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BAYREUTH**

Novel Catalytic Reactions for the Synthesis of Complex *N*-Compounds

Dissertation

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Dedicated to

Dr. Arno Herbert Karl Leinert

04.07.1938 – 17.02.2018

and

Christa Isolde Leinert

25.11.1941 – 19.01.2026

„Jeder Mensch erfindet sich früher oder später eine Geschichte,
die er, oft unter gewaltigen Opfern, für sein Leben hält, oder
eine Reihe von Geschichten, die mit Namen zu belegen sind, so
dass an ihrer Wirklichkeit scheint es, nicht zu zweifeln ist.“

Max R. Frisch

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1 SUMMARY / ZUSAMMENFASSUNG

1.1 Summary

This thesis addresses the development of novel catalytic concepts for the synthesis of complex nitrogen-containing compounds using PN₅P ligand-stabilized transition metal complexes. The work focuses on designing multi-step reaction sequences and enabling the synthesis of highly functionalized products from simple, sustainable, and widely accessible starting materials (see Figure 1).

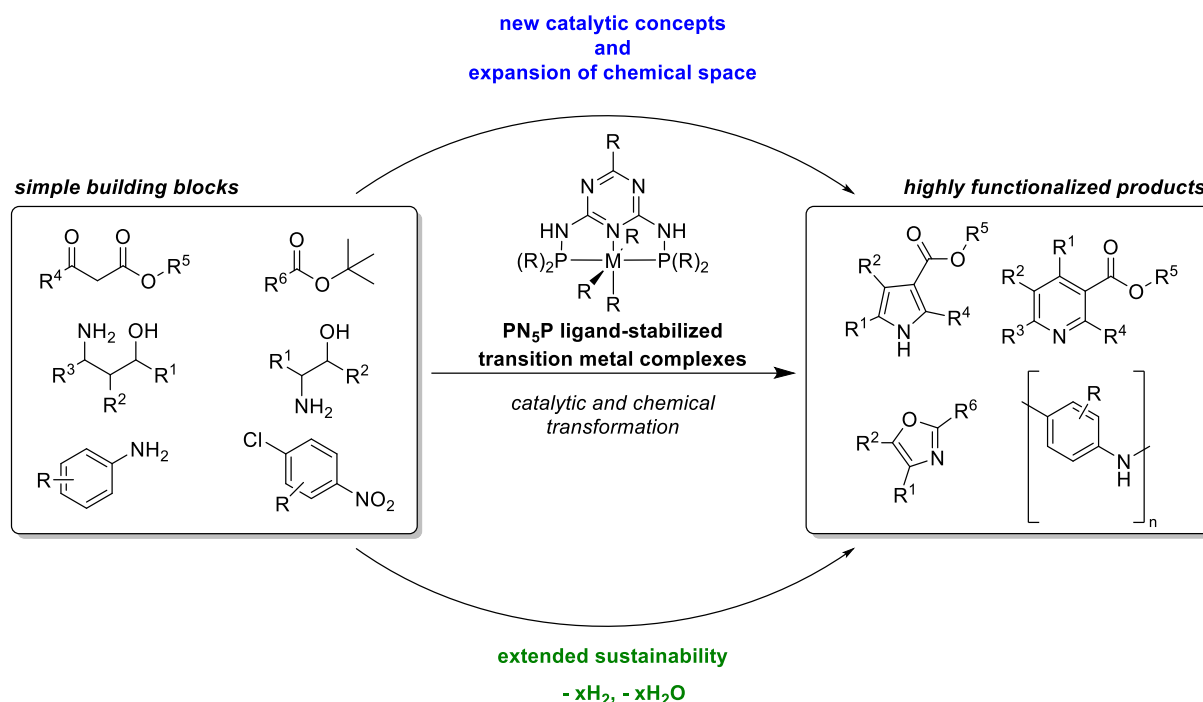


Figure 1: Schematic representation of the central philosophy of this thesis. The figure illustrates the development of novel, catalytic synthesis concepts using PN₅P ligand-stabilized transition metal complexes to transform simple and sustainable starting materials into highly functionalized nitrogen-containing products.

The PN₅P ligand-stabilized transition metal complexes used in this work are derived from dia-amino-*s*-triazine based ligands, which have been extensively investigated by the group around KEMPE in previous studies and applied in a variety of catalytic transformations. Their distinctive reactivity and selectivity, combined with the broad tunability of the ligand framework, make this class of transition metal complexes highly promising candidates for the development of new catalytic reactions.

The first part of this thesis focuses on the development of a novel *one-pot* synthesis of oxazoles. This transformation proceeds from esters and amino alcohols, both of which are abundant and broadly accessible starting materials and hydrogen is liberated in the initial step. The reaction exhibits a wide substrate scope, and – apart from the screening substrate and one drug active ingredient – the synthesized examples represent previously undisclosed compounds.

The new synthetic concept demonstrates excellent functional group tolerance, including substituents that are typically sensitive to hydrogenation, despite the presence of a hydrogenation catalyst and molecular hydrogen. Manganese (pre)catalyst **[Mn-I]** mediates the reaction most effectively – even more efficiently than related Ir or Ru catalysts (see Figure 2).

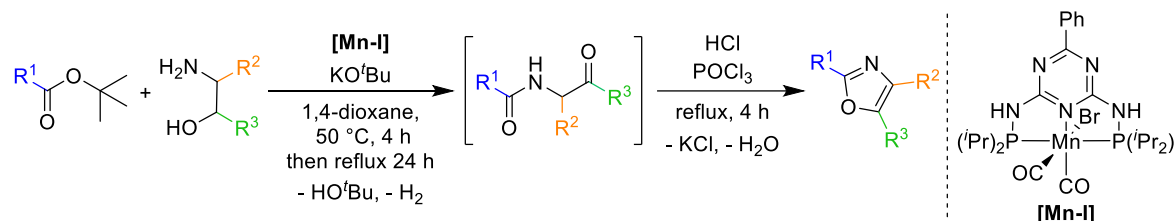


Figure 2: General concept of the established *one-pot* synthesis of oxazoles.

The second part of this work addresses a catalytic variant of the KNORR pyrrole synthesis for the preparation of pyrrole and pyridine derivatives starting from amino alcohols and 1,3-ke-toesters. The reaction is most efficiently mediated by a Mn-based (pre)catalyst **[Mn-I]** in combination with a simple acid catalyst. The synthesis of highly functionalized products and their potential applications is demonstrated, and 35 of the 43 compounds obtained have not been previously reported in the literature (see Figure 3).

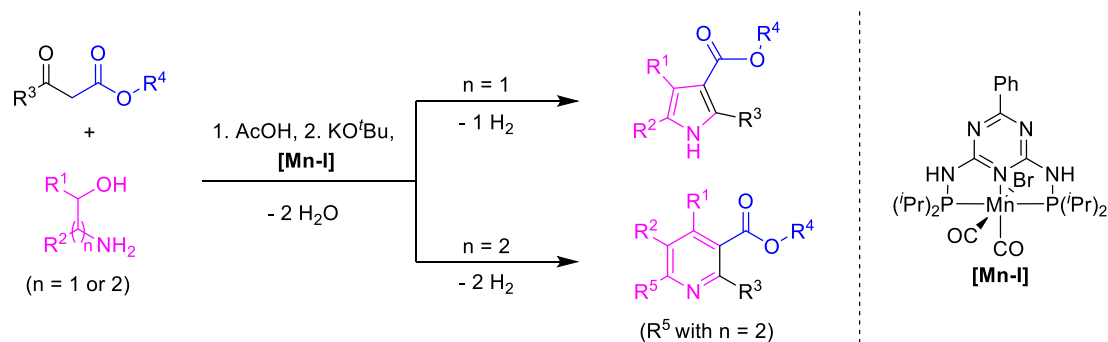


Figure 3: Principle for the catalytic synthesis of pyrroles and pyridines.

The third chapter is based on the establishment of a protecting group free iterative concept for the synthesis of sequence-defined and functionalized polyamines. The two key steps of the process are the Pd-catalyzed aryl amination using a PEPPSI-*i*Pr Pd (pre)catalyst and the selective reduction of the nitro group with a highly active Ir (pre)catalyst **[Ir-I]** (see Figure 4). Incorporating a selective *N*-functionalization step after the aryl amination further enhances the chemical stability, solubility, and overall degree of functionalization of the products. Based on these findings, a three-step process was established that enables the synthesis of higher functionalized polyamine derivatives.

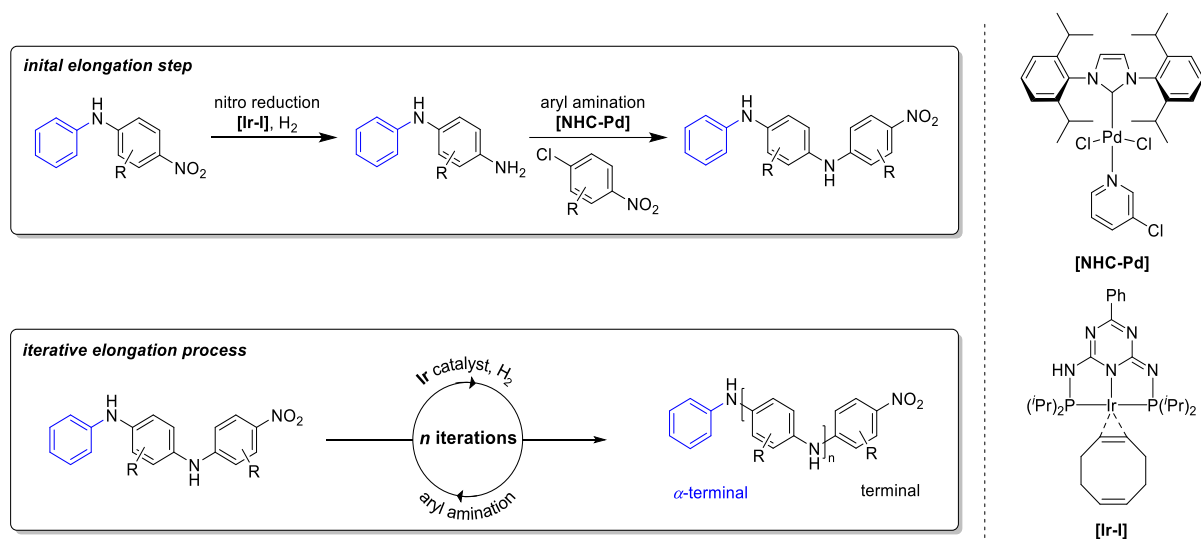


Figure 4: Iterative synthesis of sequence-defined and conjugated polyamines via a catalytic two-step process.

1.2 Zusammenfassung

Diese Dissertation befasst sich mit der Entwicklung neuartiger katalytischer Konzepte für die Synthese komplexer stickstoffhaltiger Verbindungen unter Verwendung von PN_5P -ligand-stabilisierten Übergangsmetallkomplexen. Der Fokus der Arbeit liegt auf der Entwicklung mehrstufiger Reaktionssequenzen zur Synthese hochfunktionalisierter Produkte aus einfachen, nachhaltigen und breit zugänglichen Ausgangsmaterialien (siehe Abbildung 1).

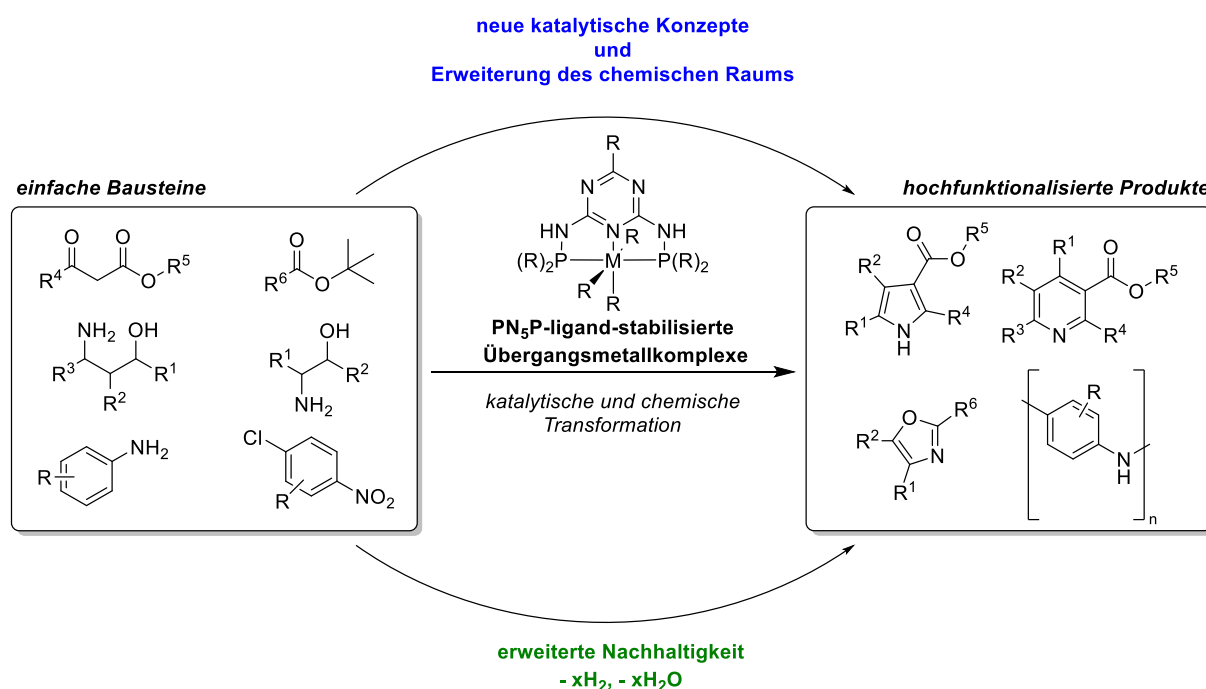


Abbildung 1: Schematische Darstellung der zentralen Philosophie dieser Dissertation. Die Abbildung veranschaulicht die Entwicklung neuartiger katalytischer Synthesekonzepte unter Verwendung von PN_5P -ligand-stabilisierten Übergangsmetallkomplexen, um einfache und nachhaltige Ausgangsmaterialien in strukturell komplexe, stickstoffhaltige Produkte umzuwandeln.

