72	7,17	8,41	119771	52,65	2345536	49,68
2	9,21	8,66	9,92	107728	47,35	2376075	50,32

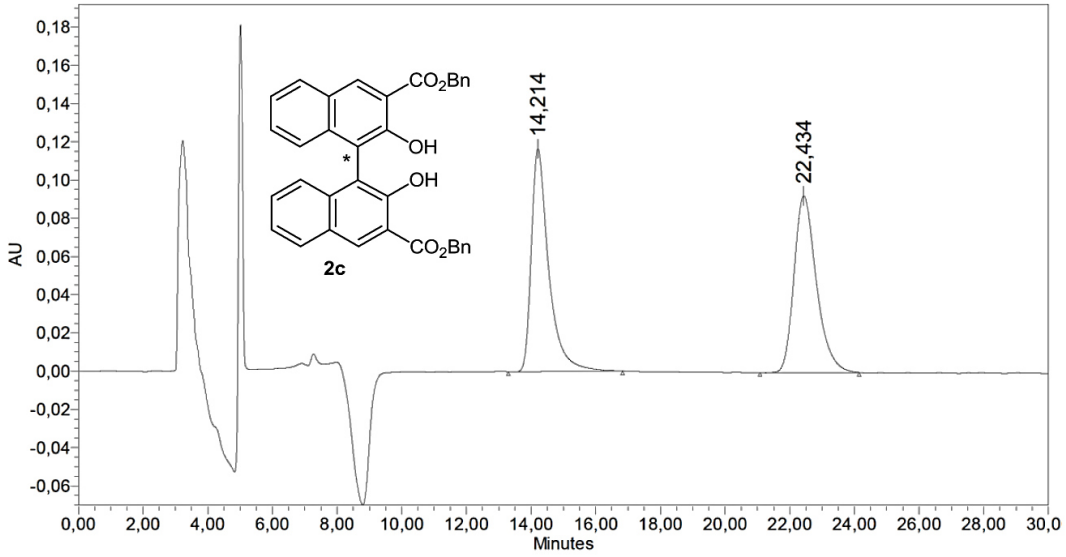
(*M*)-**2b** (75% ee, see Table 6, entry 6):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	7,94	7,55	8,56	32123	15,08	635393	12,53
2	9,45	8,87	10,54	180955	84,92	4435080	87,47

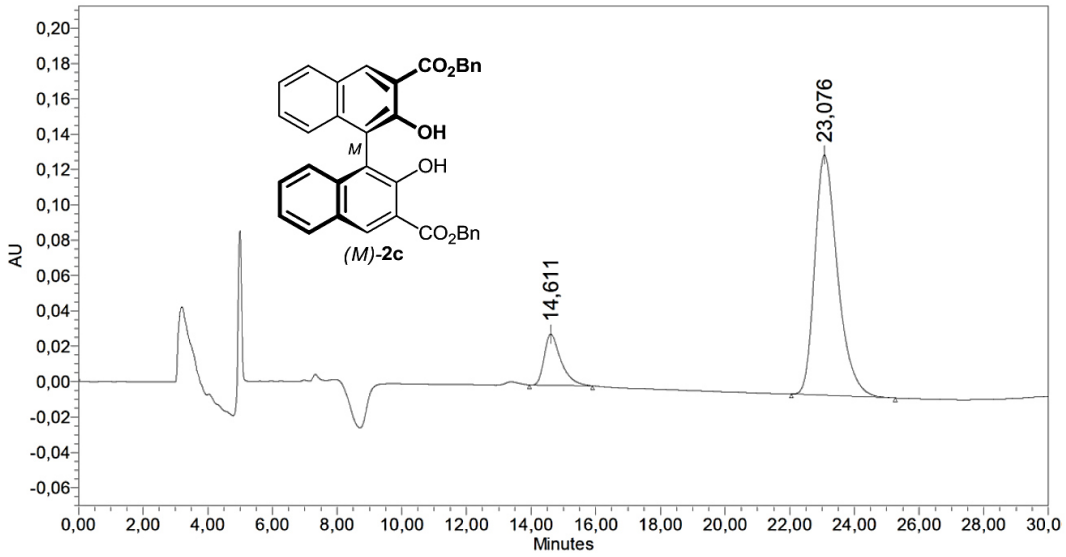
2c (racemic sample):

HPLC conditions: Chiralpak AD-H, *n*-hexane/*i*PrOH 90:10, 1.0 mL/min, 254 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	14,21	13,30	16,83	116514	55,77	4335003	49,44
2	22,43	21,08	24,15	92415	44,23	4433449	50,56

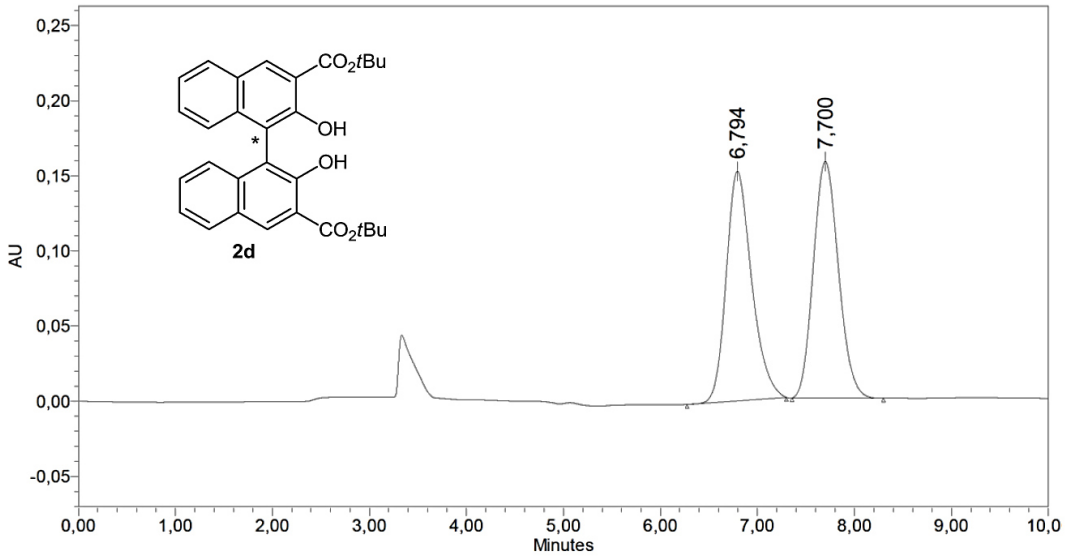
(*M*)-**2c** (73% ee, see Table 6, entry 3):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	14,61	13,95	15,90	28958	17,56	1031877	13,39
2	23,08	22,05	25,27	135948	82,44	6673526	86,61

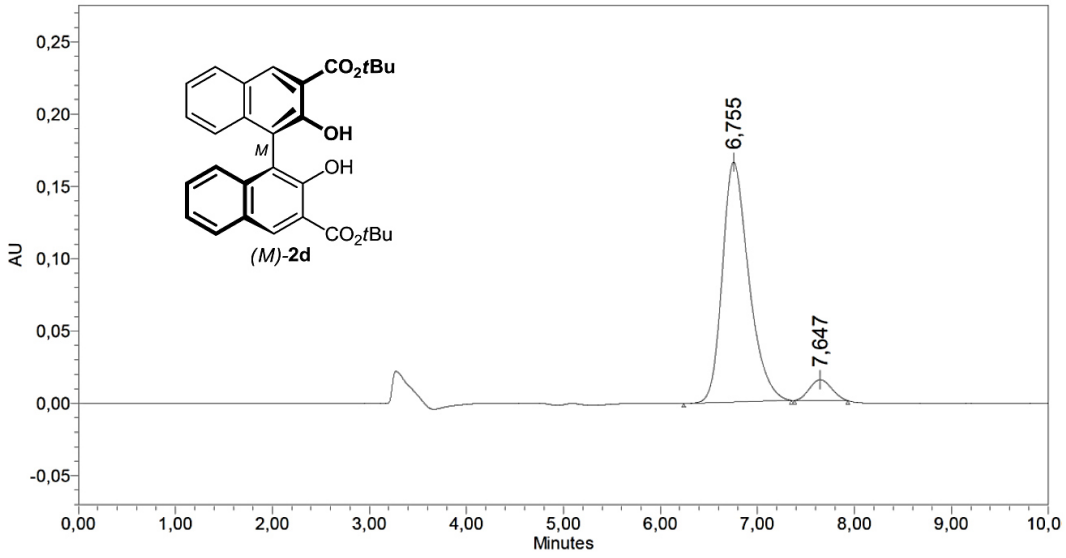
2d (racemic sample):

HPLC conditions: Chiralpak AD-H, *n*-hexane/*i*PrOH 98:02, 1.0 mL/min, 254 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	6,79	6,28	7,30	152769	49,25	2781976	49,62
2	7,70	7,36	8,30	157444	50,75	2824828	50,38

(*M*)-**2d** (87% ee, see Table 6, entry 9):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	6,76	6,24	7,35	165996	92,04	3139680	93,28
2	7,65	7,38	7,93	14360	7,96	226201	6,72

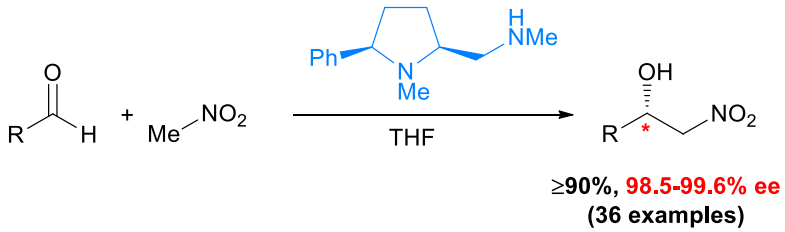
6.3 (2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a chiral diamine ligand for copper(II)-catalysed Henry reactions with superb enantiocontrol

Dagmar Scharnagel,‡ Felix Prause,‡ Johannes Kaldun,‡ Robert G. Haase and Matthias Breuning*

Organic Chemistry Laboratory, University of Bayreuth, Universitätsstraße 30, 95447 Bayreuth, Germany.

‡ These authors contributed equally to this work.

* Matthias.Breuning@uni-bayreuth.de



Published in: *Chem. Commun.* **2014**, *50*, 6623–6625.

http://pubs.rsc.org/en/content/articlelanding/2014/cc/c4cc02429j#!divAbstract

doi: 10.1039/C4CC02429J

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

(2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a chiral diamine ligand for copper(II)-catalysed Henry reactions with superb enantiocontrol†

Cite this: *Chem. Commun.*, 2014, 50, 6623

Received 2nd April 2014,
Accepted 1st May 2014

DOI: 10.1039/c4cc02429j

www.rsc.org/chemcomm

Dagmar Scharnagel,‡ Felix Prause,‡ Johannes Kaldun,‡ Robert G. Haase and Matthias Breuning*

A *cis*-2-aminomethyl-5-phenylpyrrolidine, which is easily available from methyl Boc-L-pyroglutamate, was found to be a highly efficient chiral ligand for Cu(II)-catalysed Henry reactions. Excellent yields (>90%) and superb levels of enantiocontrol (98.5–99.6% ee) were reached with aromatic, heteroaromatic, vinylic, and aliphatic aldehydes (36 examples).

The Henry (or nitroaldol) reaction is a powerful tool for C–C bond formation, because it permits rapid access to valuable synthetic intermediates such as 1,2-amino alcohols and α-hydroxy acids.[1] Tremendous advances have been made over the last two decades in the development of enantioselective versions of this reaction.[2] Among the many highly efficient systems based on heterobimetal,[3] transition metal,[4–6] organo[7] and enzyme[8] catalysis, chirally modified copper complexes have received particular attention due to the wide structural variability of the ligands (diamines, amino alcohols, amino imines, amino pyridines, imino pyridines, Schiff bases, box-type ligands, salen-type ligands, and others),[5,6] the ease of preparation and the, in part, high levels of stereocontrol reached. Several of these catalysts permit 99% ee in the addition of nitromethane to some of the aldehydes tested,[5] but none is capable of providing 99% ee for the majority of substrates. Herein we present the first copper catalyst that fulfils this demand, giving, for the addition of nitromethane to a broad range of aldehydes, the corresponding ß-nitro alcohols in high yield and excellent 99% ee.

In the course of our studies on bicyclic diamines[9] we became interested in 2-aminomethylpyrrolidines of general type **1** (Fig. 1), which carry an additional *cis*-aryl group in 5-position, as compared to proline derived diamines. Chelation of a metal with **1** will lead to a rigid bicyclic system, in which the aryl substituent is forced into an *endo*-position directly on top of the active metal site.

Organic Chemistry Laboratory, University of Bayreuth, Universitätsstraße 30, 95447 Bayreuth, Germany. E-mail: matthias.breuning@uni-bayreuth.de

† Electronic supplementary information (ESI) available: Detailed experimental procedures, HPLC- and NMR spectra. See DOI: 10.1039/c4cc02429j

‡ These authors contributed equally to this work.

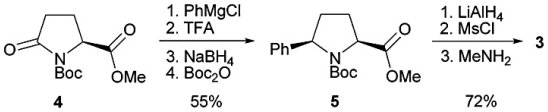
Fig. 1 *cis*-2-Aminomethyl-5-arylpyrrolidines **1** and **3** and a square-pyramidal metal complex of **1**, **2**.

As illustrated by complex **2**, such a shielding might be of particular importance in asymmetric transition metal catalysts preferring Jahn–Teller distorted octahedral geometries, because it selectively blocks one apical position and thereby reduces the number of possible transition states. The equatorial coordination sites L^1_{eq} and L^2_{eq} are still differentiated by the intrinsic steric and electronic properties of the C_1-symmetric diamine **1**, which might offer another advantage over C_2-symmetric ligands.

Copper(II)-catalysed Henry reactions, which are supposed to proceed *via* such a pentacoordinate intermediate,[10] might provide an ideal test system to probe the potential of the diamines **1**.[11] After investigating some derivatives, we quickly identified the simple compound **3** as the ligand of choice for these reactions.[12]

Diamine **3** is easily accessible from commercially available methyl Boc-L-pyroglutamate (**4**, Scheme 1). Treatment of **4** with phenylmagnesium chloride and re-cyclisation of the resulting, ring-opened ketone delivered the diastereomerically pure pyrrolidine **5** after crystallization.[13] Exhaustive reduction followed by OH/NHMe exchange afforded the target molecule **3** in overall seven simple steps and 40% yield.

The enantioselective Henry reactions between the aromatic aldehydes **6a–u** and nitromethane (11 equivalents) were performed on a 1 mmol scale in THF at −25 °C (Table 1, entries 1–21).



Scheme 1 Synthesis of diamine **3** from pyroglutamate **4**.

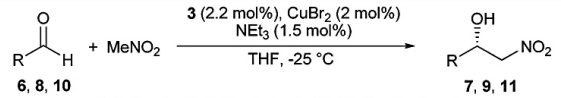
The copper(II) complex [**3**·$CuBr_2$], prepared prior to use by stirring $CuBr_2$ with a slight excess of pyrrolidine **3** in THF, was used as the chiral catalyst and NEt_3 (1.5 mol%) as the base. Under these conditions[12] and in the presence of just 2 mol% [**3**·$CuBr_2$], the Henry products **7a–u** were formed within 18 to 67 h in excellent 92–99% yield. Outstanding 99% ee, in several cases even more than 99.5% ee, were obtained with electronically more or less neutral (**6a–g**), electron-deficient (**6h–o**) and electron-rich (**6p–u**) aromatic aldehydes, carrying substituents in *ortho*-, *meta*-, or *para*-position.

Hetarylic aldehydes **8a–f** were also treated with nitromethane under these conditions (Table 1, entries 22–27). And again, the Henry products **9a–f** were obtained in excellent yields (90–99%) and superb >99.0% ee, irrespective of the heterocycle (furyl, thiophenyl, or NBoc-pyrryl) and the substitution pattern.

The α,β-unsaturated aldehydes **10a** and **10b** solely afforded the 1,2-addition products **11a** and **11b**. The latter one is the only compound tested within this context that delivered less than 99.0% ee, namely 98.7%.

In all cases, the *re*-face of the aldehyde was attacked by the nitronate; the, in part, opposite absolute stereo descriptors in the products are a formal consequence of the CIP-notation.

Table 1 Aromatic, heteroaromatic and vinylic aldehyde scope[a]



6, **8**, **10** **7**, **9**, **11**

6, **7**: R = Ar; **8**, **9**: R = hetaryl; **10**, **11**: R = 1-alkenyl

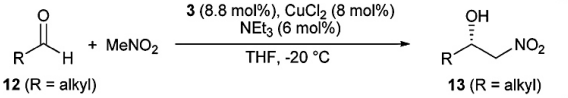
Entry	Compounds	R	Time (h)	Yield[b] (%)	ee[c] (%) (config.)
1	**6a, 7a**	Ph	24	92	99.3 (*S*)
2	**6b, 7b**	2-Me-Ph	18	99	99.2 (*S*)
3	**6c, 7c**	3-Me-Ph	20	99	99.5 (*S*)
4	**6d, 7d**	4-Me-Ph	22	93	99.4 (*S*)
5	**6e, 7e**	4-Ph-Ph	38	99	99.6 (*S*)
6	**6f, 7f**	1-Naphthyl	65	99	99.4 (*S*)
7	**6g, 7g**	2-Naphthyl	42	99	99.0 (*S*)
8	**6h, 7h**	2-O_2N-Ph	20	97	99.0 (*S*)
9	**6i, 7i**	3-O_2N-Ph	22	95	99.4 (*S*)
10	**6j, 7j**	4-O_2N-Ph	21	94	99.4 (*S*)
11	**6k, 7k**	2-Cl-Ph	18	99	99.6 (*S*)
12	**6l, 7l**	3-Cl-Ph	19	96	99.5 (*S*)
13	**6m, 7m**	4-Cl-Ph	42	95	99.5 (*S*)
14	**6n, 7n**	4-F-Ph	20	99	99.6 (*S*)
15	**6o, 7o**	4-NC-Ph	21	94	99.6 (*S*)
16	**6p, 7p**	2-MeO-Ph	42	97	99.5 (*S*)
17	**6q, 7q**	3-MeO-Ph	48	99	99.3 (*S*)
18	**6r, 7r**	4-MeO-Ph	67	99	99.2 (*S*)
19	**6s, 7s**	2,4-$(MeO)_2$-Ph	48	98	99.3 (*S*)
20	**6t, 7t**	2,5-$(MeO)_2$-Ph	39	99	99.6 (*S*)
21	**6u, 7u**	3,4-$(MeO)_2$-Ph	40	93	99.1 (*S*)
22	**8a, 9a**	2-Furyl	40	91	99.6 (*R*)
23	**8b, 9b**	5-Me-2-furyl	112	96	99.5 (*R*)[d]
24	**8c, 9c**	3-Furyl	72	99	99.4 (*S*)
25	**8d, 9d**	2-Thiophenyl	86	95	99.2 (*R*)
26	**8e, 9e**	NBoc-2-pyrryl	21	99	99.5 (*R*)
27	**8f, 9f**	NBoc-3-indolyl	160	90	99.4 (*S*)
28	**10a, 11a**	(*E*)-PhCH=CH	120	90	99.3 (*S*)
29	**10b, 11b**	(*E*)-1-Penten-1-yl	90	97	98.7 (*S*)[d]

[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL ≈ 11 eq.). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral phase; absolute configurations were established by comparison with literature data. [d] Absolute configuration was assigned based on a *re*-face attack on the aldehyde.

Aliphatic aldehydes **12** provided significantly lower enantioselectivities and yields under these conditions. Nonanal (**12b**), for example, delivered the Henry product **13b** in unsatisfying 53% yield and 94.5% ee after 40 h. In order to compensate the lower reactivity, we raised the amount of catalyst to 8 mol% and the temperature to −20 °C, which afforded **13b** in good 86% yield, but low 92.1% ee. Finally, a significant increase in the level of chirality transfer was observed by changing the copper salt from $CuBr_2$ to $CuCl_2$.[14] Under these modified conditions, both, linear (**12a–c**) and α-branched (**12d–g**) aliphatic aldehydes provided the Henry products **13a–g** in excellent 98.5–99.5% ee and >95% yield (Table 2).

The stereochemical outcome of the Henry reactions can be explained *via* the transition state **14** (Fig. 2). As mentioned earlier, the aryl group of the chiral ligand **3** blocks the upper apical position at the Cu(II) ion, thus leaving three open coordination sites, two equatorial ones and one apical one. Based on the known model,[10] the nitronate should bind apically for maximum activation, since its negative charge is less stabilised in this position by the copper ion. Of the two higher Lewis-acidic equatorial sites, the aldehyde should coordinate to the one next to the pyrrolidine moiety for two reasons: (i) this allows the sterically more demanding counter ion X to occupy the less congested position next to the aminomethyl group[9b] and (ii) with the weaker electron donating secondary amine opposite, the electrophilicity of the carbonyl group is increased thus facilitating a nucleophilic attack. Furthermore, the aldehyde must be oriented inwards in order to avoid severe steric repulsions with the chiral backbone. The C–C bond formation will presumably proceed *via* a six-membered,

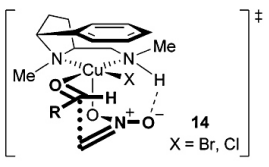
Table 2 Aliphatic aldehyde scope[a]



12 (R = alkyl) **13** (R = alkyl)

Entry	Compounds	R	Time (h)	Yield[b] (%)	ee[c] (%) (config.)
1	**12a, 13a**	*n*Bu	40	95	98.5 (*S*)
2	**12b, 13b**	*n*Oct	60	97	98.6 (*S*)
3	**12c, 13c**	$PhCH_2CH_2$	40	95	99.5 (*S*)
4	**12d, 13d**	iPr	44	96	99.1 (*S*)
5	**12e, 13e**	*c*Pent	44	99	98.9 (*S*)
6	**12f, 13f**	*c*Hex	44	99	99.4 (*S*)
7	**12g, 13g**	*t*Bu	44	99	98.6 (*S*)

[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL ≈ 11 eq.). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral phase; absolute configurations were established by comparison with literature data.



14
X = Br, Cl

Fig. 2 Proposed transition state **14**.

chair-shaped transition state, thus obviating repulsions between the nitronate-oxygen and the pyrrolidine *N*-methyl group.[15] It might be possible that this arrangement receives some further stabilisation and rigidness by an intramolecular hydrogen bridge between the nitronate oxygen and the NH-proton of the chiral ligand. Thus, the steric and electronic properties of the diamine ligand apparently create close to perfect preconditions for the experimentally observed, almost exclusive *re*-face attack of the nitronate on the aldehyde carbonyl group.

In summary, the *cis*-5-phenyl substituted 2-aminomethyl-pyrrolidine **3**, which is accessible in just a few steps from methyl Boc-L-pyroglutamate (**4**), was successfully utilized as the chiral ligand in $CuBr_2$- and $CuCl_2$-catalysed Henry reactions. Excellent isolated yields (>90%) and superb enantioselectivities (98.5–99.6% ee) were obtained with a wide variety of aromatic, heteroaromatic, vinylic and aliphatic aldehydes (36 examples). Further studies are ongoing.[16]

Financial support of the German research foundation (DFG) is gratefully acknowledged.

Notes and references

1 Reviews: (*a*) F. A. Luzzio, *Tetrahedron*, 2001, **57**, 915; (*b*) *The Nitro Group in Organic Synthesis*, ed. N. Ono, Wiley-VCH, New York, 2001.

2 Reviews: (*a*) J. Boruwa, N. Gogoi, P. P. Saikia and N. C. Barua, *Tetrahedron: Asymmetry*, 2006, **17**, 3315; (*b*) C. Palomo, M. Oiarbide and A. Laso, *Eur. J. Org. Chem.*, 2007, 2561; (*c*) Y. Alvarez-Casao, E. Marques-Lopez and R. P. Herrera, *Symmetry*, 2011, **3**, 220; (*d*) G. Blay, V. Hernández-Olmos and J. R. Pedro, *Synlett*, 2011, 1195; (*e*) G. Chelucci, *Coord. Chem. Rev.*, 2013, **257**, 1887; (*f*) N. Ananthi and S. Velmathi, *Indian J. Chem., Sect. B*, 2013, **52**, 87.

3 Selected examples: (*a*) H. Sasai, T. Suzuki, S. Arai, T. Arai and M. Shibasaki, *J. Am. Chem. Soc.*, 1992, **114**, 4418; (*b*) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 13860; (*c*) T. Nitabaru, N. Kumagai and M. Shibasaki, *Angew. Chem., Int. Ed.*, 2012, **51**, 1644; (*d*) D. Sureshkumar, K. Hashimoto, N. Kumagai and M. Shibasaki, *J. Org. Chem.*, 2013, **78**, 11494.

4 Selected examples (except Cu-catalysis): (*a*) B. M. Trost and V. S. C. Yeh, *Angew. Chem., Int. Ed.*, 2002, **41**, 861; (*b*) C. Palomo, M. Oiarbide and A. Laso, *Angew. Chem., Int. Ed.*, 2005, **44**, 3881; (*c*) J. Park, K. Lang, K. A. Abboud and S. Hong, *J. Am. Chem. Soc.*, 2008, **130**, 16484; (*d*) S. Liu and C. Wolf, *Org. Lett.*, 2008, **10**, 1831; (*e*) R. Kowalczyk, P. Kwiatkowski, J. Skarżewski and J. Jurczak, *J. Org. Chem.*, 2009, **74**, 753; (*f*) K. Lang, J. Park and S. Hong, *Angew. Chem., Int. Ed.*, 2012, **51**, 1620.

5 Cu-catalysed Henry reactions of nitromethane giving 99% ee with at least one aldehyde: (*a*) M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi and C. Ventrici, *Chem. Commun.*, 2007, 616; (*b*) T. Arai, M. Watanabe and A. Yanagisawa, *Org. Lett.*, 2007, **9**, 3595; (*c*) G. Zhang, E. Yashima and W.-D. Woggon, *Adv. Synth. Catal.*, 2009, **351**, 1255; (*d*) W. Jin, X. Li, Y. Huang, F. Wu and B. Wan, *Chem. – Eur. J.*, 2010, **16**, 8259; (*e*) G. Lai, F. Guo, Y. Zheng, Y. Fang, H. Song, K. Xu, S. Wang, Z. Zha and Z. Wang, *Chem. – Eur. J.*, 2011, **17**, 1114; (*f*) A. T. Herrmann, S. R. Martinez and A. Zakarian, *Org. Lett.*, 2011, **13**, 3636; (*g*) B. V. Subba Reddy and J. George, *Tetrahedron: Asymmetry*, 2011, **22**, 1169; (*h*) Y. Zhou, J. Dong, F. Zhang and Y. Gong, *J. Org. Chem.*, 2011, **76**, 588; (*i*) W. Jin, X. Li and B. Wan, *J. Org. Chem.*, 2011, **76**, 484; (*j*) R. I. Kureshy, A. Das, N. H. Khan, S. H. R. Abdi and H. C. Bajaj, *ACS Catal.*, 2011, **1**, 1529; (*k*) Y. Wei, L. Yao, B. Zhang, W. He and S. Zhang, *Tetrahedron*, 2011, **67**, 8552; (*l*) L. Yao, Y. Wei, P. Wang, W. He and S. Zhang, *Tetrahedron*, 2012, **68**, 9119; (*m*) D.-D. Qin, W.-H. Lai, D. Hu, Z. Chen, A.-A. Wu, Y.-P. Ruan, Z.-H. Zhou and H.-B. Chen, *Chem. – Eur. J.*, 2012, **18**, 10515; (*n*) K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen and Z. Wang, *Chem. – Eur. J.*, 2012, **18**, 12357; (*o*) A. Das, R. I. Kureshy, K. J. Prathap, M. K. Choudhary, G. V. S. Rao, N. H. Khan, S. H. R. Abdi and H. C. Bajaj, *Appl. Catal., A*, 2013, **459**, 97; (*p*) T. Deng and C. Cai, *J. Fluorine Chem.*, 2013, **156**, 183; (*q*) R. Ćwiek, P. Niedziejko and Z. Kałuża, *J. Org. Chem.*, 2014, **79**, 1222.

6 Selected recent examples of enantioselective Cu-catalysed Henry reactions: (*a*) G. Blay, V. Hernández-Olmos and J. R. Pedro, *Org. Lett.*, 2010, **12**, 3058; (*b*) T. Arai, Y. Taneda and Y. Endo, *Chem. Commun.*, 2010, **46**, 7936; (*c*) L. Cheng, J. Dong, J. You, G. Gao and J. Lan, *Chem. – Eur. J.*, 2010, **16**, 6761; (*d*) A. Chougnet, G. Zhang, K. Liu, D. Häussinger, A. Kägi, T. Allmendinger and W.-D. Woggon, *Adv. Synth. Catal.*, 2011, **353**, 1797; (*e*) M. W. Leighty, B. Shen and J. N. Johnston, *J. Am. Chem. Soc.*, 2012, **134**, 15233; (*f*) J. D. White and S. Shaw, *Org. Lett.*, 2012, **14**, 6270; (*g*) Q. Dai, N. K. Rana and J. C.-G. Zhao, *Org. Lett.*, 2013, **15**, 2922; (*h*) D.-D. Qin, W. Yu, J.-D. Zhou, Y.-C. Zhang, Y.-P. Ruan, Z.-H. Zhou and H.-B. Chen, *Chem. – Eur. J.*, 2013, **19**, 16541.

7 Selected recent examples: (*a*) D. Uraguchi, S. Nakamura and T. Ooi, *Angew. Chem., Int. Ed.*, 2010, **49**, 7562; (*b*) K. Kanagaraj, P. Suresh and K. Pitchumani, *Org. Lett.*, 2010, **12**, 4070; (*c*) Q. Dai, H. Huang and J. C.-G. Zhao, *J. Org. Chem.*, 2013, **78**, 4153; (*d*) A. Quintavalla, M. Lombardo, S. P. Sanap and C. Trombini, *Adv. Synth. Catal.*, 2013, **355**, 938; (*e*) S. Kitagaki, T. Ueda and C. Mukai, *Chem. Commun.*, 2013, **49**, 4030; (*f*) M. T. Corbett and J. S. Johnson, *Angew. Chem., Int. Ed.*, 2014, **53**, 255.

8 M. Gruber-Khadjawi, T. Purkarthofer, W. Skranc and H. Griengl, *Adv. Synth. Catal.*, 2007, **349**, 1445.

9 (*a*) M. Breuning, D. Hein, M. Steiner, V. H. Gessner and C. Strohmann, *Chem. – Eur. J.*, 2009, **15**, 12764; (*b*) M. Breuning, M. Steiner, C. Mehler, A. Paasche and D. Hein, *J. Org. Chem.*, 2009, **74**, 1407; (*c*) M. Breuning and D. Hein, *Eur. J. Org. Chem.*, 2013, 7575.

10 D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692.

11 Enantioselective, Cu-catalysed Henry reactions using proline-derived ligands: (*a*) B. V. Subba Reddy, S. Madhusudana Reddy, S. Manisha and C. Madan, *Tetrahedron: Asymmetry*, 2011, **22**, 530; (*b*) D. Lu, Y. Zhou, Y. Li, S. Yan and Y. Gong, *J. Org. Chem.*, 2011, **76**, 8869; (*c*) B. Ni and J. He, *Tetrahedron Lett.*, 2013, **54**, 462; (*d*) Y. Zhou, Y. Zhu, S. Yan and Y. Gong, *Angew. Chem., Int. Ed.*, 2013, **52**, 10265; (*e*) H. Yuan, J. Hu and Y. Gong, *Tetrahedron: Asymmetry*, 2013, **24**, 699; (*f*) H. A. Sema, G. Bez and S. Karmakar, *Appl. Organomet. Chem.*, 2014, **28**, 290; (*g*) Ref. 5*e*, *h* and *n*.

12 Details about the diamine screening and the optimization of the reactions conditions as well as further mechanistic investigations will be reported elsewhere.

13 Synthesis of related compounds: (*a*) M.-C. Fournie-Zaluski, P. Coric, V. Thery, W. Gonzalez, H. Meudal, S. Turcaud, J.-B. Michel and B. P. Roques, *J. Med. Chem.*, 1996, **39**, 2594; (*b*) A. Momotake, H. Togo and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1193; (*c*) A. C. Rudolph, R. Machauer and S. F. Martin, *Tetrahedron Lett.*, 2004, **45**, 4895.

14 A similar effect on the ee was not observed with aromatic aldehydes.

15 A boat-type transition state cannot fully be excluded, but seems less likely.

16 Initial studies on Henry reactions with other nitroalkanes revealed acceptable to good diastereoselectivities and excellent enantioselectivities in the major *syn*-diastereomer. The reaction of benzaldehyde (**6a**) with nitropropane, for example, afforded the corresponding ß-nitro alcohol in 99% yield with a *syn*/*anti* ratio of 79 : 21 and 98% ee in the major diastereomer.

Electronic Supplementary Material (ESI) for ChemComm.

(2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a Chiral Diamine Ligand for Copper(II)-Catalysed Henry Reactions with Superb Enantiocontrol

Dagmar Scharnagel, Felix Prause, Johannes Kaldun, Robert G. Haase, and Matthias Breuning*

Organic Chemistry Laboratory
University of Bayreuth
Universitätsstraße 30
95447 Bayreuth, Germany
E-mail: Matthias.Breuning@uni-bayreuth.de

Table of Contents

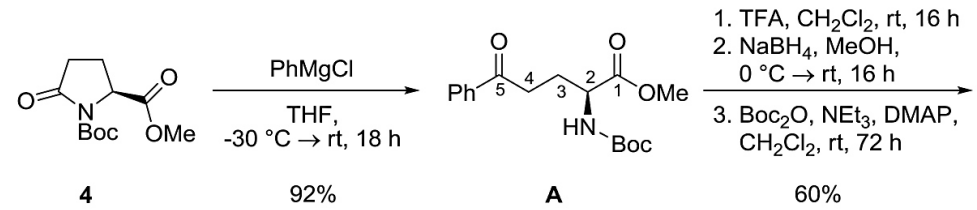
1. General Information

All reactions were carried out under an argon atmosphere with dry solvents. Anhydrous tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), methanol (MeOH), and nitromethane ($MeNO_2$) were prepared using standard procedures.[1]

Commercially available reagents (highest quality available) were used as received. All liquid aldehydes used in enantioselective Henry reactions were distilled prior to use in order to remove any accompanying acid impurities. Reactions were monitored by thin layer chromatography (TLC) on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey-Nagel, particle size 40–63 μm) was used for column chromatography.

Melting points (m.p.) were measured on a Stuart SMP10 digital melting point apparatus and are uncorrected. Optical rotations ($[\alpha]_D^T$) were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance 400 or a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^1H and ^{13}C NMR data were made on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared (IR) spectra were recorded on a Jasco FT-IR-410 or a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra (HRMS) on a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization) or on a Finnigan MAT 90 using EI (electron ionisation. 70 eV).

2. Synthesis of the Diamine 3



2.1. (*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-oxo-5-phenylpentanoate (A)

PhMgCl (25 wt% in THF, 31.6 mL, 60.0 mmol) was added at -30 °C to a solution of **4** (12.2 g, 50.0 mmol) in abs. THF (150 mL). The reaction mixture was slowly warmed to rt and stirred for 18 h. After addition of sat. aq. NH_4Cl (2 mL), the solvent was removed and the residue was diluted with

1 *Purification of Laboratory Chemicals*, eds. W. L. F. Armarego and D. D. Perrin, 4th ed., Butterworth-Heinemann, Oxford, 2000.

CH_2Cl_2 (200 mL). Sat. aq. NH_4Cl (180 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (180 mL) and the aqueous layer was re-extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Column chromatography (silica gel, petrol ether/ EtOAc 1:0 → 2:1) delivered a mixture of the keto ester **A** and the corresponding 2,3-dihydropyrrole. This mixture was dissolved in MeOH (280 mL) and H_2O (35 mL), treated with TsOH•H_2O (210 mg), and stirred for 1 d at rt. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (250 mL), washed with sat. aq. $NaHCO_3$ (2 × 150 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure afforded keto ester **A** (14.8 g, 46.0 mmol, 92%) as a white solid, $[\alpha]_D^{25}$ = 14.6 (c = 1.13 in $CHCl_3$) [ref[2]: $[\alpha]_D^{20}$ = –14.8 (c = 1.13 in $CHCl_3$) for *ent*-**A**]. The NMR data of **A** were in full agreement with those given in ref.[2]

2.2. (2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-phenylpyrrolidine-1,2-dicarboxylate (5)

A solution of the keto ester **A** (12.1 g, 37.6 mmol) in abs. CH_2Cl_2 (370 mL) was treated at rt with TFA (57.9 mL, 85.7 g, 752 mmol) and stirred overnight. The solvent was removed under reduced pressure and the resulting orange oil was diluted five times with CH_2Cl_2 (300 mL) and evaporated again, in order to remove excess TFA. $NaBH_4$ (2.70 g, 71.4 mmol) was slowly added at 0 °C to a solution of the residue in MeOH (300 mL). After stirring for 16 h at rt, the solvent was removed. The resulting orange oil was diluted four times with MeOH (260 mL) and evaporated again. The residue was suspended in abs. CH_2Cl_2 (1000 mL) and NEt_3 (7.49 mL, 5.71 g, 56.4 mmol), Boc_2O (12.3 g, 56.4 mmol), and DMAP (50.0 mg, 409 µmol) were added at rt. After 3 d of stirring, sat. aq. NH_4Cl (1000 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL) and the combined organic layers were dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, petrol ether/EtOAc 1:0 → 0:1) afforded an 86:14 mixture of **5** and its 5-epimer, which was crystallized from CH_2Cl_2/Et_2O/pentane (1:4:14) to give diastereomerically pure **5** (6.90 g, 22.6 mmol, 60%) as colourless needles.

R_f = 0.37 (petrol ether/EtOAc 3:1); m.p. 100–101 °C; $[\alpha]_D^{21}$ = 25.7 (c = 1.00 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$):* δ = 1.14 (s, 5.4H, $C(CH_3)_3$), 1.41 (s, 3.6H, $C(CH_3)_3$), 2.03 (m, 2H, 3-H, 4-H), 2.19 (m, 1H, 3-H), 2.31 (m, 1H, 4-H), 3.81 (s, 3H, OMe), 4.35 (m, 0.4H, 2-H), 4.49 (m, 0.6H, 2-H), 4.74 (m, 0.6H, 5-H), 4.98 (m, 0.4H, 5-H), 7.21 (m, 1H, Ph-H), 7.32 (m, 2H, Ph-H), 7.54 ppm (m, 2H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$):* δ = 28.1, 28.4 ($C(CH_3)_3$), 28.9, 29.1 (C-3), 34.6, 35.7 (C-4), 52.1, 52.3 (OMe), 60.4, 60.9 (C-2), 62.3, 63.2 (C-5), 80.2, 80.4 ($C(CH_3)_3$), 126.1, 126.5, 126.8, 128.2, 128.4 (CH-Ph), 143.2, 144.2 (C_q-Ph), 153.9, 154.6 (NCO_2), 173.8 ppm (CO_2Me); IR (ATR): $\tilde{\nu}$ = 3734 (w), 3628 (w), 2981 (w), 2951 (w), 1747 (m), 1684 (s), 1605 (w), 1398 (s), 1352 (m), 1197 (s), 1155 (s), 1121 (m), 1083 (m), 757 (m), 704 cm^{-1} (m); HRMS (ESI, pos.): *m/z* calcd. for $[C_{17}H_{23}NO_4 + Na]^+$: 328.1519, found: 328.1518. *Mixture of rotamers due to hindered rotation of the carbamate group.

2 J. Ackermann, M. Matthes and C. Tamm, *Helv. Chim. Acta*, 1990, **73**, 122.

2.3. (2*S*,5*R*)-2-Hydroxymethyl-1-methyl-5-phenylpyrrolidine (B)

$LiAlH_4$ (2.46 g, 64.8 mmol) was added at 0 °C to a solution of **5** (3.30 g, 10.8 mmol) in abs. THF (100 mL). After 1 h, the reaction mixture was heated to reflux for 16 h. The solution was diluted with Et_2O (80 mL) and carefully treated with sat. aq. Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was thoroughly washed with CH_2Cl_2/MeOH (9:1, 700 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2/MeOH 95:5) delivered alcohol **B** (1.98 g, 10.4 mmol, 96%) as a colourless oil.

R_f = 0.33 (Et_2O); $[\alpha]_D^{26}$ = 79.6 (c = 0.50 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (m, 1H, 4-H), 1.97 (m, 2H, 3-H), 2.08 (m, 1H, 4-H), 2.18 (s, 3H, NMe), 2.68 (m, 1H, 2-H), 2.80 (br s, 1H, OH), 3.42 (dd, *J* = 10.0, 6.5 Hz, 1H, 5-H), 3.51 (dd, *J* = 10.8, 1.9 Hz, 1H, CH*H*OH), 3.77 (dd, *J* = 10.8, 3.4 Hz, 1H, C*H*HOH), 7.25 (m, 1H, Ph-H), 7.33 ppm (m, 4H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.4 (C-3), 34.6 (C-4), 38.5 (NMe), 61.7 (CH_2OH), 66.6 (C-2), 72.5 (C-5), 127.30, 127.33, 128.5 (CH-Ph), 143.1 ppm (C_q-Ph); IR (ATR): $\tilde{\nu}$ = 3414 (w), 2947 (w), 2871 (w), 2842 (w), 2783 (w), 1603 (w), 1451 (m), 1075 (m), 1027 (s), 755 (s), 699 cm^{-1} (s); HRMS (ESI, pos.): *m/z* calcd. for $[C_{12}H_{17}NO + H]^+$: 192.1383, found: 192.1384.

2.4. (2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine (3)

MsCl (731 µL, 1.08 g, 9.44 mmol) and NEt_3 (1.80 mL, 1.30 g, 12.9 mmol) were added at 0 °C to a solution of the alcohol **B** (1.64 g, 8.58 mmol) in abs. CH_2Cl_2 (20 mL). The reaction was allowed to warm to rt and stirred for further 16 h. Aqeous $MeNH_2$ (11 M in H_2O, 23.0 mL, 257 mmol), NEt_3 (521 mg, 719 µL, 5.15 mmol), and MeOH (30 mL) were added and stirring was continued for 1 d. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2/10% aq. NH_3 in MeOH 95:5 → 85:15) delivered diamine **3** (1.31 g, 6.41 mmol, 75%) as a yellowish oil.

R_f = 0.53 (Et_2O, deact. SiO_2); $[\alpha]_D^{29}$ = 51.2 (c = 1.00 in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 (m, 1H, 4-H), 1.84 (m, 1H, 3-H), 1.96 (m, 2H, 3-H, NH), 2.05 (m, 1H, 4-H), 2.15 (s, 3H, NMe), 2.52 (s, 3H, HN*Me*), 2.61 (m, 1H, 2-H), 2.69 (dd, *J* = 11.4, 5.6 Hz, 1H, C*H*HN), 2.75 (dd, *J* = 11.4, 3.6 Hz, 1H, C*H*HN), 3.27 (dd, *J* = 9.6, 6.6 Hz, 1H, 5-H), 7.22 (m, 1H, Ph-H), 7.33 ppm (m, 4H, Ph-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.0 (C-3), 34.4 (C-4), 37.2 (HNMe), 39.4 (NMe), 55.3 (CH_2N), 65.8 (C-2), 72.7 (C-5), 127.1, 127.5, 128.4 (CH-Ph), 144.0 ppm (C_q-Ph); IR (ATR): $\tilde{\nu}$ = 2943 (w), 2872 (w), 2838 (w), 2783 (w), 1603 (w), 1451 (w), 1133 (w), 1073 (w), 1039 (w), 755 (m), 698 cm^{-1} (s); HRMS (ESI, pos.): *m/z* calcd. for $[C_{13}H_{20}N_2 + H]^+$: 205.1699, found: 205.1700.

3. Enantioselective Henry Reactions

3.1. General Remarks

Preparation of the racemic ß-nitro alcohols: These compounds were prepared by treatment of the aldehyde (500 µmol) at rt with nitromethane (300 µL) in the presence of NEt_3 (6.0 µL, 43 µmol) and a $CuCl_2$(tmda) complex, prepared from $CuCl_2$ (1.3 mg, 10 µmol) and TMEDA (1.5 µL, 10 µmol) in MeOH (300 µL). Purification by column chromatography (silica gel, hexanes/EtOAc 8:1 → 4:1) afforded the analytically pure β-nitro alcohols, the NMR spectroscopic data of which were identically with those given in literature.[3]

Solutions used in the enantioselective Henry reactions: In order to ensure maximum accuracy, solutions were prepared for all catalytically used reagents:

- $CuBr_2$ in MeOH (66.7 mM) from anhyd. $CuBr_2$ (44.7 mg, 200 µmol) and abs. MeOH (3.00 mL)
- $CuCl_2$ in MeOH (267 mM) from anhyd. $CuCl_2$ (53.8 mg, 400 µmol) and abs. MeOH (1.50 mL)
- Diamine **3** in THF (36.7 mM) from **3** (22.5 mg, 110.0 µmol) and abs. THF (3.00 mL)
- Diamine **3** in THF (147 mM) from **3** (45.0 mg, 220.0 µmol) and abs. THF (1.50 mL)
- NEt_3 in $MeNO_2$ (1.50 M) from NEt_3 (20.8 µL, 15.2 mg, 150 µmol) and $MeNO_2$ (79 µL)

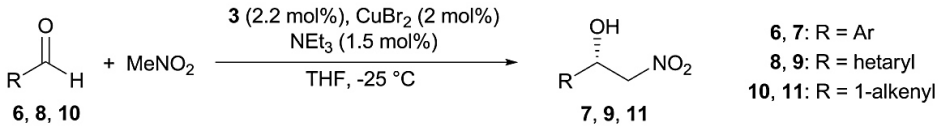
Measurement of the enantiomeric excess (ee): The ee of each ß-nitro alcohol was determined by HPLC (Knauer HPLC pump type 64.00, Knauer UV/Vis variable wavelength monitor type A0293) on chiral phase (Daicel Chiralcel OD-3, Daicel Chiralpak AD-H, Daicel Chiralcel OJ-H). The accuracy of integration was ± 0.1%. Some of the enantioselective Henry reactions were done up to five times, for example with benzaldehyde (**6a**), 2-nitrobenzaldehyde (**6h**), 2-methoxybenzaldehyde (**6p**), valeraldehyde (**12a**), and 3-phenylpropanal (**12c**). In all cases, virtually the same excellent enantiomeric excesses were measured (Δee = ± 0.2%).

Determination of the absolute configuration of the major enantiomer: For all known ß-nitro alcohols, the absolute configuration of the major enantiomer was assigned by comparison of the order of the measured retention times on HPLC with the literature-known ones, measured under identical conditions (same chiral phase and solvent system).[3] The absolute configuration of the major enantiomer of the new products **9b** and **11b** was tentatively assigned under the assumption that the sense of asymmetric induction was the same as for all other derivatives (*re*-attack on the carbonyl group).

---

3 (*a*) M. Breuning, D. Hein, M. Steiner, V. H. Gessner and C. Strohmann, *Chem.-Eur. J.*, 2009, **15**, 12764; (*b*) W. Jin, X. Li and B. Wan, *J. Org. Chem.*, 2011, **76**, 484; (*c*) Y. Q. Ji, G. Qi and Z. M. A. Judeh, *Eur. J. Org. Chem.*, 2011, 4892; (*d*) Y. Zhou, J. Dong, F. Zhang and Y. Gong, *J. Org. Chem.*, 2011, **76**, 588; (*e*) L. Yao, Y. Wei, P. Wang, W. He and S. Zhang, *Tetrahedron*, 2012, **68**, 9119; (*f*) R. Kowalczyk, P. Kwiatkowski, J. Skarżewski and J. Jurczak, *J. Org. Chem.*, 2009, **74**, 753; (*g*) L. Zhang, H. Wu, Z. Yang, X. Xu, H. Zhao, Y. Huang and Y. Wang, *Tetrahedron*, 2013, **69**, 10644; (*h*) B. V. S. Reddy and J. George, *Tetrahedron: Asymmetry*, 2011, **22**, 1169; (*i*) Y. Zhou and Y. Gong, *Eur. J. Org. Chem.*, 2011, 6092; (*j*) M. Liu, S. Ma, Z. Tian, H. Wu, L. Wu, X. Xu, Y. Huang and Y. Wang, *Tetrahedron: Asymmetry*, 2013, **24**, 736; (*k*) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen and H. Hiemstra, *Angew. Chem. Int. Ed.*, 2006, **45**, 929; (*l*) A. Gualandi, L. Cerisoli, H. Stoeckli-Evans and D Savoia, *J. Org. Chem.*, 2011, **76**, 3399; (*m*) Y. Sohtome, Y. Hashimoto, K. Nagasawa, *Adv. Synth. Catal.*, 2005, **347**, 1643.

3.2. General Procedure I (Aromatic, Heteroaromatic, and Vinylic Aldehydes)



A solution of anhyd. $CuBr_2$ (66.7 mM in MeOH, 300 µL, 4.47 mg, 20.0 µmol, 2.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of the diamine **3** (36.7 mM in abs. THF, 600 µL, 4.49 mg, 22.0 µmol, 2.2 mol%), $MeNO_2$ (600 µL, 684 mg, 11.2 mmol, 11.2 eq.) and the aldehyde **6**, **8**, or **10** (1.00 mmol, 1.00 eq.) were added successively at rt. The mixture was ultrasonicated for 10 min to give a clear, brownish solution and then cooled to –25 °C. NEt_3 (1.5 M in $MeNO_2$, 10.0 µL, 1.52 mg, 15.0 µmol, 1.5 mol%) was added and the resulting blue-green solution was stirred until TLC-control indicated complete consumption of the aldehyde (18–160 h). The crude reaction mixture was purified by column chromatography (silica gel, hexanes/EtOAc 8:1 → 4:1) delivering β-nitro alcohol **7**, **9**, or **11**.

Table S1. Experimental data and details of HPLC analysis on chiral phase.

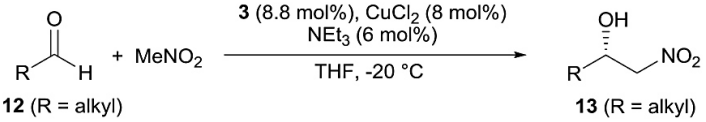
			Reaction Conditions			Enantiomer Analysis: HPLC Conditions					
Entry	Com-pounds	R	t [h]	Yield [%][a]	ee [%][b] (Config.)[c]	Column[d]	Solvent System *n*-Hexane/*i*PrOH	Flow [ml/min]	t_r (*R*) [min][e]	t_r (*S*) [min][e]	Ref.[f]
1	**6a**, **7a**	Ph	24	92	99.3 (*S*)	OD-3	85:15	0.8	12.6	14.9	3a
2	**6b**, **7b**	2-Me-Ph	18	99	99.2 (*S*)	OD-3	85:15	0.9	10.3	16.2	3b
3	**6c**, **7c**	3-Me-Ph	20	99	99.5 (*S*)	OD-3	90:10	0.9	14.4	16.7	3c
4	**6d**, **7d**	4-Me-Ph	22	93	99.4 (*S*)	OD-3	90:10	0.9	17.7	22.5	3c
5	**6e**, **7e**	4-Ph-Ph	38	99	99.6 (*S*)	OD-3	85:15	0.9	16.1	18.5	3c
6	**6f**, **7f**	1-naphthyl	65	99	99.4 (*S*)	OD-3	85:15	0.9	14.8	22.3	3b
7	**6g**, **7g**	2-naphthyl	42	99	99.0 (*S*)	OD-3	80:20	0.9	24.5	36.5	3b
8	**6h**, **7h**	2-O_2N-Ph	20	97	99.0 (*S*)	OD-3	80:20	0.7	11.5	12.2	3a
9	**6i**, **7i**	3-O_2N-Ph	22	95	99.4 (*S*)	OD-3	85:15	0.9	18.2	20.6	3d
10	**6j**, **7j**	4-O_2N-Ph	21	94	99.4 (*S*)	OD-3	85:15	0.9	18.6	22.7	3a
11	**6k**, **7k**	2-Cl-Ph	18	99	99.6 (*S*)	OD-3	97: 3	0.9	25.9	27.0	3a
12	**6l**, **7l**	3-Cl-Ph	19	96	99.5 (*S*)	OD-3	90:10	0.9	17.1	22.0	3c
13	**6m**, **7m**	4-Cl-Ph	42	95	99.5 (*S*)	OD-3	85:15	0.9	11.5	14.1	3a
14	**6n**, **7n**	4-F-Ph	20	99	99.6 (*S*)	OD-3	90:10	0.9	13.7	16.2	3e
15	**6o**, **7o**	4-NC-Ph	21	94	99.6 (*S*)	OD-3	80:20	0.9	12.9	14.6	3f
16	**6p**, **7p**	2-MeO-Ph	42	97	99.5 (*S*)	OD-3	90:10	0.9	14.0	16.8	3a
17	**6q**, **7q**	3-MeO-Ph	48	99	99.3 (*S*)	OD-3	85:15	0.9	19.3	25.6	3b

Table S1. (Continued).

Entry	Com-pounds	R	Reaction Conditions			Enantiomer Analysis: HPLC Conditions					
			t [h]	Yield [%][a]	ee [%][b] (Config.)[c]	Column[d]	Solvent System *n*-Hexane/*i*PrOH	Flow [ml/min]	t_r (*R*) [min][e]	t_r (*S*) [min][e]	Ref.[f]
18	**6r**, **7r**	4-MeO-Ph	67	99	99.2 (*S*)	OD-3	85:15	0.9	15.9	19.7	3a
19	**6s**, **7s**	2,4-$(MeO)_2$-Ph	48	98	99.3 (*S*)	OD-3	80:20	0.9	10.0	15.2	3g
20	**6t**, **7t**	2,5-$(MeO)_2$-Ph	39	99	99.6 (*S*)	OD-3	85:15	0.9	11.0	11.8	3h
21	**6u**, **7u**	3,4-$(MeO)_2$-Ph	40	93	99.1 (*S*)	OD-3	80:20	0.9	16.8	21.3	3i
22	**8a**, **9a**	2-furyl	40	91	99.6 (*R*)	AD-H	95:5	0.6	39.6	37.8	3d
23	**8b**, **9b**	5-Me-2-furyl	112	96	99.5 (*R*)	AD-H	95:5	0.6	30.4	33.0	–[g]
24	**8c**, **9c**	3-furyl	72	99	99.4 (*S*)	AD-H	90:10	0.9	15.8	21.7	3j
25	**8d**, **9d**	2-thiophenyl	86	95	99.2 (*R*)	OJ-H	85:15	0.9	30.6	26.0	3h
26	**8e**, **9e**	*N*Boc-2-pyrryl	21	99	99.5 (*R*)	OD-3	90:10	0.9	7.7	7.0	3k
27	**8f**, **9f**	*N*Boc-3-indolyl	160	90	99.4 (*S*)	OD-3	90:10	0.9	14.2	12.1	3l
28	**10a**, **11a**	(*E*)-PhCH=CH	120	90	99.3 (*S*)	OD-3	85:15	0.9	36.0	31.5	3h
29	**10b**, **11b**	(*E*)-1-pen-ten-1-yl	90	97	98.7 (*S*)	OJ-H	97:3	0.9	22.5	25.5	–[g]

[a] Isolated yield. [b] Determined by HPLC analysis on a chiral phase. [c] The absolute configuration of the major enantiomer was determined by comparison of the order of the measured retention times on HPLC with the literature-known ones, measured under identical conditions.[3] [d] OD-3: Daicel Chiralcel OD-3; AD-H: Daicel Chiralpak AD-H; OJ-H: Daicel Chiralcel OJ-H. [e] Retention time. [f] References, in which data for the HPLC analysis on chiral phase are given. [g] The absolute configuration of the major enantiomer was tentatively assigned under the assumption of a *re*-attack on the carbonyl group.

3.3. General Procedure II (Aliphatic Aldehydes)



12 (R = alkyl) **13** (R = alkyl)

A solution of anhyd. $CuCl_2$ (267 mM in MeOH, 300 µL, 10.8 mg, 80.0 µmol, 8.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of the diamine **3** (147 mM in abs. THF, 600 µL, 18.0 mg, 88.0 µmol, 8.8 mol%), $MeNO_2$ (600 µL, 684 mg, 11.2 mmol, 11.2 eq.) and aldehyde **12** (1.00 mmol, 1.00 eq.) were successively added at rt. The mixture was ultra-sonicated for 10 min to give a clear, greenish solution and then cooled to –20 °C. NEt_3 (1.5 M in $MeNO_2$, 40 µL, 6.08 mg, 60.0 µmol, 6.0 mol%) was added and the resulting blue solution was stirred until TLC-control indicated complete consumption of the aldehyde (40–60 h). The crude reaction mixture was purified by column chromatography (silica gel, pentane/Et_2O 8:1 → 4:1) delivering β-nitro alcohol **13**.

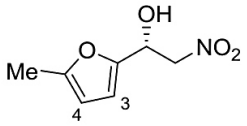
Table S2. Experimental data and details of HPLC analysis on chiral phase.

			Reaction Conditions			Enantiomer Analysis: HPLC Conditions					
Entry	Com-pounds	R	t [h]	Yield [%][a]	ee [%][b] (Config.)[c]	Column[d]	Solvent System *n*-Hexane/*i*PrOH	Flow [ml/min]	t_r (*R*) [min][e]	t_r (*S*) [min][e]	Ref.[f]
1	**12a**, **13a**	*n*Bu	40	95	98.5 (*S*)	OJ-H	97:3	0.8	21.9	22.9	3b
2	**12b**, **13b**	*n*Oct	60	97	98.6 (*S*)	AD-H	95:5	0.8	14.3	20.2	3h
3	**12c**, **13c**	$PhCH_2CH_2$	40	95	99.5 (*S*)	AD-H	90:10	0.9	13.1	16.3	3b
4	**12d**, **13d**	*i*Pr	44	96	99.1 (*S*)	OD-3	97:3	0.9	15.8	17.5	3m
5	**12e**, **13e**	*c*Pent	44	99	98.9 (*S*)	OD-3	98:2	0.9	23.8	24.9	3b
6	**12f**, **13f**	*c*Hex	44	99	99.4 (*S*)	AD-H	95:5 (EtOH)	0.9	34.3	31.1	–[g]
7	**12g**, **13g**	*t*Bu	44	99	98.6 (*S*)	OD-3	97:3	0.9	12.8	15.0	3m

[a] Isolated yield. [b] Determined by HPLC analysis on a chiral phase. [c] The absolute configuration of the major enantiomer was determined by comparison of the order of the measured retention times on HPLC with the literature-known ones, measured under identical conditions.[3] [d] OD-3: Daicel Chiralcel OD-3; AD-H: Daicel Chiralpak AD-H; OJ-H: Daicel Chiralcel OJ-H. [e] Retention time. [f] References, in which the data for the HPLC analysis on chiral phase are given. [g] The absolute configuration of the major enantiomer was assigned by comparison of the measured sign of the optical rotation with the literature-known one.[3b]

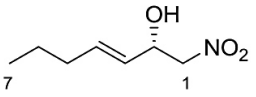
3.4. Characterization of New ß-Nitro Alcohols

3.4.1. (*R*)-1-(5-Methylfuran-2-yl)-2-nitroethanol (9b)



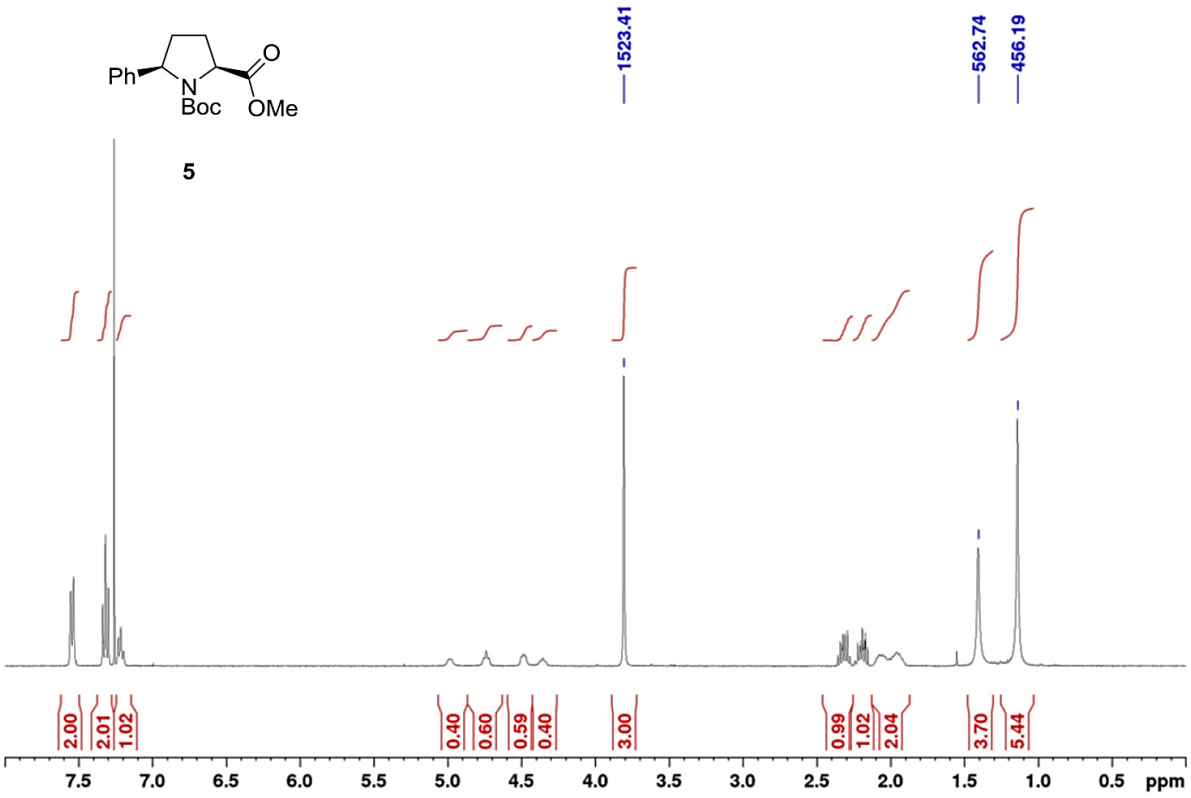
Ee = 99.5%; R_f = 0.32 (petrol ether/EtOAc 4:1); $[\alpha]_D^{28}$ = 50.1 (c = 1.0 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (s, 3H, CH_3), 2.78 (br s, 1H, OH), 4.64 (dd, *J* = 13.5, 3.4 Hz, 1H, C*H*H), 4.78 (dd, *J* = 13.5, 9.3 Hz, 1H, C*H*H), 5.40 (dd, *J* = 9.3, 3.3 Hz, 1H, C*H*OH), 5.95 (m, 1H, 4-H), 6.26 ppm (d, *J* = 3.1 Hz, 1H, 3-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6 (CH_3), 65.0 (COH), 78.6 (CH_2), 106.7 (C-4), 109.3 (C-3), 148.9 (C-2), 153.3 ppm (C-5); IR (ATR): $\tilde{\nu}$ = 3409 (w), 2925 (w), 1698 (w), 1550 (s), 1421 (w), 1379 (m), 1019 (m), 788 (m), 705 (m), 631 cm^{-1} (m); HRMS (EI, 70 eV, peak match): *m/z* calcd. for $[C_7H_9NO_4]^{\bullet+}$: 171.0526, found: 171.0526.

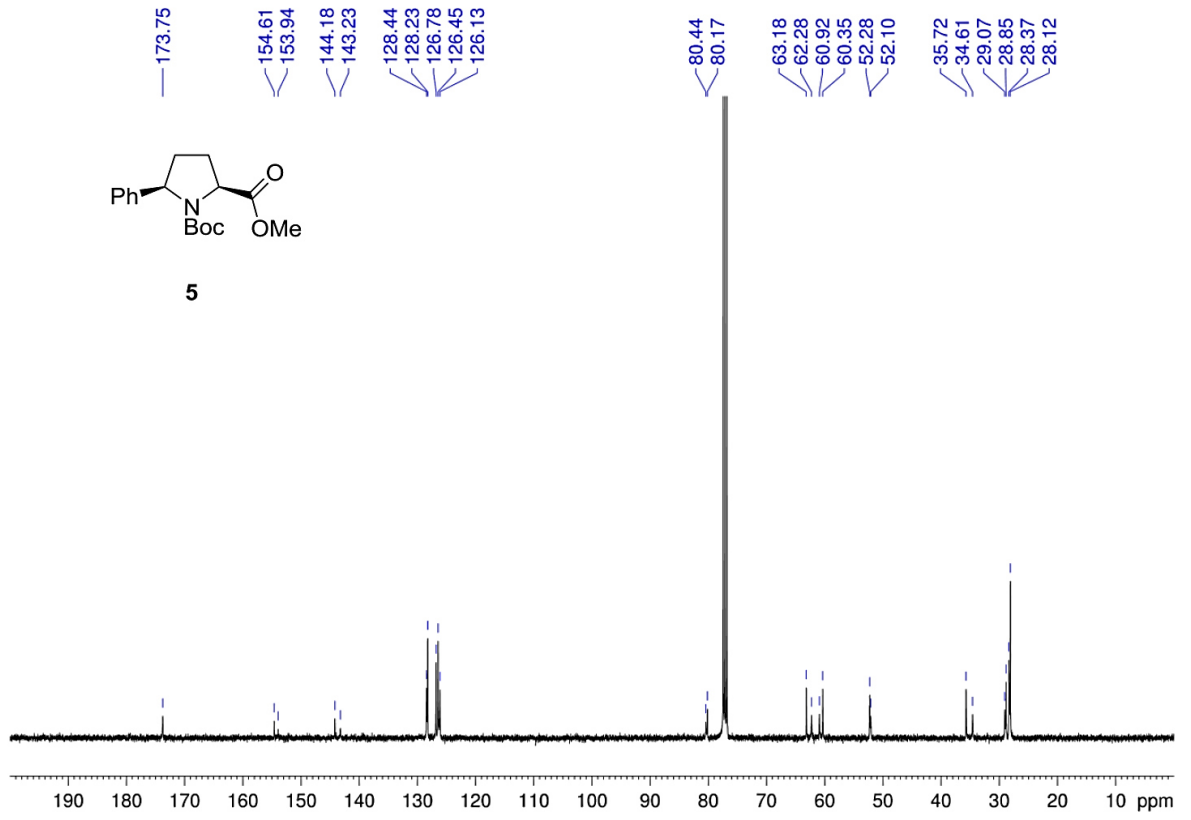
3.4.2. (*S*,*E*)-1-Nitrohept-3-en-2-ol (11b)



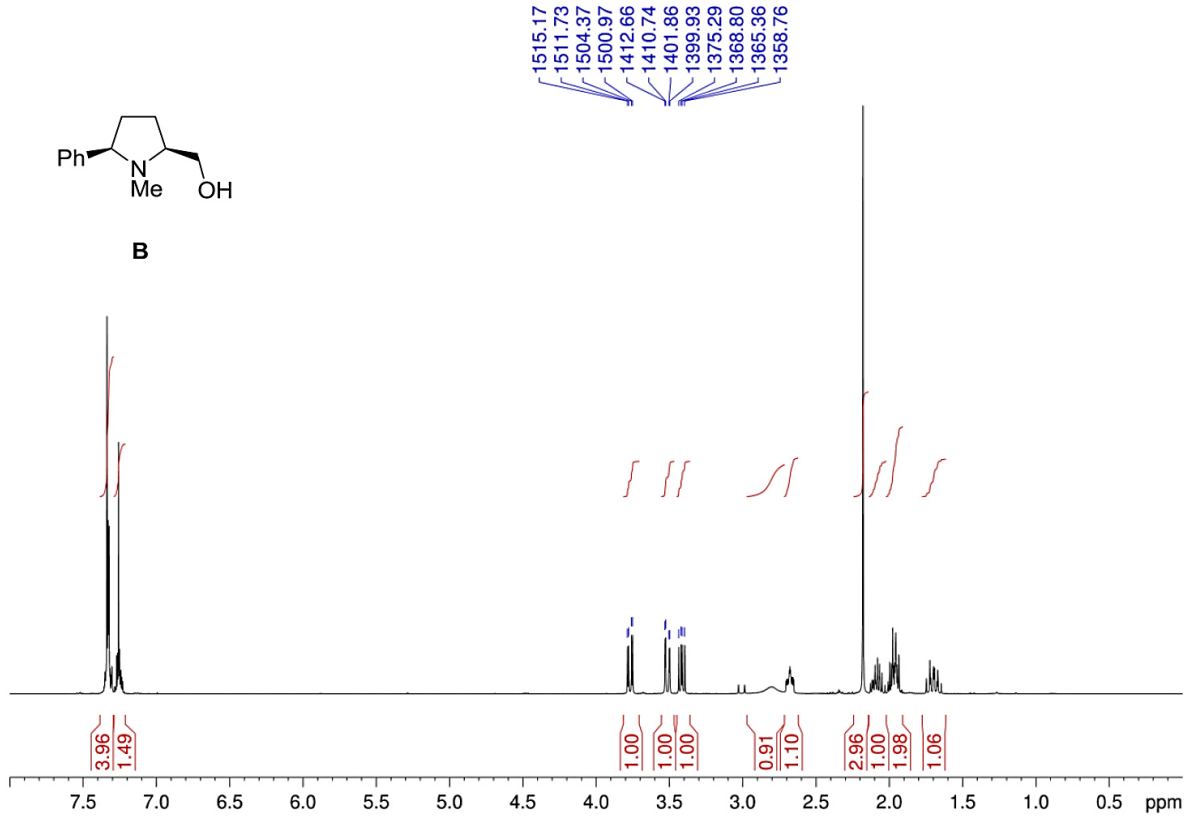
Ee = 98.7%; R_f = 0.21 (petrol ether/EtOAc 8:1); $[\alpha]_D^{28}$ = –1.4 (c = 1.00 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3H, 7-H), 1.41 (sext, *J* = 7.4 Hz, 2H, 6-H), 2.04 (q, *J* = 7.2 Hz, 2H, 5-H), 2.42 (d, *J* = 4.4 Hz, 1H, OH), 4.42 (m, 2H, CH_2NO_2), 4.82 (m, 1H, C*H*OH), 5.44 (ddt, *J* = 15.4, 6.7, 1.5 Hz, 1H, 3-H), 5.88 ppm (dtd, *J* = 15.4, 6.8, 1.0 Hz, 1H, 4-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7 (C-7), 22.1 (C-6), 34.4 (C-5), 69.8 (C-2), 80.2 (C-1), 126.3 (C-3), 136.1 ppm (C-4); IR (ATR): $\tilde{\nu}$ = 3415 (w), 2960 (w), 2932 (w), 2874 (w), 1671 (w), 1549 (s), 1379 (m), 1057 (w), 969 (m), 887 (w), 737 cm^{-1} (w); HRMS (EI, 70 eV, peak match): *m/z* calcd. for $[C_7H_{13}NO_3 - HNO_2]^{\bullet+}$: 112.0885, found: 112.0883.

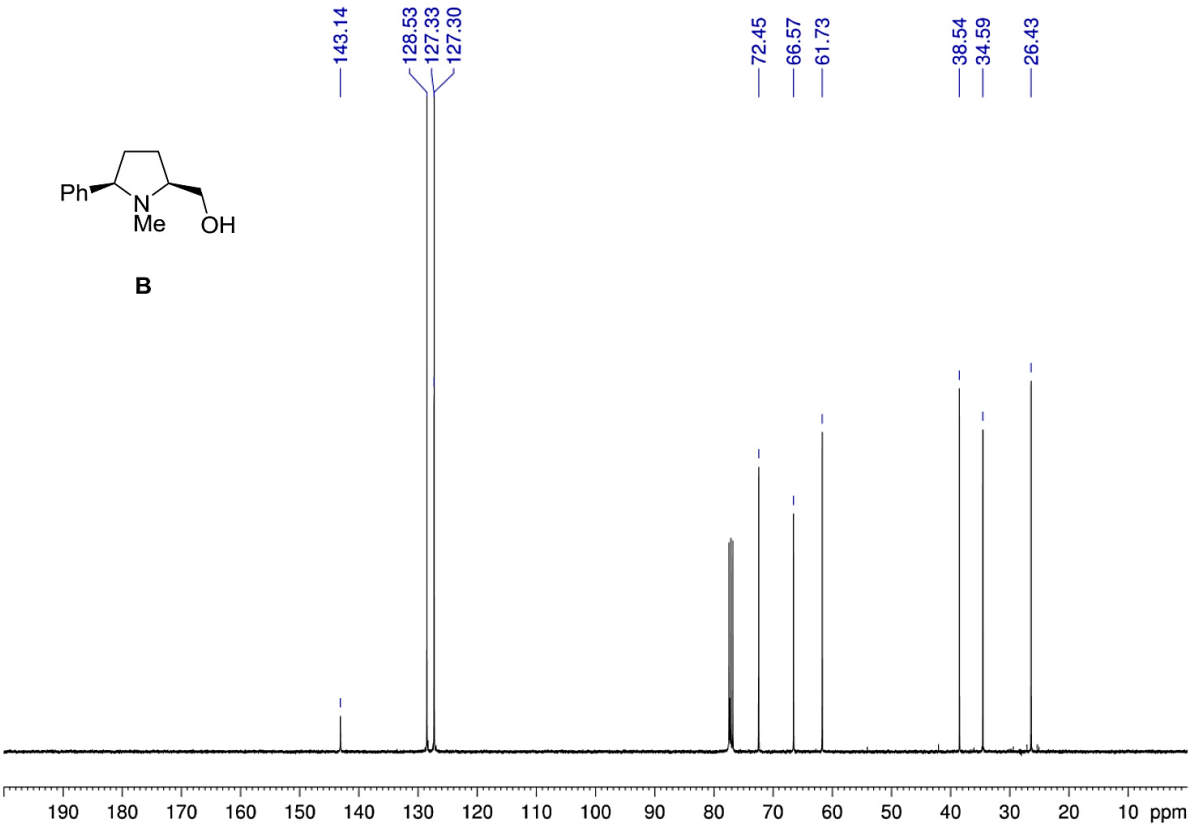
4. Copies of ^{1}H and ^{13}C NMR Spectra

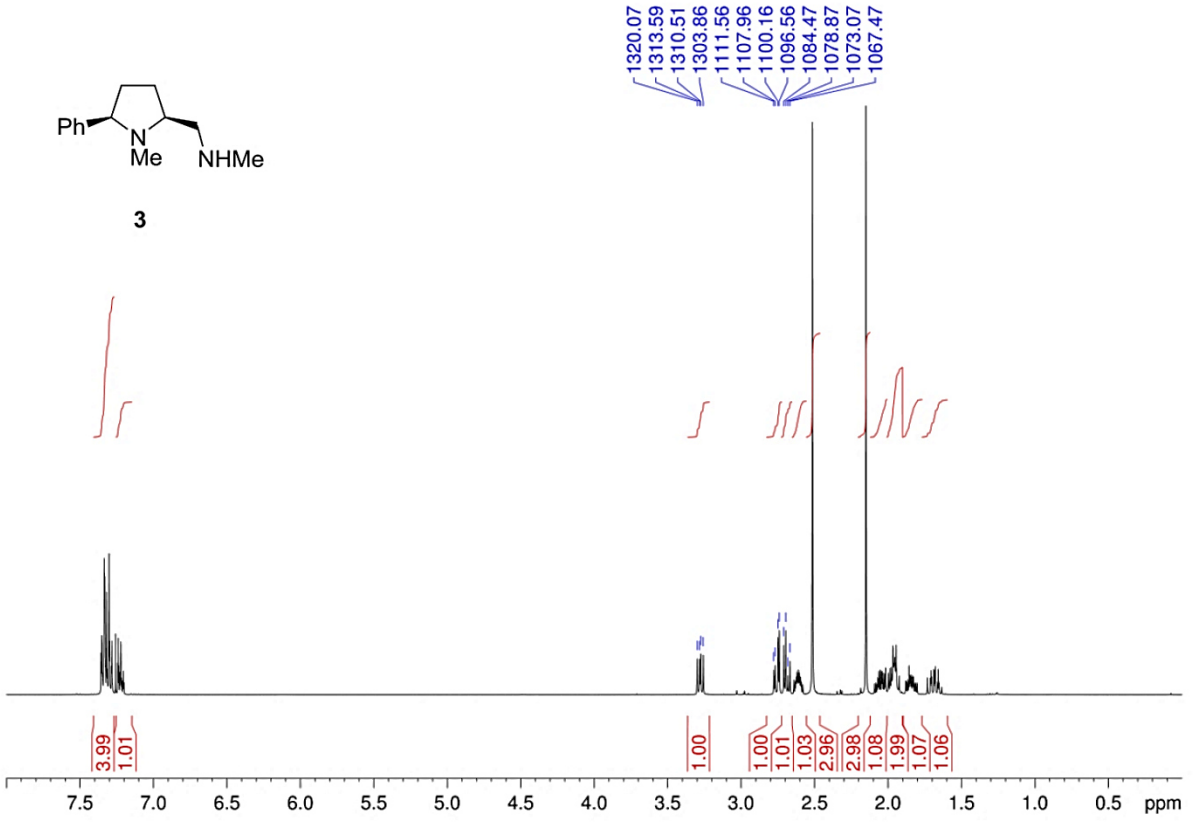


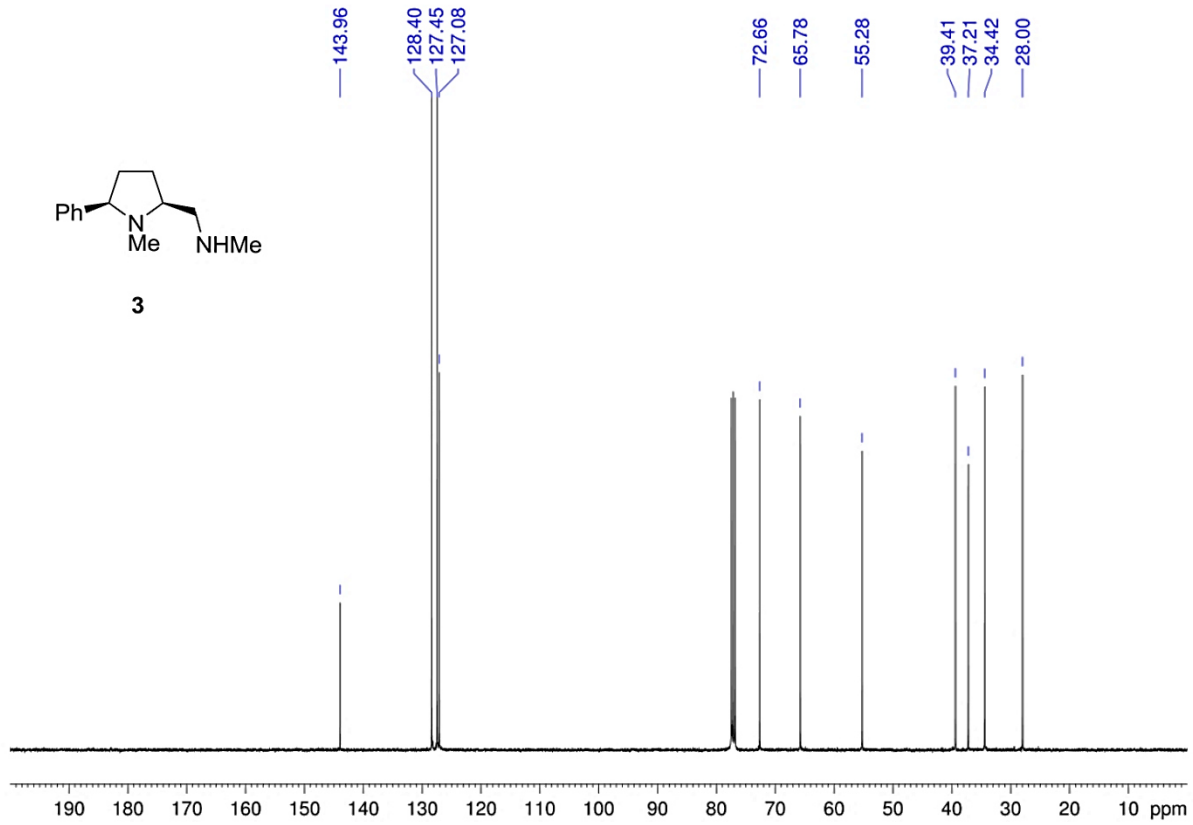


11

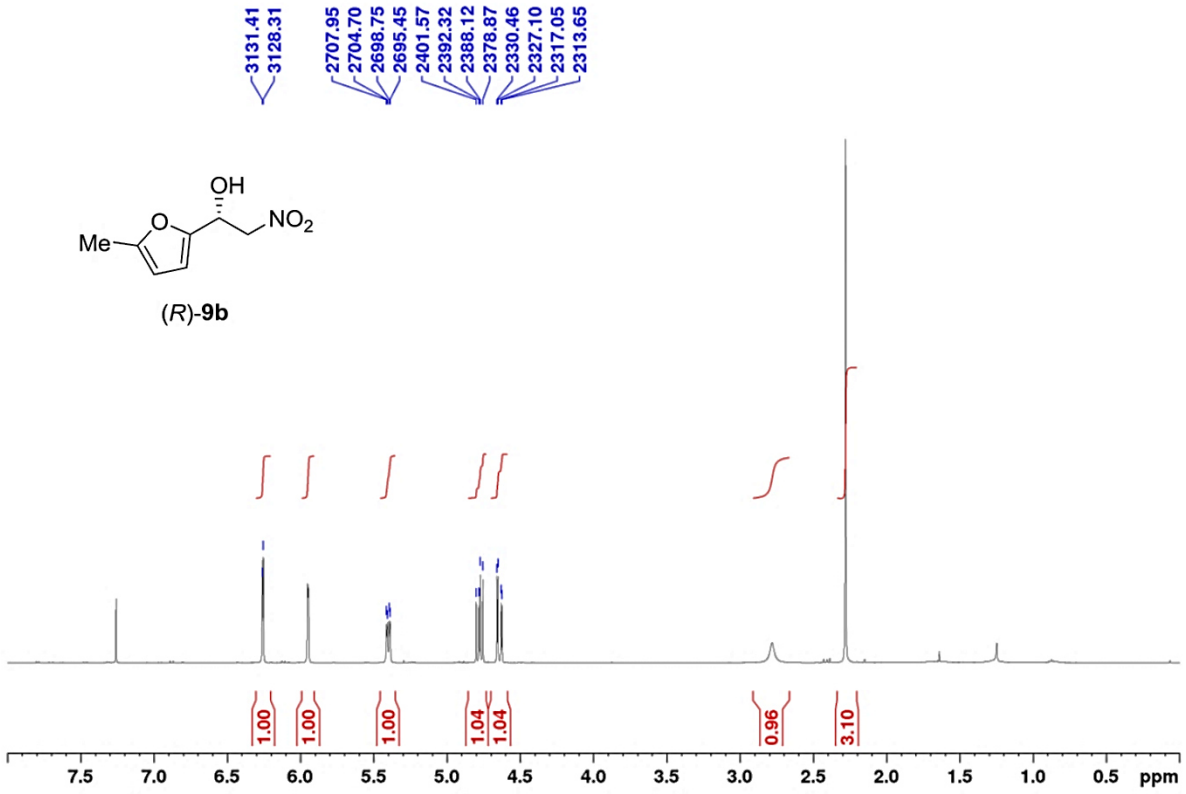

1515.17
1511.73
1504.37
1500.97
1412.66
1410.74
1401.86
1399.93
1375.29
1368.80
1365.36
1358.76
Ph
N
Me
OH
B
3.96
1.49
1.00
1.00
1.00
0.91
1.10
2.96
1.00
1.98
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

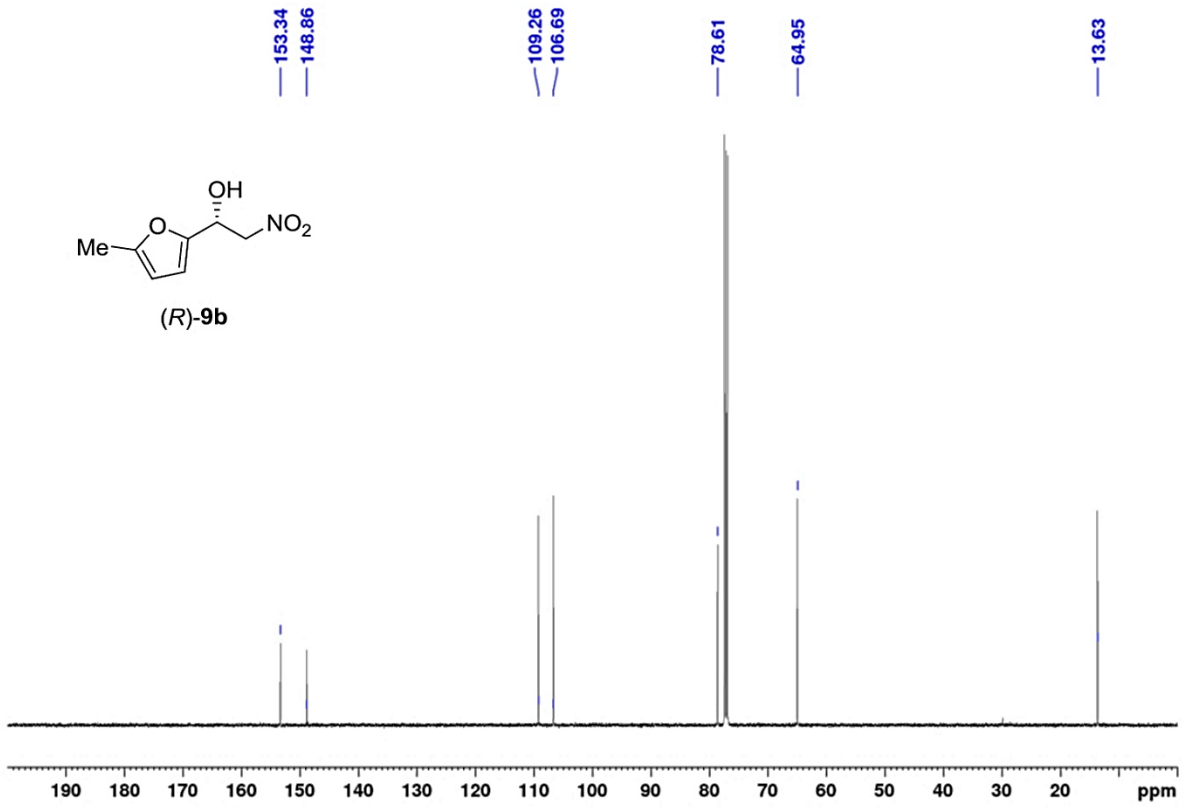

143.14
128.53
127.33
127.30
72.45
66.57
61.73
38.54
34.59
26.43
Ph
N
Me
OH
B
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

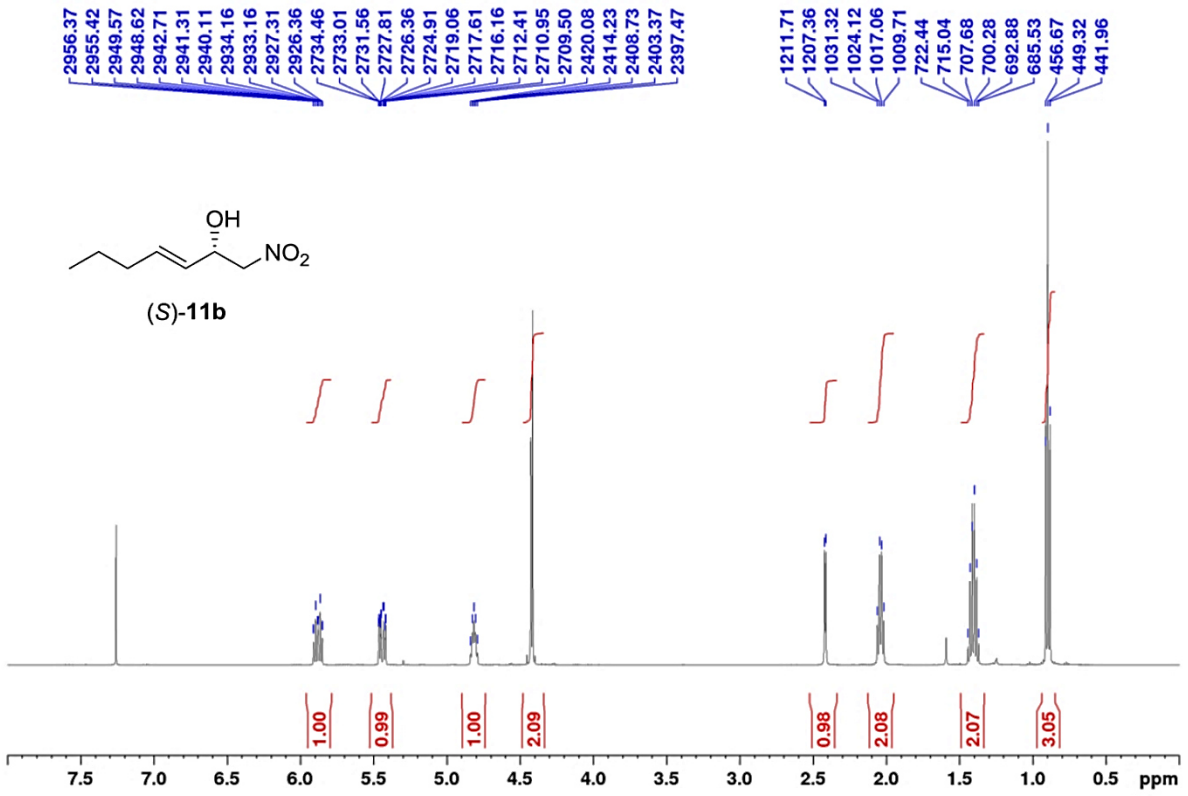

1320.07
1313.59
1310.51
1303.86
1111.56
1107.96
1100.16
1096.56
1084.47
1078.87
1073.07
1067.47
Ph
N
Me
NHMe
3
3.99
1.01
1.00
1.00
1.01
1.03
2.96
2.98
1.08
1.99
1.07
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

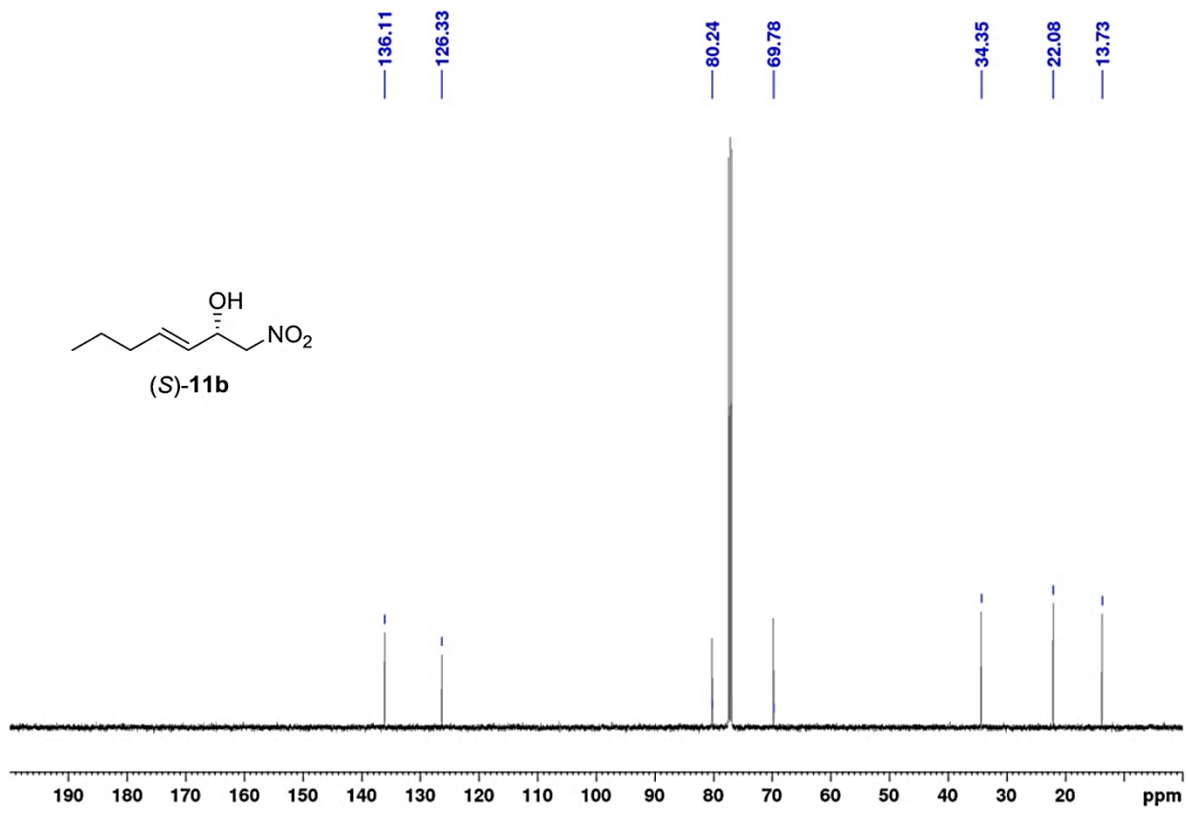

143.96
128.40
127.45
127.08
72.66
65.78
55.28
39.41
37.21
34.42
28.00
Ph
N
Me
NHMe
3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

