# Sustainable Synthesis with Alcohols – from Rare Noble to Earth-Abundant Metal Catalysts

Dissertation

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**Abbreviations**

| | |
|---|---|
| ADC | Acceptor-free Dehydrogenative Condensation |
| äq | Äquivalente |
| $BAr^F_4$ | tetrakis[3,5-bis(trifluoromethyl)phenyl]borate |
| BH | Borrowing Hydrogen |
| br. | broad |
| Bu | butyl |
| calcd. | calculated |
| cod | *cis,cis*-1,5-cyclooctadiene |
| COE | cyclooctene |
| Cy | cyclohexyl |
| d | doublet |
| DIBAL-H | diisobutyl aluminumhydride |
| EI | electron ionization |
| eq | equivalents |
| ESI+ | electrospray ionization (positive ion mode) |
| Et | ethyl |
| EWG | electron withdrawing group |
| FID | flame ionization detector |
| GC | gas chromatography |
| HA | Hydrogen Autotransfer |
| HRMS | high resolution mass spectrometry |
| Me | methyl |
| MS | mass spectrometry |
| Ms | methanesulfonyl |
| Ph | phenyl |
| PMP | *para*-methoxyphenyl |
| ppm | parts per million |
| Pr | propyl |
| *p*-Tol | *para*-Tolyl |
| Py | pyridyl |
| q | quartet |
| quint | quintet |
| R | typical moieties (e.g. aliphatic, aromatic moieties or hydrogen) |
| s | singlet |
| spt | septet |
| sxt | sextet |
| *t*-AmOH | *tert*-amyl alcohol (2-methyl-2-butanol) |
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| Ts | *p*-toluenesulfonyl |
| δ | chemical shift [ppm] |

# 1 Zusammenfassung

Inhalt der vorliegenden Arbeit sind nachhaltige, katalytische Synthesemethoden wichtiger Verbindungsklassen ausgehend von Alkoholen als nachhaltige Ressource. Der Schlüssel für alle vorgestellten Reaktionen ist der Einsatz von Übergangsmetallkomplexen (basierend auf Ir, Co und Mn), die durch $PN_5P$-Pincerliganden stabilisiert werden (Abbildung 1). Diese Liganden basieren auf kommerziell erhältlichen Triazin-Grundkörpern, wodurch eine Bibliothek verschieden substituierter Liganden einfach zugänglich ist.

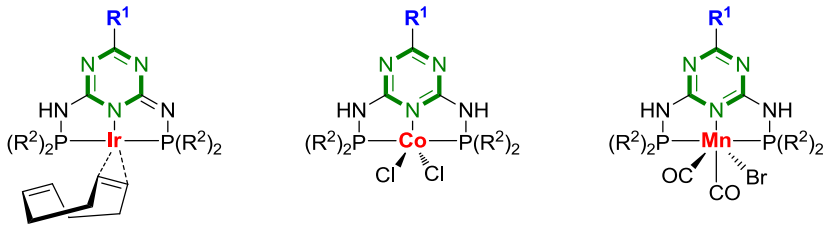
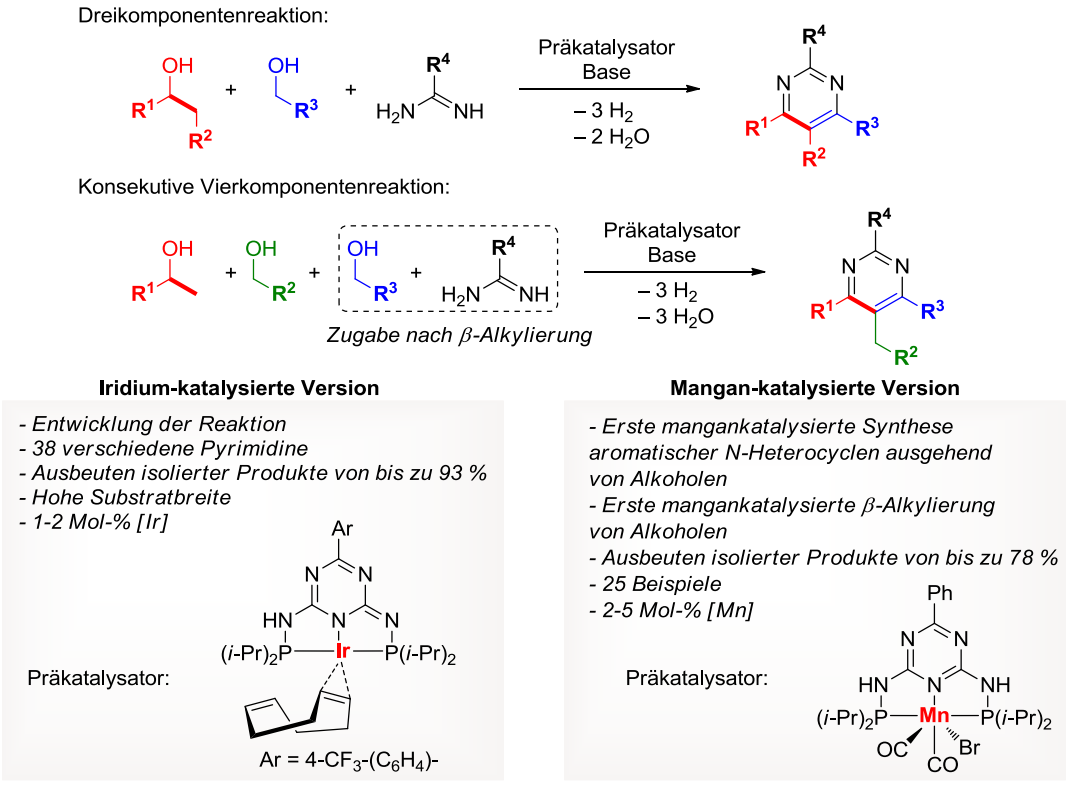



Abbildung 1. Strukturen von Übergangsmetallkomplexen, die in dieser Arbeit Verwendung finden.

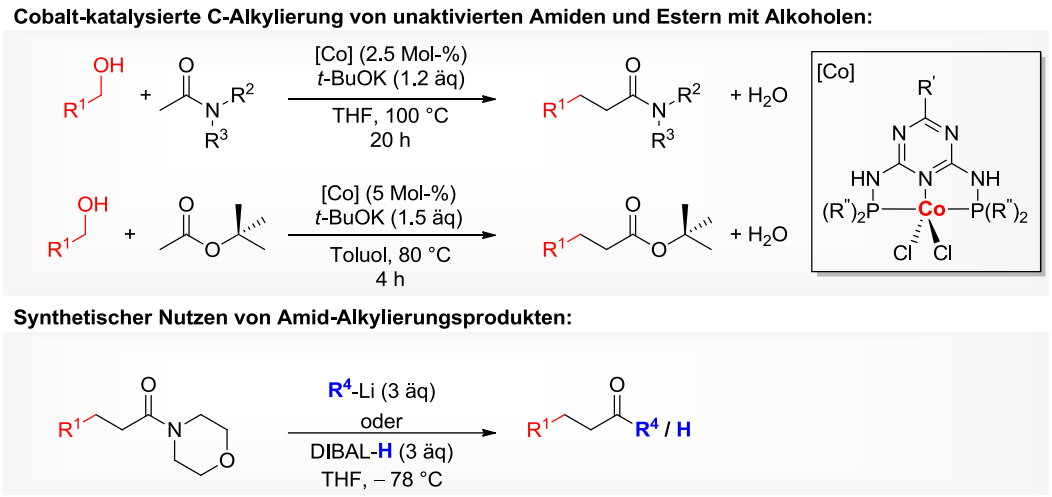
Diese Komplexe sind imstande, Borrowing Hydrogen / Hydrogen Autotransfer (BH/HA) Reaktionen und/oder Akzeptorfreie Dehydrierende Kondensationen (ADC) zu katalysieren. Von der Arbeitsgruppe Kempe wurden kürzlich Methoden zur Synthese verschiedener aromatischer N-Heterocyclen aus Alkoholen basierend auf dem ADC-Konzept entwickelt. Im Rahmen der vorliegenden Arbeit wurde eine nachhaltige Mehrkomponentensynthese von Pyrimidinen erarbeitet (Schema 1).




Schema 1. Mehrkomponentensynthese von Pyrimidinen ausgehend von Alkoholen und Amidinen.

Die vorgestellte Synthese kombiniert BH/HA und ADC-Reaktionen, um teilweise oder vollständig substituierte Pyrimidine aus bis zu drei Alkoholen und einem Amidin (oder Guanidin) zu erhalten. Diese Synthese wurde unter Benutzung eines $PN_5P$-Ligand-stabilisierten Iridiumkomplexes, der von der Arbeitsgruppe Kempe entwickelt wurde, entdeckt und ausgearbeitet. Für verschiedene Substitutionsmuster wurden jeweils die besten Reaktionsbedingungen ermittelt, was die Synthese von insgesamt 38 verschiedenen Pyrimidinen in isolierten Ausbeuten von bis zu 93 % erlaubte.

Ein noch nachhaltigerer Ansatz stellt der Ersatz von teuren und seltenen Edelmetallen durch breit verfügbare und günstige Basismetalle wie Cobalt dar. Um dieser weiteren Anforderung für eine nachhaltigere Chemie nachzukommen, wurde als nächstes eine Cobalt-katalysierte C-C-Knüpfungsreaktion durch α-Alkylierung von Acetamiden und *tert*-Butylacetat durch Alkohole basierend auf dem BH/HA Konzept entwickelt (Schema 2). Diese Reaktionen konnten bisher nur durch den Einsatz von Edelmetallkatalysatoren realisiert werden. Aus einer Bibliothek von PNP Ligand-stabilisierten Cobaltkomplexen wurde für beide Reaktionen jeweils ein aktiver Präkatalysator identifiziert. Diese Bibliothek erlaubte es außerdem, auf anspruchsvolle Substrate durch die gezielte Auswahl eines anderen geeigneten Präkatalysators zu reagieren. Neben der Synthese von insgesamt 22 Beispielen für die Alkylierung von Amiden bzw. 12 für die von Estern wurde anhand von Folgereaktionen der synthetische Nutzen der auf diese Art und Weise erhaltenen Verbindungen aufgezeigt. Im Rahmen dieses Projekts wurden insgesamt 40 Produkte hergestellt.

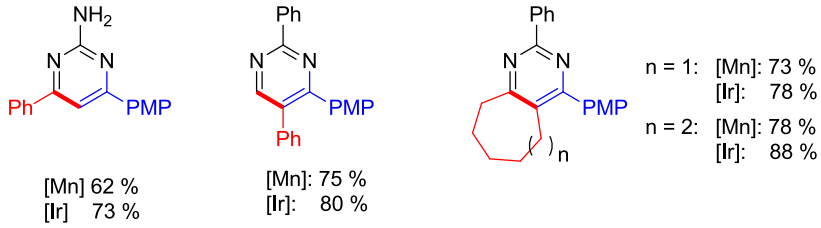



Schema 2. Oben: Cobalt-katalysierte Alkylierung von Acetamiden und *tert*-Butylacetat durch Alkohole. Unten: Synthetischer Nutzen von Alkylierungsprodukten durch Synthese von Ketonen und Aldehyden.

Die vorher genannten Cobalt-Komplexe waren allerdings nicht in der Lage, ADC-Reaktionen zu katalysieren. Erst im Jahr 2016 wurde das Potential von Mangan, dem dritthäufigsten Metall im Erdmantel, für (De-)Hydrierreaktionen erkannt. In dieser Arbeit wurde die zuvor beschriebene Pyrimidinsynthese mit einem $PN_5P$-Ligand stabilisierten Mangankomplex und damit eine der ersten Mangan-katalysierten Synthesen aromatischer N-Heterocyclen ausgehend von Alkoholen erarbeitet.

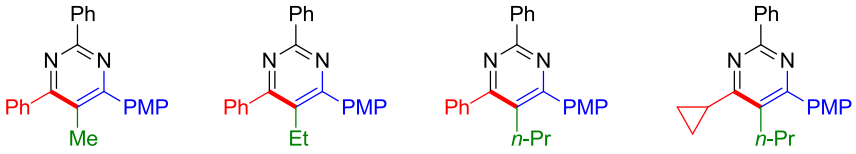
Der Mangankomplex war imstande, sowohl die Dreikomponenten- als auch die konsekutive Vierkomponentensynthese, welche auf einer vorangeschalteten β-Alkylierungsreaktion zwischen zwei Alkoholen beruht, zu katalysieren (siehe Schema 1). Auch eine Mangan-katalysierte Knüpfungsreaktion zwischen zwei Alkoholen war bisher nicht bekannt. Die ähnliche Reaktivität (bezogen auf die Art der Reaktion) des Mangankatalysators im Vergleich zu dem Iridiumkatalysator für beide einzelnen Reaktionen lässt den Schluss zu, dass Mangan das Potential hat, Iridium oder andere Edelmetalle in solchen Reaktionen zu ersetzen (Abbildung 2).

***Dreikomponentensynthese*** *(ausgewählte Beispiele):*




*Reaktionsbedingungen:* [Ir]: 1 Mol-% Präkatalysator, *t*-BuOK or KOH (0.7-1.1 äq) *tert*-amyl Alkohol, 24 h Rückfluss
[Mn]: 2 Mol-% Präkatalysator, *t*-BuOK (1.1-1.5 äq) 1,4-Dioxan, 24 h Rückfluss

***Konsekutive Vierkomponentensynthese*** *(ausgewählte Beispiele):*




*Reaktionsbedingungen:* [Ir]: 1-2 Mol-% Präkatalysator, *t*-BuOK (2.0 äq) *tert*-amyl Alkohol/1,4-Dioxan, 4 + 24 h Rückfluss
[Mn]: 5 Mol-% Präkatalysator, *t*-BuOK (2.0 äq) 1,4-Dioxan, 5 + 20 h Rückfluss

Abbildung 2. Vergleich von Ausbeuten ausgewählter Pyrimidine, die durch Iridium- oder Mangankatalysierte Akzeptorfreie Dehydrierende Kondensation ausgehend von Alkoholen und Amidinen (bzw. Guanidin) zugänglich sind. Bezüglich der Farbgebung, siehe Schema 1. Isolierte Ausbeuten sind gezeigt.

# 2 Summary

The scope of the present work includes sustainable catalytic synthetic methods of important classes of compounds starting from alcohols as a renewable resource. The key for all the reactions presented is the use of transition metal complexes (based on Ir, Co and Mn) stabilized by $PN_5P$ pincer ligands (Figure 1). These ligands are based on commercially available triazine cores, from which a library of differently substituted ligands is accessible.

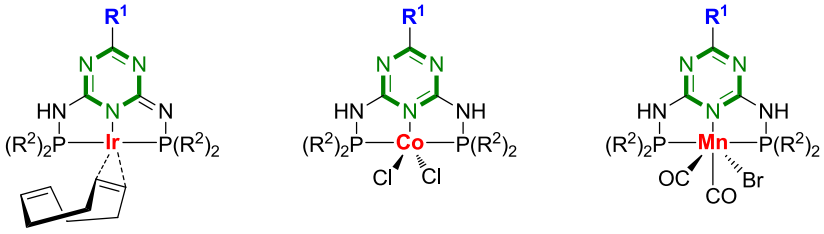
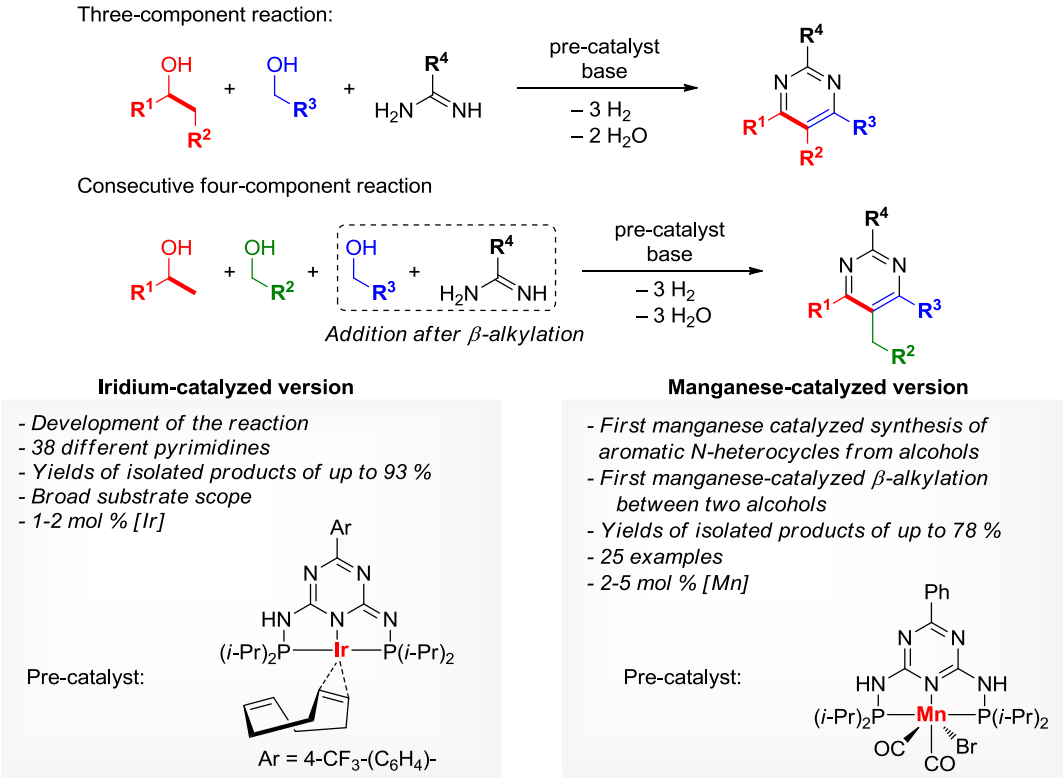



Figure 1. Structures of transition-metal complexes used within this thesis.

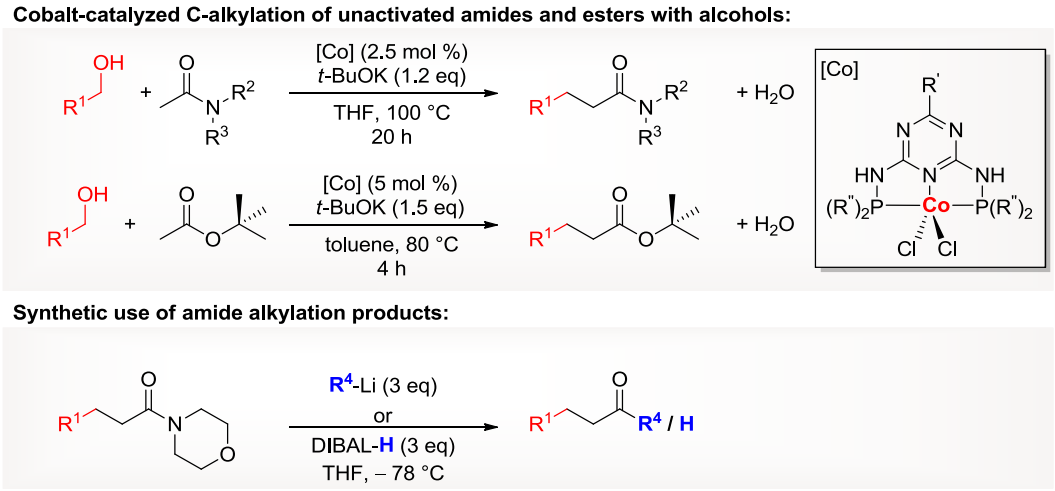
These complexes can catalyze Borrowing Hydrogen / Hydrogen Autotransfer (BH/HA) reactions and/or Acceptor-free Dehydrogenative Condensations (ADC). The Kempe group recently reported methods for the synthesis of diverse aromatic N-heterocycles from alcohols based on the ADC concept. Within this work, a sustainable multicomponent pyrimidine synthesis from alcohols and amidines was developed (Scheme 1).




Scheme 1. Multicomponent synthesis of pyrimidines from alcohols and amidines.

The synthesis presented combines BH/HA and ADC reactions to obtain partially or fully substituted pyrimidines from up to three alcohols and an amidine (or guanidine). This synthesis was discovered and elaborated using a $PN_5P$ ligand-stabilized iridium complex developed by the Kempe group. After identification of the ideal reaction conditions for different substitution patterns, 38 different pyrimidines were synthesized in isolated yields of up to 93 %.

An even more sustainable approach is the replacement of precious and rare noble metals in such reactions by broadly available and cheap base metals such as cobalt. To comply with this requisition for a more sustainable chemistry, a cobalt-catalyzed C-C bond formation reaction was elaborated next. It is based on the α-alkylation of acetamides and *tert*-butyl acetate with alcohols, according to the BH/HA concept (Scheme 2). These reactions have only been realized so far using noble metal catalysts. An active pre-catalyst for each of the two reactions was identified from a library of PNP ligand-stabilized cobalt complexes. This library also allowed a response to challenging substrates by choosing another suitable pre-catalyst. In addition to the synthesis of 22 examples of the alkylation of amides and 12 examples of the alkylation of esters, the synthetic use of compounds synthesized by this method was demonstrated by follow-up reactions. A total of 40 products was synthesized within this project.




Scheme 2. Top: Cobalt-catalyzed alkylation of acetamides and *tert*-butyl acetate by alcohols. Bottom: Synthetic use of alkylation products by synthesis of ketones and aldehydes.

However, the cobalt complexes mentioned previously could not catalyze ADC reactions. The potential of manganese, the third most abundant metal in the earth's crust, for (de-)hydrogenation reactions was only discovered recently in 2016. The pyrimidine synthesis described earlier was elaborated using a $PN_5P$ ligand-stabilized manganese complex and the reaction represents one of the first manganese-catalyzed syntheses of aromatic N-heterocycles from alcohols. The manganese complex could catalyze both the three-component and the consecutive four-component synthesis, which is based on a preceding β-alkylation reaction between two alcohols. In addition, a manganese-catalyzed bond formation between two alcohols has not been reported before. The similar reactivity (regarding the type of reaction) of the

manganese catalyst compared to the iridium catalyst for both distinct reactions suggests that manganese has the potential to replace iridium or other noble metals in such reactions (Figure 2).

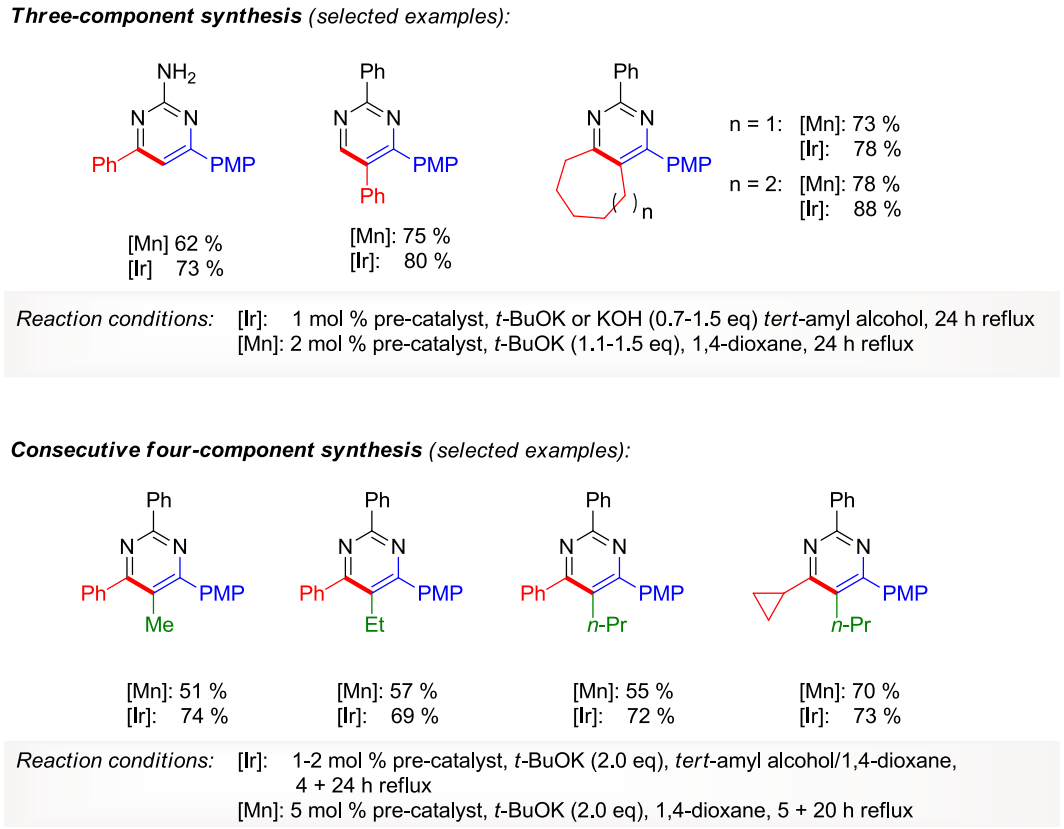



Figure 2. Comparison of yields for selected pyrimidines, which can be synthesized by iridium- or manganese-catalyzed Acceptor-free Dehydrogenative Condensation starting from alcohols and amidines (or guanidines, respectively). See Scheme 1 for coloring. Isolated yields are shown.

# 3 Introduction

## 3.1 Motivation

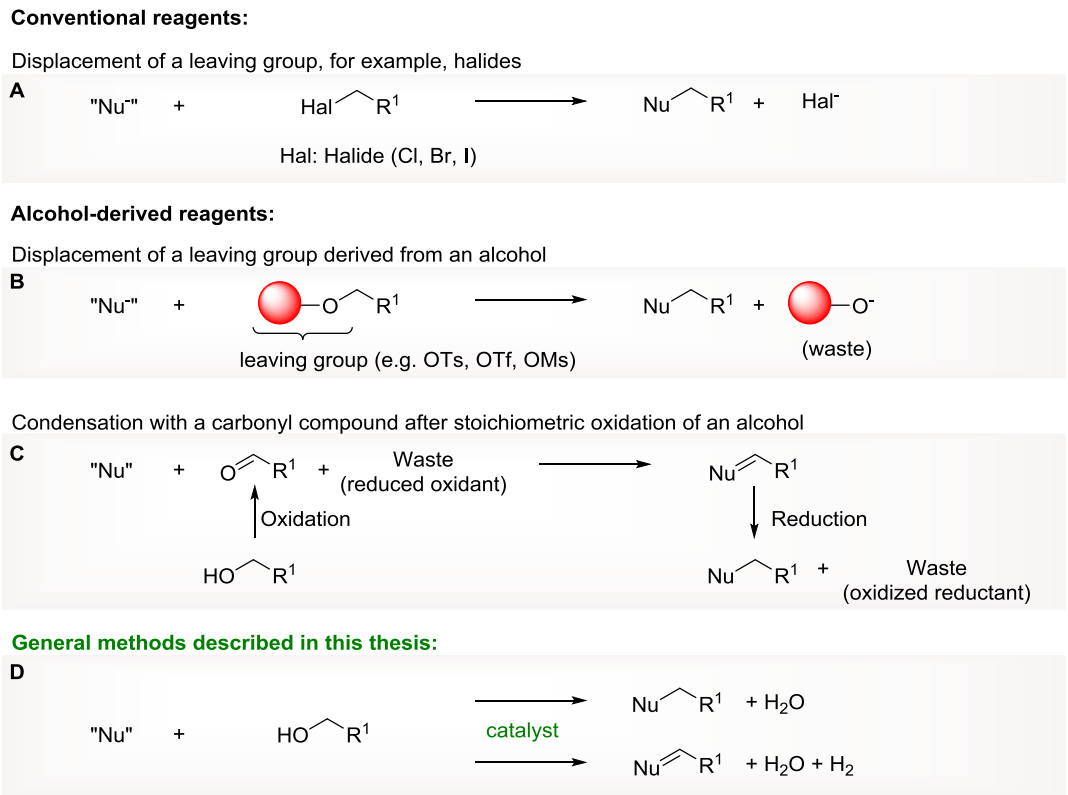
The decreasing capacity of limited crude oil resources and environmental concerns have made a rethink of established methods of producing chemicals important.[1] This fact may conform to the public's general low opinion of chemicals and chemical companies. However, one should recall that the production of chemical compounds is not only the basis of our high standard of living, but also the basis of the earth's human population.[2] Many approaches are used to render manufacturing processes as effective as possible, such as using so-called *Verbund* (combination) sites, where the stream of products, waste and energy are closely connected to each other, for example, one facility can use the side products of another process.[3] In order to make the manufacturing process more sustainable on a molecular level, the concept of green chemistry arose in the late 1990s, which can be applied to all industry sectors.[4] In the course of this concept, twelve principles were introduced by Anastas and Warner in 1998 (Table 1).[5] These are supposed to provide a framework for the design of chemical reactions and processes.

Table 1. The twelve principles of green chemistry.[5]

| | |
|---|---|
| **1.** Prevent waste | **7.** Use of renewable feedstock |
| **2.** Atom economy | **8.** Reduce derivatives |
| **3.** Less hazardous synthesis | **9.** Catalysis |
| **4.** Design of safer chemicals | **10.** Degradation |
| **5.** Safe solvents and auxiliaries | **11.** Real-time analysis for pollution prevention |
| **6.** Energy efficiency | **12.** Inherent safer chemistry for accident prevention |

Catalysis, as one principle, is a key technology which can help to render the production of chemicals more environmentally benign and to assist the discovery of "green" methods for the synthesis of chemical compounds. In fact, catalysis can be seen as a basis for many other green chemistry principles. This thesis focuses on sustainable synthesis with alcohols using transition metal complexes as catalysts. Alcohols are very promising resources, since they can be obtained from indigestible and abundantly available lignocellulosic biomass,[6] which does not compete with the food chain (principle #7). This biomass can be catalytically converted into pyrolysis oil, from which alcohols and polyols can be obtained.[7] However, these compounds are drastically different from oil-derived materials due to their high oxygen content. On the one hand, alcohols are comparably unreactive, which can be seen as an advantage regarding principle #4, on the other hand, they need to be activated to be used in organic synthesis.[8] Scheme 3 gives a general overview of conventional (**A**) and alcohol-derived reagents (**B**-**D**) that can be used for C-C or C-N bond formations. Alcohols are typically activated by conversion of the hydroxyl group into a leaving group (Scheme 3, **B**) or by oxidation (**C**). Bond formations that rely on

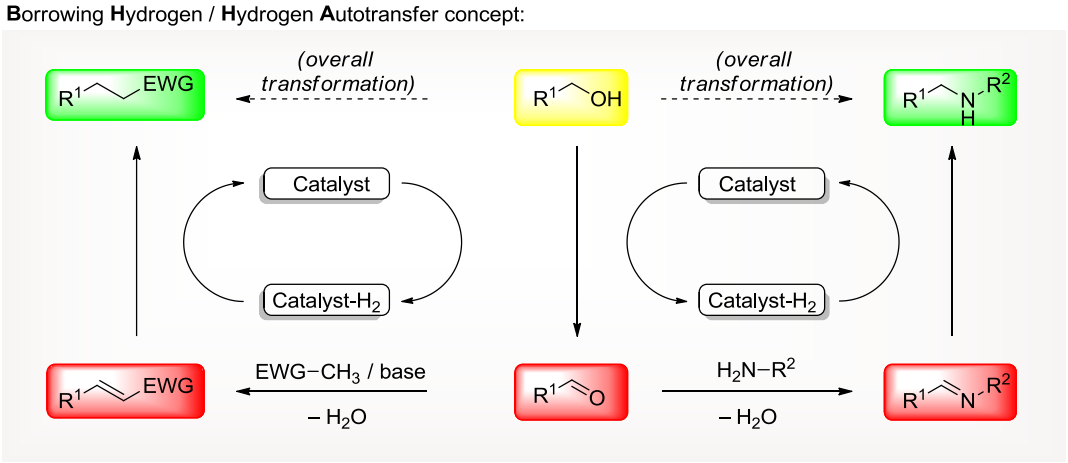
these methods are, therefore, accompanied by large amounts of waste, for example, by displacement of the leaving group or by using stoichiometric amounts of oxidants. Thus, the development of catalytic methods that allow converting alcohols directly into important classes of chemicals (Scheme 3, **D**) has emerged as a very important field of research.[9] In addition, the development of alcohol conversion reactions has the potential to advance the discovery of novel reactions, enhance existing synthetic concepts or lead to the discovery unique reactivity profiles. The Borrowing Hydrogen or Hydrogen Autotransfer (BH/HA) concept is a key method to accomplish alcohol activation in a sustainable or green manner by means of catalysis. The methodology permits the substitution of a hydroxyl group to create a new C-N or C-C bond in a redox-neutral fashion with water as the sole by-product. A related concept is Acceptor-free Dehydrogenative Condensation (ADC), which allows unsaturated compounds to be obtained from alcohols with the liberation of hydrogen and water as the by-products. Notably, these methods comply with several of the green chemistry principles denoted in Table 1. In addition to the use of abundantly available alcohols, the reactions are usually accompanied by low by-product formation and proceed with high atom economy. The BH/HA and ADC concepts are discussed in more detail in the next chapters with a focus on transformations related to the scope of this thesis.




Scheme 3. Methods for bond formations using conventional reagents (**A**), alcohol-derived reagents by displacement of leaving groups (**B**) or by a two-step oxidation and reduction sequence (**C**), and general catalytic methods using alcohols as reported in this thesis (**D**). Nu = A suitable nucleophile, e.g. an amine or a deprotonated CH-acidic compound;

## 3.2 Borrowing Hydrogen / Hydrogen Autotransfer

The Borrowing Hydrogen / Hydrogen Autotransfer concept was pioneered by Watanabe[10] and Grigg[11] in 1981. The mechanism (Scheme 4) involves a transition-metal complex as catalyst that is used to dehydrogenate an alcohol to the corresponding carbonyl compound (ketone or aldehyde) and the hydrogen is temporarily transferred to the metal complex. The more reactive carbonyl compound can be attacked by a nucleophile (e.g. an amine or the anion of a CH-acidic compound) and an unsaturated compound is obtained after elimination of water. The hydrogenation of the unsaturated intermediate by the catalyst with the hydrogen obtained from the initial dehydrogenation step closes the catalytic cycle and yields the corresponding saturated alkylation product. Typically, this type of reaction involves the use of noble metals that are also used for hydrogenation reactions. The catalysts used are based, in most cases, on iridium or ruthenium. The alkylation of amines and CH-acidic compounds by alcohols provides access to important compounds by selective C-N and C-C bond formations.[12]



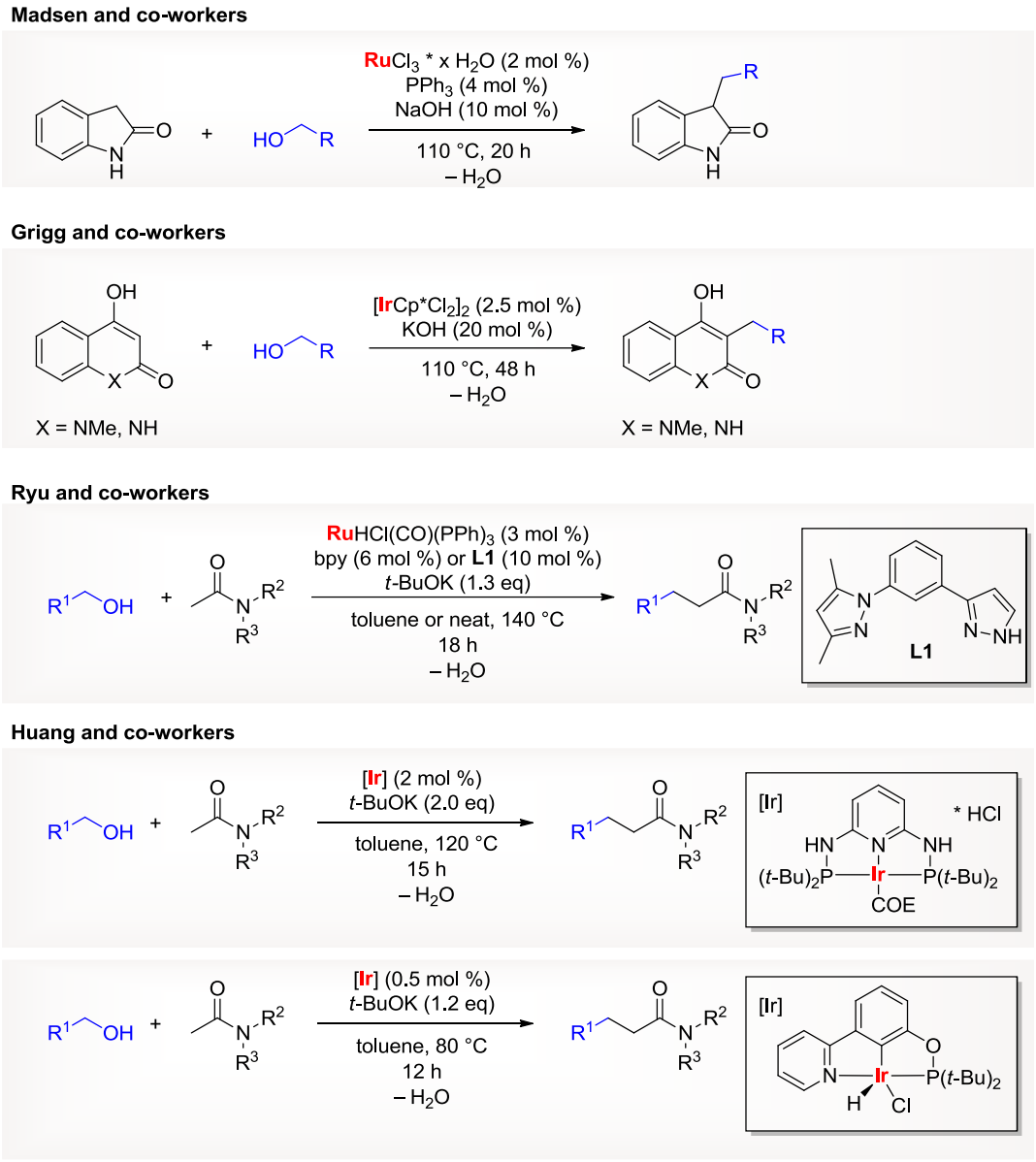

Scheme 4. The Borrowing Hydrogen / Hydrogen Autotransfer concept exemplified for the alkylation of amines with alcohols and the alkylation of CH-acidic compounds with alcohols. EWG: Electron-withdrawing group.

Reactions of interest for this work that rely on the BH/HA concept are exemplarily shown in the next chapters.

## 3.3 Alpha-alkylation of amides and esters

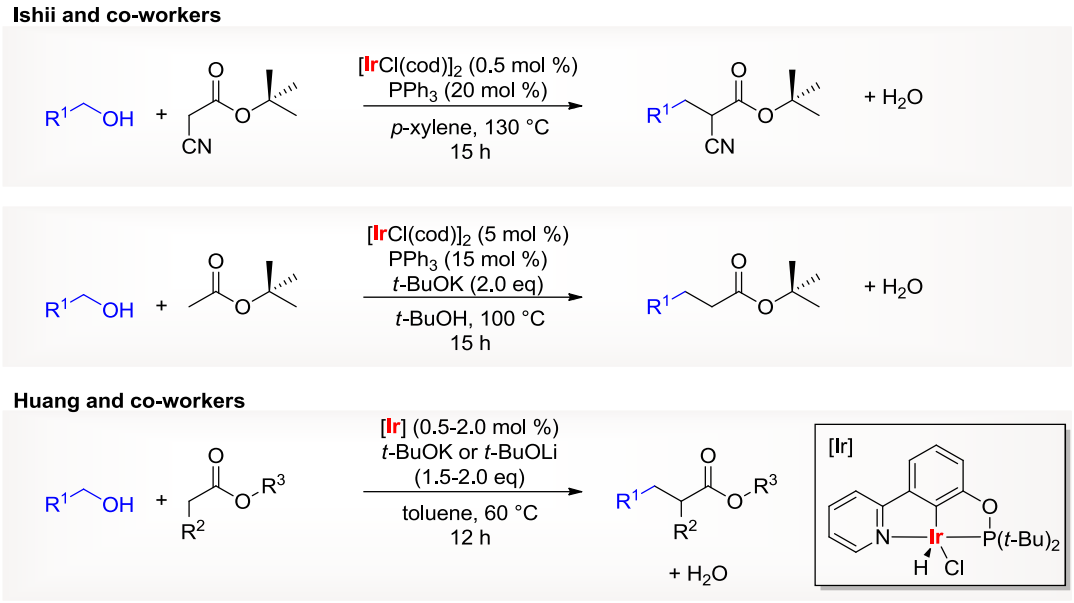
Amides and esters are valuable intermediates or products in chemical research as well as in the industry. Simple amides and esters are easily accessible and even used as solvents. The alkylation of such substrates with alcohols is an elegant method to obtain the corresponding high-value alkylation products. Prior to this work, alpha alkylation of amides and esters has only been achieved using noble metal catalysts. Amides have a low CH-acidic nature and their alkylation requires relatively harsh reaction conditions. Prominent examples include the alkylation of cyclic and therefore activated substrates such as 2-indanone,[13] 4-hydroxy-2-quinolones and quinolin-4(1H)-one[14] (Scheme 5, top). Alkylation of

unactivated amides has been achieved by the groups of Ryu[15] and Huang[16] (Scheme 5, bottom) and all reactions relied on the use of ruthenium or iridium complexes as catalysts.




Scheme 5. Alkylation of activated and unactivated amides with alcohols using noble metal catalysts.

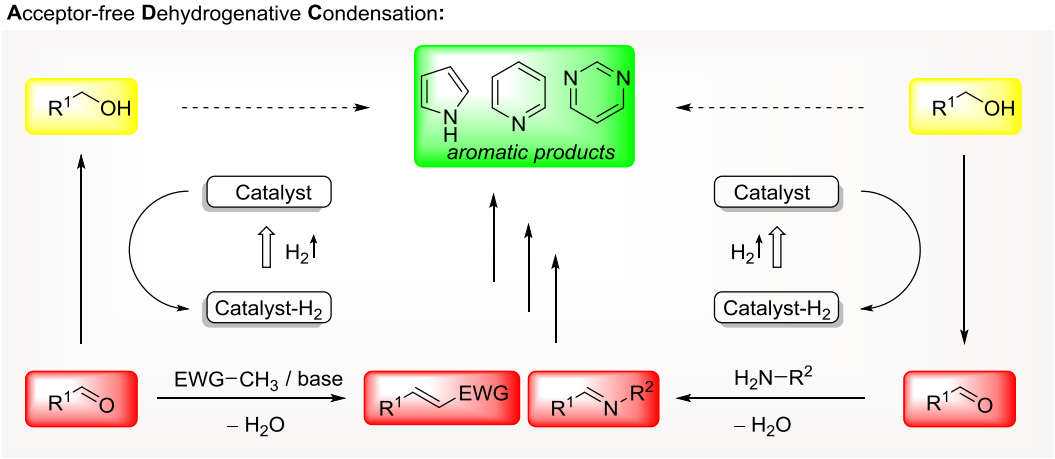
Alkylation of esters with alcohols (Scheme 6) is a more difficult reaction since side-reactions such as transesterification with the alcohols employed are expected under basic reaction conditions. Ishii and co-workers reported on the base-free alkylation of activated *tert*-butyl 2-cyanoacetate[17] and on the alkylation of *tert*-butyl acetate[18] with alcohols using *t*-BuOK as the base and *t*-BuOH as solvent in order to exclude any transesterification products. The reaction with the highest substrate scope was reported by the Huang group (Scheme 6, bottom).[19] Notably, many different esters underwent selective alkylation with alcohols in combination with a NCP ligand-stabilized iridium complex.




Scheme 6. Alkylation of activated and unactivated esters with alcohols using noble metal catalysts.

## 3.4 Acceptor-free Dehydrogenative Condensation

A concept related to BH/HA reactions is Acceptor-free Dehydrogenative Condensation (ADC).[20] As with the BH/HA concept, alcohol activation takes place by transition-metal catalyzed dehydrogenation and the carbonyl compound can undergo a condensation reaction to give an unsaturated product (Scheme 7).

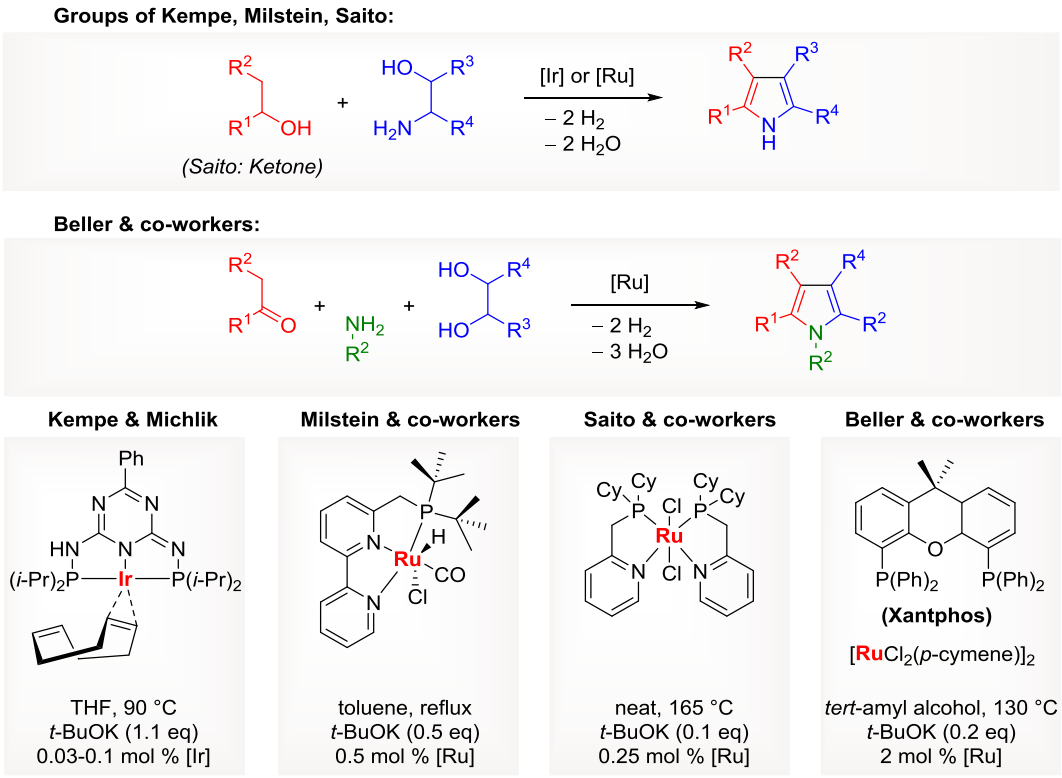



Scheme 7. Acceptor-free Dehydrogenative Condensation (ADC) to obtain unsaturated products from alcohols under release of molecular $H_2$. Cyclisation of unsaturated products may be used to obtain aromatic products. EWG: Electron-withdrawing group.

However, the catalytic cycle is closed by release of molecular hydrogen from the metal hydride complex, which allows unsaturated compounds like olefins or imines to be obtained since the reduction of the unsaturated compound is suppressed. The extrusion of dihydrogen out of the reaction mixture is the driving force for the thermodynamically disfavored reaction. When this reaction is combined with a

subsequent cyclisation reaction of the unsaturated compound, aromatic compounds can be obtained by this method.

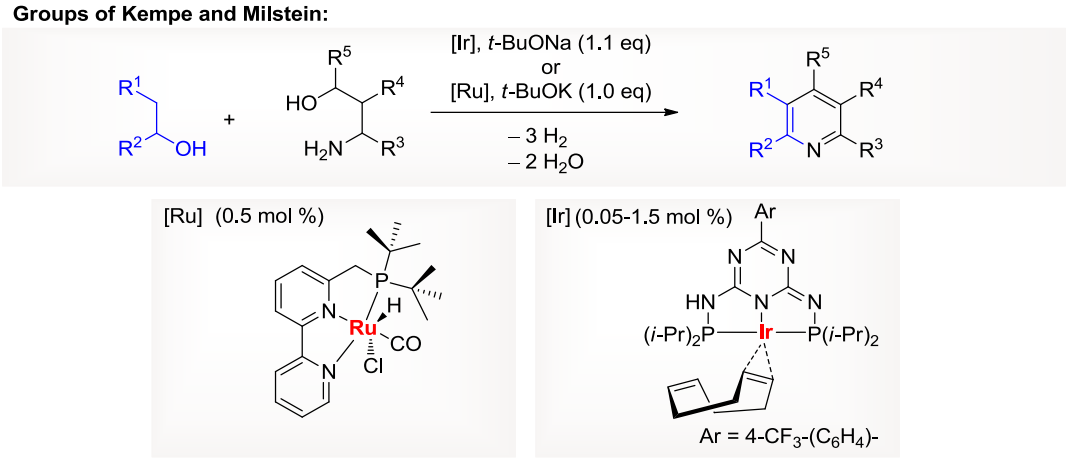
ADC reactions have recently gained much attention when they were shown to be a very elegant method to construct privileged motifs such as aromatic N-heterocycles.[21] The first few examples on the synthesis of pyrroles from alcohols via this method were reported by the groups of Beller,[22] Milstein,[23] Saito,[24] and Kempe[21] (Scheme 8). The synthetic approach by Kempe and Milstein is based on the selective coupling of an alcohol with an 1,2-amino alcohol. A similar strategy was pursued by the Saito group starting from a ketone and an 1,2-amino alcohol. The Beller group used a conceptually similar approach and reported a ruthenium catalyzed three-component reaction using a ketone, an amine and a 1,2-dialcohol for the construction of the corresponding pyrroles in a selective manner.



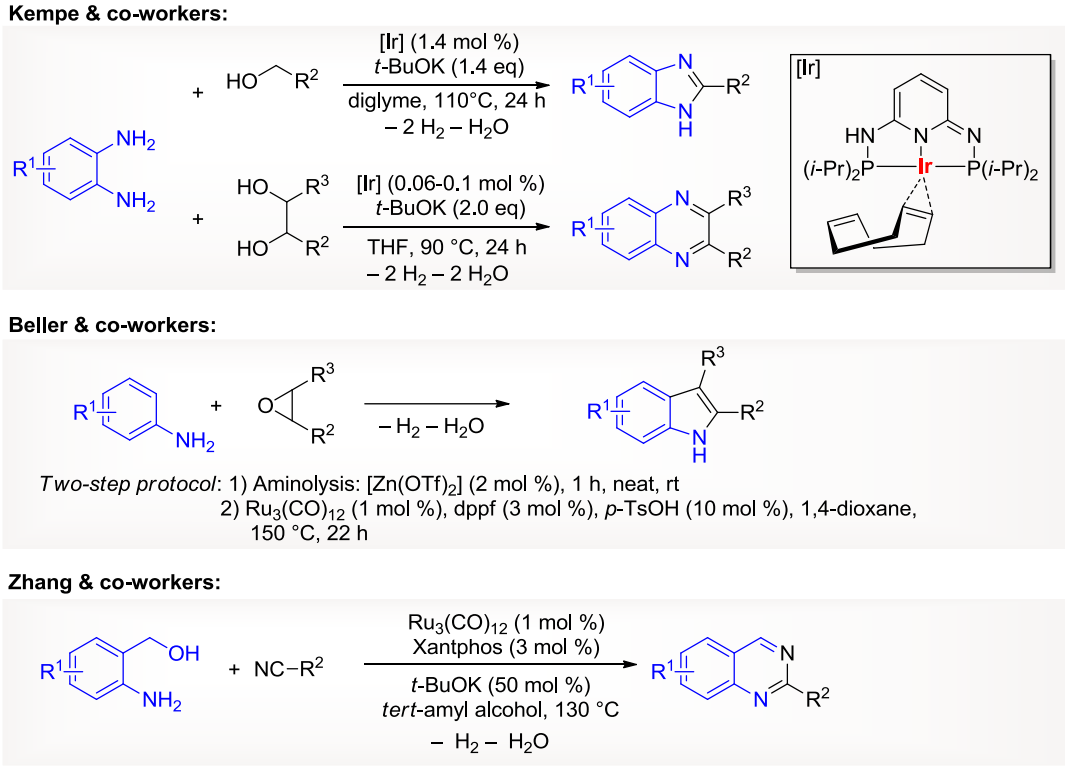

Scheme 8. ADC-based syntheses of pyrroles from alcohols by iridium or ruthenium catalyzed C-C and C-N bond formation, used (pre-)catalysts and reaction conditions. Cy: Cyclohexyl;

Inspired by these synthetic concepts, further syntheses of aromatic N-heterocycles from alcohols or alcohol intermediates were reported soon after. Starting from a secondary alcohol and a 1,3-amino alcohol, the synthesis of pyridines catalyzed by iridium or ruthenium complexes becomes feasible and was reported by the groups of Kempe[25] and Milstein[26] (Scheme 9). The Kempe group also reported on the synthesis of benzimidazoles and quinoxalines starting from 1,2-phenylenediamine derivatives and a primary alcohol or a 1,2-dialcohol, respectively (Scheme 10, top).[27] An elegant access to the indole motif was reported by the Beller group (Scheme 10, middle).[28] The synthesis involves the aminolysis of an epoxide catalyzed by a lewis acid as the first step. In the second step, the resulting 1,2-amino alcohol

becomes dehydrogenated by a ruthenium catalyst and subsequently undergoes C-C bond formation to construct the indole 5-ring. The Zhang group reported on the construction of arylquinazolines from 2-aminobenzyl alcohols and aromatic nitriles (Scheme 10, bottom).[29] The reaction involves nucleophilic attack of the aromatic amine at the nitrile carbon and subsequent dehydrogenation of the alcohol followed by a condensation that affords the corresponding quinazoline.




Scheme 9. Synthesis of pyridines from alcohols and 1,3-amino alcohols catalyzed by ruthenium (Milstein & co-workers) or iridium (Kempe & Michlik) complexes.



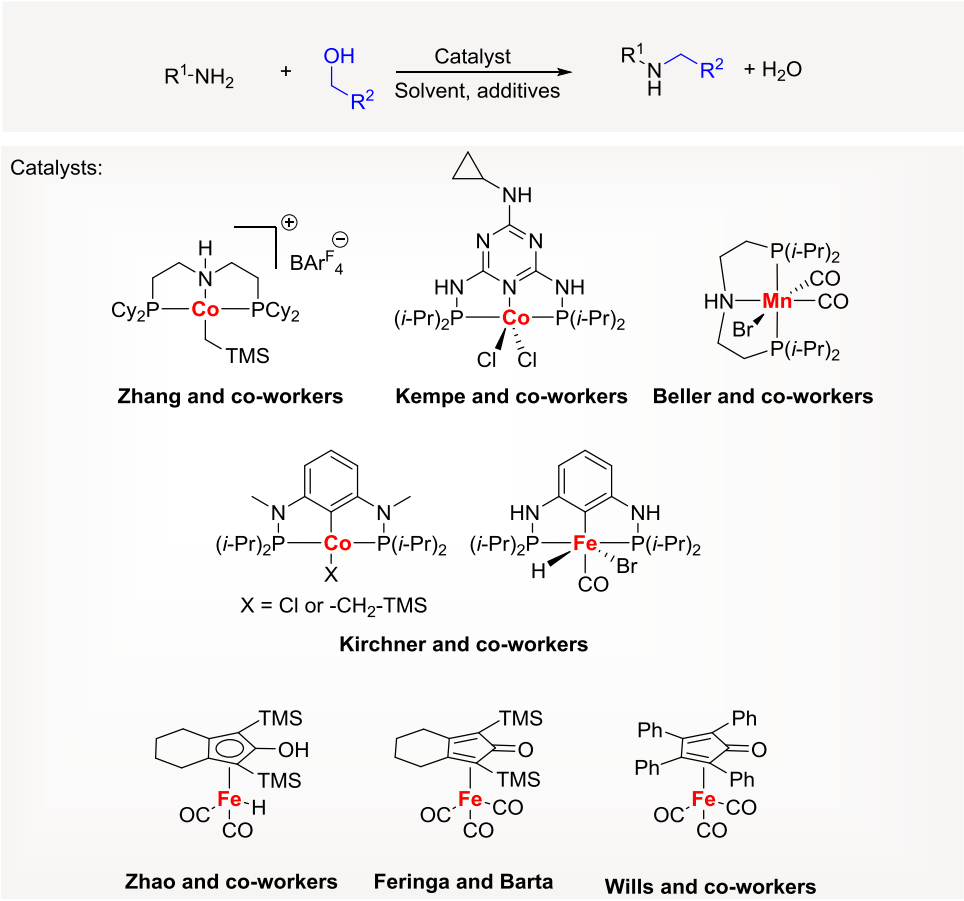

Scheme 10. Further examples of the synthesis of N-heterocycles by Acceptor-free Dehydrogenative Condensation. Dppf: 1,1'-Bis(diphenylphosphino)ferrocene.

The work within this thesis will demonstrate, that a combination of BH/HA and ADC reactions can also be used for the synthesis of highly substituted pyrimidines from alcohols and amidines or guanidines.[30]

## 3.5 Base-metal catalyzed BH/HA and ADC reactions

Despite the advantages of BH/HA and ADC reactions, such as the use of alcohols as sustainable resources, high atom-economy, low formation of by-products and formation of $H_2$ as a valuable by-product, the use of precious metals may limit the use of these reactions in terms of economy and ecology. Thus, the replacement of these metals by non-precious base metals, such as iron, cobalt and manganese, is a highly desirable goal.

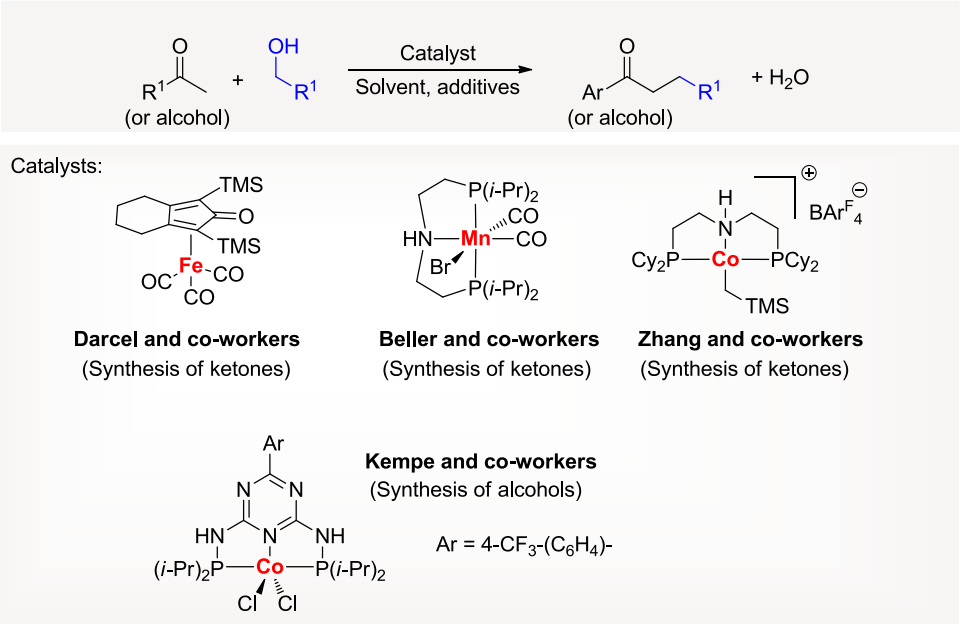
Amine alkylation with alcohols is among the most investigated BH/HA-type reactions and considerable progress has been achieved in the base-metal catalyzed versions by the groups of Zhang,[31] Beller,[32] Kempe,[33] Kirchner,[34] Zhao,[35] Feringa and Barta,[36] and Wills.[37] Complexes of iron, cobalt and manganese, stabilized by PNP ligands as well as Knoelker-type iron complexes are used to accomplish amine alkylation reactions (Scheme 11).




Scheme 11. Overview of selected base metal complexes used as catalysts for amine alkylation with alcohols.

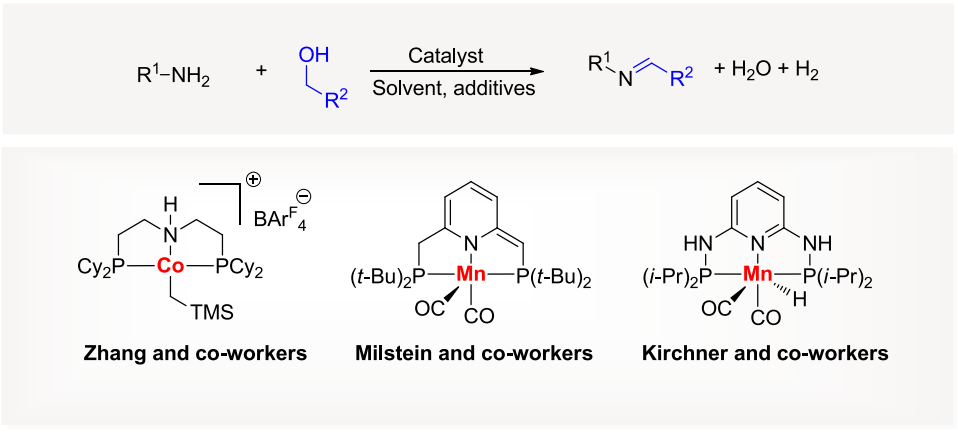
Base metal catalyzed BH/HA versions for the construction of C-C bonds are less explored and the most prominent reports demonstrate the α-alkylation of ketones with alcohols (Scheme 12). Darcel and co-workers used a Knoelker-type iron complex to achieve the alkylation of aromatic ketones in moderate to good isolated yields.[38] The Beller group used a manganese complex stabilized by a PNP pincer ligand

for the same reaction and an extended substrate scope.[39] Zhang and co-workers also reported the alkylation of ketones with alcohols using a cationic PNP cobalt complex.[40] The Kempe group used a $PN_5P$ ligand-stabilized cobalt complex to achieve the alkylation of secondary alcohols with primary alcohols.[41] Reported in this thesis is that well-defined transition metal complexes of earth-abundant cobalt are active catalysts for both the alkylation of amides and esters.[42] Prior to this work, the alkylation of these substrate classes has only been reported using noble metal catalysts (see section 3.3).




Scheme 12. Alkylation of unactivated ketones or alcohols with primary alcohols catalyzed by base-metal complexes.

Reports on ADC reactions catalyzed by base-metal complexes are also rare. The Zhang group used their PNP ligand-stabilized cationic cobalt complex, which can catalyze the alkylation of amines (Scheme 11) and ketones (Scheme 12), for the synthesis of imines from alcohols and amines accompanied by the release of $H_2$ (Scheme 13).[43]




Scheme 13. Overview of selected base-metal complexes used as catalysts for Acceptor-free Dehydrogenative Condensation of amines with alcohols to form imines.

The different selectivity (imine or amine) was obtained by variation of the reaction conditions. It took until the year 2016 to demonstrate that well-defined manganese complexes are very promising candidates as catalysts for ADC reactions. The Milstein group first reported on the use of a manganese dicarbonyl complex stabilized by a de-aromatized pyridine based PNP ligand for the synthesis of imines from amines and alcohols.[44] The Kirchner group soon reported a structurally similar complex, which can catalyze the same transformation.[34b] As it will be shown within a later chapter in this thesis, such manganese complexes can be applied for the construction of N-heterocycles from alcohols and it will be demonstrated that they show similar reactivity as noble iridium catalysts with regard to the type of chemical transformation conducted.[45]

## 3.6 References


1 M. Poliakoff, P. Licence, *Nature* **2007**, *450*, 810-812.

2 V. Smil, Enriching the Earth: Fritz Haber, Carl Bosch, and the Transformation of World Food Production, MIT Press, **2000**.

3 https://www.basf.com/en/microsites/factbook-2016/basf-group/verbund.html, accessed on April, 18, 2017

4 M. Poliakoff, P. Anastas, *Nature* **2001**, *413*, 257.

5 P. T. Anastas, J. C. Warner, Green Chemistry: Theory and Practice, Oxford University Press: New York, **1998**

6 (a) J. Zakzeski, P. C. Bruijnincx, A. L. Jongerius, B. M. Weckhuysen, *Chem. Rev.* **2010**, *110*, 3552-3599. (b) A. Corma, S. Iborra, A. Velty, *Chem. Rev.* **2007**, *107*, 2411-2502.

7 (a) T. P. Vispute, H. Zhang, A. Sanna, R. Xiao, G. W. Huber, *Science* **2010**, *330*, 1222-1227. (b) M. Besson, P. Gallezot, C. Pinel, *Chem. Rev.* **2014**, *114*, 1827-1870.

8 A. J. Watson, J. M. Williams, *Science* **2010**, *329*, 635-636.

9 J. Schranck, A. Tlili, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 7642-7644.

10 Y. Watanabe, Y. Tsuji, Y. Ohsugi, *Tetrahedron Lett.* **1981**, *22*, 2667-2670.

11 R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, *J. Chem. Soc., Chem. Commun.* **1981**, 611.

12 For selected reviews, see: (a) G. Guillena, D. J. Ramon, M. Yus, *Angew. Chem. Int. Ed.* **2007**, *46*, 2358-2364. (b) M. H. S. A. Hamid, P. A. Slatford, J. M. J. Williams, *Adv. Synth. Catal.* **2007**, *349*, 1555-1575. (c) T. D. Nixon, M. K. Whittlesey, J. M. Williams, *Dalton Trans* **2009**, 753-762. (d) G. E. Dobereiner, R. H. Crabtree, *Chem. Rev.* **2010**, *110*, 681-703. (e) R. Yamaguchi, K.-i. Fujita, M. Zhu, *Heterocycles* **2010**, *81*, 1093-1140. (f) Y. Ishii, Y. Obora, *Synlett* **2010**, *2011*, 30-51. (g) F. Alonso, P. Riente, M. Yus, *Acc. Chem. Res.* **2011**, *44*, 379-391. (h) T. Suzuki, *Chem. Rev.* **2011**, *111*, 1825-1845. (i) Y. Obora, *ACS Catal.* **2014**, *4*, 3972-3981. (j) K.-I. Shimizu, *Catal. Sci. Technol.* **2015**, *5*, 1412-1427.

13 T. Jensen, R. Madsen, *J. Org. Chem.* **2009**, *74*, 3990-3992

14 R. Grigg, S. Whitney, V. Sridharan, A. Keep, A. Derrick, *Tetrahedron* **2009**, *65*, 7468-7473.

15 T. Kuwahara, T. Fukuyama, I. Ryu, *RSC Advances* **2013**, *3*, 13702-13704

16 (a) L. Guo, Y. Liu, W. Yao, X. Leng, Z. Huang, *Org. Lett.* **2013**, *15*, 1144-1147. (b) W. Yao, X. Ma, L. Guo, X. Jia, A. Hu, Z. Huang, *Tetrahedron Lett.* **2016**, *57*, 2919-2921.

17 M. Morita, Y. Obora, Y. Ishii, *Chem. Commun.* **2007**, 2850-2852.

18 Y. Iuchi, Y. Obora, Y. Ishii, *J. Am. Chem. Soc.* **2010**, *132*, 2536-2537.

19 L. Guo, X. Ma, H. Fang, X. Jia, Z. Huang, *Angew. Chem. Int. Ed.* **2015**, *54*, 4023-4027.

20 C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712.

21 S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140-144.

22 (a) M. Zhang, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 597-601. (b) M. Zhang, X. Fang, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2013**, *135*, 11384-11388.

23 D. Srimani, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2013**, *52*, 4012-4015.

24 K. Iida, T. Miura, J. Ando, S. Saito, *Org. Lett.* **2013**, *15*, 1436-1439.

25 (a) S. Michlik, R. Kempe, *Angew. Chem. Int. Ed.* **2013**, *52*, 6326-6329. (b) T. Hille, T. Irrgang, R. Kempe, *Angew. Chem. Int. Ed.* **2017**, *56*, 371-374.

26 D. Srimani, Y. Ben-David, D. Milstein, *Chem. Commun.* **2013**, *49*, 6632-6634.

27 T. Hille, T. Irrgang, R. Kempe, *Chem. Eur. J.* **2014**, *20*, 5569-5572.

28 M. Peña-López, H. Neumann, M. Beller, *Chem. Eur. J.* **2014**, *20*, 1818-1824.

29 M. Chen, M. Zhang, B. Xiong, Z. Tan, W. Lv, H. Jiang, *Org. Lett.* **2014**, *16*, 6028-6031.

30 N. Deibl, K. Ament, R. Kempe, *J. Am. Chem. Soc.* **2015**, *137*, 12804-12807.

31 G. Zhang, Z. Yin, S. Zheng, *Org. Lett.* **2016**, *18*, 300-303.

32 S. Elangovan, J. Neumann, J. B. Sortais, K. Junge, C. Darcel, M. Beller, *Nat. Commun.* **2016**, *7*, 12641

33 S. Rösler, M. Ertl, T. Irrgang, R. Kempe, *Angew. Chem. Int. Ed.* **2015**, *54*, 15046-15050.

34 (a) M. Mastalir, G. Tomsu, E. Pittenauer, G. Allmaier, K. Kirchner, *Org. Lett.* **2016**, *18*, 3462-3465. (b) M. Mastalir, M. Glatz, N. Gorgas, B. Stöger, E. Pittenauer, G. Allmaier, L. F. Veiros, K. Kirchner, *Chem. Eur. J.* **2016**, *22*, 12316-12320.

35 H. J. Pan, T. W. Ng, Y. Zhao, *Chem. Commun.* **2015**, *51*, 11907-11910.

36 T. Yan, B. L. Feringa, K. Barta, *Nat. Commun.* **2014**, *5*, 5602.

37 A. J. Rawlings, L. J. Diorazio, M. Wills, *Org. Lett.* **2015**, *17*, 1086-1089.

38 S. Elangovan, J. B. Sortais, M. Beller, C. Darcel, *Angew. Chem. Int. Ed.* **2015**, *54*, 14483-14486.

39 M. Peña-López, P. Piehl, S. Elangovan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 14967-14971.

40 G. Zhang, J. Wu, H. Zeng, S. Zhang, Z. Yin, S. Zheng, *Org. Lett.* **2017**, *19*, 1080-1083.

41 F. Freitag, T. Irrgang, R. Kempe, *Chem. Eur. J.* **2017**, *23*, 12110-12113.

42 N. Deibl, R. Kempe, *J. Am. Chem. Soc.* **2016**, *138*, 10786-10789.

43 G. Zhang, S. K. Hanson, *Org. Lett.* **2013**, *15*, 650-653.

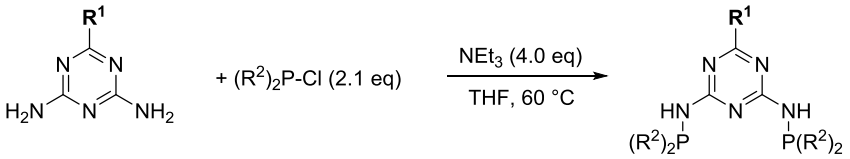
44 A. Mukherjee, A. Nerush, G. Leitus, L. J. Shimon, Y. Ben-David, N. A. Espinosa Jalapa, D. Milstein, *J. Am. Chem. Soc.* **2016**, *138*, 4298-4301.

45 N. Deibl, R. Kempe, *Angew. Chem. Int. Ed.* **2017**, *56*, 1663-1666; *Angew. Chem.* **2017**, *129*, 1685-1688.

# 4 Overview of thesis results

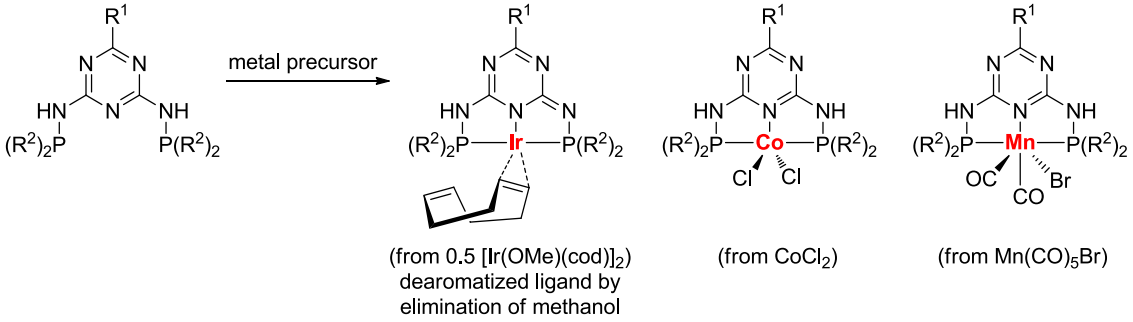
## 4.1 Synopsis

This thesis consists of three different projects that feature the conversion of alcohols into important organic compounds. The reactions presented are based on the use of $PN_5P$ ligand-stabilized iridium, cobalt and manganese complexes. These complexes are used for Borrowing Hydrogen / Hydrogen Autotransfer reactions and – in part – for Acceptor-free Dehydrogenative Condensations. The ligands used in this work were prepared on a gram scale by the reaction of commercially available triazine diamines with the corresponding phosphine chloride, mediated by triethylamine as a base (Scheme 14).




Scheme 14. Synthesis of $PN_5P$ ligands, starting from triazine diamines.

The reaction of the $PN_5P$ ligand with a suitable metal precursor allows the straightforward synthesis of the corresponding complexes (Scheme 15).

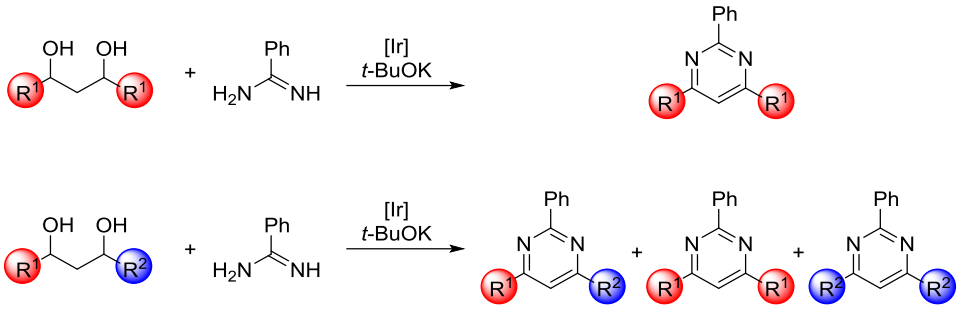



Scheme 15. Synthesis of PNP ligand-stabilized complexes of the transition metals iridium, cobalt and manganese.

### 4.1.1 A Sustainable Multicomponent Pyrimidine Synthesis

A multicomponent pyrimidine synthesis was discovered (Scheme 16) and optimized (Table 2) based on the syntheses of aromatic N-heterocycles from alcohols described recently. At the outset, an iridium-catalyzed two-component reaction between a symmetric 1,3-diol and an amidine was investigated (Scheme 16, top), which gave the expected pyrimidine product in reasonable yields. When unsymmetrical 1,3-diols were used in this reaction, a mixture of three differently substituted pyrimidine products was obtained (Scheme 16, bottom). This result suggested that a retro-aldol reaction takes place under the reaction conditions. It was then envisioned that the 1,3-diol could be replaced by a secondary and a primary alcohol. The two alcohols are dehydrogenated by the iridium catalyst and the

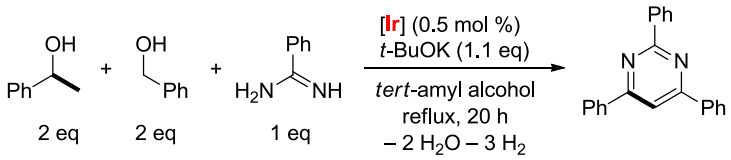
corresponding carbonyl compounds can undergo a base-mediated aldol condensation reaction to give an α,β-unsaturated ketone, which can react with the amidine to yield the pyrimidine.

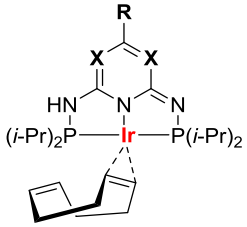



Scheme 16. Reaction discovery by investigation of the reaction between 1,3-dialcohols and benzamidine catalyzed by an iridium complex (e.g. [Ir]-**A**, Table 2).

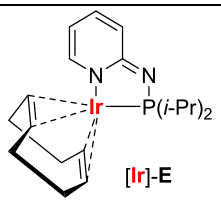
The reaction between 1-phenylethanol, benzyl alcohol and benzamidine (Table 2, top) was used as a model system and common reaction parameters were optimized. The screening of a library of iridium complexes identified pre-catalyst [**Ir**]-**A** (Table 2) as the most active for this transformation.

Table 2. Pre-catalyst screening for the iridium-catalyzed pyrimidine synthesis. Yields were determined by GC with dodecane as the internal standard.



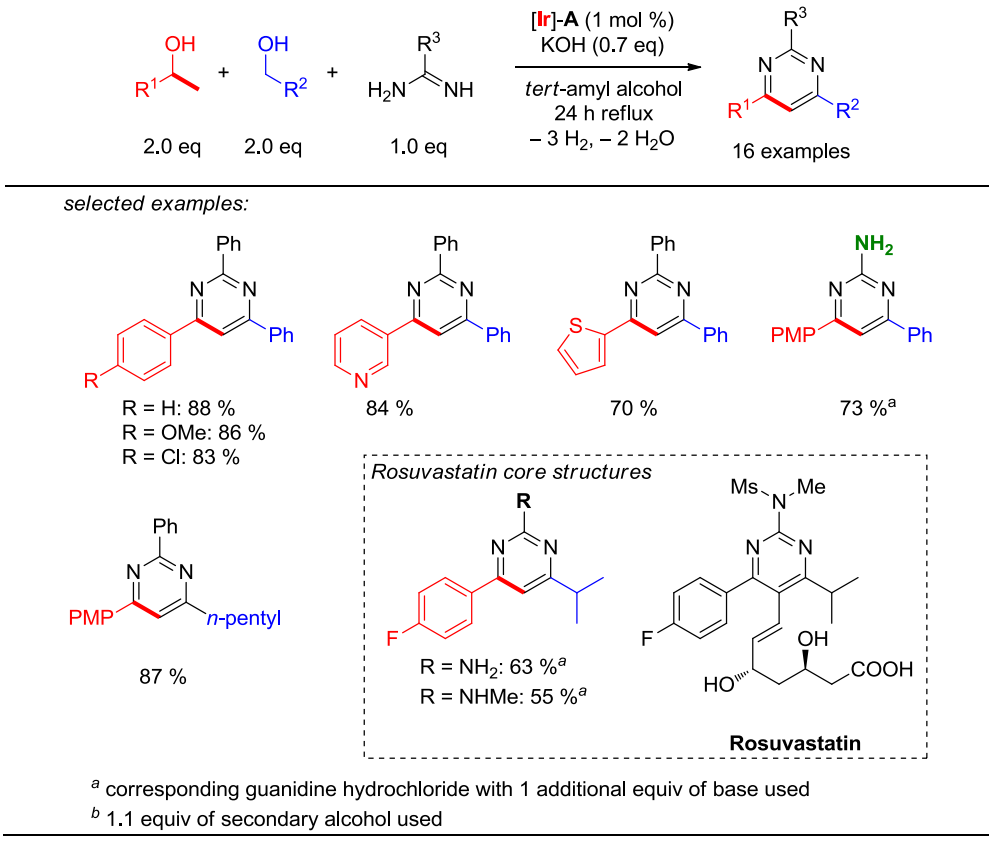

| Complex | R | X | Yield |
|---|---|---|---|
| [**Ir**]-**A** | 4-$CF_3$-($C_6H_4$)- | N | 83 % |
| [**Ir**]-**B** | Ph | N | 79 % |
| [**Ir**]-**C** | Me | N | 75 % |
| [**Ir**]-**D** | H | CH | 64 % |
| [**Ir**]-**E** | - | - | 45 % |
| [**Ir**Cl(cod)]$_2$ | | | 43 % |
| [**Ir**(OMe)(cod)]$_2$ | | | 37 % |




This three-component reaction was used to identify the general substrate scope of the reaction (see Table 3 for selected examples). Sixteen examples were synthesized according to this three-component protocol, starting from 1-substituted ethanol derivatives and another primary alcohol. The reaction tolerated a broad range of typical functional groups and heterocyclic motifs. Notably, the application of guanidine was tolerated and allowed the synthesis of the corresponding 2-aminopyrimidine. Furthermore, two core-pyrimidines of the drug Rosuvastatin were synthesized using the reaction

presented. The β-alkylation product of a secondary alcohol with a primary alcohol was identified as a side product in this reaction. This observation was leveraged in a later stage of the synthesis.

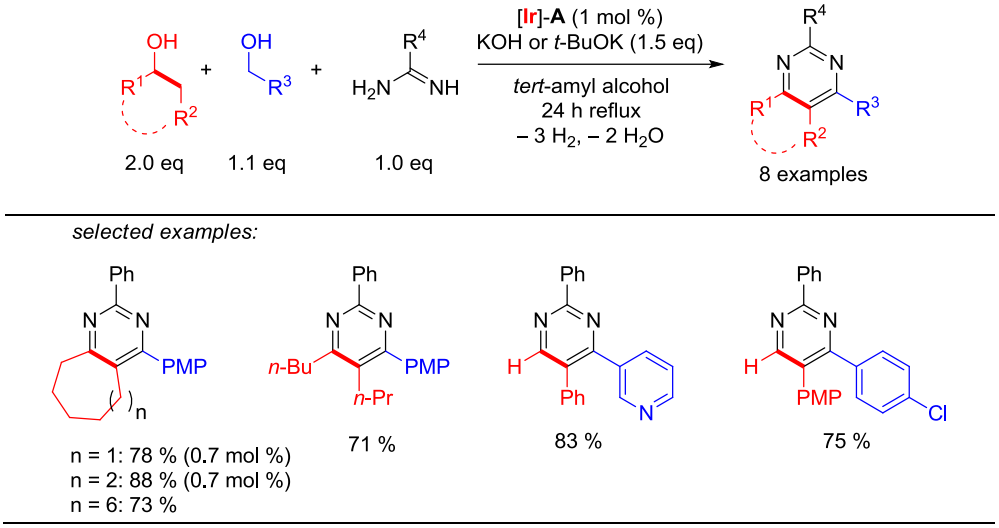
Table 3. Three-component synthesis of pyrimidines from alcohols and amidines or guanidines catalyzed by an iridium complex. Yields of isolated products are shown.




[a] corresponding guanidine hydrochloride with 1 additional equiv of base used
[b] 1.1 equiv of secondary alcohol used

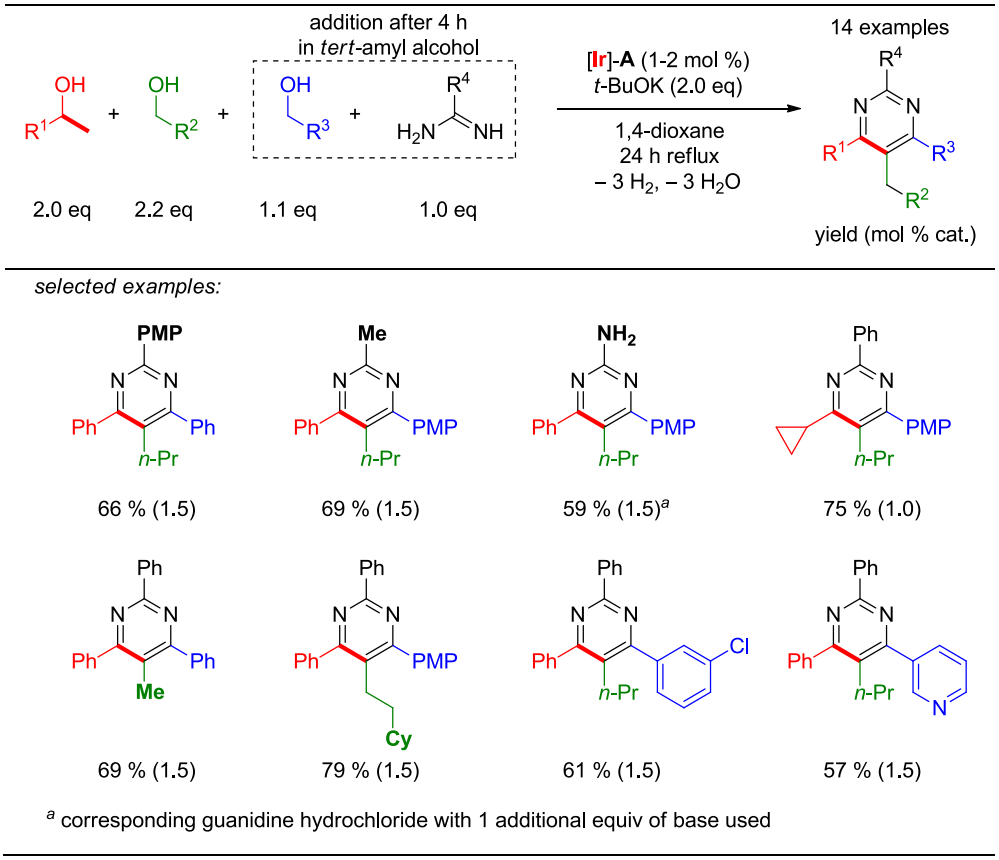
The next transformation to be investigated within this project was whether secondary alcohols with a substituent in the β-position can also be employed in this reaction (Table 4, top). The alkylation of a secondary carbon atom by means of BH/HA or ADC methods is known to be a more difficult procedure. The application of these compounds would allow the synthesis of fully substituted pyrimidines by the three-component protocol. After optimization of the reaction conditions, the synthesis of pyrimidines via alkylation of a methylene group was successful. The best yields were obtained when *t*-BuOK was used as a base and the amount was increased to 1.5 equiv. Since no saturated β-alkylation side product was observed during the reaction, the amount of primary alcohol could be lowered from 2.0 to 1.1 equiv. With these conditions, fully substituted pyrimidines were synthesized in isolated yields of up to 88 % (Table 4). The use of two primary alcohols, of which one contributes the C2 fragment to the pyrimidine core, allowed a different substitution pattern (2,4,5-trisubstituted pyrimidines) to be obtained. For the latter reaction, the best yield was obtained when KOH was used as a base.

Table 4. Synthesis of pyrimidines from alcohols with alkylation of methylene carbon atoms. Yields of isolated products are shown.




All observations made in the syntheses described previously were then used to develop a consecutive four-component pyrimidine synthesis from three alcohols and an amidine or guanidine (Table 5).

Table 5. Synthesis of tetrasubstituted pyrimidines from three alcohols and an amidine or guanidine by a consecutive four-component-synthesis. Yields of isolated products are shown.



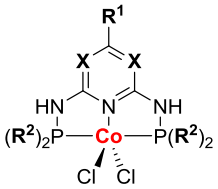
Firstly, a secondary alcohol and a primary alcohol were reacted under the typical reaction conditions for 4 hours to give the β-alkylation product which occurred as a side product in the three-component synthesis. Afterwards, another primary alcohol and an amidine (guanidine) were added to the reaction. After further optimization of the base amount and solvent, the substrate scope was explored. Fourteen differently substituted pyrimidines were synthesized by varying each reactant. A total of 38 different pyrimidine products were synthesized within this project.

### 4.1.2 General and Mild Cobalt-Catalyzed C-Alkylation of Amides and Esters with Alcohols

An even more sustainable approach for BH/HA and ADC reactions would be the replacement of rare noble metals with metals occurring abundantly. Cobalt-complexes have been reported for key steps of the BH/HA concept (like hydrogenation and dehydrogenation). The Kempe group also reported cobalt complexes, stabilized by PNP ligands, as active catalysts for the hydrogenation of C=O bonds and for the alkylation of amines with alcohols.

Further applications of these complexes were investigated within this work, leading to the first base metal-catalyzed alkylation of unactivated amides and esters with alcohols. Cobalt complex **[Co]-1c** (5 mol-%, Table 6) was used and typical reaction parameters, such as solvent, base, base amount and temperature, were optimized for both the alkylation of amides and esters to establish the best reaction conditions. Subsequently, the library of PNP ligand-stabilized cobalt complexes (Table 6) was tested to find the most active pre-catalyst for each reaction (Table 7).

Table 6. PNP ligand-stabilized cobalt dichloride complexes used to identify the best reaction conditions.

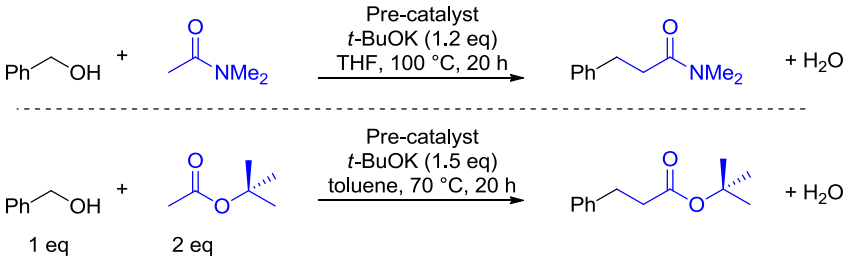



| Complex | $R^1$ | $R^2$ | X |
|---|---|---|---|
| [Co]-**1a** | H | *i*-Pr | N |
| [Co]-**1b** | Me | *i*-Pr | N |
| [Co]-**1c** | Ph | *i*-Pr | N |
| [Co]-**1d** | 4-$CF_3$-($C_6H_4$)- | *i*-Pr | N |
| [Co]-**1e** | $C_3H_5$-NH- | *i*-Pr | N |
| [Co]-**1f** | Me | Cy | N |
| [Co]-**1g** | H | *i*-Pr | CH |
| [Co]-**1h** | Me | *i*-Pr | CH |
| [Co]-**1i** | H | Ph | CH |

With the optimized conditions in hand, the substrate scope for the alkylation of amides with alcohols was explored using **[Co]-1e** because it is cheaper than **[Co]-1f** and performed equally. Many typical functional groups and motifs (e.g. aromatic, heteroaromatic and aliphatic moieties) were tolerated for the amide alkylation with alcohols (Table 8). A very intriguing finding was that when *t*-BuONa instead of *t*-BuOK was used, the reaction tolerated chlorine-substituted phenyl moieties, whereas de-

chlorination occurred under the standard conditions. Regarding problematic substrates, such as alcohols with strongly coordinating pyridine moieties, a more stable pre-catalyst (**[Co]-1f**) was chosen from the library, which permitted the corresponding products to be obtained in good to high yields.

Table 7. Pre-catalyst screening for C-alkylation of amides and esters with alcohols. Yields were determined by GC with dodecane as the internal standard.




| [Co] Pre-catalyst | Yield [%] | |
|---|---|---|
| | **Amide** | **Ester** |
| **[Co]-1a** | 7 | 13 |
| **[Co]-1b** | 49 | 43 |
| **[Co]-1c** | 25 | 50 |
| **[Co]-1d** | 41 | 60 |
| **[Co]-1e** | 69 | 42 |
| **[Co]-1f** | 74 | 45 |
| **[Co]-1g** | 0 | 31 |
| **[Co]-1h** | 0 | 24 |
| **[Co]-1i** | 0 | 0 |
| $CoCl_2$ | 0 | 0 |

The best results were obtained with tertiary amides and a secondary amide required harsher reaction conditions. A total of 22 different amides were synthesized in isolated yields of up to 93 %. Next, the alkykation of *tert*-butyl acetate with alcohols was investigated (Table 9, top). This reaction turned out to be more difficult, as esters are prone to undergo side reactions, such as self-condensation or transesterification, which diminishes the yield. After the optimization of reaction conditions, the peak of product yield was obtained when the amount of *tert*-butyl acetate was adjusted to 4 equiv with respect to the alcohol with toluene as the solvent. However, a decrease in yield was noted when the reaction was run in neat *tert*-butyl acetate. Having pinpointed the best reaction conditions and an active precatalyst (**[Co]-1d**, Table 7), twelve compounds were synthesized using this method (see Table 9 for selected examples). Reaction monitoring by GC and GC-MS indicated that *tert*-butyl acetate undergoes transesterification with the alcohol used and the reaction equilibrium is shifted towards the C-alkylated *tert*-butyl ester by transesterification with *t*-BuOH/*t*-BuOK. This reaction is restricted to *tert*-butyl acetate due to the reaction conditions applied (*t*-BuOK as the base). As with the alkylation of amides, the base had to be changed to *t*-BuONa for chlorine substituents to be tolerated.

Table 8. Cobalt-catalyzed C-alkylation of acetamides with alcohols. Yields of isolated products are shown.

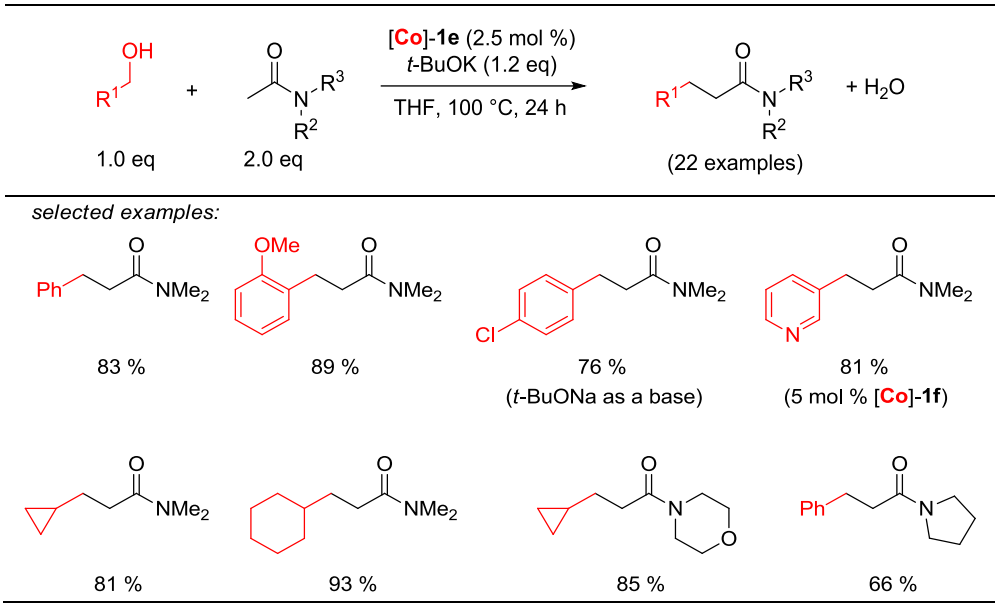
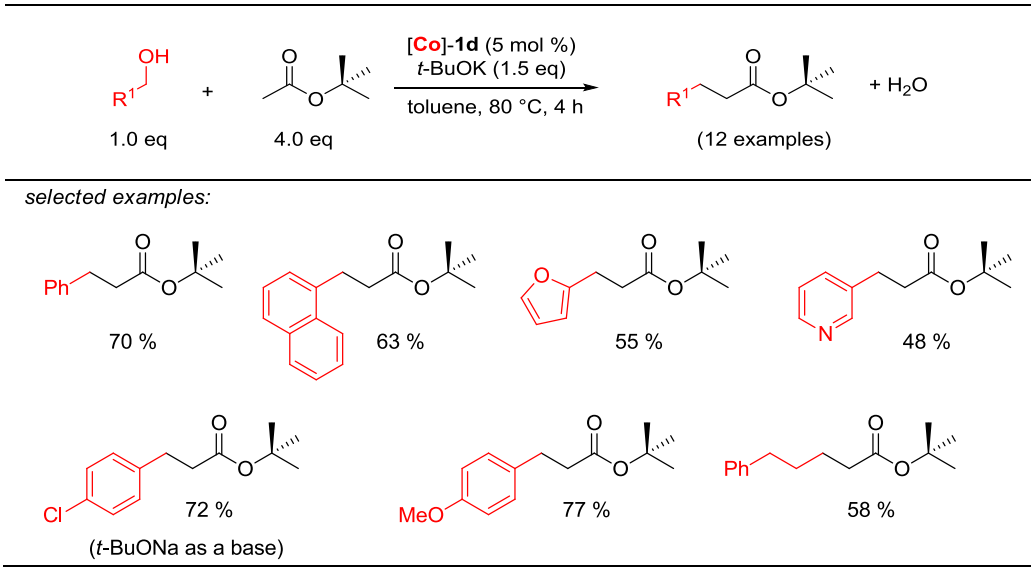
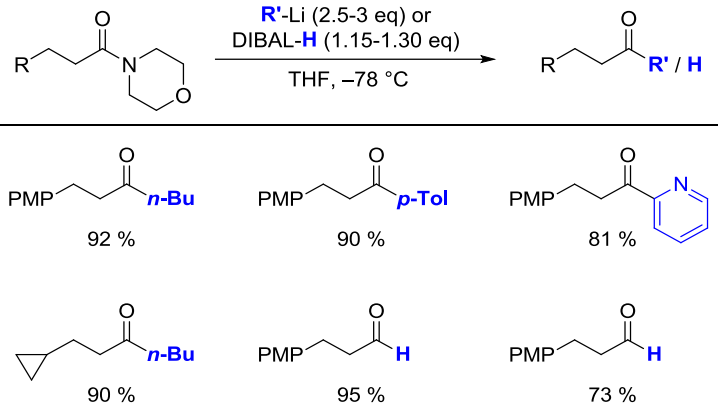



Table 9. Cobalt-catalyzed C-alkylation of *tert*-butyl acetate with alcohols. Yields of isolated products are shown.




In order to show the applicability of the amide alkylation products, some alkylated morpholino amides were reacted with organolithium compounds to yield the corresponding ketones or with DIBAL-H to give the aldehyde (Table 10). The amide starting material used was prepared on a 5 and 10 mmol scale and no variation in yield was detected, suggesting the reaction can be scaled up to some degree.

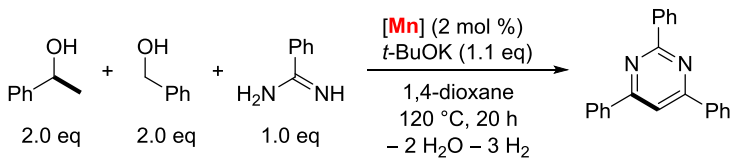
Table 10. Derivatization of amide substrates. Yields of isolated products are shown.

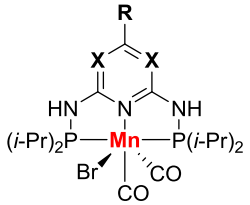



### 4.1.3 Manganese-Catalyzed Multicomponent Synthesis of Pyrimidines from Alcohols and Amidines

The cobalt complexes mentioned earlier were tested for the pyrimidine synthesis described in section 4.1.1 and no activity in this typical ADC-reaction was observed. However, manganese(I) complexes stabilized by pincer ligands have recently been reported for hydrogenation, BH/HA and ADC reactions by the groups of Beller, Milstein and Kempe. Thus, their potential in the synthesis of N-heterocycles from alcohols was explored. Using a library of PNP ligand-stabilized manganese complexes, developed by the Kempe group, a base metal-catalyzed version of the multicomponent pyrimidine synthesis from alcohols was elaborated (Table 11, top). After screening of common reaction parameters and identification of the best pre-catalyst ([Mn]-**B**, Table 11), the scope and limitations of the manganese-catalyzed version were explored.

Table 11. Pre-catalyst screening of manganese complexes for the three-component pyrimidine synthesis. Yields were determined by GC analysis with dodecane as the internal standard.

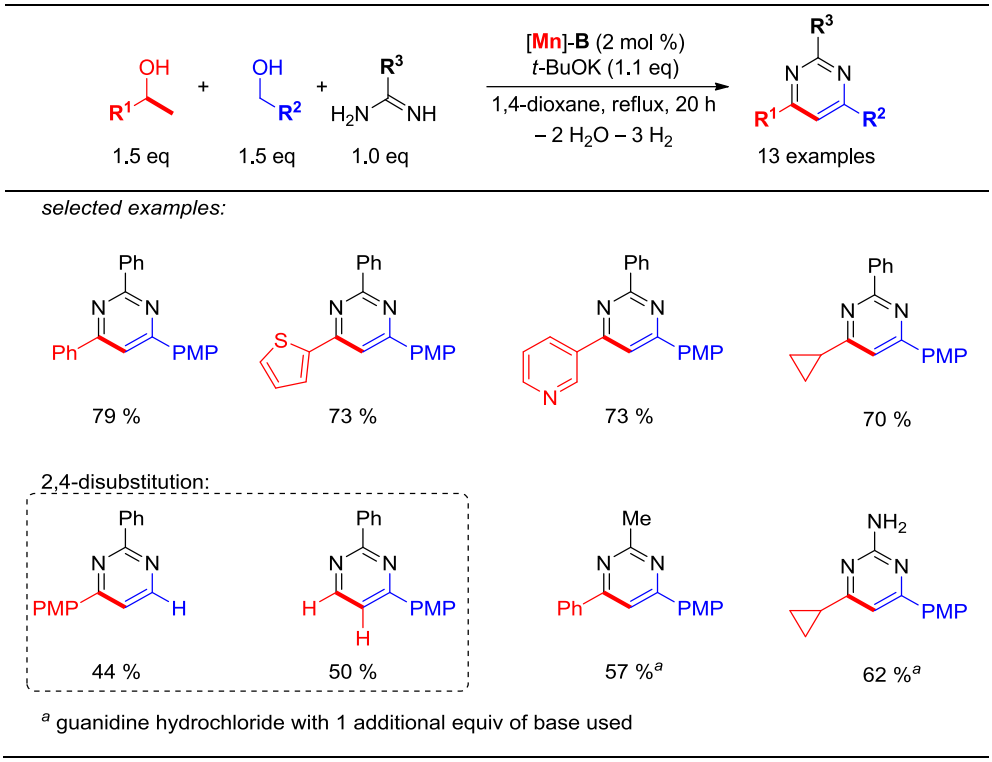



| Complex | R | X | Yield |
|---|---|---|---|
| [Mn]-**A** | Me | N | 83 % |
| [Mn]-**B** | Ph | N | 96 % |
| [Mn]-**C** | 4-$CF_3$-($C_6H_4$)- | N | 85 % |
| [Mn]-**D** | H | N | 92 % |
| [Mn]-**E** | $C_3H_5$-NH- | N | 89 % |
| [Mn]-**F** | H | CH | 48 % |
| [Mn]-**G** | Me | CH | 54 % |

The three-component synthesis (Table 12) tolerated several aromatic (e.g. phenyl moieties with different substituents as well as heterocyclic motifs) and aliphatic moieties.

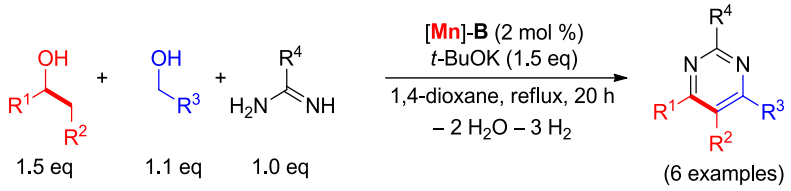
Table 12. Selected examples of pyrimidines synthesized by manganese-catalyzed three-component reaction. Isolated yields are shown.



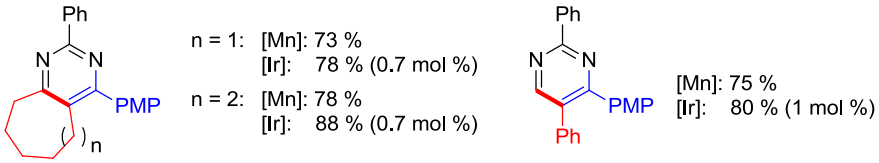

An approach towards 2,4-disubstituted pyrimidines was also elaborated within this work. This substitution pattern turned out to be challenging, since it relies on the use of ethanol and another primary alcohol, or methanol in combination with a secondary alcohol. The former version (using ethanol) gave the corresponding product in 50 % (vs. 44 % from methanol) isolated yield.

The next step was to explore the scope of the reaction when secondary alcohols are employed (Table 13, top). It should be noted, that the cobalt-catalyzed amide and ester alkylation described in section 4.1.2 allowed no methylene carbon atoms to be connected on either side of the reactants (only acetamides, *tert*-butyl acetate and primary alcohols were tolerated). The manganese-catalyzed protocol allowed the alkylation of secondary carbon atoms and the yields of some products were comparable with the iridium-catalyzed version (Table 13). Finally, the manganese-complex (**[Mn]-B**) was used in the consecutive four-component synthesis (Table 14, top). Exemplarily, six compounds were synthesized using this synthetic protocol. Even low-boiling alcohols (methanol, ethanol) could be used in the first β-alkylation reaction. The scope and comparison with the iridium-catalyzed version – if applicable – is shown in Table 14.

Table 13. Selected examples of pyrimidines synthesized by manganese-catalyzed multicomponent reaction. Comparison of yields with the iridium-catalyzed version is shown for selected compounds that have been synthesized in both projects. Yields of isolated products are shown.

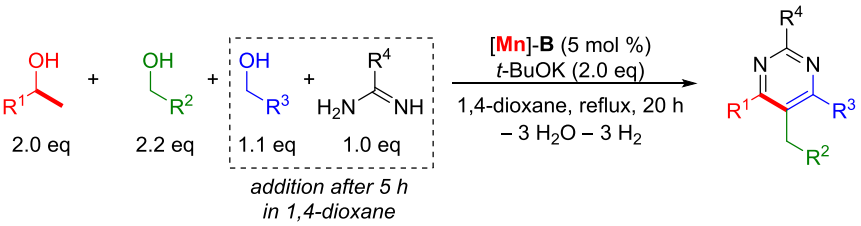


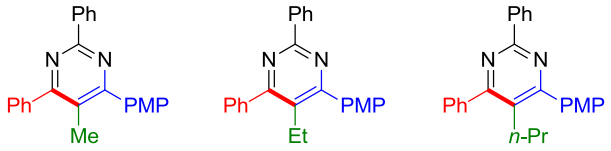

*selected examples and comparison with iridium-catalyzed version:*




Conditions for [Ir]: *tert*-amyl alcohol, *t*-BuOK or KOH (1.5 eq), 24 h reflux.

Table 14. Tetrasubstituted pyrimidines synthesized by the manganese-catalyzed consecutive four-component synthesis and comparison with the iridium catalyzed version for compounds that have been prepared in both projects. Yields of isolated products are shown.

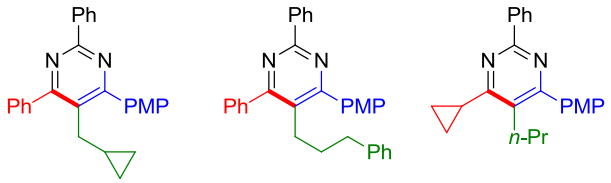



[Mn]: 51 %
[Ir]: 74 %

[Mn]: 57 %
[Ir]: 69 %

[Mn]: 55 %
[Ir]: 72 %




[Mn]: 63 %

[Mn]: 56 %

[Mn]: 70 %
[Ir]: 73 %

Conditions for [Ir]: 1-2 mol % pre-catalyst, 2.0 eq *t*-BuOK, 1,4-dioxane, reflux addition of remaining starting material after 4 h in *tert*-amyl alcohol, 24 h reflux

In summary, one of the first manganese-catalyzed syntheses of N-heterocycles from alcohols via the ADC-concept was elaborated within this project. Furthermore, an unprecedented manganese-catalyzed version of the β-alkylation (via HA/BH) between two alcohols and subsequent ADC-reactions allowed the synthesis of tetrasubstituted pyrimidines in a consecutive manner.

## 4.2 Individual contributions to joint publications

The results presented in this thesis were obtained in collaboration with others and were published as indicated below. In the following, the contributions of all co-authors and contributors to the publications are specified. The asterisk denotes the corresponding author.

**Chapter 5**

This work was published in Journal of the American Chemical Society (*J. Am. Chem. Soc.* **2015**, *137*, 12804-12807) with the title "**A Sustainable Multicomponent Pyrimidine Synthesis**".

Authors: Nicklas Deibl, Kevin Ament and Rhett Kempe*

I synthesized and characterized all compounds presented in the final version of the manuscript. Kevin Ament was involved in an early stage of the design of the reaction during his B.Sc thesis and a master module. Thomas Dietel and Mikhail Butovskii performed the X-ray analysis and solved the crystal structure of compound 6f in the manuscript. Rainer Schobert commented on the manuscript. Rhett Kempe supervised this work and co-wrote the manuscript with me.

**Chapter 6**

This work was published in Journal of the American Chemical Society (*J. Am. Chem. Soc.* **2016**, *138*, 10786-10789) with the title "**General and Mild Cobalt-Catalyzed C-Alkylation of Unactivated Amides and Esters with Alcohols**".

Authors: Nicklas Deibl and Rhett Kempe*

I conceived the concept, performed the synthetic experiments and analyzed the spectroscopic data. Robin Fertig helped with purification of some compounds during a master module. Rhett Kempe supervised this work and co-wrote the manuscript with me.

**Chapter 7**

This work was published in Angewandte Chemie International Edition (*Angew. Chem. Int. Ed.* **2017**, 56, 1663-1666) with the title "**Manganese-Catalyzed Multicomponent Synthesis of Pyrimidines from Alcohols and Amidines**".

Authors: Nicklas Deibl and Rhett Kempe*

I conceived the concept, performed the synthetic experiments and analyzed the spectroscopic data. Franziska Frielingsdorf helped with screening of reaction conditions during a B.Sc practical course. Rhett Kempe supervised this work and co-wrote the manuscript with me. I translated the manuscript for publication in the German version of Angewandte Chemie.

# 5 A Sustainable Multicomponent Pyrimidine Synthesis

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# A Sustainable Multicomponent Pyrimidine Synthesis

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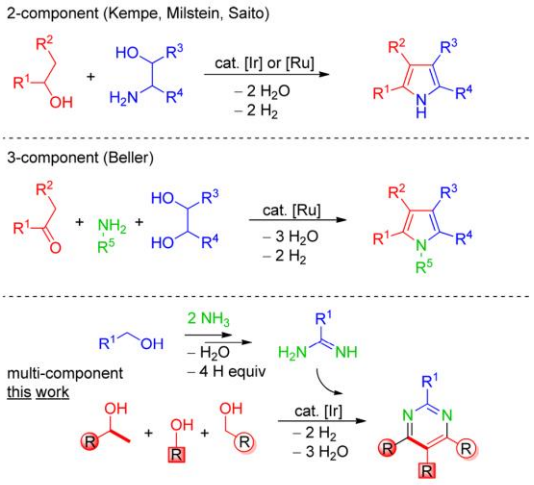
Supporting Information

**ABSTRACT:** Since alcohols are accessible from indigestible biomass (lignocellulose), the development of novel preferentially catalytic reactions in which alcohols are converted into important classes of fine chemicals is a central topic of sustainable synthesis. Multicomponent reactions are especially attractive in organic chemistry as they allow the synthesis of large libraries of diversely functionalized products in a short time when run in a combinatorial fashion. Herein, we report a novel, regioselective, iridium-catalyzed multicomponent synthesis of pyrimidines from amidines and up to three (different) alcohols. This reaction proceeds via a sequence of condensation and dehydrogenation steps which give rise to selective C−C and C−N bond formations. While the condensation steps deoxygenate the alcohol components, the dehydrogenations lead to aromatization. Two equiv of hydrogen and water are liberated in the course of the reactions. $PN_5P$−Ir−pincer complexes, recently developed in our laboratory, catalyze this sustainable multicomponent process most efficiently. A total of 38 different pyrimidines were synthesized in isolated yields of up to 93%. Strong points of the new protocol are its regioselectivity and thus the immediate access to pyrimidines that are highly and unsymmetrically decorated with alkyl or aryl substituents. The combination of this novel protocol with established methods for converting alcohols to nitriles now allows to selectively assemble pyrimidines from four alcohol building blocks and 2 equiv of ammonia.

Dwindling fossil carbon resources and environmental concerns associated with their use call for alternative ways to produce fine chemicals. Out of the available biomass, lignocellulose is especially attractive since it is abundantly available[1] and food chain competition is negligible. Since lignocellulose can be catalytically processed to alcohols,[2] the development of novel catalytic reactions converting alcohols into important classes of compounds is highly desirable.[3] Aromatic N-heterocyclic compounds have a wide range of applications and also feature prominently in medicinal chemistry.[4] Recently, a sustainable 2-component synthesis of pyrroles from alcohols has been reported by the groups of Milstein, Saito, and us (Scheme 1, top).[3,5,6] Diversely functionalized pyridines have been synthesized similarly.[7] In parallel, Beller and coworkers disclosed a 3-component pyrrole synthesis using the same conceptual approach (Scheme 1, middle).[8] These alcohol-to-heterocycle reactions proceed via a combination of dehydrogenation and condensation (acceptor-less dehydrogenative condensation) and represent a novel and sustainable approach to construct C−C and C−N multiple bonds.[9] Condensation steps deoxygenate the alcohols and dehydrogenation allows aromatization. Multicomponent reactions[10] are especially attractive among the transition-metal-mediated or -catalyzed syntheses of aromatic N-heterocycles.[11] Large libraries of diversely substituted products can be synthesized without constructing sophisticated educts. We became interested in developing a 4-component reaction where amidines and three (different) alcohol components are selectively connected to pyrimidines (Scheme 1, bottom). Based on the already known catalytic methodology to synthesize nitriles from alcohols,[12] the selective assembly of pyrimidines just from alcohols and ammonia (Scheme 1, bottom) becomes feasible.

**Scheme 1. Recently Introduced Syntheses of Aromatic N-Heterocycles from Alcohols (Top and Middle) and the Pyrimidine Synthesis Described Here (Bottom)**




Herein, we report on a novel iridium-catalyzed multicomponent pyrimidine synthesis. Alcohols and 1 equiv of an amidine are selectively linked via C−C and C−N bond formation steps. Two equiv of hydrogen and water are liberated in the course of this sustainable reaction. The synthesis protocol is especially useful with regard to the formation of diversely and selectively arylated and/or alkylated pyrimidines.

Initially, we investigated the 3-component reaction of 1-substituted ethanol derivatives with primary alcohols (Table 1, top). The two alcohols get oxidized by the Ir catalyst with release

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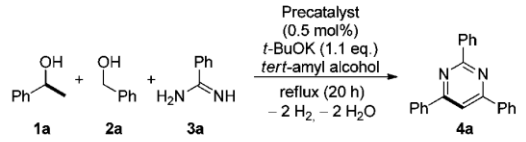
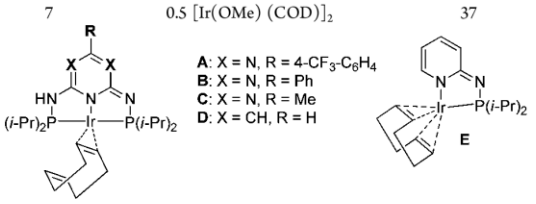
**Table 1. Catalyst Screening**[a]



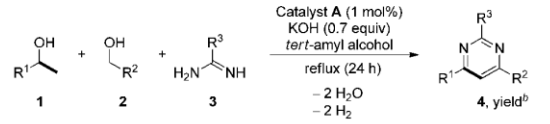

| entry | precatalyst | yield (%)[b] |
|---|---|---|
| 1 | **A** | 83 |
| 2 | **B** | 79 |
| 3 | **C** | 75 |
| 4 | **D** | 64 |
| 5 | **E** | 45 |
| 6 | 0.5 $[IrCl(COD)]_2$ | 43 |
| 7 | 0.5 $[Ir(OMe)(COD)]_2$ | 37 |

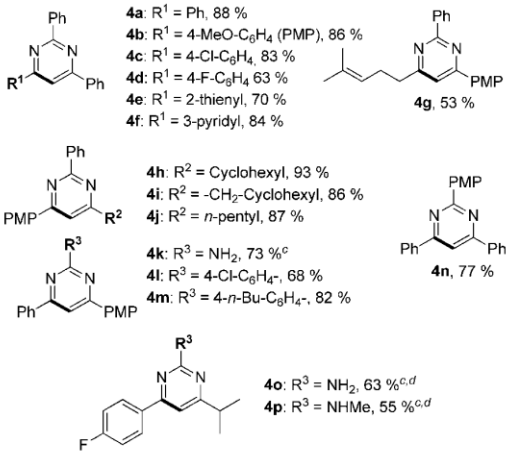



[a]Reaction conditions: 1-Phenyl ethanol (2 mmol), benzyl alcohol (2 mmol), benzamidine (1 mmol), *t*-BuOK (1.1 mmol), *tert*-amyl alcohol (3 mL), catalyst (0.005 mmol), 20 h reflux under inert atmosphere. [b]Yield was determined by GC with dodecane as internal standard. COD = 1,5-Cyclooctadiene, Me = methyl, Ph = phenyl, *i*-Pr = isopropyl, Bu = butyl.

of dihydrogen. A subsequent base-mediated aldol condensation may afford an $\alpha,\beta$-unsaturated ketone intermediate, which in turn could react with the amidine.[4] The C-alkylation by alcohols[13] (borrowing hydrogen or hydrogen autotransfer concept) represents a frequently used C−C bond formation strategy, but to date there are only a few reactions described where the unsaturated primary product is directly used as a reaction intermediate (e.g., for 1,4-addition of a nucleophile).[14] We recently extended the $\beta$-alkylation concept to methyl-*N*-heteroarenes.[15] The optimal conditions (solvent, base, and catalyst) for the 3-component reaction were identified by thoroughly investigating the reaction of 1-phenylethanol, benzyl alcohol, and benzamidine (Table 1). For instance, we found that the reaction should be run with KOH or *t*-BuOK as the base in *tert*-amyl alcohol under reflux (screening details in Supporting Information). Precatalysts **A** and **B** (Table 1, entries 1, 2) gave the highest yield of 2,3,5-triphenylpyrimidine (**4a**) in the screening reaction. Based on the convenience of $^{19}F$ NMR spectroscopy, catalyst **A** was selected. A substrate ratio of 2 equiv of each alcohol with respect to the amidine was found to give the highest yield of pyrimidine. Noticed side-reactions were self-condensation of the secondary alcohol (upon oxidation) and irreversible reduction of the conjugated C=C double bond of the unsaturated ketone. However, the amidine reacts preferably with a less-substituted $\alpha,\beta$-unsaturated ketone compared to an unsaturated ketone which is derived from multiple alkylations. When the reaction was run with 0.5 equiv KOH (w/r to the amidine), complete conversion of the alcohols was observed for the screening reaction. A catalyst loading of 1 mol % with respect to the amidine (0.25 mol % with respect to alcohols) was chosen to allow for a broad range of alcohols. Having pinpointed these optimal conditions, we then addressed the scope of possible substrates for this 3-component reaction (Table 2, compounds **4a**−**p**). Variation of the secondary alcohol led to compounds

**Table 2. Synthesis of Tri-Substituted Pyrimidines via 3-Component Reaction**[a]




[a]Reaction conditions: Secondary alcohol (2 mmol), primary alcohol (2 mmol), amidine (1 mmol), KOH (0.7 mmol), catalyst **A** (0.01 mmol), *tert*-amyl alcohol (3 mL), 24 h reflux under inert atmosphere. PMP = *para*-methoxyphenyl. [b]Yields of isolated products. [c]additional 1.0 equiv KOH to trap HCl from guanidine hydrochloride. [d]1.1 equiv of secondary alcohol.

**4a**−**g** (Table 2). Aryl chlorides, heterocycles like pyridine and thiophene, as well as olefins were tolerated. Very good isolated yield was obtained for most pyrimidine products. Compound **4g** (olefinic functional group) was isolated in lower yield since alkylation can occur on the primary and secondary carbon atom. No reduction of the double bond was observed (GC-MS analysis). The primary alcohol was then varied to introduce branched (**4h**, Cy = cyclohexyl) or linear aliphatic moieties (**4i**,**j**) in again very good isolated yields. Last, the amidine moiety was varied. The use of guanidine (as the hydrochloride along with an additional equiv of KOH) gave the pyrimidine **4k**, and gratifyingly no N-alkylation of the amino function was observed under the reaction conditions used. Substituents (*n*-butyl, methoxy, chloride) at the phenyl ring of benzamidine gave rise to the products **4l**−**n**. The application of 1-(4-fluorophenyl)-ethanol, isobutanol, and guanidine or methyl guanidine hydrochloride afforded the core pyrimidines **4o** and **4p** of the drug rosuvastatin, which acts as a HMG-CoA reductase inhibitor and is used to treat high cholesterol levels. In this case, the amount of secondary alcohol could be lowered to 1.1 equiv since no saturated $\beta$-alkylation product was observed. After having addressed the 2,4,6-substitution, we became interested in employing secondary alcohols carrying a substituent at the $\beta$-position. The significantly more challenging alkylation of a secondary carbon atom gives access to fully substituted pyrimidines. An optimization of the substrate ratio in the reaction between cycloheptanol, *para*-methoxybenzyl alcohol and benzamidine, which afforded pyrimidine **5b** (Table 3), indicated that the amount of primary alcohol can be lowered from 2.0 to 1.1 equiv. When a secondary carbon atom is alkylated,



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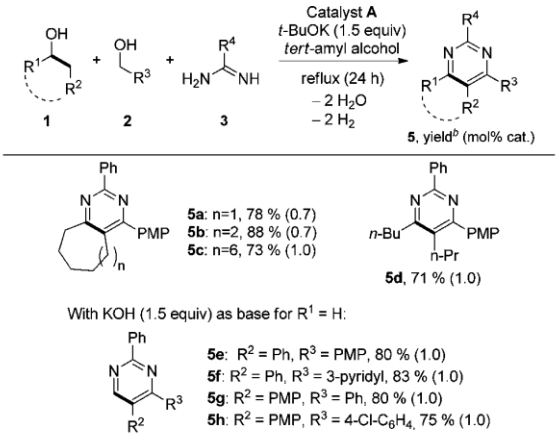
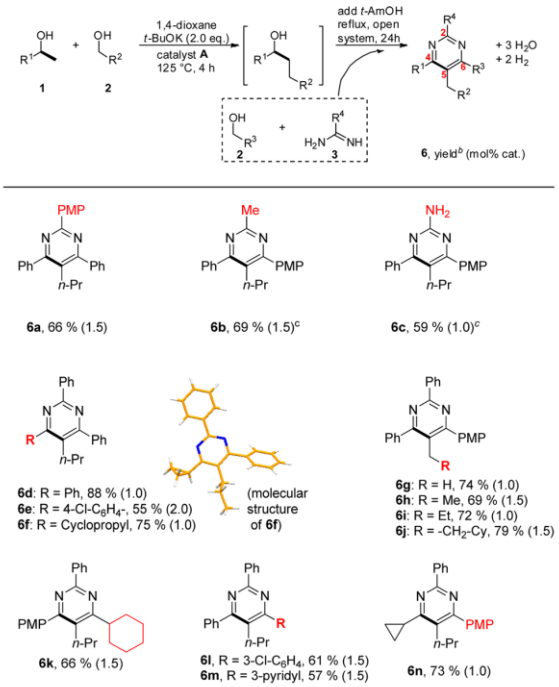
**Table 3. Synthesis of Pyrimidines via Alkylation of Methylene Groups**[a]




[a]Reaction conditions: Secondary alcohol (2 mmol), primary alcohol (1.1 mmol), amidine (1 mmol,), *t*-BuOK (1.5 mmol), catalyst A (0.007−0.010 mmol), *tert*-amyl alcohol (3 mL), 24 h reflux under inert atmosphere. KOH (1.5 mmol) was used for 2,4,5-substituted pyrimidines. [b]Yields of isolated products.

**Table 4. Synthesis of Tetra-Substituted Pyrimidines by a Consecutive 4-Component Reaction**[a]




[a]Reaction conditions: Secondary alcohol (2 mmol), primary alcohol (2.2 mmol), *t*-BuOK (2.0 mmol), catalyst **A** (0.01−0.02 mmol), 1,4-dioxane (1−2 mL), 4 h at 125 °C (oil bath). Then addition of remaining starting materials: primary alcohol (1.1 mmol), amidine (1.0 mmol) in *tert*-amyl alcohol (2 mL), 24 h reflux under inert atmosphere. [b]Yields of isolated products. Cy = cyclohexyl. [c]Corresponding amidine or guanidine hydrochloride (respectively) along with 1 additional equiv of *t*-BuOK was used.

reduction of the $\alpha,\beta$-unsaturated ketone is significantly slower as the C=C bond is less accessible for the Ir catalyst. With these optimal conditions established, we prepared pyrimidines with a fused carbocycle (Table 3, **5a−c**) from cyclic alcohols and **5d** from nonan-5-ol. 2,4,5-substituted pyrimidines (**5e−h**) were obtained by employing two primary alcohols of which one contributes the C-2 fragment to the pyrimidine core. For this reaction, the use of KOH was found to be superior compared to *t*-BuOK, and most of the examples were isolated in very good yields.

Based on the efficient and selective alkylation of a secondary carbon atoms (synthesis of **5a−h**, Table 3), a consecutive 4-component reaction becomes feasible. In the first step, the "secondary carbon atom" is formed by selective $\beta$-alkylation of the methyl group of 1-substituted ethanol derivatives (Table 4, top, left). Addition of a third alcohol and the amidine building block can give rise to fully substituted pyrimidines. Since this synthesis features four starting materials and four catalyst operations (three oxidations, one reduction), suitable reaction conditions had to be found. The reaction between 1-phenylethanol, 1-propanol, and the later addition of benzamidine and benzyl alcohol was chosen as the model reaction. We found that the $\beta$-alkylation reaction proceeds within <4 h if 1,4-dioxane and *t*-BuOK were used as solvent and base, respectively.

The optimal ratio for the $\beta$-alkylation reaction was 1 equiv of secondary alcohol and 1.1 equiv of primary alcohol. The complete conversion of the secondary alcohol is important, because its reaction with the later added third alcohol component would lead to 5-unsubstituted pyrimidines and thus to a product mixture. It should be noted, that the $\beta$-alkylation reaction can be run in either a pressurized tube or an open system (reflux condenser). In no case, a product with a C=C bond was observed (GC-MS monitoring). Next, the addition of a solution of benzamidine and benzyl alcohol was investigated, and *tert*-amyl alcohol (2 mL/mmol amidine) turned out to be optimal as the solvent. A base screening indicated, that *t*-BuOK is most efficient, as is catalyst **A** in 1−2 mol % loading. With these reaction conditions in hand, we started exploring the substrate scope of the consecutive 4-component reaction (Table 4). First, the "N−C−N" substituent was varied. Aryl (**6a**), alkyl (**6b**), and an amino function (**6c**, from guanidine) can be introduced in this position. Second, the substituent at the 4-position was varied by employing different 1-substituted ethanol derivatives which, in addition to this substituent, contribute two carbon atoms to the pyrimidine ring (for numbering, see Table 4, top right). Aromatic (**6d,e**) as well as aliphatic substituents (**6f**) were tolerated. Third, different primary alcohols were used in the first reaction as a source of the respective residues at the 5-position (**6g−j**). Notably, the use of methanol gave rise to a primary quasi-benzylic functional group at the pyrimidine in 5-position which is interesting for further functionalization reactions. Fourth, the remaining substituent at C-6, which is introduced with the primary alcohol added last, was varied. Aliphatic (**6k**) and (hetero)aromatic (**6l−n**) substituents can be introduced. Based on the examples listed in Table 4 and the modular synthesis concept of the consecutive 4-component reaction, a virtual library of more than 300 compounds (5 × 4 × 4 × 4-doublings) has been created.

In summary, we introduced a novel sustainable multicomponent pyrimidine synthesis. Alcohols and amidines can be assembled in 3- or consecutive 4-component reactions. The selective C−C and C−N bond formations proceed with the



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liberation of 2 equiv of dihydrogen (acceptor-less dehydrogenation) and the elimination of water (condensation). Unsymmetrically and fully substituted pyrimidines are accessible. The synthesis protocol is especially useful in forming selectively alkylated and/or arylated pyrimidines. The synthesis of 4-(4-fluorophenyl)-6-isopropylpyrimidin-2-amine underlines the applicability of the novel reactions to the synthesis of important pharmaceuticals. The Ir catalyst used and the optimized reaction conditions allow the presence of a wide range of typical organic functional groups.

## ■ ASSOCIATED CONTENT

### Supporting Information

. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b09510.

Experimental procedures, spectroscopic and crystallographic data (PDF)
Crystallographic data (CIF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) Tuck, C. O.; Perez, E.; Horvath, I. T.; Sheldon, R. A.; Poliakoff, M. *Science* **2012**, *337*, 695−699.

(2) (a) Vispute, T. P.; Zhang, H.; Sanna, A.; Xiao, R.; Huber, G. W. *Science* **2010**, *330*, 1222−1227. (b) Besson, M.; Gallezot, P.; Pinel, C. *Chem. Rev.* **2014**, *114*, 1827−1870.

(3) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140−144.

(4) Joule, J. A., Mills, K. In *Heterocyclic Chemistry*, 5th ed.; Wiley: Chichester, UK, 2010.

(5) (a) Srimani, D.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012−4015. (b) Iida, K.; Miura, T.; Ando, J.; Saito, S. *Org. Lett.* **2013**, *15*, 1436−1439.

(6) Reported pyrrole synthesis is based on contributions by Ishii and Crabtree: (a) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539−4542. (b) Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H. *Organometallics* **2011**, *30*, 4174−4179.

(7) (a) Michlik, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 6326−6329. (b) Srimani, D.; Ben-David, Y.; Milstein, D. *Chem. Commun.* **2013**, *49*, 6632−6634. (c) Ruch, S.; Irrgang, T.; Kempe, R. *Chem. - Eur. J.* **2014**, *20*, 13279−13285.

(8) (a) Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 597−601. (b) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135*, 11384−11388.

(9) Schranck, J.; Tlili, A.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7642−7644.

(10) Recent reviews on multicomponent synthesis of heterocycles, see: (a) D'Souza, D. M.; Müller, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1095−1108. (b) Balme, G.; Bouyssi, D.; Monteiro, N. *Heterocycles* **2007**, *73*, 87−124. (c) Arndtsen, B. A. *Chem. - Eur. J.* **2009**, *15*, 302−313. (d) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402−4421. (e) Jiang, B.; Rajale, T.; Wever, W.; Tu, S. J.; Li, G. *Chem. - Asian J.* **2010**, *5*, 2318−2335. (f) Estevez, V.; Villacampa, M.; Menendez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633−4657. (g) Allais, C.; Grassot, J.-M.; Rodriguez, J.; Constantieux, T. *Chem. Rev.* **2014**, *114*, 10829−10868.

(11) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084−3213.