Die in dieser Arbeit verwendeten PN_5P -ligand-stabilisierten Übergangsmetallkomplexe basieren auf Diamino-*s*-Triazin-abgeleiteten Liganden, die in früheren Studien von der Arbeitsgruppe um KEMPE untersucht und in einer Vielzahl katalytischer Transformationen eingesetzt wurden. Ihre ausgeprägte Reaktivität und Selektivität, kombiniert mit der breiten Anpassungsfähigkeit des Ligandensystems, machen diese Klasse von Übergangsmetallkomplexen zu vielversprechenden Kandidaten für die Entwicklung neuer katalytischer Reaktionen.

Im Mittelpunkt des ersten Teils der Arbeit steht die Entwicklung einer neuartigen *one-pot*-Synthese von Oxazolen ausgehend von 1,2-Aminoalkoholen und *tert*-Butylestern. Während der katalytischen Dehydrierung wird elementarer Wasserstoff freigesetzt. Keines der synthetisierten Verbindungen, mit Ausnahme des Screening-Substrats und der Wirkstoff eines vermarkteten Arzneimittels, sind Verbindungen, die bisher in der Literatur veröffentlicht wurden.

Das neue Konzept zeigt eine sehr gute Toleranz gegenüber funktionellen Gruppen, einschließlich hydrierempfindlichen Substituenten. Der verwendete (Prä)katalysator **[Mn-I]** weist die höchste Effektivität und Selektivität in der katalytischen Dehydrierung auf (siehe Abbildung 2).

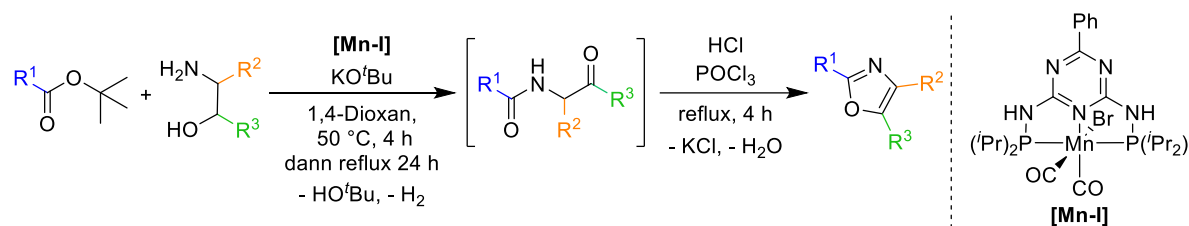


Abbildung 2: Allgemeines Konzept der konsekutiven *one-pot*-Synthese von Oxazolen.

Der zweite Teil der Arbeit beschäftigt sich mit einer katalytischen Variante der KNORR-Pyrrol-Synthese zur Herstellung von Pyrrol- und Pyridinderivaten ausgehend von Aminoalkoholen und 1,3-Ketoestern. (Prä)katalysator **[Mn-I]** und ein einfacher Säurekatalysator vermitteln die Reaktion auf effiziente Weise. Die Synthese von hochfunktionalisierten Verbindungen wurde demonstriert, und 35 der 43 isolierten Verbindungen wurden in der Literatur noch nicht beschrieben. Weiterhin werden verschiedene Anwendungsmöglichkeiten des Synthesekonzepts und der resultierenden Bausteine gezeigt (siehe Abbildung 3)

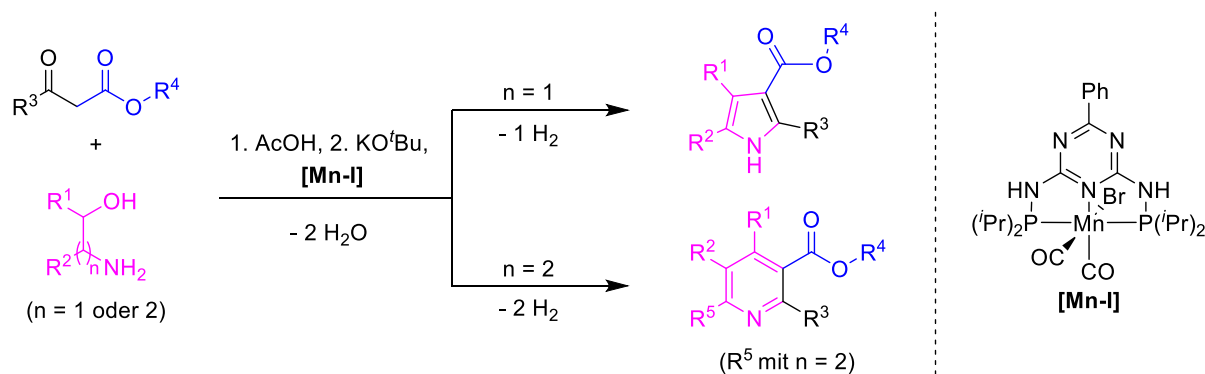


Abbildung 3: Grundprinzip der Synthese von Pyrrolen und Pyridinen.

Das dritte Kapitel beschäftigt sich mit der Etablierung eines schutzgruppenfreien, iterativen Konzepts zur Synthese sequenzdefinierter und funktionalisierter Polyamine. Die beiden zentralen Reaktionsschritte des Verfahrens sind die Pd-katalysierte Arylaminierung unter Verwendung eines PEPPSI- $i\text{-Pr}$ Pd-(Prä)Katalysators sowie die selektive Reduktion der Nitrogruppe mit einem hochaktiven Ir-(Prä)Katalysator **[Ir-I]** (siehe Abbildung 4). Die Einführung eines selektiven *N*-Funktionalisierungsschritts nach der Arylaminierung verbessert zusätzlich die chemische Stabilität, Löslichkeit und den funktionalen Umfang der Produkte. Aufbauend auf diesen Ergebnissen konnte ein dreistufiger Prozess etabliert werden, der die Synthese höher funktionalisierter Polyaminderivate ermöglicht.

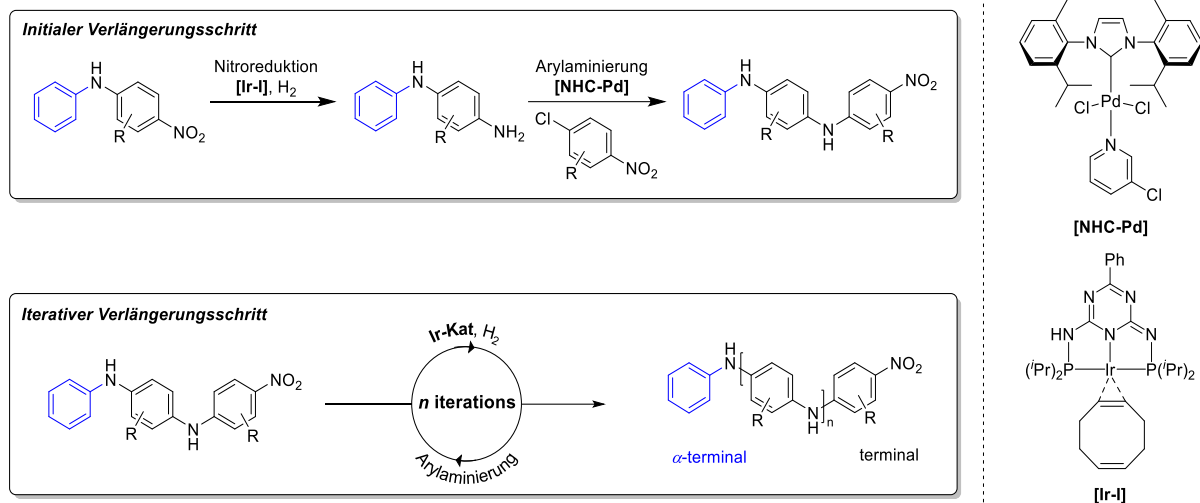


Abbildung 4: Iterative Synthese von sequenzdefinierten Polyaminen mittels katalytischem zweistufigen Prozess.

2 INTRODUCTION

The efficient and sustainable synthesis of complex organic compounds from easily accessible building blocks is one of the most exciting challenges in modern chemistry. The exploration of new reaction pathways or the minimization of by-products and/or waste products are two fundamental starting points and necessary first steps on the way to more atom-economically efficient chemical transformations.^[1]

The goal of reducing the consumption of raw materials and the generation of waste in chemical processes has become one of the main tasks of the global research community of chemists, partly due to changes in civil society. As a result, the production of the countless substances required for the uncomplicated continuation of a peaceful social order must be made more efficient. Chemistry as a scientific discipline is omnipresent. It appears in materials development and production, in healthcare and in research into new active drugs.^[1]

In all these areas, the establishment of new chemo-, regio-, diastereo- and enantioselective processes is essential to consistently meet the challenges of the 21st century. An important aspect that plays a role in organic chemistry and large-scale production is catalysis. Homogeneous transition metal complexes, which can be adapted both electronically and sterically by varying the metal and/or ligands, are of particular interest here (see Figure 5).^[1]

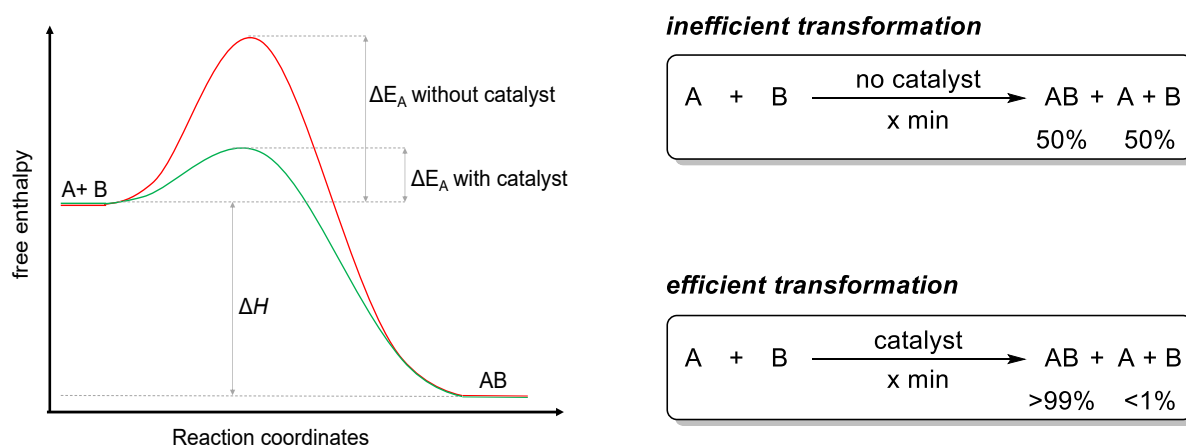


Figure 5: Comparison between catalyzed and non-catalyzed process of a reaction of the form $A + B \rightarrow AB$.

In recent decades, catalytic processes have been developed that are not only efficient and highly selective but also use renewable biomass or its resulting platform chemicals as starting compounds.^[2] Although the development of oil as a cheap source of fuel in the 19th century was one of the main reasons for the industrialization of the world and had a significant impact on raising the living standards of many people in emerging economies, the situation has changed drastically since then.