13


3131.41
3128.31
2707.95
2704.70
2698.75
2695.45
2401.57
2392.32
2388.12
2378.87
2330.46
2327.10
2317.05
2313.65
OH
O
NO2
Me
(R)-9b
1.00
1.00
1.00
1.04
1.04
0.96
3.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

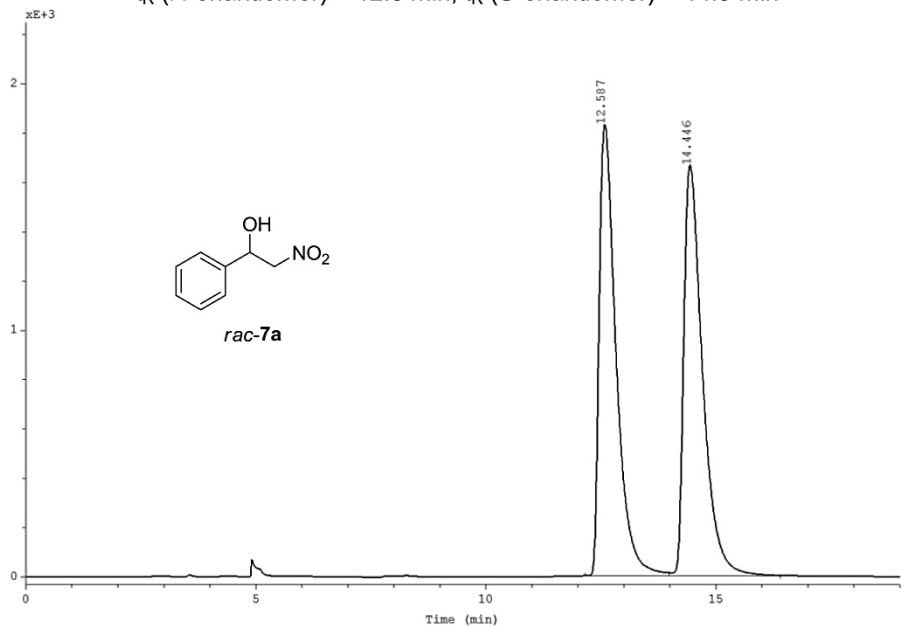

153.34
148.86
109.26
106.69
78.61
64.95
13.63
OH
O
NO2
Me
(R)-9b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


2956.37
2955.42
2949.57
2948.62
2942.71
2941.31
2940.11
2934.16
2933.16
2927.31
2926.36
2734.46
2733.01
2731.56
2727.81
2726.36
2724.91
2719.06
2717.61
2716.16
2712.41
2710.95
2709.50
2420.08
2414.23
2408.73
2403.37
2397.47
1211.71
1207.36
1031.32
1024.12
1017.06
1009.71
722.44
715.04
707.68
700.28
692.88
685.53
456.67
449.32
441.96
OH
NO2
(S)-11b
1.00
0.99
1.00
2.09
0.98
2.08
2.07
3.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

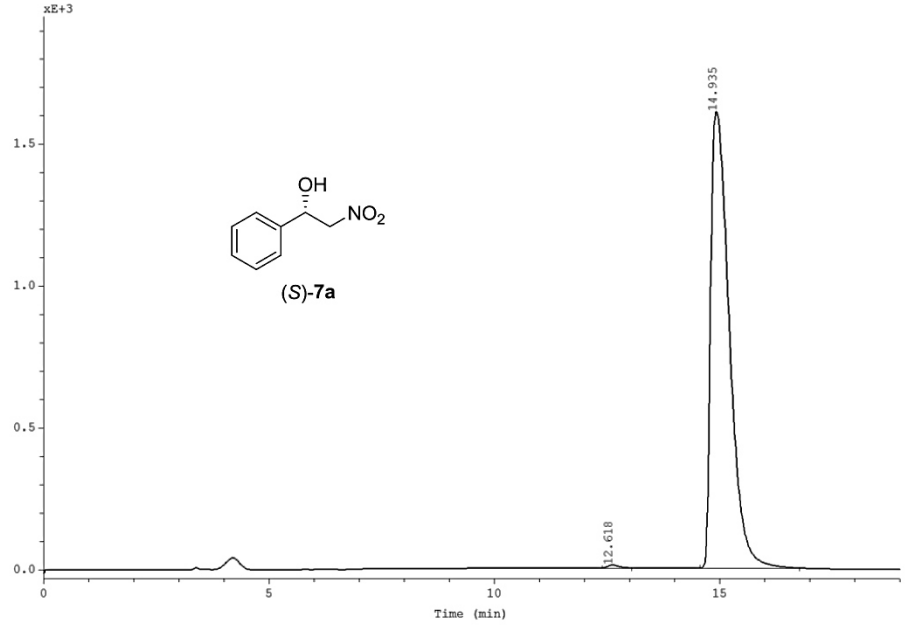

136.11
126.33
80.24
69.78
34.35
22.08
13.73
OH
NO2
(S)-11b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

5. Copies of HPLC Spectra

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.8 mL/min, 215 nm:
t_R (*R*-enantiomer) = 12.6 min; t_R (*S*-enantiomer) = 14.9 min



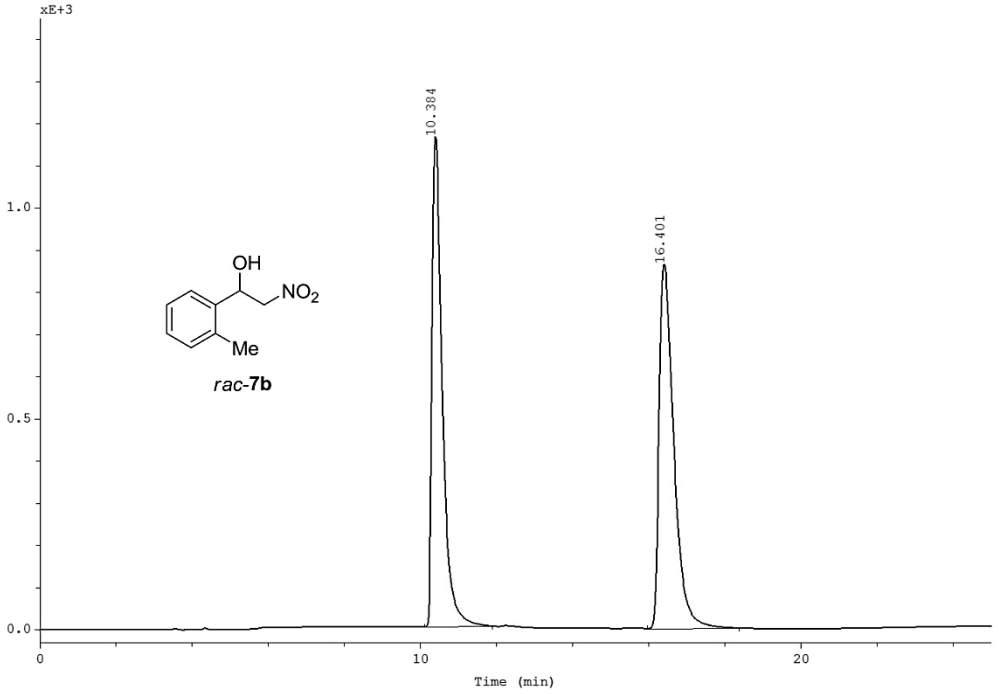
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.59	12.16	13.98	1831.20	780.62	52.38	49.81
2	14.45	13.98	16.40	1665.09	786.54	47.62	50.19



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.62	12.39	13.05	10.32	2.86	0.64	0.37
2	14.93	14.56	16.77	1609.83	767.79	99.36	99.63

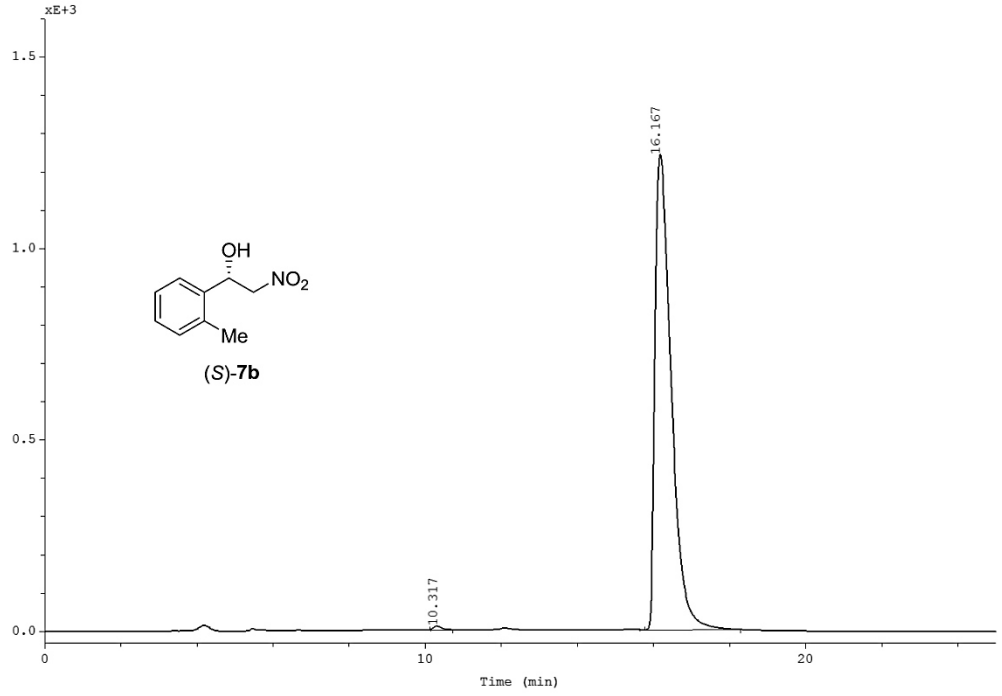
16

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 10.3 min; t_R (*S*-enantiomer) = 16.2 min



rac-**7b**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.38	10.10	11.88	1162.30	364.12	57.35	48.51
2	16.40	15.96	18.37	864.51	386.44	42.65	51.49

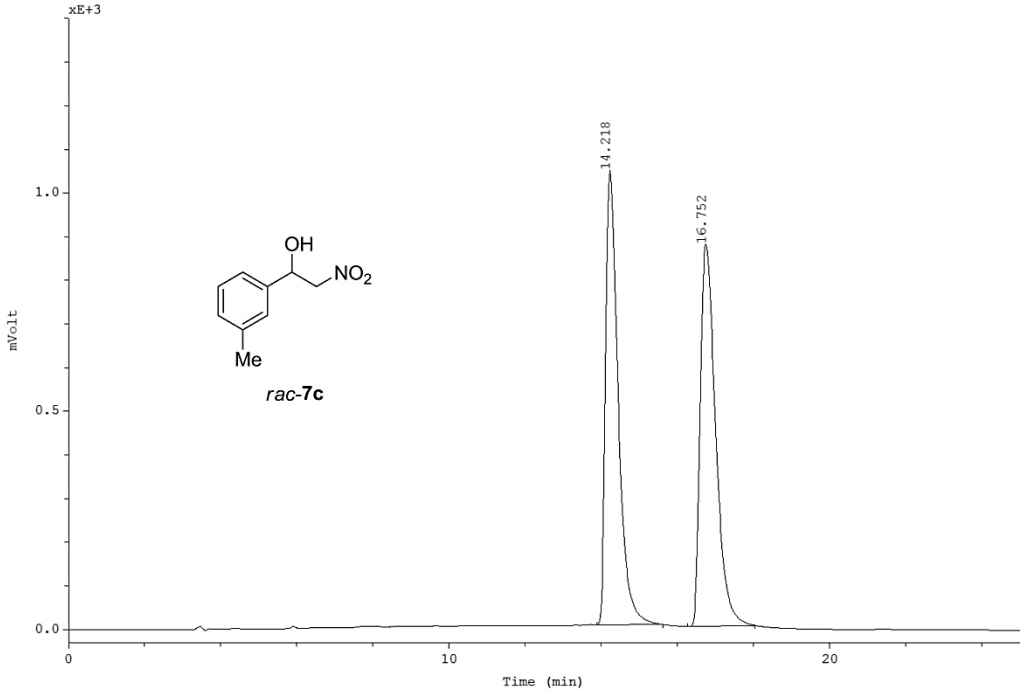


(*S*)-**7b**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.32	10.12	10.72	9.85	2.43	0.79	0.40
2	16.17	15.76	18.29	1240.90	613.36	99.21	99.60

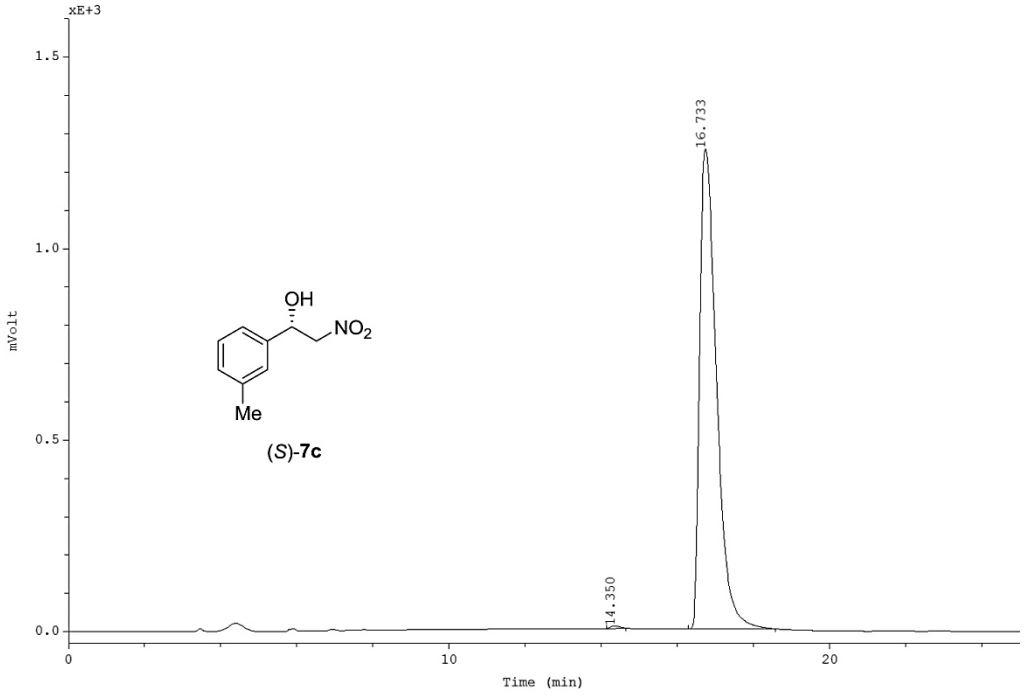
17

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.4 min; t_R (*S*-enantiomer) = 16.7 min



rac-**7c**

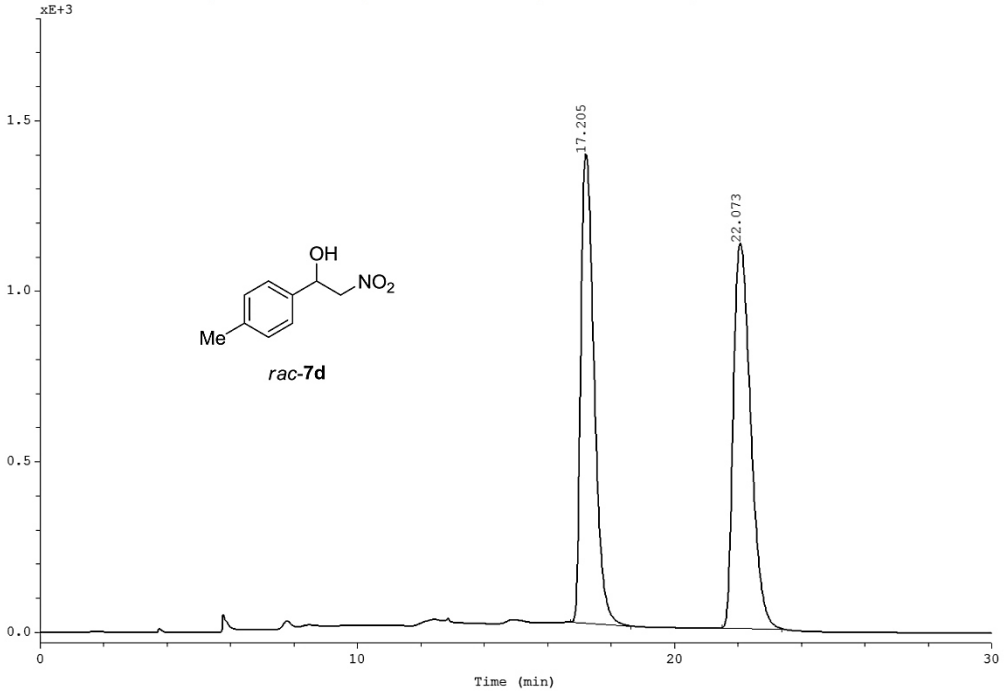
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.22	13.88	15.62	1040.79	401.61	54.35	49.45
2	16.75	16.26	18.03	874.27	410.58	45.65	50.55



(*S*)-**7c**

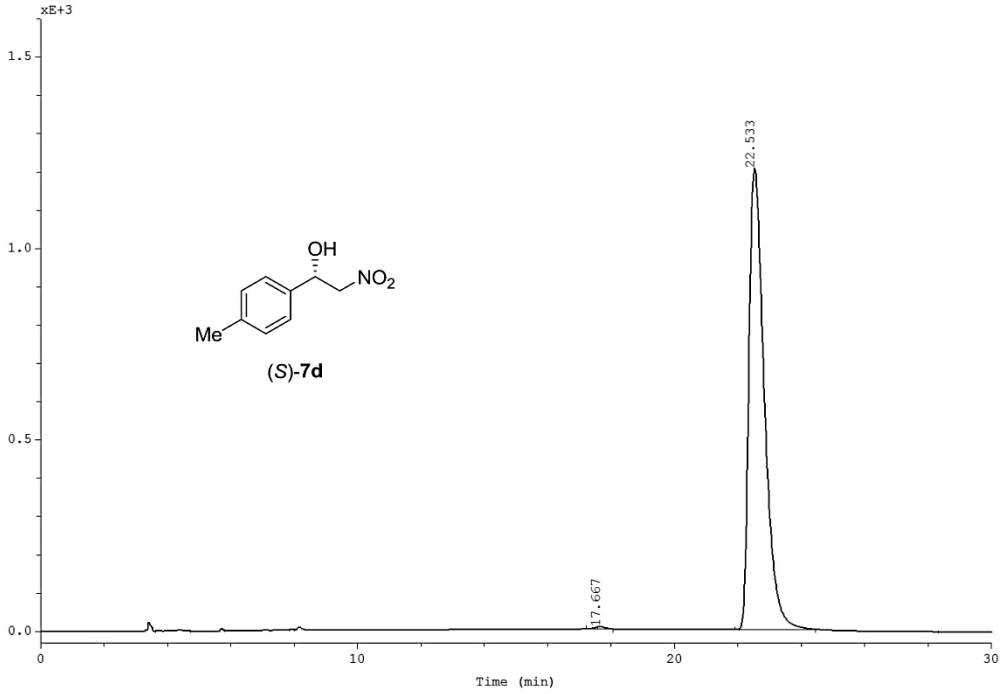
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.35	14.14	14.63	6.58	1.75	0.52	0.27
2	16.73	16.28	18.57	1253.18	640.34	99.48	99.73

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 17.7 min; t_R (*S*-enantiomer) = 22.5 min



rac-**7d**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	17.20	16.73	18.62	1376.24	672.41	54.93	48.51
2	22.07	21.49	23.38	1129.06	713.66	45.07	51.49

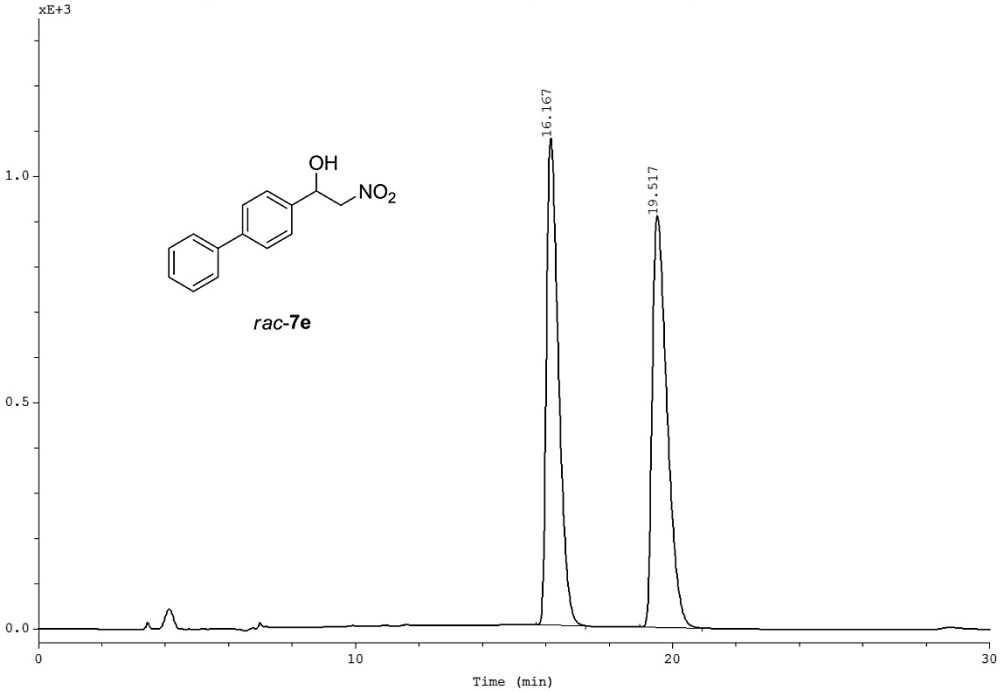


(*S*)-**7d**

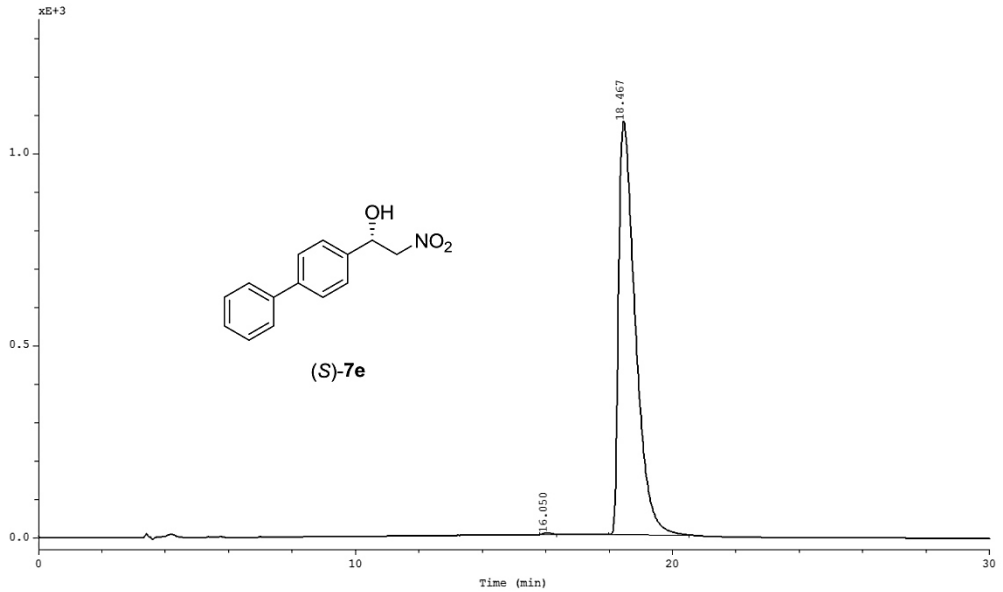
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	17.67	17.22	18.05	5.47	1.93	0.45	0.28
2	22.53	21.91	24.46	1205.63	679.96	99.55	99.72

19

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 16.1 min; t_R (*S*-enantiomer) = 18.5 min



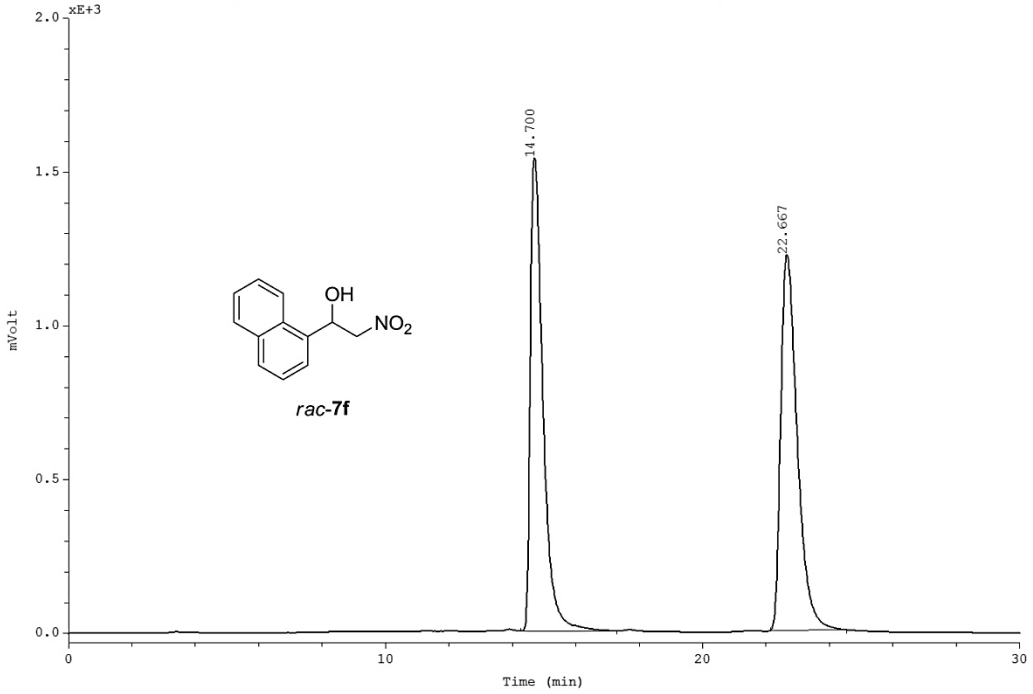
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.17	15.69	17.25	1076.49	474.73	54.17	48.99
2	19.52	18.96	20.93	910.74	494.41	45.83	51.01



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.05	15.80	16.34	4.32	1.28	0.40	0.19
2	18.47	17.98	20.53	1076.75	655.12	99.60	99.81

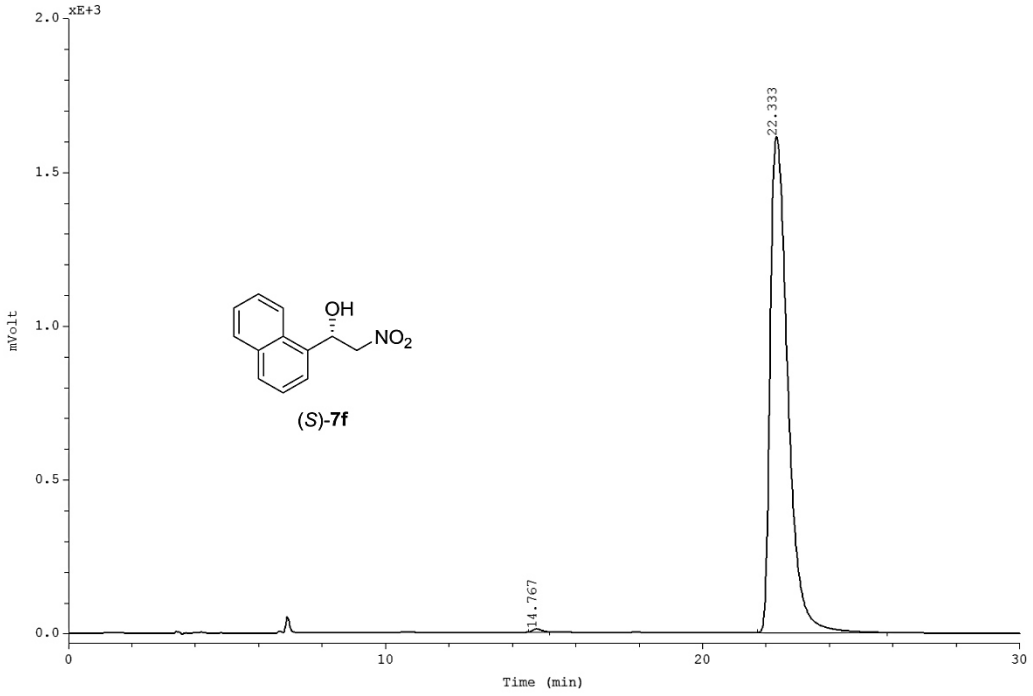
20

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.8 min; t_R (*S*-enantiomer) = 22.3 min



rac-**7f**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.70	14.27	17.29	1538.67	714.07	55.73	49.21
2	22.67	22.15	24.54	1222.22	737.10	44.27	50.79

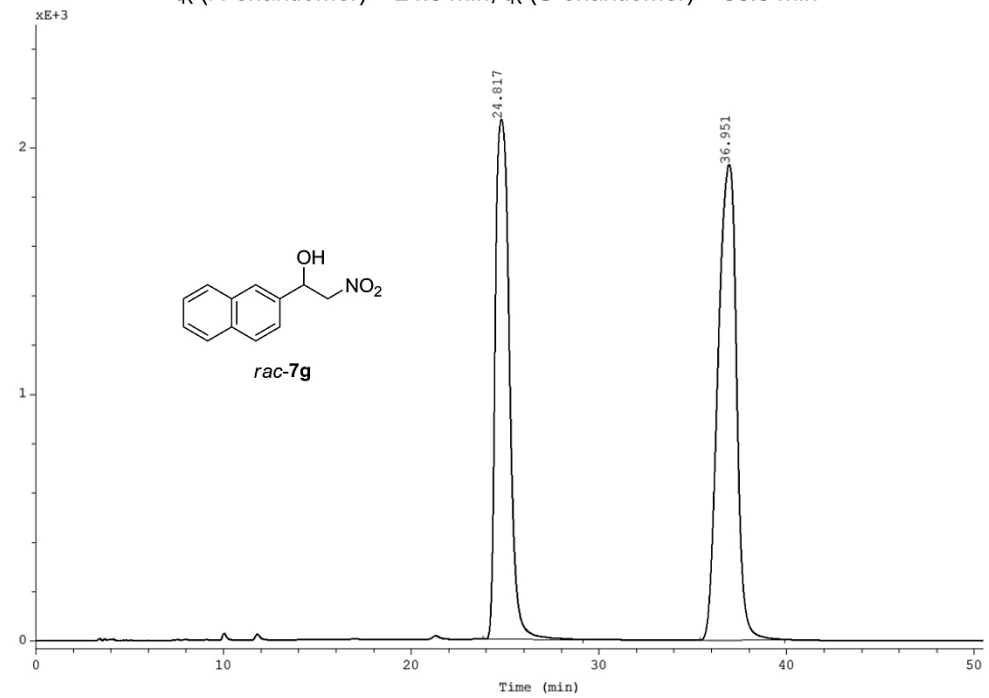


(*S*)-**7f**

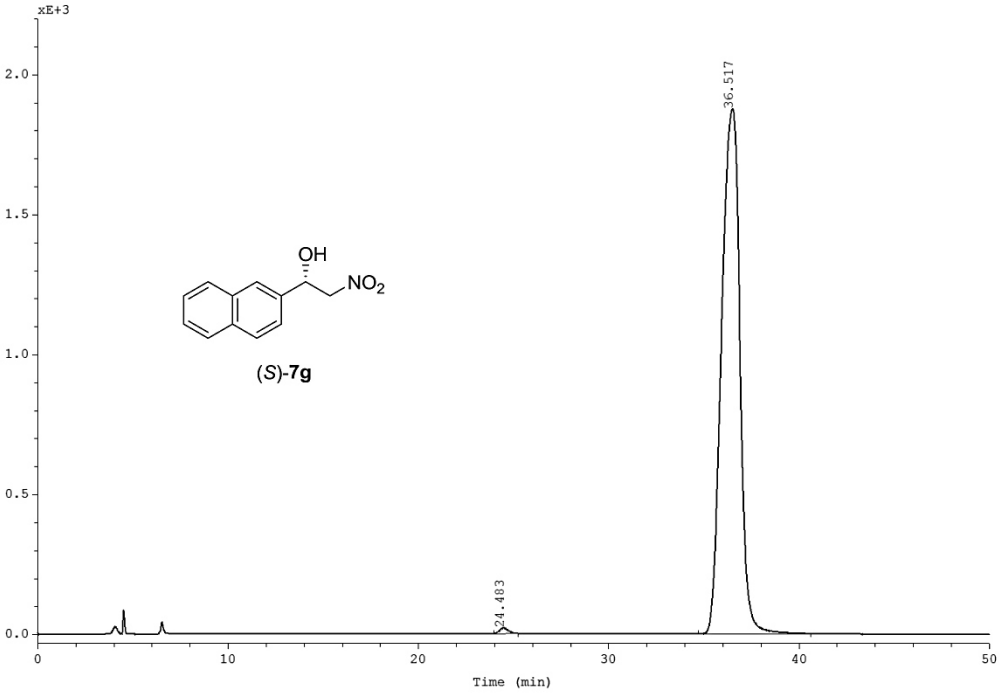
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.77	14.51	15.17	9.96	3.19	0.61	0.31
2	22.33	21.74	25.83	1613.72	1040.01	99.39	99.69

21

Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 24.5 min; t_R (*S*-enantiomer) = 36.5 min

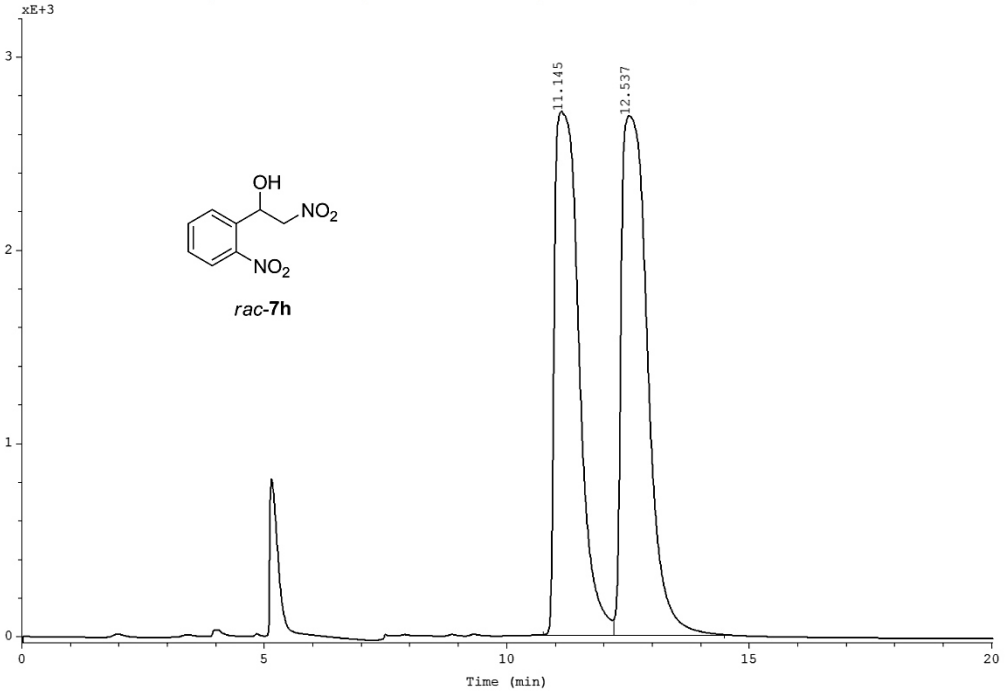


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	24.82	23.83	29.16	2108.09	1822.63	52.23	45.19
2	36.95	35.41	39.89	1928.16	2210.96	47.77	54.81

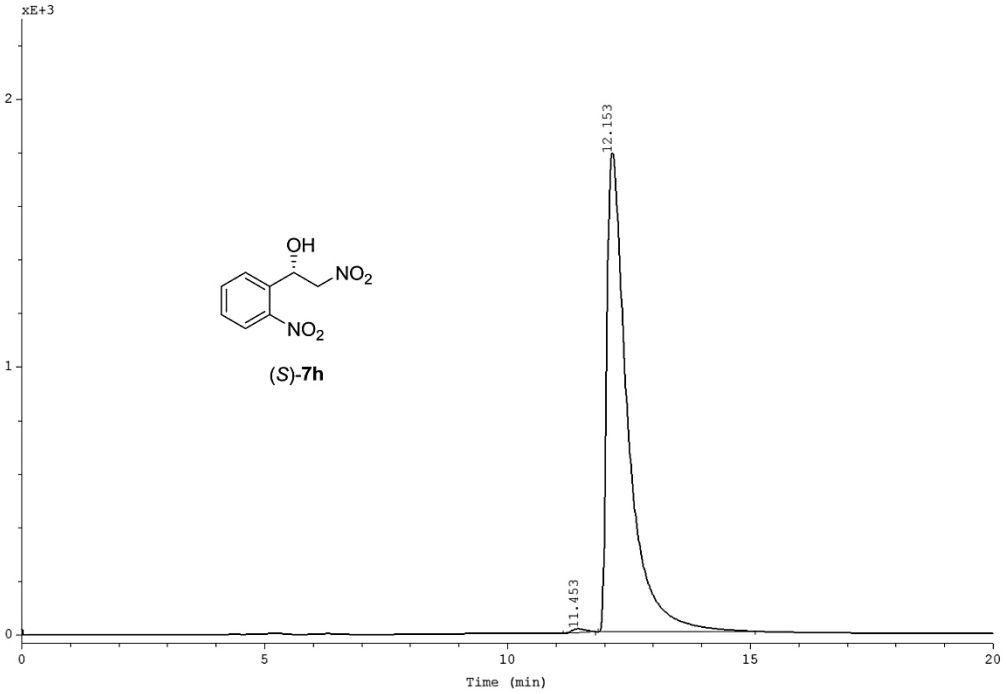


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	24.48	23.96	25.23	19.78	10.91	1.04	0.52
2	36.52	34.72	40.61	1874.37	2081.89	98.96	99.48

Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.7 mL/min, 215 nm:
t_R (*R*-enantiomer) = 11.5 min; t_R (*S*-enantiomer) = 12.2 min



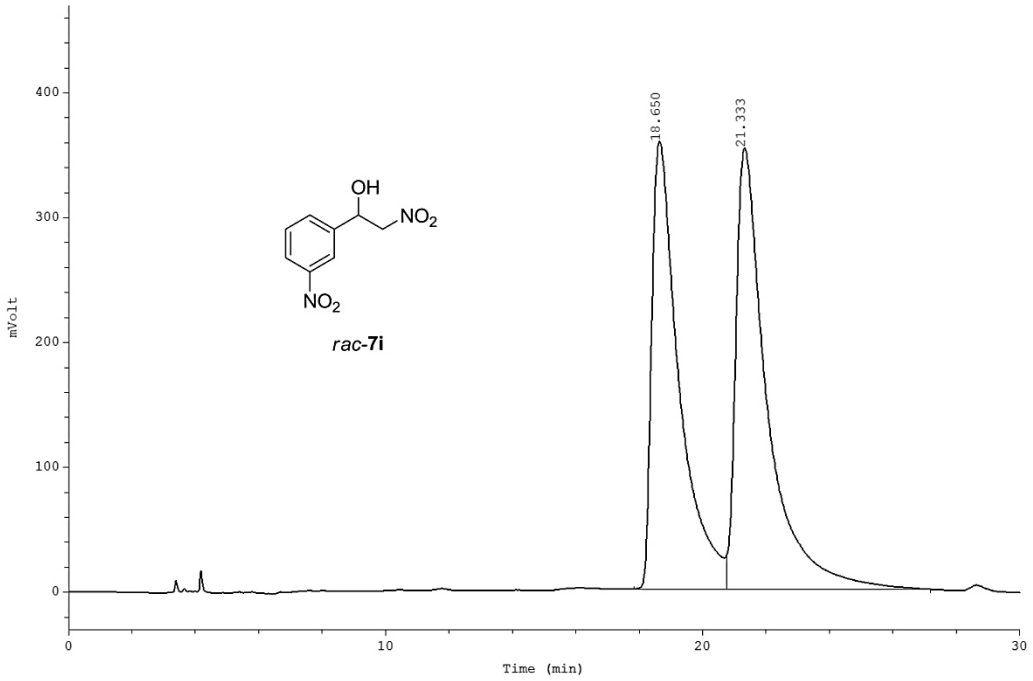
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.14	10.76	12.21	2710.17	1575.84	50.22	48.33
2	12.54	12.21	14.49	2686.59	1684.53	49.78	51.67



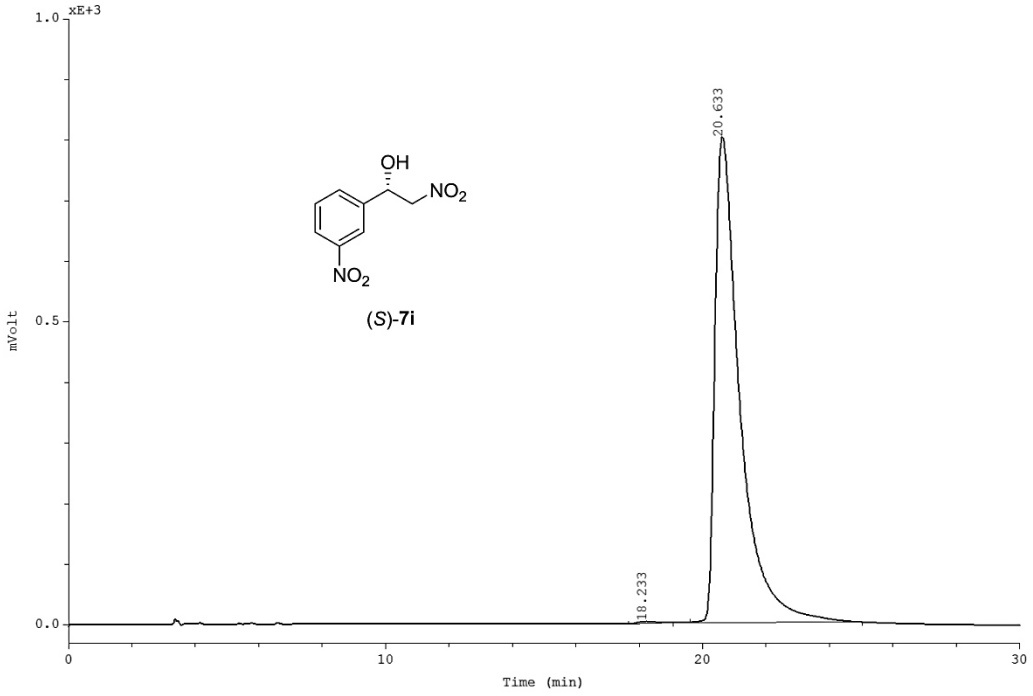
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.45	11.14	11.81	13.83	4.51	0.77	0.50
2	12.15	11.87	15.10	1785.65	897.70	99.23	99.50

23

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 18.2 min; t_R (*S*-enantiomer) = 20.6 min

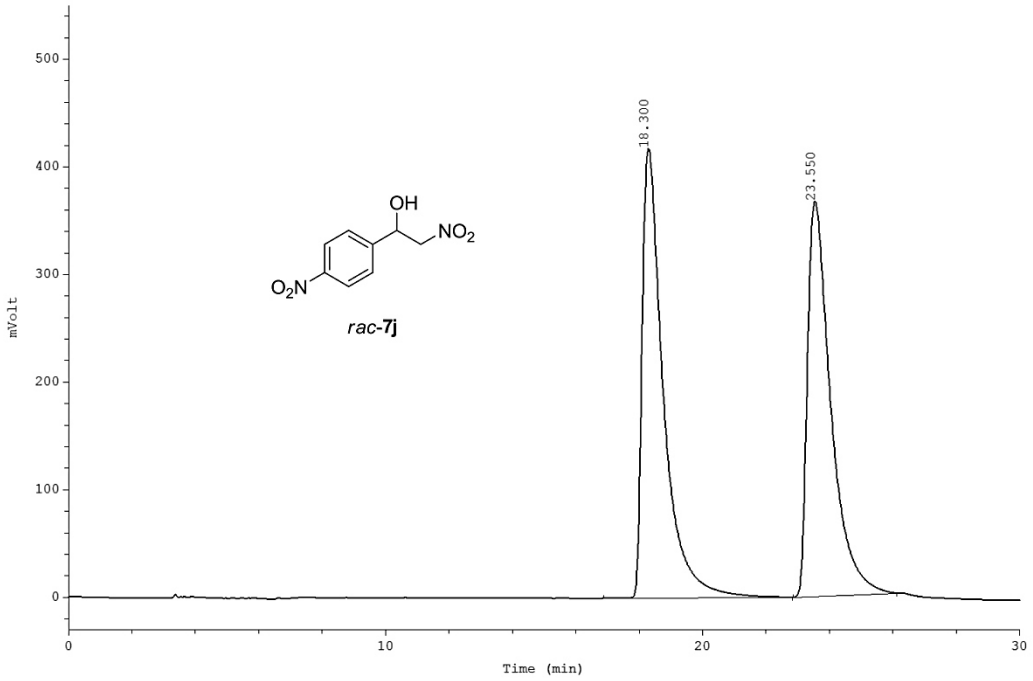


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	18.65	17.84	20.75	358.87	360.39	50.38	47.07
2	21.33	20.75	27.19	353.53	405.22	49.63	52.93



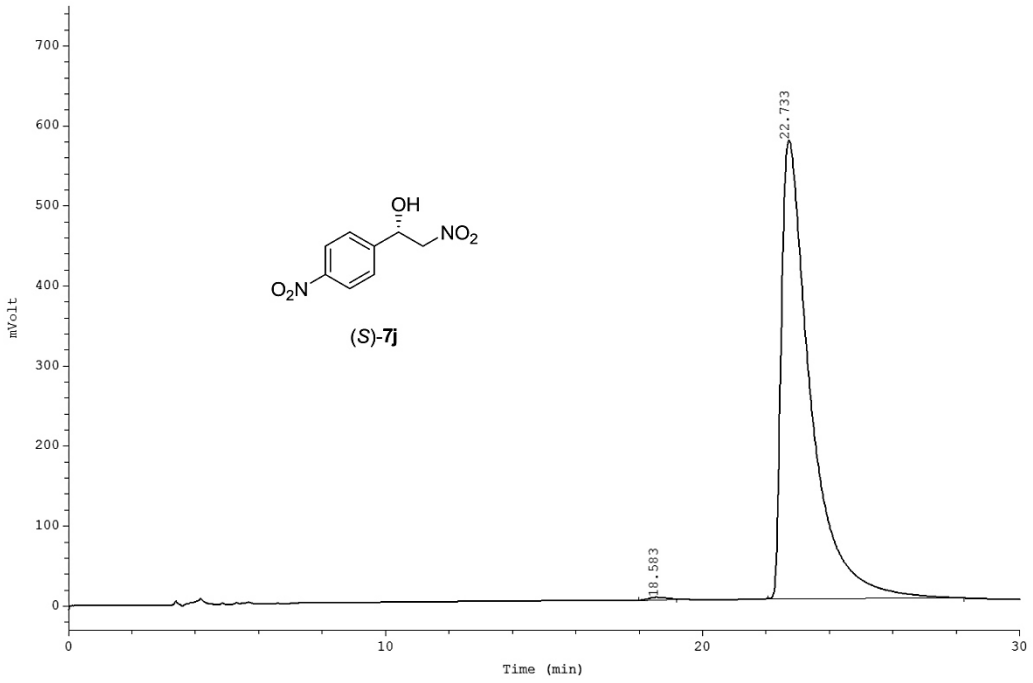
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	18.23	17.65	19.07	3.39	2.19	0.42	0.30
2	20.63	19.62	25.04	800.89	729.32	99.58	99.70

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 18.6 min; t_R (*S*-enantiomer) = 22.7 min



rac-**7j**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	18.30	16.88	22.83	418.14	325.02	53.25	50.94
2	23.55	22.87	26.12	367.11	313.04	46.75	49.06

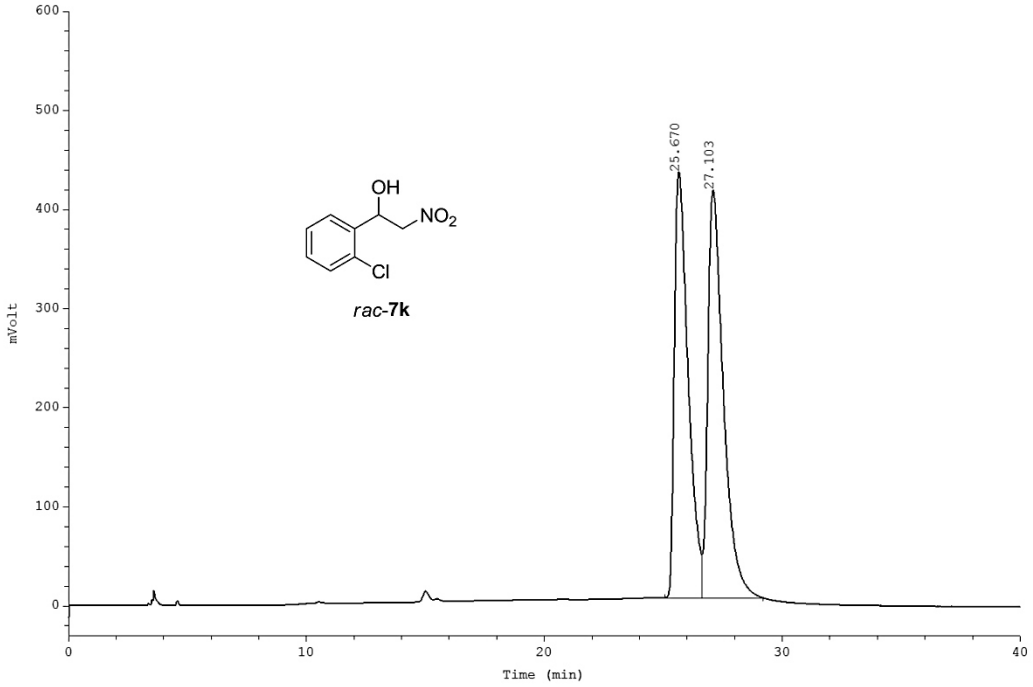


(*S*)-**7j**

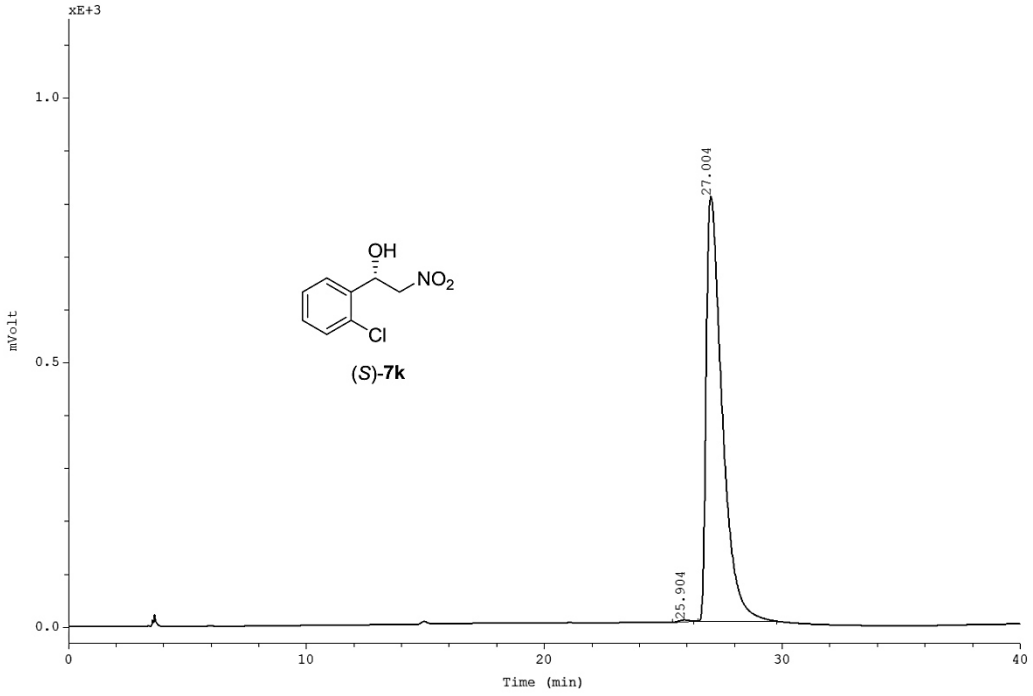
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	18.58	17.98	19.18	2.84	1.78	0.49	0.29
2	22.73	22.06	28.24	573.10	607.04	99.51	99.71

25

Chiralcel OD-3, *n*-hexane/*i*PrOH 97:3, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 25.9 min; t_R (*S*-enantiomer) = 27.0 min

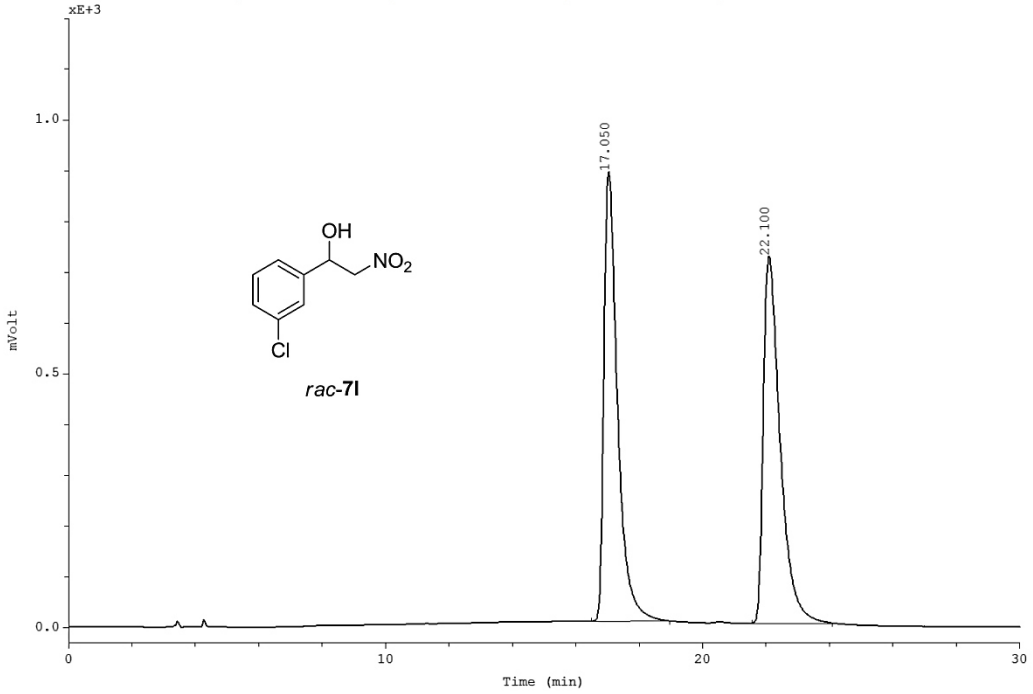


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	25.67	25.06	26.63	429.59	287.24	51.07	47.77
2	27.10	26.63	29.20	411.57	314.01	48.93	52.23



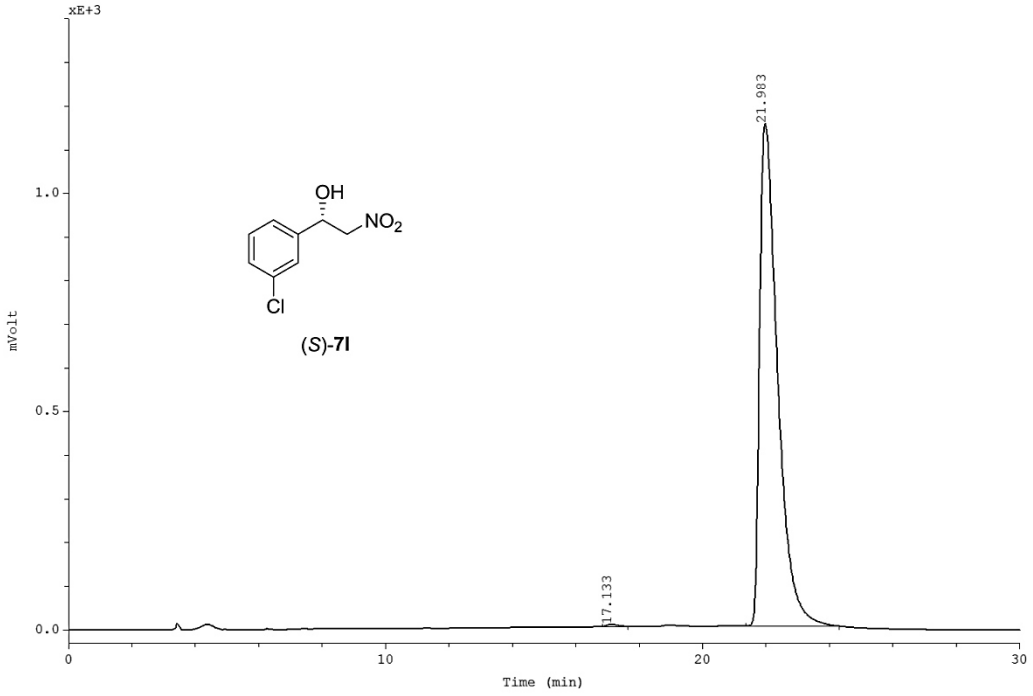
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	25.90	25.39	26.29	3.15	1.40	0.39	0.22
2	27.00	26.44	29.77	803.87	625.77	99.61	99.78

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 17.1 min; t_R (*S*-enantiomer) = 22.0 min



rac-**7l**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	17.05	16.49	18.96	885.84	441.20	55.04	49.73
2	22.10	21.55	24.10	723.73	445.92	44.96	50.27

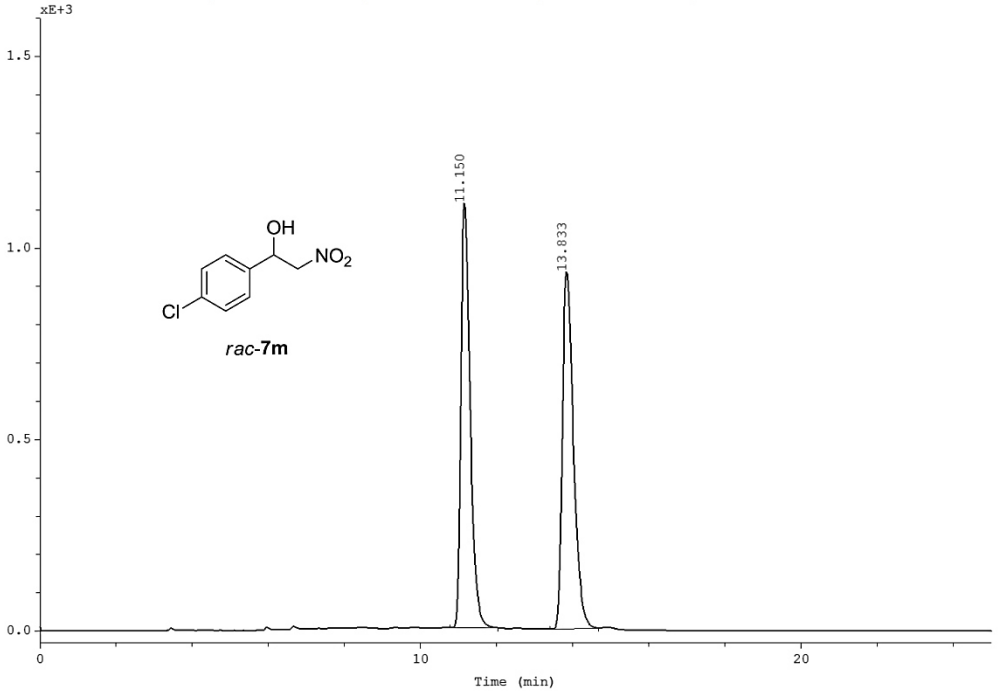


(*S*)-**7l**

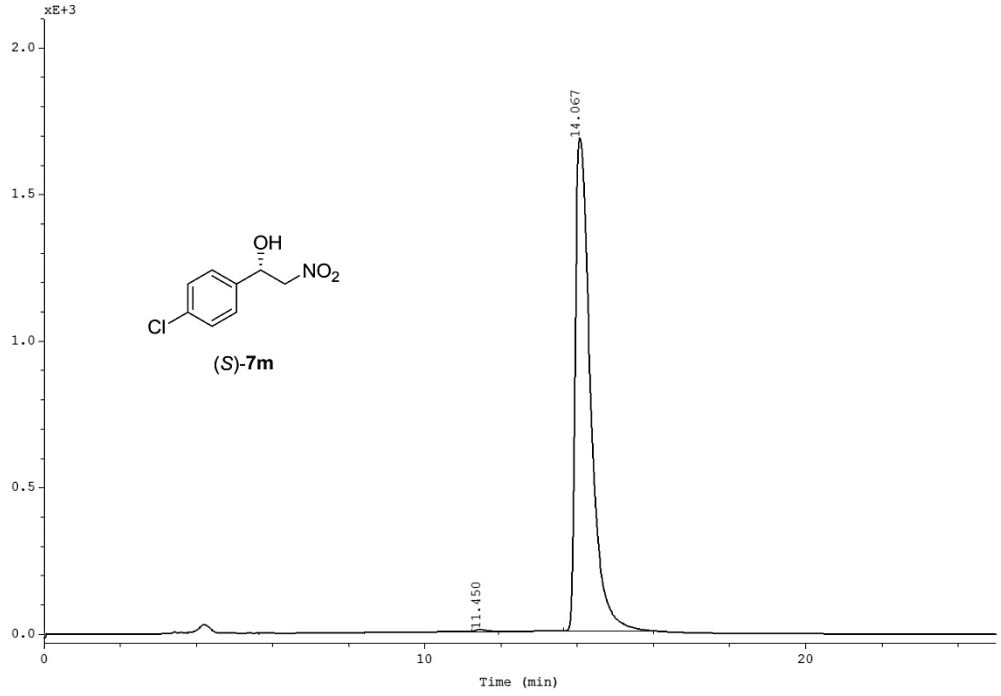
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	17.13	16.85	17.65	4.84	1.90	0.42	0.25
2	21.98	21.37	24.31	1150.93	758.59	99.58	99.75

27

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 11.5 min; t_R (*S*-enantiomer) = 14.1 min

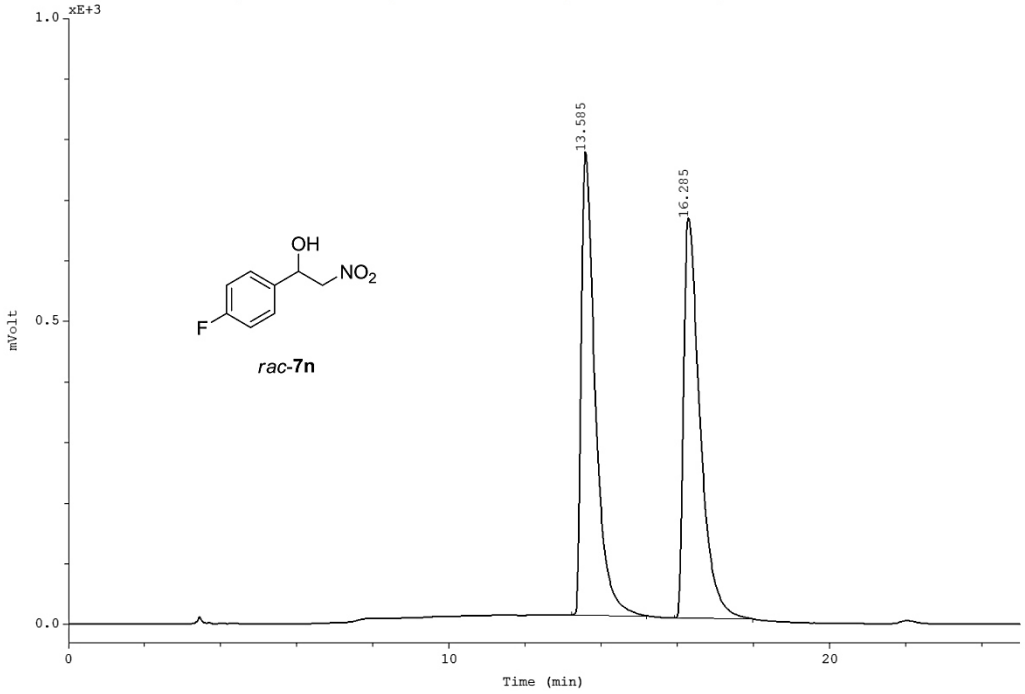


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.15	10.76	12.04	1108.84	312.44	54.33	49.86
2	13.83	13.40	14.67	932.05	314.24	45.67	50.14



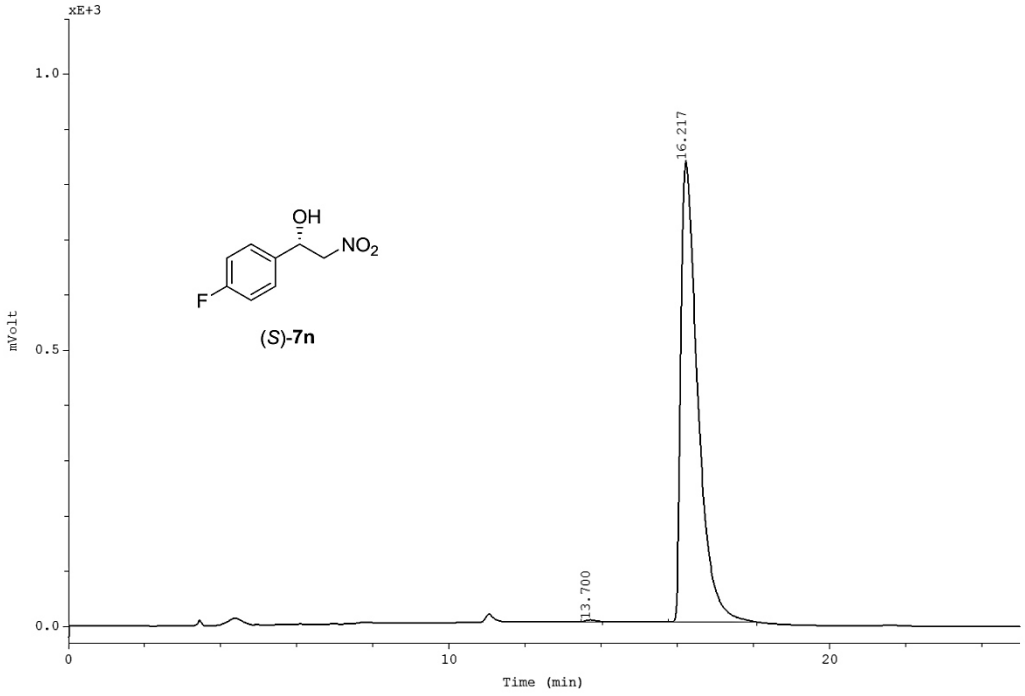
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.45	11.22	11.94	7.00	2.13	0.41	0.27
2	14.07	13.64	16.01	1681.56	784.33	99.59	99.73

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 13.7 min; t_R (*S*-enantiomer) = 16.2 min



rac-**7n**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.58	13.22	15.19	765.06	327.09	53.66	49.66
2	16.28	15.92	17.98	660.77	331.63	46.34	50.34

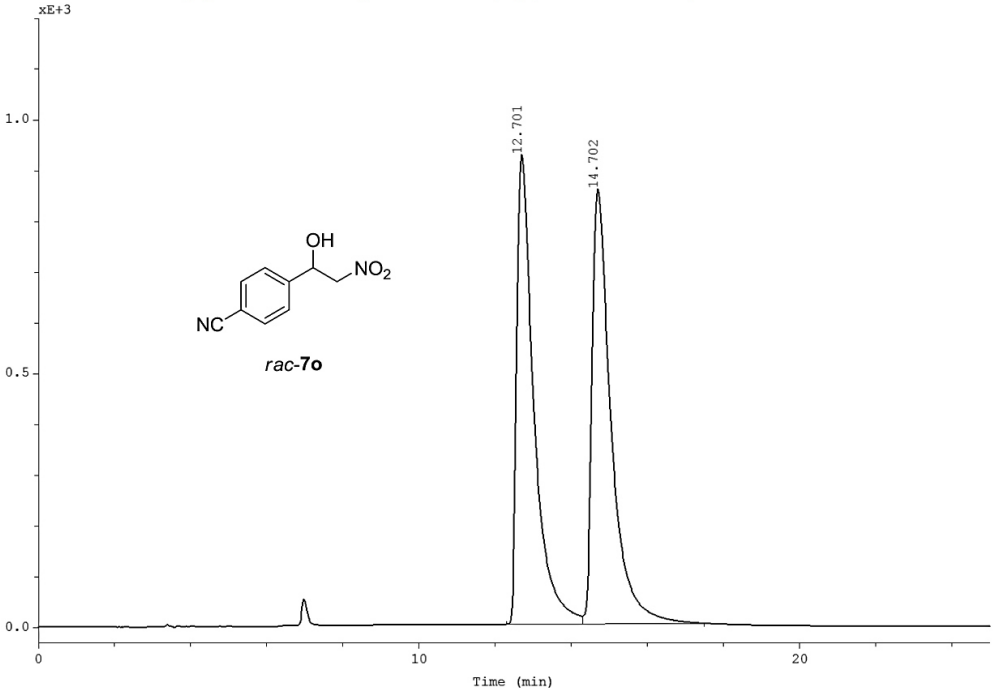


(*S*)-**7n**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.70	13.47	14.02	2.98	0.86	0.36	0.20
2	16.22	15.75	18.08	835.16	430.87	99.64	99.80

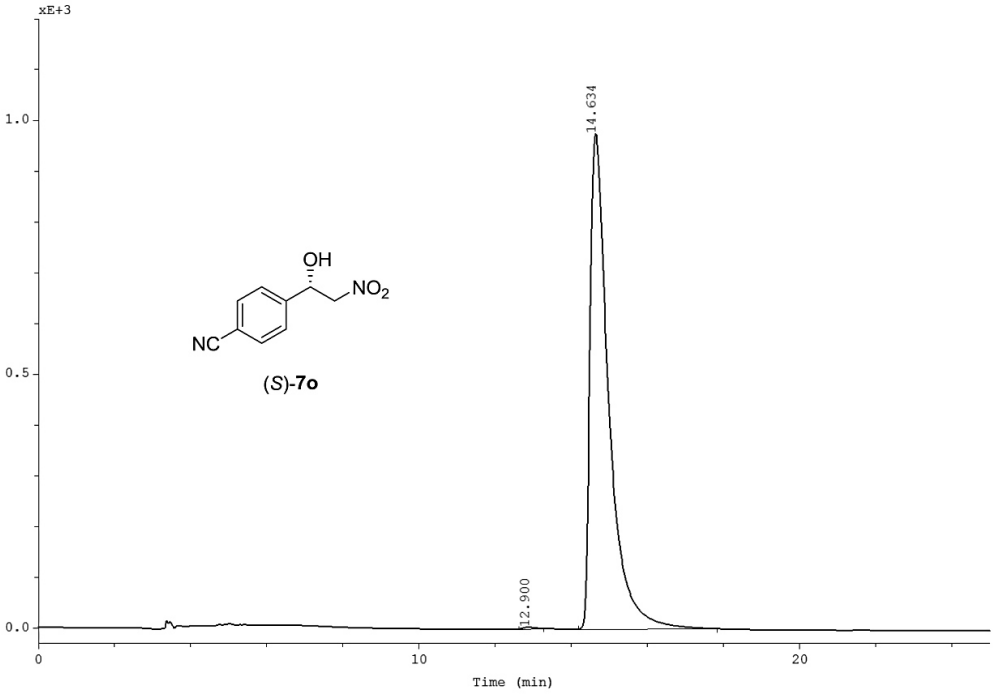
29

Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 12.9 min; t_R (*S*-enantiomer) = 14.6 min



rac-**7o**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.70	12.29	14.30	926.32	488.62	51.93	49.44
2	14.70	14.30	17.49	857.36	499.75	48.07	50.56

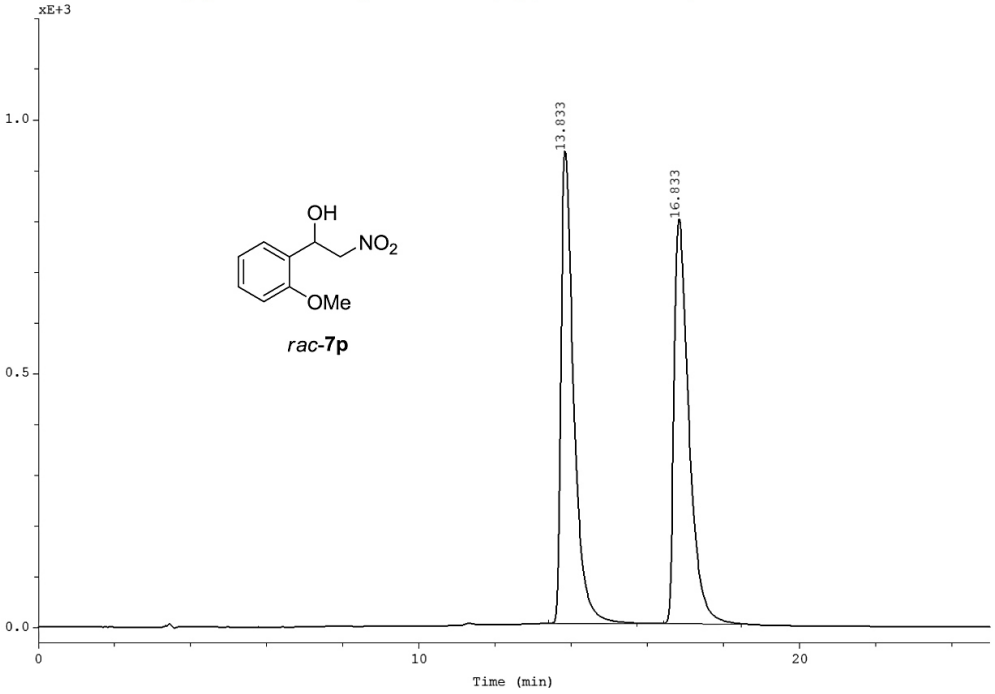


(*S*)-**7o**

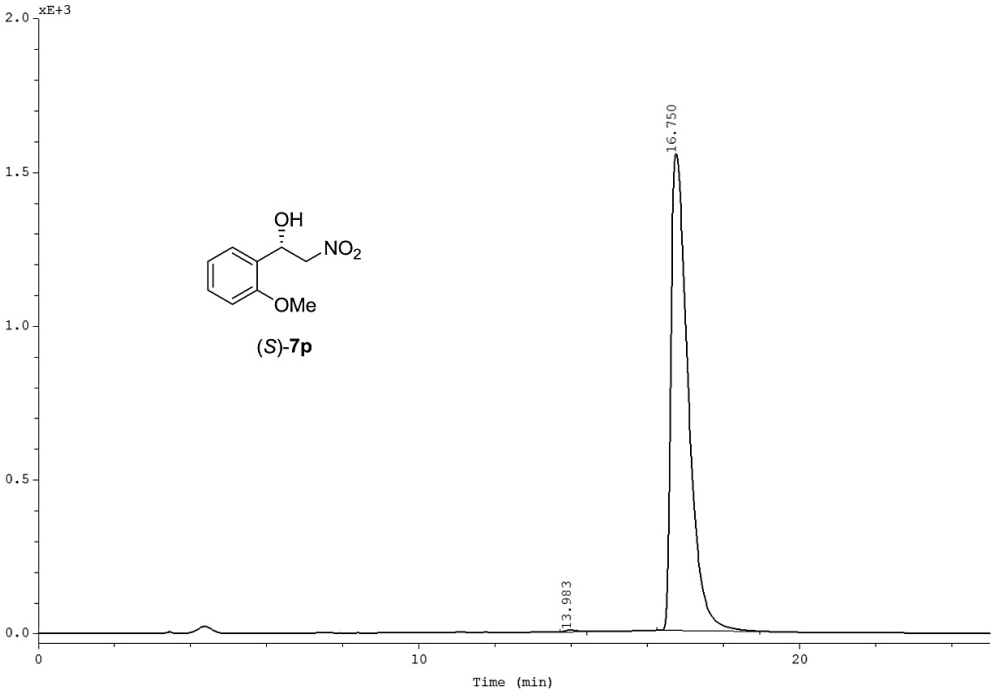
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.90	12.61	13.27	3.26	1.16	0.33	0.21
2	14.63	14.19	17.83	976.92	560.04	99.67	99.79

30

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.0 min; t_R (*S*-enantiomer) = 16.8 min



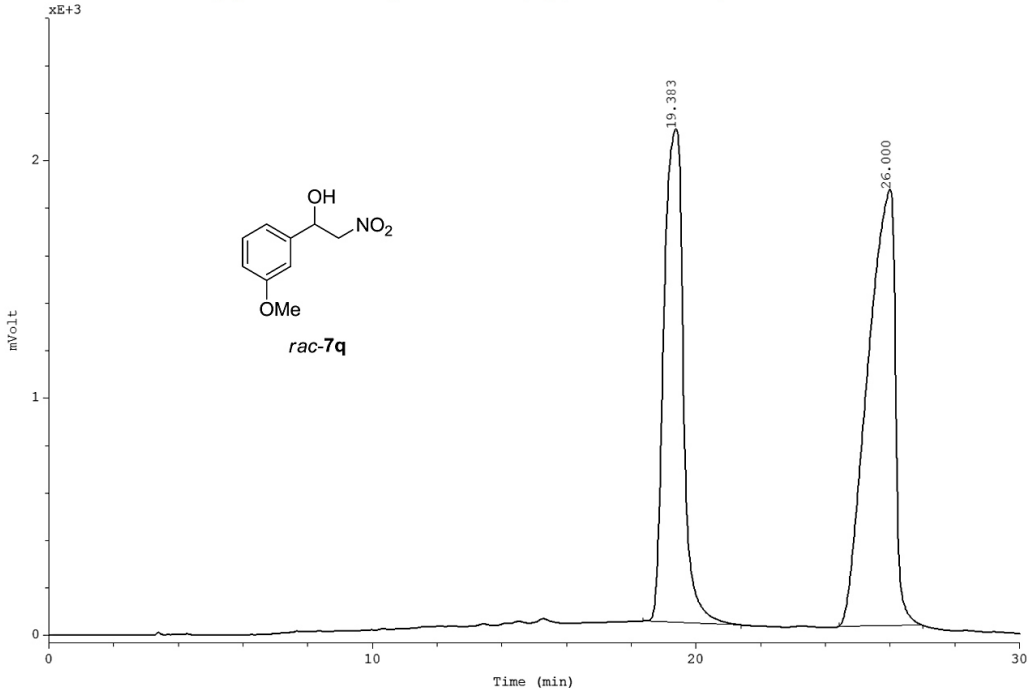
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.83	13.40	15.72	930.88	359.90	53.83	49.96
2	16.83	16.42	18.45	798.32	360.49	46.17	50.04



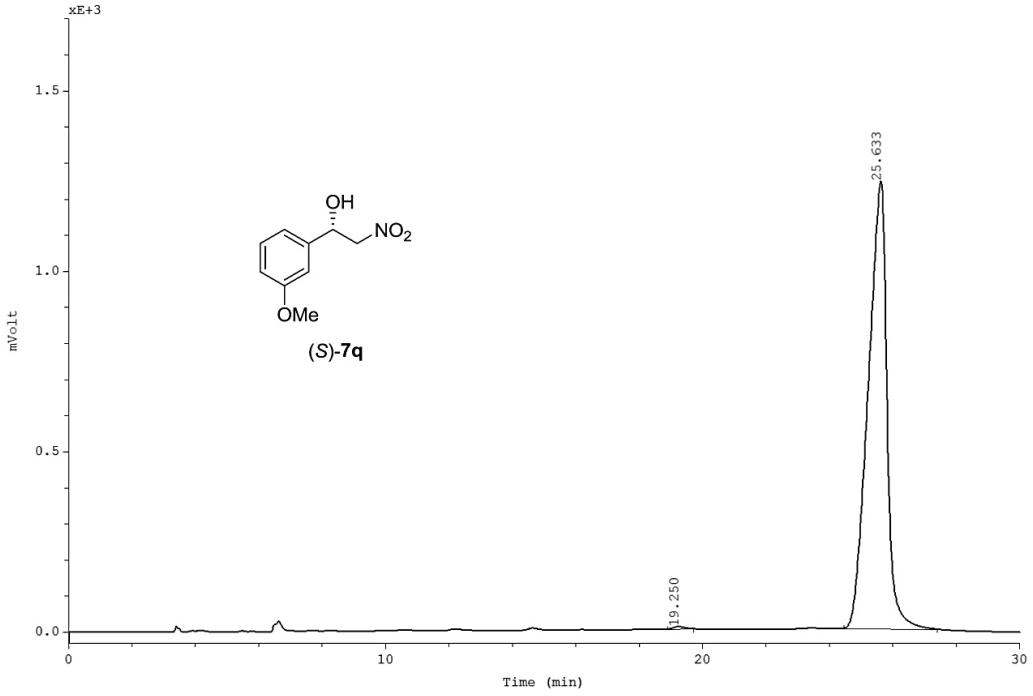
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.98	13.70	14.40	6.16	1.98	0.40	0.24
2	16.75	16.25	18.95	1551.47	812.47	99.60	99.76

31

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 19.3 min; t_R (*S*-enantiomer) = 25.6 min



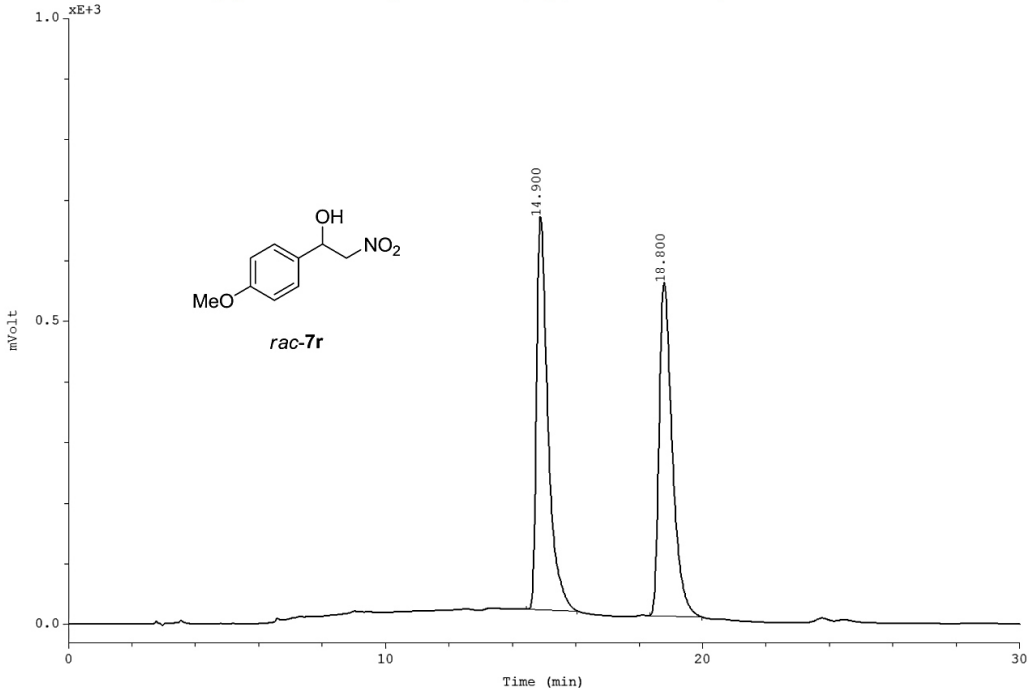
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	19.38	18.37	21.40	2079.65	1442.60	53.08	44.33
2	26.00	24.43	27.00	1838.34	1811.85	46.92	55.67



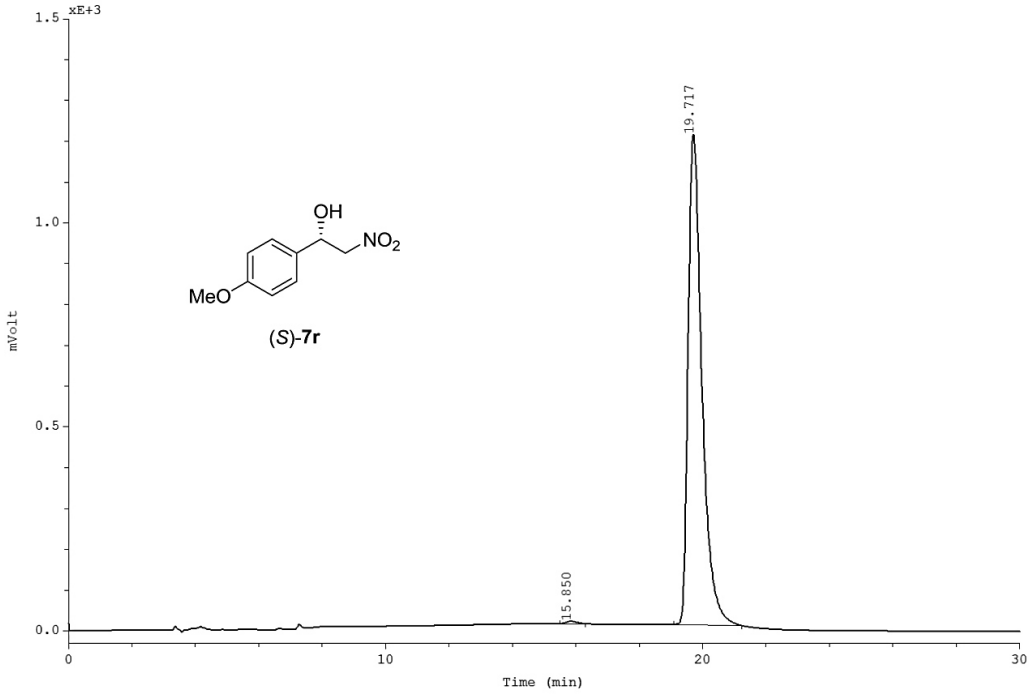
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	19.25	18.89	19.73	6.90	2.83	0.55	0.33
2	25.63	24.46	27.41	1240.99	848.65	99.45	99.67

32

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 15.9 min; t_R (*S*-enantiomer) = 19.7 min



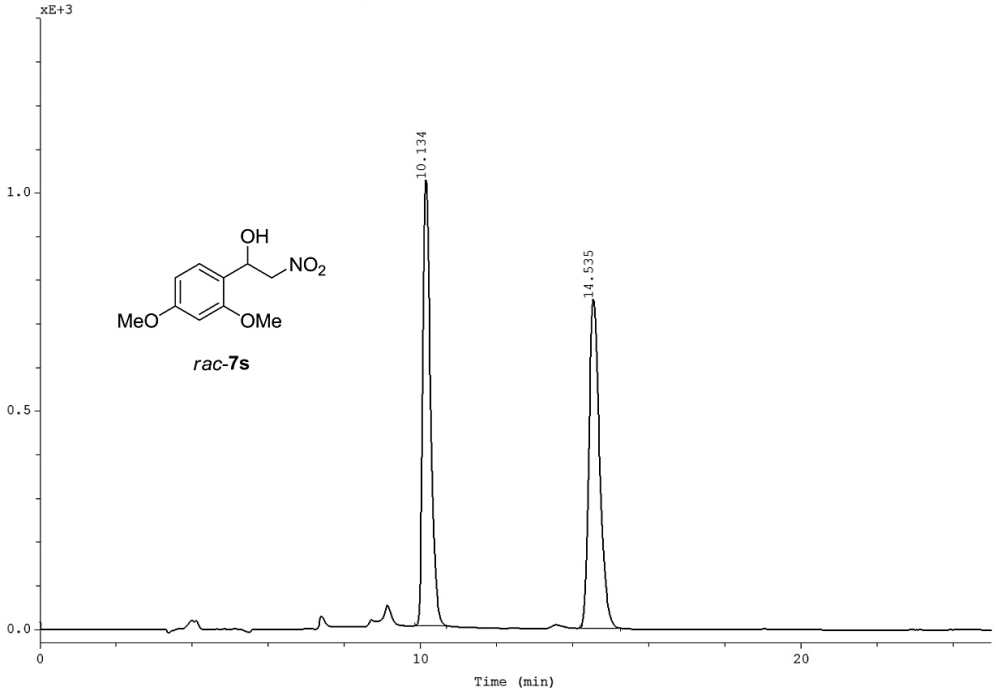
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.90	14.45	16.05	647.93	270.08	54.07	50.51
2	18.80	18.35	19.98	550.39	264.57	45.93	49.49



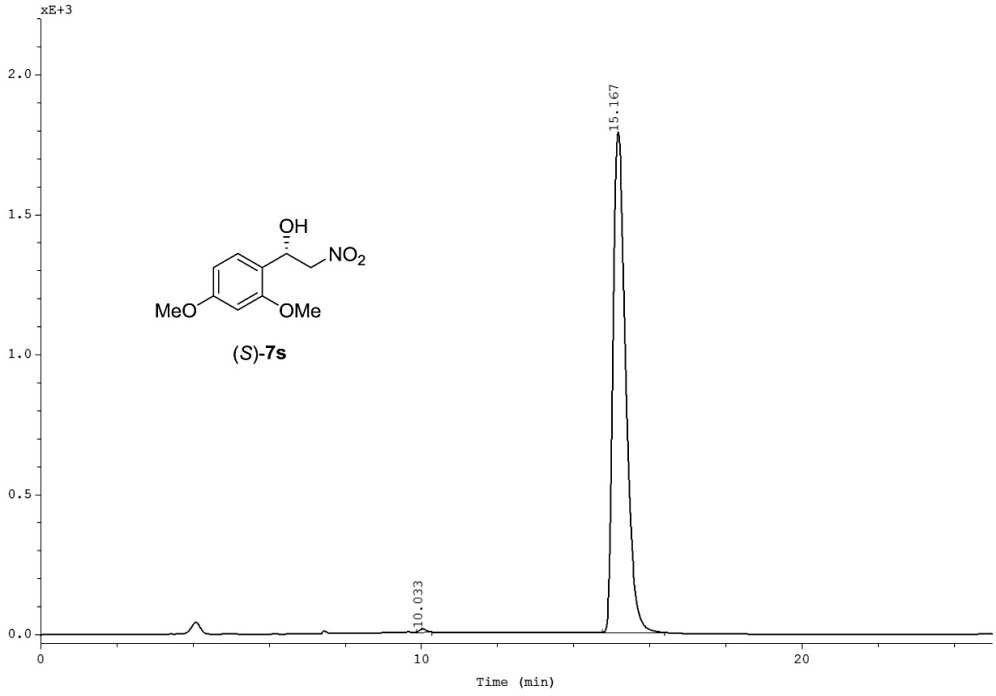
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.85	15.50	16.29	6.18	2.31	0.51	0.38
2	19.72	19.10	21.24	1201.58	607.87	99.49	99.62