(12) For selected examples see: (a) Oishi, T.; Yamaguchi, K.; Mizuno, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6286−6288. (b) Yamaguchi, K.; He, J.; Oishi, T.; Mizuno, N. *Chem. - Eur. J.* **2010**, *16*, 7199−7207. (c) Dornan, L. M.; Cao, Q.; Flanagan, J. C. A.; Crawford, J. J.; Cook, M. J.; Muldoon, M. J. *Chem. Commun.* **2013**, *49*, 6030−6032. (d) Kim, J.; Stahl, S. S. *ACS Catal.* **2013**, *3*, 1652−1656. (e) Yin, W.; Wang, C.; Huang, Y. *Org. Lett.* **2013**, *15*, 1850−1853. (f) Dighe, S. U.; Chowdhury, D.; Batra, S. *Adv. Synth. Catal.* **2014**, *356*, 3892−3896. (g) Jagadeesh, R. V.; Junge, H.; Beller, M. *Nat. Commun.* **2014**, *5*, 1−8.

(13) For selected reviews on C-alkylation by alcohols see: (a) Guillena, G.; Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358−2364. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555−1575. (c) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. *Dalton Trans.* **2009**, 753−762. (d) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681−703. (e) Yamaguchi, R.; Fujita, K.-i.; Zhu, M. *Heterocycles* **2010**, *81*, 1093−1140. (f) Ishii, Y.; Obora, Y. *Synlett* **2011**, *2011*, 30−51. (g) Alonso, F.; Riente, P.; Yus, M. *Acc. Chem. Res.* **2011**, *44*, 379−391. (h) Suzuki, T. *Chem. Rev.* **2011**, *111*, 1825−1845. (i) Obora, Y. *ACS Catal.* **2014**, *4*, 3972−3981. (j) Shimizu, K.-I. *Catal. Sci. Technol.* **2015**, *5*, 1412−1427. (k) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712.

(14) Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 1642−1645.

(15) Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924−925.




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Supporting Information

# A Sustainable Multi-Component Pyrimidine Synthesis

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# 1 General Considerations

Air- and moisture sensitive reactions were carried out under nitrogen or argon atmosphere using standard Schlenk techniques or a glove box. Dry solvents were obtained from a solvent purification system (activated alumina cartridges) or purchased from Acros. Chemicals were purchased from commercial vendors and used without purification if not noted otherwise. NMR-Spectra were collected on Varian INOVA 300 (300 MHz for $^{1}$H, 75 MHz for $^{13}$C) or Bruker Avance III HD 500 (500 MHz for $^{1}$H, 125 MHz for $^{13}$C) instruments. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$: 7.26 ppm ($^{1}$H), 77.16 ppm ($^{13}$C)). Coupling constants (*J*) are reported in Hz (coupling patterns: d = doublet, t = triplet, q = quartet, sxt = sextet, spt = septet, m = multiplet). GC analyses were carried out on an Agilent 6890N Network GC system equipped with a HP-5 column (30 m x 0.32 mm x 0.25 µm) and GC-MS analyses on an Agilent 7890A GC system equipped with a HP-5MS column (30 m x 0.32 mm x 0.25 µm) and a 5975C inert MSD detector (EI, 70 eV). Flash column chromatography was conducted on Macherey-Nagel silica gel 60 (40–63 µm particle size). Elemental analysis was performed on an Elementar Vario El *III* Instrument. X-Ray analysis was performed on a Stoe IPDS-II diffractometer [λ(Mo-Kα)= 0.71073 Å] equipped with an Oxford Cryostream low temperature unit. Structure solution and refinement were accomplished with SIR971,[1] SHELXL-20132[2] and WinGX3.[3]

All compounds were characterized by $^{1}$H and $^{13}$C NMR analysis. Spectroscopic data of known compounds were compared with literature data and new compounds were further characterized by elemental analysis.

**Purification/preparation of chemicals**: *t*-BuOK was dried at 70 °C for 3 days under high vacuum and stored in a glove box. KOH was purchased from Sigma-Aldrich (puriss. p.a., Reag. Ph. Eur., ≥85%,) and pestled inside a glove box to give a fine powder. *Tert*-amyl alcohol (*t*-AmOH) was purchased from Acros and stored over molecular sieves inside a glove box. Benzamidine was purchased as the hydrochloride hydrate. All amidine salts were extracted ($CH_2Cl_2$ vs. 1 M aq. NaOH) and dried under high vacuum prior to use.

All used ligands and catalysts were prepared as reported previously by our group.[4]

# 2 General procedures (GP) for the synthesis of pyrimidines from alcohols and amidines

## 2.1 Three-component-reaction with alkylation of a methyl group (GP-1)

Amidine (1.0 eq.), KOH (0.7 eq.), secondary alcohol (2.0 eq.), primary alcohol (2.0 eq.) and catalyst (0.01 eq, 1 mol%, from 0.01 M stock solution in *t*-AmOH) were mixed in *t*-AmOH

(3 mL/mmol amidine total volume) using a nitrogen-filled glove box and heated to reflux for 24 h under inert atmosphere in an open system. The reaction was cooled, quenched with water (1 mL) and extracted with ethyl acetate (3 x 20 mL). The crude reaction mixture was analyzed by GC-MS and after drying and evaporation of solvent the remainder was subjected to flash column chromatography on silica gel.

## 2.2 Three-component-reaction with alkylation of a methylene group (GP-2)

Amidine (1.0 eq.), *t*-BuOK (unless noted otherwise) (1.5 eq.), secondary alcohol (2.0 eq.), primary alcohol (1.1 eq.) and catalyst (0.7-1.0 mol%, from 0.01 M stock solution in *t*-AmOH) were mixed in *t*-AmOH (3 mL/mmol amidine total volume) using a nitrogen-filled glove box and heated to reflux for 24 h under inert atmosphere in an open system. The reaction was cooled, quenched with water (1 mL) and extracted with ethyl acetate (3 x 20 mL). The crude reaction mixture was analyzed by GC-MS and after drying and evaporation of solvent the remainder was subjected to flash column chromatography on silica gel.

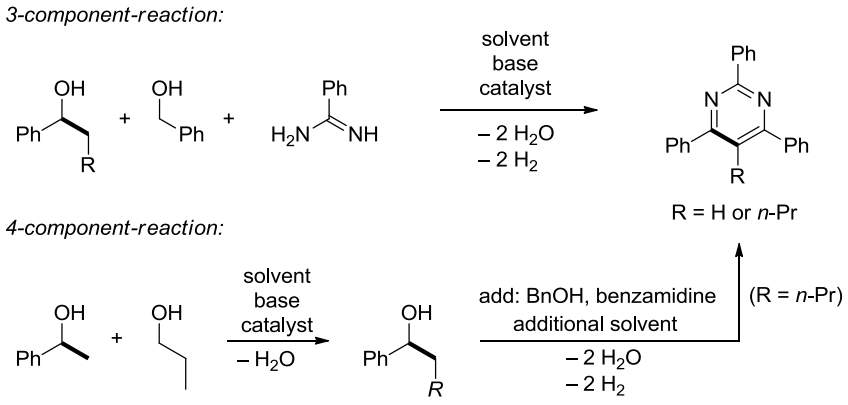
## 2.3 Consecutive four-component-reaction (GP-3)

A pressure tube (Ace pressure tube, 38 mL volume) was charged with a magnetic stirring bar, secondary alcohol (2.0 eq.), primary alcohol (2.2 eq.), *t*-BuOK (2.0 eq.) catalyst **A** (as a 0.01 M stock solution in 1,4-dioxane, 1.0-2.0 mL depending on catalyst loading) under an inert atmosphere (glove-box). The tube was closed with a Teflon® cap and immersed into a pre-heated oil bath (125 °C). After 4 hours the reaction was cooled and amidine (1.0 eq.), primary alcohol (1.1 eq.) and *t*-AmOH (2 mL) were added under inert atmosphere (glove box). The mixture was heated to reflux under inert atmosphere in an open system for 24 h. The reaction was cooled, quenched with water (1 mL) and extracted with ethyl acetate (3 x 20 mL). The crude reaction mixture was analyzed by GC-MS and after drying and evaporation of solvent the remainder was subjected to flash column chromatography on silica gel.

**Alternative procedure (GP-4)**: A two-necked Schlenk tube was charged with a magnetic stirring bar, secondary alcohol (2.0 eq.), primary alcohol (2.2 eq.), *t*-BuOK (2.0 eq.) and catalyst **A** (as a 0.01 M stock solution in 1,4-dioxane) using a glove box. The tube was sealed, taken out of the glove box and a reflux condenser was attached under argon stream. The mixture was heated to a gentle reflux for three hours under inert atmosphere in an open system to give the β-alkylation product. After cooling, a solution of amidine (1.0 eq.), primary alcohol (1.1 eq.) in *t*-AmOH (2 mL/mmol amidine) was added by syringe and the reaction mixture was heated to reflux for further 24 h. Work-up was conducted as described above.

# 3 Screening reactions

In order to identify the ideal reaction conditions the following reactions were investigated (on 0.5 or 1 mmol scale):




**General screening procedure:**

**3-Component-reaction.** In a nitrogen-filled glove box a glass tube (38 mL volume) was charged with a magnetic stirring bar, base, solvent, catalyst (as a 0.01 M stock solution in the appropriate solvent), secondary alcohol (1-phenyl ethanol or 1-phenyl propanol), primary alcohol (benzyl alcohol) and benzamidine. Starting point for substrate ratio: amidine (1 eq.): alcohols (2 eq.). The glass tube was connected to a pressure equalizer (bubble counter). The mixture was heated to a gentle reflux for 20 h using a pre-heated oil bath (125 °C). After cooling and addition of water (1 mL) and dodecane (GC-standard) the mixture was extracted with ethyl acetate (25 mL) and a small amount of the organic phase was analyzed by GC.

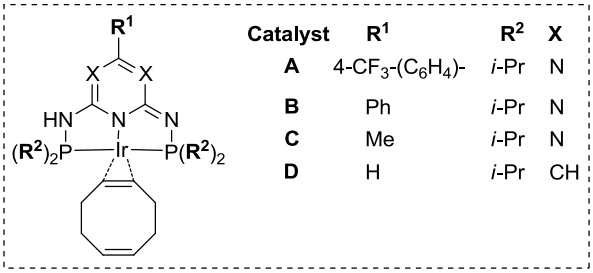
**4-Component-reaction.** In a nitrogen-filled glove box a pressure tube (Ace pressure tube, 38 mL) was charged with a magnetic stirring bar, base, solvent, catalyst (1 mol%, 1 mL from a 0.01 M stock solution in the appropriate solvent), 1-phenyl ethanol (2.0 mmol), 1-propanol (2.2 mmol) and tightly sealed with a Teflon® cap. The tube was immersed into a pre-heated oil bath (125 °C) for 4 h and then cooled to RT. Benzyl alcohol, benzamidine and additional solvent were added inside a glove-box and a pressure equalizer (bubble counter) was attached. The reaction mixture was heated to reflux for 20 h. Work-up as described above.

**Table S 1.** Solvent screening.

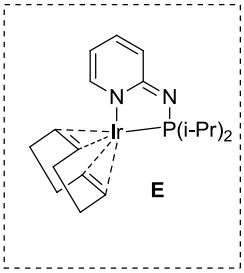
| Entry | Solvent | R(of 2° alc.) | Yield [%] |
|---|---|---|---|
| **1** | ***tert*-amyl alcohol** | **H** | **73** |
| 2 | toluene | H | 58 |
| 3 | 1,4-dioxane | H | 65 |
| 4 | diglyme | H | 72 |
| **5** | ***tert*-amyl alcohol** | ***n*-Pr** | **56** |
| 6 | toluene | *n*-Pr | 45 |
| 7 | 1,4-dioxane | *n*-Pr | 53 |
| 8 | diglyme | *n*-Pr | 44 |

*Reaction conditions*: *t*-BuOK (1.1 eq.), 0.5 mol% catalyst **A**, 3 mL solvent/mmol amidine.

**Table S 2.** Catalyst screening.




| Catalyst | $R^1$ | $R^2$ | X |
|---|---|---|---|
| **A** | 4-$CF_3$-($C_6H_4$)- | *i*-Pr | N |
| **B** | Ph | *i*-Pr | N |
| **C** | Me | *i*-Pr | N |
| **D** | H | *i*-Pr | CH |




**F:** 0.5 [Ir(OMe)(COD)]$_2$ **G:** 0.5 [Ir(Cl)(COD)]$_2$

| Entry | Catalyst | R (of 2° alc.) | Yield [%] |
|---|---|---|---|
| **1** | **A** | H | **83** |
| 2 | **B** | H | 79 |
| 4 | **C** | H | 75 |
| 5 | **D** | H | 64 |
| 6 | **E** | H | 45 |
| 7 | **F** | H | 37 |
| 8 | **G** | H | 43 |
| **9** | **A** | *n*-Pr | **64** |
| 10 | **B** | *n*-Pr | 63 |
| 12 | **C** | *n*-Pr | 44 |
| 13 | **D** | *n*-Pr | 6 |

*Reaction conditions*: 0.5 mol% catalyst, 3 mL *t*-AmOH/mmol amidine; R = H: *t*-BuOK (1.1 eq.), R = *n*-Pr: *t*-BuOK (1.5 eq.).

**Table S 3.** Base screening

| Entry | Base (1.1 eq.) | R (of 2° alc.) | Yield [%] |
|---|---|---|---|
| 1 | *t*-BuOLi | H | 20 |
| 2 | *t*-BuONa | H | 58 |
| 3 | *t*-BuOK | H | 86 |
| **4** | **KOH** | **H** | **93** |
| 5 | $Cs_2CO_3$ | H | 22 |
| 6 | KHMDS | H | 70 |

*Reaction conditions*: 0.5 mol% catalyst **A**, 3 mL *t*-AmOH/mmol amidine.

**Table S 4.** Base amount screening

| Entry | Base amount (eq. KOH) | R(of 2° alc.) | Yield [%] |
|---|---|---|---|
| 1 | *None* | H | 0 |
| 2 | 0.10 | H | 37 |
| 3 | 0.20 | H | 36 |
| **4** | **0.50** | **H** | **93** |
| 5 | 1.1 | H | 100 |
| 6 | 1.5 | H | 94 |
| 7 | 2.0 | H | 93 |
| 8 | 0.75 | n-Pr | 18 |
| 9 | 1.1 | *n*-Pr | 69 |
| 10 | 1.5 | *n*-Pr | 68 |
| 11 | 1.7 | *n*-Pr | 73 |
| 12 | 2.0 | *n*-Pr | 75 |

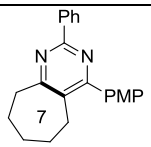
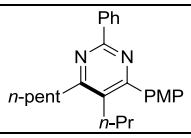
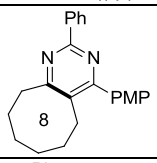
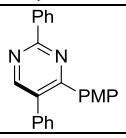
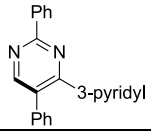
*Reaction conditions*: 0.5 mol% catalyst **A**, 3 mL *t*-AmOH/mmol amidine.

**Table S 5.** Screening of substrate-ratio for the 3-component-reaction with alkylation of a methyl group

| Entry | Amidine : 2° Alc : 1° Alc | R(of 2° alc.) | Yield [%] |
|---|---|---|---|
| 1 | 1.0 : 2.0 : 1.1 | H | 74 |
| 2 | 1.0 : 1.5 : 1.1 | H | 72 |
| 3 | 1.0 : 1.1 : 1.5 | H | 89 |
| 4 | 1.0 : 1.1 : 2.0 | H | 96 |
| **5** | **1.0 : 2.0 : 2.0** | **H** | **99** |
| 6 | 1.0 : 1.1 : 1.1 | H | 72 |
| 7 | 1.0 : 2.0 : 1.5 | H | 90 |

*Reaction conditions*: 0.5 mol% catalyst **A**, 3 mL *t*-AmOH/mmol amidine, KOH (1.1 eq.).

**Table S 6.** Comparison of bases and base amounts of selected products where alkylation of a secondary alcohol was involved.

| Entry | Product | Conditions | Isolated yield [%] |
|---|---|---|---|
| 1 |  | **1.5 eq. *t*-BuOK** | **78** |
| 2 | | 1.5 eq. KOH | 70 |
| 3 | | 1.1 eq. KOH | 55 |
| 4 |  | 1.5 eq. *t*-BuOK | 71 |
| 5 | | 1.1 eq. KOH | 56 |
| 6 |  | **1.5 eq. *t*-BuOK** | **88** |
| 7 | | 1.5 eq. KOH | 79 |
| 8 |  | 1.5 eq. *t*-BuOK | 75 |
| 9 | | **1.5 eq. KOH** | **80** |
| 10 |  | 1.5 eq. t-BuOK | 70 |
| 11 | | **1.5 eq. KOH** | **83** |

*Reaction conditions:* Sec. alcohol (2.0 mmol), prim. alcohol (1.1 mmol), benzamidine (1.0 mmol), catalyst **A** (0.7-1 mol%), base, *t*-AmOH (3 mL), 24 h reflux under inert atmosphere, open system.

## Screenings concerning the 4-component reaction

**Table S 7.** Screening of catalyst loading for the β-alkylation reaction for quantitative conversion within 4 hours.

| Catalyst amount [mol %] | Conversion of 1-phenylethanol |
|---|---|
| 0.4 | 89 % |
| **0.6** | **quantitative** |
| 0.8 | quantitative |
| 1.0 | quantitative |

Reaction conditions: 1-Phenylethanol (2 mmol), 1-propanol (2.2 mmol), *t*-BuOK (0.55 mmol), catalyst **A** in *t*-AmOH (3 mL) were heated for 4 h at 130 °C oil bath temperature (sealed tube).

**Table S 8.** Solvent/base screening for the β-alkylation reaction.

| Entry | Solvent | Base | Conversion of 1-phenylethanol |
|---|---|---|---|
| 1 | *t*-AmOH | KOH | 91 % |
| 2 | *t*-AmOH | *t*-BuOK | 94 % |
| 3 | 1,4-dioxane | KOH | 87 % |
| 4 | 1,4-dioxane | *t*-BuOK | **quantitative** |

Reaction conditions: 1-Phenylethanol (1 mmol), 1-propanol (1.1 mmol), base (1.1 mmol), catalyst **A** (0.5 mol%) in solvent (1 mL) were heated for 4 h at 125 °C oil bath temperature.

**Table S 9.** Screening of solvent in which remaining starting material is added (4-component-reaction)

| Entry | Solvent | Yield |
|---|---|---|
| **1** | ***tert*-amyl alcohol** | **55 %** |
| 2 | 1,4-dioxane | 46 % |

*Reaction conditions*: 1-Phenyl ethanol (2.0 mmol), 1-propanol (2.2 mmol), *t*-BuOK (2.0 mmol), and catalyst **A** (1 mol%) in 1,4-dioxane (1 mL) were heated in a pressure tube for 3 h. After cooling, benzyl alcohol (1.1 mmol) and benzamidine (1.0 mmol) were added as a solution in the mentioned solvent (2 mL). 20 h reflux under inert atmosphere in an open system.

**Table S 10.** Screening of the base amount for the 4-component reaction.

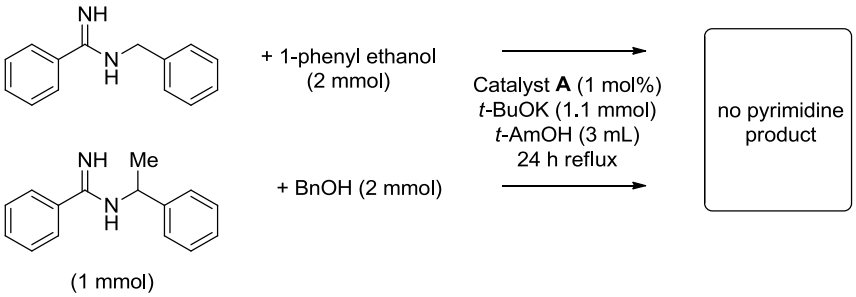
| Entry | Base amount (*t*-BuOK) w/r to amidine | Yield |
|---|---|---|
| 1 | 1.3 | 56 % |
| 2 | 1.5 | 77 % |
| 3 | 1.7 | 74 % |
| **4** | **2.0** | **89 %** |
| 5 | 2.2 | 77 % |

Reaction conditions: 2 mmol 1-phenylethanol, 2.2 mmol 1-propanol, *t*-BuOK in *t*-AmOH (2 mL) were heated in a sealed tube for 4 h at 130 °C oil bath temperature. Then addition of 1.0 mmol benzamidine and 2.0 mmol benzyl alcohol, 20 h reflux under inert atmosphere in an open system.

**Table S 11.** Screening of primary alcohol amount for the 4-component-reaction

| Entry | Equivalents 1° Alcohol | Yield |
|---|---|---|
| **1** | **1.1** | **89 %** |
| 2 | 1.3 | 73 % |
| 3 | 1.5 | 76 % |
| 4 | 1.7 | 71 % |
| 5 | 2.0 | 68 % |

*Reaction conditions*: 1-Phenyl ethanol (2.0 mmol), 1-propanol (2.2 mmol), *t*-BuOK (2.0 mmol), and catalyst **A** (1 mol%) in 1,4-dioxane (1 mL) were heated in a pressure tube for 2 h. After cooling, benzamidine (1.0 mmol), benzyl alcohol (1.1-2.0 mmol) and *t*-AmOH (2 mL) were added. 20 h reflux under inert atmosphere in an open system.




**Scheme S 1.** Control experiment to rule out a mechanism which involves sequential N-alkylation followed by C-C/C-N bond formation

# 4 Reaction details

**Reaction without glove-box technique and precautions with reagents (preparation of *6i*):**

This reaction was run with chemicals (base and alcohols) which have been stored under air in the laboratory. Benzamidine was extracted from the hydrochloride hydrate ($CH_2Cl_2$ vs. 1M NaOH) and dried under vacuum. Catalyst A was weighed under air. Dry solvents were used, however (*t*-AmOH (99%) has been stored over molecular sieve and dry 1,4-dioxane from Acros was used).

An oven-dried 25 mL Schlenk tube was cooled under a low stream of argon and charged with a magnetic stirring bar. The solid materials were transferred with argon stream turned off [t-BuOK (224 mg, 2 mmol) and catalyst **A** (8 mg, 0.01 mmol)]. Afterwards, the tube was purged with argon and the liquid materials were added under low argon stream [1-phenyl ethanol (242 µL, 2.0 mmol), 1-propanol (165 µL, 2.2 mmol) and 1,4-dioxane (1 mL)]. A reflux condenser was attached under argon stream and the top of the condenser was connected to a pressure equalizer (bubble counter). The reaction mixture was heated to a gentle reflux for 3 h 45 min. Afterwards, the reaction was cooled (low argon stream), the reflux condenser was removed to inject a solution of benzamidine (120 mg, 1 mmol), 4-methoxybenzyl alcohol (136 µL) in *tert*-Amyl alcohol (2 mL). The reflux condenser was re-attached and the reaction mixture was heated to reflux for further 24 h. Work-up was conducted as mentioned in the general procedure. Column chromatography (pentane/diethyl ether 20:1 → 30:1) yielded the title compound ***6i*** (208 mg, 0.547 mmol, 55 %) as a white solid.

**3-component-reaction (10 mmol scale, preparation of *5a*):**

Under dry $N_2$ atmosphere (glove box) an oven-dried 50 mL Schlenk tube was charged with a magnetic stirring bar, cycloheptanol (20 mmol, 2.40 mL), 4-methoxybenzyl alcohol (11 mmol 1.36 mL), benzamidine (10 mmol, 1.20 g), catalyst **A** (55 mg, 0.7 mmol, 0.7 mol%) and *tert*-amyl alcohol (20 mL). The tube was sealed, taken out of the glove box and a reflux condenser was attached under argon stream. A pressure equalizer (bubble counter) was connected to the top outlet of the condenser and the reaction mixture was heated to reflux for 24 h. Within few minutes of heating the color of the reaction mixture turned from red to yellow. After cooling, the reaction was quenched with water (20 mL) and extracted with ethyl acetate (3x 100 mL). The combined organic phase was dried over $Na_2SO_4$, concentrated by rotary evaporation and subjected to column chromatography (column dimensions: height 23 cm, diameter 4 cm, packed with pentane). Gradient elution (pentane/diethyl ether, 25:1 → 20:1) gave the title compound ***5a*** (2.55 g, 7.72 mmol, 77%) as a white solid. (1 mmol scale: 78 %)

**Consecutive 4-component-reaction (10 mmol scale, preparation of *6i*):**

Under dry $N_2$ atmosphere (glove box) an oven-dried 100 mL two-necked round-bottom flask with gas inlet was charged with a magnetic stir bar, 1-phenyl ethanol (20 mmol, 2.42 mL), 1-propanol (22 mmol, 1.65 mL), *t*-BuOK (20 mmol, 2.24 g), catalyst **A** (0.1 mmol, 79 mg) and 1,4-dioxane (10 mL). One neck of the flask was sealed with a rubber septum and the other was sealed with a glass stopper. After the flask was removed from the glove box, a reflux condenser was attached under a stream of argon. After 3.5 h a small amount of the reaction mixture was analyzed by GC analysis which showed complete consumption of 1-phenyl ethanol. After cooling (low argon stream), a mixture of benzamidine (10 mmol, 1.20 g) and 4-methoxybenzyl alcohol (11 mmol, 1.36 mL) in *tert*-amyl alcohol (20 mL) was added by syringe through the rubber septum leading to a dark reaction mixture. The reaction was heated to reflux for further 24 h. After cooling, the reaction was quenched with water (20 mL) and extracted with ethyl acetate (3x 100 mL). The combined organic phase was dried over $Na_2SO_4$, concentrated by rotary evaporation and subjected to column chromatography (column dimensions: diameter 4 cm, height 23 cm, packed with pentane). Gradient elution (pentane/diethyl ether, 40:1 to remove excess β-alkylation product, then pentane/diethyl ether 30:1) gave the title compound ***6i*** (2.35 g, 6.18 mmol, 62 %) as a white solid. (1 mmol scale: 72 %)

**Comments on substrate scope:**

1) For the consecutive 4-component reaction, the isolation via column chromatography can be difficult if the polarity of the β-alkylation product (1st step) is similar to that of the final product. Here, recrystallization is an alternative as shown for **6f**.

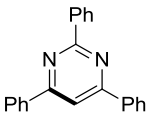
2) The order in which the substituents are introduced can result in higher polarity differences. For example, compound **6i** can prepared from 1-phenyl ethanol, 1-propanol and *para*-methoxybenzyl alcohol or from 1-(*para*-methoxyphenyl)-ethanol, 1-propanol and benzyl alcohol. In the latter case, the β-alkylation product had a similar polarity as the pyrimidine product and was difficult to separate.

3) It is more efficient for this reaction if sensitive functional groups are introduced in the last step and not via β-alkylation.

# 5 Characterization data of pyrimidine derivatives

**3-Component-Reaction (all substrates were prepared according to GP-1 unless noted otherwise)**

*2,4,6-triphenylpyrimidine (**4a**)*

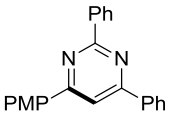



1 mmol scale. Purification by column chromatography (pentane/diethyl ether, 60:1). Yield 271 mg (0.880 mmol, 88 %) white solid.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.67 - 8.82 (m, 2 H), 8.21 - 8.38 (m, 4 H), 8.03 (s, 1 H), 7.45 - 7.66 (m, 9 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 164.9, 164.6, 138.3, 137.7, 130.9, 130.8, 129.1, 128.61, 128.58, 127.5, 110.4 ppm.

*4-(4-methoxyphenyl)-2,6-diphenylpyrimidine (**4b**)*



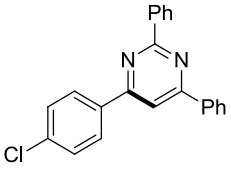

1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 20:1). Yield: 289 mg (0.855 mmol, 86 %) white solid.

Yield with *t*-BuOK (1.1 eq.): 84%
$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.68 - 8.78 (m, 2 H), 8.23 - 8.35 (m, 4 H), 7.96 (s, 1 H), 7.48 - 7.61 (m, 6 H), 7.03 - 7.11 (m, 2 H), 3.91 (s, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 164.6, 164.3, 162.0, 138.4, 137.8, 130.8, 130.7, 130.1, 129.0, 128.9, 128.6, 128.5, 127.4, 114.4, 109.5, 55.5 ppm.

Elemental analysis (%) for $C_{23}H_{24}N_2O$ calcd: C 80.20, H 7.02, N 8.13; found: C 80.22, H 7.05, N 7.91

*4-(4-chlorophenyl)-2,6-diphenylpyrimidine (**4c**)*



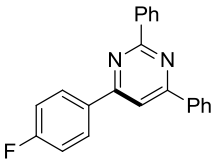

1 mmol scale. Purification by column chromatography (pentane/diethyl ether, 50:1). Yield: 282 mg (0.825 mmol, 83 %) white solid.

Yield with *t*-BuOK (1.1 eq.): 72 %
$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.65 - 8.75 (m, 2 H), 8.27 - 8.32 (m, 2 H), 8.22 - 8.27 (m, 2 H), 7.98 (s, 1 H), 7.47 - 7.62 (m, 8 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 165.1, 164.7, 163.6, 138.1, 137.5, 137.1, 136.1, 131.0 130.9, 129.3, 129.1, 128.7, 128.61, 128.60, 127.4, 110.1 ppm.

Elemental analysis (%) for $C_{22}H_{15}ClN_2$ calcd: C 77.08, H 4.41, N 8.17; found: C 77.16, H 4.48, N 8.04

*4-(4-fluorophenyl)-6-(4-methoxyphenyl)-2-phenylpyrimidine (**4d**)*

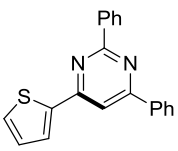



1 mmol scale. Purification by column chromatography (pentane/diethyl ether, 60:1). Yield: 201 mg (0.617 mmol, 62 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.68 - 8.76 (m, 2 H), 8.22 - 8.34 (m, 4 H), 7.95 (s, 1 H), 7.49 - 7.63 (m, 6 H), 7.18 - 7.30 (m, 2 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 165.7, 165.0, 164.6, 163.7, 138.2, 137.6, 133.79, 133.77, 131.0, 130.9, 129.5, 129.4, 129.1, 128.60, 128.59, 127.4, 116.2, 116.0, 110.0 ppm.

*2,4-diphenyl-6-(thiophen-2-yl)pyrimidine (**4e**)*



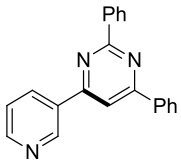

Purification by column chromatography (pentane/diethyl ether, 50:1). Yield: 221 mg (0.704 mmol, 70 %) off-white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.63 - 8.73 (m, 2 H), 8.23 - 8.32 (m, 2 H), 7.93 (dd, *J*=3.81, 1.07 Hz, 1 H), 7.86 (s, 1 H), 7.48 - 7.61 (m, 7 H), 7.21 (dd, *J*=5.04, 3.81 Hz, 1 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 164.7, 164.6, 159.8, 143.5, 137.9, 137.5, 131.0, 130.9, 129.9, 129.1, 128.6, 128.5, 127.4, 127.2, 108.6 ppm.

Elemental analysis (%) for $C_{20}H_{14}N_2S$ calcd: C 76.40, H 4.49, N 8.91; found: C 76.28, H 4.58, N 8.93

*2,4-diphenyl-6-(pyridin-3-yl)pyrimidine (**4f**)*



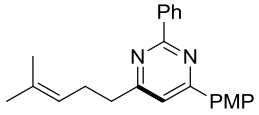

1 mmol scale. Purification by column chromatography (pentane/ethyl acetate, 7:3). Yield: 260 mg (0.841 mmol, 84 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 9.47 (s, 1 H), 8.79 (d, *J*=3.66 Hz, 1 H), 8.68 - 8.75 (m, 2 H), 8.61 (dt, *J*=7.93, 1.98 Hz, 1 H), 8.26 - 8.34 (m, 2 H), 8.04 (s, 1 H), 7.53 - 7.61 (m, 6 H), 7.51 (dd, *J*=7.78, 4.73 Hz, 1 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 165.2, 164.8, 162.5, 151.6, 148.7, 137.8, 137.2, 134.8, 133.2, 131.1, 130.9, 129.0, 128.6, 128.5, 127.3, 123.8, 110.3 ppm.

Elemental analysis (%) for $C_{21}H_{15}N_3$ calcd: C 81.53, H 4.89, N 13.58; found: C 81.48, H 5.11, N 13.54

*4-(4-methoxyphenyl)-6-(4-methylpent-3-en-1-yl)-2-phenylpyrimidine (**4g**)*




1 mmol scale, purification by column chromatography (pentane/diethyl ether, 30:1). Yield: 182 mg (0.529 mmol, 53 %) white solid.

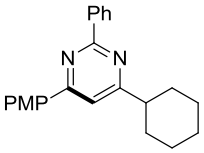
Yield with *t*-BuOK (1.1 eq.): 49 %

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.60 - 8.67 (m, 2 H), 8.20 - 8.26 (m, 2 H), 7.48 - 7.58 (m, 3 H), 7.40 (s, 1 H), 7.03 - 7.09 (m, 2 H), 5.23 - 5.31 (m, 1 H), 3.92 (s, 3 H), 2.91 (t, *J*=7.63 Hz, 2 H), 2.59 (q, *J*=7.32 Hz, 2 H), 1.73 (s, 3 H), 1.65 (s, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 170.8, 164.2, 163.2, 161.9, 138.6, 132.9, 130.4, 130.0, 128.8, 128.5, 123.3, 114.3, 112.8, 55.5, 38.4, 27.4, 25.8, 17.9 ppm.

Elemental analysis (%) for $C_{23}H_{24}N_2O$ calcd: C 80.20, H 7.02 N 8.13; found: C 80.21, H 7.09, N 7.80

*4-cyclohexyl-6-(4-methoxyphenyl)-2-phenylpyrimidine (**4h**)*




1 mmol scale. Purification by column chromatography (pentane/diethyl ether, 25:1). Yield: 321 mg (0.932 mmol, 93 %) white solid.

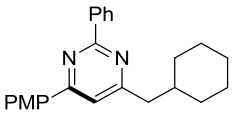
Yield with *t*-BuOK (1.1 eq.): 84 %

$^1$H NMR (300 MHz, $CDCl_3$) δ = 8.58 - 8.69 (m, 2 H), 8.16 - 8.26 (m, 2 H), 7.45 - 7.57 (m, 3 H), 7.39 (s, 1 H), 7.00 - 7.08 (m, 2 H), 3.89 (s, 3 H), 2.78 (tt, *J*=11.79, 3.47 Hz, 1 H), 2.04 - 2.11 (m, 2 H), 1.93 (dt, *J*=13.12, 3.20 Hz, 2 H), 1.78 - 1.85 (m, 1 H), 1.69 (qd, *J*=12.51, 3.05 Hz, 2 H), 1.48 (qt, *J*=12.82, 3.36 Hz, 2 H), 1.37 (tt, *J*=12.66, 3.51 Hz, 1 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 175.2, 164.0, 163.4, 161.8, 138.7, 130.3, 130.2, 128.8, 128.5, 114.2, 111.0, 55.5, 46.4, 32.3, 26.5, 26.2 ppm.

Elemental analysis (%) for $C_{23}H_{24}N_2O$ calcd: C 80.20, H 7.02, N 8.13; found: C 80.22, H 7.05, N 7.91

*4-(cyclohexylmethyl)-6-(4-methoxyphenyl)-2-phenylpyrimidine (**4i**)*




1 mmol scale. Purification by column chromatography (pentane/diethyl ether, 25:1). Yield: 308 mg (0.860 mmol, 86 %) white solid.

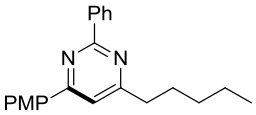
Yield with *t*-BuOK (1.1 eq.): 79 %

$^1$H NMR (500 MHz, $CDCl_3$) δ = 8.52 - 8.66 (m, 2 H), 8.15 - 8.25 (m, 2 H), 7.43 - 7.57 (m, 3 H), 7.34 (s, 1 H), 6.99 - 7.09 (m, 2 H), 3.90 (s, 3 H), 2.73 (d, *J*=7.17 Hz, 2 H), 1.86 - 2.02 (m, 1 H), 1.60 - 1.83 (m, 5 H), 1.14 - 1.36 (m, 3 H), 0.98 - 1.14 (m, 2 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 170.4, 164.3, 163.1, 161.9, 138.7, 130.4, 128.8, 128.53, 128.49, 114.3, 113.5, 55.6, 46.3, 38.1, 33.4, 26.6, 26.4 ppm.

Elemental analysis (%) for $C_{24}H_{26}N_2O$ calcd: C 80.41, H 7.31, N 7.81; found: C 80.47, H 7.32, N 7.71

*4-(4-methoxyphenyl)-6-pentyl-2-phenylpyrimidine (**4j**)*




1 mmol scale. Purification by column chromatography (pentane/diethyl ether, 25:1). Yield: 288 mg (0.867 mmol, 87 %) white solid.

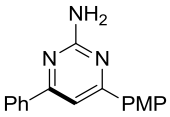
Yield with *t*-BuOK (1.1 eq.): 80 %

$^1$H NMR (500 MHz, $CDCl_3$) δ = 8.54 - 8.66 (m, 2 H), 8.17 - 8.26 (m, 2 H), 7.44 - 7.57 (m, 3 H), 7.39 (s, 1 H), 6.98 - 7.09 (m, 2 H), 3.89 (s, 3 H), 2.79 - 2.91 (m, 2 H), 1.82 - 1.91 (m, 2 H), 1.36 - 1.48 (m, 4 H), 0.89 - 0.98 (m, 3 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 171.5, 164.2, 163.3, 161.9, 138.6, 130.4, 128.8, 128.5, 128.4, 114.3, 112.6, 55.5, 38.4, 31.7, 28.7, 22.7, 14.2 ppm.

Elemental analysis (%) for $C_{22}H_{24}N_2O$ calcd: C 79.48, H 7.28, N 8.43; found: C 79.27, H 7.35, N 8.11

*4-(4-methoxyphenyl)-6-phenylpyrimidin-2-amine (**4k**)*

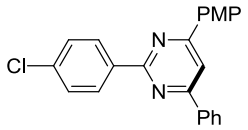



Purification by column chromatography (pentane/MTBE, 2:1 → 1.5:1). Yield: 197 mg (0.730 mmol, 73 %) white solid.

$^1$H NMR (500 MHz, $CDCl_3$) δ = 8.01 - 8.08 (m, 4 H), 7.45 - 7.54 (m, 3 H), 7.42 (s, 1 H), 6.98 - 7.04 (m, 2 H), 5.18 (br. s., 2 H), 3.88 (s, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 166.1, 165.8, 163.7, 161.8, 138.1, 130.5, 130.3, 128.9, 128.8, 127.2, 114.2, 103.7, 55.6 ppm.

*2-(4-chlorophenyl)-4-(4-methoxyphenyl)-6-phenylpyrimidine (**4l**)*

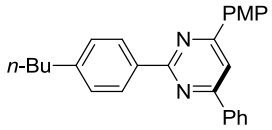



1 mmol scale. Purification by column chromatography (pentane/diethyl ether, 40:1). Yield: 253 mg (0.680 mmol, 68 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.57 - 8.72 (m, 2 H), 8.16 - 8.31 (m, 4 H), 7.89 - 7.93 (m, 1 H), 7.51 - 7.59 (m, 3 H), 7.46 - 7.51 (m, 2 H), 7.01 - 7.09 (m, 2 H), 3.90 (s, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 164.6, 164.3, 163.5, 162.1, 137.6, 136.9, 136.8, 130.9, 129.9, 129.8, 129.0, 128.9, 128.7, 127.3, 114.4, 109.6, 55.6 ppm.

*2-(4-butylphenyl)-4-(4-methoxyphenyl)-6-phenylpyrimidine (**4m**)*



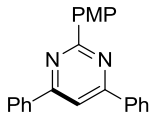

1 mmol scale. Purification by column chromatography (pentane/diethyl ether, 40:1). Yield: 324 mg (0.822 mmol, 82 %) highly viscous colorless oil.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.57 - 8.71 (m, 2 H), 8.20 - 8.36 (m, 4 H), 7.93 (s, 1 H), 7.48 - 7.63 (m, 3 H), 7.35 (d, *J*=8.54 Hz, 2 H), 6.98 - 7.12 (m, 2 H), 3.91 (s, 3 H), 2.67 - 2.78 (m, 2 H), 1.63 - 1.72 (m, 2 H), 1.41 (dq, *J*=15.03, 7.40 Hz, 2 H), 0.96 (t, *J*=7.32 Hz, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 164.6, 164.5, 164.2, 162.0, 145.8, 138.0, 136.0, 130.7, 130.2, 129.0, 128.9, 128.7, 128.5, 127.4, 114.3, 109.2, 55.5, 35.8, 33.7, 22.5, 14.1 ppm.

Elemental analysis (%) for $C_{27}H_{26}N_2O$ calcd: C 82.20, H 6.64, N, 7.10; found: C 82.43, H 6.72, N 6.98

*2-(4-methoxyphenyl)-4,6-diphenylpyrimidine (**4n**)*



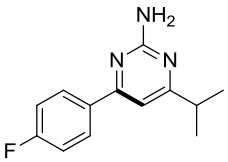

1 mmol scale. Purification by column chromatography (pentane/diethyl ether, 40:1). Yield: 259 mg (0.766 mmol, 77 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.64 - 8.75 (m, 2 H), 8.23 - 8.35 (m, 4 H), 7.96 (s, 1 H), 7.48 - 7.62 (m, 6 H), 7.00 - 7.11 (m, 2 H), 3.91 (s, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 164.8, 164.4, 162.0, 137.8, 131.1, 130.8, 130.3, 129.0, 127.4, 113.9, 109.8, 55.5 ppm.

Elemental analysis (%) for $C_{23}H_{18}N_2O$ calcd: C 81.63, H 5.36, N 8.28; found: C 81.54, H 5.46, N 8.18

*4-(4-fluorophenyl)-6-isopropylpyrimidin-2-amine (**4o**)*

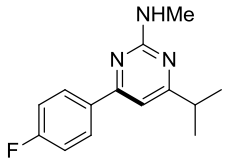



For this reaction 2.1 mmol KOH were used (1.1 eq + 1.0 eq. to trap HCl from guanidine hydrochloride). 1 mmol scale, purification by column chromatography (pentane/diethyl ether, 6/4). Yield: 146 mg (0.632 mmol, 63 %) white solid.
$^1$H NMR (500 MHz, $CDCl_3$) δ = 7.93 - 8.02 (m, 2 H), 7.08 - 7.17 (m, 2 H), 6.87 (s, 1 H), 5.23 (br. s., 2 H), 2.86 (spt, *J*=6.90 Hz, 1 H), 1.29 (d, *J*=6.90 Hz, 6 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 117.9, 165.3, 164.6, 163.4, 134.09, 134.06, 129.2, 115.9, 115.7, 104.4, 36.3, 21.87, 21.86 ppm.

*Alternative procedure*: 1-(4-fluorophenyl)-ethanol (**1.10 mmol**), isobutanol (2.00 mmol), guanidine hydrochloride (1.00 mmol), KOH (1.70 mmol), catalyst **A** (0.01 mmol), *tert*-amyl alcohol (3 mL) were heated to reflux for 24 h under inert atmosphere in an open system. GC-FID analysis showed the same response factor for the product relative to an internal standard.

*4-(4-fluorophenyl)-6-isopropyl-N-methylpyrimidin-2-amine (**4p**)*




This compound was prepared with a different substrate ratio from methyl guanidine hydrochloride (1 mmol), 1-(4-fluorophenyl)ethanol (**1.1 mmol**), isobutanol (2.0 mmol), KOH (1.7 mmol), catalyst **A** (0.01 mmol) in *tert*-amyl alcohol (3 mL) under reflux for 24 h. Purification by column chromatography (pentane/diethyl ether, 9:1). Yield: 140 mg (0.571 mmol, 57 %) white solid.

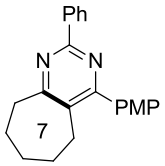
Synthesis according to GP-1 with 2.1 eq. KOH (to trap HCl from the hydrochloride) gave the title compound in 55 % isolated yield.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.98 - 8.10 (m, 2 H), 7.07 - 7.19 (m, 2 H), 6.81 (s, 1 H), 5.20 (d, *J*=4.69 Hz, 1 H), 3.06 (d, *J*=5.27 Hz, 3 H), 2.85 (spt, *J*=7.0 Hz, 1 H), 1.29 (d, *J*=7.0 Hz, 6 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 177.4, 165.9, 163.8, 163.4, 162.6, 134.4, 129.1, 129.0, 115.8, 115.5, 103.0, 36.3, 28.5, 21.9 ppm.

**3-Component-Reaction (alkylation of methylene groups)**

*4-(4-methoxyphenyl)-2-phenyl-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyrimidine (**5a**)*



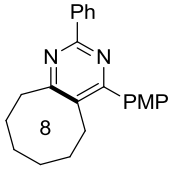

Synthesis according to GP-2. 1 mmol scale, 0.7 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 30:1 → 20:1). Yield: 257 mg (0.779 mmol, 78 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.49 (dd, *J*=7.78, 1.68 Hz, 2 H), 7.50 - 7.64 (m, 2 H), 7.35 - 7.52 (m, 3 H), 6.93 - 7.10 (m, 2 H), 3.88 (s, 3 H), 3.08 - 3.23 (m, 2 H), 2.83 - 3.00 (m, 2 H), 1.89 - 2.01 (m, 2 H), 1.78 - 1.89 (m, 2 H), 1.65 - 1.78 (m, 2 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 172.8, 164.0, 161.1, 160.3, 138.3, 131.8, 130.9, 130.3, 130.1, 128.5, 128.2, 113.8, 55.5, 39.5, 32.4, 29.3, 27.9, 26.3 ppm.

Elemental analysis (%) for $C_{22}H_{22}N_2O$ calcd: C 79.97, H 6.71, N 8.48; found: C 79.77, H 6.75, N 8.30

*4-(4-methoxyphenyl)-2-phenyl-5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidine (**5b**)*



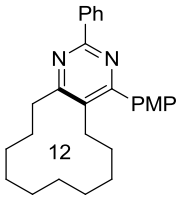

Synthesis according to GP-2. 1 mmol scale, 0.7 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 20:1). Yield: 302 mg (0.878 mmol, 88 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.49 (dd, *J*=7.78, 1.68 Hz, 7 H), 7.49 - 7.63 (m, 2 H), 7.38 - 7.49 (m, 3 H), 6.95 - 7.05 (m, 2 H), 3.88 (s, 3 H), 2.98 - 3.11 (m, 2 H), 2.82 - 2.94 (m, 2 H), 1.93 (quin, *J*=6.03 Hz, 5 H), 1.58 - 1.71 (m, 2 H), 1.39 - 1.56 (m, 4 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 170.8, 165.2, 161.6, 160.1, 138.4, 132.2, 130.4, 130.0, 128.7, 128.5, 128.2, 113.7, 55.5, 35.1, 31.5, 30.5, 26.7, 26.4, 26.0 ppm.

Elemental analysis (%) for $C_{23}H_{24}N_2O$ calcd: C 80.20, H 7.02; N 8.13; found: C 80.22, H 6.92, N 8.15

*4-(4-methoxyphenyl)-2-phenyl-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[d]pyrimidine (**5c**)*



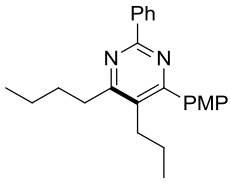

Synthesis according to GP-2. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 25:1 → 20:1). Yield: 292 mg (0.730 mmol, 73 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.43 - 8.55 (m, 2 H), 7.50 - 7.57 (m, 2 H), 7.40 - 7.48 (m, 3 H), 6.97 - 7.04 (m, 2 H), 3.88 (s, 3 H), 2.92 (t, *J*=7.71 Hz, 2 H), 2.82 (t, *J*=7.70 Hz, 2 H), 2.00 - 2.13 (m, 2 H), 1.36 - 1.60 (m, 12 H), 1.29 (q, *J*=1.00 Hz, 2 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 170.1, 166.2, 161.0, 160.0, 138.4, 132.7, 130.1, 130.0, 129.0, 128.4, 128.2, 113.8, 55.5, 32.3, 28.2, 27.8, 27.0, 26.9, 26.1, 25.91, 25.88, 23.30, 23.28 ppm.

Elemental analysis (%) for $C_{27}H_{32}N_2O$ calcd: C 80.96, H 8.05, N 6.99; found: C 80.63, H 8.15, N 6.49

*4-butyl-6-(4-methoxyphenyl)-2-phenyl-5-propylpyrimidine (**5d**)*



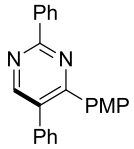

Synthesis according to GP-2. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 40:1 → 30:1). Yield: 254 mg (0.706 mmol, 71 %) colorless oil which solidified upon standing.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.38 - 8.59 (m, 2 H), 7.49 - 7.58 (m, 2 H), 7.40 - 7.49 (m, 3 H), 6.97 - 7.06 (m, 2 H), 3.89 (s, 3 H), 2.82 - 2.95 (m, 2 H), 2.63 - 2.75 (m, 2 H), 1.82 - 1.96 (m, 2 H), 1.41 - 1.60 (m, 4 H), 1.02 (t, *J*=7.32 Hz, 3 H), 0.89 (t, *J*=7.30 Hz, 3 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 169.8, 165.5, 161.0, 160.0, 138.4, 132.4, 130.3, 130.0, 128.4, 128.2, 113.7, 110.1, 55.5, 34.5, 31.1, 30.2, 24.0, 23.0, 14.4, 14.3 ppm.

Elemental analysis (%) for $C_{24}H_{28}N_2O$ calcd: C 79.96, H 7.83, N 7.77; found: C 79.98, H 7.94, N 7.56

*4-(4-methoxyphenyl)-2,5-diphenylpyrimidine (**5e**)*




Synthesis according to GP-2. KOH (1.5 eq.) was used as the base. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 20:1 → 10:1). Yield: 270 mg (0.799 mmol, 80 %) white solid.

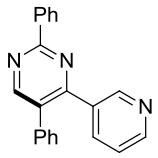
Yield with *t*-BuOK: 75 %

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.74 (s, 1 H), 8.54 - 8.62 (m, 2 H), 7.47 - 7.59 (m, 5 H), 7.33 - 7.42 (m, 3 H), 7.27 - 7.32 (m, 2 H), 6.79 - 6.86 (m, 2 H), 3.82 (s, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 163.2, 162.9, 160.8, 158.8, 137.8, 137.2, 131.8, 130.7, 130.4, 130.3, 129.4, 129.0, 128.7, 128.4, 128.0, 113.7, 55.4 ppm.

Elemental analysis (%) for $C_{23}H_{18}N_2O$ calcd: C 81.63; H 5.36; N 8.28; found: C 81.76, H 5.36, N 8.30

*2,5-diphenyl-4-(pyridin-3-yl)pyrimidine (**5f**)*




Synthesis according to GP-2. KOH (1.5 eq.) was used as the base. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 255 mg (0.825 mmol, 83 %) white solid.

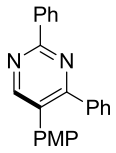
Yield with *t*-BuOK: 70 %

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.85 - 8.88 (m, 1 H), 8.83 (s, 1 H), 8.57 - 8.64 (m, 3 H), 7.88 (dt, *J*=7.93, 1.98 Hz, 1 H), 7.52 - 7.58 (m, 3 H), 7.38 - 7.44 (m, 3 H), 7.25 - 7.31 (m, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 163.7, 160.7, 159.1, 151.0, 150.3, 137.31, 137.29, 135.9, 133.8, 131.2, 131.1, 129.4, 129.2, 128.8, 128.5, 128.4, 123.0 ppm.

Elemental analysis (%) for $C_{21}H_{15}N_3$ calcd: C 81.53; H 4.89; N 13.58; found: C 81.23, H 4.93, N 13.36

*5-(4-methoxyphenyl)-2,4-diphenylpyrimidine (**5g**)*



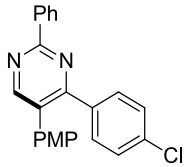

Synthesis according to GP-2. KOH (1.5 eq.) was used as the base. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 30:1 → 20:1). Yield: 271 mg (0.802 mmol, 80 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.78 (s, 1 H), 8.58 (m, 2 H), 7.59 (m, 2 H), 7.46 - 7.55 (m, 3 H), 7.29 - 7.41 (m, 3 H), 7.14 - 7.21 (m, 2 H), 6.85 - 6.92 (m, 2 H), 3.83 (s, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 163.3, 163.0, 159.6, 158.8, 138.2, 137.7, 130.7, 130.63, 130.58, 130.1, 129.4, 128.9, 128.7, 128.34, 128.25, 114.4, 55.4 ppm.

Elemental analysis (%) for $C_{23}H_{18}N_2O$ calcd: C 81.63, H 5.36, N 8.28; found: C 81.63, H 5.41, N 8.06

*4-(4-chlorophenyl)-5-(4-methoxyphenyl)-2-phenylpyrimidine (**5h**)*




Synthesis according to GP-2. KOH (1.5 eq.) was used as the base. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 20:1). Yield: 279 mg (0.750 mmol, 75 %) white solid.

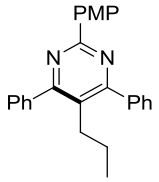
$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.74 - 8.80 (m, 1 H), 8.51 - 8.59 (m, 2 H), 7.47 - 7.56 (m, 5 H), 7.27 - 7.33 (m, 2 H), 7.13 - 7.20 (m, 2 H), 6.88 - 6.94 (m, 2 H), 3.84 (s, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 163.1, 162.1, 159.7, 158.9, 137.5, 136.7, 135.7, 131.4, 130.8, 130.6, 130.5, 128.7, 128.55, 128.48, 128.3, 114.6, 55.4 ppm.

Elemental analysis (%) for $C_{23}H_{17}ClN_2O$ calcd: C 74.09, H 4.60, N 7.51; found: C 73.89, H 4.81, N 7.27

## 4-Component-Reaction

*2-(4-methoxyphenyl)-4,6-diphenyl-5-propylpyrimidine (**6a**)*



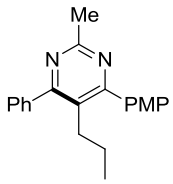

Synthesis according to GP-3. 1 mmol scale, 1.5 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 30:1). Yield: 249 mg (0.655 mg, 66 %) white solid.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.43 - 8.56 (m, 2 H), 7.60 - 7.68 (m, 4 H), 7.42 - 7.57 (m, 6 H), 6.91 - 7.00 (m, 2 H), 3.86 (s, 3 H), 2.72 - 2.83 (m, 2 H), 1.07 - 1.24 (m, 2 H), 0.56 (t, *J*=7.32 Hz, 3 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 167.3, 161.7, 161.1, 140.0, 130.7, 130.0, 128.9, 128.8, 128.4, 127.6, 113.8, 55.5, 30.4, 23.4, 14.1 ppm.

Elemental analysis (%) for $C_{26}H_{24}N_2O$ calcd: C 82.07, H 6.36, N 7.36; found: C 81.80, H 6.64, N 7.06

*4-(4-methoxyphenyl)-2-methyl-6-phenyl-5-propylpyrimidine (**6b**)*



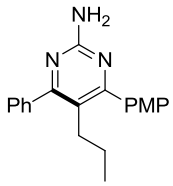

Synthesis according to GP-3. 1 mmol scale, 1.5 mol% catalyst **A**. Acetamidine hydrochloride along with 1 eq. *t*-BuOK was added in the last step. Purification by column chromatography (pentane/ethyl acetate, 4:1). Yield: 220 mg (0.691 mmol, 69 %) colorless viscous oil which solidified upon standing.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.34 - 7.56 (m, 7 H), 6.98 (d, *J*=8.79 Hz, 2 H), 3.82 (s, 3 H), 2.75 (s, 3 H), 2.68 (s, 2 H), 1.13 (sxt, *J*=7.50 Hz, 2 H), 0.54 (t, *J*=7.32 Hz, 3 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 167.2, 166.8, 164.4, 160.0, 139.5, 131.8, 129.9, 128.6, 128.4, 127.2, 113.8, 55.3, 30.1, 25.9, 23.1, 13.9 ppm.

Elemental analysis (%) for $C_{21}H_{22}N_2O$ calcd: C 79.21, H 6.96, N 8.80; found: C 78.80, H 6.87, N 8.62

*4-(4-methoxyphenyl)-6-phenyl-5-propylpyrimidin-2-amine (**6c**)*



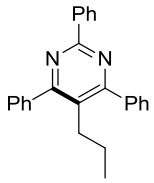

Synthesis according to GP-3. 1 mmol scale, 1 mol% catalyst **A**. Guanidine hydrochloride along with 1 eq. *t*-BuOK was added in the last step. Purification by column chromatography (pentane/ethyl acetate 1:1). Yield: 188 mg (0.589 mmol, 59 %) pale yellow solid.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.33 - 7.54 (m, 7 H), 6.92 - 7.02 (m, 2 H), 5.40 (s, 2 H), 3.85 (s, 3 H), 2.43 - 2.58 (m, 2 H), 1.08 (s, 2 H), 0.52 (t, *J*=7.32 Hz, 3 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 168.6, 168.3, 160.5, 160.0, 139.7, 132.12, 132.07, 129.7, 128.5, 128.4, 128.2, 120.5, 113.8, 55.4, 29.8, 23.7, 14.0 ppm.

Elemental analysis (%) for $C_{20}H_{21}N_3O$ calcd: C 75.21, H 6.63, N 13.16; found: C 74.98, H 6.77, N 12.76

*2,4,6-triphenyl-5-propylpyrimidine (**6d**)*



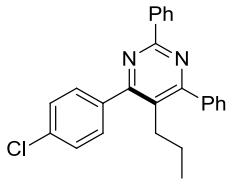

Synthesis according to GP-3. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/ diethyl ether, 50:1 → 40:1). Yield: 288 mg (0.822 mmol, 82 %) white solid.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.45 - 8.65 (m, 2 H), 7.59 - 7.75 (m, 4 H), 7.41 - 7.58 (m, 9 H), 2.70 - 2.89 (m, 2 H), 1.18 (dd, *J*=15.82, 7.61 Hz, 2 H), 0.58 (t, *J*=7.32 Hz, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 167.4, 161.3, 139.8, 138.0, 130.4, 128.93, 128.89, 128.5, 128.4, 30.5, 23.3, 14.0 ppm.

Elemental analysis (%) for $C_{25}H_{22}N_2$ calcd: C 85.68, H 6.33, N 7.99; found: C 85.64, H 6.60, N 7.92

*4-(4-chlorophenyl)-2,6-diphenyl-5-propylpyrimidine (**6e**)*

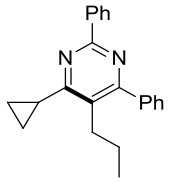



Synthesis according to GP-3. 1 mmol scale, 2 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 60:1). Yield: 210 mg (0.547 mmol, 55 %) white solid.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.43 - 8.65 (m, 2 H), 7.57 - 7.71 (m, 4 H), 7.40 - 7.57 (m, 8 H), 2.71 - 2.86 (m, 2 H), 1.12 - 1.23 (m, 2 H), 0.59 (t, *J*=7.32 Hz, 3 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 167.7, 166.2, 161.4, 139.6, 138.2, 130.5, 130.4, 129.0, 128.9, 128.8, 128.5, 128.38, 128.35, 30.4, 23.4, 14.1 ppm.
Elemental analysis (%) for $C_{25}H_{21}ClN_2$ calcd: C 78.01, H 5.50, N 7.28; found: C 78.05, H 5.53, N 7.24

*4-cyclopropyl-2,6-diphenyl-5-propylpyrimidine (**6f**)*

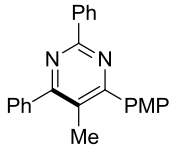



Synthesis according to GP-3. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 100:1). Yield: 252 mg (0.802 mmol, 80 %) colorless crystals suitable for X-ray analysis upon evaporation.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.37 - 8.51 (m, 2 H), 7.35 - 7.60 (m, 8 H), 2.71 - 2.84 (m, 2 H), 2.16 - 2.31 (m, 1 H), 1.56 - 1.73 (m, 2 H), 1.37 - 1.45 (m, 2 H), 1.06 - 1.16 (m, 2 H), 0.89 (t, *J*=7.32 Hz, 3 H) ppm.
$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 170.1, 165.1, 160.9, 140.0, 138.4, 130.1, 128.9, 128.6, 128.4, 128.3, 128.15, 128.12, 30.1, 24.0, 14.3, 13.7, 11.3 ppm.

Elemental analysis (%) for $C_{22}H_{22}N_2$ calcd: C 84.04, H 7.05, N 8.91; found: C 83.94, H 7.02, N 8.81

*4-(4-methoxyphenyl)-5-methyl-2,6-diphenylpyrimidine (**6g**)*



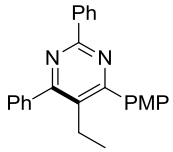

Synthesis according to GP-3. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 40:1 → 20:1). Yield: 259 mg (0.736 mmol, 74 %) white solid.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.48 - 8.66 (m, 2 H), 7.68 - 7.84 (m, 4 H), 7.38 - 7.60 (m, 6 H), 6.97 - 7.13 (m, 2 H), 3.90 (s, 3 H), 2.42 (s, 3 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 166.9, 166.4, 161.4, 160.5, 139.4, 138.1, 131.6, 131.1, 130.2, 129.5, 129.1, 128.4, 128.3, 128.2, 126.1, 122.9, 113.7, 55.4, 18.1 ppm.

Elemental analysis (%) for $C_{24}H_{20}N_2O$ calcd: C 81.79, H 5.72, N 7.95; found: C 81.12, H 6.13, N 7.74

*5-ethyl-4-(4-methoxyphenyl)-2,6-diphenylpyrimidine (**6h**)*



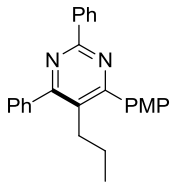

Synthesis according to GP-3. 1 mmol scale, 1.5 mol% catalyst **A**. Purification by column chromatography (pentane/ diethyl ether, 40:1 → 30:1). Yield: 251 mg (0.686 mmol, 69 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.46 - 8.59 (m, 2 H), 7.58 - 7.71 (m, 4 H), 7.37 - 7.56 (m, 6 H), 6.97 - 7.12 (m, 2 H), 3.90 (s, 3 H), 2.88 (q, *J*=7.63 Hz, 2 H), 0.80 (t, *J*=7.48 Hz, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 167.3, 166.7, 161.3, 160.3, 139.9, 138.0, 132.2, 130.4, 130.3, 129.8, 128.9, 128.8, 128.5, 128.4, 113.9, 55.5, 21.8, 14.6 ppm.

Elemental analysis (%) for $C_{25}H_{22}N_2O$ calcd: C 81.94, H 6.05, N 7.64; found: C 81.72, H 6.19, N 7.58

*4-(4-methoxyphenyl)-2,6-diphenyl-5-propylpyrimidine (**6i**)*



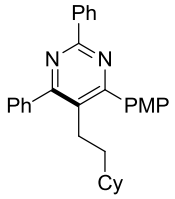

Synthesis according to GP-3. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/ diethyl ether, 40:1 → 20:1) Yield: 274 mg (0.721 mmol, 72 %) white solid.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.49 - 8.63 (m, 2 H), 7.60 - 7.73 (m, 4 H), 7.38 - 7.58 (m, 6 H), 6.99 - 7.11 (m, 2 H), 3.90 (s, 3 H), 2.76 - 2.92 (m, 2 H), 1.10 - 1.26 (m, 2 H), 0.59 (t, *J*=7.32 Hz, 3 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 167.4, 166.9, 161.2, 160.2, 139.9, 138.0, 132.3, 130.5, 130.3, 128.9, 128.8, 128.4, 128.34, 128.27, 113.9, 55.5, 30.5, 23.2, 14.1 ppm.

Elemental analysis (%) for $C_{26}H_{24}N_2O$ calcd: C 82.07, H 6.36, N 7.36; found: C 82.08, H 6.49, N 7.26

*5-(2-cyclohexylethyl)-4-(4-methoxyphenyl)-2,6-diphenylpyrimidine (**6j**)*

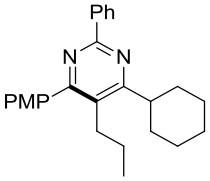



Synthesis according to GP-3. 1 mmol scale, 1.5 mol% catalyst **A**. Purification by column chromatography (pentane/ diethyl ether, 30:1) Yield: 353 mg (0.788 mmol, 79 %) white solid.
$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.47 - 8.62 (m, 2 H), 7.59 - 7.72 (m, 4 H), 7.37 - 7.56 (m, 6 H), 6.96 - 7.11 (m, 2 H), 3.90 (s, 3 H), 2.74 - 2.94 (m, 2 H), 1.51 (d, *J*=9.37 Hz, 3 H), 1.21 - 1.37 (m, 2 H), 0.93 - 1.14 (m, 5 H), 0.85 (td, *J*=6.88, 3.22 Hz, 1 H), 0.43 - 0.64 (m, 2 H) ppm.

$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 166.8, 160.2, 139.8, 138.0, 132.2, 130.5, 130.3, 128.9, 128.8, 128.44, 128.40, 128.3, 113.8, 55.5, 37.5, 37.4, 32.8, 26.5, 26.2, 25.8 ppm.

Elemental analysis (%) for $C_{31}H_{32}N_2O$ calcd: C 83.00, H 7.19, N 6.24; found: C 82.55, H 7.20, N 6.33.

*4-cyclohexyl-6-(4-methoxyphenyl)-2-phenyl-5-propylpyrimidine (**6k**)*



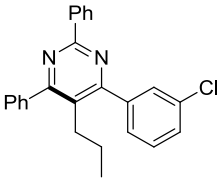

Synthesis according to GP-3. 1 mmol scale, 1.5 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 40:1). Yield: 254 mg (0.657 mmol, 66 %) white solid.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.48 - 8.57 (m, 2 H), 7.49 - 7.55 (m, 2 H), 7.40 - 7.48 (m, 3 H), 6.97 - 7.04 (m, 2 H), 3.89 (s, 3 H), 2.88 - 2.99 (m, 1 H), 2.62 - 2.72 (m, 2 H), 1.87 - 2.01 (m, 4 H), 1.81 (d, *J*=9.00 Hz, 3 H), 1.35 - 1.57 (m, 5 H), 0.90 (t, *J*=7.32 Hz, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 173.3, 165.8, 161.0 160.0, 138.6, 132.7, 130.3, 130.0, 128.4, 128.2, 127.5, 113.7, 55.5, 42.1, 32.5, 30.0, 26.7, 26.2, 24.8, 14.4 ppm.

Elemental analysis (%) for $C_{26}H_{30}N_2O$ calcd: C 80.79, H 7.82, N 7.25; found: C 80.43, H 7.83, N 7.19

*4-(3-chlorophenyl)-2,6-diphenyl-5-propylpyrimidine (**6l**)*



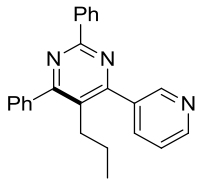

Synthesis according to GP-3. 1 mmol scale, 1.5 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 80:1 → 60:1). Yield: 234 mg (0.608 mmol, 61 %) viscous colorless oil which solidified upon standing.

$^{1}$H NMR (500 MHz, $CDCl_3$) δ = 8.34 - 8.47 (m, 2 H), 7.44 - 7.58 (m, 3 H), 7.23 - 7.42 (m, 9 H), 2.57 - 2.70 (m, 2 H), 0.96 - 1.11 (m, 2 H), 0.45 (t, *J*=7.32 Hz, 3 H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$) δ = 167.7, 165.9, 161.4, 141.4, 139.5, 137.6, 134.4, 130.5, 129.7, 129.1, 128.98, 128.97, 128.8, 128.48, 128.45, 128.37, 128.3, 127.0, 30.3, 23.3, 14.0 ppm.

Elemental analysis (%) for $C_{25}H_{21}ClN_2$ calcd: C 78.01, H 5.50, N 7.28; found: C 77.81, H 5.59, N 6.98

*2,4-diphenyl-5-propyl-6-(pyridin-3-yl)pyrimidine (**6m**)*

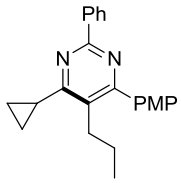



Synthesis according to GP-3. 1 mmol scale. 1.5 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 1:1). Yield: 199 mg (0.566 mmol, 57 %) white solid.

$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.94 (s, 2 H), 8.74 (s, 2 H), 8.47 - 8.58 (m, 2 H), 8.01 (dt, *J*=7.76, 1.98 Hz, 1 H), 7.60 - 7.70 (m, 4 H), 7.40 - 7.57 (m, 14 H), 2.75 - 2.87 (m, 2 H), 1.09 - 1.28 (m, 2 H), 0.59 (t, *J*=7.32 Hz, 3 H) ppm.
$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 167.9, 164.3, 161.6, 150.0, 149.7, 139.4, 137.6, 136.5, 135.6, 130.6, 129.1, 128.9, 128.8, 128.58, 128.55, 128.4, 123.4, 30.4, 23.5, 14.0 ppm.

Elemental analysis (%) for $C_{24}H_{21}N_3$ calcd: C 82.02, H 6.02, N 11.96; found: C 81.83, H 5.91, N 11.93

*4-cyclopropyl-6-(4-methoxyphenyl)-2-phenyl-5-propylpyrimidine (**6n**)*




Synthesis according to GP-3. 1 mmol scale, 1 mol% catalyst **A**. Purification by column chromatography (pentane/diethyl ether, 40:1). Yield: 250 mg (0.726 mmol, 73 %) white solid.

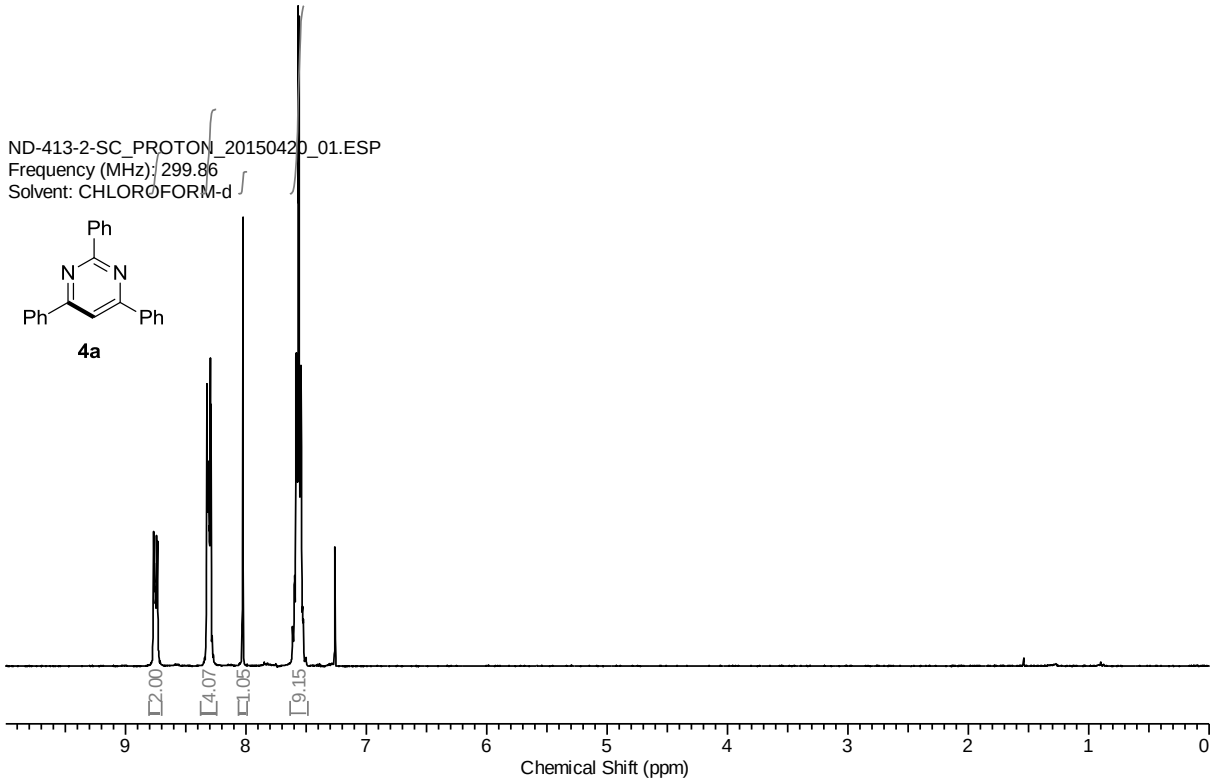
$^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.38 - 8.52 (m, 8 H), 7.35 - 7.58 (m, 5 H), 6.96 - 7.07 (m, 2 H), 3.88 (s, 1 H), 2.74 - 2.88 (m, 2 H), 2.16 - 2.30 (m, 2 H), 1.57 - 1.74 (m, 4 H), 1.35 - 1.44 (m, 2 H), 1.05 - 1.15 (m, 2 H), 0.92 (t, *J*=7.32 Hz, 3 H) ppm.

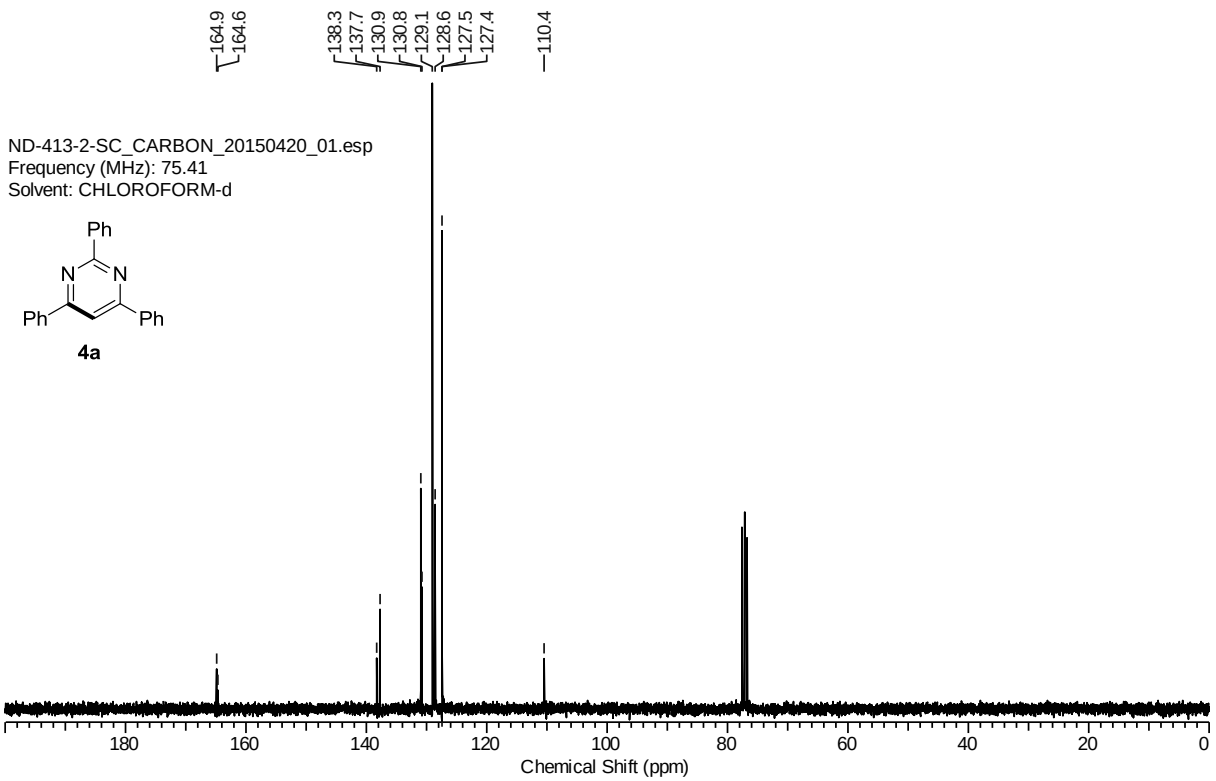
$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 170.0, 164.6, 160.8, 160.0, 138.5, 132.4, 130.4, 130.0, 128.3, 128.1, 128.0, 113.7, 55.5, 30.2, 24.0, 14.4, 13.7, 11.2 ppm.

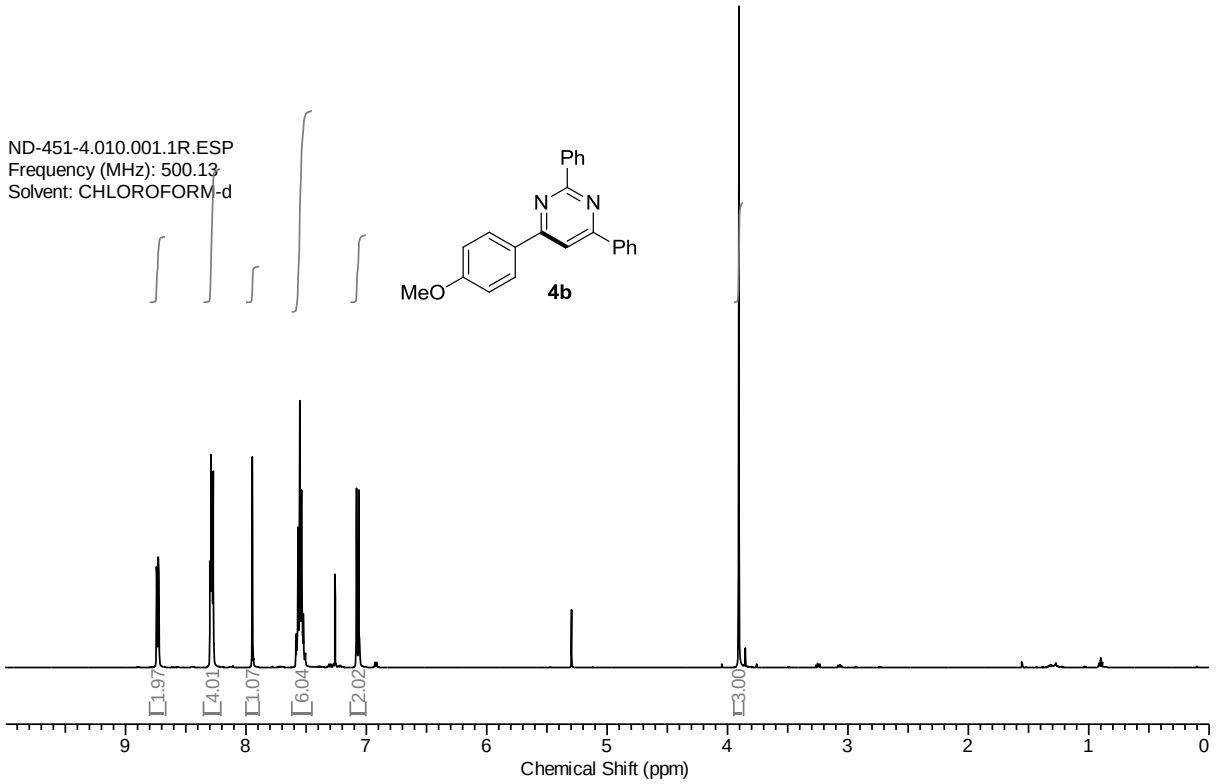
Elemental analysis (%) for $C_{23}H_{24}N_2O$ calcd: C 80.20, H 7.02; N 8.13; found: C 80.34, H 7.13, N 8.29

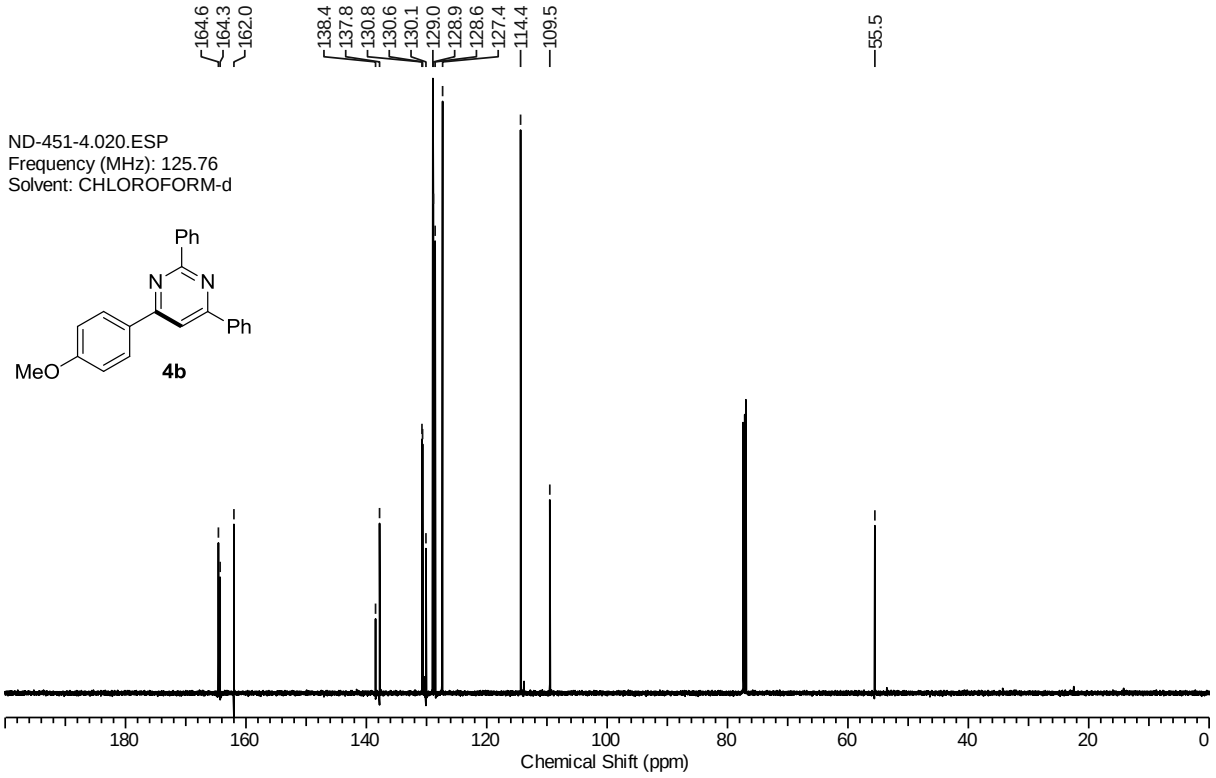
# 6 NMR-Spectra

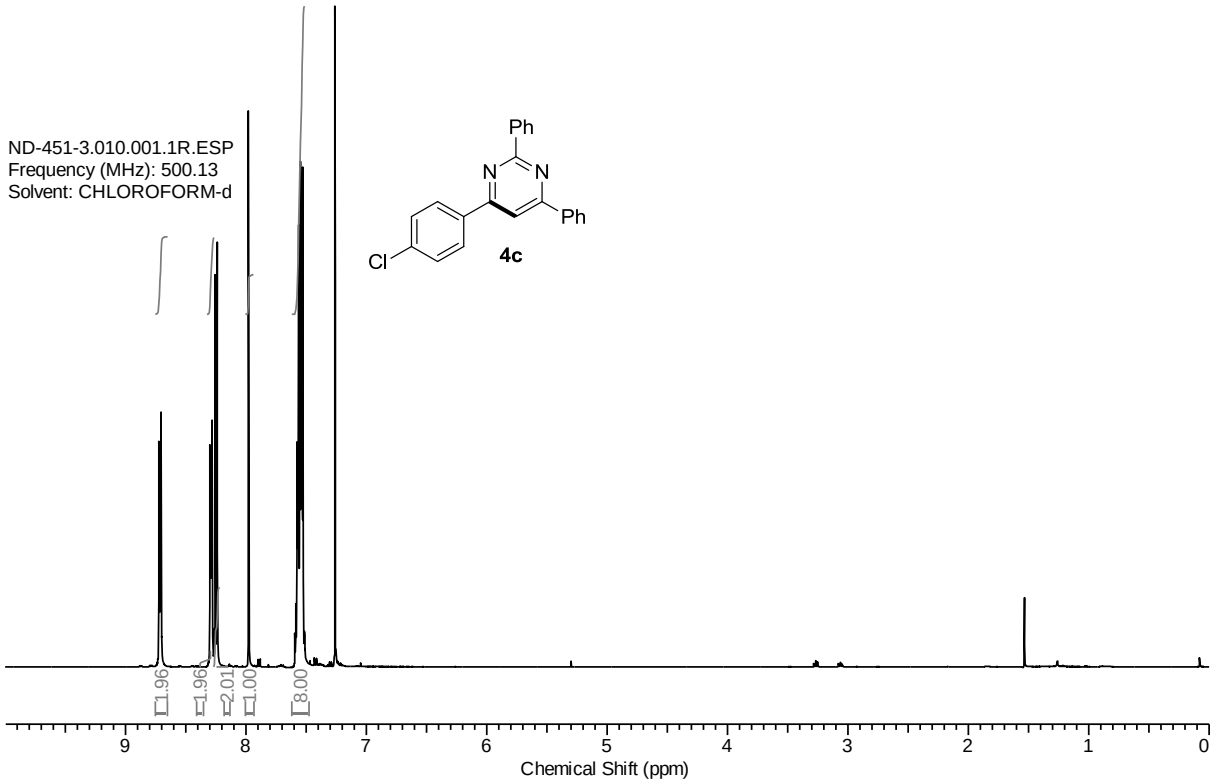
**3-component-reaction, Me alkylation**




ND-451-4.010.001.1R.ESP
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
Ph
MeO
4b
1.97
4.01
1.07
6.04
2.02
3.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


164.6
164.3
162.0
138.4
137.8
130.8
130.6
130.1
129.0
128.9
128.6
127.4
114.4
109.5
55.5
ND-451-4.020.ESP
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
MeO
4b
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)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N
Ph
Cl
4c
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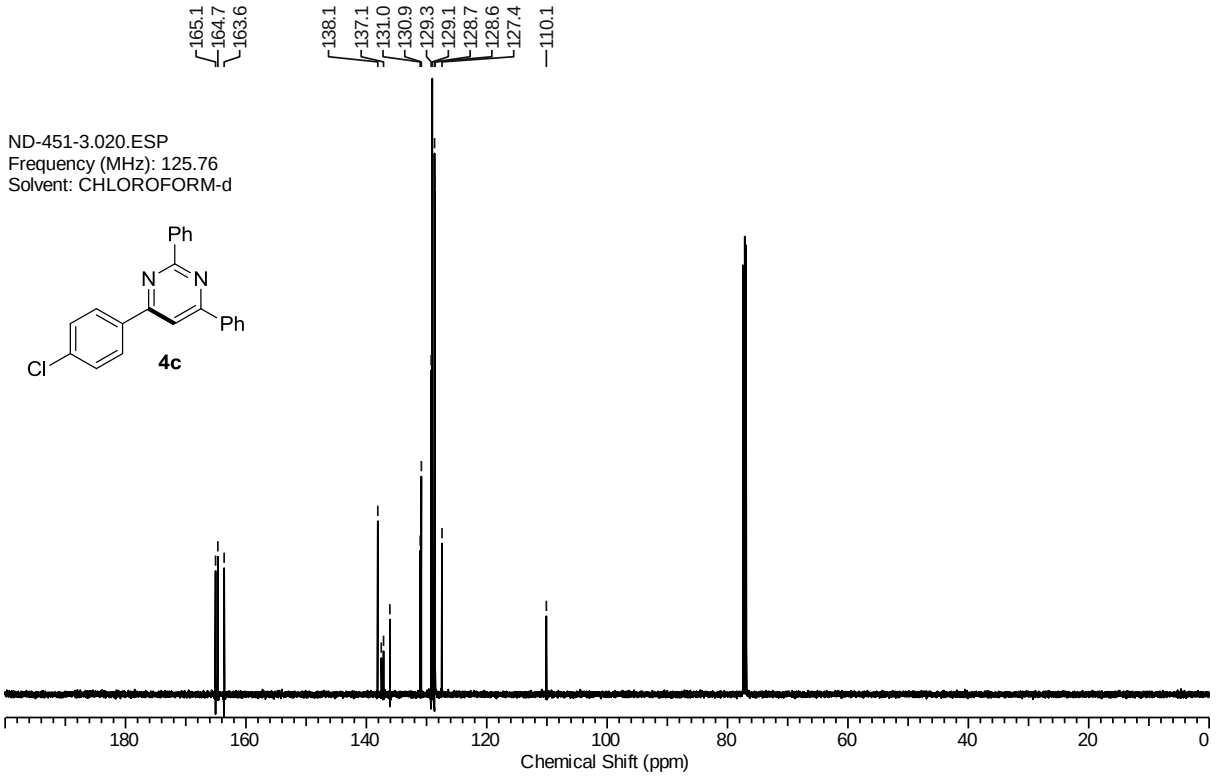
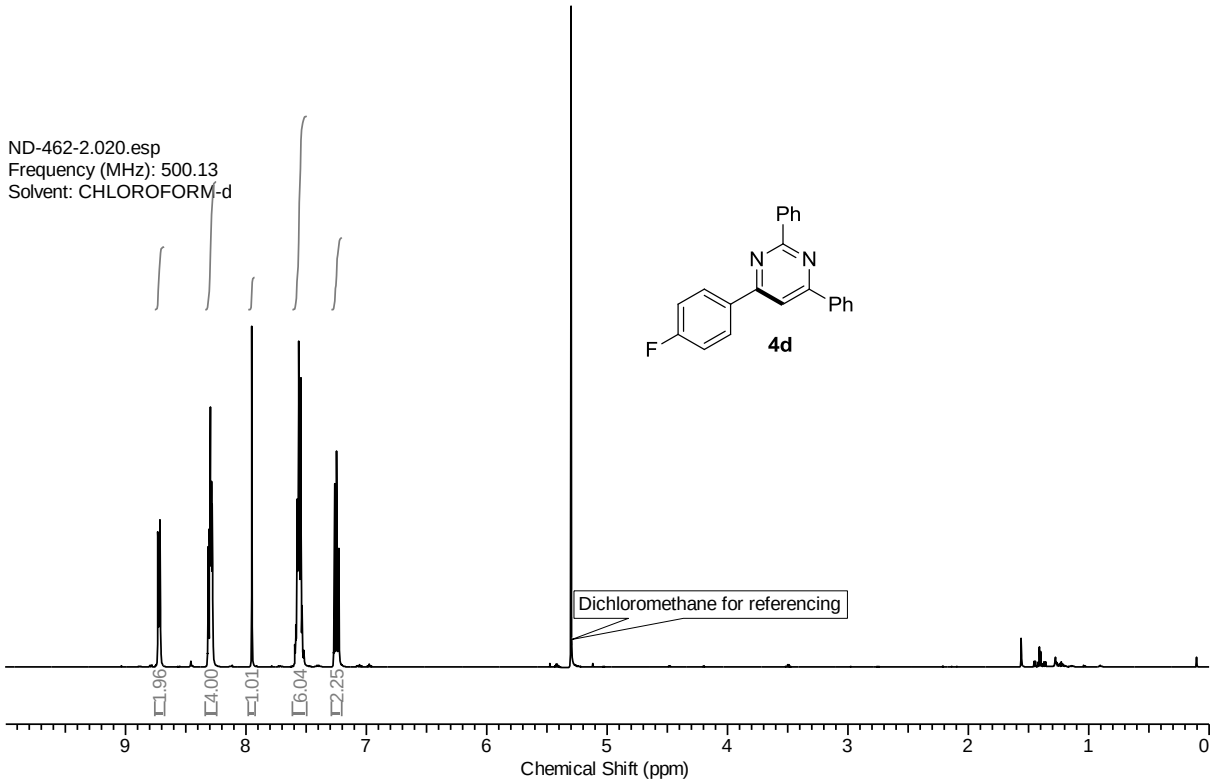
1.00
8.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


165.1
164.7
163.6
138.1
137.1
131.0
130.9
129.3
129.1
128.7
128.6
127.4
110.1
ND-451-3.020.ESP
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
Cl
4c
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


ND-462-2.020.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
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N
N
Ph
F
4d
Dichloromethane for referencing
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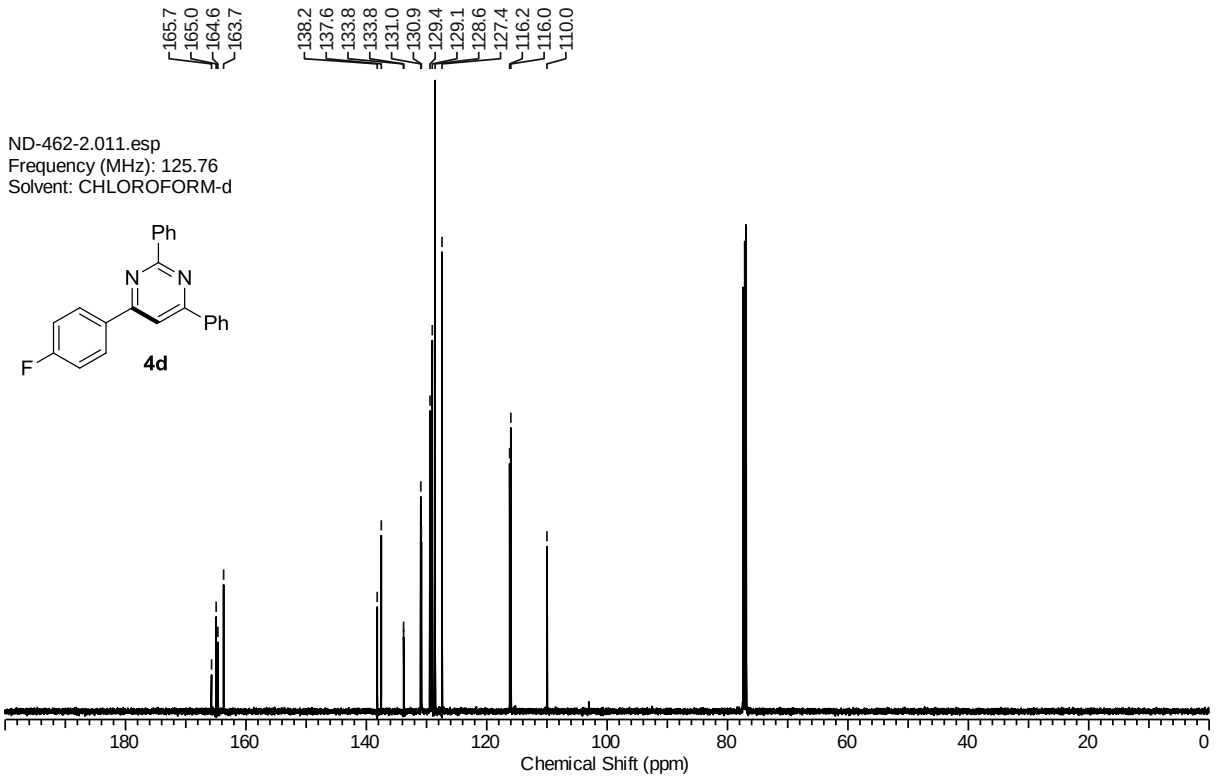
1.01
6.04
2.25
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


165.7
165.0
164.6
163.7
138.2
137.6
133.8
133.8
131.0
130.9
129.4
129.1
128.6
127.4
116.2
116.0
110.0
ND-462-2.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
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N
Ph
F
4d
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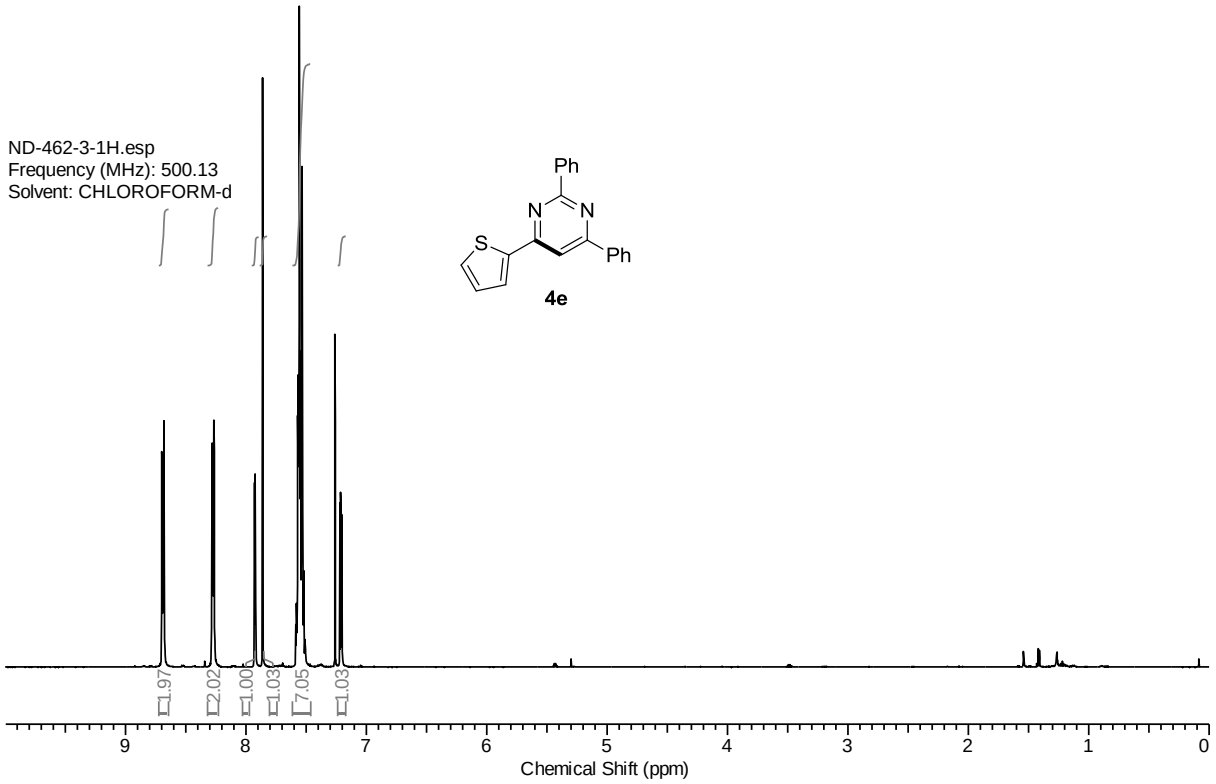
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)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N
S
Ph
4e
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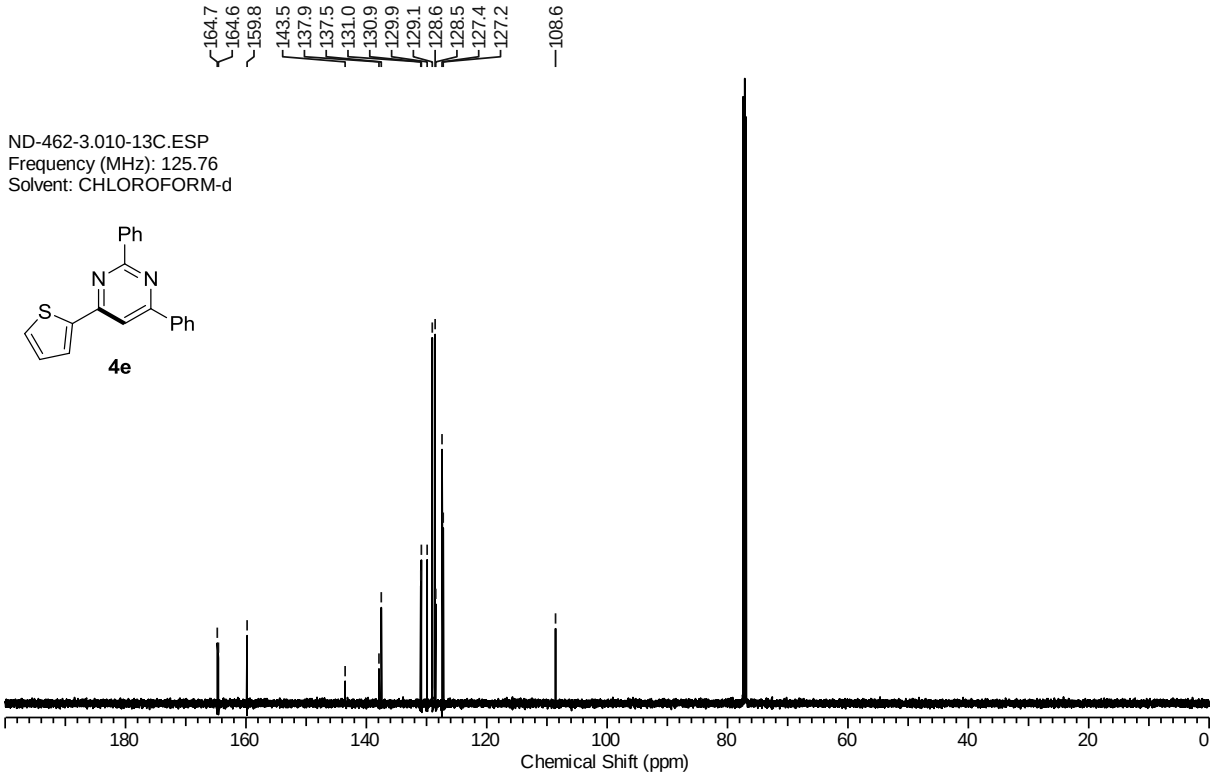
1.00
1.03
7.05
1.03
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


164.7
164.6
159.8
143.5
137.9
137.5
131.0
130.9
129.9
129.1
128.6
128.5
127.4
127.2
108.6
ND-462-3.010-13C.ESP
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
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N
S
Ph
4e
180
160
140
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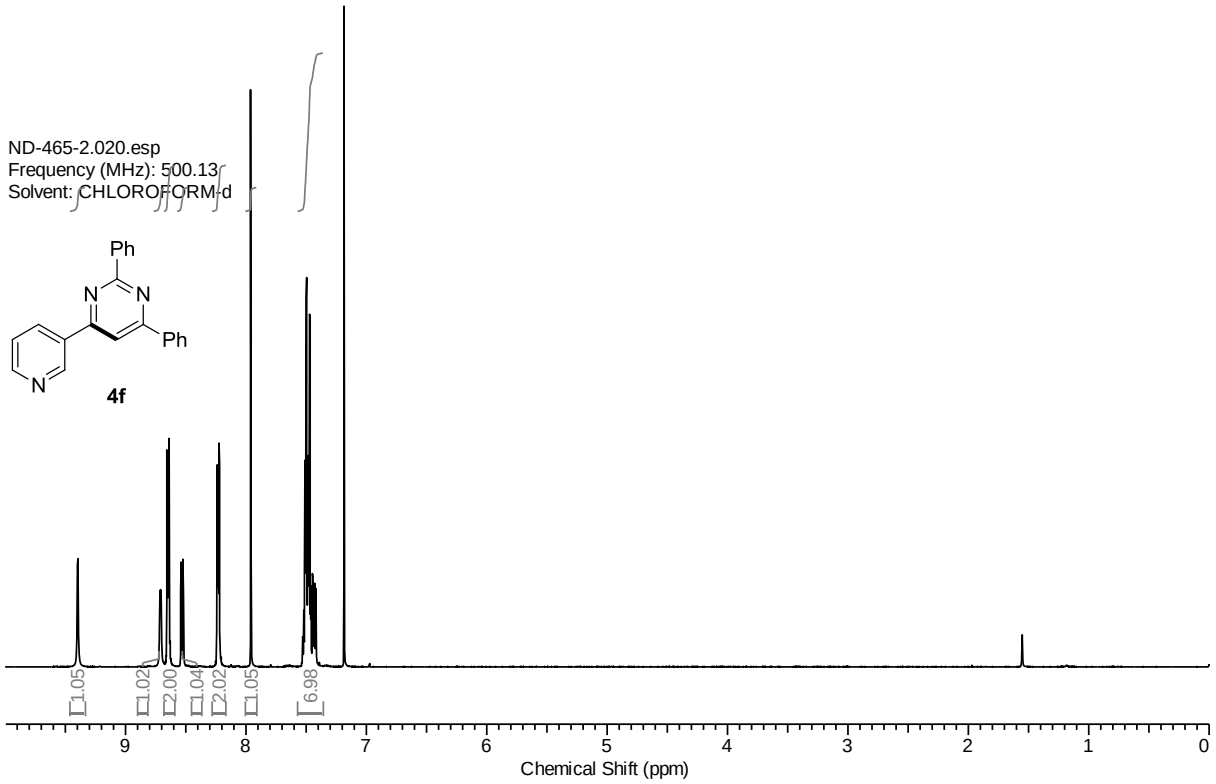
100
80
60
40
20
0
Chemical Shift (ppm)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Ph
N
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1.02
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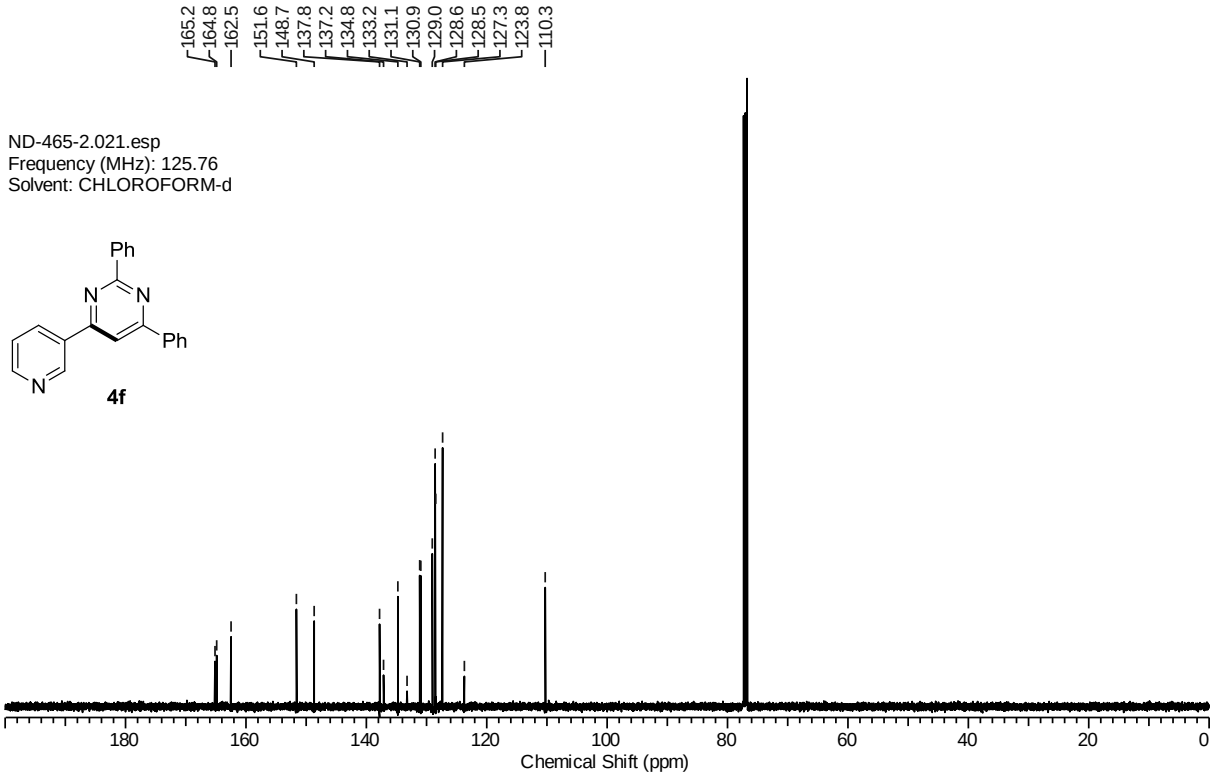
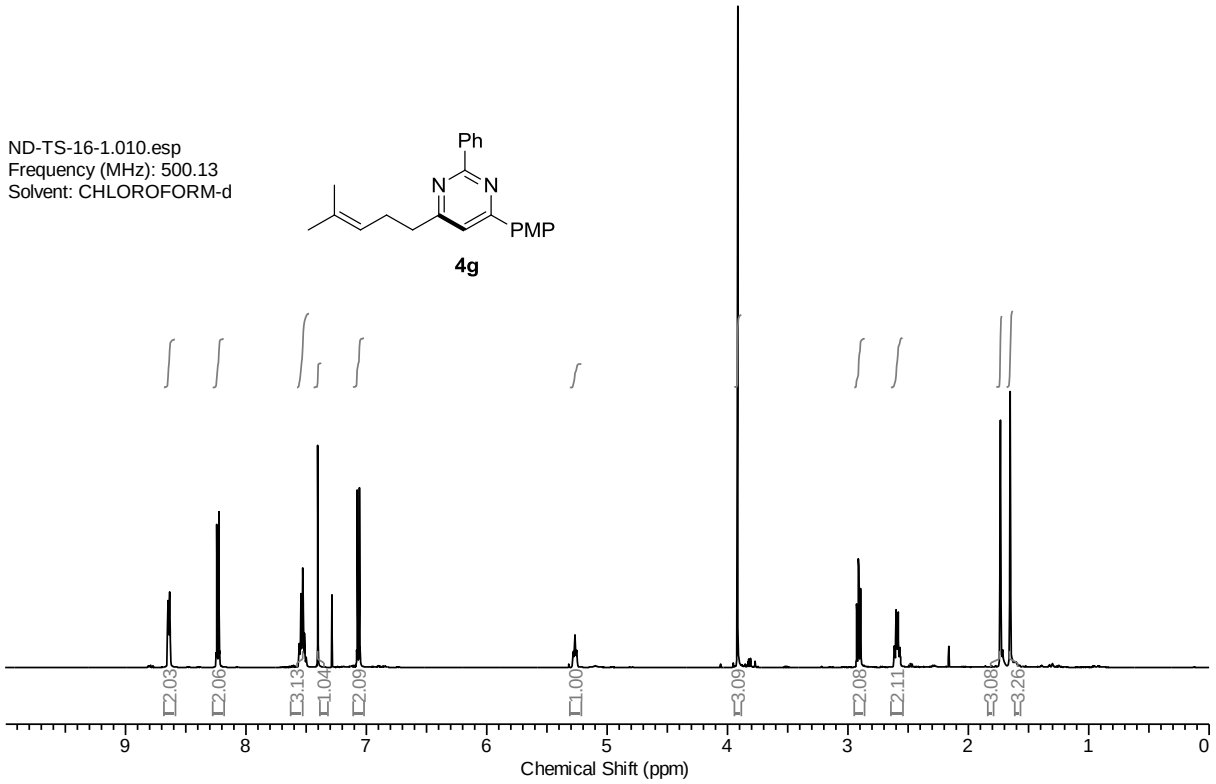
2.02
1.05
6.98
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


165.2
164.8
162.5
151.6
148.7
137.8
137.2
134.8
133.2
131.1
130.9
129.0
128.6
128.5
127.3
123.8
110.3
ND-465-2.021.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
N
4f
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)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Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
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N
PMP
4g
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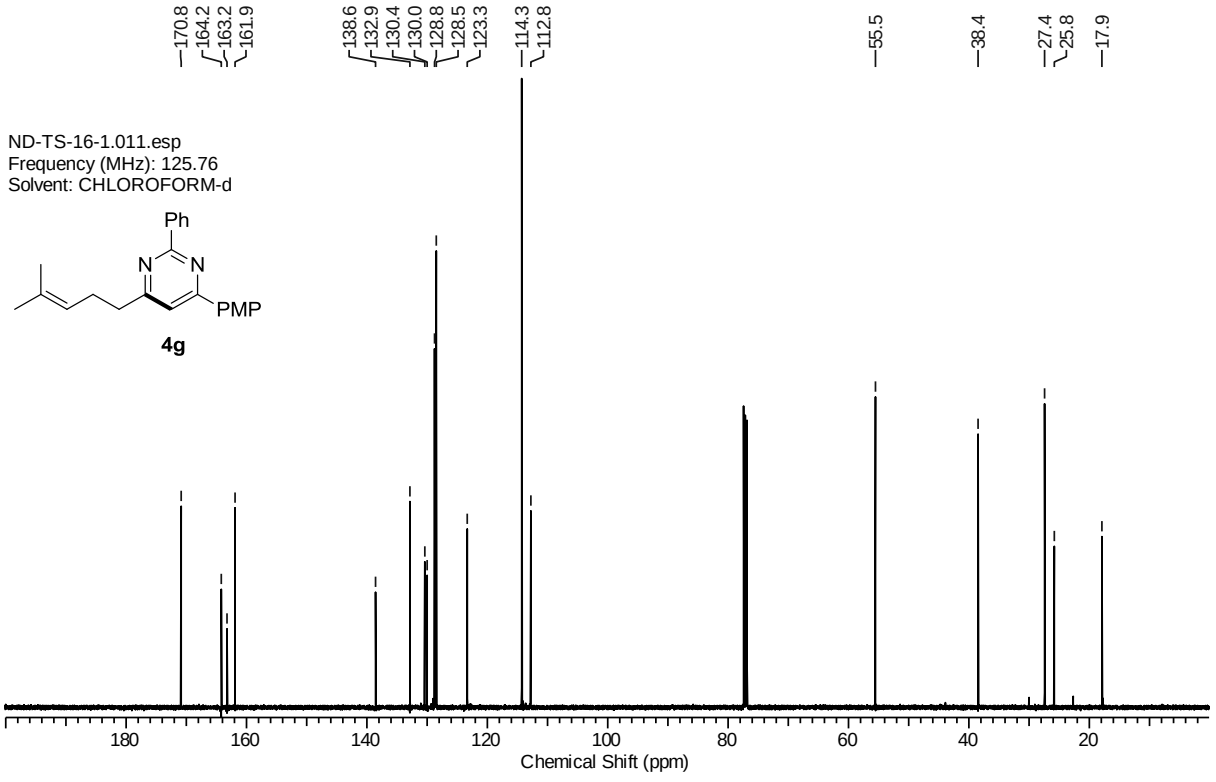
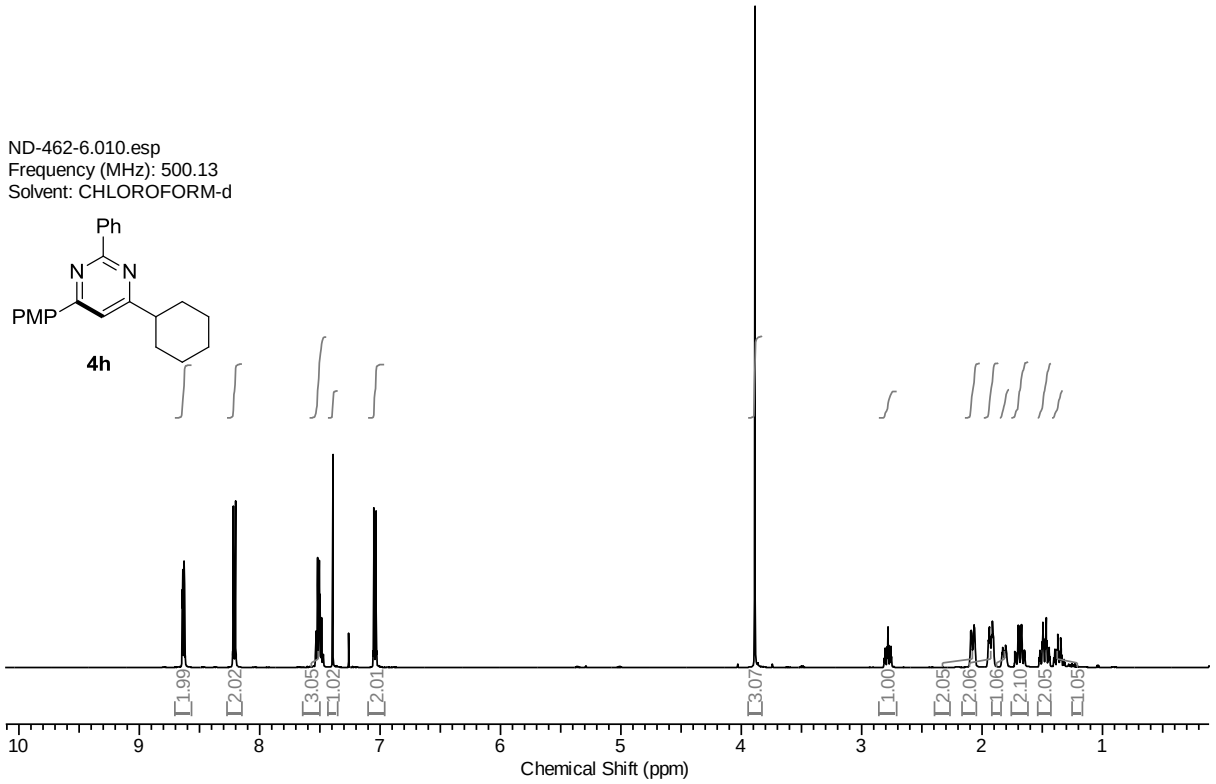
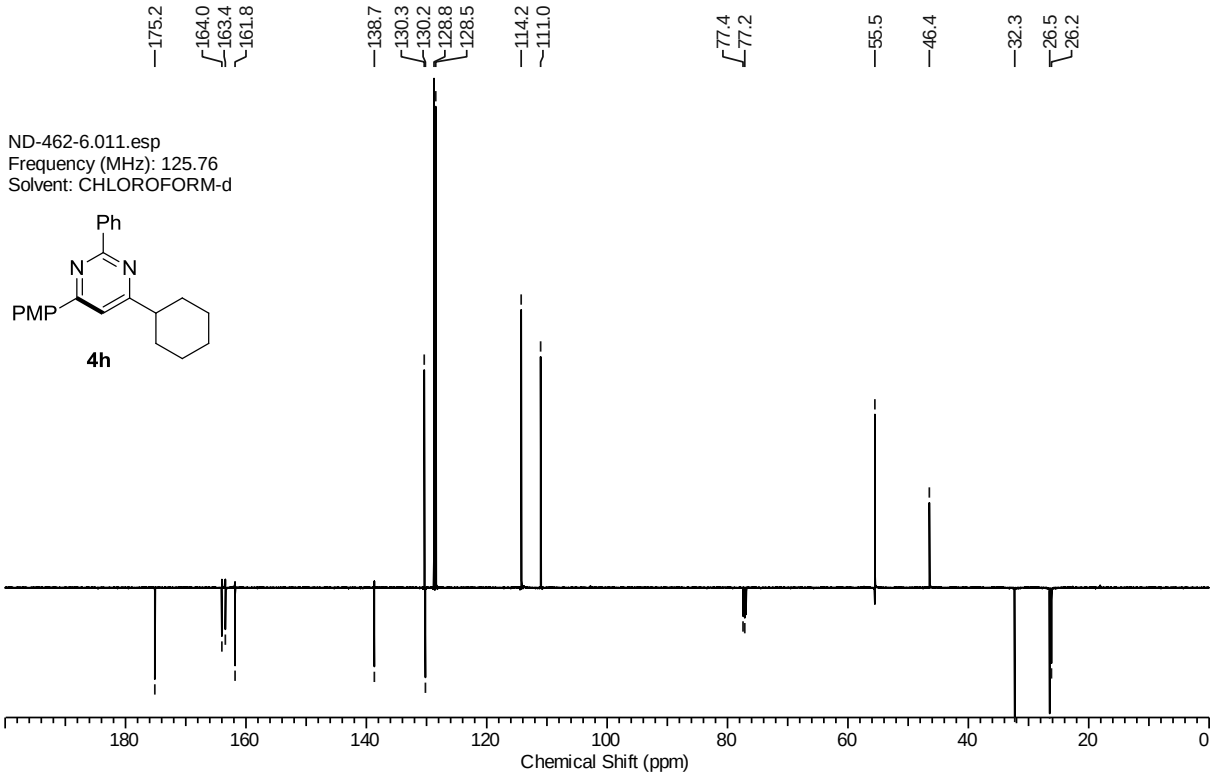
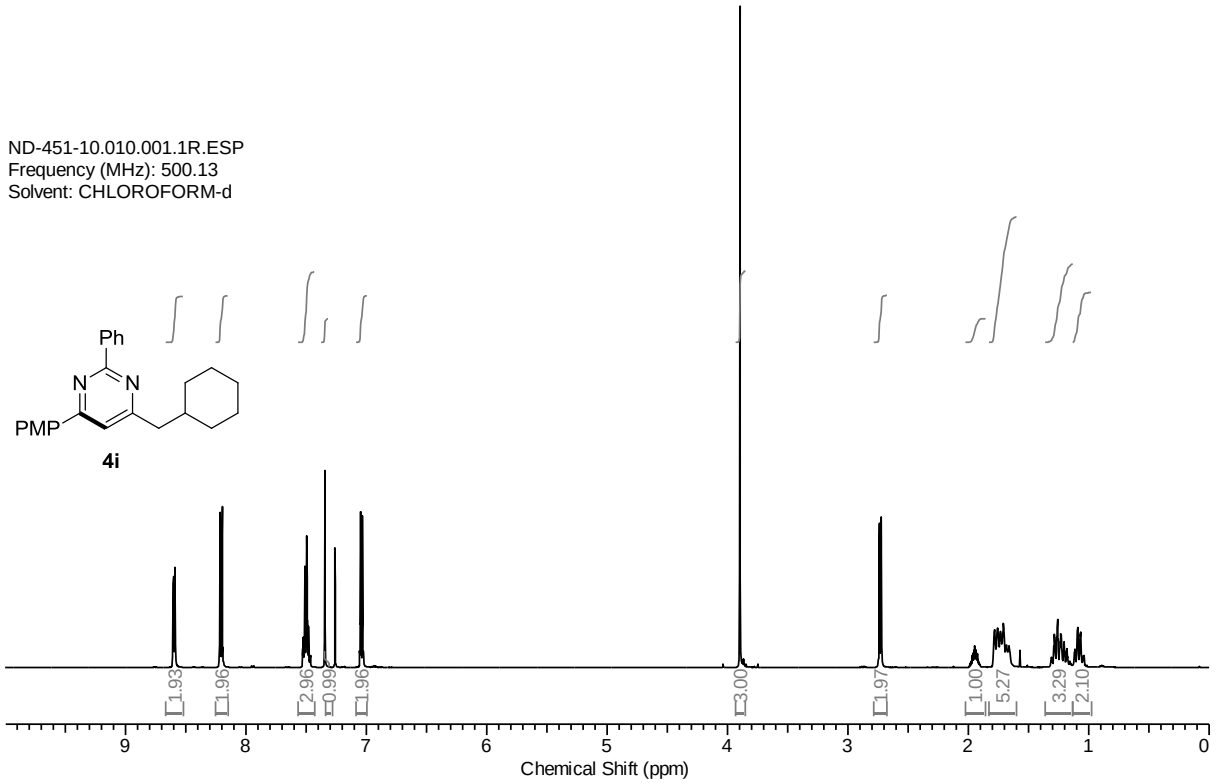
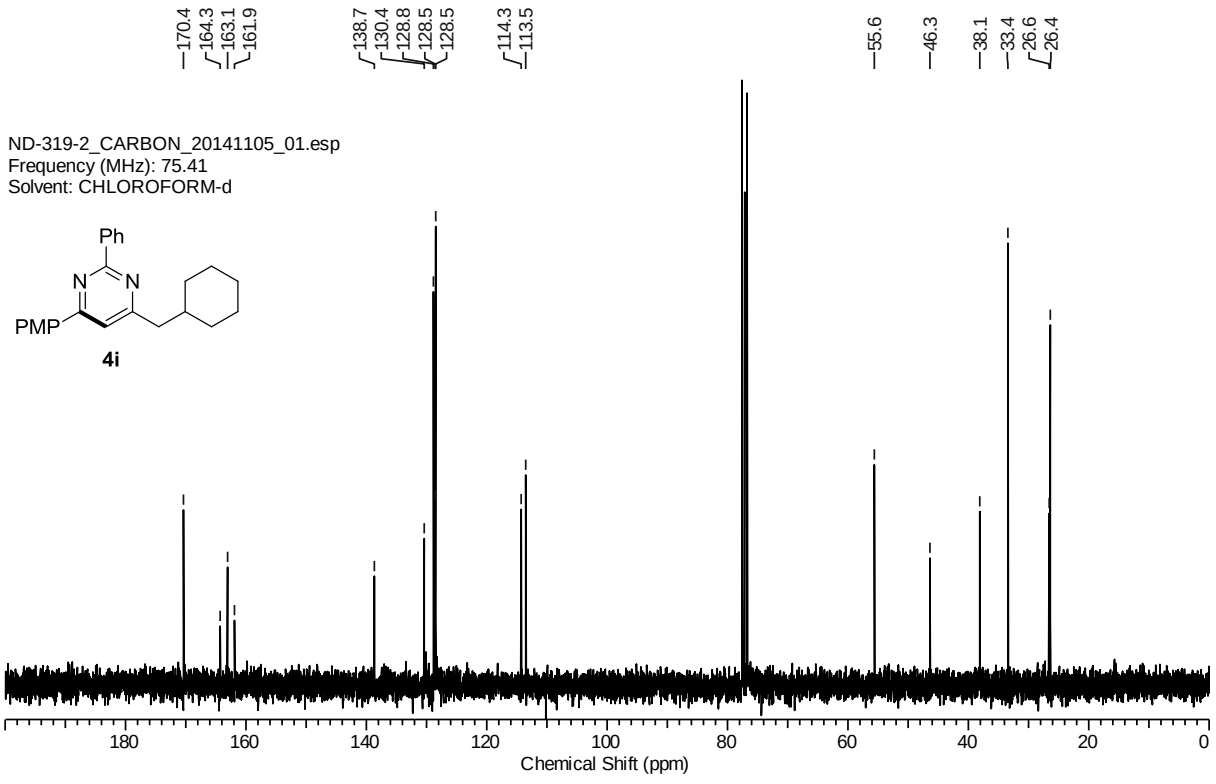
2.09
1.00
3.09
2.08
2.11
3.08
3.26
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

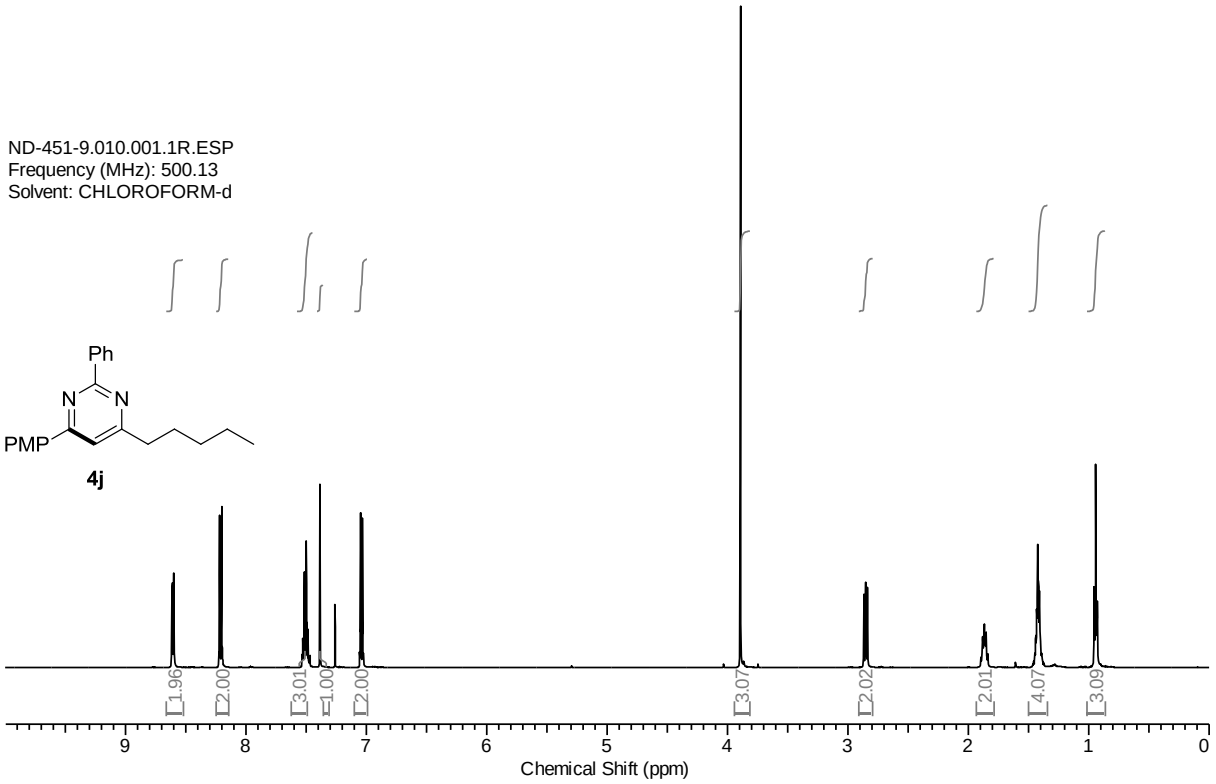

170.8
164.2
163.2
161.9
138.6
132.9
130.4
130.0
128.8
128.5
123.3
114.3
112.8
55.5
38.4
27.4
25.8
17.9
ND-TS-16-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4g
180
160
140
120
100
80
60
40
20
Chemical Shift (ppm)

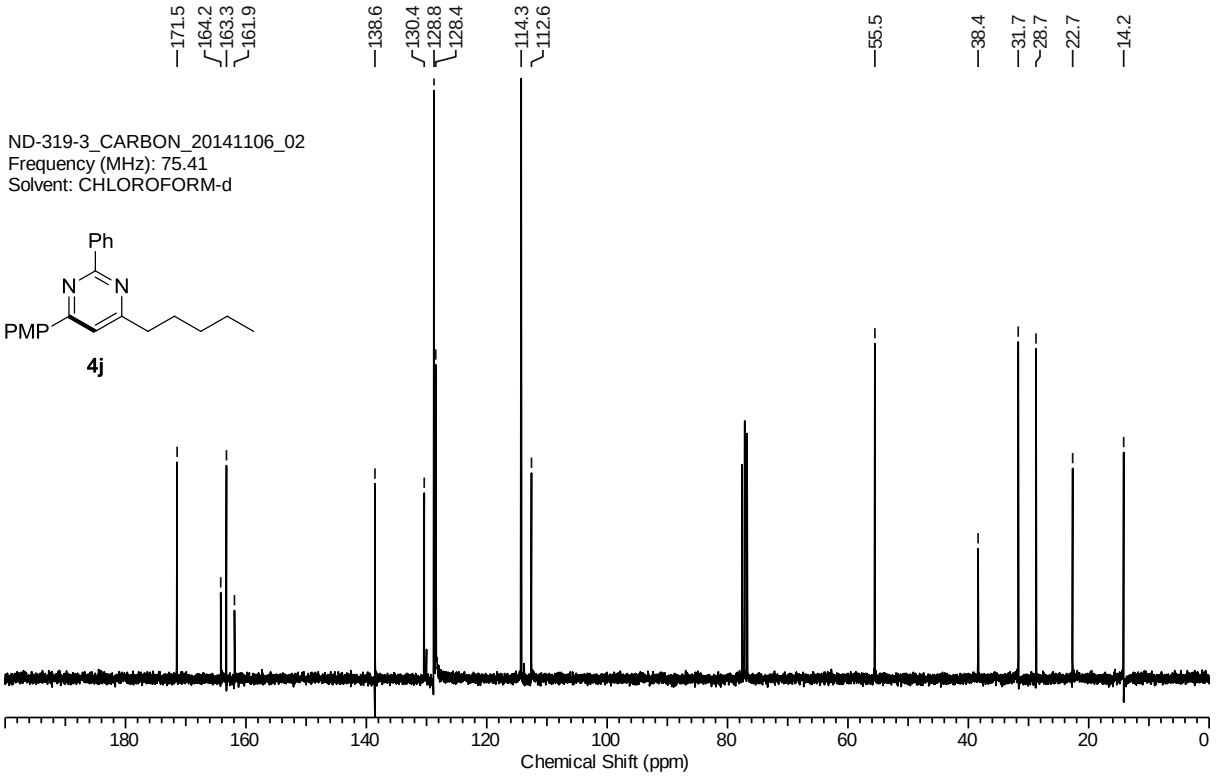

ND-462-6.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4h
1.99
2.02
3.05
1.02
2.01
3.07
1.00
2.05
2.06
1.06
2.10
2.05
1.05
10
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