Almost 200 years later, with dwindling oil resources, daily oil consumption of around 100 million barrels of oil per day and global energy and environmental crises as well as geopolitical crises and conflicts arising, it is essential to develop new ecological and energy efficient processes for the sustainable production of fuels.^{[3],[4],[5]}

However, not only fuel production from sustainable sources, but also the production of chemicals from renewable resources has become a highly relevant topic in the last two decades. This is because one of the most crucial elements for the chemical industry is carbon. However, most chemical substances containing carbon are currently still produced from finite fossil resources such as oil and coal.^{[6],[7]} As a result, interdisciplinary research groups are working intensively on the task of replacing traditional innovations that are used in the planning and implementation of chemical synthesis with more efficient systems. One requirement for these innovative approaches is that they are profitable from an economic and ecological point of view and can therefore be implemented without government regulations or subsidies. This expansion, which demands an extremely high degree of innovation and creativity from the chemist, was defined as green chemistry by P. T. ANASTAS and J. C. WARNER in 1998 and specified by setting out twelve principles.^[8] In addition to safety aspects, the principles mentioned by the two authors include the avoidance of waste, the implementation of atom- and energy efficient reactions, the use of renewable resources, the preferential use of catalysts and the avoidance of derivatization reagents. The catalysis mentioned by P. T. ANASTAS and J. C. WARNER and the use of renewable resources play a special role here.^[8]

In view of this, numerous new catalytic methods to produce chemicals from renewable sources have been researched and substantiated as promising alternatives in recent years^{[2],[6],[7]} Among other things, the use and processing of biomass, or more precisely lignocellulose as a barely utilized waste product of the food industry, has been intensively investigated in research.^[9]

Lignocellulose has several properties that make this specific type of biomass so interesting. Firstly, it is indigestible for humans, which prevents potential competition with the food supply. Secondly, lignocellulose is available in massive quantities.^[9] Lignocellulose can be used as a starting compound to produce organic fine chemicals such as alcohols. For this purpose, the cheap fuel obtained from biomass is converted step by step using an integrated catalytic approach.^[9] The so-called pyrolysis oil is converted into a wide variety of chemical raw materials in individual steps through hydrogenation processes and the use of zeolite catalysts. Successive hydrogenation can increase the intrinsic hydrogen content and produce a variety of polyols and alcohols.^[9]

Due to the development of simple, energy efficient methods for converting large quantities of biomass into a variety of basic chemical substances, the development of reactions that convert these sustainably produced substrates into essential bulk and fine chemicals has become a central topic in green chemistry. In homogeneous catalysis in particular, many new methods have been developed in the last decade to further use and functionalize these various products.

Individual research groups have developed new and pioneering concepts, such as borrowing hydrogen/hydrogen-auto transfer (BH/HA) catalysis or the acceptorless dehydrogenation methodology (see Figure 6).^{[10],[11]}

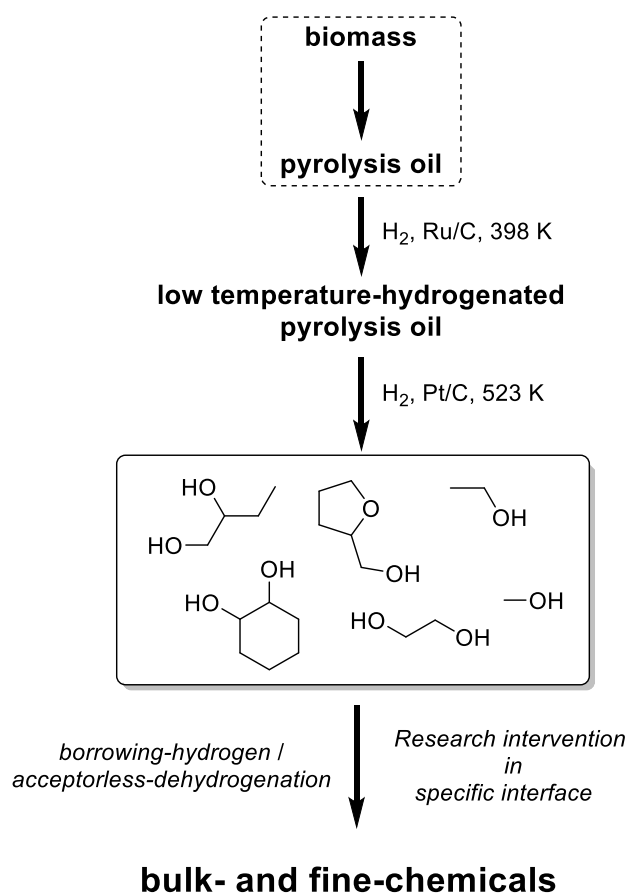


Figure 6: Intervention of current research for the synthesis of fine chemicals derived from biomass.

For example, a primary or secondary alcohol function is first dehydrogenated. In some cases, the two hydrogen atoms are formally bonded to the catalyst center and their ligand system as proton (H^+) and hydride (H^-). The carbonyl function thus formed can react with a nucleophile to form an unsaturated intermediate by condensation with the release of water. In the final step, the unsaturated intermediate is reduced by the catalyst used, formally returning the previously bound hydrogen, and the complex is returned to its catalytically active state.^{[12],[13]} By suppressing the final reduction step, unsaturated carbonyl, imine or olefin derivatives are accessible through this reaction sequence. This variation of the borrowing-hydrogen methodology is known as acceptorless dehydrogenation. The unsaturated products formed in this way can often be used as reactive intermediates for further synthetic modifications. In this case, the catalyst is regenerated by releasing dihydrogen, which is produced as an economically and ecologically valuable by-product (see Figure 7).^{[12],[13]}

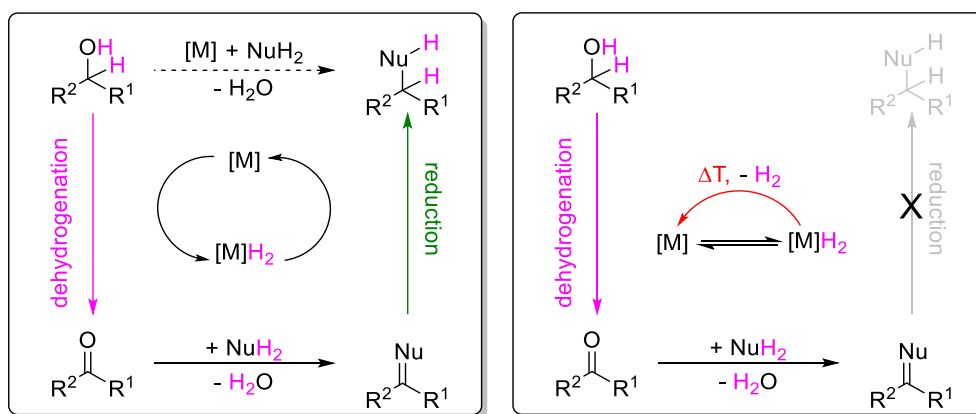
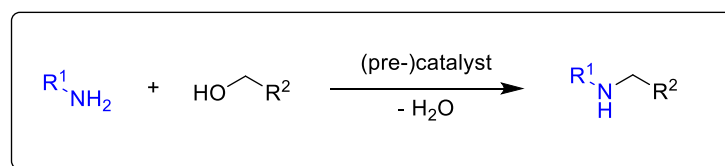


Figure 7: Borrowing hydrogen concept (left). Acceptorless dehydrogenation process (right).

In addition to the release of non-toxic by-products, a particular feature of catalysis using borrowing-hydrogen or acceptorless dehydrogenation methodology is the possible use of unreactive alcohols that can hardly be used for C-C couplings, which can be converted into synthetically more valuable substrates in an energy and atom efficient manner (see Figure 8).^{[12],[13]} Developing new synthesis concepts based on this developed concept is therefore of high importance.

alkylation of amines with alcohols



alkylation of secondary alcohols with alcohols

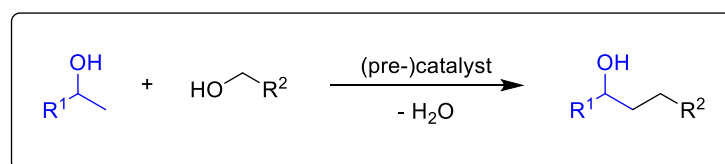


Figure 8: Synthetic concepts involving BH/HA-catalysis to transform alcohols into valuable compounds.

While borrowing hydrogen or acceptorless dehydrogenation methodology deals with the synthesis of complex molecules from sustainable starting substances, iterative synthesis focuses on efficient, optimized reaction sequences that can be repeated as often as required. This results in complex higher molecular weight compounds with interesting properties in a simple and optimized way.^[14]

The principle of iterative synthesis is clearly inspired by nature. For example, many biosynthetic pathways of natural (macro)molecules are inherently modular, suggesting that such structures and their associated functions should be accessible using a generalized iterative synthesis approach. Furthermore, most natural products, which are the source of inspiration for more than 50% of all human therapeutics, are derived from only a few major biosynthetic pathways, each involving the iterative assembly of a small number of discrete molecular building blocks.^{[14],[15]}

For instance, polyketides, an important class of biologically active compounds, are biosynthesized from malonyl-CoA and methyl-malonyl-CoA. The iterative sequence of decarboxylative CLAISEN condensation and other intermediate biosynthesis steps can be used to form a wide range of chemical structures (see Figure 9).^[16]

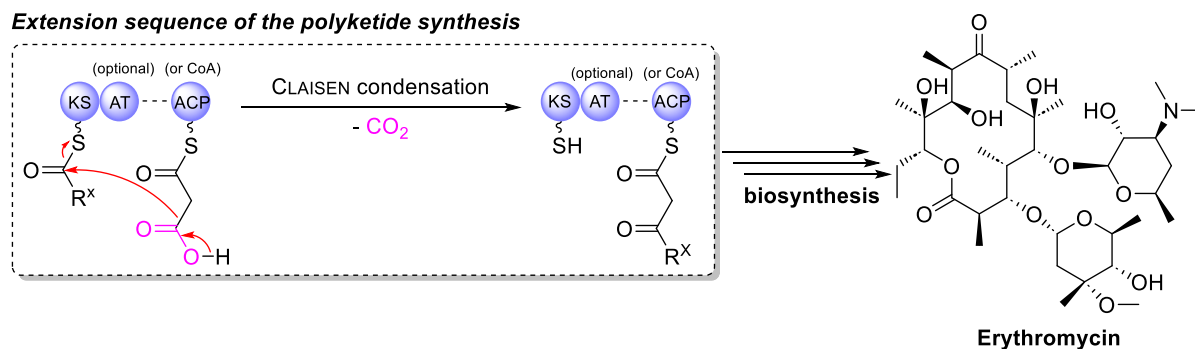


Figure 9: Schematic representation of the biosynthesis of polyketides by iterative extension of the polyketide chain using decarboxylative CLAISEN condensation (left). Erythromycin: A representative example of a structurally complex polyketide natural product (right).

Researchers have therefore been attempting to apply this principle of nature to chemical processes for quite some time. The revolutionary solid-phase peptide synthesis for example utilizes the iterative synthesis concept. Here, the individual amino acid building blocks are linked together in an automated synthesis protocol (see Figure 10).^{[14],[17],[18]}

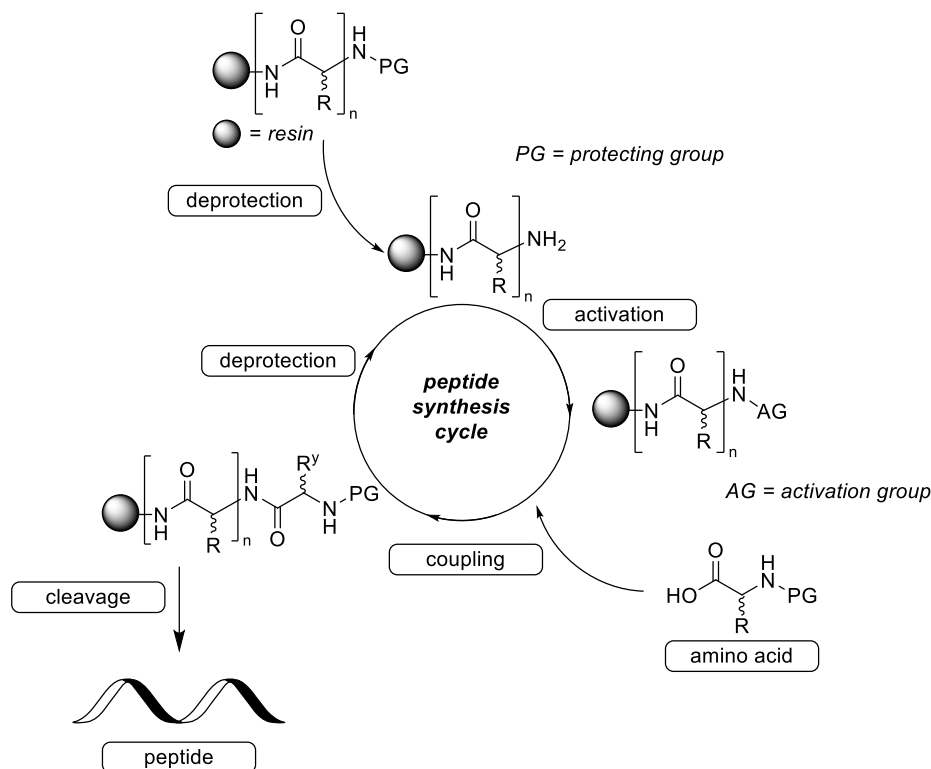


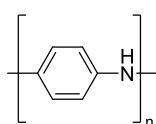
Figure 10: Schematic concept of the solid phase peptide synthesis.