33

Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 10.0 min; t_R (*S*-enantiomer) = 15.2 min

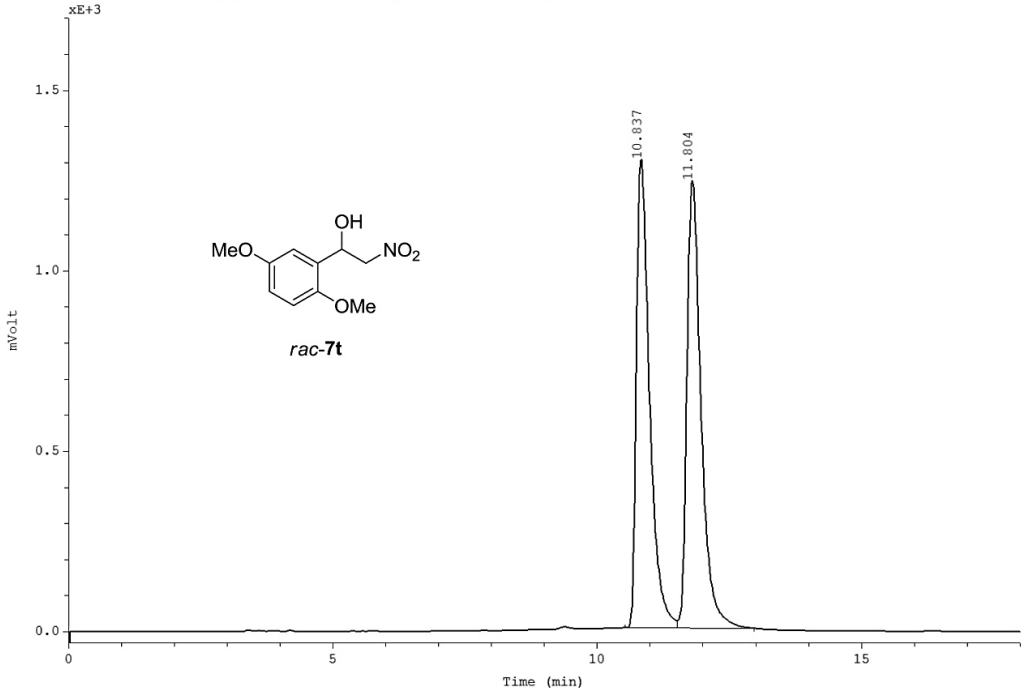


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.13	9.85	10.67	1021.08	241.17	57.55	49.55
2	14.53	14.19	15.25	753.08	245.51	42.45	50.45



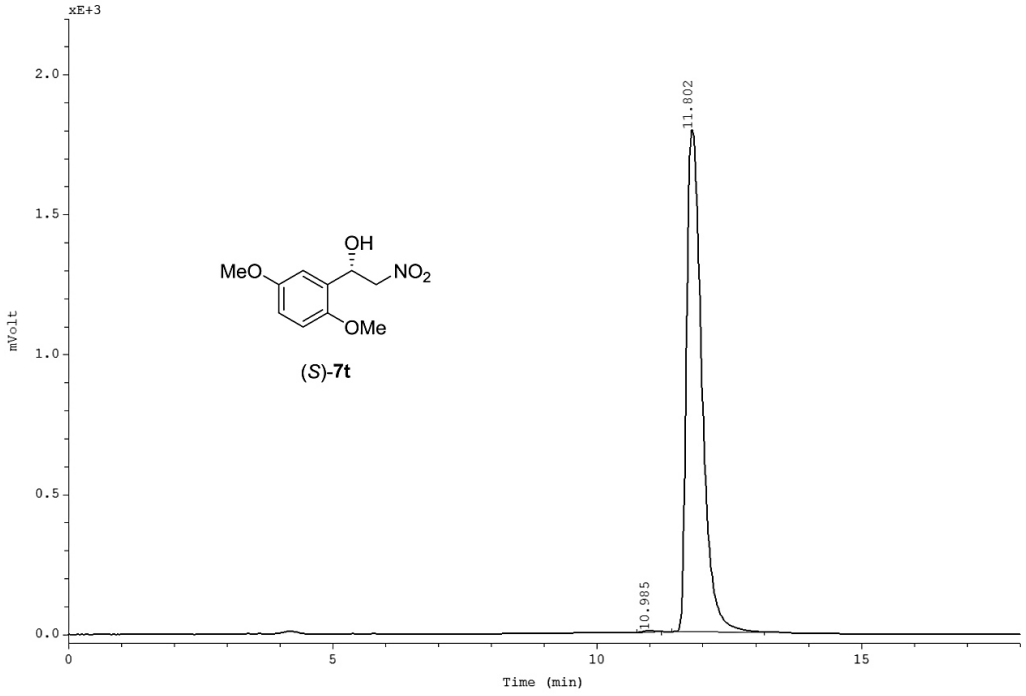
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.03	9.87	10.27	12.70	2.55	0.71	0.37
2	15.17	14.75	16.39	1787.89	693.02	99.29	99.63

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 11.0 min; t_R (*S*-enantiomer) = 11.8 min



rac-**7t**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.84	10.52	11.51	1298.70	376.34	51.14	49.35
2	11.80	11.51	12.97	1240.72	386.27	48.86	50.65

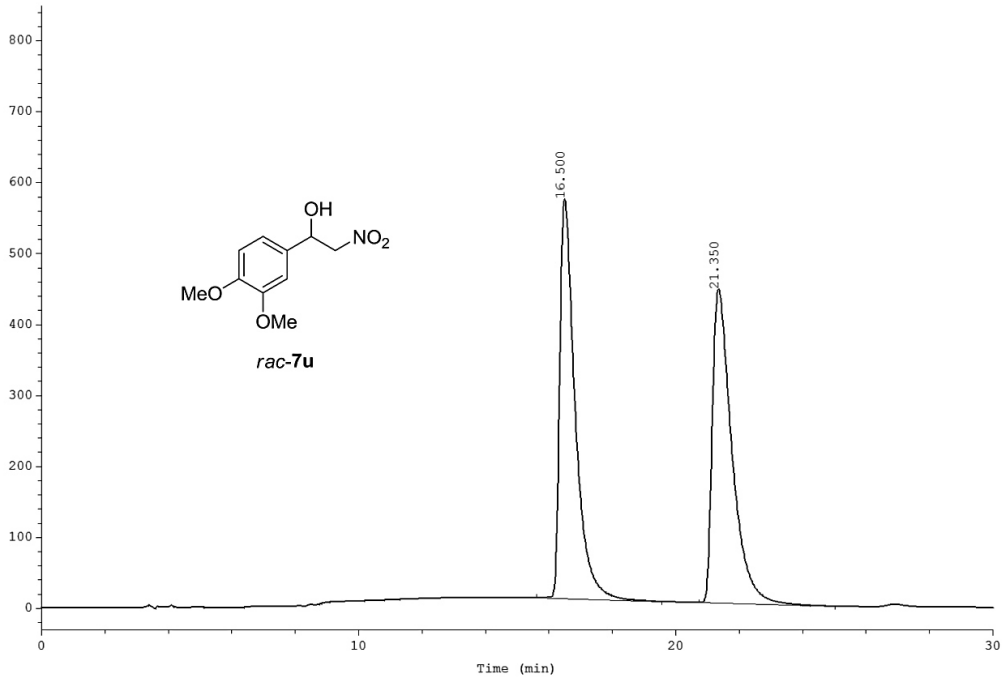


(*S*)-**7t**

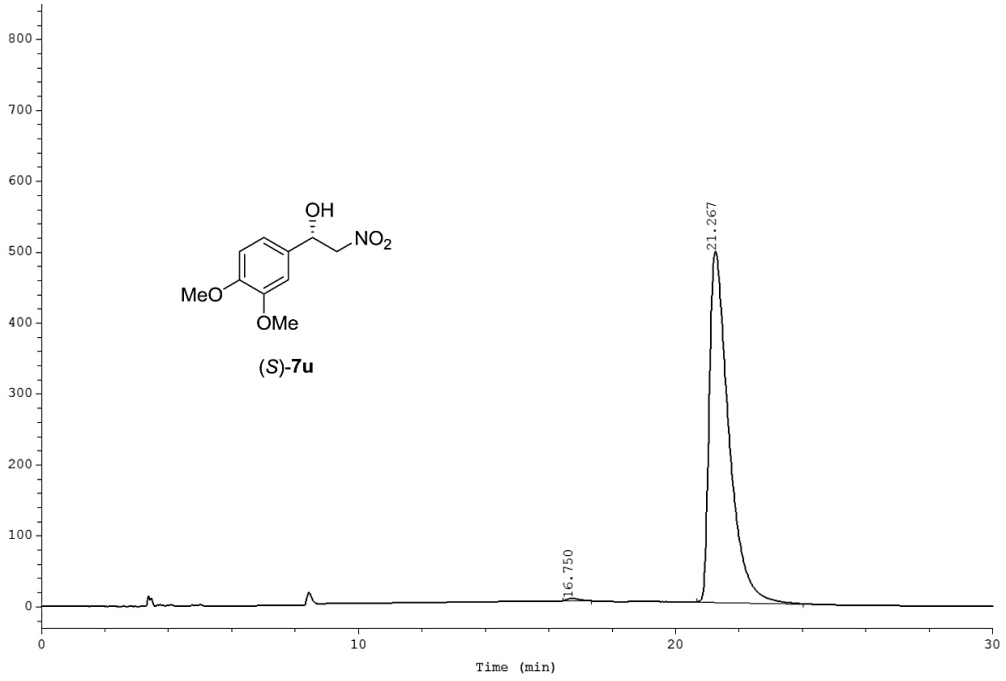
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.99	10.75	11.22	4.93	1.15	0.27	0.19
2	11.80	11.41	13.16	1795.31	604.90	99.73	99.81

35

Chiralcel OD-3, *n*-hexane/*i*PrOH 80:20, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 16.8 min; t_R (*S*-enantiomer) = 21.3 min

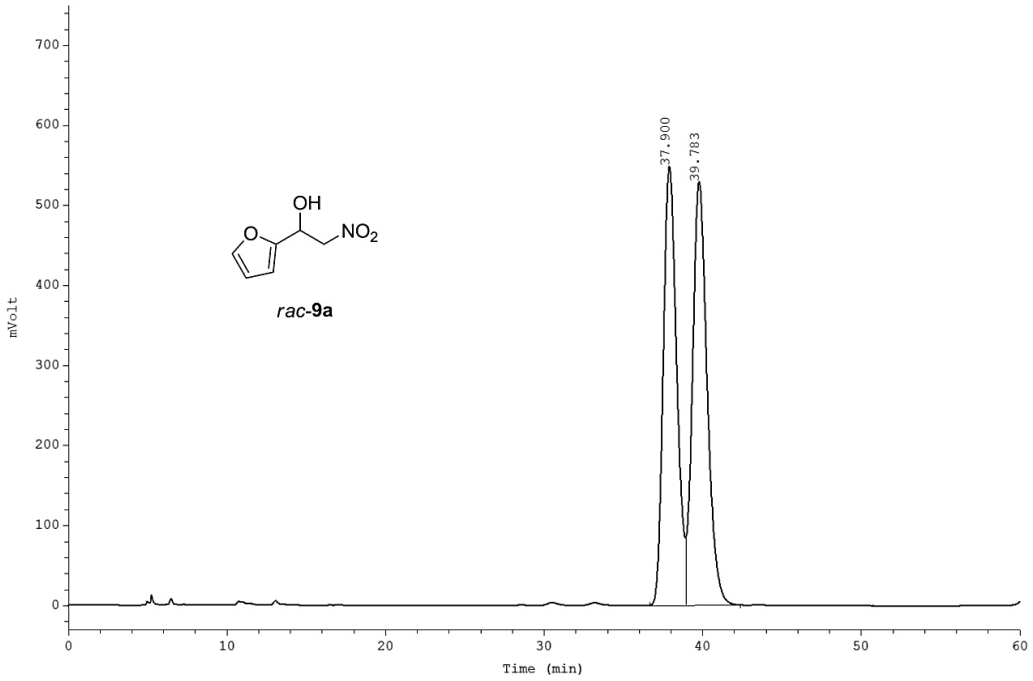


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.50	15.62	19.57	562.53	317.77	55.98	50.06
2	21.35	20.75	25.02	442.42	317.03	44.02	49.94



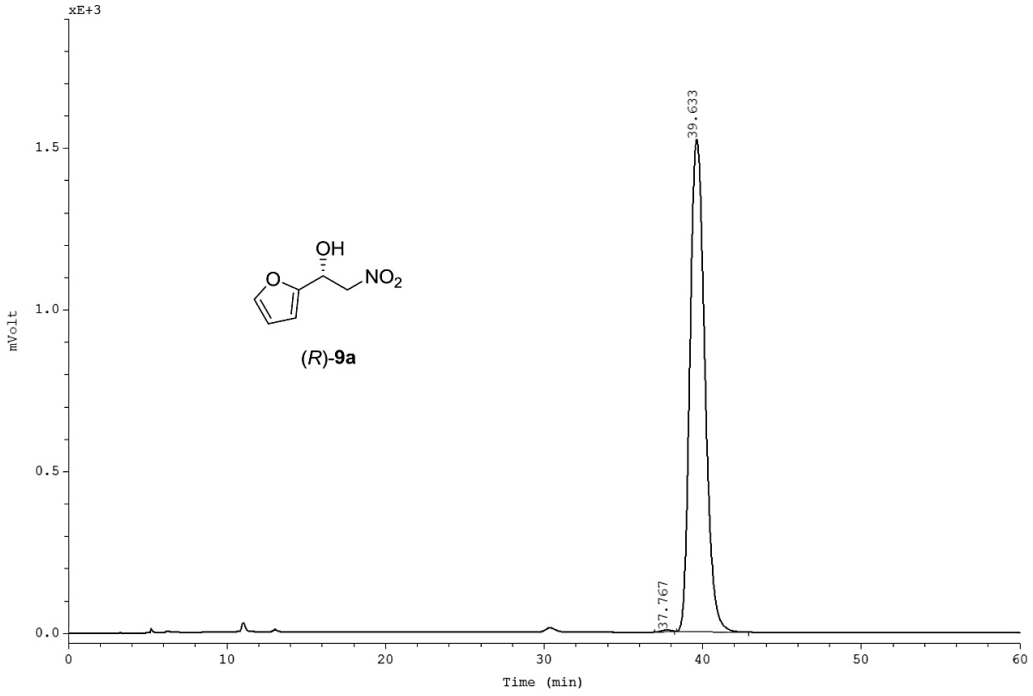
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.75	16.44	17.35	3.40	1.51	0.68	0.43
2	21.27	20.67	24.03	494.65	350.63	99.32	99.57

Chiralpak AD-H, *n*-hexane/*i*PrOH 95:5, 0.6 mL/min, 215 nm:
t_R (*R*-enantiomer) = 39.6 min; t_R (*S*-enantiomer) = 37.8 min



rac-**9a**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	37.90	36.68	38.94	549.10	537.37	50.93	48.66
2	39.78	38.94	42.36	529.03	567.03	49.07	51.34

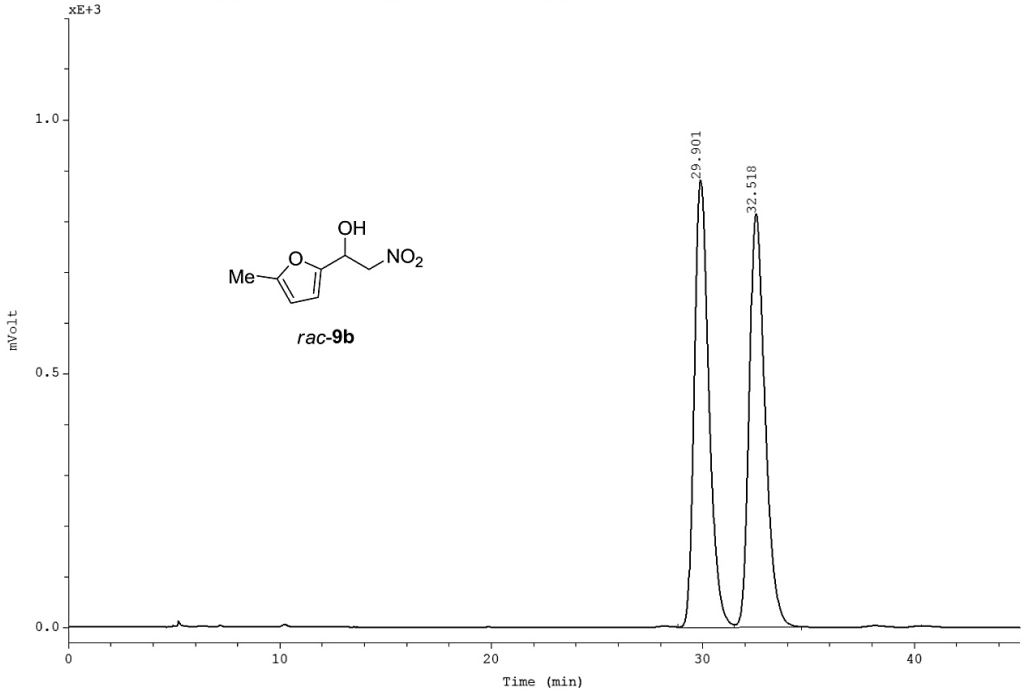


(*R*)-**9a**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	37.77	36.95	38.24	5.00	3.40	0.33	0.20
2	39.63	38.35	42.90	1521.85	1658.92	99.67	99.80

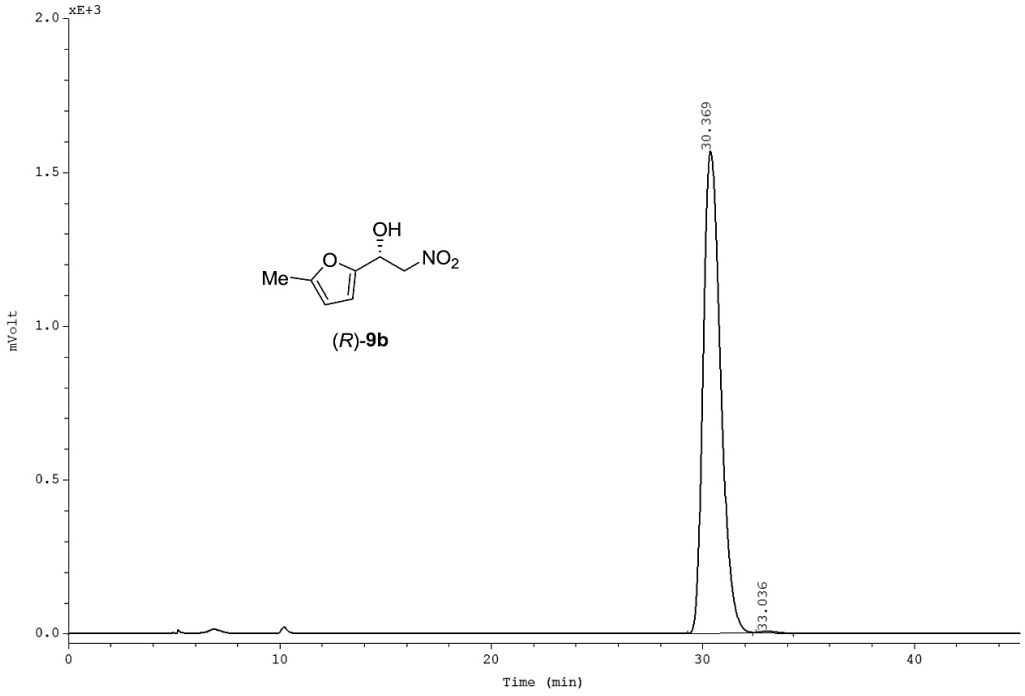
37

Chiralpak AD-H, *n*-hexane/*i*PrOH 95:5, 0.6 mL/min, 215 nm:
t_R (*R*-enantiomer) = 33.0 min; t_R (*S*-enantiomer) = 30.4 min



rac-**9b**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	29.90	28.81	31.49	881.34	704.76	51.98	49.91
2	32.52	31.49	34.67	814.19	707.39	48.02	50.09

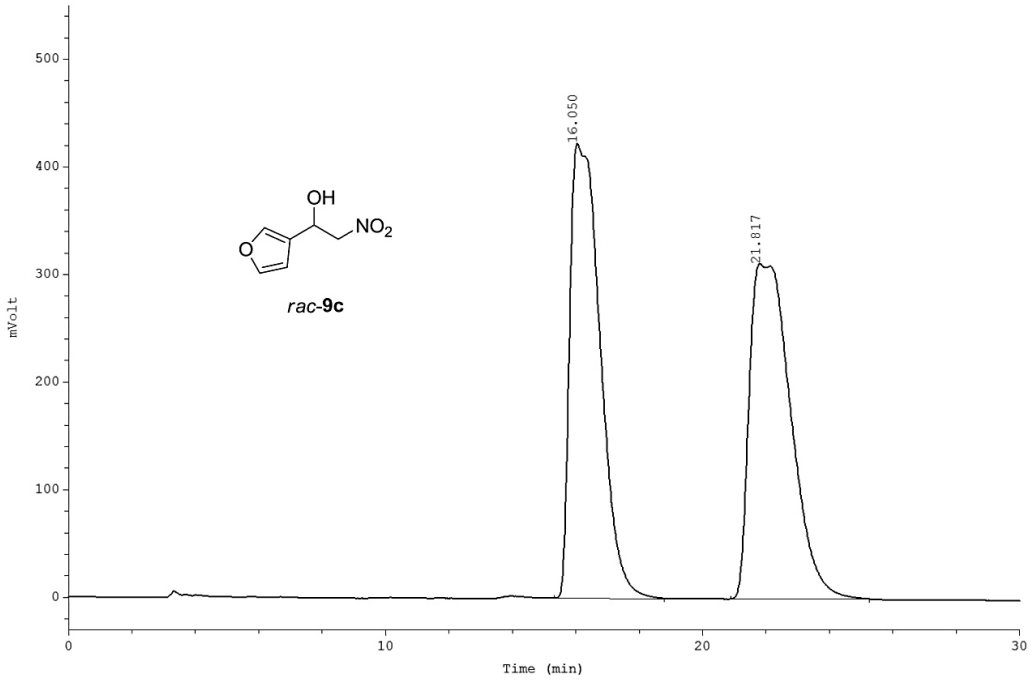


(*R*)-**9b**

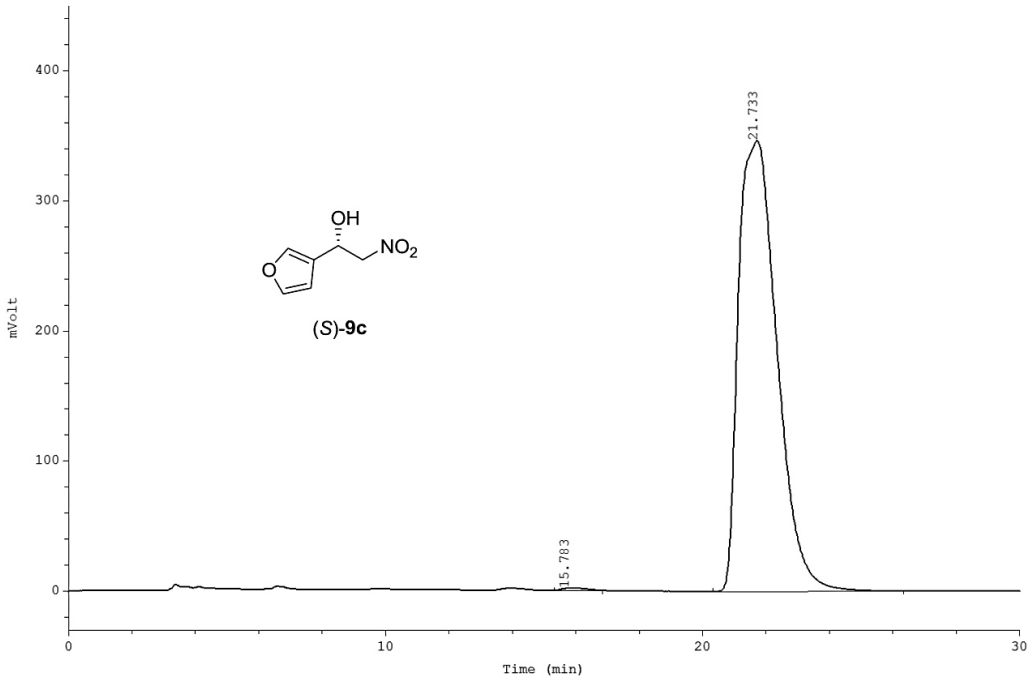
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	30.37	29.26	32.36	1567.98	1501.65	99.68	99.74
2	33.04	32.50	34.28	4.96	3.95	0.32	0.26

38

Chiralpak AD-H, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 15.8 min; t_R (*S*-enantiomer) = 21.7 min



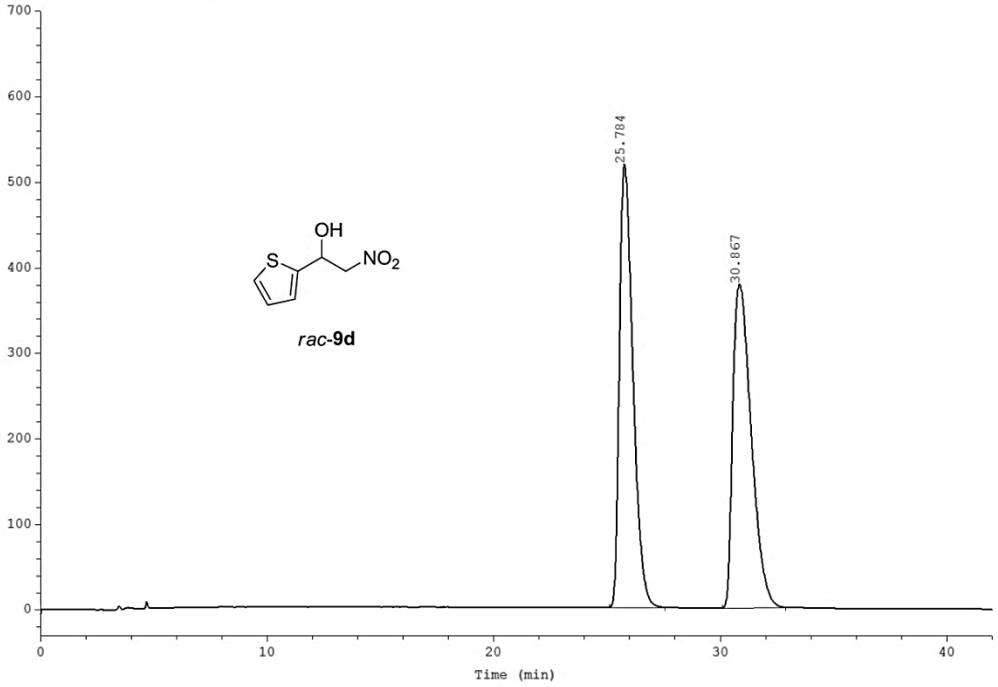
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	16.05	15.32	18.78	422.76	467.62	57.58	49.86
2	21.82	20.89	25.26	311.45	470.22	42.42	50.14



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.78	15.33	16.85	1.63	1.49	0.47	0.30
2	21.73	20.32	26.35	346.55	486.01	99.53	99.70

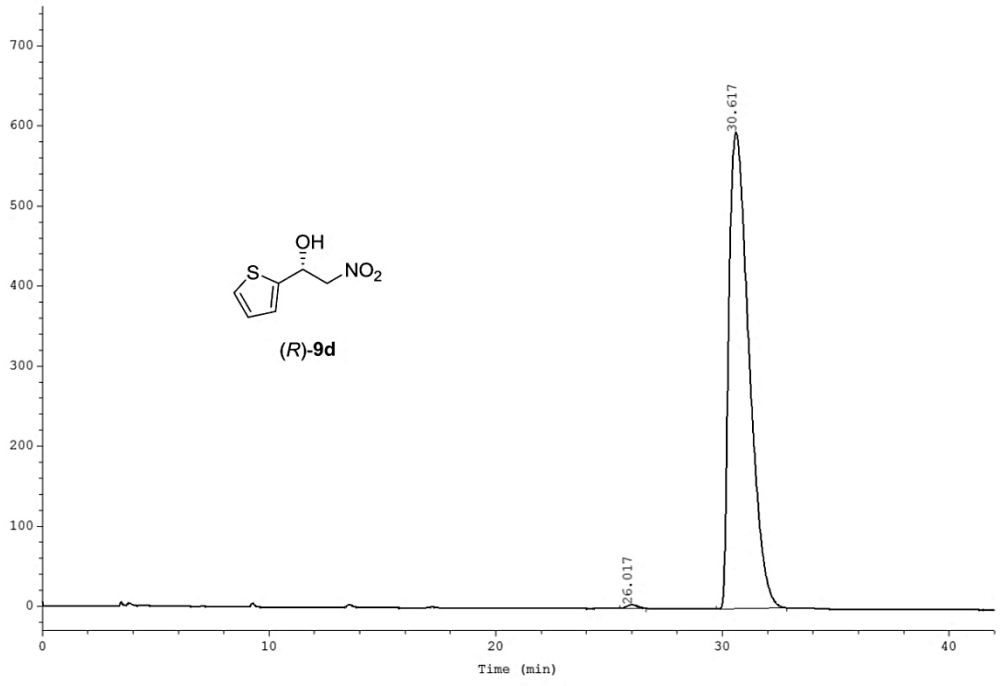
39

Chiralcel OJ-H, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 30.6 min; t_R (*S*-enantiomer) = 26.0 min



rac-**9d**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	25.78	25.11	27.55	518.41	358.24	57.78	50.07
2	30.87	30.10	32.90	378.74	357.22	42.22	49.93

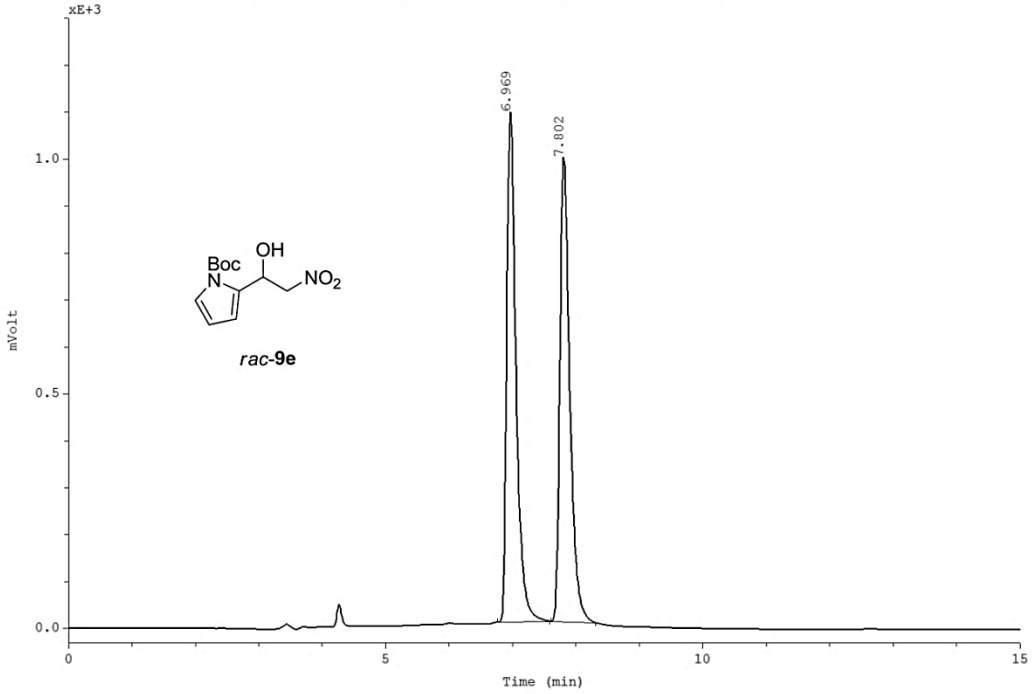


(*R*)-**9d**

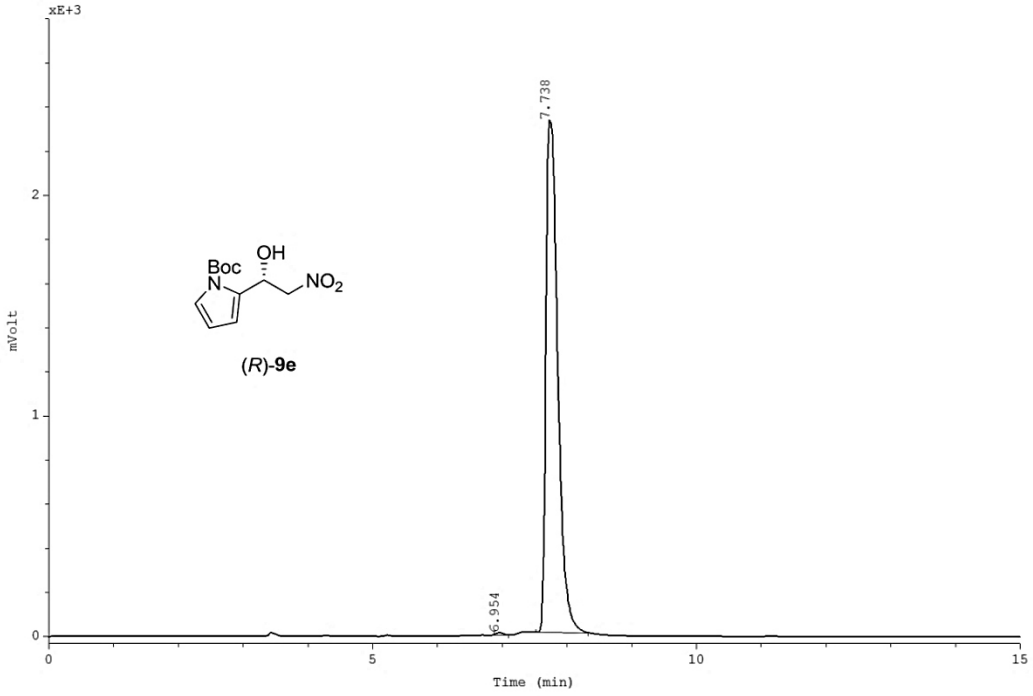
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	26.02	25.47	26.63	4.47	2.43	0.75	0.40
2	30.62	29.74	32.85	595.05	609.21	99.25	99.60

40

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 7.0 min; t_R (*S*-enantiomer) = 7.7 min



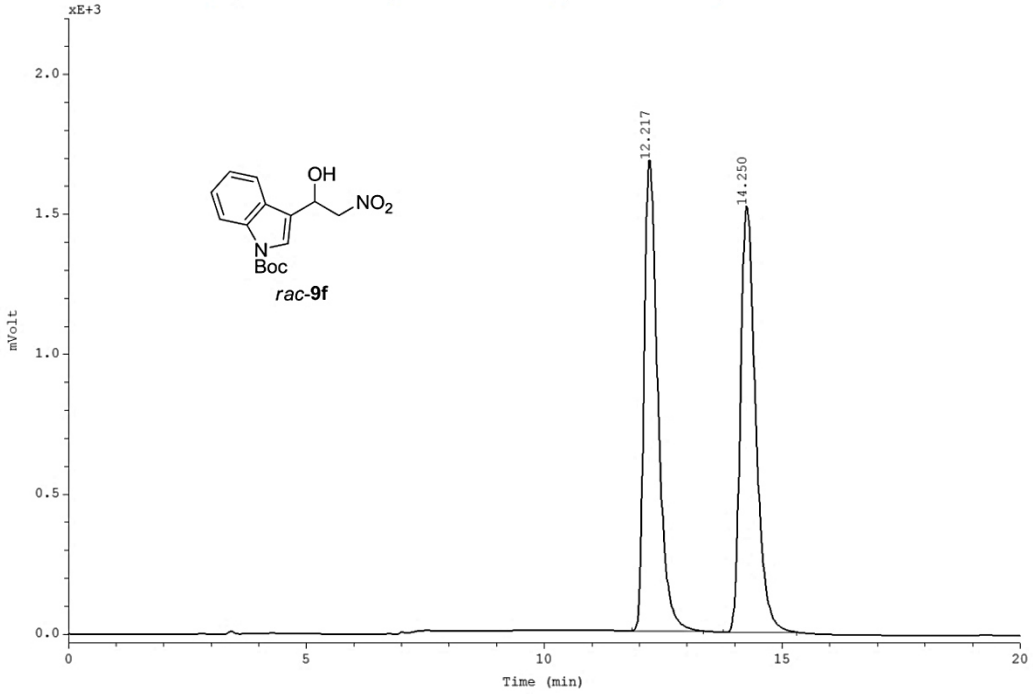
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	6.97	6.77	7.58	1086.31	183.21	52.32	50.30
2	7.80	7.60	8.31	990.06	181.02	47.68	49.70



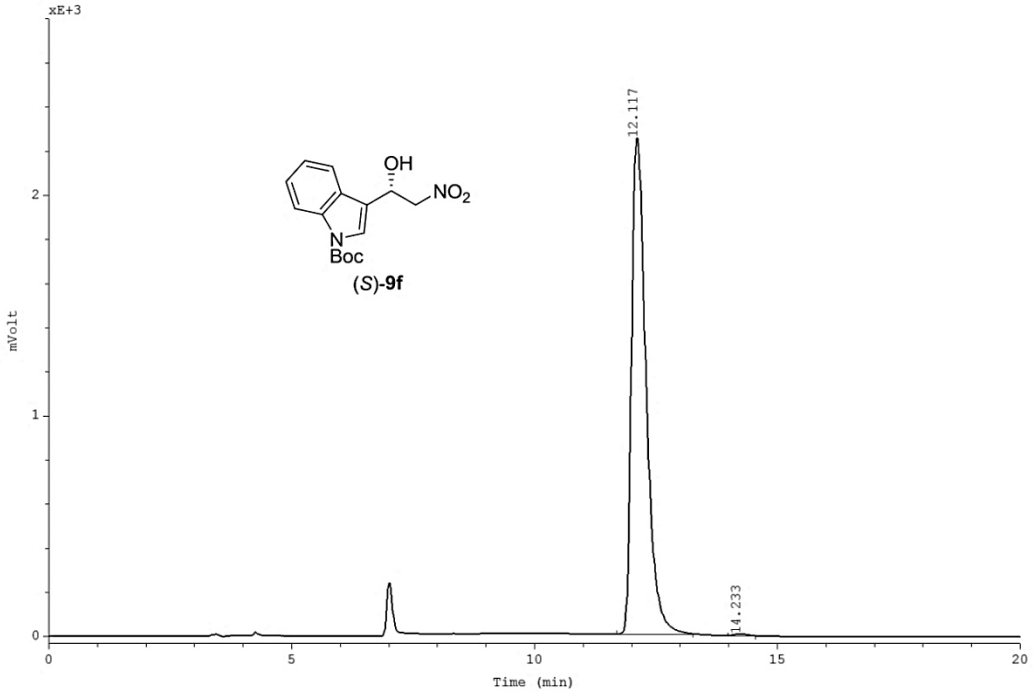
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	6.95	6.87	7.10	9.41	1.17	0.40	0.24
2	7.74	7.52	8.33	2321.72	495.29	99.60	99.76

41

Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.2 min; t_R (*S*-enantiomer) = 12.1 min



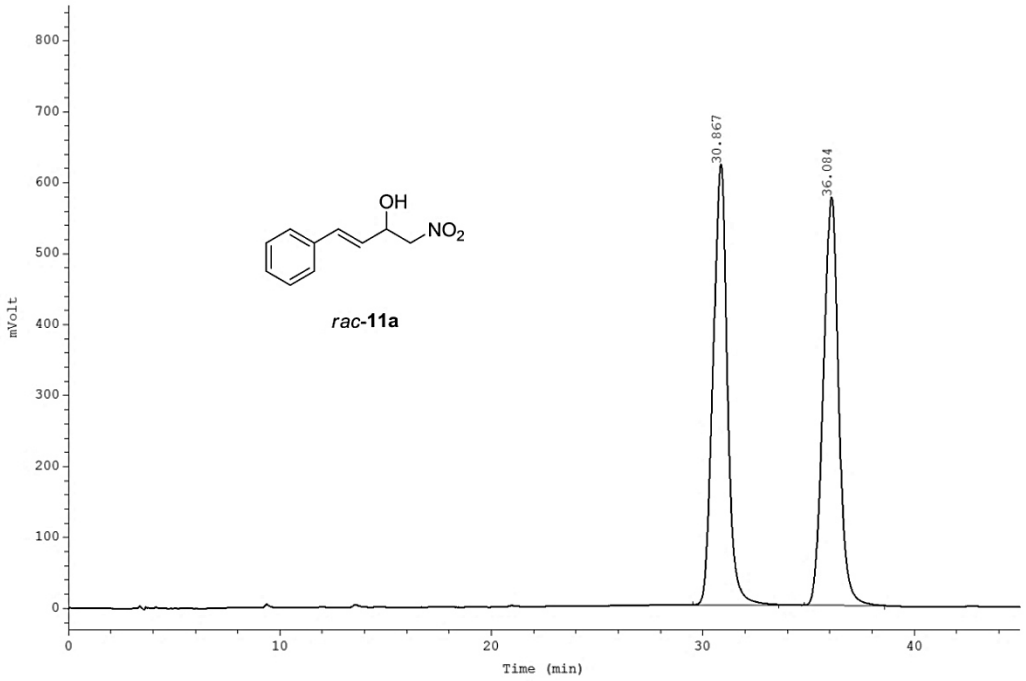
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.22	11.84	13.34	1682.54	565.18	52.47	49.94
2	14.25	13.77	15.30	1524.37	566.65	47.53	50.06



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.12	11.70	13.27	2250.06	783.35	99.63	99.68
2	14.23	13.98	14.55	8.47	2.51	0.37	0.32

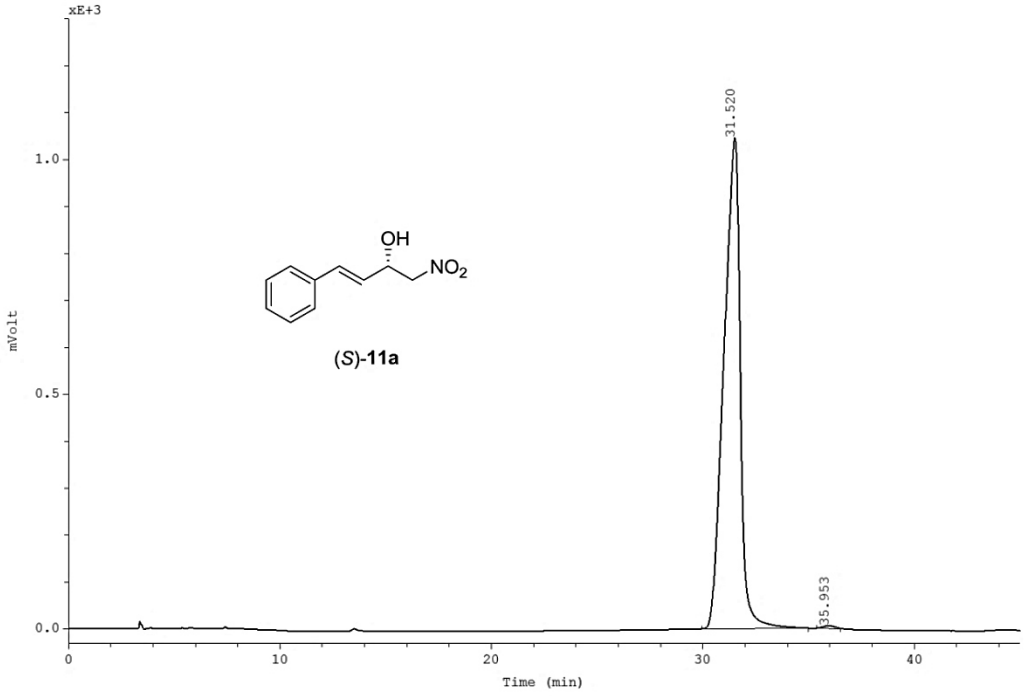
42

Chiralcel OD-3, *n*-hexane/*i*PrOH 85:15, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 36.0 min; t_R (*S*-enantiomer) = 31.5 min



rac-**11a**

	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	30.87	29.52	33.58	621.43	485.83	51.91	49.96
2	36.08	34.78	38.58	575.59	486.64	48.09	50.04

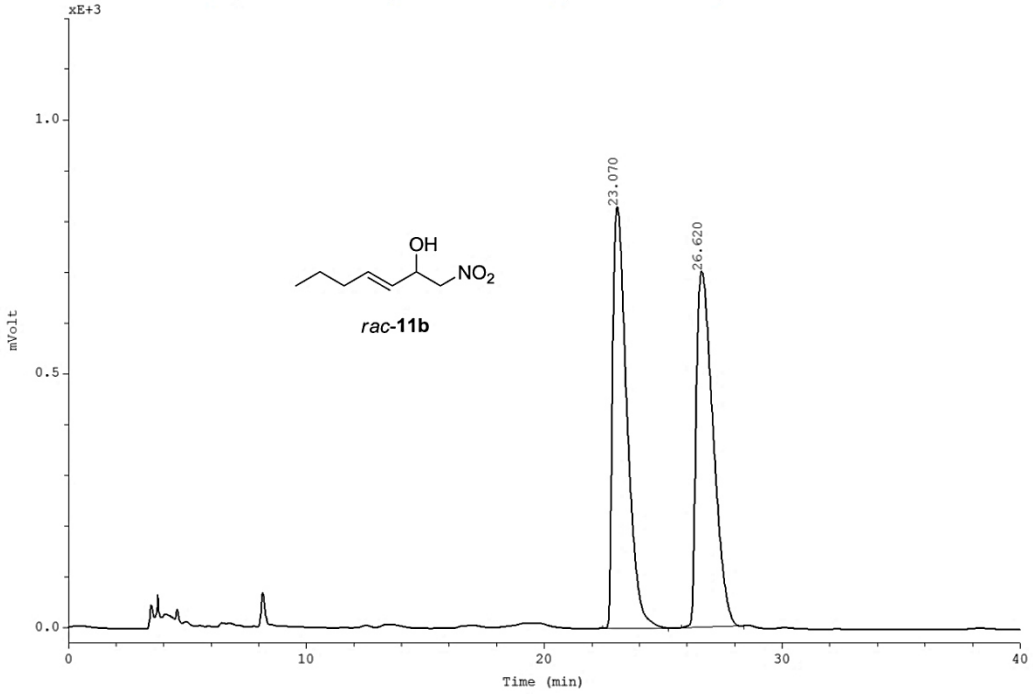


(*S*)-**11a**

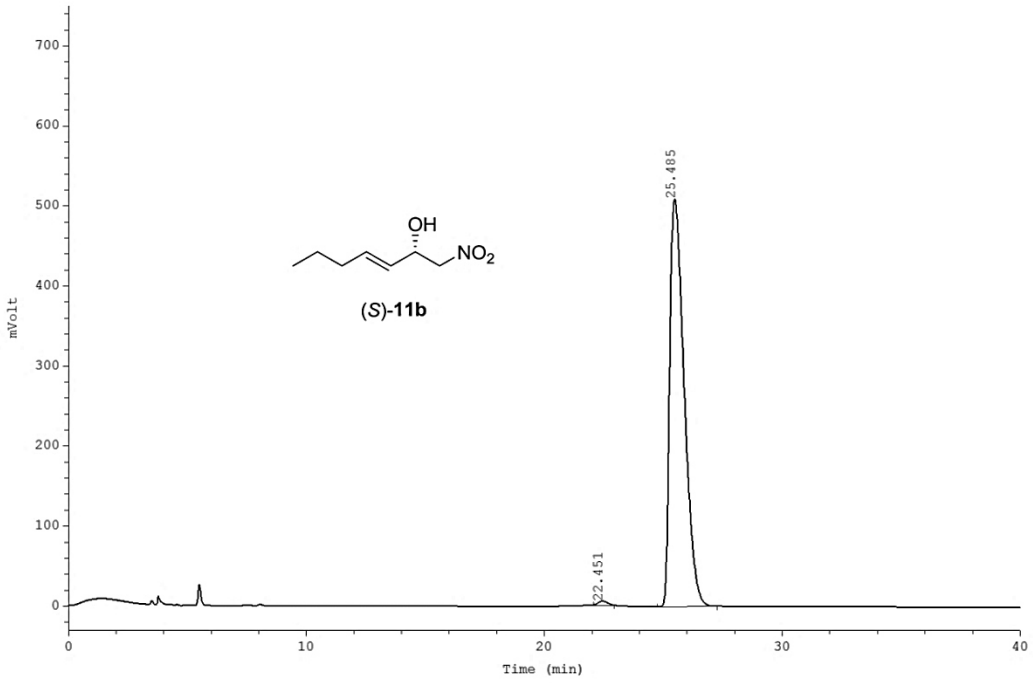
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	31.52	29.94	34.99	1045.52	934.68	99.48	99.65
2	35.95	35.38	36.52	5.44	3.33	0.52	0.35

43

Chiralcel OJ-H, *n*-hexane/*i*PrOH 97:3, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 22.5 min; t_R (*S*-enantiomer) = 25.5 min

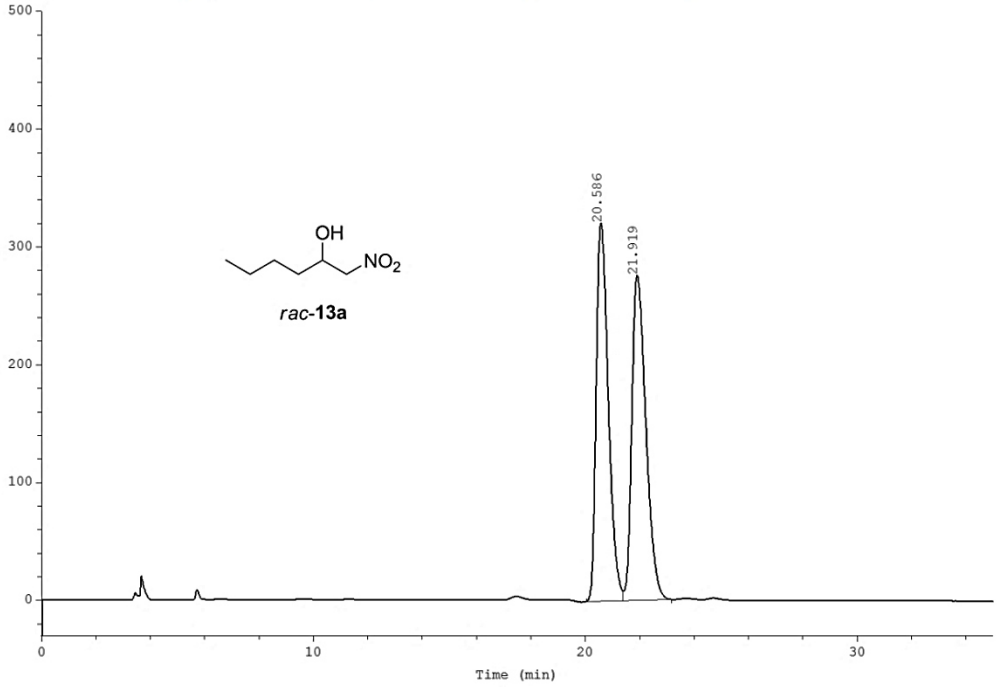


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	23.07	22.46	25.22	830.90	580.25	54.23	50.12
2	26.62	25.76	28.38	701.41	577.57	45.77	49.88

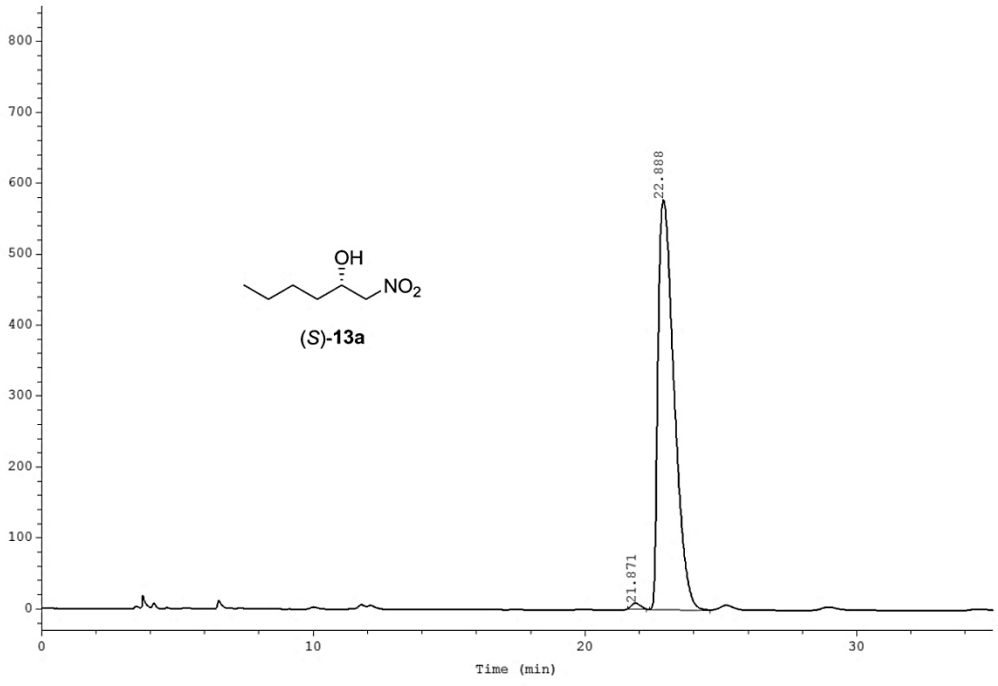


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	22.45	22.07	22.93	4.99	2.26	0.97	0.63
2	25.49	24.74	27.26	509.37	358.45	99.03	99.37

Chiralcel OJ-H, *n*-hexane/*i*PrOH 97:3, 0.8 mL/min, 215 nm:
t_R (*R*-enantiomer) = 21.9 min; t_R (*S*-enantiomer) = 22.9 min



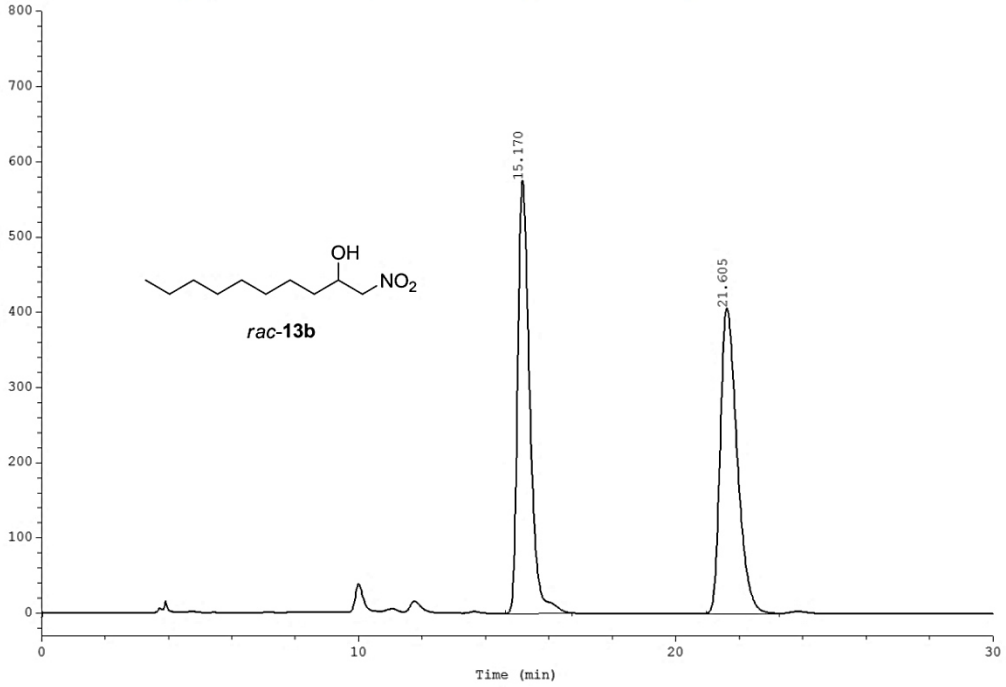
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	20.59	20.03	21.39	321.23	165.68	53.77	49.84
2	21.92	21.39	23.17	276.19	166.73	46.23	50.16



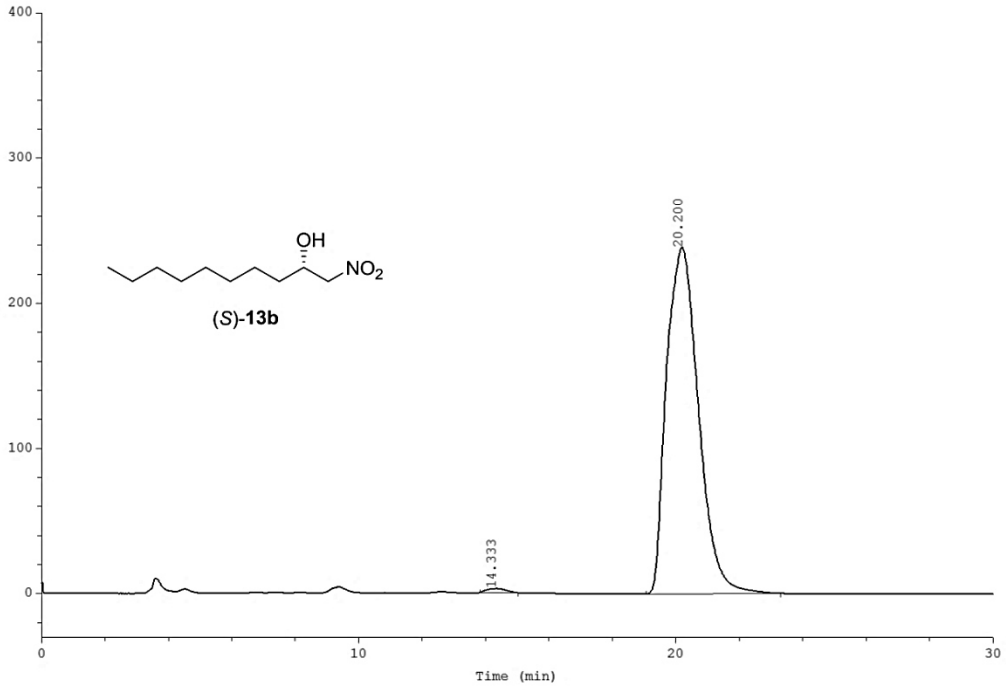
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	21.87	21.57	22.26	8.10	2.99	1.38	0.75
2	22.89	22.38	24.59	577.72	395.15	98.62	99.25

45

Chiralpak AD-H, *n*-hexane/*i*PrOH 95:5, 0.8 mL/min, 215 nm:
t_R (*R*-enantiomer) = 14.3 min; t_R (*S*-enantiomer) = 20.2 min

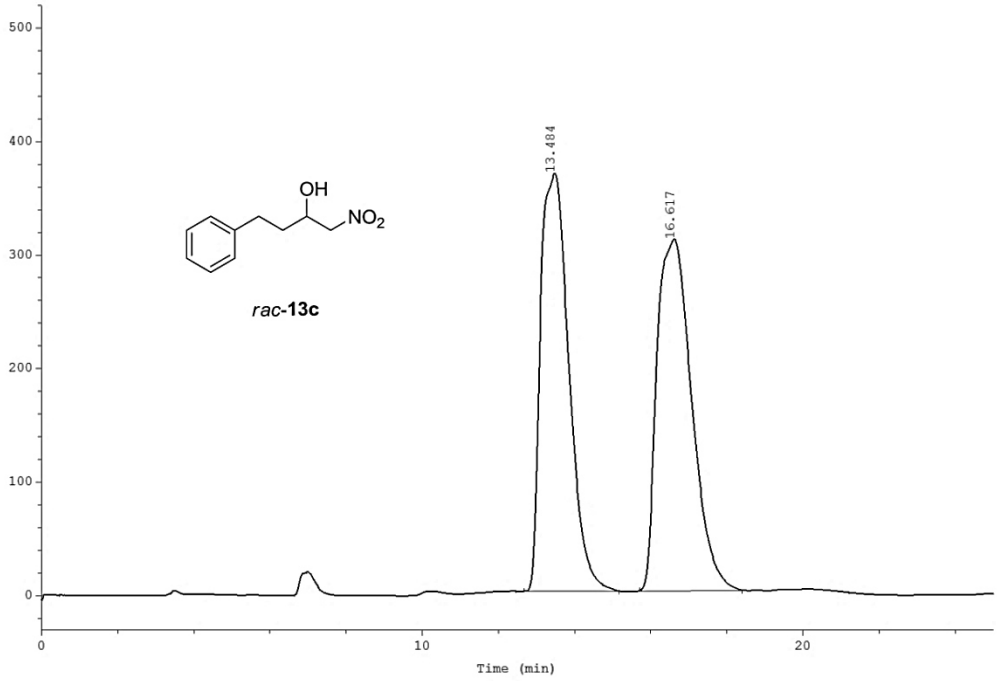


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.17	14.63	16.73	575.42	253.40	58.61	50.30
2	21.61	20.95	23.25	406.28	250.38	41.39	49.70

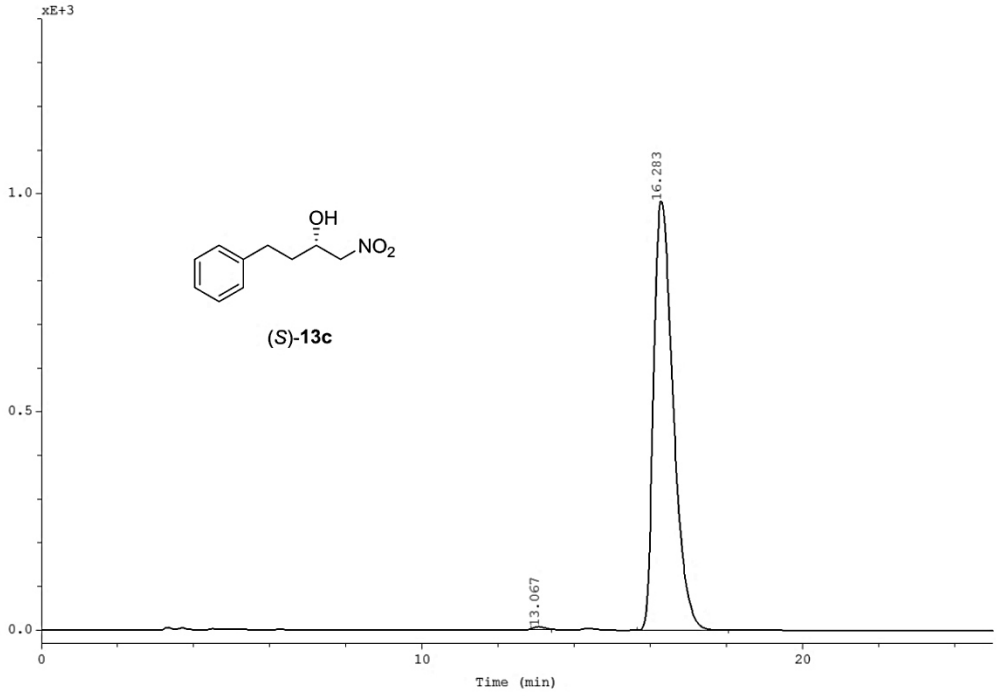


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.33	13.82	15.03	2.80	1.96	1.16	0.70
2	20.20	19.06	23.30	238.45	278.10	98.84	99.30

Chiralpak AD-H, *n*-hexane/*i*PrOH 90:10, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 13.1 min; t_R (*S*-enantiomer) = 16.3 min



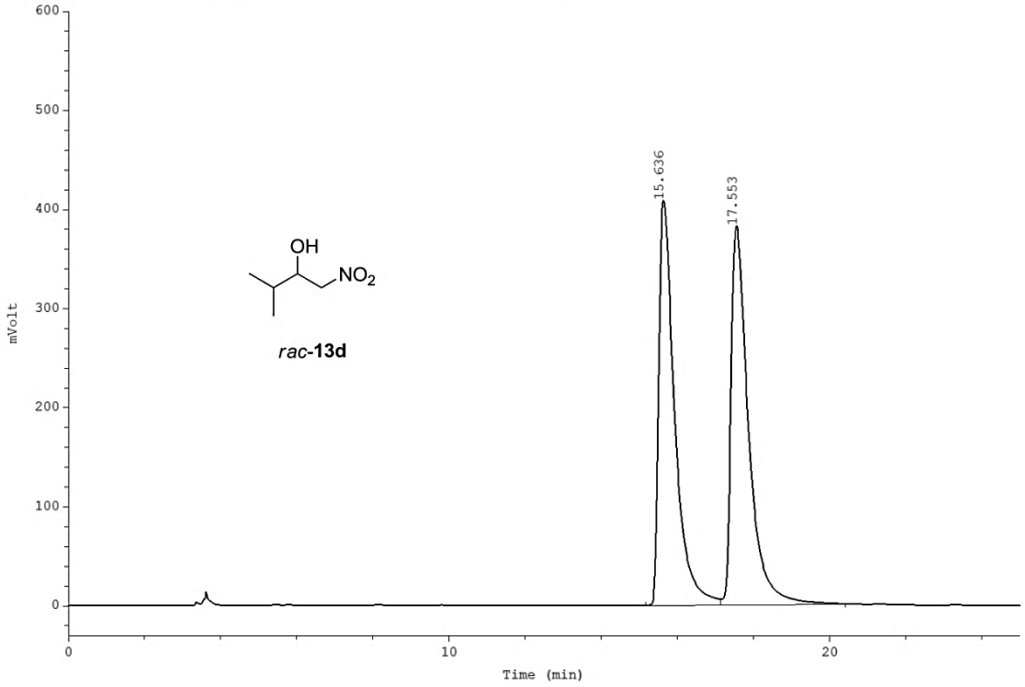
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.48	12.67	15.16	368.44	316.71	54.32	49.22
2	16.62	15.70	18.40	309.79	326.70	45.68	50.78



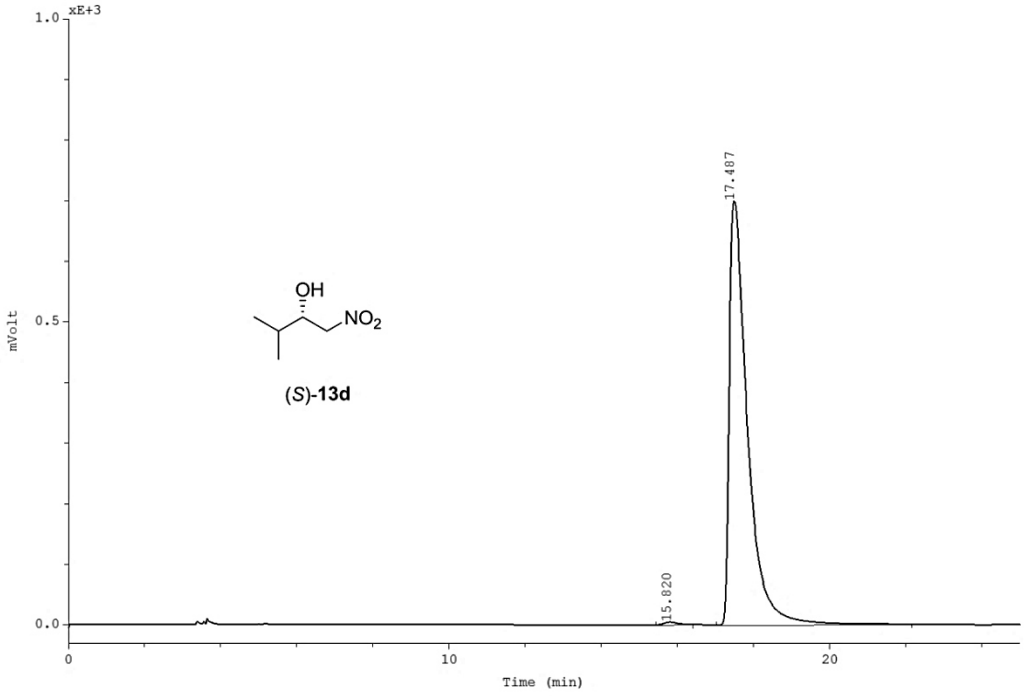
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.07	12.85	13.40	5.26	1.60	0.53	0.27
2	16.28	15.66	18.04	983.87	584.21	99.47	99.73

47

Chiralcel OD-3, *n*-hexane/*i*PrOH 97:3, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 15.8 min; t_R (*S*-enantiomer) = 17.5 min



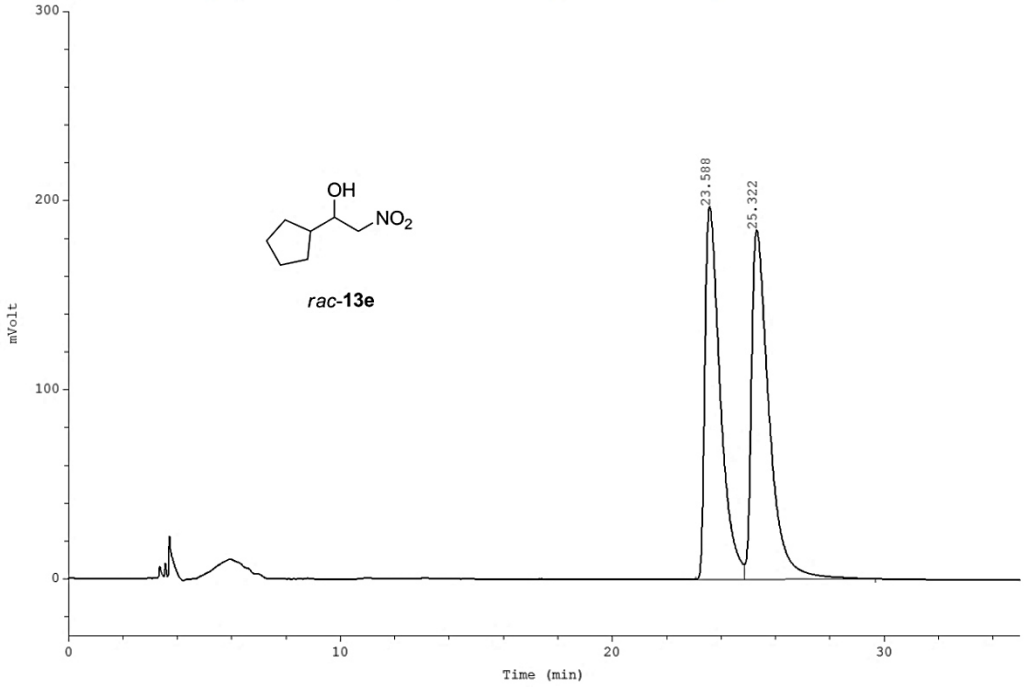
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.64	15.16	17.13	408.93	198.55	51.68	49.29
2	17.55	17.13	20.40	382.40	204.27	48.32	50.71



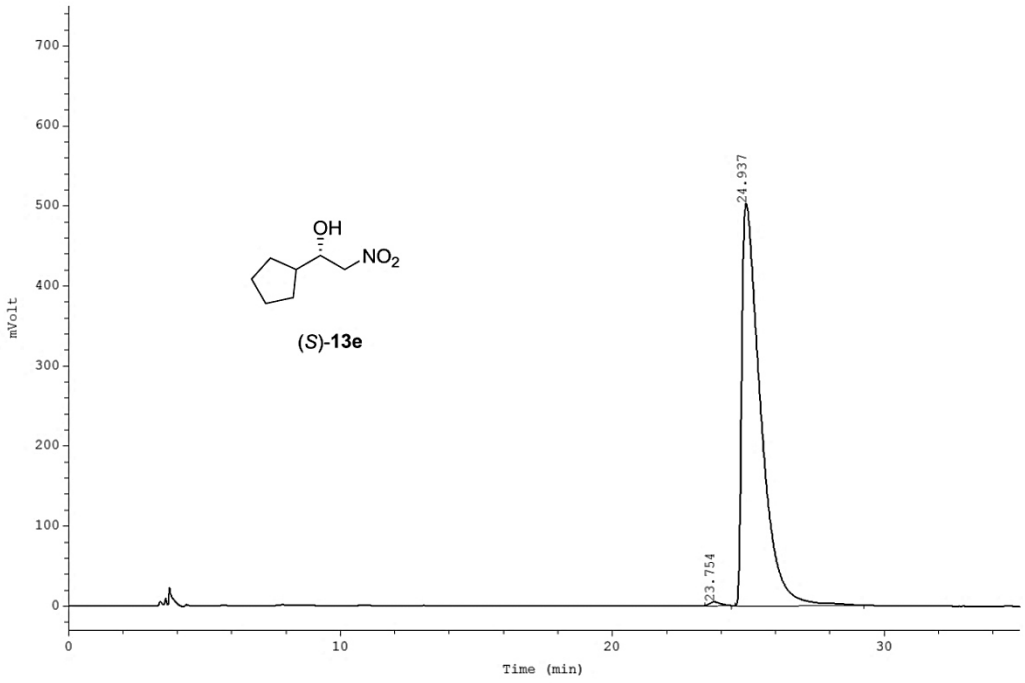
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.82	15.42	16.41	4.62	1.80	0.66	0.46
2	17.49	17.03	22.15	700.05	387.99	99.34	99.54

48

Chiralcel OD-3, *n*-hexane/*i*PrOH 98:2, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 23.8 min; t_R (*S*-enantiomer) = 24.9 min



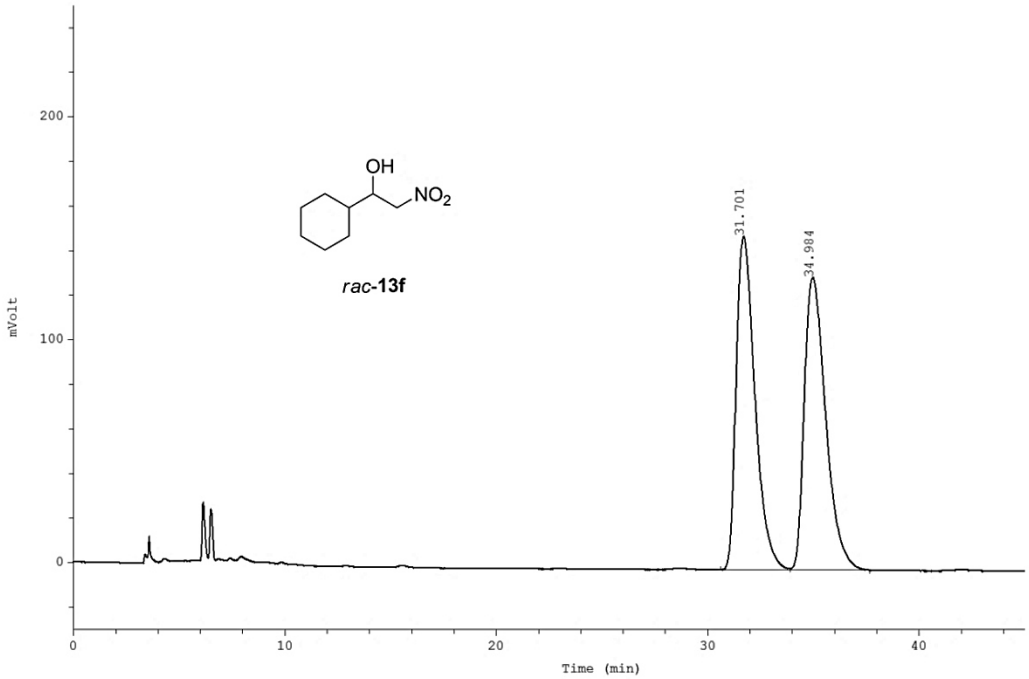
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	23.59	23.07	24.85	197.21	128.56	51.64	48.22
2	25.32	24.85	29.67	184.70	138.07	48.36	51.78



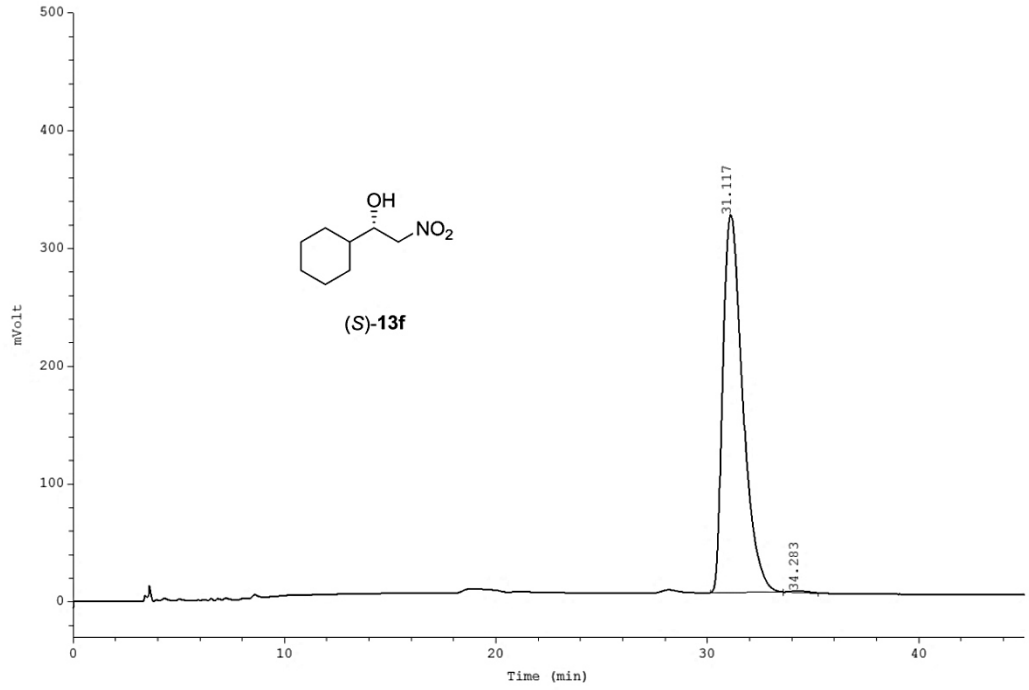
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	23.75	23.39	24.38	4.75	2.26	0.94	0.56
2	24.94	24.49	29.25	502.62	402.83	99.06	99.44

49

Chiralpak AD-H, *n*-hexane/EtOH 95:5, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 34.3 min; t_R (*S*-enantiomer) = 31.1 min

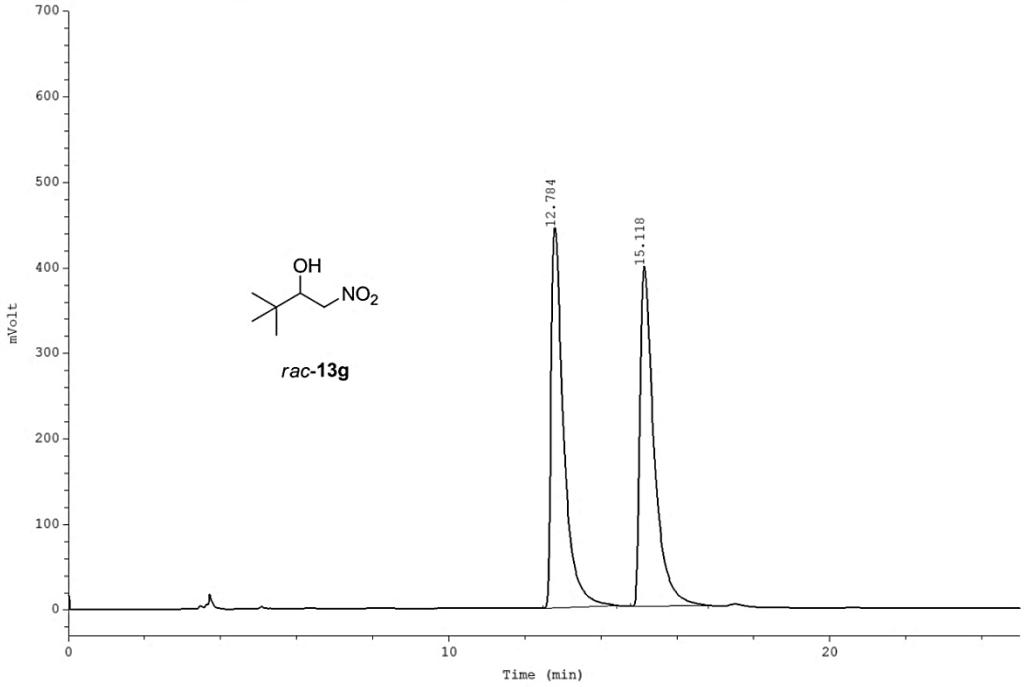


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	31.70	30.62	33.89	149.54	154.21	53.28	50.01
2	34.98	33.89	37.65	131.14	154.14	46.72	49.99

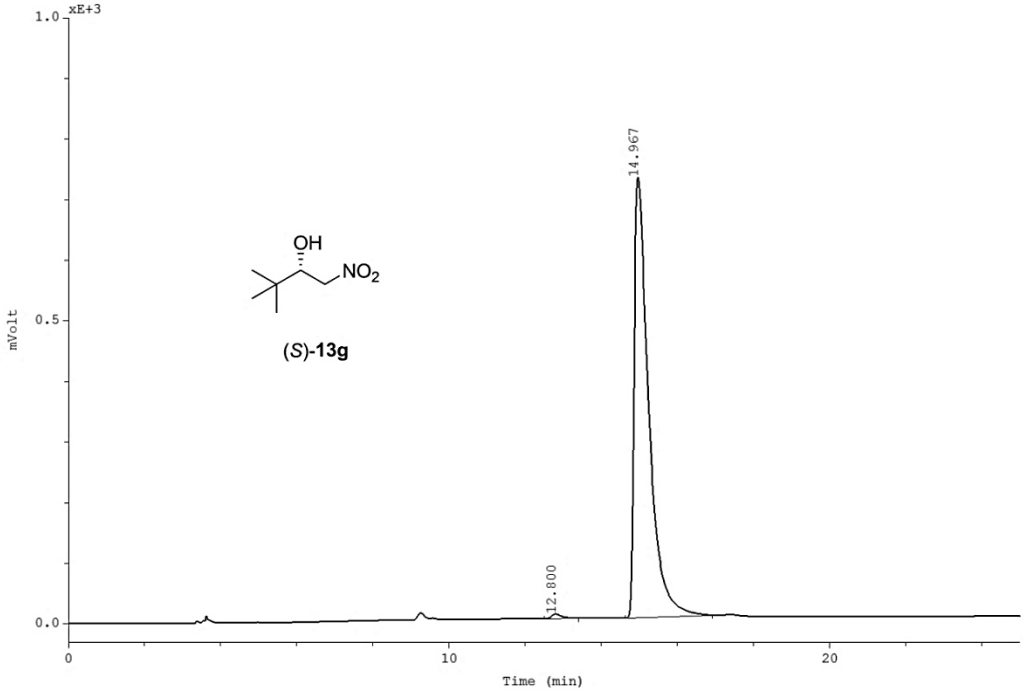


	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	31.12	30.13	33.59	320.98	349.59	99.62	99.70
2	34.28	33.59	35.23	1.23	1.05	0.38	0.30

Chiralcel OD-3, *n*-hexane/*i*PrOH 97:3, 0.9 mL/min, 215 nm:
t_R (*R*-enantiomer) = 12.8 min; t_R (*S*-enantiomer) = 15.0 min



	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.78	12.46	14.40	444.95	169.74	52.80	49.77
2	15.12	14.76	16.80	397.69	171.30	47.20	50.23



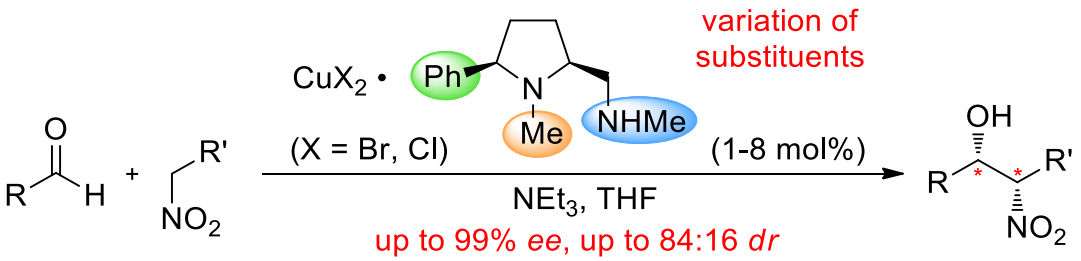
	Ret.time [min]	Start [min]	End [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.80	12.49	13.40	7.22	2.22	0.98	0.68
2	14.97	14.61	16.92	726.51	322.98	99.02	99.32

6.4 Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions

Johannes Kaldun, Felix Prause, Dagmar Scharnagel, Frederik Freitag and Matthias Breuning*

Organic Chemistry Laboratory, University of Bayreuth, Universitätsstraße 30, 95447 Bayreuth, Germany.

* Matthias.Breuning@uni-bayreuth.de



Published in: *ChemCatChem* **2016**, *8*, 1846–1856.

http://onlinelibrary.wiley.com/doi/10.1002/cctc.201600240/full

doi: 10.1002/cctc.201600240

ChemPubSoc Europe

DOI: 10.1002/cctc.201600240

CHEMCATCHEM Full Papers

Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions

Johannes Kaldun, Felix Prause, Dagmar Scharnagel, Frederik Freitag, and Matthias Breuning*[a]

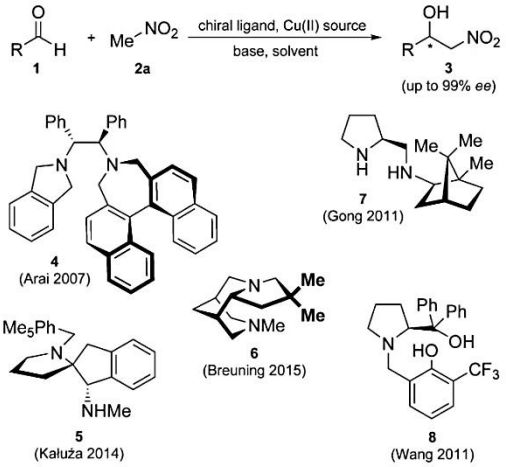
Dedicated to Prof. Dr. Dr. h.c. mult. Gerhard Bringmann on the occasion of his 65th birthday.

The development of a new catalytic system for enantioselective Henry reactions, which permits superb 99% *ee* with a broad variety of aldehydes, is presented. In-depth structure–selectivity investigations with 33 5-*cis*-substituted prolinamines, prepared from methyl Boc-L-pyroglutamate, revealed that an aromatic or sterically demanding aliphatic substituent in 5-*cis* position is crucial for high levels of stereocontrol, while bulkier substituents at the nitrogen atoms diminish both, enantioselectivities and reaction rates. The scope of the prime catalyst was expanded to gram-scale and diastereomeric Henry reactions (up to 84:16 *dr*, 99% *ee*). In the course of mechanistic studies, it was proven that the resulting β-nitro alcohols are configurationally stable under the reaction conditions. In addition, competition experiments were used to determine the relative reaction rates of some of the prolinamine-modified catalysts.

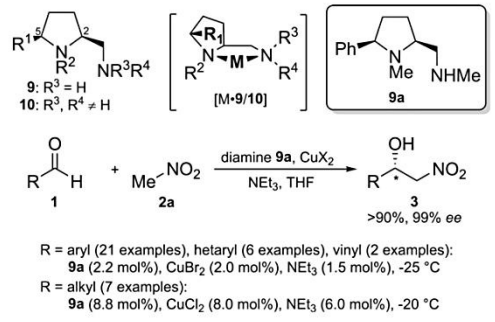
Introduction

The enantioselective Henry (nitro aldol) reaction[1] has drawn much attention as an asymmetric carbon–carbon bond forming reaction,[2] which triggered the development of many efficient catalytic systems based on heterobimetal[3] and transition-metal[4–6] complexes.[7] Chirally modified copper complexes received particular interest because of the wide structural variability of successful ligands, among them diamines, amino alcohols, amino imines, amino pyridines, imino pyridines, Schiff bases, box-type ligands, and salen-type ligands.[5,6,8,9] Examples of diamines (**4**–**7**)[5a,j,p,8a] and ligands containing the proline motif (**7**, **8**)[5j,m] that permit 99% *ee* in the addition of nitromethane (**2a**) to at least one aldehyde substrate **1** are shown in Scheme 1. Notably, Gong's ligand **7**,[5j] which belongs to the most potent ones for this reaction, combines both structural features.

As part of our ongoing work on conformationally rigid diamines[8,10] and encouraged by the stereodiscriminating power of **7**, we became interested in prolinamines of general type **9** and **10** (Scheme 2),[11] which possess, as compared to other proline-derived ligands, an additional substituent R^1 in 5-*cis* position. Upon chelation of a metal M, a bicyclic complex [M·**9**/**10**] will be formed with the substituent R^1 shielding the upper left face, which might permit enhanced levels of stereocontrol in asymmetric transformations. This assumption was recently corroborated by copper-catalyzed, enantioselective Henry reac-



Scheme 1. The enantioselective, copper-catalyzed Henry reaction and a selection of diamine (**4**–**7**)[5a,j,p,8a] and proline-derived (**7**,**8**)[5j,m] ligands that give 99% *ee* with at least one aldehyde substrate.



Scheme 2. The proline-derived diamines **9** and **10**, their metal complexes [M·**9**/**10**], and enantioselective, copper-catalyzed Henry reactions in the presence of the chiral diamine **9a**.[9]

[a] *J. Kaldun, F. Prause, D. Scharnagel, F. Freitag, Prof. M. Breuning*
Organic Chemistry Laboratory
University of Bayreuth
Universitätsstraße 30, 95447 Bayreuth (Germany)
E-mail: Matthias.Breuning@uni-bayreuth.de

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/cctc.201600240.

ChemPubSoc Europe

CHEMCATCHEM Full Papers

tions of nitromethane (**2a**) with a series of aromatic, heteroaromatic, vinylic, and aliphatic aldehydes **1**.[9,12] The $CuCl_2$ and $CuBr_2$ complexes of the simple prolinamine **9a** (R^1 = Ph; R^2, R^4 = Me; R^3 = H) provided the corresponding β-nitro alcohols **3** with superb, as yet unrivalled 99% *ee* in all cases (36 examples). Herein we present the development of the catalytic system CuX_2·**9a**, whose optimization included in-depth structure-enantioselectivity investigations with more than 30 diamines of types **9** and **10**. In addition, further studies on the substrate scope, some mechanistic investigations on the origin of the excellent enantioselectivities reached, and the preparation of the new diamines used in this study are described.

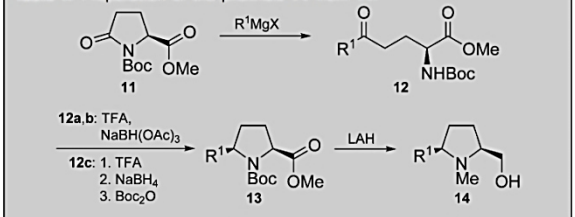
Results and Discussion

Synthesis of the prolinamines

A fast and variable access to prolinamines of type **9** and **10** was essential for the extensive ligand screening planned. We recently developed several routes to this class of diamines that all start from commercially available methyl Boc-L-pyroglutamate (**11**), but differ in the order of introduction of the substituents R^1–R^4, thus permitting a maximum of flexibility.[11] The new prolinamines used in this study were prepared with focus on a late-stage installation of the exocyclic amino function NR^3R^4, which is most easily achieved by hydroxy–amine exchange on the stage of the prolinol precursors **14**.

The substituent R^1 in 5-*cis* position was attached by chemoselective Grignard addition to the pyrrolidine carbonyl group in **11** and reductive cyclization of the resulting β-amino ketones **12** (Table 1). In accordance with earlier results,[11] the yield of the initial addition step strongly depended on the steric hindrance of the Grignard reagent. Good 78% were reached with 3,5-Me_2PhMgBr, whereas just mediocre 37% and 31% were obtained with the more bulky secondary alkyl Grignards *c*PentMgBr and *c*HexMgCl, respectively. The aliphatic β-amino ketones **12a** and **12b** were directly cyclized to the corresponding prolines **13a** and **13b** by using $NaBH(OAc)_3$ as the reductant, whereas ring closure of the aromatic derivative **12c** required a deprotection–reductive cyclization–reprotection sequence.[11] The *cis* diastereoselectivity was high in cyclizations (*dr* > 90:10). Final exhaustive reduction with LAH in refluxing THF afforded the prolinol intermediates **14a–c** in 91–95% yield.