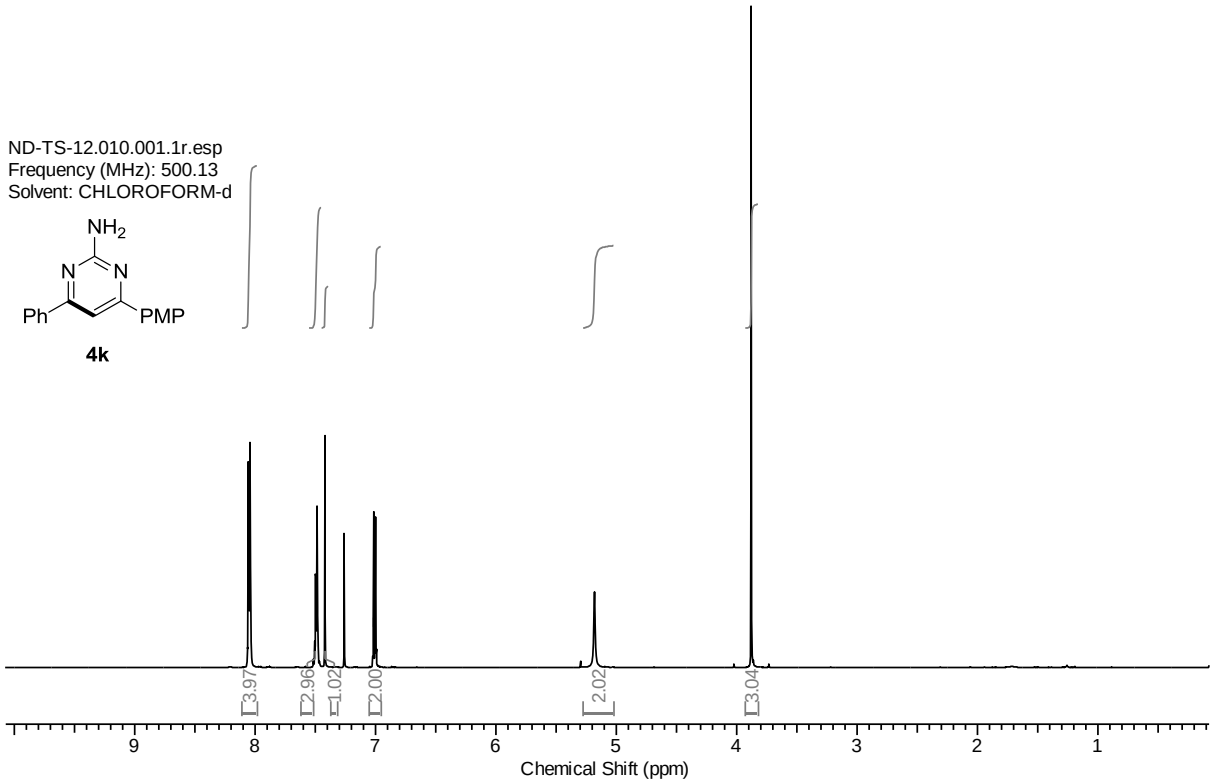

175.2
164.0
163.4
161.8
138.7
130.3
130.2
128.8
128.5
114.2
111.0
77.4
77.2
55.5
46.4
32.3
26.5
26.2
ND-462-6.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4h
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

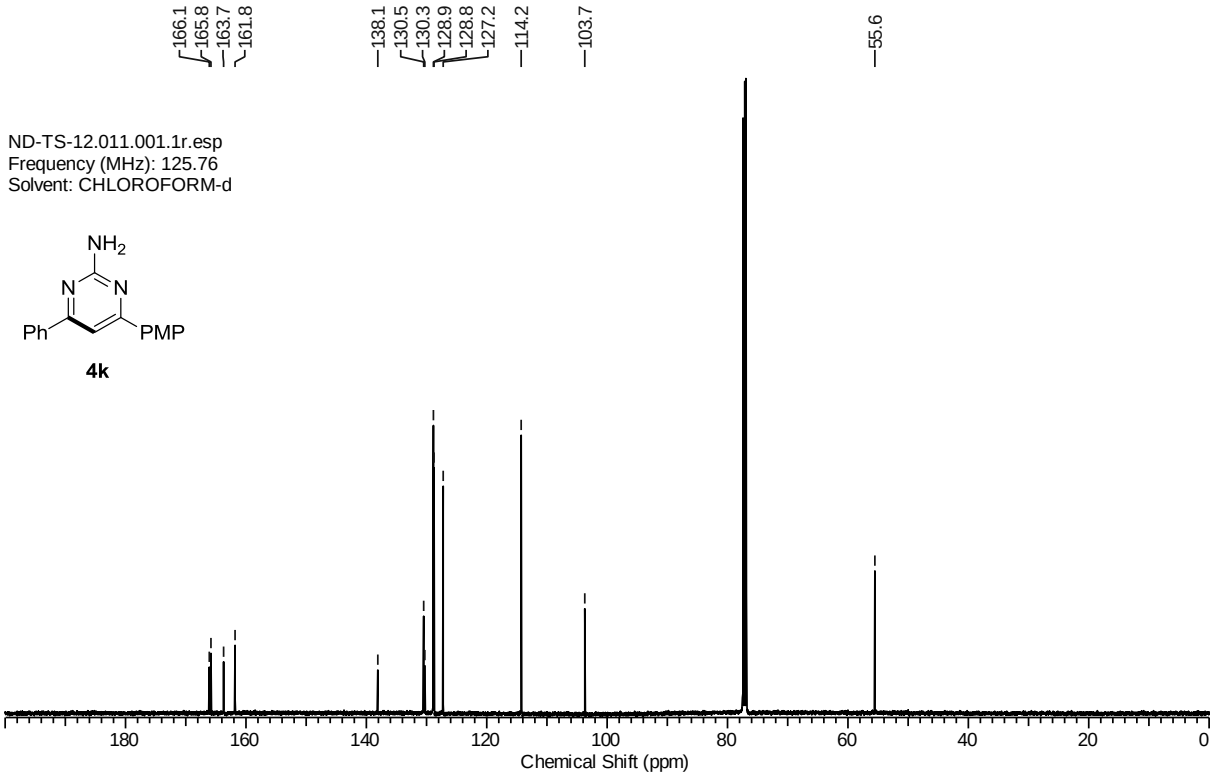

ND-451-10.010.001.1R.ESP
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4i
1.93
1.96
2.96
0.99
1.96
3.00
1.97
1.00
5.27
3.29
2.10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

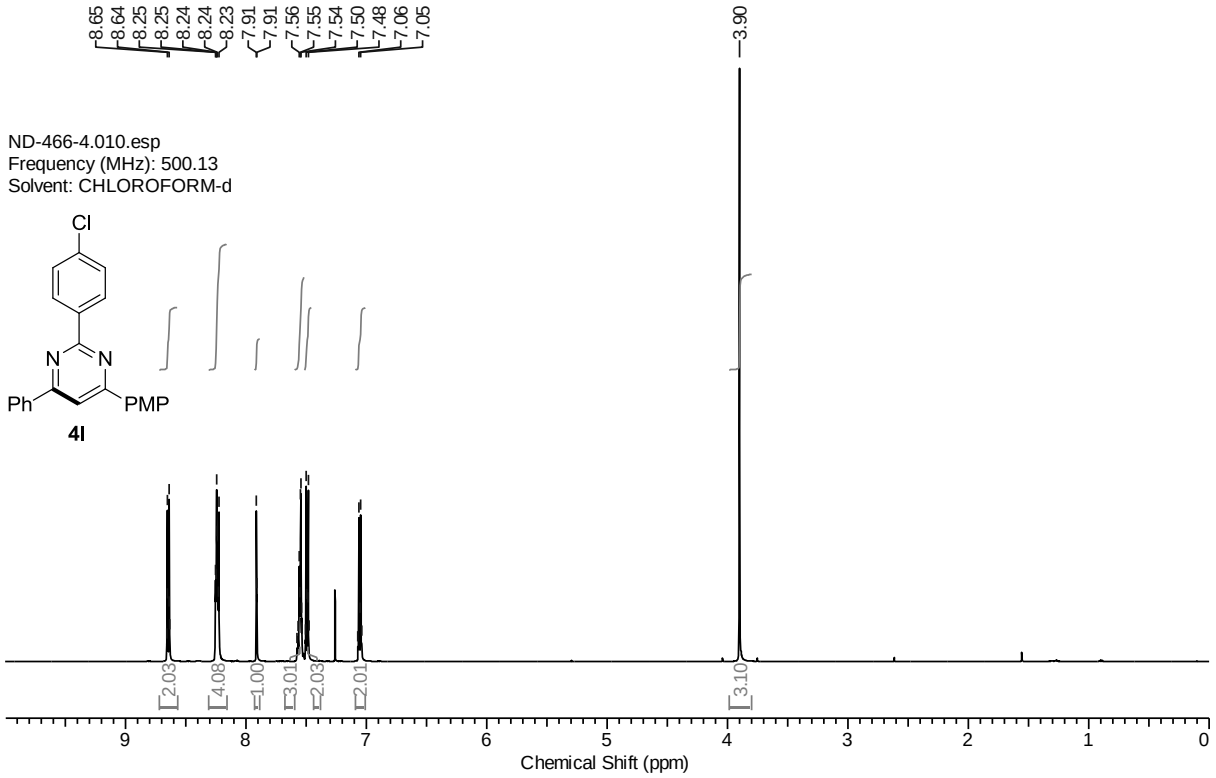

170.4
164.3
163.1
161.9
138.7
130.4
128.8
128.5
128.5
114.3
113.5
55.6
46.3
38.1
33.4
26.6
26.4
ND-319-2_CARBON_20141105_01.esp
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4i
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

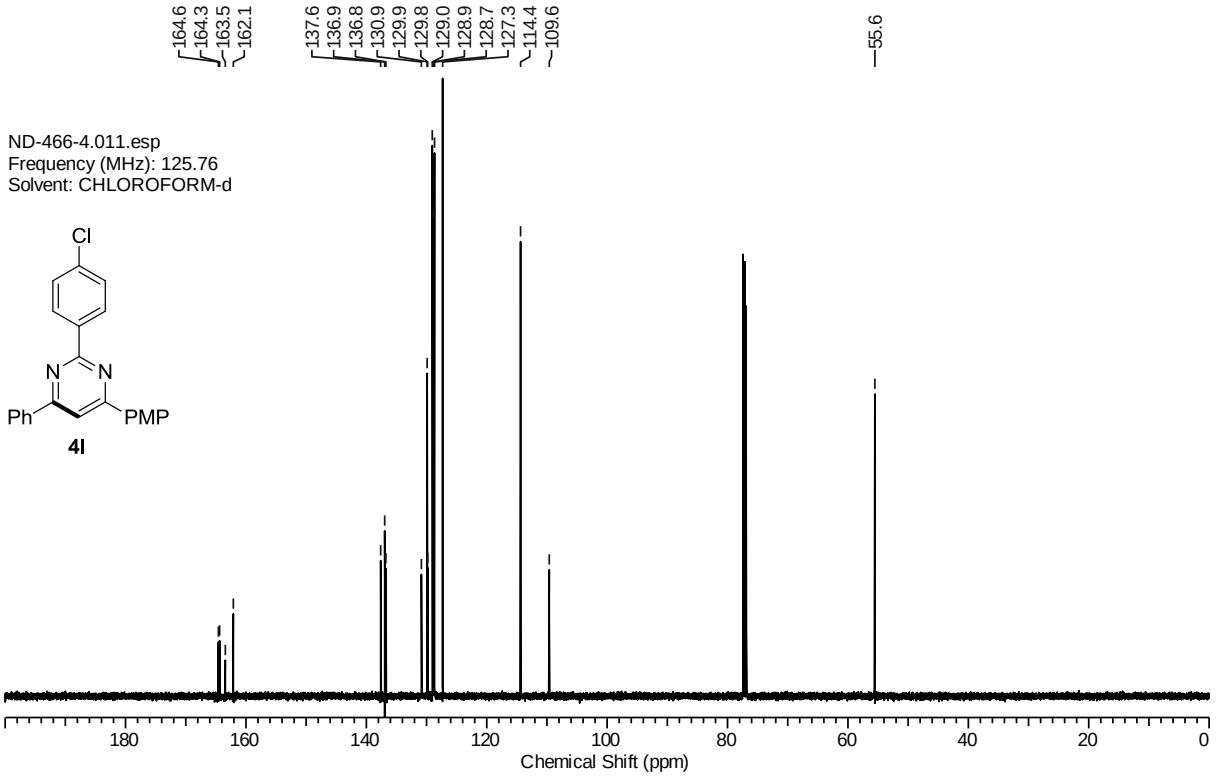

ND-451-9.010.001.1R.ESP
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4j
1.96
2.00
3.01
1.00
2.00
3.07
2.02
2.01
4.07
3.09
Chemical Shift (ppm)

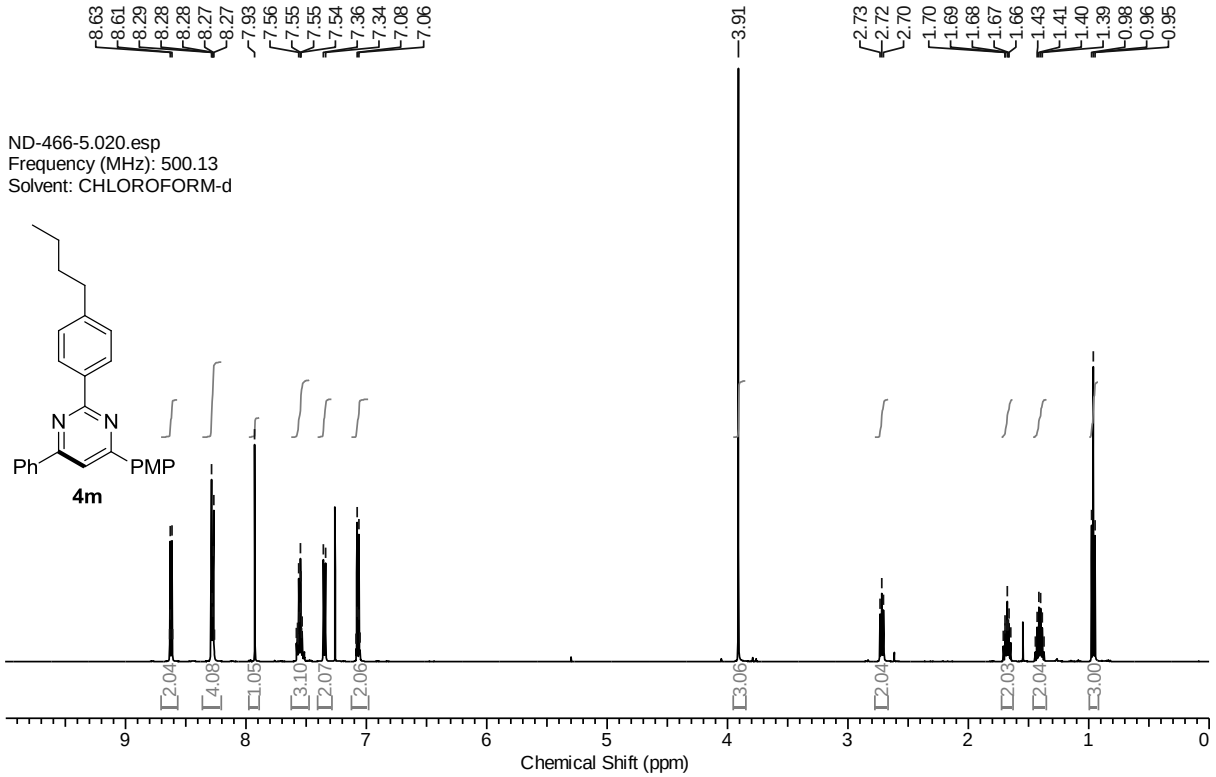

171.5
164.2
163.3
161.9
138.6
130.4
128.8
128.4
114.3
112.6
55.5
38.4
31.7
28.7
22.7
14.2
ND-319-3_CARBON_20141106_02
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4j
Chemical Shift (ppm)

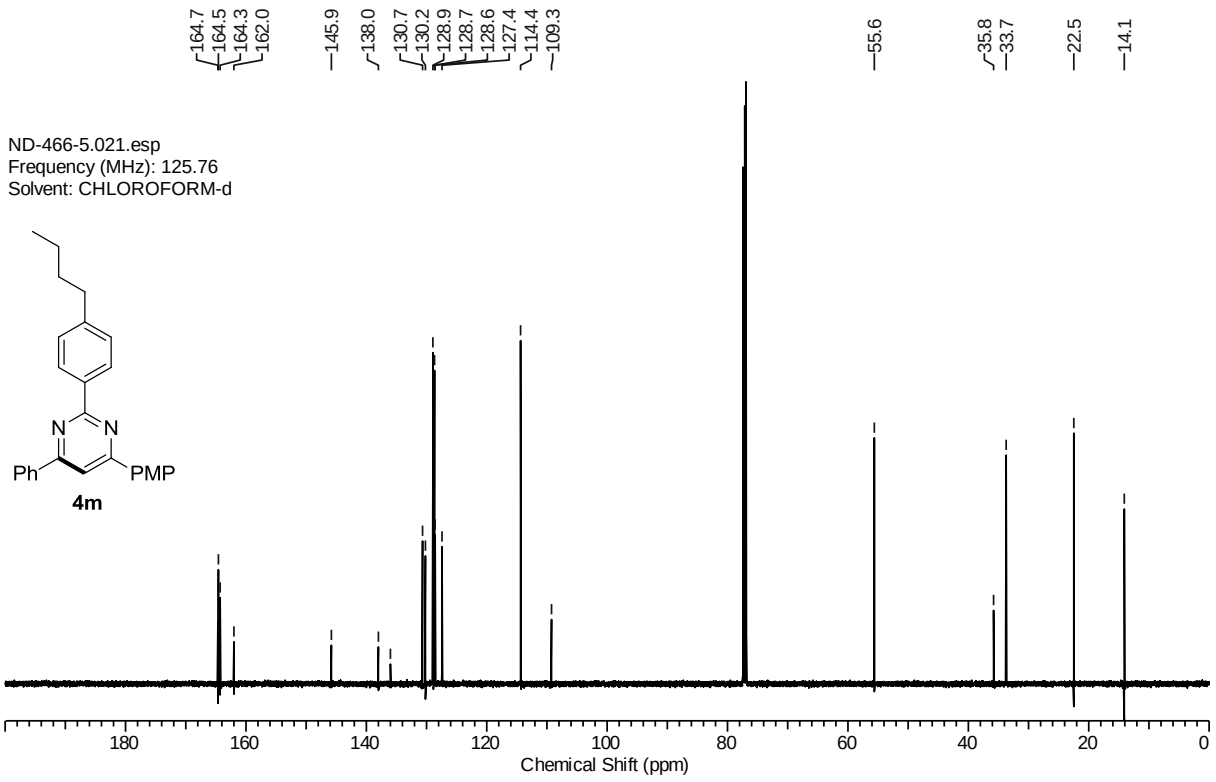

ND-TS-12.010.001.1r.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
NH2
N
N
Ph
PMP
4k
3.97
2.96
1.02
2.00
2.02
3.04
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

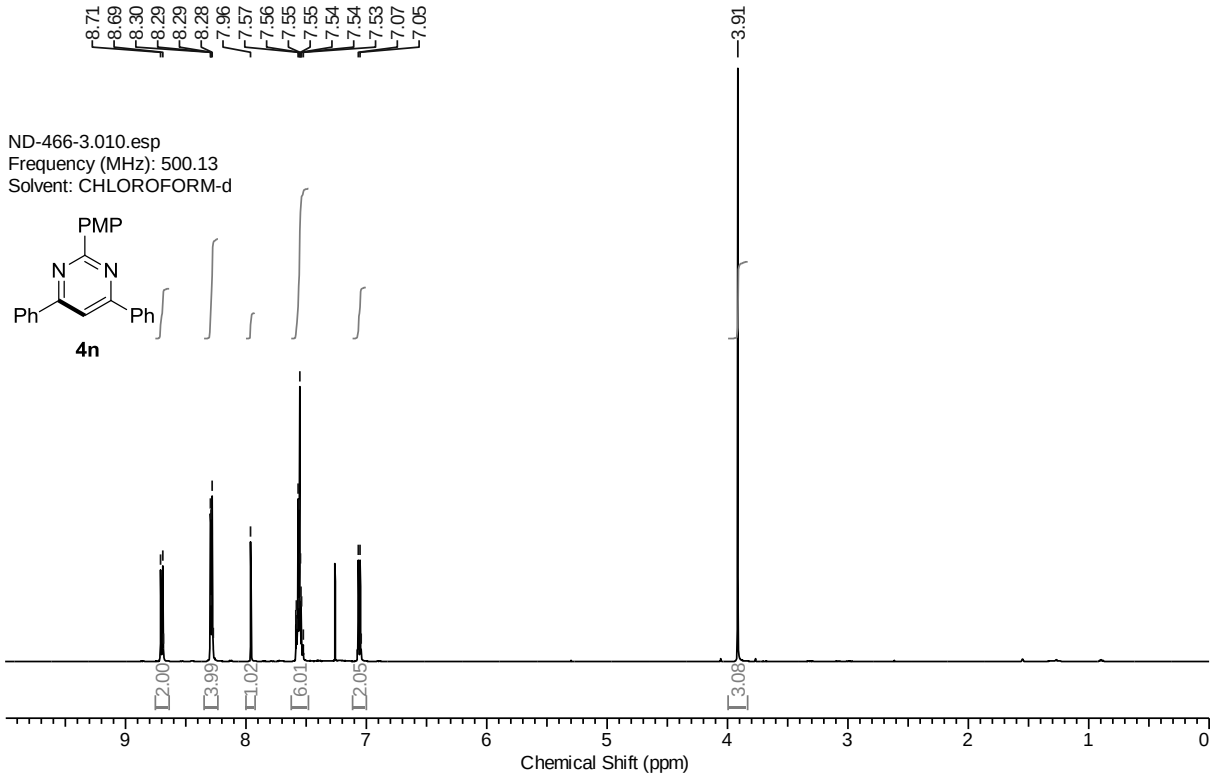

166.1
165.8
163.7
161.8
138.1
130.5
130.3
128.9
128.8
127.2
114.2
103.7
55.6
ND-TS-12.011.001.1r.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
NH2
N
N
Ph
PMP
4k
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

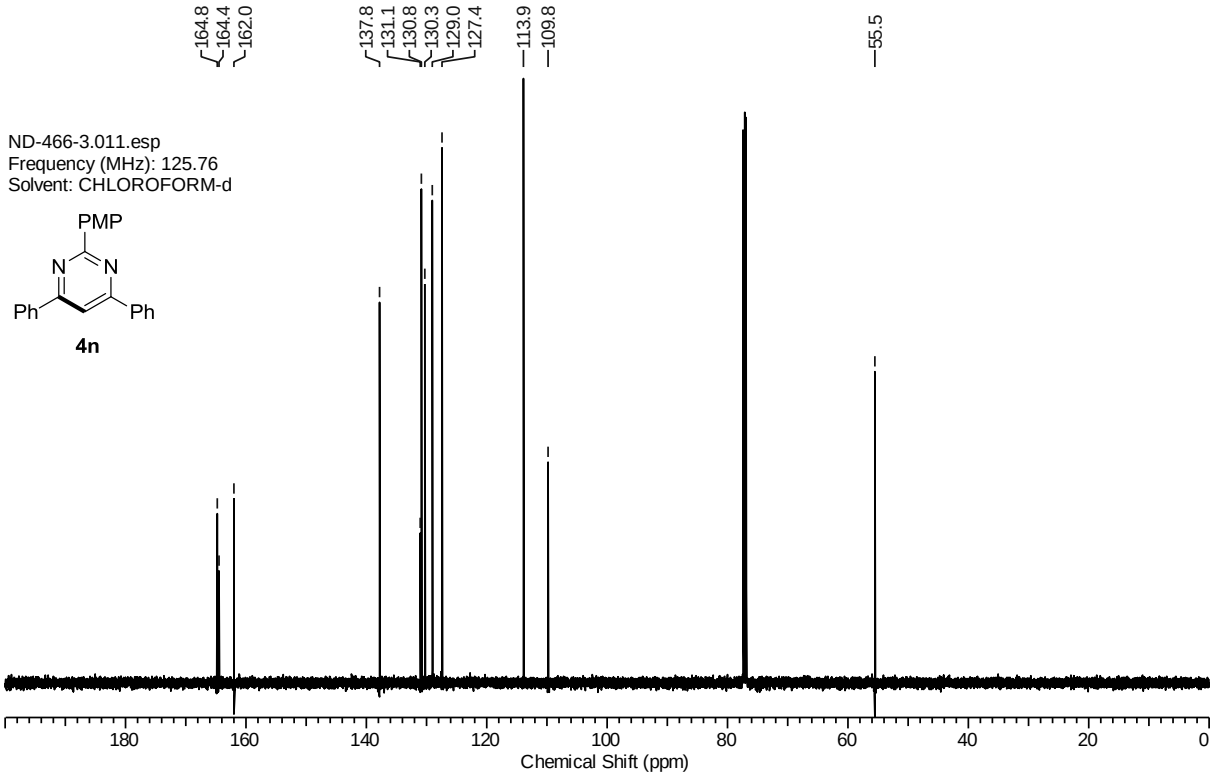

8.65
8.64
8.25
8.25
8.24
8.24
8.23
7.91
7.91
7.56
7.55
7.54
7.50
7.48
7.06
7.05
3.90
ND-466-4.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Cl
N
N
Ph
PMP
4l
2.03
4.08
1.00
3.01
2.03
2.01
3.10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

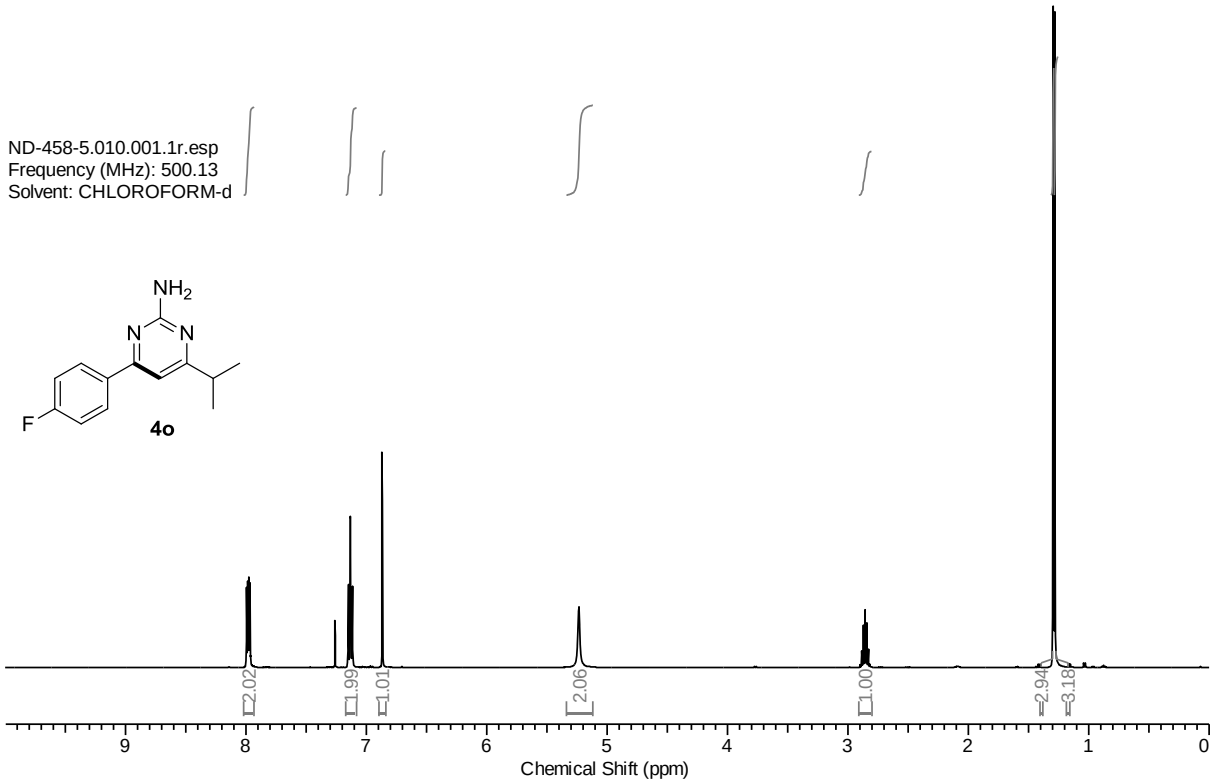

164.6
164.3
163.5
162.1
137.6
136.9
136.8
130.9
129.9
129.8
129.0
128.9
128.7
127.3
114.4
109.6
55.6
ND-466-4.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Cl
N
N
Ph
PMP
4l
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

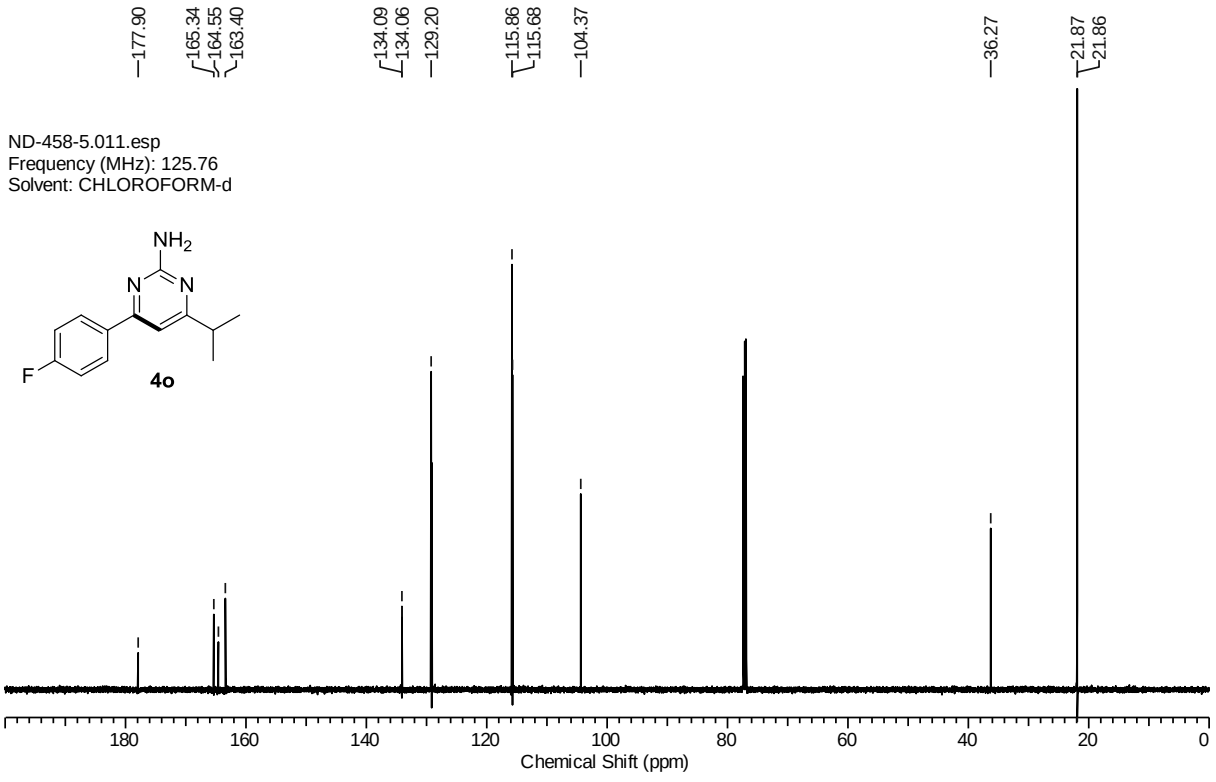

8.63
8.61
8.29
8.28
8.28
8.27
8.27
7.93
7.56
7.55
7.55
7.54
7.36
7.34
7.08
7.06
3.91
2.73
2.72
2.70
1.70
1.69
1.68
1.67
1.66
1.43
1.41
1.40
1.39
0.98
0.96
0.95
ND-466-5.020.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
N
N
Ph
PMP
4m
2.04
4.08
1.05
3.10
2.07
2.06
3.06
2.04
2.03
2.04
3.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

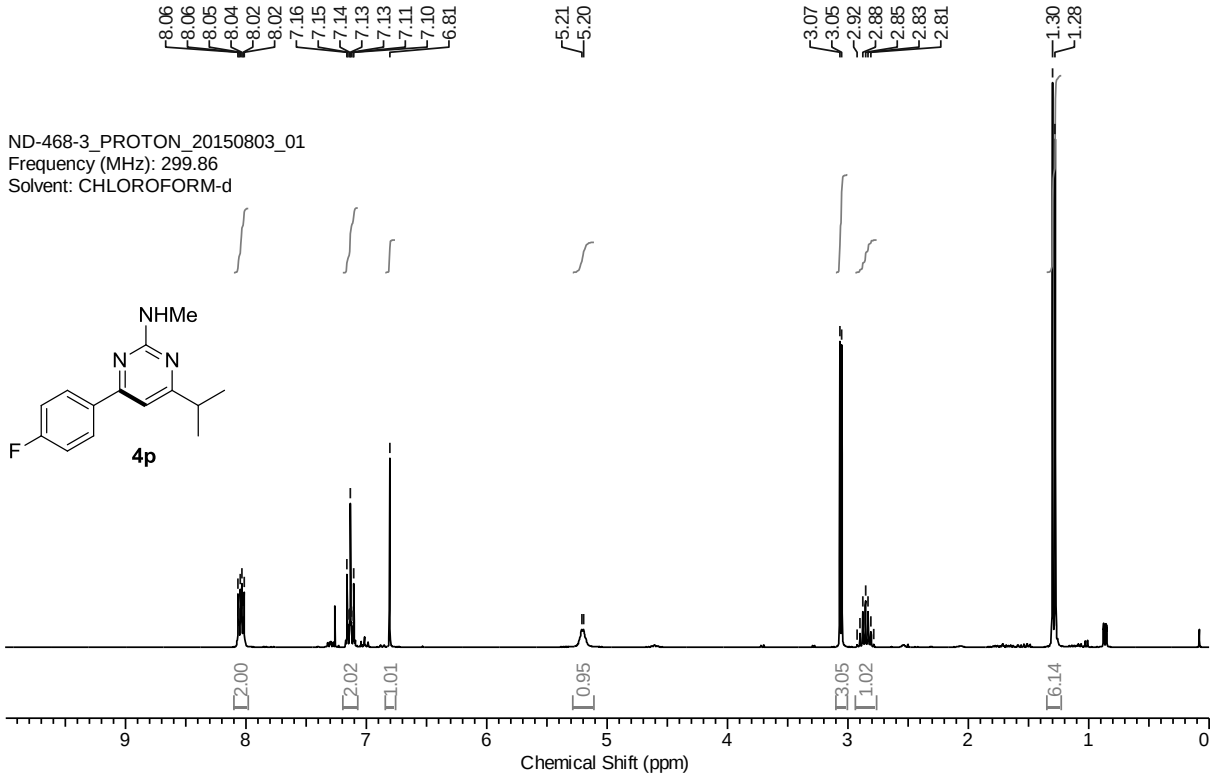

164.7
164.5
164.3
162.0
145.9
138.0
130.7
130.2
128.9
128.7
128.6
127.4
114.4
109.3
55.6
35.8
33.7
22.5
14.1
ND-466-5.021.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
N
N
Ph
PMP
4m
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

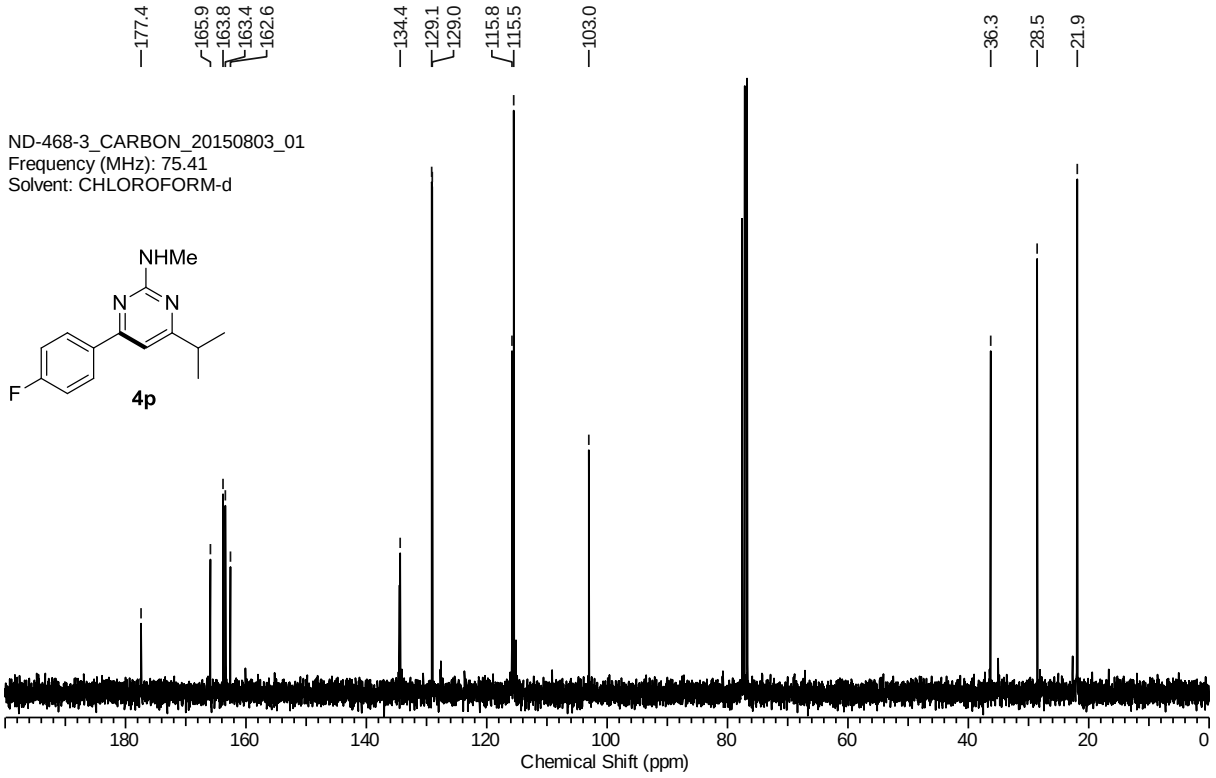

8.71
8.69
8.30
8.29
8.29
8.28
7.96
7.57
7.56
7.55
7.55
7.54
7.54
7.53
7.07
7.05
3.91
ND-466-3.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
PMP
N
N
Ph
Ph
4n
2.00
3.99
1.02
6.01
2.05
3.08
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


164.8
164.4
162.0
137.8
131.1
130.8
130.3
129.0
127.4
113.9
109.8
55.5
ND-466-3.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
PMP
N
N
Ph
Ph
4n
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

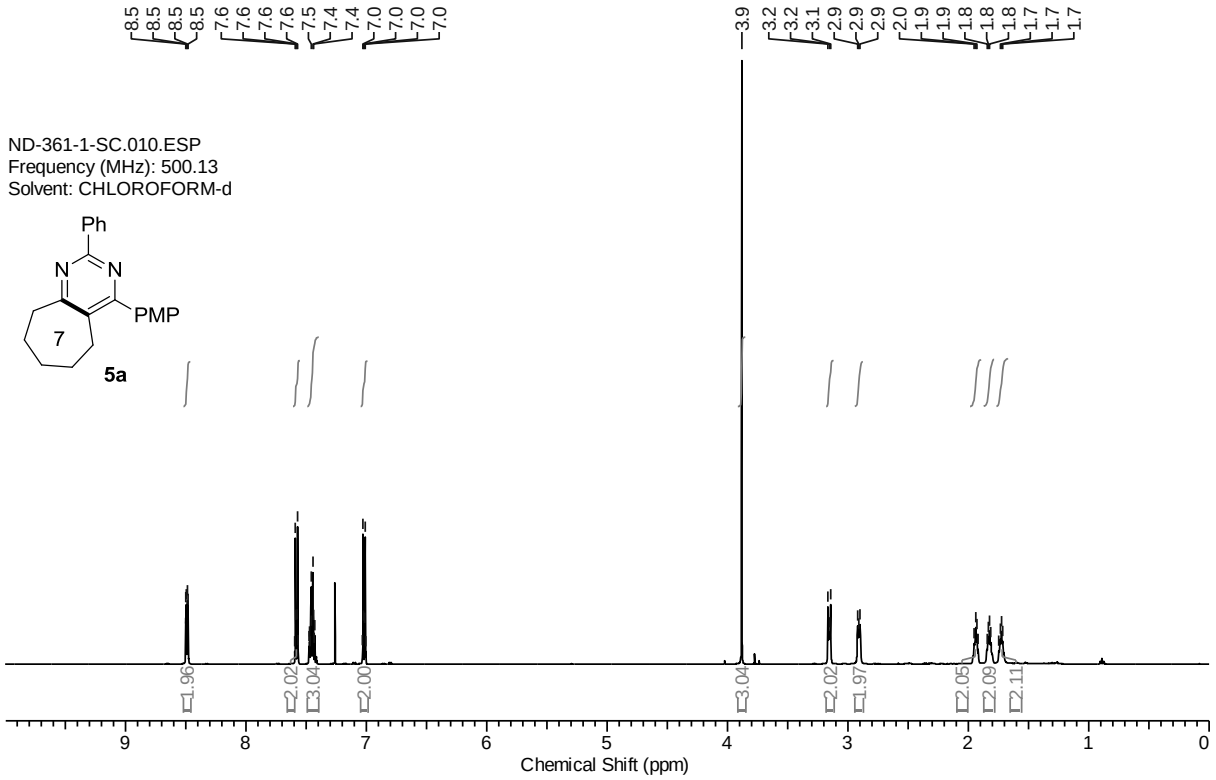

ND-458-5.010.001.1r.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
NH2
N
N
F
4o
2.02
1.99
1.01
2.06
1.00
2.94
3.18
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

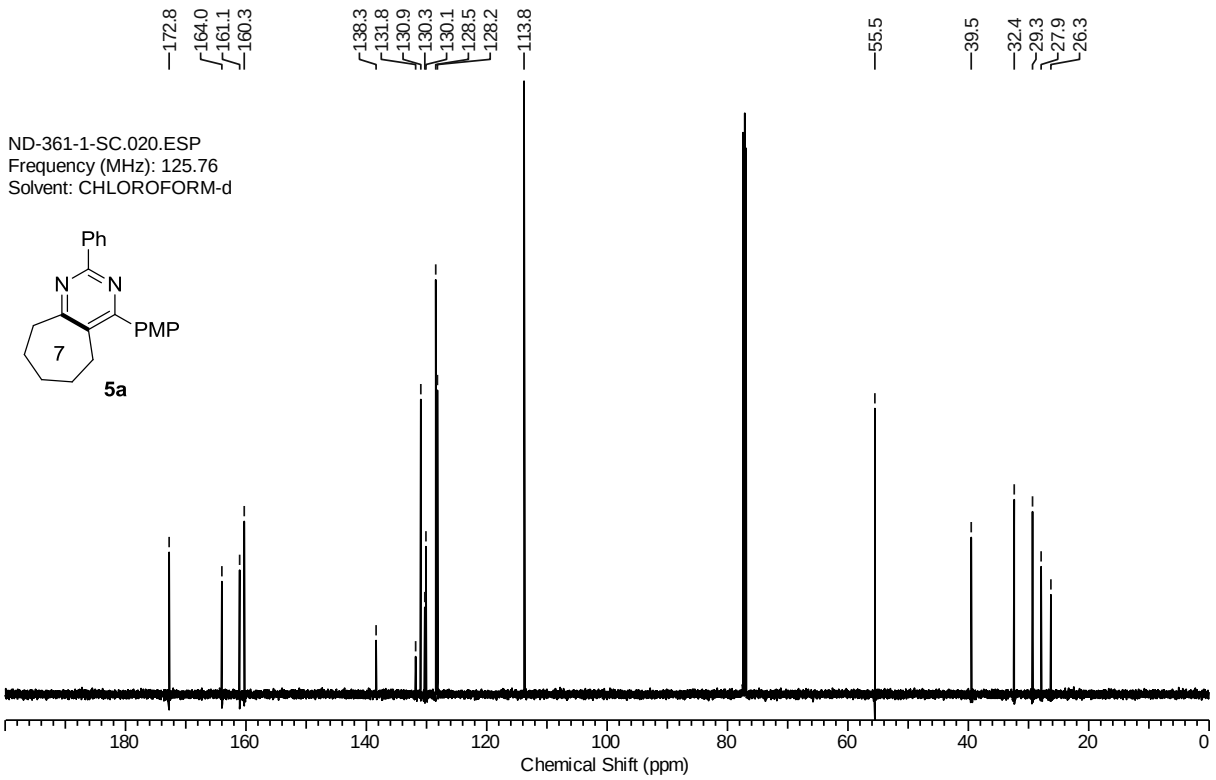

177.90
165.34
164.55
163.40
134.09
134.06
129.20
115.86
115.68
104.37
36.27
21.87
21.86
ND-458-5.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
NH2
N
N
F
4o
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

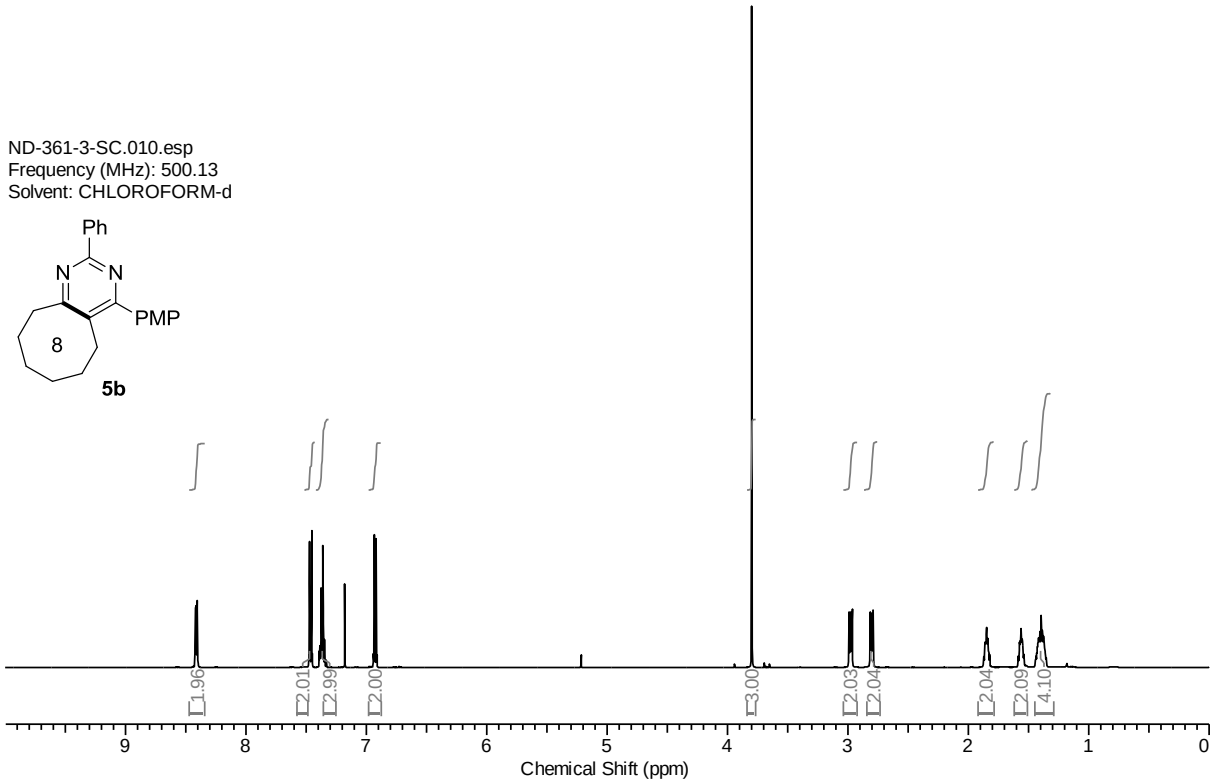

8.06
8.06
8.05
8.04
8.02
8.02
7.16
7.15
7.14
7.13
7.13
7.11
7.10
6.81
5.21
5.20
3.07
3.05
2.92
2.88
2.85
2.83
2.81
1.30
1.28
ND-468-3_PROTON_20150803_01
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
NHMe
N
N
F
4p
2.00
2.02
1.01
0.95
3.05
1.02
6.14
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

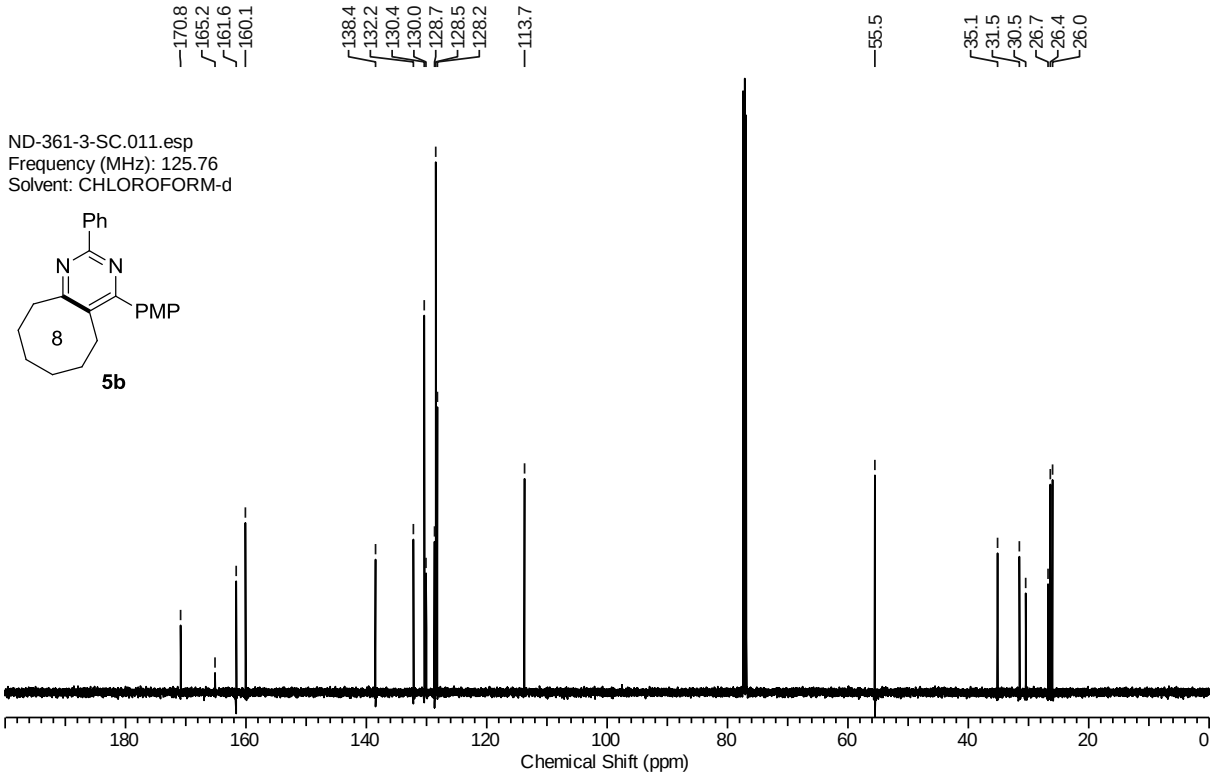

177.4
165.9
163.8
163.4
162.6
134.4
129.1
129.0
115.8
115.5
103.0
36.3
28.5
21.9
ND-468-3_CARBON_20150803_01
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
NHMe
N
N
F
4p
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

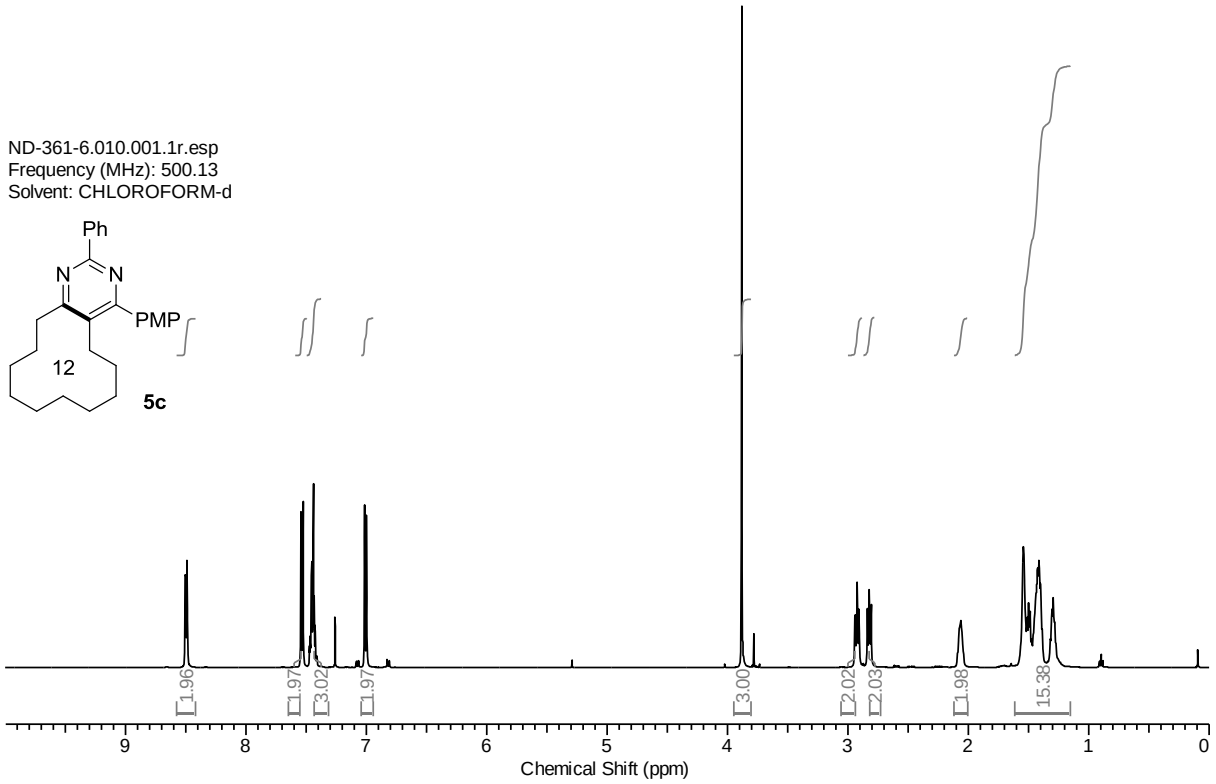
**3-component-reaction, $CH_2$-alkylation**

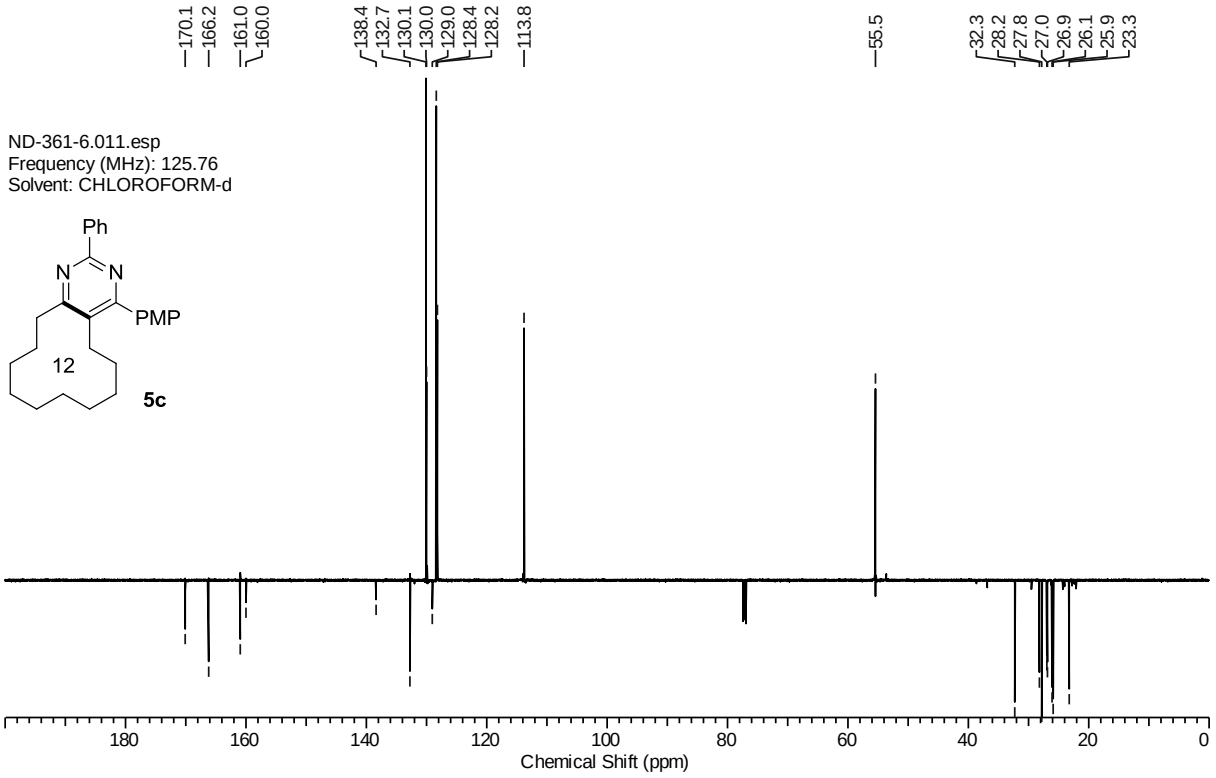


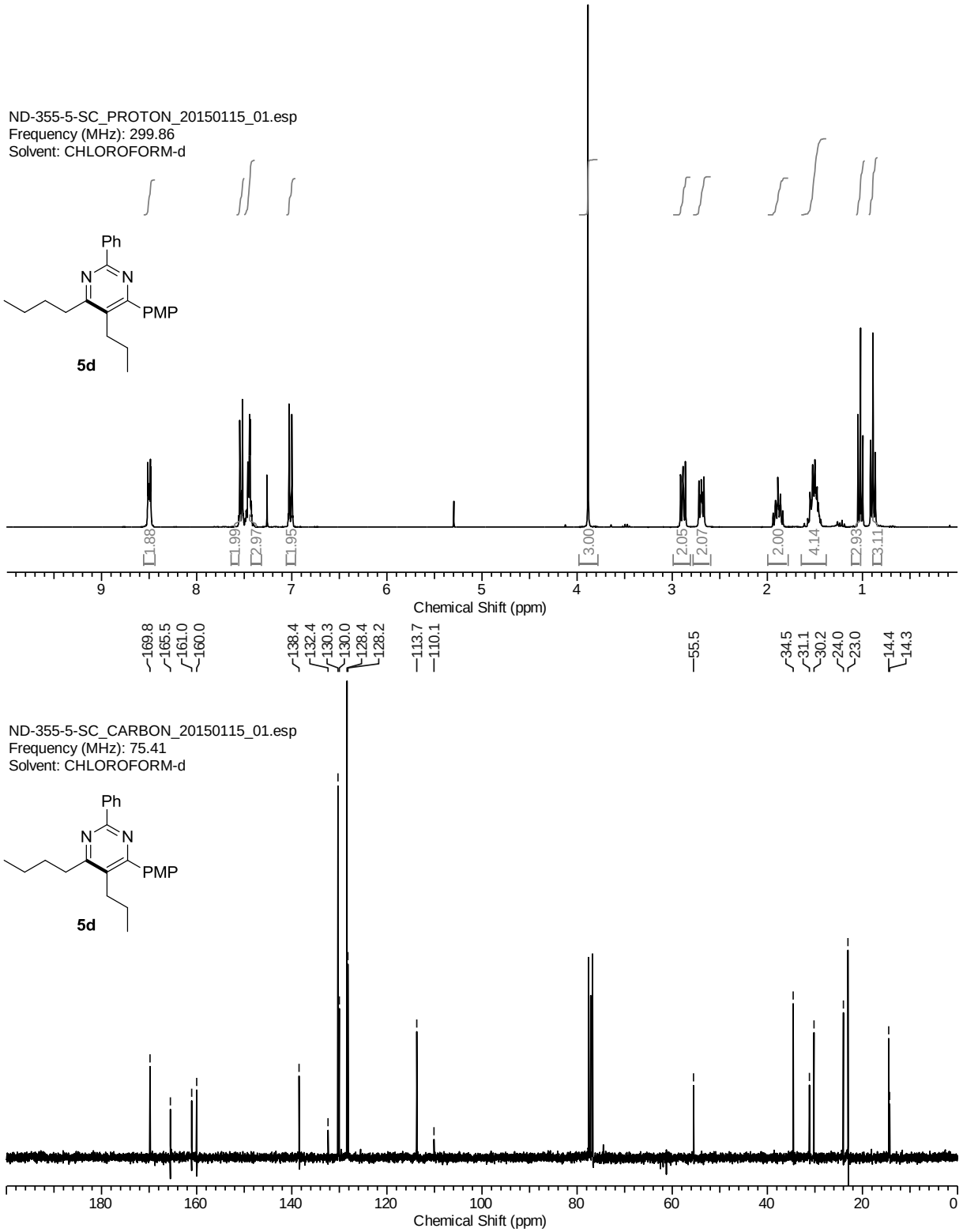



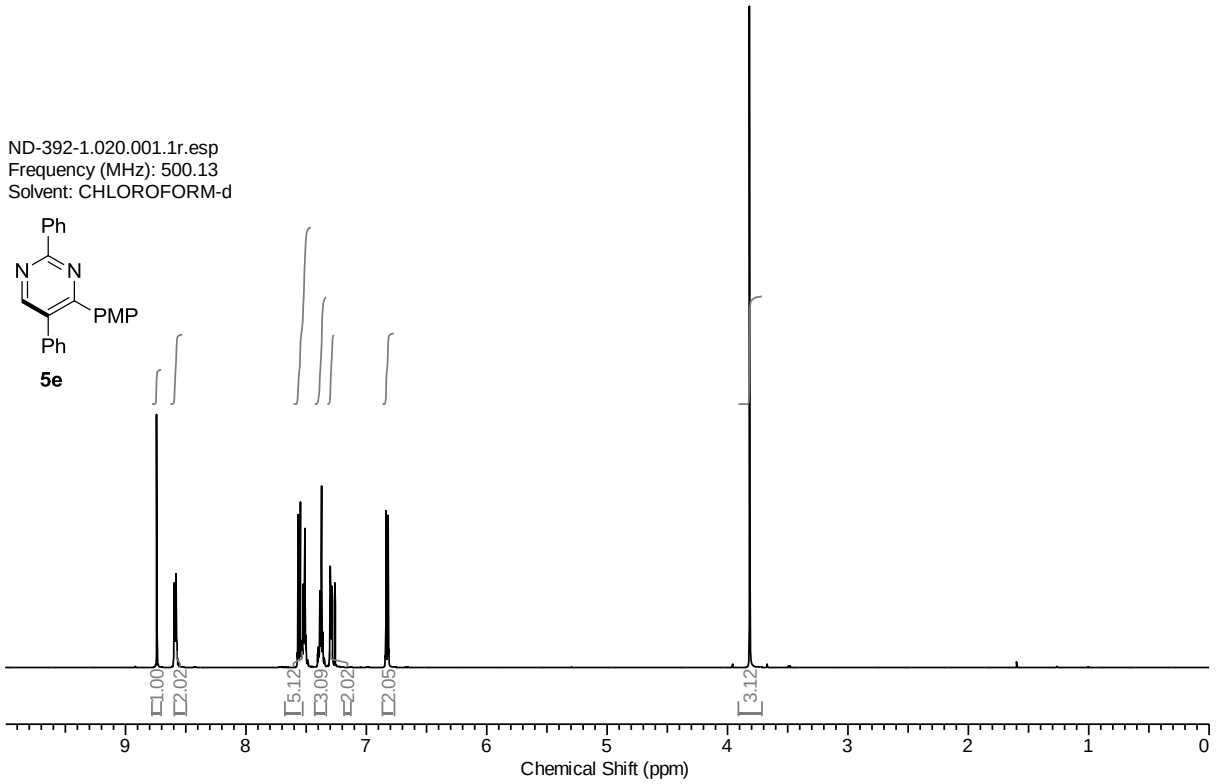

ND-361-3-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
8
5b
1.96
2.01
2.99
2.00
3.00
2.03
2.04
2.04
2.09
4.10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

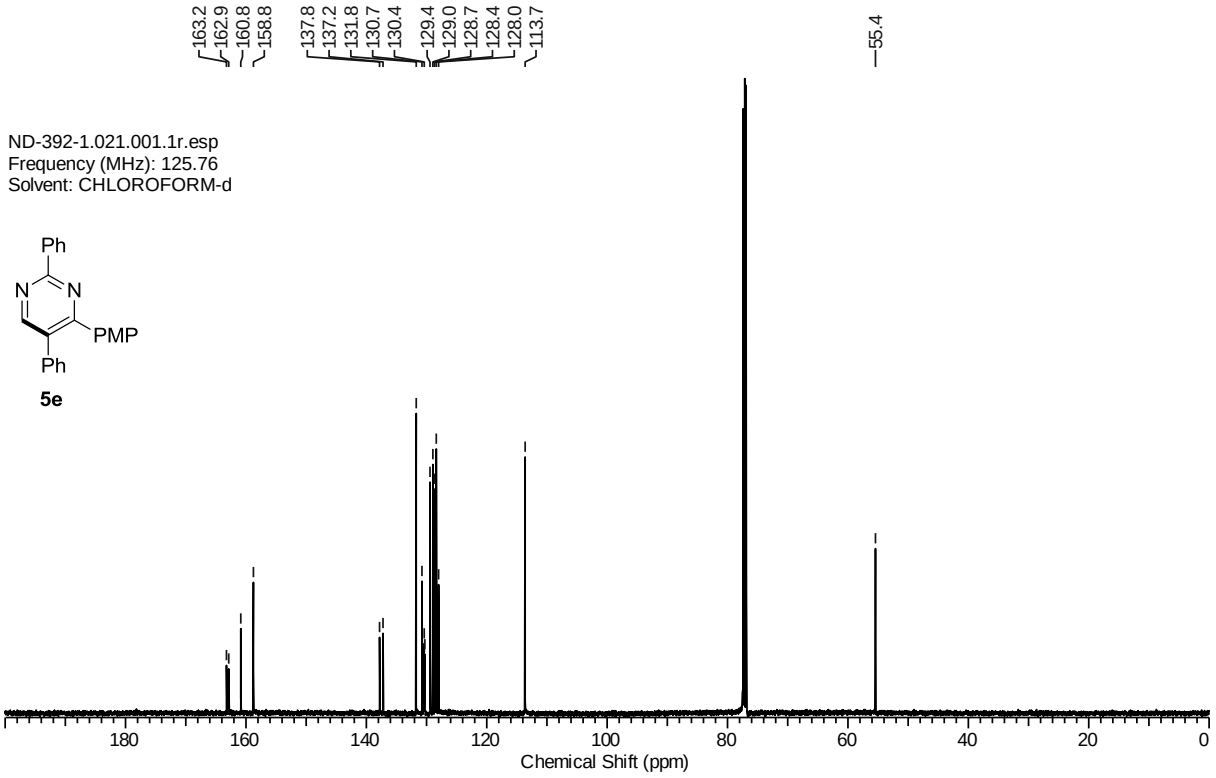

170.8
165.2
161.6
160.1
138.4
132.2
130.4
130.0
128.7
128.5
128.2
113.7
55.5
35.1
31.5
30.5
26.7
26.4
26.0
ND-361-3-SC.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
8
5b
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

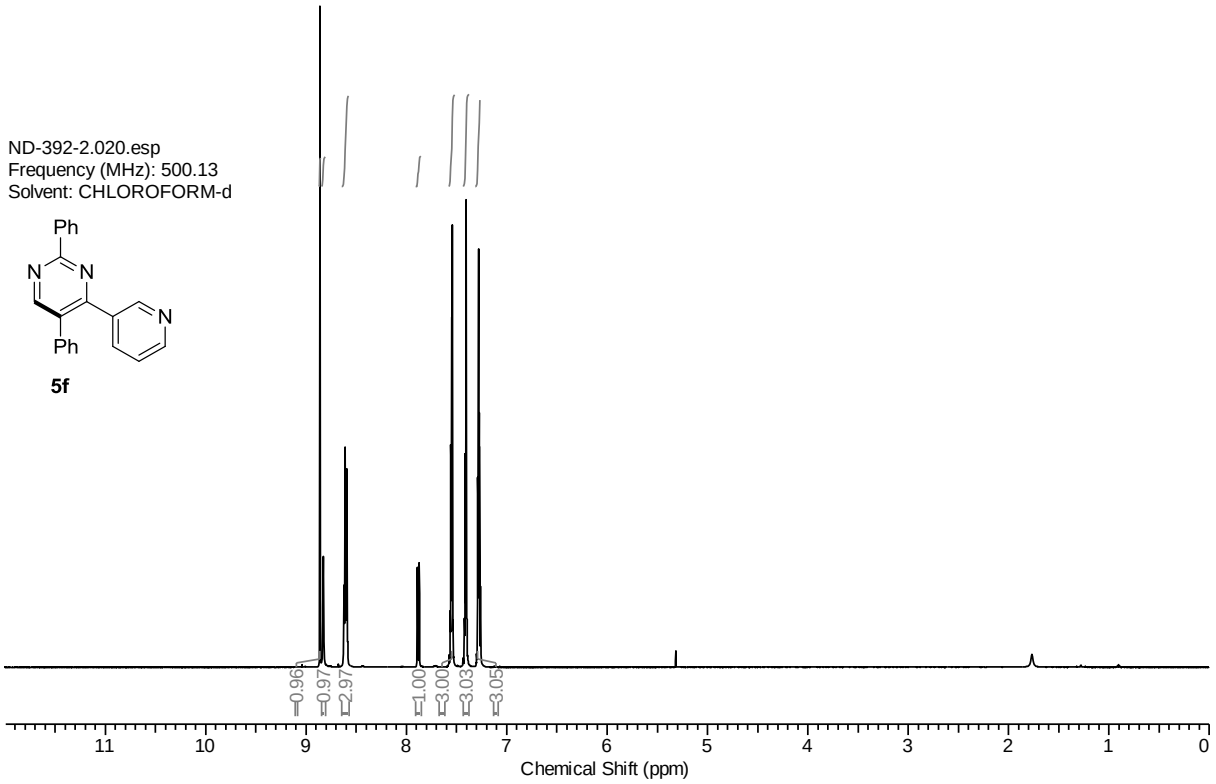

ND-361-6.010.001.1r.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
12
5c
1.96
1.97
3.02
1.97
3.00
2.02
2.03
1.98
15.38
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

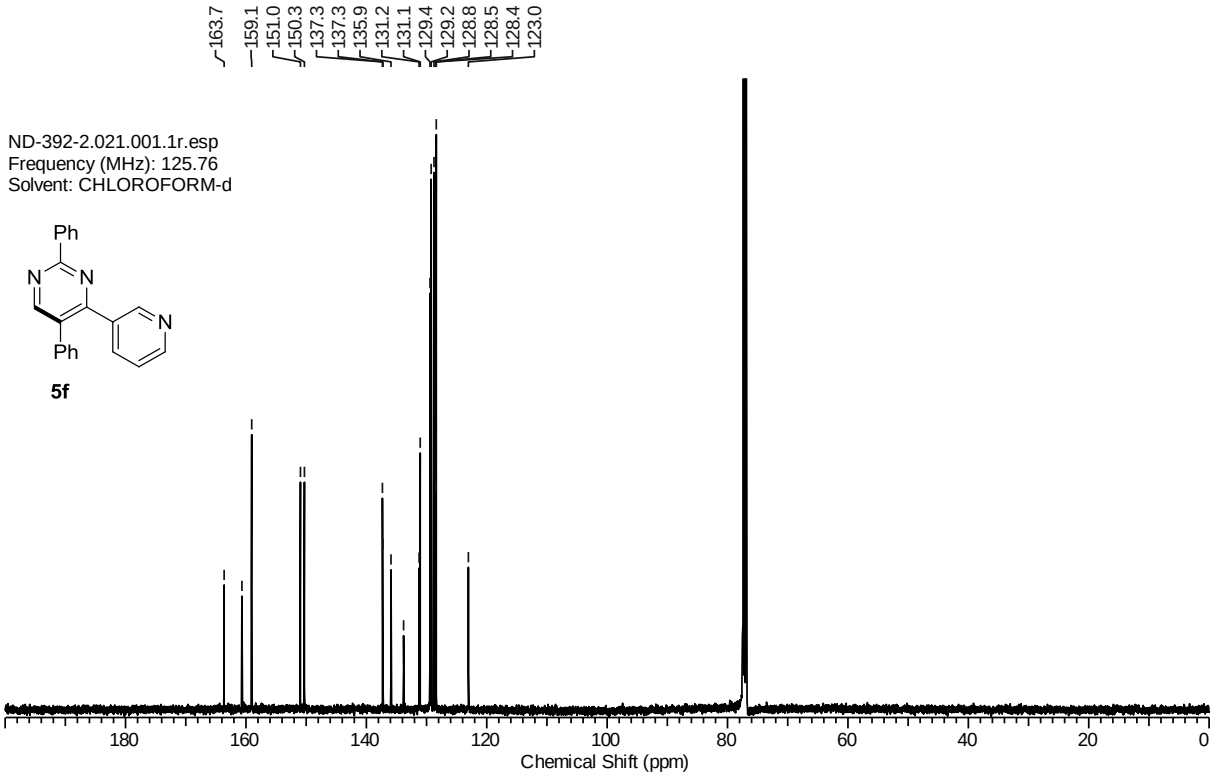

170.1
166.2
161.0
160.0
138.4
132.7
130.1
130.0
129.0
128.4
128.2
113.8
55.5
32.3
28.2
27.8
27.0
26.9
26.1
25.9
23.3
ND-361-6.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
12
5c
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

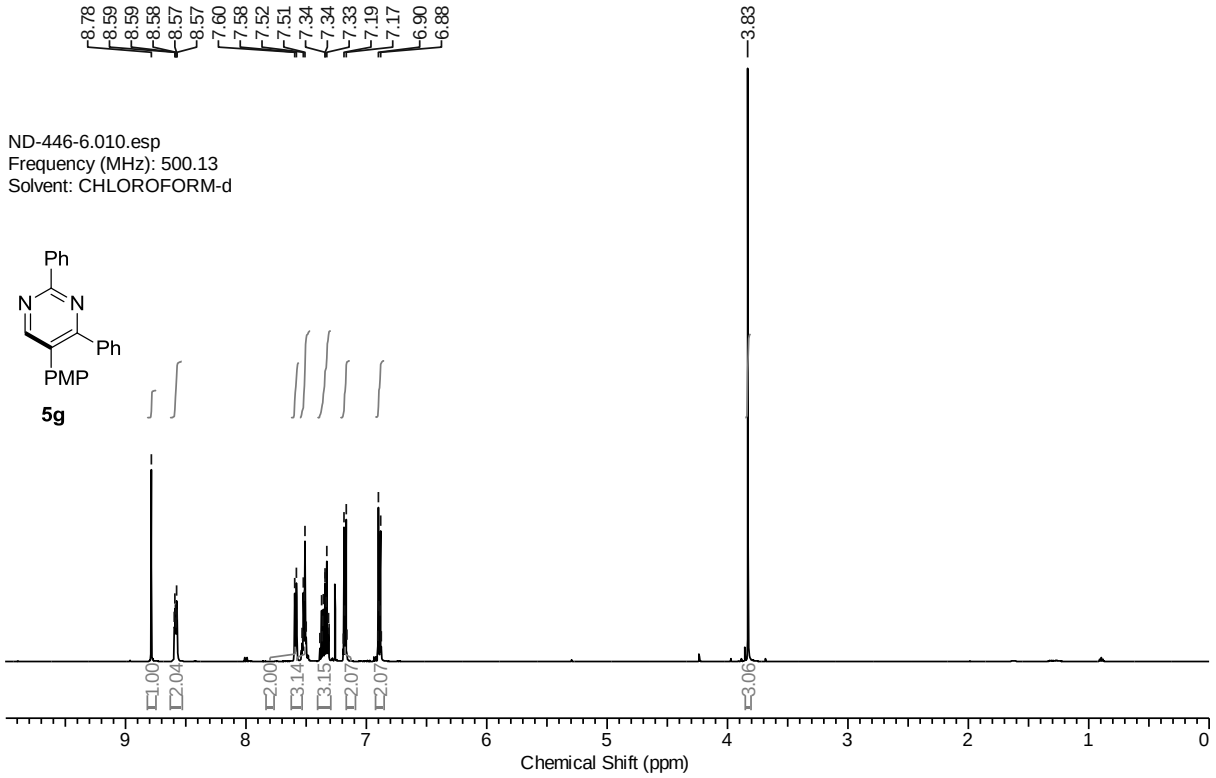

ND-355-5-SC_PROTON_20150115_01.esp
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
Ph
N
N
PMP
5d
1.88
1.99
2.97
1.95
3.00
2.05
2.07
2.00
4.14
2.93
3.11
Chemical Shift (ppm)
169.8
165.5
161.0
160.0
138.4
132.4
130.3
130.0
128.4
128.2
113.7
110.1
55.5
34.5
31.1
30.2
24.0
23.0
14.4
14.3
ND-355-5-SC_CARBON_20150115_01.esp
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
Chemical Shift (ppm)

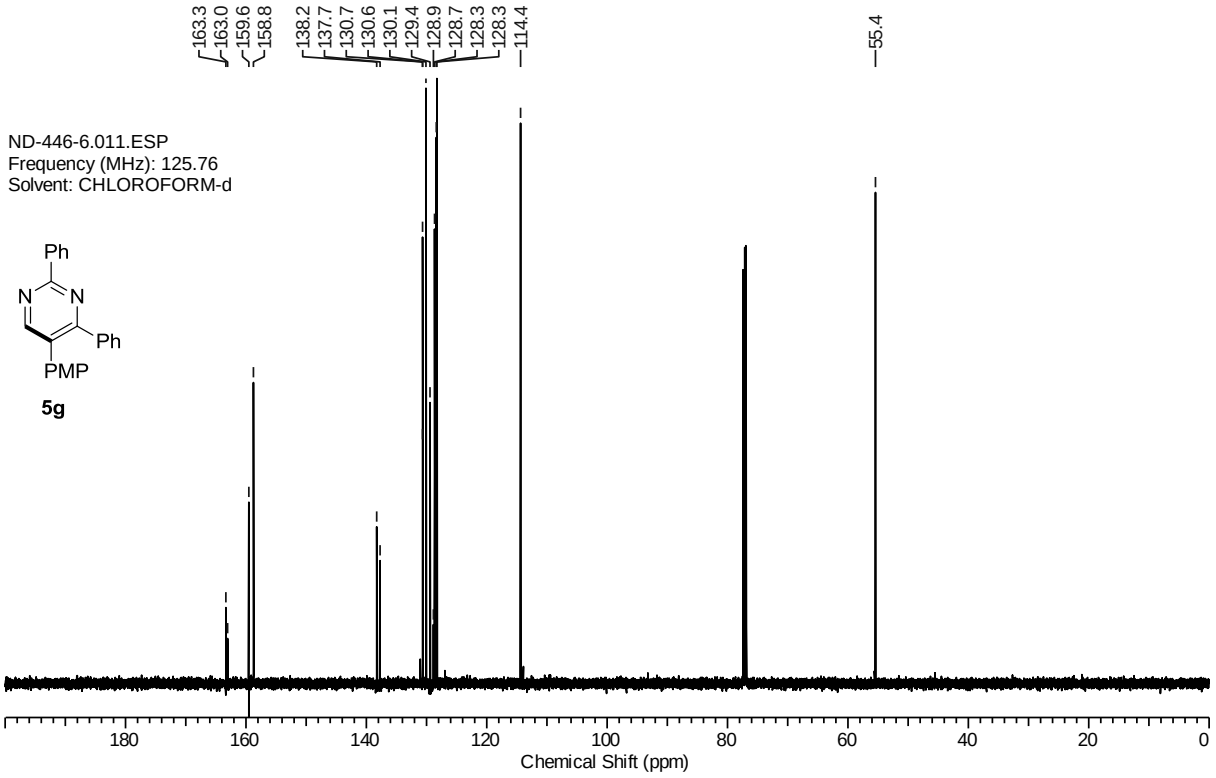

ND-392-1.020.001.1r.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
Ph
5e
1.00
2.02
5.12
3.09
2.02
2.05
3.12
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

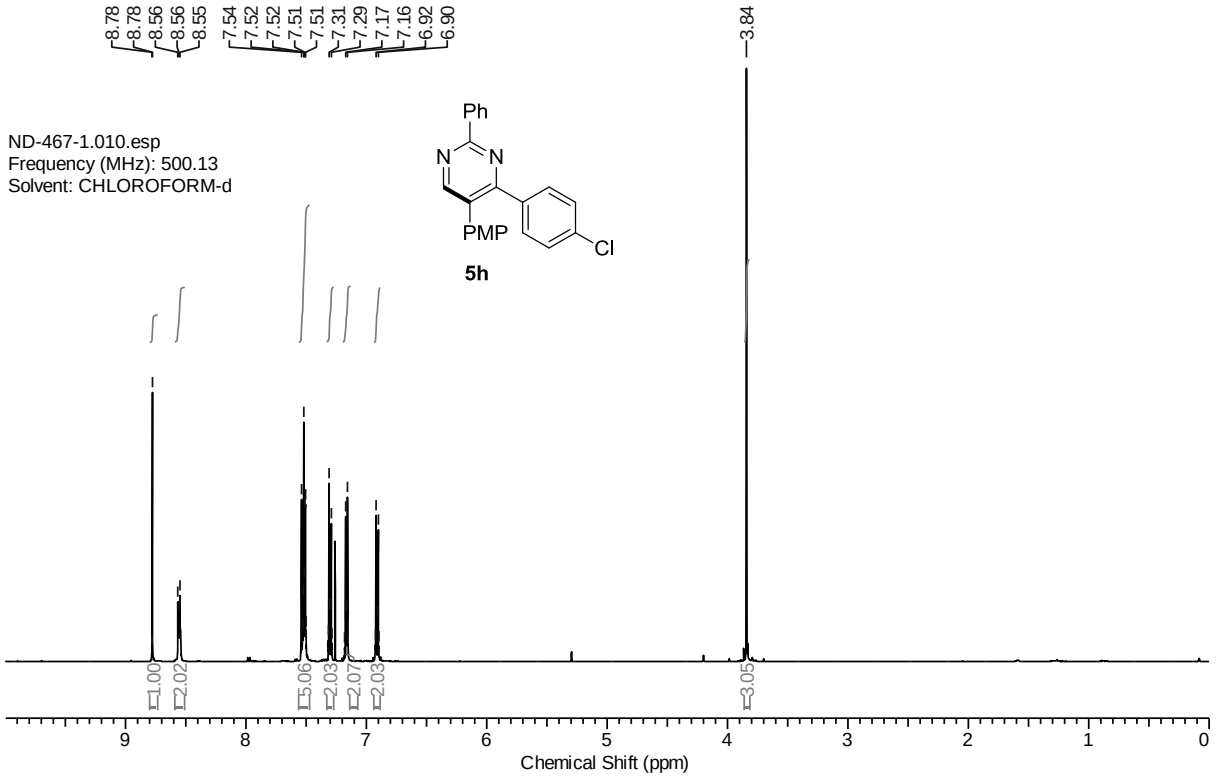

163.2
162.9
160.8
158.8
137.8
137.2
131.8
130.7
130.4
129.4
129.0
128.7
128.4
128.0
113.7
55.4
ND-392-1.021.001.1r.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
Ph
5e
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

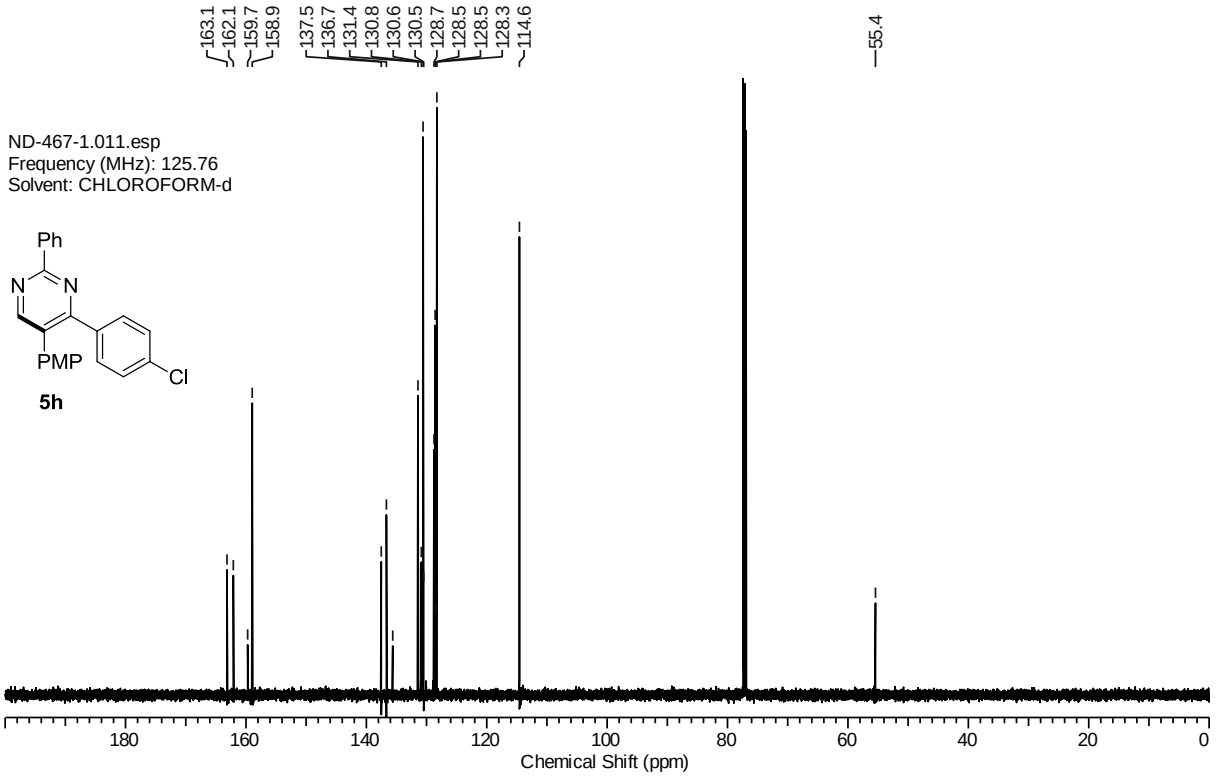

ND-392-2.020.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
N
Ph
5f
0.96
0.97
2.97
1.00
3.00
3.03
3.05
11
10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


163.7
159.1
151.0
150.3
137.3
137.3
135.9
131.2
131.1
129.4
129.2
128.8
128.5
128.4
123.0
ND-392-2.021.001.1r.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
N
Ph
5f
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

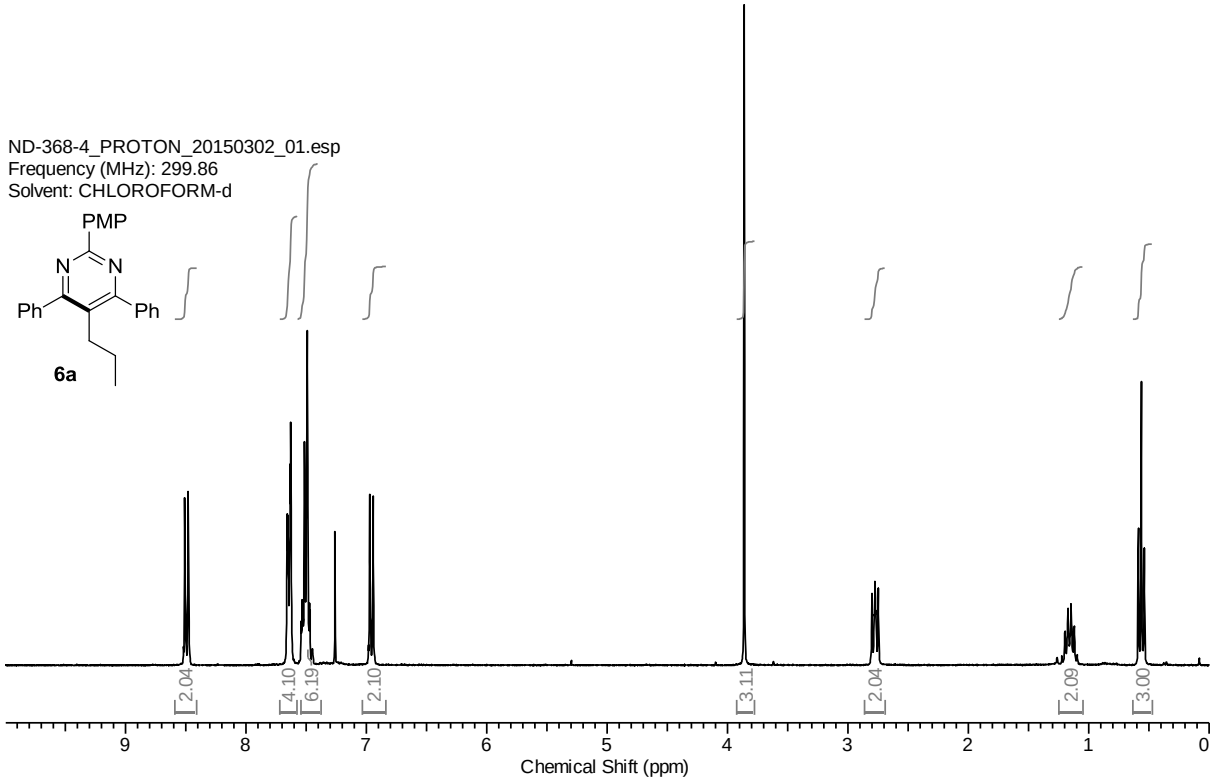

8.78
8.59
8.59
8.58
8.57
8.57
7.60
7.58
7.52
7.51
7.34
7.34
7.33
7.19
7.17
6.90
6.88
3.83
ND-446-6.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
5g
1.00
2.04
2.00
3.14
3.15
2.07
2.07
3.06
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

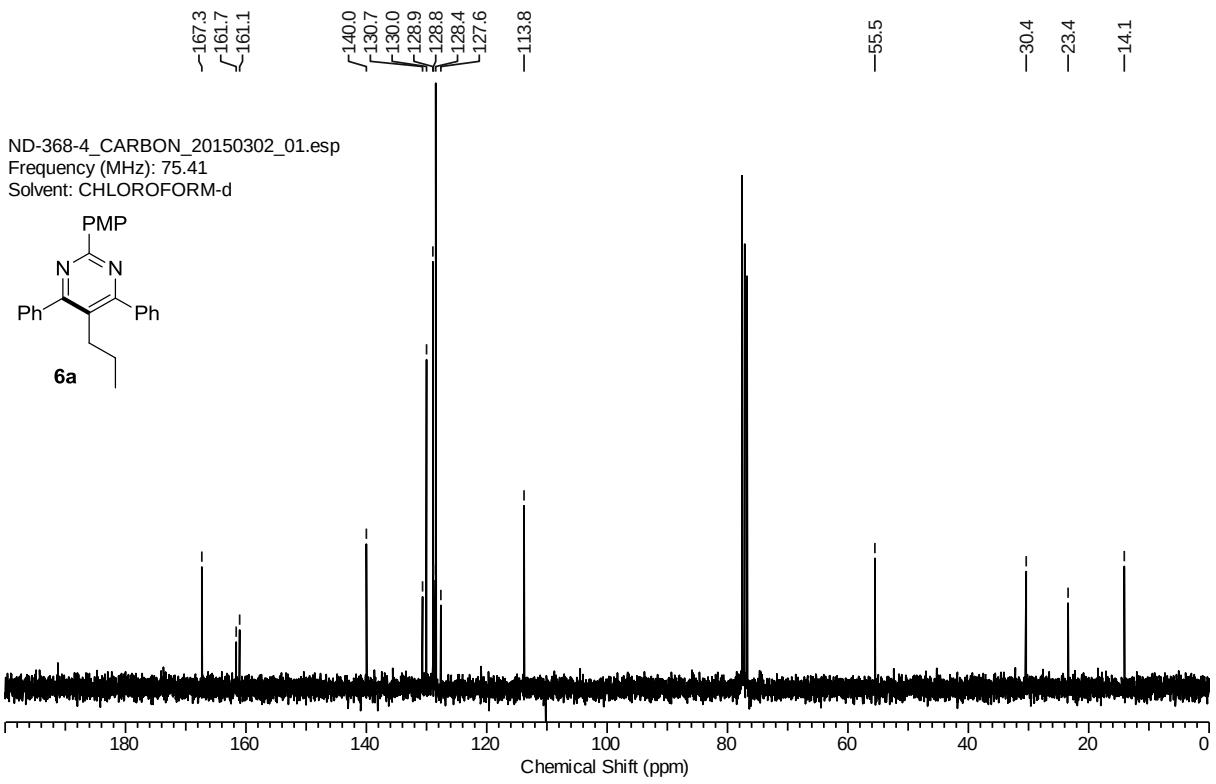

163.3
163.0
159.6
158.8
138.2
137.7
130.7
130.6
130.1
129.4
128.9
128.7
128.3
128.3
114.4
55.4
ND-446-6.011.ESP
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
5g
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

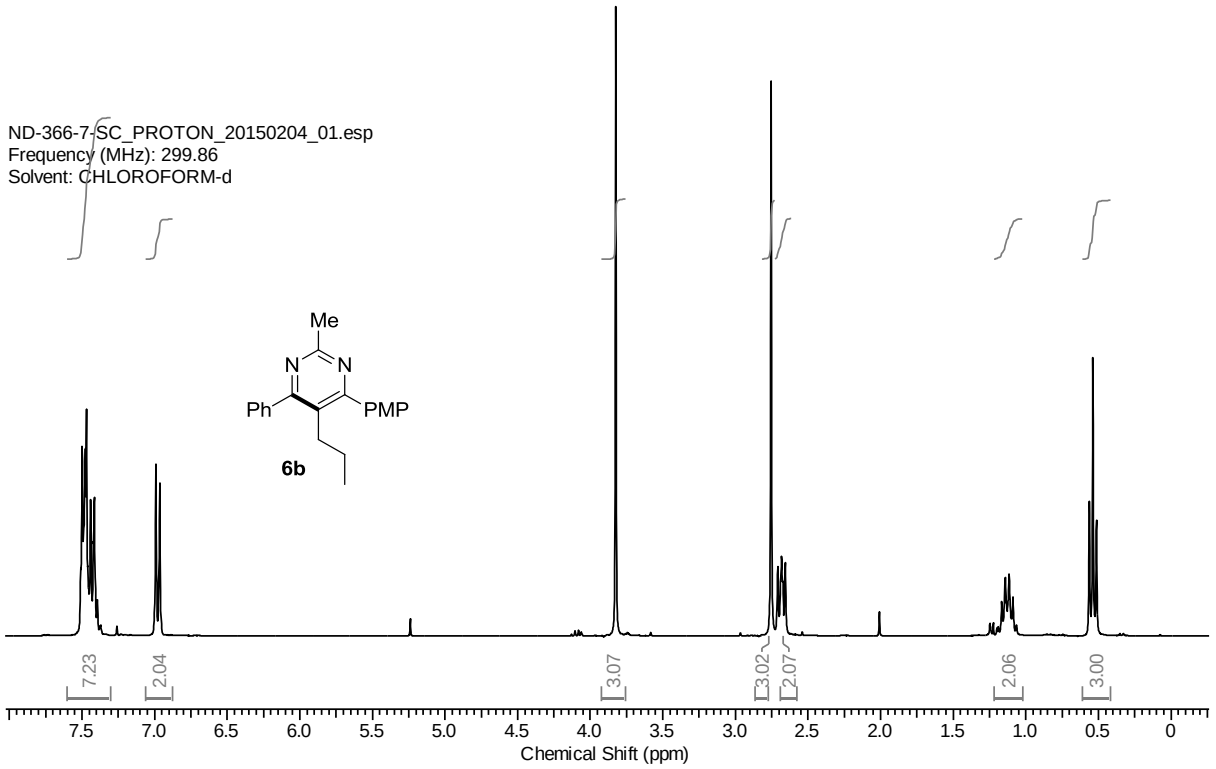

8.78
8.78
8.56
8.56
8.55
7.54
7.52
7.52
7.51
7.51
7.31
7.29
7.17
7.16
6.92
6.90
3.84
ND-467-1.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
Cl
5h
1.00
2.02
5.06
2.03
2.07
2.03
3.05
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

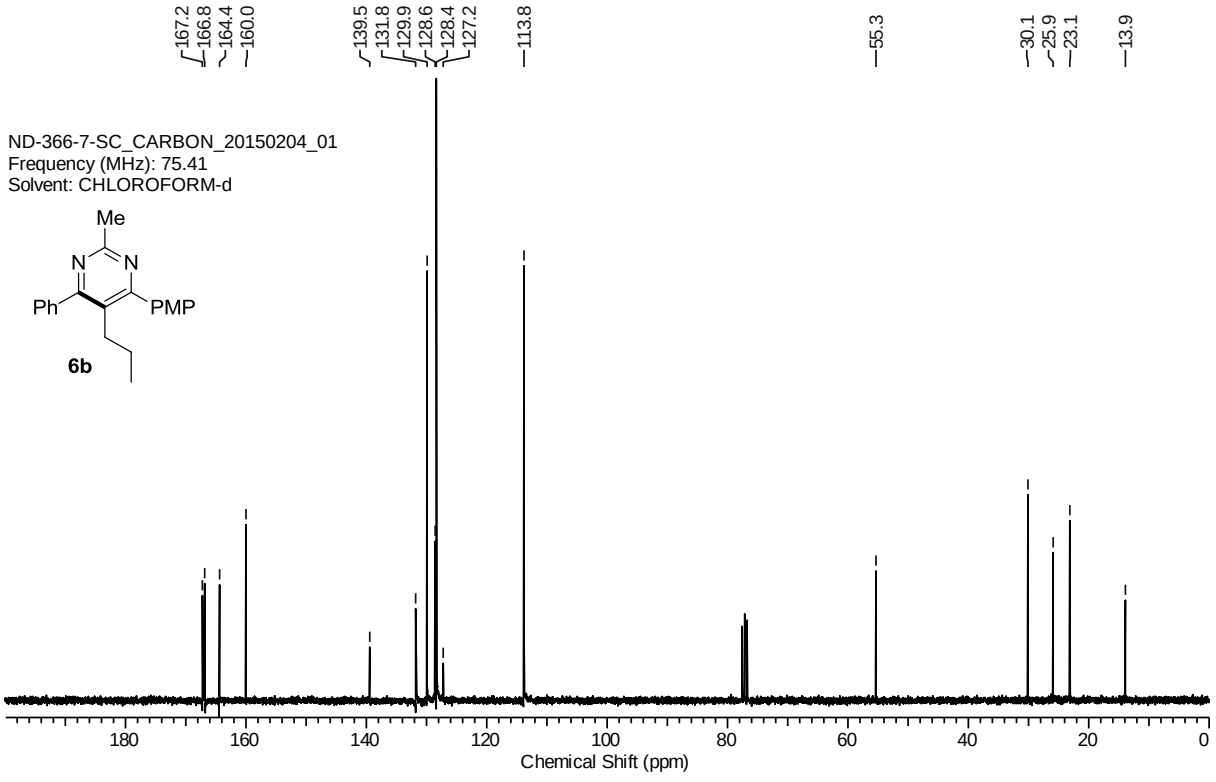

163.1
162.1
159.7
158.9
137.5
136.7
131.4
130.8
130.6
130.5
128.7
128.5
128.5
128.3
114.6
55.4
ND-467-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
Cl
5h
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

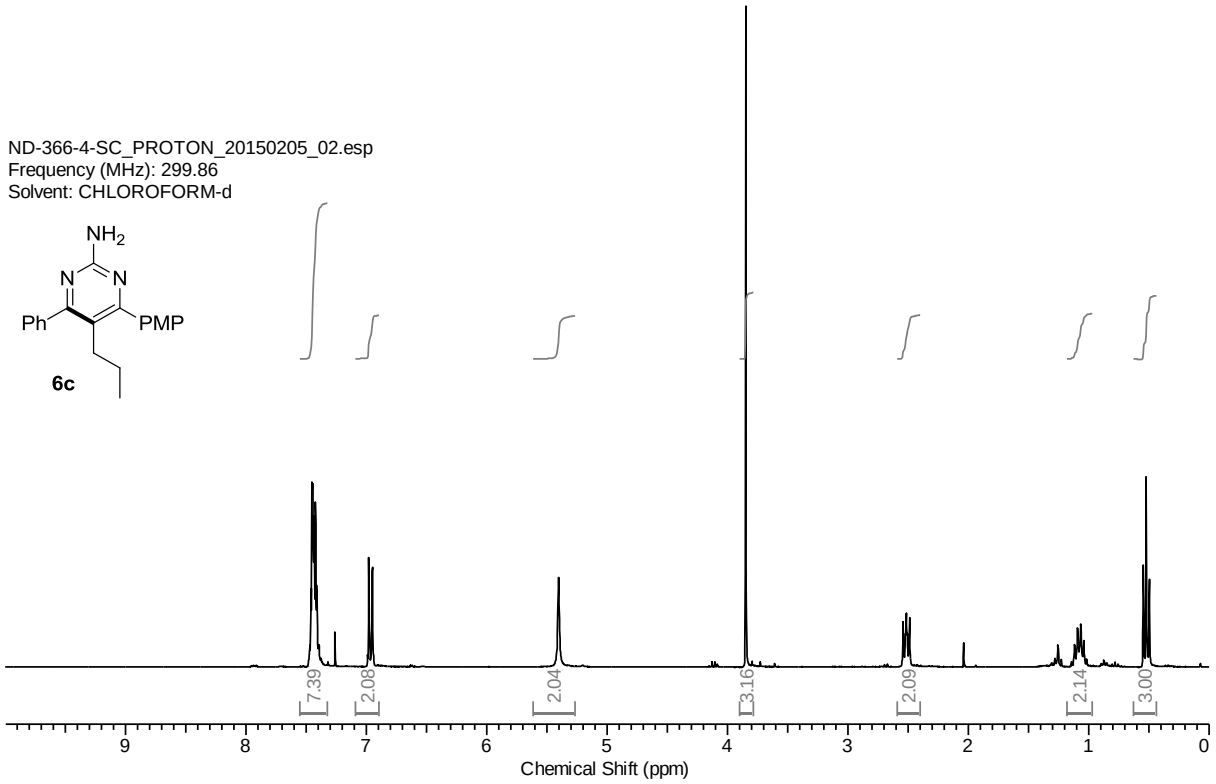
**Consecutive 4-component-reaction**

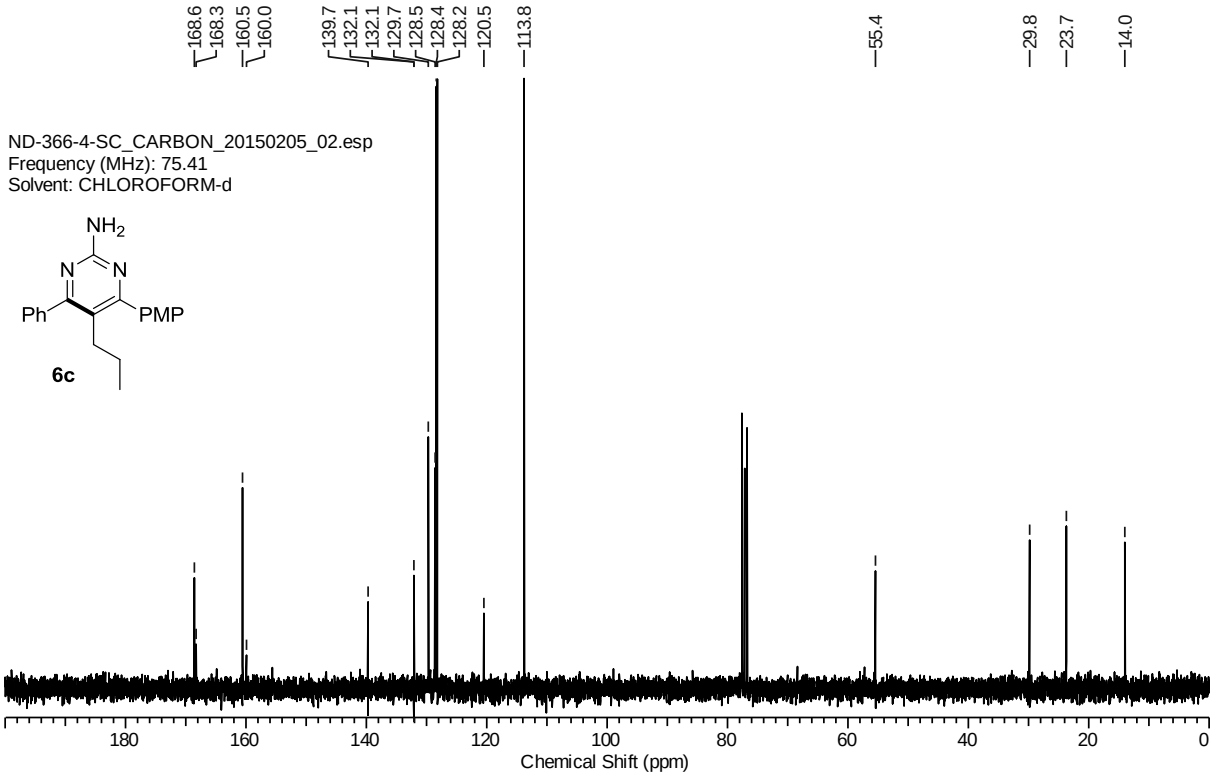


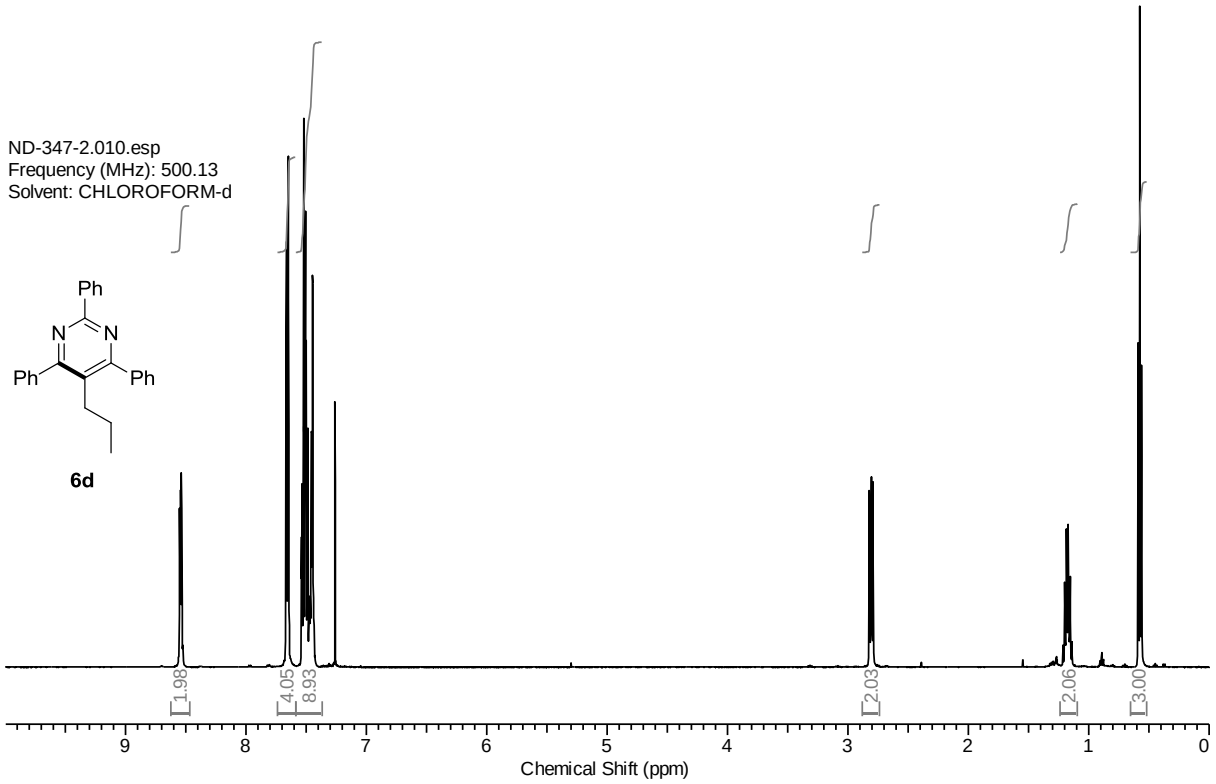



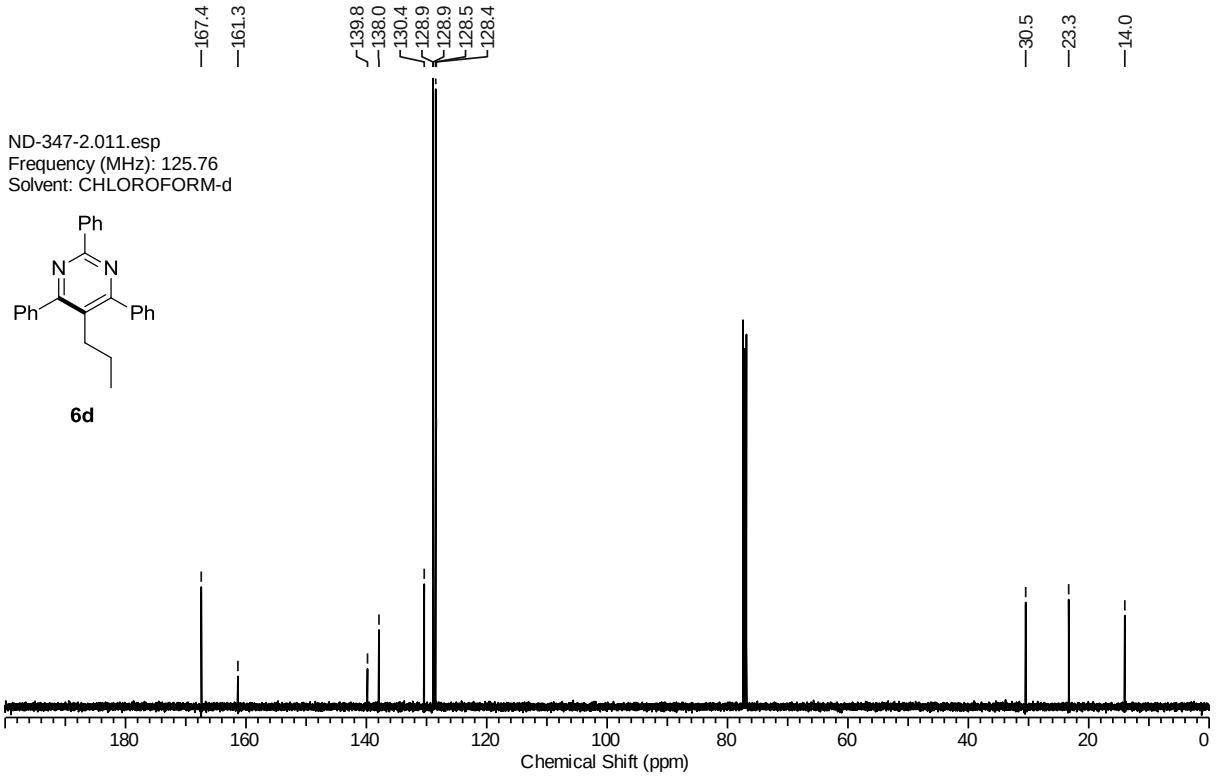

ND-366-7-SC_PROTON_20150204_01.esp
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
Me
N
N
Ph
PMP
6b
7.23
2.04
3.07
3.02
2.07
2.06
3.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)

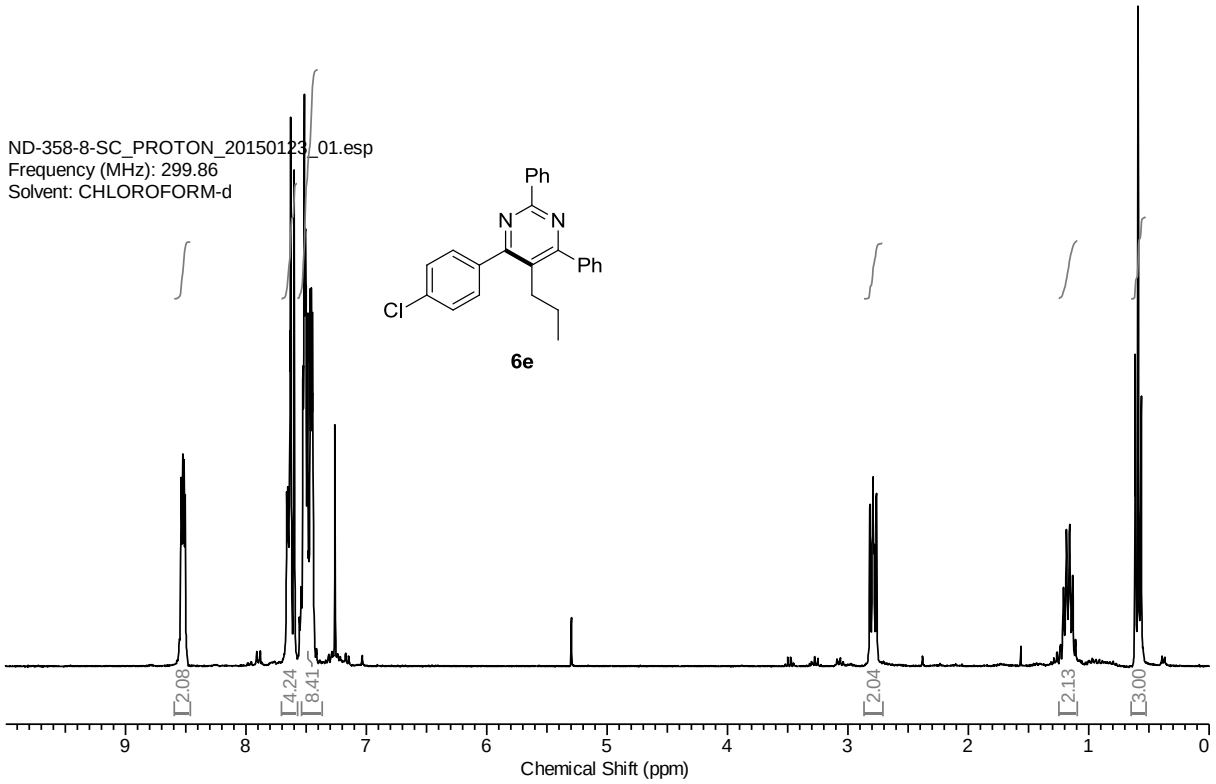

167.2
166.8
164.4
160.0
139.5
131.8
129.9
128.6
128.4
127.2
113.8
55.3
30.1
25.9
23.1
13.9
ND-366-7-SC_CARBON_20150204_01
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
Me
N
N
Ph
PMP
6b
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

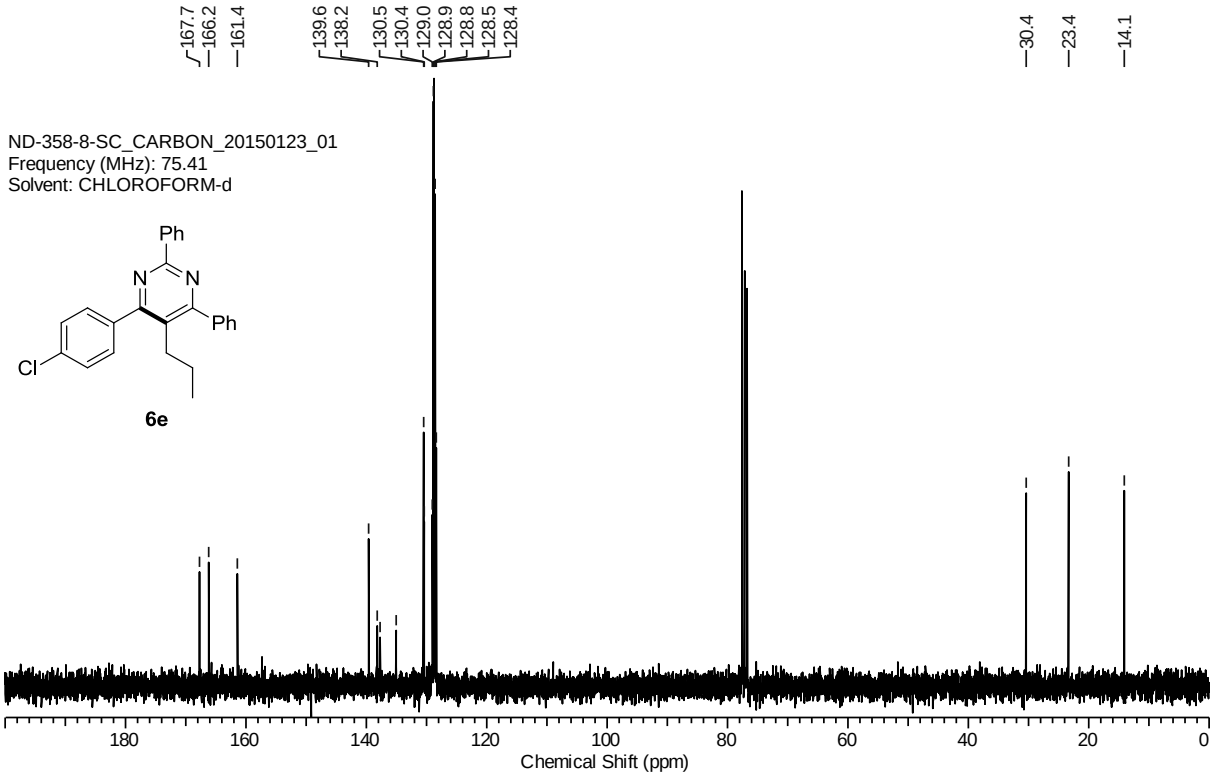

ND-366-4-SC_PROTON_20150205_02.esp
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
NH2
N
N
Ph
PMP
6c
7.39
2.08
2.04
3.16
2.09
2.14
3.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

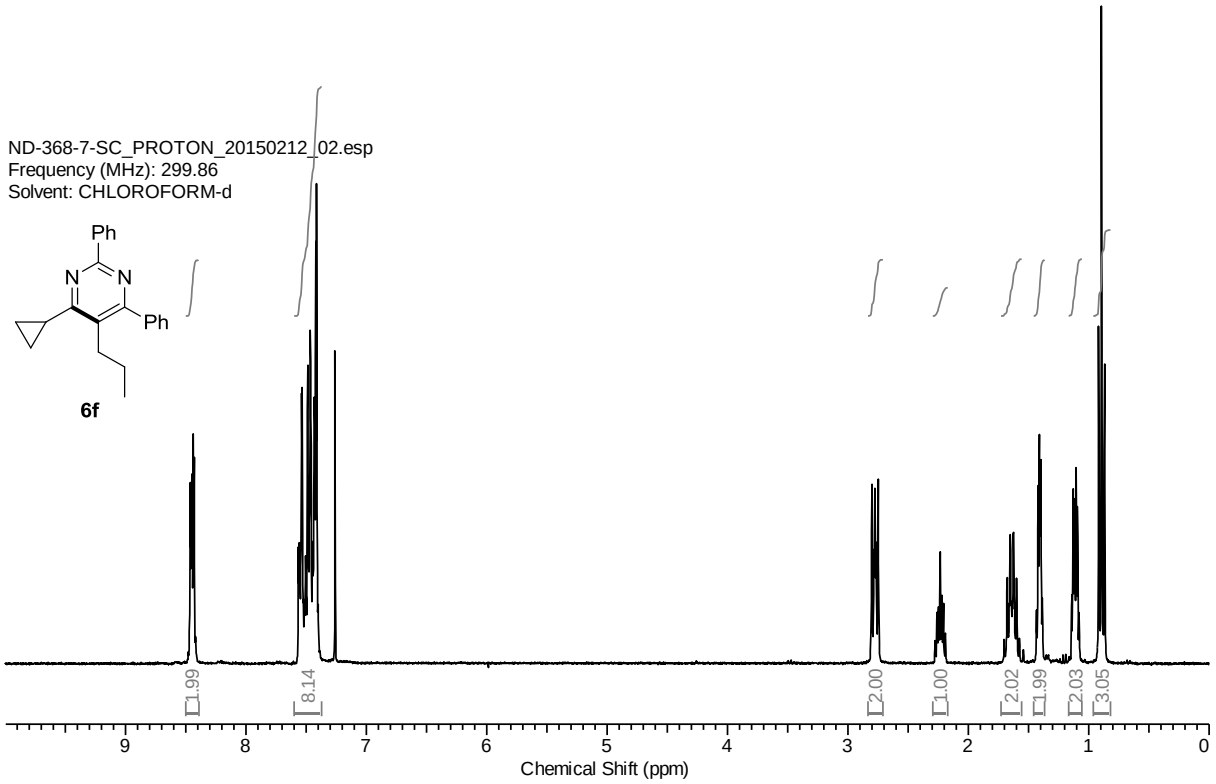

168.6
168.3
160.5
160.0
139.7
132.1
132.1
129.7
128.5
128.4
128.2
120.5
113.8
55.4
29.8
23.7
14.0
ND-366-4-SC_CARBON_20150205_02.esp
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
NH2
N
N
Ph
PMP
6c
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

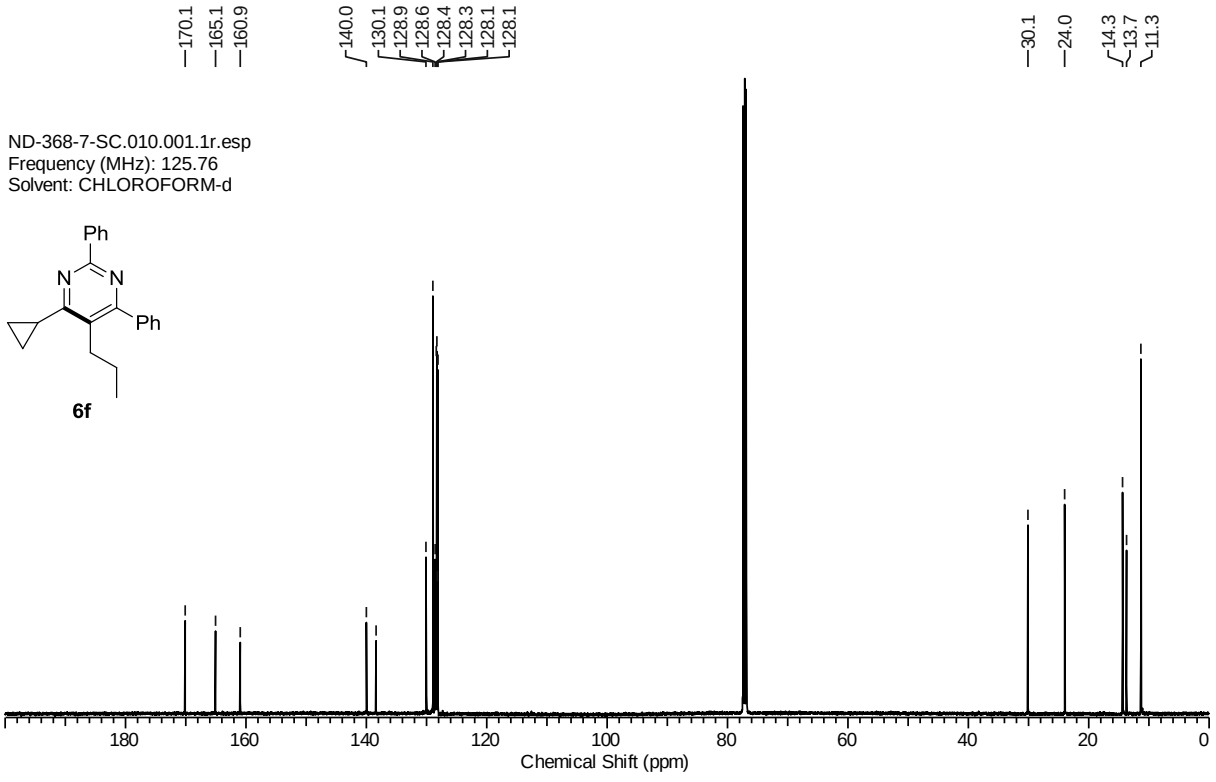

ND-347-2.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
Ph
Ph
6d
1.98
4.05
8.93
2.03
2.06
3.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

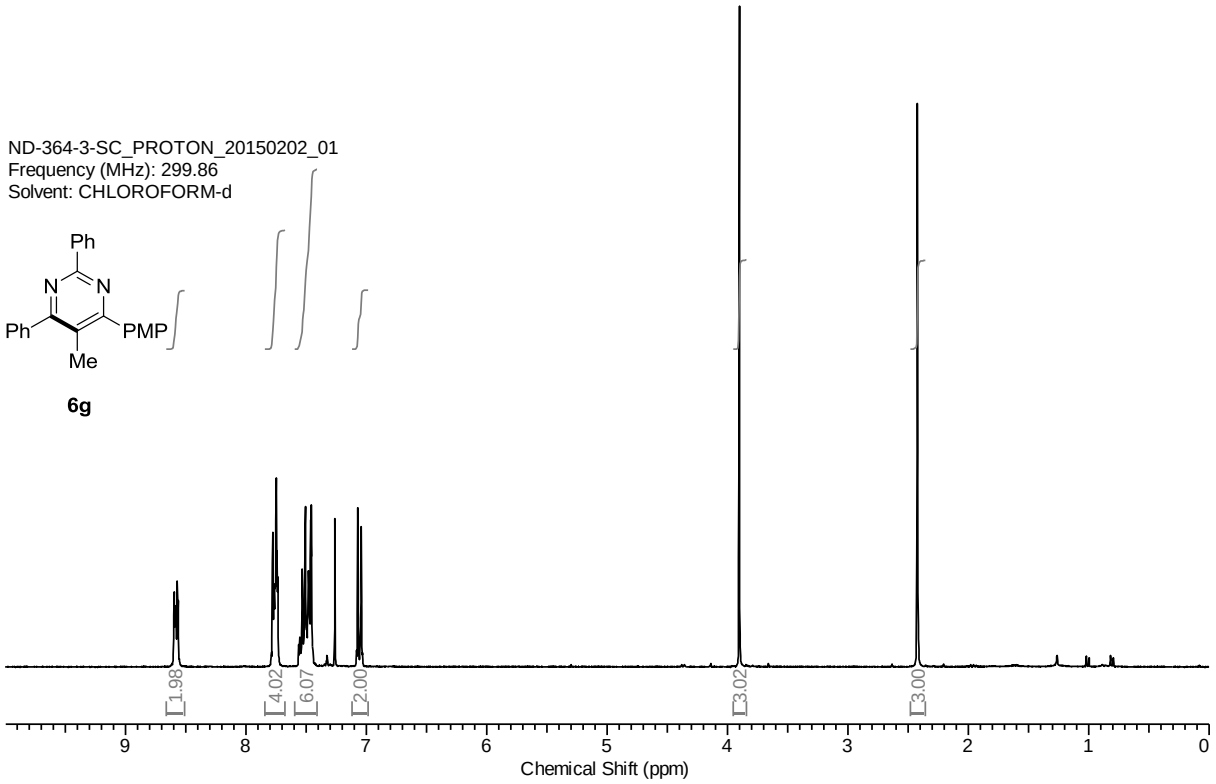

167.4
161.3
139.8
138.0
130.4
128.9
128.9
128.5
128.4
30.5
23.3
14.0
ND-347-2.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
Ph
6d
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