Orthogonal protection group chemistry and functional group activation play a crucial role. This makes it possible to construct sequence-defined amino acid chains with specific properties (see Figure 10).^[14,17,18]

The iterative synthesis concept can be used not only for the synthesis of low-molecular compounds or peptides. Material components, usually consisting of polycyclic systems, also exhibit a high degree of modularity. Although they fulfill a wide range of different functions, they often consist of common, repeating substructural motifs such as oligoarenes or oligothiophenes.^{[19],[20]}

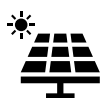
One of the most promising nitrogen containing conductive materials are oligo- and polyanilines. These kinds of organic materials are especially interesting because of their wide range of applications (see Figure 11).^{[21],[22],[23],[24],[25]}

applications of polyaniline materials

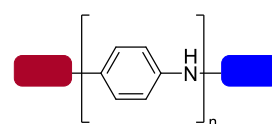


polyaniline

- electronics
- (bio)sensors
- OLED materials
- electrode materials



applications of oligoaniline materials



oligoaniline composites

- bioimaging
- drug delivery
- tissue engineering
- antimicrobial therapy



Figure 11: Applications for oligo- and polyaniline materials.

Currently, there is only limited synthetic access to functionalized oligo- and polyanilines. It would therefore be of great interest to develop new (catalytic) synthesis concepts for this class of substances to provide access to tailor-made materials for specific applications.

3 STATE OF THE ART

3.1 The concept of acceptorless dehydrogenation catalysis

In recent years, acceptorless dehydrogenation catalysis (ADC) has emerged as one of the most important and influential concepts in organometallic catalysis.^{[10],[26]}

The dehydrogenation of hydrogen-rich organic molecules is in most cases a thermodynamically unfavorable process.^{[27],[28],[29]} As a result, stoichiometric quantities of oxidants such as oxygen, potassium peroxo monosulphates, peroxides, metal oxides or hypervalent iodine compounds are often used for the dehydrogenation of organic substrates.^[30] All these oxidation methods, especially the use of hypervalent iodine compounds, peroxides or metal oxides, have poor atomic economy and lead to the uneconomical formation of by-products (see Figure 12). Research into novel methods for the dehydrogenation of hydrogen-rich organic substrates is therefore a highly relevant topic in the field of green and sustainable chemistry.

The concept of acceptorless dehydrogenation thus provides a wide range of ecologically and economically efficient reaction profiles and synthetic methods with the release of hydrogen as the only by-product (see Figure 12).^[31] In particular, the catalytic dehydrogenation of alcohols to the corresponding carbonyl moiety is an attractive area of application for the acceptorless dehydrogenation concept. Traditionally, methods such as SWERN-, PARIKH-DOERING-, DESS-MARTIN or JONES-oxidation are used in classical synthetic chemistry to generate the corresponding keto, aldehyde, or acid function. All these reactions require stoichiometric amounts of oxidant and often result in toxic by-products.^[30]

In contrast, many transition metal complexes have been developed in recent years that are capable of selectively dehydrating alcohol functions (siehe Figure 12).^{[32],[33]} In particular, (pre)catalysts with PNP pincer ligands often showed high activity and selectivity.

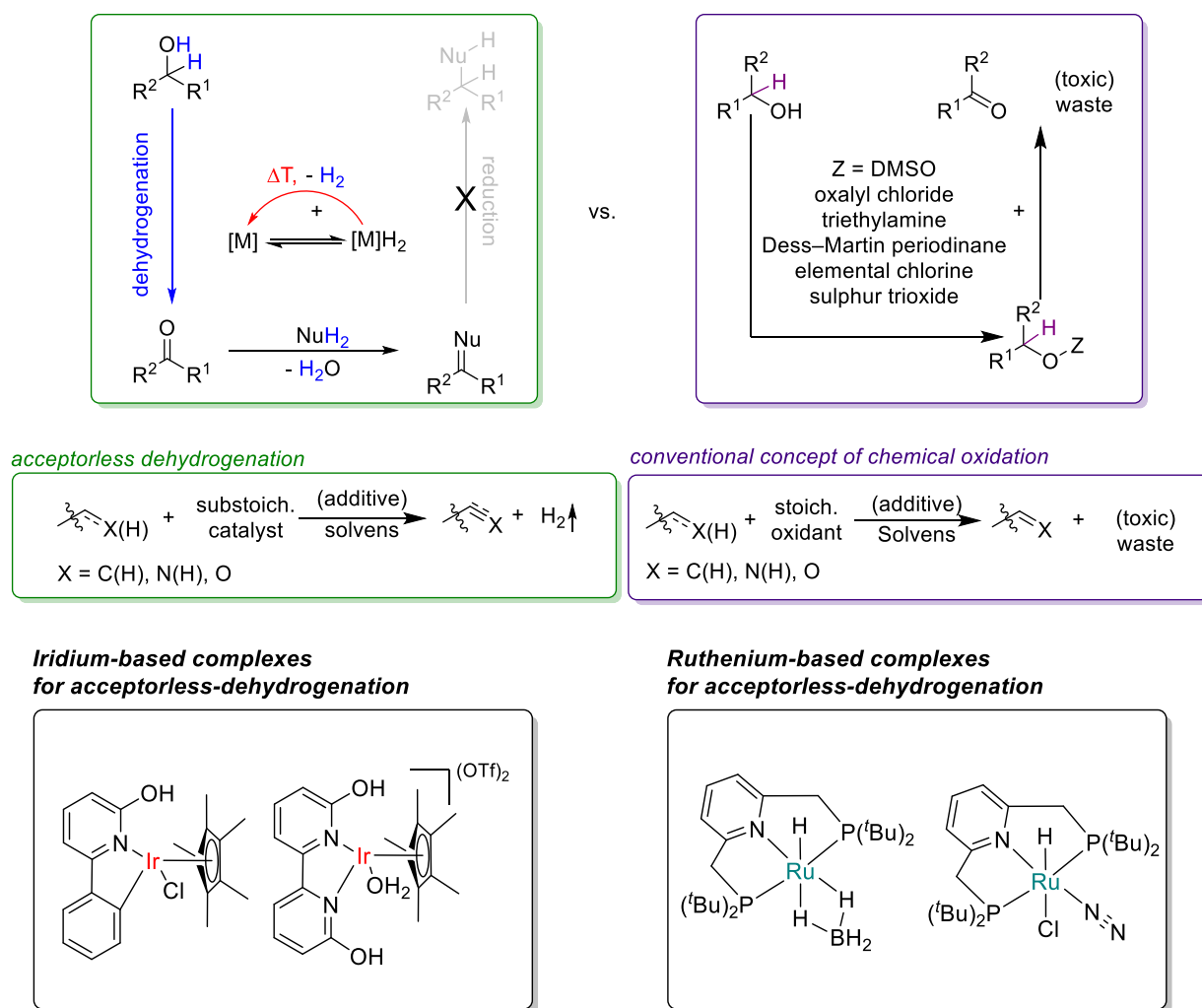


Figure 12: Comparison of *acceptorless dehydrogenation catalysis* with conventional oxidation methods (top). Selected precious metal catalysts (bottom).

3.2 Synthesis of heterocyclic compounds via ADC

3.2.1 Overview: synthesis of *N*-heterocyclic compound classes via ADC

N-heterocyclic compounds are one of the most important substance classes in organic and pharmaceutical chemistry. They are components of drugs, natural substances, and functional materials as well as polymers. The concept of ADC is particularly attractive for the synthesis of *N*-heterocycles, as alcohols and amino alcohols from renewable resources can be used as starting compounds.

In 1991, WATANABE's group published a novel synthesis of benzoxazoles and benzimidazoles using a Ru catalyst.^[34] From there on various groups have published catalytic syntheses of *N*-heterocycles based on acceptorless dehydrogenation concept, with each work differing in the type of catalyst system, the general reaction conditions, and substitution possibilities. In 2011, the group around CRABTREE published a possibility to convert symmetrical 1,4-diols and primary amines into the corresponding pyrroles.^[35] The groups led by KEMPE, MILSTEIN and SAITO used secondary alcohols and 1,2-amino alcohols for their pyrrole syntheses.^{[36],[37],[38]} BELLER and co-workers established a synthesis concept whereby fully substituted pyrroles were accessible.^[39] Subsequently, further syntheses of aromatic *N*-heterocycles were published. These included pyridines^{[40],[41]}, quinolines^{[40],[42]}, 3-amino pyridines^[43], benzimidazoles^[44], 2-aryl quinazolines^[45], quinoxalines^[44] and pyrimidines^[46] (see Figure 13).

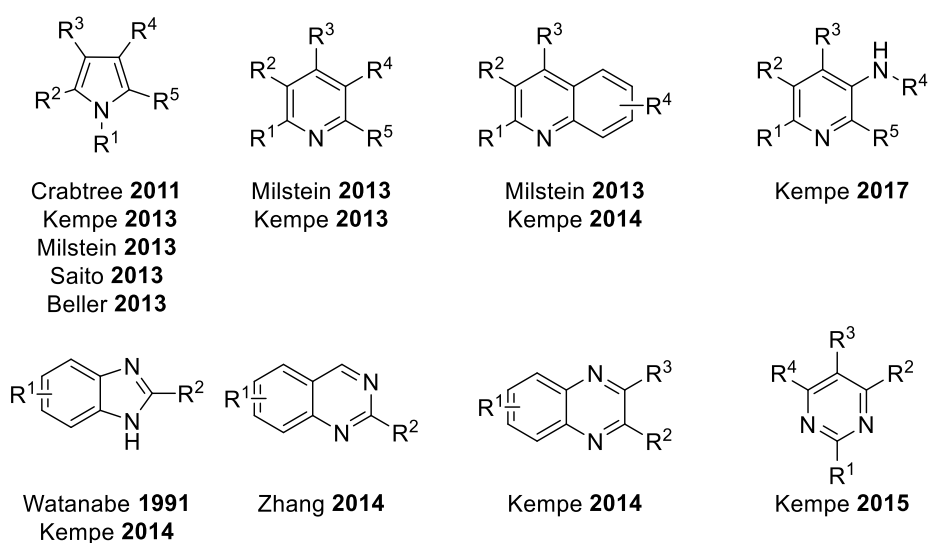


Figure 13: Synthesis of *N*-heterocycles via ADC using precious metal catalysts.

In the following sections, individual publications are discussed in detail to provide a deeper insight into the concepts mentioned.

3.2.2 Iridium- and ruthenium-catalyzed synthesis of pyrroles via ADC

In 2013, KEMPE and his colleagues published a new method for converting secondary alcohols with amino alcohols into various pyrrole derivatives. The iridium complex used was able to selectively eliminate hydrogen to subsequently yield the desired pyrrole derivatives by condensation (see Figure 14).^[36]

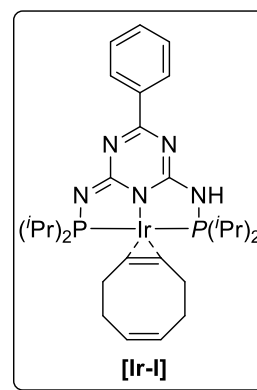
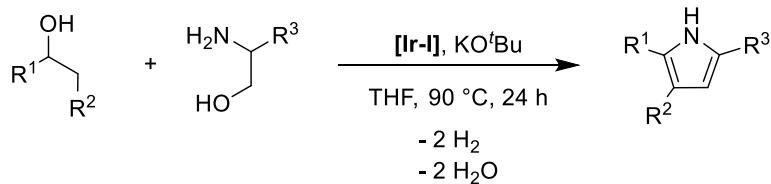
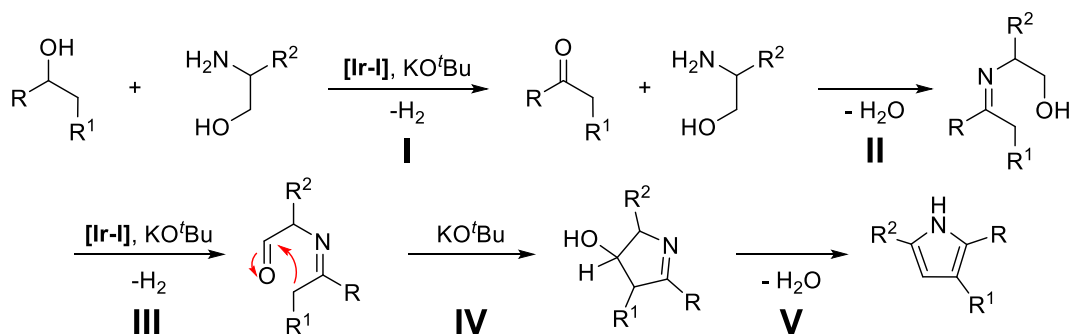
General reaction conditons**Postulated mechanism**

Figure 14: Synthesis of pyrrole derivatives according to MICHLIK *et al.* (top). Postulated mechanism (bottom).