Table 1. Preparation of the prolinols **14** from **11**.

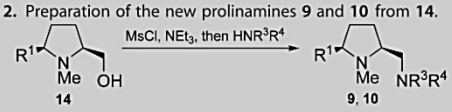


Entry	R^1	Yield of **12**[a] [%]	Yield of **13**[a] [%]	Yield of **14**[a] [%]
1	*c*Pent	37 (**12a**)	90 (**13a**)	92 (**14a**)
2	*c*Hex	31 (**12b**)	70 (**13b**)	95 (**14b**)
3	3,5-Me_2Ph	78 (**12c**)	59 (**13c**)[b]	91 (**14c**)

[a] Isolated yield. [b] 93:7 mixture of **13c** and its C5-epimer.

The alcohols **14a–c** thus prepared and the known derivatives **14d** (R^1 = Me)[11] and **14e** (R^1 = Ph)[9] were converted into the prolinamines **9** and **10** by mesylation of the hydroxy function and subsequent amination with an excess of the respective amine HNR^3R^4 (Table 2). The conversions of these reactions were good,[13] but the high polarity of the resulting diamines led to, in part, significant losses during column chromatographic purification, thus lowering the isolated yields to 50–76%.

Table 2. Preparation of the new prolinamines **9** and **10** from **14**.



Entry	**14**	R^1	**9, 10**	NR^3R^4	Yield [%][a]
1	**a**	*c*Pent	**9b**	NHMe	54
2	**b**	*c*Hex	**9c**	NHMe	56
3	**c**	3,5-Me_2Ph	**9d**	NHMe	76
4[b]	**d**	Me	**9e**	NHMe	52[c]
5[d]	**e**	Ph	**9f**	NHAc	78[c]
6[d]	**e**	Ph	**9g**	NHMs	80[c]
7	**e**	Ph	**9h**	$NH(CH_2)_2OH$	50
8	**e**	Ph	**9i**	$NH(CH_2)_2OMe$	73
9	**a**	*c*Pent	**10a**	NMe_2	57
10	**b**	*c*Hex	**10b**	NMe_2	57
11	**c**	3,5-Me_2Ph	**10c**	NMe_2	73

[a] Isolated yield. [b] Two-step sequence: 1. MsCl, NEt_3, then HN(Me)Bn; 2. H_2, $Pd(OH)_2$/C. [c] Yield over two steps. [d] Two-step sequence: 1. MsCl, NEt_3, then NH_3-MeOH (85%)[11] 2. for **9f**: Ac_2O, NEt_3; for **9g**: MsCl, NEt_3.

Notably, the direct preparation of **9e** (R^1 = Me, NR^3R^4 = NHMe, Table 2 entry 4) from **14d** by using the standard procedure, mesylation and amination with methylamine, failed. The pronounced volatility of the product made a removal of a higher boiling solvent such as MeOH, which was required as co-eluent in the chromatography of **9e**, practically impossible. We circumvented this problem by amination of **14d** with benzylmethylamine, giving the less polar and less volatile *N*-benzyl derivative of **9e**, which could be purified. Hydrogenolytic debenzylation under acidic conditions, basic extraction into Et_2O, and careful evaporation delivered **9e** in high purity and acceptable 52% yield over two steps. Finally, the amides **9f** and **9g** were synthesized by a two-step sequence (entries 5 and 6). Amination of **14e** with ammonia afforded the corresponding primary amine,[11] which was converted into **9f** and **9g** by N-acetylation and N-mesylation, respectively.

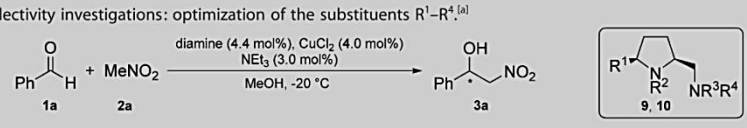
Optimization of the catalytic system

All enantioselective Henry reactions were performed under an argon atmosphere in a well-tempered cooling bath. In the case

ChemPubSoc Europe

CHEMCATCHEM Full Papers

Table 3. First structure–selectivity investigations: optimization of the substituents R^1–R^4.[a]



Entry	Diamine	R^1	R^2	NR^3R^4	*t* [h]	Yield [%][b]	*ee* [%][c]	Configuration[d]
1	**10d**	H	Me	NMe_2	24	99	71	*R*
2	**10e**	Me	Me	NMe_2	18	93	23	*S*
3	**10f**	Bn	Me	NMe_2	24	99	13	*S*
4	**10g**	*i*Pr	Me	NMe_2	40	99	84	*S*
5	**10a**	*c*Pent	Me	NMe_2	18	95	87	*S*
6	**10b**	*c*Hex	Me	NMe_2	18	93	88	*S*
7	**10h**	Ph	Me	NMe_2	20	95	84	*S*
8	**10i**	4-MeOPh	Me	NMe_2	24	99	83	*S*
9	**10j**	3,5-$(CF_3)_2$Ph	Me	NMe_2	24	93	88	*S*
10	**10c**	3,5-Me_2Ph	Me	NMe_2	18	92	90	*S*
11	**10k**	1-naphthyl	Me	NMe_2	24	72	87	*S*
12	**10l**	Ph	Me	N(Me)*t*Bu	48	0	–	–
13	**10m**	Ph	Me	pyrrolidinyl	40	99	94	*S*
14	**9a**	Ph	Me	NHMe	19	99	98	*S*
15	**9j**	Ph	Me	NHEt	48	70	98	*S*
16	**9k**	Ph	Me	NH*i*Pr	48	50	85	*S*
17	**9l**	Ph	Me	NH*t*Bu	48	25	30	*S*
18	**9m**	Ph	Me	NHPh	48	0	–	–
19	**9f**	Ph	Me	NHAc	24	0	–	–
20	**9g**	Ph	Me	NHMs	24	0	–	–
21	**9h**	Ph	Me	$NH(CH_2)_2OH$	40	35	84	*S*
22	**9i**	Ph	Me	$NH(CH_2)_2OMe$	40	34	95	*S*
23	**9n**	Ph	Me	NH_2	48	28	93	*S*
24	**9o**	Ph	H	NHMe	113	23	77	*S*
25	**9p**	Ph	Et	NHMe	40	99	98	*S*
26	**9q**	Ph	Bn	NHMe	40	32	90	*S*
27	**9r**	Ph	*i*Pr	NHMe	24	0	–	–

[a] Performed on a 1 mmol scale in MeOH (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase and rounded off to whole numbers. [d] Assigned by comparison with literature data.

of an important or unexpected result, the reaction was repeated at least twice. The enantiomeric excess of the products **3** was determined by HPLC on chiral phase with an accuracy of up to ±0.1 percentage points.

Ligand structure (I)

The initial ligand screening was done on the addition of nitromethane (**2a**) to benzaldehyde (**1a**) as the model reaction (Table 3), by using the following protocol: The chiral catalyst (4 mol%), prepared prior to use from $CuCl_2$ (4.0 mol%) and a slight excess of the chiral diamine **9** or **10** (4.4 mol%), and the aldehyde **1a** were dissolved in a 1:1 mixture of $MeNO_2$ (≈11 equivalents with respect to **1a**) and MeOH. After cooling to −20 °C, the reaction was started by addition of the ancillary base NEt_3 (3.0 mol%) and stirred for 18–113 h. Under these conditions, the most simple diamine, the 5-*cis*-unsubstituted prolinamine **10d** (R^1 = H), which furthermore possesses a pyrrolidine *N*-methyl and an exocyclic dimethylamino group ($R^{2–4}$ = Me), provided the *R*-configured β-nitro alcohol (*R*)-**3a** in acceptable 71% *ee* and excellent 99% yield after 24 h (Table 3, entry 1). The level of enantioselection reached was quite remarkable, taking the low steric differentiation around the copper atom in the catalyst into account (see complex [M·**9**/**10**] in Scheme 2, with R^1 = H, $R^{2–4}$ = Me).

In a first set of experiments we kept the methyl groups for $R^{2–4}$ and varied the 5-*cis* substituent R^1 (entries 2–11), which was assumed to exert a strong effect on the chirality transfer. And indeed, its impact is clearly seen on the sense of the asymmetric induction. Compared to the reaction with **10d** (R^1 = H), the enantiomeric product, (*S*)-**3a**, was preferentially formed with all prolinamines carrying such a substituent ($R^1 \neq$ H). The level of stereoinduction rose with an increasing steric demand of R^1. Good enantioselectivities of 83–90% *ee* were reached with all diamines that possess an α-branched aliphatic or an aromatic substituent R^1 as in **10a–c,g–k** (entries 4–11). The good chirality transfers with the aliphatic diamines also exclude a decisive role of a π–π-stacking between R^1 and the aromatic substrate benzaldehyde (**1a**). Among the promising prolinamines, we chose to continue the ligand optimization with derivatives possessing a phenyl group as R^1, since these compounds are most easily accessible (for a reinvestigation on R^1 under optimized conditions, see Table 7).

The influence of the substituents R^3 and R^4 at the exocyclic aminomethyl group was investigated next (Table 3, entries 12–23). Increasing the size of one of these substituents as in **10l** (NR^3R^4 = N(Me)*t*Bu) caused a complete breakdown in reactivity.

ChemPubSoc Europe

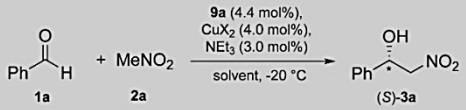
CHEMCATCHEM Full Papers

With pyrrolidinyl instead of NMe_2, improved 94% *ee* were reached. Another gain in stereocontrol was observed upon switching to the prolinamines **9**, which carry secondary aminomethyl groups NHR^4 (entries 14–22). Excellent 98% *ee* were reached with the diamines **9a** (NHMe) and **9j** (NHEt), whereas bulkier substituents R^4 as in **9k,l** (NH*i*Pr, NH*t*Bu) resulted in diminished asymmetric inductions. As a general trend, the catalytic activity significantly dropped with increasing steric demand of R^4, which is clear from the falling yields in the row **9a**, **9j**, **9k** to **9l**, even at prolonged reactions times. No product formation was observed with the anilinyl derivative **9m** (NHPh) and the amides **9f** (NHAc) and **9g** (NHMs). The potentially tridendate diamines **9h** ($NH(CH_2)_2OH$) and **9i** ($NH(CH_2)_2OMe$) and the primary diamine **9n** (NH_2) provided (*S*)-**3a** in acceptable 84–95% *ee*, but low 28–35% yield.

After having identified the NHMe group as the optimal NR^3R^4 function, we finally turned our attention to the substituent R^2 at the pyrrolidine nitrogen atom (entries 24–27). The same trend as with the NR^3R^4 group was observed: Excellent asymmetric inductions of 98% *ee* were achieved with small R^2 as in **9a** and **9p** (R^2 = Me, Et), while larger substituents R^2 as in **9q** and **9r** (R^2 = Bn, *i*Pr) or an NH function as in **9o** drastically reduced the activity of the catalyst.

In summary, the best result (98% *ee*, 99% yield) was achieved with the prolinamine **9a** possessing a phenyl substituent in 5-*cis* position, a pyrrolidine *N*-methyl group, and a 2-(methylaminomethyl) side chain. All further experiments were therefore performed with this diamine.

Table 4. Variation of the copper salt, solvent, and the solvent–$MeNO_2$ ratio.[a]



Entry	Cu Salt	Solvent	Solvent:$MeNO_2$	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	$CuCl_2$	MeOH	1:1	19	99	97.7
2	$CuCl_2$	EtOH	1:1	20	99	98.2
3	$CuCl_2$	THF	1:1	18	99	98.3
4	$CuCl_2$	$MeNO_2$	0:2	21	99	98.3
5	$CuBr_2$	MeOH	1:1	22	90	98.7
6	$CuBr_2$	EtOH	1:1	21	99	98.9
7	$CuBr_2$	THF	1:1	18	99	99.0
8	$CuBr_2$	$MeNO_2$	0:2	22	99	98.0
9[e]	$Cu(OAc)_2$[f]	MeOH	1:1	70	7	98.2
10[e]	$Cu(OAc)_2$[f]	EtOH	1:1	70	12	99.0
11[e]	$Cu(OAc)_2$[f]	THF	1:1	70	30	98.7
12[e]	$Cu(OAc)_2$[f]	$MeNO_2$	0:2	70	20	97.8
13	$Cu(OAc)_2$[f]	THF	1:1	17	88	90.8
14	$Cu(OAc)_2$[f]	MeOH	1:1	15	97	91.2
15	$CuBr_2$	THF	3:1	16	99	99.1
16	$CuBr_2$	THF	1:3	16	99	98.6
17[g]	$CuBr_2$	THF	1:1	16	99	99.0
18[h]	$CuBr_2$	THF	1:1	16	99	99.1

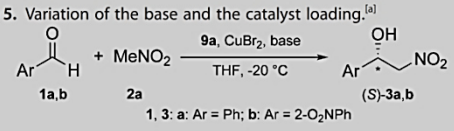
[a] Performed on a 1 mmol scale in the respective solvent–$MeNO_2$ mixture (1200 µL total, c(**1a**) = 0.83 M). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 3, entry 14. [e] No NEt_3 added. [f] Dihydrate. [g] Reaction in 600 µL solvent, c(**1a**) = 1.66 M. [h] Reaction in 2400 µL solvent, c(**1a**) = 0.42 M.

Reaction conditions

The copper source ($CuCl_2$, $CuBr_2$, and $Cu(OAc)_2$) and the solvent (MeOH, EtOH, THF, and $MeNO_2$) were varied first (Table 4, entries 1–12). The influence of both parameters on the chirality transfer was marginal, which is clear from the excellent 97.7–99.0% *ee* obtained in all cases. A distinct difference in reactivity and, thus, in the yields, was observed between the copper halide and the copper acetate complexes. In the latter Henry reactions, no NEt_3 was added since the acetate freed from the catalyst upon coordination of the substrates can act as the base.[14] The low 7–30% yield obtained after 70 h are presumably a consequence of the weaker basicity of acetate, which slows down the deprotonation of nitromethane. Addition of NEt_3 (3 mol%, entries 13 and 14) accelerated the reaction (≥88% yield after 17 h), but resulted in lower stereocontrol (91% *ee*). A closer inspection of the enantioselectivities achieved with the $CuCl_2$ and $CuBr_2$ complexes revealed the latter ones as slightly superior (98.0–99.0% *ee* vs. 97.7–98.3% *ee*). All solvents examined permitted similar levels of chirality transfer, but the reaction with $CuBr_2$ in THF seemed to proceed somewhat faster. Since this will be beneficial for lower-temperature reactions (see Table 6), we decided to continue with this combination. Changes in the solvent–$MeNO_2$ ratio from 1:1 to 3:1 and 1:3 (entries 15 and 16) as well as in the concentration from 0.83 M to 1.66 M and 0.42 M (entries 17 and 18) had no noticeable effect on yield and enantioselectivity.

A short base screening (Table 5, entries 1–3) revealed that the steric demand of the base is not of importance, which is clear from the excellent 99% yield and 99.0% *ee* reached with both, NEt_3 and $EtNiPr_2$. A sufficient basicity, however, was re-

Table 5. Variation of the base and the catalyst loading.[a]



Entry	1, 3	$CuBr_2$:**9a** : Base [mol%/mol%]	Base	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	**a**	4.0:3.0	NEt_3	18	99	99.0
2	**a**	4.0:3.0	$EtNiPr_2$	20	99	99.0
3	**a**	4.0:3.0	pyridine	20	traces	–
4	**a**	4.0:3.0	–	16	0	–
5	**a**	4.0:6.0	NEt_3	21	99	98.9
6	**a**	4.0:1.0	NEt_3	16	13	99.0
7	**a**	2.0:1.5	NEt_3	18	99	99.1
8	**a**	1.0:0.75	NEt_3	17	48	99.2
9	**a**	0.50:0.375	NEt_3	41	7	98.5
10	**b**	4.0:3.0	NEt_3	17	99	99.0
11	**b**	2.0:1.5	NEt_3	17	99	98.9
12	**b**	1.0:0.75	NEt_3	17	64	99.0
13	**b**	0.50:0.375	NEt_3	42	13	94.4

[a] Performed on a 1 mmol scale in THF (600 µL) and $MeNO_2$ (600 µL), **9a** : $CuBr_2$ = 1.1:1. [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 4, entry 7.

ChemPubSoc Europe

CHEMCATCHEM Full Papers

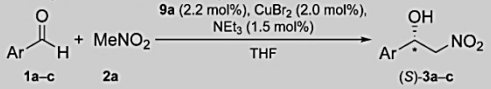
quired, because only traces of product were formed in the presence of pyridine. This observation is in good agreement with the slow reaction rates observed for the $Cu(OAc)_2$ complexes in which acetate served as the base (see Table 4, entries 9–12). As expected, there was no reaction without a base (Table 5, entry 4).

Changing the ratio catalyst–NEt_3 from standard 4:3 to 4:6 or 4:1 had little to no effect on the enantioselectivity (Table 5, entries 5 and 6). The yield, however, dropped to mere 13% if just 1 mol% of NEt_3 was used. The catalyst loading can be reduced to 2 mol% without any loss in yield and stereocontrol, if the catalyst–NEt_3 ratio is kept constant at 4:3 (entry 7). With just 1 mol% of catalyst and 0.75 mol% of base, the hitherto best enantioselection of 99.2% *ee* was achieved (entry 8). Although the 48% yield reached are just mediocre, the level of conversion is quite surprising as compared to the reaction with 4 mol% $CuBr_2$·**9a** and 1 mol% NEt_3 (see entry 6), which provided just 13% product within the same time frame, despite of the higher amounts of base and catalyst. Further lowering of the catalyst loading to 0.5 mol% resulted in a slight loss of asymmetric induction (98.5% *ee*), but a drastically reduced yield (7% after 41 h, entry 9).

At this point we checked that our optimization was not too substrate specific. As electron-deficient aldehydes might more readily undergo the uncatalyzed background reaction (vide infra), and, thus, require higher catalyst loadings, the latter experiments were repeated with 2-nitrobenzaldehyde (**1b**, entries 10–13). In the presence of 2 mol% catalyst, also this substrate provided the corresponding β-nitro alcohol (*S*)-**3b** in excellent 98.9% *ee* and 99% yield. Further reduction of the amount of catalyst to 0.5%, however, led to a significantly stronger depletion in enantioselectivity (94.4% *ee*), as compared to the analogous reaction with benzaldehyde (**1a**, see entry 9).

The last parameter, the temperature, was optimized with benzaldehyde (**1a**), 2-nitrobenzaldehyde (**1b**), and 2-methoxybenzaldehyde (**1c**) as the model substrates (Table 6). As expected, an increase in stereocontrol was observed by lowering the temperature to −30 °C, giving the β-nitro alcohols (*S*)-**3a–c** in excellent 99.1–99.5% *ee*. The reaction rates, however, markedly dropped below −25 °C, which is clear from the prolonged reaction times required and the incomplete conversion of the least reactive aldehyde **1c**. We therefore choose −25 °C as a good compromise between yield and chirality transfer.

Table 6. Optimization of the temperature.[a]



1, 3: **a**: Ar = Ph; **b**: Ar = 2-O_2NPh; **c**: Ar= 2-MeOPh

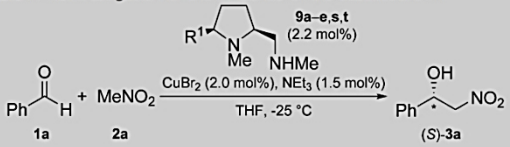
Entry	1, 3	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	**a**	−20	18	99	99.1
2[e]	**a**	−25	24	92	99.3
3	**a**	−30	66	99	99.5
4[f]	**b**	−20	17	99	98.9
5[e]	**b**	−25	20	97	99.0
6	**b**	−30	66	99	99.1
7	**c**	−20	40	99	99.2
8[e]	**c**	−25	42	97	99.5
9	**c**	−30	67	55	99.5

[a] Performed on a 1 mmol scale in THF (600 µL) and $MeNO_2$ (600 µL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 5, entry 7. [e] Data taken from Ref. [9]. [f] See Table 5, entry 11.

Ligand structure (II)

At this final stage we decided to reinvestigate the influence of the 5-*cis* substituent R^1, because there had been no clear preference for a particular group in the initial screening (see Table 3, entries 1–11). The re-evaluation was performed under the optimized reaction conditions with the secondary prolinamines **9b–e,s,t** carrying the better stereo-differentiating exocyclic NHMe group. As seen in Table 7, all derivatives of **9** with an aliphatic or aromatic substituent R^1 provided the β-nitro alcohol (*S*)-**3a** with high stereocontrol (≥96.0% *ee*), even the diamine **9e**, which possesses the small methyl group. The best stereoselection (99.3% *ee*) was achieved with the phenyl-substituted prolinamine **9a** (Table 7, entry 6), maybe as a result of the optimization process done on this compound. The surprising reversal in the sense of enantioselection, as it had been found with the tertiary diamine **10d** missing the substituent R^1 (see Table 3, entry 1), was not observed for the secondary prolinamine **9s**, which also afforded the *S*-configured product (*S*)-**3a**, albeit in low 25% *ee*.

Table 7. Reinvestigation of the influence of the substituent R^1.[a]



Entry	9	R^1	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**s**	H	18	95	25.2
2	**e**	Me	18	95	96.0
3	**t**	*i*Pr	18	99	96.9
4	**b**	*c*Pent	19	99	97.0
5	**c**	*c*Hex	18	99	97.7
6[d]	**a**	Ph	24	92	99.3
7	**d**	3,5-Me_2Ph	41	99	98.2

[a] Performed on a 1 mmol scale in THF (600 µL) and $MeNO_2$ (600 µL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] See Table 6, entry 2.

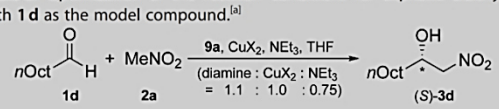
Aliphatic aldehydes

When applying the optimized conditions to the Henry reaction of the aliphatic aldehyde nonanal (**1d**), the β-nitro alcohol (*S*)-**3d** was produced in disappointing 53% yield and 94.5% *ee* (Table 8, entry 1). The yield and the level of enantioselection,

ChemPubSoc Europe

CHEMCATCHEM Full Papers

Table 8. Optimization of the reaction conditions for aliphatic aldehydes with **1d** as the model compound.[a]



Entry	Cu Salt ([mol%])	T [°C]	t [h]	Yield [%][b]	*ee* [%][c]
1	$CuBr_2$ (2)	−25	40	53	94.5
2	$CuBr_2$ (4)	−25	60	75	96.2
3	$CuBr_2$ (8)	−25	24	90	97.0
4	$CuCl_2$ (8)	−25	21	87	98.2
5[d]	$CuCl_2$ (8)	−20	60	97	98.6
6	$CuCl_2$ (8)	−10	16	77	97.1

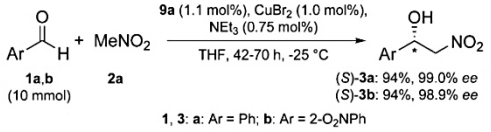
[a] Performed on a 1 mmol scale in THF (600 μL) and $MeNO_2$ (600 μL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] Data taken from ref. [9].

however, were raised by increasing the amount of catalyst to 8 mol% and the temperature to −20 °C, and by changing the copper source to $CuCl_2$. Under these conditions, the product (*S*)-**3d** was obtained in excellent 97% yield and high 98.6% *ee*. One observation made in this context is noteworthy: The enantioselectivity of the reaction at −25 °C with $CuCl_2$·**9a** as the catalyst was slightly lower than the one at −20 °C (entry 4 vs. 5). This unexpected result might have its origin in a beginning aggregation of the catalyst at −25 °C, as judged from the increasing turbidity of the reaction mixture, which would reduce the amount of active catalyst and, thus, favor the non-stereoselective background reaction. A similar effect was not observed for the complex $CuBr_2$·**9a** in the reaction with aromatic aldehydes (see Table 6).

Under the optimized conditions for aromatic aldehydes [$CuBr_2$ (2 mol%), **9a** (2.2 mol%), NEt_3 (1.5 mol%), THF/$MeNO_2$ = 1:1, −25 °C] and aliphatic aldehydes [$CuCl_2$ (8 mol%), **9a** (8.8 mol%), NEt_3 (6.0 mol%), THF/$MeNO_2$ = 1:1, −20 °C], enantioselective Henry reactions with a broad variety of substrates were performed, providing the excellent results reported earlier.[9]

Gram-scale reactions

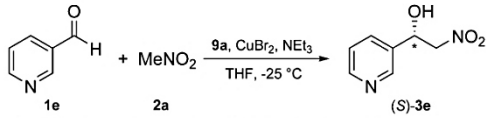
Finally, we decided to prove the practicability of our new catalytic system in gram-scale reactions (10 mmol aldehyde) with benzaldehyde (**1a**) and 2-nitrobenzaldehyde (**1b**) as the model substrates (Scheme 3). To further demonstrate its effectiveness, we cut, compared to the optimized procedure above, the amount of catalyst $CuBr_2$·**9a** in half (1 mol%), which was the minimum amount required to preserve the excellent stereocontrol (see Table 5, entries 8 and 12). Even under these enforced conditions, the Henry products (*S*)-**3a** and (*S*)-**3b** were formed in high 94% yield each. The enantiomeric excess (99.0% and 98.9% *ee*, respectively) was as good as in the small-scale reactions.



Scheme 3. Gram-scale Henry reactions of **1a** and **1b**.

Extending the substrate scope

The good performance of the prolinamine **9a** in Henry reactions prompted us to further study its scope and limitations. A tempting substrate is nicotinaldehyde (**1e**, Scheme 4) because of its basic and nucleophilic pyridine moiety, which might promote the uncatalyzed background reaction[15] and, in addition, might competitively coordinate to the catalyst, thus reducing the amount of catalytically active species. And indeed, the Henry reaction of **1e** in the presence of the catalyst $CuBr_2$·**9a** (2 mol%) proceeded sluggishly and delivered (*S*)-**3e** in unsatisfying 43% yield after 10 d and with low 82% *ee*. To accelerate the catalyzed reaction, we raised the amount of $CuBr_2$·**9a** to 15 mol%. Under these conditions, (*S*)-**3e** was obtained in improved 81% yield and acceptable 90% *ee* after 5 days.



9a (2.2 mol%), $CuBr_2$ (2.0 mol%), NEt_3 (1.5 mol%): 10 d, 43%, 82% *ee*
9a (16.5 mol%), $CuBr_2$ (15 mol%), NEt_3 (12 mol%): 5 d, 81%, 90% *ee*

Scheme 4. Henry reactions with basic nicotinaldehyde (**1e**).

Diastereo- and enantioselective Henry reactions[16] with nitroalkanes **2** (R′ ≠ H) were first studied using benzaldehyde (**1a**) as the substrate (Table 9). Owing to the lower reactivity of the nitroalkanes **2b–d** (R′ = Me, Et, CH_2OTBS), the following reactions were performed at −20 °C and with 8 mol% catalyst $CuBr_2$·**9a**. Whereas the *syn–anti* ratio in the nitroethane (**2b**) derived product **3f** was meager (60:40), acceptable ratios of 78:22 were obtained in **3g** and **3h** prepared from nitropropane (**2c**) and sterically more demanding 2-TBSO-nitroethane (**2d**), respectively. The enantioselectivities were always excellent (≥ 98% *ee*) in the major *syn* products and acceptable to good (82–93% *ee*) in the minor *anti* products. A further gain in selectivity was reached with the combination cyclohexanecarbaldehyde (**1f**)-nitropropane (**2c**), which provided the product **3i** in a good 84:16 *syn-anti* ratio and with 99% *ee* in both diastereomers. Thus, the catalyst $CuBr_2$·**9a** is also well suited for enantio- and diastereoselective Henry reactions.

Mechanistic investigations

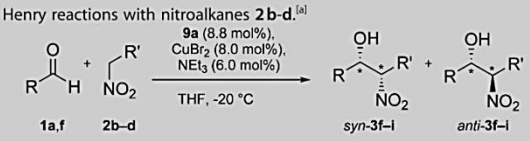
Origin of enantioselection

Next we put our focus on the origin of the enantioselection. We wanted to prove that the high levels of stereocontrol solely arise from a kinetic differentiation in the *C,C*-coupling step and that processes involving product species, as, for example, an additional resolution on the stage of the primarily

ChemPubSoc Europe

CHEMCATCHEM Full Papers

Table 9. Enantio- and diastereoselective Henry reactions with nitroalkanes **2b-d**.[a]

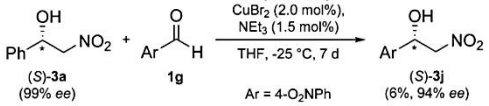


Entry	1	R	2	R′	*t* [d]	3	Yield [%][b]	*syn*:*anti*[c]	ee_{syn} [%][d]	ee_{anti} [%][d]
1	**a**	Ph	**b**	Me	4	**f**	99	60:40	99	93
2	**a**	Ph	**c**	Et	4	**g**	99	78:22	98	82
3	**a**	Ph	**d**	CH_2OTBS	7	**h**	98	78:22	99	93
4	**f**	*c*Hex	**c**	Et	7	**i**	84	84:16	99	99

[a] Performed on a 1 mmol scale in THF (600 μL) and nitroalkane **2** (8 equiv). [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC on chiral phase.

resulting, diastereomeric product–catalyst complexes, do not contribute.

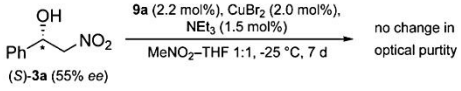
A necessary precondition for any dynamic process that influences the stereochemical outcome on the stage of the products is an equilibrium between the product species and the starting materials. The existence of such an equilibrium, although more or less fully shifted towards the products, was demonstrated by treatment of the β-nitro alcohol (*S*)-**3a** with 4-nitrobenzaldehyde (**1g**) under standard conditions (Scheme 5). The cross product **3j** observed in this reaction



Scheme 5. The formation of the cross product (*S*)-**3j** from (*S*)-**3a** and **1g** proves the reversibility of the Henry reaction under the standard reaction conditions.

must have been formed via a retro-Henry–Henry sequence. The rate of the back reaction, however, is pretty slow, which is clear from the low 6% yield obtained after 7 d. The good 94% *ee* indicates that at least the formation of (*S*)-**3j** must have been catalyzed by $CuBr_2$·**9a**.

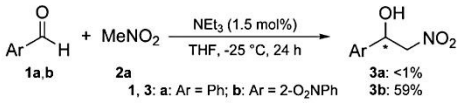
With the existence of the back reaction proven, the question remained whether this process induces any changes in the enantiopurity of the product. This cannot be the case because stirring of the scalemic β-nitro alcohol (*S*)-**3a** (55% *ee*) under standard conditions for 7 d did not noticeably alter its optical purity (Scheme 6). Thus, any scenario that affects the overall stereochemical outcome and involves product species can be safely excluded. The excellent stereodifferentiation observed must have its origin exclusively in the C,C-coupling step.



Scheme 6. The scalemic β-nitro alcohol (*S*)-**3a** (55% *ee*) is configurationally stable under standard Henry conditions.

Uncatalyzed background reaction

From the ≥98.9% *ee* reached with **1a** and **1b** in the presence of just 1 mol% of $CuBr_2$·**9a** (see Scheme 3) it follows that the catalyzed reaction must proceed at least 99 times faster than the non-stereoselective background reaction.[17] This is in good agreement with the observation that the latter one is virtually non-existing for benzaldehyde (**1a**: <1% conversion within 24 h, Scheme 7). In contrast to that, the rate of the background



Scheme 7. Uncatalyzed background reactions of **1a** and **1b**.

reaction is surprisingly high for the more electrophilic 2-nitrobenzaldehyde (**1b**, 59% conversion within 24 h). Although this does not noticeably affect the enantioselectivity of the catalyzed reaction with 1 mol% of $CuBr_2$·**9a**, it is most likely the main reason for the more pronounced loss in stereocontrol in the reaction of **1b** with 0.5 mol% catalyst, as compared to the analogous reaction of **1a** (98.5% vs. 94.4% *ee*, see Table 5, entry 9 vs. 13).

Relative reactivities of the catalysts derived from 9a and 10h

In parallel to the significantly enhanced stereocontrol reached with prolinamines of type **9** (secondary exocyclic amino group), as compared to those of type **10** (tertiary exocyclic amino group), we also observed a gain in reactivity. We therefore decided to measure the relative rates of reactions in the presence of our prime catalyst CuX_2·**9a** in comparison to those with CuX_2·**10h** (**10h**: dimethyl analogue of **9a**) under different conditions. Competition experiments, in which equimolar amounts of two chiral catalysts are used that deliver enantiomeric products, offer an experimentally simple method to do this, without the necessity of extensive kinetic studies. The relative rate constant k_{rel} can be calculated from the enantiomeric ratios of the single-catalyst and competition experiments using Equation (1):[18]

ChemPubSoc Europe

CHEMCATCHEM Full Papers

$$k_{rel} = \frac{k_{cat1}}{k_{cat2}} = \frac{(er_1 + 1)(er_{cp} - er_2)}{(er_2 + 1)(er_1 - er_{cp})} \quad (1)$$

er_1 = *S*/*R* ratio with catalyst 1
er_2 = *S*/*R* ratio with catalyst 2
er_{cp} = *S*/*R* ratio reached in the 1:1-competition experiment

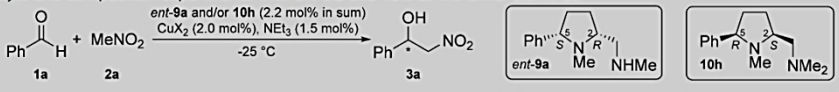
The required pseudo-enantiomeric catalyst *ent*-**9a** was prepared in analogy to **9a**, but starting from methyl Boc-D-pyroglutamate (*ent*-**11**).[9,11] The single-catalyst and competition experiments were done with the $CuBr_2$ and $CuCl_2$ catalysts derived from **10h** (2*S*,5*R*-configuration) and *ent*-**9a** (2*R*,5*S*-configuration) in THF and MeOH at −25 °C (Table 10). In THF and with $CuBr_2$·*ent*-**9a**, the product (*R*)-**3a** was obtained after 18 h in good 92% yield and excellent 99% *ee*, while the analogous reaction with $CuBr_2$·**10h** proceeded more slowly (58% yield after 43 h) and delivered the enantiomer (*S*)-**3a** with significantly lower stereocontrol (84% *ee*). The competition experiment (Table 10, entry 3) with equimolar amounts of both catalysts provided (*R*)-**3a** in 50% *ee*, clearly proving the higher catalytic activity of $CuBr_2$·*ent*-**9a**. By using Equation (1), a relative rate factor k_{rel} ($=k_{ent-9a}k_{10h}^{-1}$) of 2.73 in favor of $CuBr_2$·*ent*-**9a** was calculated. A similar k_{rel} value of 3.54 was observed for the corresponding chloro complexes $CuCl_2$·*ent*-**9a** and $CuCl_2$·**10h** (entries 4–6). MeOH as the solvent (entries 7–9) causes a general decrease in reactivity, which is clear from the prolonged reaction times required, which might be an effect of its better coordination abilities favoring a deactivation of intermediate catalyst species. In addition, the ratio k_{rel} of the reaction rates is higher: The catalytic system $CuCl_2$·*ent*-**9a** reacted 7.32 times faster than $CuCl_2$·**10h**. This furthermore underlines the existence of direct solvent-catalyst interactions—if this were not the case, the same k_{rel} values in THF and MeOH would be expected.

In the transition states of the Henry reactions with the secondary prolinamines **9**, there is the possibility of an additional hydrogen bridge between the NH function of the chiral ligand and the nitronate bound to the copper atom, which would further rigidify the system and, thus, explain the better stereocontrol observed.[9] This interaction should reduce the nucleophilicity of the nitronate and, in consequence, lower the activities of the catalysts CuX_2·**9**, as compared to CuX_2·**10**. Since the opposite effect was observed in the competition experiments, the existence of such a hydrogen bridge seems unlikely.[19] The higher enantioselectivities reached with secondary prolinamines **9** presumably originate from steric and conformational factors.

Conclusions

Several new, 5-*cis*-substituted prolinamines of type **9** and **10** were synthesized in 4–6 steps from methyl Boc-L-pyroglutamate (**11**). Their potential as the chiral ligands in enantioselective, copper-catalyzed Henry reactions was evaluated. In-depth structure–selectivity investigations with more than 30 diamines **9** and **10** revealed that an aromatic or sufficiently bulky aliphatic substituent in 5-*cis* position is crucial for high levels of stereocontrol, while larger groups at the pyrrolidine nitrogen atom or at the exocyclic aminomethyl group cause an, in part, drastic loss in reactivity and enantioselectivity. The prolinamine **9a** (R^1 = Ph; R^2 = Me; NR^3R^4 = NHMe) was found to be the chiral ligand of choice. Optimization of other reaction parameters, such as temperature, solvent, concentration and catalyst loading, led to two highly efficient catalytic systems, $CuBr_2$·**9a** for aromatic aldehydes and $CuCl_2$·**9a** for aliphatic ones. With just 2 mol% of catalyst (8 mol% in the case of aliphatic aldehydes), the superb results reported earlier (99% *ee* with 36 aldehydes) were achieved.[9] In further studies we extended the scope of $CuBr_2$·**9a** to gram-scale and diastereoselective Henry reactions (up to 84:16 *dr*, 99% *ee*). It was also proven that the stereodifferentiation originates solely from the C,C-coupling step and that the product is configurationally stable under the reaction conditions. The uncatalyzed background reaction is virtually non-existing for benzaldehyde (**1a**), but remarkably high for the more electrophilic 2-nitrobenzaldehyde (**1b**). The relative reactivity of the catalysts derived from the prolinamines **9a** and **10h** was studied by competition experiments. The complexes with **9a** reacted up to 7.32 times faster, depending on the reaction conditions. This, however, does not explain the significant increase in enantioselectivity observed

Table 10. Single-catalyst and competition experiments with *ent*-**9a** and **10h** as the chiral diamines.[a]



Entry	Diamine	Cu Salt	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]	Configuration	$k_{rel} = k_{ent-9a}k_{10h}^{-1}$[d]
1	*ent*-**9a**	$CuBr_2$	THF	18	92	99	*R*	
2	**10h**	$CuBr_2$	THF	43	58	84	*S*	
3	*ent*-**9a**/**10h** 1:1[e]	$CuBr_2$	THF	19	87	50	*R*	2.73
4	*ent*-**9a**	$CuCl_2$	THF	18	99	99	*R*	
5	**10h**	$CuCl_2$	THF	39	81	87	*S*	
6	*ent*-**9a**/**10h** 1:1[e]	$CuCl_2$	THF	19	77	58	*R*	3.54
7	*ent*-**9a**	$CuCl_2$	MeOH	40	82	98	*R*	
8	**10h**	$CuCl_2$	MeOH	39	47	85	*S*	
9	*ent*-**9a**/**10h** 1:1[e]	$CuCl_2$	MeOH	41	78	76	*R*	7.32

[a] Performed on a 1 mmol scale in THF (600 µL) and $MeNO_2$ (600 µL). [b] Isolated yield. [c] Determined by HPLC on chiral phase. [d] Calculated using Equation (**1**). [e] The catalysts derived from *ent*-**9a** and **10h** were prepared separately and mixed shortly before use.

ChemPubSoc Europe

CHEMCATCHEM Full Papers

with **9a** (NR^3R^4 = NHMe), as compared to its dimethyl analogue **10h** (NR^3R^4 = NMe_2).

Experimental Section

All reactions with moisture-sensitive reagents were performed under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[20] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey–Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey–Nagel, particle size 40–63 μm) was used for column chromatography. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^{1}H and ^{13}C NMR data were performed on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer, high-resolution mass spectra were recorded on a ThermoFisher Scientific Q-Exactive (Orbitrap) or a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization). The enantiomeric excess and the configuration of the β-nitro alcohols **3** were determined by HPLC analysis on chiral phase; the diastereomeric ratios were measured by ^{1}H NMR (for details see Supporting Information). Prolinols **14d**[11] and **14e**[9] and prolinamines **9a**,[9] **9j–m**,[12] **9n–r,t**,[11] **10e–k,m**[11] and **10l**[12] were prepared according to literature procedures. Diamines **10d** and **9s** are commercially available. The synthesis of the prolinamine **9b** and general procedures for the asymmetric Henry reactions are described here. For the preparation of all other new compounds, see Supporting information.

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-cyclopentyl-5-oxopentanoate (12a)

A solution of the pyroglutamate **11** (10.0 g, 41.1 mmol) in anhydrous THF (120 mL) was treated at −40 °C with *c*PentMgBr, prepared from bromocyclopentane (5.95 mL, 8.27 g, 55.5 mmol) and Mg (1.49 mg, 61.1 mmol) in anhydrous THF (50 mL). The reaction mixture was allowed to warm to RT overnight. Sat. aq. NH_4Cl (20 mL) was added and THF was evaporated in vacuo. The resulting aqueous suspension was partitioned between sat. aq. NH_4Cl (200 mL) and CH_2Cl_2 (200 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2×200 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 5:1) afforded amino ketone **12a** (4.75 g, 15.2 mmol, 37%) as a colorless oil. R_f = 0.27 (petroleum ether/EtOAc 6:1); $[\alpha]_D^{31}$ = −18.6 (*c* = 1.00 in MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 3375, 2952, 2871, 1745, 1706, 1513, 1366, 1146 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9H, $C(CH_3)_3$), 1.56 (m, 2H, *c*Pent-H), 1.59–1.75 (m, 4H, *c*Pent-H), 1.79 (m, 2H, *c*Pent-H), 1.89 (m, 1H, 3-*H*H), 2.10 (m, 1H, 3-H*H*), 2.55 (m, 2H, 4-H_2), 2.84 (quint., *J* = 7.9 Hz, 1H, *c*Pent-H), 3.72 (s, 3H, OCH_3), 4.26 (m, 1H, 2-H), 5.09 ppm (d, *J* = 8.0 Hz, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.1 (C-*c*Pent), 26.6 (C-3), 28.4 ($C(CH_3)_3$), 29.0, 29.1 (C-*c*Pent), 37.7 (C-4), 51.5 (C-*c*Pent), 52.5 (OCH_3), 53.1 (C-2), 80.1 ($C(CH_3)_3$), 155.6 (NCO_2), 173.1 (C-1), 212.2 ppm (C-5); HRMS (ESI, pos.) *m/z* calcd for $C_{16}H_{27}NO_5$ $[M+H]^+$ 314.19620, found 314.19637.

(2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-cyclopentylpyrrolidine-1,2-dicarboxylate (13a)

$NaBH(OAc)_3$ (5.53 g, 26.1 mmol) was added at 0 °C to a solution of the amino ketone **12a** (4.20 g, 13.4 mmol) in EtOAc (60 mL). After 10 min, TFA (6.66 mL, 9.85 g, 86.4 mmol) was added dropwise and the reaction mixture was stirred overnight at RT. Sat. aq. $NaHCO_3$ (200 mL) was added and the reaction mixture was extracted with EtOAc (3×200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (silica gel, petroleum ether–EtOAc, 15:1–4:1) provided diastereomerically pure **13a** (3.59 g, 12.1 mmol, 90%) as a colorless oil. R_f = 0.69 (petroleum ether/EtOAc 3:1); $[\alpha]_D^{32}$ = −26.5 (*c* = 1.00 in MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 2948, 2869, 1756, 1694, 1455, 1387, 1365, 1167, 1139, 1108 cm^{-1}; ^{1}H NMR* (500 MHz, $CDCl_3$): δ = 1.12 (m, 1H, *c*Pent-H), 1.36 (s, 5.4H, $C(CH_3)_3$), 1.42 (s, 3.6H, $C(CH_3)_3$), 1.49 (m, 3H, *c*Pent-H), 1.62 (m, 3H, *c*Pent-H), 1.78 (m, 3H, 4-H_2, *c*Pent-H), 1.86–2.13 (m, 2H, 3-*H*H, *c*Pent-H), 2.20 (m, 1H, 3-H*H*), 3.69 (s, 3H, OCH_3), 3.74 (m, 0.4H, 5-H), 3.86 (t, *J* = 7.9 Hz, 0.6H, 5-H), 4.17 (t, *J* = 8.6 Hz, 0.6H, 2-H), 4.29 ppm (t, *J* = 8.3 Hz, 0.4H, 2-H); ^{13}C NMR* (125 MHz, $CDCl_3$): δ = 25.0, 25.1, 25.3, 27.9 (C-*c*Pent), 28.3, 28.5 ($C(CH_3)_3$), 28.8, 28.9 (C-3, C-4), 29.5, 29.7, 30.3, 30.5, 44.6, 44.8 (C-*c*Pent), 51.9, 52.1 (OCH_3), 59.6, 60.1 (C-2), 62.4, 62.7 (C-5), 79.7, 80.0 ($C(CH_3)_3$), 154.4, 155.0 (1-CO_2), 174.1, 174.3 ppm (2-CO_2); HRMS (ESI, pos.) *m/z* calcd for $C_{16}H_{27}NO_4$ $[M+H]^+$ 298.20128, found 298.20134. * 60:40 mixture of rotamers.

(2*R*,5*S*)-2-Cyclopentyl-5-(hydroxymethyl)-1-methylpyrrolidine (14a)

$LiAlH_4$ (732 mg, 19.3 mmol) was added at 0 °C to a solution of the pyrrolidine ester **13a** (822 mg, 2.76 mmol) in anhydrous THF (25 mL). The reaction mixture was stirred for 1 h at 0 °C and then refluxed for 26 h. The resulting suspension was treated with sat. aq. Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of Celite and the filter cake was rinsed with CH_2Cl_2-MeOH (9:1, 200 mL). Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2-MeOH-NH_3 (aq., 25%), 90:9:1) provided amino alcohol **14a** (467 mg, 2.55 mmol, 92%) as a colorless oil. R_f = 0.23 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5); $[\alpha]_D^{31}$ = +22.5 (*c* = 1.00 in MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 3312, 2948, 2866, 2782, 1771, 1455, 1240, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (m, 2H, *c*Pent-H), 1.43–1.67 (m, 6H, 3-*H*H, 4-*H*H, *c*Pent-H), 1.76 (m, 4H, 3-H*H*, 4-H*H*, *c*Pent-H), 2.02 (m, 1H, *c*Pent-H), 2.32 (s, 3H, 1-CH_3), 2.51 (dd, *J* = 13.6, 6.6 Hz, 1H, 2-H), 2.58 (m, 1H, 5-H), 2.80–3.25 (br s, 1H, OH), 3.36 (d, *J* = 10.6 Hz, 1H, 5-C*H*H), 3.63 ppm (dd, *J* = 10.6, 3.5 Hz, 1H, 5-CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4 (C-*c*Pent), 25.9, 26.3 (C-3, C-4), 26.9, 27.5, 30.7 (C-*c*Pent), 39.9 (1-CH_3), 43.5 (C-*c*Pent), 61.0 (5-CH_2), 67.6 (C-5), 70.7 ppm (C-2); HRMS (ESI, pos.) *m/z* calcd for $C_{11}H_{21}NO$ $[M + H]^+$ 184.16959, found 184.16908.

(2*R*,5*S*)-2-Cyclopentyl-1-methyl-5-((methylamino)methyl)pyrrolidine (9b)

MsCl (27.8 μL, 41.1 mg, 360 μmol) and NEt_3 (136 μL, 99.4 mg, 982 μmol) were added at 0 °C to a solution of the prolinol **14a** (60.0 mg, 327 μmol) in anhydrous CH_2Cl_2 (4 mL). After 3 d at RT, an excess of methylamine (aq., 40%, 1.30 mL, 1.16 g, 9.81 mmol) and MeOH (4.0 mL) was added and stirring was continued for 3 d. Evaporation of the solvent and column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 97:2.7:0.3–95:4.5:0.5) delivered prolinamine **9b** (34.6 mg, 176 μmol, 54%) as a yellowish oil. R_f = 0.31 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1); $[\alpha]_D^{32}$ = +4.9 (*c* = 0.20 in

ChemPubSoc Europe

CHEMCATCHEM Full Papers

MeOH); IR (ATR): $\tilde{\nu}_{max}$ = 2951, 2865, 2780, 1450, 1209, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.12–1.30 (m, 2H, *c*Pent-H), 1.41–1.68 (m, 8H, 3-*H*H, 4-*H*H, *c*Pent-H, NH), 1.68–1.87 (m, 3H, 3-H*H*, 4-H*H*, *c*Pent-H), 1.97 (m, 1H, *c*Pent-H), 2.31 (s, 3H, 1-CH_3), 2.33 (m, 1H, 2-H), 2.45 (s, 3H, $NHCH_3$), 2.47 (m, 1H, 5-H), 2.53 (dd, *J* = 11.2, 6.0 Hz, 1H, 5-C*H*H), 2.64 ppm (dd, *J* = 11.2, 3.9 Hz, 1H, 5-CH*H*); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4, 26.0 (C-*c*Pent), 27.0 (C-3), 27.92 (C-4), 27.93, 30.9 (C-*c*Pent), 37.2 ($NHCH_3$), 40.9 (1-CH_3), 43.8 (C-*c*Pent), 55.7 (5-CH_2), 67.0 (C-5), 71.3 ppm (C-2); HRMS (ESI, pos.) *m/z* calcd for $C_{12}H_{24}N_2$ $[M+H]^+$ 197.20123, found 197.20218.

General procedure for the enantioselective Henry reactions of aromatic aldehydes under optimized conditions

A solution of anhydrous $CuBr_2$ (66.7 mM in MeOH, 300 µL, 4.47 mg, 20.0 µmol, 2.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of diamine **9a** (36.7 mM in anhydrous THF, 600 µL, 4.49 mg, 22.0 µmol, 2.2 mol%), $MeNO_2$ (**2a**, 600 µL, 684 mg, 11.2 mmol, 11.2 equiv), and the aldehyde **1** (1.00 mmol, 1.00 equiv) were added successively at RT. The mixture was ultrasonicated for 10 min to give a clear, brownish solution, which was cooled to −25 °C. NEt_3 (1.50 M in THF, 10.0 µL, 1.52 mg, 15.0 µmol, 1.5 mol%) was added and the resulting blue-green solution was stirred until TLC-control indicated complete consumption of the aldehyde. The crude reaction mixture was purified by column chromatography (silica gel, hexanes–EtOAc 8:1–4:1) providing β-nitro alcohol **3**. The enantiomeric excess of **3** was determined by HPLC on chiral phase.[9] All variations were done on basis of this general procedure and are indicated in the corresponding Tables and Schemes.

General procedure for the enantioselective Henry reactions of aliphatic aldehydes under optimized conditions

A solution of anhydrous $CuCl_2$ (267 mM in MeOH, 300 µL, 10.8 mg, 80.0 µmol, 8.0 mol%) was evaporated to dryness in a Schlenk tube. A solution of diamine **9a** (147 mM in anhydrous THF, 600 µL, 18.0 mg, 88.0 µmol, 8.8 mol%), $MeNO_2$ (**2a**, 600 µL, 684 mg, 11.2 mmol, 11.2 equiv), and the aldehyde **1** (1.00 mmol, 1.00 equiv) were added successively at RT. The mixture was ultrasonicated for 10 min to give a clear, brownish solution and then cooled to −20 °C. NEt_3 (1.50 M in THF, 40 µL, 6.08 mg, 60.0 µmol, 6.0 mol%) was added and the resulting blue-green solution was stirred until TLC-control indicated complete consumption of the aldehyde. The crude reaction mixture was purified by column chromatography (silica gel, pentane–Et_2O 8:1–4:1) providing β-nitro alcohol **3**. The enantiomeric excess of **3** was determined by HPLC on chiral phase.[9] All variations were done on basis of this general procedure and are indicated in the corresponding Tables and Schemes.

Acknowledgements

The financial support of the German research foundation (DFG) is gratefully acknowledged.

Keywords: aldol reactions · amines · asymmetric catalysis · copper · ligand design

[1] Reviews: a) H. Sasai in *Comprehensive Organic Synthesis Vol. 2, 2nd ed.* (Eds.: P. Knochel, G. A. Molander), Elsevier, Amsterdam, **2014**, chap. 2.13, pp. 543–570; b) F. A. Luzzio, *Tetrahedron* **2001**, *57*, 915–945; c) *The Nitro Group in Organic Synthesis* (Ed.: N. Ono), Wiley-VCH, New York, **2001**.

[2] Reviews: a) P. Drabina, L. Harmand, M. Sedlak, *Curr. Org. Synth.* **2014**, *11*, 879–888; b) R. Ballini, M. Petrini in *Science of Synthesis C-1 Building Blocks in Organic Synthesis* (Ed.: P. W. N. M. Van Leeuwen), Thieme, Stuttgart, **2014**, chap. 1.3.3, pp. 507–524; c) N. Ananthi, S. Velmathi, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2013**, *52*, 87–108; d) G. Chelucci, *Coord. Chem. Rev.* **2013**, *257*, 1887–1932; e) G. Blay, V. Hernández-Olmos, J. R. Pedro, *Synlett* **2011**, 1195–1211; f) Y. Alvarez-Casao, E. Marques-Lopez, R. P. Herrera, *Symmetry* **2011**, *3*, 220–245; g) C. Palomo, M. Oiarbide, A. Laso, *Eur. J. Org. Chem.* **2007**, 2561–2574; h) J. Boruwa, N. Gogoi, P. P. Saikia, N. C. Barua, *Tetrahedron: Asymmetry* **2006**, *17*, 3315–3326.

[3] Selected examples: a) K. Hashimoto, N. Kumagai, M. Shibasaki, *Org. Lett.* **2014**, *16*, 3496–3499; b) T. Ogawa, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2013**, *52*, 6196–6201; *Angew. Chem.* **2013**, *125*, 6316–6321; c) D. Sureshkumar, K. Hashimoto, N. Kumagai, M. Shibasaki, *J. Org. Chem.* **2013**, *78*, 11494–11500; d) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 13860–13869.

[4] Selected examples (except Cu-catalysis): a) J. Dimroth, M. Weck, *RSC Adv.* **2015**, *5*, 29108–29113; b) G.-H. Ouyang, Y.-M. He, Q.-H. Fan, *Chem. Eur. J.* **2014**, *20*, 16454–16457; c) Y.-L. Wei, K.-F. Yang, F. Li, Z.-J. Zheng, Z. Xu, L.-W. Xu, *RSC Adv.* **2014**, *4*, 37859–37867; d) Y. Liu, P. Deng, X. Li, Y. Xiong, H. Zhou, *Synlett* **2014**, *25*, 1735–1738; e) S. Wu, J. Tang, J. Han, D. Mao, X. Liu, X. Gao, J. Yu, L. Wang, *Tetrahedron* **2014**, *70*, 5986–5992; f) K. Lang, J. Park, S. Hong, *Angew. Chem. Int. Ed.* **2012**, *51*, 1620–1624; *Angew. Chem.* **2012**, *124*, 1652–1656; g) S. Liu, C. Wolf, *Org. Lett.* **2008**, *10*, 1831–1834; h) C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884; *Angew. Chem.* **2005**, *117*, 3949–3952.

[5] Cu-catalyzed Henry reactions of nitromethane giving 99% *ee* with at least one aldehyde: a) R. Ćwiek, P. Niedziejko, Z. Kałuża, *J. Org. Chem.* **2014**, *79*, 1222–1234; b) Y. Zhou, Y. Zhu, S. Yan, Y. Gong, *Angew. Chem. Int. Ed.* **2013**, *52*, 10265–10269; *Angew. Chem.* **2013**, *125*, 10455–10459; c) T. Deng, C. Cai, *J. Fluorine Chem.* **2013**, *156*, 183–186; d) A. Das, R. I. Kureshy, K. J. Prathap, M. K. Choudhary, G. V. S. Rao, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *Appl. Catal. A* **2013**, *459*, 97–105; e) D.-D. Qin, W.-H. Lai, D. Hu, Z. Chen, A.-A. Wu, Y.-P. Ruan, Z.-H. Zhou, H.-B. Chen, *Chem. Eur. J.* **2012**, *18*, 10515–10518; f) L. Yao, Y. Wei, P. Wang, W. He, S. Zhang, *Tetrahedron* **2012**, *68*, 9119–9124; g) Y. Wei, L. Yao, B. Zhang, W. He, S. Zhang, *Tetrahedron* **2011**, *67*, 8552–8558; h) R. I. Kureshy, A. Das, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *ACS Catal.* **2011**, *1*, 1529–1535; i) W. Jin, X. Li, B. Wan, *J. Org. Chem.* **2011**, *76*, 484–491; j) Y. Zhou, J. Dong, F. Zhang, Y. Gong, *J. Org. Chem.* **2011**, *76*, 588–600; k) B. V. Subba Reddy, J. George, *Tetrahedron: Asymmetry* **2011**, *22*, 1169–1175; l) A. T. Herrmann, S. R. Martinez, A. Zakarian, *Org. Lett.* **2011**, *13*, 3636–3639; m) G. Lai, F. Guo, Y. Zheng, Y. Fang, H. Song, K. Xu, S. Wang, Z. Zha, Z. Wang, *Chem. Eur. J.* **2011**, *17*, 1114–1117; n) W. Jin, X. Li, Y. Huang, F. Wu, B. Wan, *Chem. Eur. J.* **2010**, *16*, 8259–8261; o) G. Zhang, E. Yashima, W.-D. Woggon, *Adv. Synth. Catal.* **2009**, *351*, 1255–1262; p) T. Arai, M. Watanabe, A. Yanagisawa, *Org. Lett.* **2007**, *9*, 3595–3597; q) M. Bandini, F. Piccinelli, S. Tommasi, A. Umani-Ronchi, C. Ventrici, *Chem. Commun.* **2007**, 616–618.

[6] Selected recent examples of enantioselective Cu-catalyzed Henry reactions: a) P. Niedziejko, M. Szewczyk, P. Kalicki, Z. Kałuża, *Tetrahedron: Asymmetry* **2015**, *26*, 1083–1094; b) A. Das, M. K. Choudhary, R. I. Kureshy, K. Jana, S. Verma, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, B. Ganguly, *Tetrahedron* **2015**, *71*, 5229–5237; c) Y. Shi, Y. Li, J. Sun, Q. Lai, C. Wei, Z. Gong, Q. Gu, Z. Song, *Appl. Organomet. Chem.* **2015**, *29*, 661–667; d) Q. Song, X. An, T. Xia, X. Zhou, T. Shen, *C. R. Chim.* **2015**, *18*, 215–222; e) J.-L. Li, L. Liu, Y.-N. Pei, H.-J. Zhu, *Tetrahedron* **2014**, *70*, 9077–9083; f) M. Holmquist, G. Blay, M. C. Muñoz, J. R. Pedro, *Org. Lett.* **2014**, *16*, 1204–1207; g) S. J. Canipa, A. Stute, P. O'Brien, *Tetrahedron* **2014**, *70*, 7395–7403; h) X. Wang, W. Zhao, G. Li, J. Wang, G. Liu, L. Liu, R. Zhao, M. Wang, *Appl. Organomet. Chem.* **2014**, *28*, 892–899; i) P. Kiełbasiński, M. Rachwalski, S. Kaczmarczyk, S. Leśniak, *Tetrahedron: Asymmetry* **2013**, *24*, 1417–1420; j) Q. Dai, N. K. Rana, J. C.-G. Zhao, *Org. Lett.* **2013**, *15*, 2922–2925; k) M. W. Leighty, B. Shen, J. N. Johnston, *J. Am. Chem. Soc.* **2012**, *134*, 15233–15236.

[7] Selected recent examples of organocatalyzed and enzymatic Henry reactions: a) M. T. Corbett, J. S. Johnson, *Angew. Chem. Int. Ed.* **2014**, *53*, 255–259; *Angew. Chem.* **2014**, *126*, 259–263; b) K. Matsumoto, S. Asa-

ChemPubSoc Europe

CHEMCATCHEM Full Papers

kura, *Tetrahedron Lett.* **2014**, *55*, 6919 – 6921; c) M. Vlatković, L. Bernardi, E. Otten, B. L. Feringa, *Chem. Commun.* **2014**, *50*, 7773 – 7775; d) P. B. Thorat, S. V. Goswami, W. N. Jadhav, S. R. Bhusare, *Aust. J. Chem.* **2013**, *66*, 661 – 666; e) S. Kitagaki, T. Ueda, C. Mukai, *Chem. Commun.* **2013**, *49*, 4030 – 4032; f) K. Kanagaraj, P. Suresh, K. Pitchumani, *Org. Lett.* **2010**, *12*, 4070 – 4073; g) D. Uraguchi, S. Nakamura, T. Ooi, *Angew. Chem. Int. Ed.* **2010**, *49*, 7562 – 7565; *Angew. Chem.* **2010**, *122*, 7724 – 7727; h) M. Gruber-Khadjawi, T. Purkarthofer, W. Skranc, H. Griengl, *Adv. Synth. Catal.* **2007**, *349*, 1445 – 1450; i) T. Mandal, S. Samanta, C.-G. Zhao, *Org. Lett.* **2007**, *9*, 943 – 945; j) Y. Sohtome, N. Takemura, K. Takada, R. Takagi, T. Iguchi, K. Nagasawa, *Chem. Asian J.* **2007**, *2*, 1150 – 1160.

[8] a) D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, W. Milius, M. Breuning, *Chem. Eur. J.* **2015**, *21*, 12488 – 12500; b) M. Breuning, D. Hein, M. Steiner, V. H. Gessner, C. Strohmann, *Chem. Eur. J.* **2009**, *15*, 12764 – 12769.

[9] D. Scharnagel, F. Prause, J. Kaldun, R. G. Haase, M. Breuning, *Chem. Commun.* **2014**, *50*, 6623 – 6625.

[10] a) M. Breuning, D. Hein, *Eur. J. Org. Chem.* **2013**, 7575 – 7582; b) M. Breuning, A. Paasche, M. Steiner, S. Dilsky, V. H. Gessner, C. Strohmann, B. Engels, *J. Mol. Struct.* **2011**, *1005*, 178 – 185; c) M. Breuning, T. Häuser, C. Mehler, C. Däschlein, C. Strohmann, A. Oechsner, H. Braunschweig, *Beilstein J. Org. Chem.* **2009**, *5*, 81; d) M. Breuning, M. Steiner, C. Mehler, A. Paasche, D. Hein, *J. Org. Chem.* **2009**, *74*, 1407 – 1410.

[11] F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel, M. Breuning, *Synthesis* **2015**, *47*, 575 – 586.

[12] For a successful application of copper complexes of diamines **9** and **10** in enantioselective, oxidative biaryl coupling reactions, see: F. Prause, B. Arensmeyer, B. Fröhlich, M. Breuning, *Catal. Sci. Technol.* **2015**, *5*, 2215 – 2226.

[13] Rearrangements of **14** to β-amino piperidines (via the sequence mesylation-aziridinium formation-nucleophilic attack at C-2 under ring enlargement) did not occur to a significant degree.

[14] Enantioselective Henry reactions in the presence of chiral, $Cu(OAc)_2$-derived catalysts, a) without an ancillary base: Ref. 5 e,h,k,l,n–q; 6 d,h–k; 16 b,c,e,h; b) with an ancillary base: Ref. 5 a,c,g; 6 a,b; 16 d,i.

[15] Catalytic amounts of pyridine do only weakly promote the Henry reaction (see Table 5, entry 3). In the case of nicotinaldehyde (**1 e**), however, the pyridyl moiety is part of the substrate and, thus, present in a 50-fold excess with respect to the amount of catalyst (2 mol%).

[16] Selected recent examples of diastereo- and enantioselective Cu-catalyzed Henry reactions: a) H. Mei, X. Xiao, X. Zhao, B. Fang, X. Liu, L. Lin, X. Feng, *J. Org. Chem.* **2015**, *80*, 2272 – 2280; b) T. Arai, A. Joko, K. Sato, *Synlett* **2015**, *26*, 209 – 214; c) A. Das, M. K. Choudhary, R. I. Kureshy, T. Roy, N. H. Khan, S. H. R. Abdi, H. C. Bajaj, *ChemPlusChem* **2014**, *79*, 1138 – 1146; d) L. Zhang, H. Wu, Z. Yang, X. Xu, H. Zhao, Y. Huang, Y. Wang, *Tetrahedron* **2013**, *69*, 10644 – 10652; e) D.-D. Qin, W. Yu, J.-D. Zhou, Y.-C. Zhang, Y.-P. Ruan, Z.-H. Zhou, H.-B. Chen, *Chem. Eur. J.* **2013**, *19*, 16541 – 16544; f) J. D. White, S. Shaw, *Org. Lett.* **2012**, *14*, 6270 – 6273; g) K. Xu, G. Lai, Z. Zha, S. Pan, H. Chen, Z. Wang, *Chem. Eur. J.* **2012**, *18*, 12357 – 12362; h) R. Boobalan, G.-H. Lee, C. Chen, *Adv. Synth. Catal.* **2012**, *354*, 2511 – 2520; i) A. Chougnet, G. Zhang, K. Liu, D. Häussinger, A. Kägi, T. Allmendinger, W.-D. Woggon, *Adv. Synth. Catal.* **2011**, *353*, 1797 – 1806; j) L. Cheng, J. Dong, J. You, G. Gao, J. Lan, *Chem. Eur. J.* **2010**, *16*, 6761 – 6765; k) T. Arai, Y. Taneda, Y. Endo, *Chem. Commun.* **2010**, *46*, 7936 – 7938; l) Ref. 5 d,f,g,i–k,n,p; 8 a,b.

[17] From $er_{obs} = (S_{cat} + S_{bg})/(R_{cat} + R_{bg}) \geq 99.5{:}0.5$ and under the assumption of a perfect catalyst ($S_{cat}/R_{cat} = 100{:}0$) follows $v_{cat}/v_{bg} \geq 99{:}1$. In the case of a nonperfect catalyst ($S_{cat}/R_{cat} < 100{:}0$), the ratio v_{cat}/v_{bg} would be even higher. obs = observed, cat = catalyzed reaction, bg = background reaction.

[18] This formula (deduction see Supporting Information) can be used under the following assumptions, which are—most probably—fulfilled by our reactions: (i) the rate laws for the for the two catalytic cycles are identical ($v_{cat1}/v_{cat2} \approx$ constant) and do not change in the course of the reaction, (ii) there is no interaction between the catalysts that unproportionally reduces the concentration of one catalyst (as, for example, the formation of a 2:1 oligomer), and (iii) the uncatalyzed background reaction is slow (here: 1% at maximum because of the excellent 99% *ee* reached) and, thus, does not measurably lower the enantiomeric excess.

[19] The existence of a hydrogen bridge cannot be fully ruled out, because the lower steric hindrance in **9** might induce an acceleration that overcompensates any deceleration induced by the hydrogen bounding.

[20] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals, 4th ed.*, Butterworth-Heinemann, Oxford, **2000**.

Received: February 29, 2016
Published online on May 9, 2016

Heterogeneous & Homogeneous & Bio- & Nano-
CHEMCATCHEM
CATALYSIS

Supporting Information

Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions

Johannes Kaldun, Felix Prause, Dagmar Scharnagel, Frederik Freitag, and Matthias Breuning*[a]

cctc_201600240_sm_miscellaneous_information.pdf

Table of Contents

1. Derivation of equation (1)

Definitions:

- Indices 1 and 2 denote to the single-catalyst experiments with catalyst 1 and 2, respectively.
- Index cp denotes to the competition experiment using a 1:1 ratio of catalyst 1 and 2.
- [P], [S], [R] are the concentrations of the product and its *S*- and *R*-enantiomers.
- e.r. is defined as the enantiomeric ratio *S*/*R*.
- k_{rel} gives the relative rate to be calculated.

Preconditions:

- There is no (significant degree of an) enantioselectivity-eroding background reaction.
- The rate laws of the single-catalyst reactions are identical.
- There is no change in the reaction order during the course of the reaction.
- Identical reagent and catalyst concentrations are used in all experiments.
- The parallel reactions occurring in the competition experiment do not interfere. Equimolar amounts of catalyst 1 and 2 are used.

Measured values: $e.r._{.1}$, $e.r._{.2}$, and $e.r._{.cp}$

Primary equations:

(**A**) $k_{rel} = [P_1] / [P_2]$ = constant (Product distribution in non-interfering parallel reactions that obey the same rate law)

(**B**) $[P_1] = [S_1] + [R_1]$ (**C**) $[P_2] = [S_2] + [R_2]$ (**D**) $e.r._{.1} = [S_1] / [R_1]$

(**E**) $e.r._{.2} = [S_2] / [R_2]$ (**F**) $[S_{cp}] = [S_1] + [S_2]$ (**G**) $[R_{cp}] = [R_1] + [R_2]$

(**H**) $e.r._{.cp} = [S_{cp}] / [R_{cp}]$

Derivation:

- From (**A**) and (**B**) – (**E**) follows:

$$k_{rel} = [P_1] / [P_2] = ([S_1] + [R_1]) / ([S_2] + [R_2]) = (e.r._{.1} \bullet [R_1] + [R_1]) / (e.r._{.2} \bullet [R_2] + [R_2])$$
$$= (e.r._{.1} + 1) / (e.r._{.2} + 1) \bullet [R_1] / [R_2] \quad (\mathbf{J})$$

- From (**H**) and (**D**) – (**G**) follows:

$$e.r._{.cp} = [S_{cp}] / [R_{cp}] = ([S_1] + [S_2]) / ([R_1] + [R_2]) = (e.r._{.1} \bullet [R_1] + e.r._{.2} \bullet [R_2]) / ([R_1] + [R_2]) \quad (\mathbf{K})$$

- Solving (**K**) for $[R_1] / [R_2]$ gives:

$$[R_1] / [R_2] = (e.r._{.cp} - e.r._{.2}) / (e.r._{.1} - e.r._{.cp}) \quad (\mathbf{L})$$

- Substitution of $[R_1] / [R_2]$ in (**J**) with (**L**) gives equation (1):

$$k_{rel} = \frac{(e.r._{.1} + 1) \bullet (e.r._{.cp} - e.r._{.2})}{(e.r._{.2} + 1) \bullet (e.r._{.1} - e.r._{.cp})} \quad (1)$$

2. Experimental procedures for the synthesis of the prolinamine ligands 9 and 10

All reactions with moisture-sensitive reagents were carried out under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[1] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey-Nagel, particle size 40–63 µm) was used for column chromatography. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^{1}H and ^{13}C NMR data were performed on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra were recorded on a ThermoFisher Scientific Q-Exactive (Orbitrap) or a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization). The enantiomeric excess and the configuration of the ß-nitro alcohols **3** were determined by HPLC analysis on chiral phase; the diastereomeric ratios were measured by ^{1}H NMR. Prolinols **14d**[2] and **14e**[3] and prolinamines **9a**,[3] **9j**–**m**,[4] **9n**–**r**,**t**,[2] **10e–k,m**[2] and **10l**[4] were prepared according to literature procedures. Diamines **10d** and **9s** are commercially available. The preparations of **9b**, **12a**, **13a**, and **14a** and the general procedures for the enantioselective Henry reactions are given in the main article.

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-cyclohexyl-5-oxopentanoate (12b)

A solution of the pyroglutamate **11** (3.65 g, 15.0 mmol) in anhydrous THF (45 mL) was treated at -40 °C with *c*HexMgCl (1.4 M in THF, 16.1 mL, 22.5 mmol). The reaction mixture was allowed to warm to RT overnight. Sat. aq. NH_4Cl (150 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (150 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and column chromatography (silica gel, petroleum ether–EtOAc, 8:1) afforded amino ketone **12b** (1.51 g, 4.61 mmol, 31%) as a colorless oil.

R_f = 0.26 (petroleum ether/EtOAc 6:1). $[\alpha]_D^{31}$ = –17.3 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3362, 2934, 2859, 1748, 1709, 1519, 1450, 1367, 1248, 1167, 1053 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.07-1.34 (m, 5 H, *c*Hex-H), 1.39 (s, 9 H, $C(CH_3)_3$), 1.62 (m, 1 H, *c*Hex-H), 1.76 (m, 4 H, *c*Hex-H), 1.85 (m, 1 H, 3-*H*H), 2.06 (m, 1 H, 3-H*H*), 2.29 (m, 1 H, *c*Hex-H), 2.43-2.59 (m, 2 H, 4-H_2), 3.70 (s, 3 H, OCH_3), 4.22 (m, 1 H, 2-H), 5.09 (d, *J* = 7.9 Hz, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.7, 25.8 (C-*c*Hex), 26.4 (C-3), 28.3 ($C(CH_3)_3$), 28.5 (C-*c*Hex), 36.5 (C-4), 50.9 (C-*c*Hex), 52.5 (OCH_3), 53.1 (C-2), 80.0 ($C(CH_3)_3$), 155.5 (NCO_2), 173.1 (C-1), 213.0 (C-5) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{17}H_{29}NO_5$ $[M + H]^+$ 328.21185, found 328.21179.

[1] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, 4th Ed., Butterworth-Heinemann, Oxford, **2000**.
[2] F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel, M. Breuning, *Synthesis* **2015**, *47*, 575-586.
[3] D. Scharnagel, F. Prause, J. Kaldun, R. G. Haase and M. Breuning, *Chem. Commun.* **2014**, *50*, 6623-6625.
[4] F. Prause, B. Arensmeyer, B. Fröhlich, M. Breuning, *Catal. Sci. Technol.* **2015**, *5*, 2215-2226.

4

(*S*)-Methyl 2-(*tert*-butoxycarbonylamino)-5-(3,5-dimethylphenyl)-5-oxopentanoate (12c)

A solution of the pyroglutamate **11** (3.65 g, 15.0 mmol) in anhydrous THF (40 mL) was treated at -40 °C with 2,5-Me_2PhMgBr (22.5 mL, 1.0 M in THF, 22.5 mmol), prepared from 1-bromo-3,5-dimethylbenzene (6.12 mL, 8.33 g, 45.0 mmol) and Mg (1.31 g, 54.0 mmol) in anhydrous THF (39 mL). The reaction mixture was allowed to warm to RT overnight. Sat. aq. NH_4Cl (100 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Column chromatography (silica gel, petroleum ether–EtOAc, 5:1–1:1 afforded amino ketone **12c** (4.09 g, 11.7 mmol, 78%) as a colorless oil.

R_f = 0.73 (petroleum ether/EtOAc 2:1). $[\alpha]_D^{31}$ = –9.1 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3376, 2985, 2934, 1748, 1714, 1686, 1520, 1437, 1367, 1247, 1161, 1051 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.41 (s, 9 H, $C(CH_3)_3$), 2.05 (m, 1 H, 3-*H*H), 2.28 (m, 1 H, 3-H*H*), 2.35 (s, 6 H, Ar-CH_3), 3.00 (ddd, *J* = 17.8, 8.3, 6.0 Hz, 1 H, 4-*H*H), 3.10 (ddd, *J* = 17.8, 8.2, 6.6 Hz, 1 H, 4-H*H*), 3.74 (s, 3 H, OCH_3), 4.38 (m, 1 H, 2-H), 5.18 (d, *J* = 8.1 Hz, 1 H, NH), 7.19 (s, 1 H, Ar-H), 7.54 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.3 (Ar-CH_3), 27.1 (C-3), 28.4 ($C(CH_3)_3$), 34.7 (C-4), 52.6 (OCH_3), 53.2 (C-2), 80.1 ($C(CH_3)_3$), 125.9 (CH-Ar), 132.9 (CH-Ar), 136.8, 138.3 (C_q-Ar), 155.6 (NCO_2), 173.1 (C-1), 199.4 (C-5) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{19}H_{27}NO_5$ $[M + H]^+$ 350.19620, found 350.19601.

(2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-cyclohexylpyrrolidine-1,2-dicarboxylate (13b)

$NaBH(OAc)_3$ (615 mg, 2.90 mmol) was added at 0 °C to a solution of the amino ketone **12b** (731 mg, 2.23 mmol) in EtOAc (12 mL). After 10 min, TFA (739 µL, 1.09 g, 9.59 mmol) was added dropwise and the reaction mixture was stirred overnight at RT. Sat. aq. $NaHCO_3$ (50 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Column chromatography (silica gel, petroleum ether–EtOAc, 10:1–5:1) provided diastereomerically pure **3b** (488 mg, 1.57 mmol, 70%) as a colorless oil.

R_f = 0.47 (petroleum ether/EtOAc 6:1). $[\alpha]_D^{31}$ = –9.9 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2924, 2852, 1756, 1695, 1449, 1366, 1253, 1162, 1108 cm^{-1}. ^{1}H NMR* (500 MHz, $CDCl_3$) δ = 0.86 (m, 1 H, *c*Hex-H), 0.93-1.12 (m, 2 H, *c*Hex-H), 1.17 (m, 2 H, *c*Hex-H), 1.36 (s, 5.7 H, $C(CH_3)_3$), 1.42 (s, 3.3 H, $C(CH_3)_3$), 1.44-1.66 (m, 2 H, 4-*H*H, *c*Hex-H), 1.66-1.92 (m, 7 H, 3-*H*H, 4-H*H*, *c*Hex-H), 2.14 (m, 1 H, 3-H*H*), 3.59 (t, *J* = 7.0 Hz, 0.4 H, 5-H), 3.68 (s, 3 H, OCH_3), 3.69 (m, 0.6 H, 5-H), 4.14 (m, 0.6 H, 2-H), 4.27 (t, *J* = 8.2 Hz, 0.4 H, 2-H) ppm. ^{13}C NMR* (125 MHz, $CDCl_3$) δ = 26.3, 26.4 (C-4), 26.5, 26.6, 26.7, 26.9 (C-*c*Hex), 28.3, 28.5 ($C(CH_3)_3$), 27.7, 29.1 (C-3), 29.30, 29.34, 30.2, 30.5 (C-*c*Hex), 41.3, 41.5 (C-*c*Hex), 51.9, 52.1 (OCH_3), 59.8, 60.3 (C-2), 63.4, 63.5 (C-5), 79.8, 79.9 ($C(CH_3)_3$), 154.6, 155.2 (1-CO_2), 173.9, 174.2 (2-CO_2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{17}H_{29}NO_4$ $[M + H]^+$ 312.21693, found 312.21677. * 60:40 mixture of rotamers.

(2*S*,5*R*)-1-*tert*-Butyl 2-methyl 5-(3,5-dimethylphenyl)pyrrolidine-1,2-dicarboxylate (13c)

A solution of the amino ketone **12c** (4.01 g, 11.5 mmol) in abs. CH_2Cl_2 (115 mL) was treated at RT with TFA (17.7 mL, 26.1 g, 229 mmol) and stirred overnight. The solvent was removed under reduced pressure and the resulting orange oil was diluted five times with CH_2Cl_2 (150 mL) and evaporated again, in order to remove excess TFA. $NaBH_4$ (866 mg, 22.9 mmol) was slowly added at 0 °C to a solution of the residue in MeOH (180 mL). After stirring overnight at RT, the solvent was removed. The resulting oil was diluted four times with MeOH (150 mL) and evaporated again. The residue was suspended in anhydrous CH_2Cl_2 (230 mL) and NEt_3 (2.39 mL, 1.74 g, 17.2 mmol), Boc_2O (3.76 g, 17.2 mmol), and DMAP (70.0 mg, 573 µmol) were added at RT. After stirring overnight, sat. aq. NH_4Cl (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL) and the combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, petrol ether–EtOAc, 5:1) afforded a 93:7 mixture of pyrrolidine **13c** and its C5-epimer 5-*epi*-**13c** (2.25 g, 6.79 mmol, 59%) as a colorless oil.

R_f = 0.43 (petroleum ether/EtOAc 5:1). $[\alpha]_D^{32}$ = +21.0 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2974, 2934, 1754, 1694, 1607, 1455, 1390, 1366, 1200, 1160, 1119 cm^{-1}. ^1H NMR* (500 MHz, $CDCl_3$) δ = 1.15 (s, 5 H, $C(CH_3)_3$), 1.41 (s, 4 H, $C(CH_3)_3$), 1.93 (m, 1 H, 4-*H*H), 2.06 (m, 1 H, 3-*H*H), 2.17 (m, 1 H, 3-H*H*), 2.27 (m, 1 H, 4-H*H*), 2.31 (s, 6 H, Ar-CH_3), 3.80 (s, 3 H, OCH_3), 4.34 (m, 0.46 H, 2-H), 4.46 (dd, *J* = 8.2, 4.6 Hz, 0.54 H, 2-H), 4.66 (m, 0.58 H, 5-H), 4.91 (dd, *J* = 7.6, 3.4 Hz, 0.53 H, 5-H), 6.85 (s, 1 H, Ar-H), 7.16 (s, 2 H, Ar-H) ppm. ^{13}C NMR* (125 MHz, $CDCl_3$) δ = 21.4, 21.5 (Ar-CH_3), 28.0, 28.2 ($C(CH_3)_3$), 28.7, 28.9 (C-3), 34.5, 35.4 (C-4), 51.9, 52.1 (OCH_3), 60.2, 60.8 (C-2), 62.1, 62.9 (C-5), 79.9, 80.2 ($C(CH_3)_3$), 123.8, 124.2, 128.2, 128.5 (CH-Ar), 137.4, 137.7, 143.2, 143.9 (C_q-Ar), 153.8, 154.5 (1-CO_2), 173.5, 173.7 (2-CO_2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{19}H_{27}NO_4$ $[M + H]^+$ 334.20128, found 334.20122. * 55:45 mixture of rotamers; signals of the minor diastereomer are not listed.

Reduction of the esters 13 with LAH

General procedure (GP-1): $LiAlH_4$ (7.0 equiv.) was added at 0 °C to a solution of the pyrrolidine ester **13** (1.0 equiv.) in anhydrous THF (5.5 mL/mmol **13**). The reaction mixture was stirred for 1 h at 0 °C and then refluxed for 20–35 h. The resulting suspension was diluted with Et_2O (6 mL/mmol **13**) and treated with sat. aq. Na_2SO_4 until H_2 evolution ceased. The resulting mixture was filtered through a pad of celite® and the filter cake was rinsed with CH_2Cl_2–MeOH (9:1, 75 mL/mmol **13**). Evaporation of the solvent and column chromatography provided amino alcohol **14**.

(2*R*,5*S*)-2-Cyclohexyl-5-(hydroxymethyl)-1-methylpyrrolidine (14b) According to GP-1, pyrrolidine ester **13b** (1.60 g, 5.12 mmol) was reduced with LAH (1.36 g, 35.8 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 9:1–4:1), prolinol **14b** (956 mg, 4.84 mmol, 95%) as a colorless oil.

R_f = 0.31 (CH_2Cl_2/MeOH 95:5). $[\alpha]_D^{32}$ = +30.5 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3353, 2922, 2851, 2787, 1653, 1448, 1051, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 0.88-1.04 (m, 2 H, *c*Hex-H), 1.05-1.29 (m, 3 H, *c*Hex-H), 1.45-1.81 (m, 10 H, 3-H_2, 4-H_2, *c*Hex-H), 2.30 (s, 3 H, 1-CH_3), 2.38 (m, 1 H, 2-H), 2.59 (m, 1 H, 5-H), 3.00-3.85 (br s, 1 H, OH), 3.38 (dd, *J* = 10.8, 2.1 Hz, 1 H, 5-C*H*H), 3.65 (dd, *J* = 10.8, 3.5 Hz, 1 H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.3, 26.2, 26.38 (C-*c*Hex), 26.42 (C-4), 26.9 (C-*c*Hex), 27.0 (C-3), 31.2 (C-*c*Hex), 39.7 (C-*c*Hex), 39.9 (1-CH_3), 61.0 (5-CH_2), 67.6 (C-5), 72.0 (C-2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{12}H_{23}NO$ $[M + H]^+$ 198.18524, found 198.18439.

(2*R*,5*S*)-2-(3,5-Dimethylphenyl)-5-(hydroxymethyl)-1-methylpyrrolidine (14c) According to GP-1, a 93:7 mixture of the pyrrolidine ester **13c** and its C5-epimer (2.25 g, 6.75 mmol) was reduced with LAH (1.79 g, 47.2 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH, 19:1–9:1), prolinol **14c** (1.35 g, 6.16 mmol, 91%) as a colorless oil.

R_f = 0.43 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5). $[\alpha]_D^{32}$ = +75.9 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3392, 2945, 2863, 2782, 1771, 1606, 1456, 1240, 1151, 1082, 1035 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.67 (m, 1 H, 3-*H*H), 1.95 (m, 2 H, 4-H_2), 2.05 (m, 1 H, 3-H*H*), 2.16 (s, 3 H, 1-CH_3), 2.31 (s, 6 H, Ar-CH_3), 2.65 (m, 1 H, 5-H), 2.75-3.00 (br s, 1 H, OH), 3.34 (t, *J* = 7.7 Hz, 1 H, 2-H), 3.50 (d, *J* = 10.5 Hz, 1H, 5-C*H*H), 3.77 (d, *J* = 9.7 Hz, 1 H, 5-CH*H*), 6.90 (s, 1 H, Ar-H), 6.94 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.0 (Ar-*C*H_3), 26.0 (C-4), 33.9 (C-3), 38.5 (1-CH_3), 61.9 (5-CH_2), 66.5 (C-5), 72.2 (C-2), 124.7, 128.6 (CH-Ar), 137.3, 142.5 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{21}NO$ $[M + H]^+$ 220.16959, found 220.16992.

Mesylation and amination of the prolinols 14

General procedure (GP-2): MsCl (1.10–1.50 equiv.) and NEt_3 (3.0 equiv.) were added at 0 °C to a solution of the prolinol **14** (1.0 equiv.) in anhydrous CH_2Cl_2 (12 mL/mmol **14**). After 1–3 d at RT, an excess of the amine (5–30 equiv.) was added and stirring was continued for 3 d. Evaporation of the solvent and column chromatography provided prolinamines **9** and **10**.

(2*R*,5*S*)-2-Cyclohexyl-1-methyl-5-((methylamino)methyl)pyrrolidine (9c) According to GP-2, prolinol **14b** (64.5 mg, 327 µmol) was mesylated and treated with methylamine (aq., 40%, 1.30 mL, 1.16 g, 9.81 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 97:2.7:0.3), prolinamine **9c** (38.7 mg, 184 µmol, 56%) as a yellowish oil.

R_f = 0.32 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{32}$ = +13.5 (*c* = 0.50 in MeOH). IR (ATR) ν_{max} = 2925, 2851, 2783, 1769, 1448, 1241, 1130, 1056 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 0.80-1.03 (m, 2 H, 3-*H*H, *c*Hex-H), 1.05-1.30 (m, 3 H, *c*Hex-H), 1.41 (m, 1 H, *c*Hex-H), 1.56 (m, 4 H, 3-H*H*, 4-*H*H, *c*Hex-H), 1.61-1.87 (m, 6 H, 4-H*H*, *c*Hex-H, NH), 2.19 (ddd, *J* = 12.0, 7.5, 4.8 Hz, 1 H, 2-H), 2.22 (s, 3 H, 1-CH_3), 2.43 (s, 3 H, NHCH_3), 2.45 (m, 1 H, 5-H), 2.52 (dd, *J* = 11.2, 5.7 Hz, 1 H, 5-C*H*H), 2.61 (dd, *J* = 11.2, 3.8 Hz, 1 H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.0, 26.5,

26.6, 27.1, 27.2 (C-*c*Hex), 27.9 (C-4), 31.3 (C-3), 37.1 ($NHCH_3$), 40.3 (C-*c*Hex), 40.6 (1-CH_3), 55.0 (5-CH_2), 66.2 (C-5), 72.0 (C-2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{13}H_{26}N_2$ $[M + H]^+$ 211.21688, found 211.21688.

(2*R*,5*S*)-2-(3,5-Dimethylphenyl)-1-methyl-5-((methylamino)methyl)pyrrolidine (9d) According to GP-2, prolinol **14c** (71.7 mg, 327 µmol) was mesylated and treated with methylamine (aq., 40%, 1.30 mL, 1.16 g, 9.81 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 90:9:1), prolinamine **9d** (58.0 mg, 250 µmol, 76%) as a yellowish oil.

R_f = 0.44 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{32}$ = +52.6 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3320, 2943, 2837, 2779, 1650, 1606, 1466, 1203, 1134, 1046 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.68 (m, 1 H, 3-*H*H), 1.82 (m, 1 H, 4-*H*H), 1.91-2.06 (m, 2 H, 3-H*H*, 4-H*H*), 2.14 (s, 3H, 1-CH_3), 2.30 (s, 6 H, Ar-CH_3), 2.52 (s, 3 H, NHCH_3), 2.56 (m, 1 H, 5-H), 2.68 (dd, *J* = 11.4, 5.8 Hz, 5-C*H*H), 2.76 (m, 1 H, 5-CH*H*), 3.18 (dd, *J* = 9.8, 6.6 Hz, 1 H, 2-H), 6.87 (s, 1 H, Ar-H), 6.95 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.5 (Ar-CH_3), 27.9 (C-4), 34.2 (C-3) 37.1 ($NHCH_3$), 39.5 (1-CH_3), 55.0 (5-CH_2), 65.6 (C-5), 72.7 (C-2), 125.2, 128.9 (CH-Ar), 137.9, 143.6 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{15}H_{24}N_2$ $[M + H]^+$ 233.20123, found 233.20236.

(2*S*,5*S*)-1,2-Dimethyl-5-((methylamino)methyl)pyrrolidine (9e) According to GP-2, prolinol **14d** (100 mg, 774 µmol) was mesylated and treated with *N*-methylbenzylamine (2.00 mL, 1.88 g, 15.5 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5), (2*S*,5*S*)-2-((benzyl(methyl)amino)methyl)-1,5-dimethylpyrrolidine (113 mg, 486 µmol, 63%) as colorless oil.

R_f = 0.35 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{26}$ = –49.1 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2962, 2836, 2778, 1495, 1453, 1372, 1205, 1126, 1022 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.08 (d, *J* = 6.1 Hz, 3 H, 5-CH_3), 1.33 (m, 1 H, 4-*H*H), 1.50 (m, 1 H, 3-*H*H), 1.81 (m, 1 H, 4-H*H*), 1.92 (m, 1 H, 3-H*H*), 2.18 (m, 1 H, 5-H), 2.20 (s, 3 H, 1-CH_3), 2.30 (s, 3 H, NCH_3), 2.35 (dd, *J* = 11.6, 8.3 Hz, 1 H, 2-C*H*H), 2.40 (m, 1 H, 2-H), 2.54 (dd, *J* = 11.6, 3.5 Hz, 1 H, 2-CH*H*), 3.41 (d, *J* = 13.1 Hz, 1 H, NC*H*HPh), 3.57 (d, *J* = 13.1 Hz, 1 H, NCH*H*Ph), 7.23 (m, 1 H, Ph-H), 7.30 (m, 4 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.0 (5-CH_3), 28.7 (C-3), 31.6 (C-4), 39.5 (1-CH_3), 43.2 NCH_3), 63.0 (2-CH_2), 63.2 (C-5), 63.3 (N*C*H_2Ph), 65.3 (C-2), 127.0, 128.3, 129.2 (CH-Ph), 139.3 (C_q-Ph) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{15}H_{24}N_2$ $[M + H]^+$ 233.20123, found 233.20061.

A solution of this prolinamine (58.0 mg, 250 µmol) in MeOH (2 mL) was treated with 10% HCl in MeOH (1 mL) and 20% $Pd(OH)_2$/C (48 mg, 68.4 µmol) was added. After hydrogenation (1 bar) for 2 h at 60 °C the mixture was filtered over a plug of celite® and the solvent was evaporated. The crude product was partitioned between 20% aq. KOH (4 mL) and Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (5 × 10 mL) and the combined organic

layers were dried over $MgSO_4$. Careful removal of the solvent at 40 °C/100 mbar (note: the product is highly volatile!) provided prolinamine **9e** (23.0 mg, 161 µmol, 83%) as a colorless oil.