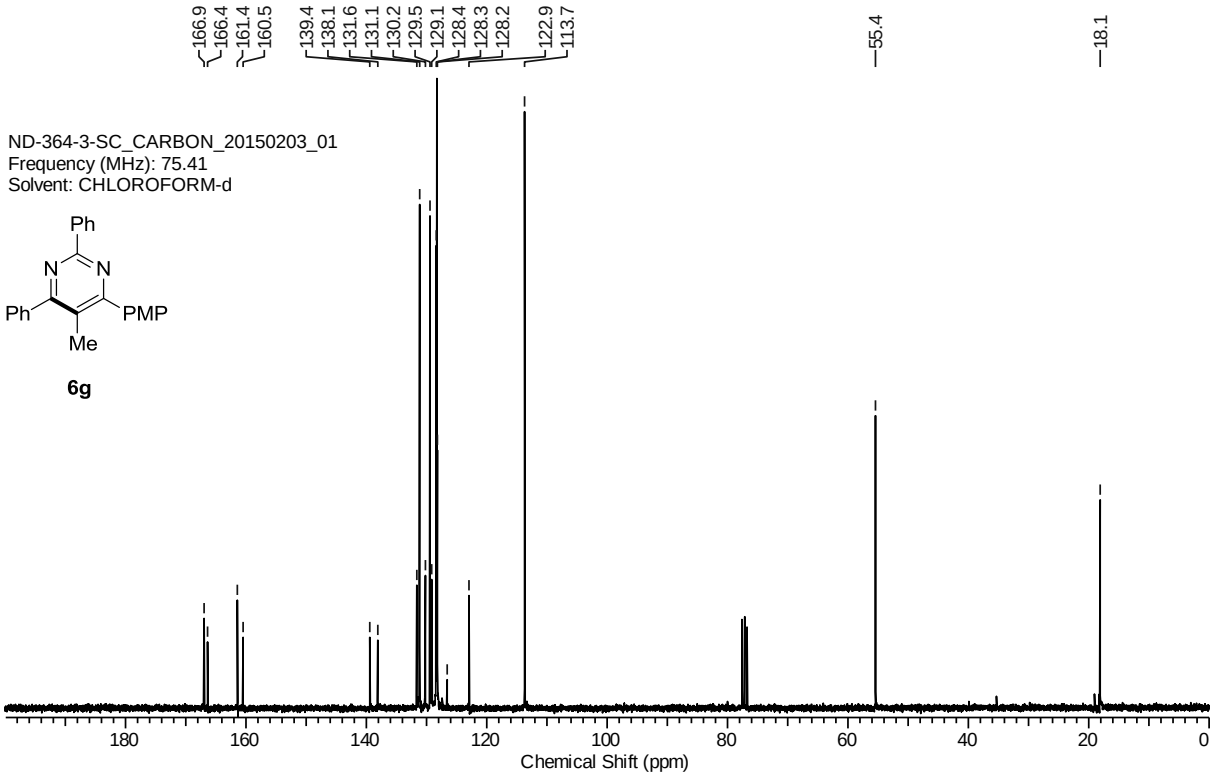

ND-358-8-SC_PROTON_20150123_01.esp
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
Ph
N
N
Ph
Cl
6e
2.08
4.24
8.41
2.04
2.13
3.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

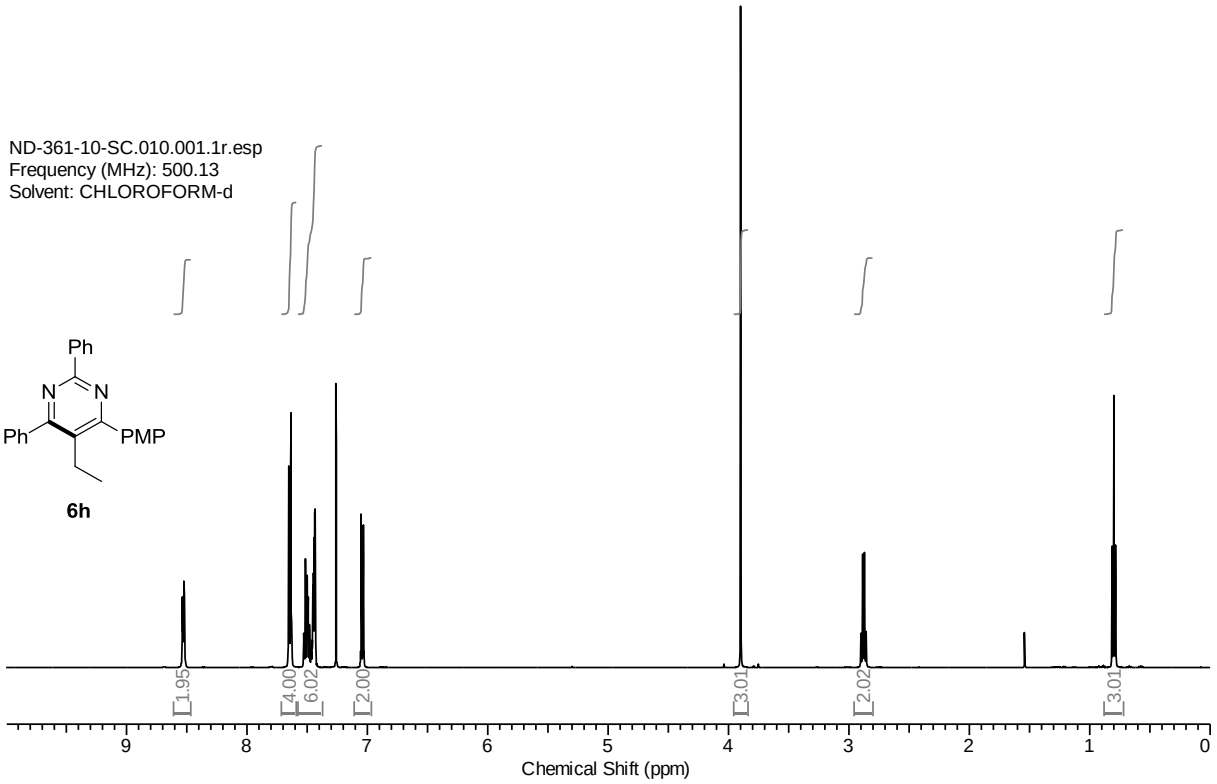

167.7
166.2
161.4
139.6
138.2
130.5
130.4
129.0
128.9
128.8
128.5
128.4
30.4
23.4
14.1
ND-358-8-SC_CARBON_20150123_01
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
Ph
N
N
Ph
Cl
6e
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

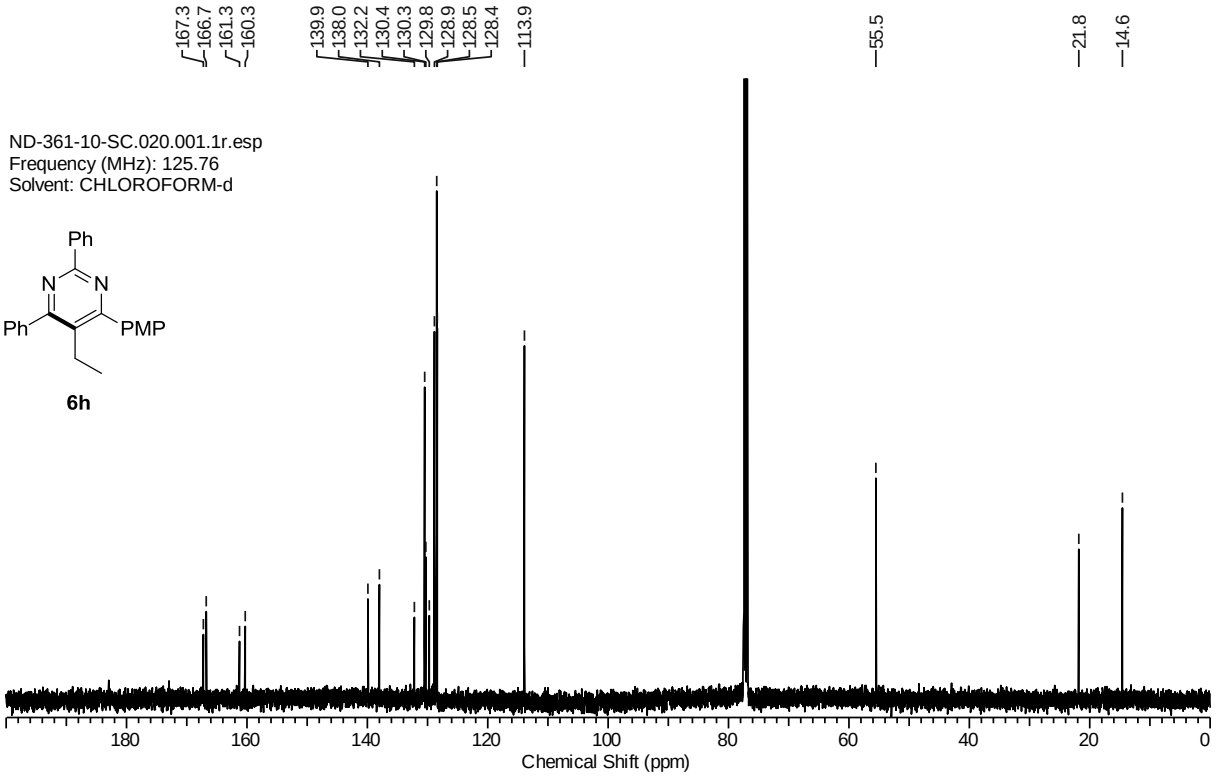

ND-368-7-SC_PROTON_20150212_02.esp
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
Ph
N
N
Ph
6f
1.99
8.14
2.00
1.00
2.02
1.99
2.03
3.05
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

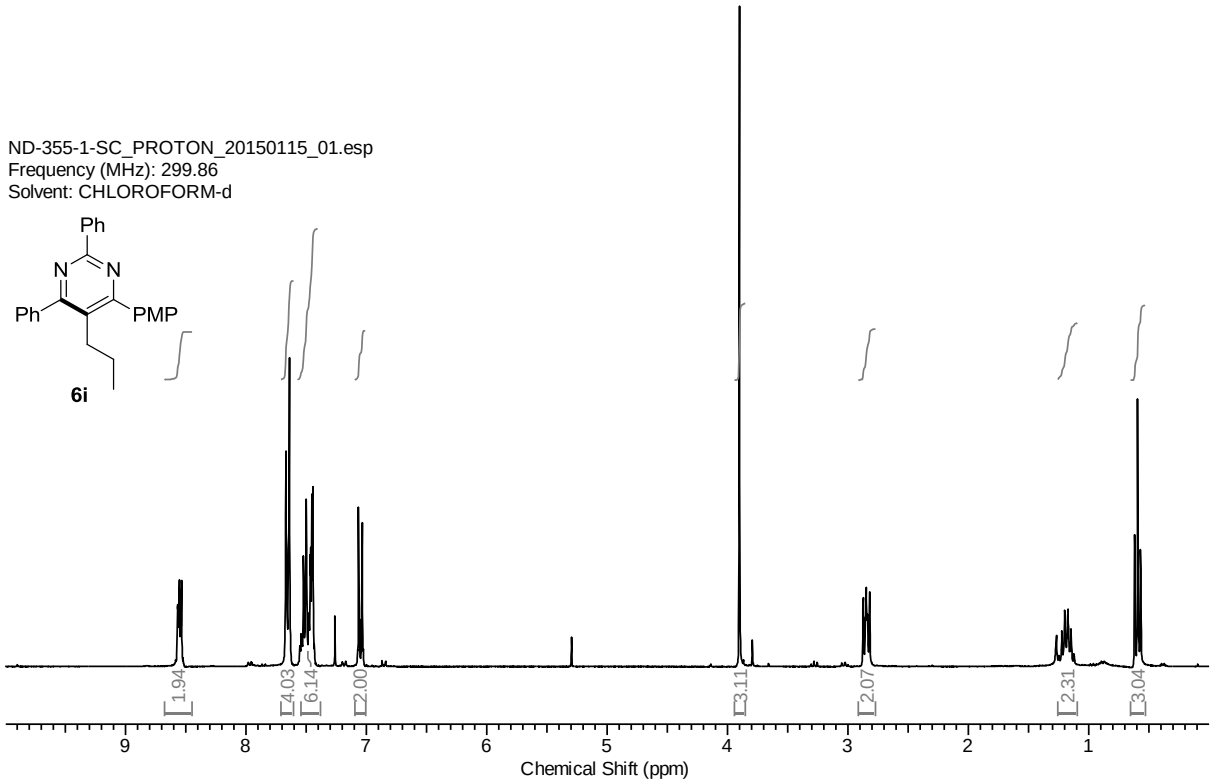

170.1
165.1
160.9
140.0
130.1
128.9
128.6
128.4
128.3
128.1
128.1
30.1
24.0
14.3
13.7
11.3
ND-368-7-SC.010.001.1r.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
6f
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

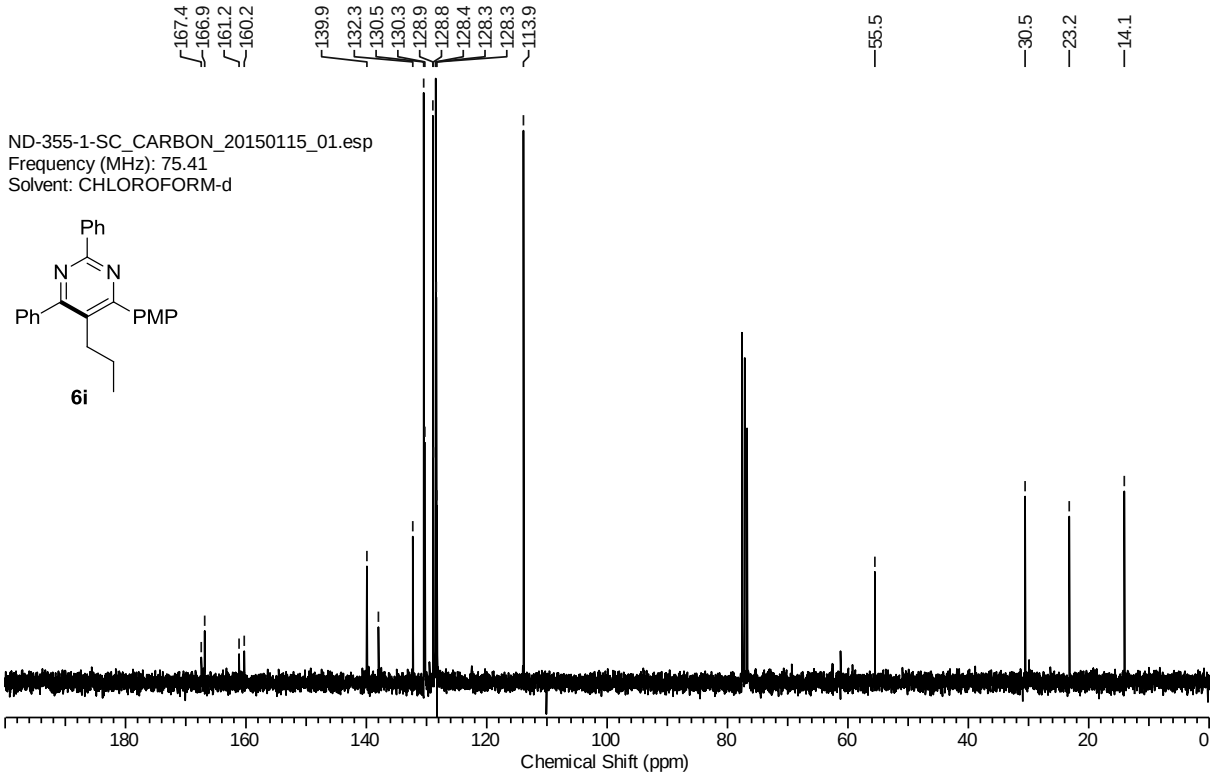

ND-364-3-SC_PROTON_20150202_01
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
Me
6g
1.98
4.02
6.07
2.00
3.02
3.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

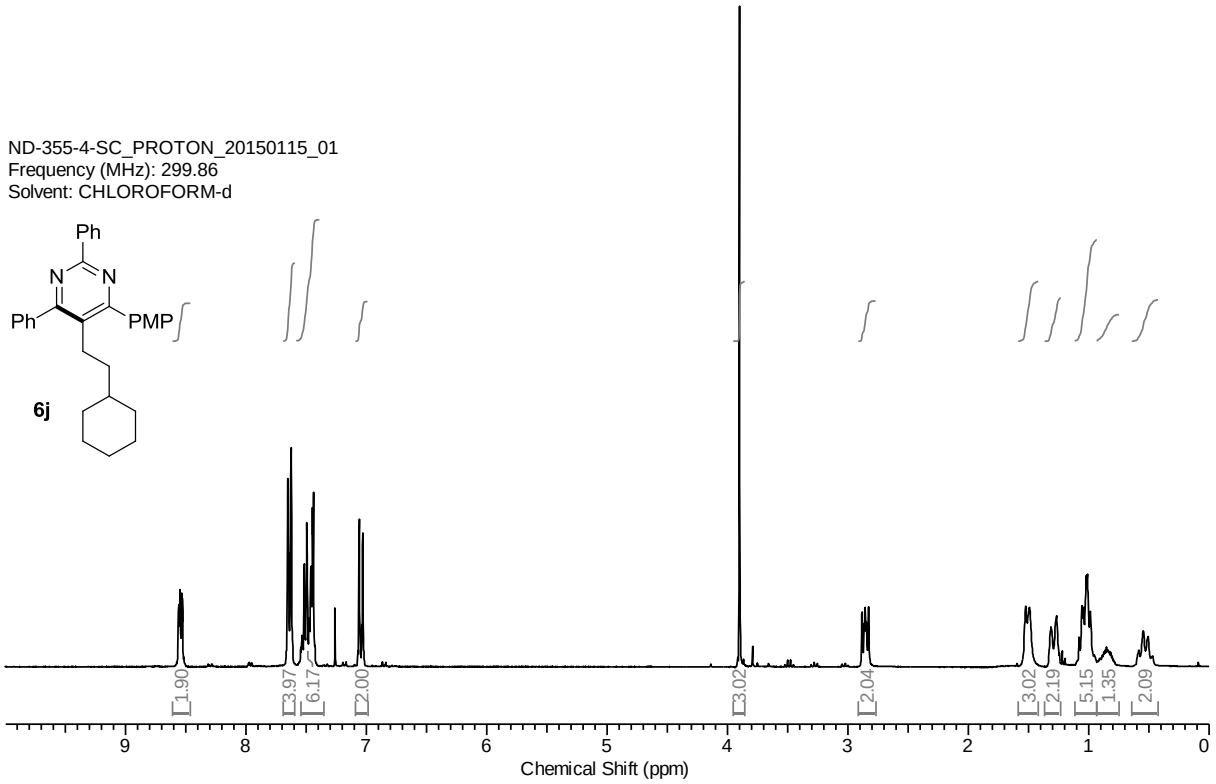

166.9
166.4
161.4
160.5
139.4
138.1
131.6
131.1
130.2
129.5
129.1
128.4
128.3
128.2
122.9
113.7
55.4
18.1
ND-364-3-SC_CARBON_20150203_01
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
Me
6g
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

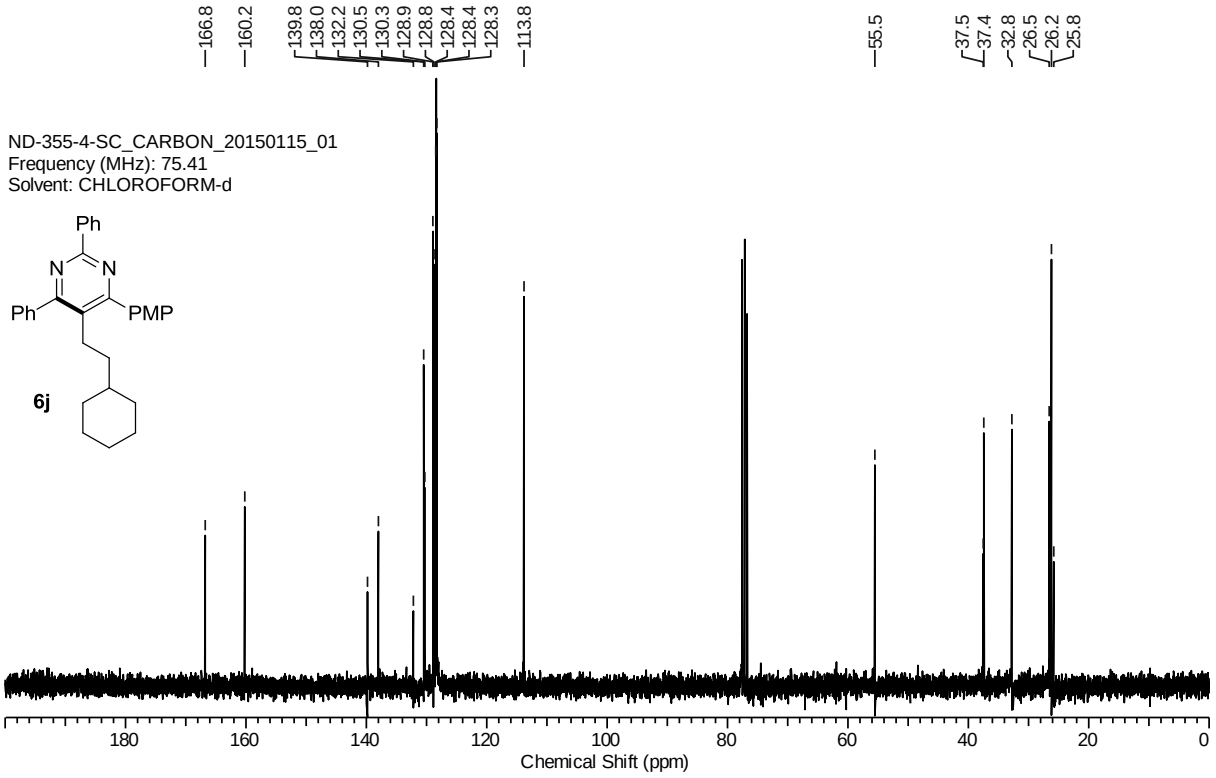

ND-361-10-SC.010.001.1r.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
6h
1.95
4.00
6.02
2.00
3.01
2.02
3.01
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

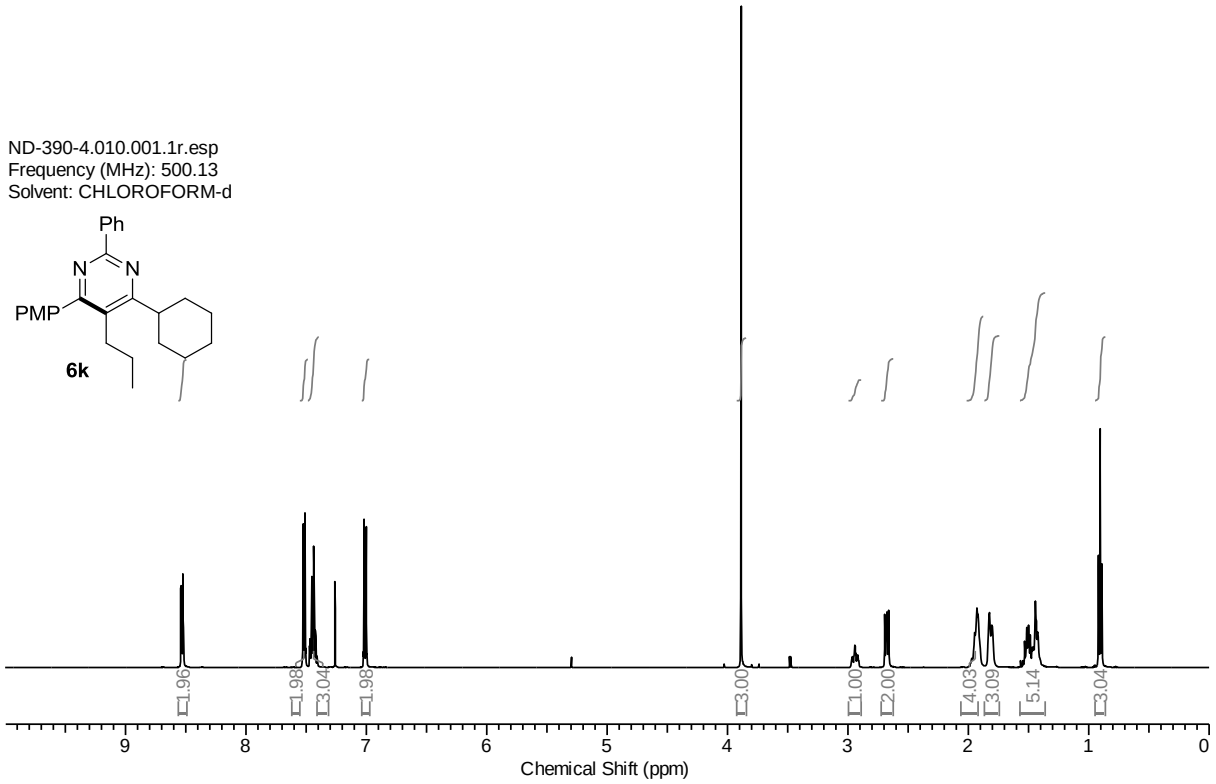

167.3
166.7
161.3
160.3
139.9
138.0
132.2
130.4
130.3
129.8
128.9
128.5
128.4
113.9
55.5
21.8
14.6
ND-361-10-SC.020.001.1r.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
6h
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

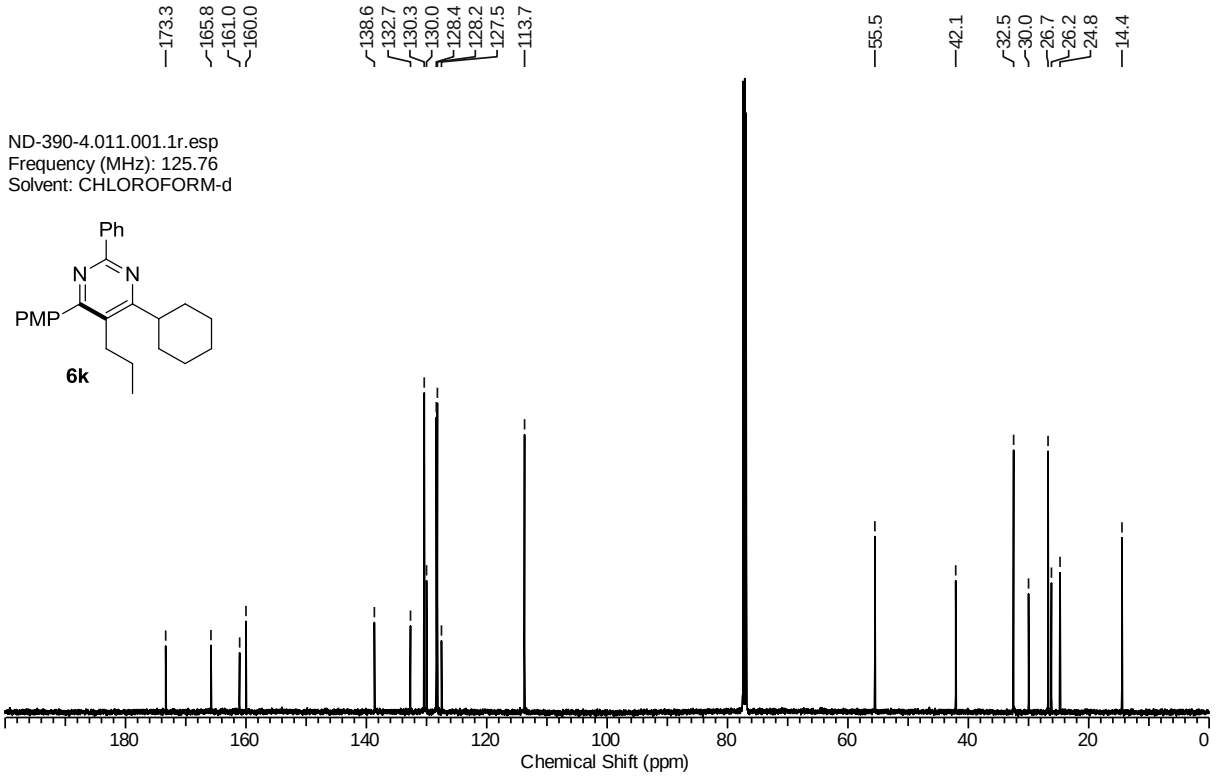

ND-355-1-SC_PROTON_20150115_01.esp
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
6i
1.94
4.03
6.14
2.00
3.11
2.07
2.31
3.04
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

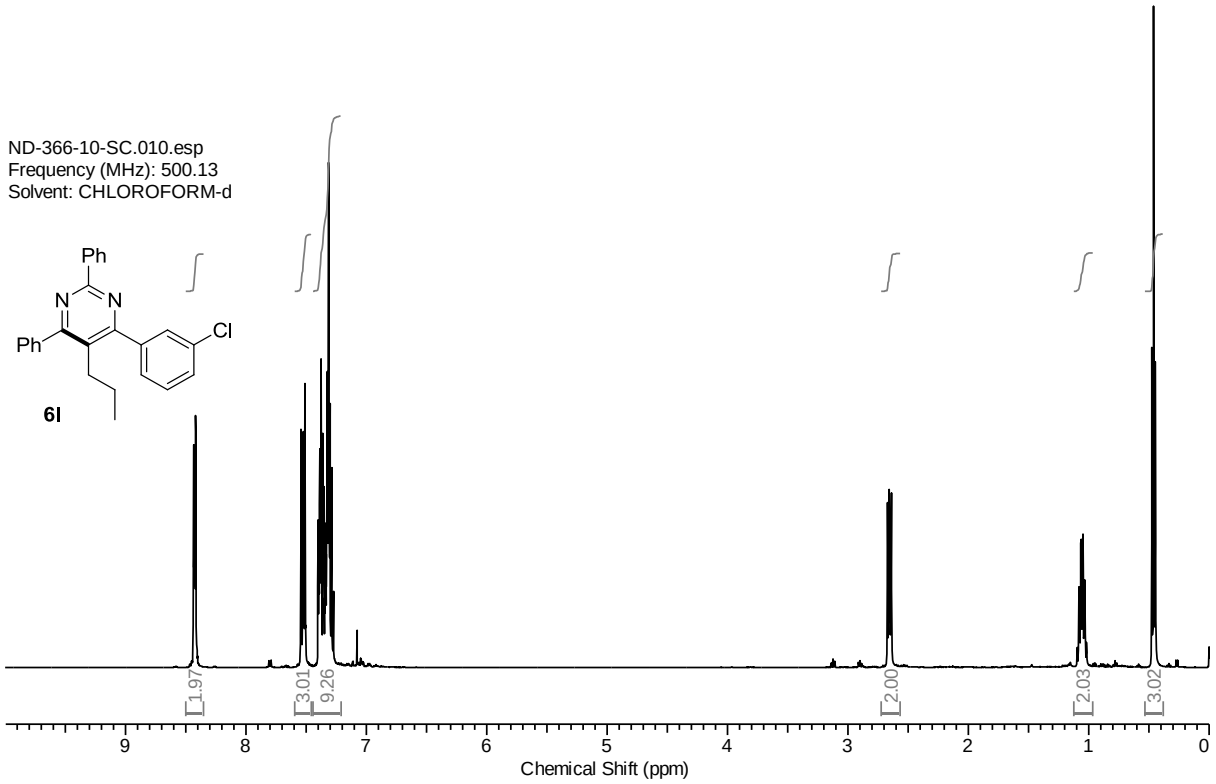

167.4
166.9
161.2
160.2
139.9
132.3
130.5
130.3
128.9
128.8
128.4
128.3
128.3
113.9
55.5
30.5
23.2
14.1
ND-355-1-SC_CARBON_20150115_01.esp
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
6i
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

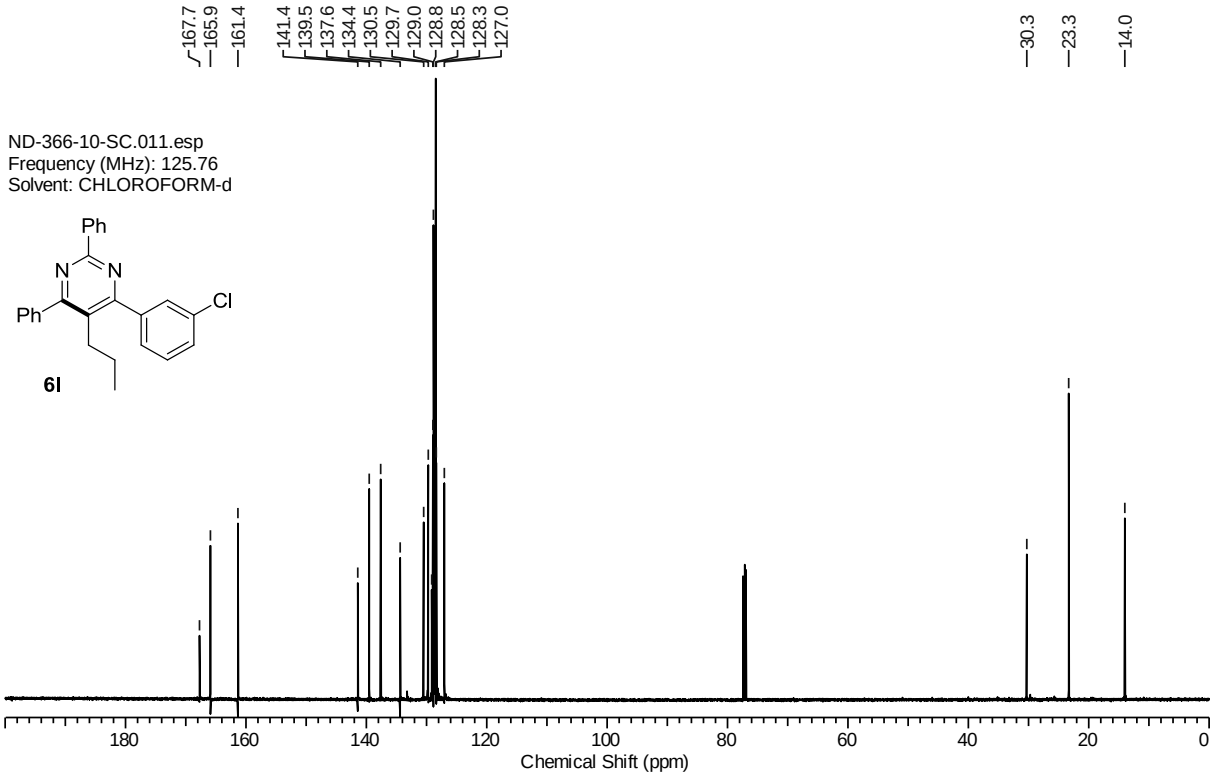

ND-355-4-SC_PROTON_20150115_01
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
6j
1.90
3.97
6.17
2.00
3.02
2.04
3.02
2.19
5.15
1.35
2.09
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


166.8
160.2
139.8
138.0
132.2
130.5
130.3
128.9
128.8
128.4
128.4
128.3
113.8
55.5
37.5
37.4
32.8
26.5
26.2
25.8
ND-355-4-SC_CARBON_20150115_01
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
6j
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


ND-390-4.010.001.1r.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
6k
1.96
1.98
3.04
1.98
3.00
1.00
2.00
4.03
3.09
5.14
3.04
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


173.3
165.8
161.0
160.0
138.6
132.7
130.3
130.0
128.4
128.2
127.5
113.7
55.5
42.1
32.5
30.0
26.7
26.2
24.8
14.4
ND-390-4.011.001.1r.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
6k
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


ND-366-10-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
Ph
Cl
6l
1.97
3.01
9.26
2.00
2.03
3.02
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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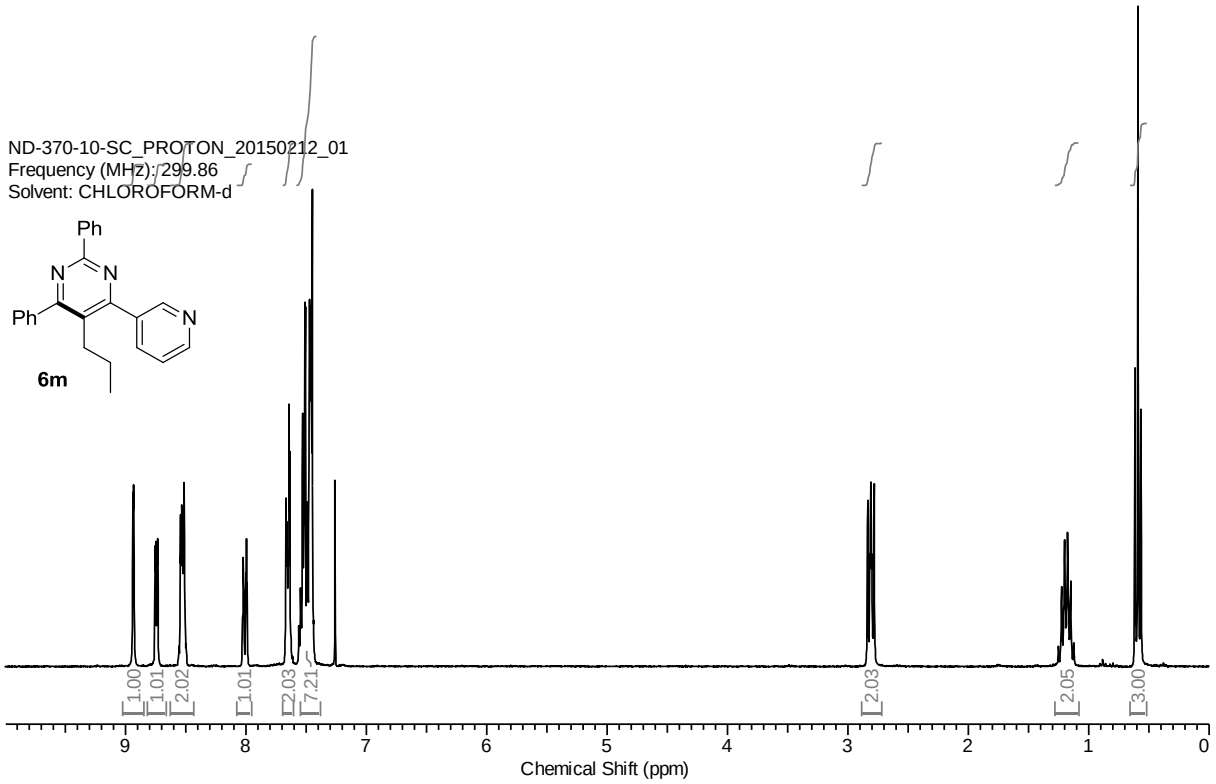
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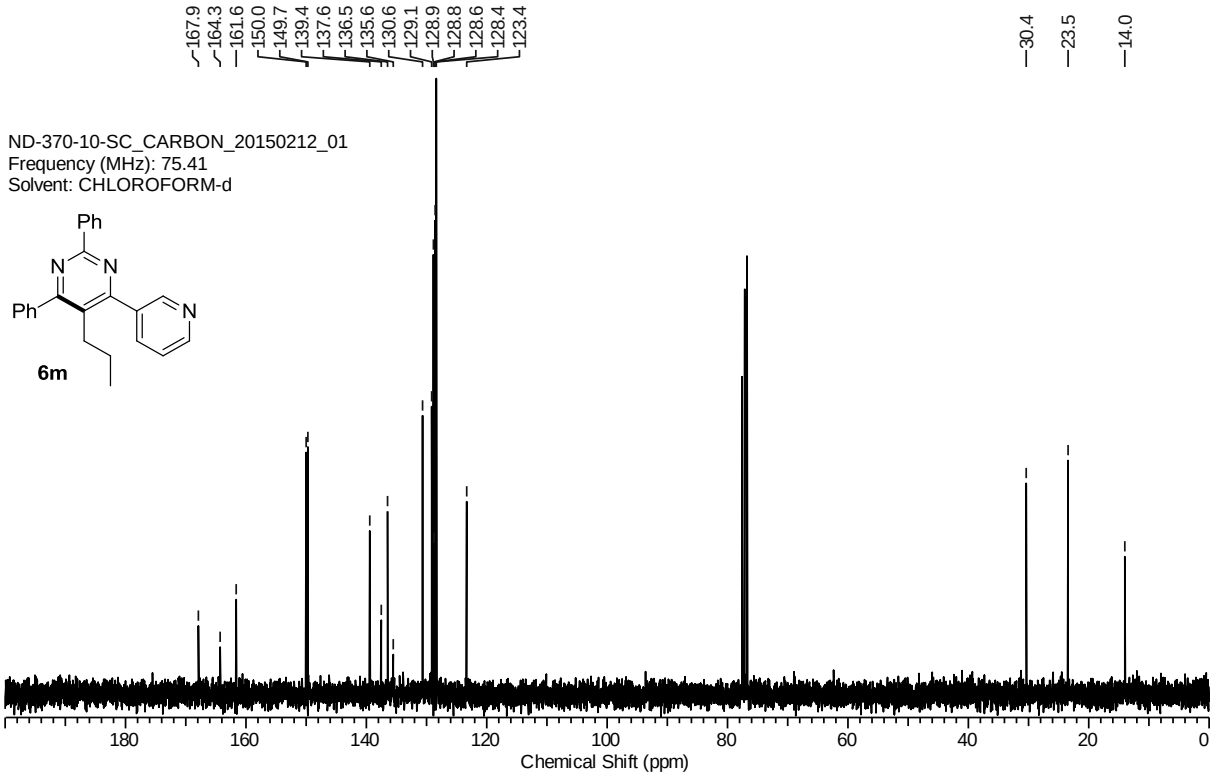
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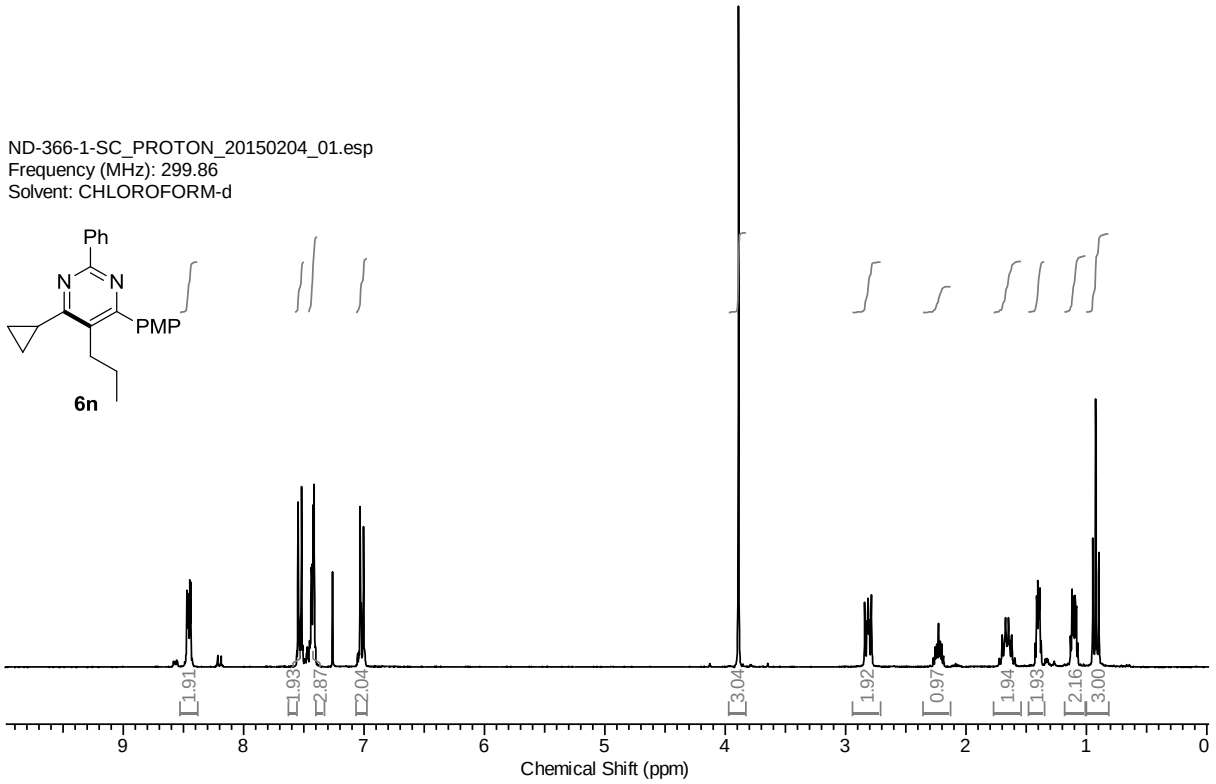
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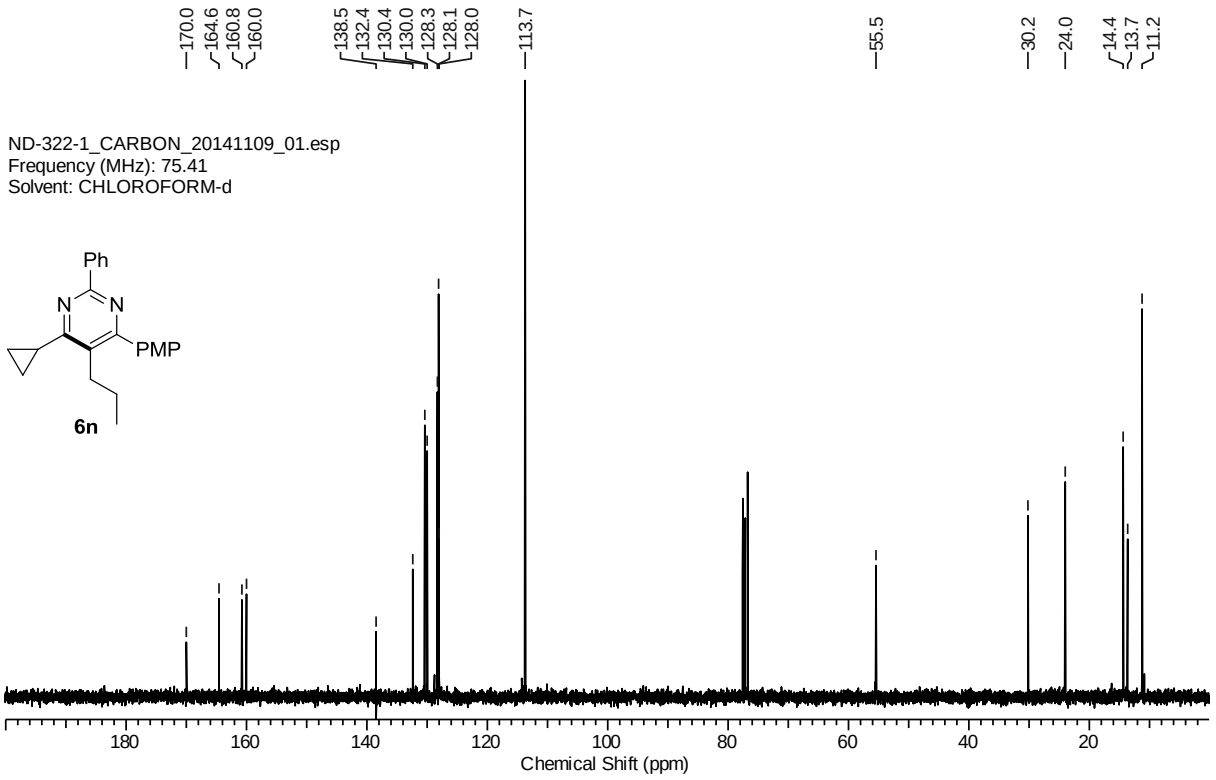
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Chemical Shift (ppm)

[1] Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115-119.
[2] Sheldrick, G. M. *Acta Crytallogr. A.* **2008**, *64*, 122-122.
[3] Farrugia, L. J. J. Appl. Crystallogr. 1999, 32, 837-838.
[4] (a) Michlik, S.; Kempe, R. *Angew. Chem. Int. Ed.* **2013**, 52, 6326-6329. (b) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, 5, 140-144.

# 6 General and Mild Cobalt-Catalyzed C-Alkylation of Unactivated Amides and Esters with Alcohols

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# General and Mild Cobalt-Catalyzed C-Alkylation of Unactivated Amides and Esters with Alcohols

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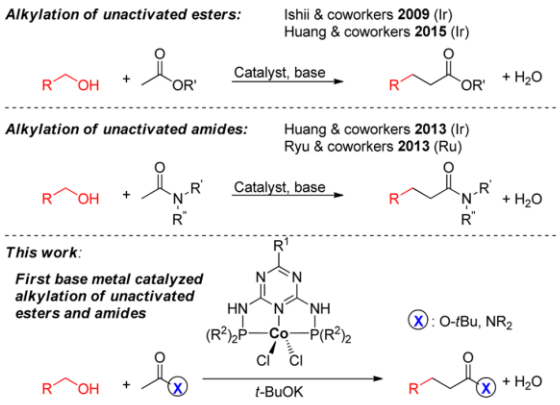
Supporting Information

**ABSTRACT:** The borrowing hydrogen or hydrogen autotransfer methodology is an elegant and sustainable or green concept to construct carbon−carbon bonds. In this concept, alcohols, which can be obtained from barely used and indigestible biomass, such as lignocellulose, are employed as alkylating reagents. An especially challenging alkylation is that of unactivated esters and amides. Only noble metal catalysts based on iridium and ruthenium have been used to accomplish these reactions. Herein, we report on the first base metal-catalyzed α-alkylation of unactivated amides and esters by alcohols. Cobalt complexes stabilized with pincer ligands, recently developed in our laboratory, catalyze these reactions very efficiently. The precatalysts can be synthesized easily from commercially available starting materials on a multigram scale and are self-activating under the basic reaction conditions. This Co catalyst class is also able to mediate alkylation reactions of both esters and amides. In addition, we apply the methodology to synthesize ketones and to convert alcohols into aldehydes elongated by two carbon atoms.

For the construction of carbon−carbon bonds, α-alkylation of carbonyl compounds is a fundamental method.[1] In the course of such a transformation, a base is used to deprotonate the carbonyl compound, and the anion is trapped with a reactant which bears a leaving group, such as a halide. The borrowing hydrogen (BH) or hydrogen autotransfer (HA) concept is an elegant and operationally easy method for C−C bond formation using alcohols as the electrophile.[2] Alcohols are especially appealing building blocks, since they can be obtained from indigestible, abundantly available and barely used biomass, such as lignocellulose.[3] A transition-metal complex is used to oxidize the alcohols to the corresponding carbonyl compounds, and a subsequent condensation reaction with a CH-acidic compound yields an unsaturated intermediate that is reduced by the catalyst with the hydrogen obtained from the oxidation step. Only water is released in these reactions, rendering them green or sustainable apart from the use of alcohols as an alkylating agent. Derivatives of carboxylic acids, such as esters and amides, are valuable intermediates and products both in industry and academia. An elegant approach to modify ordinary and broadly available amides and esters is the α-alkylation by alcohols. Here, even solvents commonly used and other amides and esters can be converted into more sophisticated and valuable products. However, alkylations of these substrate classes have proved to be challenging. Amides have a comparably low CH-acidic nature due to resonance stabilization, and esters can readily undergo side reactions. To date, both α-alkylations of activated[4] and unactivated[5] amides and of activated[6] and unactivated[7] esters with alcohols have only been reported using iridium or ruthenium catalysts (Scheme 1).

**Scheme 1. Recent Methods for the Alkylation of Unactivated Amides and Esters with Alcohols and the Work Using Co Catalysts, Stabilized by $PN_5P$ Ligands, Described Herein**[a]




[a] $R^1$ = 4-$CF_3$-$C_6H_4$, NH-$C_3H_5$, methyl; $R^2$ = *i*-Pr, cyclohexyl.

The substitution of noble metals by earth-abundant and inexpensive base metals is a key challenge in transition-metal-mediated catalysis. Cobalt complexes have recently been reported as catalysts in key reaction steps of the BH/HA concept, such as hydrogenation (olefins,[8] ketones,[9] carboxylic acids,[10] nitriles,[11] esters,[12] $CO_2$[13]) and dehydrogenation[14]. Our group recently reported C-alkylations based on BH/HA[15] and on the sustainable syntheses of N-heterocycles based on $PN_5P$-stabilized Ir complexes.[3c,16] Using the same ligand class, we also reported on the first Co-catalyzed alkylation of aromatic amines by alcohols.[17] Related $PN_3P$-pincer ligands were introduced by Haupt and coworkers[18] and the broad applicability of this ligand class was demonstrated by Kirchner and coworkers.[19] Herein, we report on the first α-alkylation of unactivated amides and esters by alcohols applying base metal catalysts. Cobalt complexes stabilized with $PN_5P$ ligands (Scheme 1, bottom) are efficient catalysts for both reactions. The

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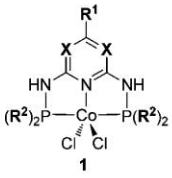
precatalysts can be synthesized in two steps in almost quantitative yield beginning with commercially available starting materials on a gram scale and become activated under the basic reaction conditions.[9a,17a] In addition, we describe the application of the alkylation of amides to synthesize unsymmetrically substituted ketones and to convert alcohols into aldehydes, which are extended by two carbon atoms.

The reaction between benzyl alcohol (**2a**) and *N*,*N*-dimethylacetamide (**3a**) to give **5a** was thoroughly investigated to find broadly applicable reaction conditions for the Co-catalyzed amide alkylation proposed (Tables 1 and 2). Starting with catalyst **1c** (Table 1, 5 mol %), common reaction parameters, such as solvent, base, base amount, substrate ratio, and temperature, were investigated (see the SI). Afterward, a screening of the Co complexes **1a**–**i** (2.5 mol %) was applied in the synthesis of the model compound **5a** (Table 2). While precatalysts **1a**–**d** (entries 1–4) gave unsatisfying yields, **1e** and **1f** (entries 5 and 6) gave the highest yields of the alkylation product. Alcohol conversion was quantitative for both precatalysts. Complex **1e** is less expensive (*i*-Pr moieties of the P atom), possesses very good solubility in THF or dioxane at RT, and is, therefore, very convenient to handle as a stock solution. Thus, **1e** was selected eventually. Most interestingly, **1g**–**i**, which are based on a pyridine core, and $CoCl_2$ failed to catalyze the reaction (entries 7–10). In summary, the reaction can be conducted with 2.5 mol % **1e** in THF at 100 °C (closed system) with 1.2 equiv *t*-BuOK as the base and a 2-fold excess of amide with respect to the alcohol. Notably, these conditions are milder than those for the Ir-catalyzed approach reported by Huang and coworkers (toluene, 120 °C, 2 equiv base, 2 mol % Ir).[5a] Mechanistic investigations of the model reaction (Table 2) indicate that alcohol oxidation is rate-limiting and reduction of the double bond is comparably fast. The key to a selective reaction is a low concentration of the unsaturated intermediate (*N*,*N*-dimethylcinnamamide) since it undergoes multiple side reactions with educts and products (see SI for details). The metal base (metal-to-Co ratio 2:1) is used to activate the dichloro complexes via double deprotonation of the ligand and removal of chloro ligands (salt elimination).[9a] The double deprotonation option is a unique feature of the ligand class used herein. Taking note of these optimized conditions, we started to explore the substrate scope of the amide alkylation (Table 3). The screening product **5a** was isolated in 83% yield. Methyl substituents in the *ortho*, *meta*, and *para*-positions of the

**Table 1. Co Complexes Used Herein to Identify the Best Reaction Conditions**[a]

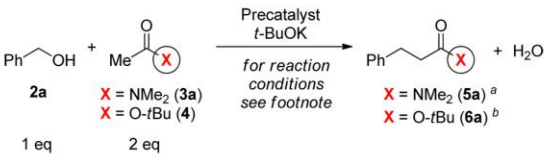


1

| Complex | R¹ | R² | X |
|---|---|---|---|
| **1a** | H | *i*-Pr | N |
| **1b** | Me | *i*-Pr | N |
| **1c** | Ph | *i*-Pr | N |
| **1d** | 4-$CF_3$-$C_6H_4$ | *i*-Pr | N |
| **1e** | NH-$C_3H_5$ | *i*-Pr | N |
| **1f** | Me | Cy | N |
| **1g** | H | *i*-Pr | CH |
| **1h** | Me | *i*-Pr | CH |
| **1i** | H | Ph | CH |

[a]Cy = cyclohexyl.

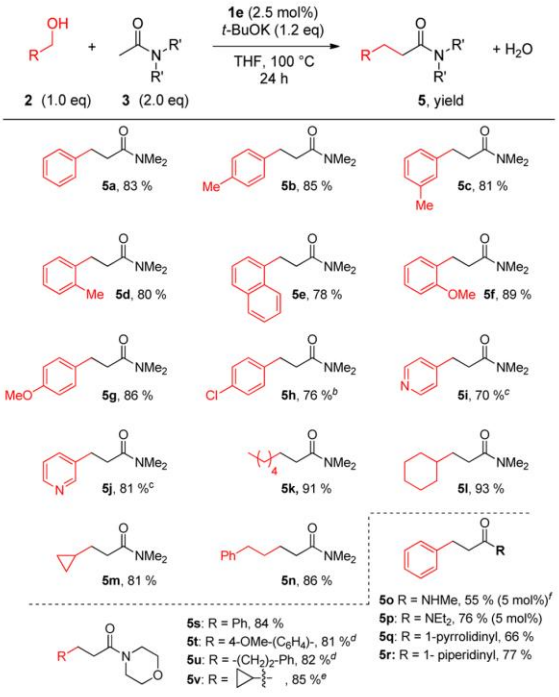
**Table 2. Catalyst Screening for Amide and Ester Alkylation**




| | | yield [%][c] | |
|---|---|---|---|
| entry | [Co] precatalyst | **5a** | **6a** |
| 1 | **1a** | 7 | 13 |
| 2 | **1b** | 49 | 43 |
| 3 | **1c** | 25 | 50 |
| 4 | **1d** | 41 | 60 |
| 5 | **1e** | 69 | 42 |
| 6 | **1f** | 74 | 45 |
| 7 | **1g** | 0 | 31 |
| 8 | **1h** | 0 | 24 |
| 9 | **1i** | 0 | 0 |
| 10 | $CoCl_2$ | 0 | 0 |

[a]Benzyl alcohol (1 mmol), *N*,*N*-dimethylacetamide (2 mmol), *t*-BuOK (1.2 mmol), THF (4 mL), [Co] (0.025 mmol), 20 h at 100 °C (oil bath temperature). [b]Benzyl alcohol (1 mmol), *tert*-butyl acetate (2 mmol), toluene (1 mL), [Co] (0.02 mmol), 20 h at 70 °C (oil bath temperature). [c]Determined by GC with dodecane as an internal standard.

**Table 3. Product Scope for Amide Alkylation**[a]




[a]Alcohol (1 mmol), amide (2 mmol), *t*-BuOK (1.2 mmol), **1e** (0.025 mmol), and THF (4 mL) were heated for 24 h at 100 °C (oil bath) in a closed system. Yields are of isolated products. [b]*t*-BuONa was used as a base. [c]**1f** (5 mol %) was used. [d]10 mmol scale. [e]5 mmol scale. [f]1,4-dioxane, 120 °C, 1.5 equiv *t*-BuOK.



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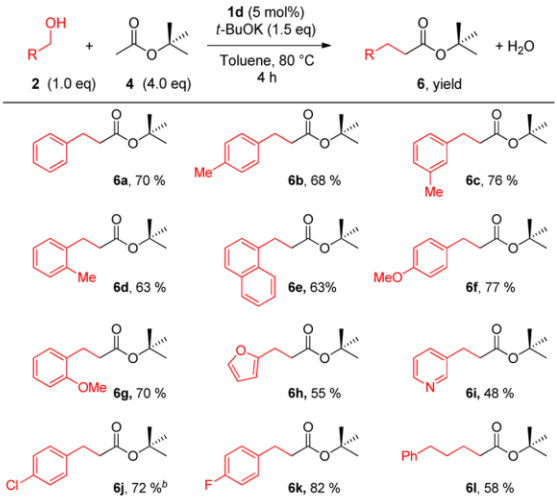
phenyl ring furnished **5b–d** in again very good yields (80–85%, respectively), and application of 1-naphthyl methanol gave **5e** in 78% yield. Methoxy-substituted benzyl alcohols gave the corresponding products in excellent yields (89% and 86% for **5f** and **5g**, respectively). When 4-chlorobenzyl alcohol was subjected to the reaction conditions, partial dechlorination was observed by GC analysis, and the products were inseparable by column chromatography. However, the change to *t*-BuONa (instead of *t*-BuOK) under otherwise identical reaction conditions furnished **5h** as the only product in 76% isolated yield. 3- and 4-pyridine methanol also proved to be challenging alcohols, and low conversions were obtained under the standard conditions. However, with the diverse Co-complex library as a toolbox, the application of **1f** with higher catalyst loading (5 mol %) gave the alkylation products **5i** in acceptable 70% and **5j** in good 81% yield. When aliphatic (branched and linear) alcohols were used in this reaction (products **5k–n**), the highest yields of up to 93% were obtained. In order to C-alkylate a secondary amide, the reaction conditions had to be adjusted, and **5o** was obtained in 55% yield when the reaction was run in 1,4-dioxane at 120 °C with 1.5 equiv *t*-BuOK and 5 mol % **1e**. Further variation of the amide moiety gave **5p–r** in good yields (66–77%, respectively) and the very interesting N-morpholino amides **5s–v** (*vide infra*) in very good yields, even on a higher scale (10 mmol, >2 g for **5t,u**). The latter compounds exhibit a similar reactivity to Weinreb amides (R-CO-N(Me)OMe) which failed to react.

Taking note of the good performance of the Co catalysts for the amide alkylation, we focused on acetates as the coupling partner (Table 4, top). The reaction between benzyl alcohol and *tert*-butyl acetate was investigated to find suitable reaction conditions (Table 1, synthesis of **6a**; see the SI for details). A catalyst screening identified precatalyst **1d** (entry 4) to be the most active for this transformation. The peak of product yield was obtained when the amount of *tert*-butyl acetate (**4**) was increased to four equiv. When the reaction was conducted in neat *tert*-butyl acetate, the yield dropped. In summary, the reaction should be run in toluene at 80 °C with 1.5 equiv of *t*-BuOK, four equiv of *tert*-butyl acetate and complex **1d** (5 mol %). *tert*-Butyl acetate undergoes fast transesterification, and the equilibrium is shifted to the alkylated *tert*-butyl esters **6** with the consumption of the primary alcohol (see SI for details). Having pinpointed the reaction conditions, we explored the substrate scope of this reaction (Table 4). The application of benzyl and methylbenzyl alcohols and 1-naphthyl methanol gave the ester alkylation products **6a–e** in 63–76% isolated yields, respectively. The use of electron-rich methoxybenzyl alcohols furnished the corresponding products in good yields as well (77% and 70% for **6f,g**, respectively). The application of methanol bearing heteroaromatic substituents (furyl, pyridyl) also gave the C-alkylation products, albeit in lower yields (55% for **6h** and 48% for **6i**). In order to obtain the chlorine-substituted product **6j** free of side products (72% yield), *t*-BuONa had to be used as the base (*t*-BuOK: 48% isolated yield). The use of 4-fluorobenzyl alcohol gave an excellent yield (**6k**, 82%). Ester **6l** could be obtained in 58% yield using 3-phenyl-1-propanol.

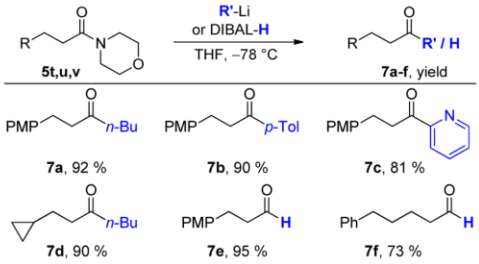
Finally, we became interested in exploring the applicability of amide alkylation products synthesized via Co catalysis to expand the scope of the BA/HA methodology[16a,20] (Table 5).

**Table 4. Product Scope for Ester Alkylation**[a]




[a]Alcohol (1 mmol), *tert*-butyl acetate (4 mmol), *t*-BuOK (1.5 mmol), toluene (1 mL), **1d** (5 mol %), 4 h at 80 °C (oil bath). Yields are of isolated products. [b]*t*-BuONa was used as a base.

**Table 5. Derivatization of Amide Substrates**[a]




[a]THF, − 78 °C, R′-Li (2.5–3 equiv) or diisopropylaluminum hydride (DIBAL-H, 1.15–1.30 equiv), 1 h reaction time. Yields are of isolated products. PMP = *para*-methoxyphenyl, *p*-Tol = *para*-tolyl, Bu = butyl.

N-morpholino amides **5t–v** were converted into the corresponding ketones **7a–d** using alkyl and aryl Li reagents, and only monoaddition was observed (as opposed to esters). The reaction of **5t** and **5u** with diisobutyl aluminumhydride (DIBAL-H) at −78 °C gave aldehydes **7e** and **7f** in 95% and 73% yields, respectively.

In summary, we report on the first base metal-catalyzed C-alkylation of unactivated amides and esters by alcohols. The reaction is catalyzed most efficiently by $PN_5P$-stabilized Co complexes developed in our laboratory. These catalysts are easy to synthesize on a large scale from commercially available starting materials. The catalysts are self-activating under the reaction conditions needed to accomplish the alkylations. The method is characterized by mild reaction conditions and good functional group tolerance. A key to a broad substrate scope is also the library of easily accessible $PN_5P$-Co catalysts. Amide alkylation products were obtained in up to 93% isolated yields with catalyst loadings nearly the same as those reported for Ir, but under milder reaction conditions and applying less base. The demanding ester alkylation reaction gave the corresponding products in moderate to good yields. So far, different catalyst classes have been applied to $\alpha$-alkylate amides and esters. Finally, further transformations of the amide alkylation



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products into compounds with other functional groups (ketone, aldehyde) showcase the value of the products obtained by this method. Eight novel compounds out of 40 examples have been synthesized.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06448.

Experimental procedures and spectroscopic data (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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## ■ REFERENCES


(1) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press: Oxford, 2001.

(2) For selected reviews on C-alkylation by alcohols, see: (a) Huang, F.; Liu, Z.; Yu, Z. *Angew. Chem., Int. Ed.* **2016**, *55*, 862−875. (b) Nandakumar, A.; Midya, S. P.; Landge, V. G.; Balaraman, E. *Angew. Chem., Int. Ed.* **2015**, *54*, 11022−11034. (c) Shimizu, K.-I. *Catal. Sci. Technol.* **2015**, *5*, 1412−1427. (d) Obora, Y. *ACS Catal.* **2014**, *4*, 3972−3981. (e) Gunanathan, C.; Milstein, D. *Science* **2013**, *341*, 1229712. (f) Alonso, F.; Riente, P.; Yus, M. *Acc. Chem. Res.* **2011**, *44*, 379−391. (g) Suzuki, T. *Chem. Rev.* **2011**, *111*, 1825−1845. (h) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681−703. (i) Yamaguchi, R.; Fujita, K.-I.; Zhu, M. *Heterocycles* **2010**, *81*, 1093−1140. (j) Obora, Y.; Ishii, Y. *Synlett* **2011**, *2011*, 30−51. (k) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. *Dalton Trans.* **2009**, *7*, 753−762. (l) Guillena, G.; Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358−2364. (m) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555−1575.

(3) (a) Vispute, T. P.; Zhang, H.; Sanna, A.; Xiao, R.; Huber, G. W. *Science* **2010**, *330*, 1222−1227. (b) Tuck, C. O.; Perez, E.; Horvath, I. T.; Sheldon, R. A.; Poliakoff, M. *Science* **2012**, *337*, 695−699. (c) Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140−144.

(4) (a) Jensen, T.; Madsen, R. *J. Org. Chem.* **2009**, *74*, 3990−3992. (b) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 7468−7473.

(5) (a) Guo, L.; Liu, Y.; Yao, W.; Leng, X.; Huang, Z. *Org. Lett.* **2013**, *15*, 1144−1147. (b) Kuwahara, T.; Fukuyama, T.; Ryu, I. *RSC Adv.* **2013**, *3*, 13702−13704.

(6) (a) Grigg, R.; Whitney, S.; Sridharan, V.; Keep, A.; Derrick, A. *Tetrahedron* **2009**, *65*, 7468−7473. (b) Ledger, A. E. W.; Slatford, P. A.; Lowe, J. P.; Mahon, M. F.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, *7*, 716−722. (c) Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2007**, *7*, 2850−2852.

(7) (a) Guo, L.; Ma, X.; Fang, H.; Jia, X.; Huang, Z. *Angew. Chem., Int. Ed.* **2015**, *54*, 4023−4027. (b) Iuchi, Y.; Obora, Y.; Ishii, Y. *J. Am. Chem. Soc.* **2010**, *132*, 2536−2537.

(8) (a) Friedfeld, M. R.; Shevlin, M.; Margulieux, G. W.; Campeau, L. C.; Chirik, P. J. *J. Am. Chem. Soc.* **2016**, *138*, 3314−3324. (b) Chirik, P. J. *Acc. Chem. Res.* **2015**, *48*, 1687−1695. (c) Friedfeld, M. R.; Margulieux, G. W.; Schaefer, B. A.; Chirik, P. J. *J. Am. Chem. Soc.* **2014**, *136*, 13178−13181. (d) Lin, T. P.; Peters, J. C. *J. Am. Chem. Soc.* **2014**, *136*, 13672−13683. (e) Lin, T. P.; Peters, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 15310−15313. (f) Monfette, S.; Turner, Z. R.; Semproni, S. P.; Chirik, P. J. *J. Am. Chem. Soc.* **2012**, *134*, 4561−4564. (g) Knijnenburg, Q.; Horton, A. D.; Heijden, H. v. d.; Kooistra, T. M.; Hetterscheid, D. G. H.; Smits, J. M. M.; Bruin, B. d.; Budzelaar, P. H. M.; Gal, A. W. *J. Mol. Catal. A: Chem.* **2005**, *232*, 151−159.

(9) (a) Rösler, S.; Obenauf, J.; Kempe, R. *J. Am. Chem. Soc.* **2015**, *137*, 7998−8001. (b) Gartner, D.; Welther, A.; Rad, B. R.; Wolf, R.; Jacobi von Wangelin, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 3722−3726. (c) Zhang, G.; Vasudevan, K. V.; Scott, B. L.; Hanson, S. K. *J. Am. Chem. Soc.* **2013**, *135*, 8668−8681. (d) Zhang, G.; Hanson, S. K. *Chem. Commun.* **2013**, *49*, 10151−10153. (e) Zhang, G.; Scott, B. L.; Hanson, S. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12102−12106.

(10) Korstanje, T. J.; van der Vlugt, J. I.; Elsevier, C. J.; de Bruin, B. *Science* **2015**, *350*, 298−302.

(11) Mukherjee, A.; Srimani, D.; Chakraborty, S.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2015**, *137*, 8888−8891.

(12) Srimani, D.; Mukherjee, A.; Goldberg, A. F.; Leitus, G.; Diskin-Posner, Y.; Shimon, L. J.; Ben David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2015**, *54*, 12357−12360.

(13) (a) Federsel, C.; Ziebart, C.; Jackstell, R.; Baumann, W.; Beller, M. *Chem. - Eur. J.* **2012**, *18*, 72−75. (b) Jeletic, M. S.; Mock, M. T.; Appel, A. M.; Linehan, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 11533−11536.

(14) Zhang, G.; Hanson, S. K. *Org. Lett.* **2013**, *15*, 650−653.

(15) Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132*, 924−925.

(16) (a) Deibl, N.; Ament, K.; Kempe, R. *J. Am. Chem. Soc.* **2015**, *137*, 12804−12807. (b) Hille, T.; Irrgang, T.; Kempe, R. *Chem. - Eur. J.* **2014**, *20*, 5569−5572. (c) Michlik, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 6326−6329.

(17) (a) Rösler, S.; Ertl, M.; Irrgang, T.; Kempe, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 15046−15050. Nearly parallel, Zhang et al. introduced a different Co catalyst which was able to alkylate aliphatic and aromatic amines: (b) Zhang, G.; Yin, Z.; Zheng, S. *Org. Lett.* **2016**, *18*, 300−303.

(18) (a) Schirmer, W.; Flörke, U.; Haupt, H. J. *Z. Anorg. Allg. Chem.* **1987**, *545*, 83−97. (b) Li, H.; Zheng, B.; Huang, K.-W. *Coord. Chem. Rev.* **2015**, *293*−*294*, 116−138.

(19) Selected examples of recent publications: (a) Murugesan, S.; Stoger, B.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *Angew. Chem., Int. Ed.* **2016**, *55*, 3045−3048. (b) Bertini, F.; Gorgas, N.; Stöger, B.; Peruzzini, M.; Veiros, L. F.; Kirchner, K.; Gonsalvi, L. *ACS Catal.* **2016**, *6*, 2889−2893. (c) Gorgas, N.; Stöger, B.; Veiros, L. F.; Kirchner, K. *ACS Catal.* **2016**, *6*, 2664−2672. (d) Gorgas, N.; Stöger, B.; Veiros, L. F.; Pittenauer, E.; Allmaier, G.; Kirchner, K. *Organometallics* **2014**, *33*, 6905−6914. (e) Murugesan, S.; Stöger, B.; Carvalho, M. D.; Ferreira, L. P.; Pittenauer, E.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *Organometallics* **2014**, *33*, 6132−6140. (f) de Aguiar, S. R.; Stoger, B.; Pittenauer, E.; Puchberger, M.; Allmaier, G.; Veiros, L. F.; Kirchner, K. *J. Organomet. Chem.* **2014**, *760*, 74−83.

(20) Frost, J. R.; Cheong, C. B.; Akhtar, W. M.; Caputo, D. F.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2015**, *137*, 15664−15667.




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Supporting Information

# General and Mild Cobalt-Catalyzed C-Alkylation of Unactivated Amides and Esters with Alcohols

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# 1 General Methods

Air- and moisture sensitive reactions were carried out under nitrogen or argon atmosphere using standard Schlenk techniques or a glove box. Dry solvents were obtained from a solvent purification system (activated alumina cartridges) or purchased from Acros. Chemicals were purchased from commercial vendors and used without purification if not noted otherwise. NMR-Spectra were collected at ambient temperature (23 °C) on Varian INOVA 300 (300 MHz for $^{1}$H, 75 MHz for $^{13}$C) or Bruker Avance III HD 500 (500 MHz for $^{1}$H, 126 (125.76) MHz for $^{13}$C) instruments. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$: 7.26 ppm ($^{1}$H), 77.16 ppm ($^{13}$C)). Coupling constants (*J*) are reported in Hz (coupling patterns: d = doublet, t = triplet, q = quartet, sxt = sextet, spt = septet, m = multiplet). GC analyses were carried out on an Agilent 6890N Network GC system equipped with a HP-5 column (30 m x 0.32 mm x 0.25 μm) or on an Agilent 6850 GC system equipped with a Optima17 column (30 m x 0.32mm x 25μm). GC-MS analyses were carried out on an Agilent 7890A GC system equipped with a HP-5MS column (30 m x 0.32 mm x 0.25 μm) and a 5975C inert MSD detector. Flash column chromatography was conducted on Macherey-Nagel silica gel 60 (40–63 μm particle size). Elemental analysis was performed on an Elementar Vario El *III* Instrument. High resolution mass spectra (HRMS) were obtained from a Thermo Fisher Scientific Q-Exactive (Orbitrap) instrument in ESI+ mode.

MTBE = Methyl *tert*-butyl ether.
DIBAL-H = Diisopropylaluminum hydride.

*t*-BuOK was dried under high vacuum at 70 °C and stored in a glove box.

The identity and purity of all compounds was characterized by $^{1}$H and $^{13}$C NMR spectroscopy and GC-MS. Unknown compounds were further characterized by HRMS or elemental analysis. Ambiguous NMR spectra were confirmed by two-dimensional methods.
Compounds **5i, 5m, 5v, 6e, 6g, 7a, 7c, 7d** were previously not described in the literature.

Ligands[1] and Co-complexes[2] were prepared according to methods previously reported by our group. Representative procedures are also given below.

# 2 General procedures

**Typical procedure for ligand preparation**: Under inert gas atmosphere a round-bottom flask with gas inlet was charged with a magnetic stirring bar and a solution of the

corresponding triazine or pyridine diamine (1 eq) in abs. THF (~0.1 M). The solution was cooled to 0 °C and the corresponding chlorophosphine (2.1 eq) was added dropwise by syringe through a septum maintaining a positive inert gas pressure. Afterwards triethylamine (4 eq) was added dropwise by syringe. The flask was sealed and the reaction was warmed to room temperature and then heated to 60 °C overnight. After cooling, triethyl ammoniumchloride was allowed to settle and the organic phase was isolated by filtration. The salt cake was washed with THF once and the combined organic phases were concentrated and dried under high vacuum giving the PNP ligand. In most cases no further purification was required. Otherwise, the ligands can be recrystallized in a small amount of hot toluene.

**Co-complex preparation**. Under inert gas atmosphere (glove box) a Schlenk tube was charged with a magnetic stirring bar and a suspension of $CoCl_2$ (1 eq) in THF (~0.12 M). The PNP-ligand (1 eq) was dissolved in THF (~0.12 M) and added to the stirred suspension of $CoCl_2$ in one portion leading to an instant color change. The Schlenk tube was sealed, removed from the glove box and heated to 60 °C overnight.
Complexes **1e, 1f** were isolated upon concentration in vacuo. Complex **1d** precipitated from the reaction mixture and the solvent was concentrated to half volume, the organic phase was removed and the remainder was dried under high vacuum.

**Amide alkylation (1 mmol scale)**. Using a glove box (dry $N_2$ atmosphere), an oven dried 10 mL top screw vial was charged with a magnetic stirring bar, *t*-BuOK (1.2 mmol, 134.4 mg, 1.2 eq), alcohol (1 mmol, 1.0 eq), catalyst **1e** (1 mL from a 0.025 M stock solution in THF, 0.025 mmol, 2.5 mol%), amide (2 mmol, 2.0 eq) and THF (3.0 mL). The vial was sealed, removed from the glove box and the reaction mixture was heated to 100 °C (oil bath temperature) for 24 h. The reaction mixture was quenched with water (1 mL) and extracted with diethyl ether (3x 10 mL). The organic phase was analyzed with GC and GC-MS to monitor consumption of alcohol and product formation. The combined organic phases were dried over $Na_2SO_4$, evaporated and the amide product was purified using a small column of silica gel and pentane/ethyl acetate as the eluent.

As shown for product **5t**, the reaction gives the same yields when run on higher scale (10 mmol).

*Version without pre-synthesized complex (1 mmol scale reaction)*: In an analogous manner as described above, a 10 mL top screw vial was charged with a magnetic stirring bar and $CoCl_2$ (0.025 mmol, 3.25 mg, 2.5 mol%). A solution of the corresponding ligand (0.025 mmol, 9.96 mg) in THF (1 mL) was added. After stirring for 2 min, a deep purple solution was obtained. Afterwards, the remaining components were added and the reaction was conducted and

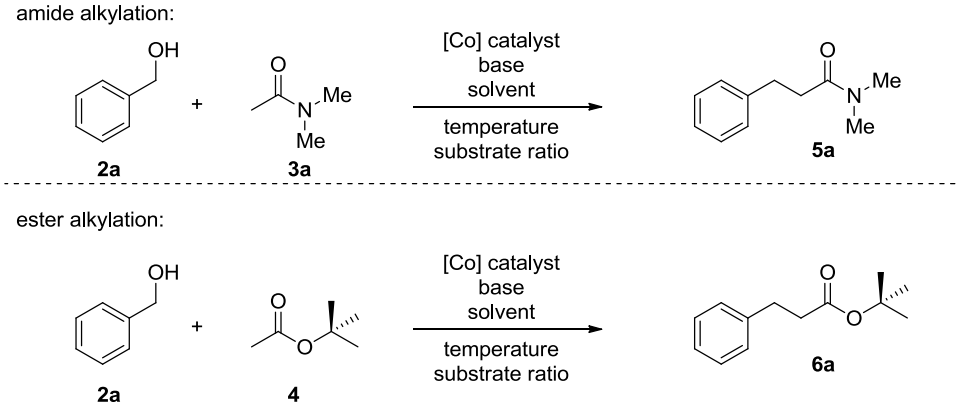
subjected to work up as described above. Amide **5a** was isolated in 81 % yield (143 mg, 0.808 mmol).

**Ester alkylation**. Using a glove box (dry $N_2$ atmosphere), an oven dried glass tube (38 mL volume) was charged with a magnetic stirring bar, *t*-BuOK (1.5 mmol, 168 mg, 1.5 eq), alcohol (1 mmol, 1.0 eq), catalyst **1d** (31 mg, 0.05 mmol, 5 mol%), *tert*-butyl acetate (4 mmol, 4.0 eq) and toluene (1 mL). The tube was sealed with a teflon cap, removed from the glove box and the reaction mixture was heated to 80 °C (oil bath temperature) for 4 h. The reaction mixture was quenched with water (1 mL) and extracted with diethyl ether (3x 10 mL). The organic phase was analyzed with GC and GC-MS to monitor consumption of alcohol and product formation. The combined organic phases were dried over $Na_2SO_4$, evaporated and the ester product was purified using flash column chromatography.

*Note*: Since the reaction mixture gets viscous during the reaction, efficient stirring is necessary. Therefore, a reaction tube with higher diameter is beneficial.

# 3 Screening reactions

In order to find the optimal reaction conditions for ester and amide alkylation, the following reactions were investigated.




*Typical screening procedure*: Using a nitrogen-filled glove box, a 10 mL top-screw vial was charged with a magnetic stirring bar, the corresponding starting materials, base, catalyst and solvent. The vial was sealed, removed from the glove box and the reaction mixture was immersed into a pre-heated oil bath. Afterwards, the reaction was cooled, water (1 mL), diethyl ether (5 mL) and dodecane (GC-standard) were added. After shaking, an aliquot of the organic phase was analyzed by GC-FID to determine the yield based on the internal standard method. For further details, see the table footnotes.
For catalyst screening, see article.

## 3.1 Amide alkylation

Table S 1. Solvent Screening

| Entry | Solvent | Yield (GC) |
|---|---|---|
| **1** | **THF** | **71 %** |
| 2 | 1,4-dioxane | 58 % |
| 3 | toluene | 52 % |
| 4 | *tert*-amyl alcohol | 48 % |
| 5 | Diglyme | 57 % |

*Reaction Conditions*: *N*,*N*'-Dimethylacetamide (2 mmol), benzyl alcohol (1 mmol), precatalyst **1c** (0.05 mmol, 5 mol%), *t*-BuOK (1.0 mmol), solvent (2 mL), pressure tube, 100 °C oil bath, 19 h reaction time.

Table S 2. Base Screening

| Entry | Base | Yield (GC) |
|---|---|---|
| 1 | *t*-BuOLi | 28 % |
| 2 | *t*-BuONa | 63 % |
| **3** | ***t*-BuOK** | **65 %** |
| 4 | KOH | 0 % |
| 5 | KH | 45 % |
| 6 | $Cs_2CO_3$ | 0 % |
| 7 | KHMDS | 23 % |

*Reaction Conditions*: *N*,*N*'-Dimethylacetamide (2 mmol), benzyl alcohol (1 mmol), precatalyst **1c** (0.05 mmol, 5 mol%), base (1.0 mmol), THF (2 mL), pressure tube, 100 °C oil bath, 19 h reaction time.

Table S 3. Base Amount Screening

| Entry | Base amount [eq.] | Yield (GC) |
|---|---|---|
| 1 | 0.1 | 0 % |
| 2 | 0.2 | 0 % |
| 3 | 0.5 | 25 % |
| 4 | 1.0 | 55 % |
| **5** | **1.2** | **66 %** |
| 6 | 1.5 | 65 % |
| 7 | 1.7 | 69 % |
| 8 | 2.0 | 69 % |

*Reaction Conditions*: *N,N'*-Dimethylacetamide (2 mmol), benzyl alcohol (1 mmol), precatalyst **1c** (0.05 mmol, 5 mol%), *t*-BuOK (0.1-2.0 mmol), THF (3 mL), pressure tube, 100 °C oil bath, 19 h reaction time.

Table S 4. Screening of substrate ratio

| Entry | $Me_2NAc$ : BnOH ratio | Yield (GC) |
|---|---|---|
| 1 | 1.0 : 1.0 | 58 % |
| 2 | 1.5 : 1.0 | 64 % |
| **3** | **2.0 : 1.0** | **68 %** |
| 4 | 1.0 : 1.5 | 39 % |
| 5 | 1.0 : 2.0 | 35 % |

*Reaction Conditions*: *N,N'*-Dimethylacetamide (1-2 mmol), benzyl alcohol (1-2 mmol), precatalyst **1c** (0.05 mmol, 5 mol%), *t*-BuOK (1.2 mmol), THF (2 mL), pressure tube, 100 °C oil bath, 19 h reaction time.

Table S 5. Temperature Screening

| Entry | Temperature | Yield (GC) |
|---|---|---|
| 1 | 60 °C | 40 % |
| 2 | 80 °C | 65 % |
| **3** | **100 °C** | **67 %** |

*Reaction Conditions:* N,N'-Dimethylacetamide (2 mmol), benzyl alcohol (1 mmol), precatalyst **1c** (0.05 mmol, 5 mol%), *t*-BuOK (1.2 mmol), THF (2 mL), pressure tube, 100 °C oil bath, 19 h reaction time.

## 3.2 Ester Alkylation

Table S 6. Solvent Screening

| Entry | Solvent | Yield (GC) |
|---|---|---|
| 1 | THF | 24 % |
| **2** | **Toluene** | **40 %** |
| 3 | *tert*-amyl alcohol | 8 % |
| 4 | 1,4-dioxane | 27 % |
| 5 | Diglyme | 13 % |

Reaction Conditions: tert-butyl acetate (2.0 mmol), benzyl alcohol (1.0 mmol), solvent (2 mL), *t*-BuOK (1 mmol), precatalyst **1c** (0.05 mmol, 5 mol%), 80 °C oil bath, sealed tube, 20 h

Table S 7. Base Screening

| Entry | Base (1.0 eq.) | Yield (GC) |
|---|---|---|
| 1 | *t*-BuOLi | *n/d* |
| 2 | *t*-BuONa | 37 % |
| **3** | ***t*-BuOK** | **38 %** |
| 4 | KOH | *n/d* |
| 5 | KH | 18 % |
| 6 | $Cs_2CO_3$ | *n/d* |
| 7 | KHMDS | 15 % |

Reaction Conditions: tert-butyl acetate (2.0 mmol), benzyl alcohol (1.0 mmol), toluene (2 mL), base (1 mmol), precatalyst **1c** (0.05 mmol, 5 mol%), 70 °C, sealed tube, 20 h
n/d = not detected

Table S 8. Base Amount Screening

| Entry | Base amount (eq) | Yield (GC) |
|---|---|---|
| 1 | 0.10 | *n/d* |
| 2 | 0.20 | *n/d* |
| 3 | 0.50 | 15 % |
| 4 | 1.00 | 43 % |
| 5 | 1.20 | 53 % |
| **6** | **1.50** | **60 %** |
| 7 | 1.70 | 57 % |
| 8 | 2.00 | 53 % |

Reaction Conditions: tert-butyl acetate (2.0 mmol), benzyl alcohol (1.0 mmol), toluene (2 mL), t-BuOK (0.1-2.0 mmol), precatalyst **1c** (0.05 mmol, 5 mol%), 70 °C, sealed tube, 20 h
*n/d* = not detected

Table S 9. Screening of substrate ratio

| Entry | *t*-BuOAc/BnOH ratio | Yield (GC) |
|---|---|---|
| 1 | 2.0 : 1.0 | 55 % |
| **2** | **4.0 : 1.0** | **90 %** |
| 3 | 6.0 : 1.0 | 90 % |
| 4 | Neat ester (1.5 mL) | 52 % |

Reaction Conditions: *tert*-butyl acetate (2.0-1.0 mmol), benzyl alcohol (1.5-1.0 mmol), toluene (2 mL), t-BuOK (1.5 mmol), precatalyst **1d** (0.05 mmol, 5 mol%), 70 °C, sealed tube, 20 h.
(Screening with optimized catalyst **1d**)

The reaction can be run within a temperature range of 70-100 °C without high variations in yield (Table S 10). 80 °C was chosen eventually to account for a broad scope.

Table S 10. Screening of temperature

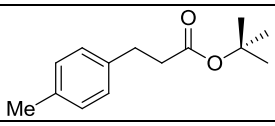
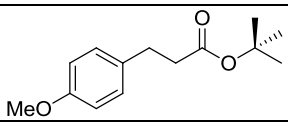
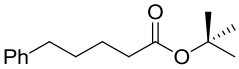
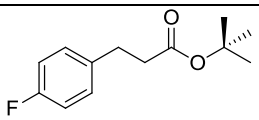
| Entry | Temperature | Isolated yield of **6a** |
|---|---|---|
| 1 | 70 °C | 70 % |
| 2 | 100 °C | 71 % |

Reaction Conditions: *tert*-butyl acetate (4 mmol), benzyl alcohol (1 mmol), toluene (1 mL), *t*-BuOK (1.5 mmol), precatalyst **1d** (0.05 mmol, 5 mol%), 70 °C, sealed tube, 4 h.

The reaction was found to be complete in 4 hours. For the following products, the isolated yields were compared for different reaction times (4 h vs. 12 h) and catalyst loadings (3 mol%

vs. 5 mol%,). No significant variations were detected and 4 h reaction time was chosen eventually (Table S 11).

Table S 11. Comparison of reaction conditions.

| Entry | Product | Conditions | Isolated yield |
|---|---|---|---|
| 1 |  | cat. **1d** (5 mol%), 4 h | 68 % |
| 2 | | cat. **1d** (3 mol%), 12 h | 69 % |
| 3 |  | cat. **1d** (5 mol%), 4 h | 77 % |
| 4 | | cat. **1d** (3 mol%), 12 h | 68 % |
| 5 |  | cat**. 1d** (5 mol%), 4 h | 58 % |
| 6 | | cat. **1d** (3 mol%), 12 h | 56 % |
| 7 |  | cat. **1d** (5 mol%), 4 h | 82 % |
| 8 | | cat. **1d** (3 mol%), 12 h | 75 % |

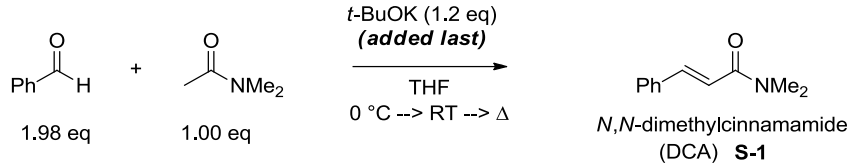
Reaction Conditions: *tert*-butyl acetate (4 mmol), alcohol (1 mmol), toluene (1 mL), *t*-BuOK (1.5 mmol), precatalyst **1d** (3 or 5 mol%), 80 °C oil bath, sealed tube, 4 or 12 h.

## 3.3 Mechanistic Investigations

### 3.3.1 Amide alkylation

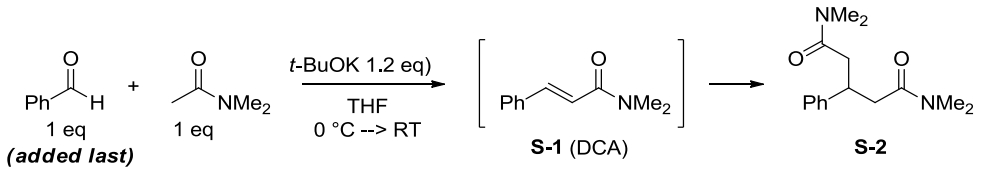
#### 3.3.1.1 Synthesis of *N,N*-dimethylcinnamamide

In order to obtain deeper mechanistic insight into the alkylation reaction, we first prepared *N,N*-dimethylcinnamamide (**S-1**, Scheme S 1, see also synthesis section) which is believed to be a central intermediate in the catalytic cycle.




Scheme S 1. Preparation of N,N-dimethylcinnamamide.

During preparation, we noticed formation of the di-amide **S-2** (Scheme S 2), which is derived from 1,4-addition of *N,N*-dimethylacetamide to DCA. **S-2** was obtained exclusively when benzaldehyde was added dropwise to the anion of *N,N*-dimethylacetamide (prepared from *N,N*-dimethylacetamide and *t*-BuOK in THF, Scheme S 2).




Scheme S 2. Attempted synthesis of N,N-dimethylcinnamamide.

The crude reaction mixture of all prepared amide substrates was analyzed by GC and in general only low amounts of side-products occurred. This result suggested that the concentration of unsaturated intermediate [DCA (**S-1**) for the model reaction] in the reaction mixture must be low (see also Figure S 2 for a typical gas-chromatogram after reaction end).

#### 3.3.1.2 Time-conversion-plot for the model reaction (amide alkylation)

The time-conversion-plot of the model-reaction of the amide alkylation reaction is depicted in Figure S 1. Yields and conversions were obtained by reaction monitoring by GC with dodecane as internal standard.

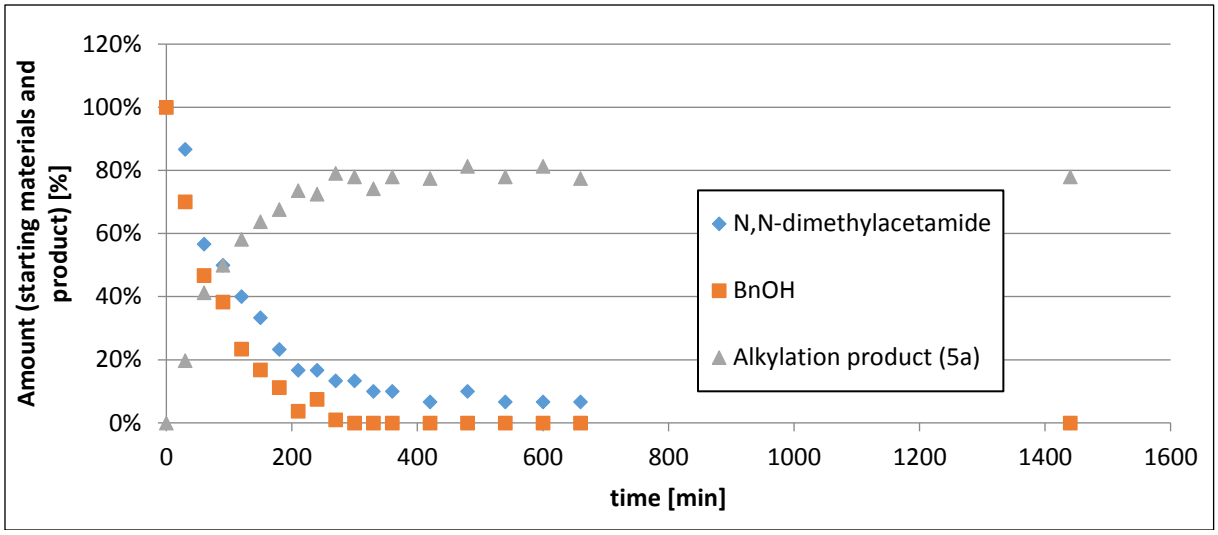
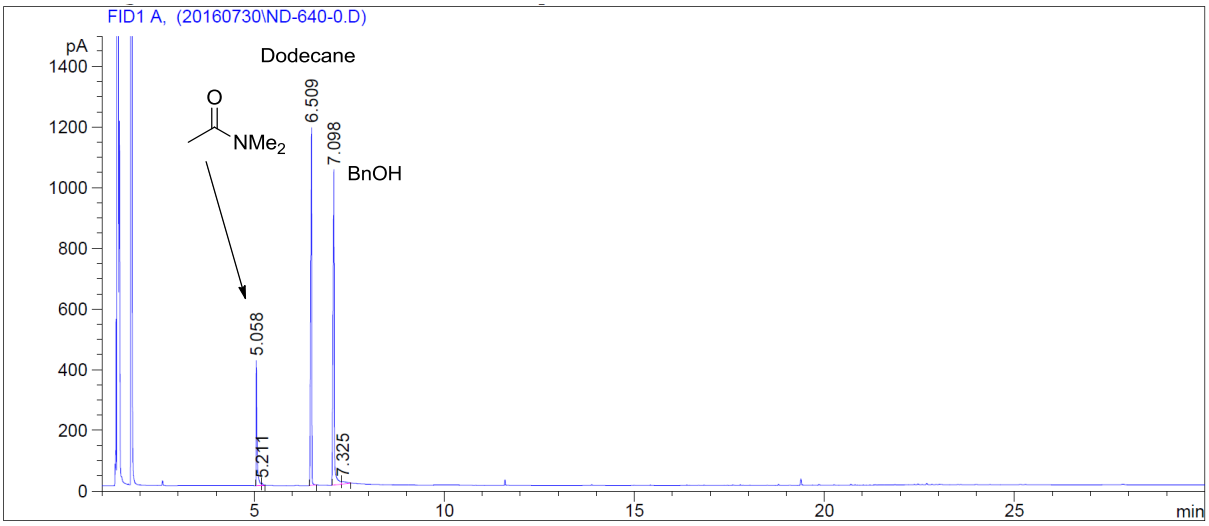



Figure S 1. Time-conversion plot of the amide alkylation reaction.

Reaction start




Reaction end (24 h)

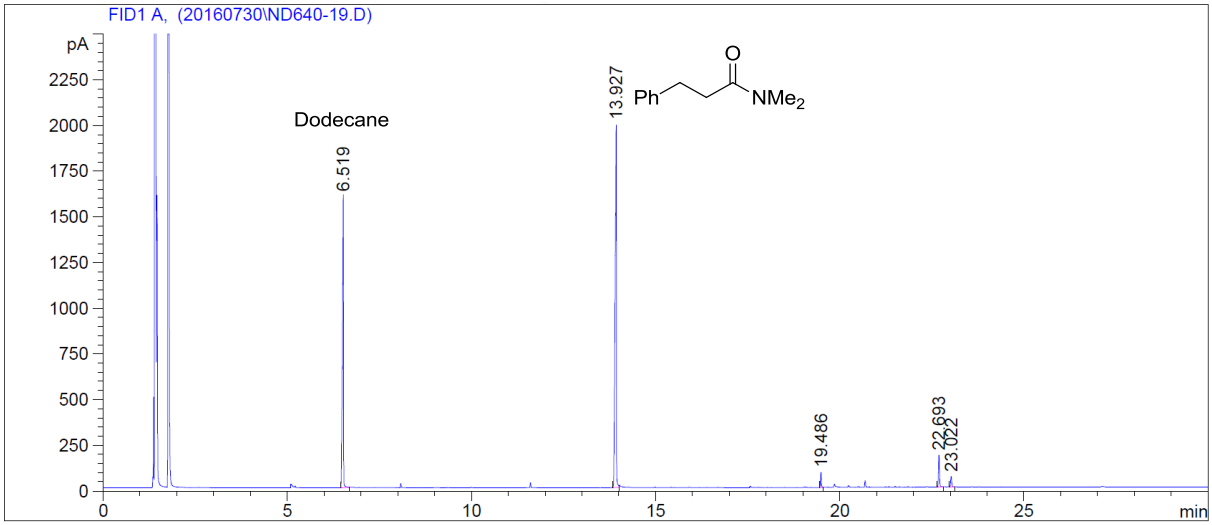


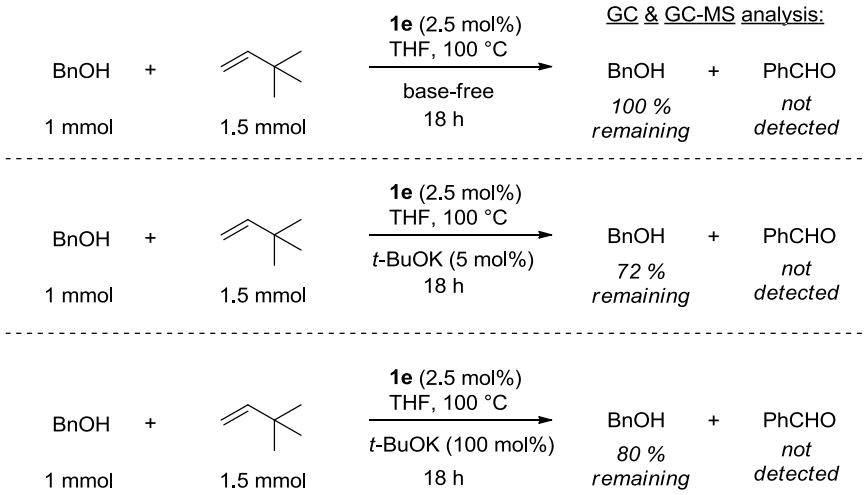

Figure S 2. Gas-chromatograms of the model reaction at reaction start and reaction end.

The following conclusions were drawn:

- No induction period was observed
- No *N*,*N*-dimethylcinnamamide intermediate was detected during the reaction which means the oxidation of alcohol is rate-determining and reduction proceeds relatively fast.
- No significant amount of side-products was observed.
- Alcohol conversion and product formation correlate.

### 3.3.1.3 Investigation of the oxidation step

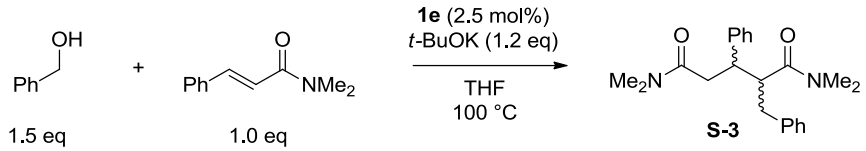
For an Ir-catalyst, the transfer hydrogenation between benzyl alcohol and 3,3-dimethylbut-1-ene is described in the literature as the only mechanistic work. When this reaction was conducted with the cobalt catalyst, no significant conversion of benzyl alcohol was observed with or without base (Scheme S 3).




Scheme S 3. Investigation of transfer hydrogenation.

### 3.3.1.4 Concerted oxidation/reduction

When the reaction between the proposed intermediate *N*,*N*-dimethylcinnamamide and benzyl alcohol under catalytic conditions was monitored, another side-product accumulated in significant amount. The product was identified by GC-MS as the 1,4-addition product between the intermediate *N*,*N*-dimethylcinnamamide and the hydrogenation product. This observation further supports the assumption that the reduction of the α,β-unsaturated intermediate proceeds before competition reactions take place since only very low amounts of this side-product are seen in the catalytic reaction (cf. the gas-chromatogram in Figure S 3 with Figure S 4).




Scheme S 4. Attempted transfer hydrogenation between benzyl alcohol and intermediate.

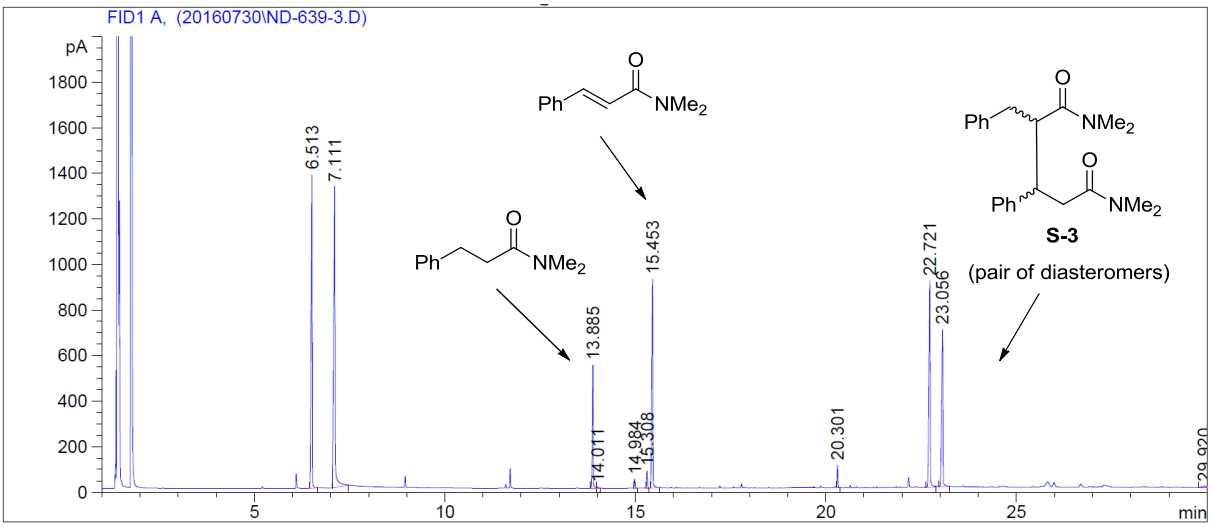



Figure S 3. Gas-chromatogram of the reaction depicted in Scheme S 4 after 1.5 h.

Comparison with catalytic reaction:

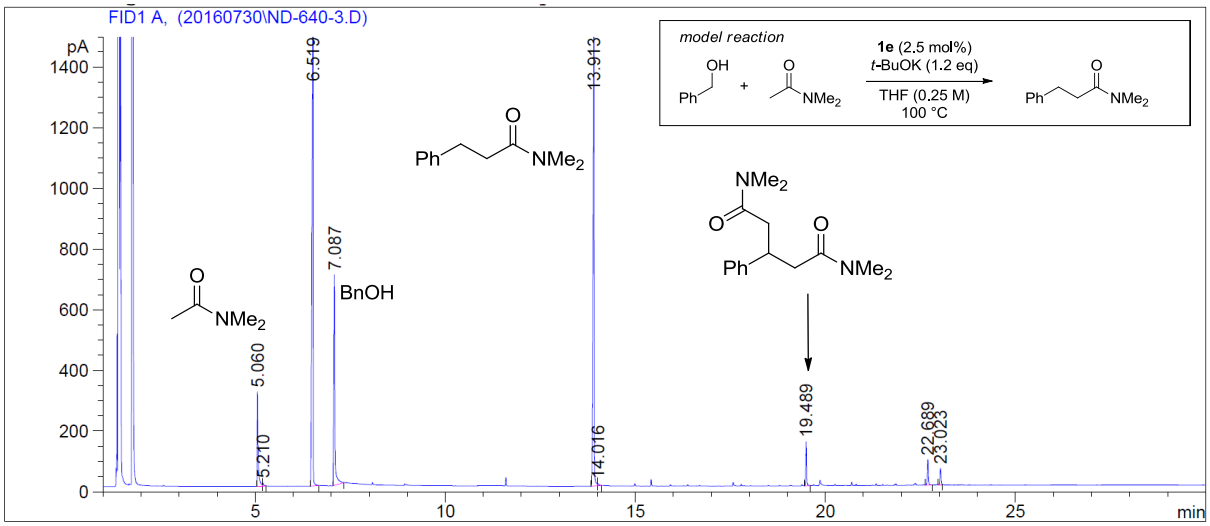
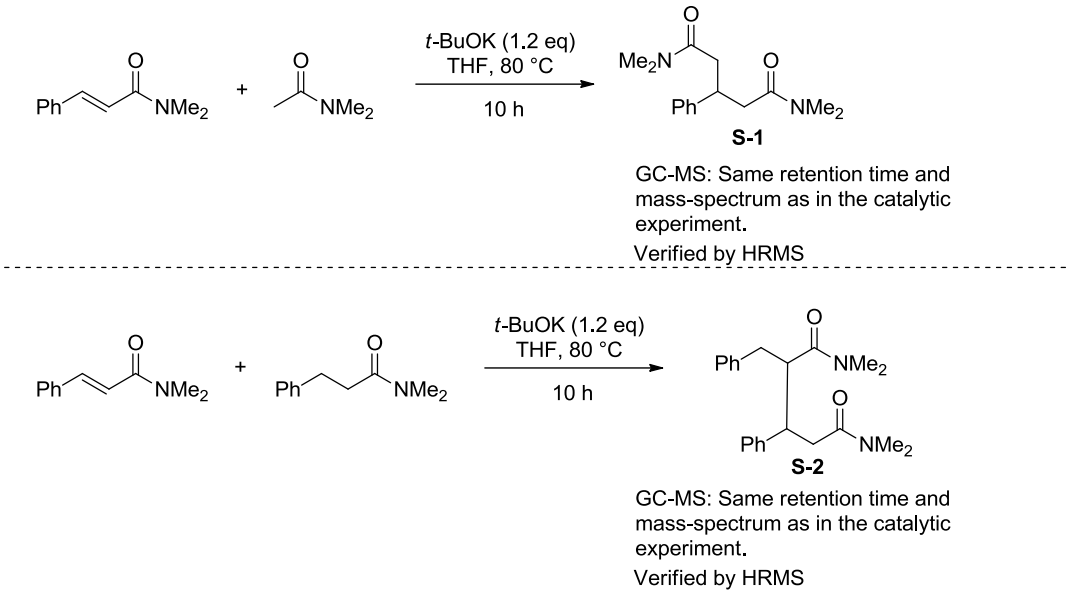



Figure S 4. Gas-chromatogram of the model reaction after 1.5 h.

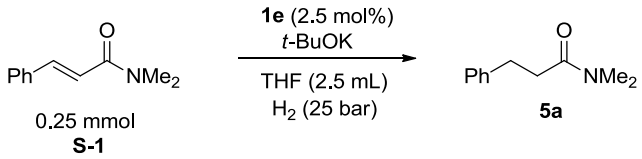
Possible 1,4-addition products were prepared independently to verify GC-measurements (Scheme S 5).




Scheme S 5. Control experiments to verify possible 1,4-addition side-products.

### 3.3.1.5 Hydrogenation experiments

DCA (**S-1**) was subjected to hydrogenation under catalytic conditions. If hydrogen equivalents are not obtained from the rate-limiting alcohol oxidation, but from molecular hydrogen, it was envisioned that fast reduction would limit 1,4-addition side-reactions.



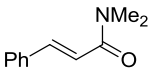

| | | |
|---|---|---|
| Conditions: | (1) 80 °C, 5 mol% *t*-BuOK, 4 h: | 30 % conversion, 20 % yield |
| | (2) 80 °C, 120 mol% *t*-BuOK, 4 h: | 100 % conversion, 41 % yield |
| | (3) 80 °C, 50 mol% *t*-BuOK, 4 h: | 100 % conversion, 61 % yield |
| | (4) 40 °C, 50 mol% *t*-BuOK, 4 h: | 100 % conversion, 42 % yield |
| | (5) 80 °C, 50 mol% *t*-BuOK, 1 h: | 100 % conversion, 60 % yield |
| | (6) 80 °C, 50 mol% *t*-BuOK, 0.5 h: | 100 % conversion, 57 % yield |
| | | *(determined by GC with dodecane as internal standard)* |

Scheme S 6. Hydrogenation experiments.

Hydrogenation proceeded even within 30 min (entry 6 in Scheme S 6) and the 1,4-addition product was not obtained.

### 3.3.1.6 Syntheses

*N,N-dimethylcinnamamide (**S-1**)*



To a stirred solution of benzaldehyde (98.9 mmol, 10 mL, 1.98 eq) and *N,N*-dimethylacetamide (50.0 mmol, 4.65 mL, 1.00 eq) in THF (200 mL) was added *t*-BuOK (60 mmol, 6.72 g, 1.2 eq) in portions at 0 °C. The reaction mixture was warmed to rt and heated

to reflux for 1 hour. After cooling, water was added until a clear solution was obtained. The reaction mixture was then concentrated and partitioned between water (50 mL) and $CH_2Cl_2$ (100 mL). After separation of the phases, the aqueous phase was extracted with $CH_2Cl_2$ (2x 100 mL). The combined organic phase was dried over $Na_2SO_4$, concentrated and purified by column chromatography (silica gel, pentane/ethyl acetate 1:1 → 1:2) to give the title compound as a crystalline white solid (2.98 g, 17.0 mmol, 34 %).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.67 (d, *J*=15.26 Hz, 1 H), 7.50 - 7.55 (m, 2 H), 7.31 - 7.40 (m, 3 H), 6.89 (d, *J*=15.26 Hz, 1 H), 3.17 (s, 3 H), 3.07 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 166.8, 142.5, 135.5, 129.7, 128.9, 127.9, 117.5, 37.6, 36.1 ppm.

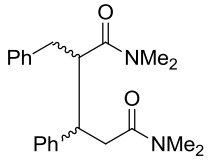
**MS** (EI, 70 eV) *m/z*: 175.1 ($M^+$), 131.1, 103.1, 77.1, 51.1.

The spectroscopic data correspond with those reported in the literature.[3]

*Note:* When the reactants were added in a different order (*N*,*N*-dimethylacetamide, *t*-BuOK, then dropwise addition of benzaldehyde (1 eq)), the corresponding 1,4-addition product **S-2** was obtained as monitored by GC-MS (*m/z* 262.1).

**Confirmation of 1,4-addition products:**

*2-benzyl-$N^1$,$N^1$,$N^5$,$N^5$-tetramethyl-3-phenylpentanediamide*

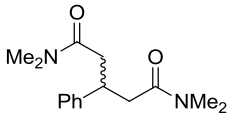



Under nitrogen atmosphere (glove box), *N*,*N*-dimethylcinnamamide (0.5 mmol, 87.5 mg, 1 eq), *N*,*N*-dimethyl-3-phenylpropanamide (0.75 mmol, 133 mg, 1.5 eq), *t*-BuOK (67 mg, 0.6 mmol, 1.2 eq) and THF (3 mL) were mixed in a 10 mL vial. The vial was sealed and the reaction mixture was heated with a 80 °C oil bath for 10.5 h. The reaction was quenched with water (2 mL) and extracted with ethyl acetate (3x 10 mL) and concentrated. The crude product was analyzed by GC-MS and LC-HRMS. The above 1,4-addition product was observed at the same retention time as in the catalytic reaction and the identity was further confirmed by HRMS.

**GC-MS** (EI, 70 eV) *m/z*: 352.2 ($M^+$), 308.2, 266.1, 216.1, 176.1, 131.1, 115.1, 103.1, 91.1, 72.1.

**HRMS** (ESI+): *m/z* calcd. for $[C_{22}H_{28}N_2O_2 + H]^+$ 353.22235; found: 353.22134.

*$N^1$,$N^1$,$N^5$,$N^5$-tetramethyl-3-phenylpentanediamide*

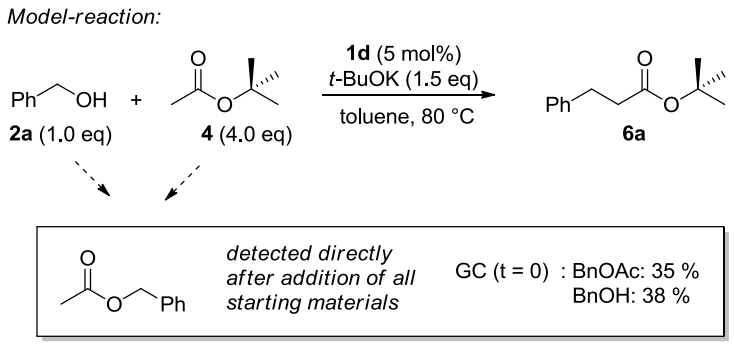


Under nitrogen atmosphere (glove box), *N*,*N*-dimethylcinnamamide (0.5 mmol, 87.5 mg, 1 eq), *N*,*N*-dimethylacetamide (1 mmol, 93 µL, 2 eq), *t*-BuOK (67 mg, 0.6 mmol, 1.2 eq) and THF (3 mL) were mixed in a 10 mL vial. The vial was sealed and the reaction mixture was heated with a 80 °C oil bath for 10.5 h. The reaction was quenched with water (2 mL) and extracted with ethyl acetate (3x 10 mL) and concentrated. The crude product was analyzed by GC-MS and LC-HRMS. The above 1,4-addition product was observed at the same retention time as in the catalytic reaction and the identity was further confirmed by HRMS.
**GC-MS** (EI, 70 eV) *m/z*: 262.1 ($M^+$), 218.1, 190.1, 176.1, 131.0, 103.0, 87.1, 72.0.
**HRMS** (ESI+): *m/z* calcd. for $[C_{15}H_{22}N_2O_2 + H]^+$ 263.17540; found: 263.17462.

## 3.3.2 Ester alkylation

### 3.3.2.1 Reaction monitoring

The reaction of the ester alkylation (model reaction) was monitored by GC with dodecane as internal standard (Scheme S 7 and Figure S 5).




Scheme S 7. Model reaction for ester alkylation and outcome of analysis of the reaction directly after addition of starting materials.

An aliquot (500 µL from a 2 mmol scale reaction) was removed from the reaction mixture immediately after addition of *tert*-butyl acetate. The aliquot was quenched with water and extracted with diethyl ether.
GC-FID and GC-MS analysis of the t = 0 min reaction sample showed a significant amount of benzyl acetate which was confirmed by GC-MS and by comparison of the retention time of an authentic sample.
This result indicates that transesterification products undergo resolution by alcohol exchange with *t*-BuOH followed by consumption of the primary alcohol in the catalytic alkylation reaction. The catalytic reaction gives one single product after 1-4 h.

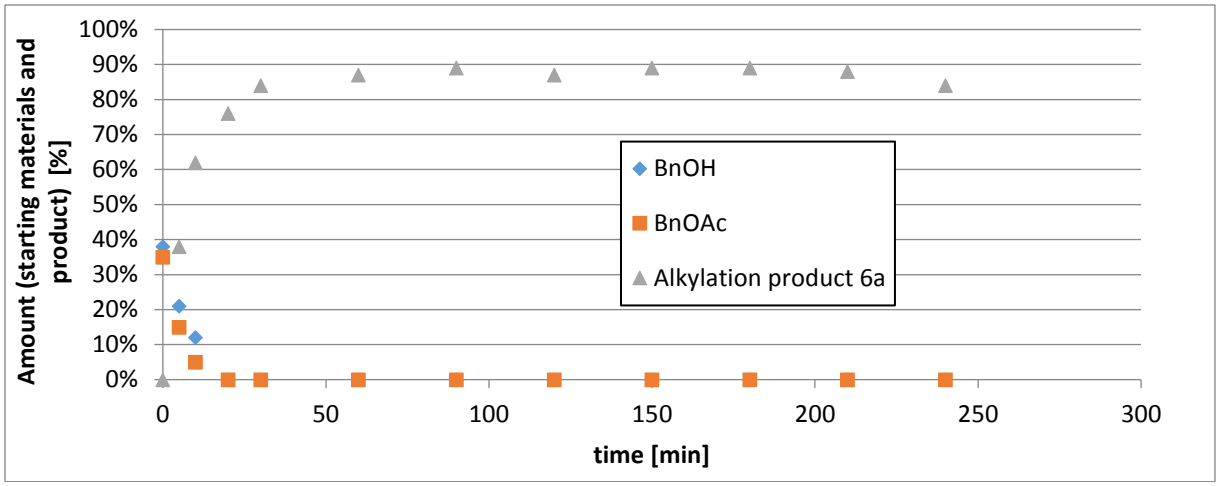
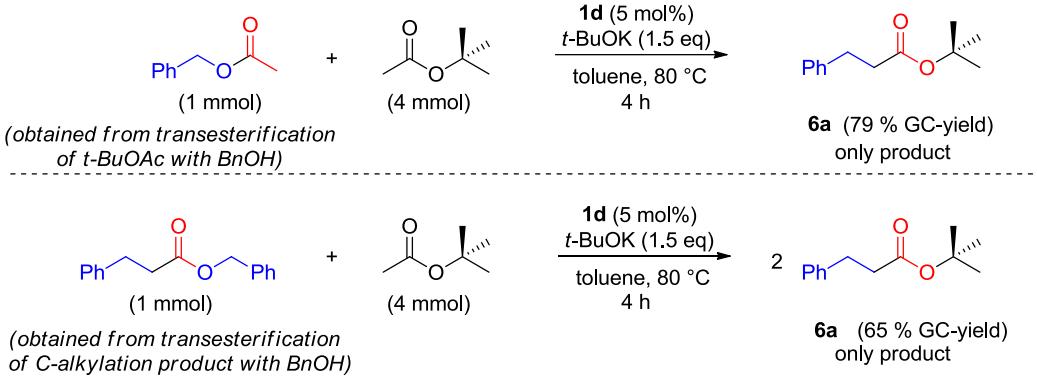



Figure S 5. Time-conversion plot for the catalytic ester alkylation (model reaction).

### 3.3.2.2 Control reactions

The corresponding transesterification products were subjected to the reaction conditions to prove the shift towards the *tert*-butyl ester.



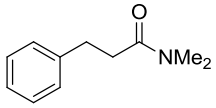

Scheme S 8. Control reactions of transesterification products under catalytic conditions.

Both benzyl acetate and benzyl 3-phenylpropanoate were converted into the alkylated *tert*-butyl ester **6a** under catalytic conditions (Scheme S 8). Conversion was quantitative and no other side-products were observed by GC analysis.

# 4 Characterization data

## 4.1 Amide alkylation products

*N,N-dimethyl-3-phenylpropanamide (**5a**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1.5). Yield: 147 mg (0.830 mmol, 83 %) colorless oil.

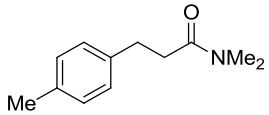
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.25 - 7.31 (m, 2 H), 7.17 - 7.24 (m, 3 H), 3.00-2.94 (m, 8 H, overlapping signals of $NMe_2$ and $CH_2$), 2.58 - 2.64 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.3, 141.6, 128.5, 126.2, 37.2, 35.4, 31.5 ppm.

**MS** (EI, 70 eV) *m/z*: 177.2 ($M^+$), 131.1, 105.1, 91.1, 72.1.

The spectroscopic data correspond to those reported in the literature.[4]

*N,N-dimethyl-3-(p-tolyl)propanamide (**5b**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1). Yield: 163 mg (0.853 mmol, 85 %) colorless oil.

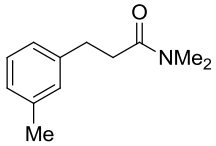
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.05 - 7.16 (m, 4 H), 2.87 - 2.98 (m, 8 H, overlapping signals of $NMe_2$ and $CH_2$), 2.54 - 2.64 (m, 2 H), 2.31 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.3, 138.5, 135.6, 129.2, 128.4, 37.2, 35.6, 35.5, 31.0, 21.1 ppm.

**MS** (EI, 70 eV) *m/z*: 191.1 ($M^+$), 147.1, 131.0, 118.1, 105.1, 91.1, 72.1.

The spectroscopic data correspond to those reported in the literature.[4]

*N,N-dimethyl-3-(m-tolyl)propanamide (**5c**)*



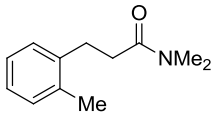

Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1). Yield: 154 mg (0.806 mmol, 81 %) colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.13 - 7.21 (m, 1 H), 6.99 - 7.07 (m, 3 H), 2.89 - 2.99 (m, 8 H overlapping signals of $NMe_2$ and $CH_2$), 2.56 - 2.65 (m, 2 H), 2.33 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.3, 141.5, 138.1, 129.3, 128.5, 126.9, 125.5, 37.2, 35.5, 31.4, 21.5 ppm.

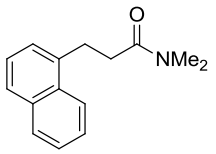
**MS** (EI, 70 eV) *m/z*: 191.2 ($M^+$), 147.1, 131.1, 119.1, 105.1, 91.1, 72.1.
The spectroscopic data correspond to those reported in the literature.[4]

*N,N-dimethyl-3-(o-tolyl)propanamide (**5d**)*



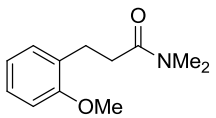

Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1). Yield: 153 mg (0.801 mmol, 80 %) colorless oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.06 - 7.21 (m, 5 H), 2.89 - 3.00 (m, 8 H, overlapping signals of $NMe_2$ and $CH_2$), 2.53 - 2.60 (m, 2 H), 2.33 (s, 3 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.4, 140.0, 136.1, 130.4, 128.9, 126.4, 126.2, 37.2, 35.5, 34.0, 28.8, 19.4 ppm.
**MS** (EI, 70 eV) *m/z*: 191.1 ($M^+$), 176.1, 162.1, 147.1, 119.1, 105.1, 91.1, 72.0.
The spectroscopic data correspond to those reported in the literature.[4]

*N,N-dimethyl-3-(naphthalen-1-yl)propanamide (**5e**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1). Yield: 176 mg (0.775 mmol, 78 %) colorless viscous oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 8.03 - 8.09 (m, 1 H), 7.86 (dd, *J*=8.39, 1.07 Hz, 1 H), 7.73 (d, *J*=7.63 Hz, 1 H), 7.45 - 7.55 (m, 2 H), 7.35 - 7.43 (m, 2 H), 3.42 - 3.48 (m, 2 H), 2.96 (s, 3 H), 2.85 (s, 3 H), 2.70 - 2.77 (m, 2 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.4, 137.8, 134.0, 131.8, 129.0, 127.1, 126.3, 126.2, 125.8, 123.7, 37.2, 35.6, 34.7, 28.6 ppm.
**MS** (EI, 70 eV) m/z: 227.1 ($M^+$), 183.1, 154.1, 141.1, 128.1, 115.1, 86.0, 72.0.
**HRMS** (ESI+) *m/z* $[C_{15}H_{17}NO + H]^+$ calcd. 228.13829, found 228.13771
The spectroscopic data correspond to those reported in the literature.[6]

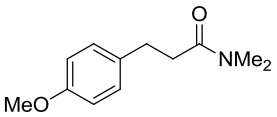
*3-(2-methoxyphenyl)-N,N-dimethylpropanamide (**5f**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1.5). Yield: 184 mg (0.889 mmol, 89 %) colorless oil.

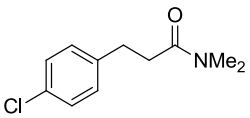
**$^1$H NMR** (500 MHz, $CDCl_3$) δ =7.15 - 7.22 (m, 2 H), 6.87 (td, *J*=7.40, 1.07 Hz, 1 H), 6.84 (d, *J*=8.24 Hz, 1 H), 3.82 (s, 3 H), 2.90 - 2.97 (m, 8 H, overlapping signals of $NMe_2$ and $CH_2$), 2.54 - 2.61 (m, 2 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.9, 157.6, 130.3, 129.8, 127.5, 120.6, 110.3, 55.3, 37.2, 35.4, 33.8, 26.8 ppm.
**MS** (EI, 70 eV) *m/z*: 207.1 ($M^+$), 192.1, 176.1, 161.1, 150.1, 134.1, 121.1, 105.1, 91.1, 72.1, 65.1.
The spectroscopic data correspond to those reported in the literature.[4]

*3-(4-methoxyphenyl)-N,N-dimethylpropanamide (**5g**)*



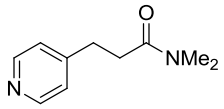

Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1→1:1.5). Yield: 177 mg (0.855 mmol, 86 %) colorless oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.07 - 7.17 (m, 2 H), 6.76 - 6.85 (m, 2 H), 3.76 (s, 3 H), 2.91-2.88 (m, 8 H, overlapping signals of $NMe_2$ and $CH_2$), 2.50 - 2.62 (m, 2 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ =172.3, 158.0, 133.6, 129.4, 113.9, 55.3, 37.2, 36.0, 35.4, 30.5 ppm.
**MS** (EI, 70 eV) *m/z*: 224.1 ($M^+$), 183.2, 154.2, 140.1, 121.1, 100.1, 87.1, 79.1, 72.1, 55.1.
The spectroscopic data correspond to those reported in the literature.[4]

*3-(4-chlorophenyl)-N,N-dimethylpropanamide (**5h**)*




*Variation from the general procedure: t*-BuONa (1.2 mmol) was used as base instead of *t*-BuOK. Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1 → 1:2). Yield: 160 mg (0.758 mmol, 76 %) colorless oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.20 - 7.25 (m, 2 H), 7.12 - 7.16 (m, 2 H), 2.89 - 2.96 (m, 8 H, overlapping signals of $CH_2$ and $NMe_2$), 2.54 - 2.60 (m, 2 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 171.9, 140.1, 131.9, 129.9, 128.6, 37.2, 35.5, 35.1, 30.7 ppm.
**MS** (EI, 70 eV) *m/z*: 211.1 ($M^+$), 167.0, 138.0, 131.0, 125.0, 103.0, 86.1, 72.0, 58.0.
The spectroscopic data correspond to those reported in the literature.[4]

*N,N-dimethyl-3-(pyridin-4-yl)propanamide (**5i**)*




*Variation from the general procedure*: Catalyst **1f** (5 mol%) was used. Purification by column chromatography (silica gel, $CH_2Cl_2$/MeOH, 100:5). Yield: 125 mg (0.702 mmol, 70 %) yellow oil.

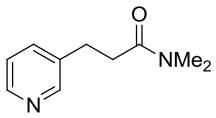
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 8.46 (d, *J*=4.88 Hz, 2 H), 7.13 (d, *J*=5.80 Hz, 2 H), 2.96-2.91 (m, 8 H, overlapping signals of $NMe_2$ and $CH_2$), 2.60 (t, *J*=7.78 Hz, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 171.3, 150.7, 149.8, 124.0, 37.2, 35.6, 33.8, 30.5 ppm.

**MS** (EI, 70 eV) *m/z*: 178.1 ($M^+$), 134.4, 106.1, 72.1.

**HRMS** (ESI+) *m/z* $[C_{10}H_{14}N_2O + H]^+$ calcd. 179.11789, found 179.11739

*N,N-dimethyl-3-(pyridin-3-yl)propanamide (**5j**)*




*Variation from the general procedure*: Catalyst **1f** (5 mol%) was used. Purification by column chromatography (silica gel, $CH_2Cl_2$/MeOH, 100:5). Yield: 144 mg (0.809 mmol, 81 %) colorless oil.

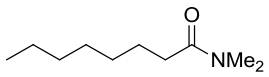
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 8.46 (s, 1 H), 8.42 (d, *J*=4.27 Hz, 1 H), 7.54 (d, *J*=7.93 Hz, 1 H), 7.18 (dd, *J*=7.93, 4.88 Hz, 1 H), 2.98-2.91 (m, 8 H, overlapping signals of $NMe_2$ and $CH_2$), 2.59 (t, *J*=7.63 Hz, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 171.5, 150.0, 147.7, 136.9, 136.2, 123.4, 37.2, 35.6, 34.7, 28.4 ppm.

**MS** (EI, 70 eV) *m/z*: 177.1 ($M^+$), 135.1, 106.1, 92.0, 72.0.

The spectroscopic data correspond to those reported in the literature.[5]

*N,N-dimethyloctanamide (**5k**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1). Yield: 156 mg (0.912 mmol, 91 %) colorless oil.

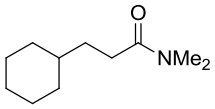
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 3.00 (s, 3 H), 2.94 (s, 3 H), 2.26 - 2.34 (m, 2 H), 1.57 - 1.67 (m, 2 H), 1.20 - 1.38 (m, 8 H), 0.82 - 0.91 (m, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 173.4, 37.4, 35.5, 33.6, 31.9, 29.6, 29.3, 25.4, 22.8, 14.2 ppm.

**MS (EI)**: *m/z* 171.2 ($M^+$), 142.1, 128.1, 114.1, 100.1, 87.1, 72.1, 57.1.

The spectroscopic data correspond to those reported in the literature.[6]

*3-cyclohexyl-N,N-dimethylpropanamide (**5l**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1). Yield: 170 mg (0.929 mmol, 93 %) colorless oil.

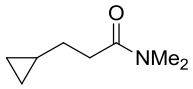
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 2.98 (s, 3 H), 2.91 (s, 3 H), 2.25 - 2.32 (m, 2 H), 1.57 - 1.74 (m, 5 H), 1.44 - 1.54 (m, 2 H), 1.04 - 1.29 (m, 4 H), 0.81 - 0.95 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 173.6, 37.6, 37.4, 35.5, 33.2, 32.7, 31.0, 26.7, 26.4 ppm.