Mechanistic and kinetic studies showed that the pyrrole is produced in three steps. After oxidation of the secondary alcohol to the ketone, the amino alcohol reacts with the resulting ketone to form the imine (**I** $\rightarrow$ **II**). This is followed by another oxidation and elimination of the hydrogen (**II** $\rightarrow$ **III**) and finally condensation and formation of the pyrrole (**III** $\rightarrow$ **IV** $\rightarrow$ **V**). The oxidation of secondary alcohols proved to be a rate-determining step, as no imine intermediate could be detected during the reaction control. Thus, the C-alkylation had to proceed significantly faster than the oxidation of alcohol to the ketone. In addition, it could be concluded that the Ir-catalyst **[Ir-I]** itself was essential for the oxidation reaction, but the base used was required for the C-C coupling reactions or condensation (see Figure 14).^[36]

In the same year, MILSTEIN and his team published the preparation of pyrroles using ruthenium precatalyst **[Ru-I]** (see Figure 15).^[37]

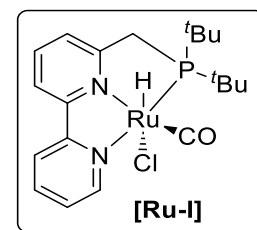
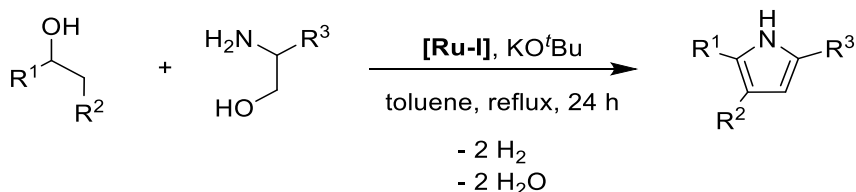
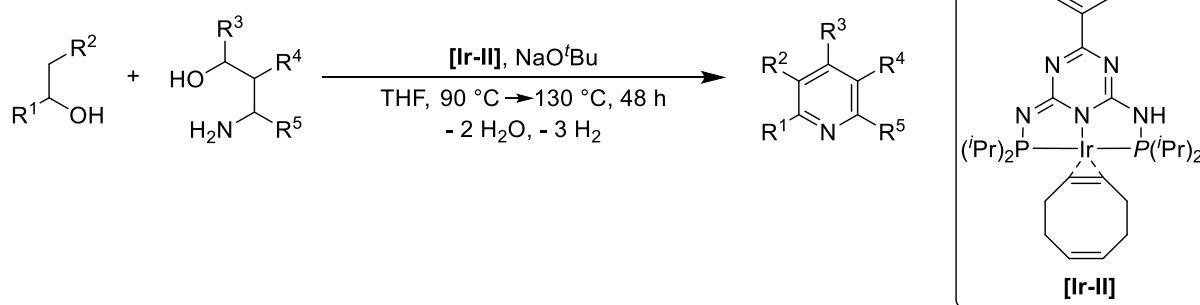


Figure 15: Ru-mediated synthesis of pyrroles using ADC according to SRIMANI *et al.*

3.2.3 Iridium-catalyzed synthesis of pyridines via ADC

Once the research community had internalized the general principle of synthesizing nitrogen-containing heterocycles using acceptorless dehydrogenation and borrowing-hydrogen catalysis, it was possible to synthesize not only pyrroles, but also several other interesting nitrogen heterocycles. In 2013, KEMPE and his colleagues published a novel synthesis of pyridines. By combining 1,3-aminoalcohols and secondary alcohols, the group was able to synthesize multi-substituted pyridine derivatives (see Figure 16).^[41]

General reaction conditions



Postulated mechanism

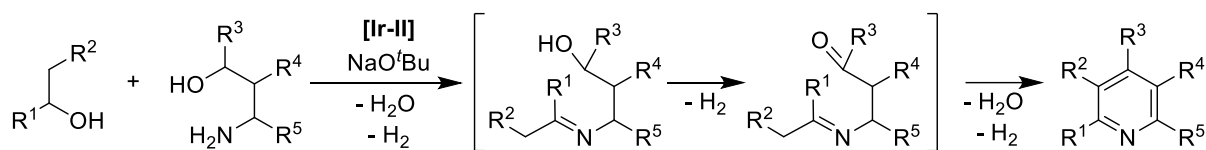


Figure 16: Ir-mediated synthesis of pyridines according to MICHLIK *et al.* (top). Postulated mechanism (bottom).

In the newly developed synthesis, the 1,3-amino alcohol reacts with the previously oxidized or dehydrated secondary alcohol in the initial step. Mechanistic studies showed that the amino alcohol used was oxidized significantly more slowly and that selective imine formation was therefore possible. In the next step, the free hydroxyl group of the amino alcohol is dehydrogenated, and the olefin is formed by base-catalyzed ring closure and water elimination. Aromatization by β -H elimination and release of H₂ led to the formation of the desired pyridine derivatives (see Figure 16).^[41]

3.2.4 Iridium-catalyzed synthesis of pyrimidines via ADC

In 2015, KEMPE and co-workers published a synthesis of pyrimidines based on the principle of ADC. They used various primary and secondary alcohols as well as amidines, which were selectively linked via C-C and C-N bond formation during the multicomponent reaction (see Figure 17).^[46]

The group first investigated the synthesis of trisubstituted pyrimidines. Later, they established a three-component reaction using secondary alcohols, primary alcohols and an amidine. Mechanistic investigations showed that the two alcohols were dehydrogenated in the first step by the catalyst used. The oxidation was followed by *in situ* aldol condensation and the formation of an α - β -unsaturated ketone intermediate. Reaction with the amidine used and dehydration by β -H elimination led to the formation of the pyrimidine (see Figure 17).^[46]

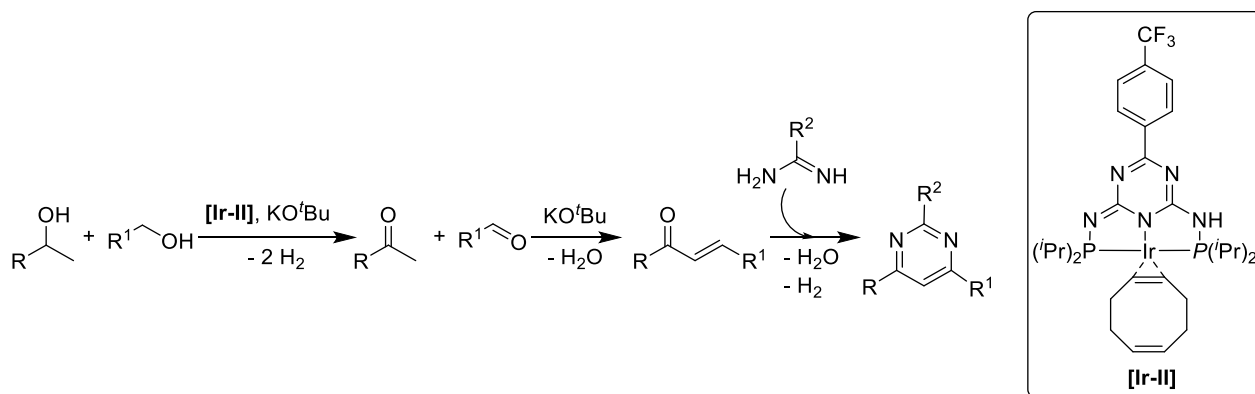


Figure 17: Ir-catalyzed multicomponent synthesis of pyrimidines according to DEIBL *et al.*

After establishing a three-component synthesis, the research group focused on the preparation of tetrasubstituted pyrimidines. For this purpose, they developed a consecutive four-component reaction, in which the stepwise addition of the individual components was crucial. In the first step of the reaction, a secondary and a primary alcohol are dehydrogenated. The subsequent *in situ* aldol condensation initially leads to an α - β -unsaturated ketone. After a longer reaction time and an adjustment of the reaction temperature, both the carbonyl group and the double bond could be reduced. A secondary alcohol was formed, which, after addition of another alcohol and the desired amidine, reacted further to form the tetrasubstituted pyrimidine derivative.^[46]

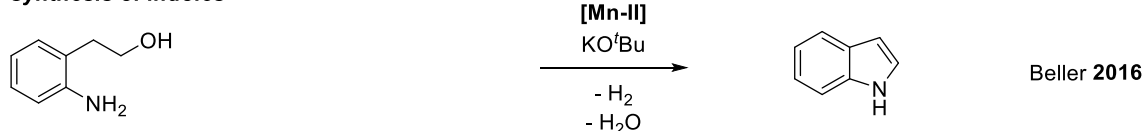
3.2.5 Manganese-catalyzed synthesis of *N*-heterocycles via ADC

In the following years, attempts were made to replace expensive precious metal catalysts with 3d-metal catalysts. Mn-based systems proved to be one of the most promising candidates. Several Mn-complexes have been therefore developed and investigated as (pre)catalysts for the synthesis of *N*-heterocycles using acceptorless dehydrogenation (see Figure 18).

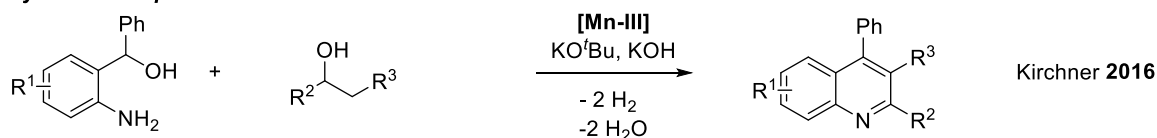
The syntheses of *N*-heterocycles described in this section demonstrate the great potential of manganese catalysts for ADC reactions. By using these highly selective (pre)catalysts and through understanding and controlling reaction conditions, novel and complex reaction sequences can often be generated, which can lead to interesting target compounds.

The BELLER group used precatalyst **[Mn-II]** for the synthesis of indole (Figure 18).^[47] KIRCHNER and his colleagues developed the synthesis of quinolines starting from 2-aminobenzyl alcohols and alcohols.^[48] The same catalyst was used by the research group to synthesize pyrimidines.^[43] KEMPE and co-workers also published a Mn-catalyzed synthesis of pyrimidines shortly thereafter.^[49] The same catalyst was also used for the first 3d-metal catalyzed synthesis of pyrroles using alcohols and amino alcohols.^[50] In 2018, SRIMANI and co-workers published a phosphine-free manganese(I) complex **[Mn-IV]** derived from a tridentate NNS ligand for the selective synthesis of 2-substituted and 1,2-disubstituted benzimidazoles by acceptorless dehydrogenative condensation of aromatic diamines with primary alcohols.^[51] In the same year, MILSTEIN and colleagues published the synthesis of quinoxalines and pyrazines using the acridine-based Mn pincer complex **[Mn-V]** (see Figure 18).^[52]

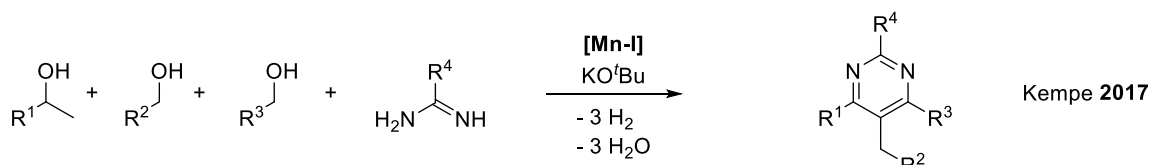
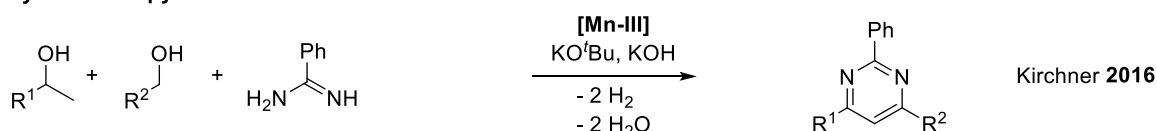
synthesis of indoles