R_f = 0.13 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{26}$ = –15.9 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3348, 2959, 2844, 2786, 1682, 1542, 1460, 1377, 1192, 1126, 1036 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.09 (d, *J* = 6.1 Hz, 3 H, 2-CH_3), 1.36 (m, 1 H, 3-*H*H), 1.59 (m, 1 H, 4-*H*H), 1.84 (m, 2 H, 3-H*H*, 4-H*H*), 2.00 (s, 1 H, NH), 2.25 (m, 1 H, 2-H), 2.27 (s, 3 H, 1-CH_3), 2.40 (m, 1 H, 5-H), 2.47 (s, 3 H, NHCH_3), 2.55 (dd, *J* = 11.4, 6.7 Hz, 1 H, 5-C*H*H), 2.74 (dd, *J* = 11.4, 3.5 Hz, 1 H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 19.3 (2-CH_3), 27.5 (C-4), 32.0 (C-3), 37.1 (NHCH_3), 39.3 (1-CH_3), 55.7 (5-CH_2), 63.0 (C-2), 66.6 (C-5) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_8H_{19}N_2$ $[M + H]^+$ 143.15428, found 143.15402.

(2*S*,5*R*)-2-((2-Hydroxyethylamino)methyl)-1-methyl-5-phenylpyrrolidine (9h) According to GP-2, prolinol **14e** (180 mg, 941 µmol) was mesylated and treated with 2-aminoethanol (282 µL, 287 mg, 4.71 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5–80:18:2), prolinamine **9h** (110 mg, 469 µmol, 50%) as a colorless oil.

R_f = 0.42 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 85:13.5:1.5). $[\alpha]_D^{29}$ = +52.9 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3299, 2946, 2837, 2784, 1491, 1452, 1078, 1058, 1033, 755, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.69 (m, 1 H, 4-*H*H), 1.86 (m, 1 H, 3-*H*H), 1.98 (m, 1 H, 3-H*H*), 2.06 (m, 1 H, 4-H*H*), 2.15 (s, 3 H, 1-CH_3), 2.63 (m, 1 H, 2-H), 2.74 (dd, *J* = 11.6, 5.5 Hz, 1 H, 2-C*H*H), 2.78-2.95 (m, 5 H, 2-CH*H*, N*H*C$H_2$$CH_2$O*H*), 3.29 (dd, *J* = 9.9, 6.6 Hz, 1 H, 5-H), 3.68 (m, 2 H, CH_2OH), 7.23 (m, 1 H, Ph-H), 7.32 (m, 4 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 27.7 (C-3), 34.3 (C-4), 39.4 (1-CH_3), 51.5 (NH*C*$H_2$$CH_2$OH), 51.8 (2-$CH_2$), 60.5 ($CH_2$OH), 65.8 (C-2), 72.6 (C-5), 127.1, 127.4, 128.4 (CH-Ph), 143.6 (C_q-Ph) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{23}N_2O$ $[M + H]^+$ 235.18049, found 235.18063.

(2*S*,5*R*)-2-((2-Methoxyethylamino)methyl)-1-methyl-5-phenylpyrrolidine (9i) According to GP-2, prolinol **14e** (225 mg, 1.18 mmol) was mesylated and treated with 2-methoxyethanamine (3.08 mL, 2.66 g, 35.4 mmol) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 98:1.8:0.2–90:9:1), prolinamine **9i** (213 mg, 858 µmol, 73%) as a colorless oil.

R_f = 0.28 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{28}$ = +52.0 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2939, 2875, 2818, 2786, 1452, 1197, 1115, 1073, 756, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.68 (m, 1 H, 4-*H*H), 1.80 (m, 1 H, 3-*H*H), 1.98 (m, 1 H, 3-H*H*), 2.05 (m, 1 H, 4-H*H*), 2.15 (s, 3 H, 1-CH_3), 2.39 (s, 1 H, NH), 2.61 (m, 1 H, 2-H), 2.71 (dd, *J* = 11.3, 6.4 Hz, 1 H, 2-C*H*H), 2.83 (dd, *J* = 11.3, 3.6 Hz, 1 H, 2-CH*H*), 2.87 (m, 2 H, NHC$H_2$$CH_2$O), 3.28 (dd, *J* = 9.7, 6.6 Hz, 1 H, 5-H), 3.38 (s, 3 H, OCH_3), 3.54 (t, *J* = 5.2 Hz, 2 H, CH_2O), 7.21 (m, 1 H, Ph-H), 7.29 (m, 2 H, Ph-H), 7.34 (m, 2 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 28.1 (C-3), 34.3 (C-4), 39.4 (1-CH_3), 49.9 (NH*C*$H_2$$CH_2$O), 53.2 (2-$CH_2$), 58.9 ($OCH_3$), 65.8 (C-2), 71.9 ($CH_2$O), 72.5 (C-5), 127.0, 127.4,

128.3 (CH-Ph), 143.9 (C_q-Ph) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{15}H_{25}N_2O$ $[M + H]^+$ 249.19614, found 249.19605.

(2*R*,5*S*)-2-Cyclopentyl-5-((dimethylamino)methyl)-1-methylpyrrolidine (10a) According to GP-2, prolinol **14a** (60.0 mg, 327 µmol) was mesylated and treated with dimethylamine (aq., 40%, 595 µL, 529 mg 4.91 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5), prolinamine **10a** (39.0 mg, 185 µmol, 57%) as a brownish oil.

R_f = 0.35 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{25}$ = –24.4 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2947, 2866, 2764, 1456, 1206, 1155 1032 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.18 (m, 2 H, *c*Pent-H), 1.48 (m, 5 H, 3-*H*H, 4-*H*H, *c*Pent-H), 1.59 (m, 2 H, *c*Pent-H), 1.72 (m, 1 H, 3-H*H*), 1.80 (m, 1 H, *c*Pent-H), 1.85-2.01 (m, 2 H, 4-H*H*, *c*Pent-H), 2.22 (s, 6 H, $N(CH_3)_2$), 2.24 (m, 2 H, 2-H, 5-C*H*H), 2.34 (s, 3 H, 1-CH_3), 2.39 (m, 2 H, 5-H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 25.3, 26.0 (C-*c*Pent), 26.9 (C-3), 28.4 (C-*c*Pent), 29.3 (C-4), 31.2 (C-*c*Pent), 41.1 (1-CH_3), 43.7 (C-*c*Pent), 46.5 ($N(CH_3)_2$), 65.2 (5-CH_2), 65.9 (C-5), 71.8 (C-2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{13}H_{26}N_2$ $[M + H]^+$ 211.21688, found 211.21620.

(2*R*,5*S*)-2-Cyclohexyl-5-((dimethylamino)methyl)-1-methylpyrrolidine (10b) According to GP-2, prolinol **14b** (61.7 mg, 327 µmol) was mesylated and treated with dimethylamine (aq., 40%, 595 µL, 529 mg 4.91 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5), prolinamine **10b** (41.4 mg, 185 µmol, 57%) as a yellow oil.

R_f = 0.37 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 90:9:1). $[\alpha]_D^{25}$ = –9.4 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2923, 2851, 2766, 1449, 1345, 1156, 1031 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 0.86-1.02 (m, 2 H, *c*Hex-H), 1.05-1.29 (m, 3 H, *c*Hex-H), 1.44 (m, 2 H, 4-*H*H, *c*Hex-H), 1.57 (m, 3 H, 3-H_2, *c*Hex-H), 1.63-1.79 (m, 4 H, *c*Hex-H), 1.90 (m, 1 H, 4-H*H*), 2.22 (m, 2 H, 2-H, 5-C*H*H), 2.27 (s, 6 H, $N(CH_3)_2$), 2.30 (s, 3 H, 1-CH_3), 2.44 (m, 2 H, 5-H, 5-CH*H*) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 24.6 (C-3), 26.5, 26.6, 27.1, 27.2 (C-*c*Hex), 29.7 (C-4), 31.3, 40.0 (C-*c*Hex), 40.8 (1-CH_3), 46.6 ($N(CH_3)_2$), 65.2 (5-CH_2), 65.4 (C-5), 72.3 (C-2) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{28}N_2$ $[M + H]^+$ 225.23253, found 225.23183.

(2S,5R)-2-((Dimethylamino)methyl)-5-(3,5-dimethylphenyl)-1-methylpyrrolidine (10c) According to GP-2, prolinol **14c** 71.7 mg, 327 µmol) was mesylated and treated with dimethylamine (aq., 40%, 595 µL, 529 mg 4.91 mmol) and MeOH (4.0 mL) to give, after column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 95:4.5:0.5), prolinamine **10c** (59.0 mg, 239 µmol, 73%) as a yellow oil.

R_f = 0.29 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5). $[\alpha]_D^{32}$ = +27.3 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 2945, 2817, 2764, 1606, 1456, 1261, 1201, 1157, 1034 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.73 (m, 2 H, 3-*H*H, 4-*H*H), 2.05 (m, 2 H, 3-H*H*, 4-H*H*), 2.19 (s, 3 H, 1-CH_3), 2.30 (s, 6 H, Ar-CH_3), 2.37 (s, 6 H, N(CH_3)$_2$), 2.46 (dd, *J* = 11.5, 7.9 Hz, 1 H, 2-C*H*H), 2.58 (m, 1 H, 2-H), 2.60 (dd, *J* = 11.5, 3.5 Hz, 1 H, 2-CH*H*) 3.17 (dd, *J* = 9.1, 6.6 Hz, 1 H, 5-H), 6.87 (s, 1 H, Ar-H), 6.95 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 21.5 (Ar-CH_3), 29.5 (C-3), 33.8 (C-4) 39.8 (1-CH_3), 46.5 (N(CH_3)$_2$), 64.6 (C-2), 65.2 (2-CH_2), 72.8 (C-5), 125.3, 128.9 (CH-Ar), 137.9, 143.4 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{16}H_{26}N_2$ $[M + H]^+$ 247.21688, found 247.21634.

(2*S*,5*R*)-2-((Acetylamino)methyl)-1-methyl-5-phenylpyrrolidine (9f)

The primary prolinamine **9n**[2] (110 mg, 578 µmol) was dissolved in anhydrous CH_2Cl_2 (5 mL), and NEt_3 (88.8 µL, 64.3 mg, 636 µmol) and Ac_2O (60.1 µL, 64.9 mg, 636 µmol) were added dropwise. The solvent was evaporated after 3 h at RT and residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 97:2.7:0.3–95:4.5:0.5) to give prolinamine **9f** (123 mg, 529 µmol, 92%) as a colorless oil.

R_f = 0.23 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 95:4.5:0.5). $[\alpha]_D^{28}$ = +10.2 (*c* = 0.50 in MeOH). IR (ATR) ν_{max} = 3289, 2949, 2843, 2782, 1647, 1549, 1452, 1368, 1279, 1193, 1041 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.61 (m, 1 H, 4-*H*H), 1.68 (m, 1 H, 3-*H*H), 1.92 (m, 1 H, 3-H*H*), 2.03 (s, 3 H, $NCOCH_3$), 2.07 (m, 1 H, 4-H*H*), 2.12 (s, 3 H, 1-CH_3), 2.66 (m, 1 H, 2-H), 3.16 (ddd, *J* = 13.7, 4.0, 2.8 Hz, 1 H, 2-C*H*H), 3.30 (dd, *J* = 9.2, 7.0 Hz, 1 H, 5-H), 3.65 (ddd, *J* = 13.7, 7.9, 2.4 Hz, 1 H, 2-CH*H*), 6.2 (s, 1 H, NH), 7.24 (m, 1 H, Ph-H), 7.31 (m, 4 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 23.4 (NCO*C*H_3), 26.7 (C-3), 34.0 (C-4), 38.5 (1-CH_3), 40.2 (2-CH_2), 64.3 (C-2), 72.0 (C-5), 127.16, 127.22, 128.5 (CH-Ph), 143.2 (C_q-Ph), 170.6 (N*C*OCH_3) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{14}H_{21}N_2O$ $[M + H]^+$ 233.16484, found 233.16491.

(2*S*,5*R*)-2-((Methanesulfonylamino)methyl)-1-methyl-5-phenylpyrrolidine (9g)

The primary prolinamine **9n**[2] (100 mg, 526 µmol) was dissolved in anhydrous CH_2Cl_2 (5 mL), and NEt_3 (80.7 µL, 58.5 mg, 578 µmol) and MsCl (44.7 µL, 66.2 mg, 578 µmol) were added dropwise. The solvent was evaporated after 1.5 h at RT and residue was purified by column chromatography (silica gel, CH_2Cl_2–MeOH–NH_3 (aq., 25%), 98:1.8:0.3) to give prolinamine **9g** (133 mg, 496 µmol, 94%) as a colorless oil.

R_f = 0.30 (CH_2Cl_2/MeOH/NH_3 (aq., 25%) 98:1.8:0.2). $[\alpha]_D^{32}$ = +31.0 (*c* = 1.00 in MeOH). IR (ATR) ν_{max} = 3257, 2958, 2790, 1490, 1397, 1326, 1309, 1163, 1147, 1020, 993 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 1.68 (m, 1 H, 4-*H*H), 1.90 (m, 1 H, 3-*H*H), 1.98 (m, 1 H, 3-H*H*), 2.08 (m, 1 H, 4-H*H*), 2.13 (s, 3 H, 1-CH_3), 2.72 (m, 1 H, 2-H), 3.01 (s, 3 H, SO_2CH_3), 3.23 (m, 1 H, 2-C*H*H), 3.30 (dd, *J* = 12.0, 3.8 Hz, 1 H, 2-CH*H*), 3.34 (dd, *J* = 9.9, 6.7 Hz, 1 H, C-5), 5.10 (d, *J* = 6.6 Hz, 1 H, NH), 7.25 (m, 1 H, Ph-H), 7.32 (m, 4 H, Ph-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ = 26.5 (C-3), 34.0 (C-4), 38.4 (1-CH_3), 39.9 (SO_2CH_3), 44.0 (2-CH_2), 64.1 (C-2), 72.1 (C-5), 127.27, 127.34, 128.5 (CH-Ph),

142.8 (C_q-Ph) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{13}H_{21}N_2O_2S$ $[M + H]^+$ 269.13183, found 269.13175.

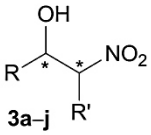
Gram-scale Henry reaction of 2a and b catalyzed by $CuBr_2$·9a

To a solution of diamine **9a** (22.5 mg, 110 µmol) in anhydrous THF (6.0 mL), anhydrous $CuBr_2$ (22.3 mg, 100 µmol), $MeNO_2$ (**2a**, 6.0 mL, 6.84 g, 112 mmol), and the respective aldehyde (**1a**: 1.06 g, 10.0 mmol, 1.01 mL; **1b**: 1.51 g, 10.0 mmol) were added successively at RT. The mixture was ultrasonicated for 10 min to give a clear, brownish solution and then cooled to -25 °C. NEt_3 (10.4 µL, 7.59 mg, 7.50 µmol) was added and the resulting blue-green solution was stirred for 70 h (**1a**) and 42 h (**1b**). The crude reaction mixture was purified by column chromatography (silica gel, hexanes/EtOAc 1:0 → 4:1) to afford the corresponding ß-nitro alcohols (**3a**: 1.57 g, 9.39 mmol, 94%, 99.0% *ee*, colorless oil; **3b**: 1.99 g, 9.39 mmol, 94%, 98.9% *ee*, yellowish solid). The enantiomeric excess of **3a**,**b** was determined by HPLC on chiral phase.[3]

3. HPLC analysis of the ß-nitro alcohols 3

Measurement of the enantiomeric excess (*ee*): The *ee* of each ß-nitro alcohol **3** was determined by HPLC (Knauer HPLC pump type 64.00, Knauer UV/VIS variable wavelength monitor type A0293 or Waters Alliance HPLC, Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralcel OD-3, Daicel Chiralpak AD-H, Daicel Chiralcel OJ-H) with accuracy of integration of up to ± 0.1%. Many of the enantioselective Henry reactions were repeated, always providing the virtually same enantiomeric excesses (Δ*ee* = ± 0.2%).

Determination of the relative and absolute configuration of the major enantiomer: For the ß-nitro alcohols **3a-g,i,j** the absolute configuration was assigned by comparison with literature data.[3,5] In the case of the product **3h**, the major enantiomer was assigned under the assumption that the sense of asymmetric induction was the same as for all other derivatives (*re*-attack on the carbonyl group, see ref. 3). The relative configuration of the diastereomeric ß-nitro alcohols **3f-i** was confirmed by comparison of the NMR spectroscopic data with those given in literature.[5]



3a–j

Table S1. HPLC analysis on chiral phase.

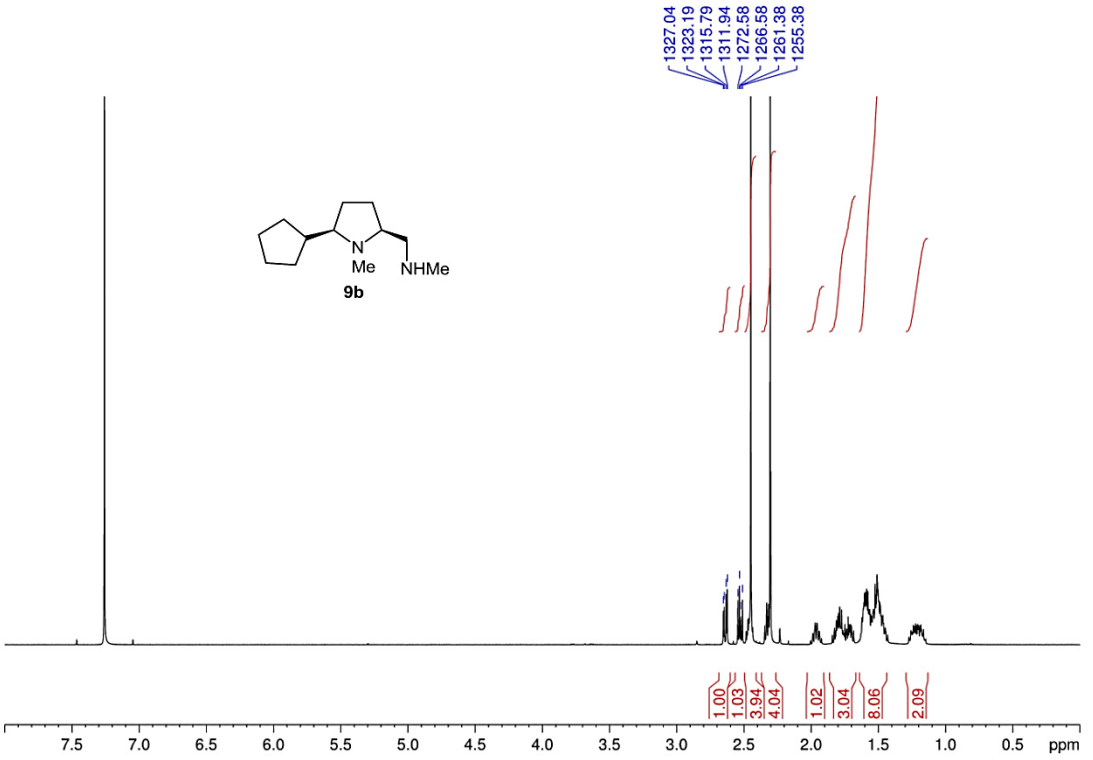
Compound	R	R'	Enantiomer Analysis: HPLC Conditions					
			Column[a]	Solvent System *n*-Hexane/*i*PrOH	Flow [ml/min]	t_r (*R*) [min][b]	t_r (*S*) [min][b]	Ref.[c]
3a	Ph	H	OD-3	85:15	0.8	12.6	14.9	[3]
3b	2-O_2N-Ph	H	OD-3	80:20	0.7	11.5	12.2	[3]
3c	2-MeO-Ph	H	OD-3	90:10	0.9	14.0	16.8	[3]
3d	*n*Oct	H	AD-H	95:5	0.8	14.3	20.2	[3]
3e	3-pyridyl	H	OJ-H	75:25	0.8	15.5	19.5	[5a]
3f	Ph	Me	AD-H	95:5	0.9	17.2 (1*R*,2*S*) 23.6 (1*R*,2*R*)	21.1 (1*S*,2*S*) 15.2 (1*S*,2*R*)	[5b,c]
3g	Ph	Et	OD-3	95:5	0.9	13.9 (1*R*,2*S*) 16.6 (1*R*,2*R*)	20.6 (1*S*,2*S*) 23.3 (1*S*,2*R*)	[5b,c]
3h[d]	Ph	CH_2OTBS	OD-3	95:5	0.9	10.4 (1*R*,2*S*) 12.2 (1*R*,2*R*)	14.2 (1*S*,2*S*) 19.3 (1*S*,2*R*)	[5d]
3i	*c*Hex	Et	AD-H	97:3[e]	0.8	19.7 (1*R*,2*S*) 62.1 (1*R*,2*R*)	20.9 (1*S*,2*S*) 23.7 (1*S*,2*R*)	[5b,c]
3j	4-O_2N-Ph	H	OD-3	85:15	0.8	18.5	23.5	[3]

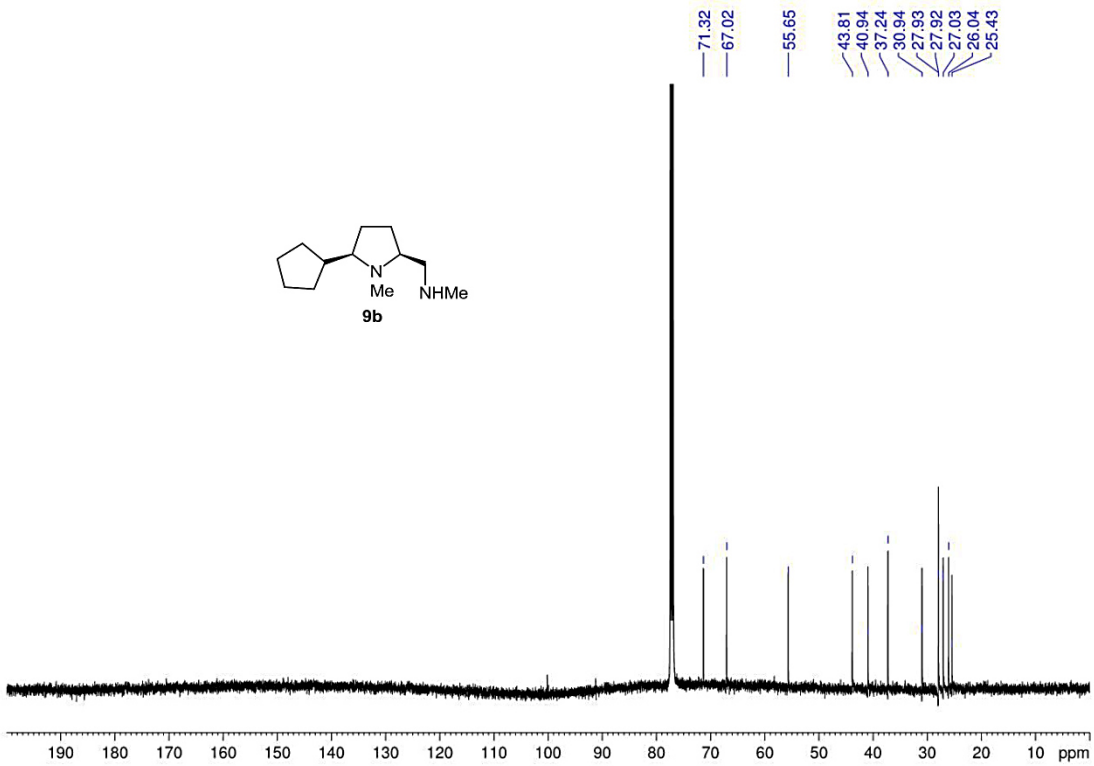
[a] OD-3: Daicel Chiralcel OD-3; AD-H: Daicel Chiralpak AD-H; OJ-H: Daicel Chiralcel OJ-H. [b] Retention time. [c] Reference data for NMR spectra and enantiomer analysis by HPLC on chiral phase.[3,5] [d] The absolute and relative configuration of the major enantiomer was tentatively assigned under the assumption of a *re*-attack on the carbonyl group. [e] As the polar eluent, EtOH was used instead of *i*PrOH.

[5] a) X.-G. Liu, J.-J. Jiang, M. Shi, *Tetrahedron: Asymmetry* **2007**, *18*, 2773-2781; b) D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, W. Milius, M. Breuning, *Chem. Eur. J.* **2015**, *21*, 12488-12500; c) Y. Zhou, J. Dong, F. Zhang, Y. Gong, *J. Org. Chem.* **2011**, *76*, 588-600; d) T. Nitabaru, A. Nojiri, M. Kobayashi, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 13860-13869.

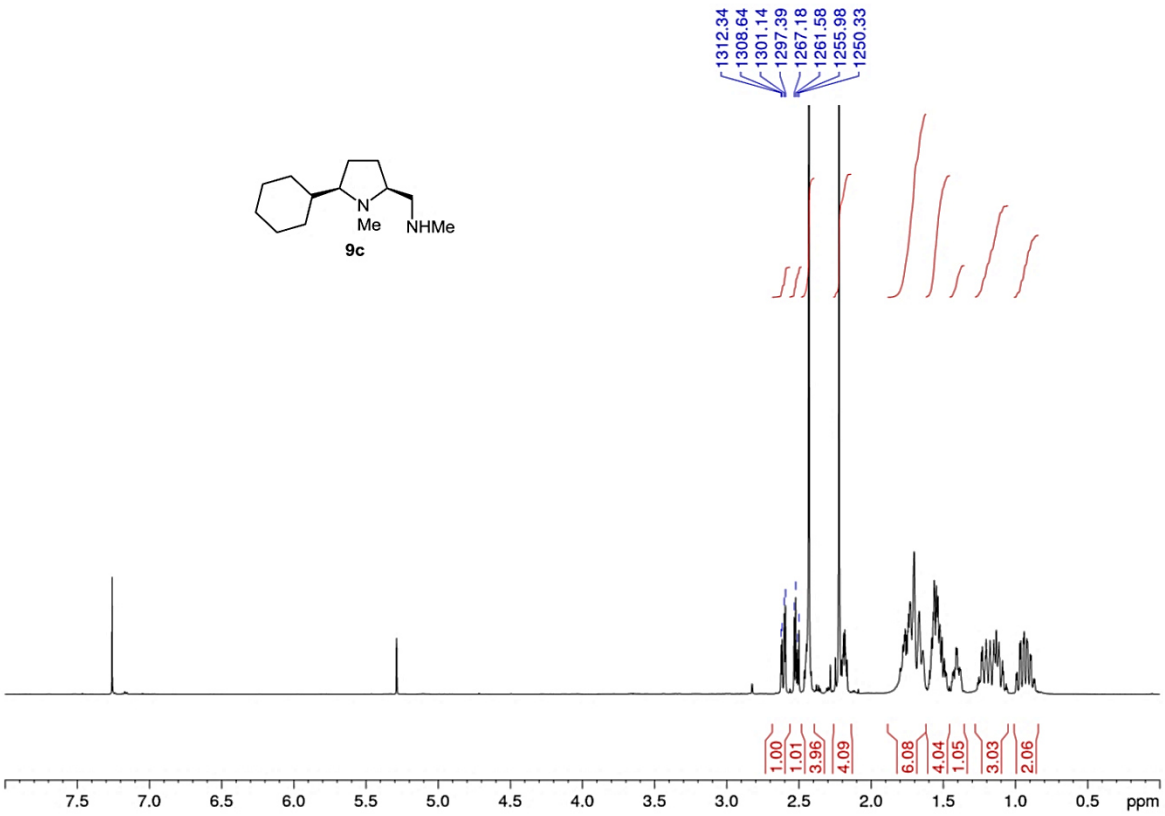
4. Copies of ^{1}H and ^{13}C NMR spectra

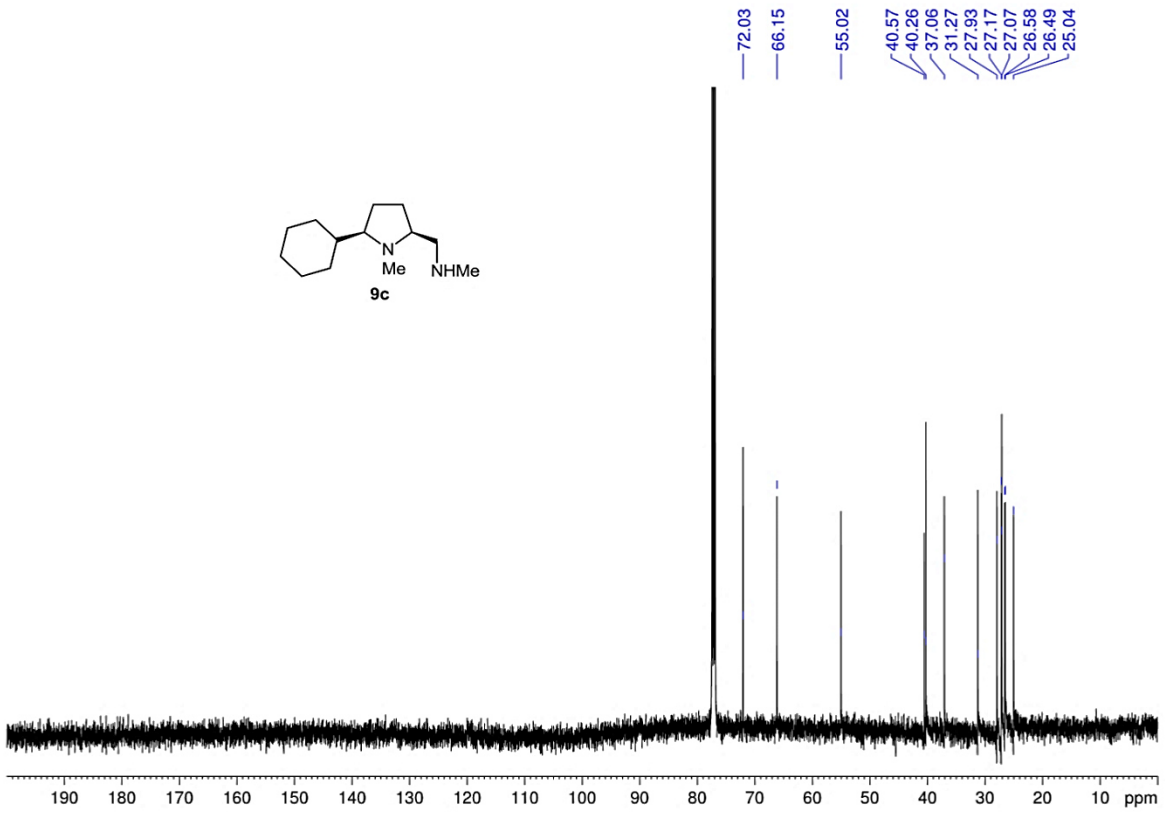
The ^{1}H and ^{13}C NMR spectra of all new compounds are listed in numerical order.



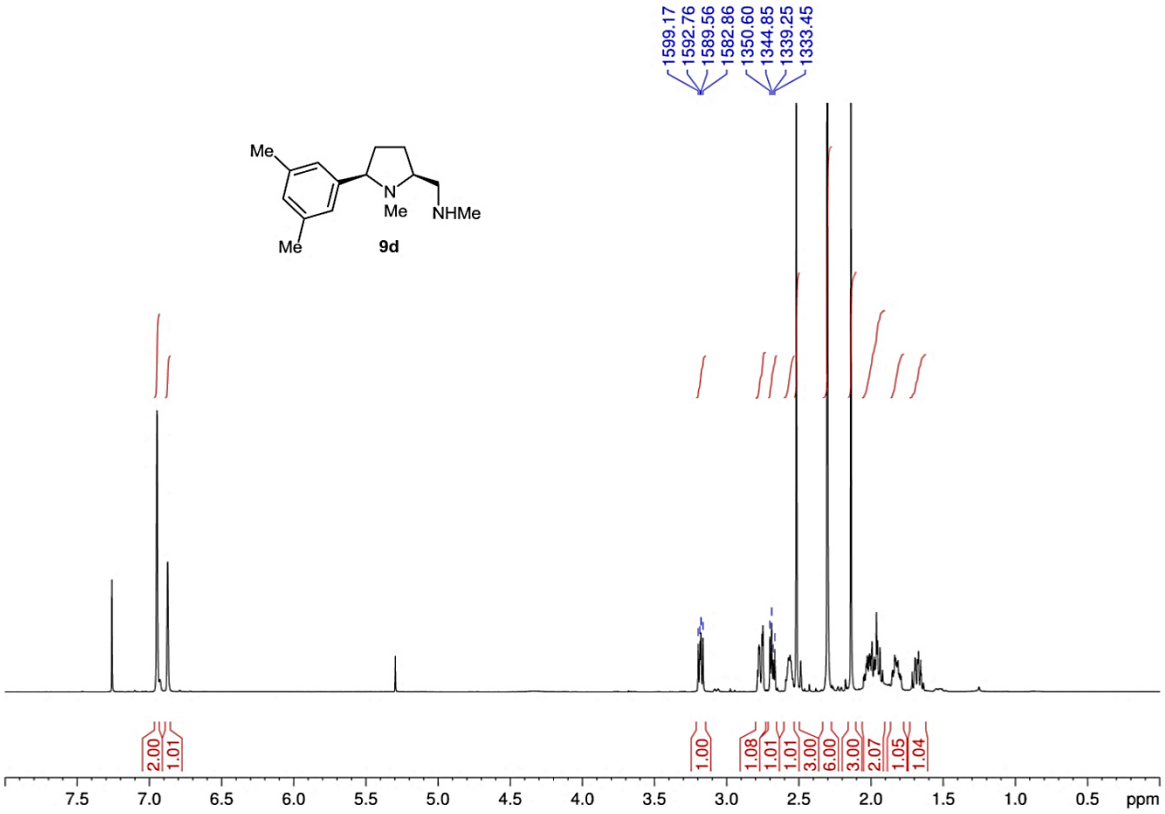


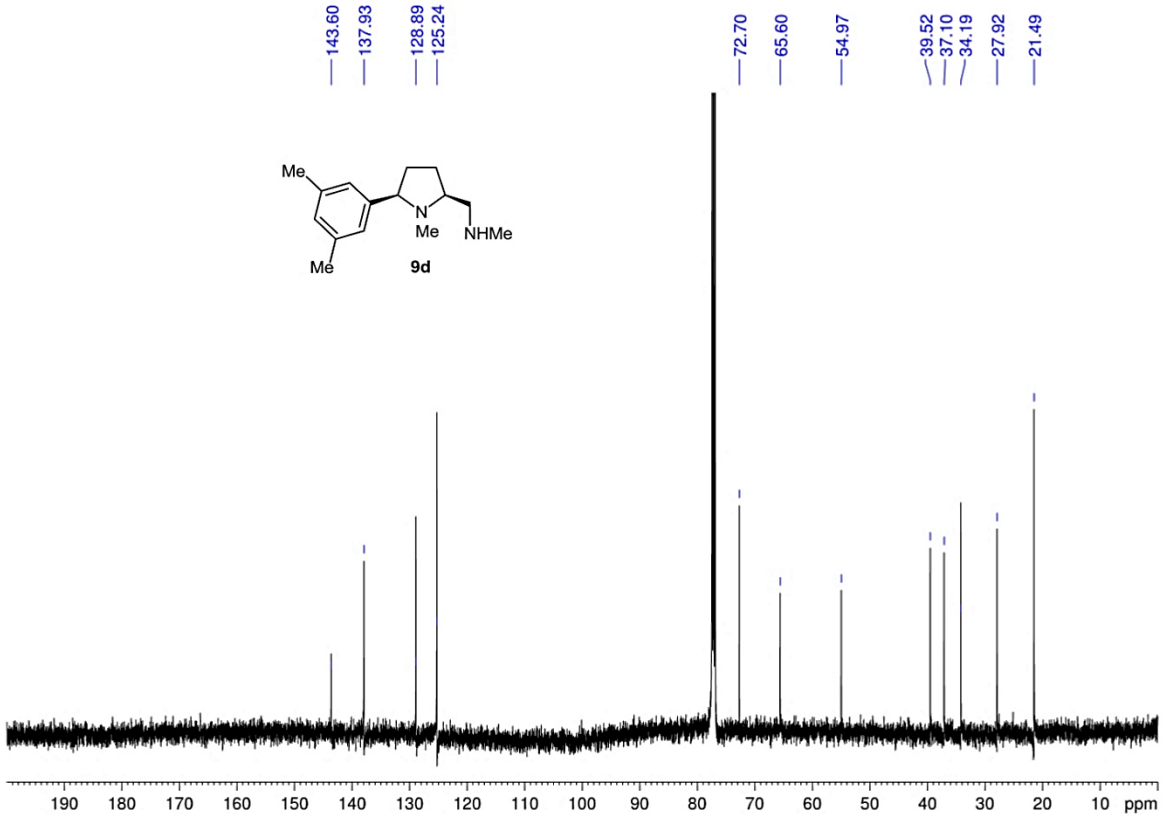
14


1312.34
1308.64
1301.14
1297.39
1267.18
1261.58
1255.98
1250.33
N
Me
NHMe
9c
1.00
1.01
3.96
4.09
6.08
4.04
1.05
3.03
2.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

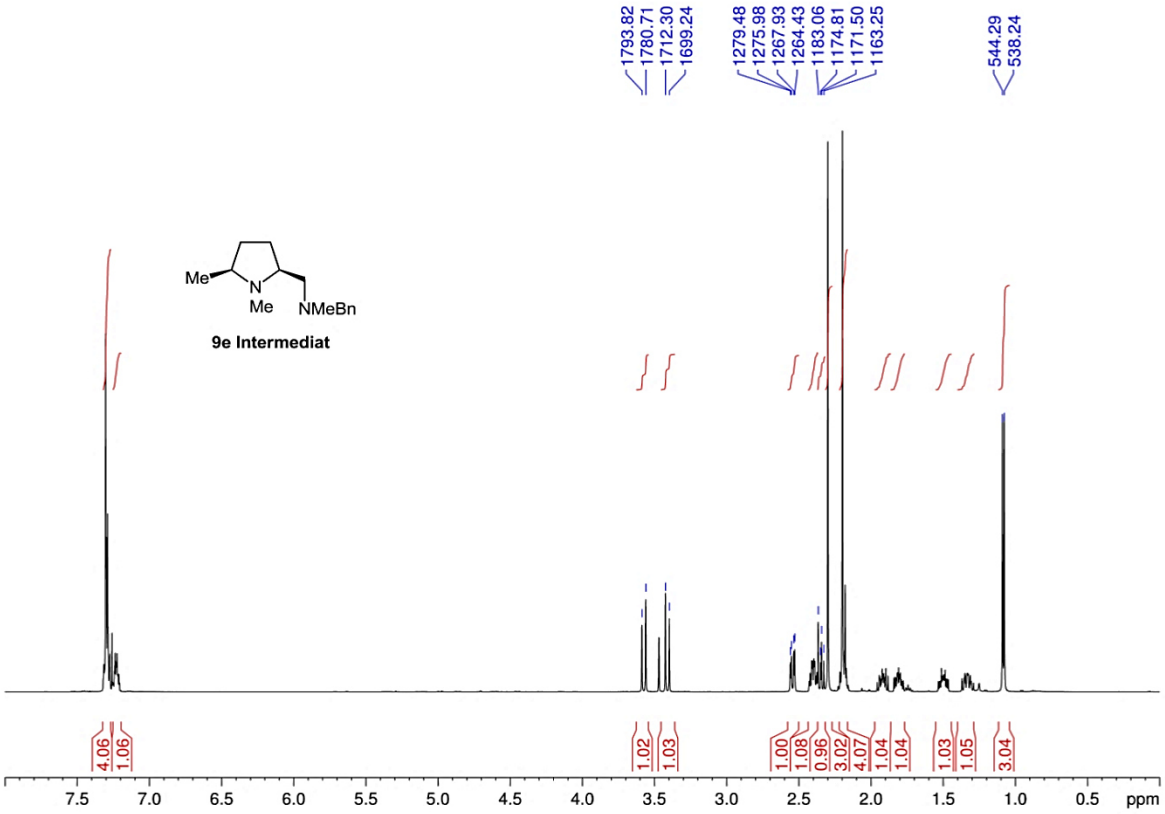

72.03
66.15
55.02
40.57
40.26
37.06
31.27
27.93
27.17
27.07
26.58
26.49
25.04
N
Me
NHMe
9c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

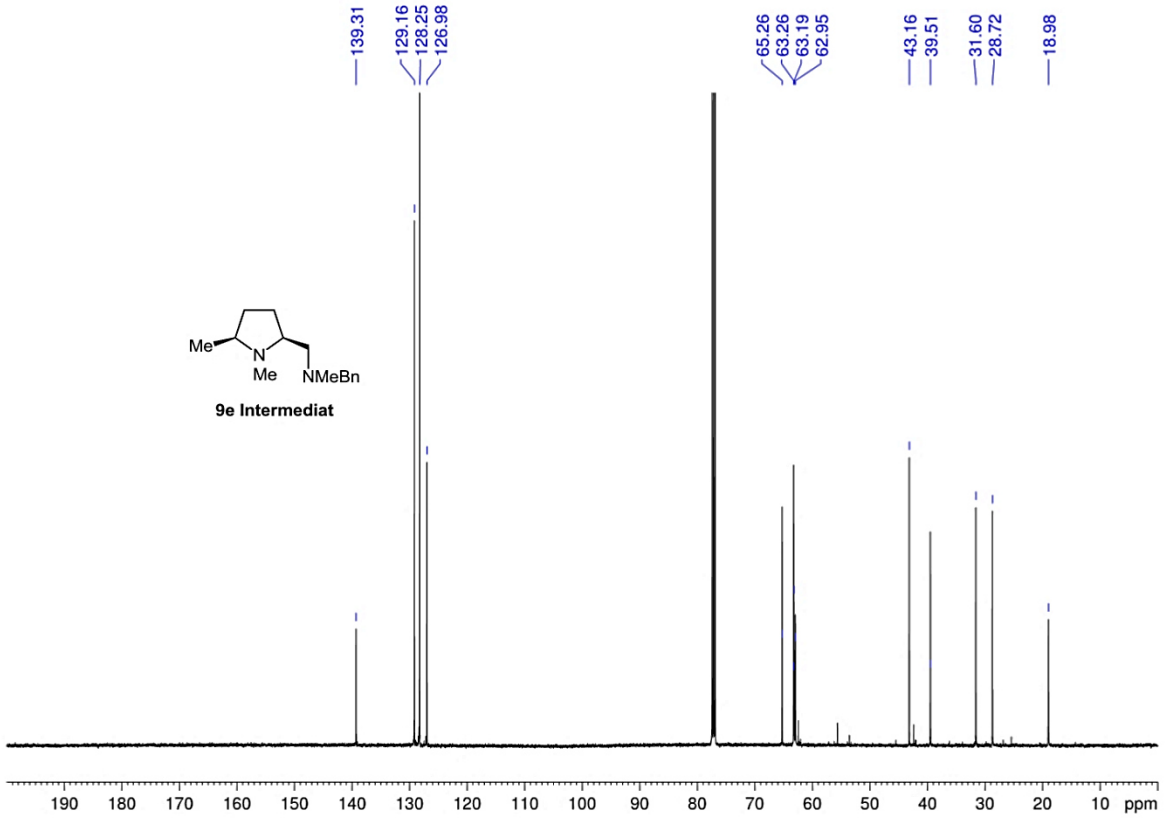
15


1599.17
1592.76
1589.56
1582.86
1350.60
1344.85
1339.25
1333.45
Me
N
Me
NHMe
Me
9d
2.00
1.01
1.00
1.08
1.01
1.01
3.00
6.00
3.00
2.07
1.05
1.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

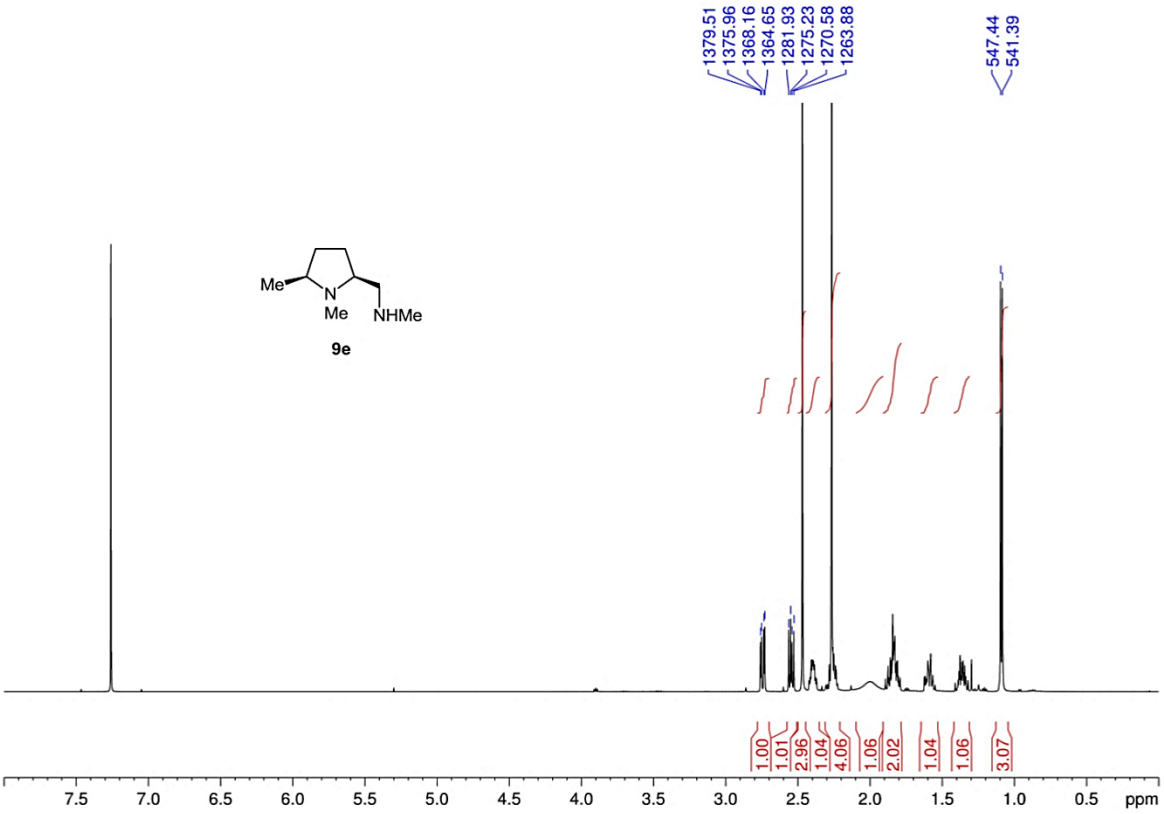

143.60
137.93
128.89
125.24
72.70
65.60
54.97
39.52
37.10
34.19
27.92
21.49
Me
N
Me
NHMe
Me
9d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

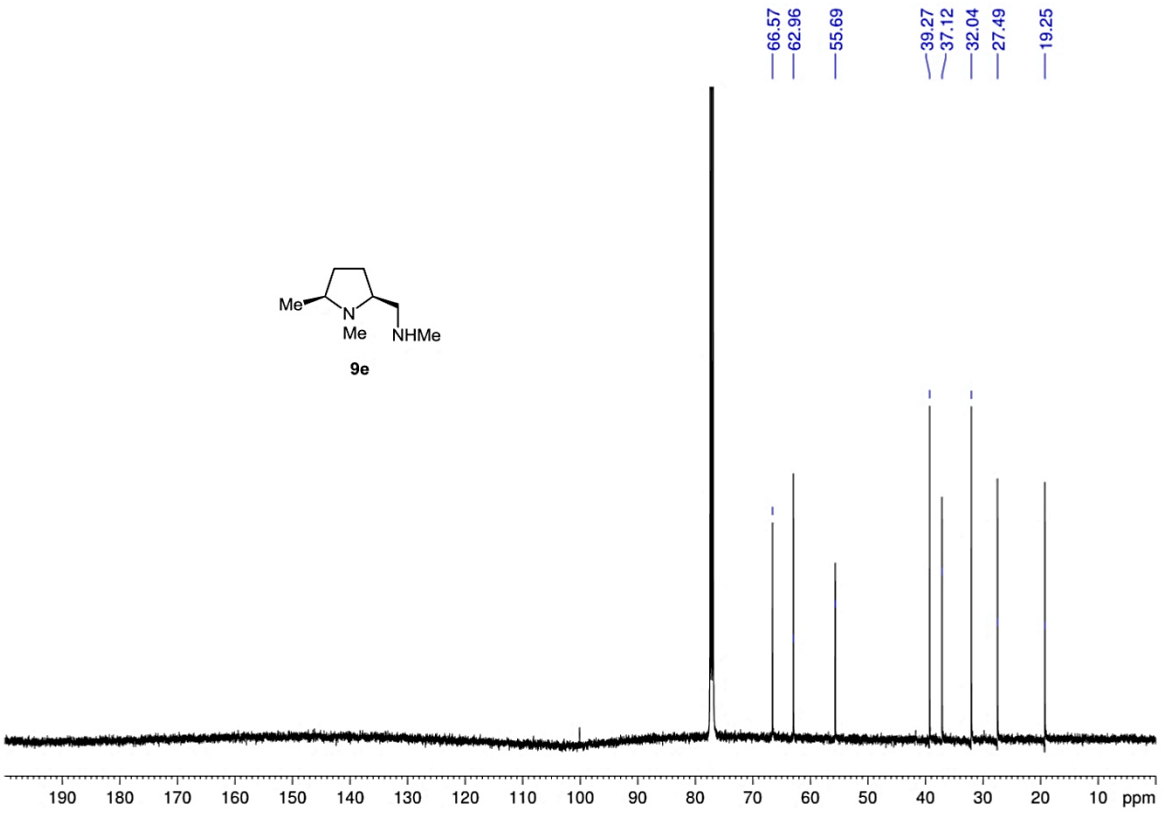
16


1793.82
1780.71
1712.30
1699.24
1279.48
1275.98
1267.93
1264.43
1183.06
1174.81
1171.50
1163.25
544.29
538.24
Me
N
Me
NMeBn
9e Intermediat
4.06
1.06
1.02
1.03
1.00
1.08
0.96
3.02
4.07
1.04
1.04
1.03
1.05
3.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

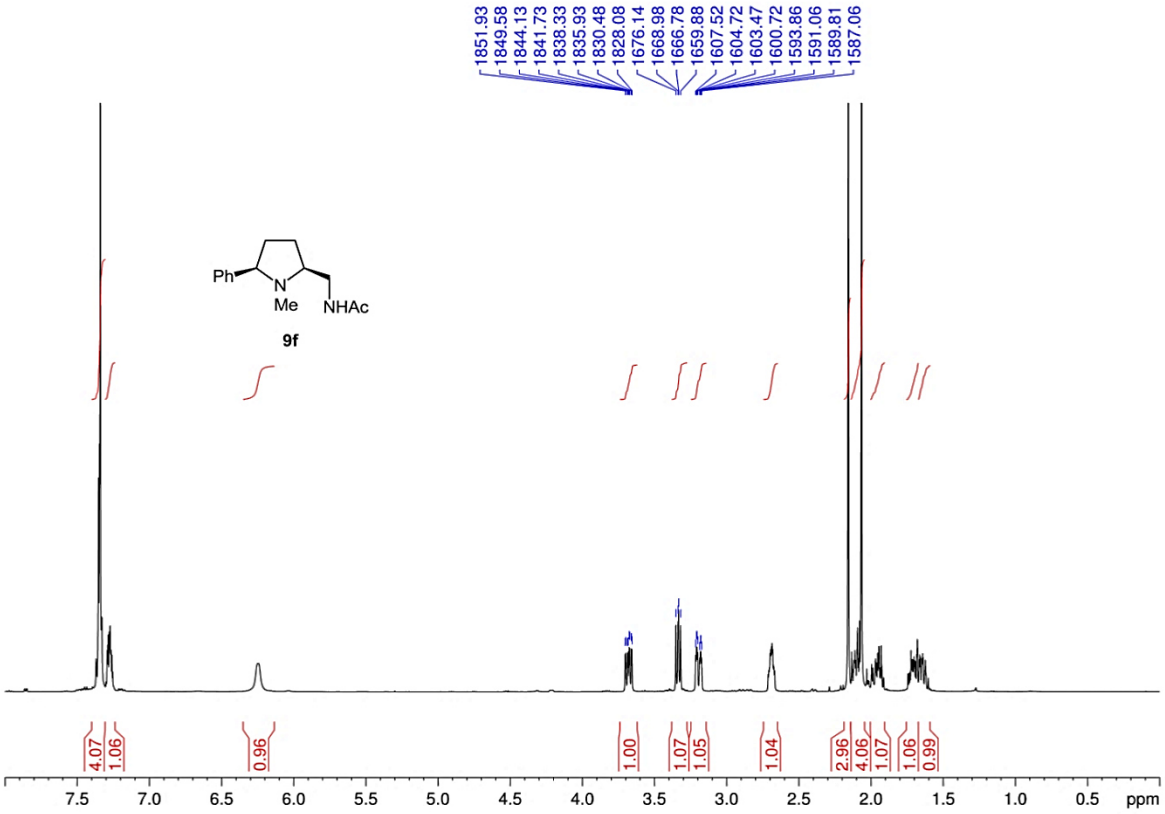

139.31
129.16
128.25
126.98
65.26
63.26
63.19
62.95
43.16
39.51
31.60
28.72
18.98
Me
N
Me
NMeBn
9e Intermediat
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

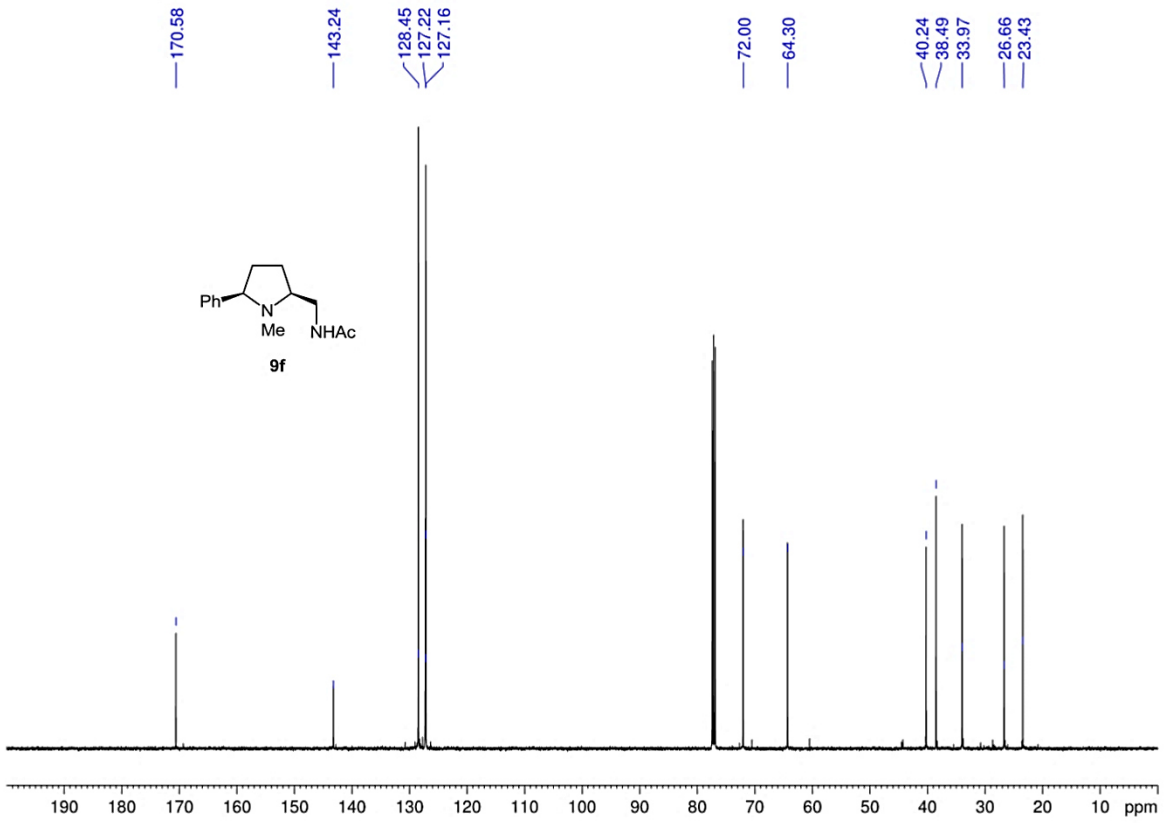
17


1379.51
1375.96
1368.16
1364.65
1281.93
1275.23
1270.58
1263.88
547.44
541.39
Me
N
Me
NHMe
9e
1.00
1.01
2.96
1.04
4.06
1.06
2.02
1.04
1.06
3.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

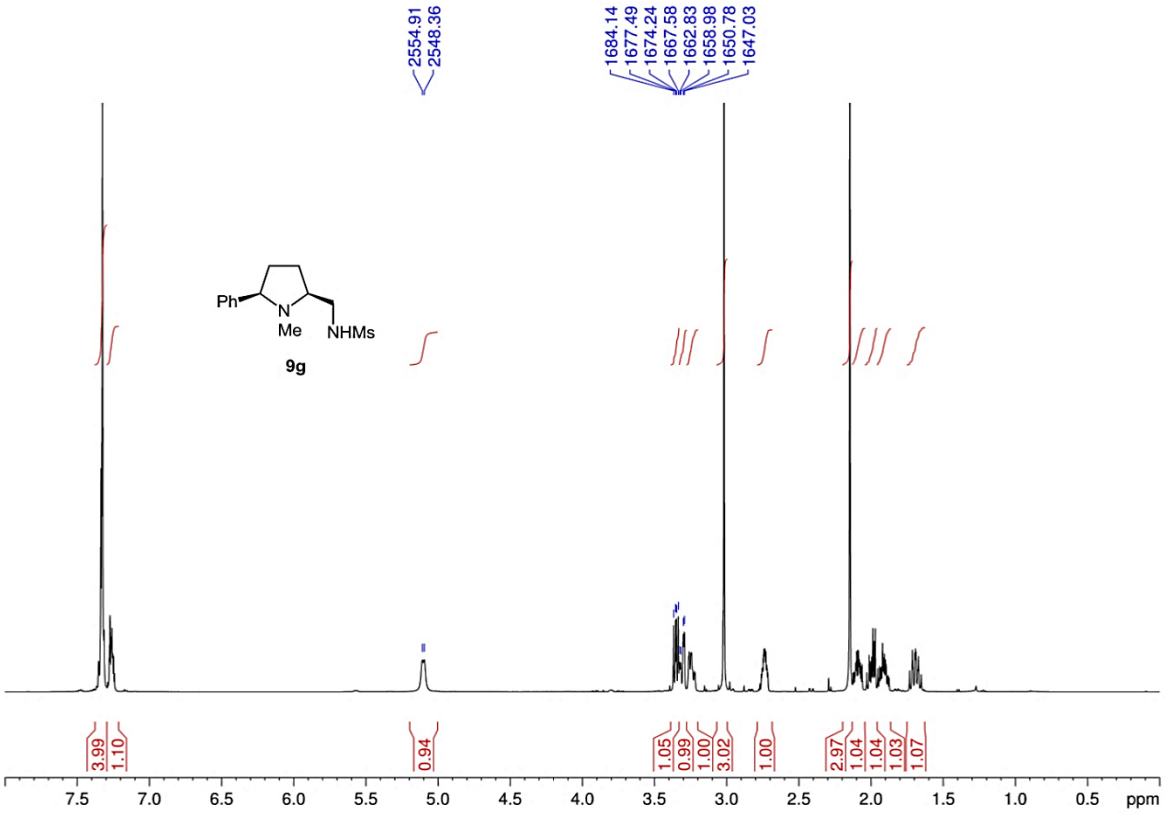

66.57
62.96
55.69
39.27
37.12
32.04
27.49
19.25
Me
N
Me
NHMe
9e
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

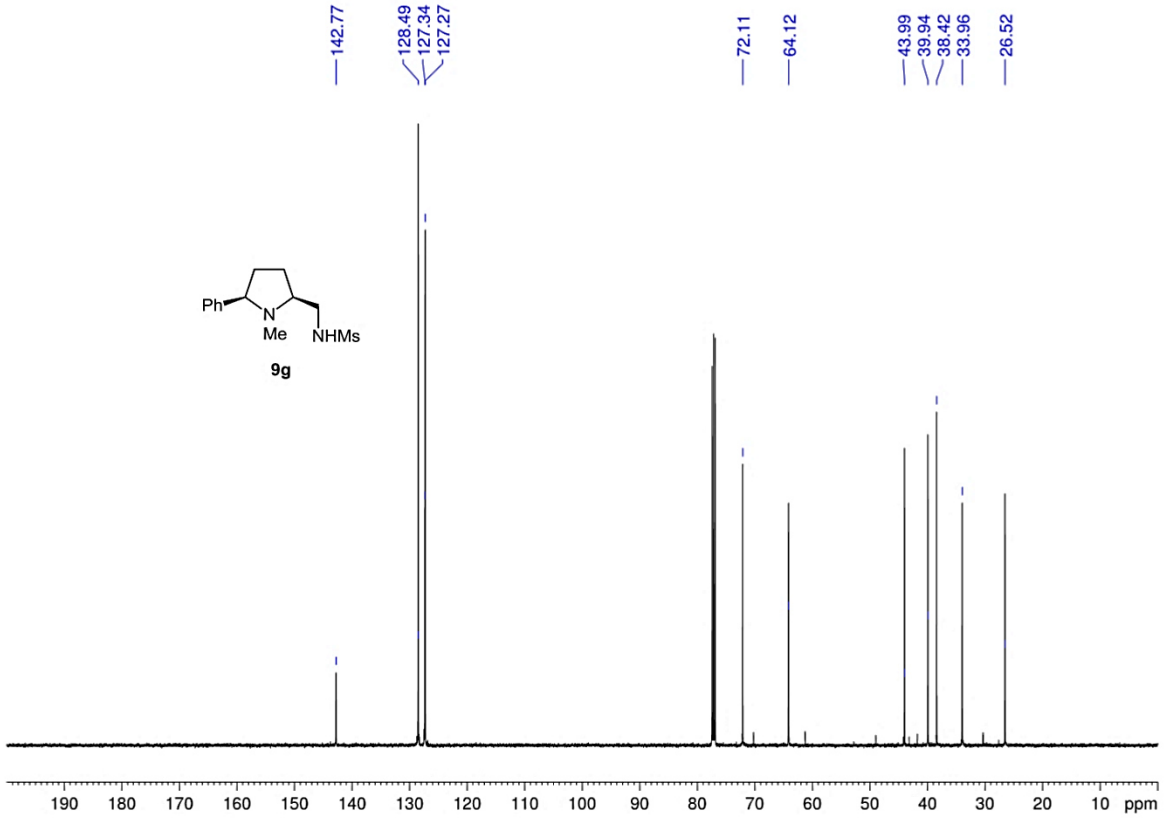
18


1851.93
1849.58
1844.13
1841.73
1838.33
1835.93
1830.48
1828.08
1676.14
1668.98
1666.78
1659.88
1607.52
1604.72
1603.47
1600.72
1593.86
1591.06
1589.81
1587.06
Ph
N
Me
NHAc
9f
4.07
1.06
0.96
1.00
1.07
1.05
1.04
2.96
4.06
1.07
1.06
0.99
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

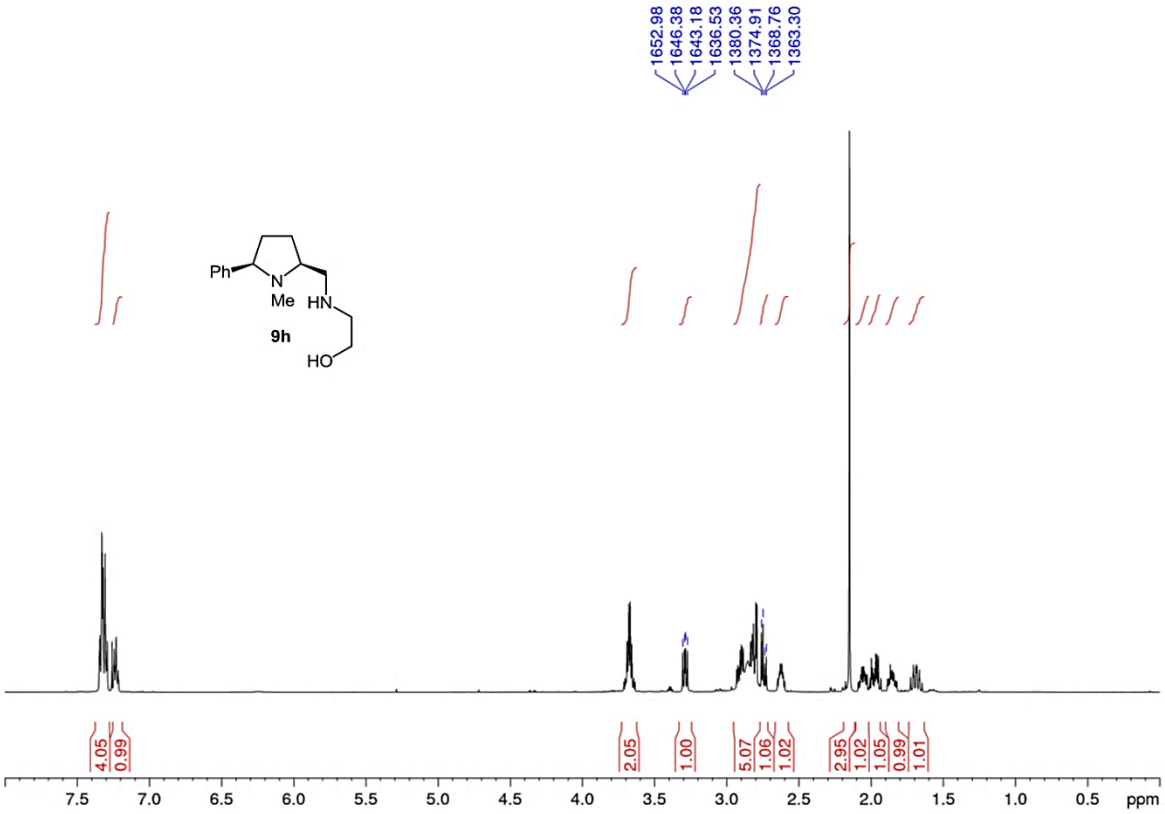

170.58
143.24
128.45
127.22
127.16
72.00
64.30
40.24
38.49
33.97
26.66
23.43
Ph
N
Me
NHAc
9f
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

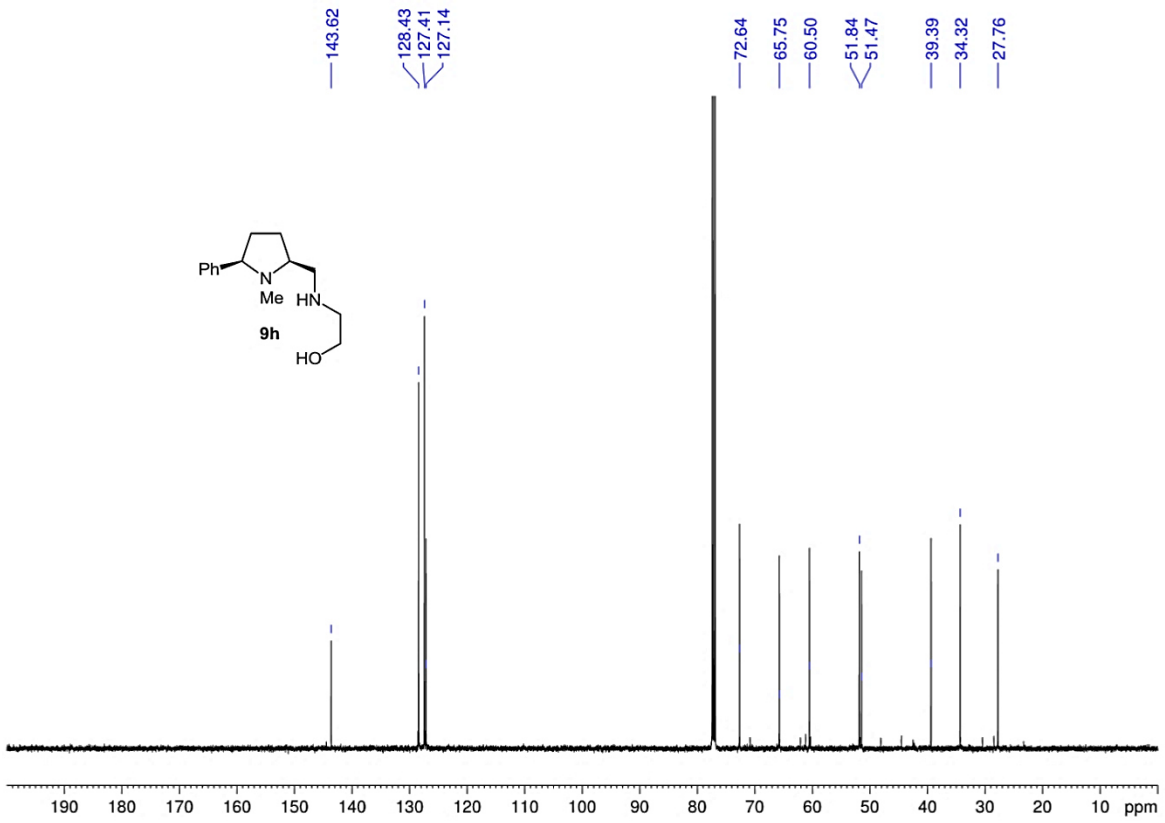
19


2554.91
2548.36
1684.14
1677.49
1674.24
1667.58
1662.83
1658.98
1650.78
1647.03
Ph
N
Me
NHMs
9g
3.99
1.10
0.94
1.05
0.99
1.00
3.02
1.00
2.97
1.04
1.04
1.03
1.07
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

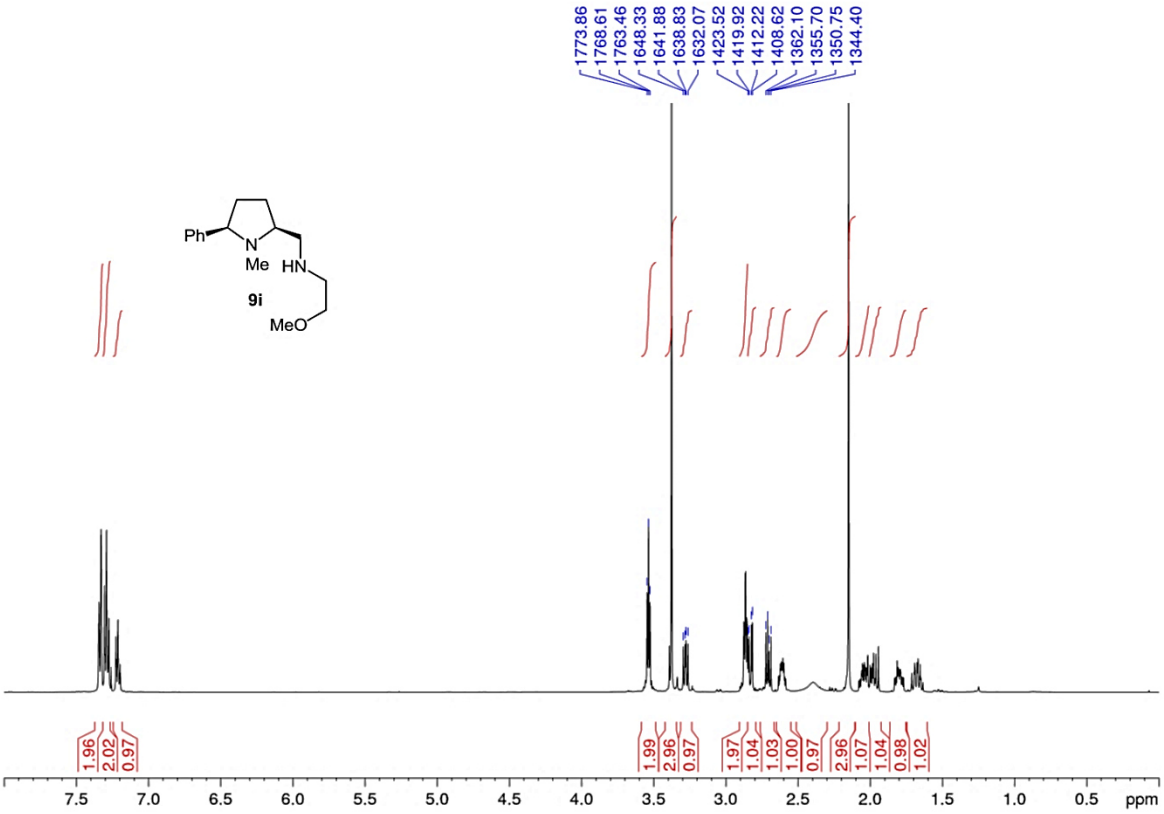

142.77
128.49
127.34
127.27
72.11
64.12
43.99
39.94
38.42
33.96
26.52
Ph
N
Me
NHMs
9g
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

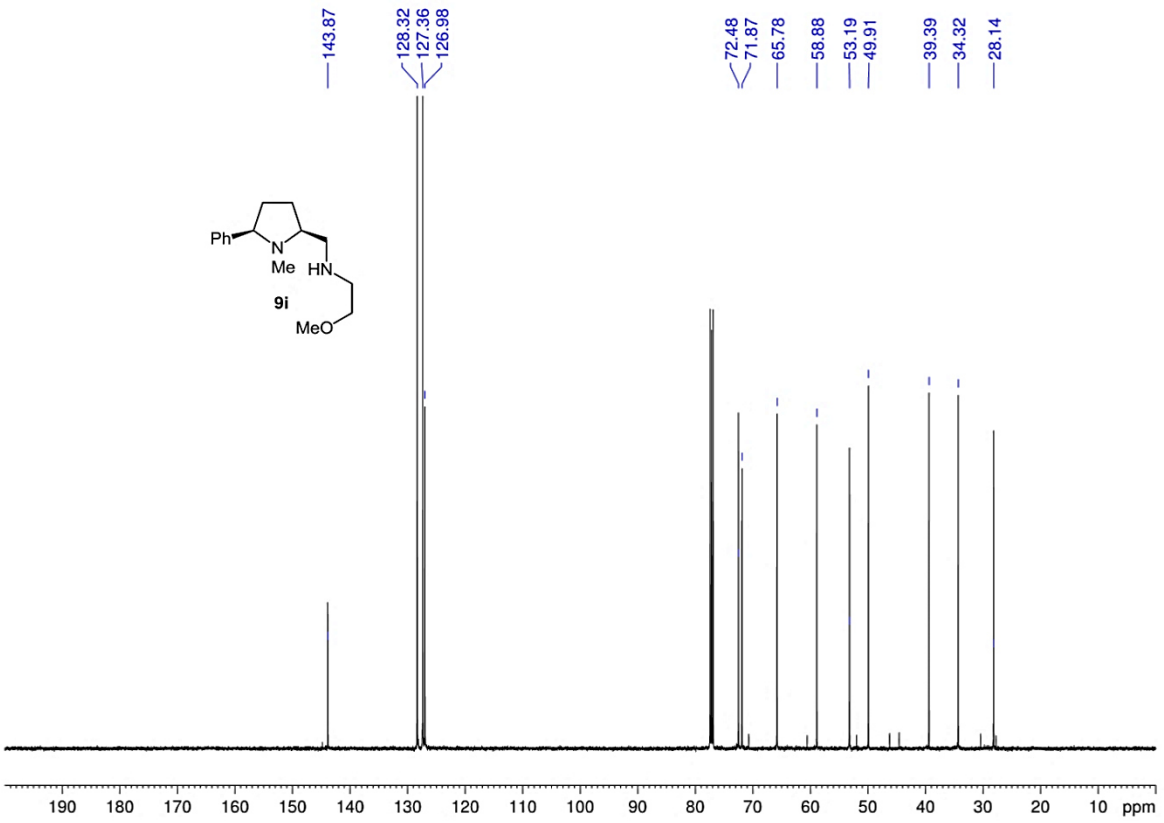
20


1652.98
1646.38
1643.18
1636.53
1380.36
1374.91
1368.76
1363.30
Ph
N
Me
HN
HO
9h
4.05
0.99
2.05
1.00
5.07
1.06
1.02
2.95
1.02
1.05
0.99
1.01
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

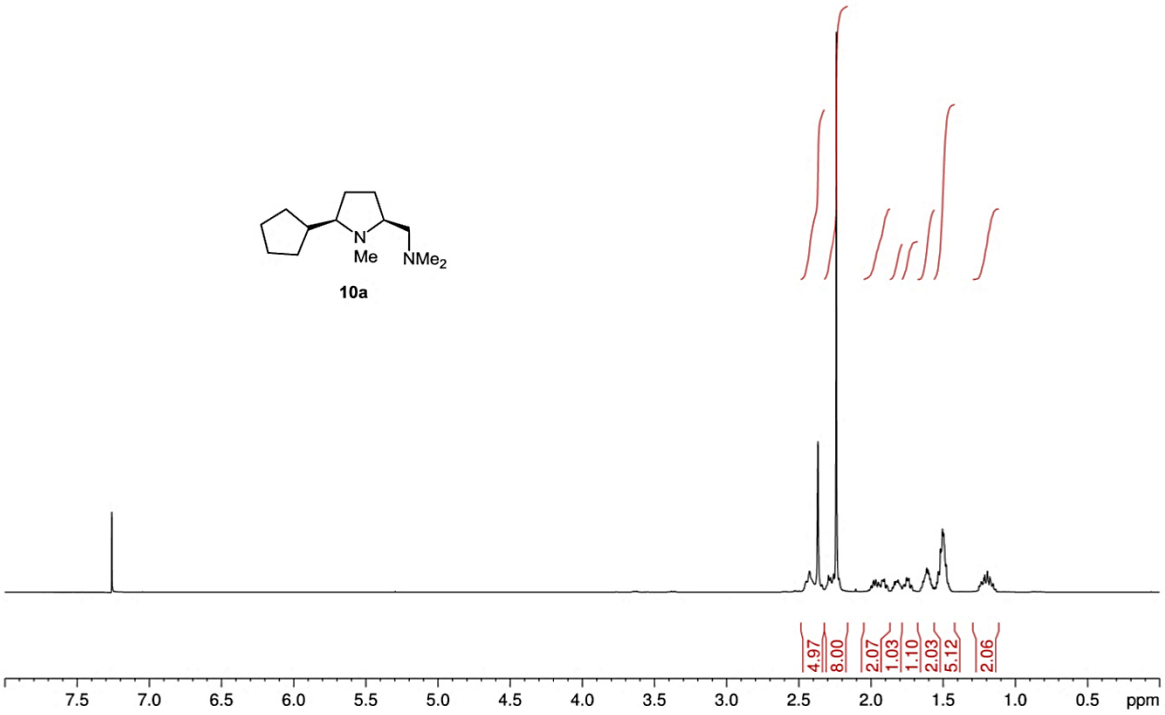

143.62
128.43
127.41
127.14
72.64
65.75
60.50
51.84
51.47
39.39
34.32
27.76
Ph
N
Me
HN
HO
9h
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

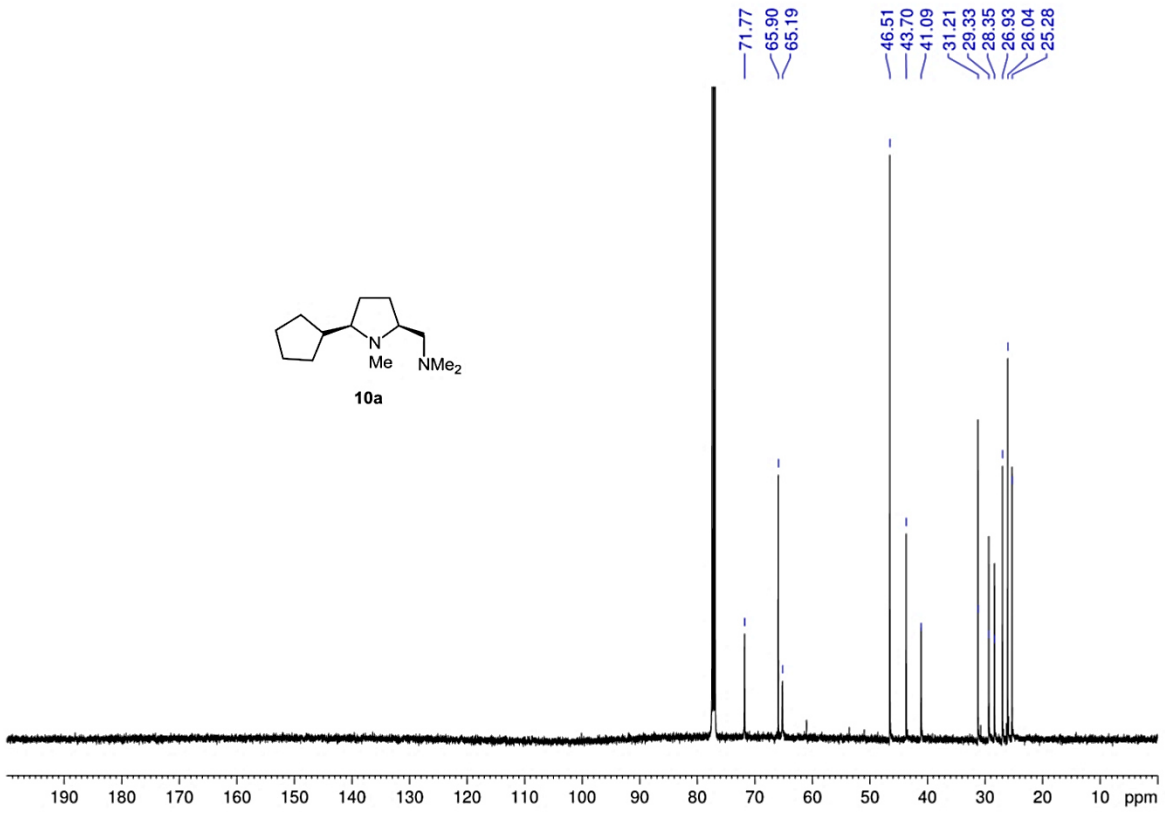
21

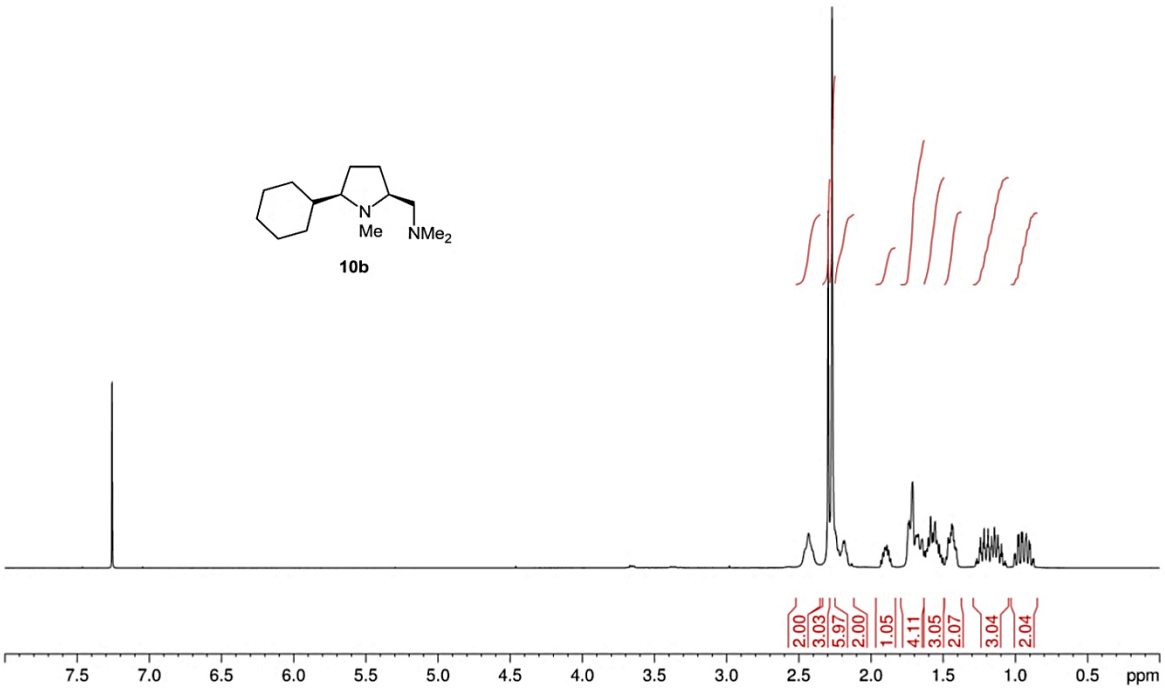

1773.86
1768.61
1763.46
1648.33
1641.88
1638.83
1632.07
1423.52
1419.92
1412.22
1408.62
1362.10
1355.70
1350.75
1344.40
Ph
N
Me
HN
9i
MeO
1.96
2.02
0.97
1.99
2.96
0.97
1.97
1.04
1.03
1.00
0.97
2.96
1.07
1.04
0.98
1.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

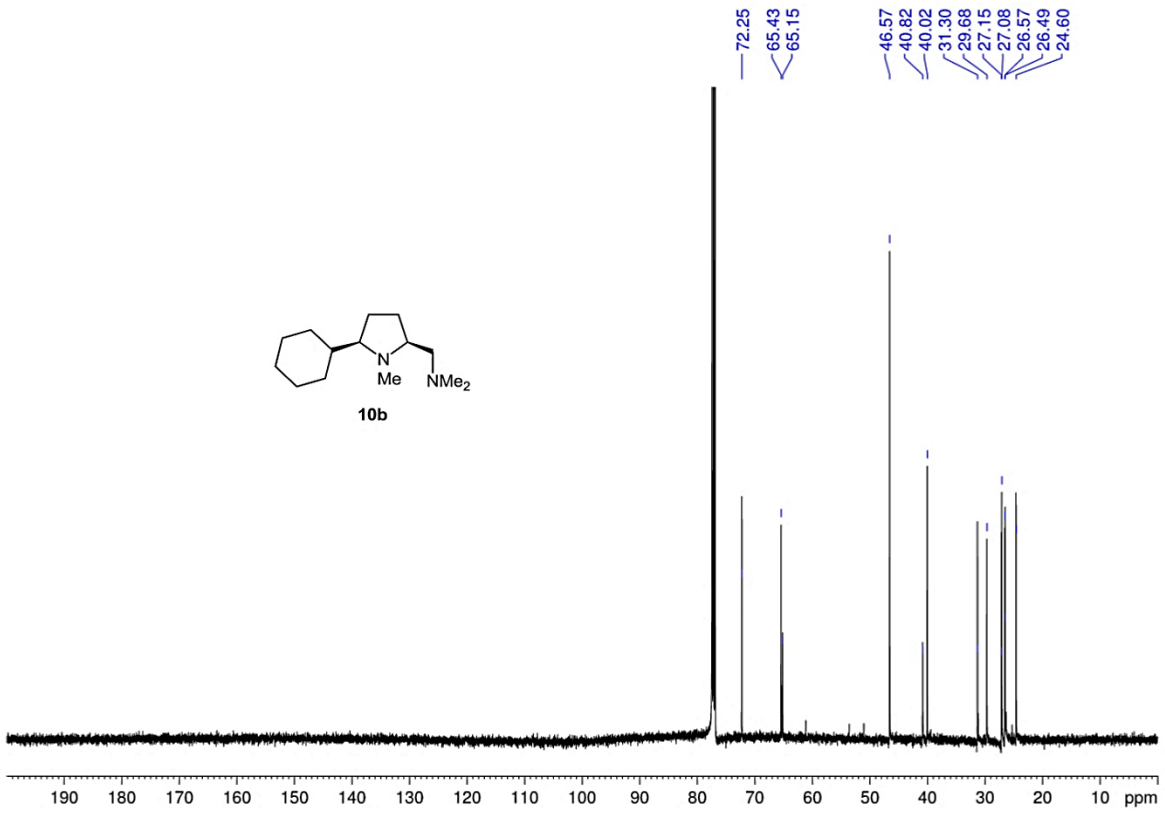

143.87
128.32
127.36
126.98
72.48
71.87
65.78
58.88
53.19
49.91
39.39
34.32
28.14
Ph
N
Me
HN
9i
MeO
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

22

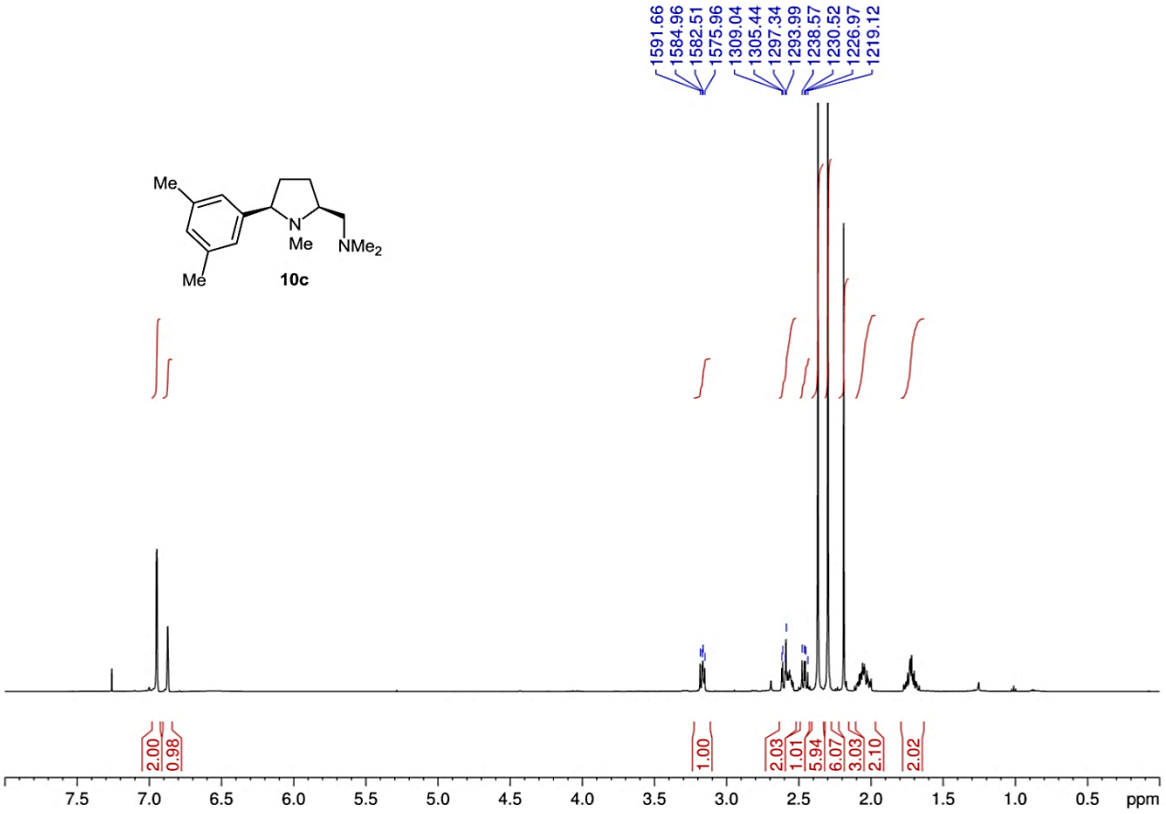

N
Me
NMe2
10a
4.97
8.00
2.07
1.03
1.10
2.03
5.12
2.06
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