**MS** (EI, 70 eV): *m/z* 183.2 ($M^+$), 154.2, 140.1, 121.1, 100.1, 87.1, 72.1, 55.1.

The spectroscopic data correspond to those reported in the literature.[4]

*3-cyclopropyl-N,N-dimethylpropanamide (**5m**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1). Yield: 114 mg (0.809 mmol, 81 %) colorless oil.

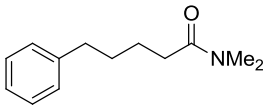
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 3.00 (s, 3 H), 2.92 (s, 3 H), 2.35 - 2.44 (m, 2 H), 1.48 - 1.54 (m, 2 H), 0.66 - 0.75 (m, 1 H), 0.37 - 0.42 (m, 2 H), 0.00 - 0.05 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 173.2, 37.4, 35.4, 33.5, 10.8, 4.6 ppm.

**MS** (EI, 70 eV) *m/z* 141.2 ($M^+$), 126.1, 113.1, 98.1, 87.1, 72.1, 55.1.

**HRMS** (ESI+) *m/z* $[C_8H_{15}NO + H]^+$ calcd. 142.12264, found 142.12217.

*N,N-dimethyl-5-phenylpentanamide (**5n**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1→1:1.5). Yield: 176 mg (0.857 mmol, 86 %) colorless oil.

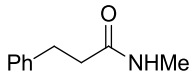
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.24 - 7.30 (m, 2 H), 7.14 - 7.21 (m, 3 H), 2.98 (s, 3 H), 2.94 (s, 3 H), 2.65 (t, *J*=7.02 Hz, 2 H), 2.30 - 2.36 (m, 2 H), 1.63 - 1.74 (m, 4 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 173.0, 142.5, 128.5, 128.4, 125.8, 37.4, 35.9, 35.5, 33.3, 31.4, 25.0 ppm.

**MS** (EI, 70 eV) *m/z*: 205.2 ($M^+$), 117.1, 100.1, 87.1, 72.1.

The spectroscopic data correspond to those reported in the literature.[4]

*N-methyl-3-phenylpropanamide (**5o**)*




Purification by column chromatography (pentane/ethyl acetate, 1:2 → 1:3). Yield: 89 mg (0.546 mmol, 55 %) crystalline white solid.

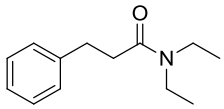
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.27 - 7.31 (m, 2 H), 7.17 - 7.23 (m, 3 H), 5.40 (br. s., 1 H), 2.97 (t, *J*=7.32 Hz, 2 H), 2.77 (d, *J*=4.88 Hz, 3 H), 2.47 (t, *J*=7.93 Hz, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.8, 141.1, 128.7, 128.5, 126.4, 38.6, 31.9, 26.4 ppm.

**MS** (EI, 70 eV) *m/z*: 163.1 ($M^+$), 133.1, 105.1, 91.1, 77.1, 65.1, 58.1, 51.1.

The spectroscopic data correspond to those reported in the literature.[4]

*N,N-diethyl-3-phenylpropanamide (**5p**)*




*Variation from the general procedure*: 5 mol% of catalyst **1d** was used. Purification by column chromatography (pentane/ethyl acetate, 1:1.5). Yield: 156 mg (0.761 mmol, 76 %) colorless oil.

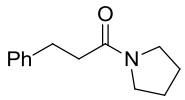
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.15 - 7.32 (m, 5 H), 3.38 (q, *J*=7.12 Hz, 2 H), 3.22 (q, *J*=7.02 Hz, 2 H), 2.96 - 3.01 (m, 2 H), 2.56 - 2.62 (m, 2 H), 1.10 (td, *J*=7.17, 4.58 Hz, 6 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 171.4, 141.8, 128.60, 128.59, 126.2, 42.0, 40.3, 35.3, 31.8, 14.4, 13.2 ppm.

**MS** (EI, 70 eV) m/z: 205.2 ($M^+$), 176.1, 133.1, 120.1, 105.1, 91.1, 72.1, 58.1.

The spectroscopic data correspond to those reported in the literature.[4]

*3-phenyl-1-(pyrrolidin-1-yl)propan-1-one (**5q**)*




Purification by column chromatography (pentane/ethyl acetate, 1:2). Yield: 133 mg (0.655 mmol, 66 %) colorless oil.

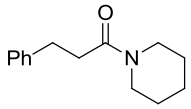
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.27 - 7.31 (m, 2 H), 7.17 - 7.25 (m, 3 H), 3.47 (t, *J*=6.87 Hz, 2 H), 3.29 (t, *J*=6.71 Hz, 2 H), 2.96 - 3.02 (m, 2 H), 2.54 - 2.59 (m, 2 H), 1.85 - 1.92 (m, 2 H), 1.79 - 1.85 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 170.9, 141.6, 128.5, 126.1, 46.6, 45.7, 36.8, 31.3, 26.1, 24.4 ppm.

**MS** (EI, 70 eV) m/z: 203.2 ($M^+$), 112.1, 91.1, 70.1, 55.1.

The spectroscopic data correspond to those reported in the literature.[7]

*3-phenyl-1-(piperidin-1-yl)propan-1-one (**5r**)*




Purification by column chromatography (pentane/ethyl acetate, 1:1). Yield: 167 mg (0.770 mmol, 77 %) colorless oil.

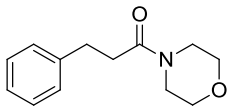
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.27 - 7.34 (m, 2 H), 7.18 - 7.27 (m, 3 H), 3.57 (t, *J*=5.80 Hz, 2 H), 3.34 (t, *J*=5.49 Hz, 2 H), 2.98 (t, *J*=7.63 Hz, 2 H), 2.63 (t, *J*=8.24 Hz, 2 H), 1.59 - 1.66 (m, 2 H), 1.50 - 1.58 (m, 2 H), 1.43 - 1.50 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 170.5, 141.5, 128.53, 128.50, 126.1, 46.7, 42.8, 35.3, 31.7, 26.4, 25.6, 24.6 ppm.

**MS** (EI, 70 eV) m/z: 217.2 ($M^+$), 126.1, 112.1, 105.1, 91.1, 84.1, 77.1, 69.1, 56.1.

The spectroscopic data correspond to those reported in the literature.[4]

*1-morpholino-3-phenylpropan-1-one (**5s**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1→1:3). Yield: 183 mg (0.836 mmol, 84 %) colorless oil which solidified upon standing (pale yellow solid).

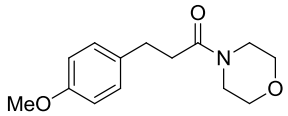
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.25 - 7.31 (m, 2 H), 7.17 - 7.22 (m, 3 H), 3.57 - 3.64 (m, 4 H), 3.47 - 3.53 (m, 2 H), 3.31 - 3.38 (m, 2 H), 2.94 - 3.00 (m, 2 H), 2.57 - 2.64 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 170.9, 141.1, 128.6, 128.5, 126.4, 126.3, 67.0, 66.5, 46.0, 42.0, 34.9, 31.5 ppm.

**MS** (EI, 70 eV) m/z: 219.2 ($M^+$), 128.1, 105.1, 91.1, 77.1, 57.1.

The spectroscopic data correspond to those reported in the literature.[4]

*3-(4-methoxyphenyl)-1-morpholinopropan-1-one (**5t**)*




*Representative procedure for 10 mmol scale reaction*: Using a glove box, a pressure tube (Ace pressure tube, 38 mL volume) was charged with a magnetic stirring bar, 4-acetyl morpholine (20 mmol, 2.30 mL, 2.0 eq), *t*-BuOK (12.0 mmol, 1.34 g, 1.2 eq), 4-methoxybenzyl alcohol (10 mmol, 1.24 mL, 1.0 eq), catalyst **1d** (0.250 mmol, 132 mg, 2.5 mol%) and THF (10 mL). The tube was sealed with a Teflon cap and immersed into a 100 °C oil bath outside the glove box for 24 hours. After cooling, the reaction mixture was quenched with half-saturated aqueous NaCl solution (10 mL) and extracted with diethyl ether (3x 100 mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated. The crude product was nearby pure as judged by $^1$H NMR analysis and was purified using a small pad (5

cm height) of silica gel eluting with pentane/ethyl acetate, 1:2 to give the product as a colorless oil (2.01 g, 8.06 mmol, 81 %).

*The reaction gave the same yields on a 1 and 5 mmol scale.*

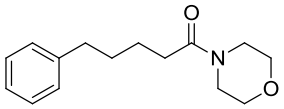
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.08 - 7.17 (m, 2 H), 6.79 - 6.87 (m, 2 H), 3.78 (s, 3 H), 3.58 - 3.67 (m, 4 H), 3.50 - 3.57 (m, 2 H), 3.31 - 3.40 (m, 2 H), 2.87 - 2.95 (m, 2 H), 2.53 - 2.62 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 171.1, 158.2, 133.2, 129.5, 114.1, 67.0, 66.6, 55.4, 46.1, 42.0, 35.2, 30.7 ppm.

**MS** (EI, 70 eV) *m/z*: 249.2 ($M^+$), 161.1, 134.1, 121.1, 108.1, 86.1, 70.1, 57.1.

The spectroscopic data correspond to those reported in the literature.[7]

*1-morpholino-5-phenylpentan-1-one (**5u**)*




*10 mmol scale*. Purification by column chromatography (pentane/ethyl acetate, 6:4 → 1:1). Yield: 2.02 g (8.17 mmol, 82 %) colorless oil.

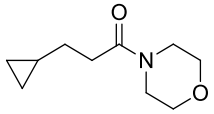
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.21 - 7.25 (m, 2 H), 7.12 - 7.19 (m, 3 H), 3.55 - 3.66 (m, 6 H), 3.35 - 3.42 (m, 2 H), 2.58 - 2.67 (m, 2 H), 2.24 - 2.34 (m, 2 H), 1.60 - 1.71 (m, 4 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ =171.7, 142.3, 128.5, 125.9, 67.1, 66.8, 46.1, 42.0, 35.8, 33.1, 31.2, 25.0 ppm.

**MS** (EI, 70 eV) *m/z*: 247.2 ($M^+$), 156.1, 142.1, 129.1, 117.1, 104.1, 91.1, 70.1, 57.2.

The spectroscopic data correspond to those reported in the literature.[8]

*3-cyclopropyl-1-morpholinopropan-1-one (**5v**)*




*5 mmol scale*. Purification by column chromatography (pentane/ethyl acetate, 1:1). Yield: 780 mg (4.26 mmol, 85 %) colorless oil.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 3.64 - 3.70 (m, 1 H), 3.58 - 3.63 (m, 1 H), 3.46 - 3.52 (m, 1 H), 2.38 - 2.45 (m, 1 H), 1.49 - 1.57 (m, 1 H), 0.67 - 0.77 (m, 1 H), 0.41 - 0.46 (m, 1 H), 0.03 - 0.08 (m, 2 H) ppm.

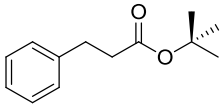
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 171.9, 67.1, 66.8, 46.2, 42.0, 33.2, 30.6, 10.8, 4.7 ppm.

**MS** (EI, 70 eV) *m/z*: 183.1 ($M^+$), 168.1, 154.1, 140.1, 129.1, 114.1, 97.1, 86.1, 70.1, 57.1.

**HRMS** (ESI+): *m/z* $[C_{10}H_{17}NO_2 + H]^+$ calcd. 184.13321, found 184.13268.

## 4.2 Ester alkylation products

*tert-butyl 3-phenylpropanoate (**6a**)*



Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1). Yield: 145 mg (0.704 mmol, 70 %) colorless oil.

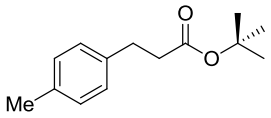
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.16 - 7.23 (m, 2 H), 7.08 - 7.15 (m, 3 H), 2.83 (t, *J*=7.78 Hz, 2 H), 2.43 - 2.49 (m, 2 H), 1.34 (s, 9 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.4, 140.9, 128.50, 128.45, 126.2, 80.4, 37.2, 31.3, 28.2 ppm.

**MS** (EI, 70 eV) *m/z*: 206.1 ($M^+$), 150.1, 133.1, 104.1, 91.1, 77.1, 57.1.

The spectroscopic data correspond to those reported in the literature.[9]

*tert-butyl 3-(p-tolyl)propanoate (**6b**)*



Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1). Yield: 149 mg (0.677 mmol, 68 %) colorless oil.

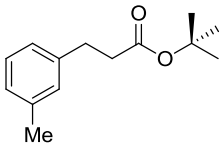
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.11 (s, 4 H), 2.89 (t, *J*=7.63 Hz, 2 H), 2.53 (t, *J*=8.24 Hz, 2 H), 2.33 (s, 3 H), 1.44 (s, 9 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.5, 137.8, 135.6, 129.2, 128.3, 80.4, 37.4, 30.8, 28.2, 21.1 ppm.

**MS** (EI, 70 eV) *m/z*: 220.2 ($M^+$), 164.1, 147.1, 118.1, 105.1, 91.1, 77.1, 65.1, 57.1

The spectroscopic data correspond to those reported in the literature.[9]

*tert-butyl 3-(m-tolyl)propanoate (**6c**)*



Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1). Yield: 168 mg (0.764 mmol, 76 %) colorless oil.

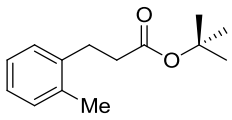
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.19 (t, J=7.48 Hz, 1 H), 6.99 - 7.06 (m, 3 H), 2.90 (t, *J*=7.93 Hz, 2 H), 2.52 - 2.58 (m, 2 H), 2.34 (s, 3 H), 1.45 (s, 9 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.4, 140.8, 138.0, 129.3, 128.4, 126.9, 125.4, 80.4, 37.2, 31.2, 28.2, 21.5 ppm.

**MS** (EI, 70 eV) *m/z*: 220.2 ($M^+$), 164.1, 147.1, 118.1, 105.1, 91.1, 77.1, 65.1, 57.2.

The spectroscopic data correspond to those reported in the literature.[9]

*tert-butyl 3-(o-tolyl)propanoate (**6d**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1). Yield: 138 mg (0.626 mmol, 63 %) colorless oil.

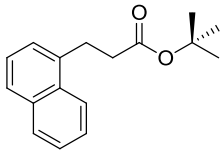
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.06 - 7.19 (m, 4 H), 2.86 - 2.96 (m, 3 H), 2.48 - 2.55 (m, 2 H), 2.34 (s, 3 H), 1.45 (s, 9 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.56, 139.0, 136.1, 130.3, 128.6, 126.4, 126.1, 80.5, 35.9, 28.6, 28.2, 19.4 ppm.

**MS** (EI, 70 eV) *m/z*: 220.2 ($M^+$), 164.1, 147.1, 119.1, 105.1, 91.1, 77.1, 65.1, 57.1.

The spectroscopic data correspond to those reported in the literature.[9]

*tert-butyl 3-(naphthalen-1-yl)propanoate (**6e**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1). Yield: 161 mg (0.629 mmol, 63 %) colorless oil.

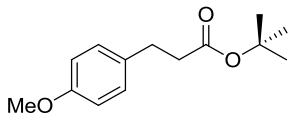
**$^1$H NMR** (500 MHz, $CDCl_3$) δ =8.06 (d, J=8.54 Hz, 1 H), 7.87 (d, J=7.93 Hz, 1 H), 7.74 (d, J=7.93 Hz, 1 H), 7.46 - 7.57 (m, 2 H), 7.34 - 7.44 (m, 2 H), 3.35 - 3.44 (m, 2 H), 2.65 - 2.73 (m, 2 H), 1.42 - 1.51 (m, 9 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.5, 136.9, 134.0, 131.8, 128.9, 127.1, 126.1, 126.0, 125.7, 123.6, 80.6, 36.5, 28.4, 28.2 ppm.

**MS** (EI, 70 eV) *m/z*: 256.1 ($M^+$), 200.1, 183.1, 153.1, 141.1, 128.1, 115.0, 77.0, 57.1.

**Elemental analysis** (%) for $C_{17}H_{20}O_2$ calcd. C 79.65, H 7.86; found: C 79.55, H 7.68.

*tert-butyl 3-(4-methoxyphenyl)propanoate (**6f**)*



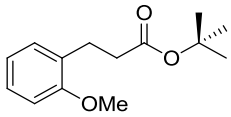

Purification by column chromatography (silica gel, pentane/diethyl ether, 30:1). Yield: 181 mg (0.767 mmol, 77 %) colorless oil.

**$^1$H NMR** (300 MHz, $CDCl_3$) δ =7.12 (d, *J*=8.20 Hz, 2 H), 6.82 (d, *J*=8.20 Hz, 2 H), 3.78 (s, 3 H), 2.85 (t, *J*=8.20 Hz, 2 H), 2.50 (t, *J*=7.61 Hz, 2 H), 1.42 (s, 9 H) ppm.

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 172.5, 133.0, 129.4, 113.9, 80.4, 55.4, 37.5, 30.4, 28.2 ppm.

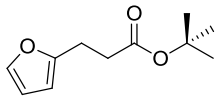
**MS** (EI, 70 eV) *m/z*: 236.1 ($M^+$), 180.1, 163.1, 137.0, 121.1, 91.1, 77.0, 57.1.
The spectroscopic data correspond to those reported in the literature.[10]

*tert-butyl 3-(2-methoxyphenyl)propanoate (**6g**)*



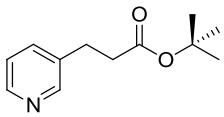

Purification by column chromatography (silica gel, pentane/diethyl ether, 40:1). Yield: 165 mg (0.699 mmol, 70 %) colorless oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.10 - 7.24 (m, 2 H), 6.78 - 6.93 (m, 2 H), 3.83 (s, 3 H), 2.84 - 2.96 (m, 2 H), 2.46 - 2.58 (m, 2 H), 1.43 (s, 9 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.9, 157.6, 130.0, 129.2, 127.5, 120.4, 110.3, 80.1, 55.3, 35.5, 28.2, 26.3 ppm.
**MS** (EI, 70 eV) *m/z*: 236.1 ($M^+$), 180.1, 163.0, 134.1, 121.1, 105.1, 91.1, 77.0, 65.1, 57.1.
**Elemental analysis** (%) for $C_{14}H_{20}O_3$ calcd. C 71.16, H 8.53; found: C 71.08, H 8.82.
Due to low polarity of the compound, no ESI+ HRMS could be obtained.

*tert-butyl 3-(furan-2-yl)propanoate (**6h**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1). Yield: 107 mg (0.546 mmol, 55 %) colorless oil.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.29 (dd, *J*=1.83, 0.92 Hz, 1 H), 6.27 (dd, *J*=3.05, 1.83 Hz, 1 H), 6.00 (dd, *J*=3.36, 0.92 Hz, 1 H), 2.92 (t, *J*=7.63 Hz, 1 H), 2.53 - 2.59 (m, 2 H), 1.43 (s, 9 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.0, 154.6, 141.2, 110.3, 105.3, 80.6, 34.0, 28.2, 23.8 ppm.
**MS** (EI, 70 eV) *m/z*: 196.1 ($M^+$), 140.0, 123.0, 94.0, 81.0, 65.1, 57.1.
The spectroscopic data correspond to those reported in the literature.[9]

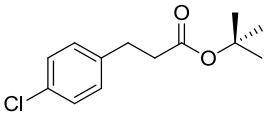
*tert-butyl 3-(pyridin-3-yl)propanoate (**6i**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1). Yield: 100 mg (0.483 mmol, 48 %) colorless oil.
**$^1$H NMR** (500 MHz, $CDCl^3$) δ = 8.35 - 8.53 (m, 2 H), 7.50 (dt, *J*=7.63, 1.83 Hz, 1 H), 7.18 (dd, *J*=7.78, 4.73 Hz, 1 H), 2.88 (t, *J*=7.63 Hz, 2 H), 2.53 (t, *J*=7.48 Hz, 2 H), 1.38 (s, 9 H) ppm.

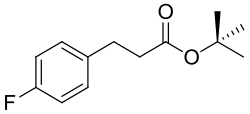
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 171.8, 150.0, 147.8, 136.1, 136.0, 123.4, 80.8, 36.6, 28.3, 28.1 ppm.
**MS** (EI, 70 eV) *m/z*: 207.1 ($M^+$), 192.1, 162.1, 151.0, 134.0, 106.1, 92.0, 78.0, 65.1, 57.1.
The spectroscopic data correspond to those reported in the literature.[11]

*tert-butyl 3-(4-chlorophenyl)propanoate (**6j**)*



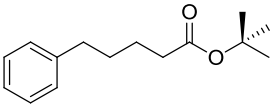

*Variation from the general procedure*: *t*-BuONa (1.5 equiv) was used as the base. Purification by column chromatography (pentane/diethyl ether, 50:1). Yield: 174 mg (0.723 mmol, 72 %) colorless oil.
**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ = 7.21 - 7.31 (m, 2 H), 7.08 - 7.20 (m, 2 H), 2.78 - 2.96 (m, 2 H), 2.46 - 2.62 (m, 2 H), 1.43 (s, 9 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.1, 139.4, 132.0, 129.8, 128.6, 80.6, 37.0, 30.6, 28.2 ppm.
**MS** (EI, 70 eV) *m/z*: 240.1 ($M^+$), 225.0, 207.0, 184.0, 167.0, 149.0, 138.0, 125.0, 112.0, 103.1, 89.0, 77.0, 57.1
The spectroscopic data correspond to those reported in the literature.[9]

*tert-butyl 3-(4-fluorophenyl)propanoate (**6k**)*




2 mL toluene were used. Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1). Yield: 184 mg (0.821 mmol, 82 %) colorless oil.
**$^{1}$H NMR** (500 MHz, $CDCl_3$) δ = 7.15 (dd, *J*=8.39, 5.34 Hz, 2 H), 6.96 (t, *J*=8.70 Hz, 2 H), 2.88 (t, *J*=7.63 Hz, 2 H), 2.51 (t, *J*=7.78 Hz, 2 H), 1.41 (s, 9 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 172.2, 162.5, 160.6, 136.54*, 136.51*, 129.9*, 129.8*, 115.3*, 115.2*, 80.6, 37.3, 30.5, 28.2 ppm.
*$^{13}$C-$^{19}$F coupling is observed.
**MS** (EI, 70 eV) *m/z*: 224.1 ($M^+$), 168.1, 151.1, 122.1, 109.1, 103.1, 96.1, 83.1, 77.1, 57.1.
The spectroscopic data correspond to those reported in the literature.[9]

*tert-butyl 5-phenylpentanoate (**6l**)*

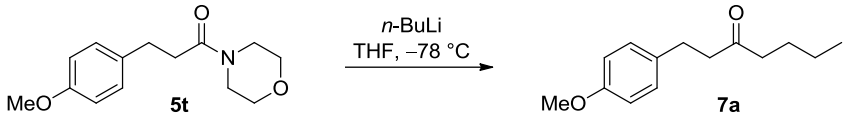



Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1). Yield: 135 mg (0.576 mmol, 58 %) colorless oil.

When conducted at 100 °C (oil bath), the reaction gave the same isolated yield.
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.15 - 7.25 (m, 10 H), 7.05 - 7.14 (m, 3 H), 2.50 - 2.59 (m, 2 H), 2.12 - 2.20 (m, 2 H), 1.56 (dt, *J*=7.32, 3.66 Hz, 4 H), 1.36 (s, 9 H) ppm.
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 173.2, 142.2, 128.5, 128.4, 125.9, 80.1, 35.8, 35.5, 31.0, 28.2, 24.9 ppm.
**MS** (EI, 70 eV) *m/z*: 234.1 ($M^+$), 178.1, 161.1, 117.1, 104.1, 91.1, 77.1, 65.0, 57.1.
The spectroscopic data correspond to those reported in the literature.[9]

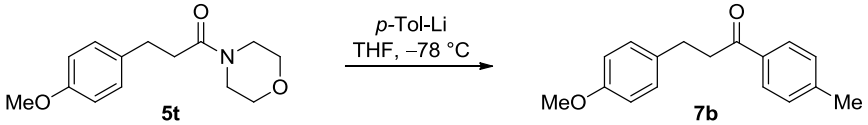
## 4.3 Follow-up products

*1-(4-methoxyphenyl)heptan-3-one (**7a**)*




To a solution of amide **5t** (255 mg, 1.02 mmol, 1 eq) in abs. THF (5 mL) was added *n*-BuLi (1.6 M in hexane, 3 mmol, 3 equiv, 1.88 mL) dropwise at –78 °C. After 3 h and 3 h 40 min aliquots of *n*-BuLi (0.5 mmol and 0.3 mmol, respectively) were added in addition. After 4 h 20 min overall reaction time the reaction was quenched with aqueous acetic acid (30 %, 5 mL), warmed to rt and extracted with diethyl ether (3x 30 mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated. Purification by column chromatography (silica gel, pentane/diethyl ether, 6:1) gave ketone **7a** as a colorless oil ( 207 mg, 0.941 mmol, 92 %).
**$^1$H NMR** (300 MHz, $CDCl_3$) δ =7.03 - 7.15 (m, 2 H), 6.76 - 6.89 (m, 2 H), 3.78 (s, 3 H), 2.78 - 2.90 (m, 2 H), 2.63 - 2.76 (m, 2 H), 2.37 (t, *J*=7.32 Hz, 2 H), 1.44 - 1.61 (m, 2 H), 1.28 (dq, *J*=14.86, 7.35 Hz, 2 H), 0.88 (t, *J*=7.32 Hz, 3 H) ppm.
**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 210.7, 158.0, 133.3, 129.3, 114.0, 55.4, 44.7, 42.9, 29.1, 26.0, 22.4, 14.0 ppm
**MS** (EI, 70 eV) *m/z*: 220.1 ($M^+$), 163.1, 135.1, 121.0, 108.0, 91.1, 85.0, 77.0, 57.1.
**HRMS** (ESI+): *m/z* $[C_{14}H_{20}O_2 + H]^+$ calcd. 221.15361, found 221.15303.

*3-(4-methoxyphenyl)-1-(pyridin-2-yl)propan-1-one (**7b**)*




To a solution of *para*-tolyl lithium (241 mg, 2.46 mmol, 3 eq.) in abs. THF (8 mL) was added a solution of 3-(4-methoxyphenyl)-1-morpholinopropan-1-one (204 mg, 0.819 mmol, 1 eq.) in abs. THF (3 mL) dropwise by syringe at –78 °C. The reaction mixture was stirred for 1 hour and was then quenched by the addition of aqueous acetic acid (30%, 5 mL). The reaction mixture was warmed to rt and extracted with MTBE (3x 30 mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated. Column chromatography (pentane/diethyl ether,

9:1) gave the title compound as a colorless oil which solidified upon standing (187 mg, 0.736 mmol, 90 %).

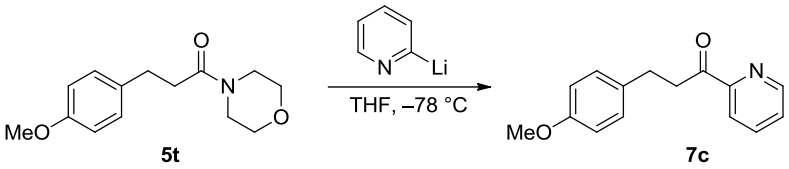
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 7.79 (d, *J*=8.24 Hz, 2 H), 7.14 - 7.23 (m, 2 H), 7.05 - 7.13 (m, 2 H), 6.72 - 6.81 (m, 2 H), 3.71 (s, 3 H), 3.11 - 3.23 (m, 2 H), 2.89 - 2.97 (m, 2 H), 2.33 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 199.1, 158.0, 143.9, 134.5, 133.5, 129.4, 128.3, 114.0, 55.3, 40.7, 29.4, 21.7 ppm.

**MS** (EI, 70 eV) *m/z*: 254.1 ($M^+$), 239.1, 135.0, 121.1, 108.1, 91.1, 77.0, 65.1, 51.0.

The spectroscopic data correspond to those reported in the literature.[12]

*3-(4-methoxyphenyl)-1-(pyridin-2-yl)propan-1-one (**7c**)*




**5t** **7c**

To a solution of 2-bromopyridine (438 mg, 264 µL, 2.77 mmol, 3.0 eq) in abs. THF (4 mL) was added *n*-butyl lithium (1.6 M in hexane, 1.44 mL, 2.30 mmol, 2.5 eq) dropwise at –78 °C and the resulting dark-orange solution was stirred for 1 hour at this temperature. Then a solution of the amide **5t** (230 mg, 0.924 mmol, 1.0 eq) in THF (3 mL) was added dropwise. After one hour the reaction was quenched by the addition of hydrochloric acid (1 M, 5 mL), diluted with MTBE and warmed to rt. The aqueous phase was extracted with MTBE (3x 30 mL) and the combined organic phase was dried over $Na_2SO_4$ and concentrated. Column chromatography (silica gel, pentane/diethyl ether, 5:1) gave the ketone as a colorless oil (180 mg, 0.747 mmol, 81 %).

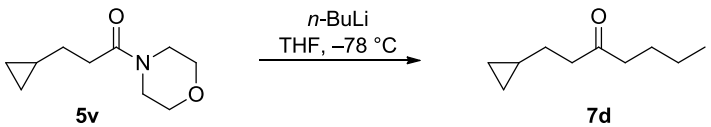
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 8.58 - 8.73 (m, 1 H), 8.03 (dt, *J*=7.78, 1.14 Hz, 1 H), 7.82 (td, *J*=7.71, 1.68 Hz, 1 H), 7.45 (ddd, *J*=7.63, 4.88, 1.22 Hz, 1 H), 7.12 - 7.24 (m, 2 H), 6.76 - 6.89 (m, 2 H), 3.77 (s, 3 H), 3.54 (t, *J*=7.63 Hz, 2 H), 3.01 (t, *J*=7.63 Hz, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 201.2, 158.0, 153.4, 149.1, 137.0, 133.6, 129.5, 127.2, 121.9, 113.9, 55.3, 39.8, 29.1 ppm.

**MS** (EI, 70 eV) *m/z*: 241.1 ($M^+$), 212.1, 121.1, 107.0, 91.1, 79.0, 65.1, 51.0.

**HRMS** (ESI+): *m/z* $[C_{10}H_{14}N_2O + H]^+$ calcd. 242.11756, found 242.11702

*1-cyclopropylheptan-3-one (**7d**)*




**5v** **7d**

To a solution of amide **5v** (267 mg, 1.46 mmol, 1 eq) in abs. THF (5 mL) was added *n*-butyl lithium (1.6 M in hexane, 2.73 mL, 4.38 mmol, 3 eq) dropwise at –78 °C. The reaction mixture was stirred at this temperature for 1 hour and was then quenched with hydrochloric

acid (1 M, 5 mL) and diluted with diethyl ether (10 mL). After warming to rt, the reaction mixture was extracted with diethyl ether (3x 10 mL), the combined phase was dried over $Na_2SO_4$ and concentrated. Column chromatography (pentane/diethyl ether, 15:1, 1st eluting fraction) gave ketone **7d** as a colorless oil (203 mg, 1.32 mmol, 90 %).

**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 2.50 (t, *J*=7.32 Hz, 2 H), 2.41 (t, *J*=7.48 Hz, 2 H), 1.55 (dt, *J*=15.18, 7.51 Hz, 2 H), 1.46 (q, *J*=7.12 Hz, 2 H), 1.31 (dq, *J*=15.03, 7.40 Hz, 2 H), 0.90 (t, *J*=7.32 Hz, 3 H), 0.61 - 0.71 (m, 1 H), 0.35 - 0.46 (m, 2 H), -0.01 - 0.05 (m, 2 H) ppm.

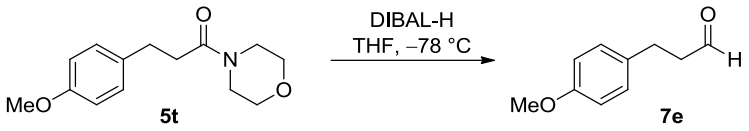
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 211.8, 42.9, 29.2, 26.1, 22.5, 14.0, 10.7, 4.6 ppm.

**MS** (EI, 70 eV) *m/z*: 154.1 ($M^+$), 139.1, 125.1, 112.1, 97.1, 83.1, 69.1, 57.1.

**Elemental analysis** (%) for $C_{10}H_{18}O$: calcd. C 77.87, H 11.76; found: C 77.76, H 12.03.

Due to low molecular weight and polarity, no ESI+ HRMS could be obtained.

*3-(4-methoxyphenyl)propanal (**7e**)*




To a solution of amide **5t** (130 mg, 0.522 mmol, 1 eq) in abs. THF (3 mL) was added DIBAL-H (1 M in hexane, 0.6 mL, 0.600 mmol, 1.15 eq) at –78 °C. The reaction was stirred for 50 min and was then quenched by the addition of an aqueous solution of Na/K tartrate and diluted with diethyl ether. The reaction was warmed to rt, the phases were separated and the aqueous phase was extracted with diethyl ether (4x 20 mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated. Column chromatography (pentane/diethyl ether, 1:1) gave the aldehyde as a colorless oil (81 mg, 0.494 mmol, 95 %).

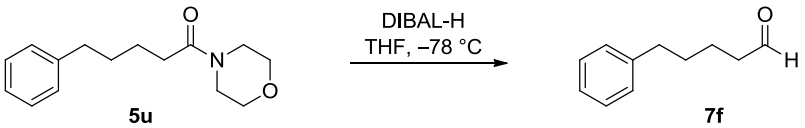
**$^1$H NMR** (300 MHz, $CDCl_3$) δ = 9.81 (t, *J*=1.46 Hz, 1 H), 7.03 - 7.18 (m, 2 H), 6.75 - 6.94 (m, 2 H), 3.78 (s, 3 H), 2.86 - 2.95 (m, 2 H), 2.69 - 2.78 (m, 2 H) ppm.

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 201.9, 158.2, 129.3, 114.1, 55.4, 45.7, 27.4 ppm.

**MS** (EI, 70 eV) *m/z*: 164.1 ($M^+$), 121.1, 108.1, 91.1, 77.1, 65.1.

The spectroscopic data correspond to those reported in the literature.[13]

5-phenylpentanal (**7f**)




To a solution of amide **5u** (245 mg, 0.991 mmol, 1 eq) in abs. THF (5 mL) was added DIBAL-H (1 M in hexane, 1.09 mL, 1.09 mmol, 1.1 eq) dropwise at –78 °C. After 1 hour the reaction was monitored by TLC and another aliquot of DIBAL-H (300 µL, 300 µmol) was added. After further 20 min the reaction mixture was quenched with an aqueous solution of citric acid (33 wt-%, 6 mL), diluted with diethyl ether (10 mL), warmed to rt and stirred for 30 min. The phases were separated and the aqueous phase was extracted with diethyl ether

(3x 10 mL). The combined organic phase was dried over $Na_2SO_4$ and concentrated. Column chromatography (pentane/diethyl ether, 15:1) gave the aldehyde **7f** as a colorless oil (117 mg, 0.722 mmol, 73 %).

The $^1$H NMR spectrum was referenced using dichloromethane (δ = 5.30 ppm) because compound- and $CDCl_3$ signals overlapped.

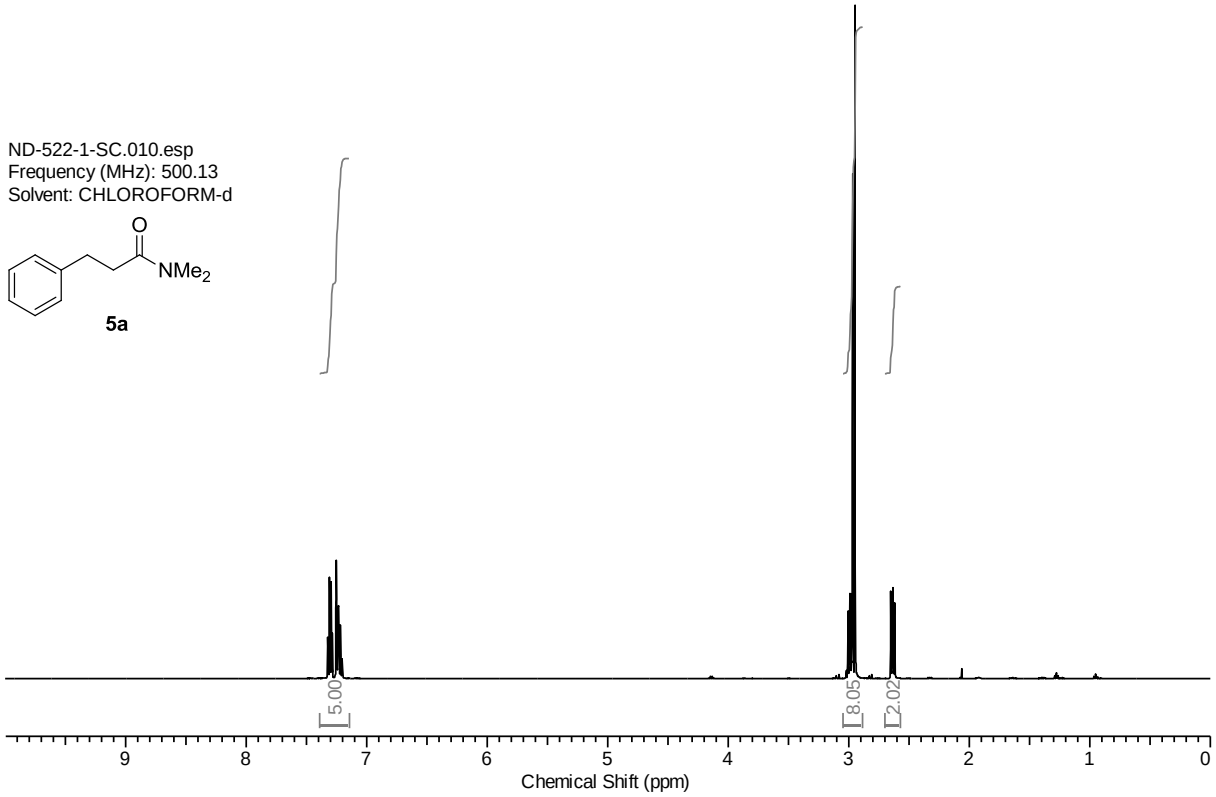
**$^1$H NMR** (500 MHz, $CDCl_3$) δ = 9.76 (t, *J*=1.83 Hz, 1 H), 7.24 - 7.33 (m, 2 H), 7.13 - 7.24 (m, 3 H), 2.57 - 2.70 (m, 2 H), 2.46 (dtd, *J*=7.06, 3.57, 3.57, 1.68 Hz, 2 H), 1.62 - 1.75 (m, 4 H) ppm.

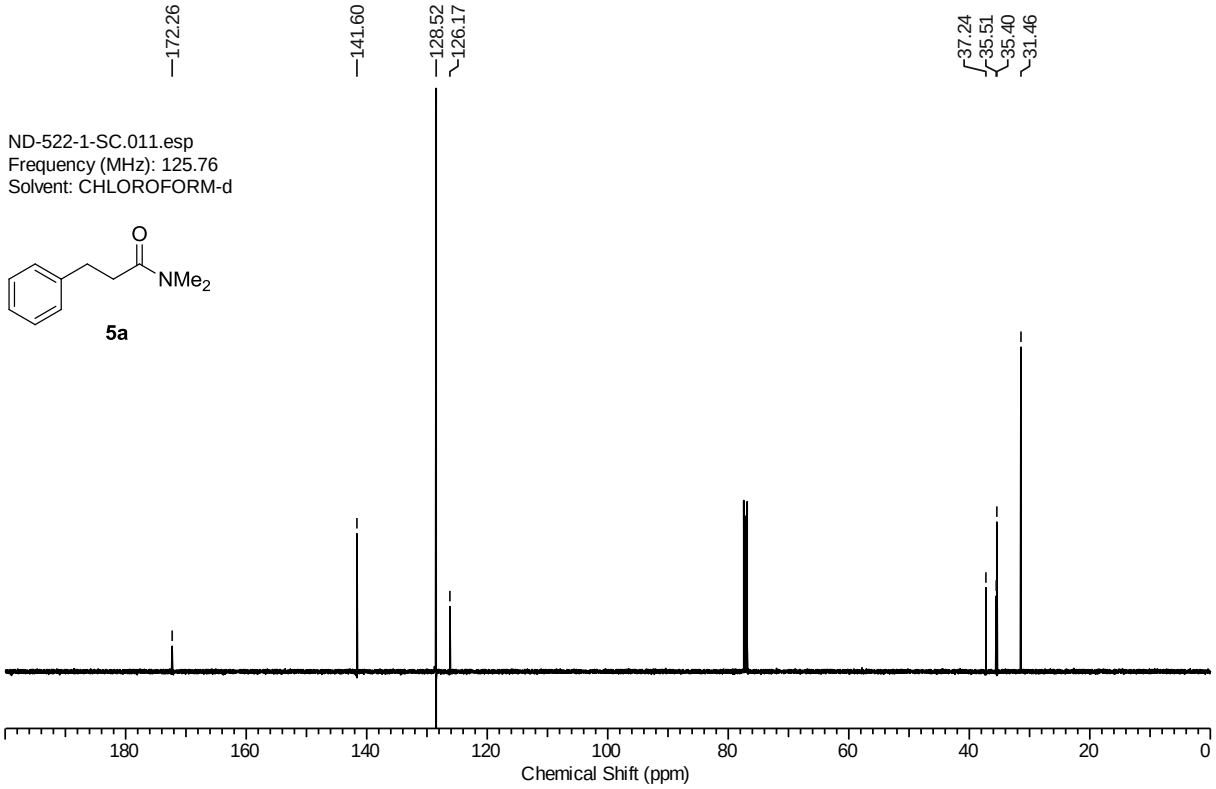
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ = 202.7, 142.1, 128.5, 126.0, 43.9, 35.8, 31.0, 21.8 ppm.

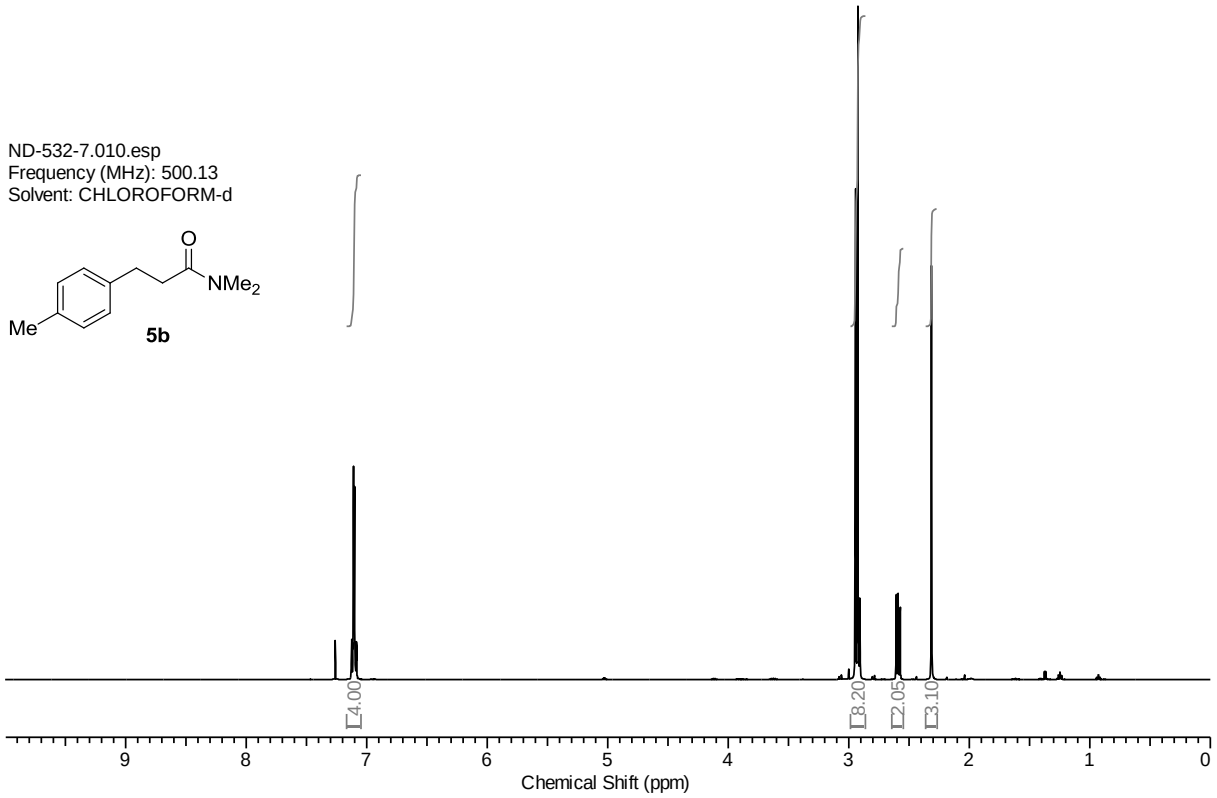
**MS** (EI, 70 eV) *m/z*: 162.1 ($M^+$), 144.1, 129.1, 117.1, 105.1, 91.1, 84.1, 77.1, 71.1, 65.1, 57.1, 51.1.

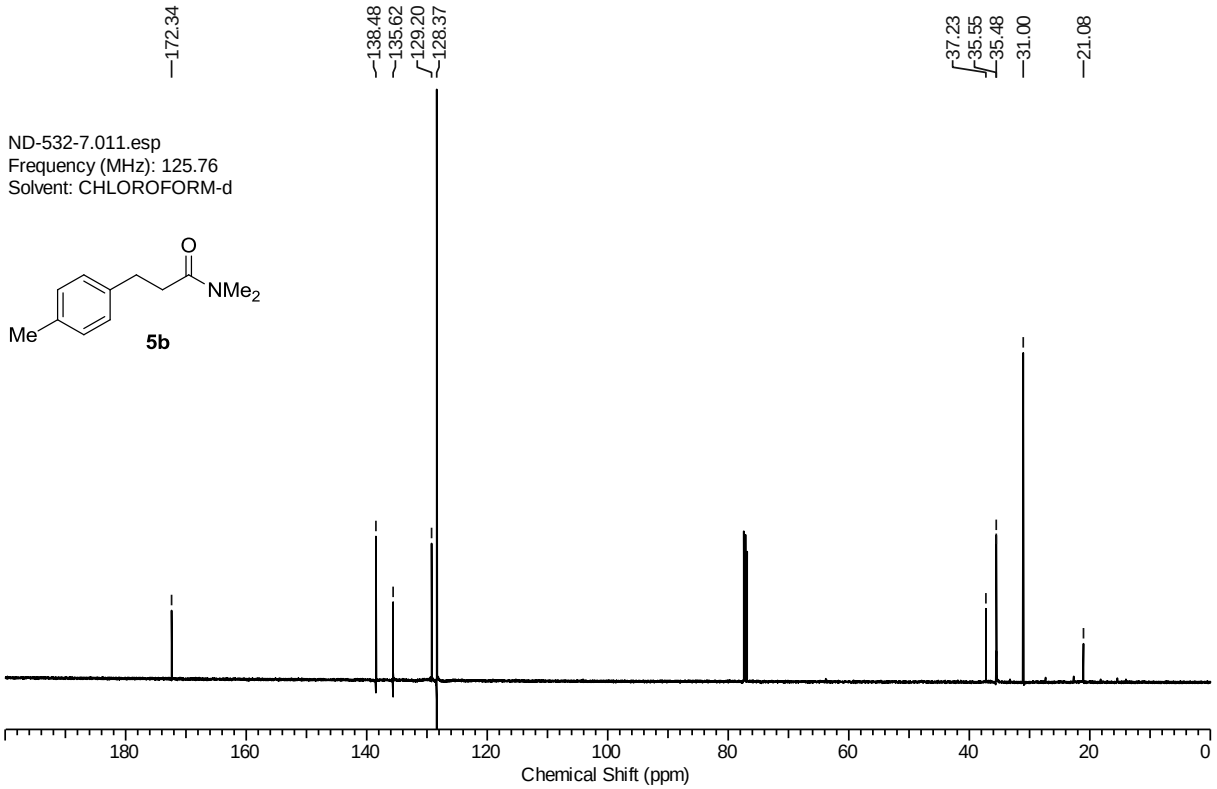
The spectroscopic data correspond to those reported in the literature.[14]

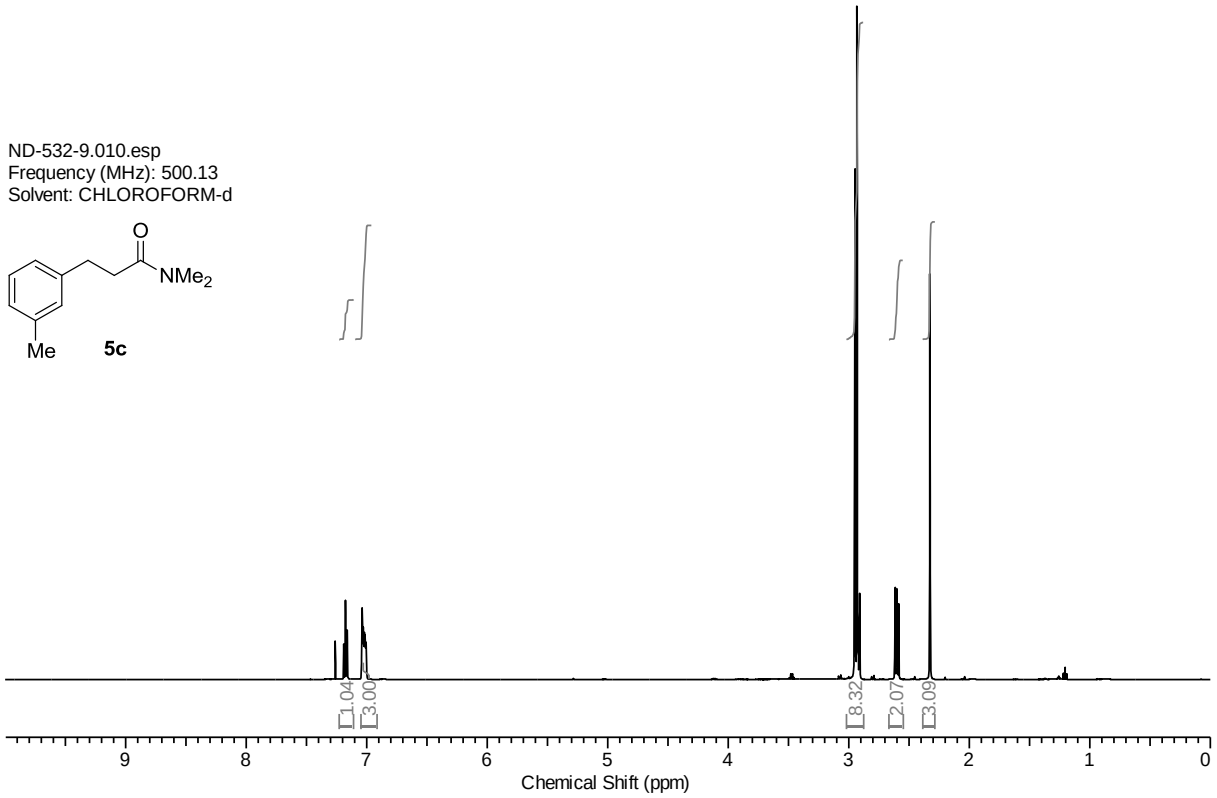
# 5 NMR-Spectra

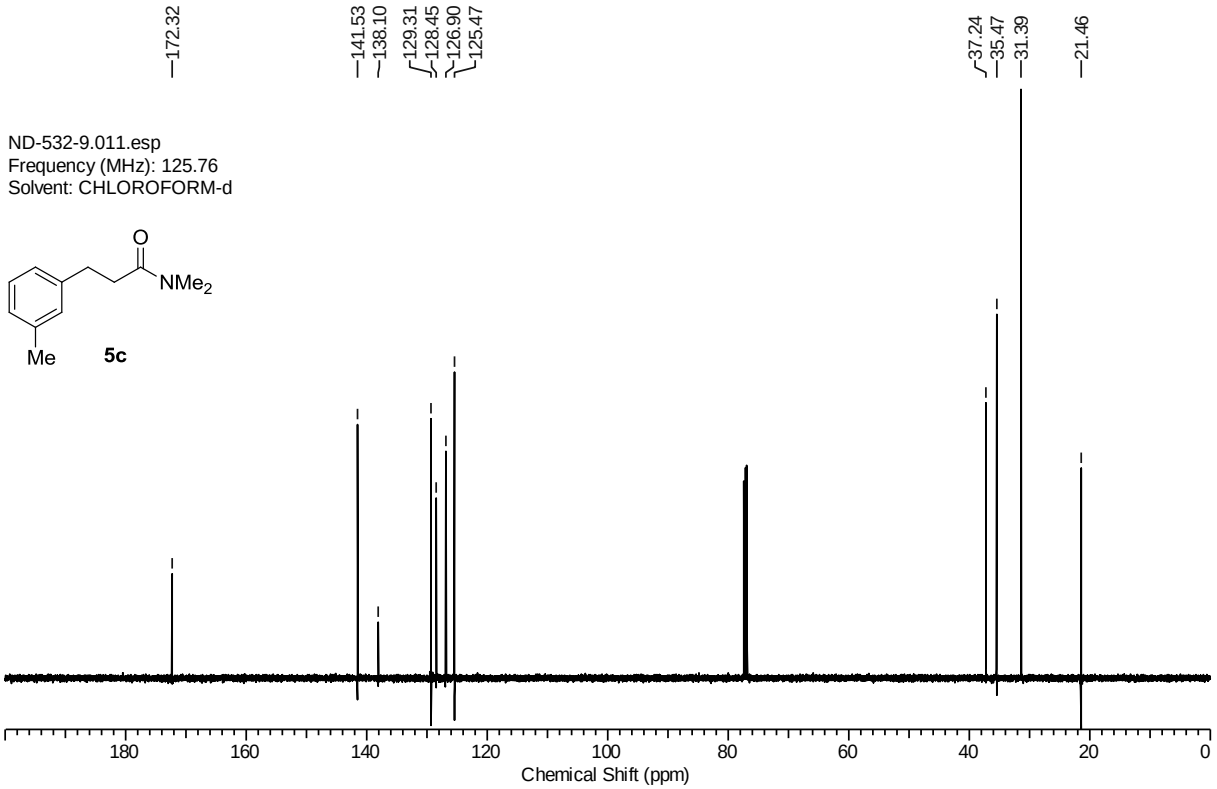


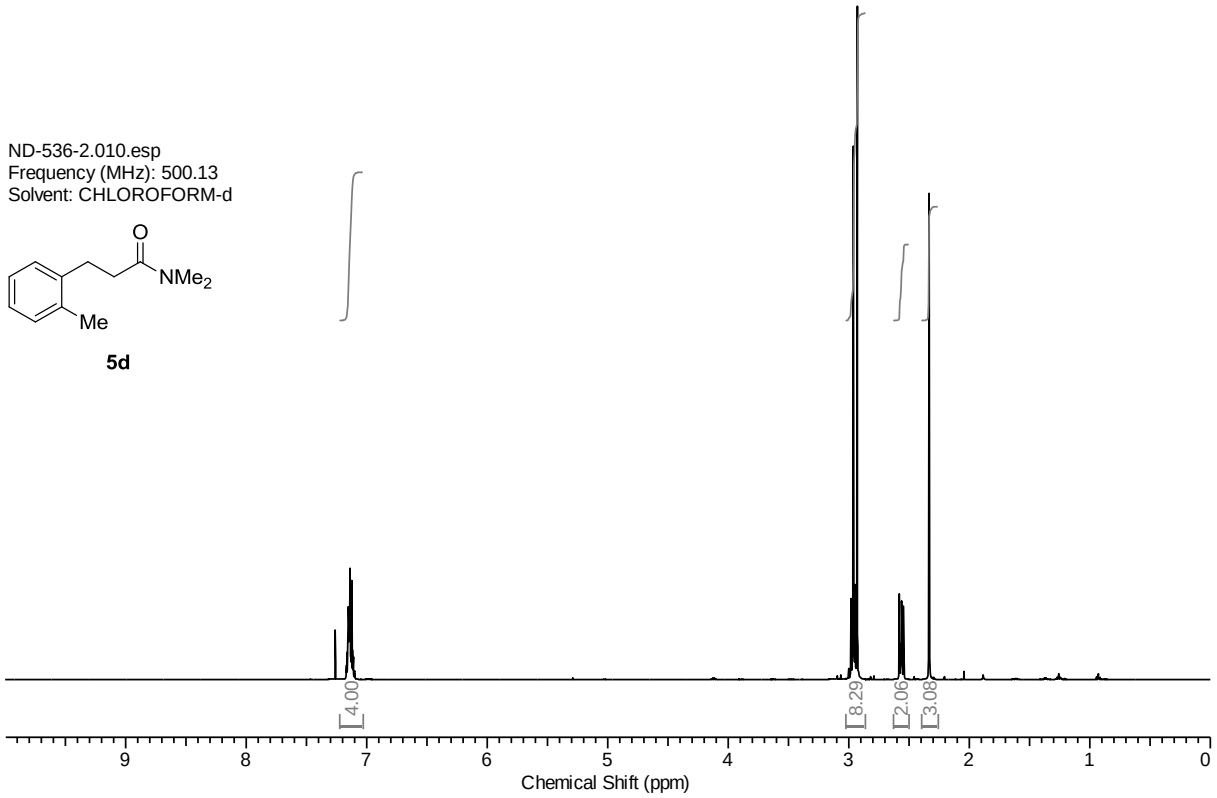



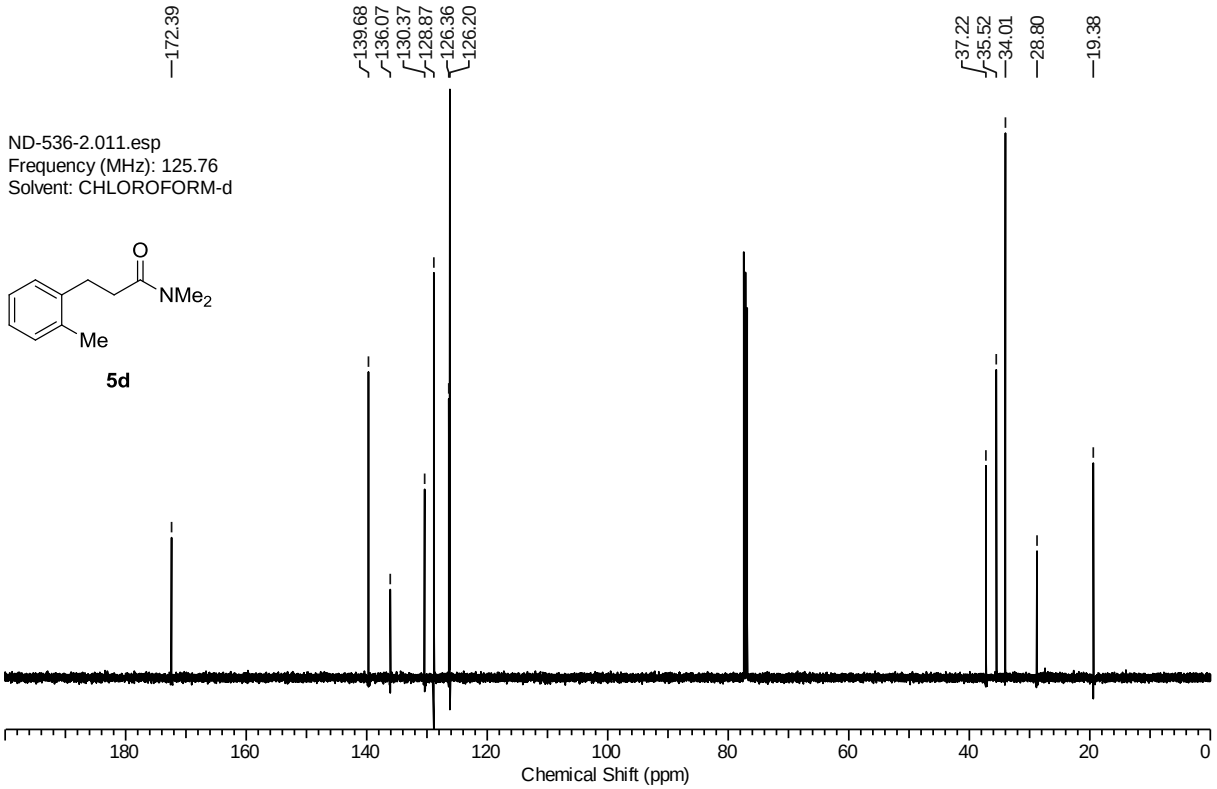

ND-532-7.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
Me
5b
4.00
8.20
2.05
3.10
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

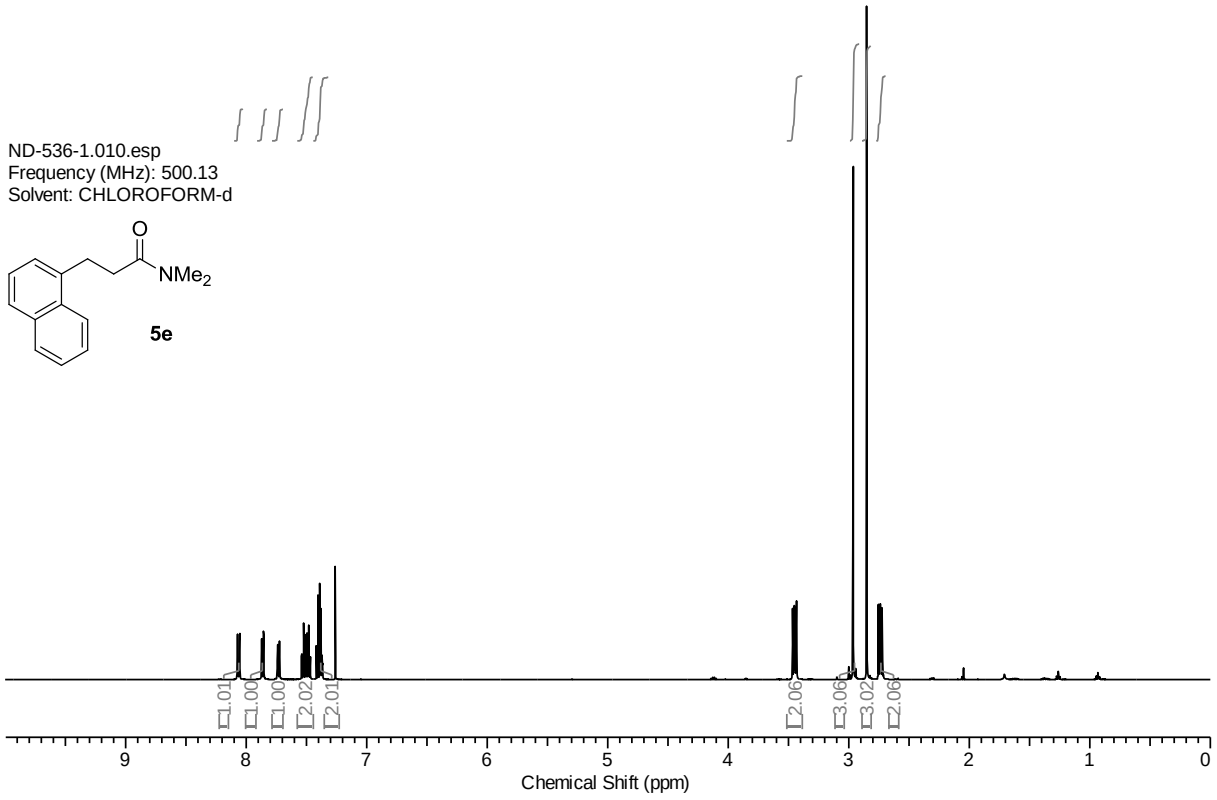

172.34
138.48
135.62
129.20
128.37
37.23
35.55
35.48
31.00
21.08
ND-532-7.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
Me
5b
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

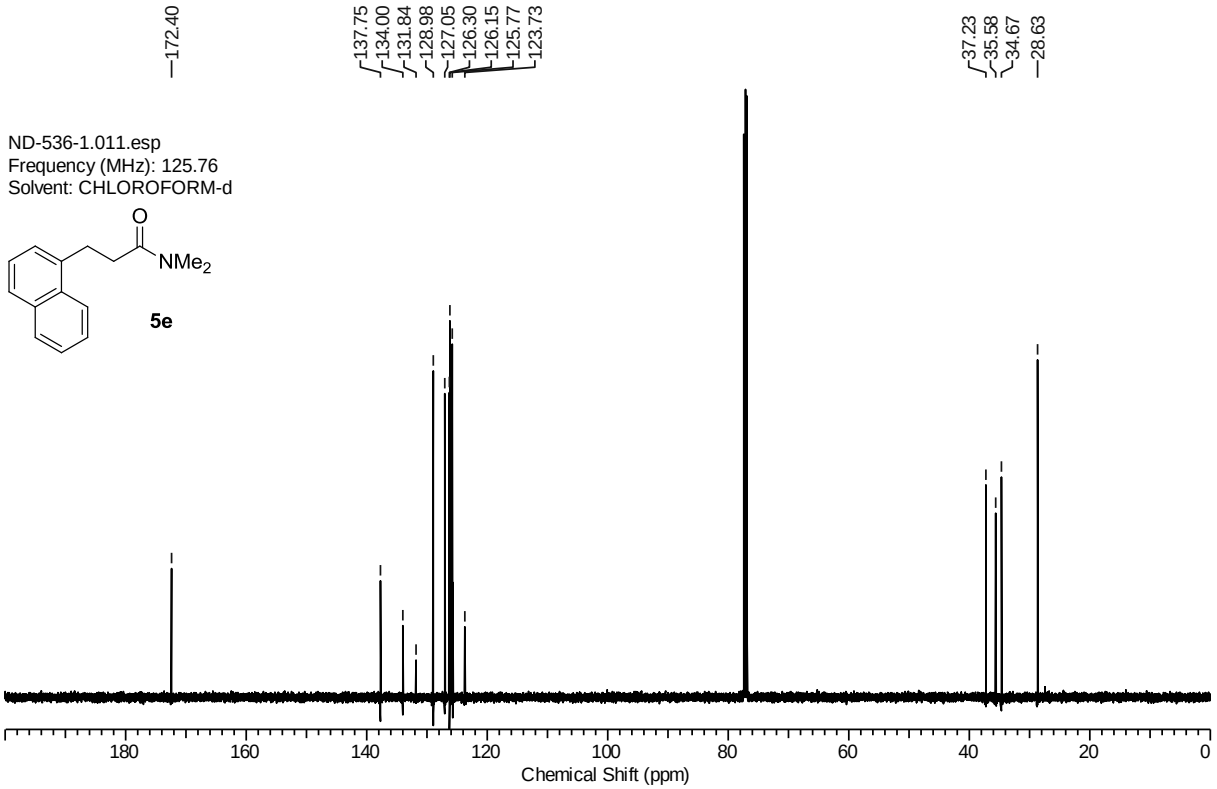

ND-532-9.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
Me
5c
1.04
3.00
8.32
2.07
3.09
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

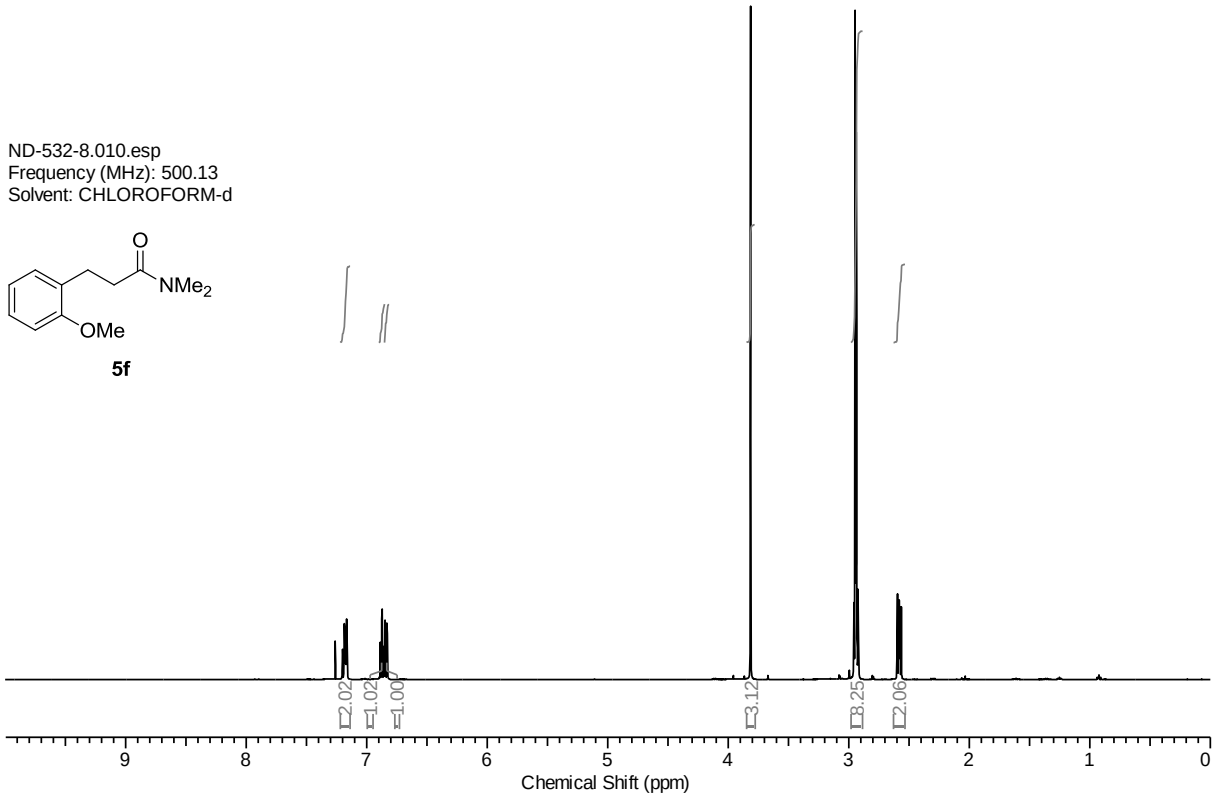

172.32
141.53
138.10
129.31
128.45
126.90
125.47
37.24
35.47
31.39
21.46
ND-532-9.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
Me
5c
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

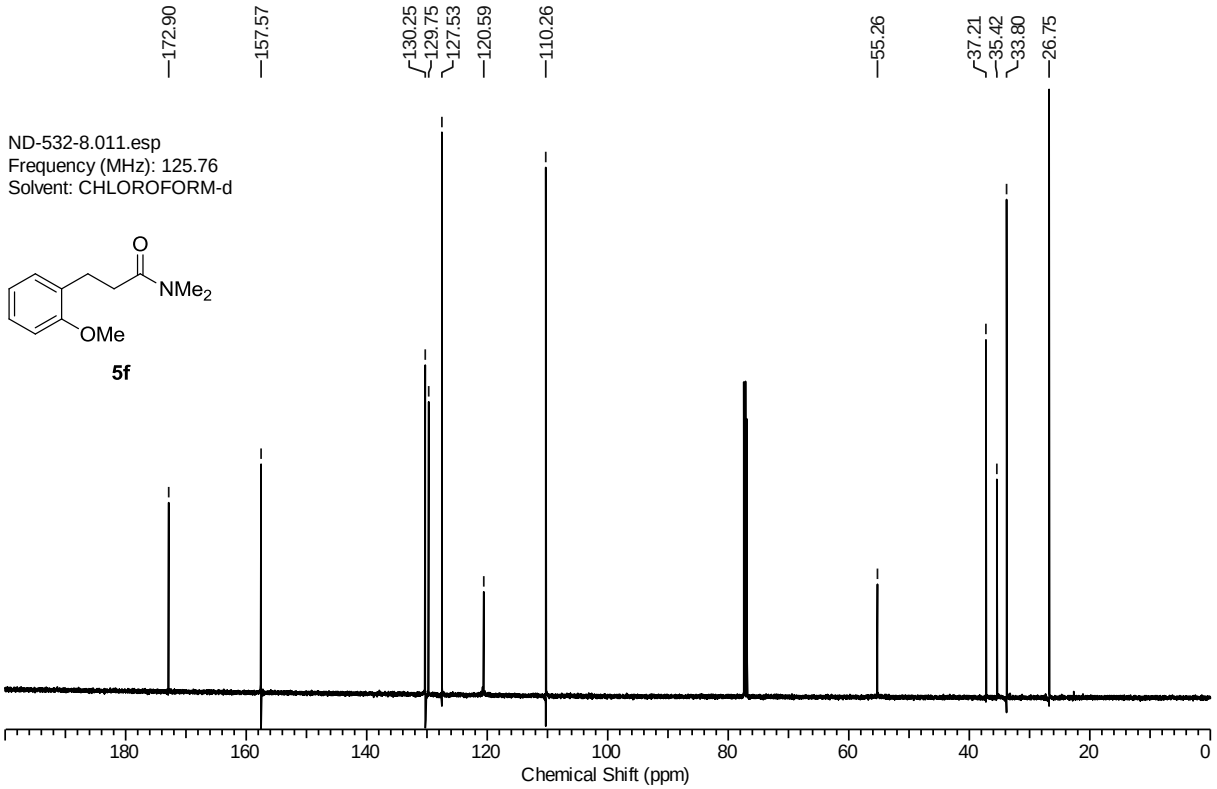

ND-536-2.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
Me
5d
4.00
8.29
2.06
3.08
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

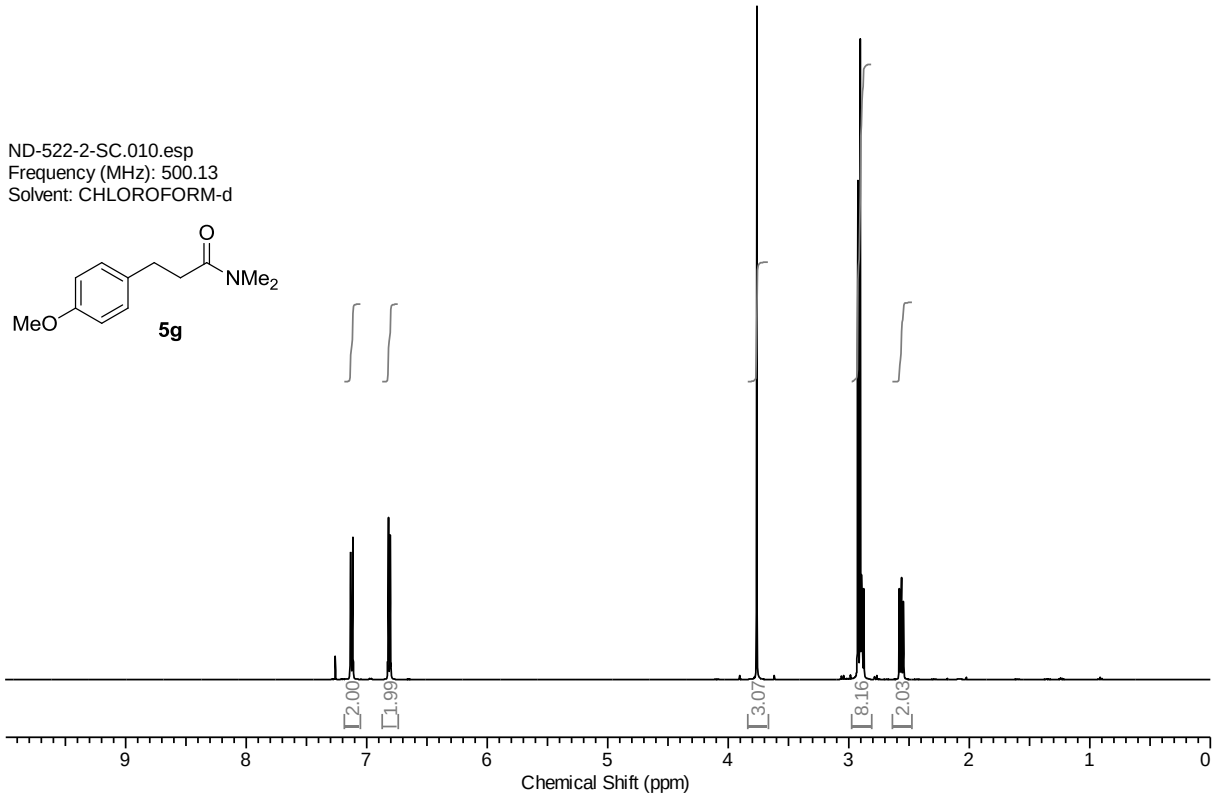

172.39
139.68
136.07
130.37
128.87
126.36
126.20
37.22
35.52
34.01
28.80
19.38
ND-536-2.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
Me
5d
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

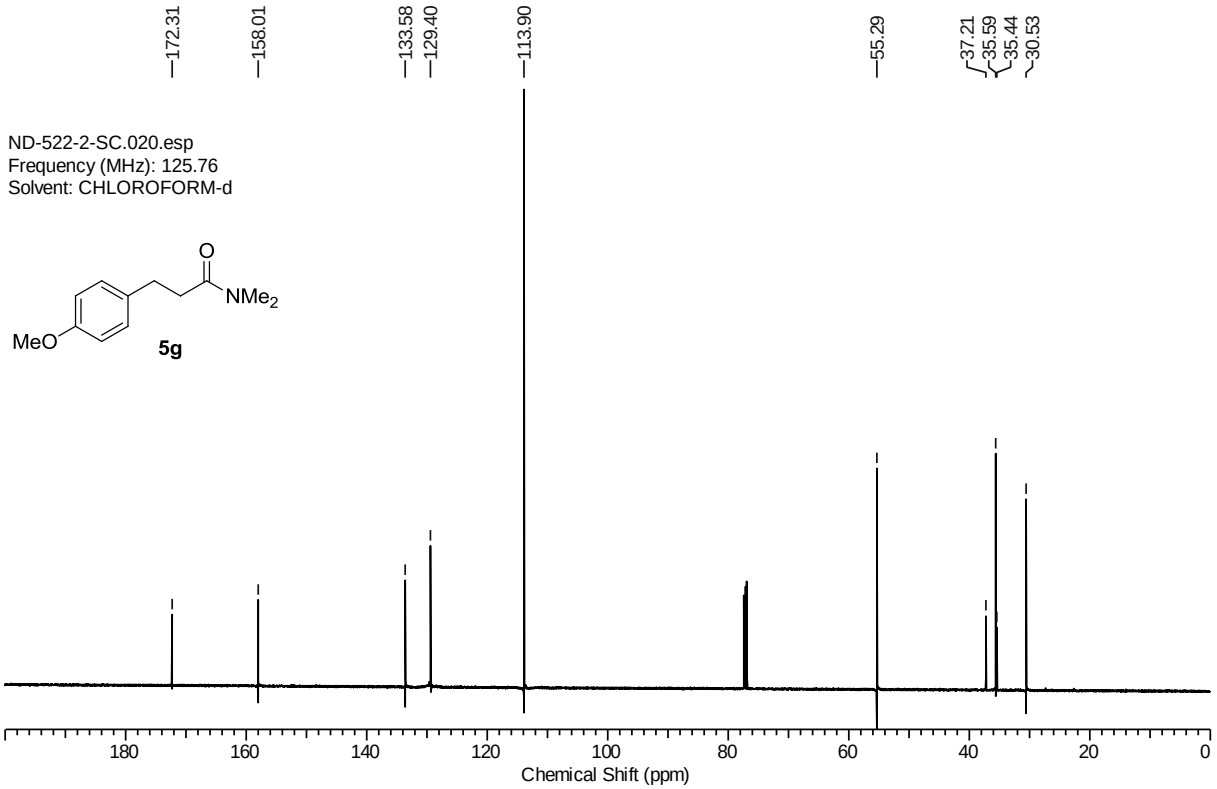

ND-536-1.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
5e
1.01
1.00
1.00
2.02
2.01
2.06
3.06
3.02
2.06
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

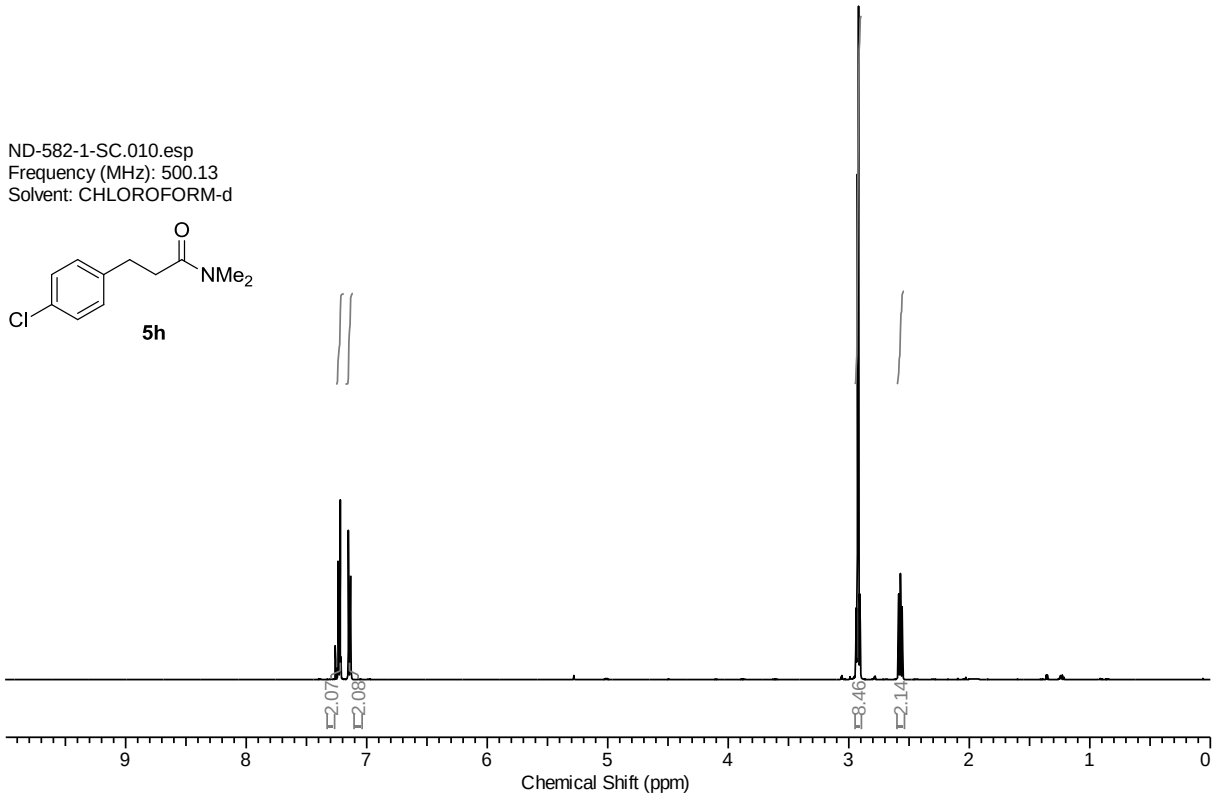

172.40
137.75
134.00
131.84
128.98
127.05
126.30
126.15
125.77
123.73
37.23
35.58
34.67
28.63
ND-536-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
5e
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

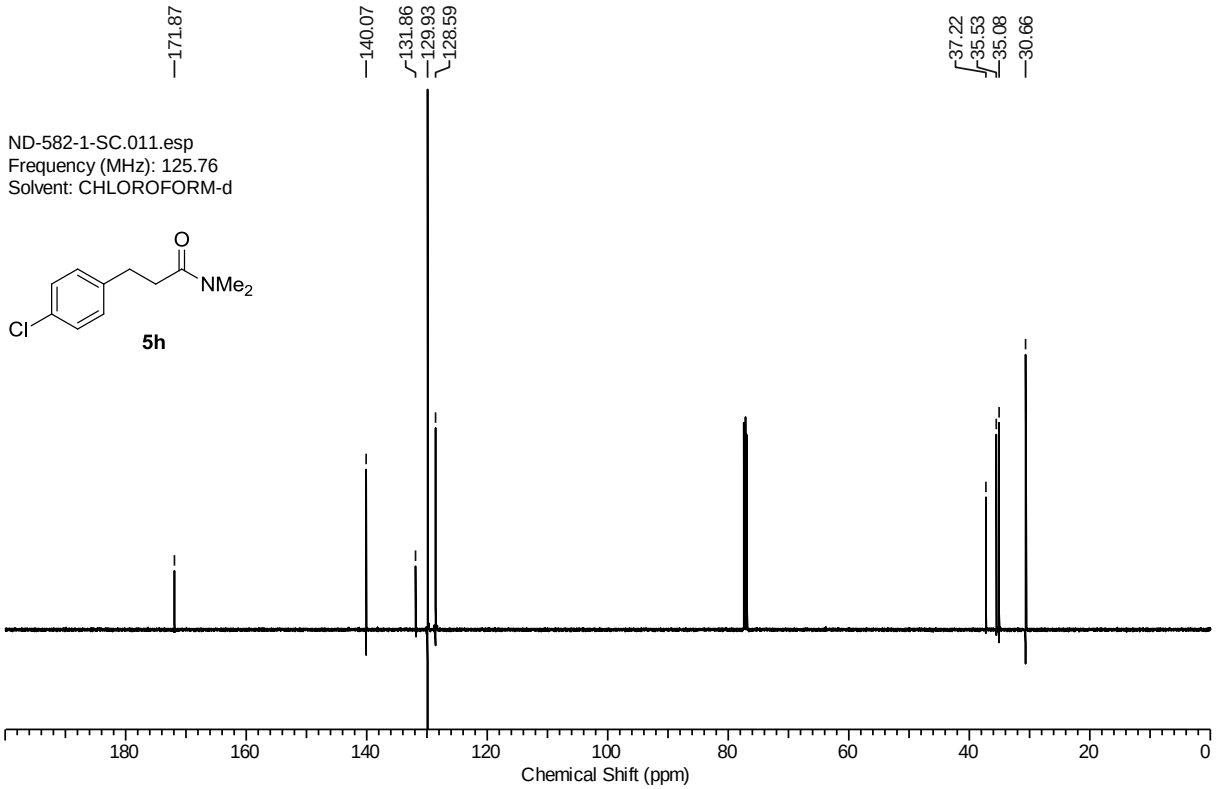

ND-532-8.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
OMe
5f
2.02
1.02
1.00
3.12
3.25
2.06
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

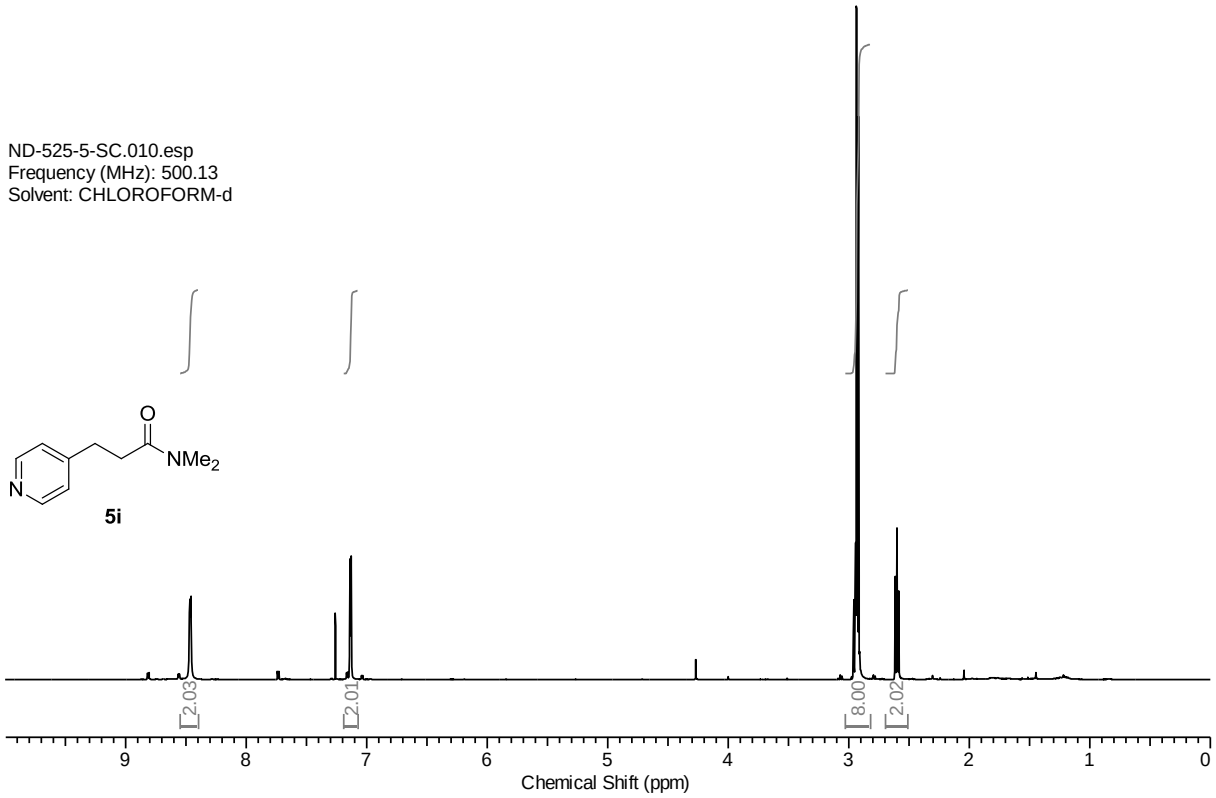

172.90
157.57
130.25
129.75
127.53
120.59
110.26
55.26
37.21
35.42
33.80
26.75
ND-532-8.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
OMe
5f
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

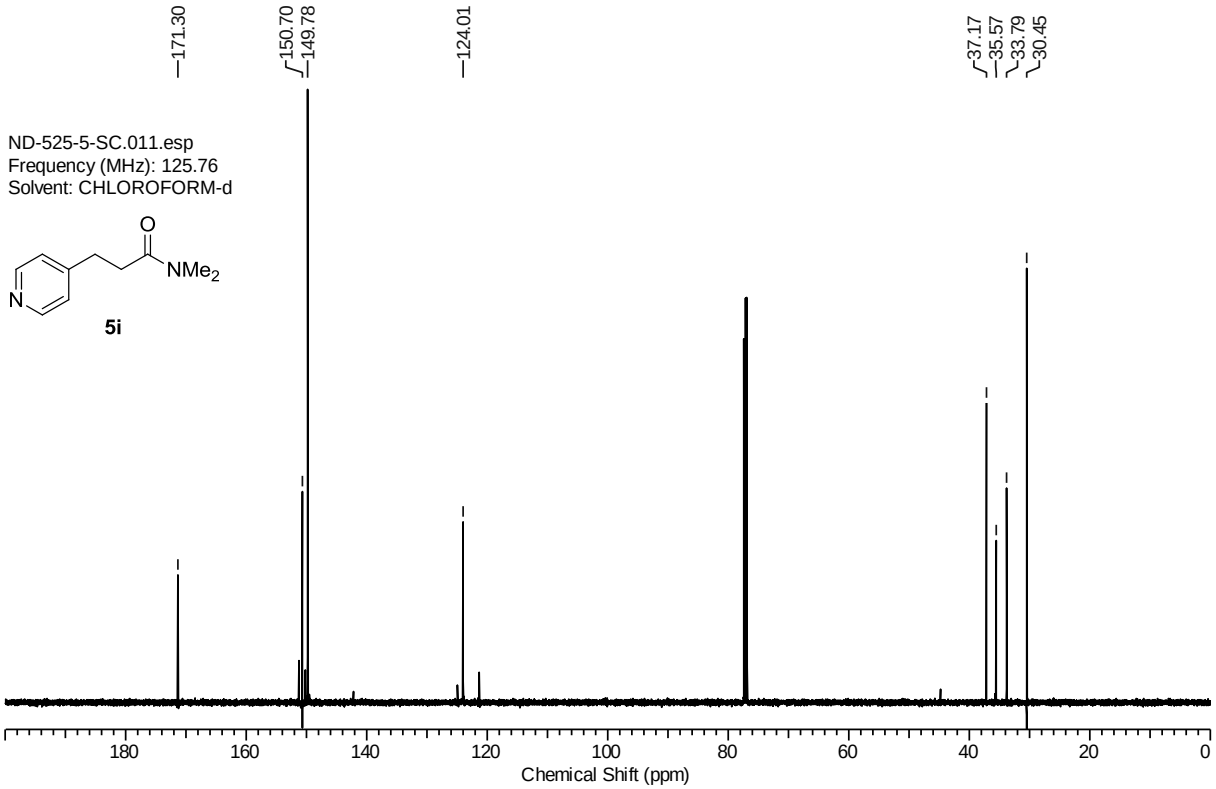

ND-522-2-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
MeO
5g
2.00
1.99
3.07
8.16
2.03
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

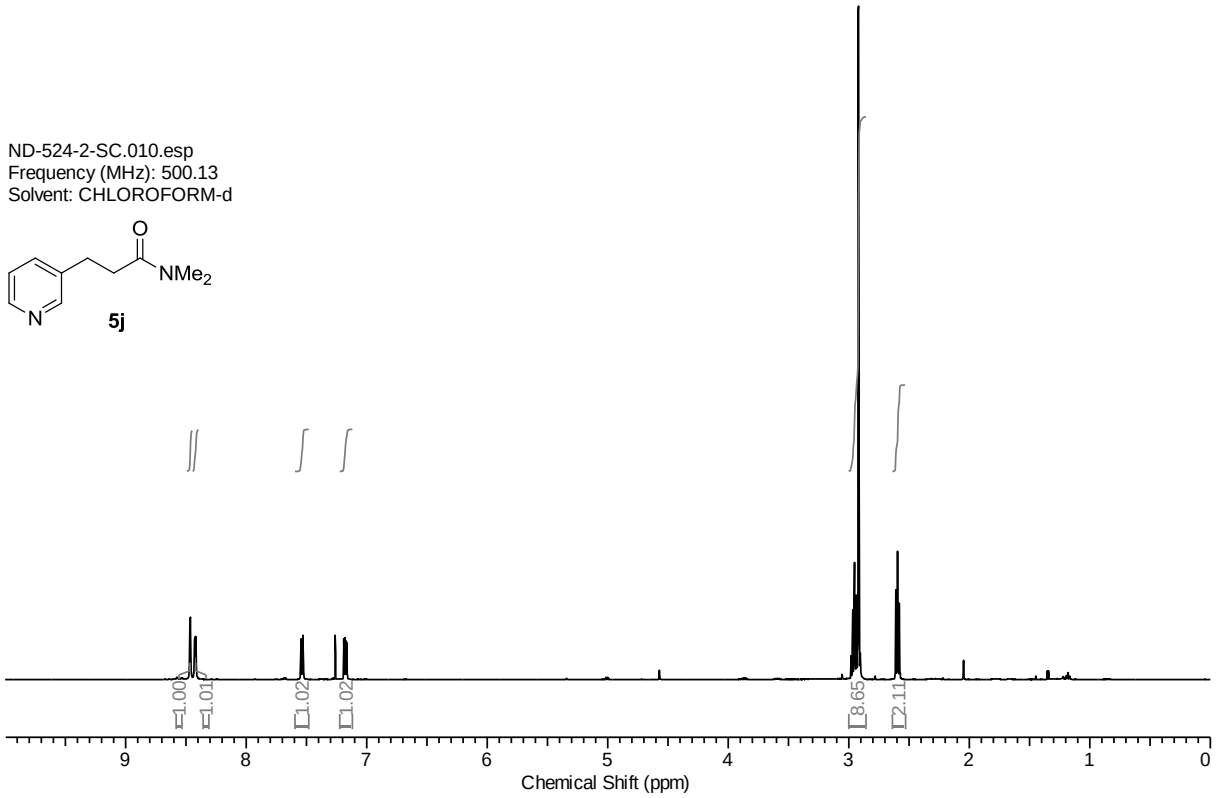

172.31
158.01
133.58
129.40
113.90
55.29
37.21
35.59
35.44
30.53
ND-522-2-SC.020.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
MeO
5g
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

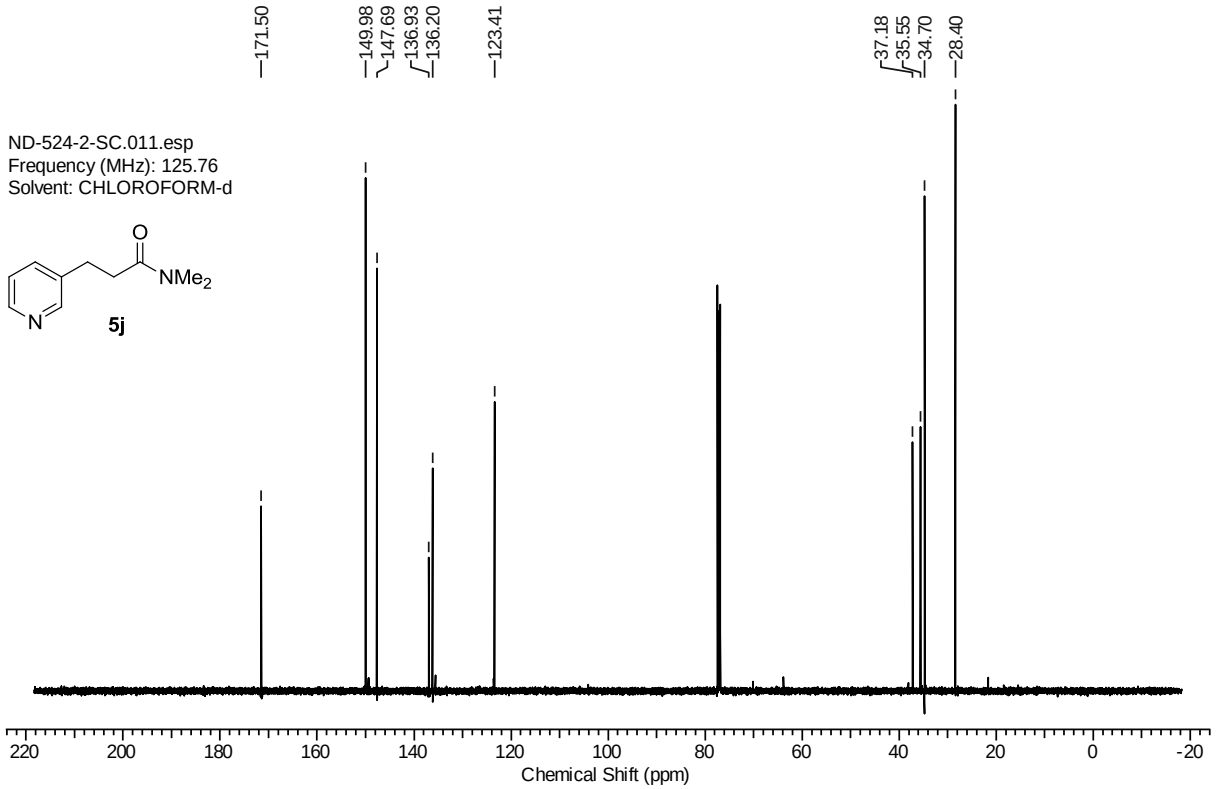

ND-582-1-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
Cl
5h
2.07
2.08
8.46
2.14
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

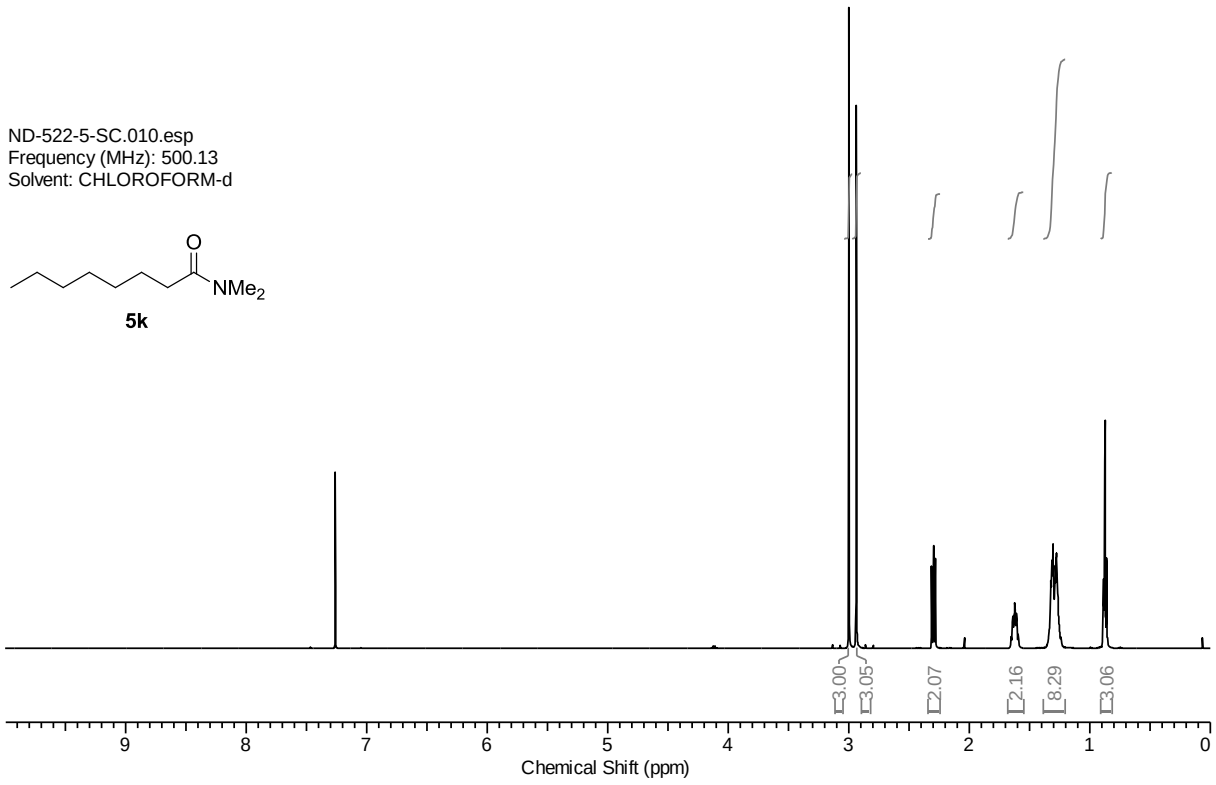

171.87
140.07
131.86
129.93
128.59
37.22
35.53
35.08
30.66
ND-582-1-SC.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
Cl
5h
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

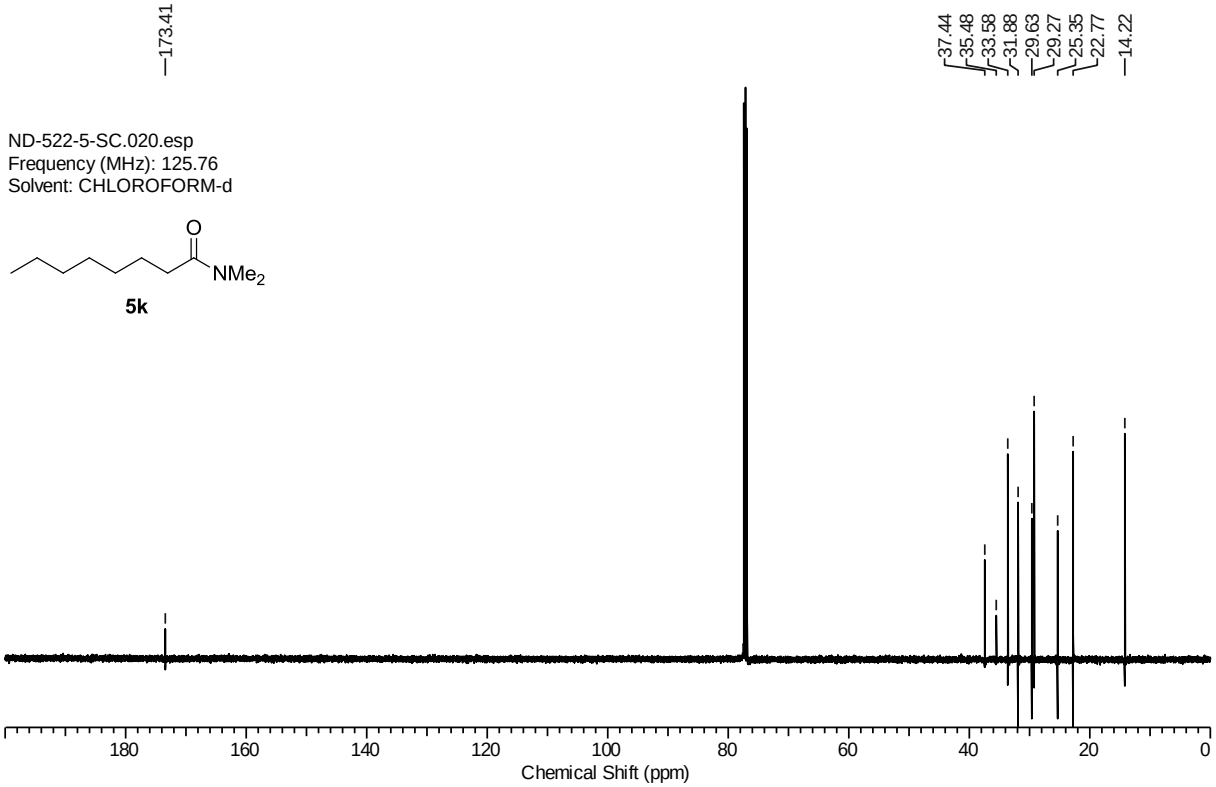

ND-525-5-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
N
5i
2.03
2.01
8.00
2.02
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

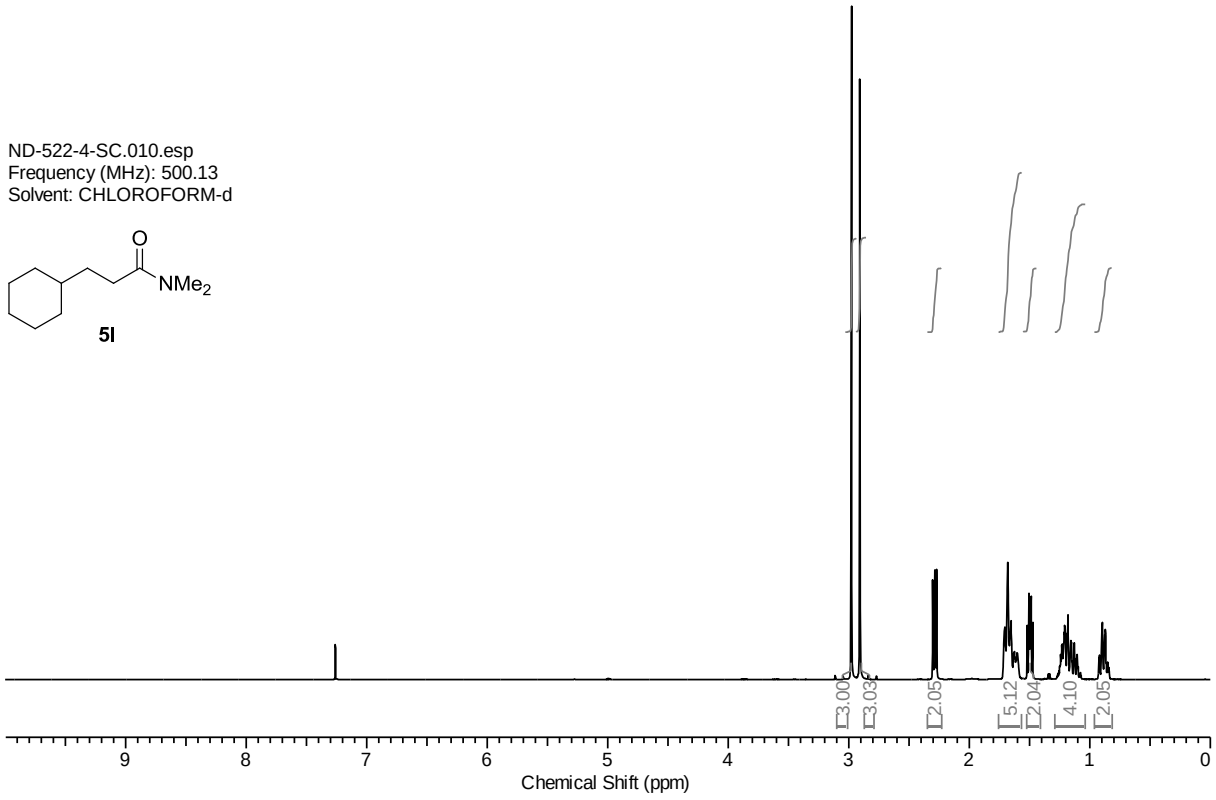

171.30
150.70
149.78
124.01
37.17
35.57
33.79
30.45
ND-525-5-SC.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
N
5i
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

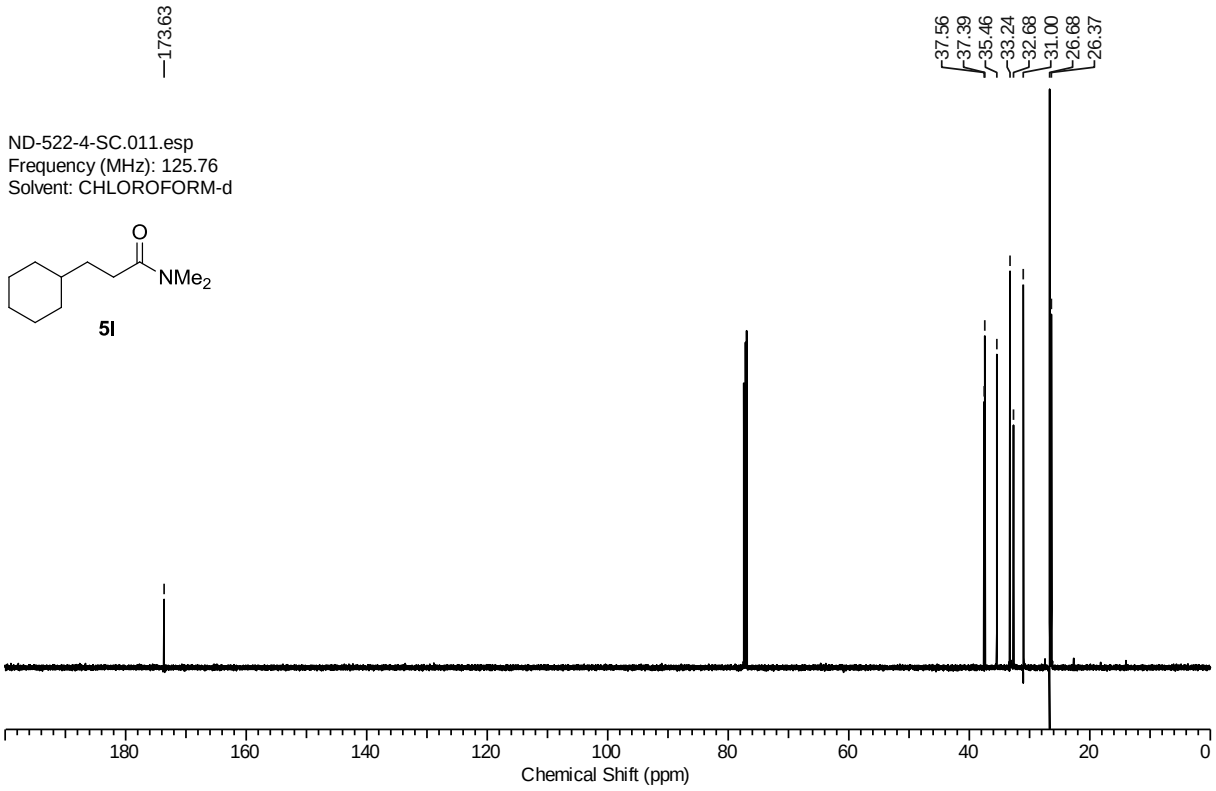

ND-524-2-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
N
5j
1.00
1.01
1.02
1.02
8.65
2.11
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

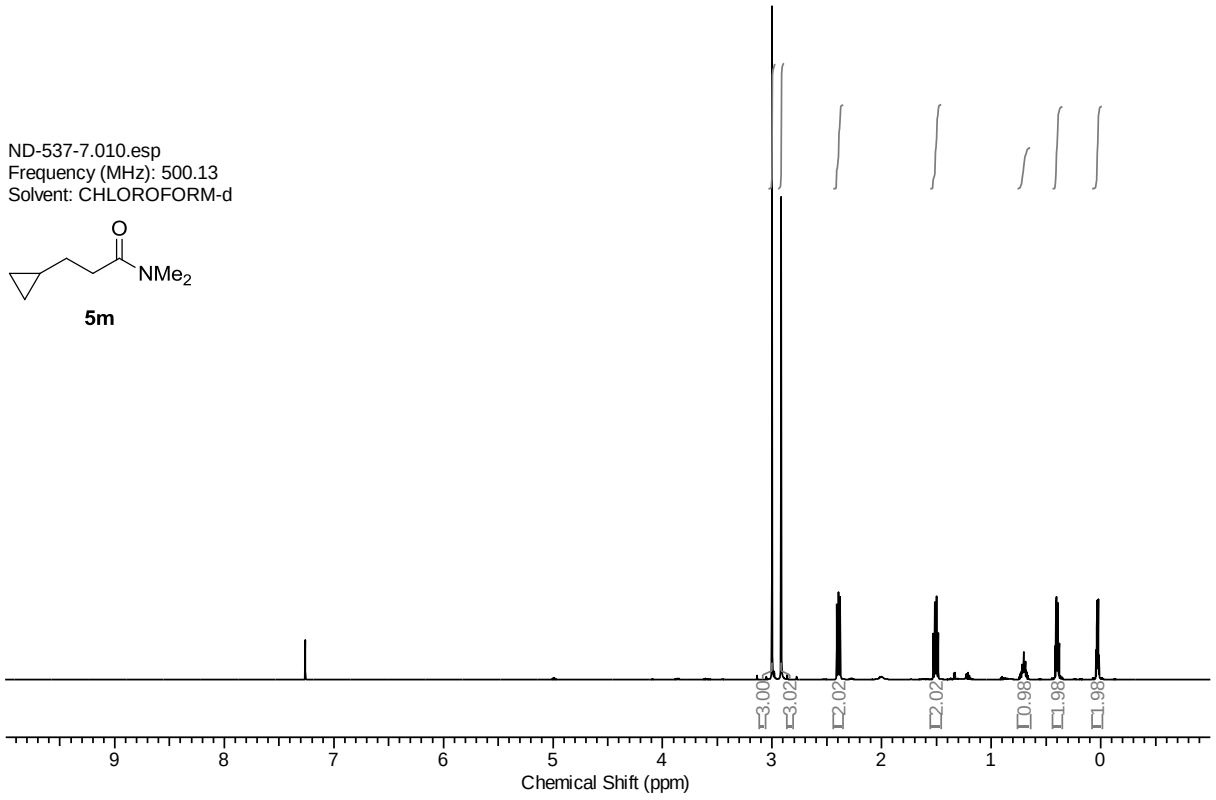

171.50
149.98
147.69
136.93
136.20
123.41
37.18
35.55
34.70
28.40
ND-524-2-SC.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
N
5j
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

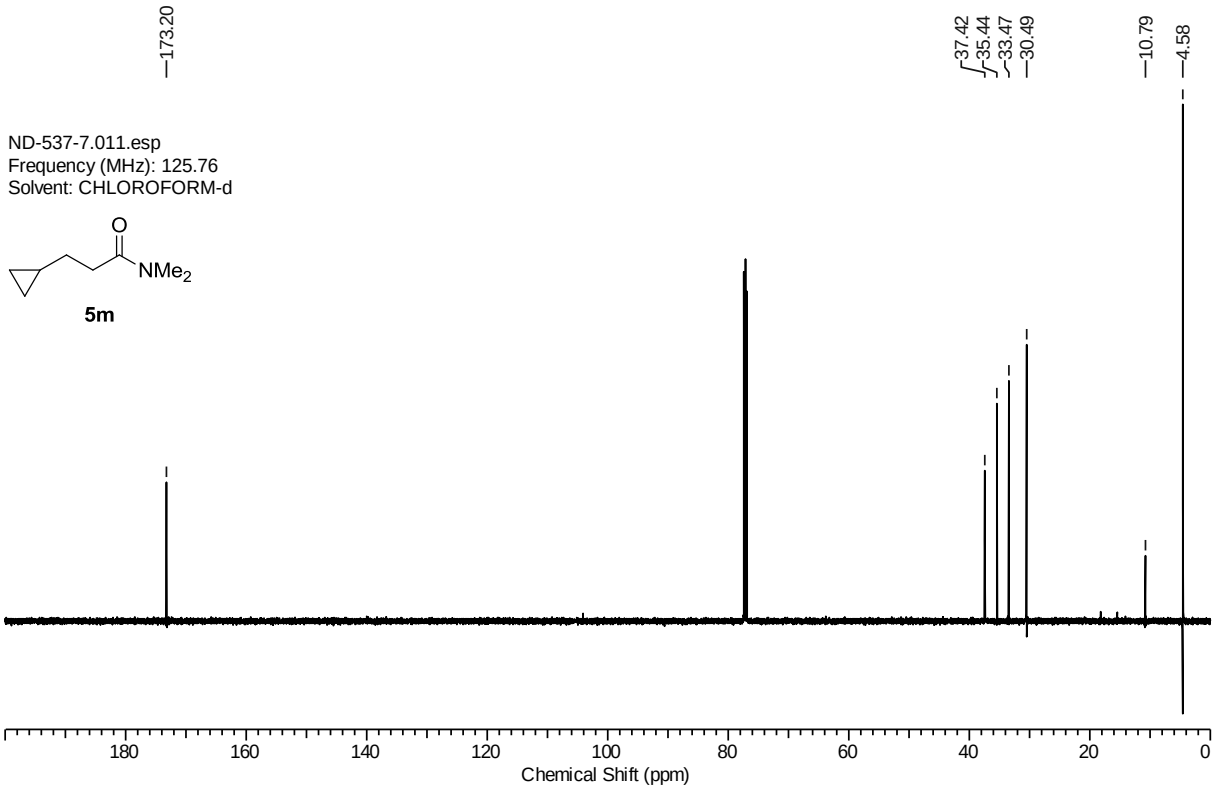

ND-522-5-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
5k
3.00
3.05
2.07
2.16
8.29
3.06
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

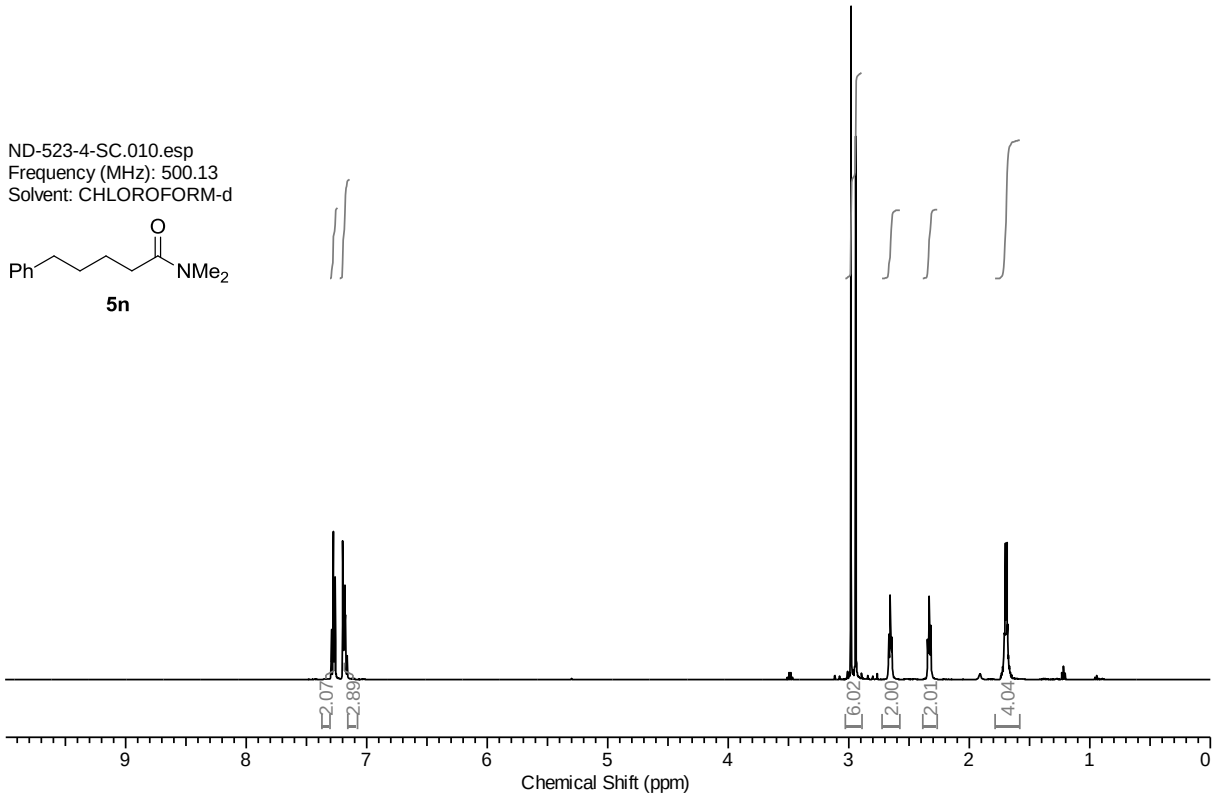

173.41
37.44
35.48
33.58
31.88
29.63
29.27
25.35
22.77
14.22
ND-522-5-SC.020.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
5k
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

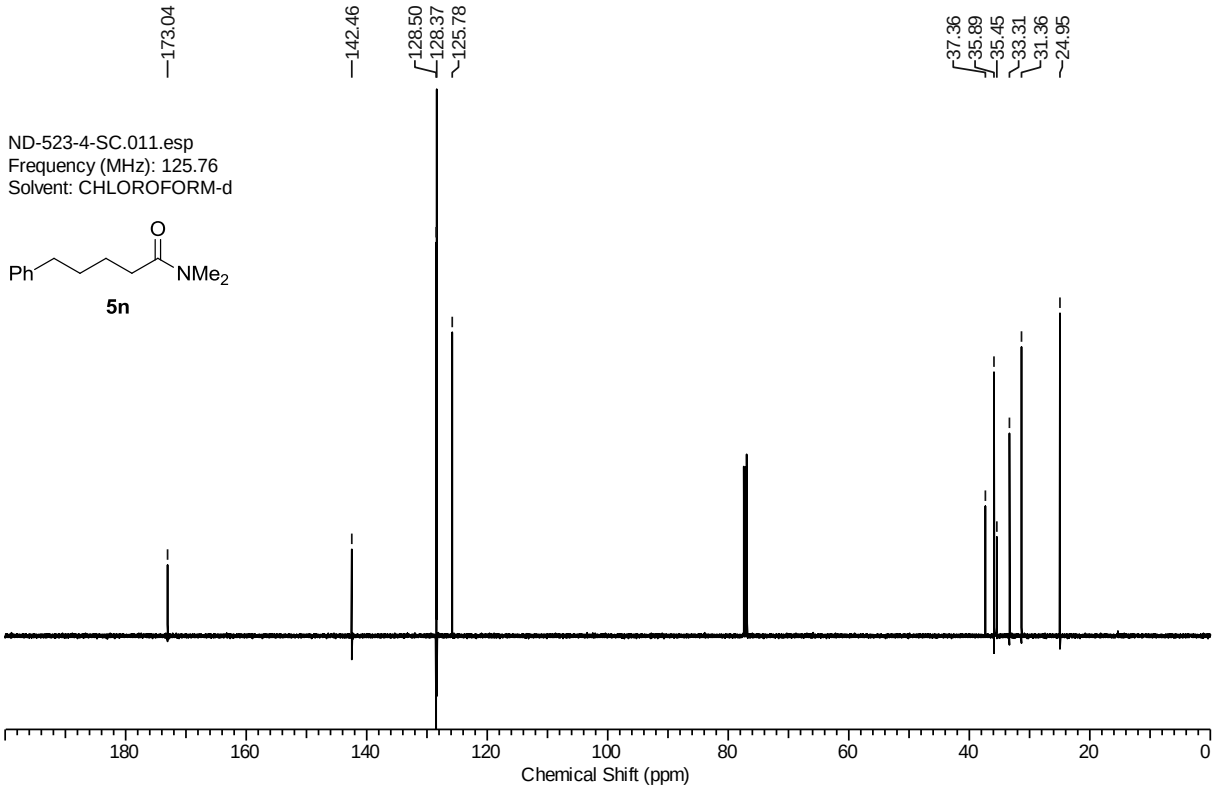

ND-522-4-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
5l
3.00
3.03
2.05
5.12
2.04
4.10
2.05
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

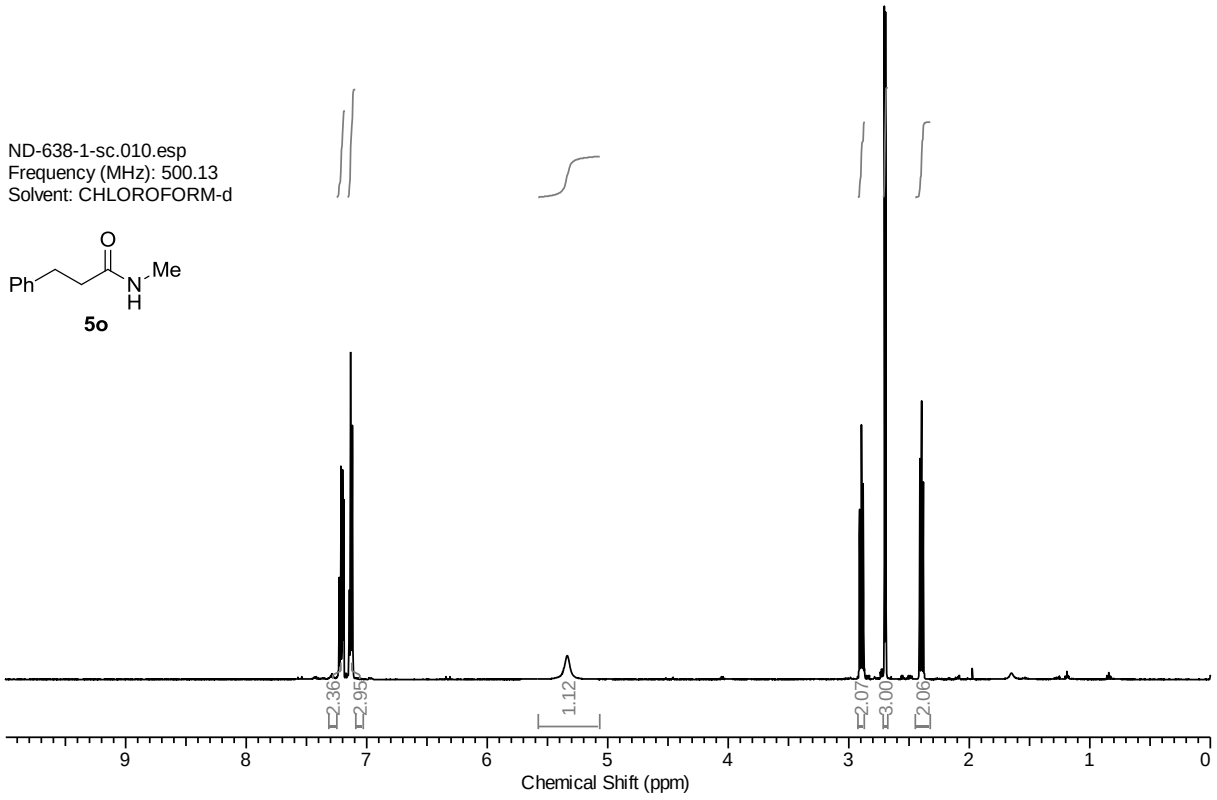

173.63
37.56
37.39
35.46
33.24
32.68
31.00
26.68
26.37
ND-522-4-SC.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
5l
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

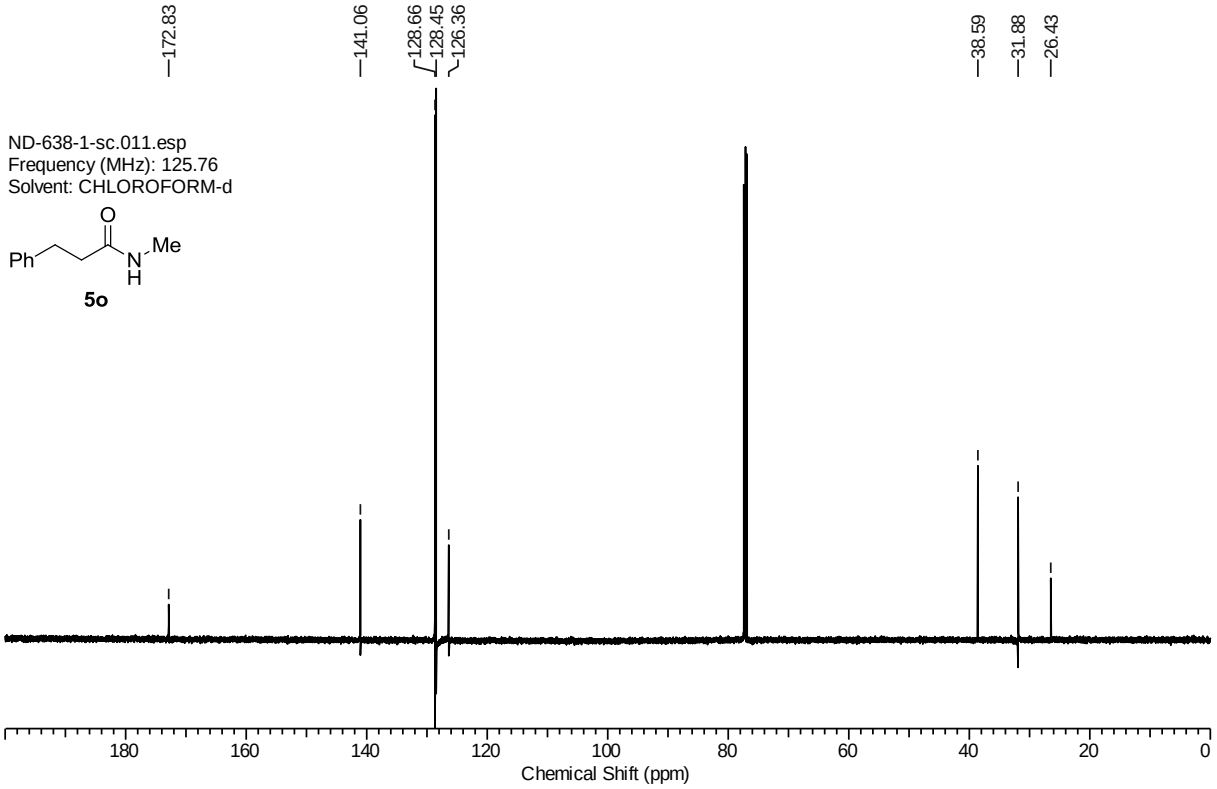

ND-537-7.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
NMe2
5m
3.00
3.02
2.02
2.02
0.98
1.98
1.98
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