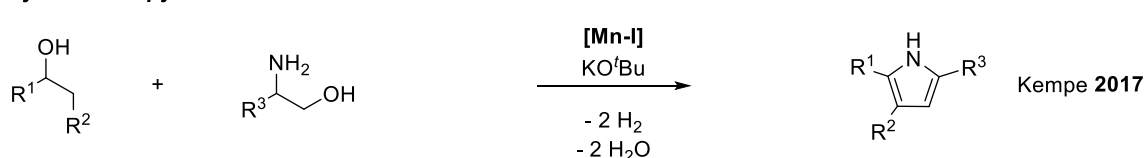
synthesis of quinolines



synthesis of pyrimidines



synthesis of pyrroles



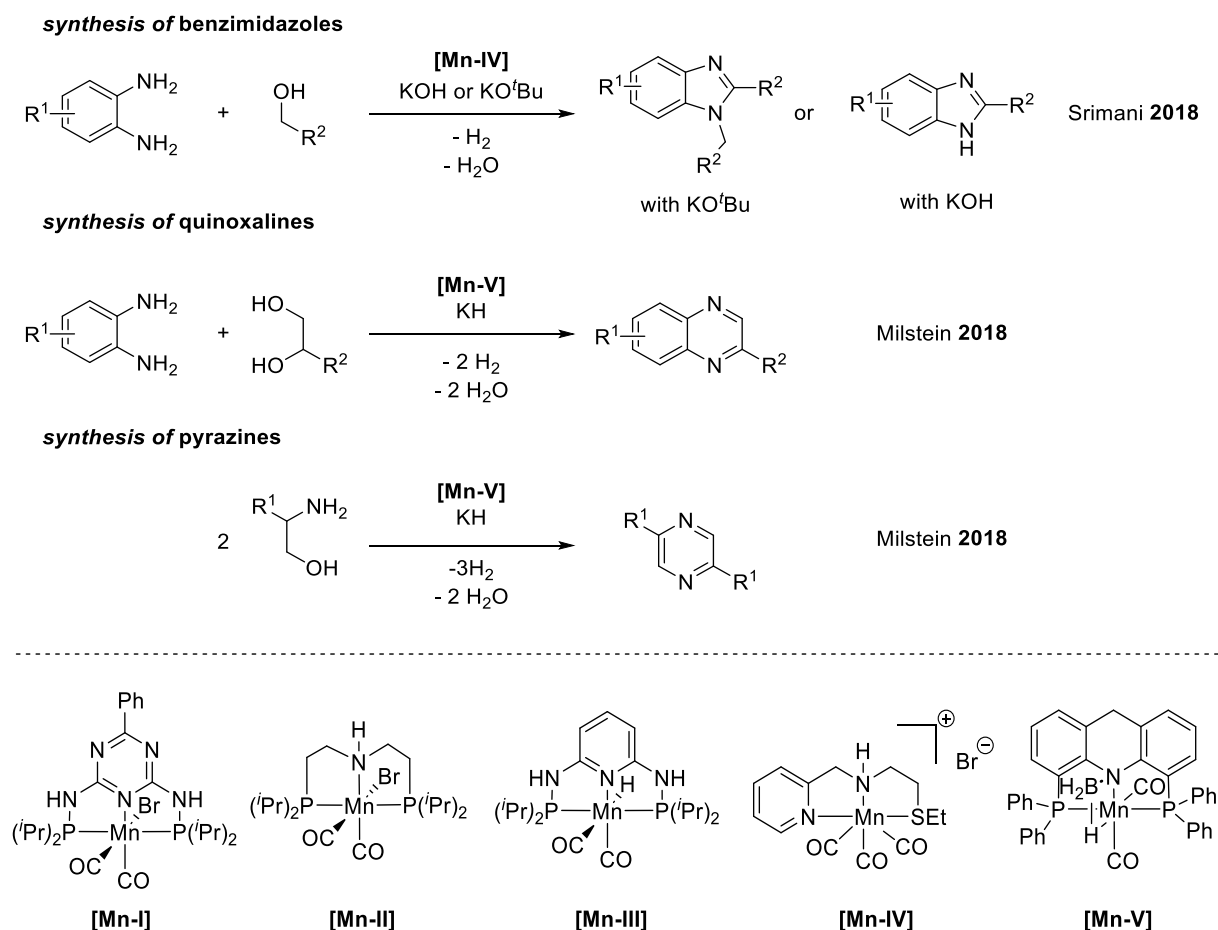


Figure 18: Dedicated overview of Mn-catalyzed synthesis of *N*-heterocycles via ADC.

3.3 Iterative synthesis

3.3.1 Synthetic methods for enforcing sequence control

Accepterless dehydrogenation catalysis enables the synthesis of highly functionalized compounds from simple and partially sustainable building blocks. Another concept in chemistry that builds on this idea is iterative synthesis. By repeating individual reaction steps in iterative sequences, it becomes possible to rapidly produce functionalized, structurally diverse, and sequence-defined compounds. In general, there are three different polymerization or synthesis methods used for the preparation of sequence-controlled compounds.

The idea of the precise macromonomer approach is characterized by the coupling of sequence-specific macromonomers, or defined individual building blocks, in periodic sequences. For example, this principle has been used to produce elastin-like polymers. The individual, previously synthesized building blocks were coupled together using a copper-catalyzed click reaction (see Figure 19).^{[53],[54]}

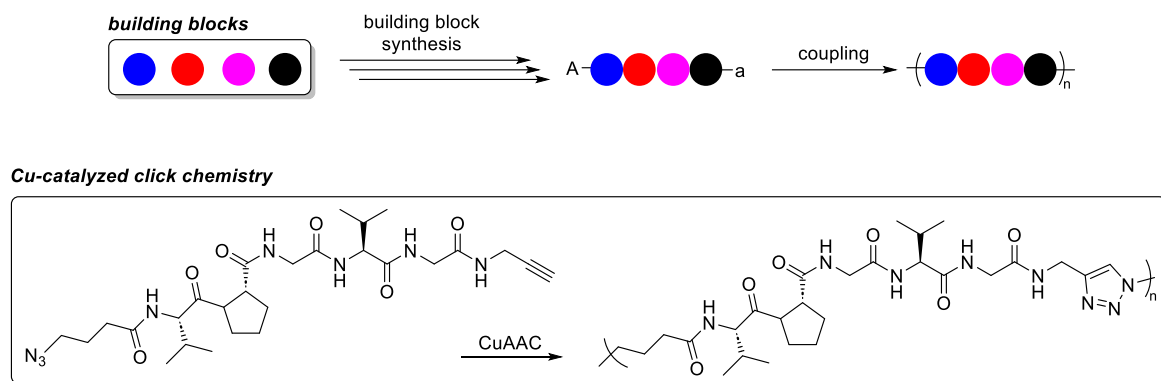
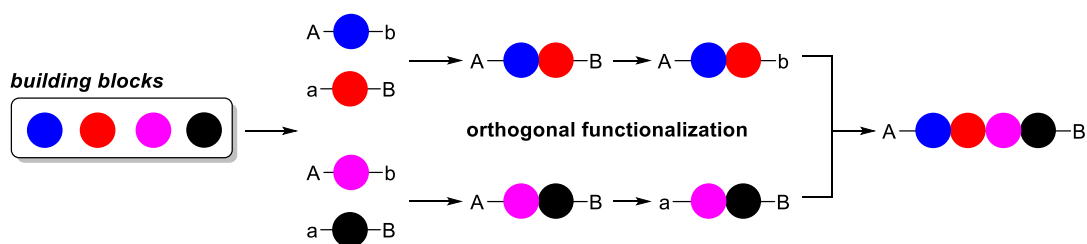


Figure 19: Coupling of defined macromonomers (top). Synthesis of elastin-like polymers using click chemistry (bottom).

In contrast, iterative exponential growth achieves the synthesis of complex oligomers or polymers through sequential addition of monomers. Using repetitive reaction conditions and orthogonal functionalization or coupling, precisely defined sequences can be constructed (see Figure 20).^{[53],[55]}



Cu-catalyzed coupling of orthogonal functional groups

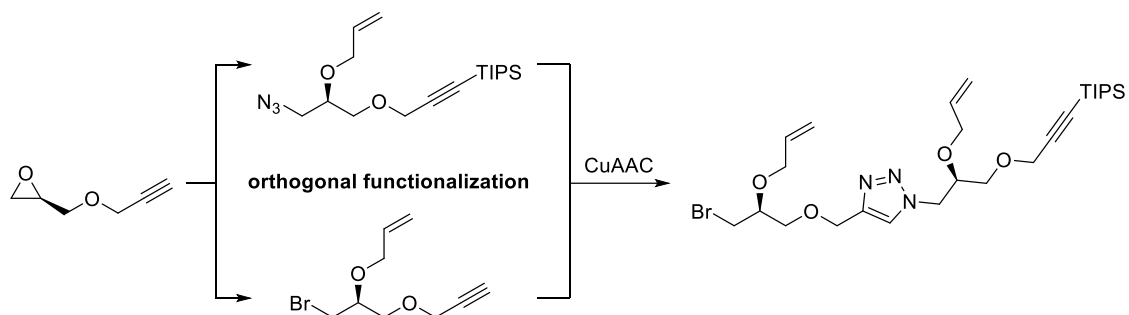


Figure 20: Principle of iterative exponential growth (top). Synthesis of uniform diblock copolymers using orthogonal functionalization and Cu-catalyzed coupling.

In addition to the previously mentioned examples, the classic iterative construction of defined polymer or oligomer sequences focuses on a linear growth. Individual building blocks are successively coupled together (see Figure 21).^{[53],[56]}

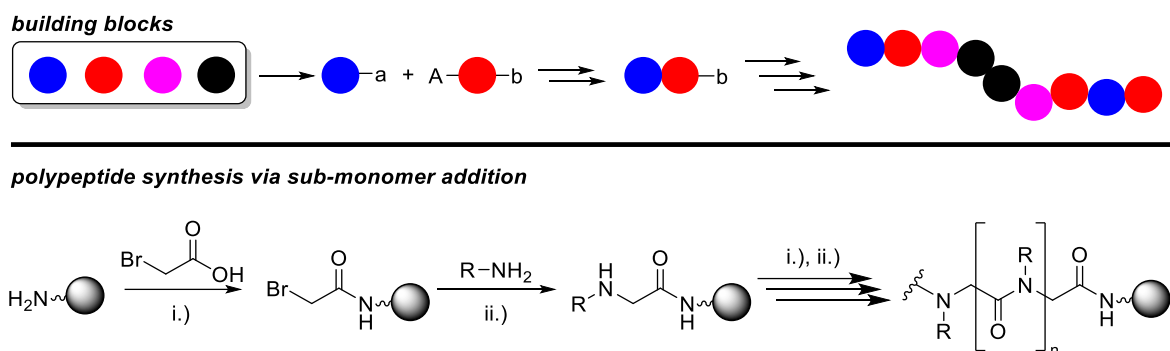


Figure 21: Principle of linear growth (top). Polypeptide synthesis via sub-monomer-addition. (bottom).

3.3.2 Synthesis of sequence defined oligoanilines

In 1998, BUCHWALD and co-workers discussed multiple approaches for the synthesis of sequence defined oligoanilines via Pd-catalyzed aryl amination (see Figure 22).^[57]

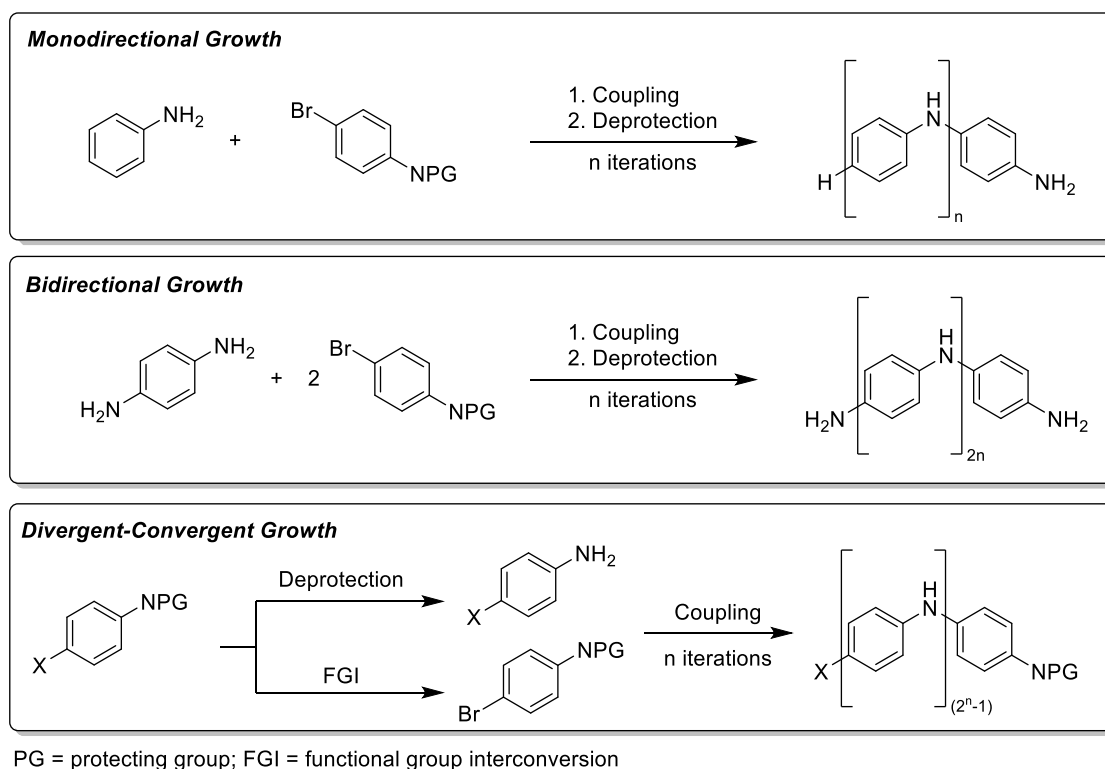


Figure 22: Approaches for the synthesis of sequence defined oligoanilines via Pd-catalyzed aryl amination.^[52]

They established a palladium-catalyzed amination sequence employing an orthogonal protecting-group strategy, which enables the controlled synthesis of oligoanilines of varying lengths and degrees of functionalization.