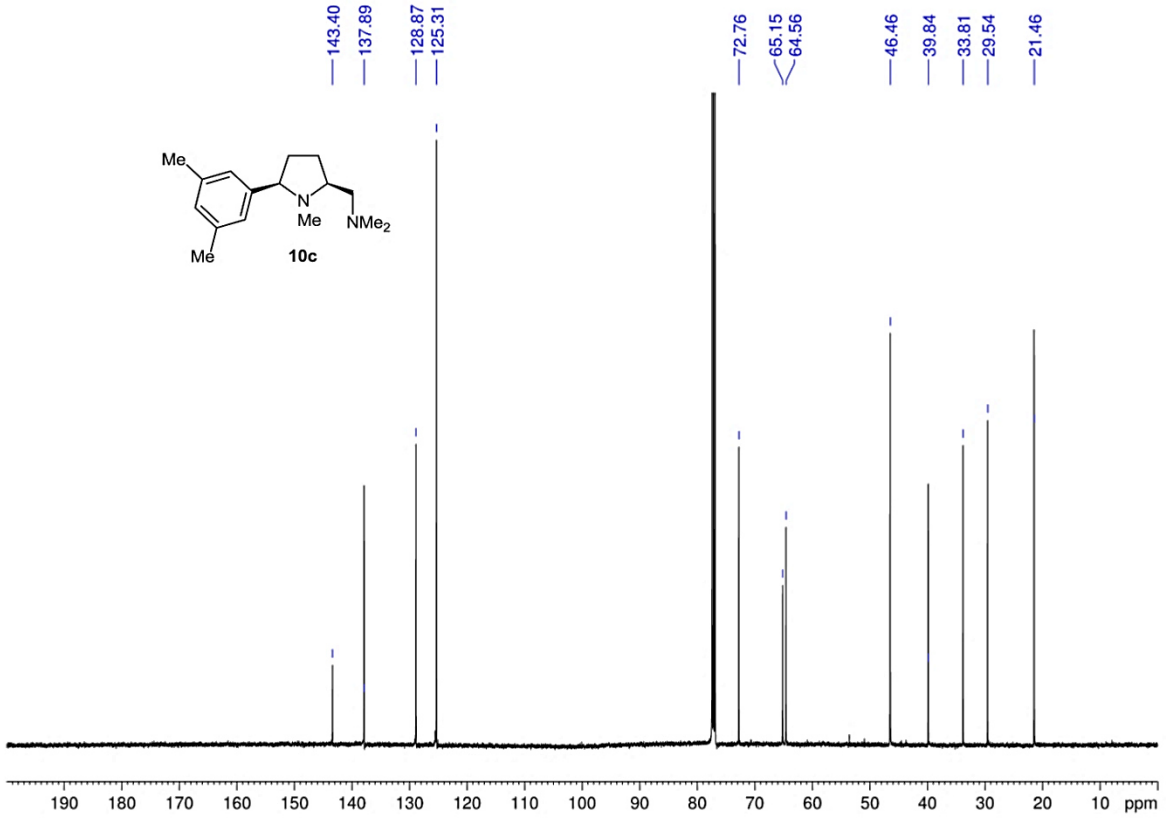

71.77
65.90
65.19
46.51
43.70
41.09
31.21
29.33
28.35
26.93
26.04
25.28
N
Me
NMe2
10a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


N
Me
NMe2
10b
2.00
3.03
5.97
2.00
1.05
4.11
3.05
2.07
3.04
2.04
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

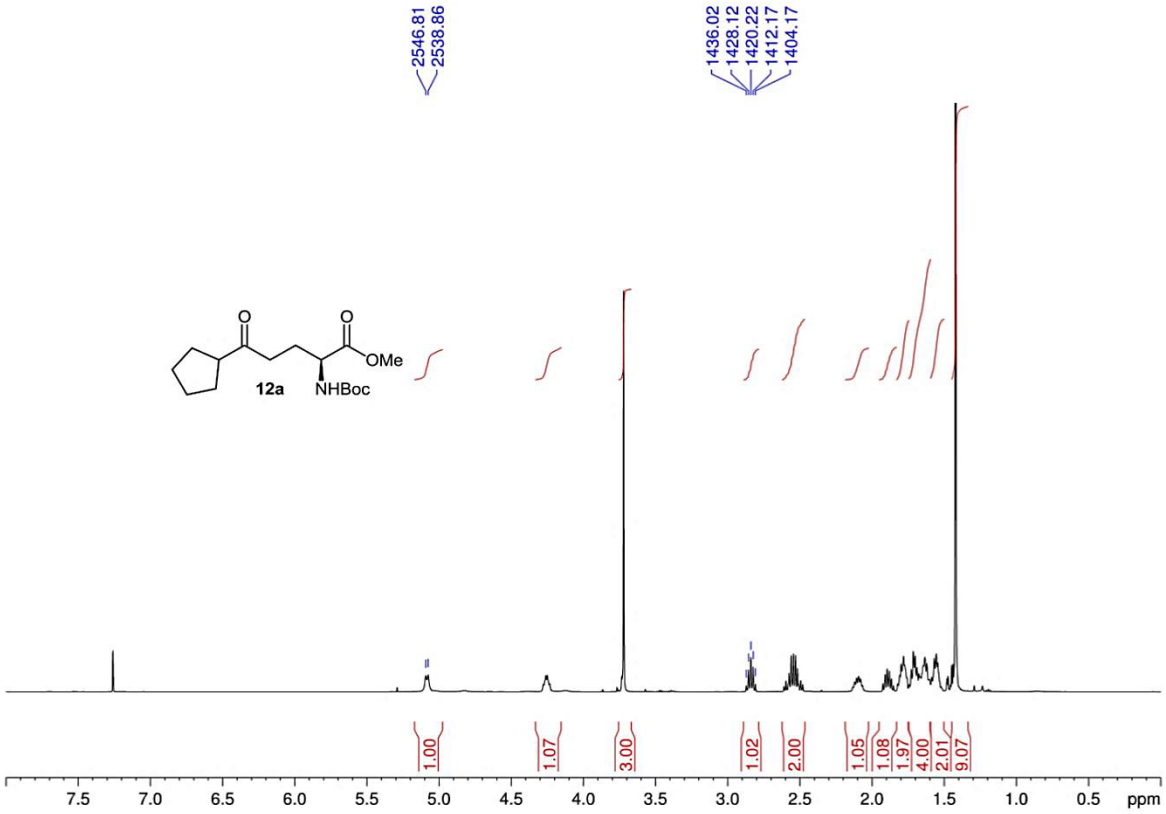

72.25
65.43
65.15
46.57
40.82
40.02
31.30
29.68
27.15
27.08
26.57
26.49
24.60
N
Me
NMe2
10b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

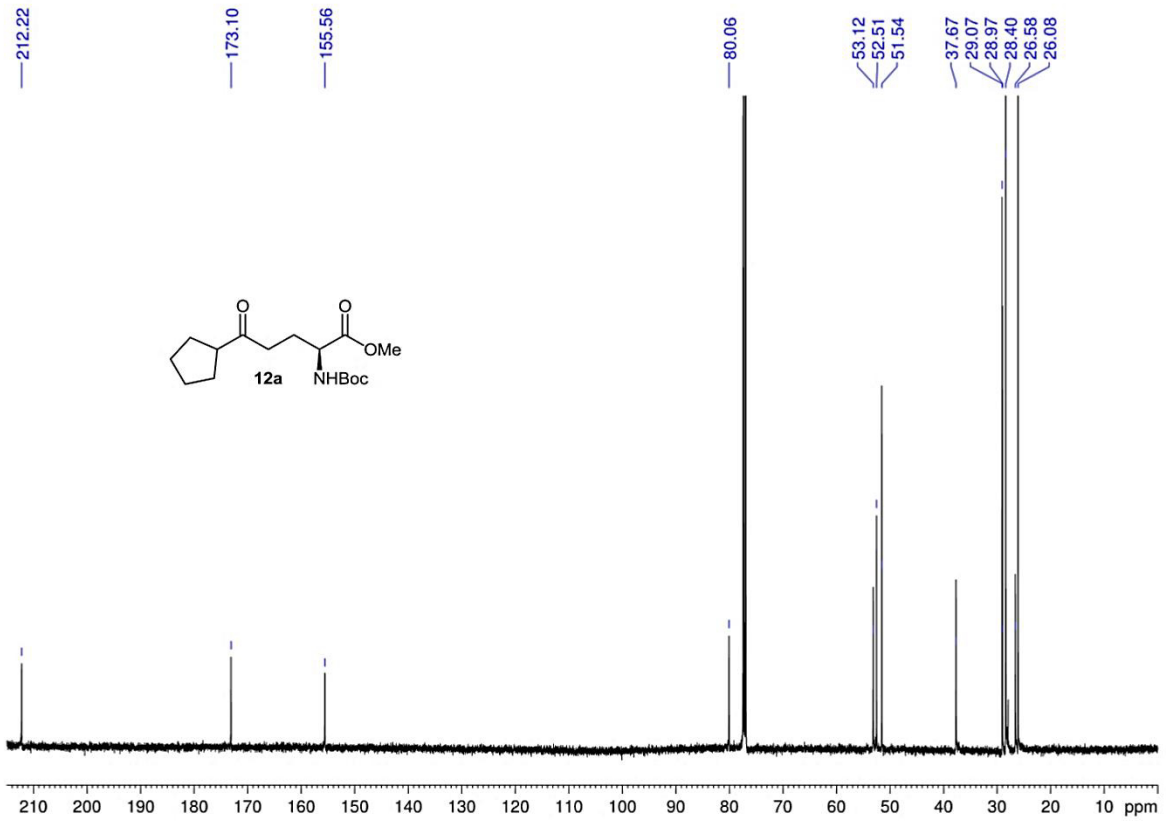
24


1591.66
1584.96
1582.51
1575.96
1309.04
1305.44
1297.34
1293.99
1238.57
1230.52
1226.97
1219.12
Me
N
Me
NMe2
Me
10c
2.00
0.98
1.00
2.03
1.01
5.94
6.07
3.03
2.10
2.02
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

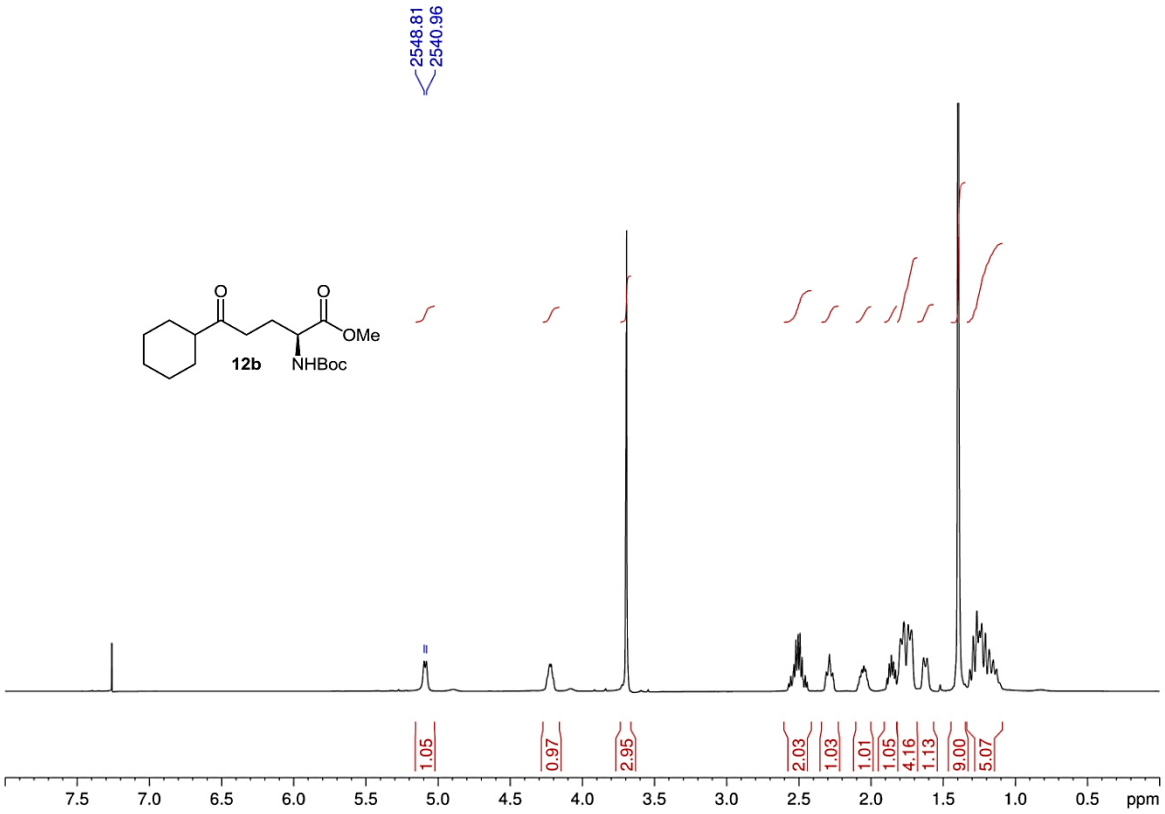

143.40
137.89
128.87
125.31
72.76
65.15
64.56
46.46
39.84
33.81
29.54
21.46
Me
N
Me
NMe2
Me
10c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

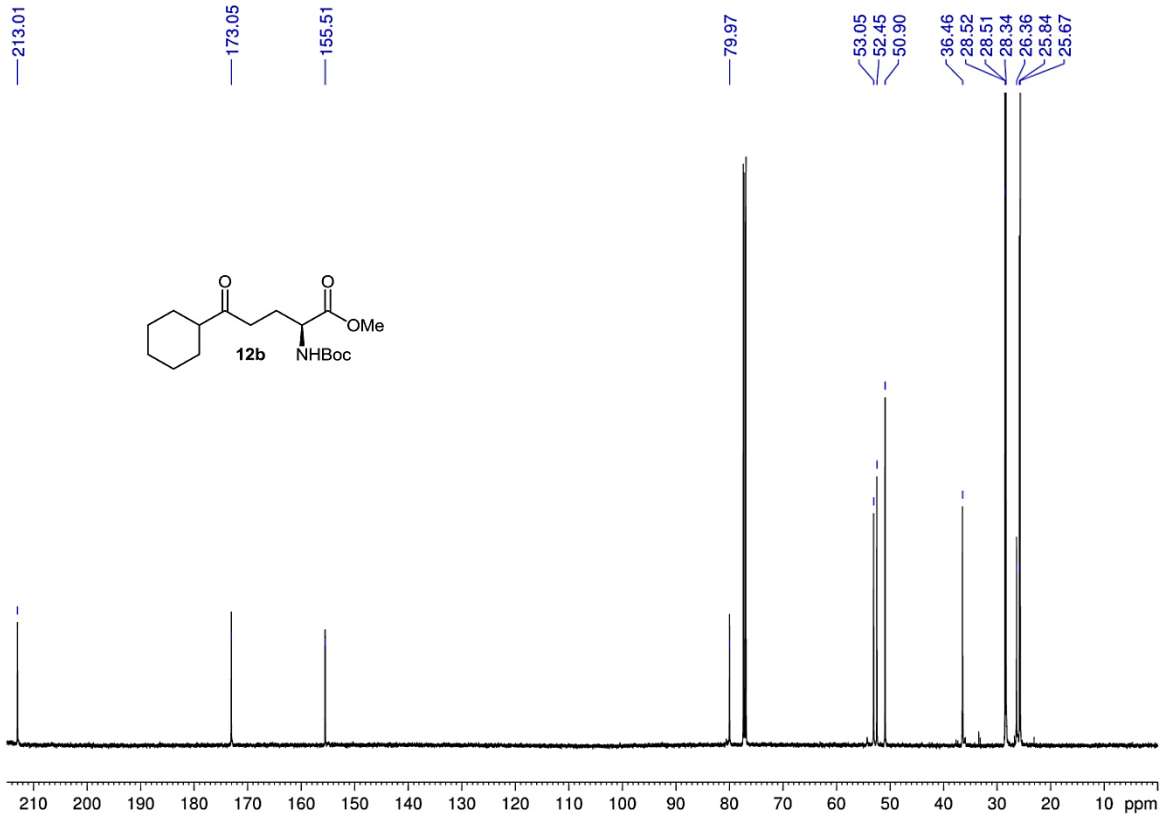
25

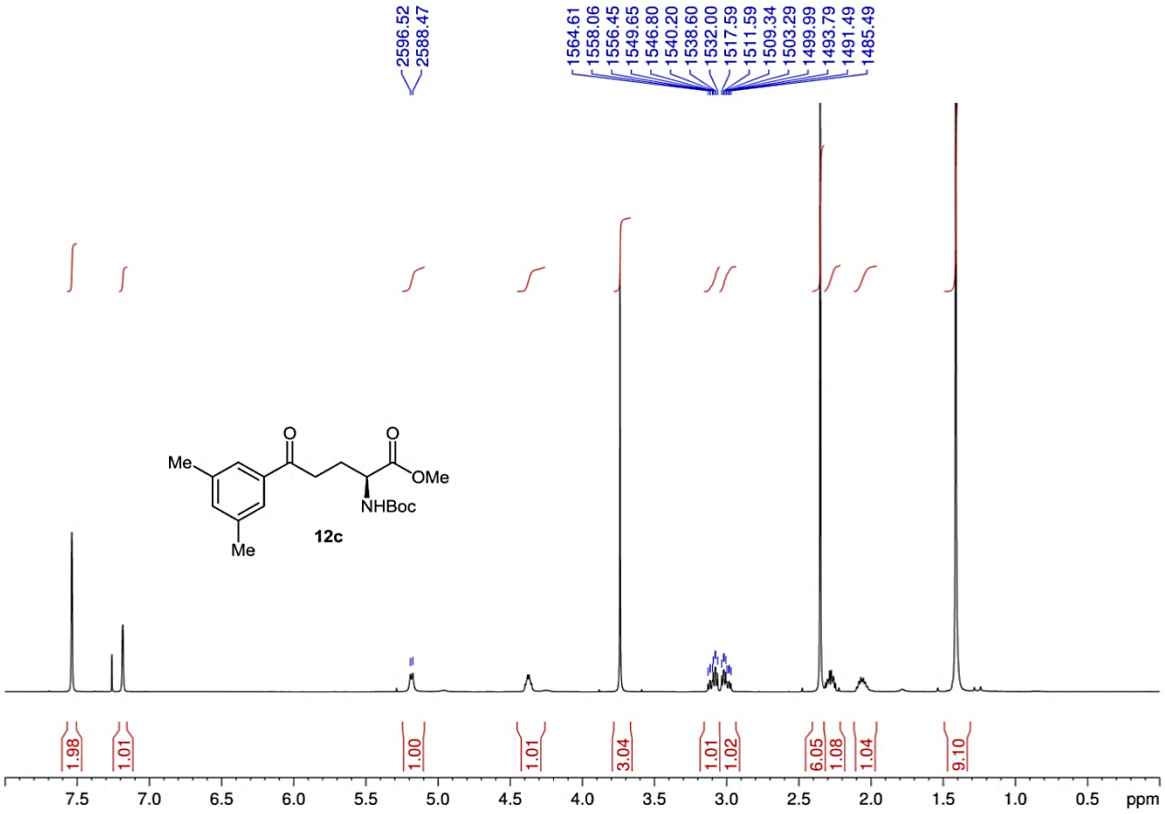

2546.81
2538.86
1436.02
1428.12
1420.22
1412.17
1404.17
O
O
OMe
12a
NHBoc
1.00
1.07
3.00
1.02
2.00
1.05
1.08
1.97
4.00
2.01
9.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

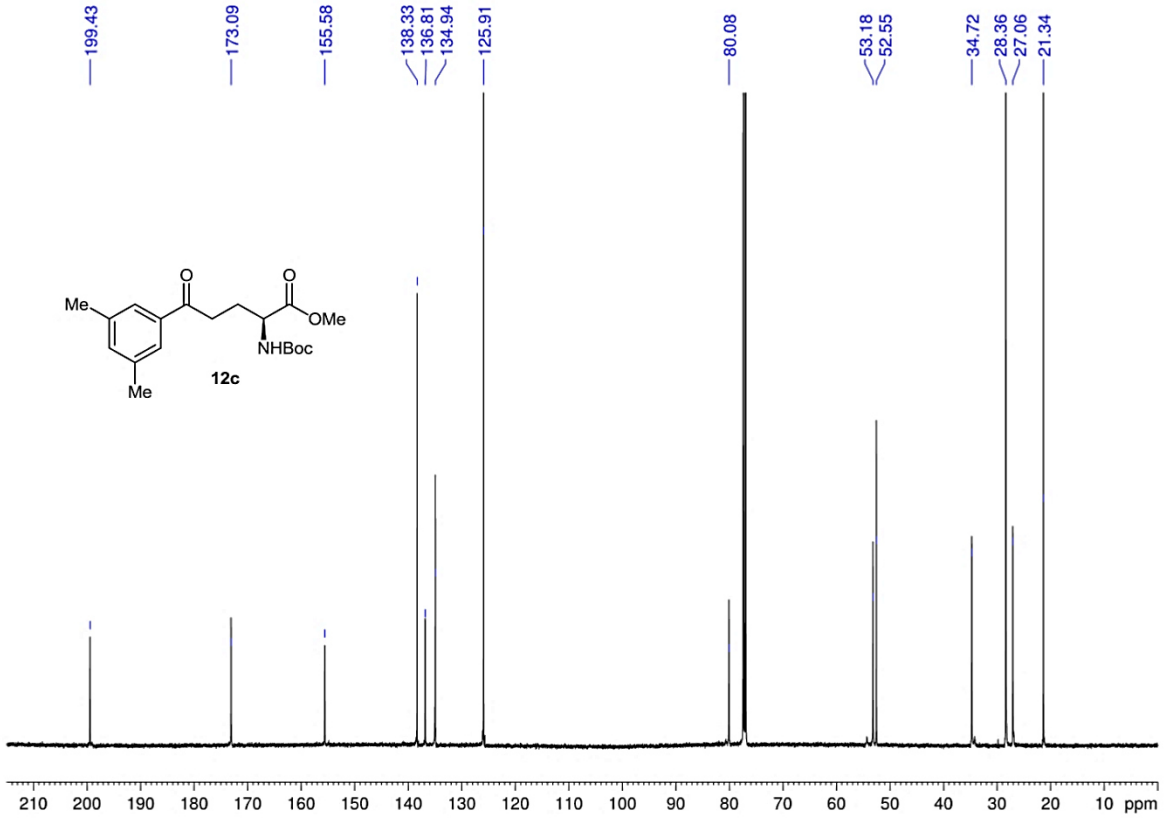

212.22
173.10
155.56
80.06
53.12
52.51
51.54
37.67
29.07
28.97
28.40
26.58
26.08
O
O
OMe
12a
NHBoc
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

26

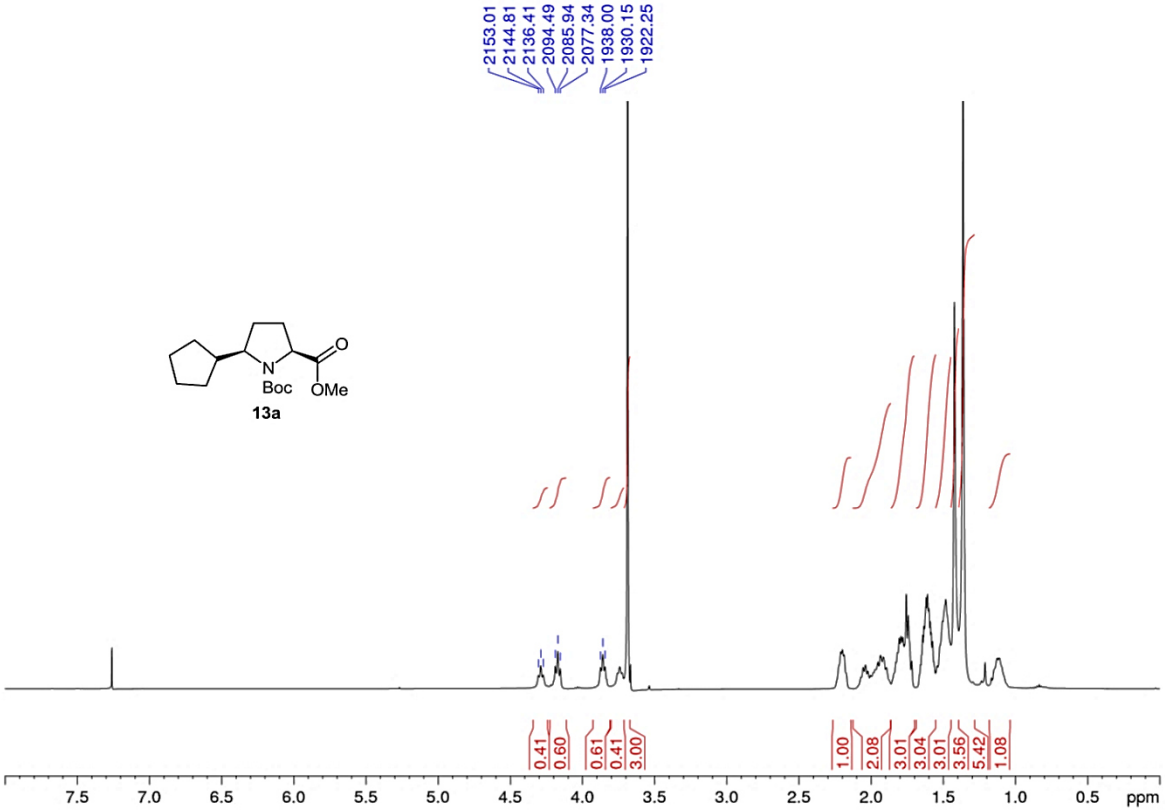

2548.81
2540.96
O
O
OMe
12b
NHBoc
1.05
0.97
2.95
2.03
1.03
1.01
1.05
4.16
1.13
9.00
5.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

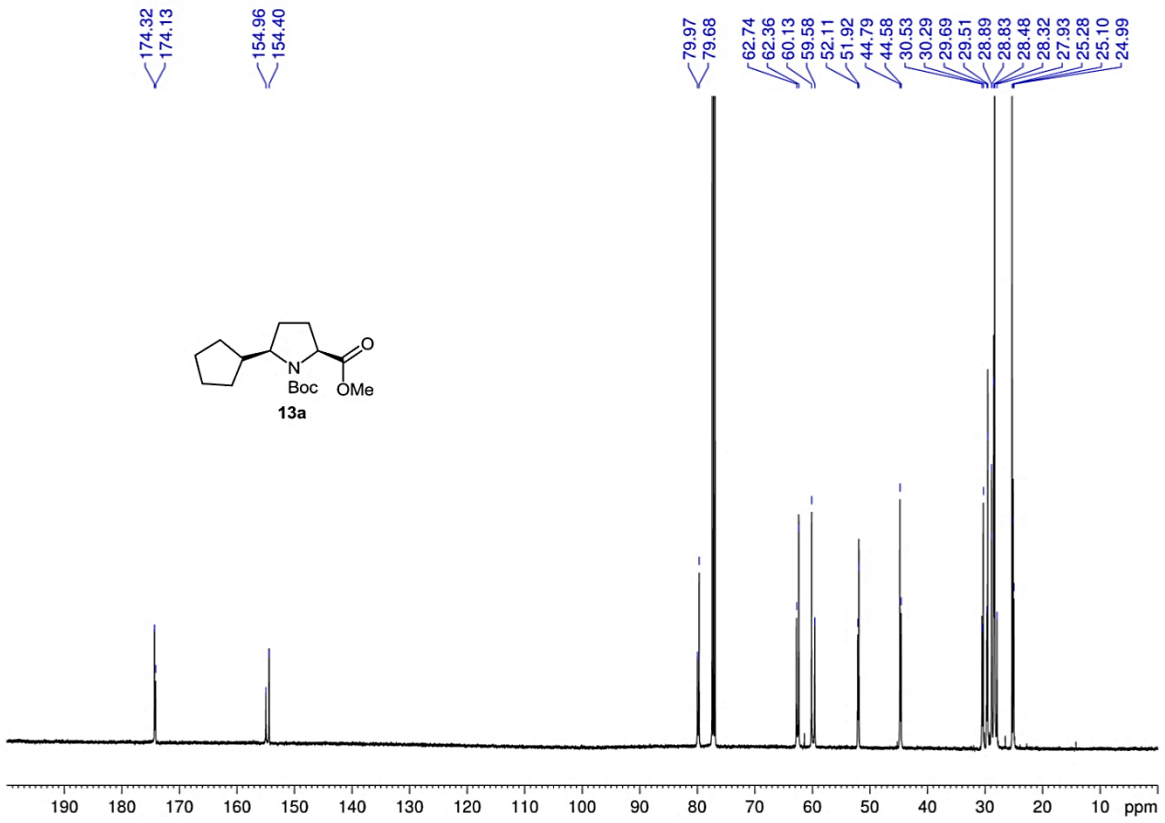

213.01
173.05
155.51
79.97
53.05
52.45
50.90
36.46
28.52
28.51
28.34
26.36
25.84
25.67
O
O
OMe
12b
NHBoc
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

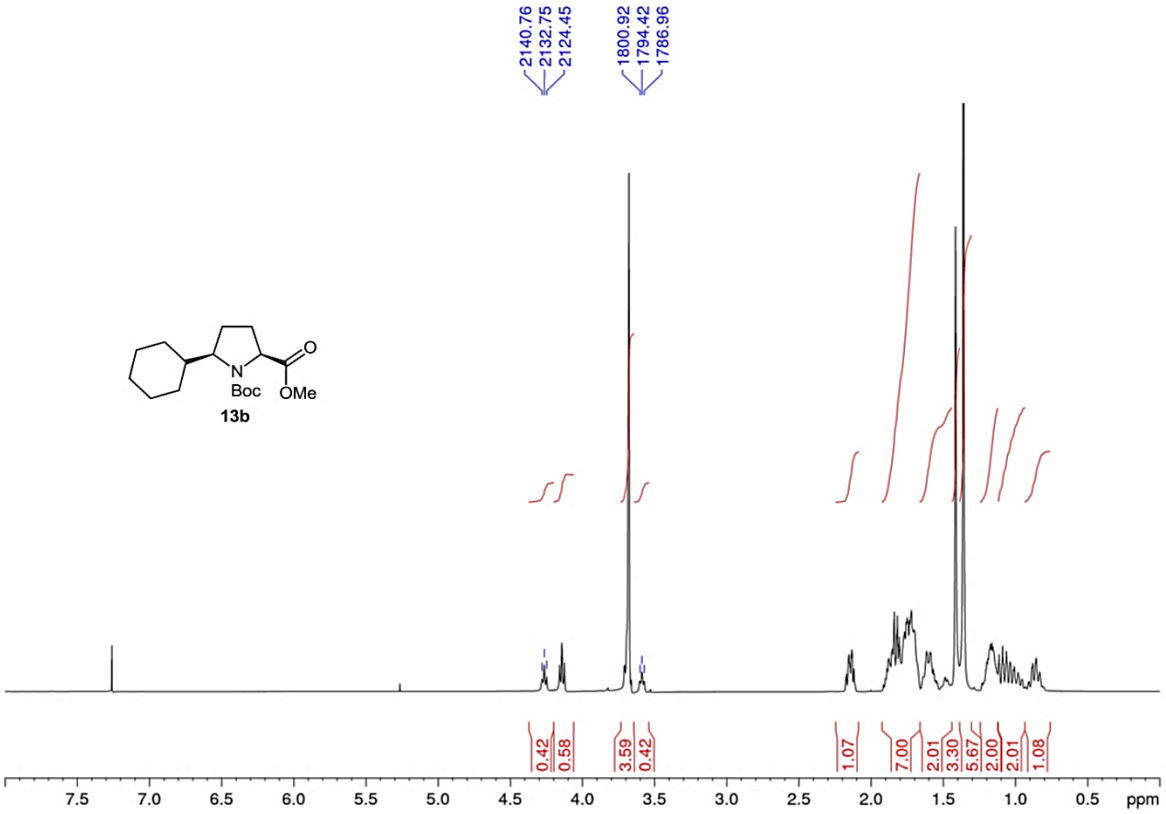

2596.52
2588.47
1564.61
1558.06
1556.45
1549.65
1546.80
1540.20
1538.60
1532.00
1517.59
1511.59
1509.34
1503.29
1499.99
1493.79
1491.49
1485.49
Me
O
O
OMe
NHBoc
Me
12c
1.98
1.01
1.00
1.01
3.04
1.01
1.02
6.05
1.08
1.04
9.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

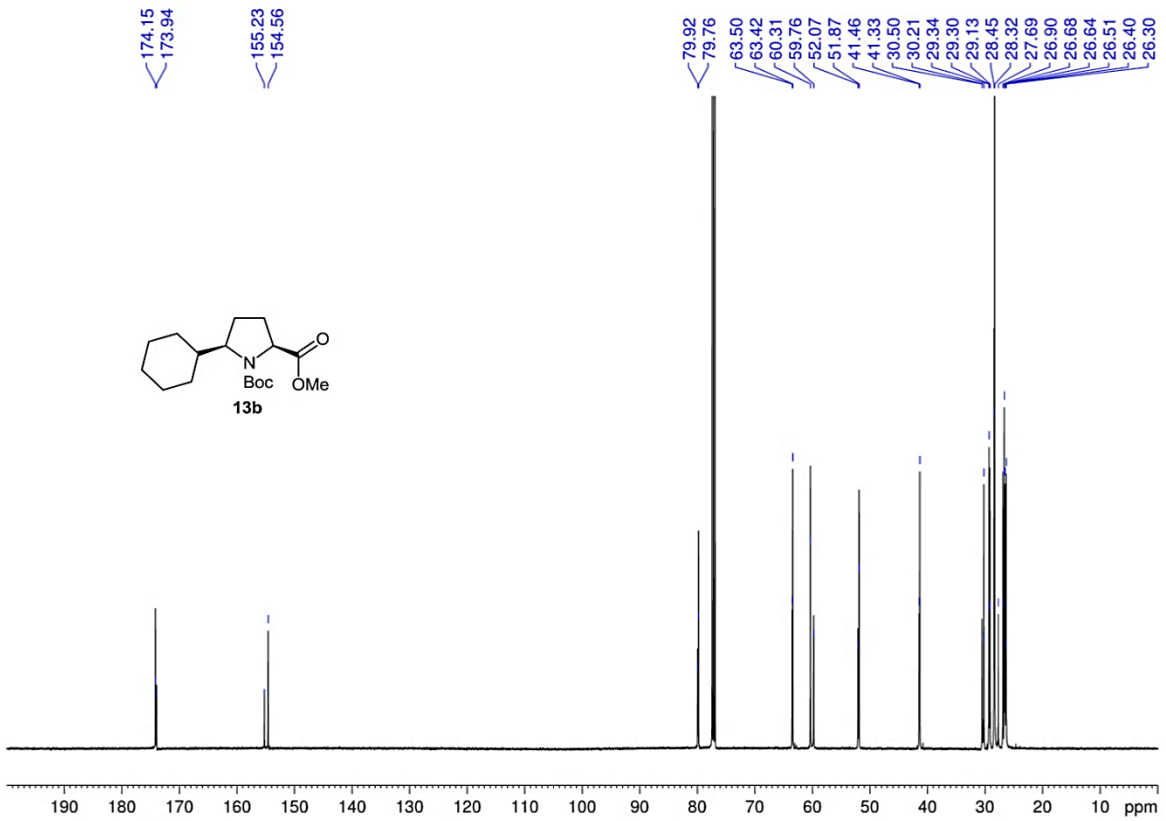

199.43
173.09
155.58
138.33
136.81
134.94
125.91
80.08
53.18
52.55
34.72
28.36
27.06
21.34
Me
O
O
OMe
NHBoc
Me
12c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

28

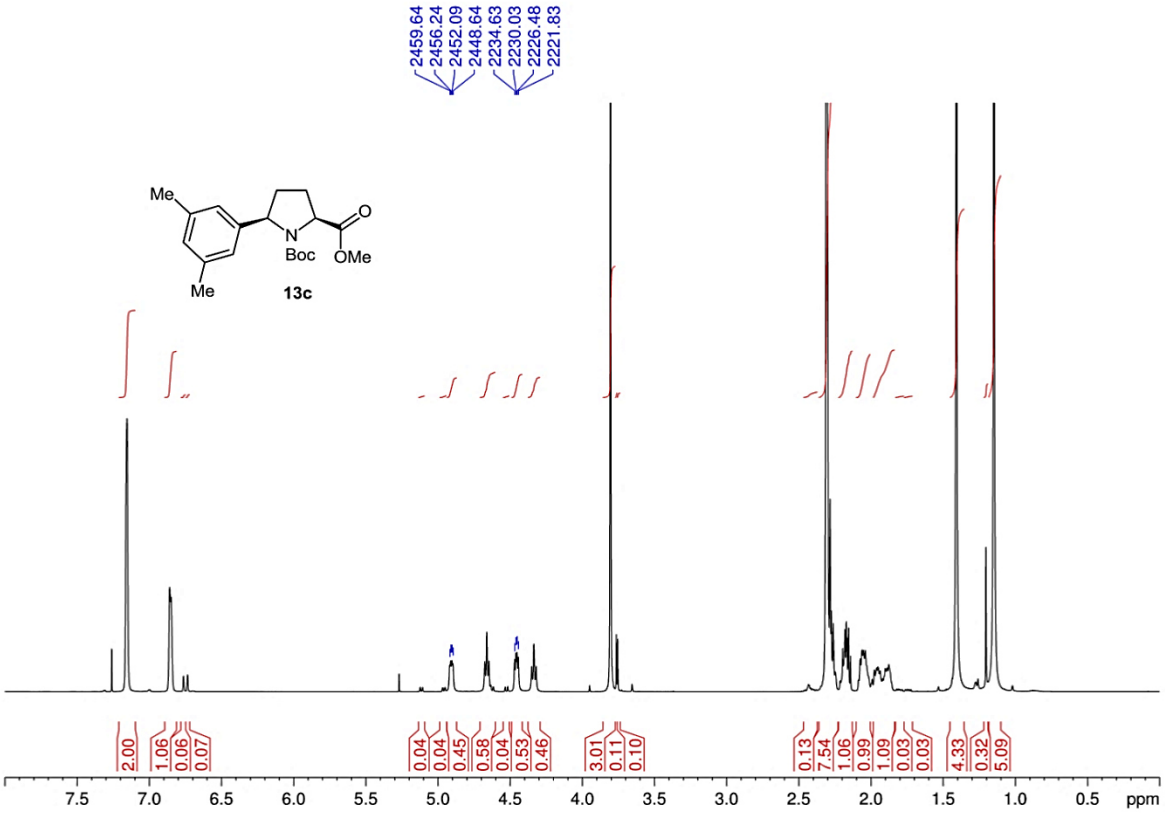

2153.01
2144.81
2136.41
2094.49
2085.94
2077.34
1938.00
1930.15
1922.25
Boc
OMe
13a
0.41
0.60
0.61
0.41
3.00
1.00
2.08
3.01
3.04
3.01
3.56
5.42
1.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

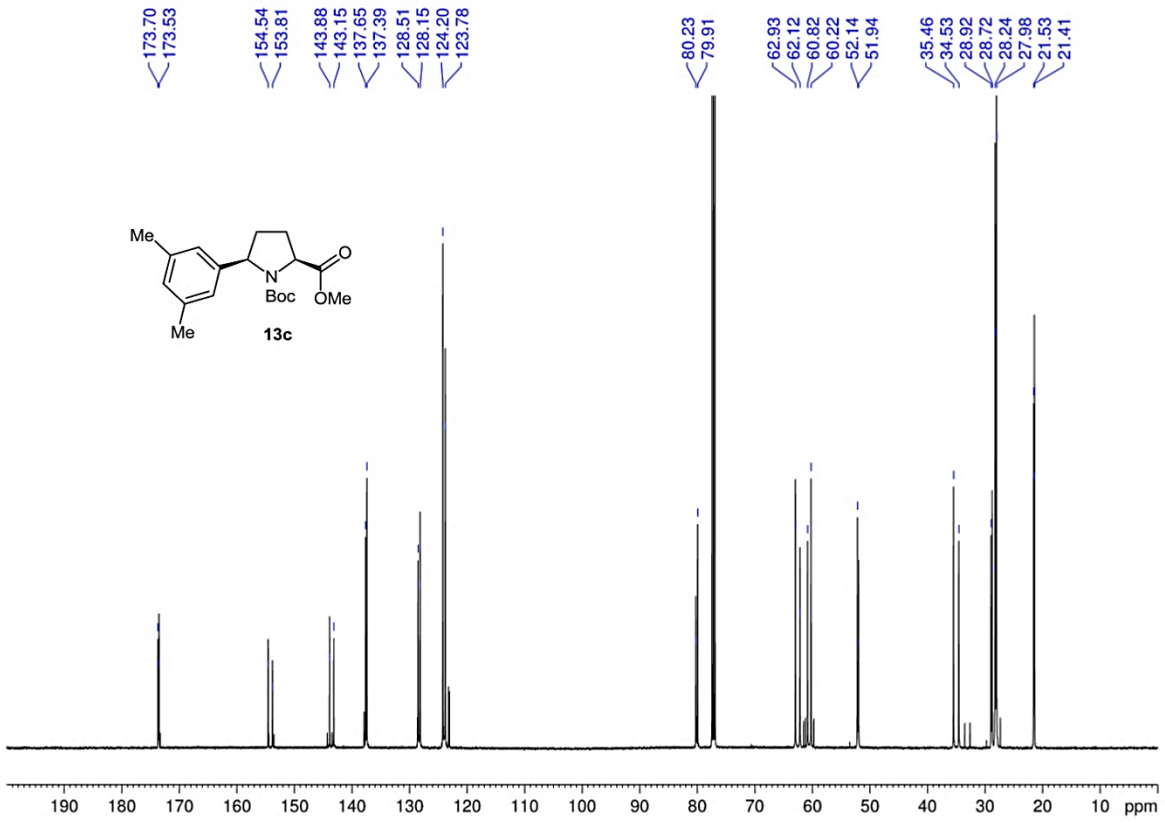

174.32
174.13
154.96
154.40
79.97
79.68
62.74
62.36
60.13
59.58
52.11
51.92
44.79
44.58
30.53
30.29
29.69
29.51
28.89
28.83
28.48
28.32
27.93
25.28
25.10
24.99
Boc
OMe
13a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

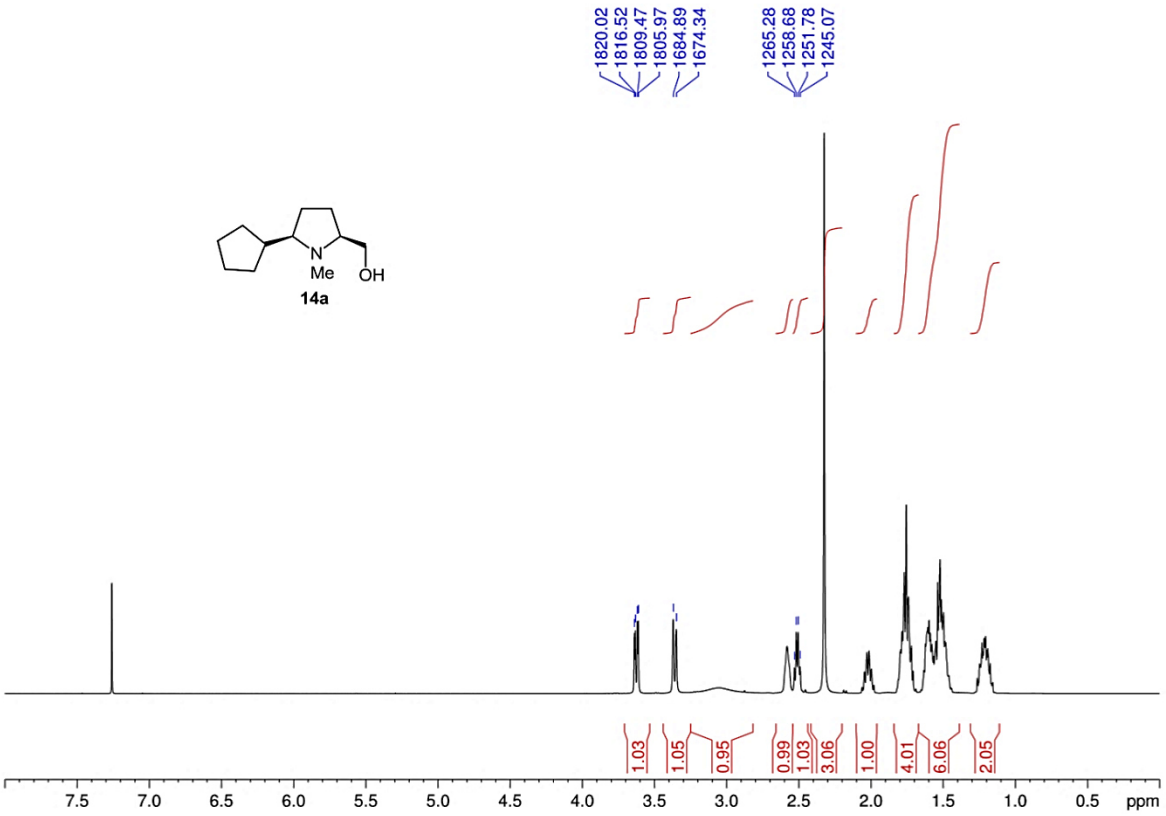

2140.76
2132.75
2124.45
1800.92
1794.42
1786.96
N
Boc
OMe
O
13b
0.42
0.58
3.59
0.42
1.07
7.00
2.01
3.30
5.67
2.00
2.01
1.08
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

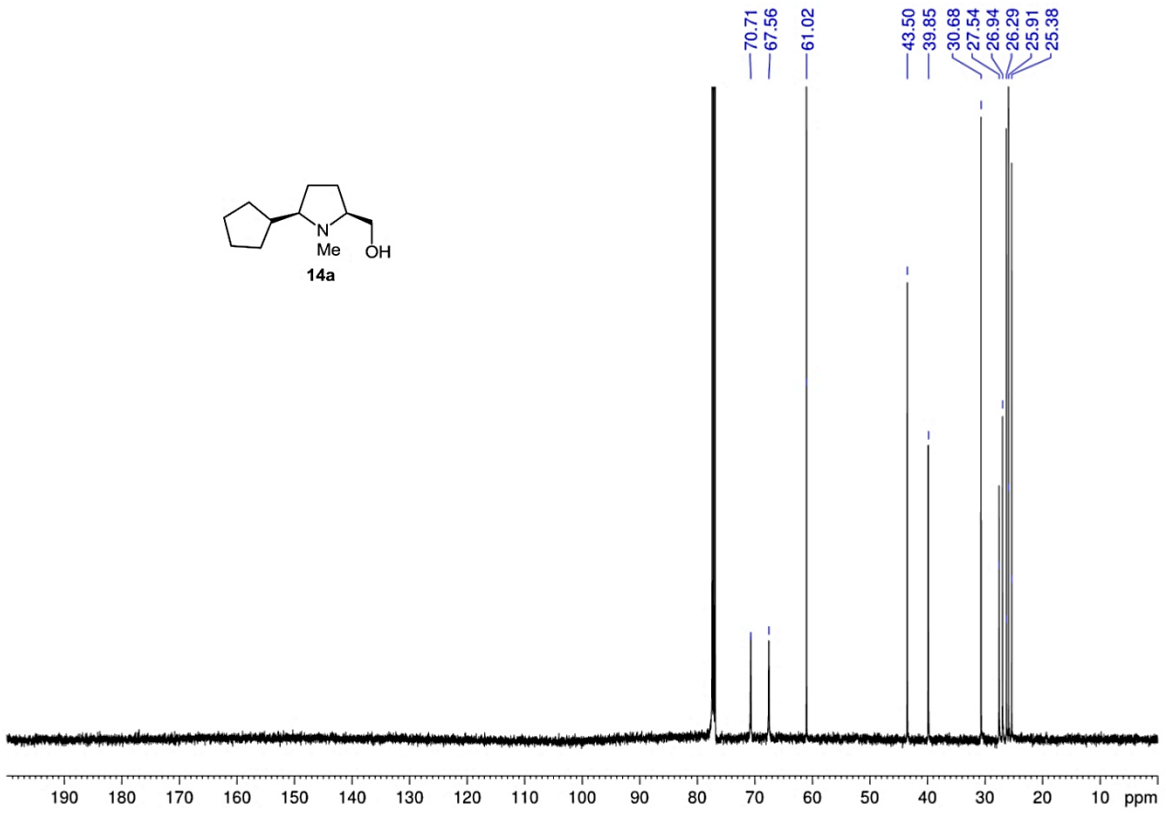

174.15
173.94
155.23
154.56
79.92
79.76
63.50
63.42
60.31
59.76
52.07
51.87
41.46
41.33
30.50
30.21
29.34
29.30
29.13
28.45
28.32
27.69
26.90
26.68
26.64
26.51
26.40
26.30
N
Boc
OMe
O
13b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

30

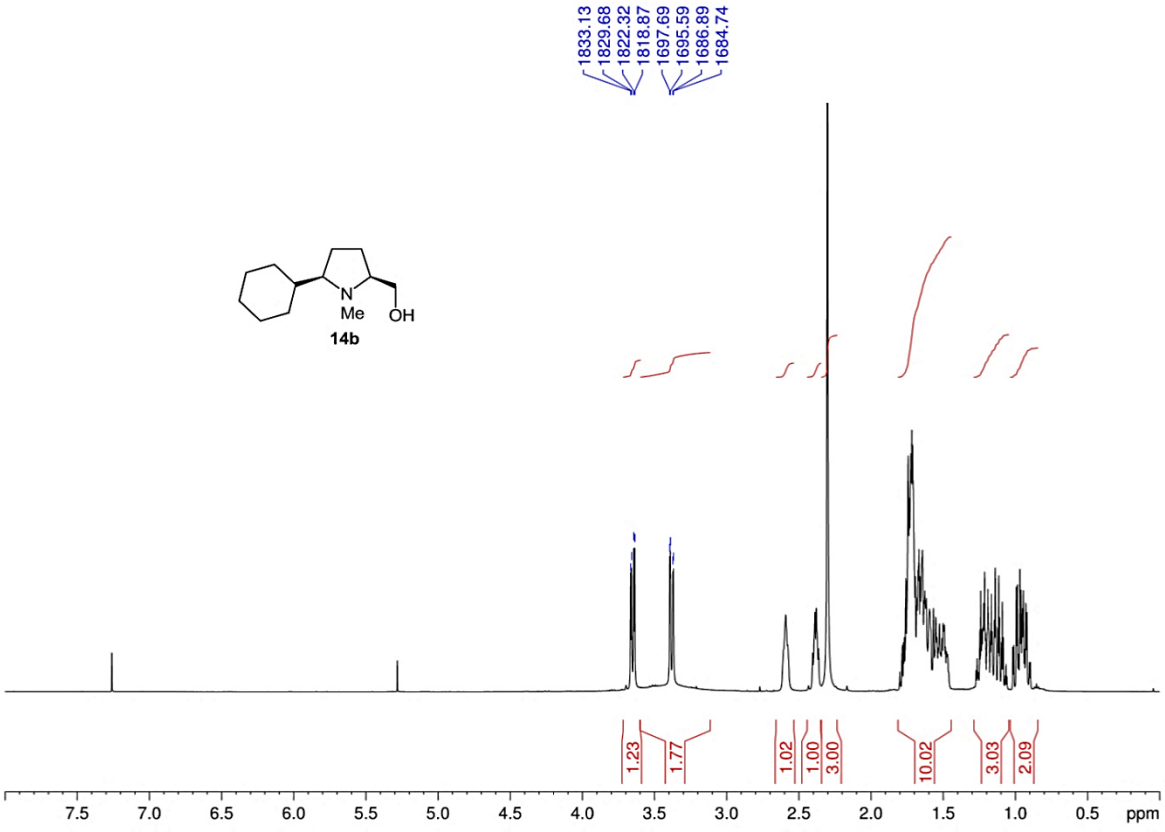

2459.64
2456.24
2452.09
2448.64
2234.63
2230.03
2226.48
2221.83
Me
N
Boc
OMe
O
Me
13c
2.00
1.06
0.06
0.07
0.04
0.04
0.45
0.58
0.04
0.53
0.46
3.01
0.11
0.10
0.13
7.54
1.06
0.99
1.09
0.03
0.03
4.33
0.32
5.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

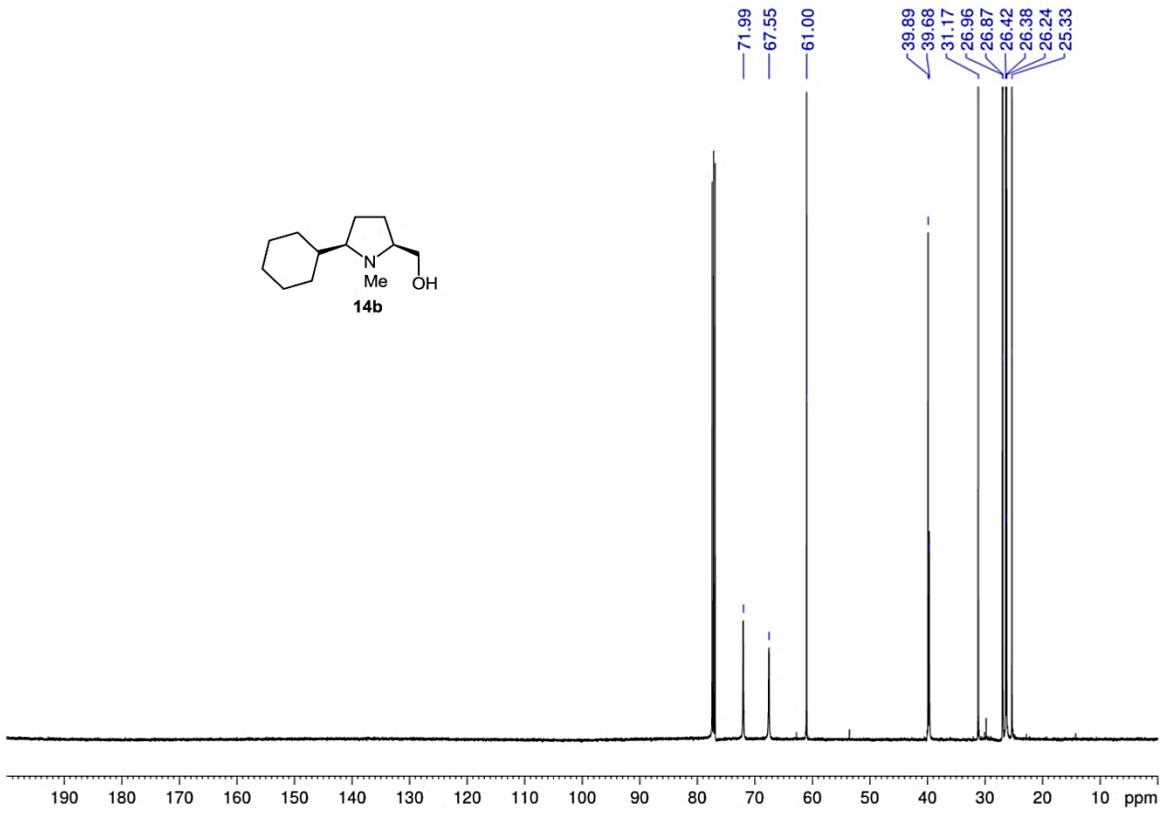

173.70
173.53
154.54
153.81
143.88
143.15
137.65
137.39
128.51
128.15
124.20
123.78
80.23
79.91
62.93
62.12
60.82
60.22
52.14
51.94
35.46
34.53
28.92
28.72
28.24
27.98
21.53
21.41
Me
N
Boc
OMe
O
Me
13c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

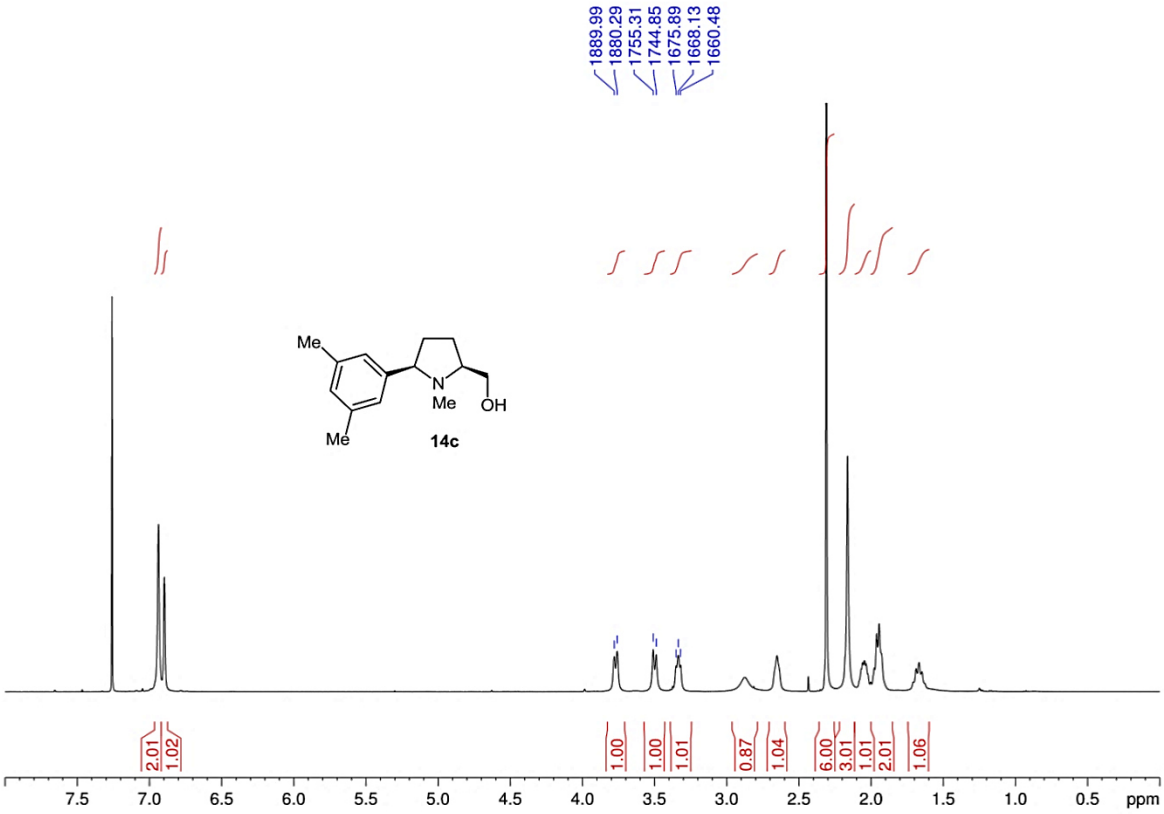

1820.02
1816.52
1809.47
1805.97
1684.89
1674.34
1265.28
1258.68
1251.78
1245.07
N
Me
OH
14a
1.03
1.05
0.95
0.99
1.03
3.06
1.00
4.01
6.06
2.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

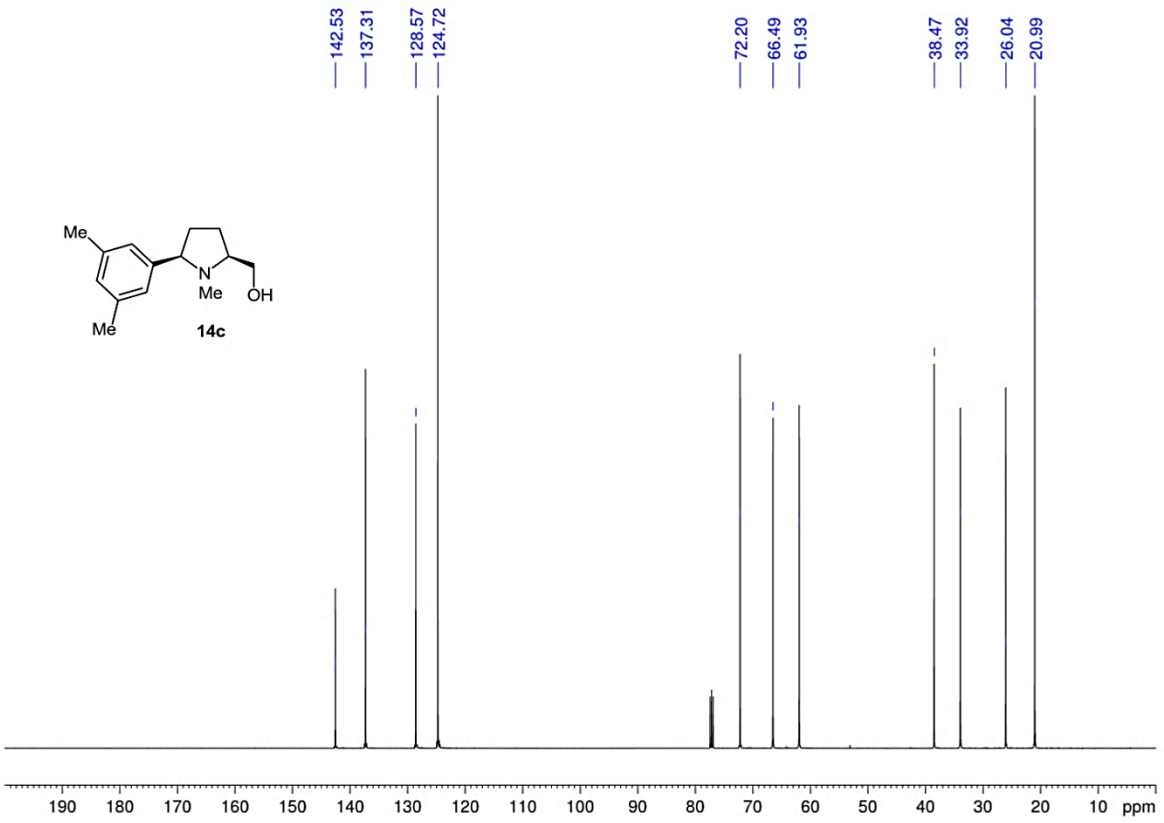

70.71
67.56
61.02
43.50
39.85
30.68
27.54
26.94
26.29
25.91
25.38
N
Me
OH
14a
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

32

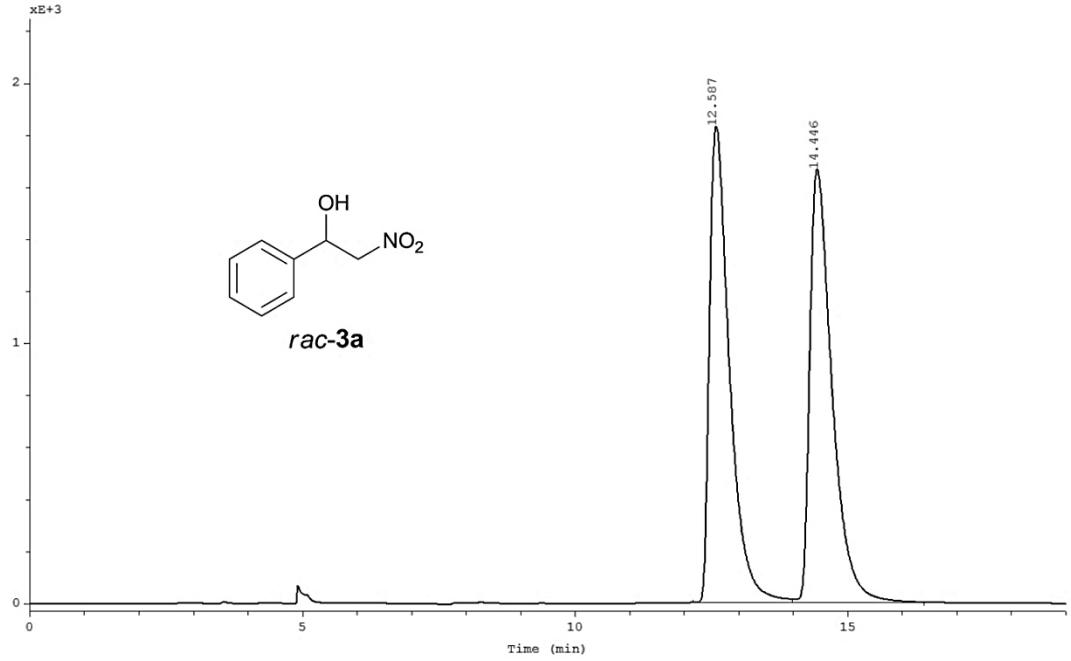

1833.13
1829.68
1822.32
1818.87
1697.69
1695.59
1686.89
1684.74
N
Me
OH
14b
1.23
1.77
1.02
1.00
3.00
10.02
3.03
2.09
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


71.99
67.55
61.00
39.89
39.68
31.17
26.96
26.87
26.42
26.38
26.24
25.33
N
Me
OH
14b
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

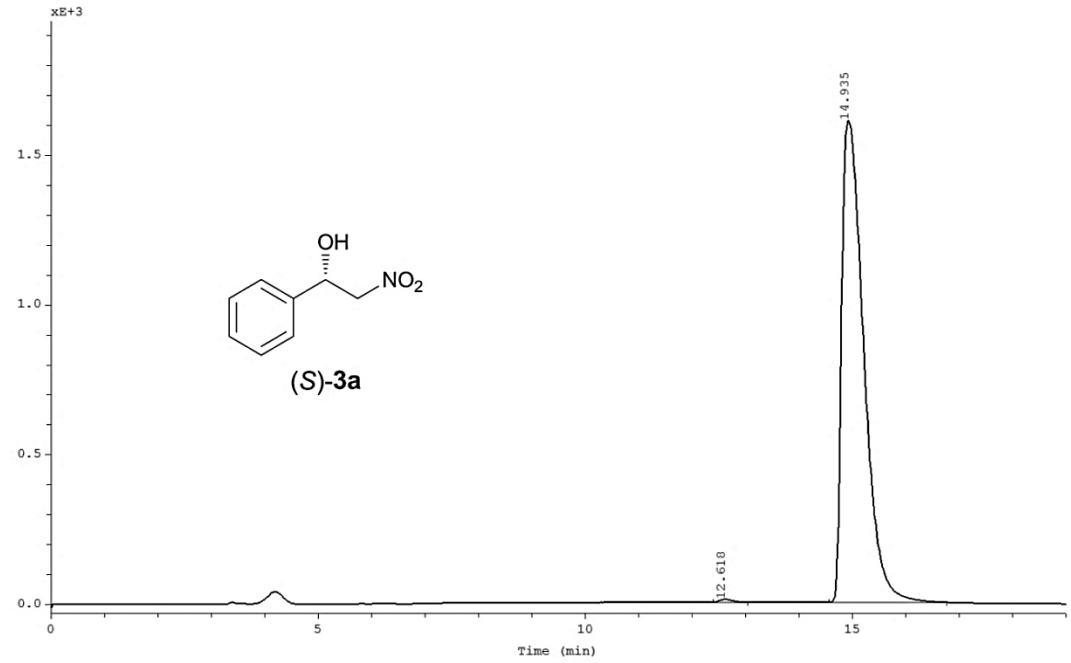

1889.99
1880.29
1755.31
1744.85
1675.89
1668.13
1660.48
Me
N
Me
OH
Me
14c
2.01
1.02
1.00
1.00
1.01
0.87
1.04
6.00
3.01
1.01
2.01
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


142.53
137.31
128.57
124.72
72.20
66.49
61.93
38.47
33.92
26.04
20.99
Me
N
Me
OH
Me
14c
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

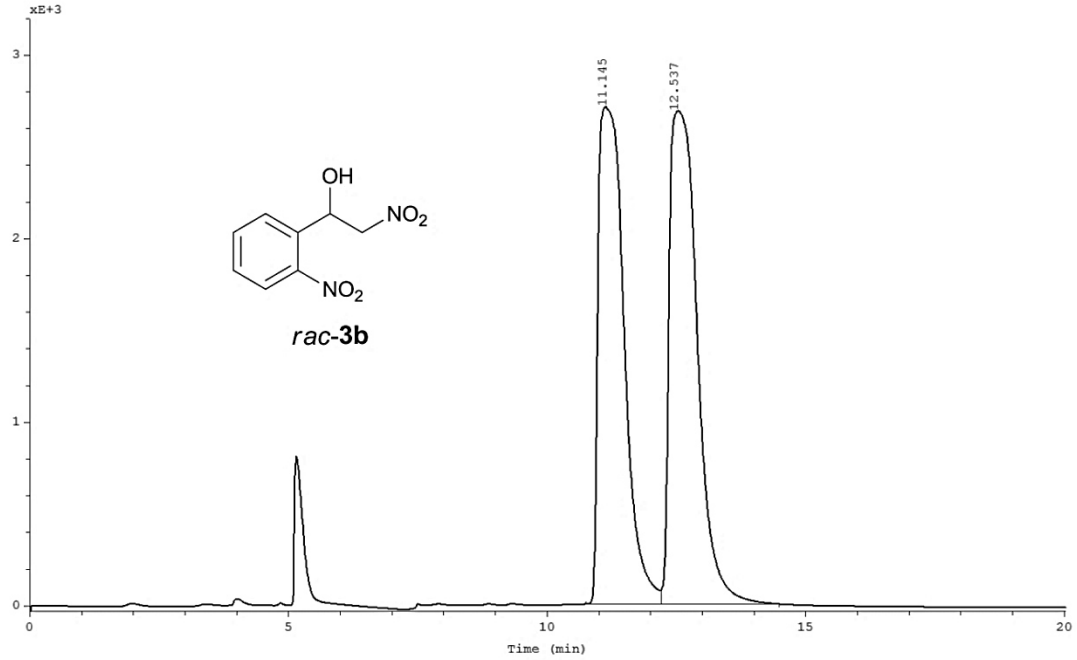
5. Copies of HPLC Spectra



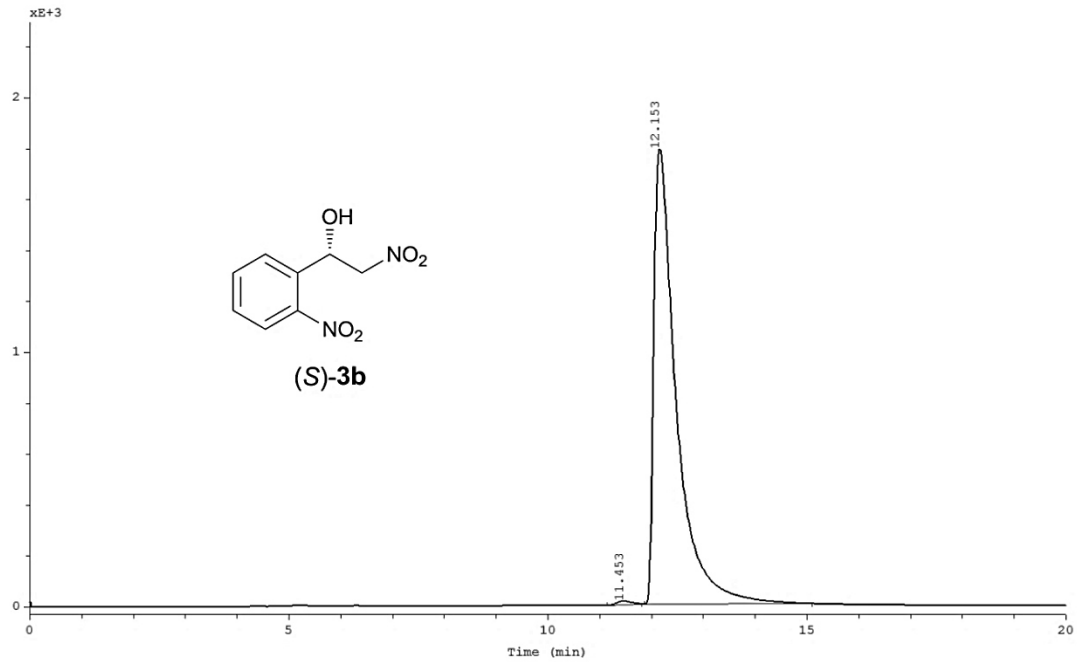
	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.59	1831.20	780.62	52.38	49.81
2	14.45	1665.09	786.54	47.62	50.19



	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	12.62	10.32	2.86	0.64	0.37
2	14.93	1609.83	767.79	99.36	99.63

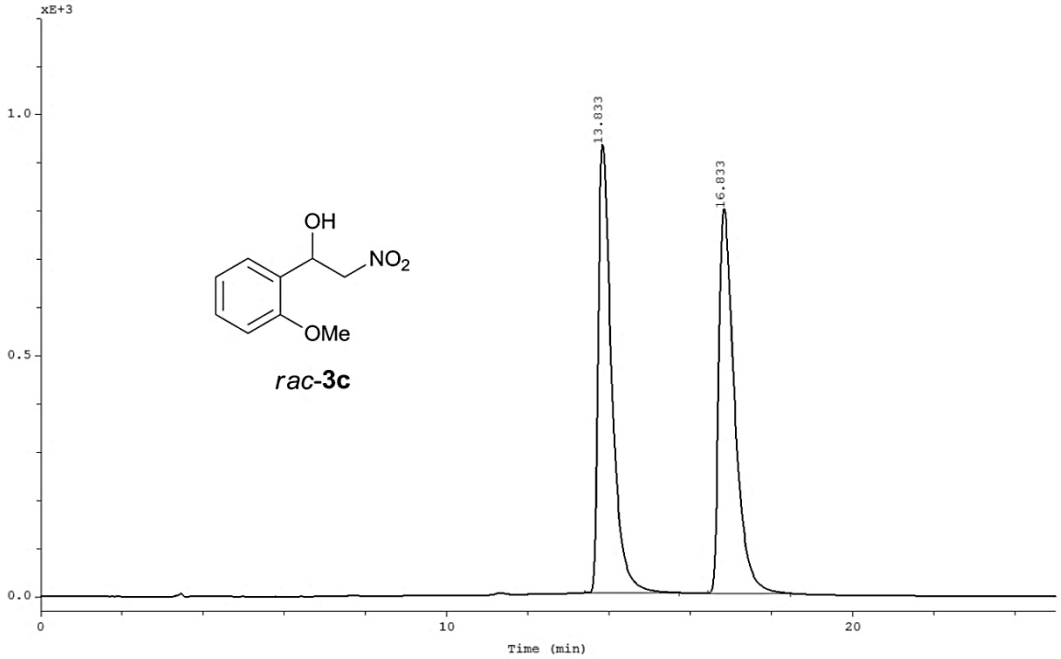


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.14	2710.17	1575.84	50.22	48.33
2	12.54	2686.59	1684.53	49.78	51.67

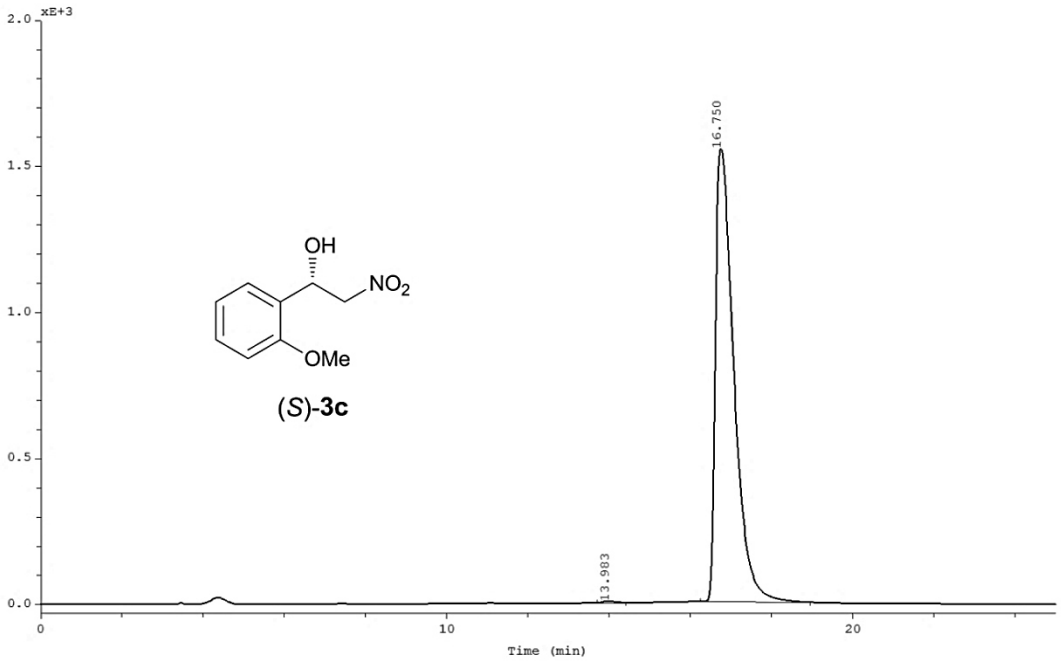


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	11.45	13.83	4.51	0.77	0.50
2	12.15	1785.65	897.70	99.23	99.50

36

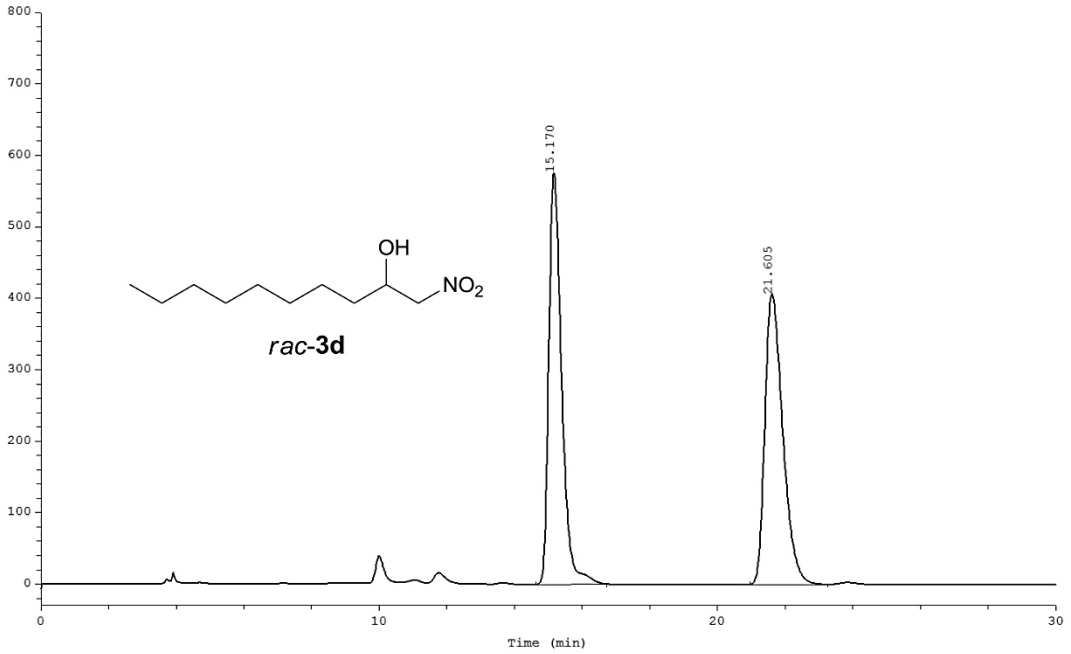


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.83	930.88	359.90	53.83	49.96
2	16.83	798.32	360.49	46.17	50.04

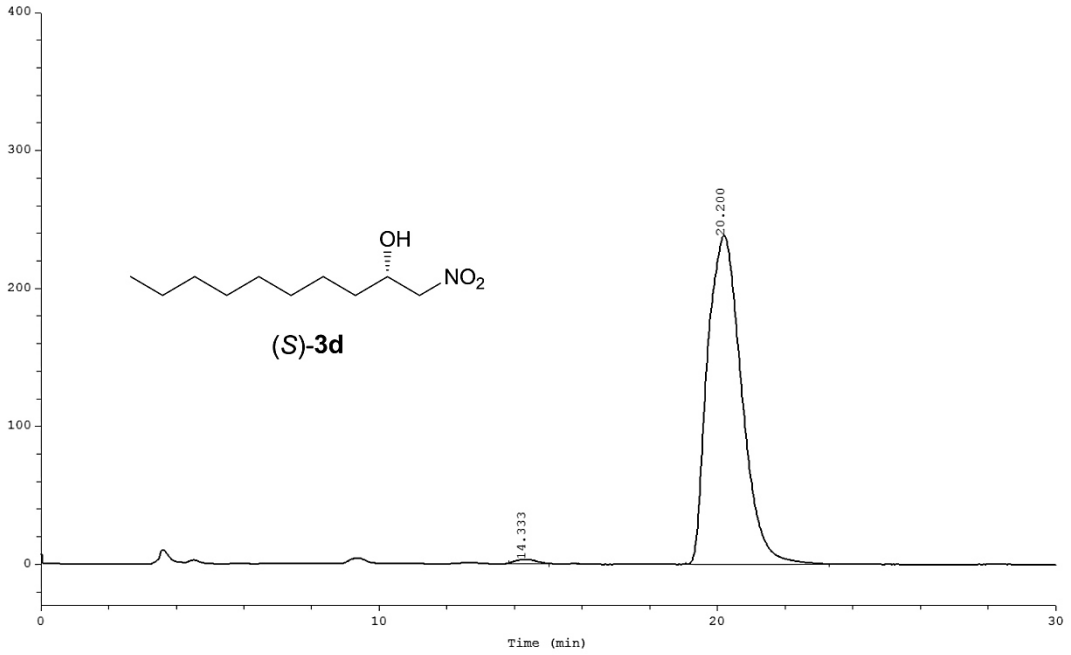


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.98	6.16	1.98	0.40	0.24
2	16.75	1551.47	812.47	99.60	99.76

37

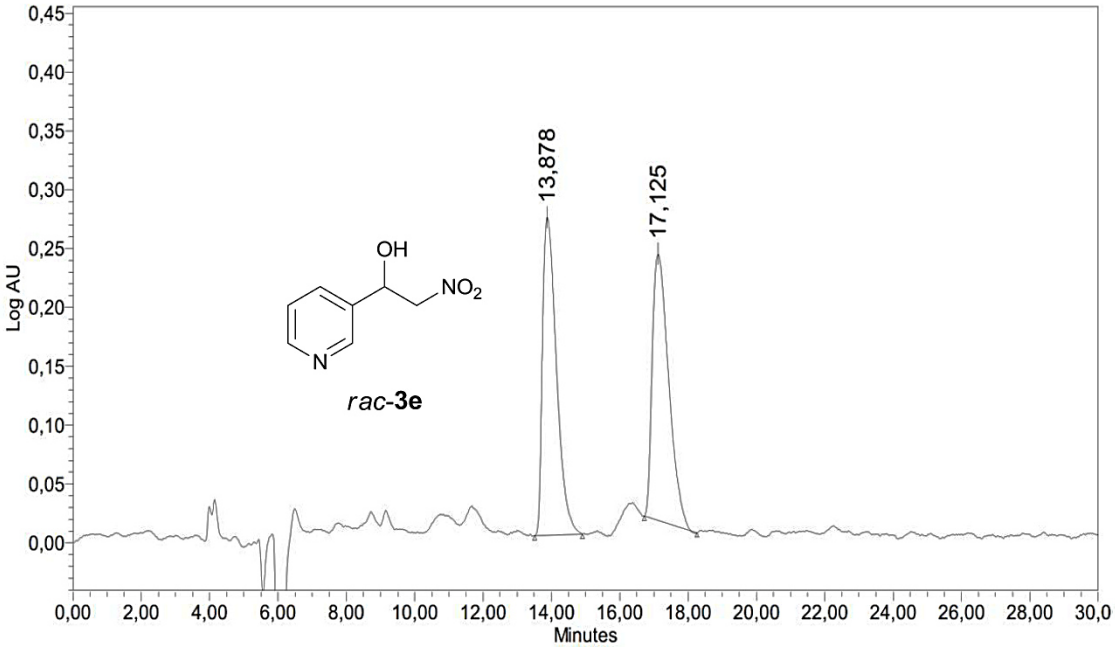


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.17	575.42	253.40	58.61	50.30
2	21.61	406.28	250.38	41.39	49.70

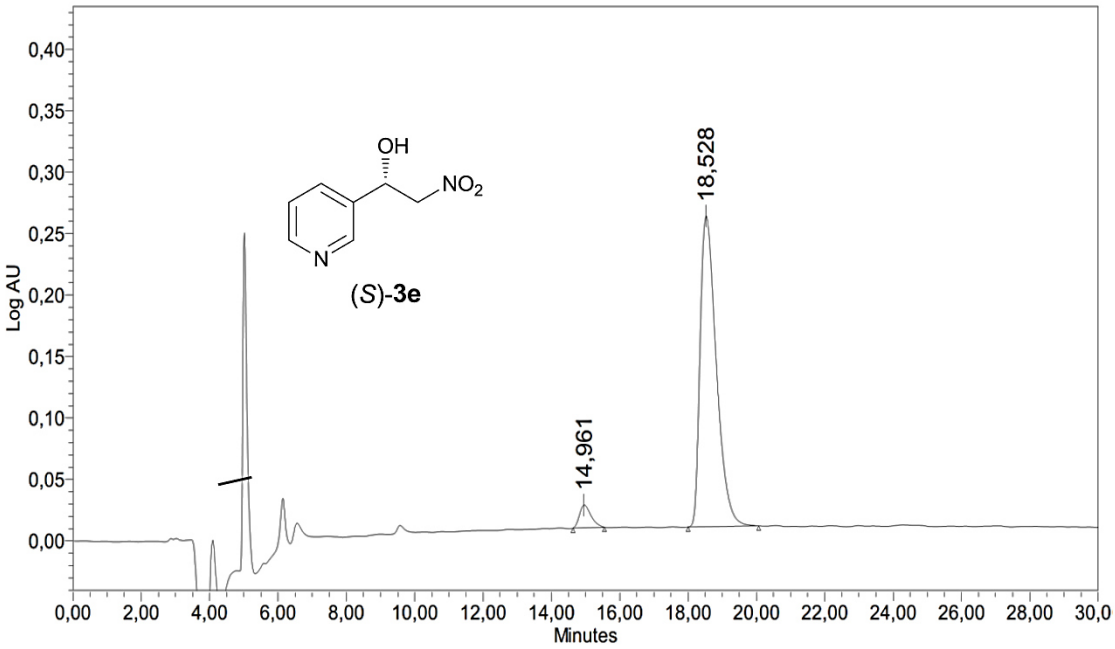


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	14.33	2.80	1.96	1.16	0.70
2	20.20	238.45	278.10	98.84	99.30

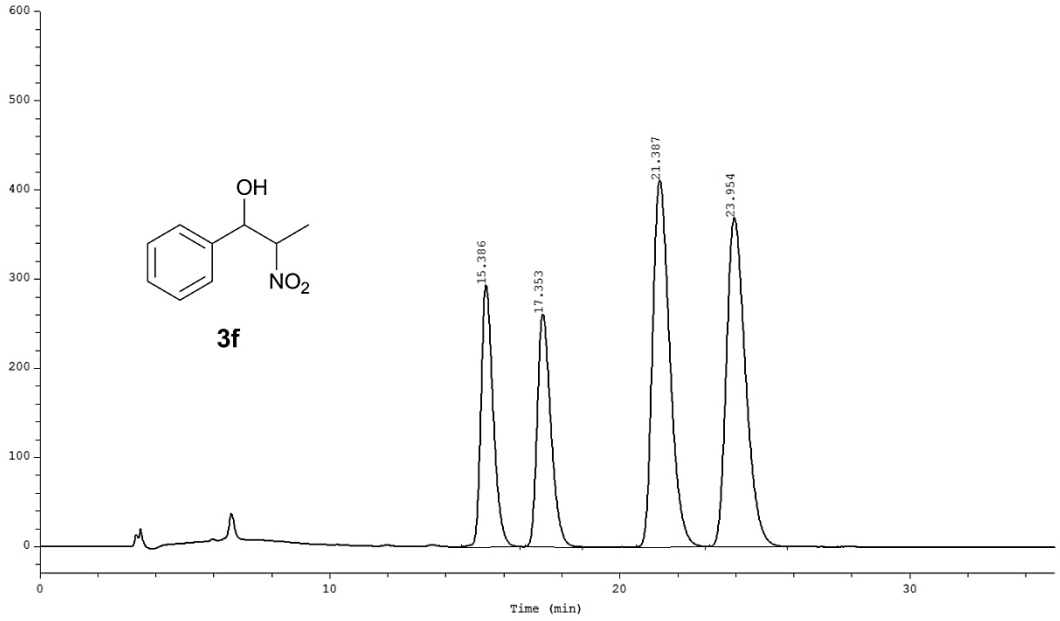
38



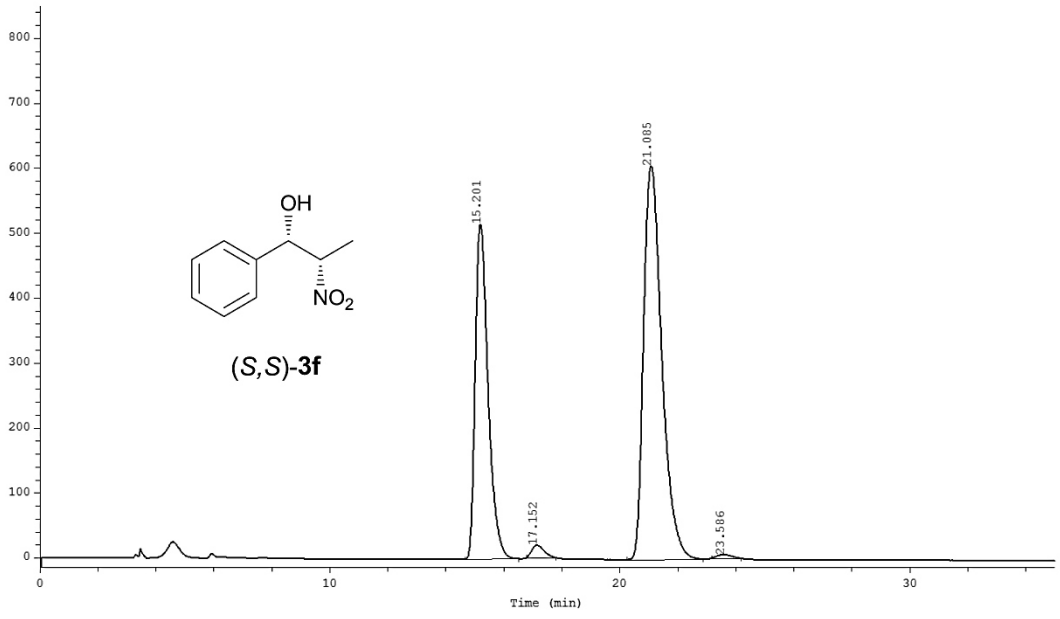
	Ret.time [min]	% Hight	% Area
1	13.88	54.39	50.27
2	17.13	45.61	49.73



	Ret.time [min]	% Hight	% Area
1	14.96	6.83	4.94
2	18.53	93.17	95.06



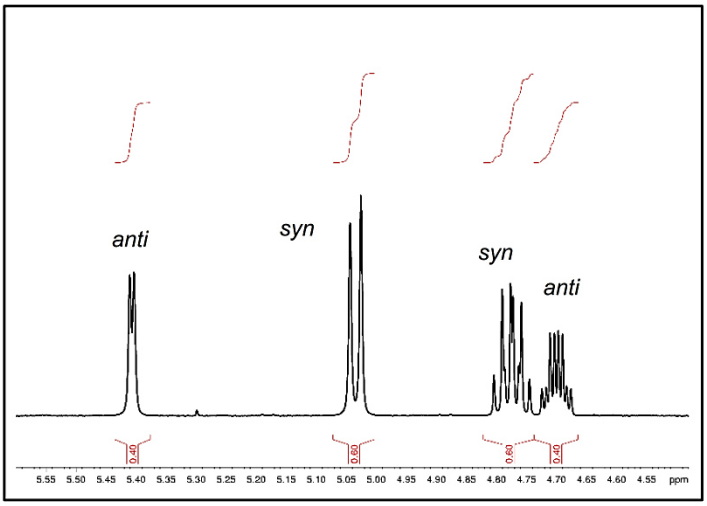
	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.39	293.77	143.47	22.00	16.87
2	17.35	261.40	142.60	19.58	16.77
3	21.39	410.97	281.80	30.78	33.14
4	23.95	369.08	282.38	27.64	33.21