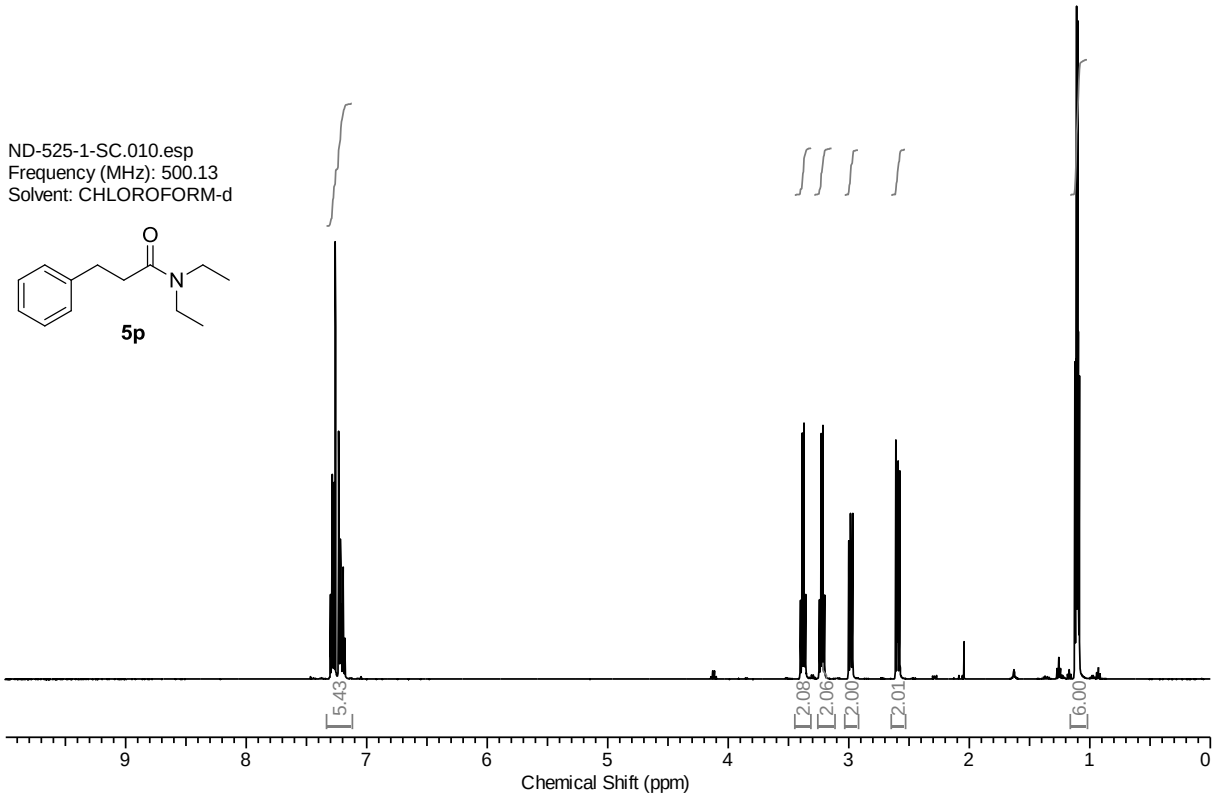

173.20
37.42
35.44
33.47
30.49
10.79
4.58
ND-537-7.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
NMe2
5m
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

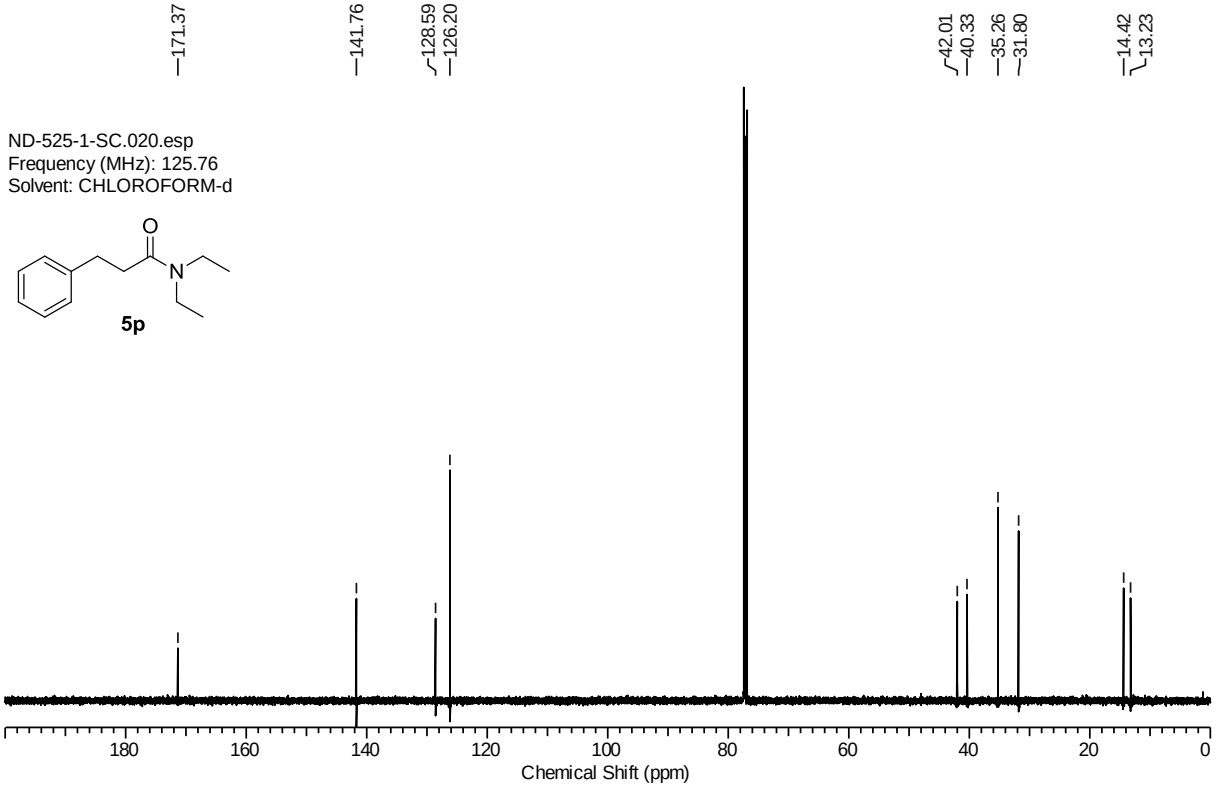

ND-523-4-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
O
NMe2
5n
2.07
2.89
6.02
2.00
2.01
4.04
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

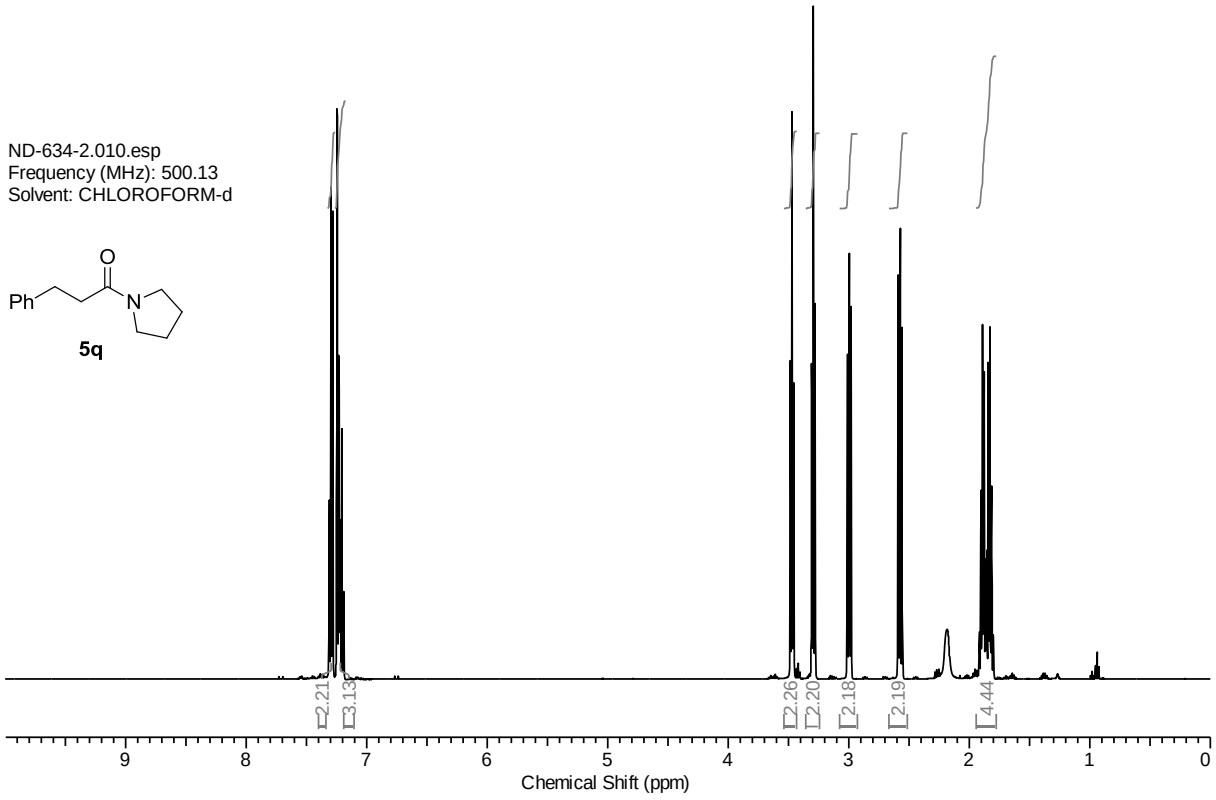

173.04
142.46
128.50
128.37
125.78
37.36
35.89
35.45
33.31
31.36
24.95
ND-523-4-SC.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
O
NMe2
5n
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

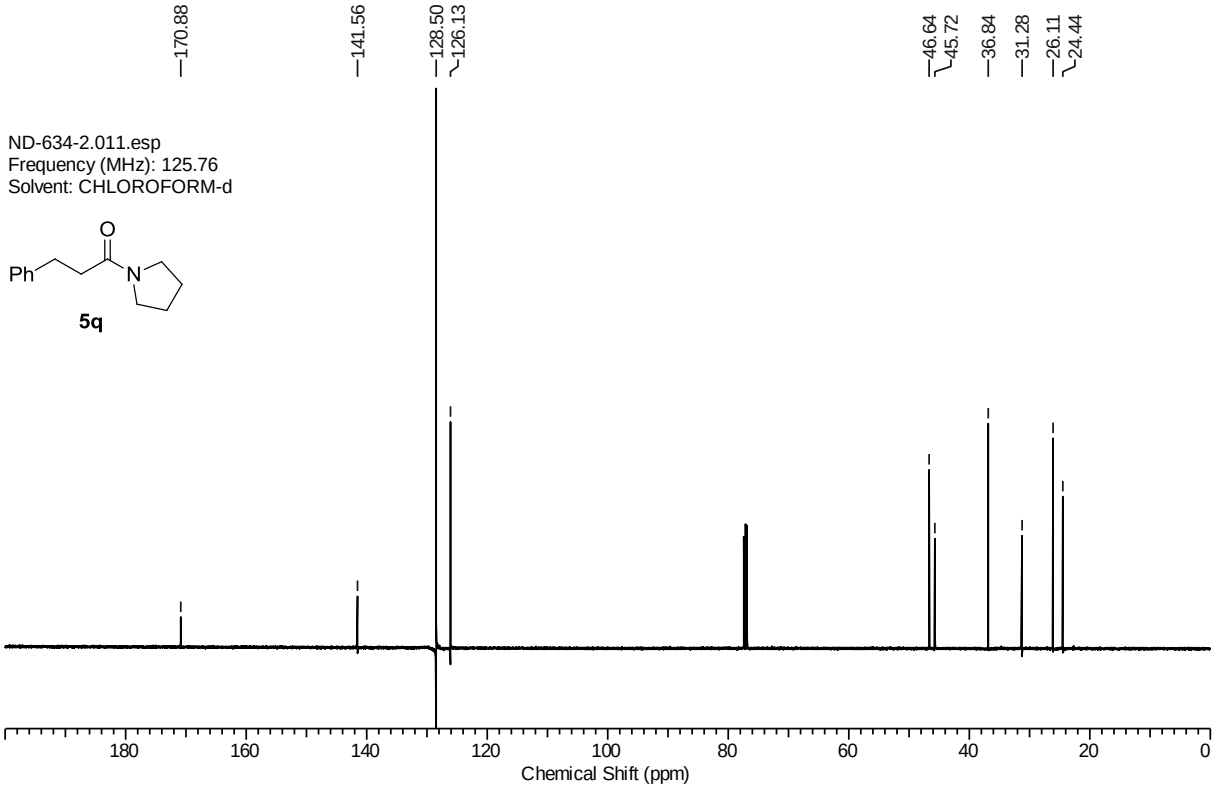

ND-638-1-sc.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
O
N
H
Me
5o
2.36
2.95
1.12
2.07
3.00
2.06
Chemical Shift (ppm)

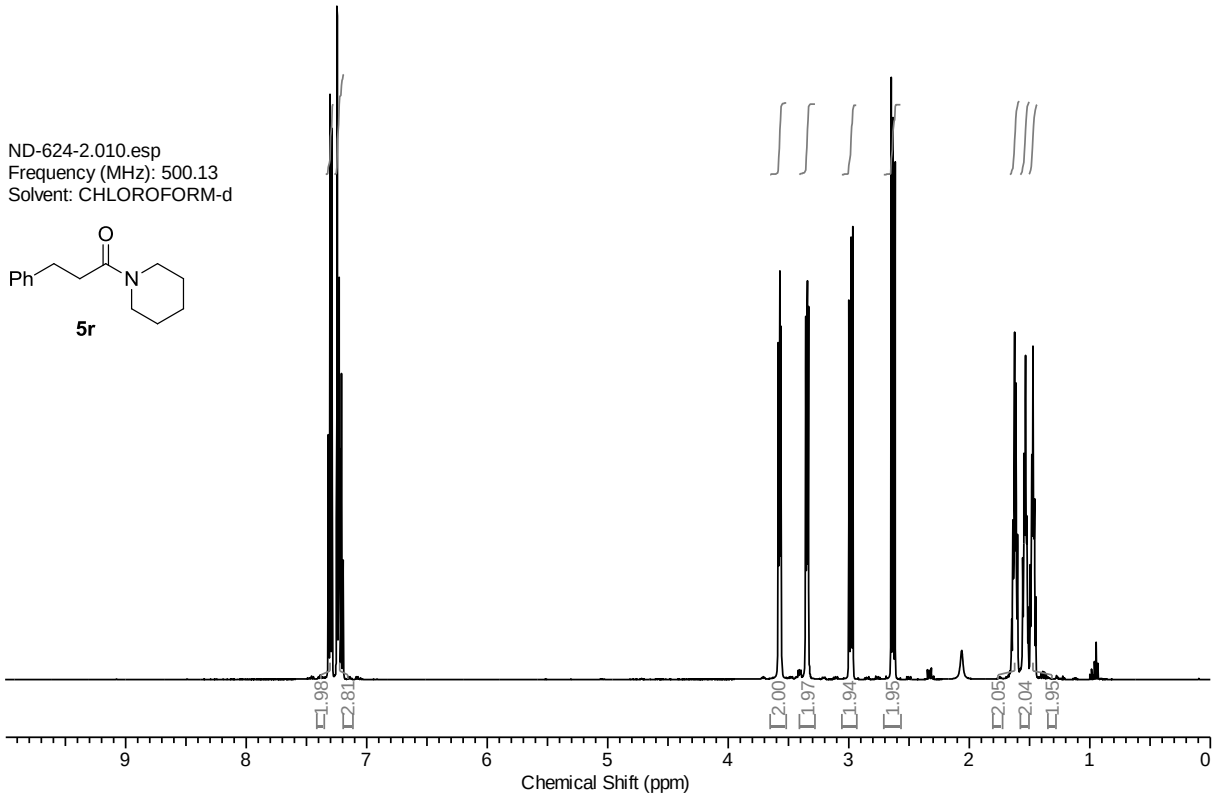

172.83
141.06
128.66
128.45
126.36
38.59
31.88
26.43
ND-638-1-sc.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
O
N
H
Me
5o
Chemical Shift (ppm)

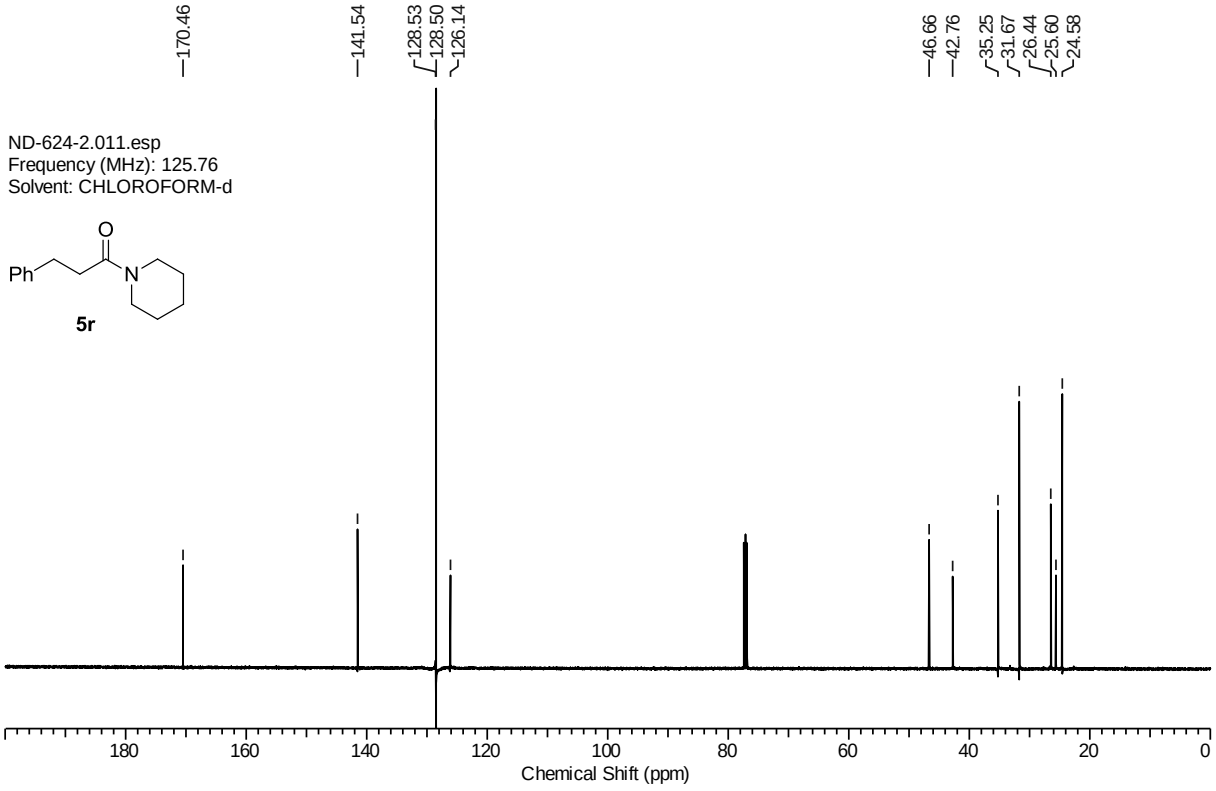

ND-525-1-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
5p
5.43
2.08
2.06
2.00
2.01
6.00
Chemical Shift (ppm)

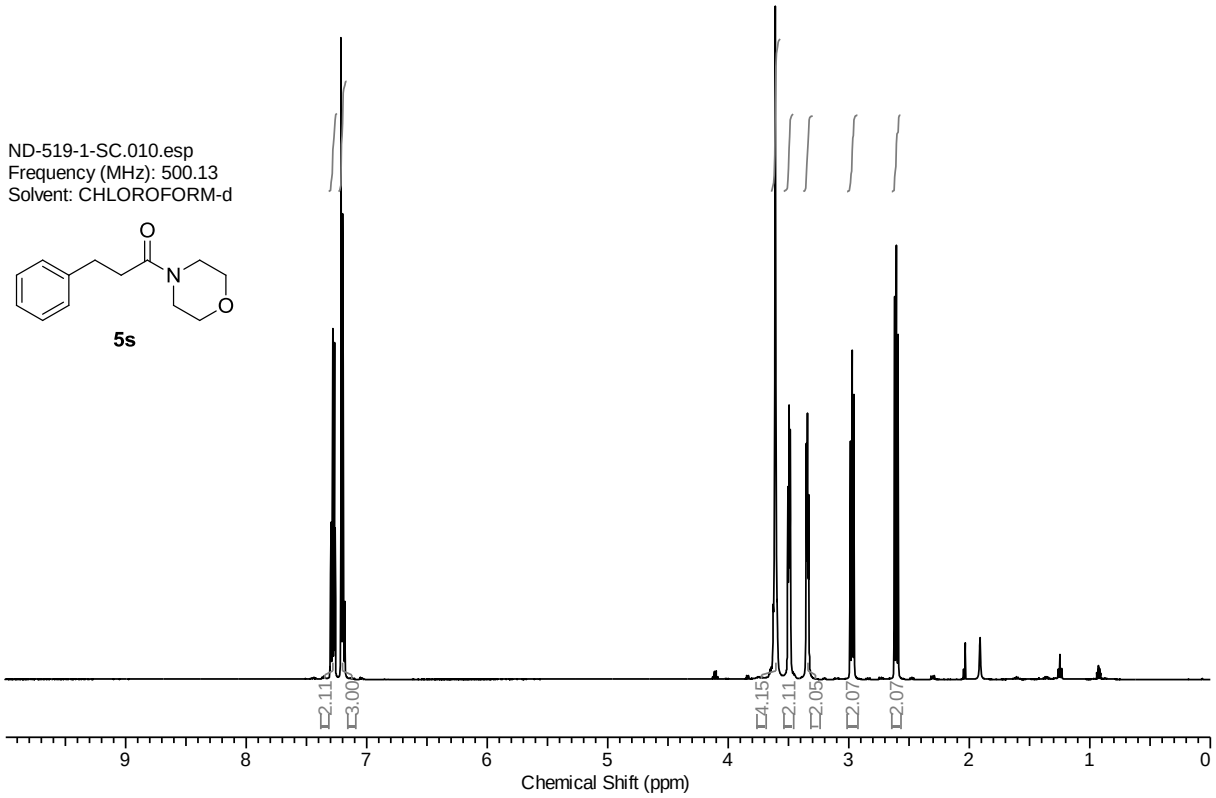

171.37
141.76
128.59
126.20
42.01
40.33
35.26
31.80
14.42
13.23
ND-525-1-SC.020.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
5p
Chemical Shift (ppm)

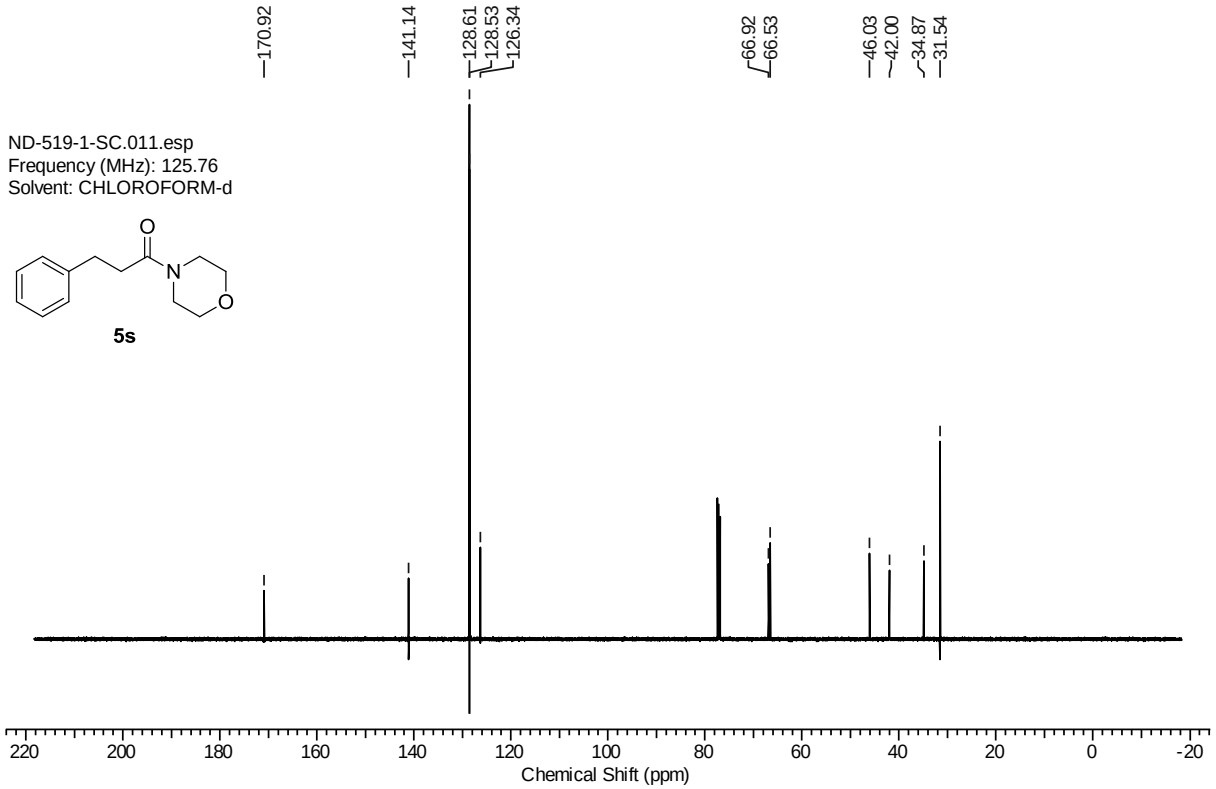

ND-634-2.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
O
N
5q
2.21
3.13
2.26
2.20
2.18
2.19
4.44
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

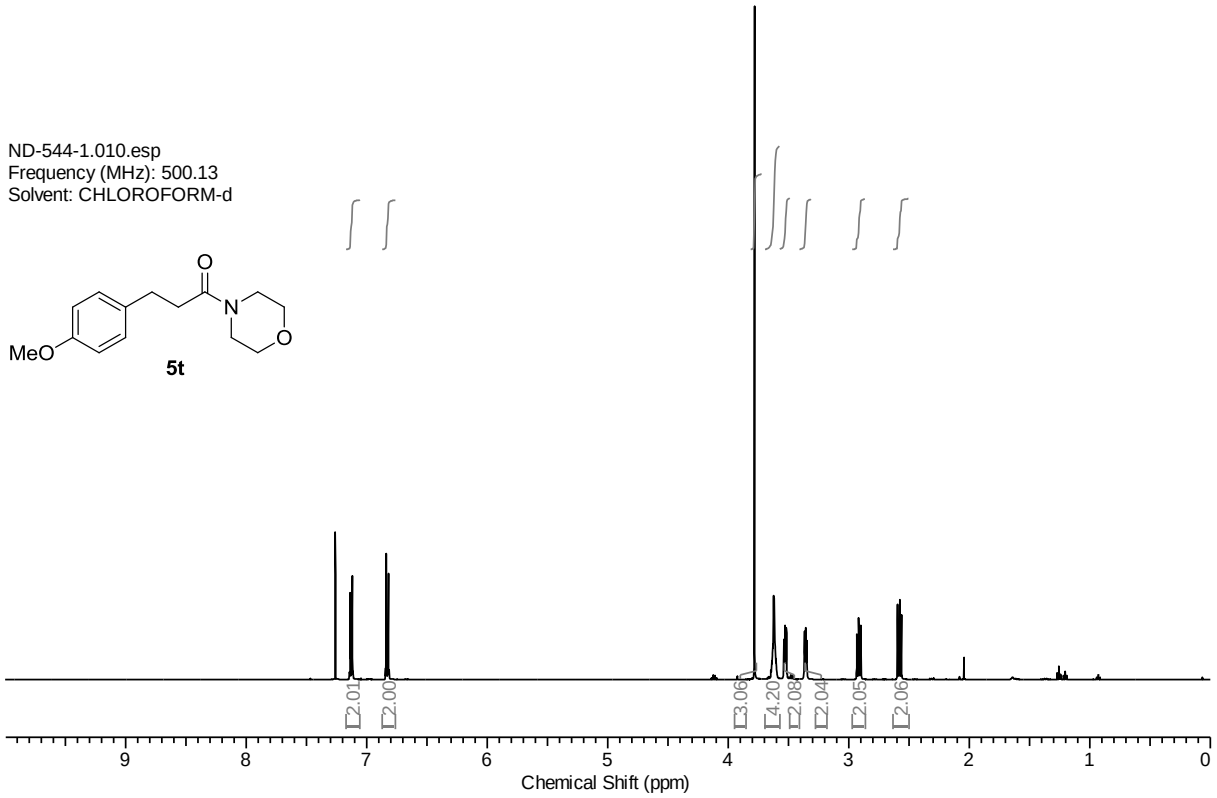

170.88
141.56
128.50
126.13
46.64
45.72
36.84
31.28
26.11
24.44
ND-634-2.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
O
N
5q
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

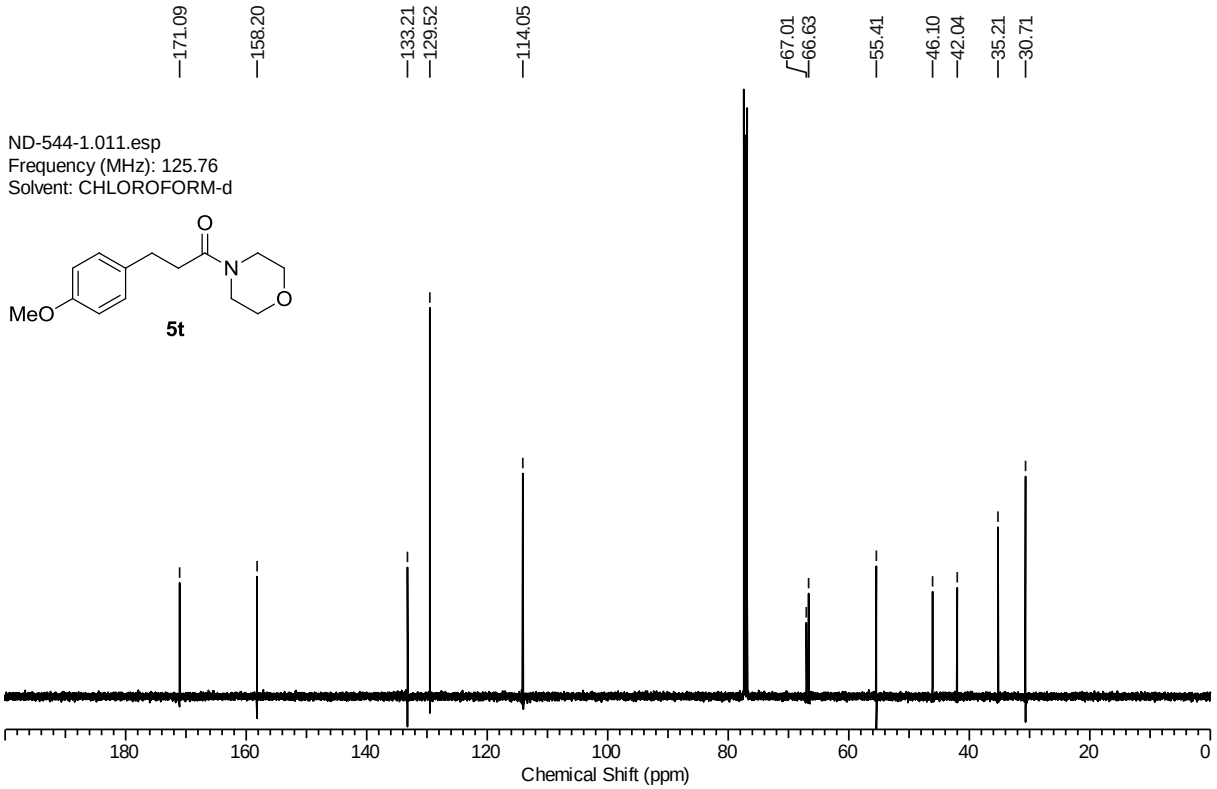

ND-624-2.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
O
N
5r
1.98
2.81
2.00
1.97
1.94
1.95
2.05
2.04
1.95
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

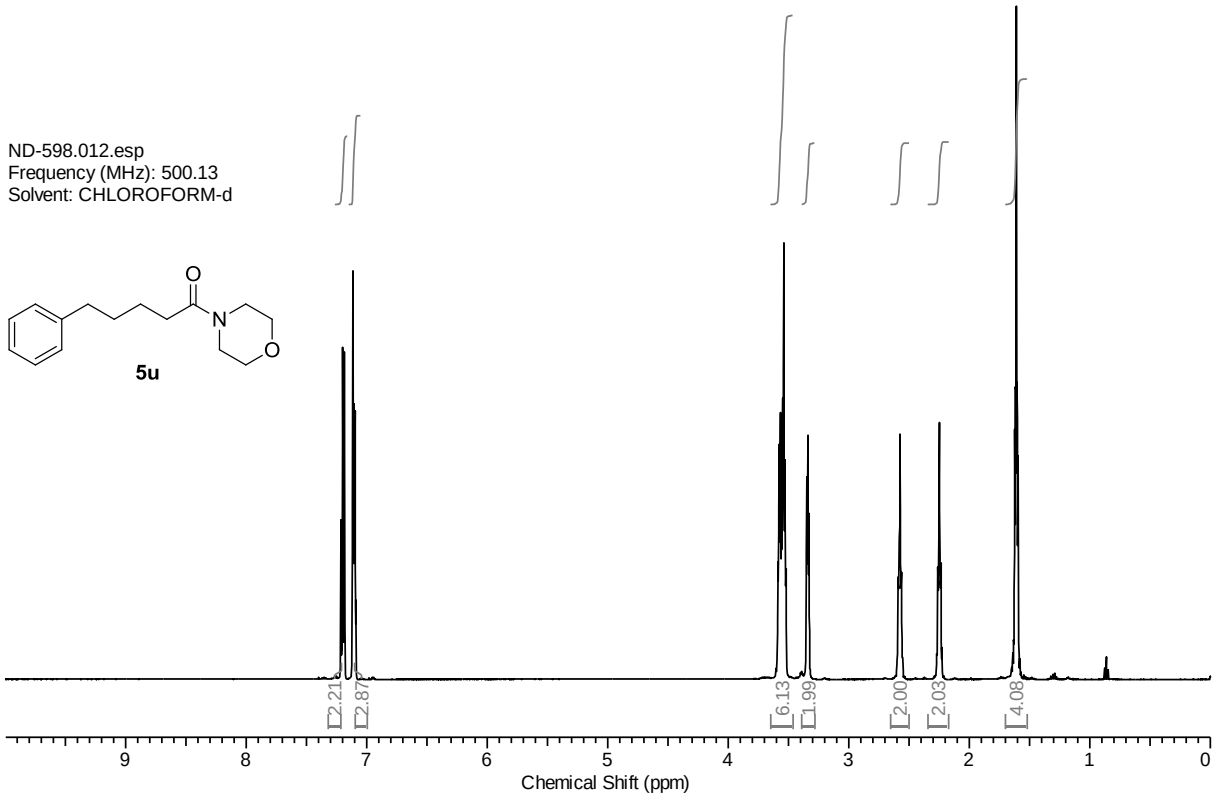

170.46
141.54
128.53
128.50
126.14
46.66
42.76
35.25
31.67
26.44
25.60
24.58
ND-624-2.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
O
N
5r
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

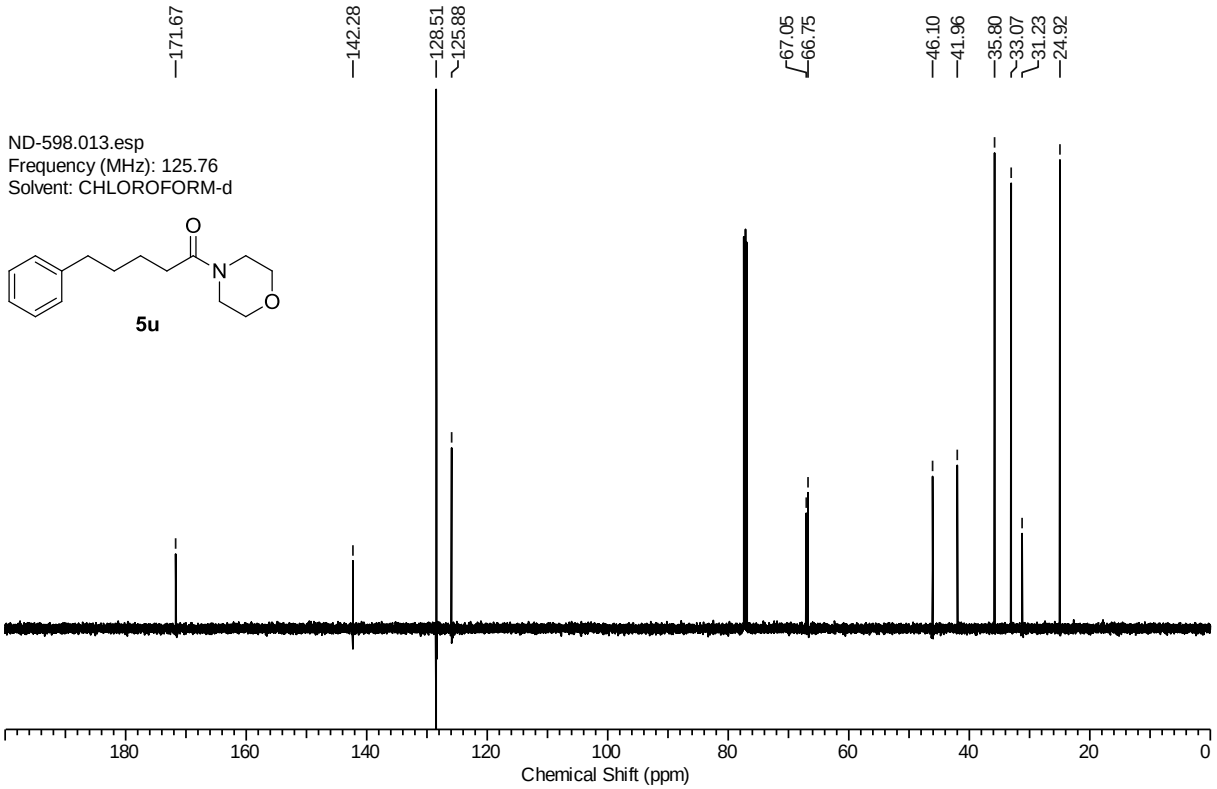

ND-519-1-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
5s
2.11
3.00
4.15
2.11
2.05
2.07
2.07
Chemical Shift (ppm)

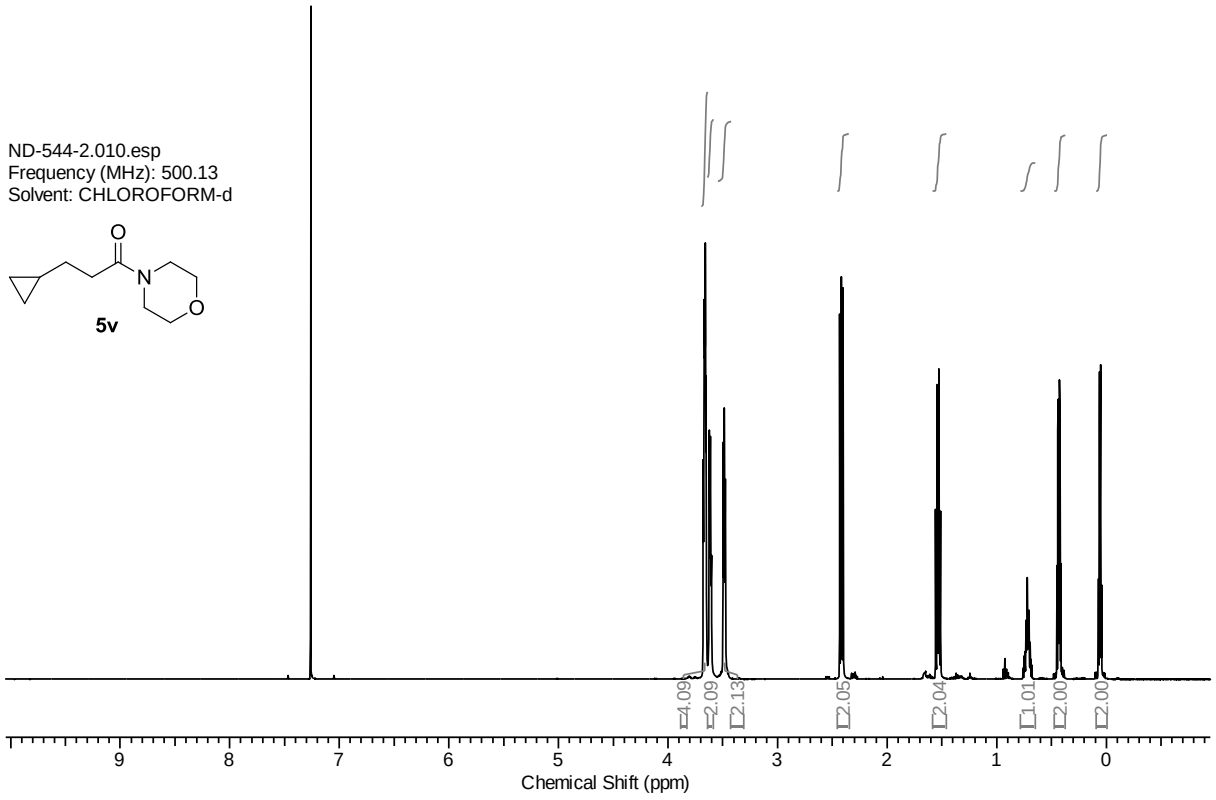

170.92
141.14
128.61
128.53
126.34
66.92
66.53
46.03
42.00
34.87
31.54
ND-519-1-SC.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
5s
Chemical Shift (ppm)

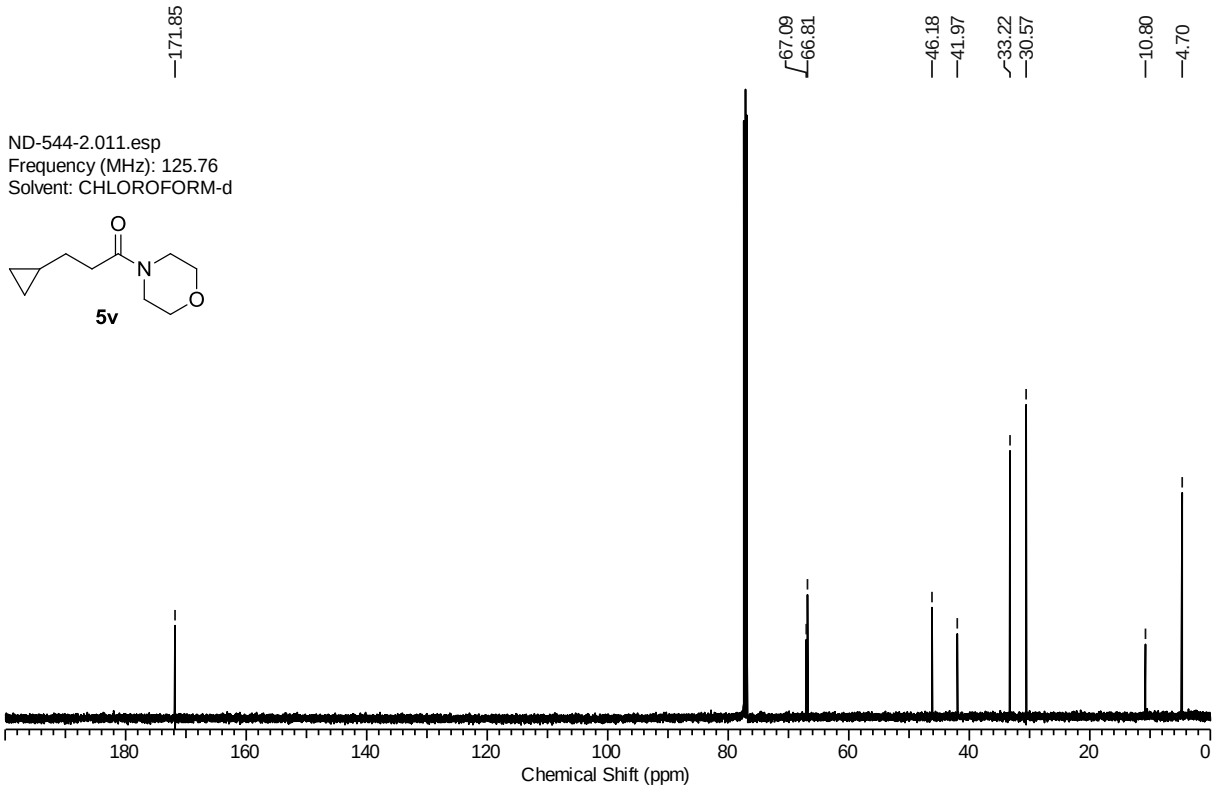

ND-544-1.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
MeO
5t
2.01
2.00
3.06
4.20
2.08
2.04
2.05
2.06
Chemical Shift (ppm)


171.09
158.20
133.21
129.52
114.05
67.01
66.63
55.41
46.10
42.04
35.21
30.71
ND-544-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
MeO
5t
Chemical Shift (ppm)

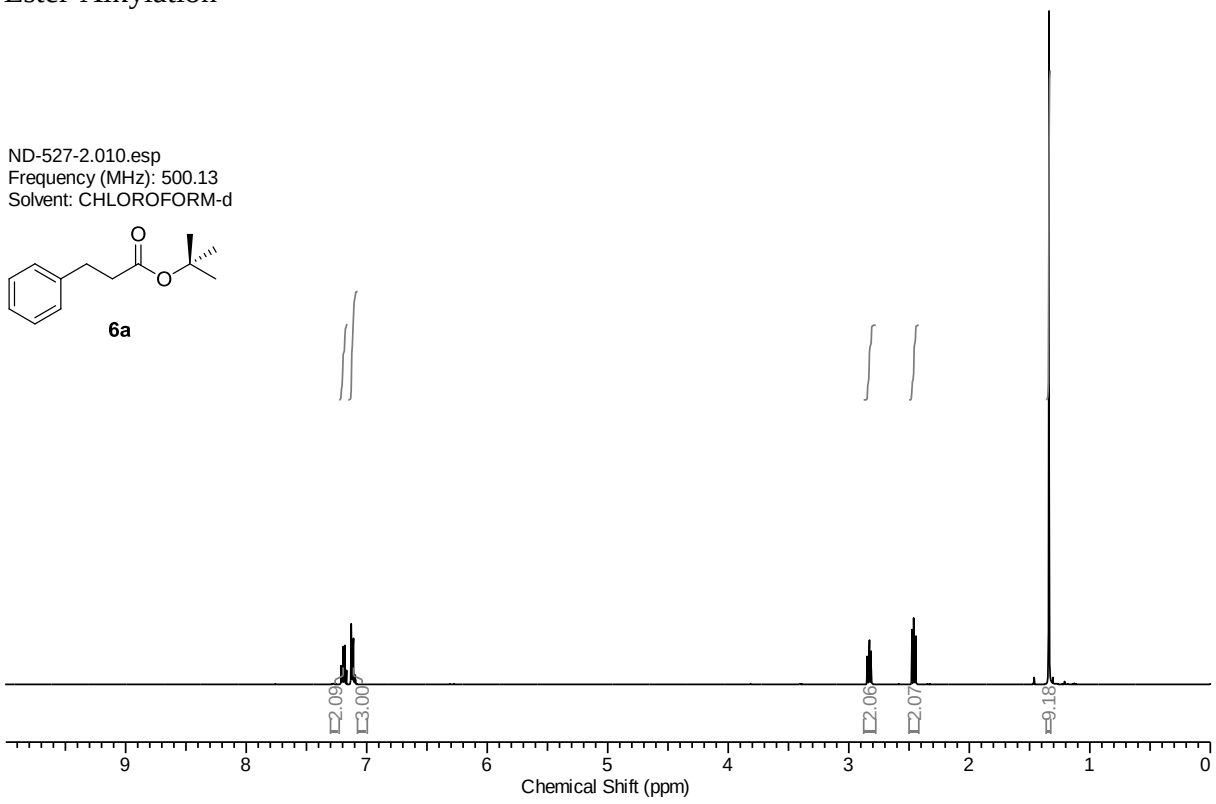

ND-598.012.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
5u
2.21
2.87
6.13
1.99
2.00
2.03
4.08
Chemical Shift (ppm)

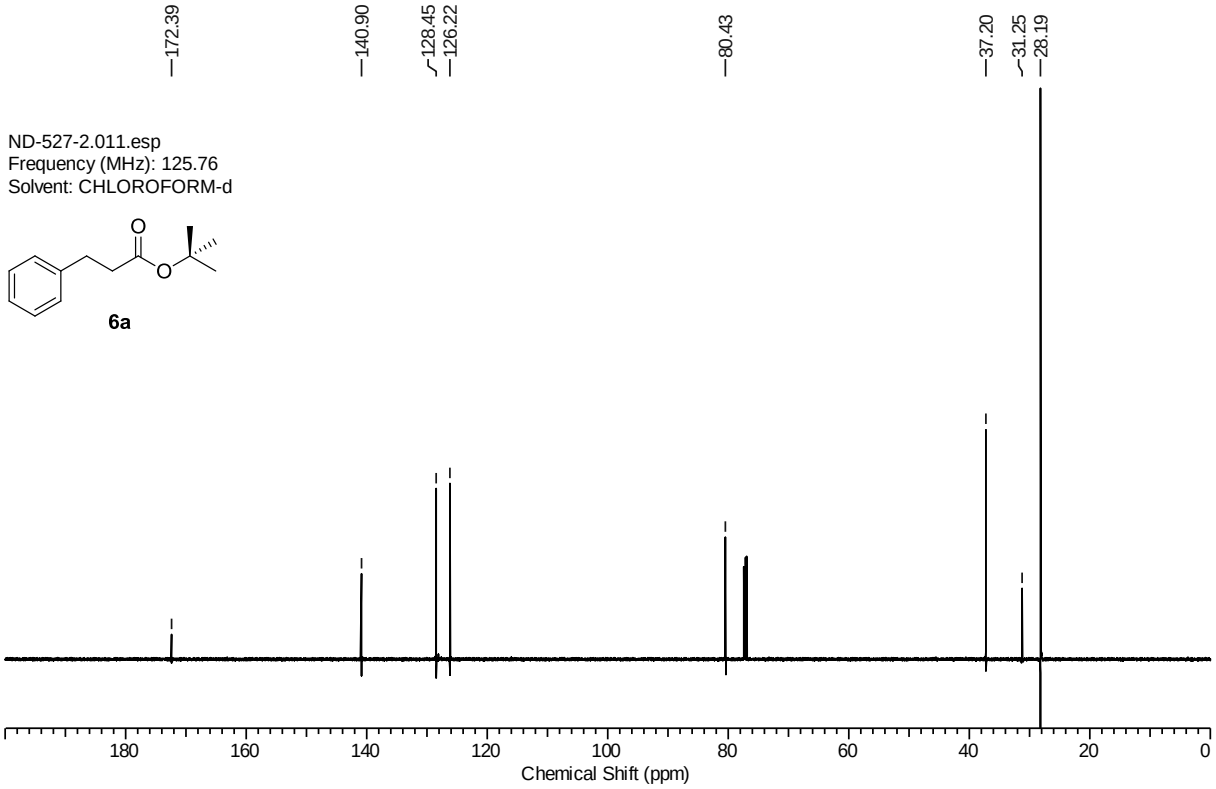

171.67
142.28
128.51
125.88
67.05
66.75
46.10
41.96
35.80
33.07
31.23
24.92
ND-598.013.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
5u
Chemical Shift (ppm)

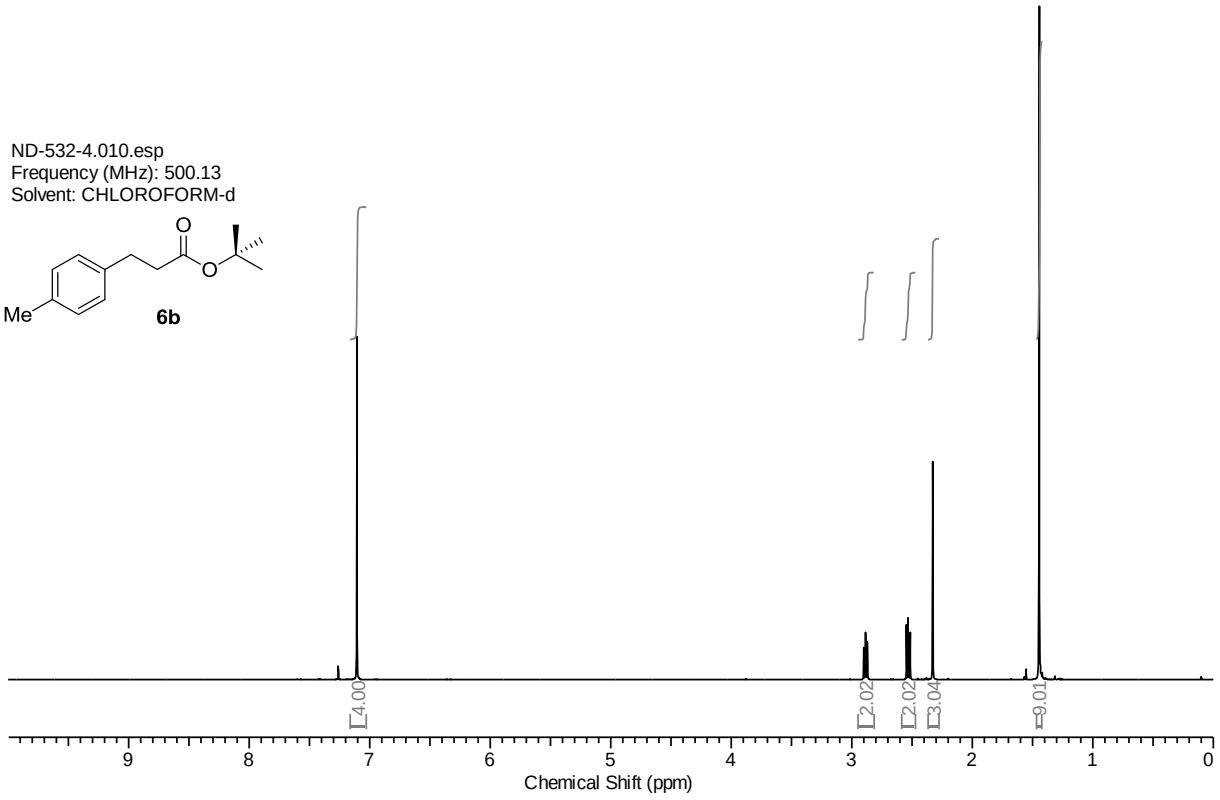

ND-544-2.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
N
O
5v
4.09
2.09
2.13
2.05
2.04
1.01
2.00
2.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

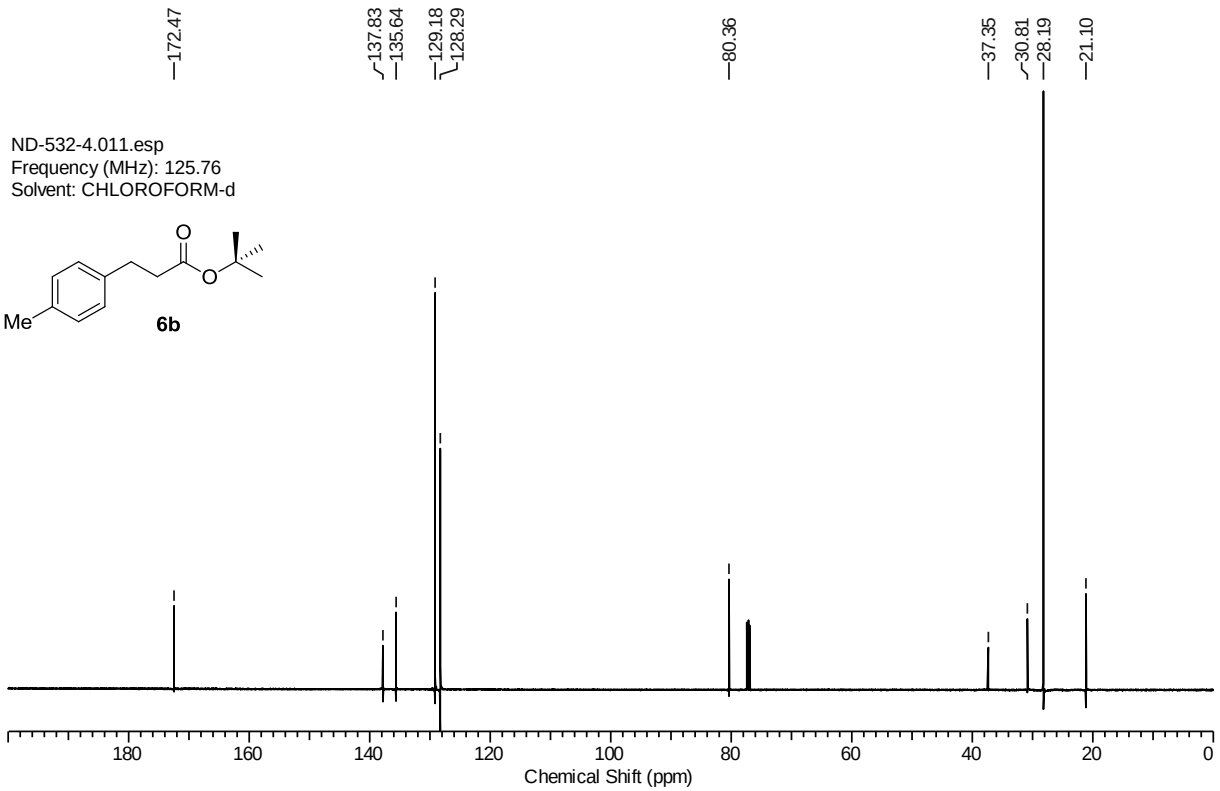

171.85
67.09
66.81
46.18
41.97
33.22
30.57
10.80
4.70
ND-544-2.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
N
O
5v
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

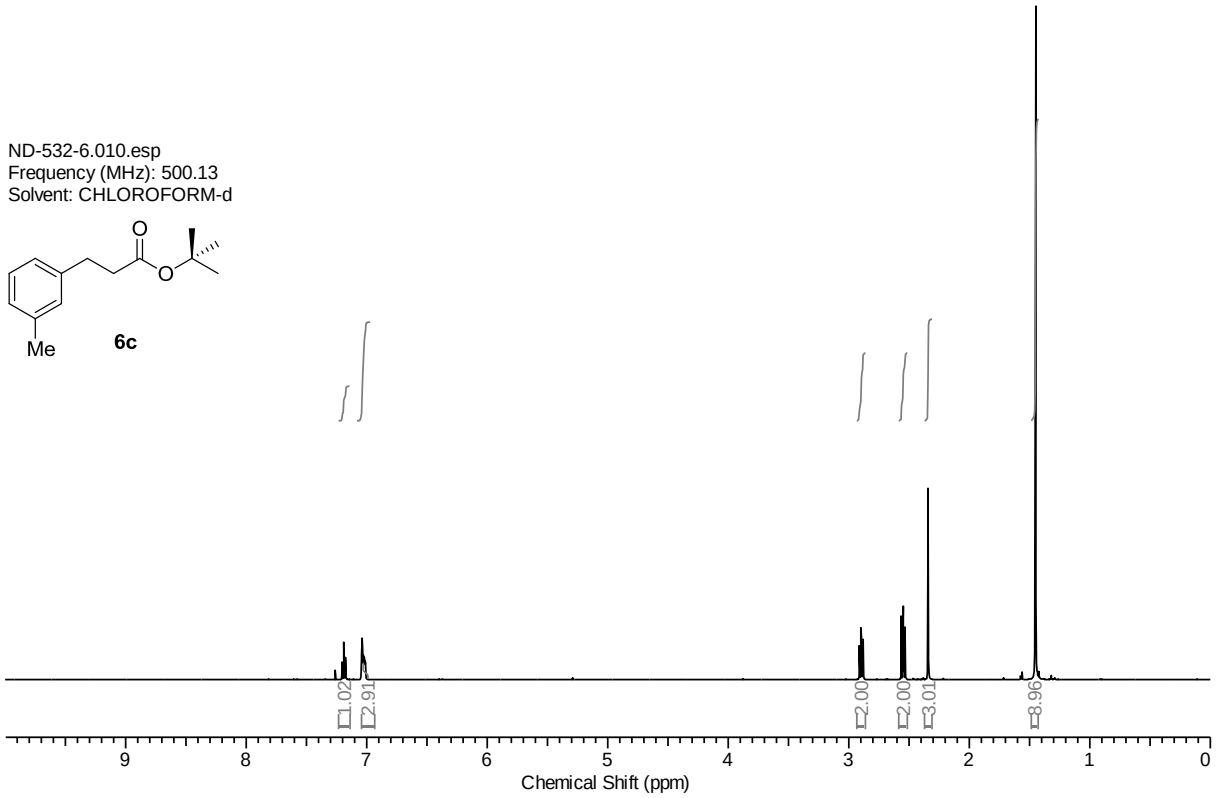
## Ester-Alkylation

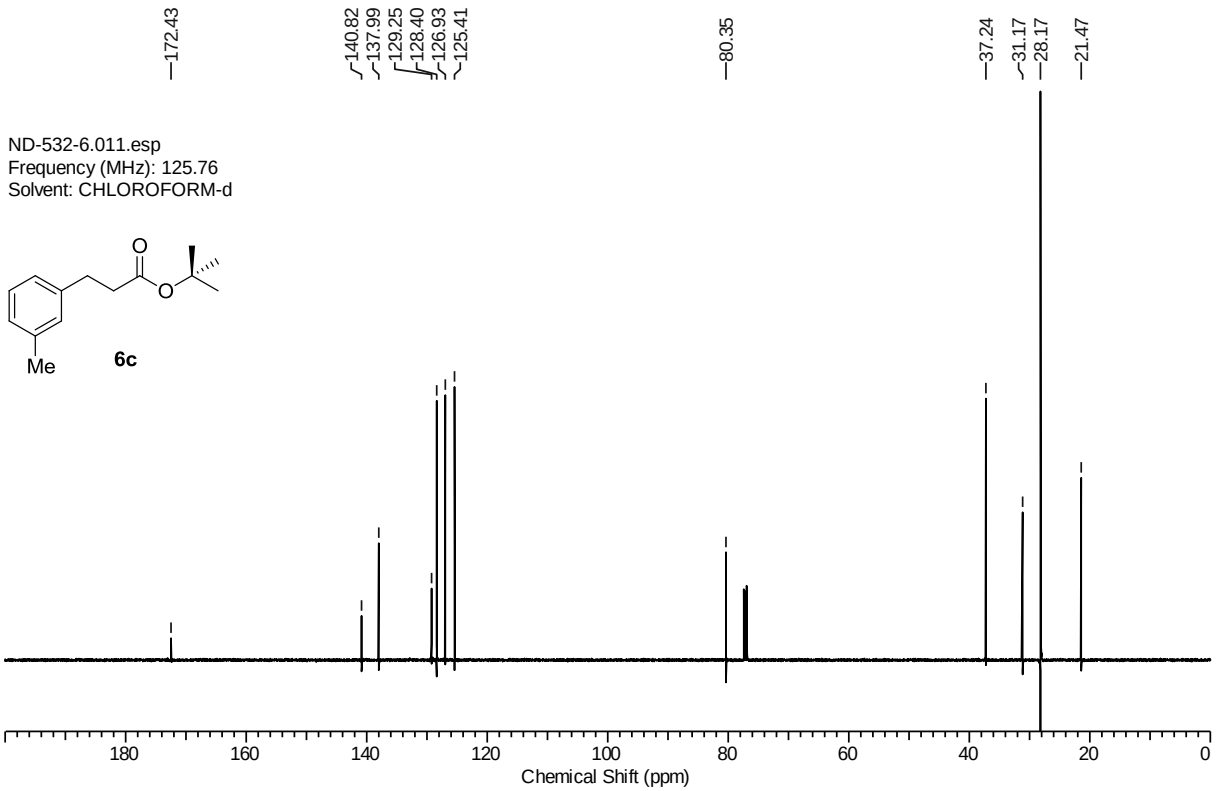


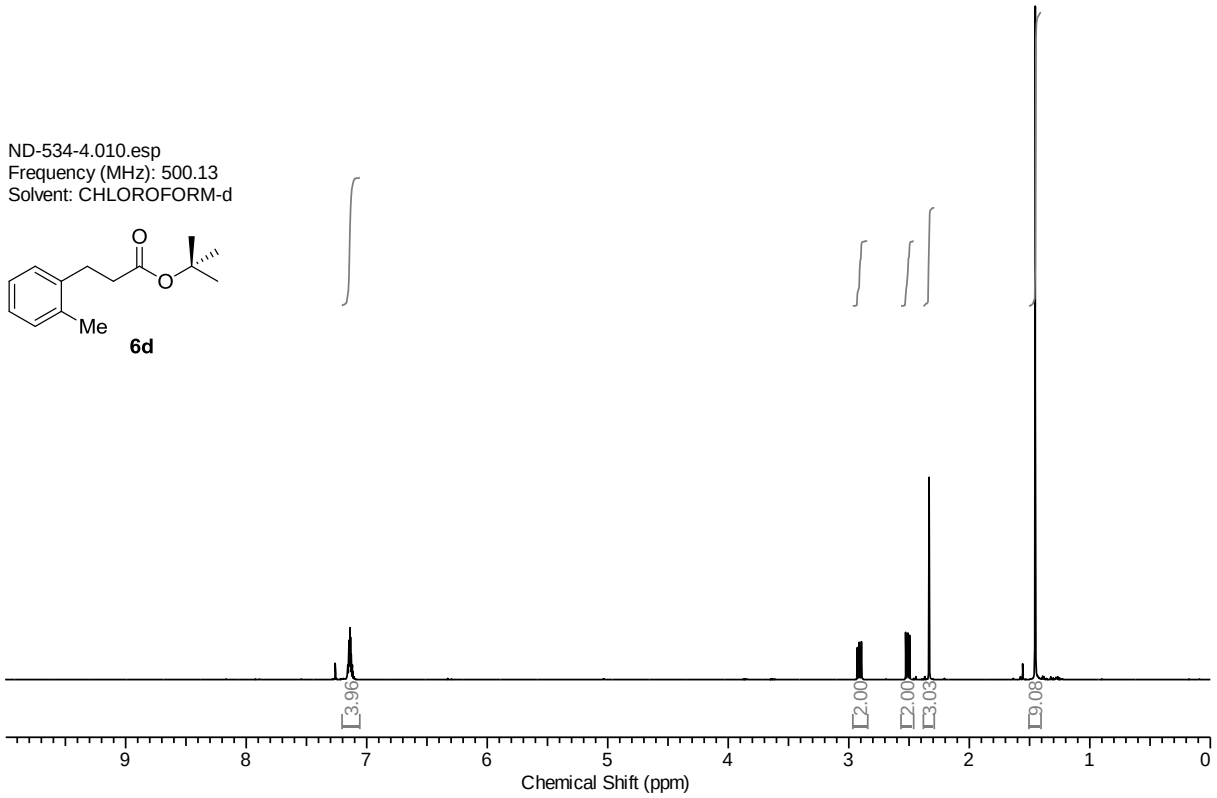



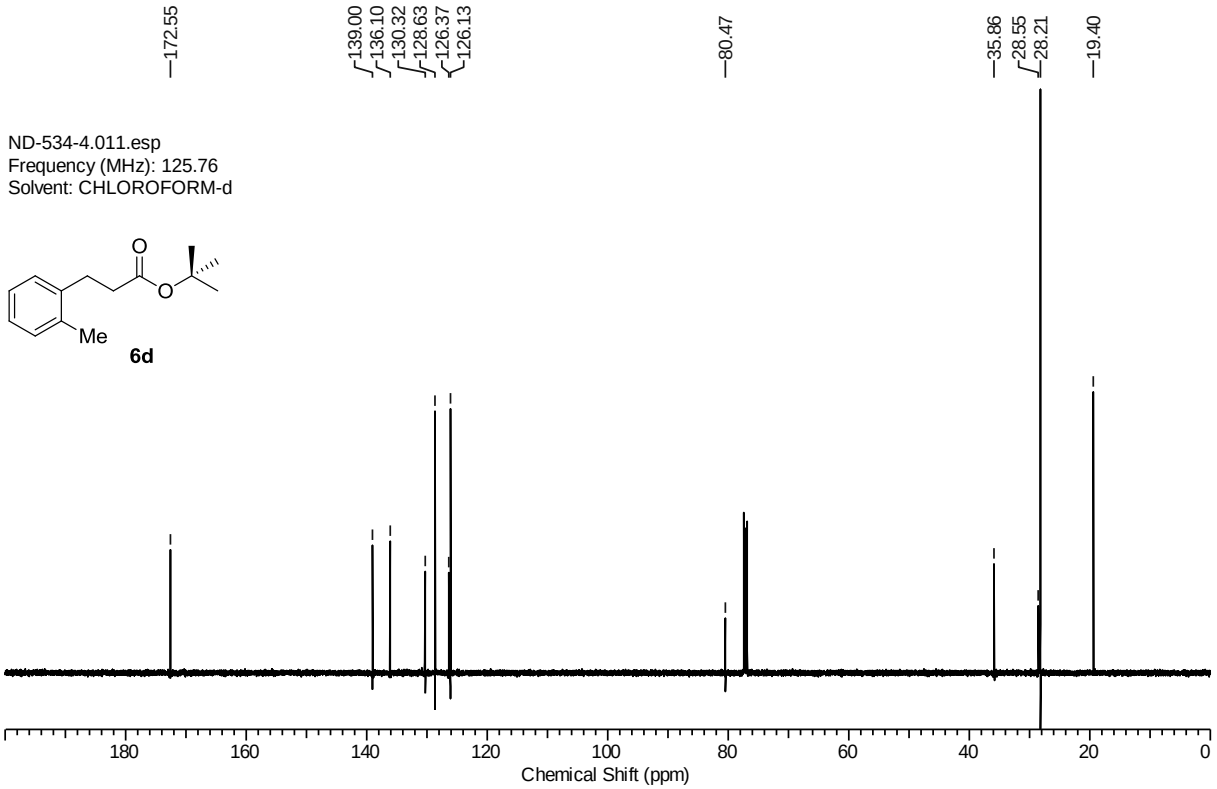

ND-532-4.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Me
6b
4.00
2.02
2.02
3.04
9.01
Chemical Shift (ppm)

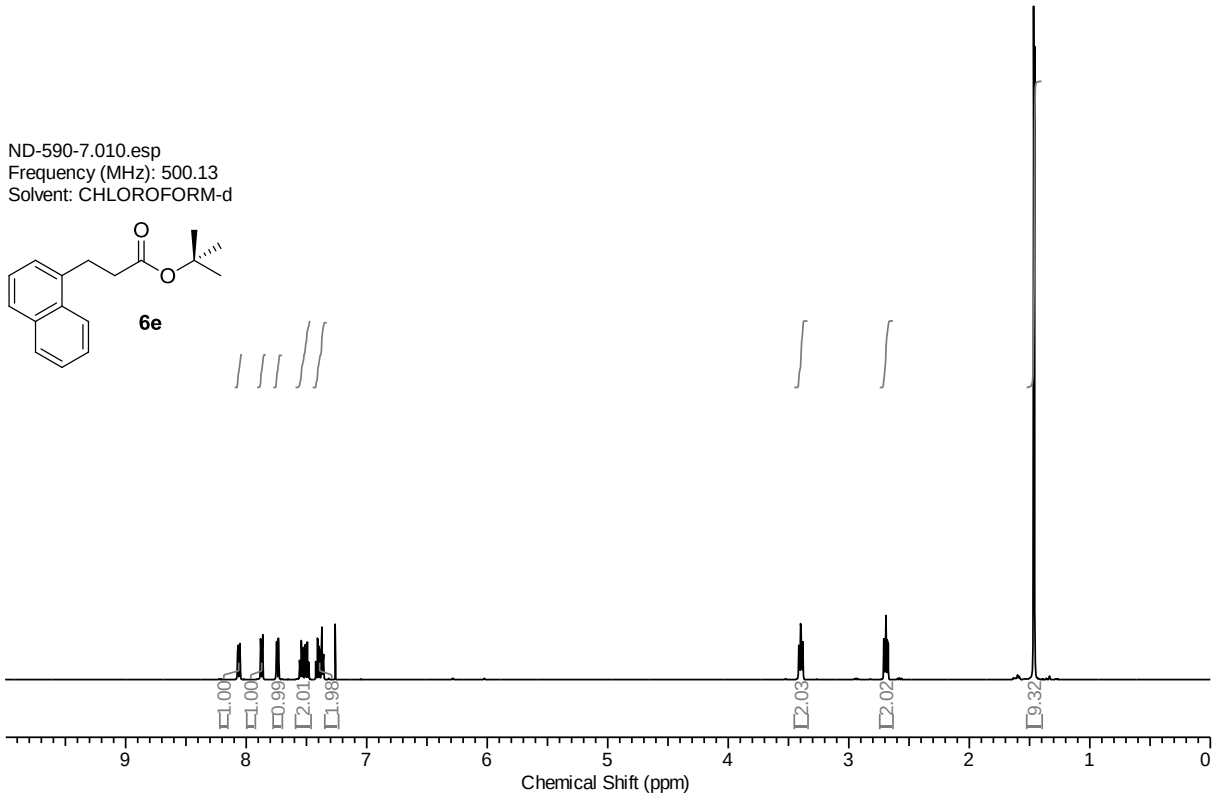

172.47
137.83
135.64
129.18
128.29
80.36
37.35
30.81
28.19
21.10
ND-532-4.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Me
6b
Chemical Shift (ppm)

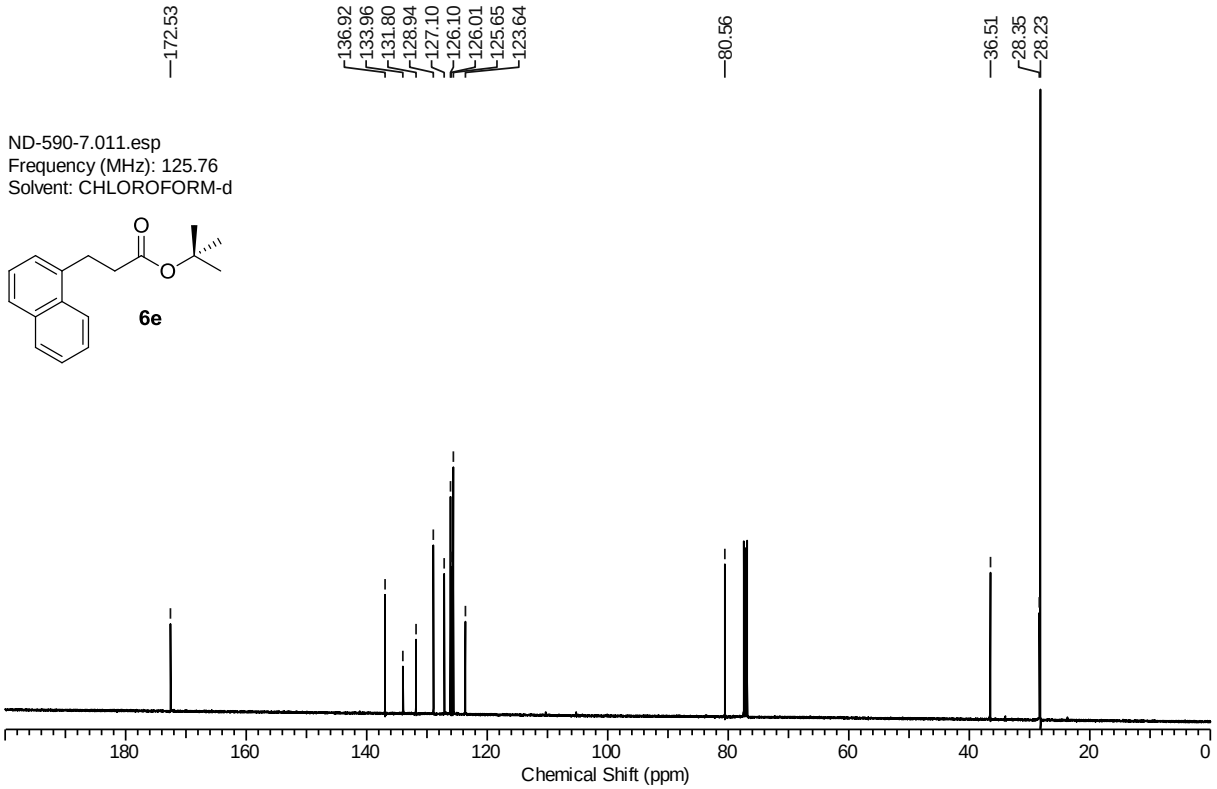

ND-532-6.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
O
Me
6c
1.02
2.91
2.00
2.00
3.01
8.96
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

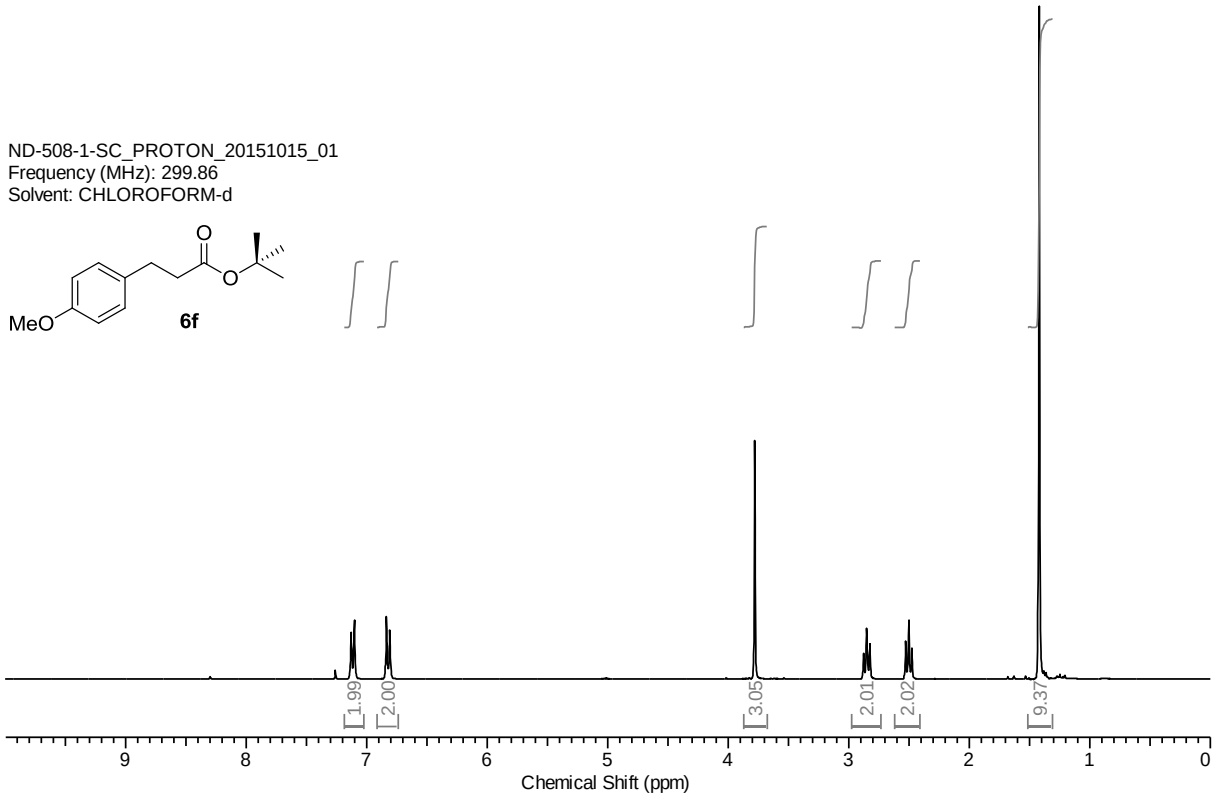

172.43
140.82
137.99
129.25
128.40
126.93
125.41
80.35
37.24
31.17
28.17
21.47
ND-532-6.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
O
Me
6c
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

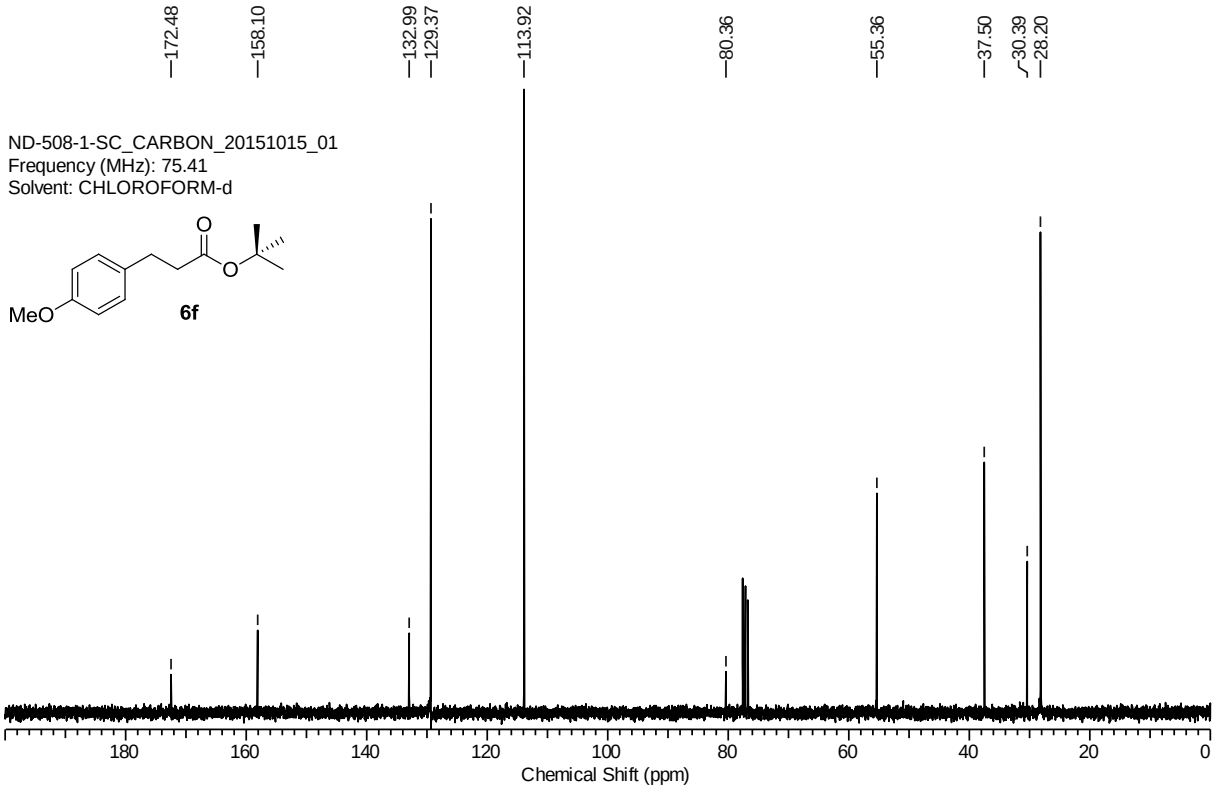

ND-534-4.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
O
Me
6d
3.96
2.00
2.00
3.03
9.08
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

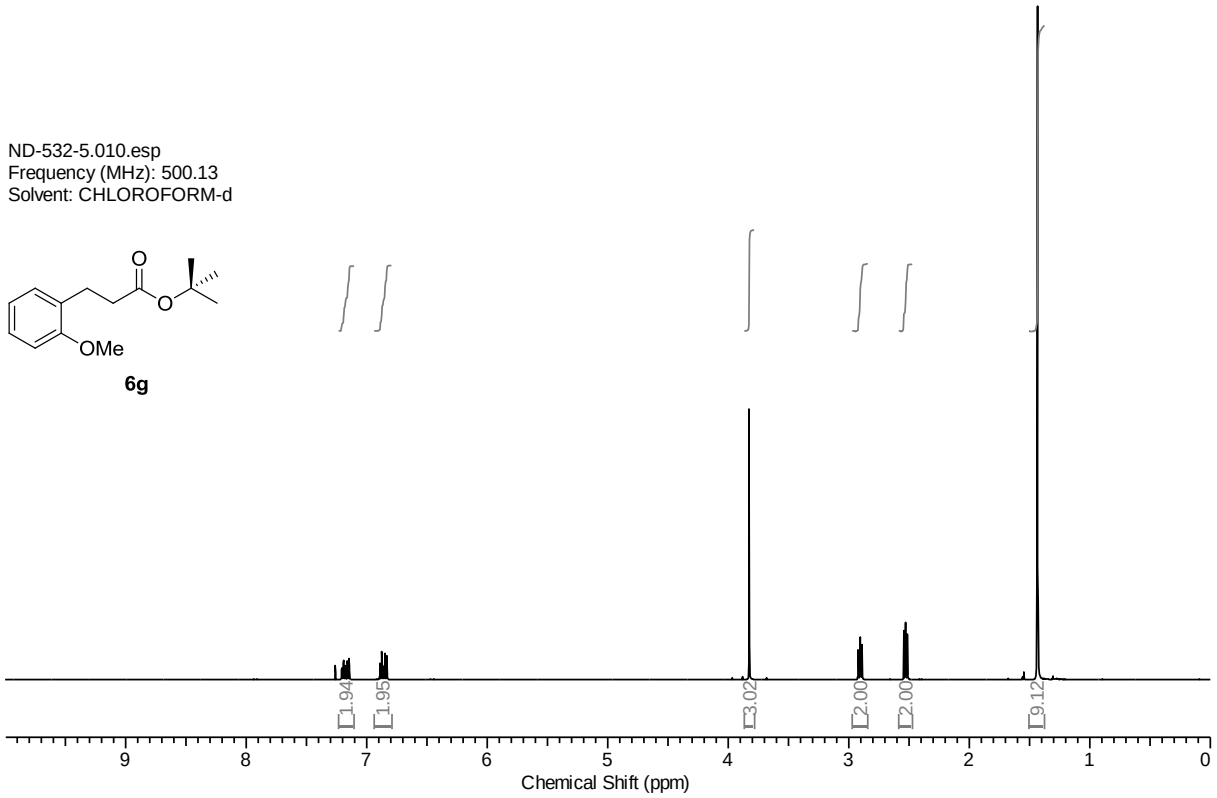

172.55
139.00
136.10
130.32
128.63
126.37
126.13
80.47
35.86
28.55
28.21
19.40
ND-534-4.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
O
Me
6d
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

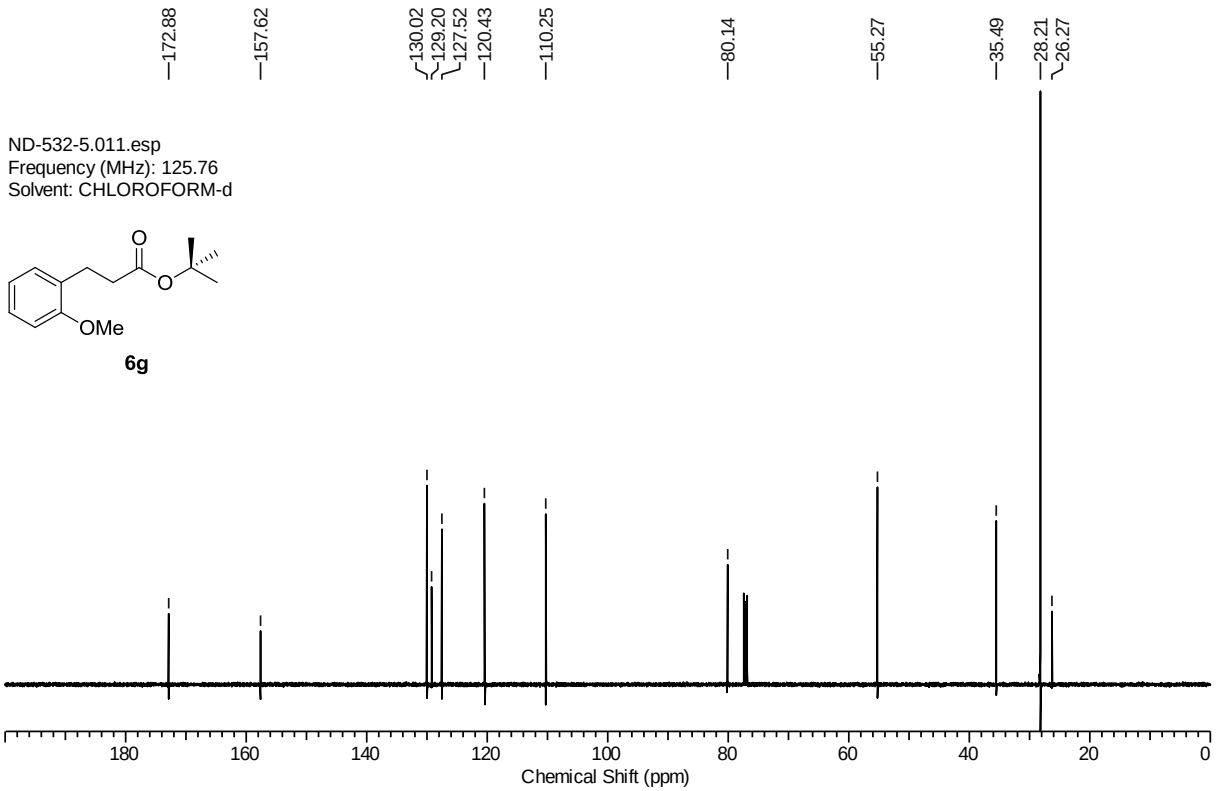

ND-590-7.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
6e
1.00
1.00
0.99
2.01
1.98
2.03
2.02
9.32
Chemical Shift (ppm)

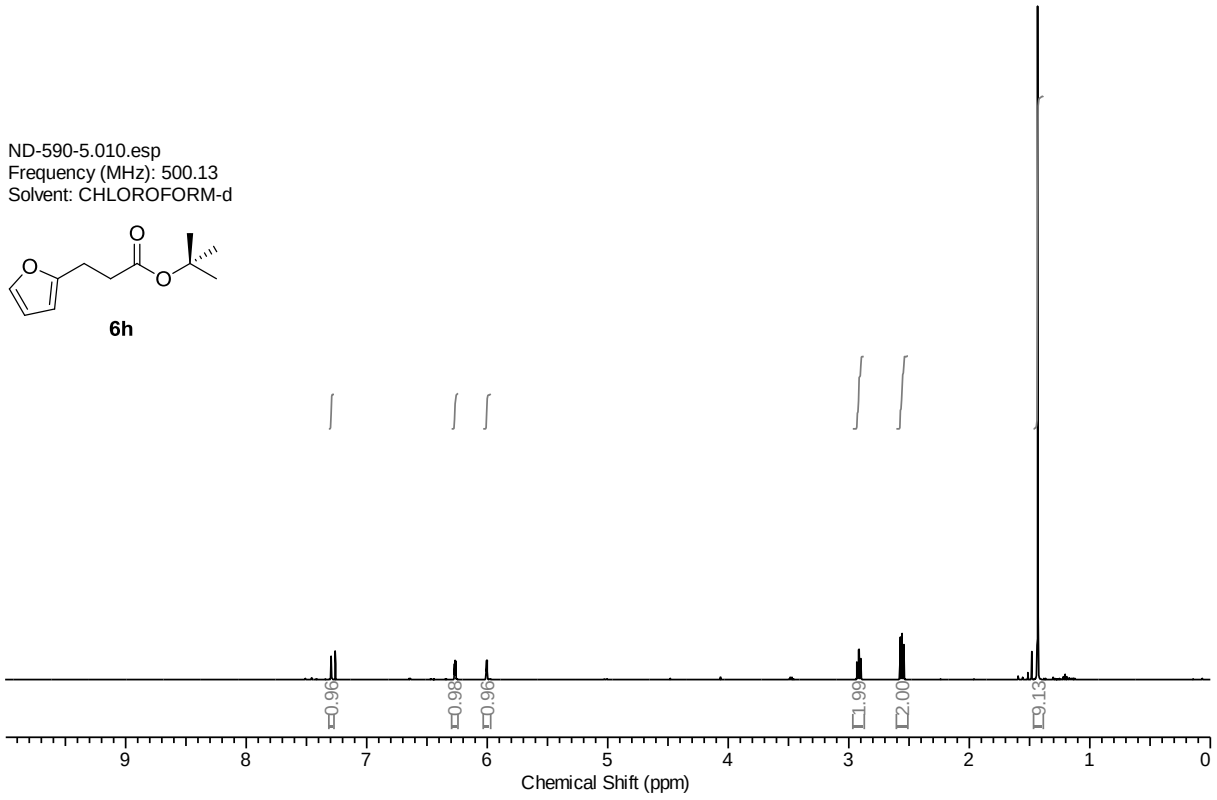

172.53
136.92
133.96
131.80
128.94
127.10
126.10
126.01
125.65
123.64
80.56
36.51
28.35
28.23
ND-590-7.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
6e
Chemical Shift (ppm)

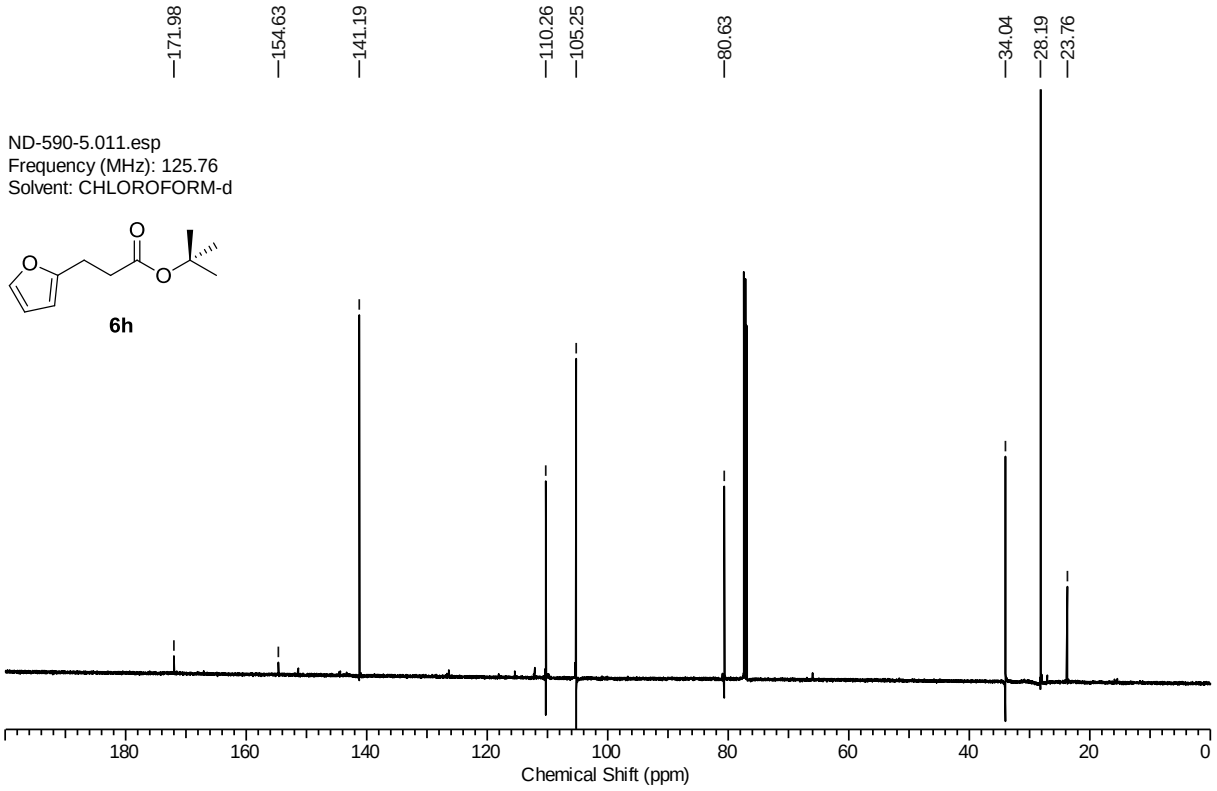

ND-508-1-SC_PROTON_20151015_01
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
MeO
6f
1.99
2.00
3.05
2.01
2.02
9.37
Chemical Shift (ppm)

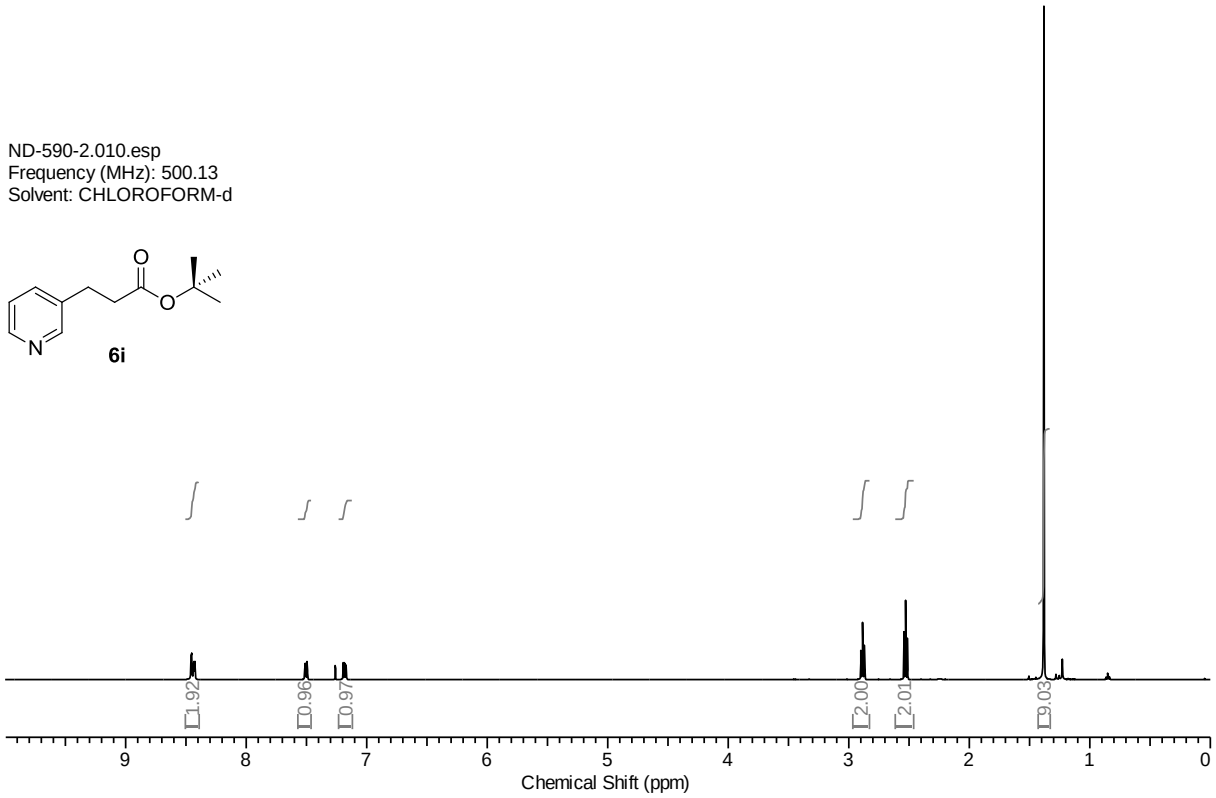

172.48
158.10
132.99
129.37
113.92
80.36
55.36
37.50
30.39
28.20
ND-508-1-SC_CARBON_20151015_01
Frequency (MHz): 75.41
Solvent: CHLOROFORM-d
MeO
6f
Chemical Shift (ppm)

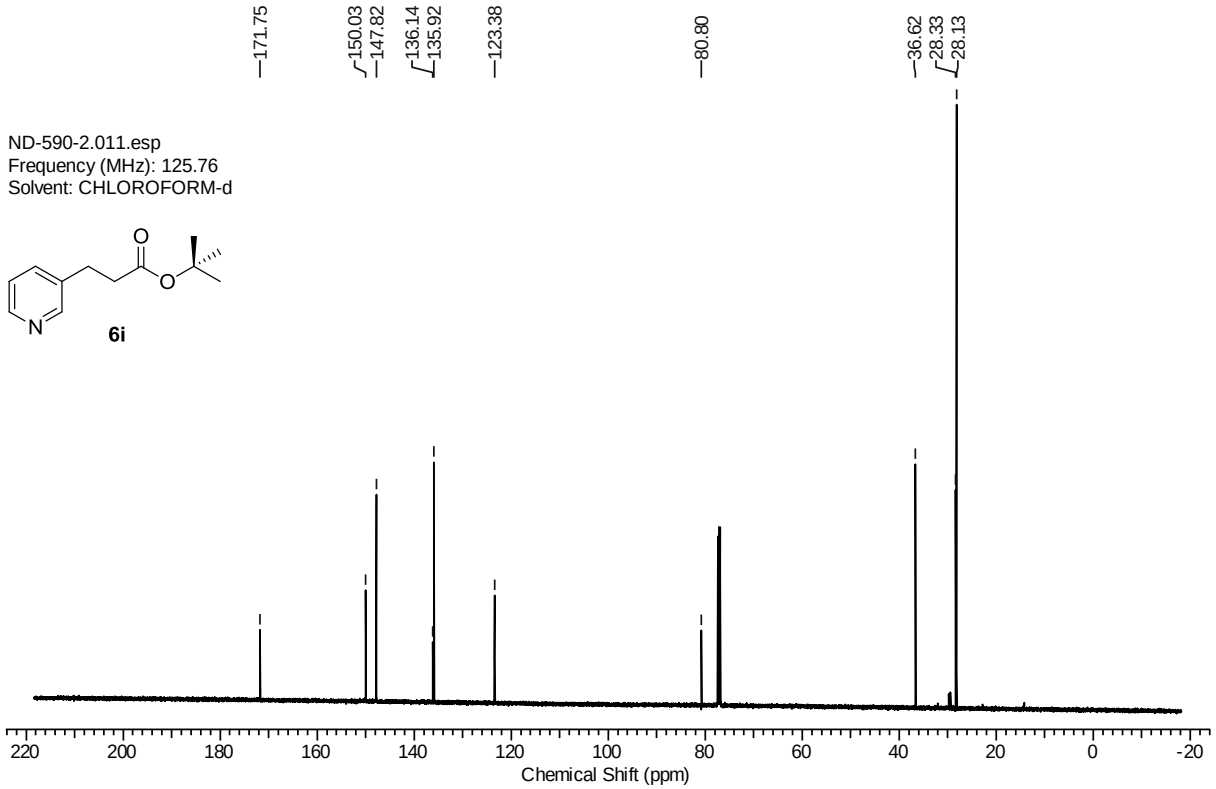

ND-532-5.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
O
OMe
6g
1.94
1.95
3.02
2.00
2.00
9.12
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

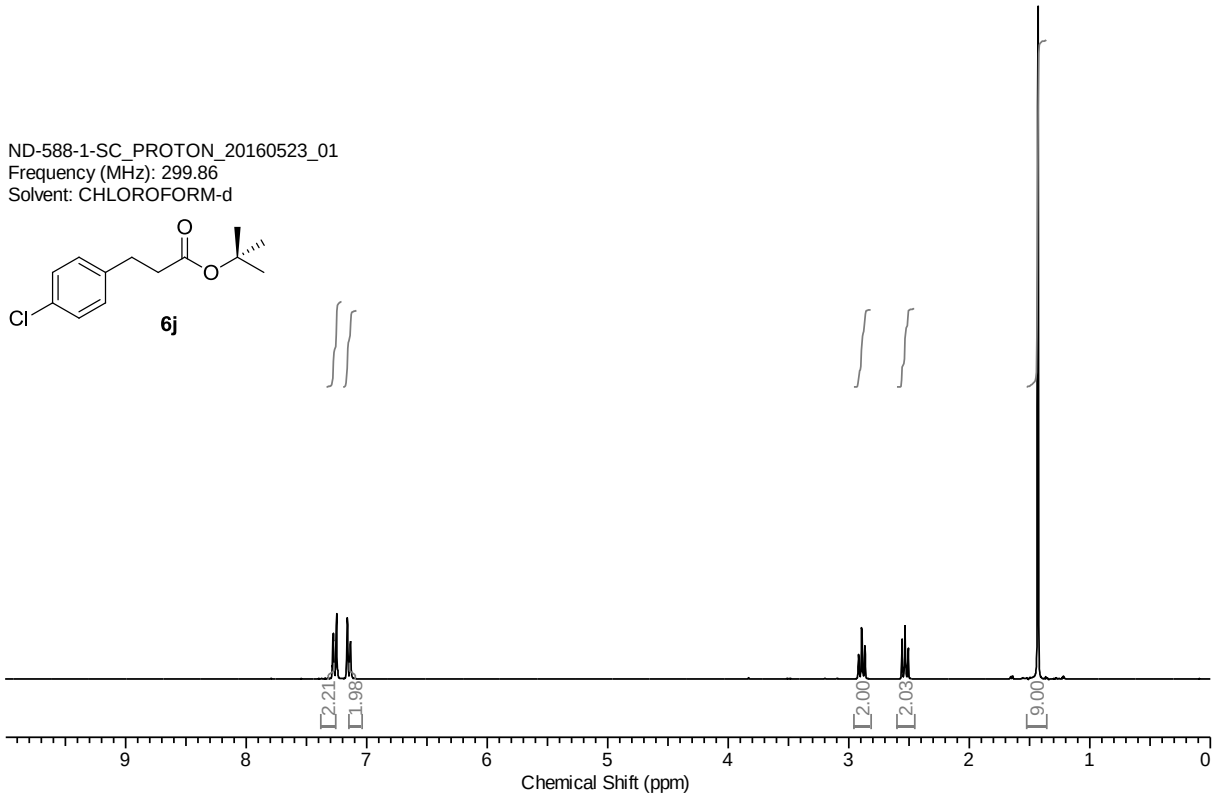

172.88
157.62
130.02
129.20
127.52
120.43
110.25
80.14
55.27
35.49
28.21
26.27
ND-532-5.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
O
OMe
6g
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

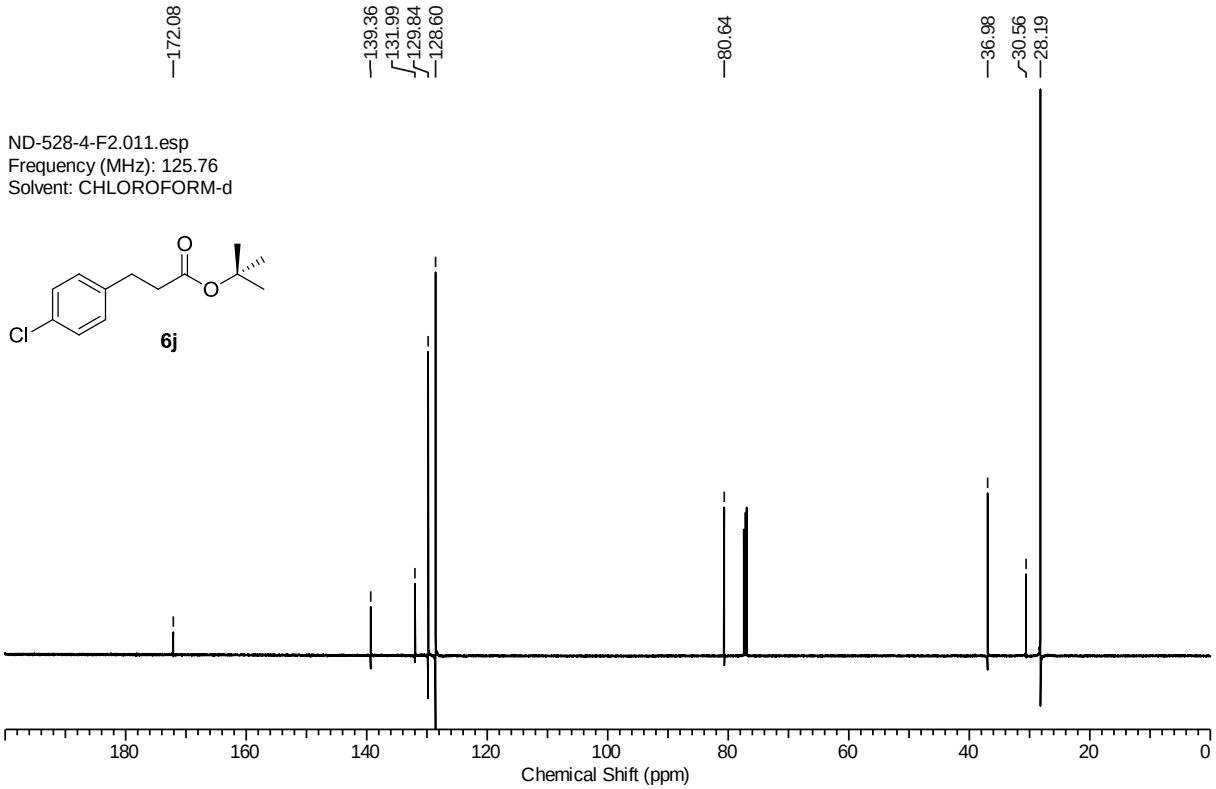

ND-590-5.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
6h
0.96
0.98
0.96
1.99
2.00
9.13
Chemical Shift (ppm)

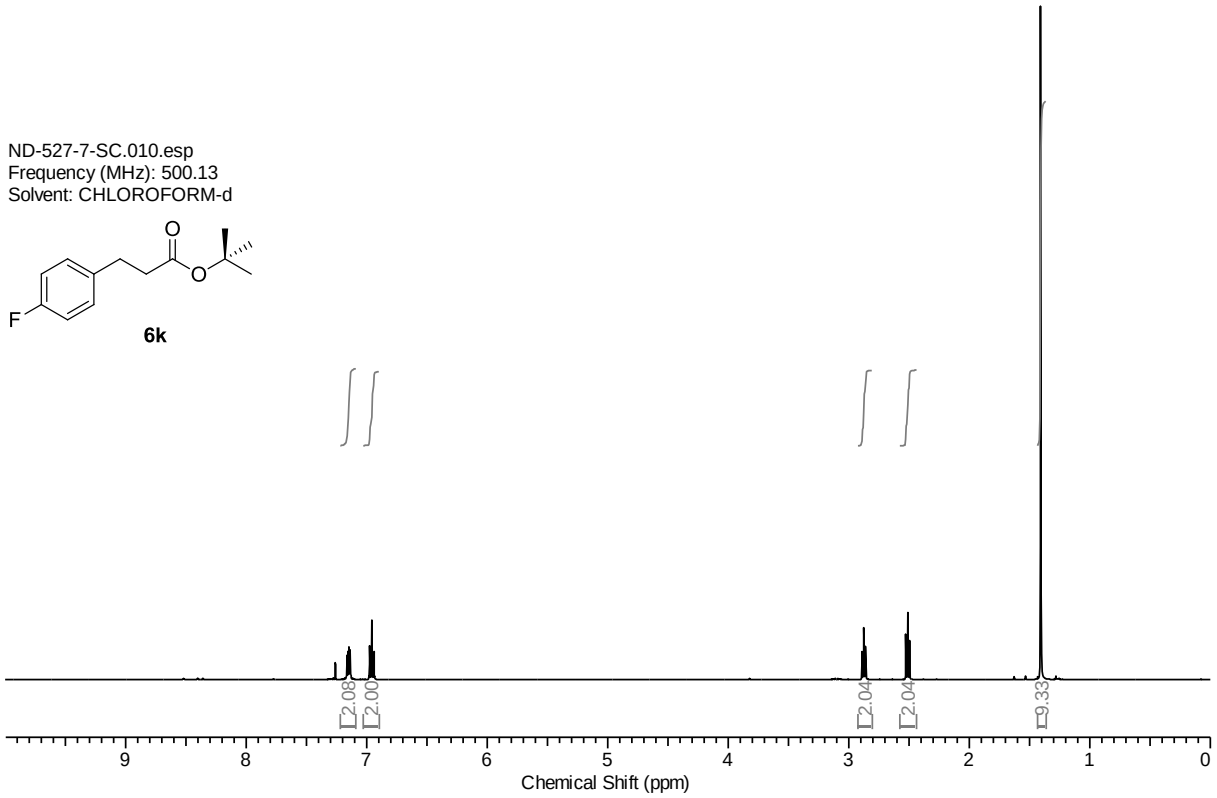

171.98
154.63
141.19
110.26
105.25
80.63
34.04
28.19
23.76
ND-590-5.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
6h
Chemical Shift (ppm)

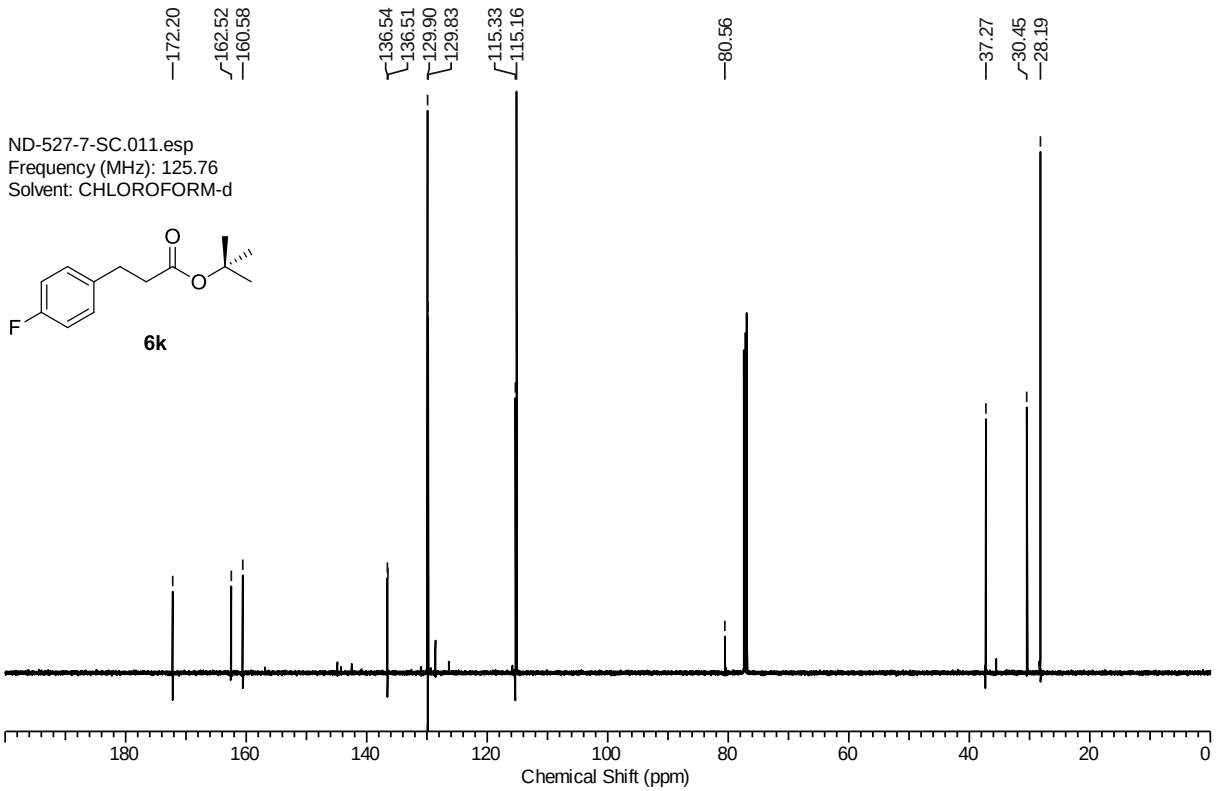

ND-590-2.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
6i
1.92
0.96
0.97
2.00
2.01
9.03
Chemical Shift (ppm)

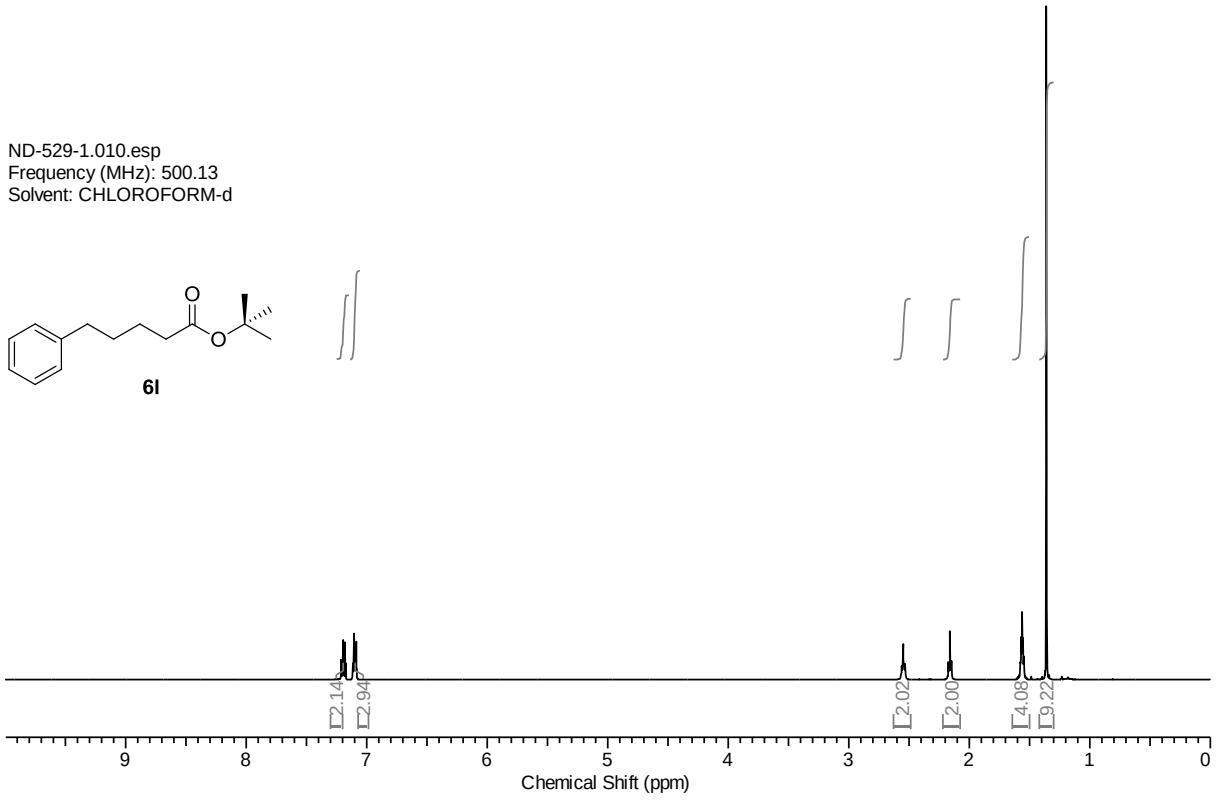

171.75
150.03
147.82
136.14
135.92
123.38
80.80
36.62
28.33
28.13
ND-590-2.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
6i
Chemical Shift (ppm)

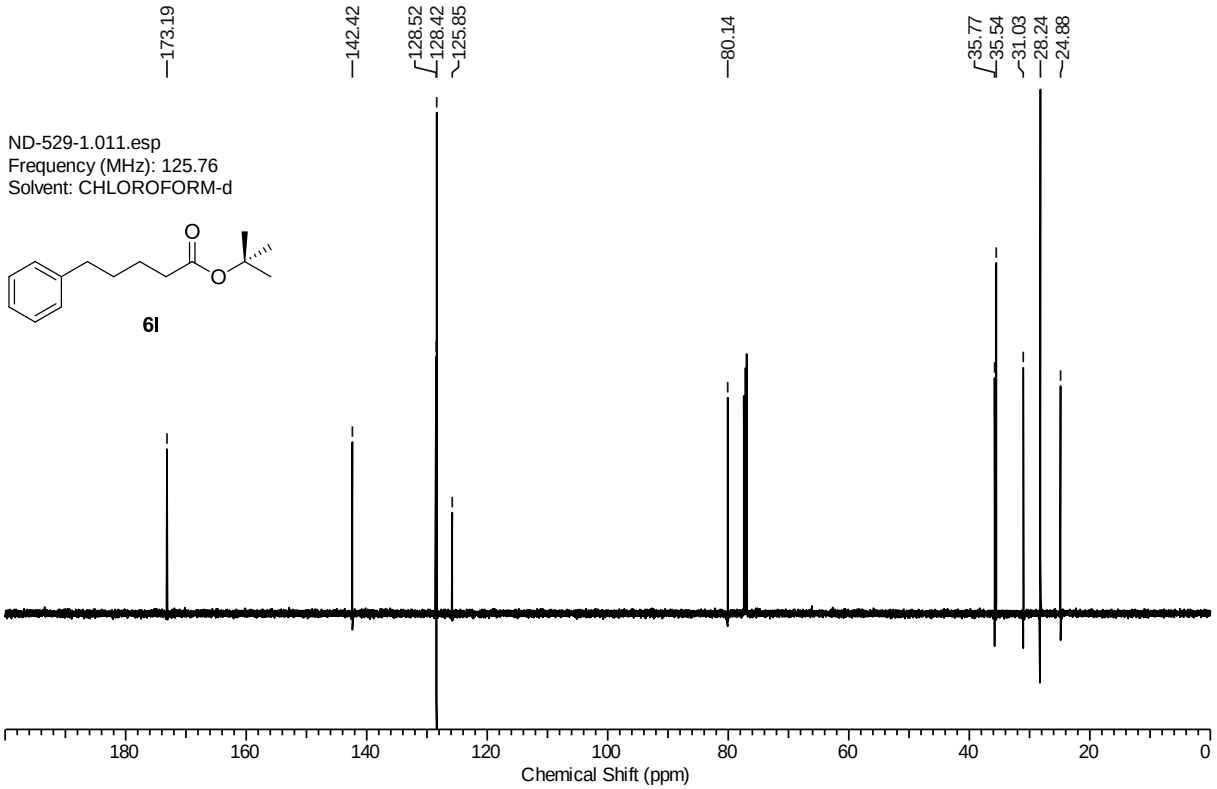

ND-588-1-SC_PROTON_20160523_01
Frequency (MHz): 299.86
Solvent: CHLOROFORM-d
O
O
Cl
6j
2.21
1.98
2.00
2.03
9.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


172.08
139.36
131.99
129.84
128.60
80.64
36.98
30.56
28.19
ND-528-4-F2.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
O
Cl
6j
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

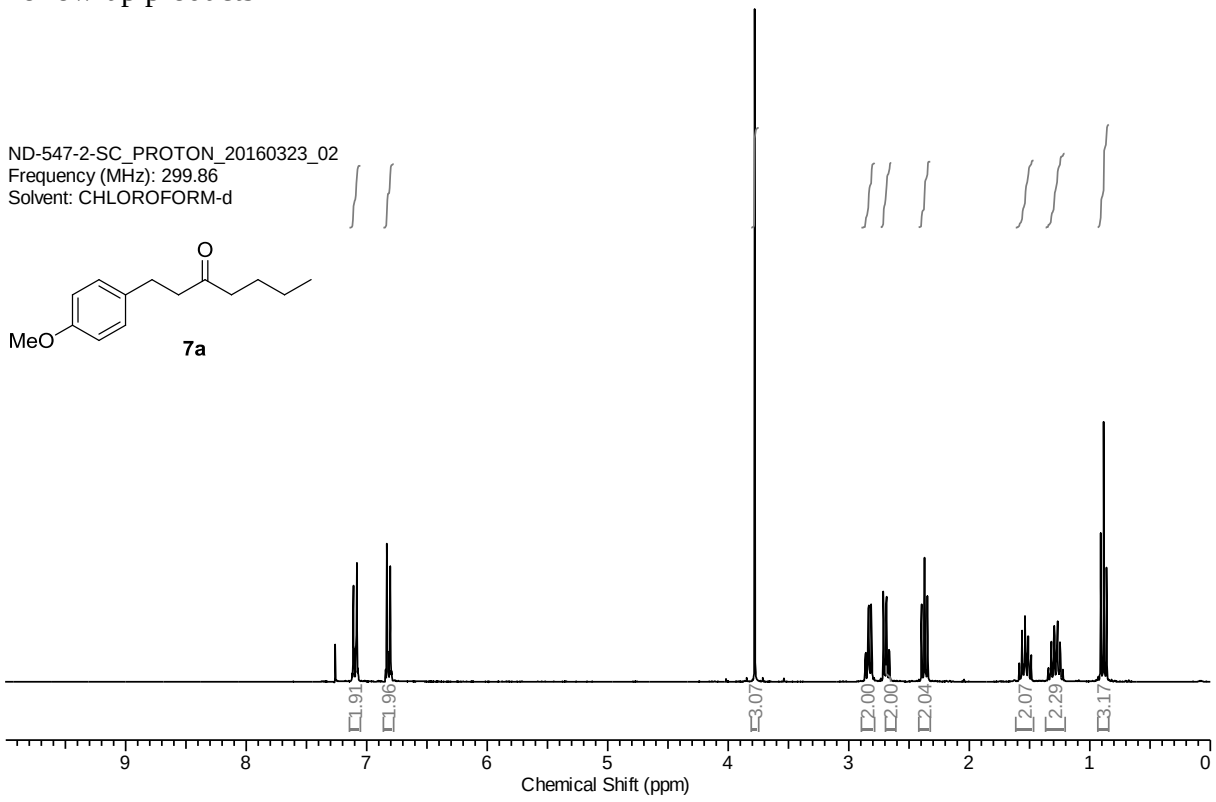

ND-527-7-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
O
F
6k
2.08
2.00
2.04
2.04
9.33
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

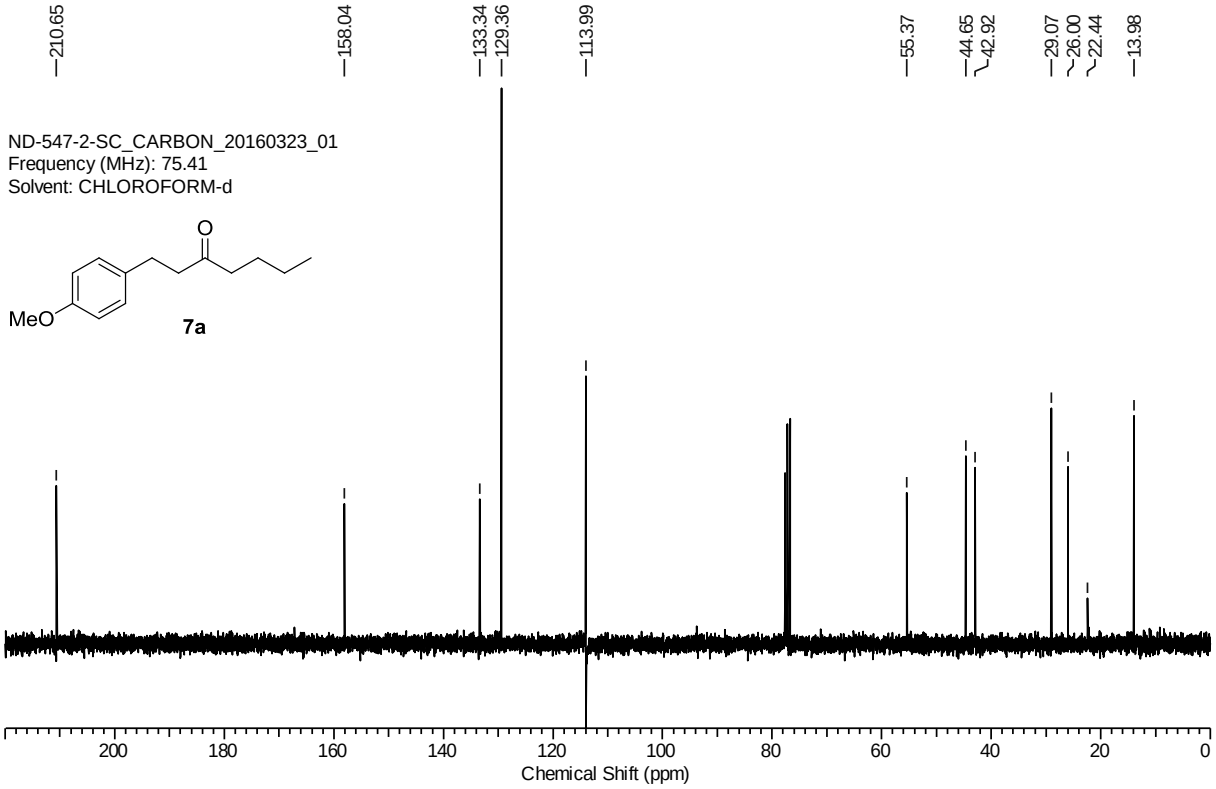

172.20
162.52
160.58
136.54
136.51
129.90
129.83
115.33
115.16
80.56
37.27
30.45
28.19
ND-527-7-SC.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
O
F
6k
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