This method affords soluble precursors that can be deprotected to yield electroactive oligomers, including phenyl-capped heptaaniline and decaaniline, end-functionalized octaanilines, and 16- and 24-mers, whose properties have been characterized by spectroscopy and electrochemical analysis. For example, they synthesized a heptamer via a bidirectional approach (see Figure 23).^[57]

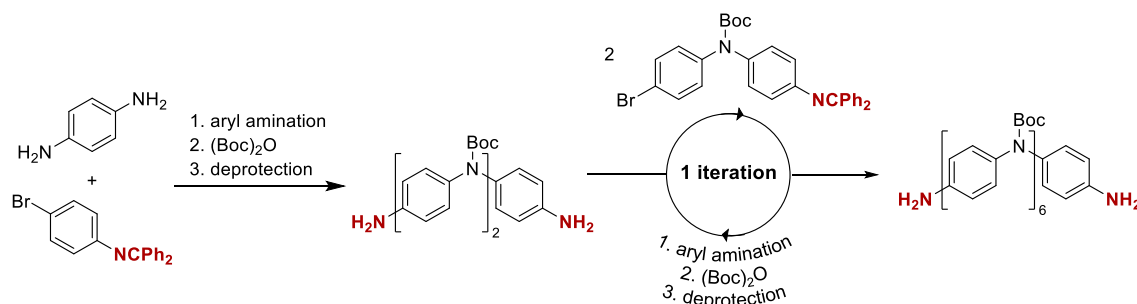
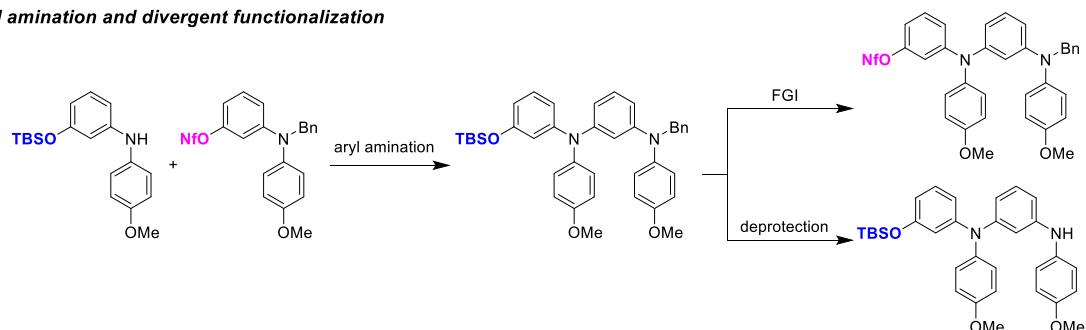


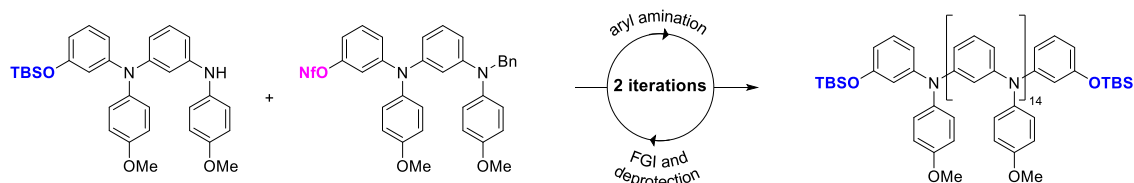
Figure 23: Bidirectional synthesis of an aniline heptamer using Pd-catalyzed aryl amination.

In the same year, HARTWIG and colleagues established a synthesis route to the largest meta-linked linear aryl amine oligomer. They used Pd catalyzed amination of aryl triflates in an exponential growth strategy. The approach uses methoxy-substituted *N*-aryl groups for solubility and NMR tracking, triaryl amine units to stabilize radical cations and prevent cross-linking, and orthogonally protected chain termini (*N*-benzylamine and TMS ether) to enable selective formation of diaryl amines and aryl nonaflates (see Figure 24).^[58]

aryl amination and divergent functionalization



iterative exponential synthesis of triaryl amine a triaryl amine oligomer



FGI = functional group interconversion

Figure 24: HARTWIGS's approach for the exponential synthesis of oligoanilines.

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5 OVERVIEW OF THESIS RESULTS

5.1 Synopsis

As previously discussed in the introduction of this thesis, the modern chemical industry faces a significant transition; while the synthesis of bulk chemicals, fine chemicals, and polymers remains essential for technological progress, conventional processes are often energy-intensive and heavily reliant on fossil resources. To minimize environmental impact and actively contribute to a more sustainable future, a structural shift toward eco-friendly, atom-efficient synthetic methodologies is required, making it a core responsibility for contemporary chemists to develop these innovative processes.

In this context, catalysis serves as a key tool by lowering activation energies and enabling alternative pathways that avoid stoichiometric, waste-generating reagents. Within this framework, the synthesis of complex, nitrogen-containing compounds such as *N*-heterocycles and polyamines presents a major challenge, as these essential building blocks for pharmaceuticals, agrochemicals, and functional materials traditionally rely on tedious multi-step sequences and harsh conditions.

To address these challenges from different synthetic angles, this doctoral work focuses on two main strategies: on one hand, it comprises the development of novel catalytic protocols for the direct synthesis of valuable *N*-heterocyclic frameworks from simple, readily available starting materials. On the other hand, this approach is expanded by establishing an innovative, iterative method for the precise synthesis of polyamines, where avoiding protecting groups and utilizing catalytic reactions minimizing both step-count and waste generation.

5.1.2 Manganese-catalyzed dehydrogenation of amido alcohols with liberation of hydrogen for the synthesis of oxazoles

As outlined in **section 3**, PN_3P ligand-stabilized complexes have demonstrated outstanding activity and selectivity in numerous studies by the KEMPE group, particularly in their use as catalysts for a broad range of hydrogenation and dehydrogenation reactions. The earliest investigations focused on Ir-based catalysts. In the following years, however, the group expanded this chemistry to include newly developed (pre)catalysts based on 3d-transition metals. Notably, they introduced a series of Mn(I) (pre)catalysts that exhibit excellent activity, high selectivity, and remarkable thermal stability in the hydrogenation of carbonyl compounds and the dehydrogenation of alcohols. Furthermore, the modular design of the PN_3P ligand family enables precise tuning of the steric and electronic properties of the catalyst system. This versatility has facilitated the development of numerous new catalytic applications and innovative synthetic methodologies.

During detailed investigations into the synthesis of 1,3-diketones from alcohols, esters, and a molecular Mn (pre)catalyst, a new concept for accessing β -ketoamides was identified. By reacting esters with amino alcohols instead of alcohols, β -hydroxyamide intermediates were formed, which could subsequently be transformed into a variety of oxazole derivatives following catalytic dehydrogenation and ROBINSON-GABRIEL cyclization. Among the numerous important compound classes in organic chemistry, *N*-heterocycles are of particular interest due to their broad range of applications, including pharmaceuticals, agrochemicals, functional materials, and both fine and bulk chemicals. Oxazoles represent a prominent subclass whose characteristic structural motif is frequently found in pharmaceuticals and organic materials. The ROBINSON-GABRIEL cyclization is one of the most important name reactions for the synthesis of oxazoles, as the regioselective intramolecular cyclization allows all three carbon atoms of the oxazole to be addressed. A major challenge in the preparation of oxazoles using the ROBINSON-GABRIEL cyclization is the synthesis of the β -ketoamides. Established methods, such as the DAKIN-WEST synthesis, suffer from the challenge of introducing various substituents. Other methods rely on toxic and explosive diazo compounds, require stoichiometric oxidants, or generally require significant synthetic effort. Considering the challenges, the simple preparation of β -ketoamides from diverse and partially sustainable starting materials, as well as the differential targeting of all three carbon atoms of the oxazole, is a highly desirable goal.

In the following, a regioselective, two-step, *one-pot* synthesis of oxazoles was established. The concept is based on *tert*-butyl esters and amino alcohols, both of which are abundant and widely available. The first step involves transesterification and catalytic dehydrogenation with Mn-(pre)catalyst **[Mn-I]** and KO^tBu in 1,4-dioxane. Subsequently, the resulting β -ketoamide is converted into the corresponding oxazole by adding POCl₃ as a cyclodehydration reagent (see Figure 25).

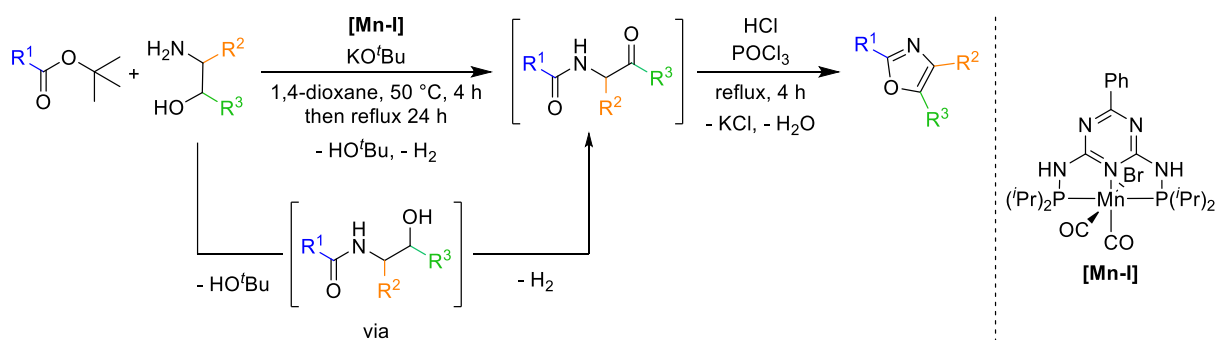


Figure 25: Synthesis of oxazole derivatives using a consecutive *one-pot* synthesis.

With optimized conditions for the newly developed two-step process, a substrate scope was established. The corresponding products could be isolated in yields up to 97 %. 44 of the 45 compounds prepared have not been previously described in the literature.

OXAPROZIN, an active ingredient of a drug, could also be obtained in moderate yields directly from the newly developed *one-pot* synthesis under adapted reaction conditions (see Figure 26).

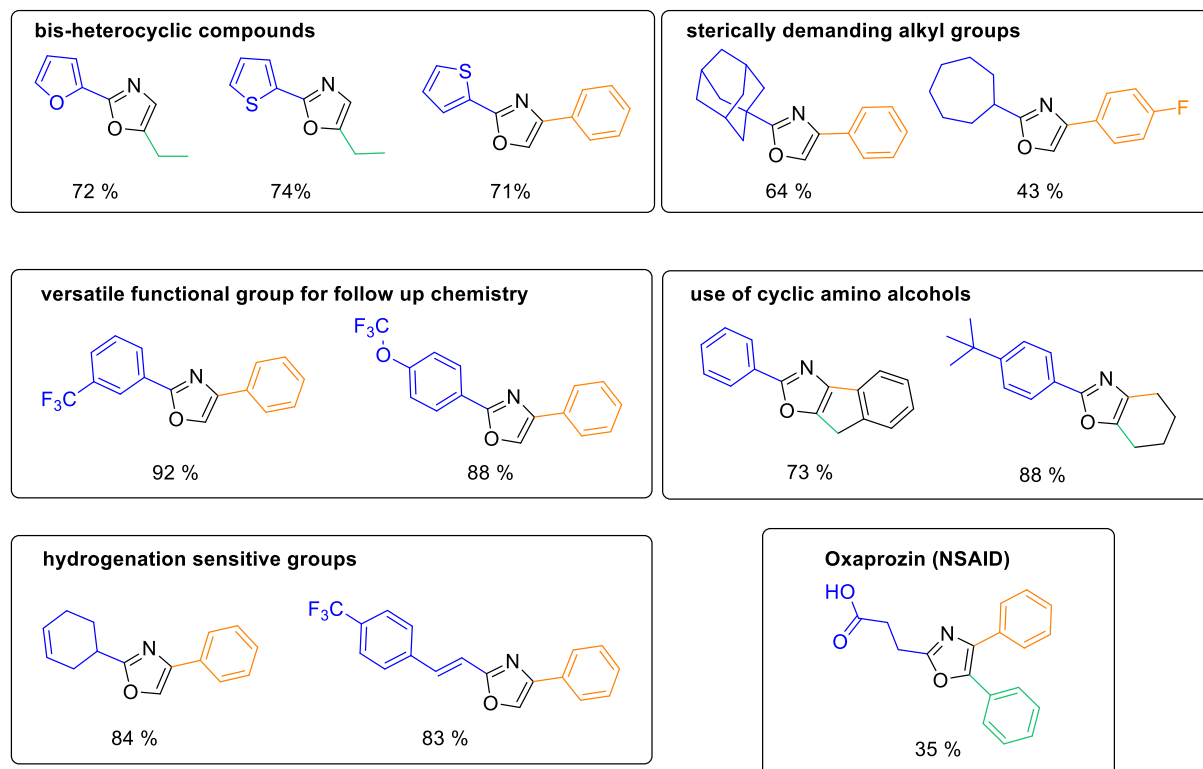


Figure 26: Selected substrate scope for the synthesis of oxazoles with isolated yields as indicated.