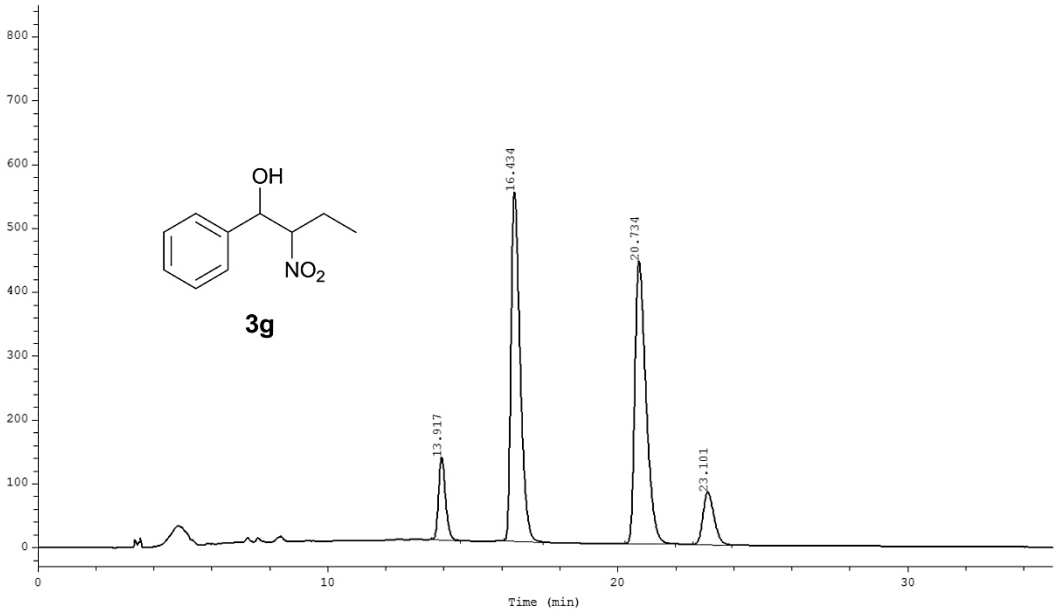


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.20	515.67	266.24	44.97	36.97
2	17.15	19.20	9.53	1.67	1.32
3	21.09	606.17	441.13	52.86	61.25
4	23.59	5.77	3.34	0.50	0.46

40

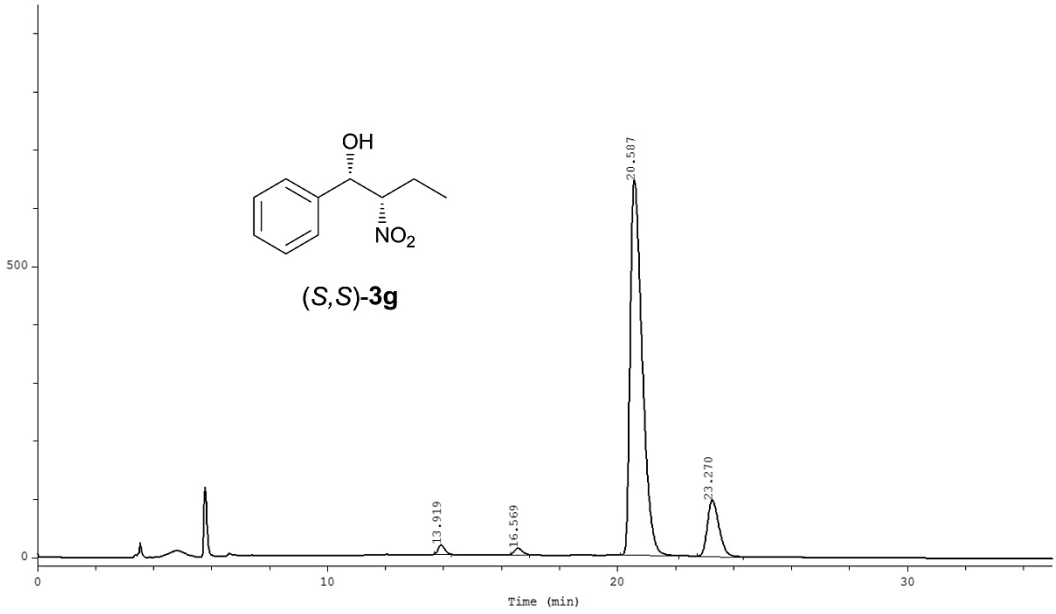
The diastereomeric ratio of **3f** was determined by ^{1}H NMR:





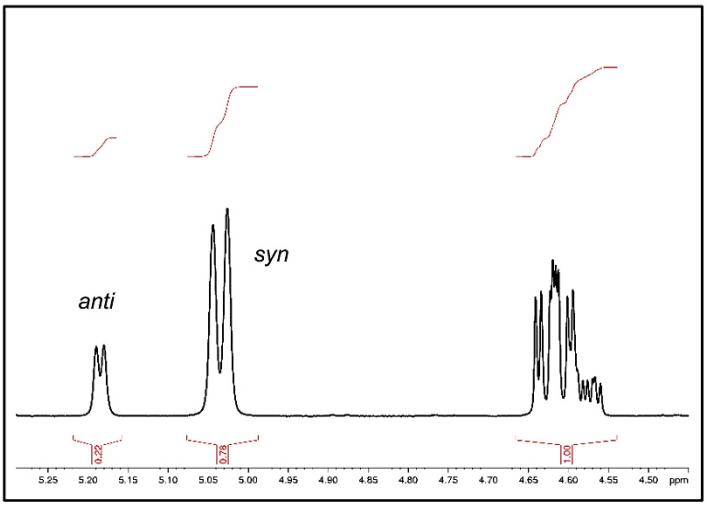
	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	15.39	293.77	143.47	22.00	16.87
2	17.35	261.40	142.60	19.58	16.77
3	21.39	410.97	281.80	30.78	33.14
4	23.95	369.08	282.38	27.64	33.21

41

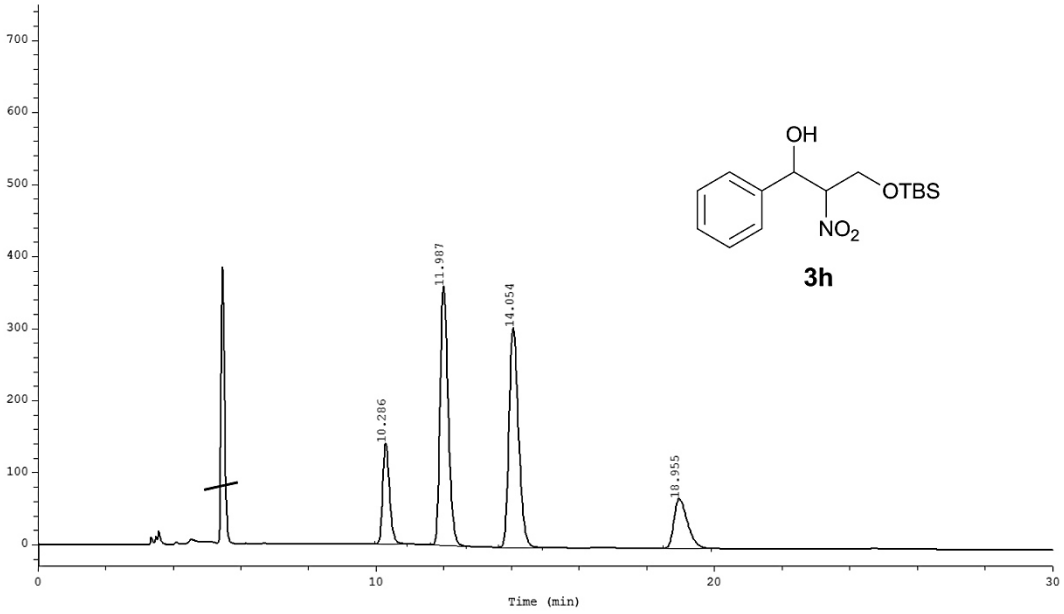


	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	13.92	15.84	4.25	2.06	1.17
2	16.57	10.99	3.48	1.43	0.96
3	20.59	644.44	309.06	83.91	85.44
4	23.27	96.77	44.95	12.60	12.43

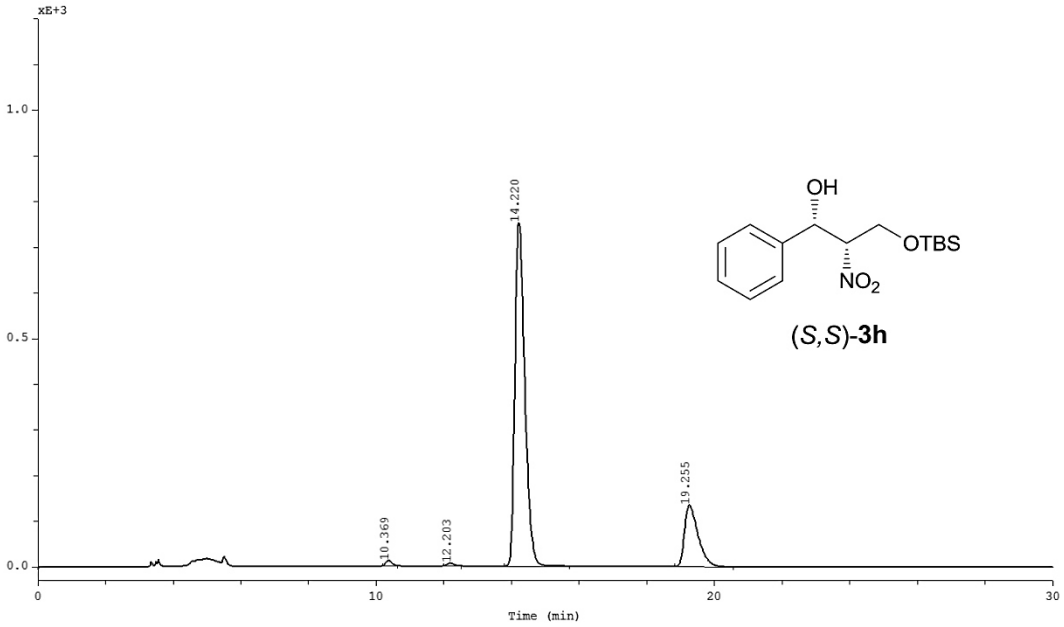
The diastereomeric ratio of **3g** was determined by ^{1}H NMR:



42

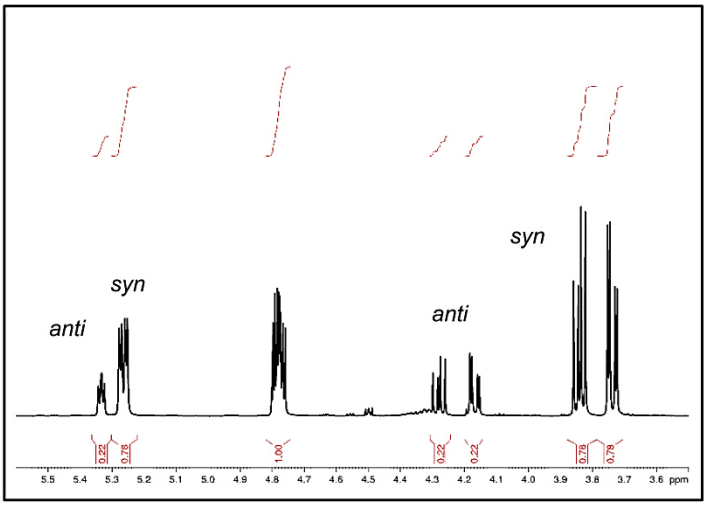


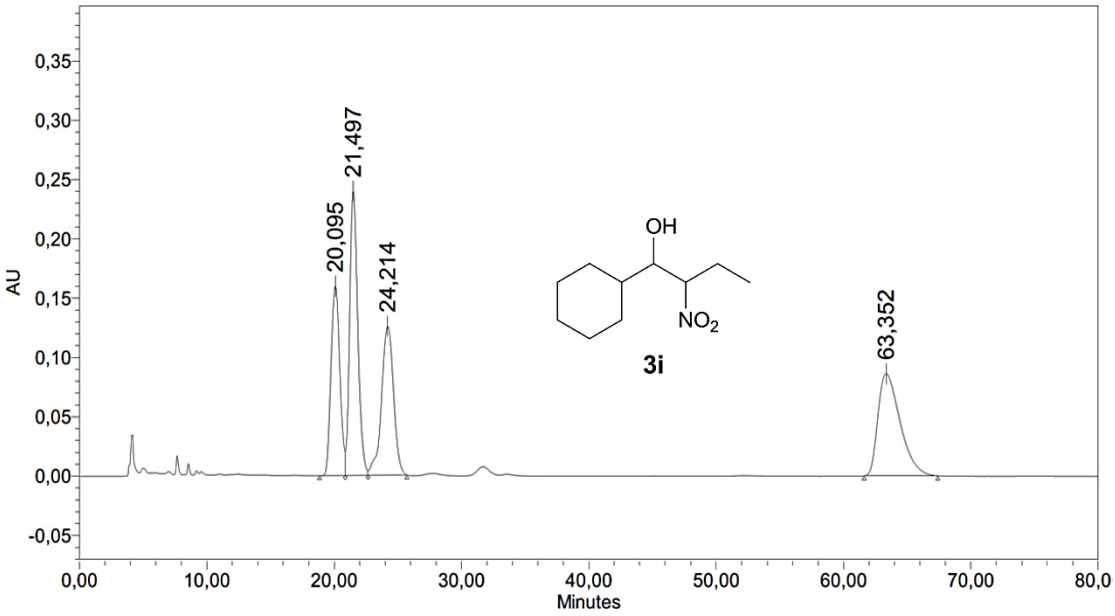
	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.29	139.69	32.53	15.99	12.34
2	11.99	359.72	99.21	41.17	37.62
3	14.05	305.18	99.84	34.92	37.86
4	18.96	69.24	32.11	7.92	12.18



	Ret.time [min]	Height [mVolt]	Area [mV*min]	% Hight	% Area
1	10.37	11.49	2.40	1.27	0.75
2	12.20	6.19	1.52	0.68	0.47
3	14.22	752.45	255.18	83.18	79.23
4	19.26	134.46	62.99	14.86	19.56

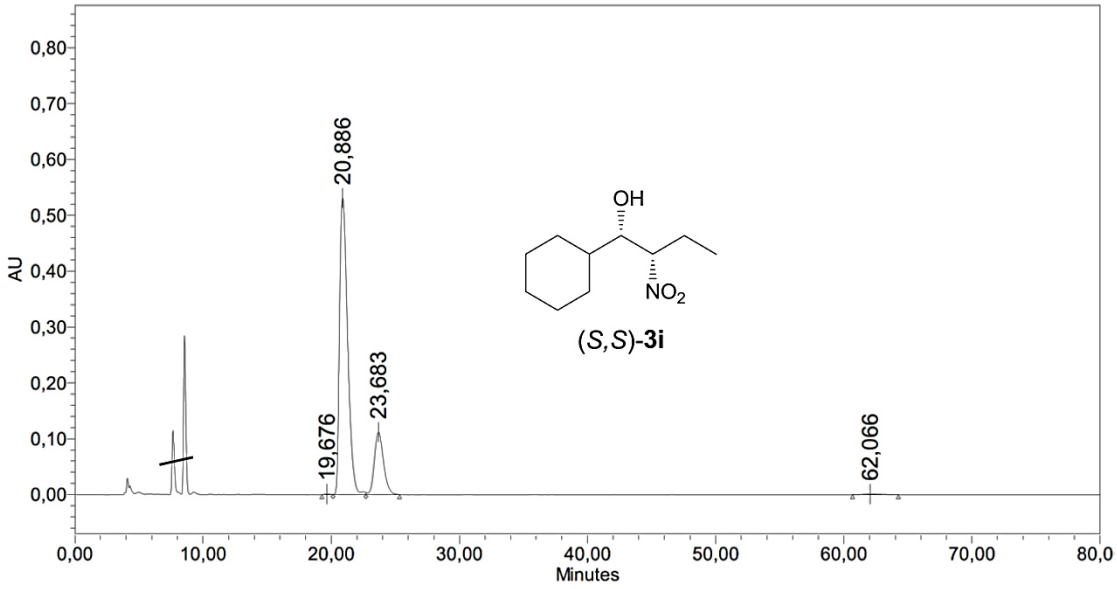
The diastereomeric ratio of **3h** was determined by ^{1}H NMR:





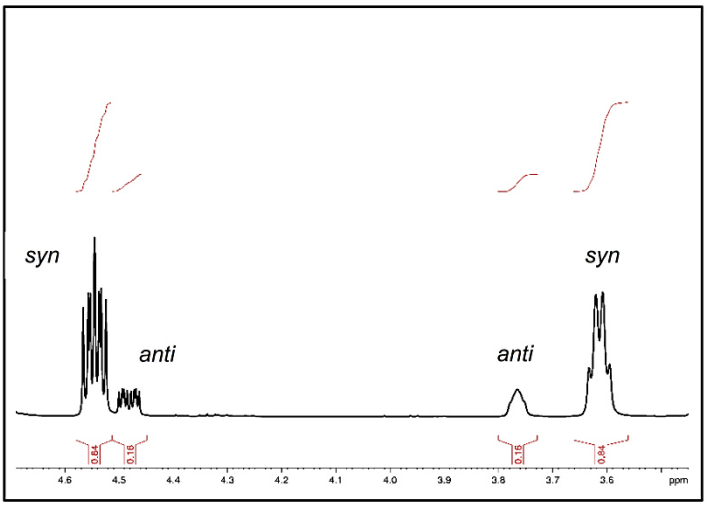
	Ret.time [min]	% Hight	% Area
1	20.09	26.14	20.73
2	21.50	39.24	28.64
3	24.21	20.54	22.47
4	63.35	14.08	28.16

44

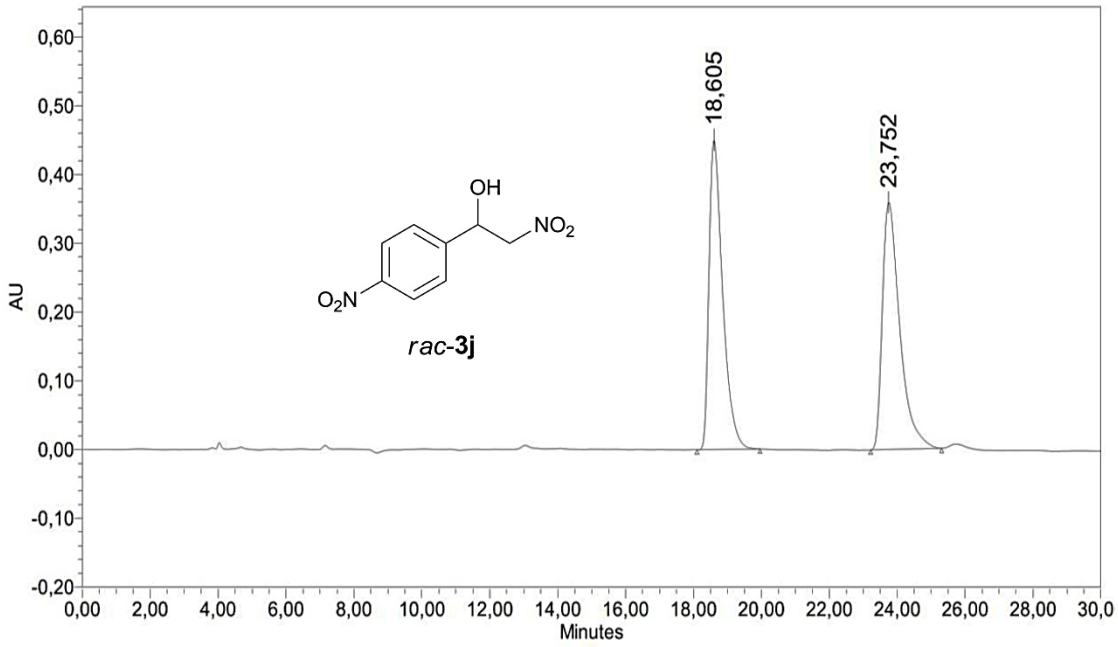


	Ret.time [min]	% Hight	% Area
1	19.68	0.12	0.08
2	20.89	82.40	80.48
3	23.68	17.34	19.13
4	62.07	0.13	0.31

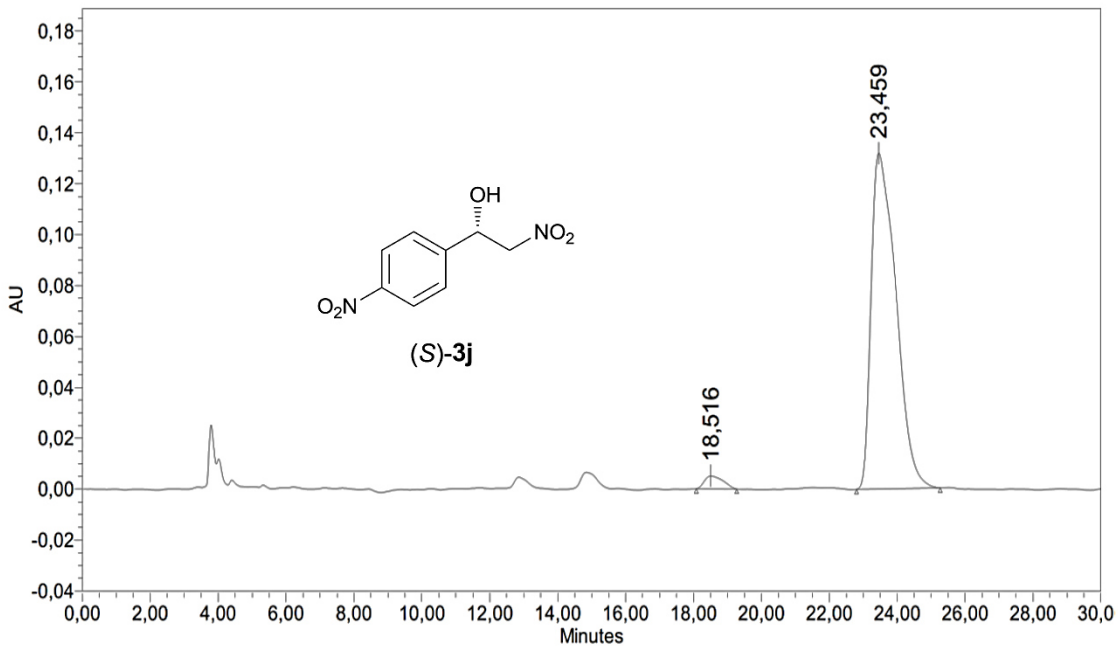
The diastereomeric ratio of **3i** was determined by ^{1}H NMR:



45



	Ret.time [min]	% Hight	% Area
1	18.61	55.61	49.57
2	23.75	44.39	50.43



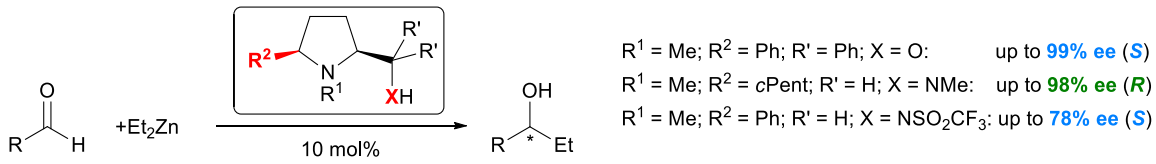
	Ret.time [min]	% Hight	% Area
1	18.52	3.68	2.80
2	23.46	96.32	97.20

6.5 Enantioselective addition of diethylzinc to aldehydes catalyzed by 5-*cis*-substituted proline derivatives

Felix Prause, Stefan Wagner and Matthias Breuning*

Organic Chemistry Laboratory, University of Bayreuth, Universitätsstraße 30, 95447 Bayreuth, Germany.

* Matthias.Breuning@uni-bayreuth.de



Manuscript to be submitted.

Abstract

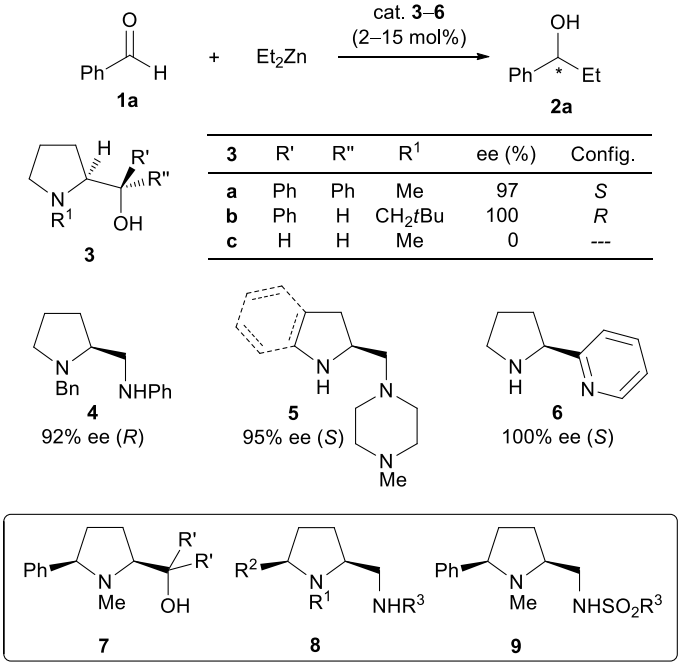
Prolinols, prolinamines, and prolinamine sulfonamides carrying a 5-*cis* substituent proved to be efficient ligands for the enantioselective addition of diethylzinc to aldehydes, providing up to 99% ee. The sense of asymmetric induction can be controlled by the nature of the exocyclic functional group (CPh_2OH vs. CH_2NHR vs. CH_2NHSO_3R). The additional 5-*cis* substituent exerts a strong beneficial effect on the chirality transfer since it rigidifies the catalyst structure. The stereochemical outcome of the reactions is discussed in detail on the respective transition states.

Key words

enantioselective catalysis, chiral ligands, pyrrolidine, diethylzinc, asymmetric addition

Introduction

The catalytic enantioselective addition of diorgano zinc reagents to aldehydes nowadays belongs to the standard repertoire of synthetic organic chemists.[1] Since the initial discovery by Oguni and Omi in 1984,[2] a plethora of chiral ligands permitting good to excellent enantioselectivities has been developed.[3] Among them are some proline derivatives, of which α,α-diphenyl-*N*-methyl-2-pyrrolidinemethanol (DPMPM, **3a**, Scheme 1), introduced by Soai and coworkers in 1987,[4] received particular attention.[5] Structure–enantioselectivity studies[4,6] on the addition of diethylzinc to benzaldehyde (**1a**) revealed that the geminal α,α-diphenyl group in **3a** is crucial for high asymmetric induction (97% ee) in favor of the *S*-configured product (*S*)-**2a**. Enantio-complementary (*R*)-**2a** can be obtained with virtually perfect stereocontrol (100% ee) in the presence of **3b**, which solely possesses an *erythro* phenyl group R' and the bulkier neopentyl group R^1 at the pyrrolidine nitrogen atom. The α-unsubstituted prolinol **3c** failed to transfer any stereo information (0% ee). More recently, it was discovered that the structurally closely related prolinamines **4**–**6** also permit good to excellent enantioselectivities (92–100% ee, *R* or *S*), even without an α-substituent.[7] The sense of asymmetric induction is governed by the substituents at the nitrogen atoms and backbone, since all proline derivatives **3**–**6** possess the same *S*-configuration at the stereocenter in the pyrrolidine.



3	R'	R''	R^1	ee (%)	Config.
a	Ph	Ph	Me	97	*S*
b	Ph	H	CH_2tBu	100	*R*
c	H	H	Me	0	---

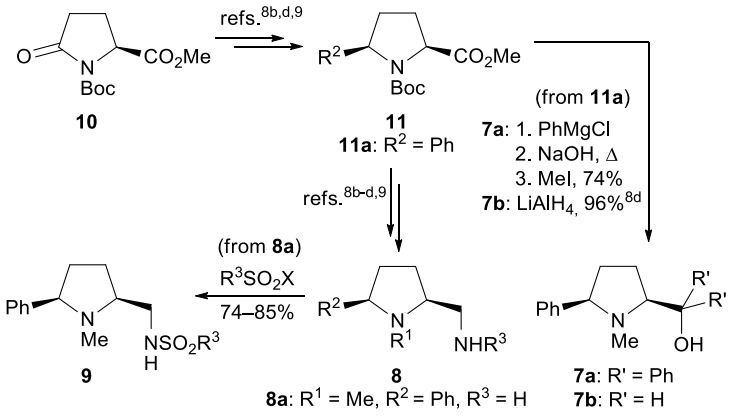
Scheme 1. Soai's prolinols **3**[4] and the prolinamines **4**–**6**,[7] all successfully used in the enantioselective addition of Et_2Zn to aldehydes (ee values refer to **1a** as the substrate), and the 5-*cis*-substituted proline derivatives **7**–**9**.

Recently, we had shown that bidentate, 2,5-*cis*-disubstituted pyrrolidines provide good to excellent asymmetric inductions when used as the chiral ligands in Cu-catalyzed Henry reactions and oxidative biaryl couplings or as the skeleton of novel tricyclic CBS reagents.[8] In continuation of these studies we decided to evaluate the prolinols **7** and prolinamines **8** and **9** in the enantioselective addition of Et_2Zn to aldehydes. We anticipated that the additional 5-*cis* substituent R^2 will be beneficial for the stereotransfer, which was confirmed by structure selectivity studies. A rationale for the observed trends and the reversals in the sense of asymmetric induction is given.

Results and discussion

Synthesis of the 5-*cis*-substituted proline derivatives

The proline derivatives **7**–**9** were prepared from methyl Boc-L-pyroglutamate (**10**) using procedures developed by us[9] and others (Scheme 2).[10,11] The 5-*cis* substituent R^2 was introduced by Grignard addition and subsequent reductive recyclization, which provided the esters **11** with good to high diastereoselectivities. Simple reduction of **11a** (R^2 = Ph) afforded the prolinol **7b** (96%),[8d] while the α,α-diphenyl derivative **7a** was synthesized by phenyl addition, *N*-deprotection, and *N*-methylation (74%). The known[8b–d,9] prolinamines **8** were accessed from **11** by Boc/R^1 exchange and conversion of the ester function into an amine. Finally, treatment of **8a** (R^1 = Me, R^2 = Ph, R^3 = H) with R^3SO_2Cl or $(R^3SO_2)_2O$ provided the new sulfonamides **9** in good 74–85% yield.



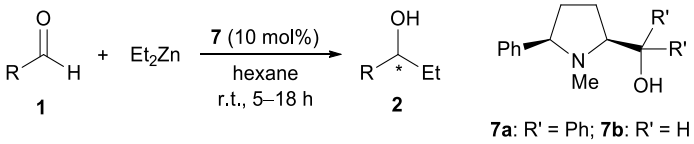
Scheme 2. Synthesis of the 5-*cis*-substituted proline derivatives **7**–**9**.[8b–d,9]

Enantioselective additions of diethylzinc to aldehydes

All enantioselective additions of Et_2Zn were carried out under standard conditions, by addition of the respective aldehyde to a mixture of the chiral ligand (2–10 mol%) and Et_2Zn (2 equiv.).

In a first set of experiments we wanted to demonstrate that the additional 5-*cis* substituent exerts a beneficial effect on the chirality transfer. Since Lüdtke and Correia[12] had recently shown that prolinol **7a**, which possesses the skeleton of **3a** plus a 5-*cis* phenyl group, permits excellent 95% ee in the arylation of *p*-tolualdehyde with phenylboronic acid, we decided to test **7a** as the chiral ligand (10 mol%) in the addition of Et_2Zn to aldehydes (Table 1).

Table 1. Addition of Et_2Zn to aldehydes **1** in the presence of the prolinols **7**.[a]



Entry	Ligand	**1**, **2**	R	Yield (%)[b]	ee (%), Config.[b]
1	**7a**	**a**	Ph	98	99 (*S*)
2[c]	**7a**	**a**	Ph	99	99 (*S*)
3	**7a**	**b**	Cy	67	96 (*S*)
4	**7a**	**c**	$Ph(CH_2)_2$	90	85 (*S*)
5	**7b**	**a**	Ph	78	25 (*R*)

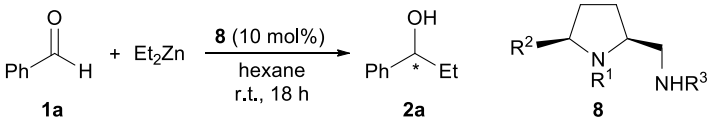
[a] The aldehyde (500 µmol) was added at r.t. to a solution of the prolinol **7** (50 µmol) and Et_2Zn (1.0 mmol) in hexane (2.0 mL). [b] Isolated yield; ee and configuration determined by HPLC on chiral phase. [c] Reaction with 2 mol% of catalyst **7a** in toluene/hexane (1:1) at 0 °C.

Good to excellent asymmetric inductions were reached with the model substrates benzaldehyde (**1a**), cyclohexyl carbaldehyde (**1b**), and hydrocinnamic aldehyde (**1c**). For **1a**, the amount of ligand **7a** was lowered to 2 mol% without any loss in chemical and optical yield. In

terms of stereoselectivity, prolinol **7a** exceeded **3a** for **1a** (**7a**: 99% ee vs. **3a**: 97% ee[4]) and, significantly, for **1b** (**7a**: 96% ee vs. **3a**: 38% ee[4]), while **3a** was slightly better with **1c** (**7a**: 85% ee vs. **3a**: 92% ee[4]). Thus, there is indeed a beneficial effect of the additional 5-*cis* substituent, at least for **1a** and **1b**. The sense of asymmetric induction (*S*) with **7a** was identical to that of **3a**. Interestingly, the α,α-unsubstituted prolinol **7b** provided in the reaction with **1a** the enantio-complementary product (*R*)-**2a**, albeit with low 25% ee. The apparently slight *R*-preference inherent to the basic skeleton **7b** must have been fully overwritten in **7a** by the stereochemical steering of the α,α-diphenyl unit.

Next we put our focus on the prolinamines **8**, which are devoid of any α-substituent, but offer the advantage of another modifiable substituent R^3 at the exocyclic amino function. In search of the optimum ligand, this substituent R^3 as well as R^1 at the pyrrolidine nitrogen atom and the 5-*cis* substituent R^2 were varied. The addition of Et_2Zn to benzaldehyde (**1a**) in the presence of **8** (10 mol%) was used as the test reaction (Table 2).

Table 2. Addition of Et_2Zn to benzaldehyde (**1a**) in the presence of the prolinamines **8**: Catalyst optimization.[a]



1a **2a** **8**

Entry	**8**	R^1	R^2	R^3	Yield (%)[b]	ee (%), Config.[b]
1	**a**	Me	Ph	H	69	12 (*R*)
2	**b**	Me	Ph	Me	81	71 (*R*)
3	**c**	Me	Ph	Et	91	4 (*R*)
4	**d**	Me	Ph	*i*Pr	91	20 (*S*)
5	**e**	H	Ph	Me	63	11 (*R*)
6	**f**	Et	Ph	Me	59	12 (*R*)
7	**g**	*i*Pr	Ph	Me	31	0 (–)
8	**h**	Bn	Ph	Me	35	4 (*S*)
9	**i**	Me	H	Me	68	45 (*R*)
10	**j**	Me	*c*Pent	Me	88	84 (*R*)
11	**k**	Me	Cy	Me	82	77 (*R*)
12	**l**	Me	Bn	Me	75	70 (*R*)
13	**m**	Me	3,5-Me_2Ph	Me	76	61 (*R*)

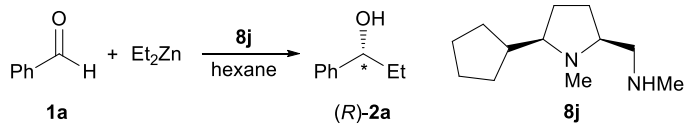
[a] The aldehyde (500 µmol) was added at r.t. to a solution of the prolinamine **8** (50 µmol) and Et_2Zn (1.0 mmol) in hexane (2.0 mL). [b] Isolated yield; ee and configuration determined by HPLC on chiral phase.

Prolinamine **8a** (R^1 = Me; R^2 = Ph, R^3 = H) carrying a primary exocyclic amino function provided the *R*-configured product (*R*)-**2a**, albeit with poor 12% ee. Significantly improved en-

antiocontrol (71% ee) was observed with diamine **8b** (R^3 = Me), which had been the ligand of choice in asymmetric Henry reactions done earlier.[8b,d] Further increase of the steric demand of R^3 (**8c**,**d**: R^3 = Et, *i*Pr) or variation of R^1 as in **8e–h** (R^1 = H, Et, *i*Pr, Bn) caused a drastic loss in stereoselectivity. Altering the 5-*cis* substituent R^2 (derivatives **8i–m**) revealed that a cyclopentyl group is most suited; prolinamine **8j** as the catalyst delivered (*R*)-**2a** in 88% yield and improved 84% ee. The necessity of a 5-*cis* substituent is obvious from the unsubstituted derivative **8i** (R^2 = H), which gave just low 45% ee. Finally, it must be noted that the sense of asymmetric induction switched from *R* to *S* when, as in **8d** and **8h**, a bulky substituent R^1 or R^3 was introduced.

The reaction conditions were optimized using prolinamine **8j** (Table 3). It was found that hexane as the solvent is slightly superior to toluene/hexane mixtures and that 20 °C are a good compromise between asymmetric induction and reaction rate. Lowering the catalyst loading from 10 to 5 or 2 mol% resulted in a loss of stereocontrol. The best yield (90%) and enantioselection (90% ee, *R*) was reached when the reaction was conducted at a concentration of *c*(**1a**) = 0.125 M.

Table 3. Optimization of the reaction conditions in the presence of **8j**.[a]



1a (*R*)-**2a** **8j**

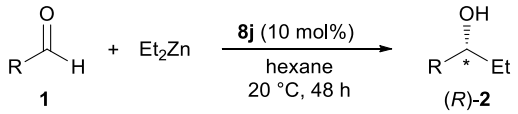
Entry	T (°C)	**8j** (mol%)	t (h)	Yield (%)[b]	ee (%)[b]
1[c]	r.t.	10	16	91	82
2	r.t.	10	18	88	84
3	30	10	21	82	84
4	20	10	16	85	88
5	10	10	16	73	88
6	0	10	72	65	90
7	20	5	72	82	87
8	20	2	72	84	82
9[d]	20	10	17	85	84
10[e]	20	10	17	90	90

[a] The aldehyde (500 µmol) was added to a solution of the prolinamine **8j** (50 µmol) and Et_2Zn (1.0 mmol) in hexane (2.0 mL). [b] Isolated yield; ee and configuration (*R*) determined by HPLC on chiral phase. [c] Reaction in toluene/hexane (1:1, 2.0 mL). [d] Reaction at double concentration. [e] Reaction at half concentration.

The scope of prolinamine **8j** is shown in Table 4. Aromatic aldehydes with electron-withdrawing (**1d**) or -donating (**1e**) groups, with *meta* (**1g**) or *para* (**1d–f**) substituents, 2-naphthyl carbaldehyde (**1i**), and hetarylic 2-thienyl carbaldehyde (**1k**) provided the *R*-configured product in >80% yield and with good 83–90% ee. *Ortho* substituents such as methyl in **1h** or an

ortho, *meta*-annelated ring as in 1-naphthyl carbaldehyde (**1j**) reduce the level of chirality transfer (80% and 60% ee, respectively). Insufficient stereocontrol was observed for vinylic cinnamic (**1l**: 17% ee) and aliphatic hydrocinnamic (**1c**: 62% ee) aldehyde. The presence of an α-branched alkyl group permitted high enantioselectivities, as obvious from the excellent 98% ee reached with cyclohexyl carbaldehyde (**1b**).

Table 4. Substrate scope of the prolinamine **8j**.[a]

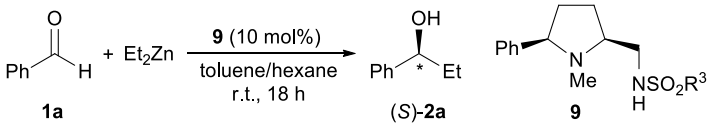


Entry	**1**, **2**	R	Yield (%)[b]	ee (%)[b]
1	**a**	Ph	90	90
2	**d**	4-ClPh	84	88
3	**e**	4-MeOPh	88	84
4	**f**	4-MePh	81	90
5	**g**	3-MePh	85	90
6	**h**	2-MePh	96	80
7	**i**	2-Naph	88	86
8	**j**	1-Naph	81	60
9	**k**	2-Thienyl	86	83
10	**l**	(*E*)-Ph-CH=CH	73	17
11	**c**	$Ph(CH_2)_2$	34	62
12	**b**	Cy	91	98

[a] The aldehyde (500 µmol) was added at 20 °C to a solution of the prolinamine **8j** (50 µmol) and Et_2Zn (1.0 mmol) in hexane (4.0 mL). [b] Isolated yield; ee and configuration (*R*) determined by HPLC on chiral phase.

Finally, the sulfonamides **9**, in which the electron-donating character of the exocyclic nitrogen atom is strongly reduced, were evaluated in the addition of Et_2Zn to benzaldehyde (**1a**, Table 5). The highest asymmetric induction (78% ee) was reached when the reaction was conducted in toluene/hexane 1:1 in the presence of the triflate **9b** (10 mol%) that carries the small and strongly electron-withdrawing CF_3 group. Larger substituents R^3 again caused an, in part, significant loss in stereocontrol. Surprisingly, the sense of the chirality transfer with **9** (*S*) is opposite to that of **8j** (*R*).

Table 5. Additions to **1a** in the presence of the prolinamine sulfonamides **9**.[a]



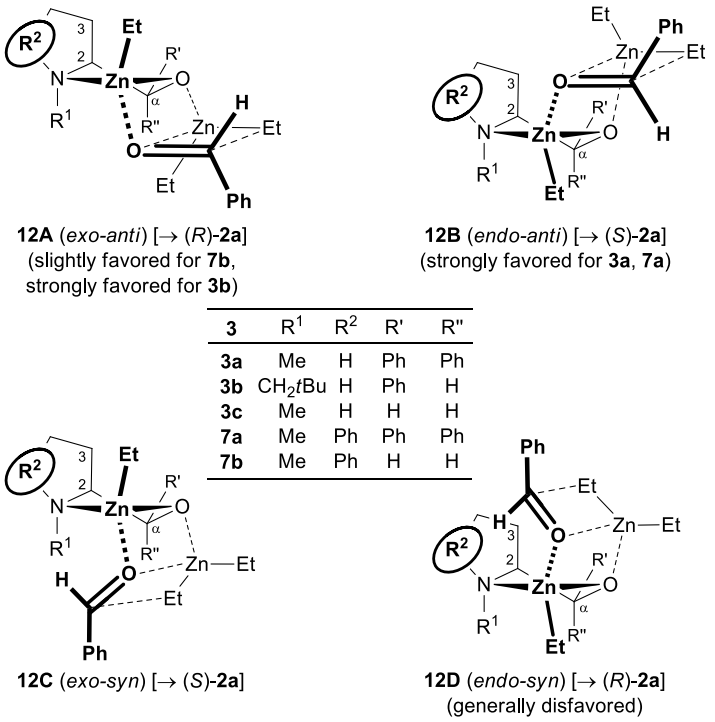
1a (*S*)-**2a** **9**

Entry	**9**	R^3	Yield (%)[b]	ee (%)[b]
1[c]	**a**	Me	70	60
2	**a**	Me	95	68
3	**b**	CF_3	84	78
4	**c**	4-MePh	90	64
5	**d**	Bn	63	72
6	**e**	2,4,6-Me_3Ph	87	17

[a] The aldehyde (500 µmol) was added at r.t. to a solution of the prolinamine sulfonamide **9** (50 µmol) and Et_2Zn (1.0 mmol) in hexane/toluene 1:1 (2.0 mL). [b] Isolated yield; ee and configuration (*S*) determined by HPLC on chiral phase. [c] Reaction in hexane (2 mL) as the solvent.

Stereochemical considerations

The stereo transfer with the proline-derived ligands **7**–**9**, including the observed switches in the sense of asymmetric induction, can be explained by inspection of the respective transition states. The following argumentation is based on quantumchemical calculations on Soai's prolinols **3**[13] and related amino alcohols,[14] which had revealed that eight transition states have to be taken into consideration. They differ in the orientation of the bicyclic catalyst core relative to the transient, inner 4-membered ring [*exo* (**12A**, **12C**) vs. *endo* (**12B**, **12D**), Figure 1, illustrated on the addition of Et_2Zn to benzaldehyde (**1a**) in the presence of the prolinols **3** and **7**] and to the outer 4-membered ring [*anti* (**12A**, **12B**) vs. *syn* (**12C**, **12D**)], and in the orientation of the aldehyde [coordination via the *trans* lone pair (**12A**–**D**) or the *cis* one (not shown)]. The latter *cis* arrangements were calculated to be, at least for aromatic aldehydes, of significantly higher energy and are, therefore, neglected in the following discussion. The same accounts for the *endo-syn* transition state **12D**, because of the strong repulsion between the coordinated reactants and the bicyclic catalyst backbone. The remaining three arrangements **12A**–**C** can be close in energy, although **12C** (*exo-syn*) is normally disfavored due to higher steric crowding. For high levels of stereotransfer, the substituents attached to the chiral ligand have to induce a sufficient difference in energy between **12A** (*exo-anti*; *R*-selective) and **12B**/**12C** (*endo-anti*/*exo-syn*; both *S*-selective).



3	R^1	R^2	R'	R''
3a	Me	H	Ph	Ph
3b	CH_2tBu	H	Ph	H
3c	Me	H	H	H
7a	Me	Ph	Ph	Ph
7b	Me	Ph	H	H

Figure 1. Possible transition states **12A**–**12D** for the ethylation of **1a** in the presence of the prolinols **3** and **7**. The disfavored transition states with *cis* coordination of the aldehyde are not shown.

The most simple prolinol, **3c** (R^1 = Me; R^2, R', R'' = H), had been shown earlier[4] not to exert any asymmetric induction at all. Apparently, there is no transition state favored by the basic prolinol skeleton, presumably due to too much conformational flexibility, despite of the bicyclic backbone. The situation changes with an additional 5-*cis* substituent R^2 such as phenyl in ligand **7b**. The phenyl group most likely occupies a pseudo-equatorial position (minimizes 1,2-repulsion), which, like an anchor, rigidifies the bicyclic catalyst backbone, forcing it into the conformation shown in Figure 1. The enforced pseudo-axial orientation of the C2–C3 bond and the increased steric hindrance in the northwestern quadrant now disfavor the *endo*-binding mode **12B**, which results in the preferred formation of the *R*-configured product via **12A**. The stereocontrol, however, is low with **7b** (25% ee) since the stereo-deteriorating *exo-syn* transition state **12C** is not sufficiently suppressed. It should be noted that the same configurational 'freeze' was achieved by Soai[4] with the α-positioned *endo* phenyl group in prolinol **3b**. The bulky neopentyl group R^1 at the pyrrolidine nitrogen atom additionally disfavors **12C**, which explains the virtually perfect asymmetric induction (100% ee) reached.

The α,α-diphenyl group in the prolinols **3a** and **7a** (R', R'' = Ph) induces a reversal in the sense of asymmetric induction. The pseudo-equatorial orientation of R' (avoids severe 1,2-repulsion with the C2–C3 bond) forces R'' into a pseudo-axial position, which efficiently shields the *exo* hemisphere and virtually excludes the arrangements **12A** and **12C**. Consequently, the reaction proceeds via transition state **12B**, leading to the *S*-configured product with excellent stereocontrol (97% ee). The additional 5-*cis* phenyl group in **7a** (R^2 = Ph) also supports this conformation (vide supra) and, therefore, augments the pseudo-axial orientation of R'', which further destabilizes stereo-deteriorating **12A**. Thus, **12B** gets even more favored,

despite an increased steric hindrance in the *endo* hemisphere due to R^2, leading to an improved asymmetric induction as compared to **3a**.

The prolinamines **8** can principally react via the transition states **13A**–**13D** (Figure 2). Their relative stabilities basically follow the order discussed above for **7b**: **13D** (*endo-syn*) << **13B** (*endo-anti*) < **13C** (*exo-syn*) < **13A** (*exo-anti*). The formal exchange of the oxygen atom in **7b** for the secondary amino group in **8** introduces a new substituent R^3, which destabilizes the majorly stereo-deteriorating arrangement **13C** because it increases the 1,2-*syn* repulsion R^3/Et in the central four-membered ring. This permitted higher levels of chirality transfer of up to a maximum of 90% ee (*R*) in the case of **8j** (R^1, R^3 = Me, R^2 = *c*Pent). However, the preference for **13A** over **13B** and **13C** and, thus, the enantioselection, is based on a fragile and delicate balance between the steric demands of the substituents R^1–R^3. Even just slightly larger ethyl groups for R^1 (**8f**) and R^3 (**8c**) cause drastic losses in asymmetric induction (≤12% ee), presumably because **13A** is destabilized by the stronger repulsion R^1/aldehyde in the *exo* hemisphere and, respectively, R^3/Et at the *endo* side. Moreover, bulkier substituents such as R^1 = Bn (**8h**) or R^3 = *i*Pr (**8d**) disfavor **13A** to the point that **13B** becomes favorable, leading to the enantio-complementary product (*S*)-**2a** in up to 20% ee. The substituent R^2 is necessary to destabilize **13B**, as obvious from the low 45% ee reached with **8i** (R^2 = H). Although there is more steric tolerance at this position (**8j**–**m**: R^2 = *c*Pent, Cy, Bn, 3,5-Me_2Ph: 90–61% ee), larger groups diminish the stereocontrol, probably since steric crowding begins to destabilize the *exo* arrangements **13A** and **13C**.

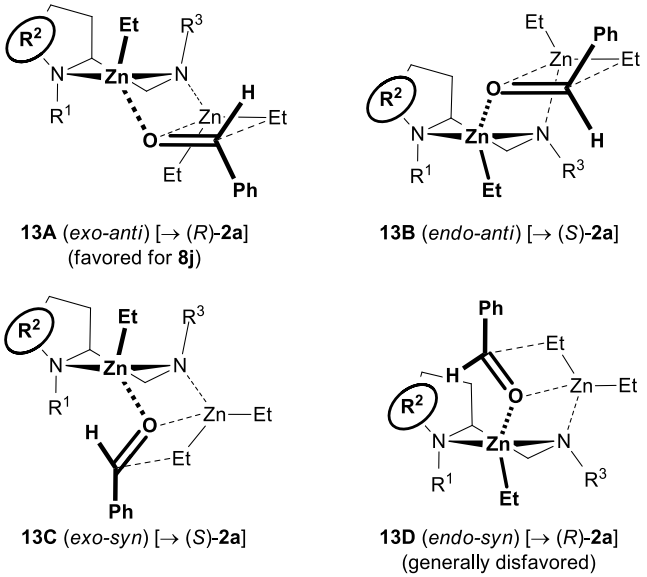
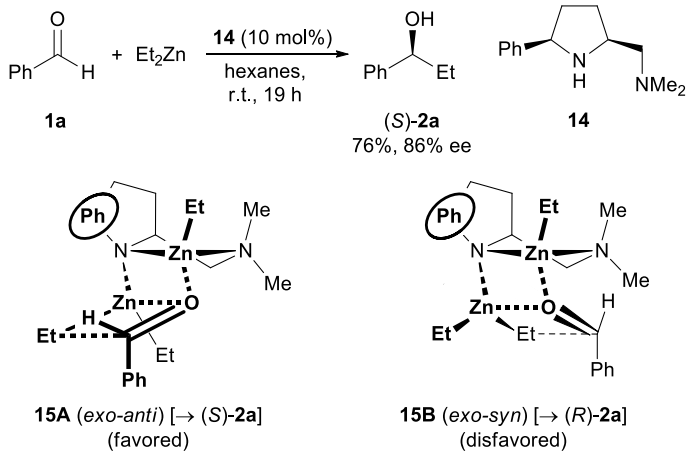


Figure 2. Possible transition states **13A**–**13D** for the ethylation of **1a** in the presence of the prolinamines **8**. The disfavored transition states with *cis* coordination of the aldehyde are not shown.

In order to find out, which of the two stereo-deteriorating transition states, **13B** (*endo-anti*) or **13C** (*exo-syn*), is primarily responsible for the non-perfect chirality transfer even with the best ligand **8j**, benzaldehyde (**1a**) was ethylated in the presence of the prolinamine **14**. This diamine, which possesses a secondary pyrrolidine nitrogen atom and a tertiary exocyclic amino

function, afforded (*S*)-**2a** in good 86% ee. The reversed sense of the asymmetric induction is a consequence of the activation of Et_2Zn by the pyrrolidine nitrogen atom in **14** (and not, as for the prolinamines **8**, by the exocyclic amine), which directs the attack to the opposite face of the coordinated benzaldehyde. Since geometric restrictions exclude *endo*-type alignments with **14**, (*S*)-**2a** must have been formed via the *exo-anti* transition state **15A** and the unwanted minor enantiomer, (*R*)-**2a**, by a competing pathway via the *exo-syn* transition state **15B**. This makes it very likely that the minor enantiomer (*S*)-**2a** of the reaction catalyzed by **8j** is formed via the corresponding *exo-syn* alignment **13C**.



Scheme 3. Addition of Et_2Zn to **1a** in the presence of prolinamine **14** and the proposed transition states **15A** and **15B**.

The exocyclic nitrogen atom in **9** is part of a sulfonamide group, which strongly reduces its ability to pre-coordinate and activate the Et_2Zn. We postulate that one of the two Lewis-basic oxygen atoms of the sulfonamide group takes this function. The observed *S*-selectivity in the ethylation of **1a** can be explained, for example, by the *endo-anti* transition state **16A**, but other arrangements are also possible, because the larger, six-membered central ring offers more conformational freedom. The flattening of the [1,3,2]-diazazincolidine, caused by the sp^2-hybridization of the sulfonamide nitrogen atom, might be a reason for the lower asymmetric inductions reached with **9** (up to 78% ee).

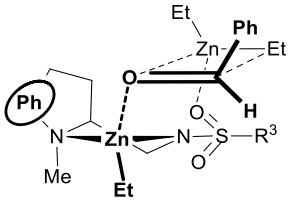


Figure 3. Proposed preferred transition state **16A** for the ethylation of **1a** in the presence of the sulfonamides **9**.

Conclusion

5-*Cis*-substituted prolinols **7**, prolinamines **8**, and prolinamine sulfonamides **9**, which are accessible from commercially available methyl Boc-L-pyroglutamate (**10**), were evaluated as the chiral ligands in the addition of Et_2Zn to aldehydes. The additional 5-*cis* substituent R^2 was found to significantly improve the chirality transfer (e.g. **8i** (R^2 = H): 45% ee vs. **8j** (R^2 = *c*Pent): 84% ee). The sense of asymmetric induction depended on the existence of α-substituents and the nature of the exocyclic functionality: While up to 99% ee in favor of the *S*-configured products were reached with the 5-*cis*,α,α-triphenyl prolinol **7a**, the enantiocomplementary, *R*-configured products were obtained with the α,α-unsubstituted prolinamines **8** (up to 98% ee for **8j**). The prolinamine sulfonamides **9** again preferentially provided the *S*-enantiomers (up to 78% ee for **9b**). Structure-selectivity studies on the prolinamines **8** revealed that even minor changes in the substituents R^1 at the pyrrolidine nitrogen atom and R^3 at the exocyclic amino function cause drastic losses in enantiocontrol. The stereochemical behavior of the ligands **7**–**9** can be explained by the respective transition states. The 5-*cis* substituent exerts a beneficial effect since it locks the catalyst structure in a favorable conformation. Of the energetically relevant transition states that differ in the relative orientation of the two transient four-membered rings formed during ethyl transfer, the *endo-anti* alignment **12B** is favored for **7a** because the α,α-diphenyl group shields the *exo* hemisphere. The prolinamines **8** react preferentially via the *exo-anti* transition state **13A**, thus avoiding steric crowding in the *endo* hemisphere. The activation of Et_2Zn in the sulfonamides **9** is proposed to occur by one of the oxygen atoms of the sulfone, leading to a six-membered inner ring during C,C-bond formation.

Experimental section

General

All reactions with moisture-sensitive reagents were carried out under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[15] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$ or vanillin. Silica gel (Macherey-Nagel, particle size 40–63 µm) was used for column chromatography. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^1H and ^{13}C NMR data were made on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra on a ThermoFisher Scientific Q-Exactive (Orbitrap) mass spectrometer using ESI (electronspray

ionization). The enantiomeric excess of the alcohols **2** was determined by HPLC analysis (Waters Alliance HPLC; Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralpak AD-H or Daicel Chiralcel OD-3).

Prolinamines **8a–h**,**j**,**k**,**m, 14** and sulfonamide **9a** were prepared according to literature procedures.[8b–d,9] Diamine **8i** is commercially available.

((2*S*,5*R*)-1-Methyl-5-phenylpyrrolidin-2-yl)diphenylmethanol (7a)

PhMgCl (20.9 mL, 2.0 M in THF, 41.7 mmol) was added at 0 °C to a solution of the ester **11a**[8d] (4.25 g, 13.9 mmol) in anhydrous THF (42 mL). After 1 d at r.t., the reaction mixture was quenched with sat. aq. NH_4Cl (20 mL) and the organic layer was removed under reduced pressure. The remaining aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The residue was suspended in EtOH (140 mL) and freshly ground NaOH (5.56 g, 139 mmol) was added at r.t. The reaction mixture was refluxed for 2 d and concentrated under reduced pressure. H_2O (80 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 90 mL). The combined organic layers were washed with brine (90 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (silica gel, hexanes:EtOAc 14:1–9:1) provided known[10a] diphenyl((2*S*,5*R*)-5-phenylpyrrolidin-2-yl)methanol (3.95 g, 12.0 mmol, 86%) as a slightly yellow solid.

The amino alcohol prepared above (880 mg, 2.67 mmol) was dissolved in DMF (11 mL) and MeI (351 µL, 796 mg, 5.61 mmol) and K_2CO_3 (812 mg, 5.87 mmol) were added at r.t. H_2O (20 mL) was added after 4 h and the mixture was extracted with Et_2O (5 × 30 mL). The combined organic layers where dried over $MgSO_4$. Removal of the solvent and column chromatography (silica gel, hexanes:EtOAc 29:1–9:1) and trituration with Et_2O (6 mL) afforded known[12] prolinol **7a** (789 mg, 2.30 mmol, 86%) as a colorless solid.

(2*R*,5*S*)-2-Benzyl-1-methyl-5-((methylamino)methyl)pyrrolidine (8l)

MsCl (86.6 µL, 129 mg, 1.12 mmol) and NEt_3 (216 µL, 157 mg, 1.55 mmol) were added at 0 °C to a solution of (2*R*,5*S*)-2-benzyl-5-(hydroxymethyl)-1-methylpyrrolidine[9] (177 mg, 862 µmol) in anhydrous CH_2Cl_2 (1.7 mL). After 1 d at r.t., H_2NMe (2.35 mL, 40 wt% in H_2O, 25.9 mmol), NEt_3 (72.1 µL, 52.3 mg, 517 µmol), and MeOH (4 mL) were added. The reaction mixture was stirred 17 h and the solvent evaporated. Column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 95:4.5:0.5–93:6.3:0.7) provided prolinamine **8l** (137 mg, 627 µmol, 73%) as an orange oil.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 90:9:1) 0.30; $[\alpha]_D^{30}$ +34.1 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 2972, 2935, 2770, 1453, 1433, 1358, 1125, 1087, 1049, 1037, 813, 757, 748, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.26 (2H, m, Ph-H), 7.18 (3H, m, Ph-H), 3.00 (1H, dd, *J* 12.2,

3.0 Hz, 2-C*H*H), 2.66 (1H, dd, *J* 11.3, 3.8 Hz, 5-C*H*H), 2.54 (1H, dd, *J* 11.2, 6.3 Hz, 5-CH*H*), 2.48 (2H, m, 2-H, 5-H), 2.44 (3H, s, $NHCH_3$), 2.43 (1H, m, 2-CH*H*), 2.38 (3H, s, 1-CH_3), 1.77 (1H, m, 4-*H*H), 1.64 (1H, m, 3-*H*H), 1.57 (1H, m, 4-H*H*), 1.45 (1H, m, 3-H*H*), 1.36–1.08 (1H, br s, NH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 140.1 (C_q-Ph), 129.4, 128.3, 126.0 (CH-Ph), 69.2 (C-2), 66.7 (C-5), 55.9 (5-CH_2), 41.2 (2-CH_2), 40.0 (1-CH_3), 37.3 ($NHCH_3$), 29.8 (C-3), 27.4 (C-4) ppm; HRMS (ESI, pos.): MH^+, found 219.1850. $C_{14}H_{23}N_2^+$ requires 219.1856.

Synthesis of the *N*-sulfonylated prolinamines 9

General procedure

NEt_3 (1.1 equiv) and the sulfonyl chloride or anhydride (1.1 equiv) were added at r.t. to a solution of the prolinamine **8a** in anhydrous CH_2Cl_2 (1 mL/100 µmol **8a**). After 2–3 h, MeOH (260 µL/100 µmol **8a**) was added. Removal of the solvent and column chromatography provided the *N*-sulfonylated prolinamine **9**.

(2*R*,5*S*)-1-Methyl-2-phenyl-5-((trifluoromethylsulfonamido)methyl)pyrrolidine (9b)

According to the GP, the prolinamine **8a** (73.7 mg, 387 µmol) was sulfonylated with trifluoromethanesulfonic anhydride to give, after column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 100:0:0–95:4.5:0.5), pyrrolidine **9b** (92.0 mg, 285 µmol, 74%) as a brownish wax.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 99:0.9:0.1) 0.56; $[\alpha]_D^{23}$ +24.9 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 3298 (br), 2952, 1389, 1367, 1230, 1185, 1146, 1032, 948, 755, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.34 (2H, m, Ph-H), 7.27 (3H, m, Ph-H), 5.22–4.00 (1H, br s, NH), 3.47 (1H, dd, *J* 12.5, 3.5 Hz, 5-C*H*H), 3.38 (2H, m, 2-H, 5-CH*H*), 2.77 (1H, m, 5-H), 2.15 (3H, s, 1-CH_3), 2.12 (1H, m, 3-*H*H), 2.03 (1H, m, 4-*H*H), 1.87 (1H, m, 4-H*H*), 1.71 (1H, m, 3-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 142.3 (C_q-Ph), 128.8, 127.7, 127.3 (CH-Ph), 120.0 (q, *J* 321.3 Hz, CF_3), 72.1 (C-2), 63.6 (C-5), 44.5 (5-CH_2), 38.2 (1-CH_3), 33.9 (C-3), 26.4 (C-4) ppm; HRMS (ESI, pos.): MH^+, found 323.1028. $C_{13}H_{18}F_3N_2O_2S^+$ requires 323.1036.

(2*S*,5*R*)-1-Methyl-2-((4-methylphenylsulfonamido)methyl)-5-phenylpyrrolidine (9c)

According to the GP, the prolinamine **8a** (70.5 mg, 371 µmol) was sulfonylated with 4-toluenesulfonyl chloride to give, after column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 100:0:0–95:4.5:0.5), pyrrolidine **9c** (105 mg, 305 µmol, 82%) as a yellowish wax.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 99:0.9:0.1) 0.43; $[\alpha]_D^{26}$ +49.4 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 3295 (br), 2951, 1598, 1493, 1454, 1427, 1323, 1152, 1069, 813, 697, 661 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.78 (2H, d, *J* 8.3 Hz, Ar-H), 7.29 (7H, m, Ar-H), 5.10 (1H, d, *J* 8.0 Hz, NH), 3.28 (1H, dd, *J* 9.9, 6.8 Hz, 5-H), 3.09 (1H, m, 2-C*H*H), 2.99 (1H, ddd, *J* 11.8, 3.9, 1.2 Hz, 2-CH*H*), 2.62 (1H, m, 2-H), 2.42 (3H, s, Ar-CH_3), 2.04 (1H, m, 4-*H*H), 1.92 (3H, s, 1-CH_3), 1.85 (2H, m, 3-H_2), 1.64 (1H, m, 4-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 143.4, 142.9, 136.8 (C_q-Ar), 129.8, 128.6, 127.5, 127.33, 127.29 (CH-Ar), 72.2 (C-5), 63.9 (C-2), 43.7 (2-CH_2), 38.2 (1-CH_3), 34.0 (C-4), 26.6 (C-3), 21.7 (Ar-CH_3) ppm; HRMS (ESI, pos.): MH^+, found 345.1623. $C_{19}H_{25}N_2O_2S^+$ requires 345.1631.

(2*S*,5*R*)-1-Methyl-2-((benzylsulfonamido)methyl)-5-phenylpyrrolidine (9d)

According to the GP, the prolinamine **8a** (73.0 mg, 384 µmol) was sulfonylated with benzylsulfonyl chloride to give, after column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 100:0:0–95:4.5:0.5), pyrrolidine **9d** (112 mg, 325 µmol, 85%) as a colorless oil.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 99:0.9:0.1) 0.29; $[\alpha]_D^{27}$ +25.3 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 3291 (br), 2949, 1455, 1327, 1151, 1125, 909, 730, 697 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.46 (2H, m, Ph-H), 7.40 (3H, m, Ph-H), 7.27 (3H, m, Ph-H), 7.20 (2H, m, Ph-H), 4.85 (1H, d, *J* 6.5 Hz, NH), 4.33 (2H, s, CH_2Ph), 3.30 (1H, dd, *J* 9.9, 6.6 Hz, 5-H), 3.12 (1H, dd, *J* 12.0, 3.9 Hz, 2-C*H*H), 3.04 (1H, m, 2-CH*H*), 2.64 (1H, m, 2-H), 2.07 (3H, s, 1-CH_3), 2.04 (1H, m, 4-*H*H), 1.89 (2H, m, 3-H_2), 1.61 (1H, m, 4-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 142.8 (C_q-Ph), 130.7 (CH-Ph), 129.7 (C_q-Ph), 129.0, 128.9, 128.5, 127.4, 127.3 (CH-Ar), 72.2 (C-5), 64.2 (C-2), 58.9 (CH_2Ph), 44.4 (2-CH_2), 38.5 (1-CH_3), 34.2 (C-4), 26.5 (C-3) ppm; HRMS (ESI, pos.): MH^+, found 345.1623. $C_{19}H_{25}N_2O_2S^+$ requires 345.1631.

(2*R*,5*S*)-1-Methyl-2-phenyl-5-((2,4,6-trimethylphenylsulfonamido)methyl)pyrrolidine (9e)

According to the GP, the prolinamine **8a** (69.4 mg, 365 µmol) was sulfonylated with 2,4,6-trimethylbenzenesulfonyl chloride to give, after column chromatography (silica gel, CH_2Cl_2:MeOH:NH_3 (aq., 25%) 100:0:0–95:4.5:0.5), pyrrolidine **9e** (107 mg, 287 µmol, 79%) as a colorless wax.

R_f (CH_2Cl_2:MeOH:NH_3 (aq., 25%) 99:0.9:0.1) 0.43; $[\alpha]_D^{29}$ +54.9 (*c* 1.0, MeOH); IR (neat): $\tilde{\nu}_{max}$ 3301 (br), 2972, 2850, 1607, 1456, 1419, 1379, 1330, 1152, 1038, 865, 758, 705, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ_H 7.33 (2H, m, Ar-H), 7.27 (3H, m, Ar-H), 6.95 (2H, s, Ar-H), 5.33 (1H, d, *J* 8.7 Hz, NH), 3.29 (1H, dd, *J* 10.0, 6.7 Hz, 2-H), 3.03 (1H, ddd, 11.5, 9.0, 2.0 Hz, 5-C*H*H), 2.91 (1H, ddd, *J* 11.5, 3.9, 1.5 Hz, 5-CH*H*), 2.67 (6H, s, Ar-CH_3), 2.63 (1H, m, 5-H), 2.29 (3H, s, Ar-CH_3), 2.05 (1H, m, 3-*H*H), 1.92 (3H, s, 1-CH_3), 1.86 (2H, m, 4-H_2), 1.67 (1H, m, 3-H*H*) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 142.8, 142.2, 139.2, 133.3 (C_q-Ar), 132.0, 128.6, 127.5, 127.3 (CH-Ar), 72.2 (C-2), 63.6 (C-5), 43.1 (5-CH_2), 38.1 (1-

CH_3), 34.1 (C-3), 26.6 (C-4), 23.0, 21.1 (Ar-CH_3) ppm; HRMS (ESI, pos.): MH^+, found 373.1936. $C_{21}H_{29}N_2O_2S^+$ requires 373.1944.

General procedure for the addition of diethylzinc to aldehydes in the presence of 8j

Et_2Zn (1.0 mL, 1.0 M in hexane, 1.00 mmol) was added to a solution of prolinamine **8j** (9.82 mg, 50.0 μmol) in hexane (3 mL). After 20 min at r.t., freshly distilled aldehyde **1** (500 μmol) was added at 20 °C and stirring was continued for 2 d. EtOAc (5 mL) and HCl (5 mL, 1.0 M in H_2O) were added, the layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL) and dried over $MgSO_4$. Evaporation of the solvent and column chromatography (hexanes:EtOAc) provided the enantiomerically enriched alcohols **2**.

Acknowledgments

Financial support by the DFG (German research foundation) is gratefully acknowledged.

Supplementary data

Supplementary data (copies of NMR spectra and HPLC chromatograms) associated with this article can be found, in the online version, at “http://...”.

References and notes

1. Reviews: (a) Bauer, T. *Coord. Chem. Rev*. **2015**, *299*, 83–150; (b) Pu, L. *Acc. Chem. Res.* **2014**, *47*, 1523–1535; (c) Hirose, T.; Kodama, K. in *Comprehensive Organic Synthesis II*; Knochel, P., Molander G. A., Johnson, J., Eds.; Elsevier: Amsterdam, 2014; Vol. 1, pp 204–266; (d) Binder, C. M.; Singaram, B. *Org. Prep. Proced. Int.* **2011**, *43*, 139–208; (e) Paixão, M. W.; Braga, A. L.; Lüdtke, D. S. *J. Braz. Chem. Soc*. **2008**, *19*, 813–830; (f) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (g) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (h) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69.

2. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824.

3. Selected, recent work in this field: (a) Wu, H.-L.; Wu, P.-Y.; Cheng, Y.-N.; Uang, B.-J. *Tetrahedron* **2016**, *72*, 2656–2665; (b) Serra, M. E. S.; Costa, D.; Murtinho, D.; Tavares, N. C. T.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2016**, *72*, 5923–5927; (c) Szakonyi, Z.; Csőr, Á.; Csámpai, A.; Fülöp, F. *Chem.–Eur. J*. **2016**, *22*, 7163–7173; (d) Nottingham, C.; Benson, R.; Müller-Bunz, H.; Guiry P. J. *J. Org. Chem.* **2015**, *80*, 10163−10176; (e) Huang, H.; Zong, H.; Bian, G.; Song, L. *J. Org. Chem.* **2015**, *80*, 12614−12619; (f) Asami, M.; Miyairi, N.; Sasahara, Y.; Ichikawa, K.-i.; Hosoda, N.; Ito, S. *Tetrahedron* **2015**, *71*, 6796−6802; (g) Li, F.; Huang, H.; Zong, H.; Bian, G.; Song, L. *Tetrahedron Lett.* **2015**, *56*, 2071–2076; (h) Naganawa, Y.; Namba, T.; Aoyama, T.; Shoji, K.; Nishiyama, H. *Chem. Commun*. **2014**, *50*, 13224−13227; (i) Gök, Y.; Kekeç, L. *Tetrahedron Lett*. **2014**, *55*, 2727–2729; (j) Prasad, K. R.; Revu, O. *Tetrahedron* **2013**, *69*, 8422–8428.

4. Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111-7115.

5. (a) Haraguchi, R.; Matsubara, S. *Org. Lett*. **2013**, *15*, 3378–3380; (b) Canales, E.; Corey, E. J. *Org. Lett*. **2008**, *10*, 3271–3273; (c) Wu, X.; Liu, X.; Zhao, G. *Tetrahedron: Asymmetry* **2005**, *16*, 2299–2305; (d) Braga, A. L.; Lüdtke, D. S.; Schneider, P. H.; Vargas, F.; Schneider, A.; Wessjohann, L. A.; Paixão, M. W. *Tetrahedron Lett*. **2005**, *46*, 7827–7830; (e) Shibata, T.; Tabira, H.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 177–178; (f) Liu, G.; Ellman, J. A. *J. Org. Chem*. **1995** , *60*, 7712–7713; (g) Watanabe, M.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3125–3128; (h) Soai, K.; Hirose, Y.; Sakata, S. *Tetrahedron: Asymmetry* **1992**, *3*, 677–680; (i) Soai, K.; Kawase, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 781–784.

6. Additional structure–enantioselectivity studies on the lithium alkoxides of **3** and related derivatives: (a) Stingl, K.; Martens, J. *Liebigs Ann. Chem*. **1994**, 491–496; (b) Mehler, T.; Martens, J.; Wallbaum, S. *Synth. Commun*. **1993**, *23*, 2691–2699; (c) Chelucci, G.; Falorni, M.; Giacomelli, G. *Tetrahedron: Asymmetry* **1990**, *1*, 843–849; (d) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233–5236; (e) Ref. 4.

7. Other prolinols and prolinamines: (a) Asami, M.; Hasome, A.; Yachi, N.; Hosoda, N.; Yamaguchi, Y.; Ito, S. *Tetrahedron: Asymmetry* **2016**, *27*, 322–329; (b) Kang, S. Y.; Park, Y. S. *Bull. Korean Chem. Soc.* **2016**, *37*, 108–111; (c) Hosoda, N.; Ito, H.; Takimoto, T.; Asami, M. *Bull. Chem. Soc. Jpn.* **2012**, *85*, 1014–1022; (d) Yang, X.; Shen, J.; Da, C.; Wang, R.; Choi, M. C. K.; Yang, L.; Wong, K.-y. *Tetrahedron: Asymmetry* **1999**, *10*, 133–138; (e) Asami, M.; Watanabe, H.; Honda, K.; Inoue, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4165–4173; (f) Wilken, J.; Kossenjans, M.; Gröger, H.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2007–2015; (g) Asami, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1687–1690; (h) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1993**, *4*, 637–640; (i) Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *47*, 8251–8258.

8. (a) Kaldun, J.; Krimalowski, A.; Breuning, M. *Tetrahedron Lett.* **2016**, *57*, 2492–2495; (b) Kaldun, J.; Prause, F.; Scharnagel, D.; Freitag, F.; Breuning, M. *ChemCatChem* **2016**, *8*, 1846–1856; (c) Prause, F.; Arensmeyer, B.; Fröhlich, B.; Breuning, M. *Catal. Sci. Technol.* **2015**, *5*, 2215–2226; (d) Scharnagel, D.; Prause, F.; Kaldun, J.; Haase, R. G.; Breuning, M. *Chem. Commun.* **2014**, *50*, 6623–6625.

9. Prause, F.; Kaldun, J.; Arensmeyer, B.; Wennemann, B.; Fröhlich, B.; Scharnagel, D.; Breuning, M. *Synthesis* **2015**, *47*, 575–586.

10. Synthesis of 5-*cis*-substituted α,α-diphenylprolinols: (a) Trost, B. M.; Miege, F. *J. Am. Chem. Soc.* **2014**, *136*, 3016–3019; (b) Nyerges, M.; Bendell, D.; Arany, A.; Hibbs, D. E.; Coles, S. J.; Hursthouse, M. B.; Groundwater, P. W.; Meth-Cohn, O. *Tetrahedron* **2005**, *61*, 3745−3753; (c) Ref. 12.

11. *Cis*-selective reductive cyclizations: (a) Pei, Z.; Li, X.; Longenecker, K.; von Geldern, T. W.; Wiedeman, P. E.; Lubben, T. H.; Zinker, B. A.; Stewart, K.; Ballaron, S. J.; Stashko, M. A.; Mika, A. K.; Beno, D. W. A.; Long, M.; Wells, H.; Kempf-Grote, A. J.; Madar, D. J.; McDermott, T. S.; Bhagavatula, L.; Fickes, M. G.; Pireh, D.; Solomon, L. R.; Lake, M. R.; Edalji, R.; Fry, E. H.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2006**, *49*, 3520−3535; (b) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301−7314; (c) Rudolph, A. C.; Machauer, R.; Martin, S. F. *Tetrahedron Lett.* **2004**, *45*, 4895−4898; (d) Momotake, A.; Togo, H.; Yokoyama, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1193−1200; (e) Xu, Y.-z.; Choi, J.; Calaza, M. I.; Turner, S.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 4069−4078; (f) Fournie-Zaluski, M.-C.; Coric, P.; Thery, V.; Gonzalez, W.; Meudal, H.; Turcaud, S.; Michel, J.-B.; Roques, B. P. *J. Med. Chem.* **1996**, *39*, 2594−2608.

12. Moro, A. V.; Tiekink, E. R. T.; Zukerman-Schpector, J.; Lüdtke, D. S.; Correia, C. R. D. *Eur. J. Org. Chem.* **2010**, 3696–3703.

13. (a) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2003**, *125*, 5130–5138; (b) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998–9006.

14. (a) Alvarez-Ibarra, C.; Luján, J. F. C.; Quiroga-Feijóo, M. L. *Tetrahedron: Asymmetry* **2010**, *21*, 2334–2345; (b) Leven, M.; Schlörer, N. E.; Neudörfl, J. M.; Goldfuss, B. *Chem.–Eur. J*. **2010**, *16*, 13443–13449; (c) Szakonyi, Z.; Balázs, Á.; Martinek, T. A.; Fülöp, F. *Tetrahedron: Asymmetry* **2006**, *17*, 199–204; (d) Jimeno, C.; Pastó, M.; Riera, A.; Pericàs, M. A. *J. Org. Chem.* **2003**, *68*, 3130−3138; (e) Panda,

M.; Phuan, P.-W.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 564−571; (f) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464–2465; (g) Vázquez, J.; Pericàs, M. A.; Maseras, F.; Lledós, A. *J. Org. Chem.* **2000**, *65*, 7303−7309; (h) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77−82; (i) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128−133; (j) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773–8776; (k) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, 117, 6327–6335; (l) Ref. 3c.

15. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, Butterworth-Heinemann: Oxford, 2000.

Supporting Information

Enantioselective addition of diethylzinc to aldehydes catalyzed by 5-*cis*-substituted proline derivatives

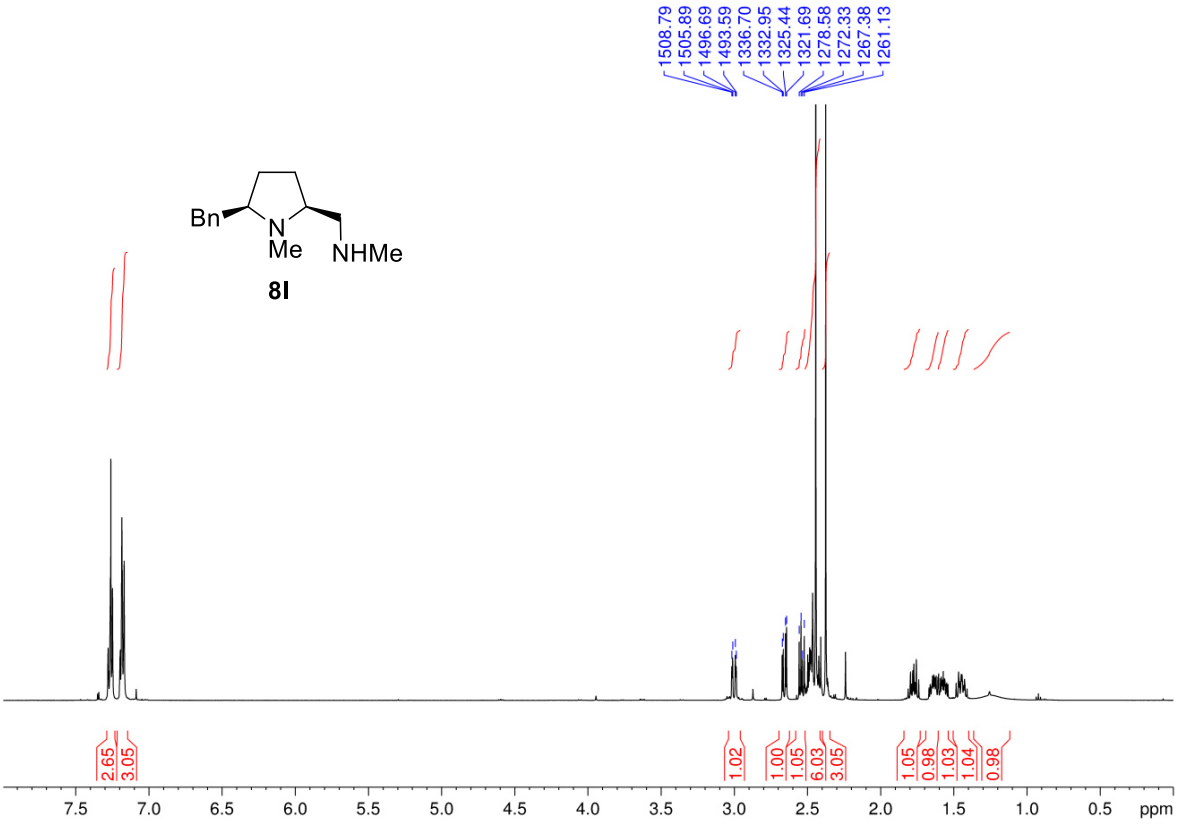
Felix Prause, Stefan Wagner and Matthias Breuning*

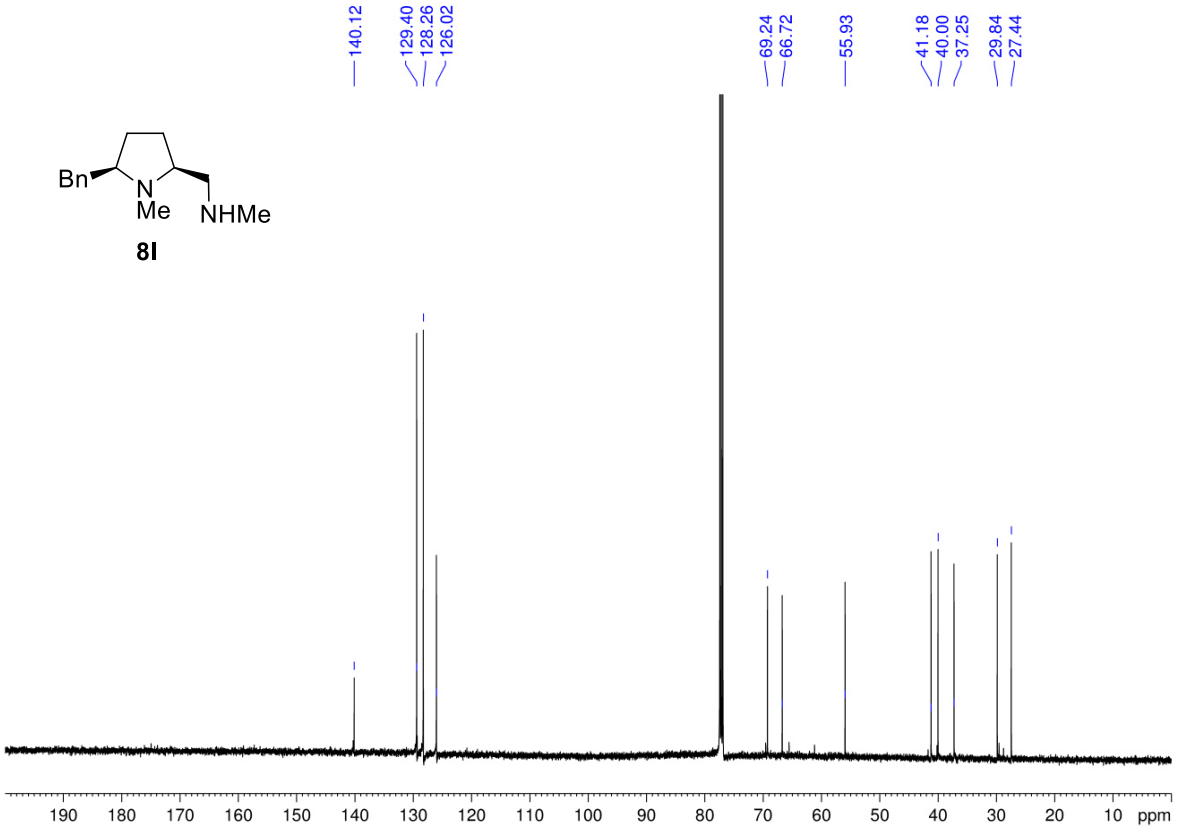
Organic Chemistry Laboratory
University of Bayreuth
Universitätsstraße 30
95447 Bayreuth, Germany
E-mail: Matthias.Breuning@uni-bayreuth.de

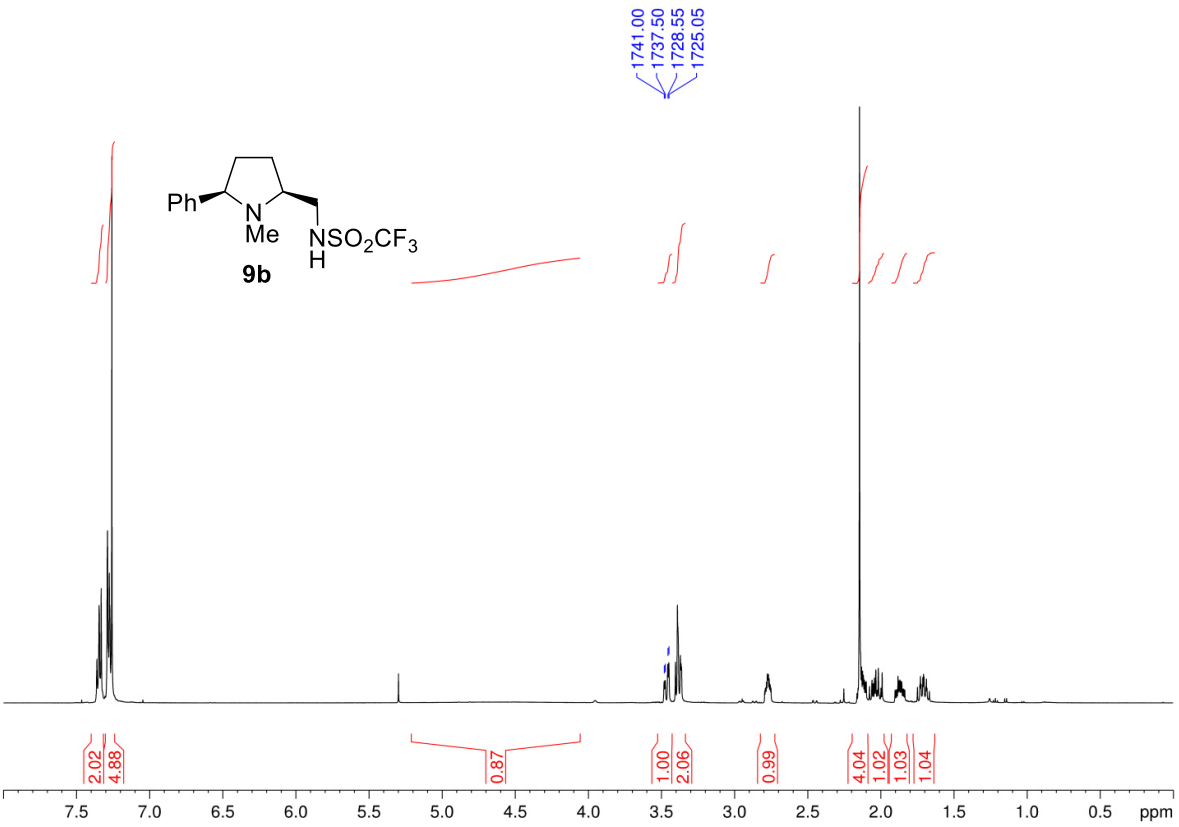
Table of Contents

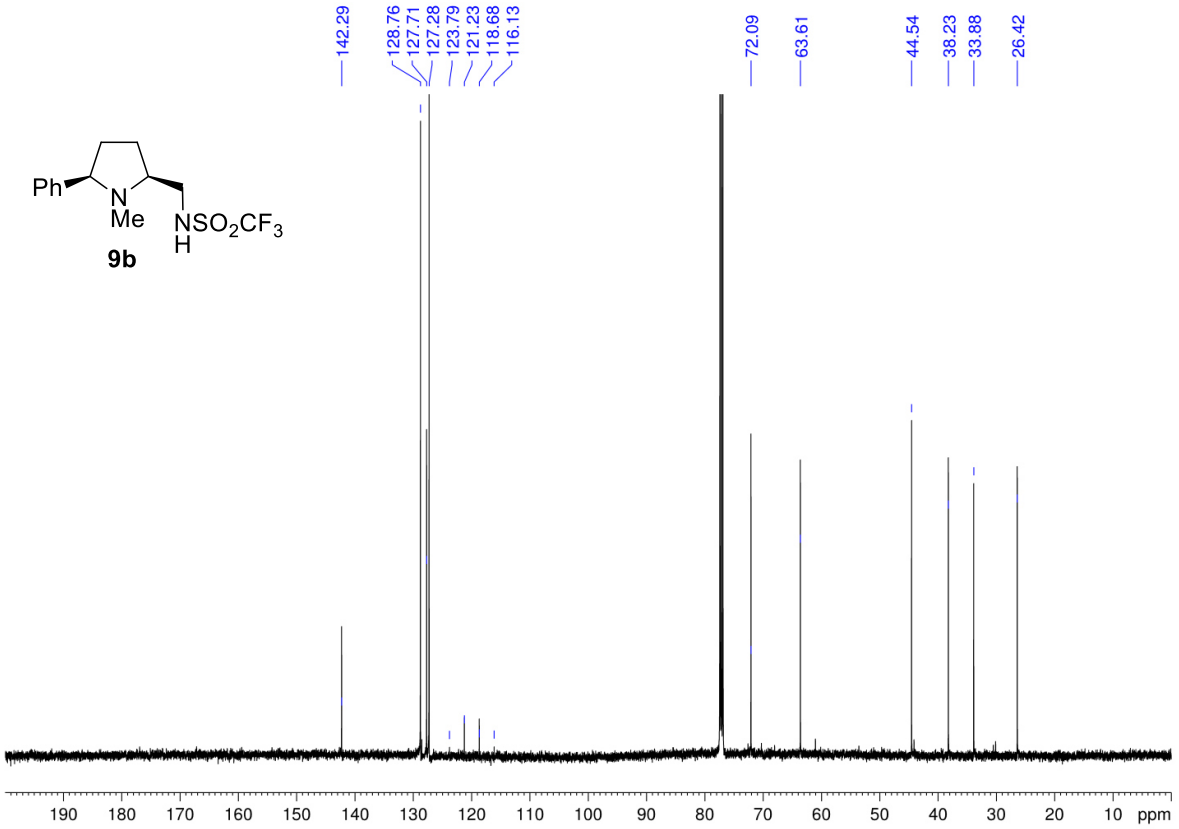
1. Copies of ^{1}H and ^{13}C NMR spectra

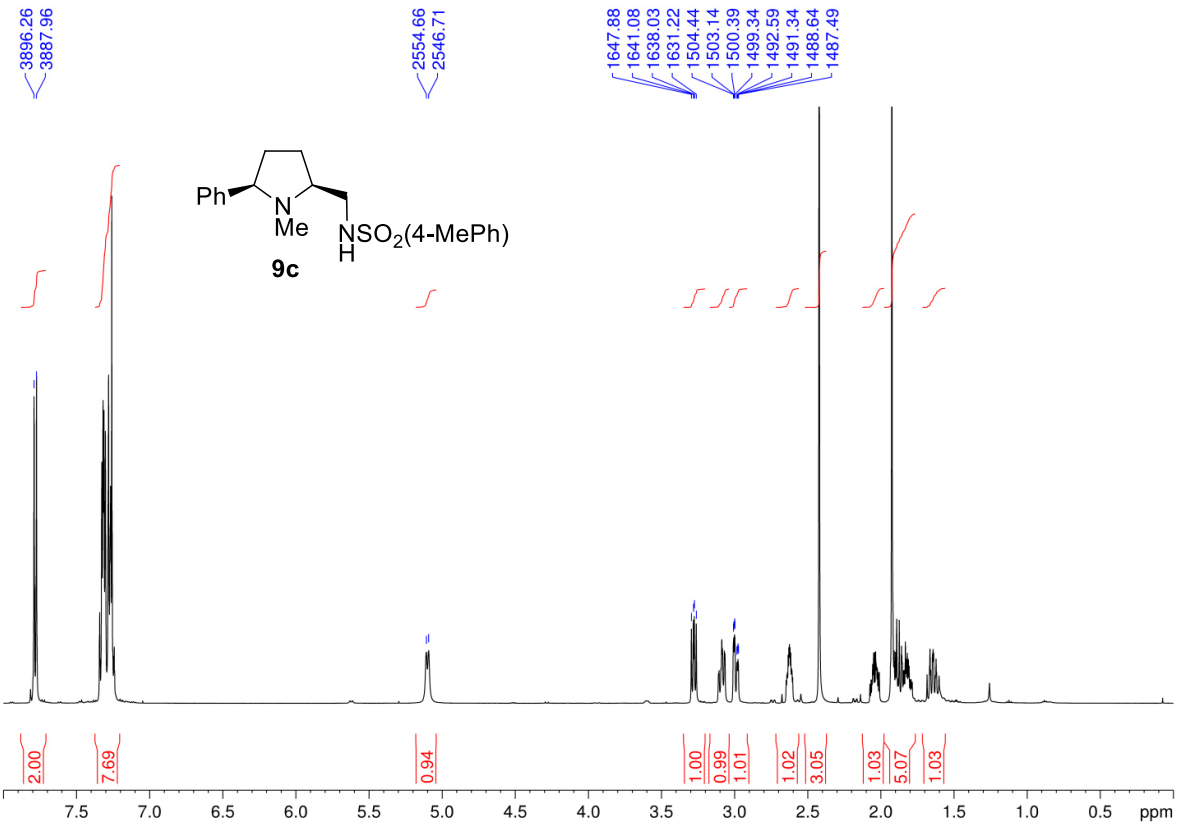
The ^{1}H and ^{13}C NMR spectra of all new compounds are listed in numerical order.