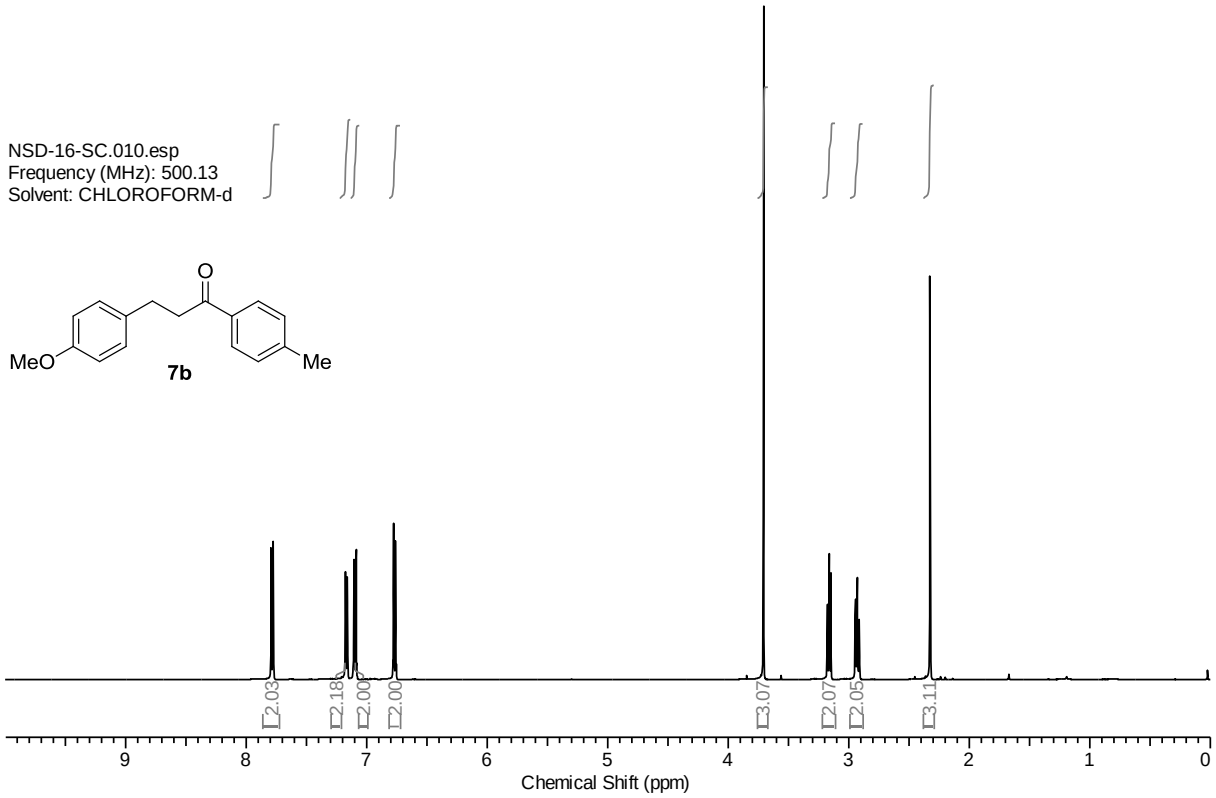

ND-529-1.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
6l
2.14
2.94
2.02
2.00
4.08
9.22
Chemical Shift (ppm)

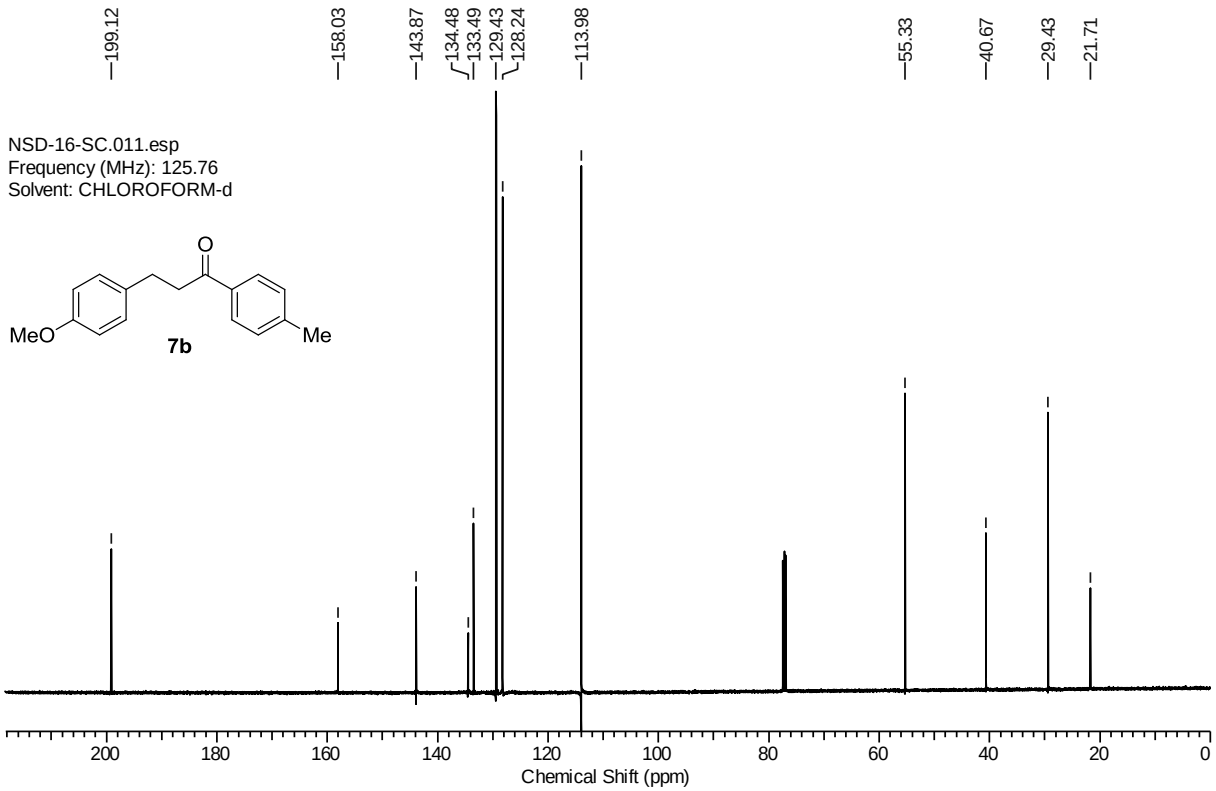

173.19
142.42
128.52
128.42
125.85
80.14
35.77
35.54
31.03
28.24
24.88
ND-529-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
6l
Chemical Shift (ppm)

Follow-up products




NSD-16-SC.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
O
MeO
Me
7b
2.03
2.18
2.00
2.00
3.07
2.07
2.05
3.11
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


199.12
158.03
143.87
134.48
133.49
129.43
128.24
113.98
55.33
40.67
29.43
21.71
NSD-16-SC.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
O
MeO
Me
7b
200
180
160
140
120
100
80
60
40
20
0
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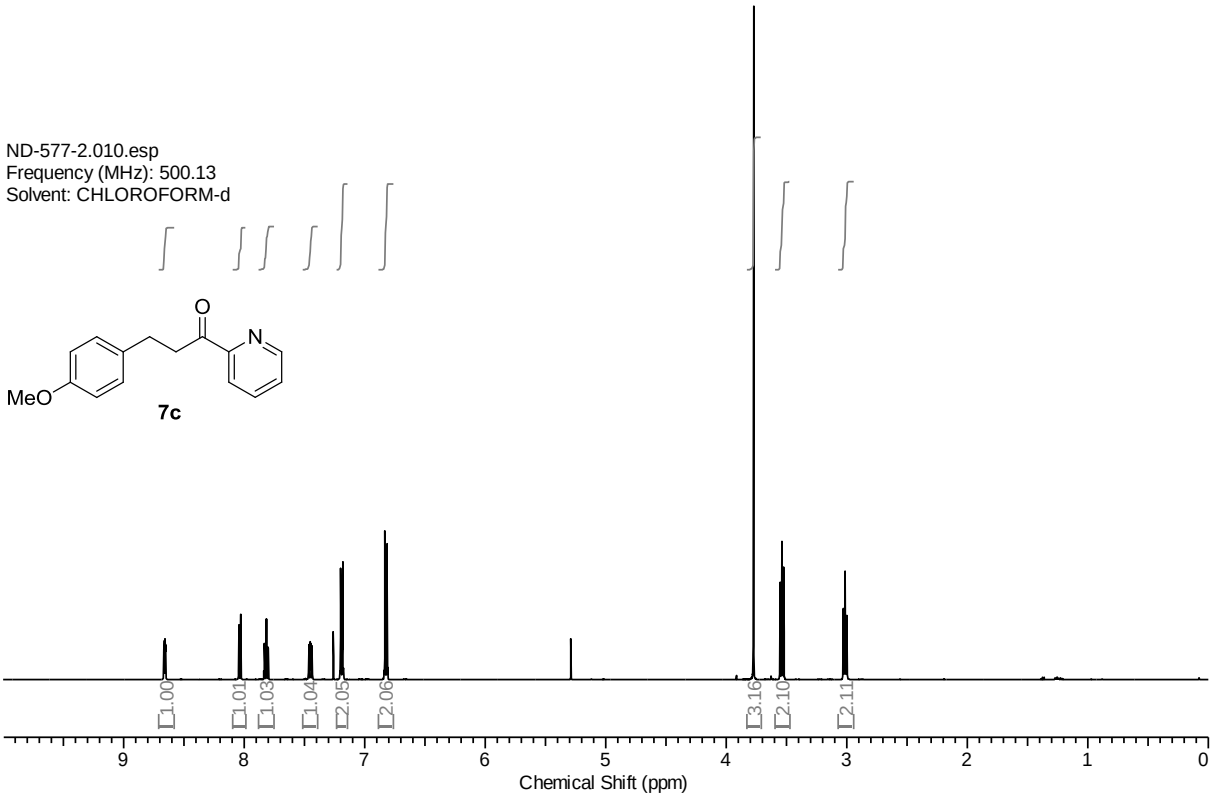
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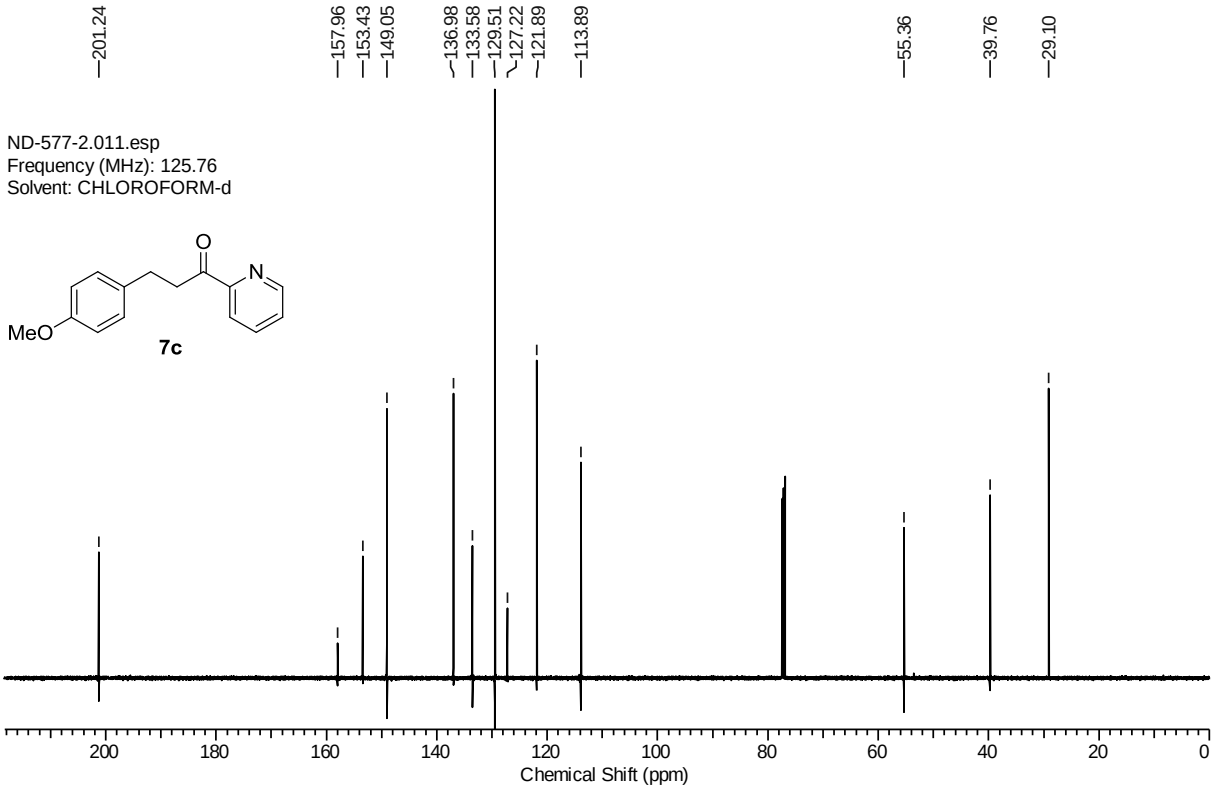
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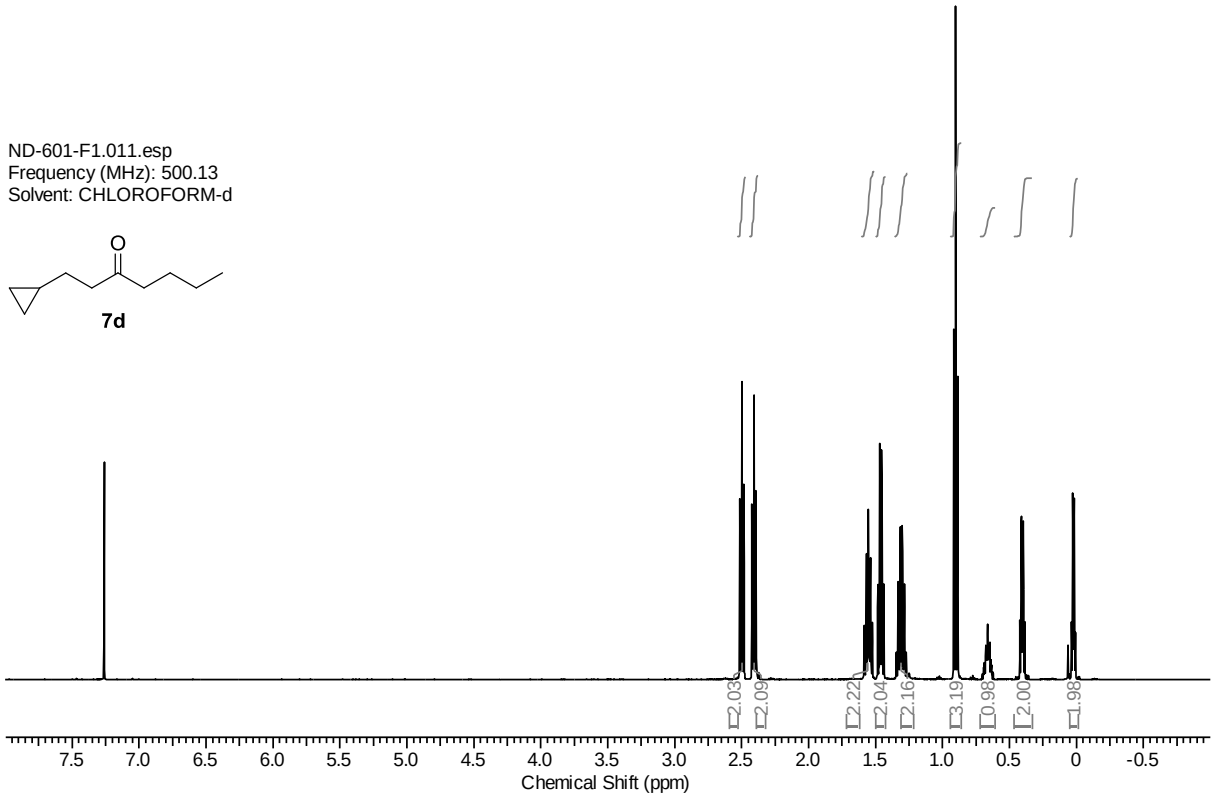
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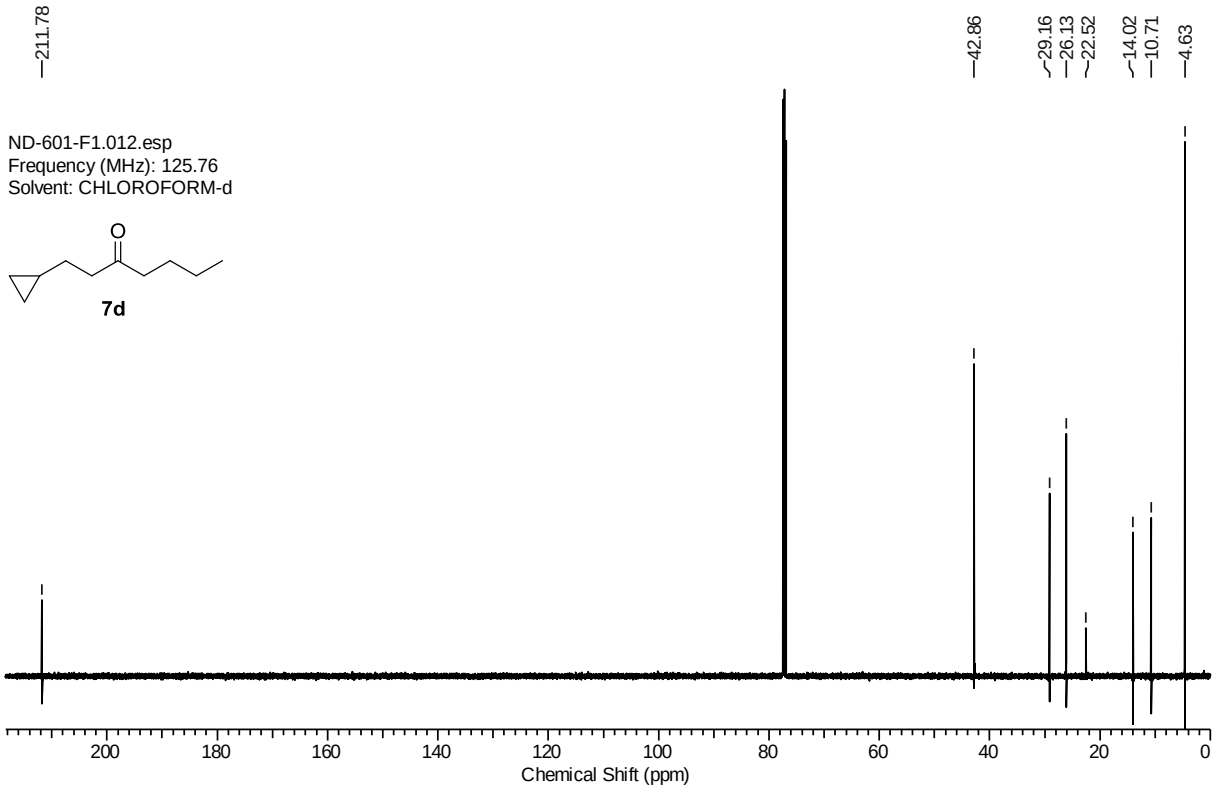
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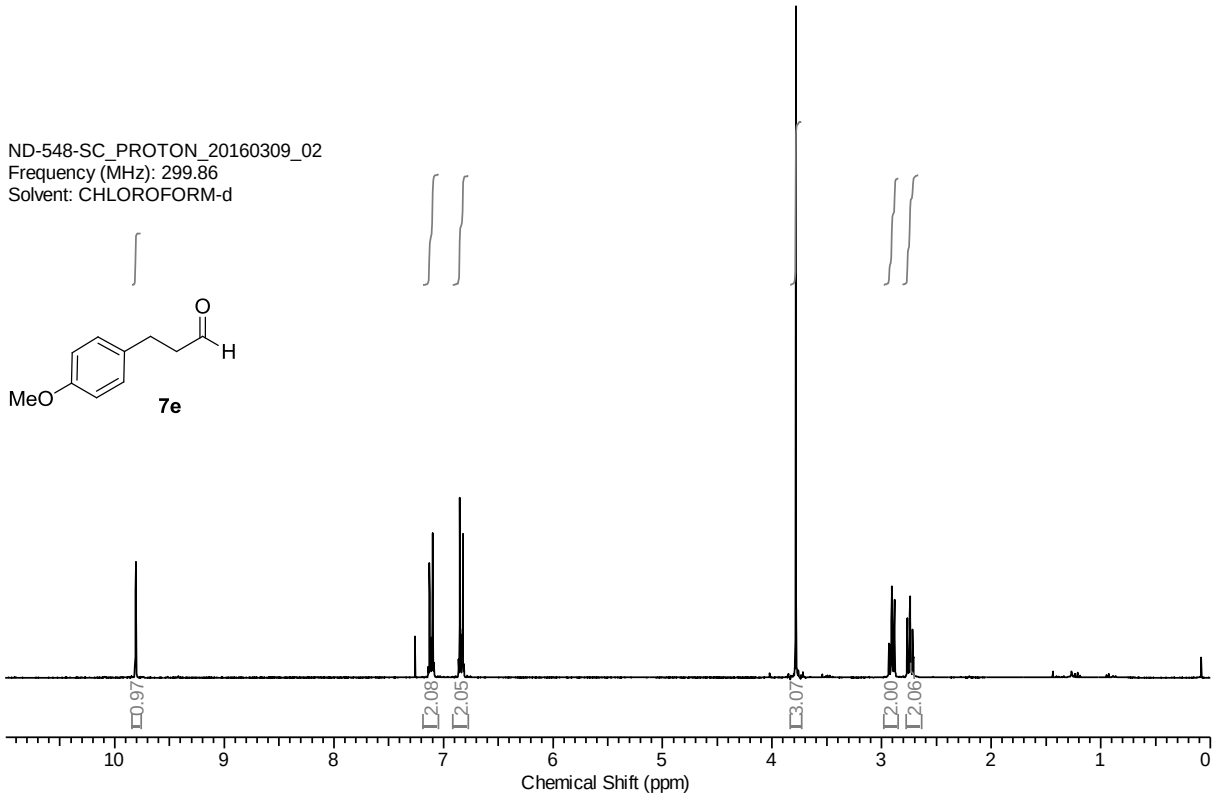
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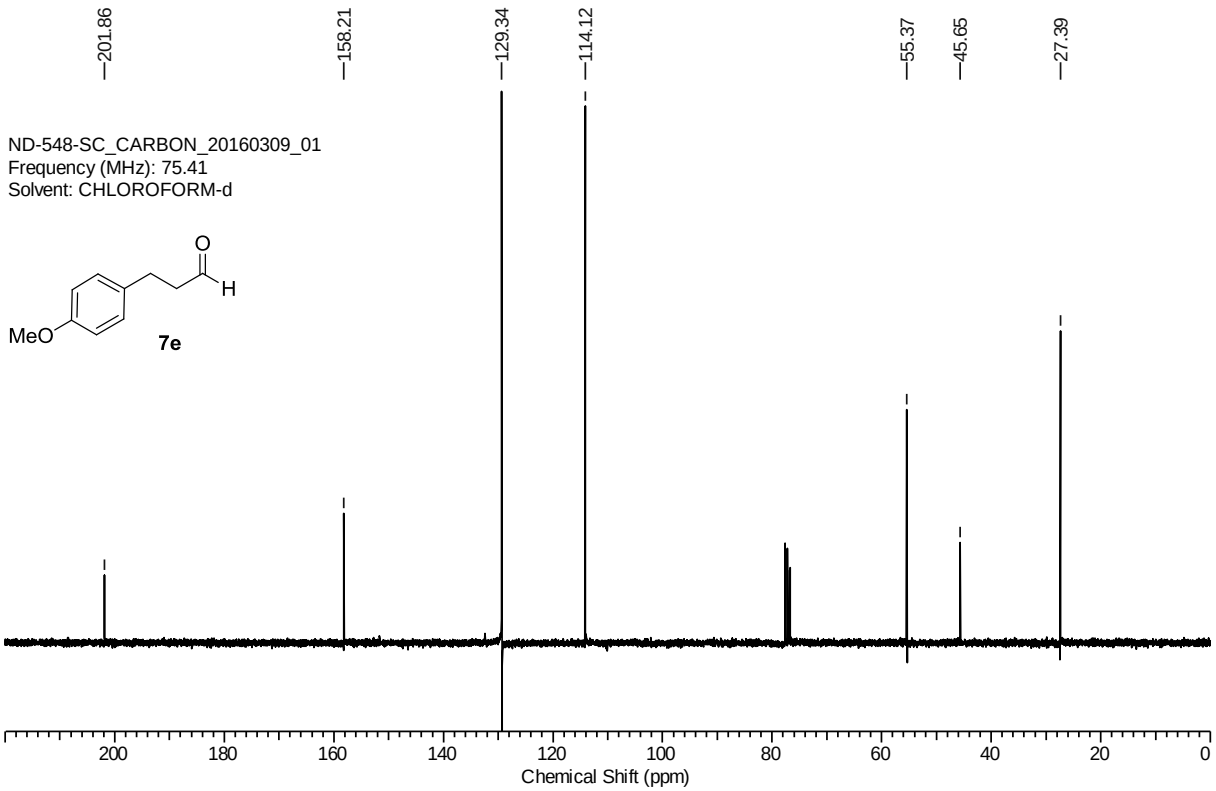
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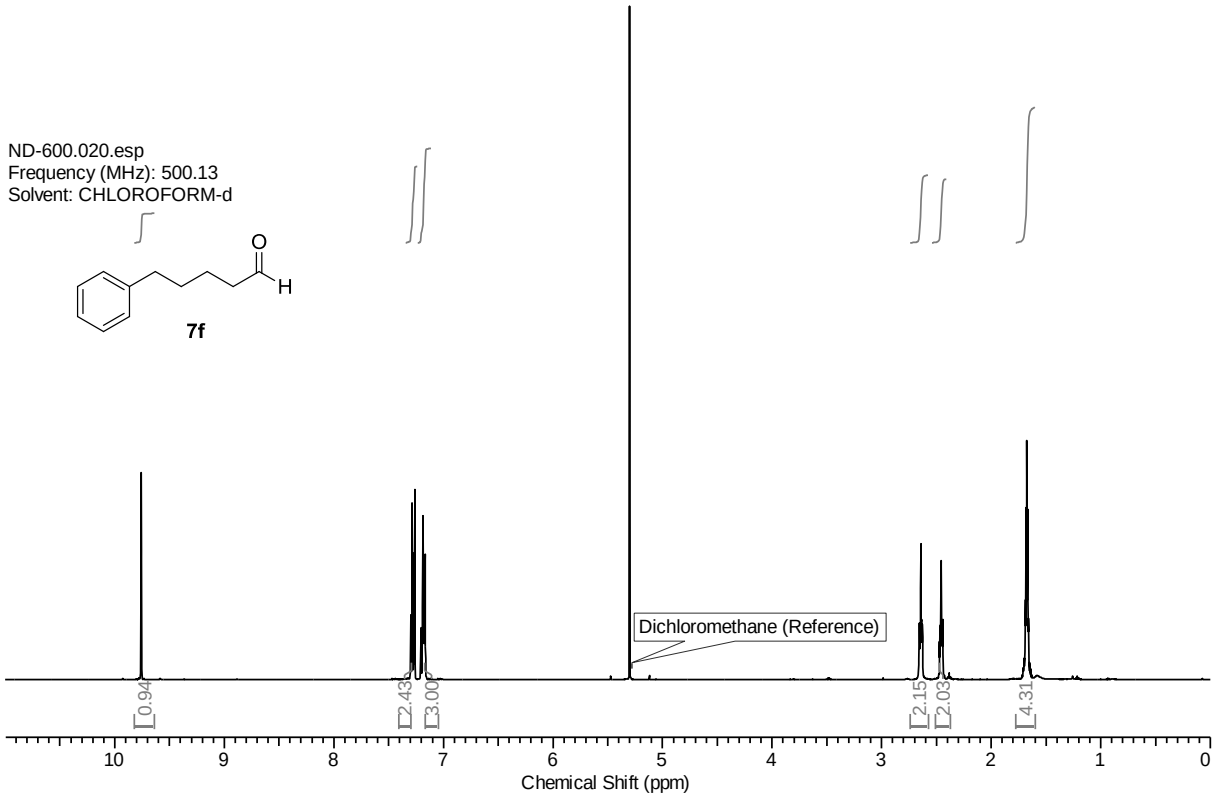
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5
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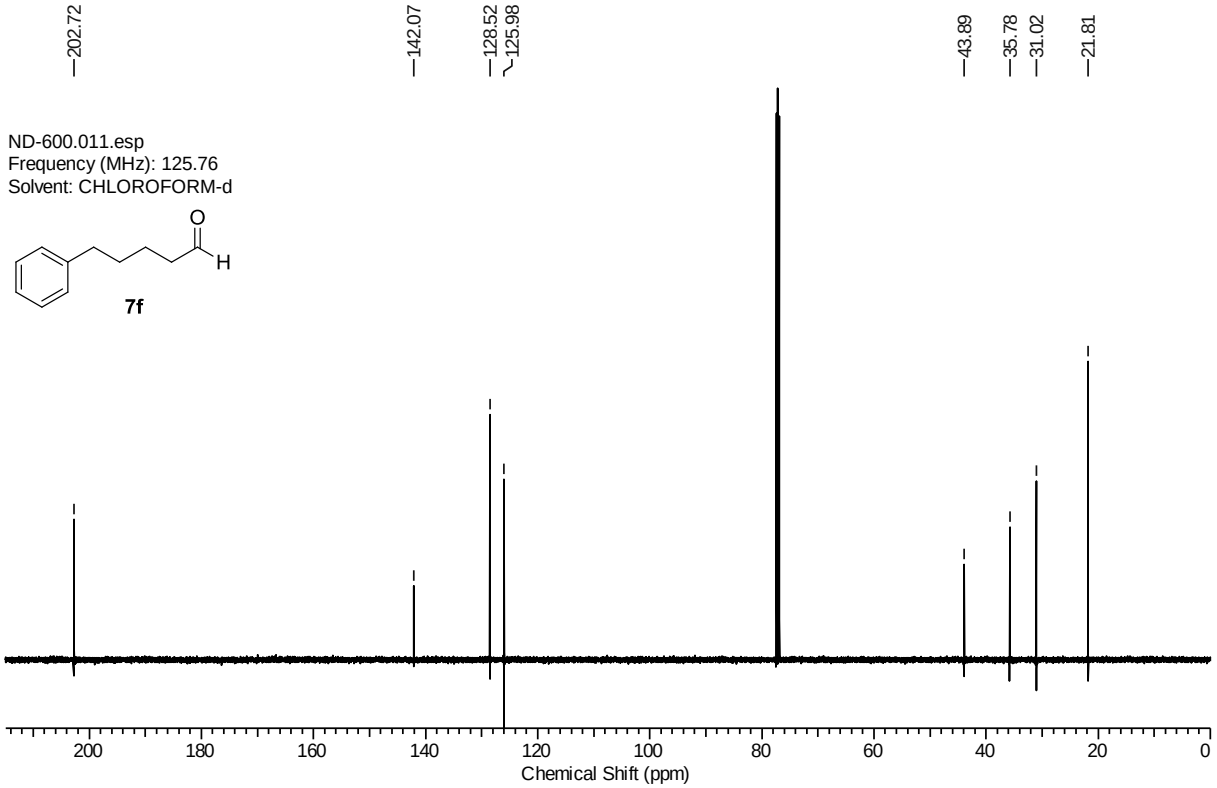
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7f
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100
80
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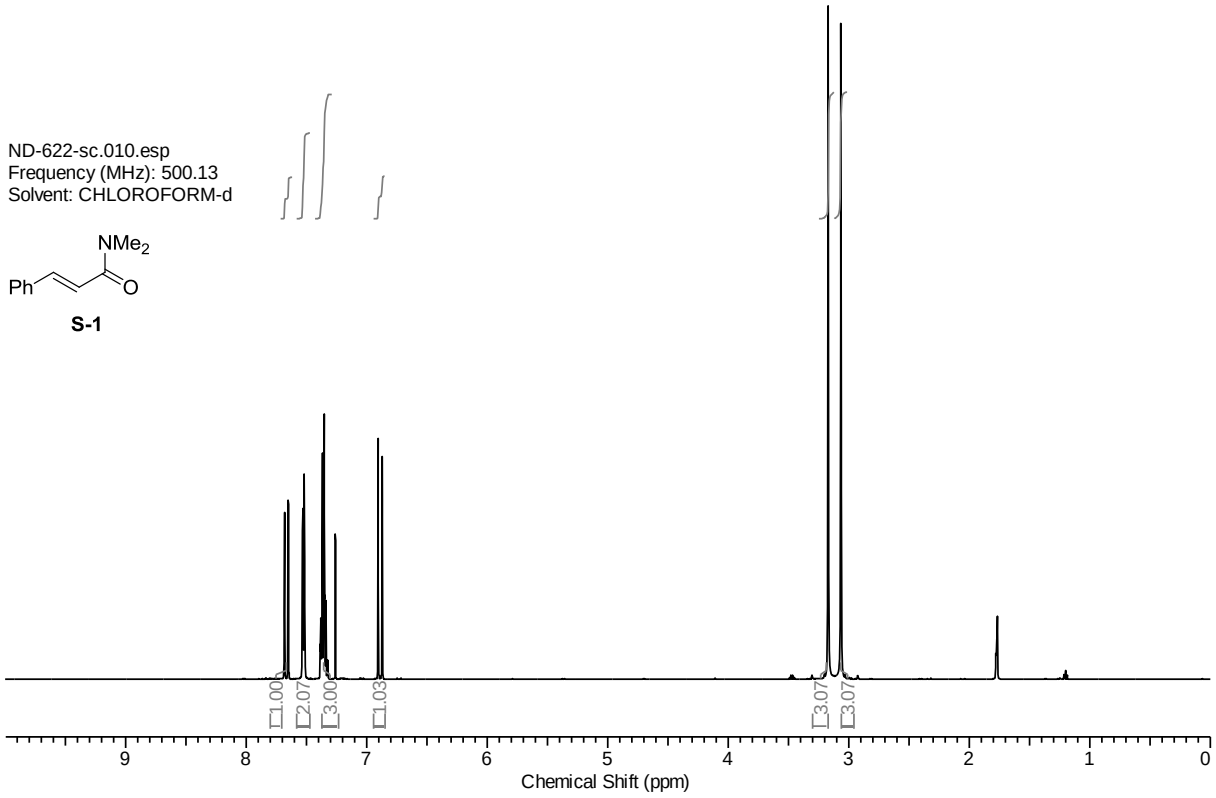
Chemical Shift (ppm)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5
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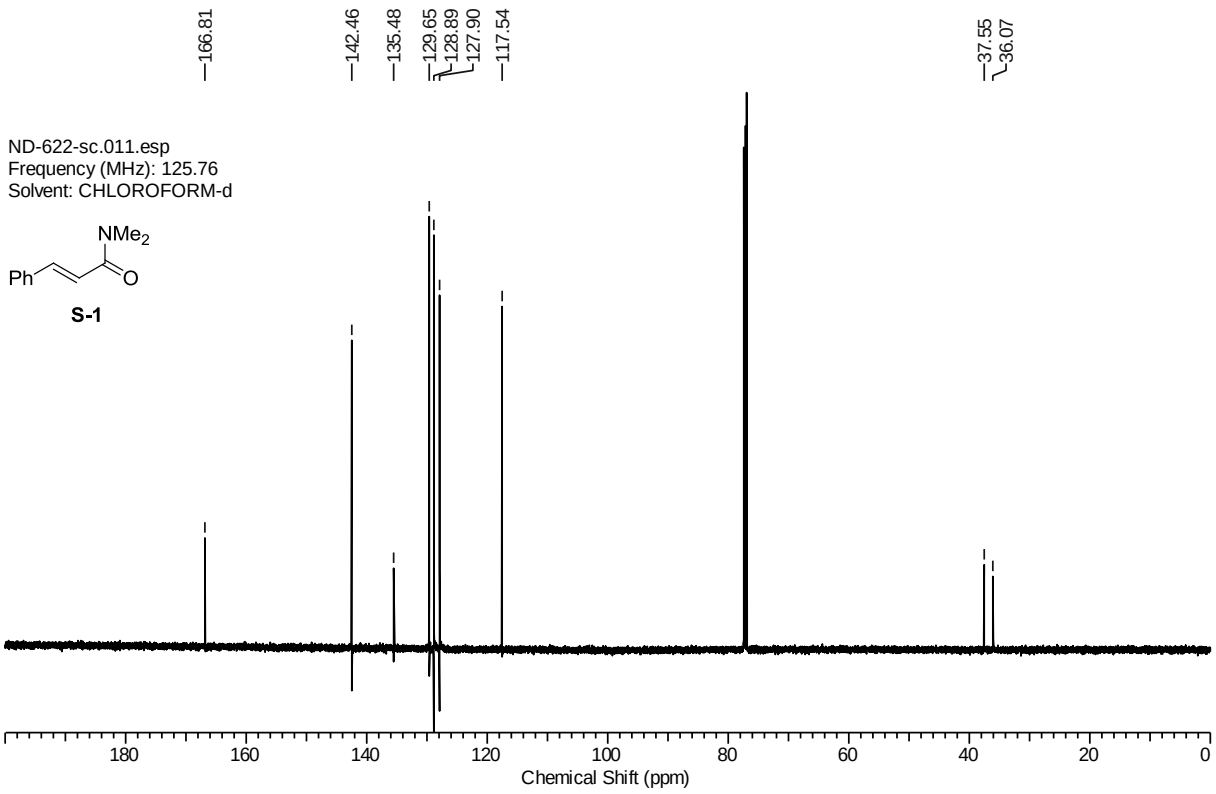
Chemical Shift (ppm)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Chemical Shift (ppm)

# 6 References

[1] (a) Michlik, S.; Kempe, R. *Nat. Chem*. **2013**, 5, 140-144. (b) Michlik, S.; Kempe, R. *Angew. Chem. Int. Ed.* **2013**, 52, 6326-6329.
[2] (a) Rösler, S.; Ertl, M.; Irrgang, T.; Kempe, R. *Angew. Chem. Int. Ed.* **2015**, *54*, 15046-15050. (b) Rösler, S.; Obenauf, J.; Kempe, R. *J. Am. Chem. Soc.* **2015**, *137*, 7998-8001.
[3] Xu, K.; Hu, Y.; Zhang, S.; Zha, Z.; Wang, Z. *Chem. Eur. J.* **2012**, *18*, 9793-9797.
[4] Guo, L.; Liu, Y.; Yao, W.; Leng, X.; Huang, Z. *Org. Lett.* **2013**, *15*, 1144-1147.
[5] Molander, G. A.; Jean-Gerard, L. *J. Org. Chem.* **2009**, *74*, 5446-5450.
[6] Kuwahara, T.; Fukuyama, T.; Ryu, I. *RSC Advances* **2013**, *3*, 13702.
[7] Wu, Z.; Hull, K. L. *Chem. Sci*. **2016**, *7*, 969-975.
[8] Kokotos, C. G.; Baskakis, C.; Kokotos, G. *J. Org. Chem.* **2008**, *73*, 8623-8626.
[9] Guo, L.; Ma, X.; Fang, H.; Jia, X.; Huang, Z. *Angew. Chem. Int. Ed.* **2015**, *54*, 4023-4027.
[10] Iuchi, Y.; Obora, Y.; Ishii, Y. *J. Am. Chem. Soc.* **2010**, *132*, 2536-2537.
[11] Salome, C.; Kohn, H. *Tetrahedron* **2009**, *65*, 456-460.
[12] Xu, Q.; Chen, J.; Tian, H.; Yuan, X.; Li, S.; Zhou, C.; Liu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 225-229.
[13] Schaubach, S.; Gebauer, K.; Ungeheuer, F.; Hoffmeister, L.; Ilg, M. K.; Wirtz, C.; Furstner, A. *Chem. Eur. J.* **2016**, *22*, 8494-8507.
[14] Kelly, C. B.; Lambert, K. M.; Mercadante, M. A.; Ovian, J. M.; Bailey, W. F.; Leadbeater, N. E. *Angew. Chem. Int. Ed.* **2015**, *54*, 4241-4245.

# 7 Manganese-Catalyzed Multicomponent Synthesis of Pyrimidines from Alcohols and Amidines

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Heterocycles

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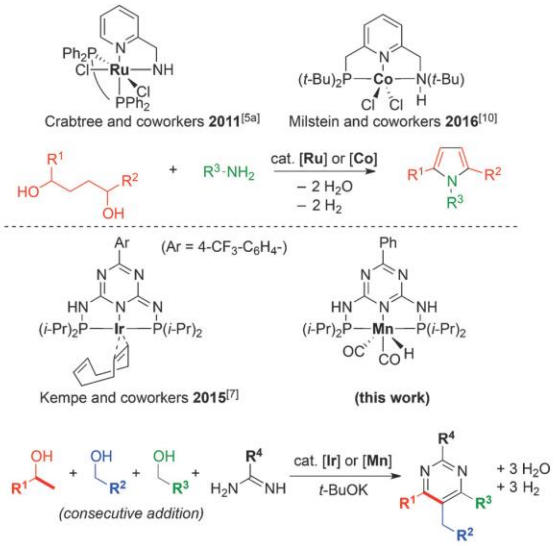
German Edition: DOI: 10.1002/ange.201611318

# Manganese-Catalyzed Multicomponent Synthesis of Pyrimidines from Alcohols and Amidines

*Nicklas Deibl and Rhett Kempe**

***Abstract:*** *The development of catalytic reactions for synthesizing different compounds from alcohols to save fossil carbon feedstock and reduce $CO_2$ emissions is of high importance. Replacing rare noble metals with abundantly available 3d metals is equally important. We report a manganese-complex-catalyzed multicomponent synthesis of pyrimidines from amidines and up to three alcohols. Our reaction proceeds through condensation and dehydrogenation steps, permitting selective C–C and C–N bond formations. β-Alkylation reactions are used to multiply alkylate secondary alcohols with two different primary alcohols to synthesize fully substituted pyrimidines in a one-pot process. Our $PN_5P$-Mn-pincer complexes efficiently catalyze this multicomponent process. A comparison of our manganese catalysts with related cobalt catalysts indicates that manganese shows a reactivity similar to that of iridium but not cobalt. This analogy could be used to develop further (de)hydrogenation reactions with manganese complexes.*

The selective linkage of alcohols to important classes of chemical compounds is an opportunity to develop more sustainable chemistry.[1] Alcohols can be obtained from indigestible and abundantly available lignocellulose biomass,[2,3] and thus the development of alcohol re-functionalization reactions can contribute to the conservation of our fossil carbon resources and the reduction of $CO_2$ emissions. A variety of reactions have been developed recently to catalytically synthesize aromatic N-heterocyclic compounds, such as pyrroles,[4,5] pyridines,[6] pyrimidines,[7] and others,[8] from alcohols.[9] These reactions have been catalyzed by rare noble metals, mostly based on Ir and Ru. A more sustainable approach would be the use of catalysts based on abundantly available 3d metals, such as Co, Fe, and Mn (nonprecious or base metals), to additionally conserve our rare noble metal resources. Milstein and co-workers recently introduced a cobalt-catalyzed synthesis of pyrroles from diols and amines[10] (Scheme 1, top). This reaction was discovered by Crabtree and co-workers using a Ru catalyst.[5a] The nonprecious metal manganese, the third most abundant metal in the earth's crust, has been overlooked in recent years with regard to catalysis involving a (de)hydrogenation step.[11] We recently introduced a variety of nonprecious metal catalysts for reactions involving (de)hydrogenation steps[11d,12–15] and




***Scheme 1.*** Synthesis of aromatic N-heterocycles from alcohols catalyzed by base-metal catalysts and corresponding methodology development using noble metals.

report here on a manganese-catalyzed version of the multicomponent reaction of alcohols and amidines to form pyrimidines[7] (Scheme 1, bottom). The reaction can be carried out to give fully substituted pyrimidines in a 3-component or a consecutive 4-component reaction. Multicomponent reactions are especially attractive in organic chemistry since they allow the synthesis of large libraries of diversely functionalized products from simple starting materials. Our synthetic method is especially useful for forming selectively alkylated and/or arylated pyrimidines. Mn catalysts stabilized by $PN_5P$ ligands[16] catalyze our reaction efficiently. Related Co catalysts are nearly inactive.

The reaction between 1-phenylethanol (**1a**), benzyl alcohol (**2a**), and benzamidine (**3a**) to pyrimidine **4a** was investigated to develop a base-metal-catalyzed version of the 3-component pyrimidine synthesis (Table 1, top). After optimization of common reaction parameters (solvent, base, base amount, substrate ratio; see the Supporting Information for details), a library of Mn complexes stabilized by $PN_5P$ or $PN_3P$ ligands was tested to find the most active precatalyst (Table 1, complexes **A**–**G**). The complexes stabilized with

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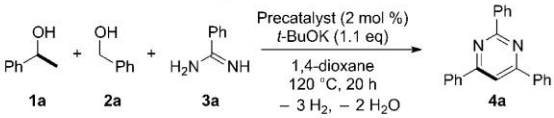
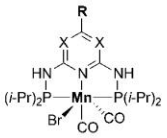
**Table 1:** Precatalyst screening of the model reaction.[a]




1a 2a 3a 4a

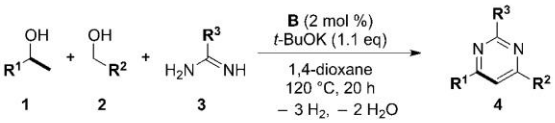
| | Precatalyst | R | X | Yield[b] of 4a |
|---|---|---|---|---|
|  | **A** | Me | N | 83% |
| | **B** | Ph | N | 96% |
| | **C** | 4-$CF_3(C_6H_4)$- | N | 85% |
| | **D** | H | N | 92% |
| | **E** | $C_3H_5NH$- | N | 89% |
| | **F** | H | CH | 48% |
| | **G** | Me | CH | 54% |

[a] Reaction conditions: 1-phenylethanol (1.0 mmol), benzyl alcohol (1.0 mmol), benzamidine (0.50 mmol), *t*-BuOK (0.55 mmol), precatalyst (0.01 mmol, 2 mol%) 1,4-dioxane (1 mL), 120°C (oil bath temperature), 20 h. [b] Yield was determined by GC with dodecane as the internal standard.

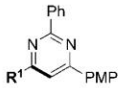
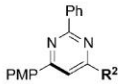
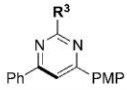
triazine-based ligands bearing a phenyl (**B**) or H (**D**) substituent in the 4-position gave the highest yield of **4a**. We also tested three cobalt complexes that were recently reported by our group[12a,13a,14] as active catalysts for borrowing hydrogen/hydrogen autotransfer (BH/HA) applications, and only unreacted starting materials were obtained (see the Supporting Information). In summary, the best yield was obtained when precatalyst **B** (2 mol%) was applied, the reaction was run in 1,4-dioxane with 1.1 equiv *t*-BuOK as the base, and an excess of alcohols (1.5–2 equiv) with respect to the amidine was used. The complexes used can be obtained on a gram scale in high yields in two steps from commercially available diamines and the corresponding Mn carbonyl precursor. With these conditions in hand, we explored the substrate scope of this 3-component reaction (Table 2). To start with, different secondary alcohols were employed, and aromatic (**4b–d**), heteroaromatic (**4e**,**f**), and aliphatic (**4g**,**h**) moieties were tolerated to give the corresponding pyrimidines in acceptable to good yields of isolated product (66–79%). When ethanol ($R^1$ = H) was used to contribute the C2 fragment, the 2,4-substituted pyrimidine **4i** was isolated in 50% yield. Through variation of the primary alcohol, aliphatic substituents were introduced to give the corresponding products **4j**,**k**. A secondary alcohol in combination with methanol as a C1 building block[17] (instead of ethanol and another primary alcohol) gave the 2,4-substituted pyrimidine **4i**. A more electron-rich *para*-methoxyphenyl group (**4l**) as well as a methyl (**4m**) and an amino group (**4n**) could be installed in the 2-position when the corresponding amidine (or guanidine) was used.

We next focused on the use of secondary alcohols with a substituent in the β-position, which can give rise to fully substituted pyrimidines. The alkylation of a secondary carbon atom by BH/HA methods is known to be more difficult,[17,18] but the corresponding pyrimidines **5** (Table 3) could be isolated in moderate to good yields with a slight increase in the base amount (1.5 equiv) and an adapted substrate ratio (1.1 equiv primary alcohol). The use of cyclic alcohols, for example, gave the corresponding products **5a–c**, which feature annulated aliphatic rings (ring size: 7, 8, or 12 carbon atoms). Two primary alcohols, of which one contributes the C2 building block, can give rise to 2,4,5-substituted pyrimidines (e.g., **5d** in good 75% yield). Fully and differently substituted pyrimidines can also be obtained as demonstrated for **5f**.

**Table 2:** Scope of the 3-component pyrimidine synthesis.[a]

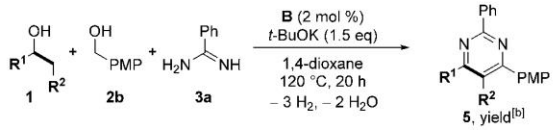



1 2 3 4

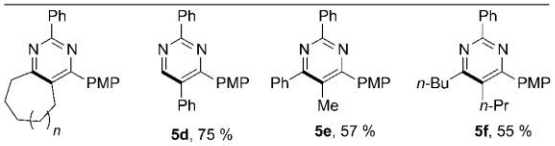
| Entry | Product | R | 4 | Yield[b] |
|---|---|---|---|---|
| 1 | | $R^1$ = Ph | **4b** | 79% |
| 2 | | $R^1$ = PMP | **4c** | 73% |
| 3 |  | $R^1$ = 3-Cl-$(C_6H_4)$- | **4d** | 71% |
| 4 | | $R^1$ = 2-thienyl | **4e** | 73% |
| 5 | | $R^1$ = 3-pyridyl | **4f** | 73% |
| 6 | | $R^1$ = *iso*-propyl | **4g** | 66% |
| 7 | | $R^1$ = cyclopropyl | **4h** | 70% |
| 8 | | $R^1$ = H | **4i** | 50% |
| 9 | | $R^2$ = cyclohexyl | **4j** | 53% |
| 10 |  | $R^2$ = *n*-pentyl | **4k** | 62% |
| 11 | | $R^2$ = H | **4i** | 44% |
| 12 | | $R^3$ = PMP | **4l**[c] | 68% |
| 13 |  | $R^3$ = Me | **4m**[c] | 57% |
| 14 | | $R^3$ = $NH_2$ | **4n**[c] | 62% |

[a] Reaction conditions: Secondary alcohol (1.5 mmol), primary alcohol (1.5 mmol), amidine/guanidine (1 mmol), *t*-BuOK (1.1 mmol), **B** (0.02 mmol, 2 mol%) 1,4-dioxane (2 mL), 120°C (oil bath temperature), 20 h. [b] Yields of isolated products. [c] Corresponding amidine or guanidine hydrochloride with 1 additional equiv of *t*-BuOK was used. PMP = *para*-methoxyphenyl.

**Table 3:** Synthesis of pyrimidines with alkylation of methylene carbon atoms.[a]




1 2b 3a




**5a**: *n* = 1, 73 %
**5b**: *n* = 2, 78 %
**5c**: *n* = 6, 53 %

**5d**, 75 % **5e**, 57 % **5f**, 55 %

[a] Reaction conditions: Secondary alcohol (1.5 mmol), primary alcohol (1.1 mmol), amidine (1.0 mmol), *t*-BuOK (1.5 mmol), **B** (0.02 mmol, 2 mol%) 1,4-dioxane (2 mL), 120°C oil bath, 20 h. [b] Yields of isolated products. PMP = *para*-methoxyphenyl.

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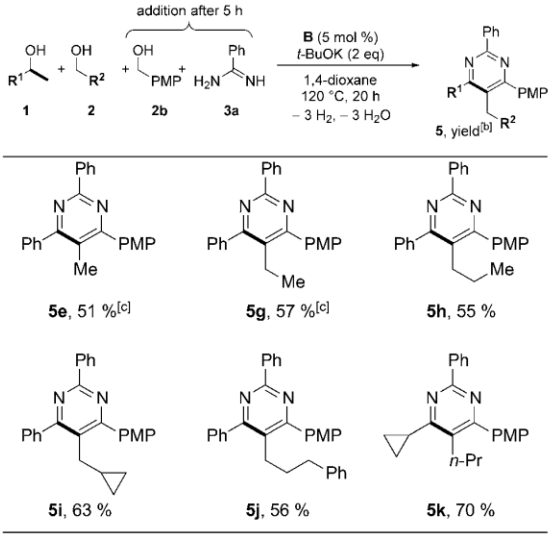
Finally, we became interested in whether the manganese catalyst is also able to catalyze a preceding β-alkylation reaction between a secondary and a primary alcohol. A manganese-catalyzed version of this reaction has not been reported, but would lead to the corresponding β-alkylated alcohol (or ketone). Subsequent addition of another primary alcohol and an amidine would give the pyrimidine in a one-pot process. Indeed, when we investigated the reaction between 1-phenylethanol (1.0 equiv) and 1-propanol (1.1 equiv) under the typical reaction conditions, the conversion of 1-phenylethanol was quantitative after 5 h (see the Supporting Information for details). Impressed by the good activity of the catalyst, we decided to use it to develop a consecutive 4-component reaction. The overall reaction to give tetrasubstituted pyrimidines **5** (Table 4, top) gave the best yields when an excess of alcohols, 2.0 equiv of *t*-BuOK (employed at the beginning), and 5 mol% precatalyst **B** (2.5 mol% with respect to the first β-alkylation reaction, since 2 equiv of alcohols are employed) were used. The primary alcohol of the β-alkylation reaction (Table 4) was varied, which allowed the installation of a quasi-benzylic methyl group (**5e**, from methanol) and longer aliphatic moieties in the pyrimidine 5-position (**5g**–**j**). For example, 1-cyclopropyl ethanol was used to install a cyclopropane moiety to the pyrimidine ring and the corresponding product **5k** was obtained in good 70% yield.

***Table 4:*** Synthesis of tetrasubstituted pyrimidines by a consecutive 4-component reaction.[a]




[a] Reaction conditions: Secondary alcohol (2.0 mmol), primary alcohol (2.2 mmol), *t*-BuOK (2.0 mmol), precatalyst **B** (0.05 mmol, 5 mol%) and 1,4-dioxane (1 mL) were heated for 5 h at 120°C (oil bath temp.). Afterwards, amidine (1.0 mmol) and primary alcohol (1.1 mmol) were added as a solution in 1,4-dioxane (2 mL) and the reaction was heated under reflux for 20 h. [b] Yields of isolated products. [c] The β-alkylation reaction was run in a closed system. PMP = *para*-methoxyphenyl.

In summary, we report the first example of a Mn-catalyzed synthesis of aromatic N-heterocycles from alcohols. This is a multicomponent reaction in which selective dehydrogenation and condensation steps lead to selective C–C and C–N bond formations. Through a 3-component reaction, fully substituted, 2,4- substituted, and 2,4,5-substituted pyrimidines can be obtained. In combination with the β-alkylation of secondary alcohols by primary alcohols, a reaction that has not yet been described for Mn catalysts, a consecutive 4-component process was developed to give fully substituted pyrimidines in a one-pot procedure. Both multicomponent methods are strong regarding the synthesis of selectively alkylated and arylated products. Precatalysts stabilized by $PN_5P$ ligands (triazine backbone) are about twice as efficient as those stabilized by $PN_3P$ ligands (pyridine backbone). Notably, both Ir[7] and Mn complexes catalyze the two distinct reactions (BH/HA and ADC) efficiently under similar reaction conditions. Co complexes stabilized by such ligands are nearly inactive in the ADC step. The (double) diagonal relationship Mn-Ru-Ir could be an explanation for the analogous catalytic reactivity between Mn and Ir observed here. Considering the many applications of Ir catalysts in (de)hydrogenation reactions, we feel that manganese has a great potential to partially replace Ir in such reactions.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** borrowing-hydrogen reactions · dehydrogenative coupling · maganese · pincer complexes · pyrimidines

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*Angew. Chem.* **2017**, *129*, 1685–1688

[1] S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140–144.
[2] C. O. Tuck, E. Perez, I. T. Horvath, R. A. Sheldon, M. Poliakoff, *Science* **2012**, *337*, 695–699.
[3] T. P. Vispute, H. Zhang, A. Sanna, R. Xiao, G. W. Huber, *Science* **2010**, *330*, 1222–1227.
[4] a) D. Srimani, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2013**, *52*, 4012–4015; *Angew. Chem.* **2013**, *125*, 4104–4107; b) M. Zhang, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 597–601; *Angew. Chem.* **2013**, *125*, 625–629; c) M. Zhang, X. Fang, H. Neumann, M. Beller, *J. Am. Chem. Soc.* **2013**, *135*, 11384–11388; d) K. Iida, T. Miura, J. Ando, S. Saito, *Org. Lett.* **2013**, *15*, 1436–1439; e) D. Forberg, J. Obenauf, M. Friedrich, S. M. Hühne, W. Mader, G. Motz, R. Kempe, *Catal. Sci. Technol.* **2014**, *4*, 4188–4192.
[5] Crabtree, as well as Ishii and co-workers have shown that a combination of dehydrogenation and condensation could lead

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to aromatic N-heterocyles such as pyrroles. Similarly, Watanabe and co-workers have described an intramolecular indole synthesis: a) K. Taguchi, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2005**, *46*, 4539 – 4542; b) N. D. Schley, G. E. Dobereiner, R. H. Crabtree, *Organometallics* **2011**, *30*, 4174 – 4179; c) Y. Tsuji, K.-T. Huh, Y. Yokoyama, Y. Watanabe, *J. Chem. Soc. Chem. Commun.* **1986**, 1575.

[6] a) S. Michlik, R. Kempe, *Angew. Chem. Int. Ed.* **2013**, *52*, 6326 – 6329; *Angew. Chem.* **2013**, *125*, 6450 – 6454; b) D. Srimani, Y. Ben-David, D. Milstein, *Chem. Commun.* **2013**, *49*, 6632 – 6634; c) S. Ruch, T. Irrgang, R. Kempe, *Chem. Eur. J.* **2014**, *20*, 13279 – 13285; d) T. Hille, T. Irrgang, R. Kempe, *Angew. Chem. Int. Ed.* **2016**, DOI: 10.1002/anie.201610071; *Angew. Chem.* **2016**, DOI: 10.1002/ange.201610071.

[7] N. Deibl, K. Ament, R. Kempe, *J. Am. Chem. Soc.* **2015**, *137*, 12804 – 12807.

[8] a) M. Chen, M. Zhang, B. Xiong, Z. Tan, W. Lv, H. Jiang, *Org. Lett.* **2014**, *16*, 6028 – 6031; b) M. Peña-López, H. Neumann, M. Beller, *Chem. Eur. J.* **2014**, *20*, 1818 – 1824; c) D. Forberg, T. Schwob, M. Zaheer, M. Friedrich, N. Miyajima, R. Kempe, *Nat. Commun.* **2016**, *7*, 13201.

[9] C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712.

[10] a) P. Daw, S. Chakraborty, J. A. Garg, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2016**, *55*, 14373 – 14377; *Angew. Chem.* **2016**, *128*, 14585 – 14589; b) For a related Fe-mediated reaction using the borrowing hydrogen or hydrogen autotransfer concept, see: T. Yan, K. Barta, *ChemSusChem* **2016**, *9*, 2321 – 2325.

[11] a) S. Elangovan, J. Neumann, J. B. Sortais, K. Junge, C. Darcel, M. Beller, *Nat. commun.* **2016**, *7*, 12641; b) S. Elangovan, M. Garbe, H. Jiao, A. Spannenberg, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 15364 – 15368; *Angew. Chem.* **2016**, *128*, 15590 – 15594; c) S. Elangovan, C. Topf, S. Fischer, H. Jiao, A. Spannenberg, W. Baumann, R. Ludwig, K. Junge, M. Beller, *J. Am. Chem. Soc.* **2016**, *138*, 8809 – 8814; d) F. Kallmeier, T. Irrgang, T. Dietel, R. Kempe, *Angew. Chem. Int. Ed.* **2016**, *55*, 11806 – 11809; *Angew. Chem.* **2016**, *128*, 11984 – 11988; e) A. Mukherjee, A. Nerush, G. Leitus, L. J. Shimon, Y. Ben-David, N. A. Espinosa Jalapa, D. Milstein, *J. Am. Chem. Soc.* **2016**, *138*, 4298 – 4301; f) M. Mastalir, M. Glatz, N. Gorgas, B. Stoger, E. Pittenauer, G. Allmaier, L. F. Veiros, K. Kirchner, *Chem. Eur. J.* **2016**, *22*, 12316 – 12320; g) N. A. Espinosa-Jalapa, A. Nerush, L. Shimon, G. Leitus, L. Avram, Y. Ben-David, D. Milstein, *Chem. Eur. J.* **2016**, DOI: 10.1002/chem.201604991; h) M. Perez, S. Elangovan, A. Spannenberg, K. Junge, M. Beller, *ChemSusChem* **2016**, DOI: 10.1002/cssc.201601057.

[12] Our contribution: a) S. Rösler, J. Obenauf, R. Kempe, *J. Am. Chem. Soc.* **2015**, *137*, 7998 – 8001; Work of others: b) T. J. Korstanje, J. I. van der Vlugt, C. J. Elsevier, B. de Bruin, *Science* **2015**, *350*, 298 – 302; c) M. S. Jeletic, M. T. Mock, A. M. Appel, J. C. Linehan, *J. Am. Chem. Soc.* **2013**, *135*, 11533 – 11536; d) A. Mukherjee, D. Srimani, S. Chakraborty, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2015**, *137*, 8888 – 8891; e) D. Gärtner, A. Welther, B. R. Rad, R. Wolf, A. Jacobi von Wangelin, *Angew. Chem. Int. Ed.* **2014**, *53*, 3722 – 3726; *Angew. Chem.* **2014**, *126*, 3796 – 3800; f) G. Zhang, K. V. Vasudevan, B. L. Scott, S. K. Hanson, *J. Am. Chem. Soc.* **2013**, *135*, 8668 – 8681; g) G. Zhang, S. K. Hanson, *Chem. Commun.* **2013**, *49*, 10151 – 10153; h) G. Zhang, B. L. Scott, S. K. Hanson, *Angew. Chem. Int. Ed.* **2012**, *51*, 12102 – 12106; *Angew. Chem.* **2012**, *124*, 12268 – 12272; i) D. Srimani, A. Mukherjee, A. F. Goldberg, G. Leitus, Y. Diskin-Posner, L. J. Shimon, Y. Ben-David, D. Milstein, *Angew. Chem. Int. Ed.* **2015**, *54*, 12357 – 12360; *Angew. Chem.* **2015**, *127*, 12534 – 12537.

[13] Our contribution: a) S. Rösler, M. Ertl, T. Irrgang, R. Kempe, *Angew. Chem. Int. Ed.* **2015**, *54*, 15046 – 15050; *Angew. Chem.* **2015**, *127*, 15260 – 15264; Work of others: b) M. Mastalir, G. Tomsu, E. Pittenauer, G. Allmaier, K. Kirchner, *Org. Lett.* **2016**, *18*, 3462 – 3465; c) Z. Yin, H. Zeng, J. Wu, S. Zheng, G. Zhang, *ACS Catal.* **2016**, *6*, 6546 – 6550; d) G. Zhang, Z. Yin, S. Zheng, *Org. Lett.* **2016**, *18*, 300 – 303.

[14] N. Deibl, R. Kempe, *J. Am. Chem. Soc.* **2016**, *138*, 10786 – 10789.

[15] T. Schwob, R. Kempe, *Angew. Chem. Int. Ed.* **2016**, *55*, 15175 – 15179; *Angew. Chem.* **2016**, *128*, 15400 – 15404.

[16] a) M. Mastalir, B. Stoger, E. Pittenauer, G. Allmaier, K. Kirchner, *Org. Lett.* **2016**, *18*, 3186 – 3189; b) F. Bertini, N. Gorgas, B. Stöger, M. Peruzzini, L. F. Veiros, K. Kirchner, L. Gonsalvi, *ACS Catal.* **2016**, *6*, 2889 – 2893; c) N. Gorgas, B. Stöger, L. F. Veiros, K. Kirchner, *ACS Catal.* **2016**, *6*, 2664 – 2672; d) S. Murugesan, B. Stoger, E. Pittenauer, G. Allmaier, L. F. Veiros, K. Kirchner, *Angew. Chem. Int. Ed.* **2016**, *55*, 3045 – 3048; *Angew. Chem.* **2016**, *128*, 3097 – 3100; e) N. Gorgas, B. Stöger, L. F. Veiros, E. Pittenauer, G. Allmaier, K. Kirchner, *Organometallics* **2014**, *33*, 6905 – 6914; f) B. Bichler, C. Holzhacker, B. Stoger, M. Puchberger, L. F. Veiros, K. Kirchner, *Organometallics* **2013**, *32*, 4114 – 4121.

[17] An application of methanol in ADC with subsequent 1,4-addition: D. Shen, D. L. Poole, C. C. Shotton, A. F. Kornahrens, M. P. Healy, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2015**, *54*, 1642 – 1645; *Angew. Chem.* **2015**, *127*, 1662 – 1665.

[18] Selected examples of alkylation of methylene carbon atoms through BH/HA methods: a) J. R. Frost, C. B. Cheong, W. M. Akhtar, D. F. Caputo, N. G. Stevenson, T. J. Donohoe, *J. Am. Chem. Soc.* **2015**, *137*, 15664 – 15667; b) L. K. Chan, D. L. Poole, D. Shen, M. P. Healy, T. J. Donohoe, *Angew. Chem. Int. Ed.* **2014**, *53*, 761 – 765; *Angew. Chem.* **2014**, *126*, 780 – 784.

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# Supporting Information

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# 1 General Methods

Air- and moisture sensitive reactions were carried out under nitrogen or argon atmosphere using standard Schlenk techniques or a glove box. Dry solvents were obtained from a solvent purification system ($Al_2O_3$ cartridges) or purchased from Acros. Chemicals were purchased from commercial vendors and used without purification if not noted otherwise. NMR-Spectra were collected on Varian INOVA 300 (300 MHz for $^1H$, 75 MHz for $^{13}C$) or Bruker Avance III HD 500 (500 MHz for $^1H$, 125.7 MHz for $^{13}C$) instruments. Chemical shifts are reported in ppm relative to the residual solvent signal ($CDCl_3$: 7.26 ppm ($^1H$), 77.16 ppm ($^{13}C$)). Coupling constants (*J*) are reported in Hz (coupling patterns: d = doublet, t = triplet, q = quartet, sxt = sextet, spt = septet, m = multiplet). GC analyses were carried out on an Agilent 6890N Network GC system equipped with a HP-5 column (30 m x 0.32 mm x 0.25 µm) or on an Agilent 6790 N equipped with an Optima 17 column (30 m x 0.32 mm x 0.25 µm). GC-MS analyses were carried out on an Agilent 7890A GC system equipped with a HP-5MS column (30 m x 0.32 mm x 0.25 µm) and a 5975C inert MSD detector. Flash column chromatography was conducted on Macherey-Nagel silica gel 60 (40–63 µm particle size). Elemental analysis was performed on an Elementar Vario El *III* Instrument. High resolution mass spectra (HRMS) were obtained from a Thermo Scientific Q-Exactive (Orbitrap) instrument in ESI+ mode.

**Purification/preparation of chemicals**: *t*-BuOK was dried at 70 °C under high vacuum Benzamidine was purchased as the hydrochloride hydrate, extracted ($CH_2Cl_2$ vs. 1 M aq. NaOH) and dried under high vacuum prior to use.

All ligands[1] and complexes[2,3] were prepared as reported previously by our group.

Pyrimidine products were analyzed by GC-MS, $^1H$ and $^{13}C$ NMR analysis and compared to authentic literature data. Unknown compounds or compounds with incomplete spectroscopic literature data were further analyzed by HRMS or elemental analysis.

The following products have not been (sufficiently) described in the literature: **4d, 4f, 4g, 4h, 4m, 5i, 5j.**

MTBE = methyl *tert*-butyl ether

# 2 General procedures for the preparation of compounds

## 2.1 General procedure for ligand preparation

**Representative procedure:** Under inert gas atmosphere a round-bottom flask with gas inlet was charged with a solution/suspension the corresponding triazine or pyridine diamine (1 eq) in abs. THF. The solution was cooled to 0 °C and diisopropyl chlorophospine (2.1 eq) was added dropwise by syringe through a septum maintaining a positive inert gas pressure. Afterwards triethylamine (4 eq) was added by syringe. The flask was sealed and the reaction was warmed to room temperature and then heated to 60 °C overnight. After cooling, triethyl ammoniumchloride was allowed to settle and the organic phase was isolated by filtration. The salt cake was washed once with THF and the combined organic phases were concentrated and dried under high vacuum giving the P,N,P ligand in good purity for direct use without further purification. Otherwise, the crude ligand can be purified by recrystallization from a small amount of hot toluene.

## 2.2 General procedure for the preparation of Manganese complexes

Using a nitrogen-filled glove box, a schlenk tube was charged with a magnetic stirring bar and a suspension of PNP-Ligand (1 eq.) and bromopentacarbonylmanganese(I) (1 eq) in toluene. The tube was sealed, removed from the glove box and a reflux condenser was attached under argon stream. The top of the condenser was connected to a bubble counter. The reaction was heated to 100 °C (oil bath) which led to a orange solution and then to precipitation of the complex. After heating overnight, the reaction was cooled and the toluene phase was removed by filtration. After drying under heating (100 °C oil bath) and high vacuum the corresponding complex was obtained typically as orange to bright yellow powder.

## 2.3 General procedure for the synthesis of pyrimidines

### 2.3.1 Three-component synthesis

***Note:*** The reactions can either be run in a closed (38 mL pressure tube) or open system (Schlenk tube with reflux condenser). No high variations in yield (10%) were detected by GC analysis on a 1 mmol scale.

When the reaction is run in an open system, alcohol conversion is nearly complete (formation of the corresponding coupling product on ketone oxidation level). When run in a closed system, excess alcohols are not completely consumed.

**Closed system:**

Using a nitrogen-filled glove box, an oven-dried pressure tube (38 mL volume) was charged with a magnetic stirring bar, *t*-BuOK (1.1 mmol, 123 mg), precatalyst **B** (0.02 mmol, 2 mol %, 1 mL from a 0.02 M stock solution), primary alcohol (1.5 mmol), secondary alcohol (1.5 mmol), amidine or guanidine (1.0 mmol) and 1,4-dioxane (2 mL). The tube was closed tightly with a teflon cap, removed from the glove box and immersed into a pre-heated oil bath (120 °C). After 20 h the reation was cooled, quenched with half-saturated brine and extracted with MTBE (4x 15 mL). A small aliquot of the organic phase was analyzed by GC-MS to monitor product formation. The combined organic phase was dried over $Na_2SO_4$ and concentrated. Purification of the remainder by column chromatography on silica gel gave the corresponding pyrimidines in the reported yields.

**Open system:**

Using a nitrogen-filled glove box, a 25 mL Schlenk tube was charged with a magnetic stirring bar, *t*-BuOK (1.1 mmol, 123 mg), precatalyst **B** (0.02, 2 mol %, 1 mL from a 0.02 M stock solution), primary alcohol (1.5 mmol), secondary alcohol (1.5 mmol), amidine or guanidine (1.0 mmol) and 1,4-dioxane (2 mL). The tube was closed with a glass stopper and removed from the glove box. A reflux condenser was evacuated and refilled with argon and then attached to the Schlenk tube maintaining an argon stream. A bubble counter was attached to the top of the condenser and the whole system was purged with argon for 15 seconds. The schlenk tube was immersed into a pre-heated oil bath (120 °C) and the reaction was allowed to run for 20 h. Work-up was conducted as described above.

### 2.3.2 Consecutive four-component synthesis

Four-component syntheses were run in 25 mL two-necked Schlenk tubes in an open system (reflux condenser).

Using a nitrogen-filled glove box, a two-necked schlenk tube (25 mL volume) was charged with a magnetic stirring bar, *t*-BuOK (2 mmol, 224 mg), precatalyst **B** (0.05 mmol), secondary alcohol (2.0 mmol), primary alcohol (2.2 mmol) and 1,4-dioxane (1 mL). One neck of the tube was closed with a rubber septum and the other neck with a glass stopper. The tube was removed from the glove box and a reflux condenser (filled with argon) was attached under argon stream. A bubble counter was attached on top of the reflux condenser and the system was purged with argon for 15 seconds. The reaction mixture was heated to reflux (120 °C oil bath) for 5 hours and then a solution (prepared in the glove box) of the remaining starting materials (primary alcohol (1.1 mmol) and amidine (1.0 mmol) in 1,4-dioxane (2 mL) was injected by syringe

through the rubber septum. The reaction mixture was allowed to run for another 20 h (reflux) and after cooling the reaction was subjected to work up as described above.

**Variation for low-boiling alcohols (methanol, ethanol):** The β-alkylation reaction was run in a closed system (sealed Schlenk flask). Afterwards, the reaction was treated as described above.

# 3 Screening of reaction conditions

*General screening procedure:* Using a nitrogen-filled glove box, a 38 mL glass pressure tube was charged with a magnetic stirring bar, base, alcohols, amidine, catalyst and solvent. The tube was closed with a teflon cap, removed from the glove box and immersed into a pre-heated (120 °C) oil bath for 20 h. The reaction was cooled, quenched with water (1 mL) and dodecane (internal standard, 100 µL for 0.5 mmol scale reaction) was added. The mixture was extracted with MTBE (20 mL) and an aliquot of the organic phase was analyzed by GC-FID to determine the yield using dodecane as the internal standard.

Table S 1. Screening of solvent

| Entry | Solvent | Yield |
|---|---|---|
| 1 | THF[a] | 0 % |
| 2 | Toluene | 32 % |
| 3 | *tert*-amyl alcohol | 55 % |
| 4 | 1,4-Dioxane | 78 % |
| 5 | Diglyme | 56 % |

Reaction conditions: 1-phenylethanol (0.75 mmol, 1.5 eq), benzyl alcohol (0.75 mmol, 1.5 eq), benzamidine hydrochloride (0.5 mmol, 1 eq), *t*-BuOK (0.5 + 0.55 mmol to trap HCl, 1.1 eq), catalyst **B** (0.01 mmol, 10 mol %) and solvent (2 mL) were heated for 20 h in a closed 38 mL pressure tube at 120 °C (oil bath).
[a] 80 °C oil bath

Table S 2. Screening of base

| Entry | Base | Yield |
|---|---|---|
| 1 | *t*-BuOLi | 0 % |
| 2 | *t*-BuONa | 9 % |
| 3 | *t*-BuOK | 78 % |
| 4 | KOH | 13 % |
| 5 | KHMDS | 62 % |

Reaction conditions: 1-phenylethanol (0.75 mmol, 1.5 eq), benzyl alcohol (0.75 mmol, 1.5 eq), benzamidine hydrochloride (0.5 mmol, 1 eq), base (0.5 + 0.55 mmol to trap HCl, 1.1 eq), catalyst **B** (0.025 mmol, 5 mol %) in 1,4-dioxane (2 mL) were heated for 20 h in a closed 38 mL pressure tube at 120 °C (oil bath).

Table S 3. Screening of base amount.

| Entry | Base amount (equiv) | Yield |
|---|---|---|
| 1 | 0.1 | 0 % |
| 2 | 0.2 | 26 % |
| 3 | 0.5 | 62 % |
| 4 | 1.1 | 79 % |
| 5 | 1.5 | 73 % |
| 6 | 2.0 | 71 % |

Reaction conditions: 1-phenylethanol (0.75 mmol, 1.5 eq), benzyl alcohol (0.75 mmol, 1.5 eq), benzamidine (free base, 0.5 mmol, 1 eq), *t*-BuOK, catalyst **B** (0.025 mmol, 5 mol %) in 1,4-dioxane (2 mL) were heated for 20 h in a closed 38 mL pressure tube at 120 °C (oil bath).

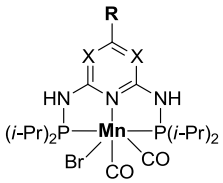
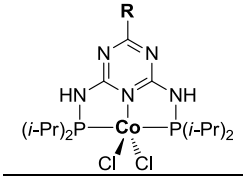
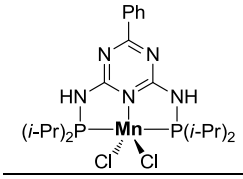
Table S 4. Screening of substrate ratio

| Entry | Ratio Amidine/2° alc/1° alc | Yield |
|---|---|---|
| 1 | 1.0 : 2.0 : 2.0 | 96 % |
| 2 | 1.0 : 1.5 : 1.5 | 79 % |
| 3 | 1.0 : 1.1 : 1.5 | 68 % |
| 4 | 1.0 : 1.5 : 1.1 | 59 % |
| 5 | 1.0 : 1.5 : 2.0 | 67 % |
| 6 | 1.0 : 2.0 : 1.5 | 75 % |

Reaction conditions: 1-phenylethanol (0.75 mmol, 1.5 eq), benzyl alcohol (0.75 mmol, 1.5 eq), benzamidine (free base, 0.5 mmol, 1 eq), *t*-BuOK, catalyst **B** (0.025 mmol, 5 mol %) in 1,4-dioxane (2 mL) were heated for 20 h in a closed 38 mL pressure tube at 120 °C (oil bath).

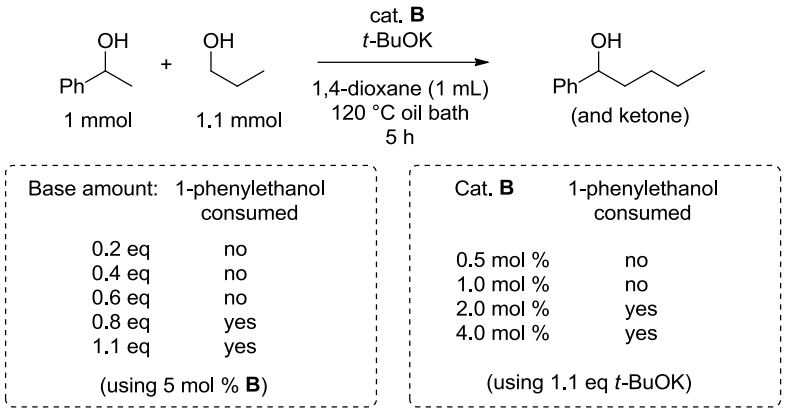
Although the screening of substrate ratio suggested to use 2 equiv of alcohols, no difference in isolated yields was observed for when 1.5 equiv of alcohols were used instead. As an example, compound **4h** was always isolated in the same yields (70 %) when either 2.0 or 1.5 equiv of alcohols were used. When 4 mol % precatalyst **B**, were used, the yield did not change as well. Thus, 1.5 equiv of alcohols was selected eventually.

Table S 5. Precatalyst Screening

| Structure | Entry | Precatalyst | R | X | Yield |
|---|---|---|---|---|---|
|  | 1 | **A** | Me | N | 83 % |
| | 2 | **B** | Ph | N | 96 % |
| | 3 | **C** | 4-$CF_3$-($C_6H_4$)- | N | 85 % |
| | 4 | **D** | H | N | 92 % |
| | 5 | **E** | $C_3H_5$-NH- | N | 89 % |
| | 6 | **F** | H | CH | 48 % |
| | 7 | **G** | Me | CH | 54 % |
|  | 8 | **H** | Me | -- | 9 % |
| | 9 | **I** | Ph | -- | 0 % |
| | 10 | **J** | $C_3H_5$-NH- | -- | 0 % |
|  | 11 | **K** | as shown | | 0 % |

Reaction conditions: 1-phenylethanol (1 mmol, 2 eq), benzyl alcohol (1 mmol, 2 eq), benzamidine (free base, 0.5 mmol, 1 eq), *t*-BuOK (0.55 mmol, 1.1 eq), catalyst (0.01 mmol, 2 mol %) in 1,4-dioxane (2 mL) were heated for 20 h in a closed 38 mL pressure tube at 120 °C (oil bath).

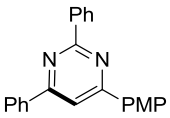
In order to establish reaction conditions that allow complete consumption of the secondary alcohol in the β-alkylation reaction within 5 hours under the typical reaction conditions, the following reaction (Scheme S 1)was investigated by GC analysis and the consumption of 1-phenylethanol was monitored (any unconsumed secondary alcohol would give the 4-unsubstituted pyrimidine in the last reaction step of the consecutive 4-component-reaction):




Scheme S 1. GC-Monitoring of the β-alkylation reaction to ensure complete consumption of 1-phenylethanol

# 4 Characterization Data

*4-(4-methoxyphenyl)-2,6-diphenylpyrimidine (**4b**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 30:1). Yield: 266 mg, (0.787 mmol, 79 %) white solid.

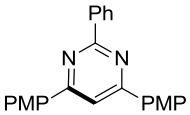
**$^1$H NMR** (500 MHz, $CDCl_3$): δ = 8.70 - 8.76 (m, 2 H), 8.22 - 8.33 (m, 4 H), 7.95 (s, 1 H), 7.48 - 7.63 (m, 6 H), 7.03 - 7.11 (m, 2 H), 3.91 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 164.6, 164.5, 164.3, 162.1, 138.4, 137.8, 130.8, 130.7, 130.0, 129.0, 128.9, 128.58, 128.55, 127.4, 114.4 109.6, 55.6 ppm.

**MS** (EI, 70 eV) *m/z*: 338.2 ($M^+$), 323.1, 235.1, 220.1, 204.1, 191.1, 165.1, 132.1, 117.4, 102.1, 89.1, 77.1.

The spectroscopic data correspond to those reported in the literature.[4]

*4,6-bis(4-methoxyphenyl)-2-phenylpyrimidine (**4c**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 40:1 → 10:1). Yield: 267 mg (0.726 mmol, 73 %) white solid.

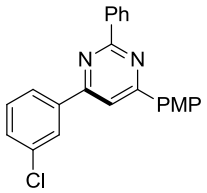
**$^1$H NMR** (500 MHz, $CDCl_3$): δ = 8.66 - 8.76 (m, 2 H), 8.22 - 8.31 (m, 2 H), 7.88 (s, 1 H), 7.47 - 7.59 (m, 2 H), 7.02 - 7.12 (m, 2 H), 3.91 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 164.3, 164.1, 138.4, 130.6, 130.2, 128.9, 128.6, 128.5, 114.4, 108.7, 55.6 ppm.

**MS** (EI, 70 eV) *m/z*: 368.1 ($M^+$), 265.1, 250.0, 234.0, 207.0, 132.1, 117.0, 103.0, 89.0, 77.0.

The spectroscopic data correspond to those reported in the literature.[5]

*4-(3-chlorophenyl)-6-(4-methoxyphenyl)-2-phenylpyrimidine (**4d**)*




Purification by column chromatography (silica gel, pentane diethyl ether, 20:1). Yield: 263 mg (0.705 mmol, 71%) white solid.

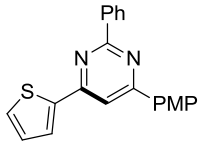
**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ = 8.60 - 8.78 (m, 2 H), 8.21 - 8.35 (m, 3 H), 8.05 - 8.20 (m, 1 H), 7.88 (s, 1 H), 7.42 - 7.64 (m, 5 H), 6.96 - 7.15 (m, 2 H), 3.91 (s, 3 H) ppm.

**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ = 164.5, 163.1, 162.2, 139.6, 138.1, 135.1, 130.8, 130.7, 130.2, 129.7, 128.9, 128.6, 127.5, 125.4, 114.4, 109.4, 55.6 ppm.

**MS** (EI, 70 eV) *m/z*: 372.1 ($M^+$), 357.1, 254.0, 234.1, 191.1, 132.1, 89.0.

**Elemental analysis (%)** for $C_{23}H_{17}ClN_2O$ calcd: C 74.09, H 4.60, N 7.51; found: C 73.82, H 4.21, N 7.30.

*4-(4-methoxyphenyl)-2-phenyl-6-(thiophen-2-yl)pyrimidine (**4e**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 30:1 → 20:1). Yield: 251 mg (0.73 mmol, 73 %) off-white solid.

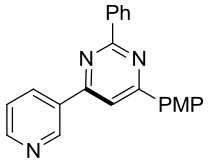
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.63 - 8.71 (m, 2 H), 8.21 - 8.29 (m, 2 H), 7.93 (dd, *J*=3.66, 1.22 Hz, 1 H), 7.80 (s, 1 H), 7.48 - 7.58 (m, 4 H), 7.21 (dd, *J*=4.88, 3.66 Hz, 1 H), 7.02 - 7.11 (m, 2 H), 3.91 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 164.4, 164.1, 162.1, 159.5, 143.6, 138.0, 130.8, 129.8, 129.7, 128.9, 128.5, 128.4, 127.0, 114.3, 107.6, 55.6 ppm.

**MS** (EI, 70 eV) *m/z*: 344.1 ($M^+$), 241.0, 226.0, 207.0, 132.0, 108.0, 89.0, 89.0, 77.0.

The spectroscopic data correspond to those reported in the literature.[5]

*4-(4-methoxyphenyl)-2-phenyl-6-(pyridin-3-yl)pyrimidine (**4f**)*




Purification by column chromatography (silica gel, pentane/ethyl acetate, 1:1). Yield: 248 mg (0.732 mmol, 73 %) pale yellow solid.

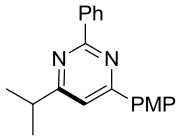
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 9.48 (br. s., 1 H), 8.79 (br. s., 1 H), 8.68 - 8.74 (m, 2 H), 8.64 (d, *J*=7.93 Hz, 1 H), 8.29 (d, *J*=8.85 Hz, 2 H), 7.97 (s, 1 H), 7.48 - 7.59 (m, 4 H), 7.09 (d, *J*=8.85 Hz, 2 H), 3.92 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 164.7, 164.6, 162.3, 138.0, 134.9, 130.9, 129.6, 129.0, 128.6, 128.5, 114.4, 109.4, 55.6 ppm.

**MS** (EI, 70 eV) *m/z*: 339.1 ($M^+$), 324.1, 235.1, 221.0, 205.0, 192.1, 132.0, 117.0, 103.0, 89.0, 76.0.

**HRMS** (ESI+) *m/z* calcd. for $[C_{22}H_{17}N_3O+H]^+$ 340.14444, found 340.14389.

*4-isopropyl-6-(4-methoxyphenyl)-2-phenylpyrimidine (**4g**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 40:1). Yield: 199 mg (0.655 mmol, 66 %) white solid.

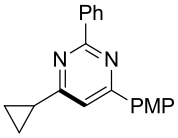
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.59 - 8.66 (m, 2 H), 8.18 - 8.25 (m, 2 H), 7.45 - 7.55 (m, 3 H), 7.41 (s, 1 H), 7.02 - 7.07 (m, 2 H), 3.90 (s, 3 H), 3.13 (spt, *J*=7.00 Hz, 1 H), 1.41 (d, *J*=7.02 Hz, 6 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 176.1, 164.0, 163.6, 161.9, 130.5, 130.2, 128.8, 128.7, 128.5, 114.3, 110.7, 55.6, 36.4, 22.1 ppm.

**MS** (EI, 70 eV) *m/z*: 304.1 ($M^+$), 289.1, 276.1, 246.1, 132.1, 104.1, 89.1, 77.1.

**HRMS** (ESI+) *m/z* calcd. for $[C_{20}H_{20}N_2O+H]^+$ 305.16484, found 305.16418.

*4-cyclopropyl-6-(4-methoxyphenyl)-2-phenylpyrimidine (**4h**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 40:1). Yield: 210 mg (0.695 mmol, 70 %) white solid.

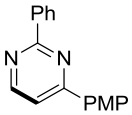
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.53 - 8.60 (m, 2 H), 8.16 - 8.23 (m, 2 H), 7.44 - 7.53 (m, 3 H), 7.40 (s, 1 H), 7.00 - 7.07 (m, 2 H), 3.89 (s, 3 H), 2.10 (m, *J*=4.27 Hz, 1 H), 1.29 - 1.35 (m, 2 H), 1.08 - 1.14 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 172.0, 163,9, 162.6, 161.8, 138.5, 130.4, 130.0, 128.8, 128.42, 128.39, 114.27, 114.25, 111.62, 55.5, 17.4, 10.9 ppm.

**MS** (EI, 70 eV) *m/z*: 302.1 ($M^+$), 198.1, 168.1, 154.1, 132.1, 104.1, 89.1, 77.1.

**HRMS (ESI+)** *m/z* calcd. for $[C_{20}H_{18}N_2O + H]^+$ 303.14919, found 303.14856

*4-(4-methoxyphenyl)-2-phenylpyrimidine (**4i**)*




Version with ethanol and 4-methoxybenzyl alcohol:

Purification by column chromatography (silica gel, pentane/diethyl ether, 7:3). Yield: 132 mg (0.504 mmol, 50 %) white solid.

Version with 1-(4-methoxyphenyl)ethanol and methanol:

Purification as above, yield: 132 mg (0.435 mmol, 44 %) white solid.

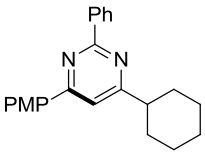
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.77 (d, *J*=5.49 Hz, 1 H), 8.55 - 8.66 (m, 2 H), 8.16 - 8.28 (m, 2 H), 7.46 - 7.61 (m, 4 H), 6.98 - 7.11 (m, 2 H), 3.89 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 164.4, 163.4, 162.1, 157.6, 138.1, 130.7, 129.4, 128.8, 128.6, 128.3, 114.3, 113.7, 55.5 ppm.

**MS** (EI, 70 eV) *m/z*: 262.1 ($M^+$), 247-1, 159.0, 132.1, 117.0, 103.0.

The spectroscopic data correspond to those reported in the literature.[6]

*4-cyclohexyl-6-(4-methoxyphenyl)-2-phenylpyrimidine (**4j**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 50:1 → 40:1). Yield:183 mg (0.532 mmol, 53 %) white solid.

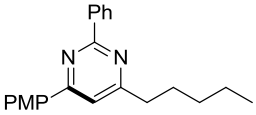
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.60 - 8.66 (m, 2 H), 8.18 - 8.24 (m, 2 H), 7.46 - 7.55 (m, 3 H), 7.39 (s, 1 H), 7.01 - 7.07 (m, 2 H), 3.89 (s, 3 H), 2.78 (tt, *J*=11.79, 3.47 Hz, 2 H), 2.04 - 2.11 (m, 2 H), 1.88 - 1.96 (m, 2 H), 1.77 - 1.85 (m, 1 H), 1.68 (qd, *J*=12.51, 3.36 Hz, 2 H), 1.48 (qt, *J*=12.82, 3.36 Hz, 2 H), 1.35 (qt, *J*=12.70, 3.36 Hz, 5 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 175.2, 164.0, 163.4, 161.8, 138.7, 130.4, 130.2, 128.8, 128.47, 128.45, 114.3, 111.1, 55.5, 46.4, 32.3, 26.5, 26.2 ppm.

**MS** (EI, 70 eV) *m/z*: 344.2 ($M^+$), 315.2, 303.1, 289.1, 276.1, 246.1, 144.6, 132.1, 104.1.

The spectroscopic data correspond to those reported in the literature.[4]

*4-(4-methoxyphenyl)-6-pentyl-2-phenylpyrimidine (**4k**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 30:1). Yield: 206 mg (0.620 mmol, 62 %) white solid.

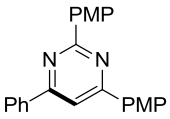
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.55 - 8.67 (m, 2 H), 8.18 - 8.24 (m, 2 H), 7.45 - 7.57 (m, 3 H), 7.39 (s, 1 H), 6.99 - 7.08 (m, 2 H), 3.89 (s, 3 H), 2.81 - 2.91 (m, 2 H), 1.80 - 1.93 (m, 2 H), 1.35 - 1.50 (m, 4 H), 0.89 - 1.00 (m, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 171.4, 164.2, 163.3, 161.9, 138.5, 130.4, 130.0, 128.8, 128.5, 128.5, 114.3, 112.6, 55.5, 38.3, 31.7, 28.7, 22.7, 14.2 ppm.

**MS** (EI, 70 eV) *m/z*: 332.2 ($M^+$), 303.1, 289.1, 276.1, 132.1, 104.1, 89.1, 77.1.

The spectroscopic data correspond to those reported in the literature.[4]

*2,4-bis(4-methoxyphenyl)-6-phenylpyrimidine (**4l**)*




1 mmol scale. Purification by column chromatography (silica gel, pentane/diethyl ether, 40:1 → 10:1). Yield: 250 mg (0.679 mmol, 68 %) white solid.

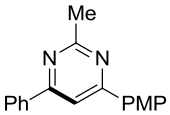
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.64 - 8.72 (m, 2 H), 8.22 - 8.31 (m, 4 H), 7.89 (s, 1 H), 7.49 - 7.59 (m, 3 H), 7.01 - 7.10 (m, 4 H), 3.91 (s, 3 H), 3.90 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 164.5, 164.20, 164.19, 162.0, 161.9, 137.9, 131.1, 130.7, 130.22, 130.16, 129.0, 128.9, 127.4, 114.3, 113.8, 108.9, 55.6, 55.5 ppm.

**MS** (EI, 70 eV) *m/z*: 368.1 ($M^+$), 353.1, 220.0, 132.0, 117.1, 102.0, 89.0, 77.0.

The spectroscopic data correspond to those reported in the literature.[7]

*4-(4-methoxyphenyl)-2-methyl-6-phenylpyrimidine (**4m**)*




1 mmol scale. Purification by column chromatography (silica gel, pentane/MTBE, 9:1 → 5:1). Yield: 156 mg (0.656 mmol, 57 %) white solid.

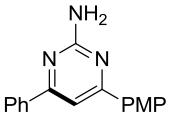
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.06 - 8.16 (m, 4 H), 7.80 (s, 1 H), 7.46 - 7.57 (m, 3 H), 6.98 - 7.05 (m, 2 H), 3.83 - 3.90 (m, 3 H), 2.85 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 168.4, 164.6, 164.3, 161.8, 137.7, 130.5, 129.8, 128.9, 128.8, 127.3, 114.3, 109.2, 55.4, 26.6 ppm.

**MS** (EI, 70 eV) *m/z*: 276.1 ($M^+$), 261.1, 235.1, 220.1, 204.1, 132.1, 117.2, 102.1, 89.1, 77.1.

**HRMS** (ESI+) *m/z* calcd. for $[C_{18}H_{16}N_2O + H]^+$ 277.13354, found 277.13312

*4-(4-methoxyphenyl)-6-phenylpyrimidin-2-amine (**4n**)*




1 mmol scale. Purification by column chromatography (silica gel, pentane/MTBE, 2:1 → 1.5:1). Yield: 172 mg (0.621 mmol, 62 %) white solid.

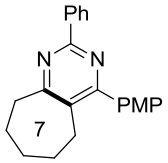
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.00 - 8.09 (m, 4 H), 7.46 - 7.54 (m, 3 H), 7.42 (s, 1 H), 6.97 - 7.04 (m, 2 H), 5.24 (br. s., 2 H), 3.88 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 166.1, 165.7, 163.5, 161.9, 137.9, 130.6, 130.1, 128.9, 128.8, 127.2, 114.26, 114.25, 103.7, 55.6 ppm.

**MS** (EI, 70 eV) *m/z*:277.1 ($M^+$), 262.0, 233.0, 220.0, 207.0, 165.0, 102.0, 89.0, 77.0.

The spectroscopic data correspond to those reported in the literature.[4]

*4-(4-methoxyphenyl)-2-phenyl-6,7,8,9-tetrahydro-5H-cyclohepta[d]pyrimidine (**5a**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 30:1 → 15:1). Yield: 240 mg (0.727 mmol, 73 %) white solid.

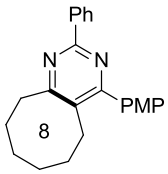
**$^{1}$H NMR** (500 MHz, CDCl3): δ = 8.49 (dd, *J*=7.93, 1.53 Hz, 2 H), 7.55 - 7.61 (m, 2 H), 7.40 - 7.49 (m, 3 H), 6.99 - 7.05 (m, 2 H), 3.88 (s, 3 H), 3.10 - 3.22 (m, 2 H), 2.85 - 2.96 (m, 2 H), 1.89 - 1.99 (m, 2 H), 1.78 - 1.88 (m, 2 H), 1.66 - 1.77 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 172.6, 163.8, 160.9, 160.1, 138.2, 131.6, 130.8, 130.2, 130.0, 128.3, 128.0, 113.6, 55.3, 39.3, 32.3, 29.1, 27.7, 26.1 ppm.

**MS** (EI, 70 eV) *m/z*: 329.2, 315.2, 301.1, 258.1, 145.1, 104.1, 91.1, 77.1.

The spectroscopic data correspond to those reported in the literature.[4]

*4-(4-methoxyphenyl)-2-phenyl-5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidine (**5b**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 30:1 → 15:1). Yield: 269 mg (0.782 mmol, 78 %) white solid.

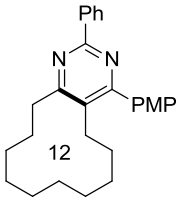
**$^{1}$H NMR** (500 MHz, CDCl3): δ = 8.44 - 8.57 (m, 2 H), 7.52 - 7.58 (m, 2 H), 7.40 - 7.50 (m, 3 H), 6.98 - 7.04 (m, 2 H), 3.88 (s, 3 H), 3.03 - 3.12 (m, 2 H), 2.84 - 2.93 (m, 2 H), 1.88 - 1.99 (m, 2 H), 1.60 - 1.69 (m, 2 H), 1.42 - 1.54 (m, 4 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ =170.8, 165.1, 161.6, 160.0, 138.4, 132.1, 130.4, 130.3, 130.0, 128.7, 128.5, 128.2, 113.7, 55.5, 35.1, 31.5, 30.5, 26.7, 26.3, 26.0 ppm.

**MS** (EI, 70 eV) *m/z*: 344.2 ($M^+$), 329.2, 315.2, 301.1, 289.1, 276.1, 183.1, 172.1, 158.1, 145.1, 128.1, 115.1, 104.1, 91.1, 77.1.

The spectroscopic data correspond to those reported in the literature.[4]

*4-(4-methoxyphenyl)-2-phenyl-5,6,7,8,9,10,11,12,13,14-decahydrocyclododeca[d]pyrimidine (**5c**)*




Purification by column chromatography (silica gel, pentande/diethyl ether, 30:1 → 20:1). Yield: 213 mg (0.533 mmol, 53 %) white solid.

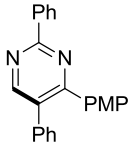
**$^1$H NMR** (500 MHz, $CDCl_3$): δ = 8.43 - 8.61 (m, 2 H), 7.52 - 7.58 (m, 2 H), 7.41 - 7.51 (m, 3 H), 6.95 - 7.06 (m, 2 H), 3.88 (s, 3 H), 2.93 (t, *J*=7.63 Hz, 2 H), 2.78 - 2.87 (m, 2 H), 2.02 - 2.13 (m, 2 H), 1.37 - 1.63 (m, 12 H), 1.24 - 1.36 (m, 3 H)

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 170.1, 166.2, 160.9, 159.9, 138.3, 132.7, 130.1, 130.00, 129.97, 128.4, 128.2, 113.7, 55.4, 34.2, 32.2, 28.2, 27.8, 26.9, 26.8, 26.0, 25.9, 25.85, 25.82, 23.22, 23.21, 22.4 ppm.

**MS** (EI, 70 eV) *m/z*: 399.1 ($M^+$), 385.2, 369.2, 257.2, 343.2, 329.2, 315.1, 303.1, 289.1, 145.0, 104.0, 77.0.

The spectroscopic data correspond to those reported in the literature.[4]

*4-(4-methoxyphenyl)-2,5-diphenylpyrimidine (**5d**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 15:1). Yield: 253 mg (0.749 mmol, 75 %) white solid.

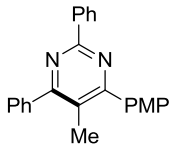
**$^1$H NMR** (500 MHz, $CDCl_3$): δ = 8.74 (s, 1 H), 8.54 - 8.63 (m, 2 H), 7.47 - 7.61 (m, 5 H), 7.33 - 7.44 (m, 3 H), 7.27 - 7.31 (m, 2 H), 6.79 - 6.87 (m, 2 H), 3.82 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 163.1, 162.9, 160.8, 158.7, 137.7, 137.1, 131.8, 130.8, 130.4, 130.2, 129.41, 129.39, 129.0, 128.68, 128.67, 128.4, 128.0, 113.7, 55.4 ppm.

**MS** (EI, 70 eV) *m/z*: 337.2, ($M^+$), 294.1, 193.1, 165.1, 102.1.

The spectroscopic data correspond to those reported in the literature.[4]

*4-(4-methoxyphenyl)-5-methyl-2,6-diphenylpyrimidine (**5e**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 9:1). Yield: 202 mg (0.574 mmol, 57 %) white solid.

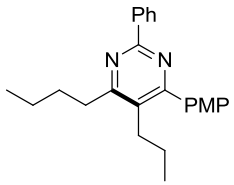
**$^1$H NMR** (500 MHz, $CDCl_3$): δ = 8.53 - 8.65 (m, 2 H), 7.71 - 7.83 (m, 4 H), 7.42 - 7.58 (m, 6 H), 7.01 - 7.12 (m, 2 H), 3.90 (s, 3 H), 2.43 (s, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 167.0, 166.4, 161.4, 160.6, 139.5, 138.1, 131.7, 131.2, 130.3, 129.53, 129.51, 129.2, 128.5, 128.4, 128.3, 123.0, 113.8, 55.5, 18.2 ppm.

**MS** (EI, 70 eV) *m/z*: 351.2 ($M^+$), 140.0, 115.1, 103.1, 77.1.

The spectroscopic data correspond to those reported in the literature.[4]

*4-butyl-6-(4-methoxyphenyl)-2-phenyl-5-propylpyrimidine (**5f**)*




**$^1$H NMR** (500 MHz, $CDCl_3$): δ = 8.47 - 8.59 (m, 2 H), 7.53 - 7.59 (m, 2 H), 7.41 - 7.50 (m, 3 H), 6.99 - 7.06 (m, 2 H), 3.89 (s, 3 H), 2.88 - 2.95 (m, 2 H), 2.68 - 2.75 (m, 2 H), 1.87 - 1.96 (m, 2 H), 1.47 - 1.59 (m, 4 H), 1.05 (t, *J*=7.32 Hz, 3 H), 0.91 (t, *J*=7.32 Hz, 3 H) ppm.

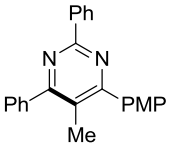
**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 169.7, 165.5, 161.0, 160.0, 138.4, 132.3, 130.3, 130.0, 128.4, 128.15, 113.7, 55.4, 34.5, 31.1, 30.2, 24.0, 23.0, 14.4, 14.2 ppm.

**MS** (EI, 70 eV) *m/z*: 359.2 ($M^+$), 345.2, 331.2, 317.2, 303.1, 287.1, 145.0, 104.1, 77.1.

The spectroscopic data correspond to those reported in the literature.[4]

**4-component-reaction:**

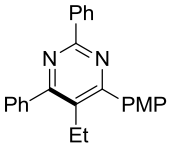
*4-(4-methoxyphenyl)-5-methyl-2,6-diphenylpyrimidine (**5e**)* via 4-CR




Variation from the standard procedure: 3 mmol methanol were used (1.5 equiv with respect to the secondary alcohol in the β-alkylation reaction). Purification by column chromatography (silica gel, pentane/diethyl ether, 20:1). Yield: 178 mg (0.506 mmol, 51 %) white solid.

For spectroscopic data, see above (preparation via 3-component-reaction).

*5-ethyl-4-(4-methoxyphenyl)-2,6-diphenylpyrimidine (**5g**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 30:1 → 20:1). Yield: 208 mg (0.568 mmol, 57 %) white solid.

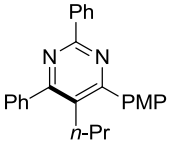
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.50 - 8.57 (m, 2 H), 7.62 - 7.69 (m, 4 H), 7.41 - 7.56 (m, 6 H), 7.02 - 7.08 (m, 2 H), 3.90 (s, 3 H), 2.89 (q, *J*=7.32 Hz, 2 H), 0.80 (t, *J*=7.48 Hz, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 167.3, 166.7, 161.2, 160.3, 139.8, 138.0, 132.1, 130.4, 130.3, 129.8, 128.88, 128.86, 128.5, 128.4, 113.9, 55.5, 218, 14.6 ppm.

**MS** (EI, 70 eV) *m/z*: 365.2 ($M^+$), 351.2, 145.1, 115.1, 77.1.

The spectroscopic data correspond to those reported in the literature.[4]

*4-(4-methoxyphenyl)-2,6-diphenyl-5-propylpyrimidine (**5h**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 30:1 → 20:1). Yield: 210 mg (0.553 mmol, 55 %) white solid.

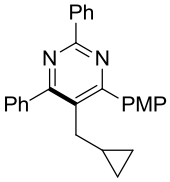
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ =8.51 - 8.59 (m, 2 H), 7.61 - 7.69 (m, 4 H), 7.42 - 7.55 (m, 6 H), 7.01 - 7.08 (m, 2 H), 3.90 (s, 3 H), 2.79 - 2.89 (m, 2 H), 1.12 - 1.26 (m, 2 H), 0.59 (t, *J*=7.32 Hz, 3 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 167.4, 166.9, 161.2, 160.3, 139.9, 137.9, 132.2, 130.5, 130.4, 128.94, 128.87, 128.47, 128.45, 128.4, 128.3, 113.89, 113.88, 55.5, 30.6, 23.2, 14.1 ppm.

**MS** (EI, 70 eV) *m/z*: 379.2 ($M^+$), 365.2, 351.2, 248.1, 145.1, 115.1, 77.1.

The spectroscopic data correspond to those reported in the literature.[3]

*5-(cyclopropylmethyl)-4-(4-methoxyphenyl)-2,6-diphenylpyrimidine (**5i**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 30:1 → 20:1). Yield: 246 mg (0.628 mmol, 63 %) white solid.

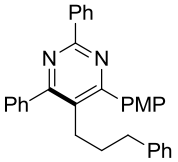
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.54 - 8.62 (m, 2 H), 7.65 - 7.72 (m, 4 H), 7.42 - 7.56 (m, 6 H), 7.02 - 7.09 (m, 2 H), 3.90 (s, 3 H), 2.86 (d, *J*=6.71 Hz, 2 H), 0.38 - 0.52 (m, 1 H), 0.07 - 0.19 (m, 2 H), -0.43 - -0.33 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 167.5, 167.0, 161.2, 160.3, 140.1, 137.9, 132.4, 130.8, 130.4, 129.3, 128.9, 128.5, 128.4, 128.1, 113.9, 55.5, 33.0, 11.4, 5.1 ppm.

**MS** (EI, 70 eV) *m/z*: 391.2 ($M^+$), 377.2, 363.2, 351.2, 315.2, 285.1, 260.1, 230.1, 115.1, 77.1.

**HRMS (ESI+)** *m/z* for $[C_{27}H_{24}N_2O + H]^+$ calcd 393.19614, found: 393.19513.

*4-(4-methoxyphenyl)-2,6-diphenyl-5-(3-phenylpropyl)pyrimidine (**5j**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 20:1). Yield: 256 mg (0.561 mmol, 56 %) white solid.

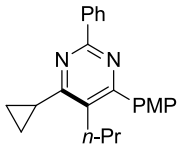
**$^{1}$H NMR** (500 MHz, $CDCl_3$): δ = 8.58 - 8.69 (m, 2 H), 7.60 - 7.73 (m, 4 H), 7.46 - 7.58 (m, 6 H), 7.13 - 7.25 (m, 3 H), 7.00 - 7.09 (m, 2 H), 6.82 - 6.91 (m, 2 H), 3.93 (s, 3 H), 2.87 - 3.00 (m, 2 H), 2.35 (t, *J*=7.32 Hz, 2 H), 1.50 - 1.64 (m, 2 H) ppm.

**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 167.3, 166.8, 161.2, 160.2, 141.3, 139.7, 137.9, 131.94, 130.34, 130.30, 128.81, 128.5, 128.4, 128.31, 128.26, 128.2, 128.0, 125.7, 113.9, 55.4, 35.5, 30.9, 28.0 ppm.

**MS** (EI, 70 eV) *m/z*: 456.2 ($M^+$), 365.2, 351.1, 338.1, 248.1, 145.1, 115.0, 91.1, 77.1

**HRMS (ESI+)** *m/z* for $[C_{32}H_{28}N_2O + H]^+$ calcd. 457.22744, found: 457.22647.

*4-cyclopropyl-6-(4-methoxyphenyl)-2-phenyl-5-propylpyrimidine (**5k**)*




Purification by column chromatography (silica gel, pentane/diethyl ether, 40:1). Yield: 241 mg (0.701 mmol, 70 %) white solid.

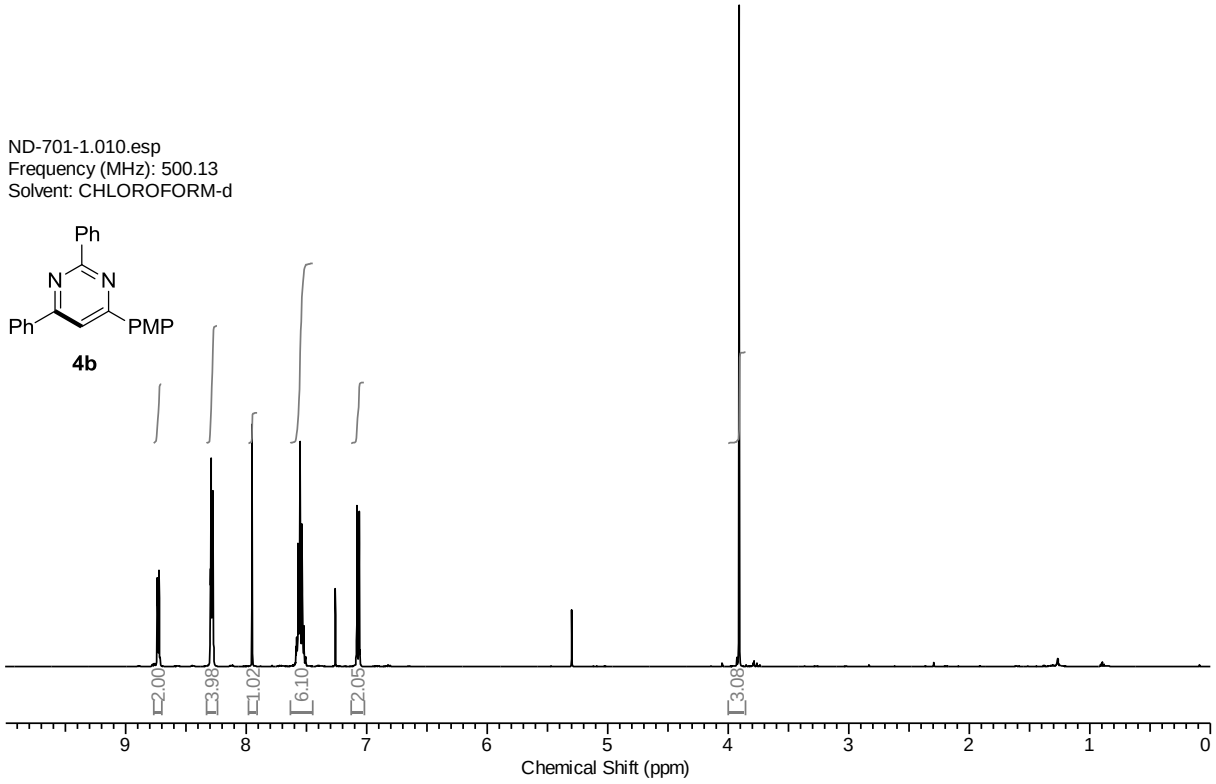
**$^1$H NMR** (500 MHz, $CDCl_3$): δ = 8.42 - 8.50 (m, 2 H), 7.51 - 7.57 (m, 2 H), 7.39 - 7.47 (m, 3 H), 6.99 - 7.07 (m, 2 H), 3.89 (s, 3 H), 2.78 - 2.85 (m, 2 H), 2.19 - 2.27 (m, 1 H), 1.61 - 1.71 (m, 2 H), 1.38 - 1.43 (m, 2 H), 1.08 - 1.14 (m, 2 H), 0.93 (t, *J*=7.32 Hz, 3 H) ppm.

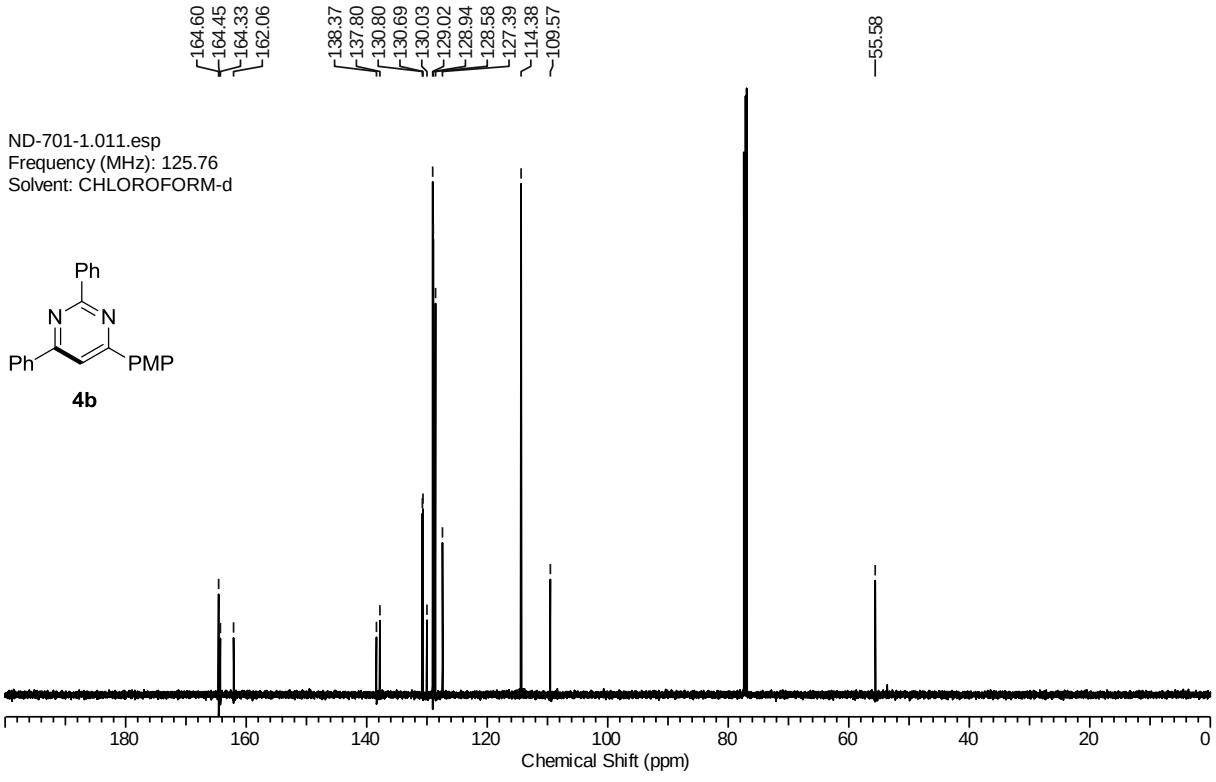
**$^{13}$C NMR** (126 MHz, $CDCl_3$): δ = 170.1, 164.5, 160.8, 160.0, 138.4, 132.4, 130.4, 130.0, 128.3, 128.1, 113.7, 55.5, 30.2, 24.0, 14.4, 13.7, 11.3 ppm.

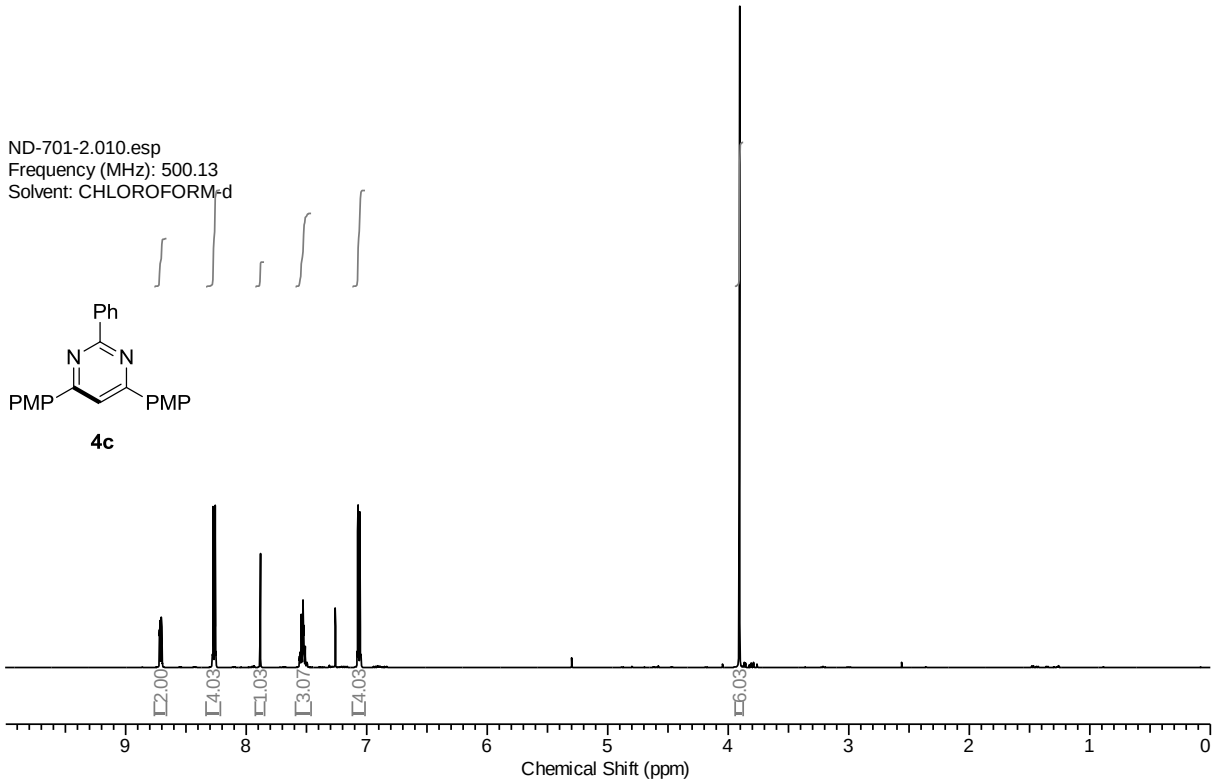
**MS** (EI, 70 eV) *m/z*: 343.3 ($M^+$), 329.2, 315.2, 301.1, 271.1, 248.1, 145.1, 104.1, 77.1.