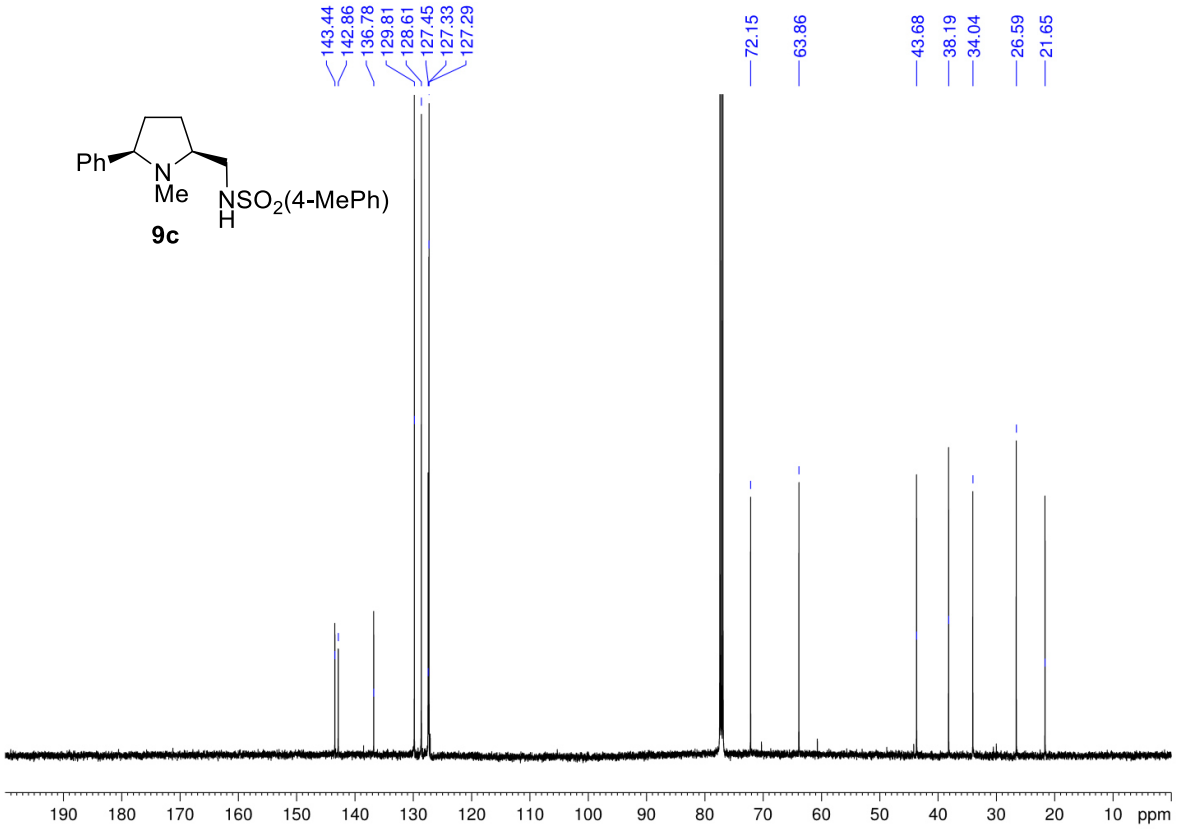


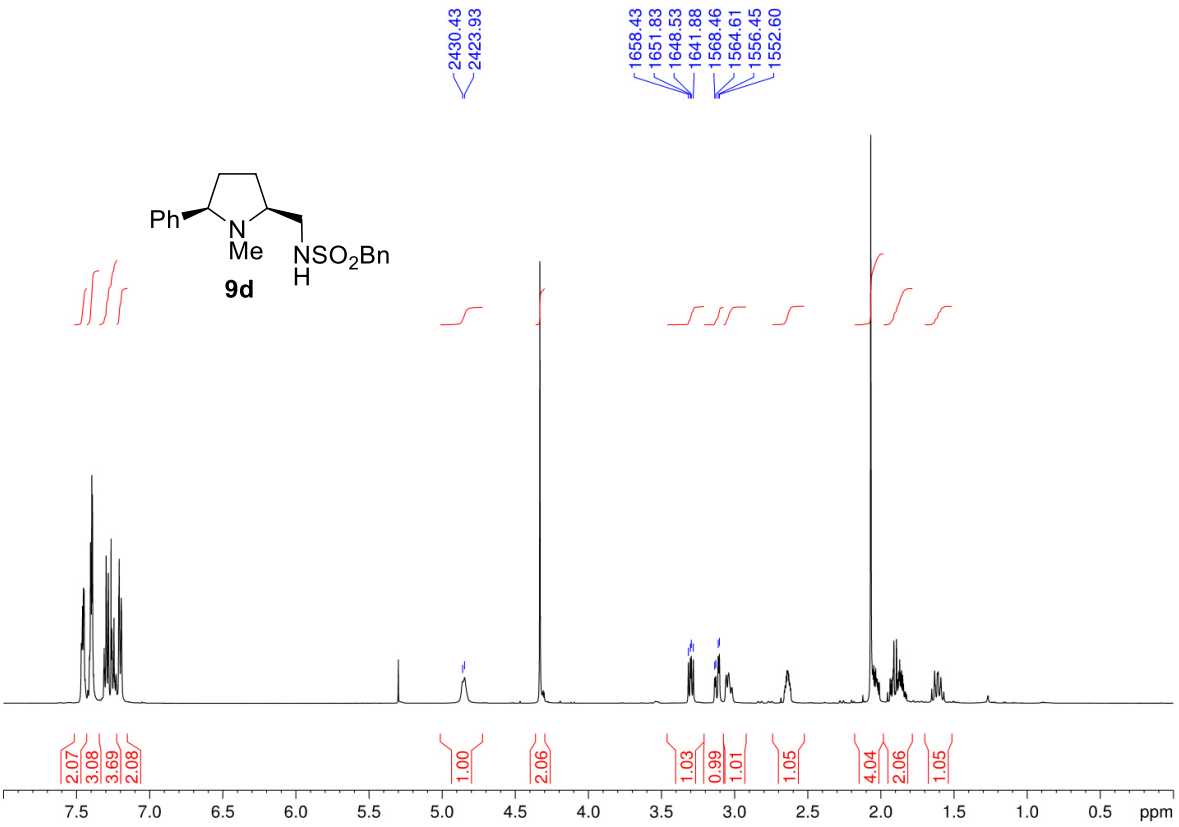


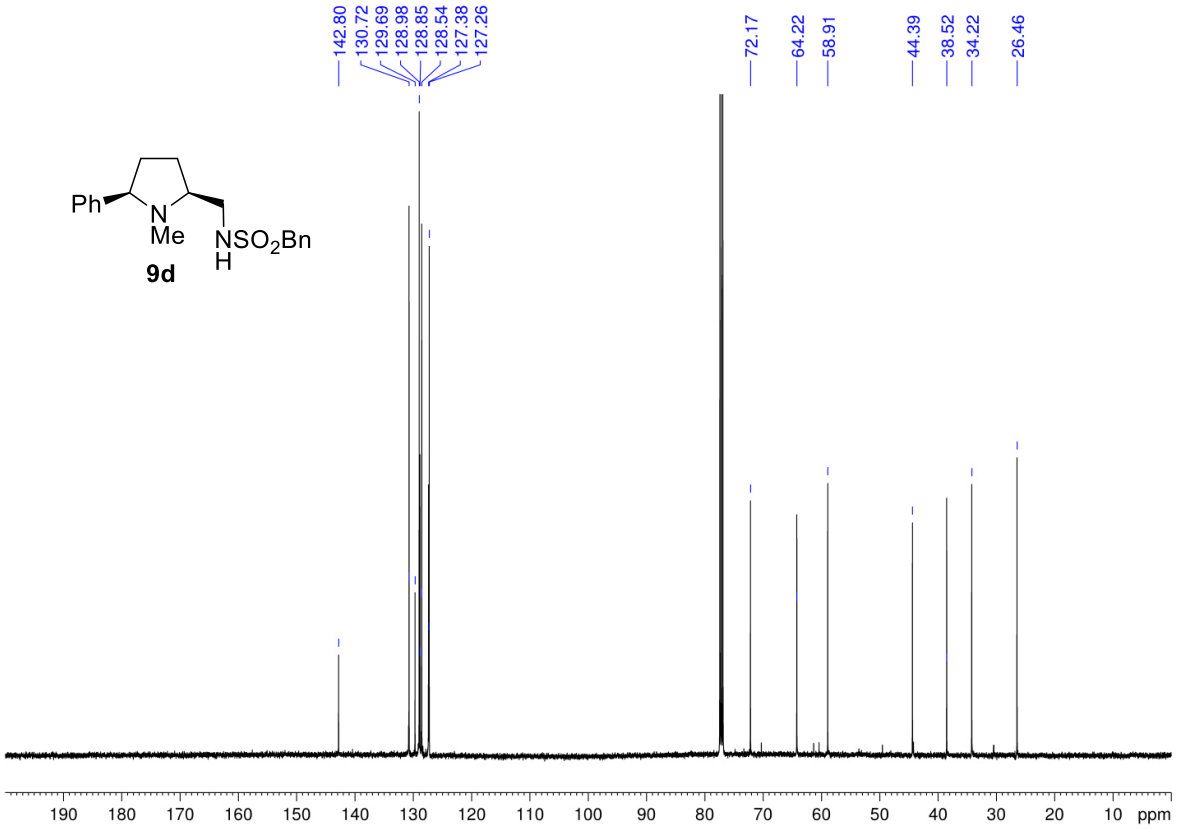

1741.00
1737.50
1728.55
1725.05
Ph
N
Me
NSO2CF3
H
9b
2.02
4.88
0.87
1.00
2.06
0.99
4.04
1.02
1.03
1.04
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

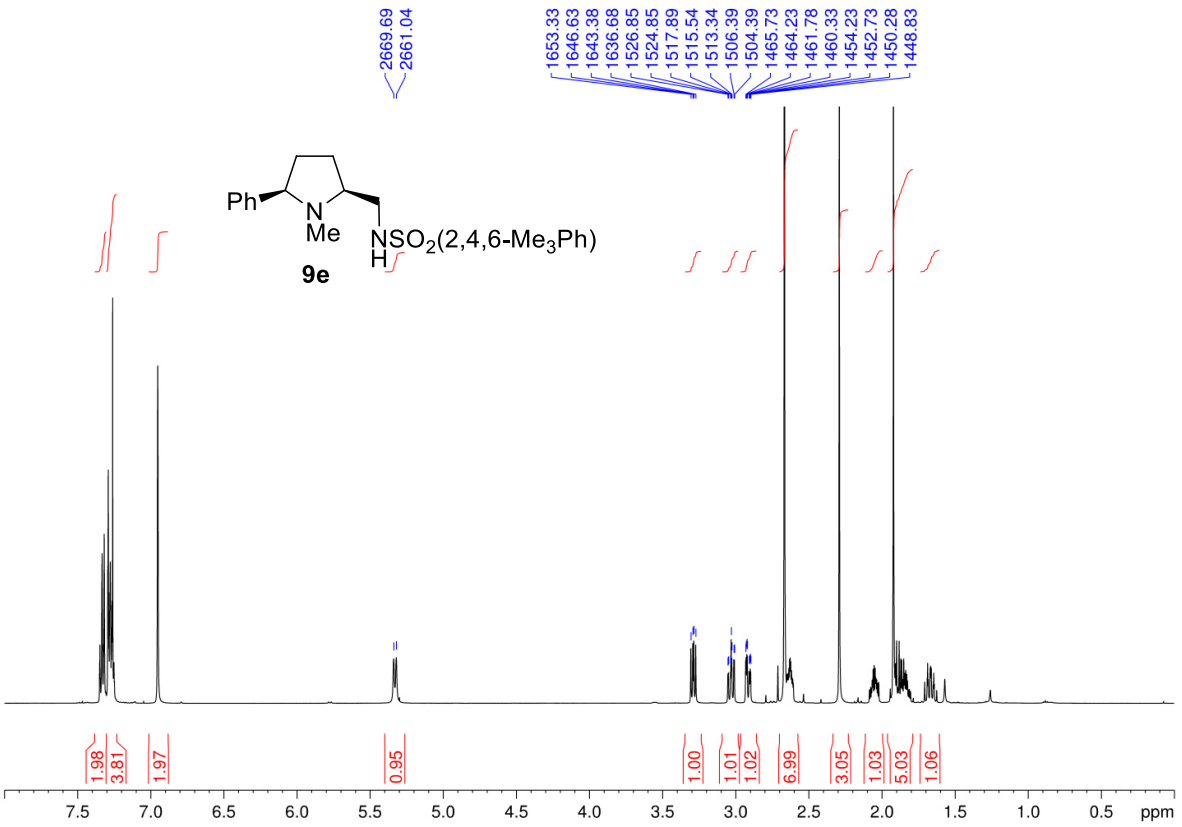

142.29
128.76
127.71
127.28
123.79
121.23
118.68
116.13
72.09
63.61
44.54
38.23
33.88
26.42
Ph
N
Me
NSO2CF3
H
9b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

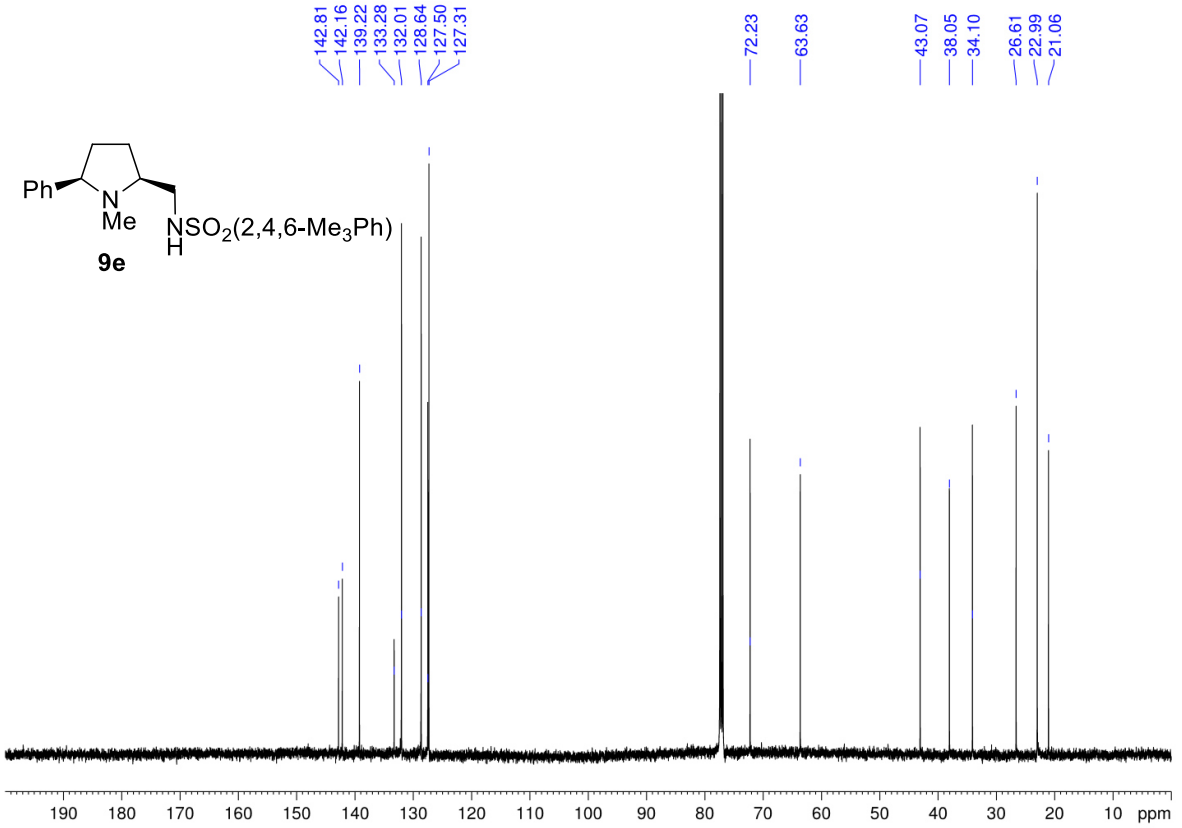

3896.26
3887.96
2554.66
2546.71
1647.88
1641.08
1638.03
1631.22
1504.44
1503.14
1500.39
1499.34
1492.59
1491.34
1488.64
1487.49
Ph
N
Me
NSO2(4-MePh)
H
9c
2.00
7.69
0.94
1.00
0.99
1.01
1.02
3.05
1.03
5.07
1.03
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


143.44
142.86
136.78
129.81
128.61
127.45
127.33
127.29
72.15
63.86
43.68
38.19
34.04
26.59
21.65
Ph
N
Me
NSO2(4-MePh)
H
9c
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


2430.43
2423.93
1658.43
1651.83
1648.53
1641.88
1568.46
1564.61
1556.45
1552.60
Ph
N
Me
NSO2Bn
H
9d
2.07
3.08
3.69
2.08
1.00
2.06
1.03
0.99
1.01
1.05
4.04
2.06
1.05
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


142.80
130.72
129.69
128.98
128.85
128.54
127.38
127.26
72.17
64.22
58.91
44.39
38.52
34.22
26.46
Ph
N
Me
NSO2Bn
H
9d
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


2669.69
2661.04
1653.33
1646.63
1643.38
1636.68
1526.85
1524.85
1517.89
1515.54
1513.34
1506.39
1504.39
1465.73
1464.23
1461.78
1460.33
1454.23
1452.73
1450.28
1448.83
Ph
N
Me
NSO2(2,4,6-Me3Ph)
H
9e
1.98
3.81
1.97
0.95
1.00
1.01
1.02
6.99
3.05
1.03
5.03
1.06
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

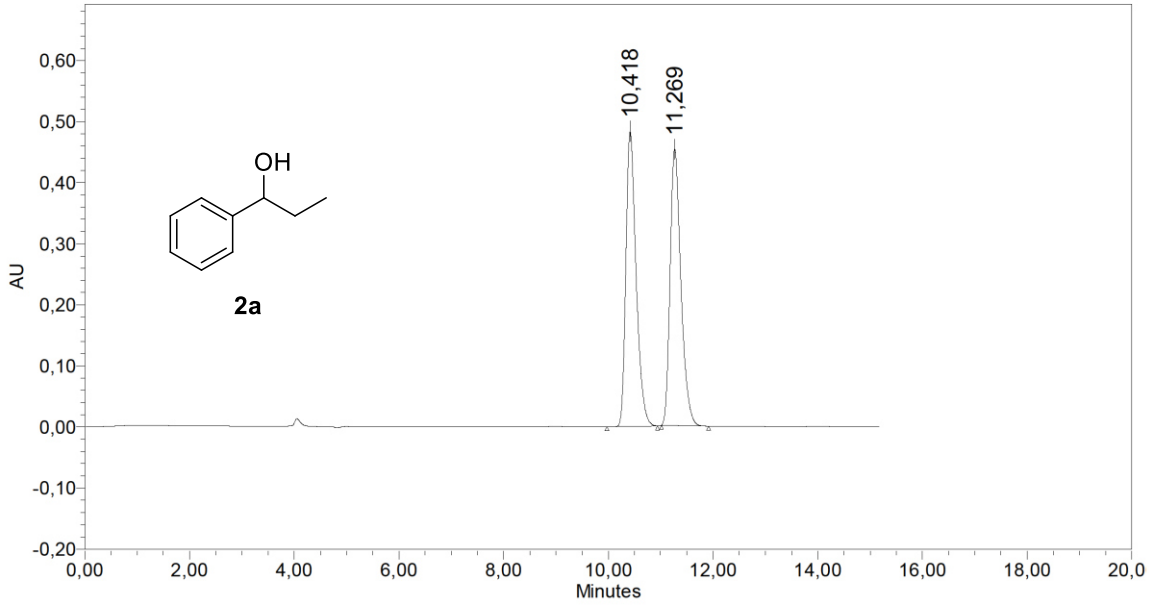

142.81
142.16
139.22
133.28
132.01
128.64
127.50
127.31
72.23
63.63
43.07
38.05
34.10
26.61
22.99
21.06
Ph
N
Me
NSO2(2,4,6-Me3Ph)
H
9e
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

2. Copies of HPLC chromatograms

The HPLC chromatograms of alcohols **2a**–**2l** are listed in numerical order.

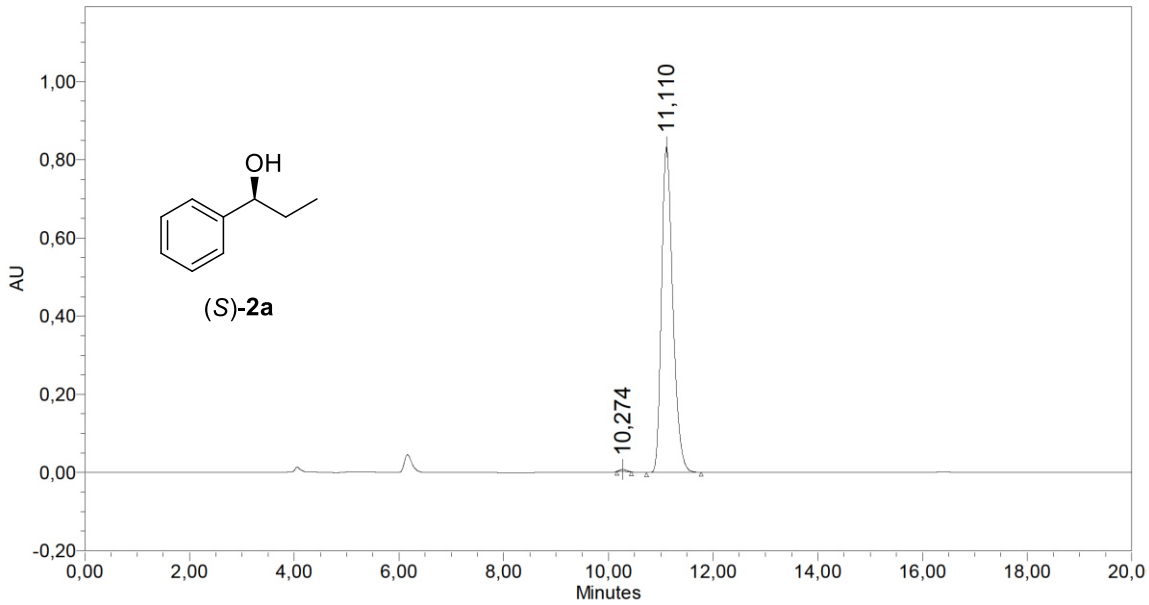
2a (racemic sample):

HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*PrOH 95:5, 0.8 mL/min, 215 nm.



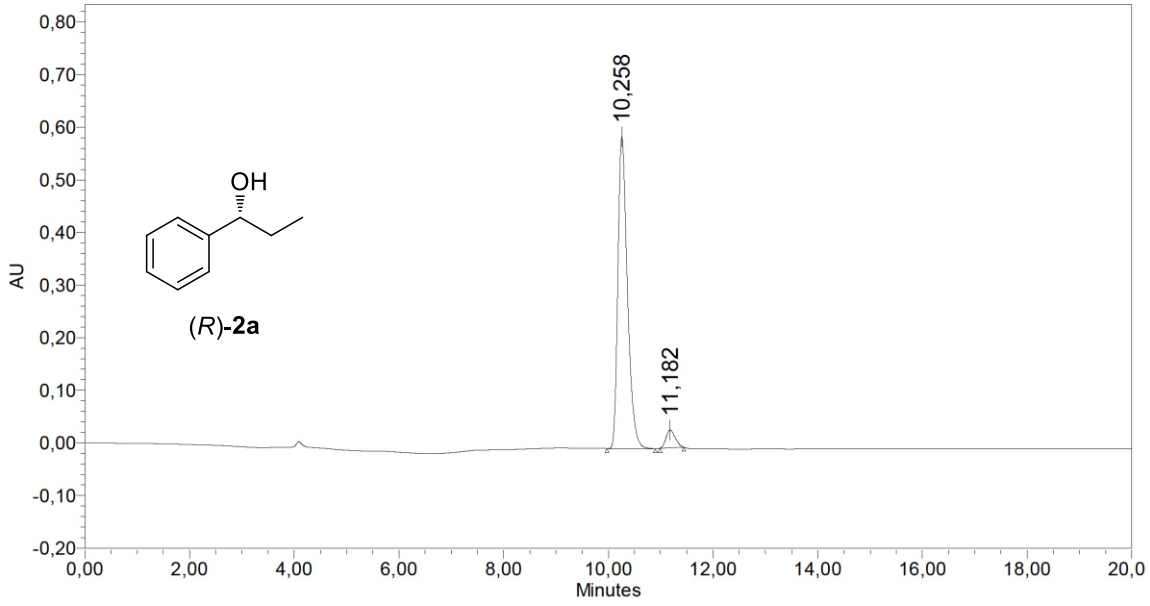
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	10,42	9,98	10,94	483233	51,62	6515589	50,11
2	11,27	11,02	11,92	452897	48,38	6487650	49,89

(*S*)-**2a** (99% ee, see Table 1, entry 1):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	10,27	10,17	10,44	5231	0,62	48516	0,39
2	11,11	10,73	11,78	833479	99,38	12476150	99,61

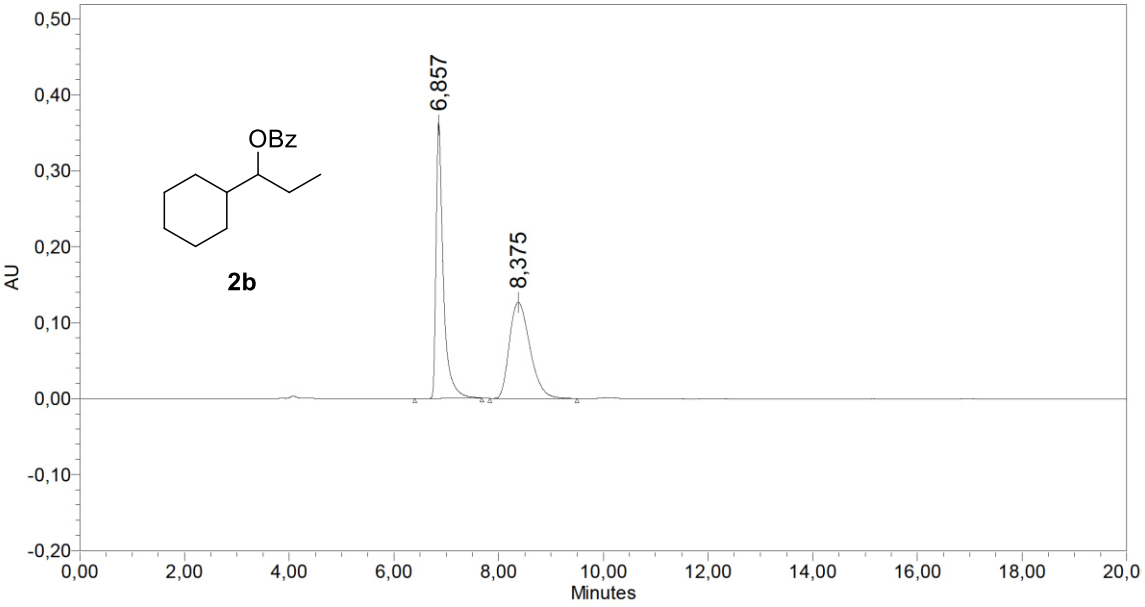
(*R*)-**2a** (90% ee, see Table 4, entry 1):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	10,26	9,98	10,90	592467	94,60	7462483	94,78
2	11,18	10,99	11,44	33840	5,40	410649	5,22

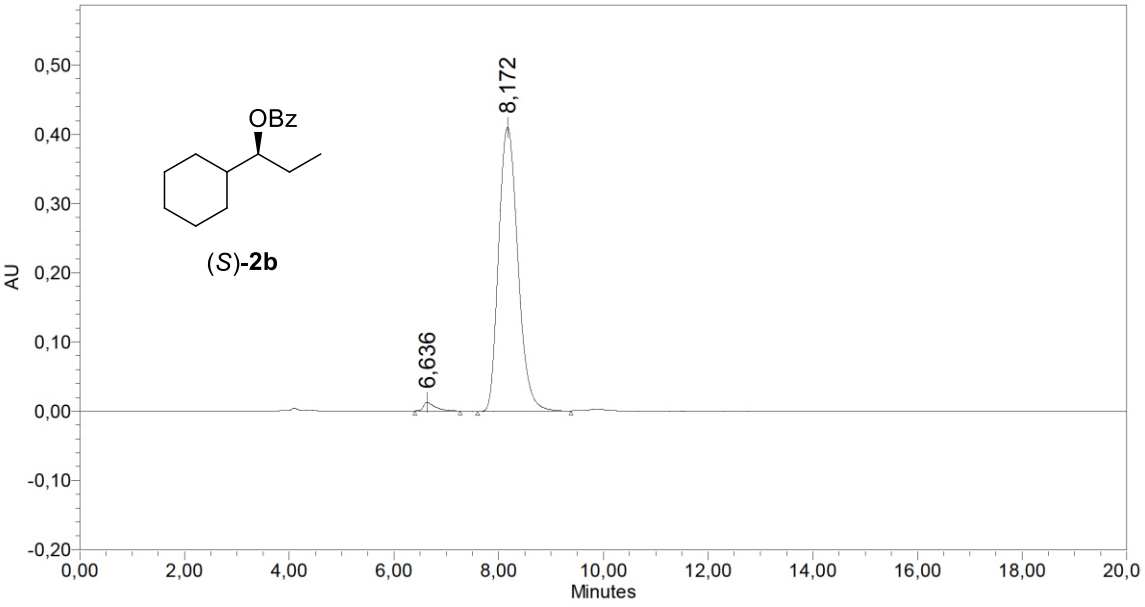
2b (racemic sample, as benzoate[1]):

HPLC conditions: Chiralpak AD-H, *n*-hexane/*i*PrOH 99:1, 0.8 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	6,86	6,40	7,68	364632	74,26	3483988	50,42
2	8,38	7,83	9,50	126357	25,74	3425732	49,58

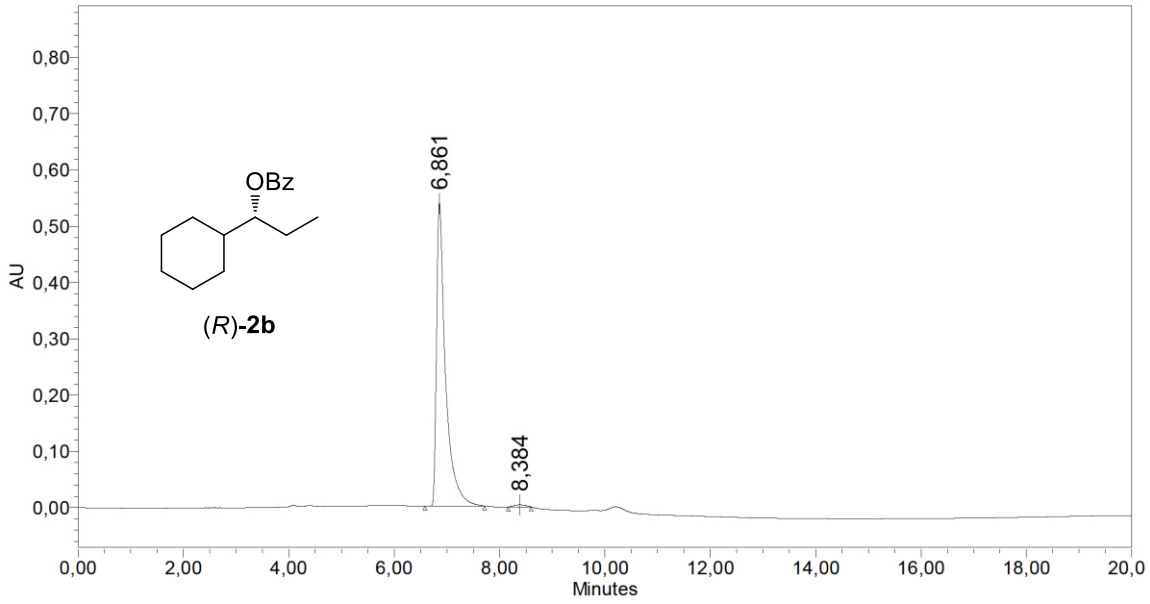
(*S*)-**2b** (96% ee, as benzoate[1], see Table 1, entry 3):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	6,64	6,40	7,27	12537	2,96	189430	1,78
2	8,17	7,60	9,38	410590	97,04	10452905	98,22

(1) Formed by reaction of 1-cyclohexyl-1-propanol with 2.0 equiv. benzoyl chloride in pyridine.

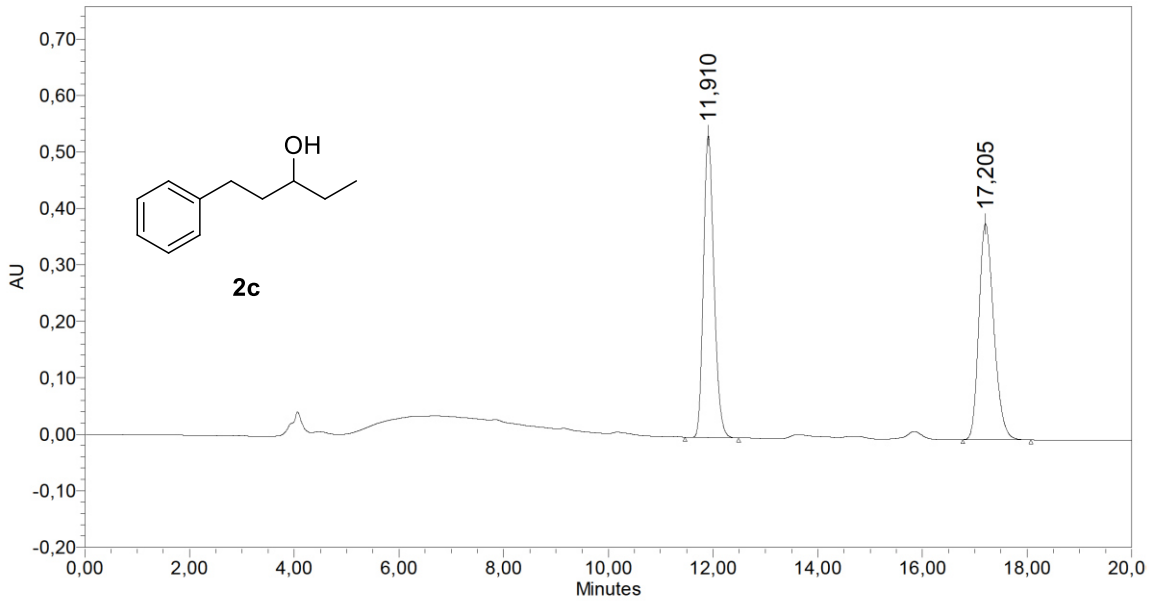
(*R*)-**2b** (98% ee, as benzoate[1], see Table 4, entry 12):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	6,86	6,58	7,72	539428	99,28	6377206	99,04
2	8,38	8,17	8,60	3912	0,72	61965	0,96

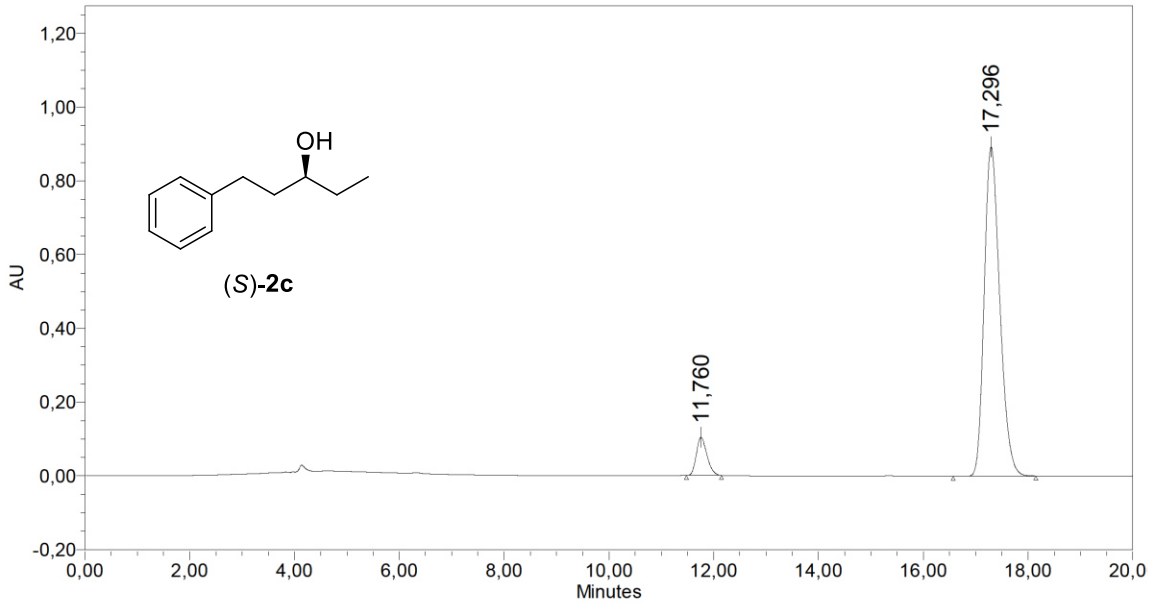
2c (racemic sample):

HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*PrOH 95:5, 0.8 mL/min, 215 nm:



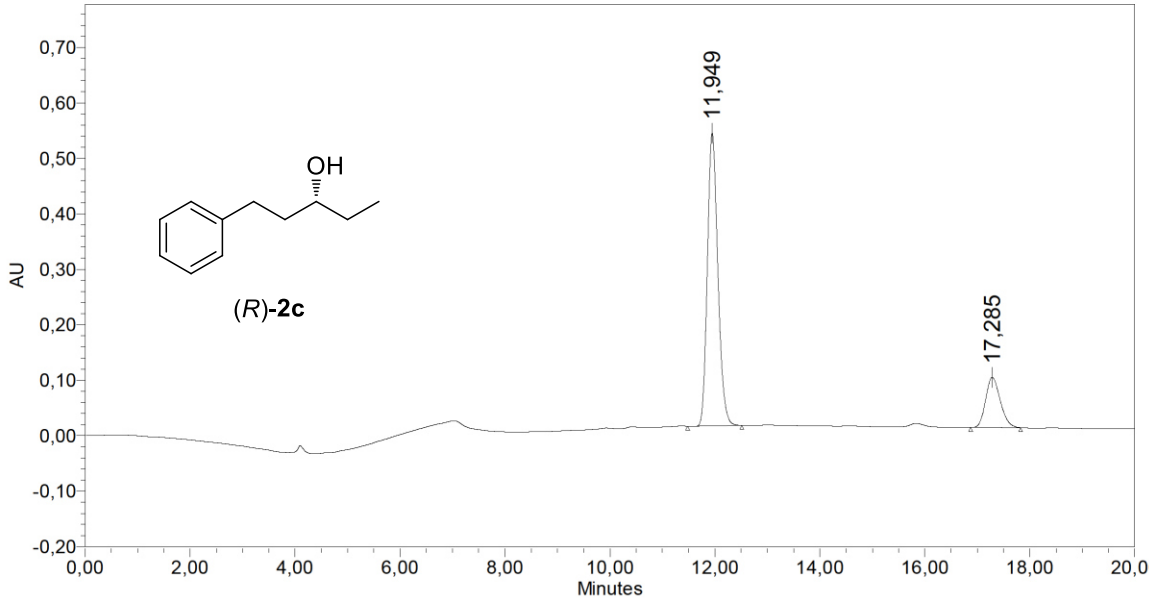
	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	11,91	11,47	12,49	535212	58,32	7431405	49,64
2	17,21	16,78	18,08	382462	41,68	7540277	50,36

(*S*)-**2c** (85% ee, see Table 1, entry 4):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	11,76	11,48	12,15	103608	10,40	1449275	7,30
2	17,30	16,58	18,15	892700	89,60	18410278	92,70

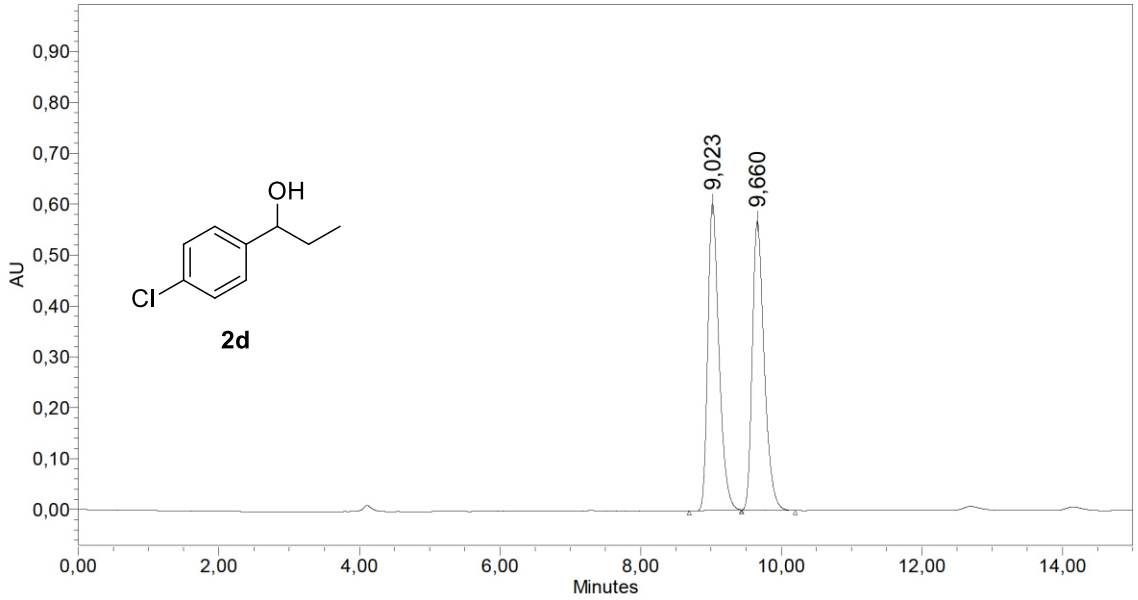
(*R*)-**2c** (62% ee, see Table 4, entry 11):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	11,95	11,48	12,52	527367	85,37	7304647	80,79
2	17,29	16,88	17,83	90390	14,63	1737170	19,21

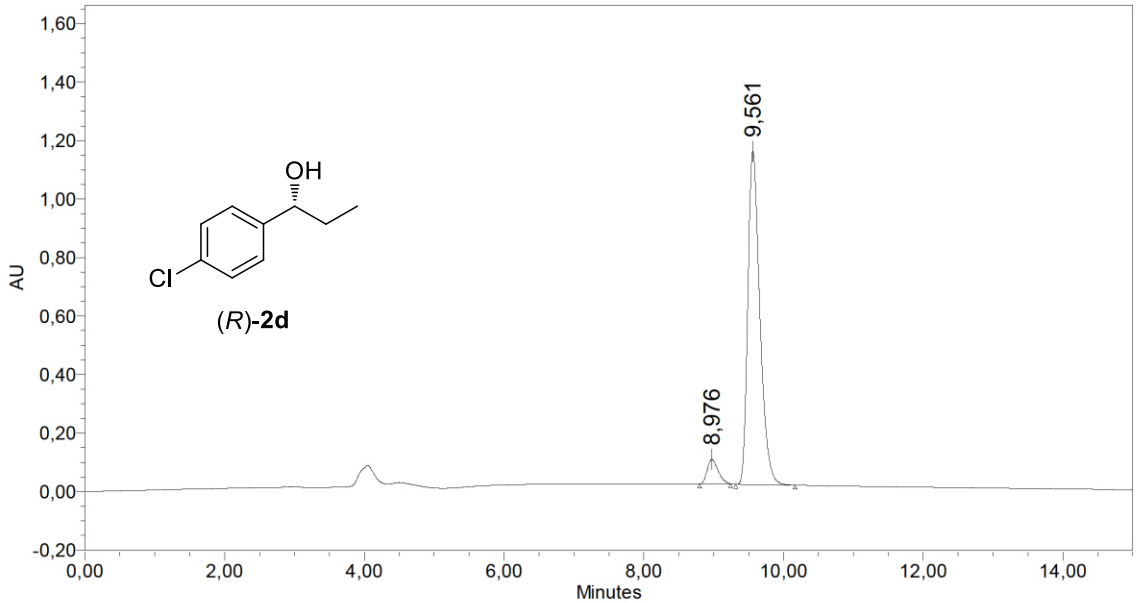
2d (racemic sample):

HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*PrOH 95:5, 0.8 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,02	8,69	9,43	603256	51,51	6650809	49,99
2	9,66	9,44	10,20	567912	48,49	6652377	50,01

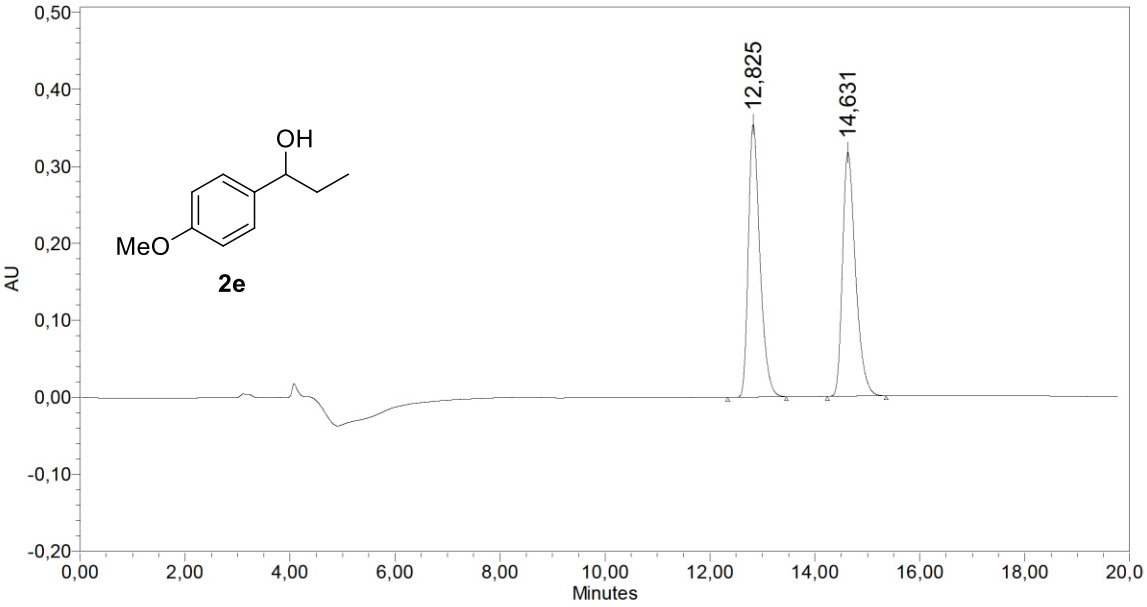
(*R*)-**2d** (88% ee, see Table 4, entry 2):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	8,98	8,80	9,24	84153	6,87	898608	6,21
2	9,56	9,32	10,17	1141545	93,13	13564453	93,79

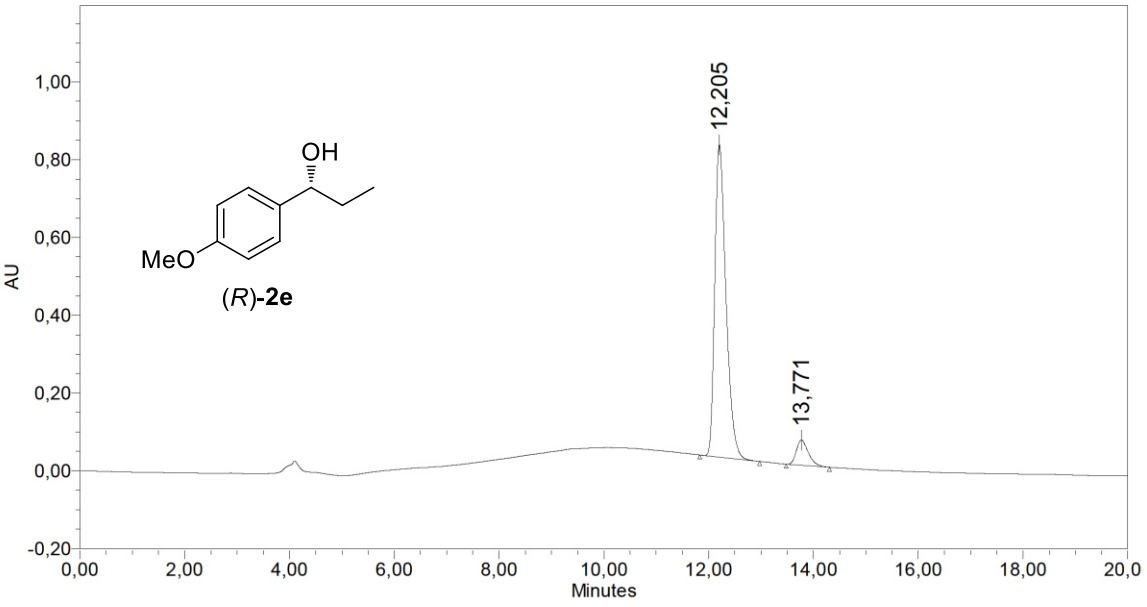
2e (racemic sample):

HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*PrOH 95:5, 0.8 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	12,83	12,34	13,46	354529	52,80	5435384	49,97
2	14,63	14,24	15,36	316936	47,20	5442232	50,03

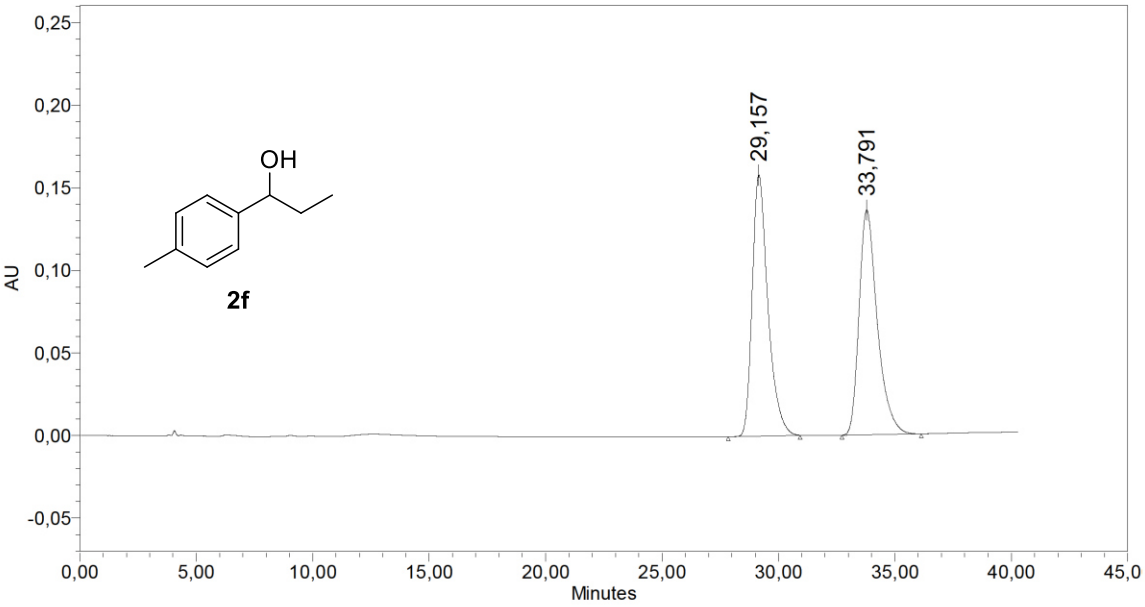
(*R*)-**2e** (84% ee, see Table 4, entry 3):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	12,21	11,83	12,98	803493	92,54	11835799	92,04
2	13,77	13,48	14,31	64734	7,46	1022928	7,96

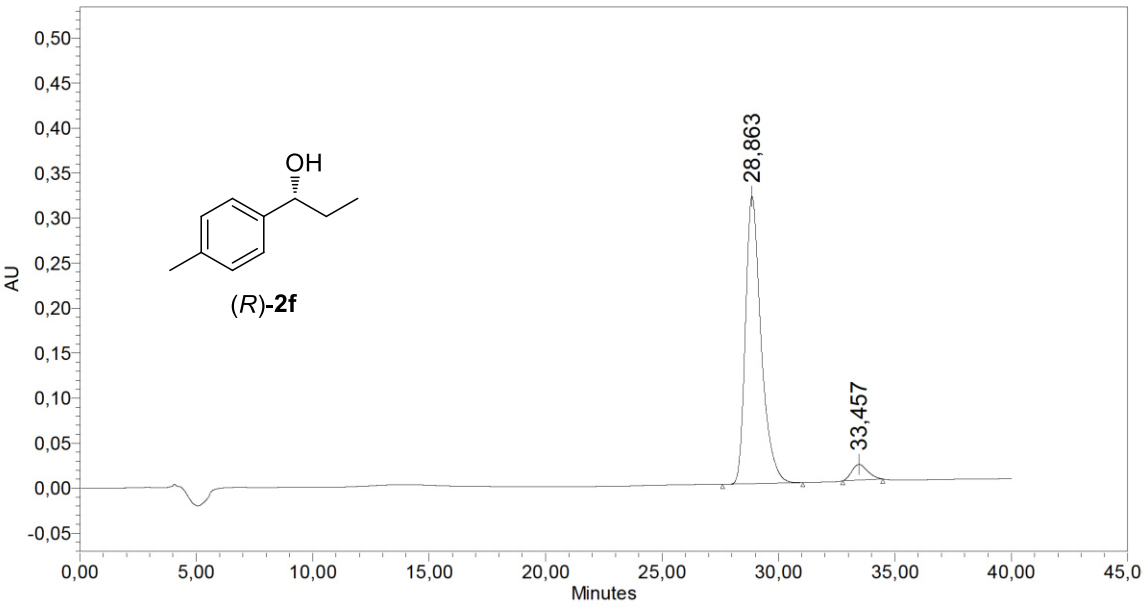
2f (racemic sample):

HPLC conditions: Chiralpak AD-H, *n*-hexane/*i*PrOH 99:1, 0.8 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	29,16	27,85	30,93	158255	53,75	7400748	50,06
2	33,79	32,73	36,13	136150	46,25	7383621	49,94

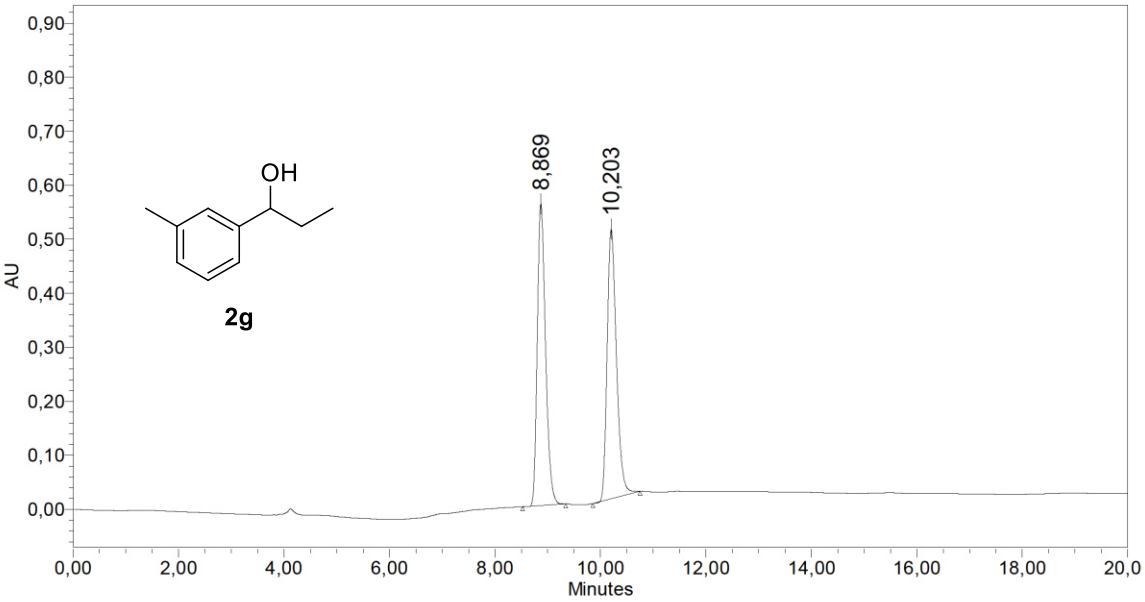
(*R*)-**2f** (90% ee, see Table 4, entry 4):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	28,86	27,60	31,05	319532	94,84	14890986	94,78
2	33,46	32,77	34,48	17369	5,16	820718	5,22

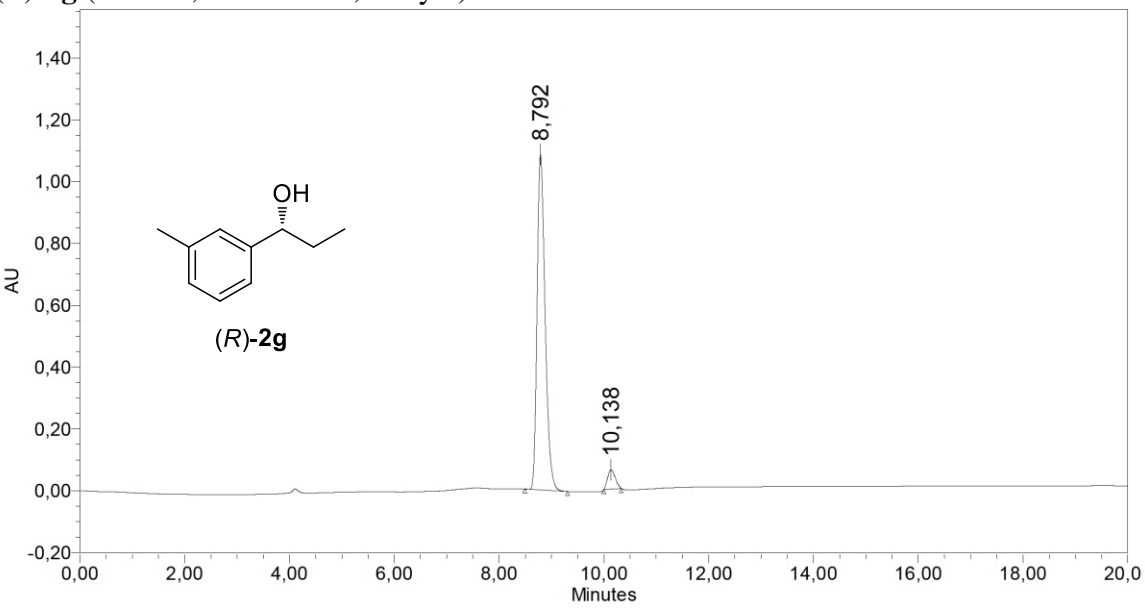
2g (racemic sample):

HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*PrOH 95:5, 0.8 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	8,87	8,53	9,34	559464	52,84	6078274	49,87
2	10,20	9,86	10,75	499394	47,16	6110411	50,13

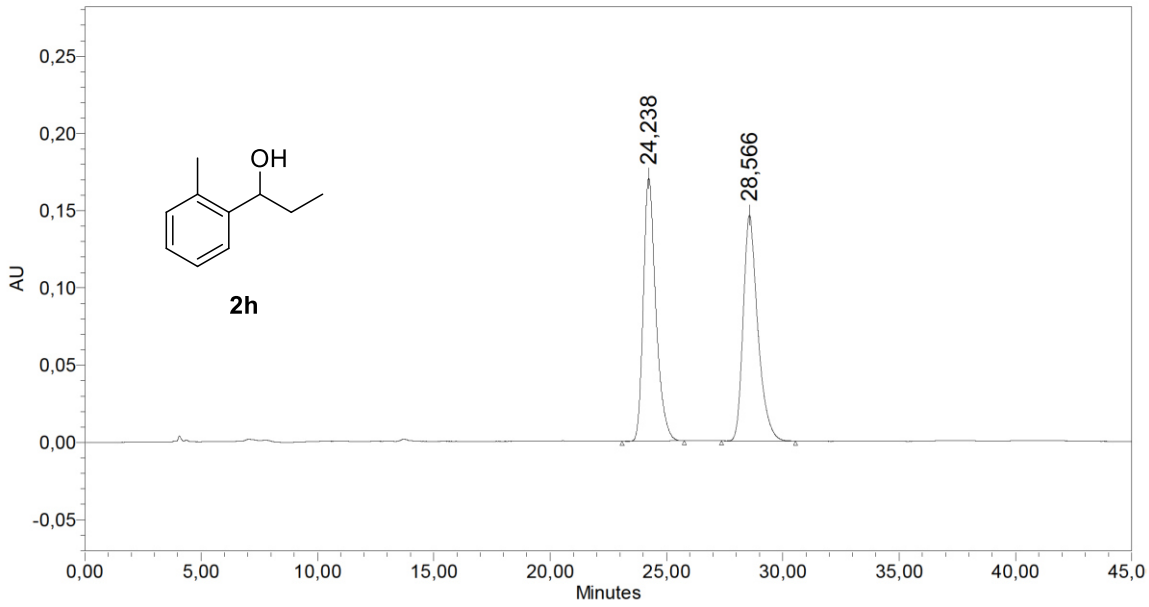
(*R*)-**2g** (90% ee, see Table 4, entry 5):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	8,79	8,49	9,31	1085669	94,58	11501954	94,83
2	10,14	10,00	10,33	62240	5,42	626722	5,17

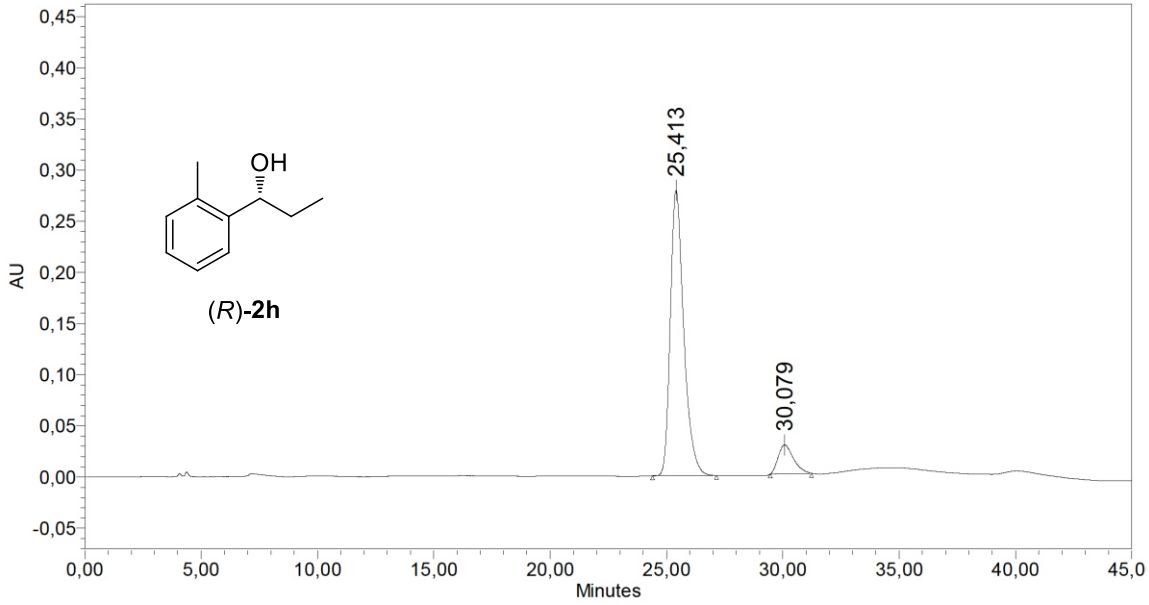
2h (racemic sample):

HPLC conditions: Chiralpak AD-H, *n*-hexane/*i*PrOH 99:1, 0.8 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	24,24	23,10	25,77	170082	53,79	6345640	49,97
2	28,57	27,37	30,55	146087	46,21	6352008	50,03

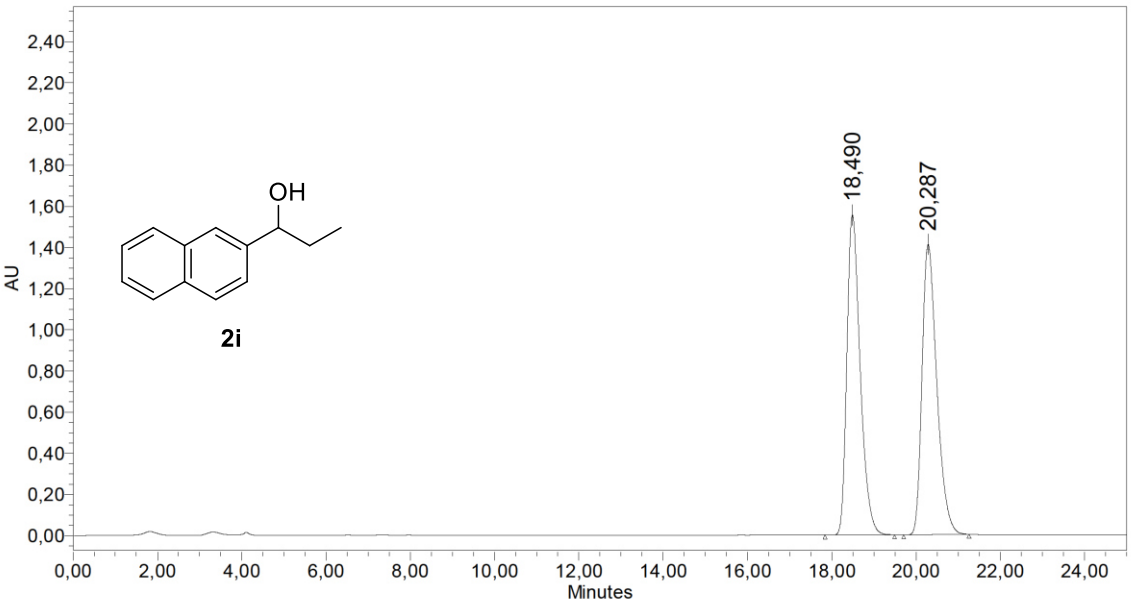
(*R*)-**2h** (80% ee, see Table 4, entry 6):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	25,41	24,40	27,15	279140	90,81	11183366	89,77
2	30,08	29,47	31,23	28245	9,19	1273833	10,23

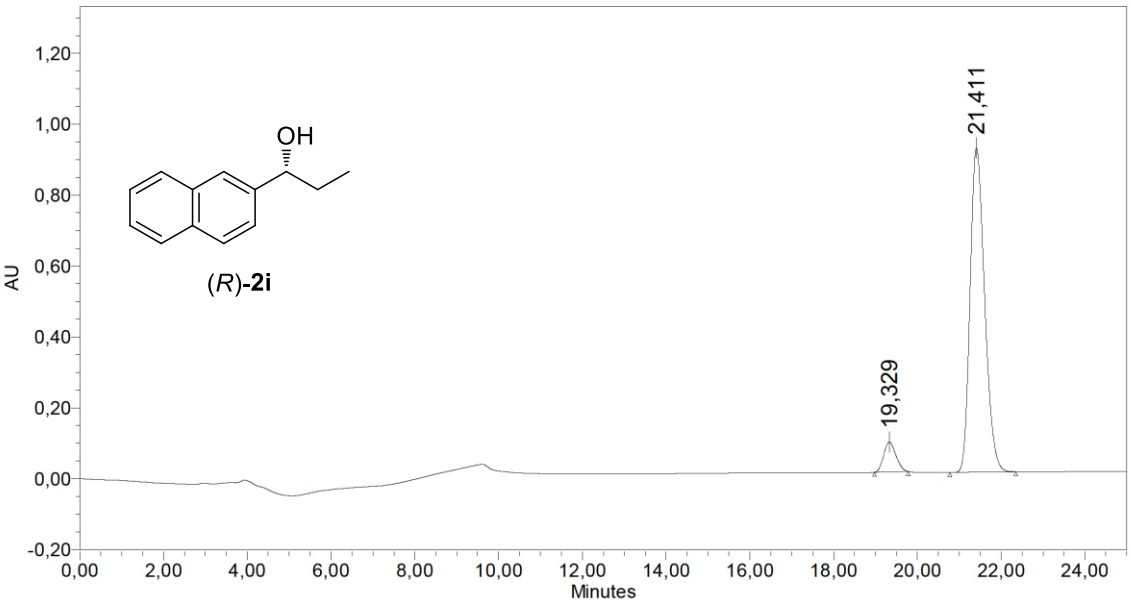
2i (racemic sample):

HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*PrOH 95:5, 0.8 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	18,49	17,84	19,49	1554322	52,42	34050792	49,89
2	20,29	19,71	21,26	1410614	47,58	34206510	50,11

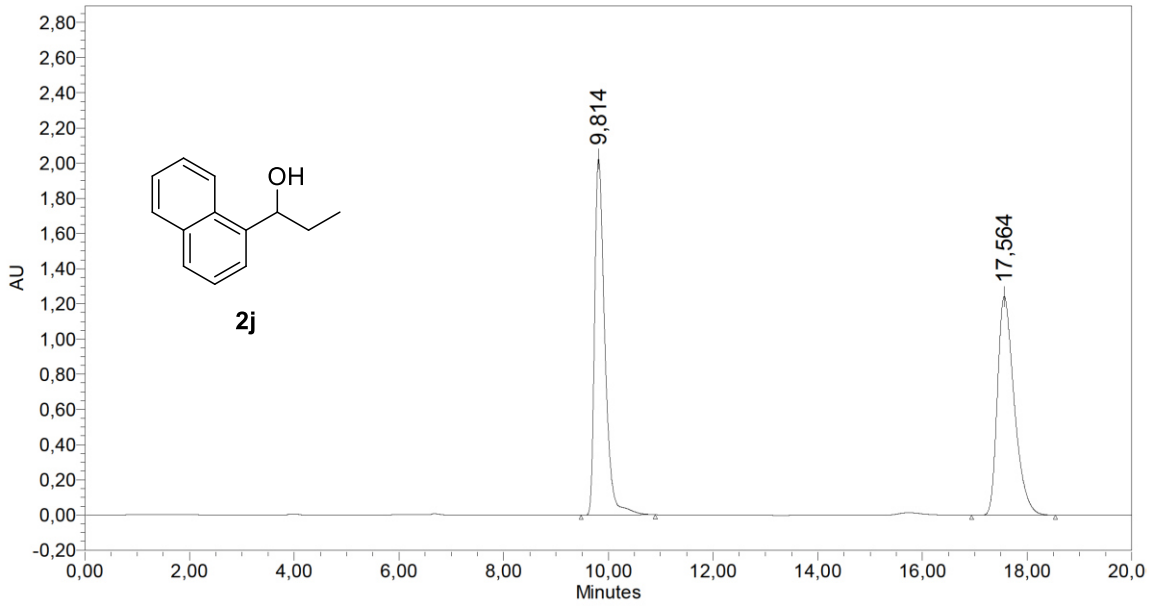
(*R*)-**2i** (86% ee, see Table 4, entry 7):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	19,33	18,98	19,78	84242	8,43	1709258	7,21
2	21,41	20,78	22,35	914621	91,57	22007572	92,79

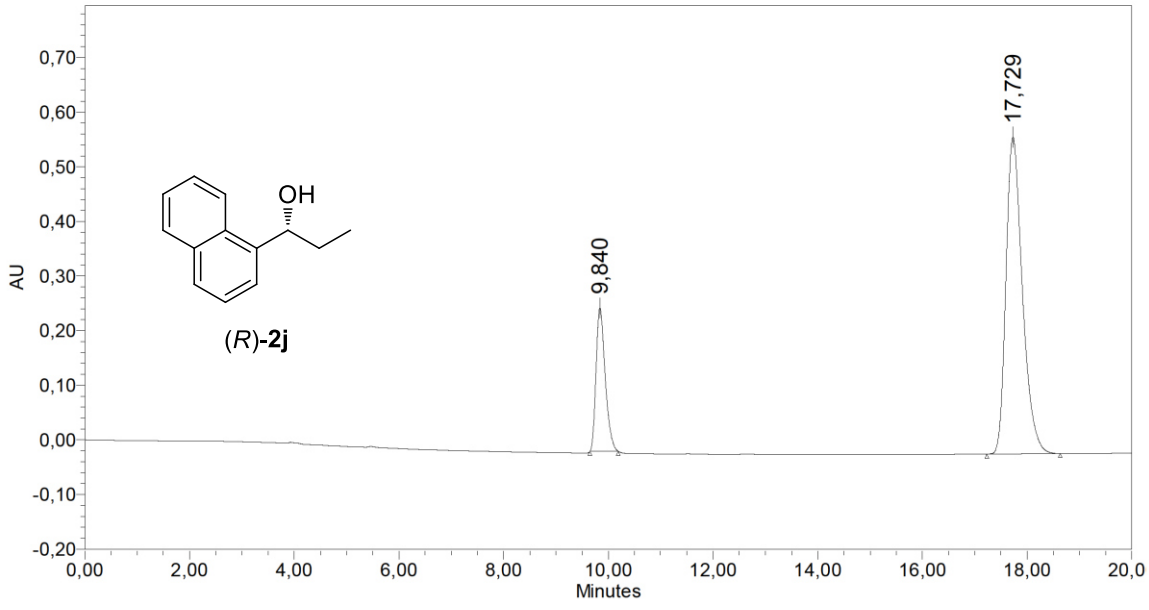
2j (racemic sample):

HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.8 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,81	9,48	10,90	2025433	61,96	27531492	49,86
2	17,56	16,94	18,54	1243257	38,04	27681393	50,14

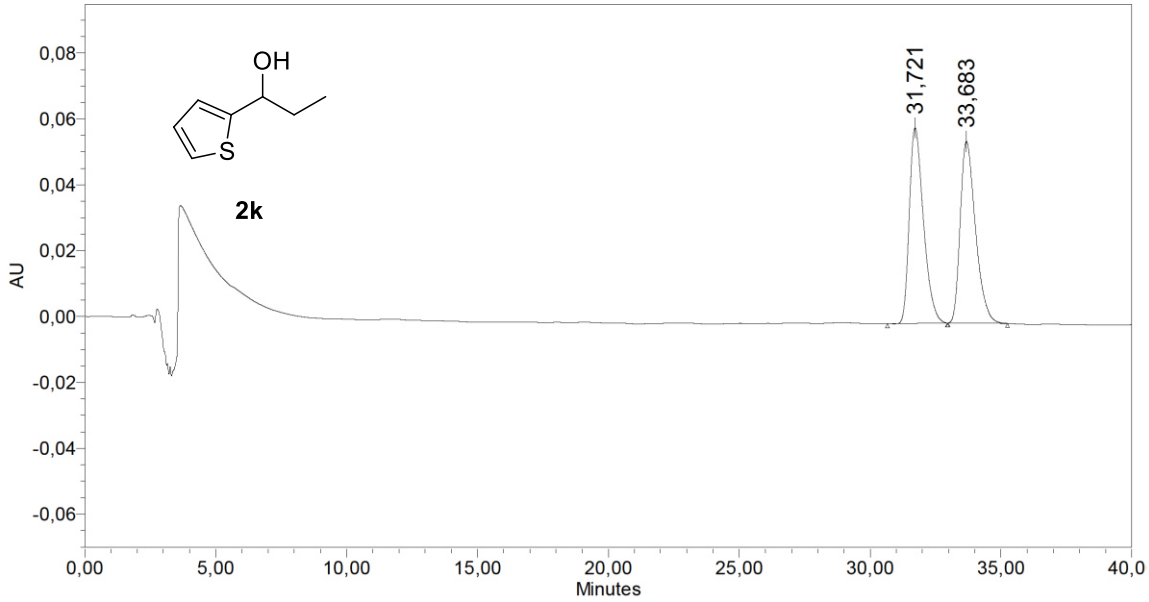
(*R*)-**2j** (60% ee, see Table 4, entry 8):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,84	9,65	10,19	262755	31,17	3182963	20,13
2	17,73	17,23	18,63	580154	68,83	12626209	79,87

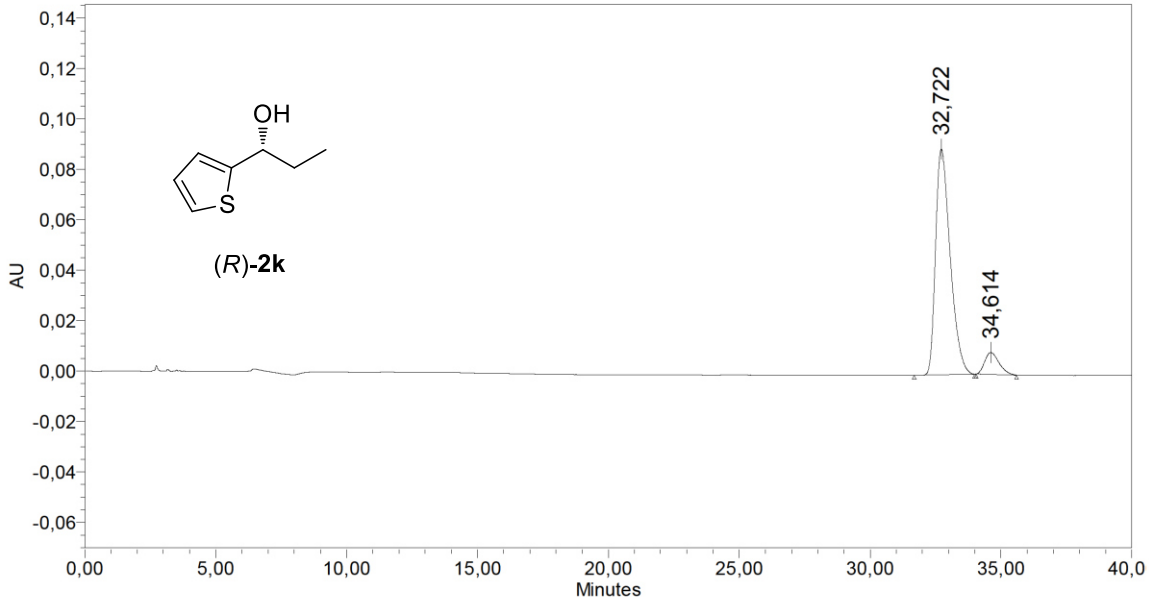
2k (racemic sample):

HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*PrOH 99.5:0.5, 1.2 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	31,72	30,67	32,96	59397	51,85	2225580	49,96
2	33,68	32,98	35,25	55155	48,15	2229092	50,04

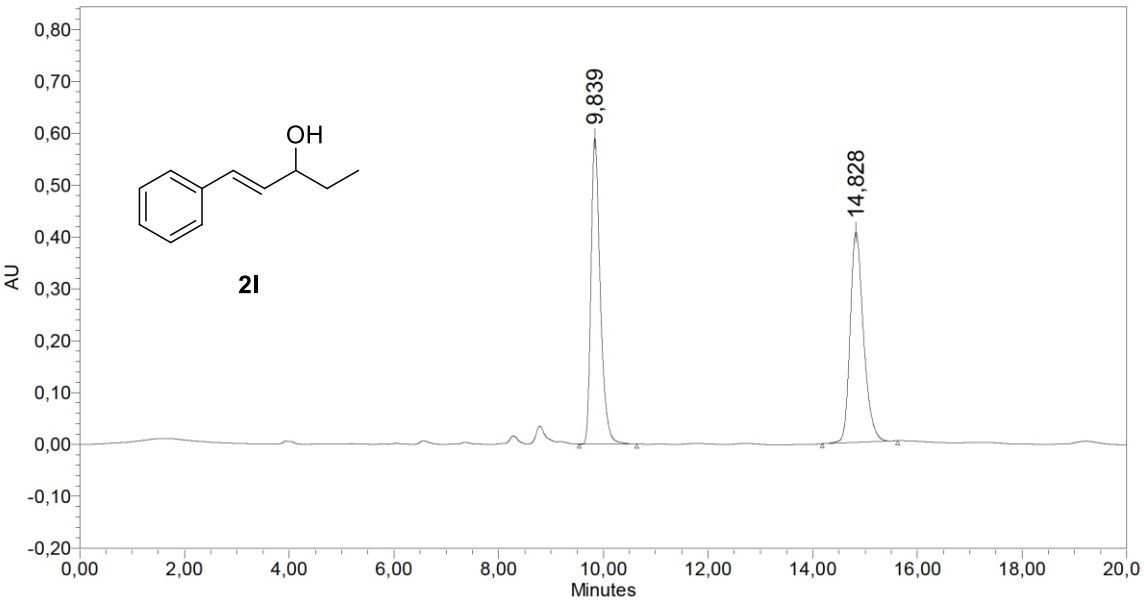
(*R*)-**2k** (83% ee, see Table 4, entry 9):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	32,72	31,69	34,00	89515	91,13	3465689	91,30
2	34,61	34,06	35,60	8712	8,87	330178	8,70

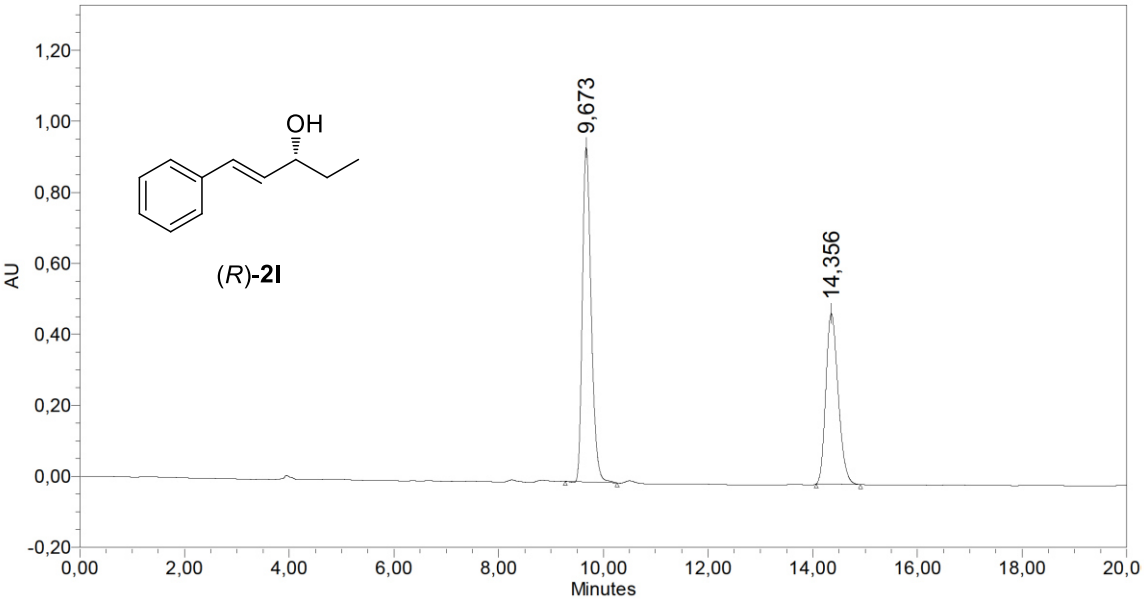
2l (racemic sample):

HPLC conditions: Chiralcel OD-3, *n*-hexane/*i*PrOH 90:10, 0.8 mL/min, 215 nm:



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,84	9,54	10,64	590122	59,28	7272881	50,41
2	14,83	14,18	15,63	405416	40,72	7153415	49,59

(*R*)-**2l** (17% ee, see Table 4, entry 10):



	Ret. Time	Start (min)	End (min)	Height	% Height	Area	% Area
1	9,67	9,28	10,27	943867	66,22	10958817	58,29
2	14,36	14,07	14,92	481572	33,78	7841574	41,71

AUFLISTUNG ALLER PUBLIKATIONEN UND MANUSKRIPTE

[6] F. Prause, S. Wagner, M. Breuning „Enantioselective addition of diethylzinc to aldehydes catalyzed by 5-*cis*-substituted proline derivatives“, Manuskript fertig zur Einreichung.

[5] J. Kaldun, F. Prause, D. Scharnagel, F. Freitag, M. Breuning, „Evaluation of 5-*cis*-Substituted Prolinamines as Ligands in Enantioselective, Copper-Catalyzed Henry Reactions“, *ChemCatChem* **2016**, *8*, 1846–1856.

[4] D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, W. Milius, M. Breuning, „The First Modular Route to Core-Chiral Bispidine Ligands and Their Application in Enantioselective Copper(II)-Catalyzed Henry Reactions“, *Chem. Eur. J.* **2015**, *21*, 12488–12500.

[3] F. Prause, B. Arensmeyer, B. Fröhlich, M. Breuning, „In-depth structure–selectivity investigations on asymmetric, copper-catalyzed oxidative biaryl coupling in the presence of 5-*cis*-substituted prolinamines“, *Catal. Sci. Technol.* **2015**, *5*, 2215–2226.

[2] F. Prause, J. Kaldun, B. Arensmeyer, B. Wennemann, B. Fröhlich, D. Scharnagel, M. Breuning, „Flexible and Modular Syntheses of Enantiopure 5-*cis*-Substituted Prolinamines from L-Pyroglutamic Acid“, *Synthesis* **2015**, *47*, 575–586.

[1] D. Scharnagel,‡ F. Prause,‡ J. Kaldun,‡ R. G. Haase, M. Breuning, „(2*S*,5*R*)-2-Methylaminomethyl-1-methyl-5-phenylpyrrolidine, a chiral diamine ligand for copper(II)-catalysed Henry reactions with superb enantiocontrol“, *Chem. Commun.* **2014**, *50*, 6623–6625.

‡ Autoren haben gleiche Beiträge geleistet.

AUFLISTUNG ALLER TAGUNGSBEITRÄGE

Poster

[4] F. Prause, J. Kaldun, D. Scharnagel, M. Breuning, „5-*cis*-Substituted Prolinamines: Modular Synthesis and Application in Enantioselective Catalysis“, GDCh-Wissenschaftsforum Chemie, Dresden, **2015**.*

* IUPAC Poster Preis

[3] D. Scharnagel, J. Goller, F. Prause, A. Müller, M. Eck, M. Breuning, „Modular Synthesis of Core-Chiral Bispidine Ligands and their Application in Asymmetric Henry Reactions“, GDCh-Wissenschaftsforum Chemie, Dresden, **2015**.

[2] D. Scharnagel, A. Müller, F. Prause, M. Eck, J. Goller, M. Breuning, „The First Modular Route to Core-Chiral Bispidine Ligands and their Application in Copper(II)-Catalyzed Asymmetric Henry Reactions“, JCF-Frühjahrssymposium, Münster, **2015**.

[1] F. Prause,‡ J. Kaldun,‡ D. Scharnagel,‡ M. Breuning, „5-*cis*-Substituted Prolinamines – Privileged Ligands for Asymmetric Henry Reactions“, ORCHEM, Weimar, **2014**.

‡ Autoren haben gleiche Beiträge geleistet.

Vorträge

[2] „Studies towards the total synthesis of Patriridoside D and other secoiridoid natural products“, 51. Doktorandenworkshop Naturstoffe: Chemie, Biologie und Ökologie, Bayreuth, **2016**.

[1] „Poster Presentation: 5-*cis*-Substituted Prolinamines: Modular Synthesis and Application in Enantioselective Catalysis“, GDCh-Wissenschaftsforum Chemie, **2015**.

DANKSAGUNG

Besonderer Dank gilt meinem Doktorvater Prof. Dr. Matthias Breuning. Zum einen für die Bereitstellung des interessanten Themas, zum anderen für die vielen ausführlichen und hilfreichen Diskussionen bei Problemen und zu guter Letzt für die mir gewährten wissenschaftlichen Freiräume.

Meinen Eltern danke ich, dass sie mir diese Arbeit ermöglichten.

Ebenfalls bedanken möchte ich mich an dieser Stelle bei meinem Mitdoktoranden Dagmar Scharnagel, Johannes Kaldun und Jessica Goller: Für das gute Arbeitsklima, das perfekte Teamwork und das gemeinsame Stemmen diverser Probleme.

Allen anderen Mitgliedern des Arbeitskreises Breuning, die über die Jahre kamen und gingen, gebührt dieser Dank ebenso. Hervorheben möchte ich hier:

Meine beiden Masteranden: Alexander Streit und Martin Völkel.

Meine Bacheloranden: Martin Völkel, Daniel Schmidmeier, Frederik Freitag, Stefan Wagner, Simon Kolb und Florian Pachel.

Meine Praktikanten: Frederik Freitag, Tobias Fröhler, Juliane Gaß, Lukas Häfner, Stefanie Hohenberger (2x), Svenja Schiemann, Daniel Schmidmeier (2x), Kevin Solinga, Martin Völkel (2x), Stefan Wagner und Johannes Wunderlich (3x); sie alle leisteten wertvolle Beiträge.

Martin Völkel und Dagmar Scharnagel möchte ich auch an dieser Stelle noch einmal für das Korrekturlesen dieser Arbeit danken.

Silvia Kastner gebührt Dank für die Lösung aller möglichen organisatorischen Probleme.

Der Zentralen Analytik, namentlich Dr. Ulrike Lacher und Kerstin Hannemann, danke ich für die Messung jeglicher Proben.

Zu guter Letzt geht ein Dank an Dr. Ulrike Lacher, die ich bei der Betreuung des 500-MHz NMR unterstützte. Auch wenn die Gründe unserer Treffen meist unerfreulich waren (irgendwas funktioniert halt an der Kiste nicht) hatte ich dabei doch viel Spaß.

Noch einmal an alle: *DANKE, THANK YOU, MERCI.*

(EIDESSTATTLICHE) VERSICHERUNGEN UND ERKLÄRUNGEN DES VERFASSERS

(§ 5 Nr. 4 PromO)

Hiermit erkläre ich, dass keine Tatsachen vorliegen, die mich nach den gesetzlichen Bestimmungen über die Führung akademischer Grade zur Führung eines Doktorgrades unwürdig erscheinen lassen.

(§ 8 S. 2 Nr. 5 PromO)

Hiermit erkläre ich mich damit einverstanden, dass die elektronische Fassung meiner Dissertation unter Wahrung meiner Urheberrechte und des Datenschutzes einer gesonderten Überprüfung hinsichtlich der eigenständigen Anfertigung der Dissertation unterzogen werden kann.

(§ 8 S. 2 Nr. 7 PromO)

Hiermit erkläre ich eidesstattlich, dass ich die Dissertation selbständig verfasst und keine anderen als die von mir angegebenen Quellen und Hilfsmittel benutzt habe.

(§ 8 S. 2 Nr. 8 PromO)

Ich habe die Dissertation nicht bereits zur Erlangung eines akademischen Grades anderweitig eingereicht und habe auch nicht bereits diese oder eine gleichartige Doktorprüfung endgültig nicht bestanden.

(§ 8 S. 2 Nr. 9 PromO)

Hiermit erkläre ich, dass ich keine Hilfe von gewerblichen Promotionsberatern bzw. -vermittlern in Anspruch genommen habe und auch künftig nicht nehmen werde.

…….....

Ort, Datum, Unterschrift (Felix Prause)