The spectroscopic data correspond to those reported in the literature.[3]

# 5 NMR Spectra

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N
PMP
PMP
4c
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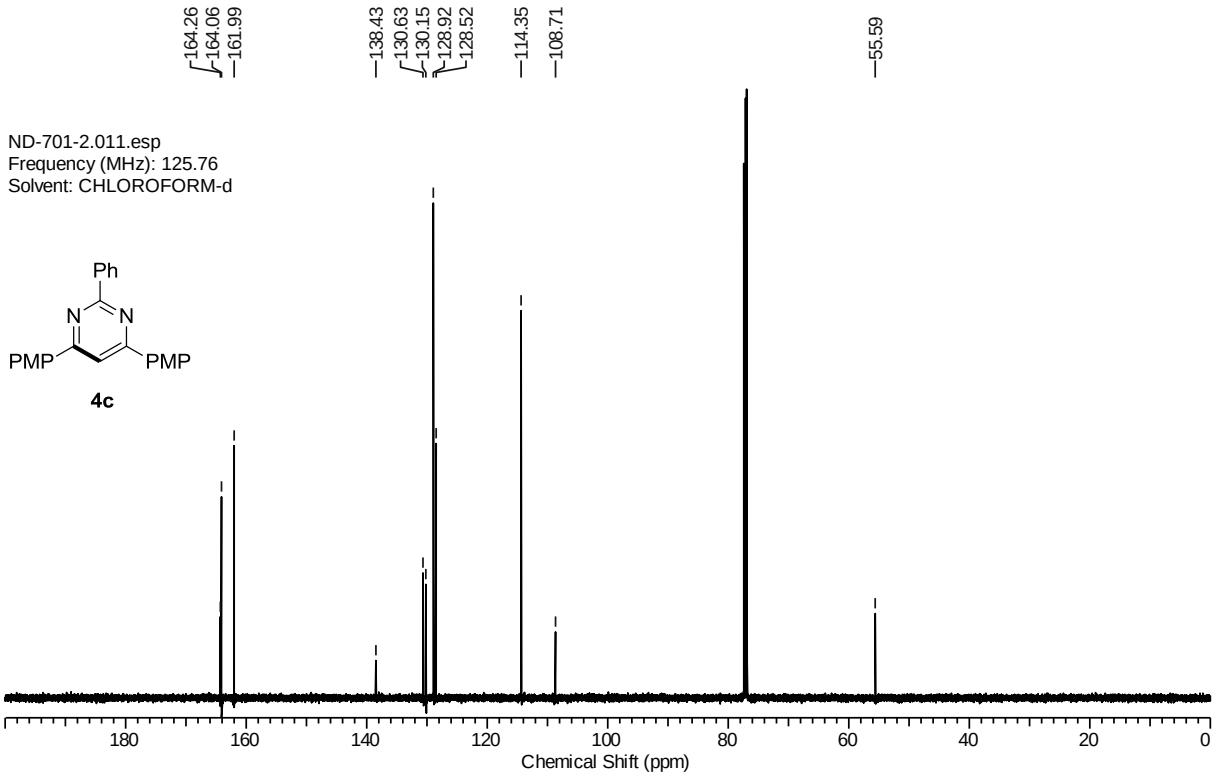
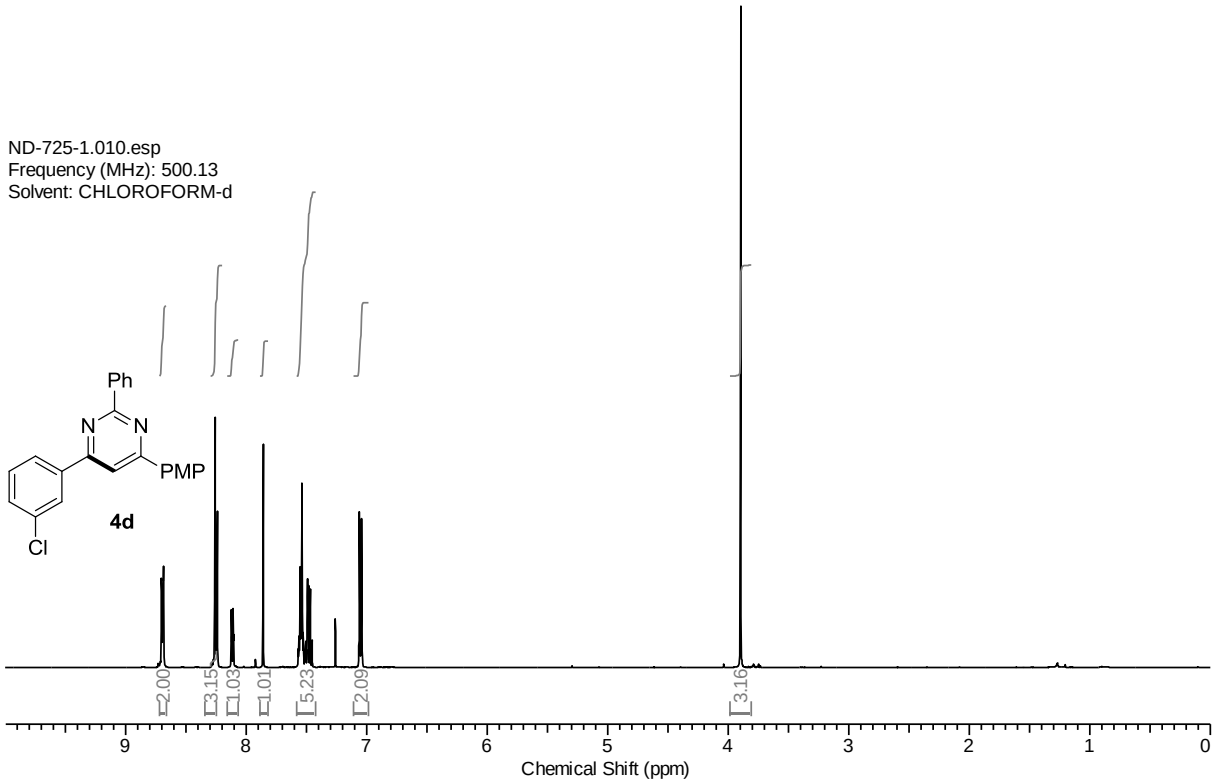
3.07
4.03
6.03
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


164.26
164.06
161.99
138.43
130.63
130.15
128.92
128.52
114.35
108.71
55.59
ND-701-2.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
PMP
4c
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)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PMP
Cl
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3.15
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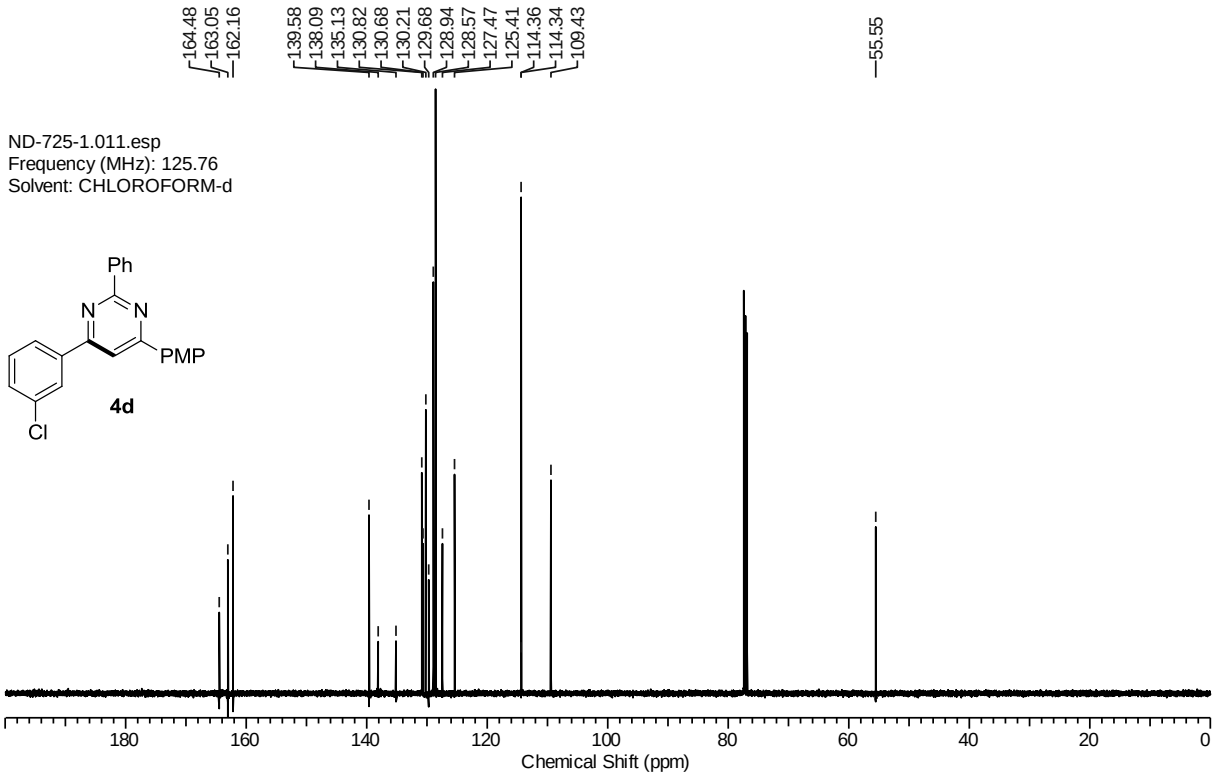
2.09
3.16
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)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139.58
138.09
135.13
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129.68
128.94
128.57
127.47
125.41
114.36
114.34
109.43
55.55
ND-725-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
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N
PMP
Cl
4d
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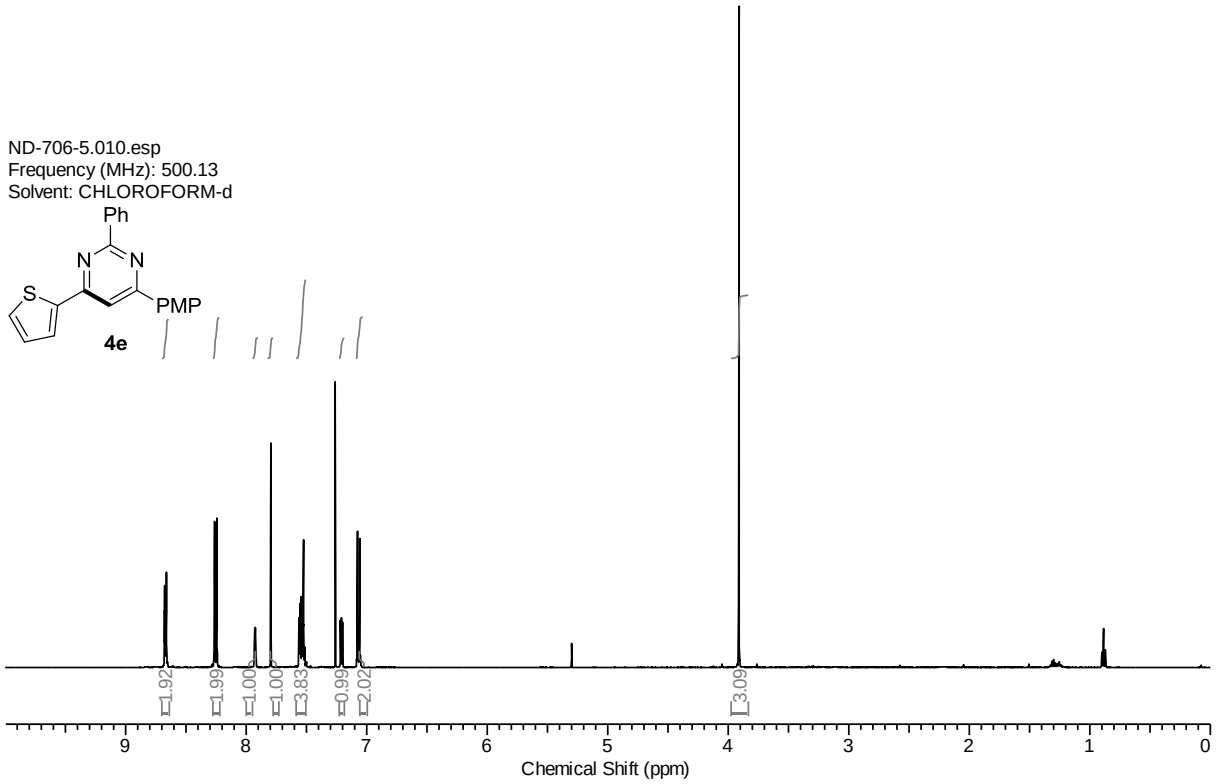
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)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Solvent: CHLOROFORM-d
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N
S
PMP
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1.00
1.00
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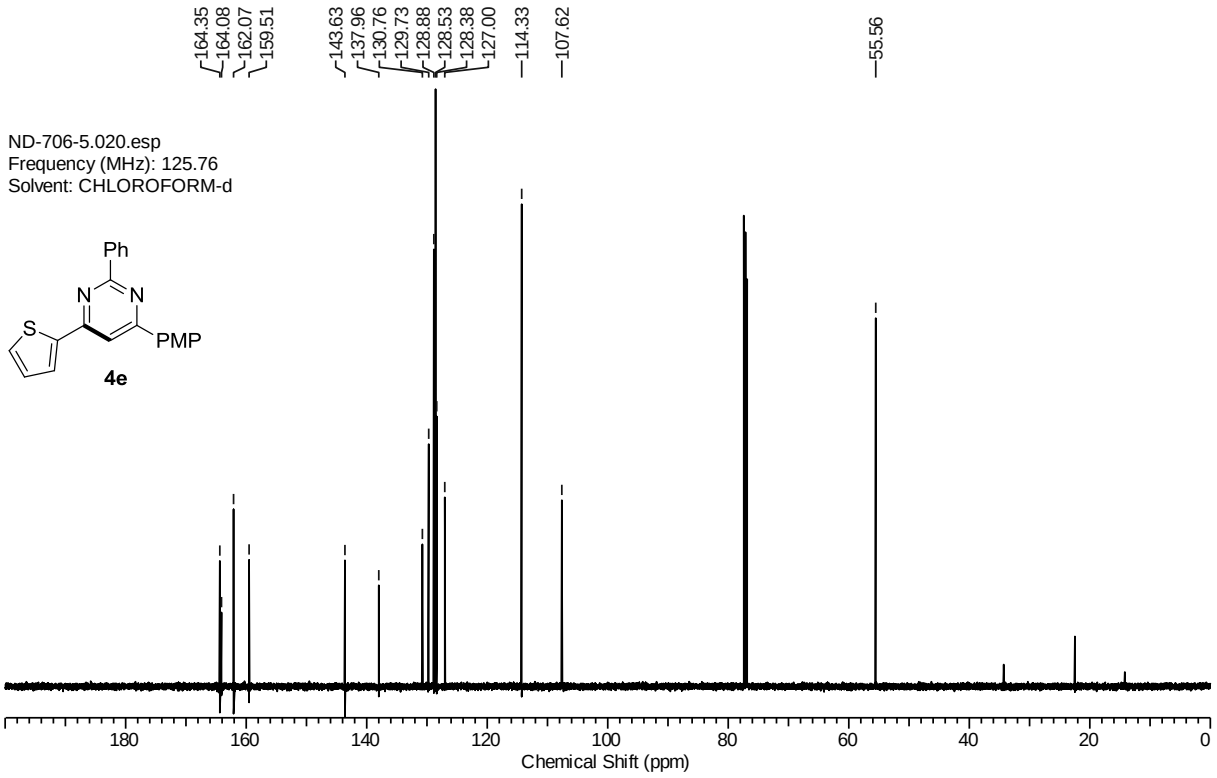
0.99
2.02
3.09
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


164.35
164.08
162.07
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143.63
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128.53
128.38
127.00
114.33
107.62
55.56
ND-706-5.020.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
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N
S
PMP
4e
180
160
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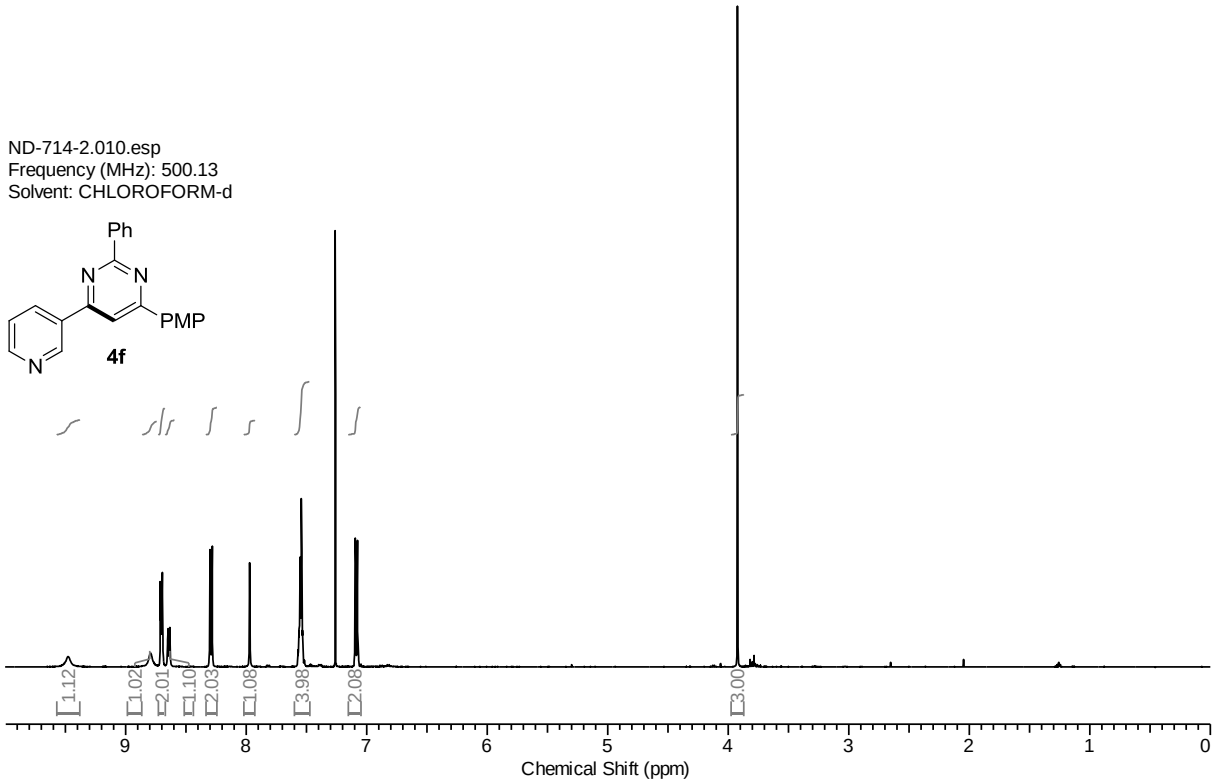
100
80
60
40
20
0
Chemical Shift (ppm)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PMP
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2.01
1.10
2.03
1.08
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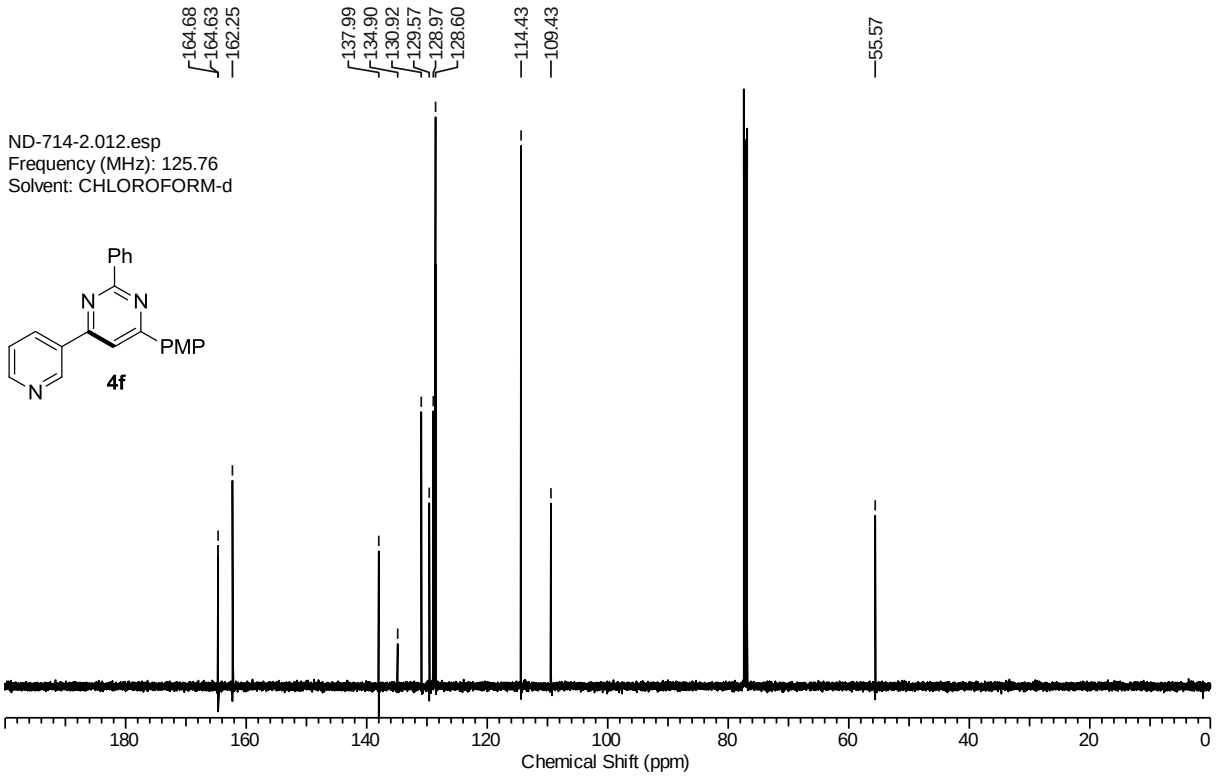
2.08
3.00
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


164.68
164.63
162.25
137.99
134.90
130.92
129.57
128.97
128.60
114.43
109.43
55.57
ND-714-2.012.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
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PMP
N
4f
180
160
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100
80
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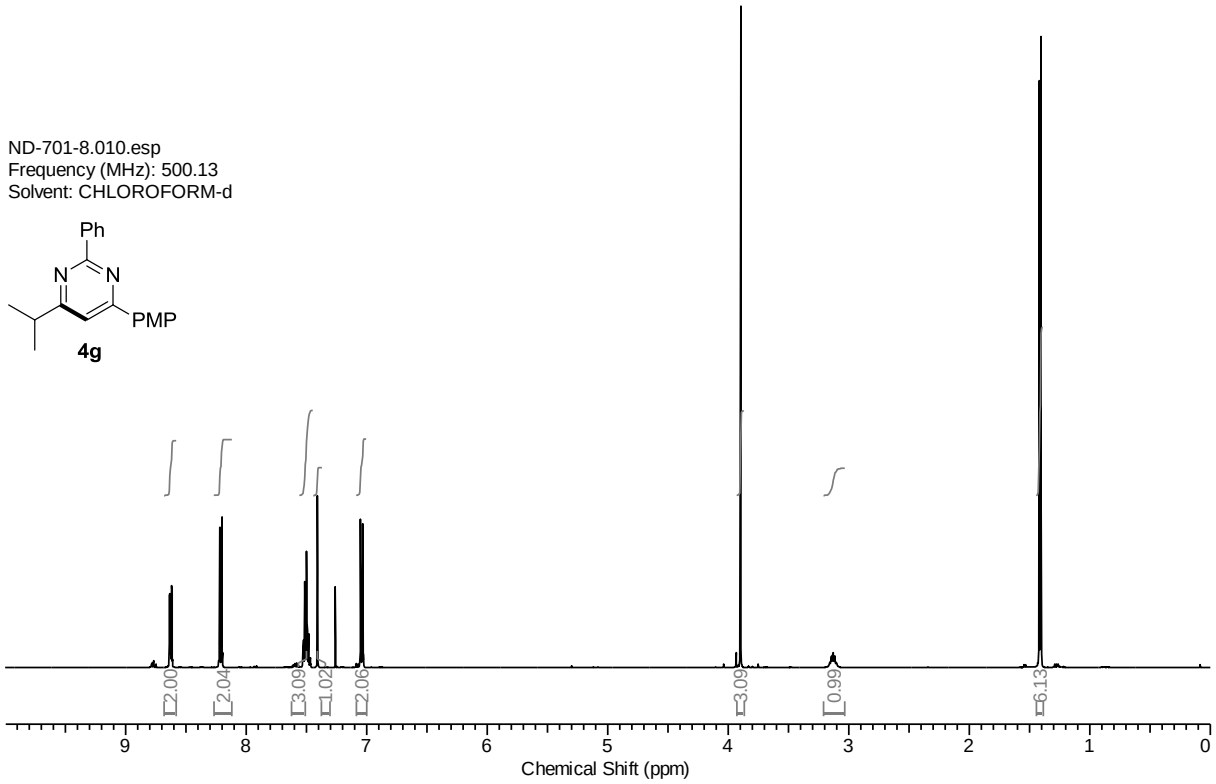
Chemical Shift (ppm)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PMP
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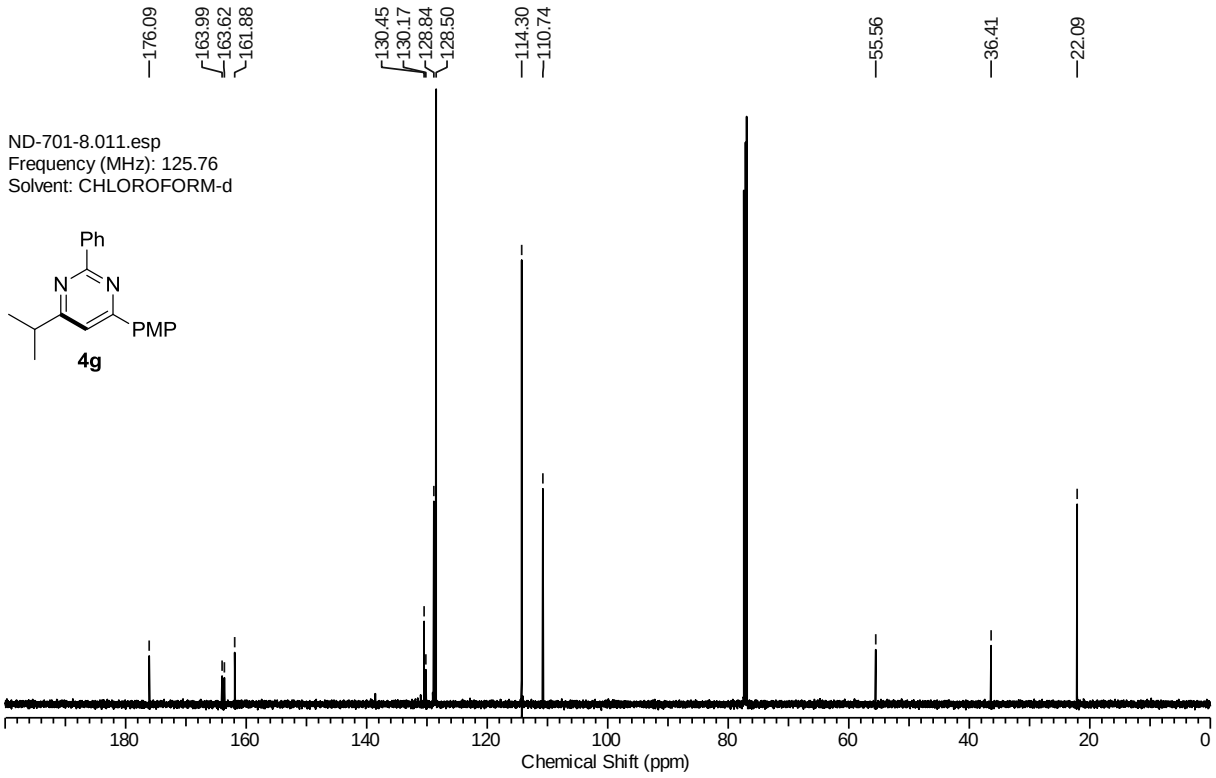
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


176.09
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55.56
36.41
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Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
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N
PMP
4g
180
160
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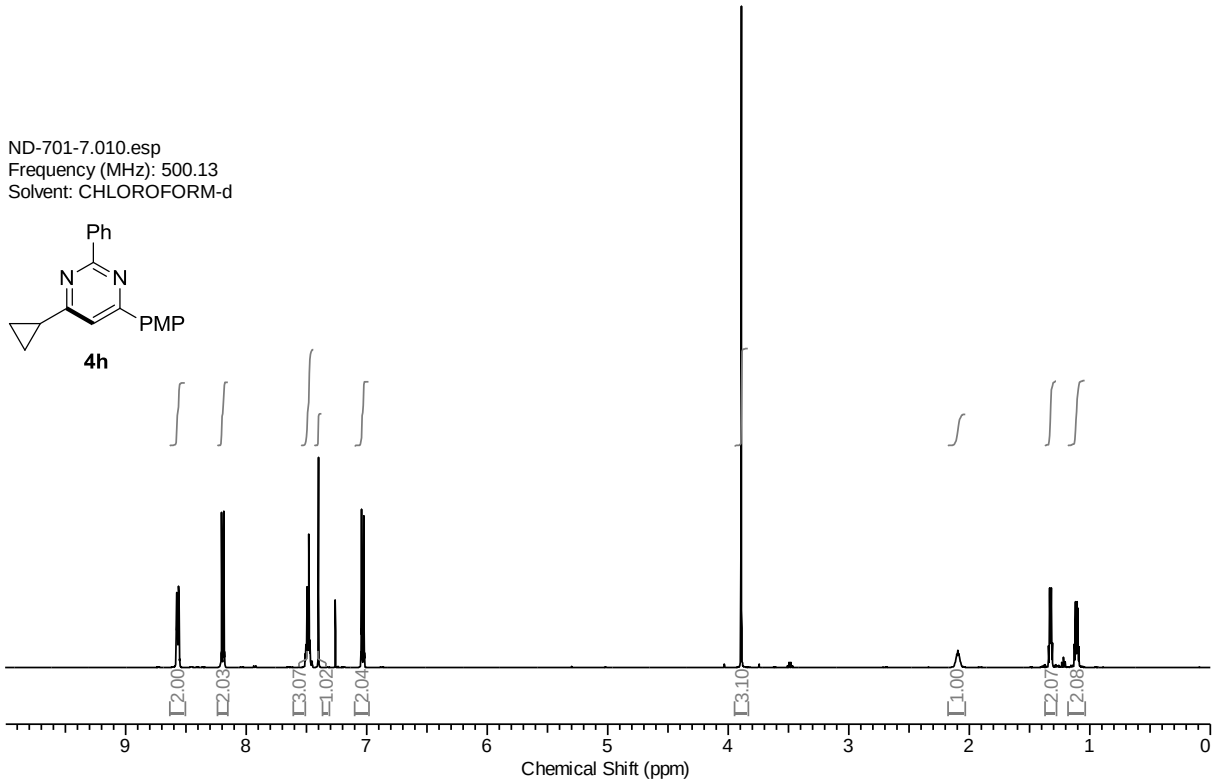
100
80
60
40
20
0
Chemical Shift (ppm)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Solvent: CHLOROFORM-d
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PMP
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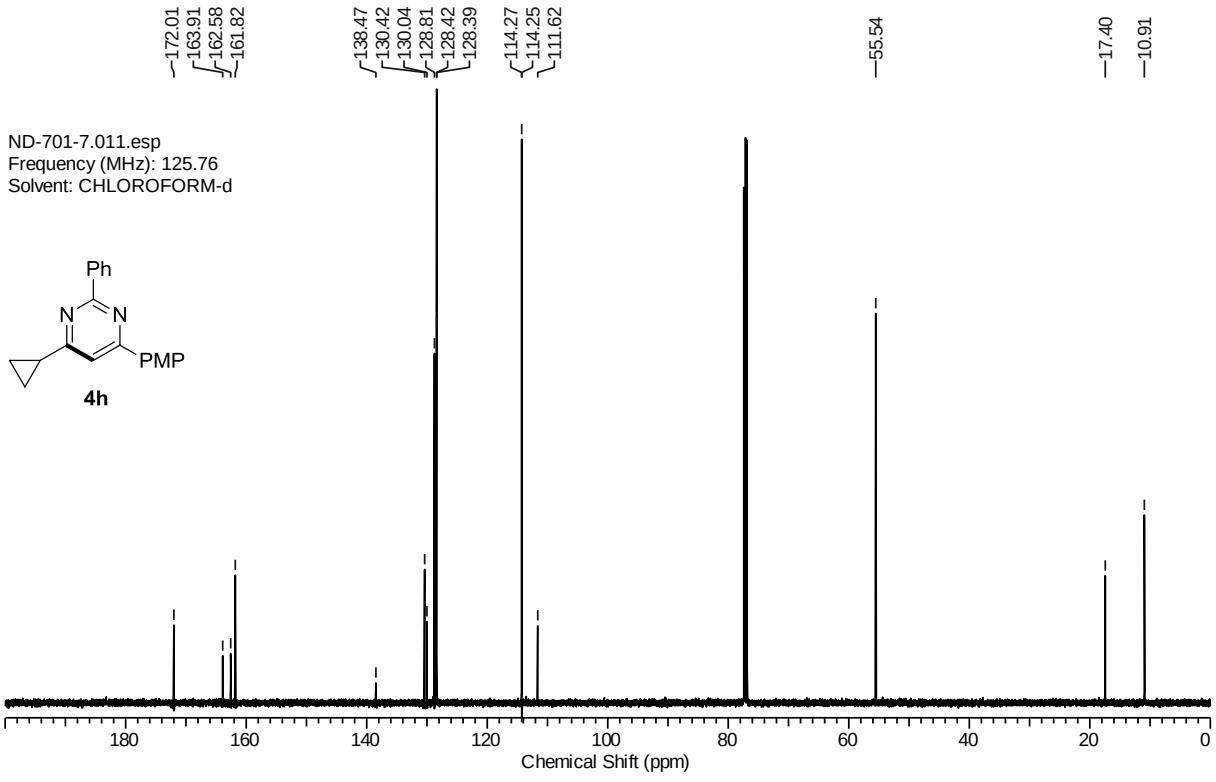
3.07
1.02
2.04
3.10
1.00
2.07
2.08
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


172.01
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161.82
138.47
130.42
130.04
128.81
128.42
128.39
114.27
114.25
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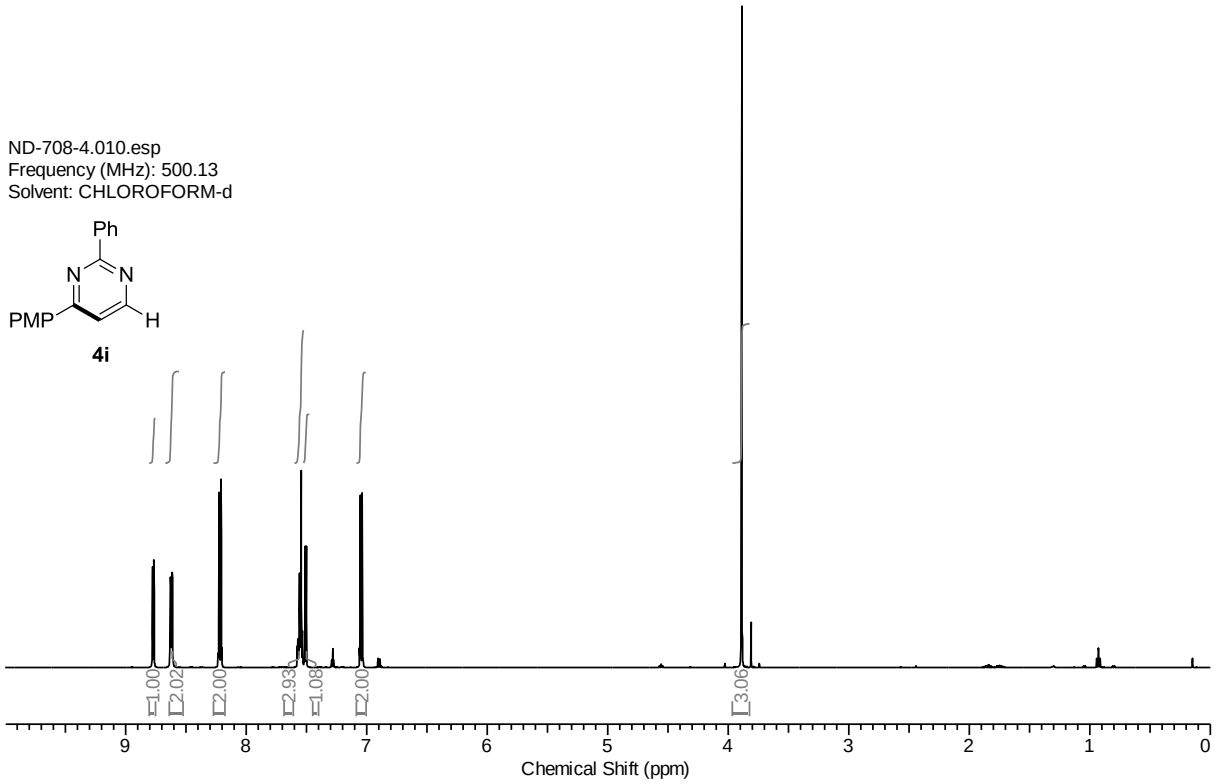
55.54
17.40
10.91
ND-701-7.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4h
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)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PMP
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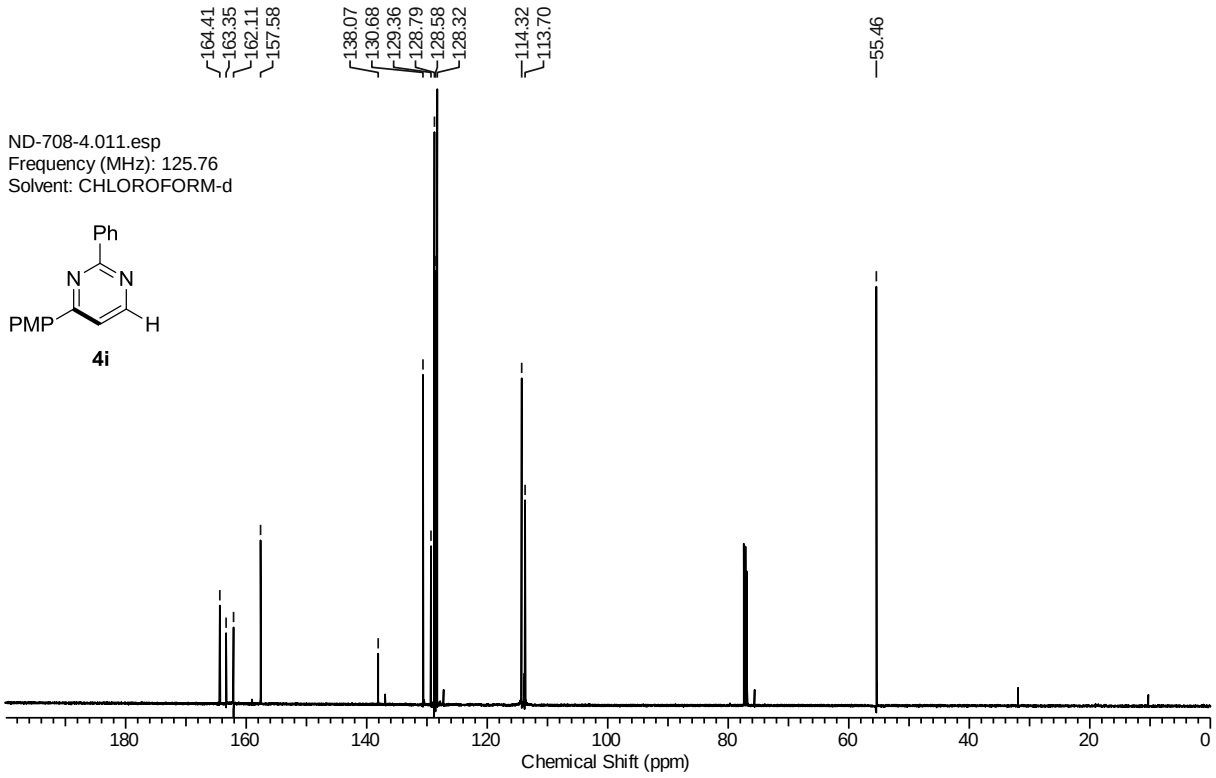
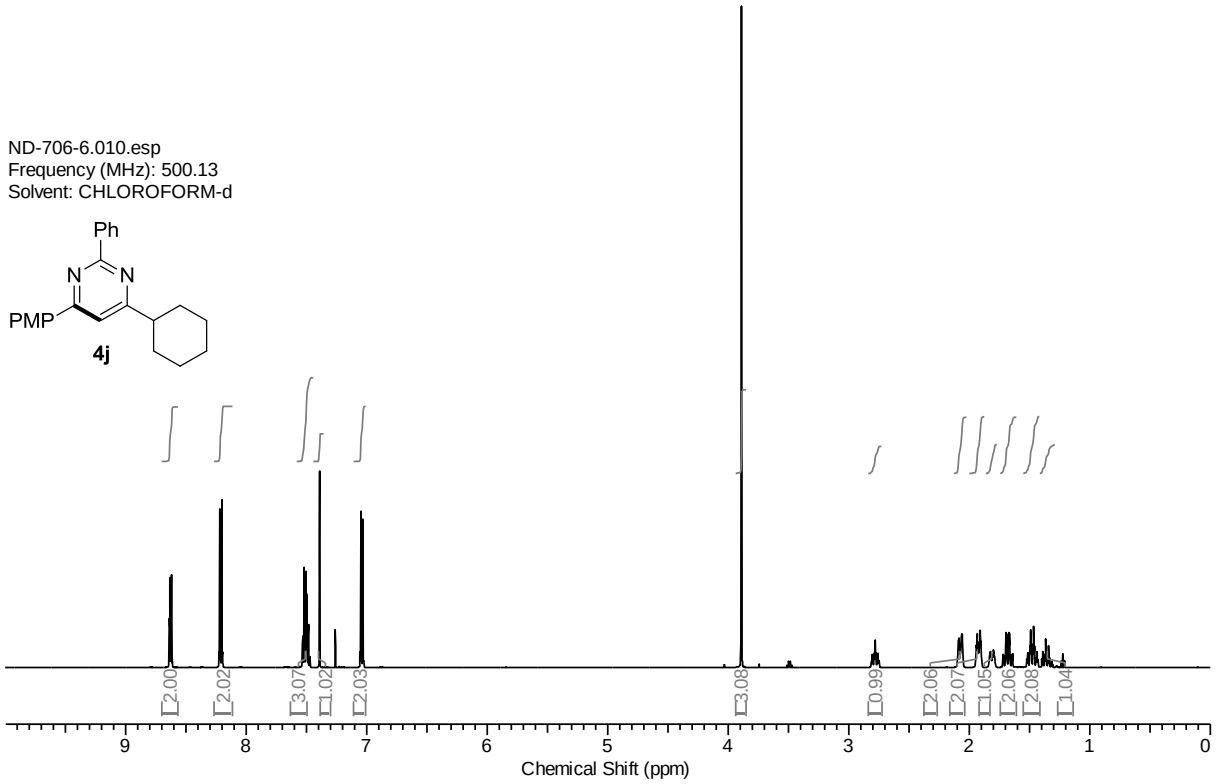
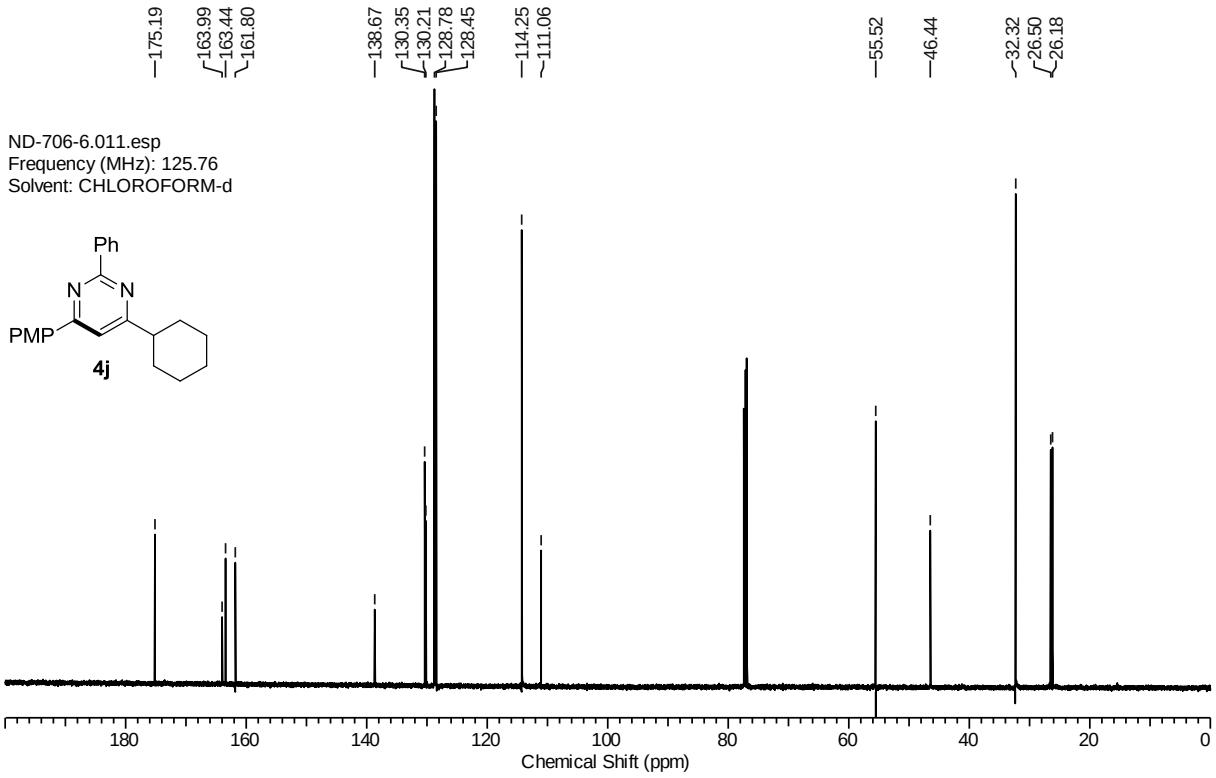
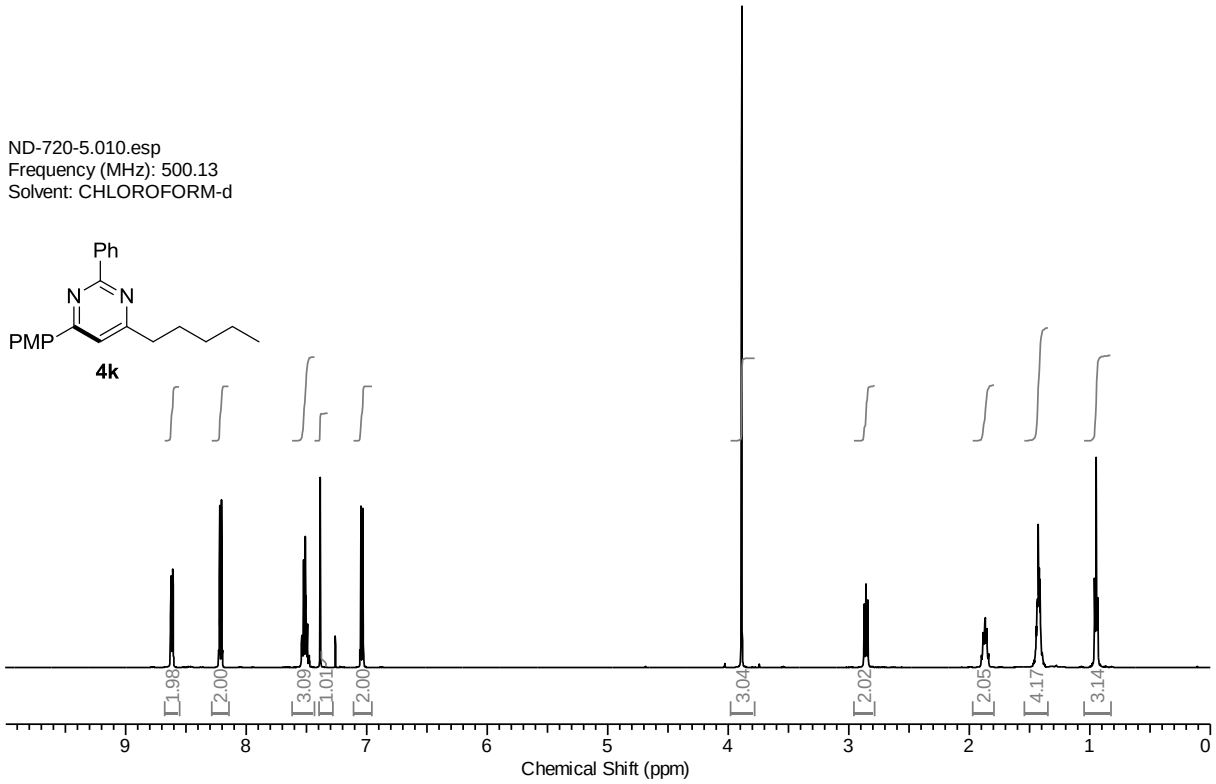
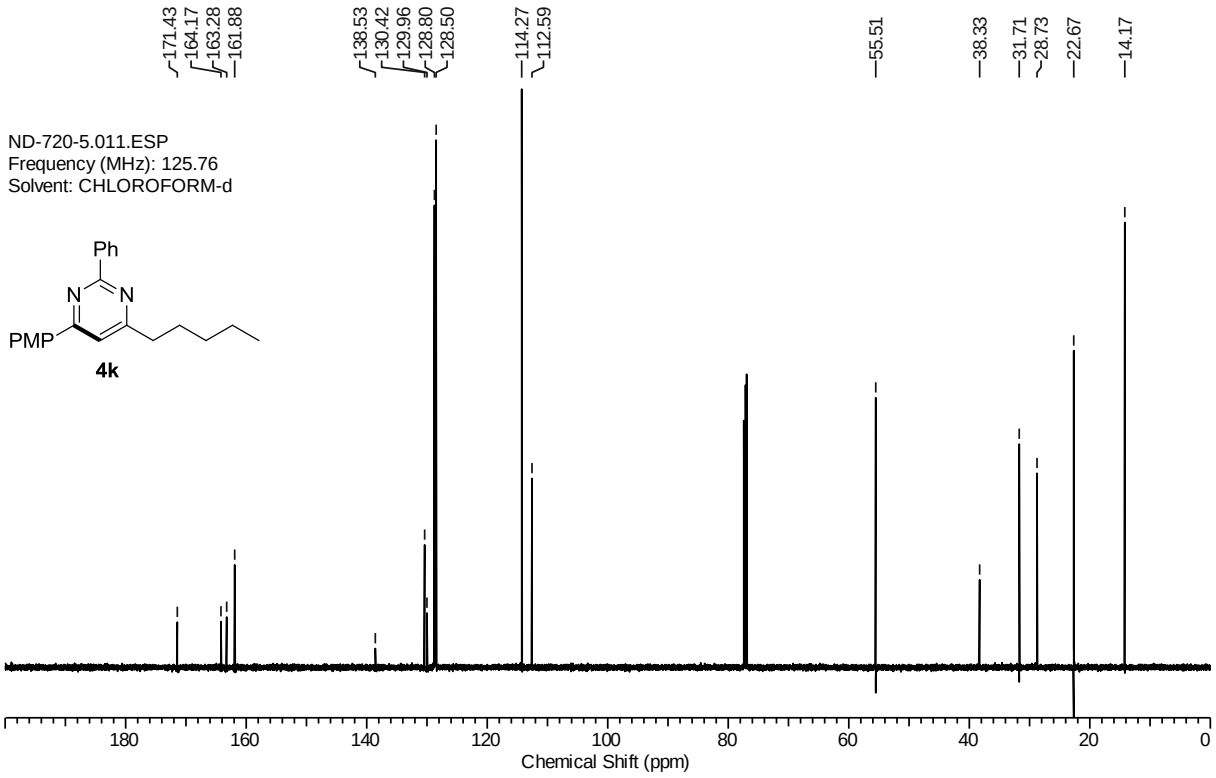
2.93
1.08
2.00
3.06
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

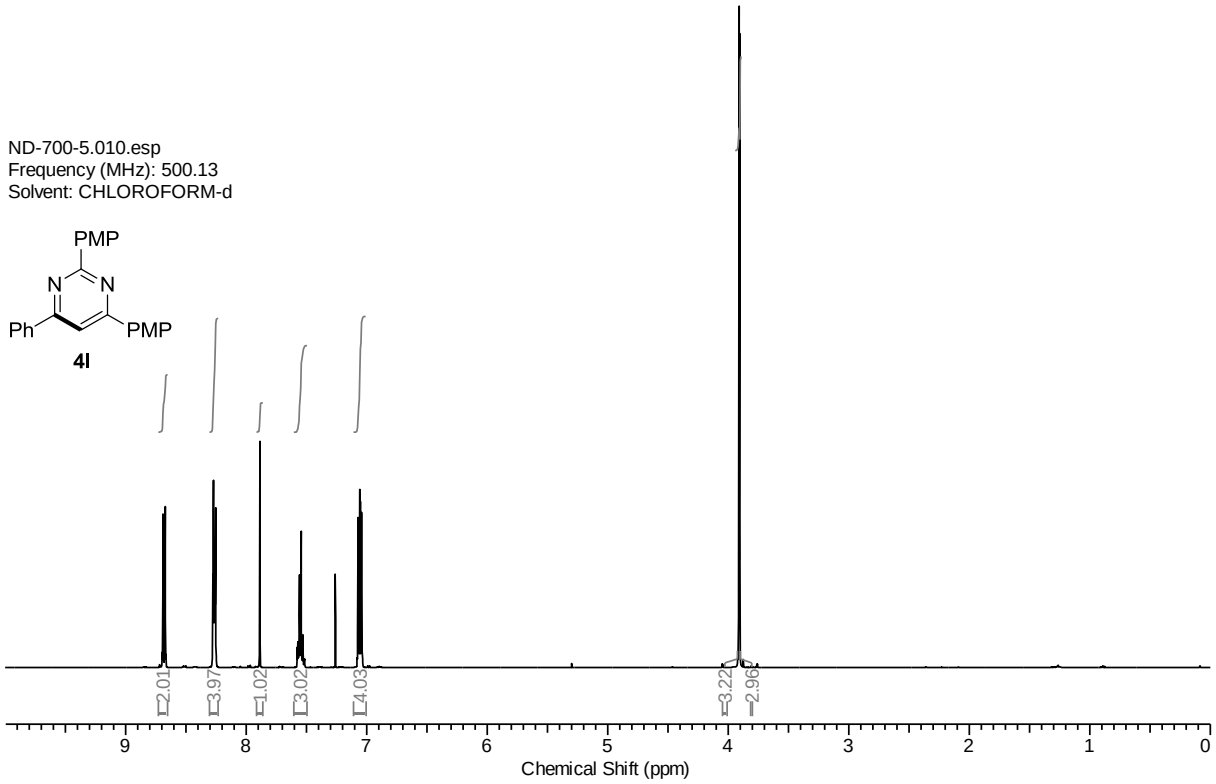

164.41
163.35
162.11
157.58
138.07
130.68
129.36
128.79
128.58
128.32
114.32
113.70
55.46
ND-708-4.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
H
4i
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

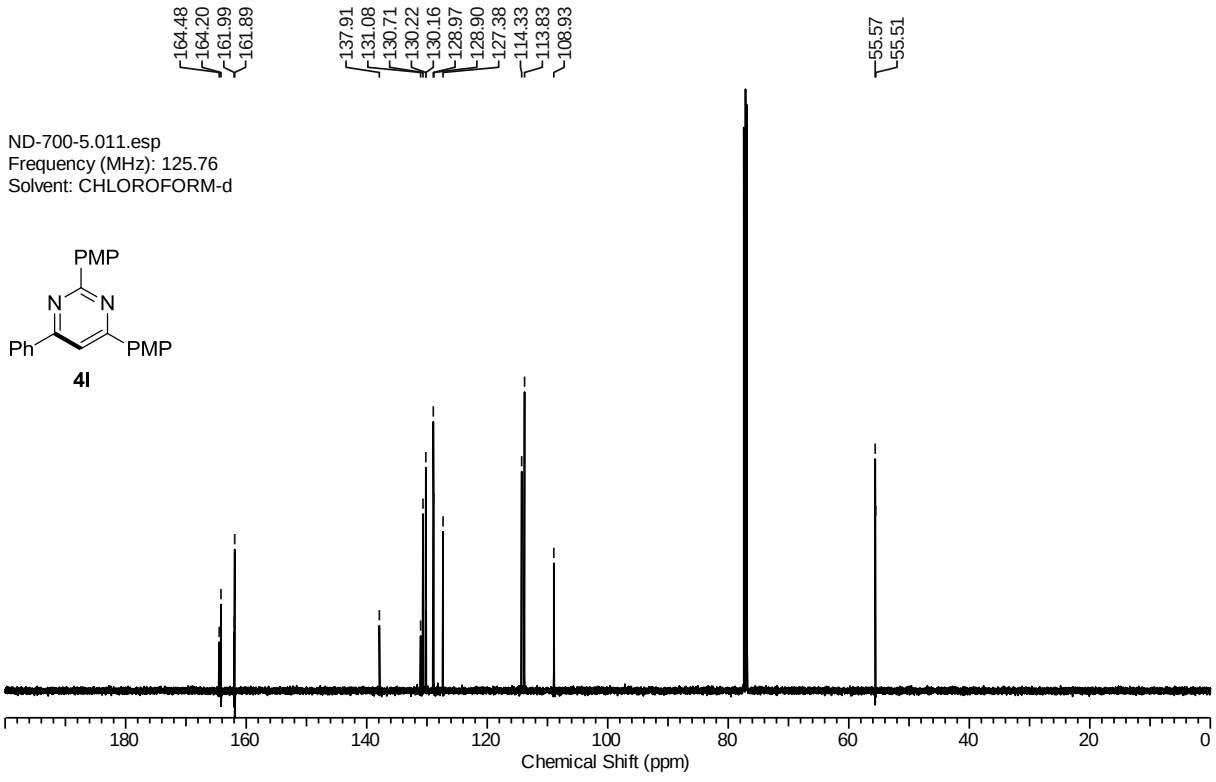

ND-706-6.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4j
2.00
2.02
3.07
1.02
2.03
3.08
0.99
2.06
2.07
1.05
2.06
2.08
1.04
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

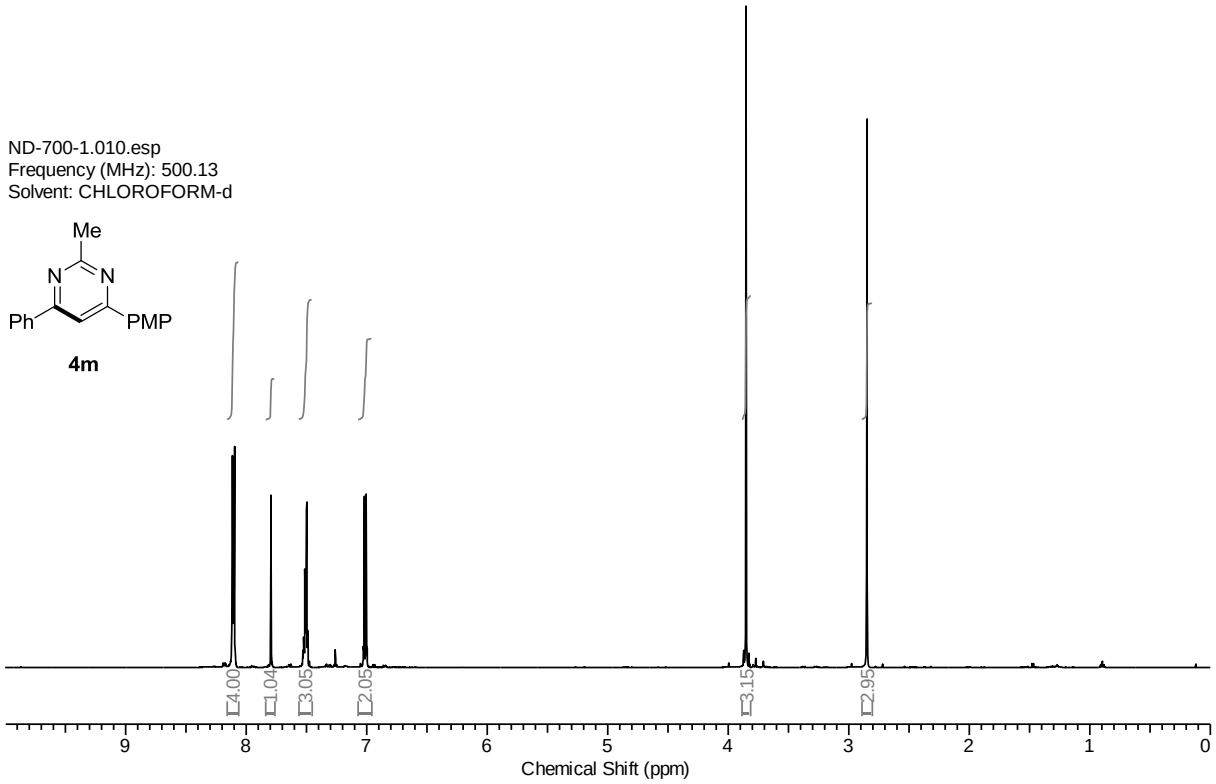

175.19
163.99
163.44
161.80
138.67
130.35
130.21
128.78
128.45
114.25
111.06
55.52
46.44
32.32
26.50
26.18
ND-706-6.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4j
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

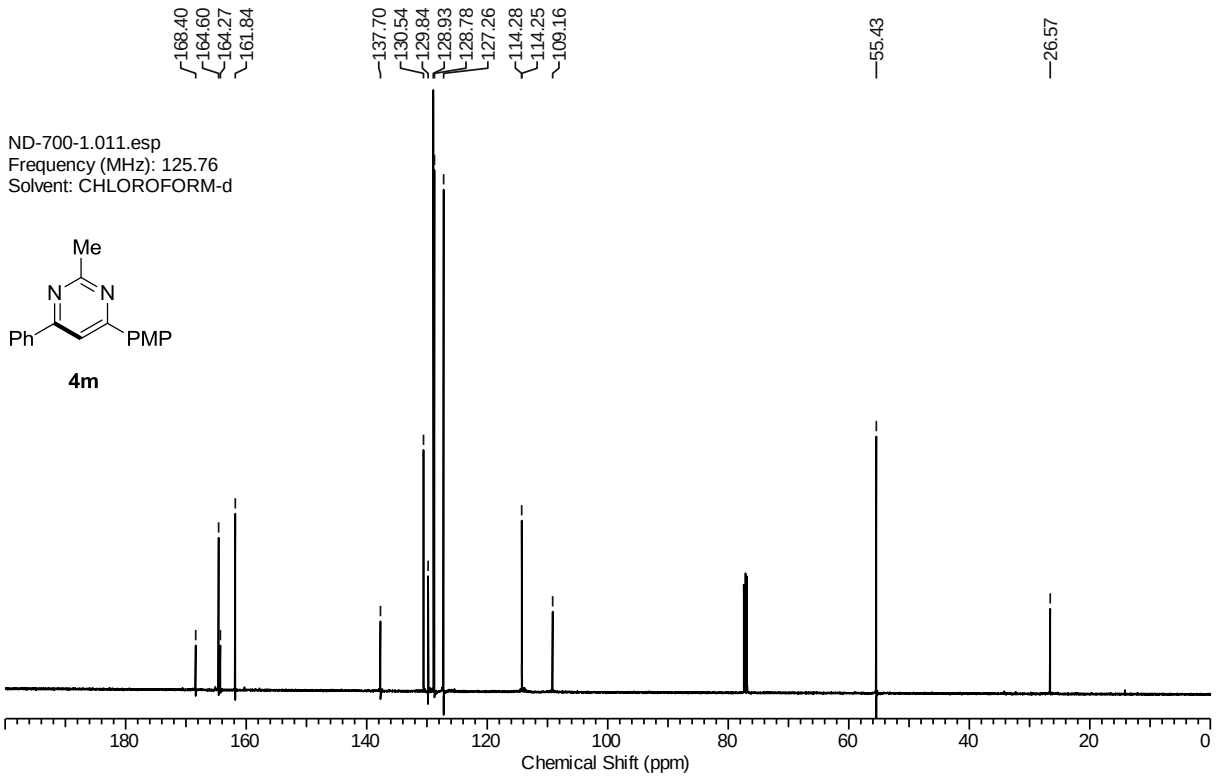

ND-720-5.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4k
1.98
2.00
3.09
1.01
2.00
3.04
2.02
2.05
4.17
3.14
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

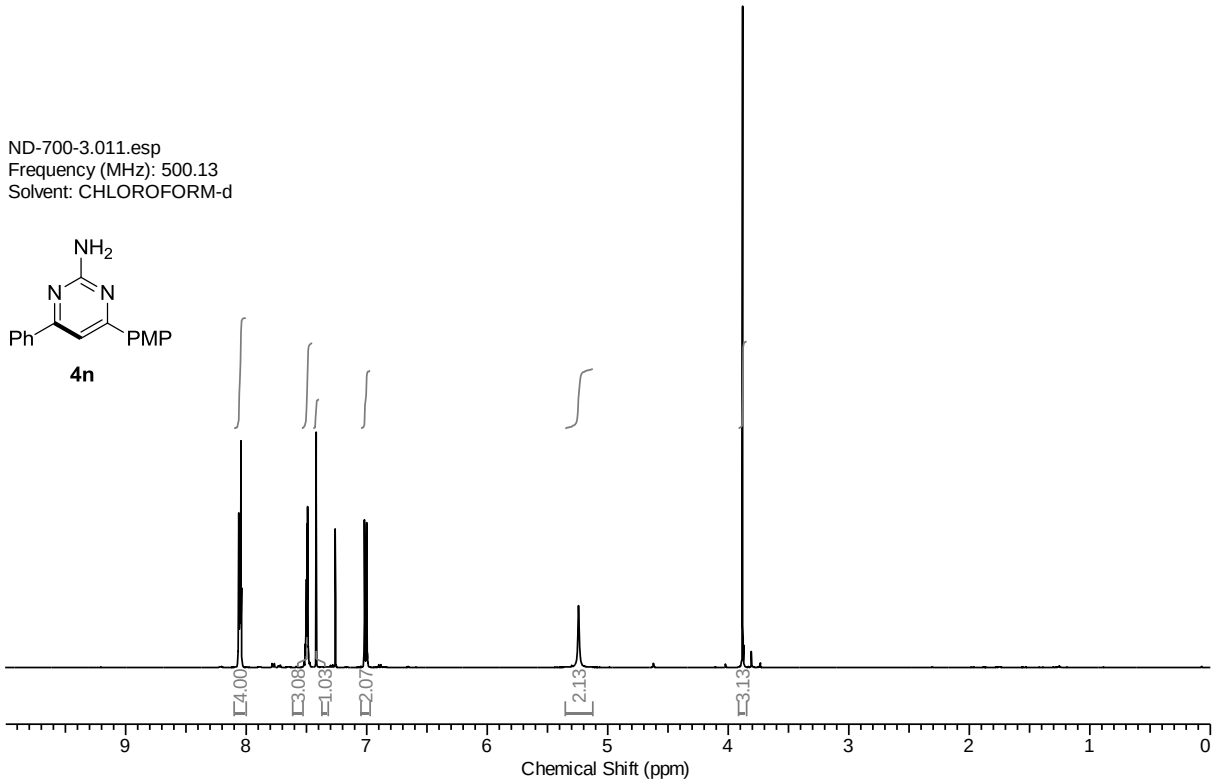

171.43
164.17
163.28
161.88
138.53
130.42
129.96
128.80
128.50
114.27
112.59
55.51
38.33
31.71
28.73
22.67
14.17
ND-720-5.011.ESP
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
4k
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

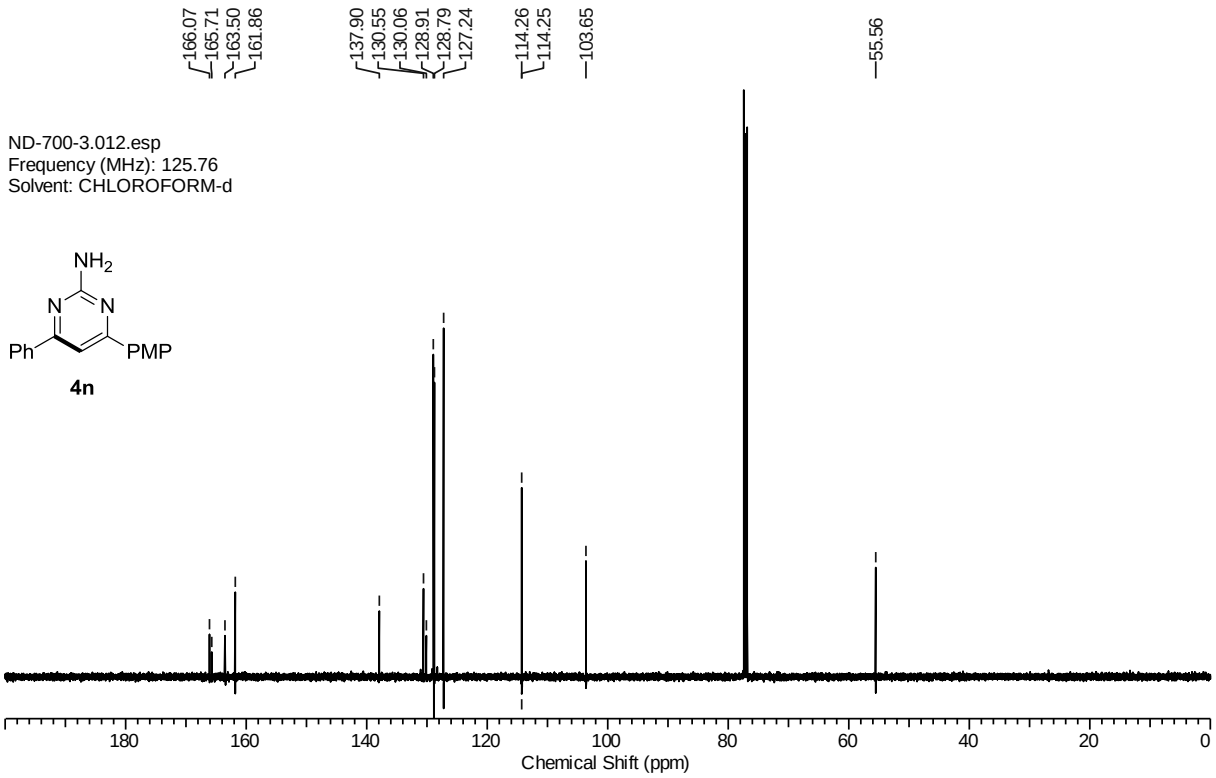

ND-700-5.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
PMP
N
N
Ph
PMP
4l
2.01
3.97
1.02
3.02
4.03
3.22
2.96
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

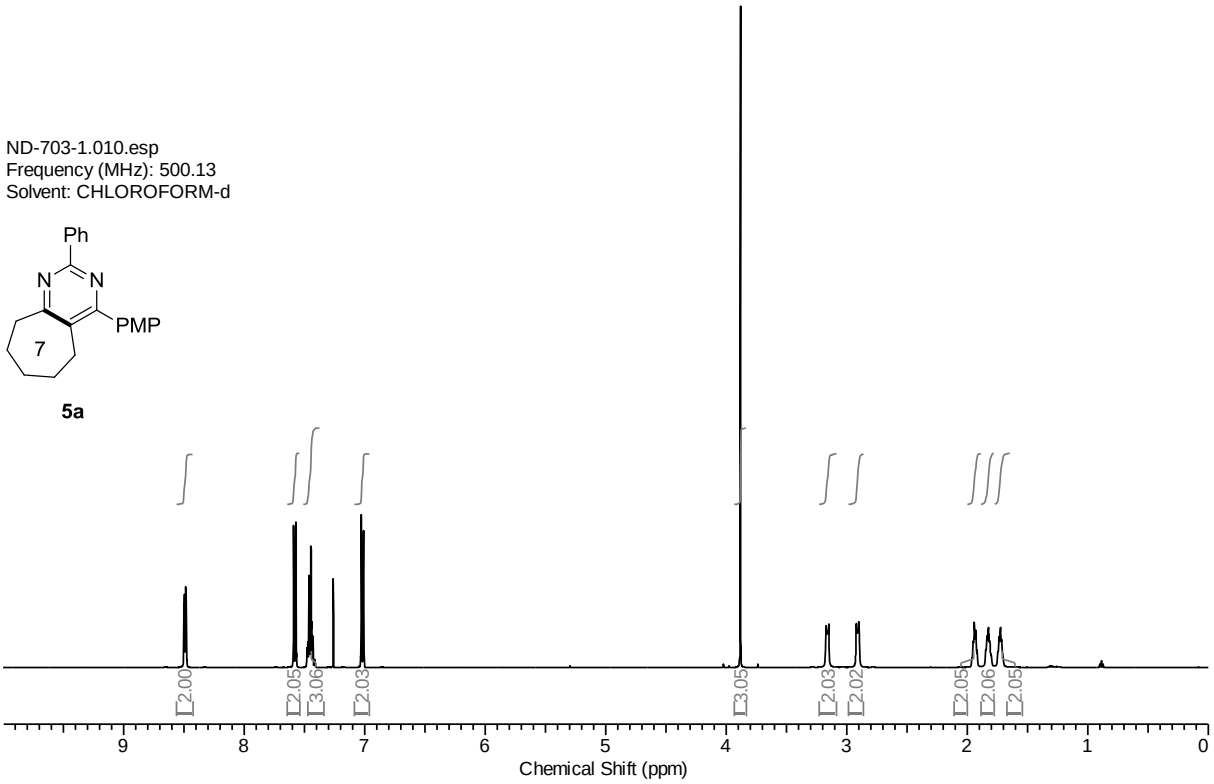

164.48
164.20
161.99
161.89
137.91
131.08
130.71
130.22
130.16
128.97
128.90
127.38
114.33
113.83
108.93
55.57
55.51
ND-700-5.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
PMP
N
N
Ph
PMP
4l
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

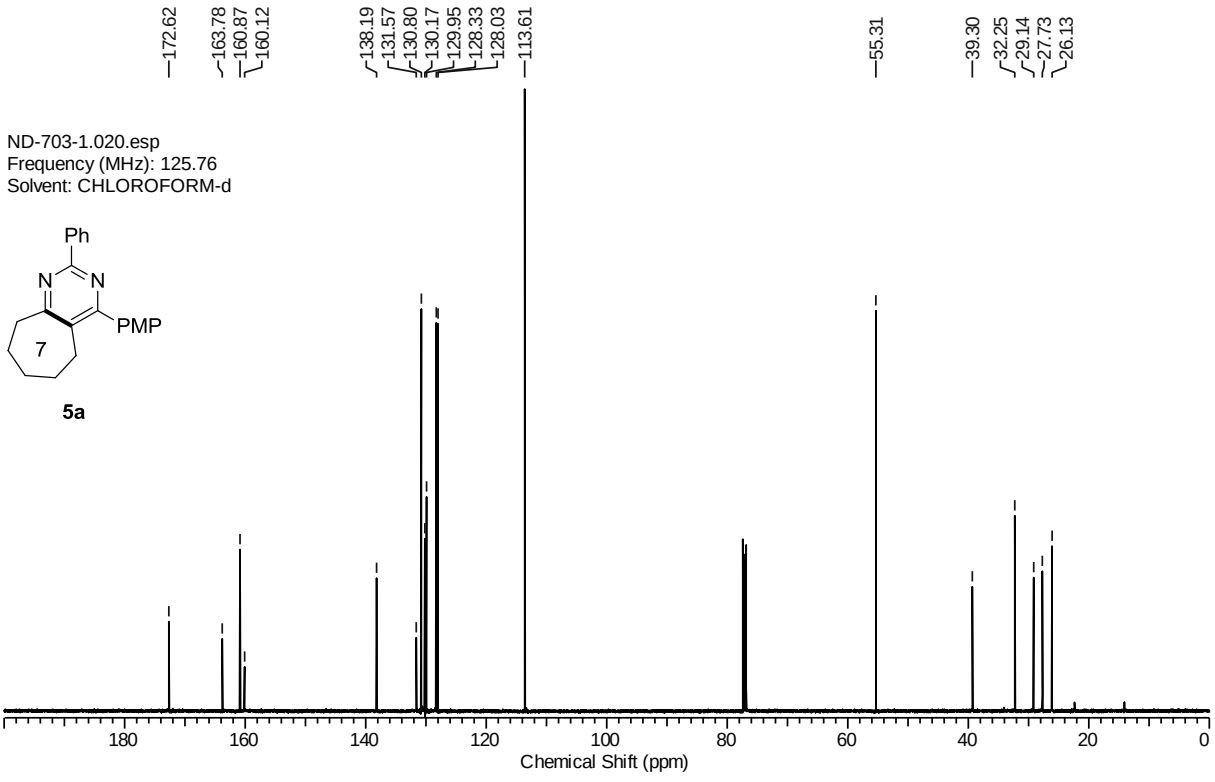

ND-700-1.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Me
N
N
Ph
PMP
4m
4.00
1.04
3.05
2.05
3.15
2.95
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

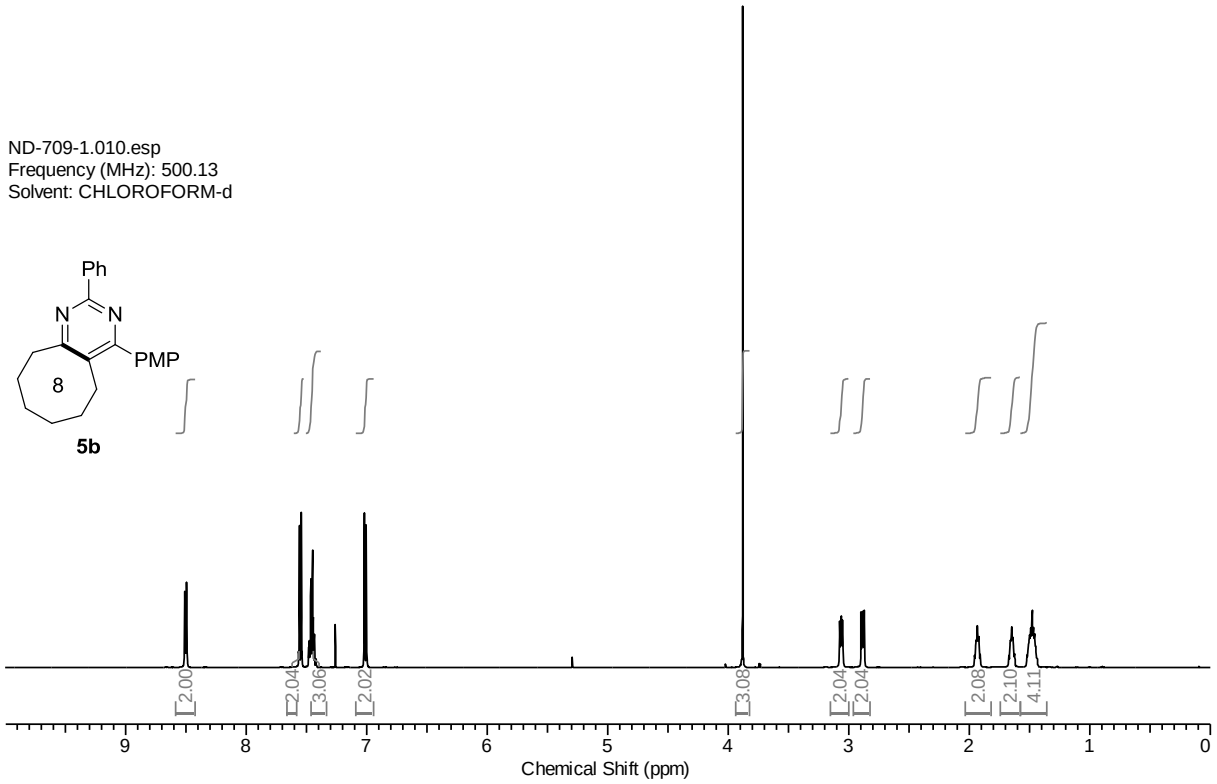

168.40
164.60
164.27
161.84
137.70
130.54
129.84
128.93
128.78
127.26
114.28
114.25
109.16
55.43
26.57
ND-700-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Me
N
N
Ph
PMP
4m
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

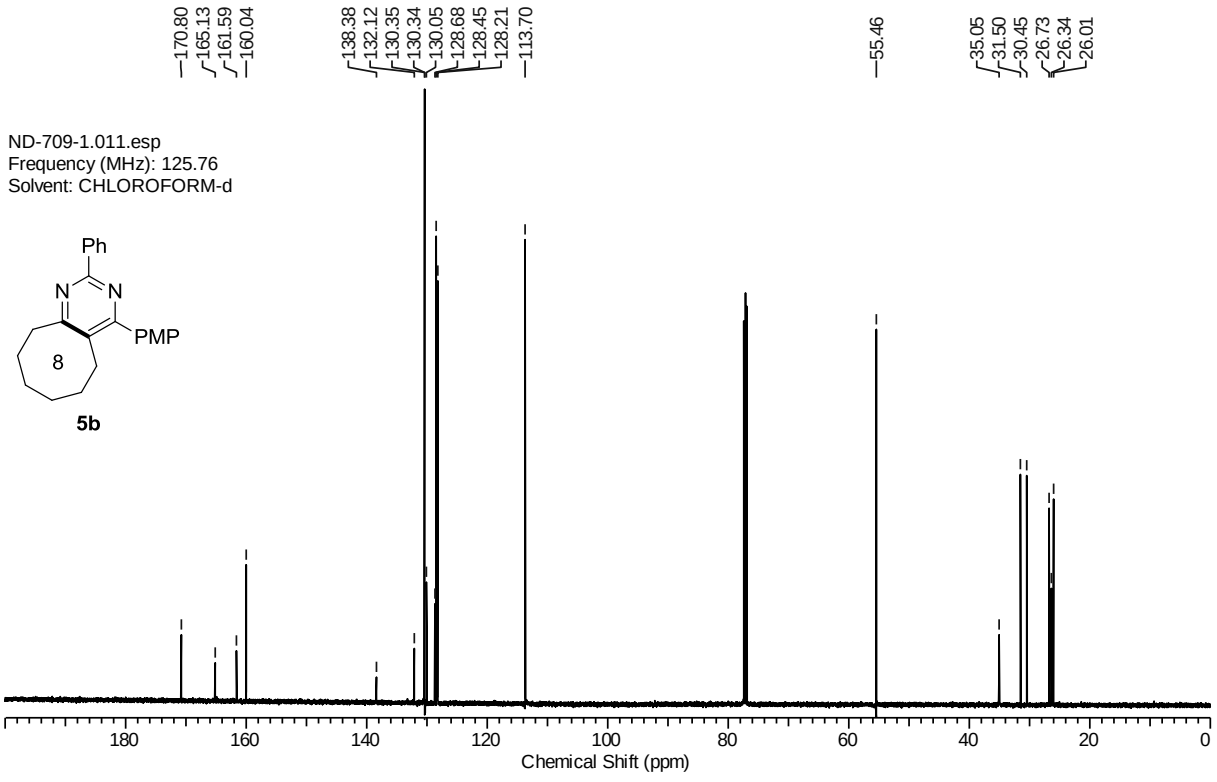

ND-700-3.011.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
NH2
N
N
Ph
PMP
4n
4.00
3.08
1.03
2.07
2.13
3.13
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

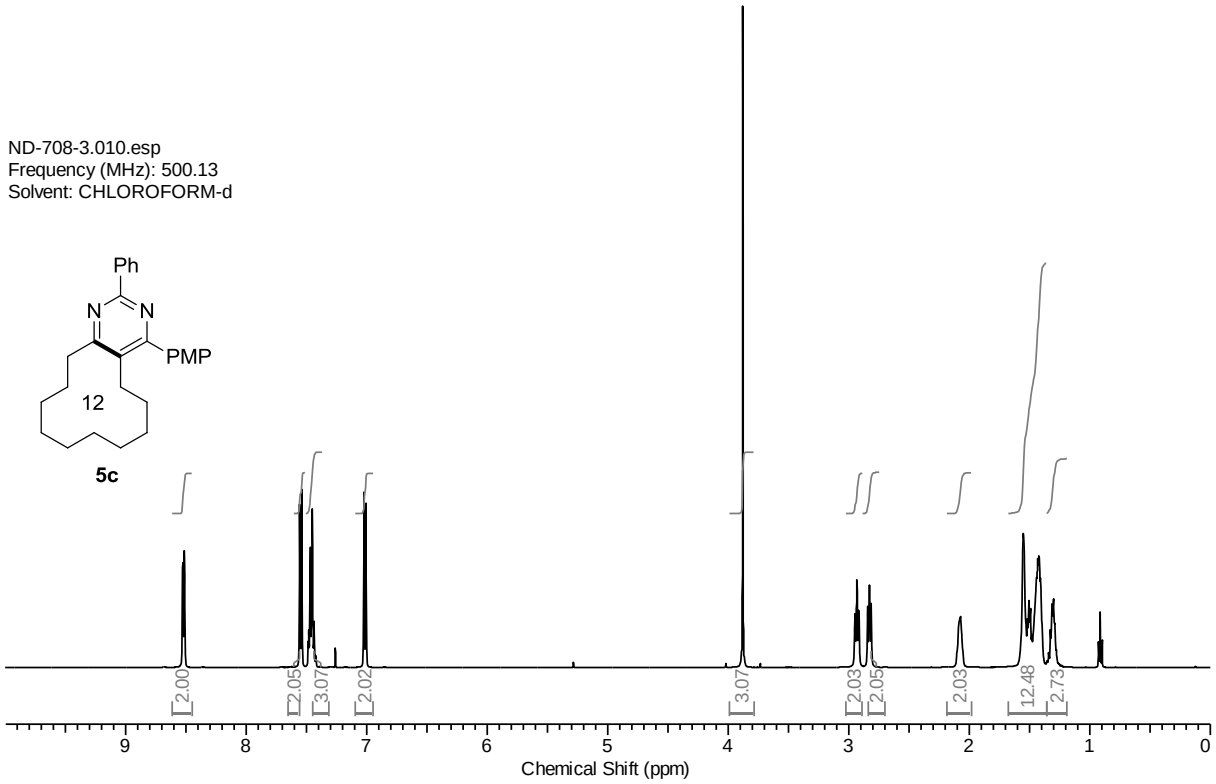

166.07
165.71
163.50
161.86
137.90
130.55
130.06
128.91
128.79
127.24
114.26
114.25
103.65
55.56
ND-700-3.012.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
NH2
N
N
Ph
PMP
4n
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

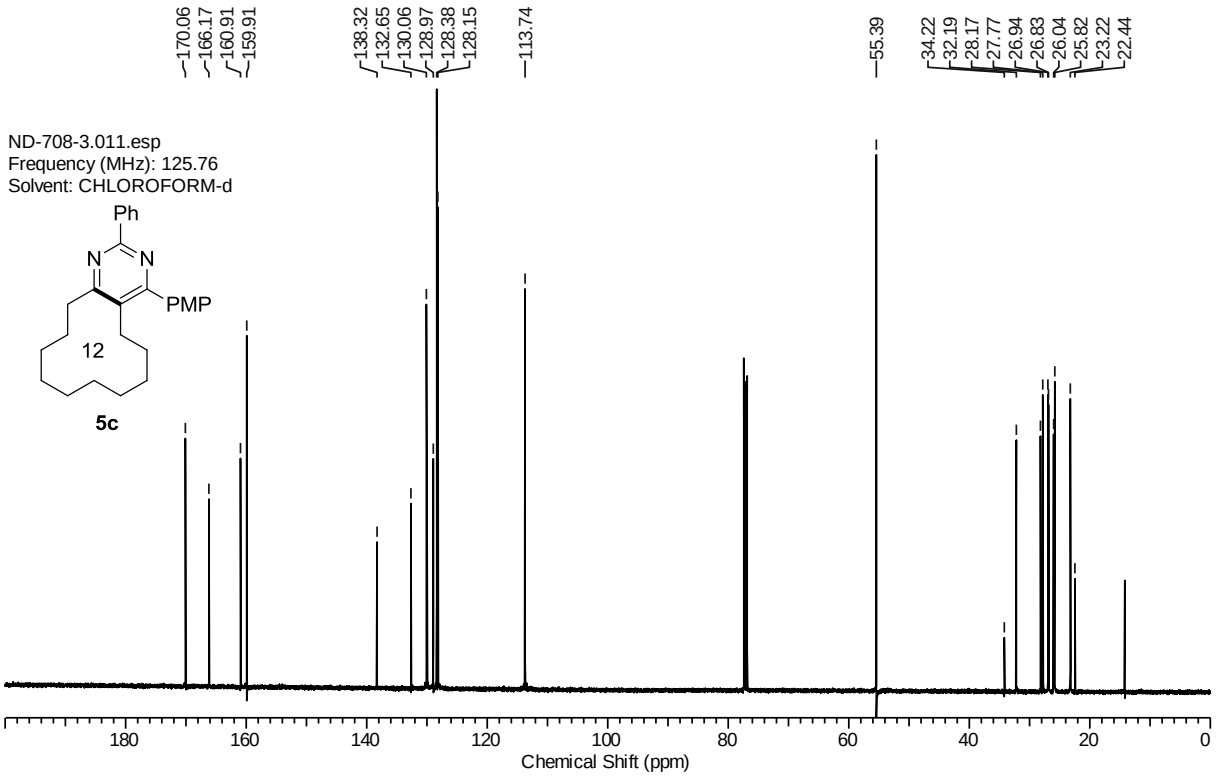

ND-703-1.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
7
5a
2.00
2.05
3.06
2.03
3.05
2.03
2.02
2.05
2.06
2.05
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

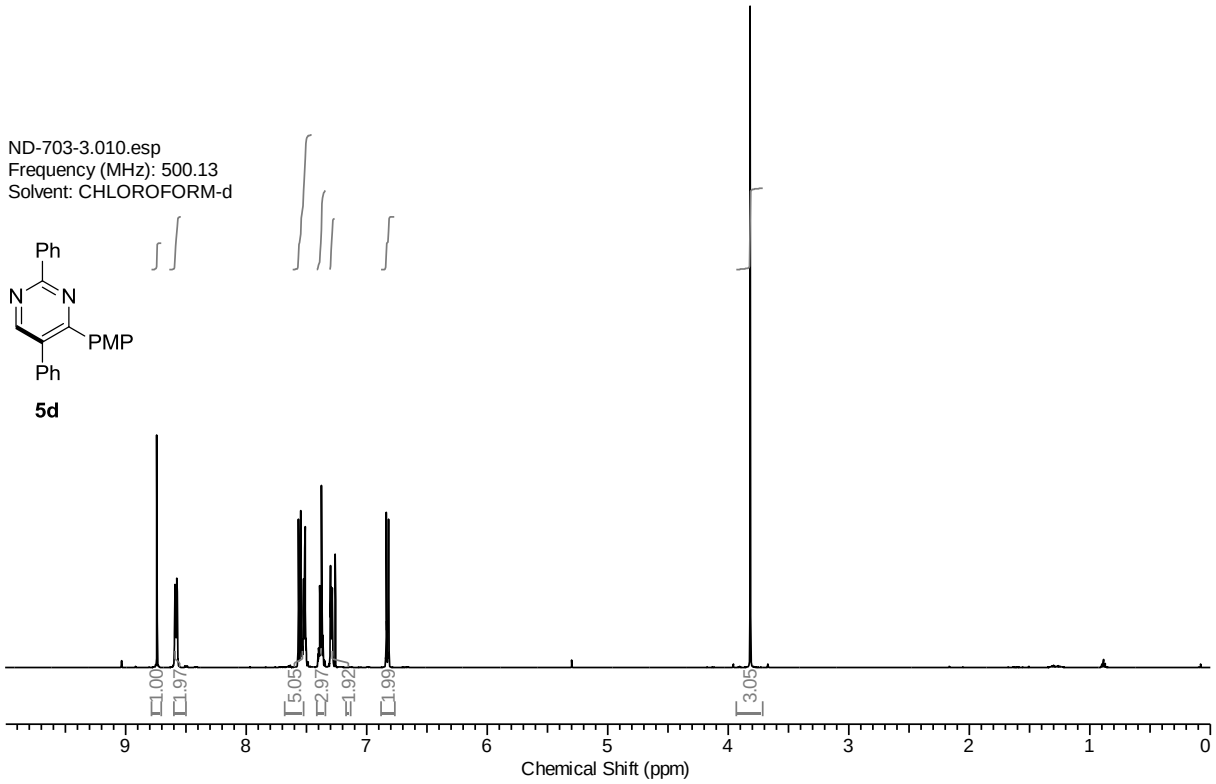

172.62
163.78
160.87
160.12
138.19
131.57
130.80
130.17
129.95
128.33
128.03
113.61
55.31
39.30
32.25
29.14
27.73
26.13
ND-703-1.020.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
7
5a
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

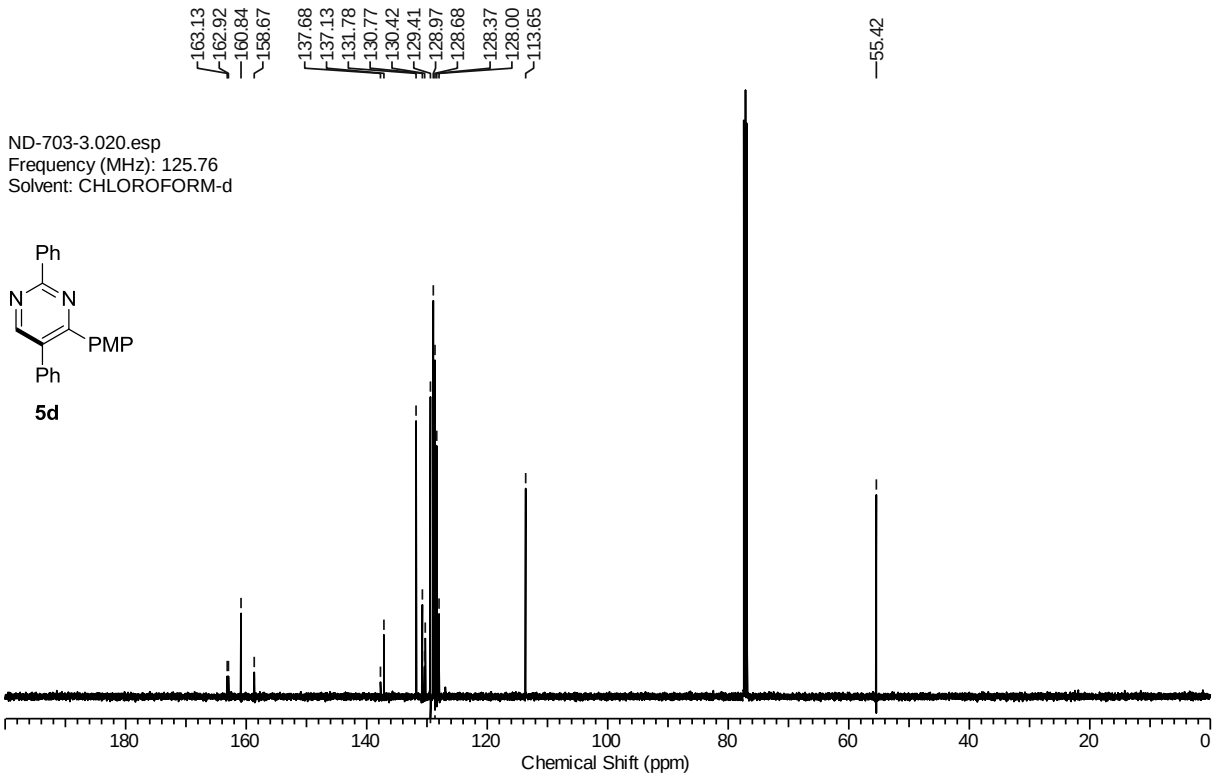

ND-709-1.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
8
5b
2.00
2.04
3.06
2.02
3.08
2.04
2.04
2.08
2.10
4.11
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

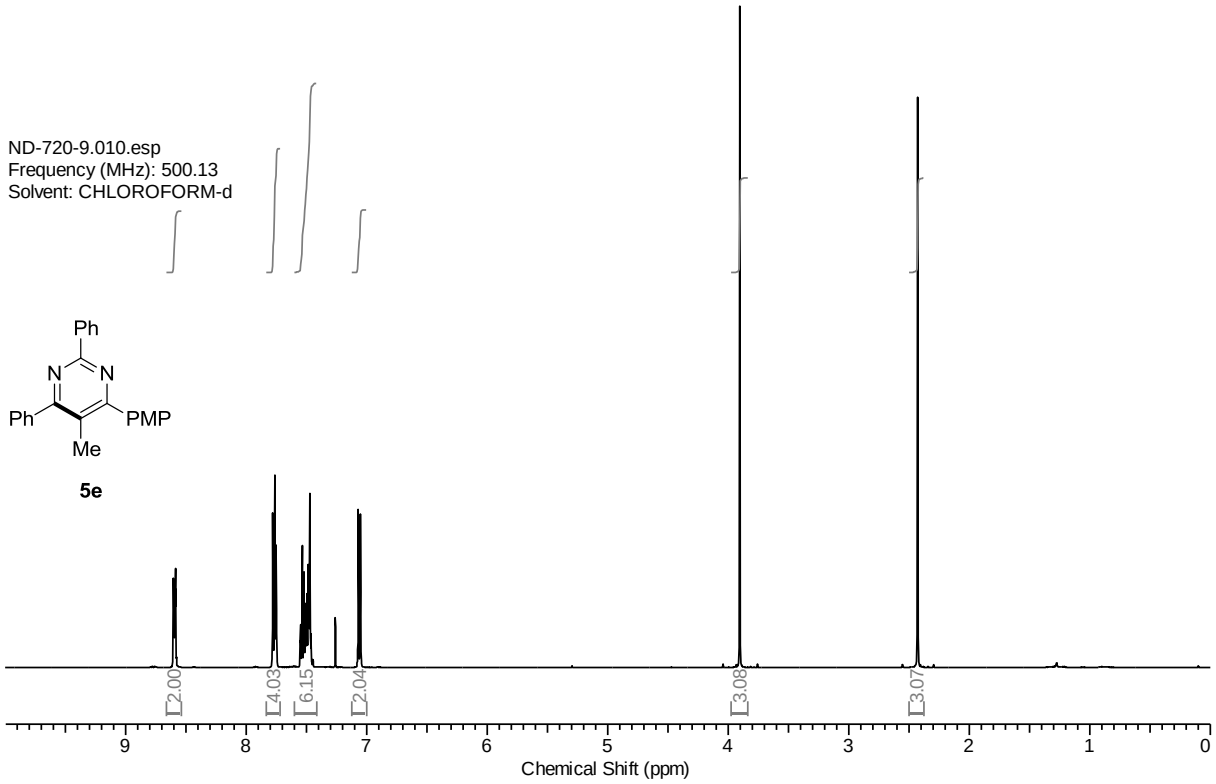

170.80
165.13
161.59
160.04
138.38
132.12
130.35
130.34
130.05
128.68
128.45
128.21
113.70
55.46
35.05
31.50
30.45
26.73
26.34
26.01
ND-709-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
8
5b
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

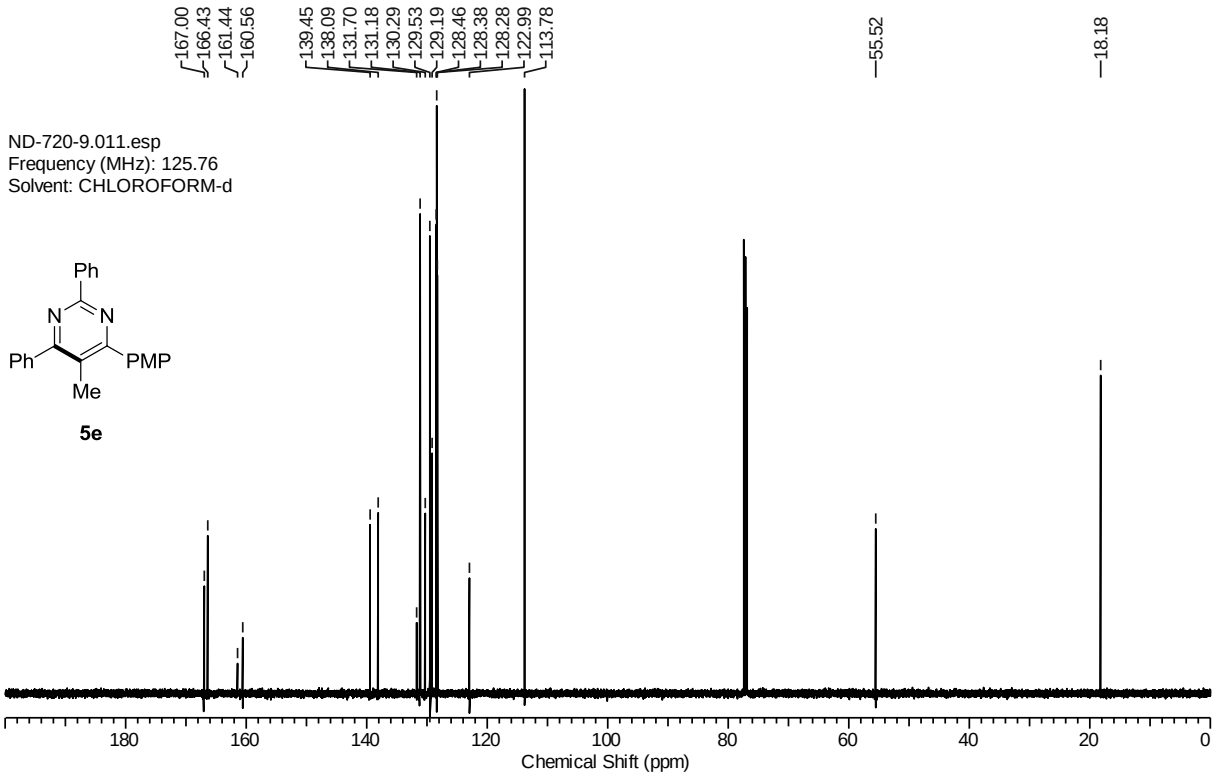

ND-708-3.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
12
5c
2.00
2.05
3.07
2.02
3.07
2.03
2.05
2.03
12.48
2.73
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

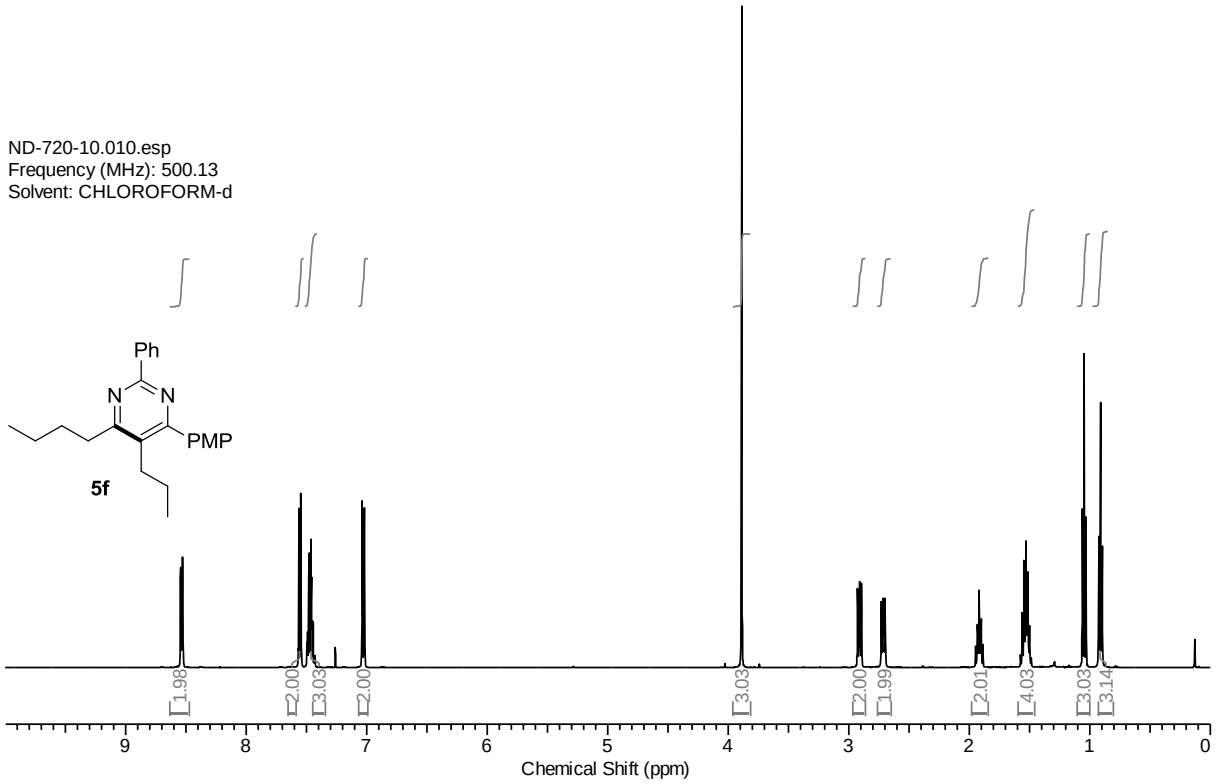

170.06
166.17
160.91
159.91
138.32
132.65
130.06
128.97
128.38
128.15
113.74
55.39
34.22
32.19
28.17
27.77
26.94
26.83
26.04
25.82
23.22
22.44
ND-708-3.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
12
5c
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

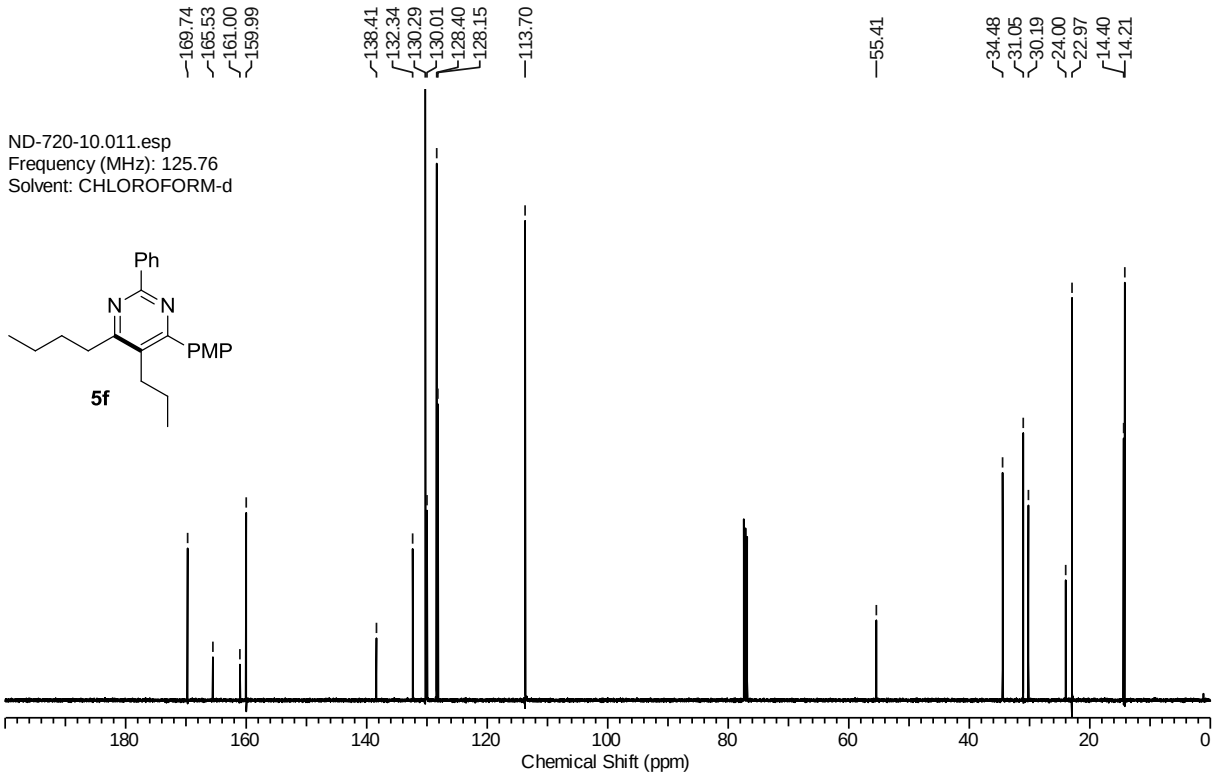

ND-703-3.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
Ph
5d
1.00
1.97
5.05
2.97
1.92
1.99
3.05
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

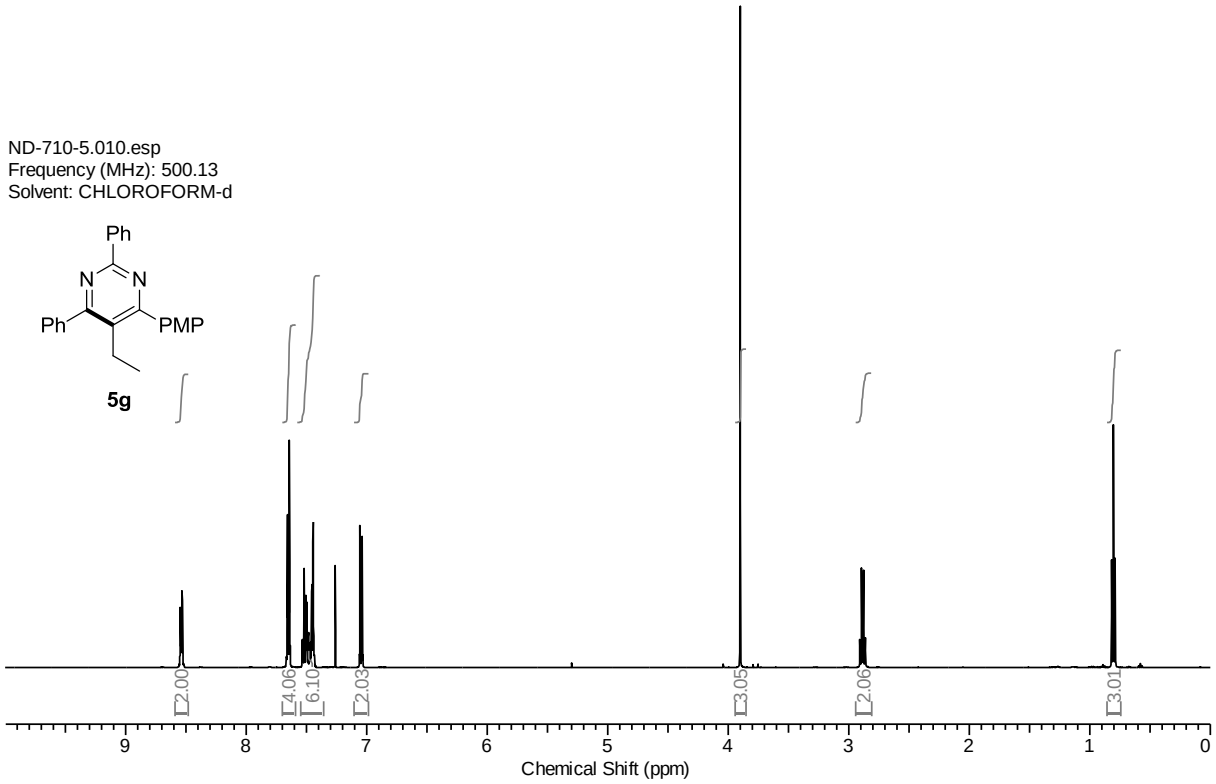

163.13
162.92
160.84
158.67
137.68
137.13
131.78
130.77
130.42
129.41
128.97
128.68
128.37
128.00
113.65
55.42
ND-703-3.020.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
Ph
5d
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

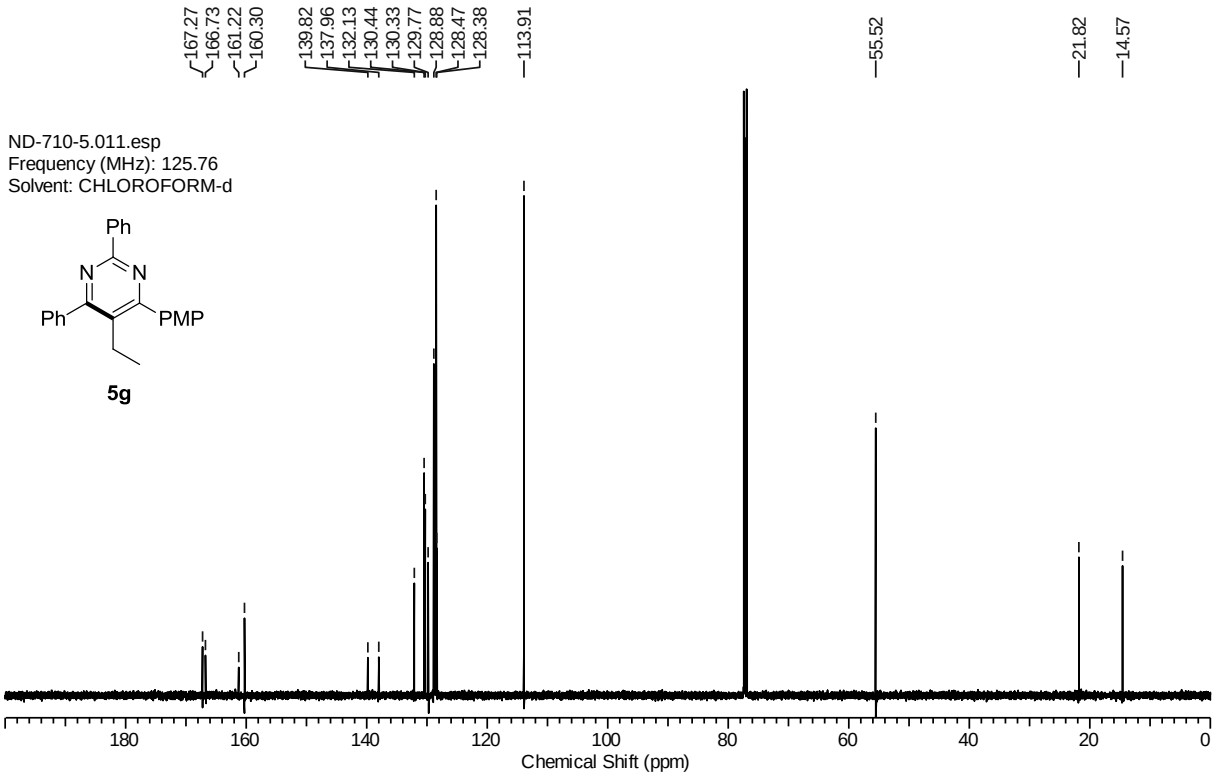

ND-720-9.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
Me
5e
2.00
4.03
6.15
2.04
3.08
3.07
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

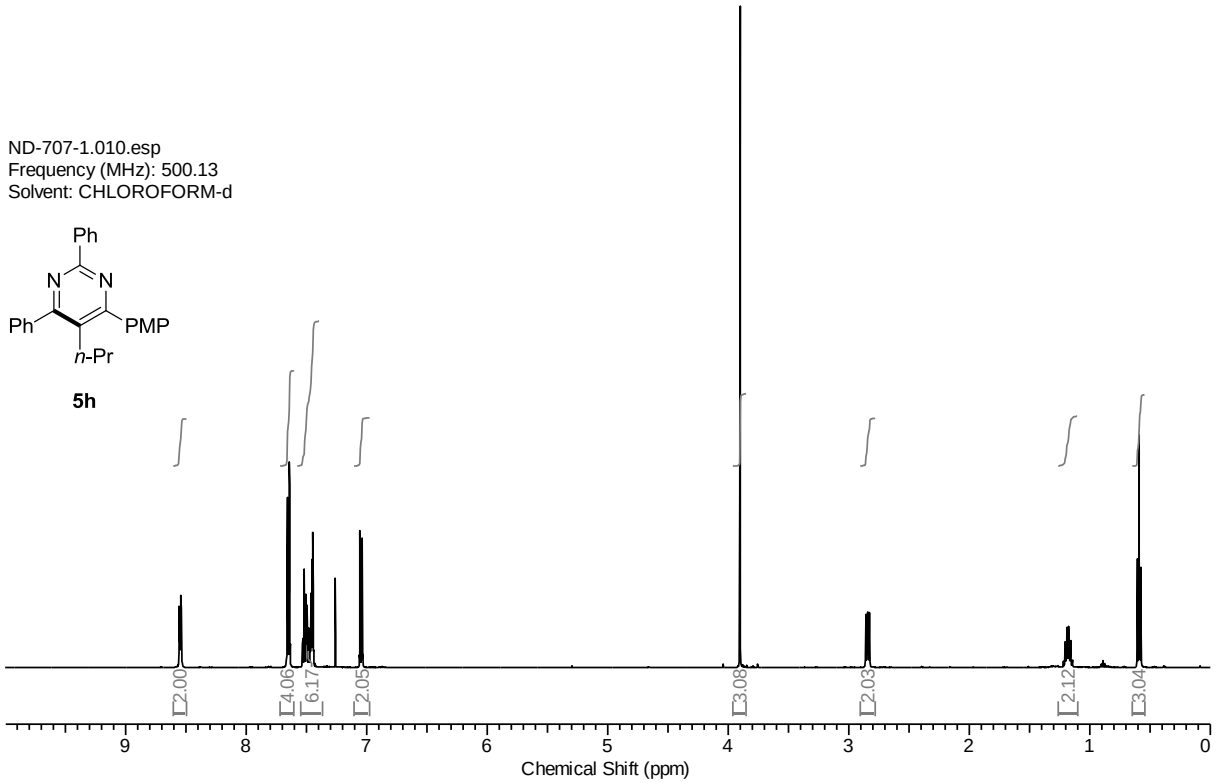

167.00
166.43
161.44
160.56
139.45
138.09
131.70
131.18
130.29
129.53
129.19
128.46
128.38
128.28
122.99
113.78
55.52
18.18
ND-720-9.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
Me
5e
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

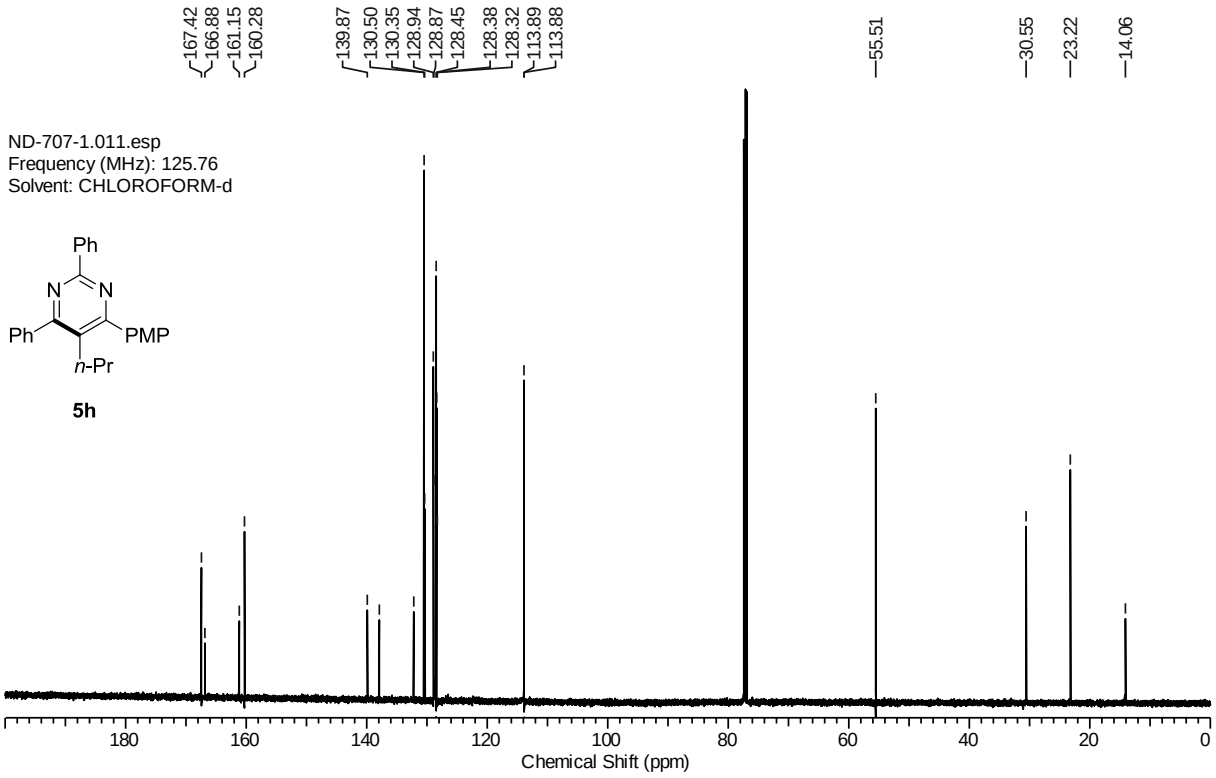

ND-720-10.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
5f
1.98
2.00
3.03
2.00
3.03
2.00
1.99
2.01
4.03
3.03
3.14
Chemical Shift (ppm)

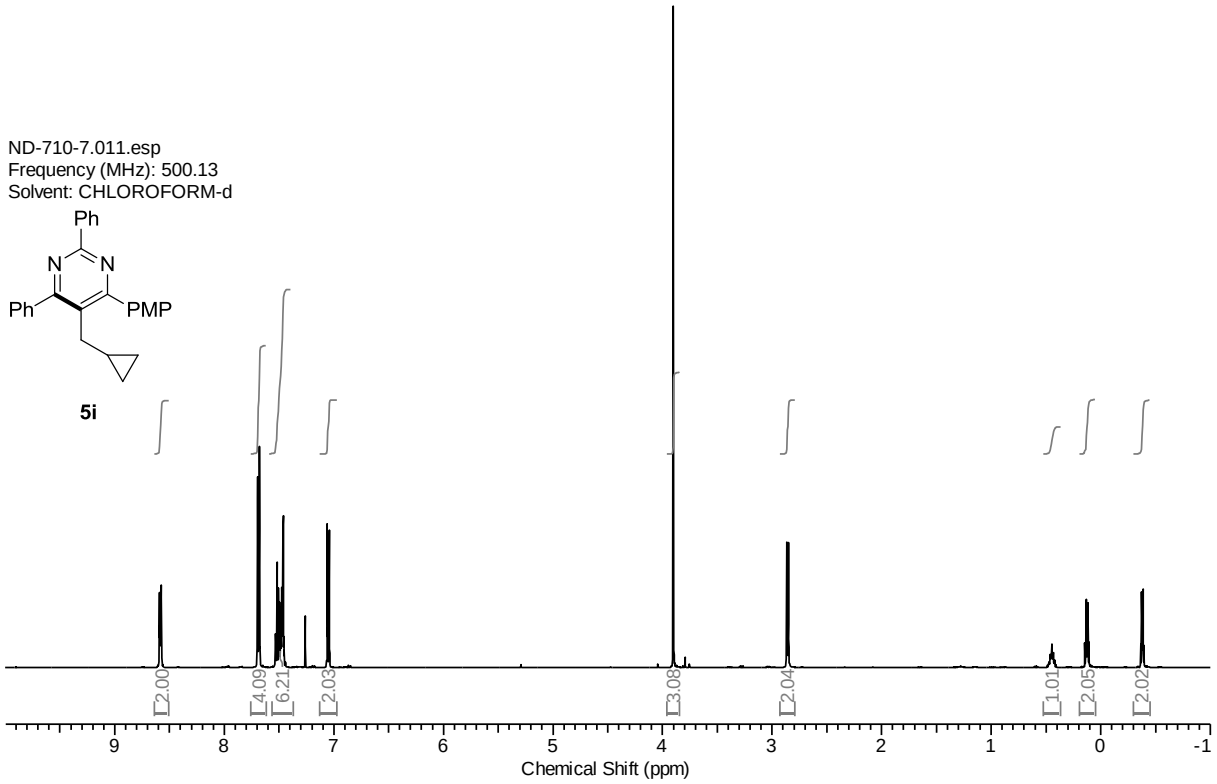

169.74
165.53
161.00
159.99
138.41
132.34
130.29
130.01
128.40
128.15
113.70
55.41
34.48
31.05
30.19
24.00
22.97
14.40
14.21
ND-720-10.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
5f
Chemical Shift (ppm)

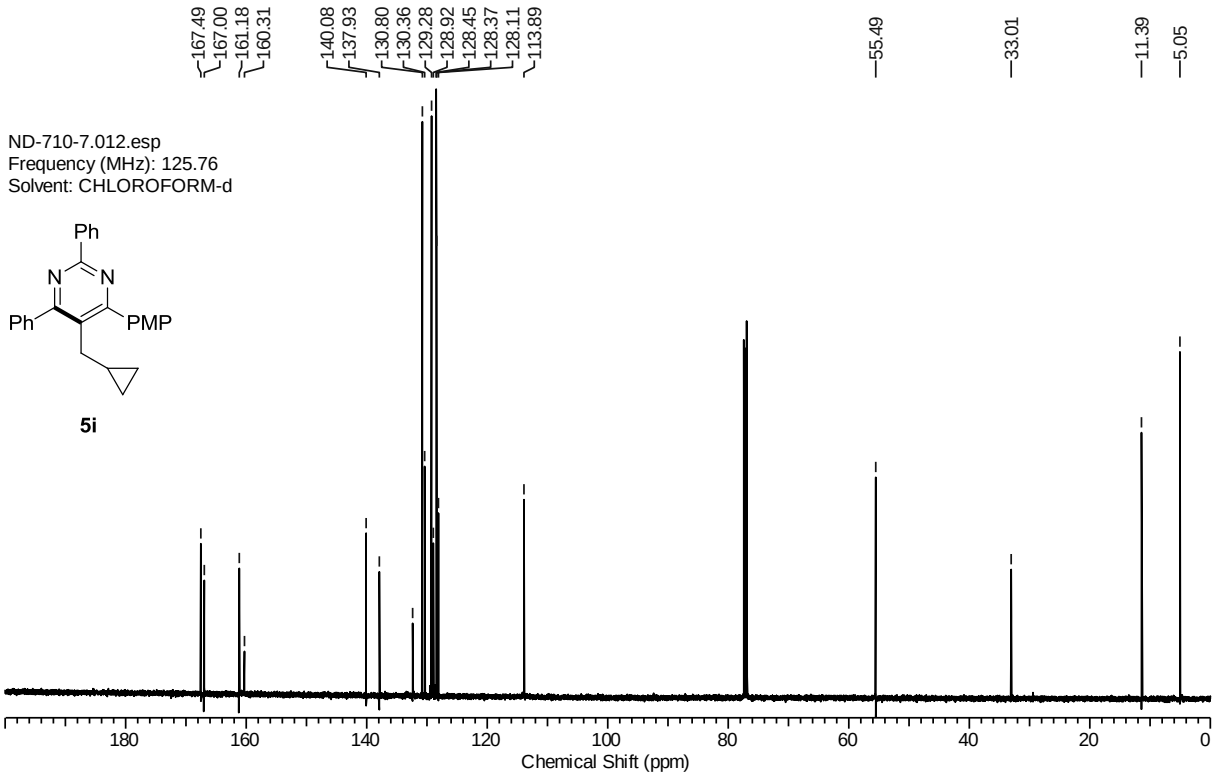

ND-710-5.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
5g
2.00
4.06
6.10
2.03
3.05
2.06
3.01
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


167.27
166.73
161.22
160.30
139.82
137.96
132.13
130.44
130.33
129.77
128.88
128.47
128.38
113.91
55.52
21.82
14.57
ND-710-5.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
5g
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


ND-707-1.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
n-Pr
5h
2.00
4.06
6.17
2.05
3.08
2.03
2.12
3.04
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)


167.42
166.88
161.15
160.28
139.87
130.50
130.35
128.94
128.87
128.45
128.38
128.32
113.89
113.88
55.51
30.55
23.22
14.06
ND-707-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
n-Pr
5h
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


ND-710-7.011.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
5i
2.00
4.09
6.21
2.03
3.08
2.04
1.01
2.05
2.02
9
8
7
6
5
4
3
2
1
0
-1
Chemical Shift (ppm)


167.49
167.00
161.18
160.31
140.08
137.93
130.80
130.36
129.28
128.92
128.45
128.37
128.11
113.89
55.49
33.01
11.39
5.05
ND-710-7.012.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
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N
Ph
PMP
5i
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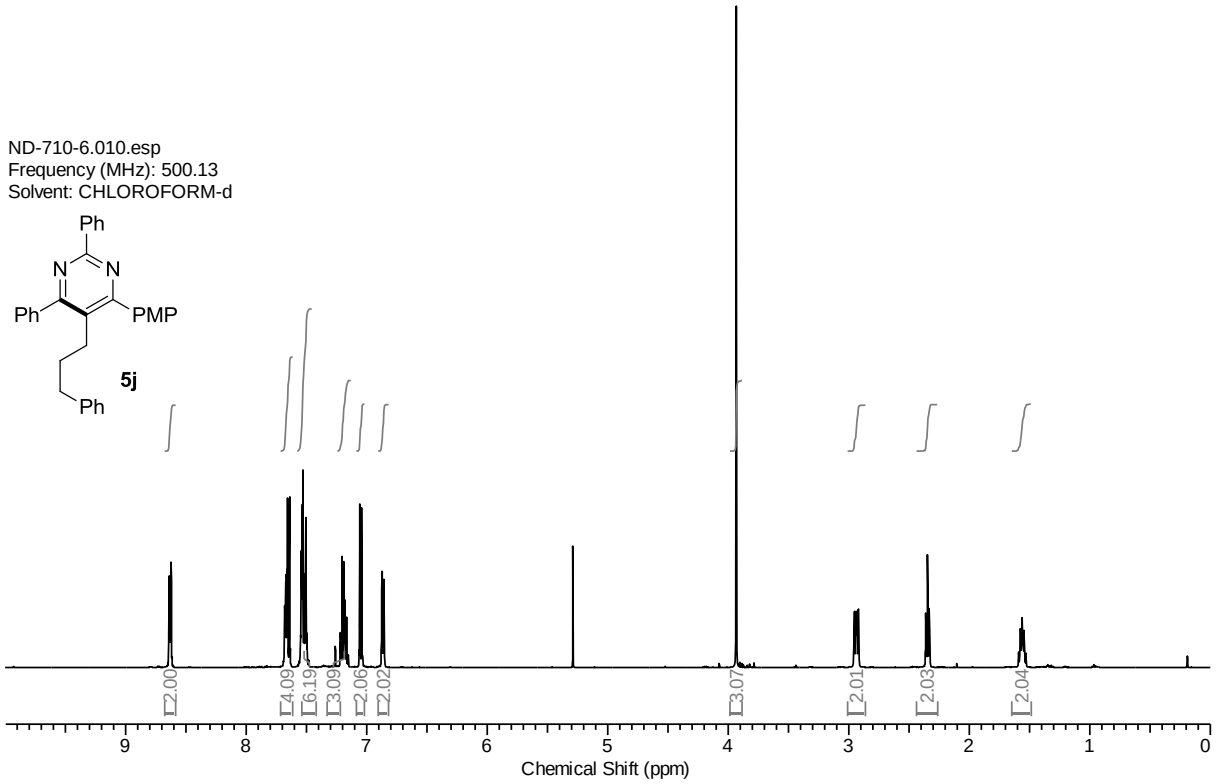
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)


ND-710-6.010.esp
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Solvent: CHLOROFORM-d
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N
N
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PMP
5j
Ph
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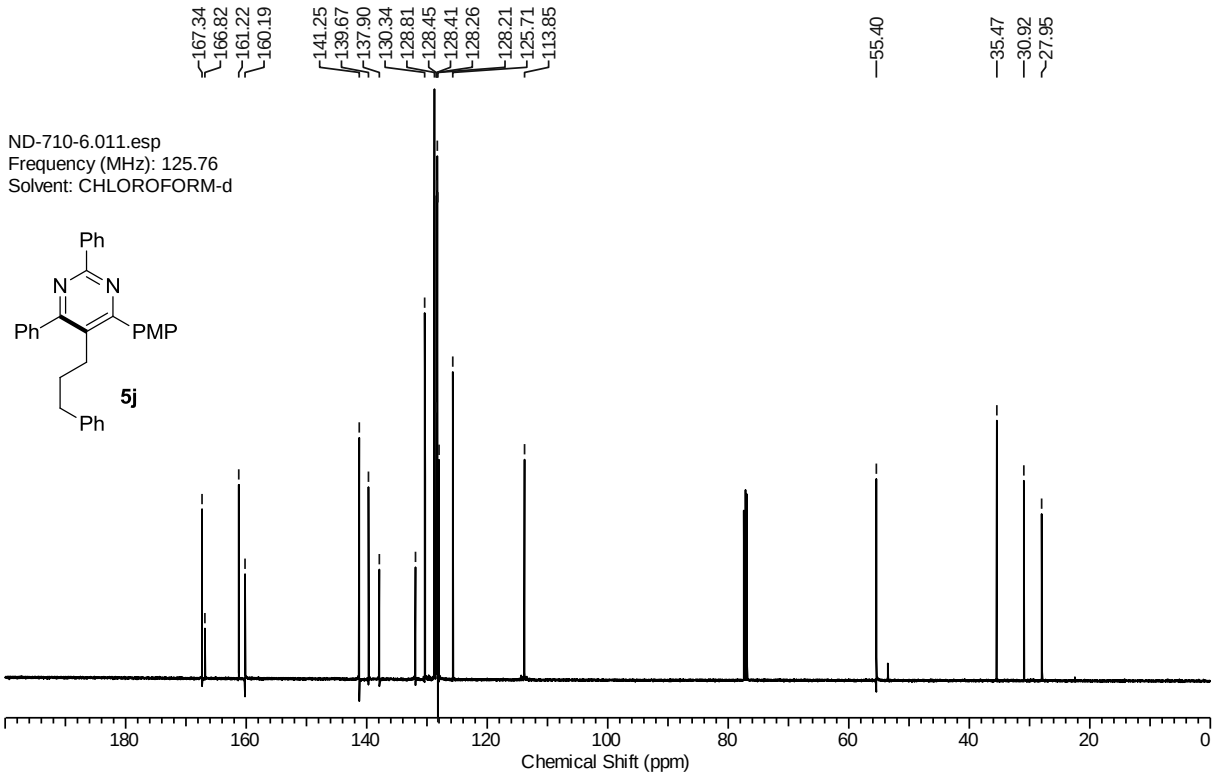
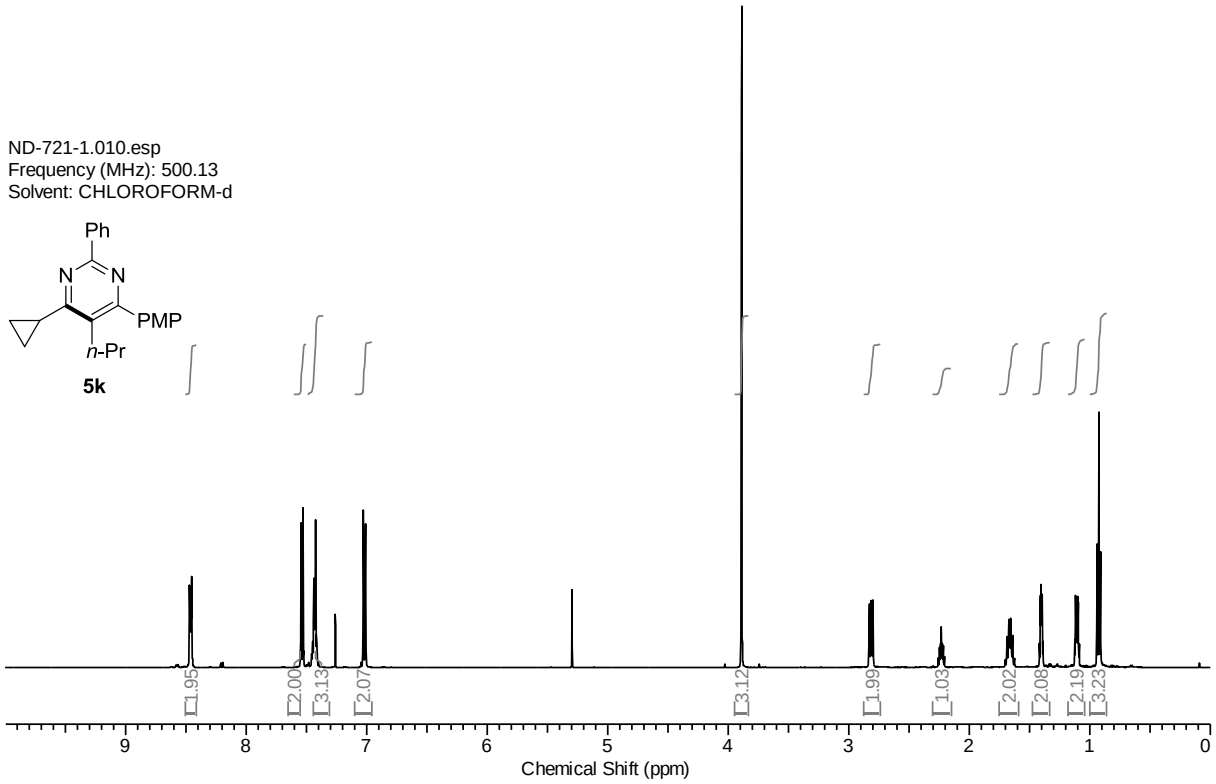
6.19
3.09
2.06
2.02
3.07
2.01
2.03
2.04
Chemical Shift (ppm)


167.34
166.82
161.22
160.19
141.25
139.67
137.90
130.34
128.81
128.45
128.41
128.26
128.21
125.71
113.85
55.40
35.47
30.92
27.95
ND-710-6.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
Ph
PMP
5j
Ph
Chemical Shift (ppm)


ND-721-1.010.esp
Frequency (MHz): 500.13
Solvent: CHLOROFORM-d
Ph
N
N
PMP
n-Pr
5k
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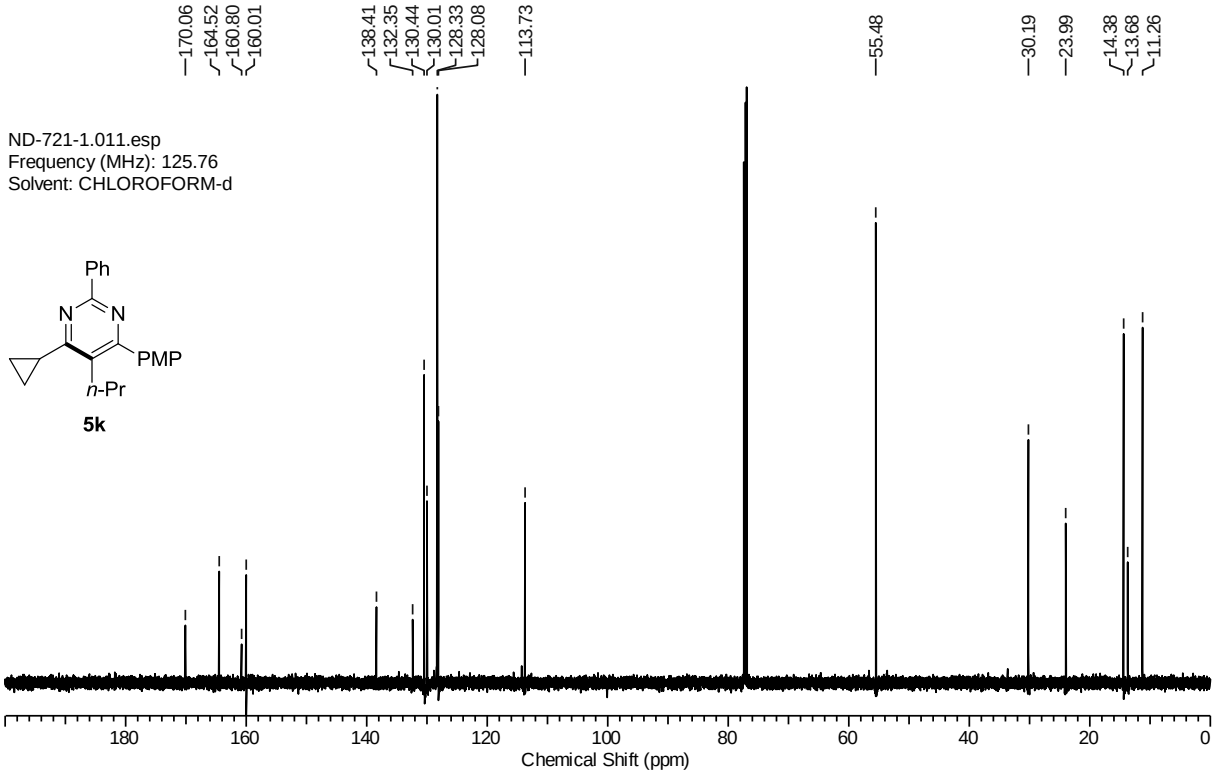
2.07
3.12
1.99
1.03
2.02
2.08
2.19
3.23
Chemical Shift (ppm)


170.06
164.52
160.80
160.01
138.41
132.35
130.44
130.01
128.33
128.08
113.73
55.48
30.19
23.99
14.38
13.68
11.26
ND-721-1.011.esp
Frequency (MHz): 125.76
Solvent: CHLOROFORM-d
Ph
N
N
PMP
n-Pr
5k
Chemical Shift (ppm)

[1] (a) S. Michlik, R. Kempe, *Nat. Chem.* **2013**, *5*, 140-144. (b) S. Michlik, R. Kempe, *Angew. Chem. Int. Ed.* **2013**, *52*, 6326-6329.
[2] F. Kallmeier, T. Irrgang, T. Dietel, R. Kempe, *Angew. Chem. Int. Ed.* **2016**, *55*, 11806-11809.
[3] S. Rösler, J. Obenauf, R. Kempe, *J. Am. Chem. Soc.* **2015**, *137*, 7998-8001.
[4] N. Deibl, K. Ament, R. Kempe, *J. Am. Chem. Soc.* **2015**, *137*, 12804-12807.
[5] M. C. Bagley, Z. Lin, S. J. A. Pope, *Tetrahedron Lett.* **2009**, *50*, 6818-6822.
[6] T. M. Gogsig, D. U. Nielsen, A. T. Lindhardt, T. Skrydstrup, *Org. Lett.* **2012**, *14*, 2536-2539.
[7] M. Adib, N. Mahmoodi, M. Mahdavi, H. R. Bijanzadeh, *Tetrahedron Lett.* **2006**, *47*, 9365-9368.

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