In the next step, various experiments were conducted to evaluate the individual reaction mechanisms. Kinetic experiments with various equivalents of KO^tBu showed that the rate of transesterification is base-dependent. Furthermore, a competition experiment was conducted to evaluate the influence of the hydroxy group. After evaluating the results, a mechanism for the formation of the β -hydroxyamides was postulated (see Figure 27).

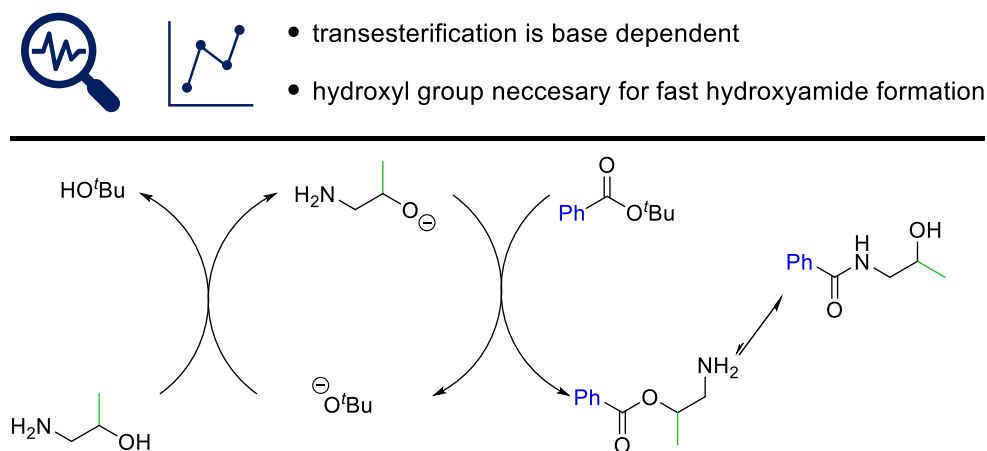


Figure 27: Summary of key mechanistic findings (top) and proposed mechanism (bottom).

Furthermore, a ¹H NMR experiment was performed to investigate the decomplexation of [Mn-H]K₂ in the presence of the β -hydroxyamide intermediate.

Comparison of the spectra of the different species showed that the addition of the intermediate leads to decomplexation of the potassium in the guanidine backbone of $[\text{Mn-H}]\text{K}_2$. This result suggests that stoichiometric amounts of potassium base are required for the formation of the active species of the catalyst (see Figure 28).

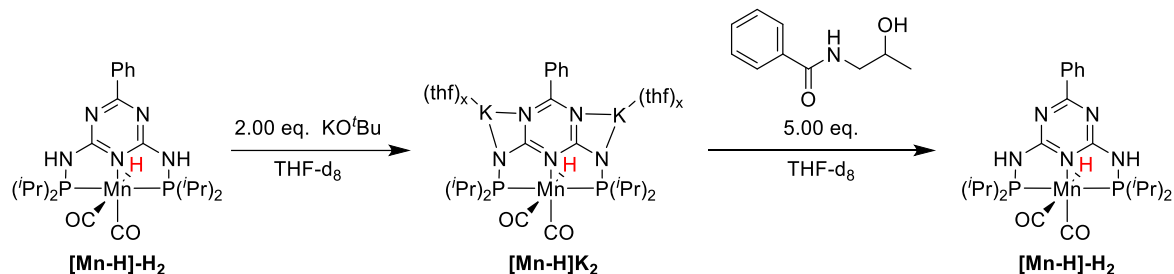


Figure 28: Experiment on the decomplexation of $[\text{Mn-H}]\text{K}_2$.

5.1.3 A catalytic version of the KNORR pyrrole synthesis permits access to pyrroles and pyridines

Building on the results of the first project, subsequent investigations examined the reactivity of 1,3-keto esters with 1,2-amino alcohols. These experiments revealed a highly selective formation of β -hydroxy enamines via condensation of the 1,3-keto ester with the corresponding amino alcohol. Catalytic dehydrogenation of the isolable intermediate afforded the respective pyrrole derivatives. At that time, numerous homogeneously and heterogeneously catalyzed PAAL-KNORR syntheses for the preparation of pyrroles had been reported; however, a catalytic variant of the original KNORR pyrrole synthesis itself had not yet been described.

In the KNORR pyrrole synthesis, substituted pyrroles are obtained from masked aminoketones and 1,3-keto esters. The reaction begins with the nitrosation of a 1,3-keto ester at its *CH*-acidic position. The resulting nitroso intermediate is then converted *in situ* under reductive conditions into the corresponding α -aminoketone, which subsequently reacts with a second equivalent of a 1,3-keto ester to yield the desired pyrrole derivative. The limitations of this synthetic sequence arise primarily from the restricted availability of suitable starting materials, the pronounced tendency of the highly reactive α -aminoketone to undergo self-condensation, and the consequently limited product diversity. In many cases, the method is effectively confined to the synthesis of symmetrical pyrrole derivatives bearing two identical ester substituents. Additionally, the nitrosation and subsequent reduction steps generate equimolar amounts of waste, and both transformations typically require harsh reaction conditions. The self-condensation of the α -aminoketone not only diminishes the yield of the desired product but also significantly reduces the overall regioselectivity of the reaction.

In the following, a catalytic two-step variant of the KNORR pyrrole synthesis was developed, which could be further expanded to a novel pyridine synthesis through the appropriate choice of amino alcohols. Both *N*-heterocycles are highly significant compound classes with a broad range of applications.

Once again, a combination of KO^tBu, 1,4-dioxane, and **[Mn-I]** proved to be the most effective system for the catalytic dehydrogenation of the β -hydroxy enamines. Using these optimized conditions, the substrate scope was explored. For the consecutive *one-pot* synthesis, acetic acid served as a simple acid catalyst to promote the condensation between the amino alcohols and the 1,3-keto esters (see Figure 29).

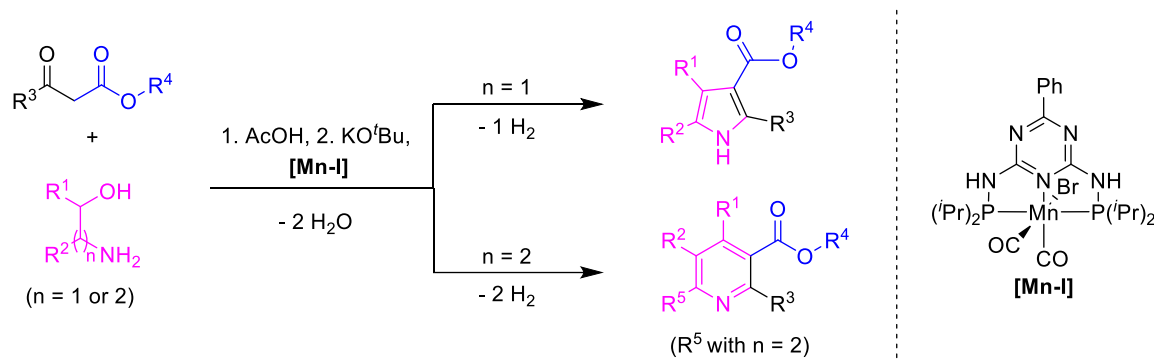


Figure 29: Established catalytic version of the KNORR pyrrole synthesis.

The resulting pyrrole and pyridine derivatives were isolated in yields of up to 97 %. Notably, the majority of the 43 compounds prepared had not been previously reported in the literature (see Figure 30).

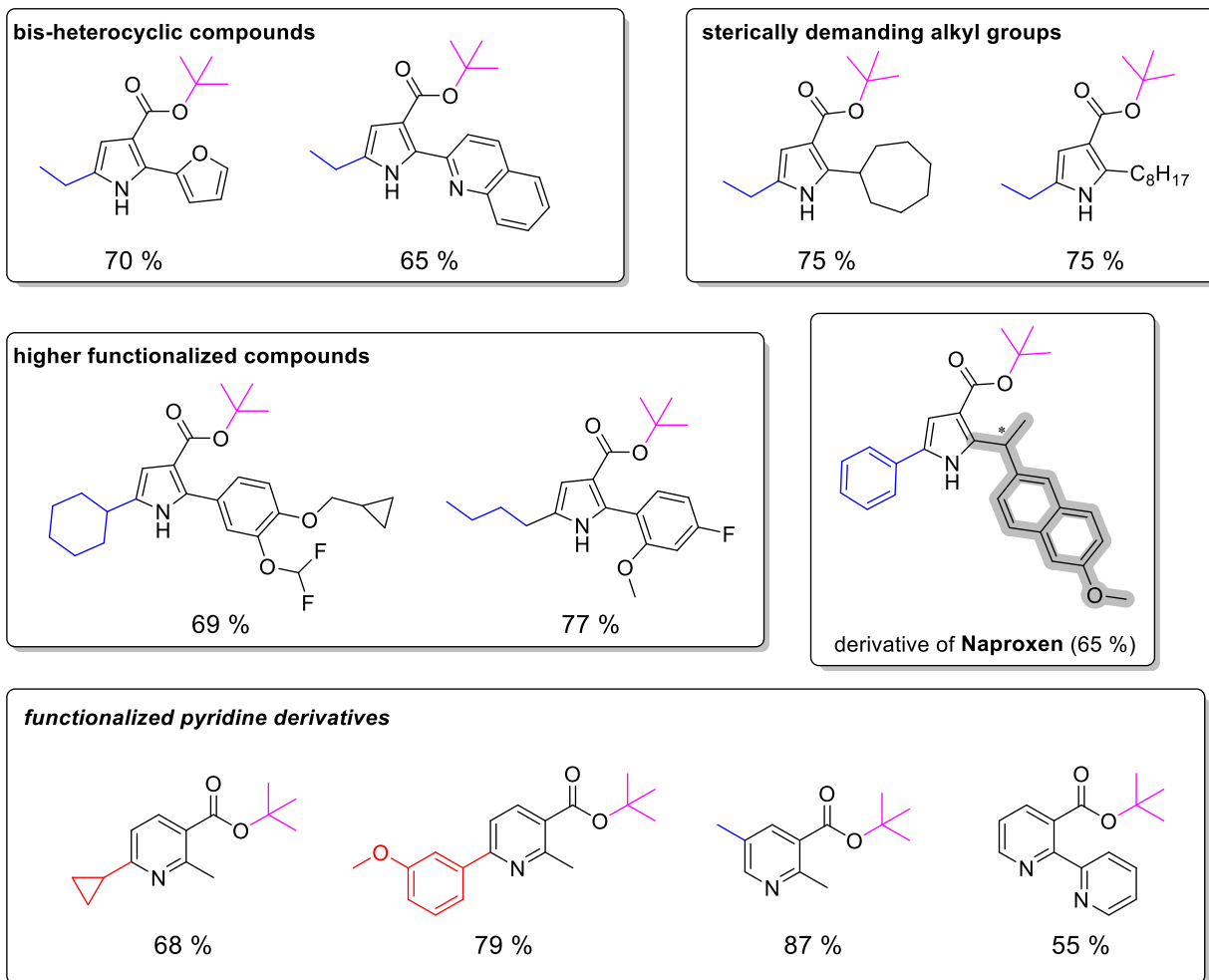
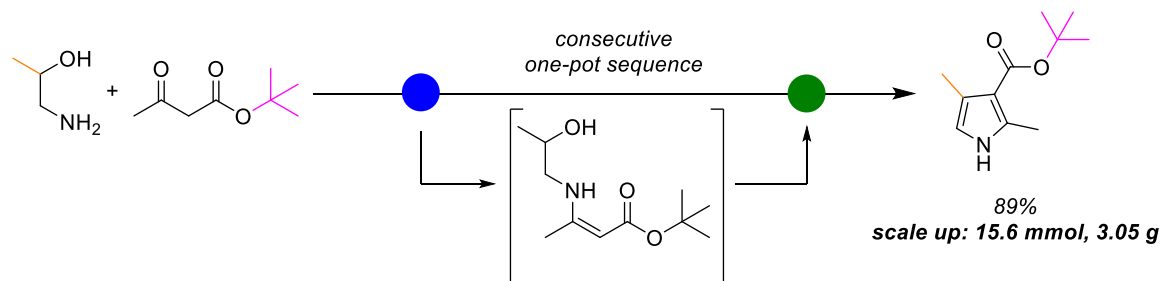


Figure 30: Selected substrate scope for the synthesis of pyrroles and pyridines with isolated yields as indicated.

To demonstrate the general applicability of the newly synthesized building blocks, SUNITINIB, an active ingredient of an anti-cancer drug, was synthesized in four steps. The starting compound was prepared on a large scale according to the developed one-pot synthesis (see Figure 31).

scale up building block synthesis



synthesis of SUNITINIB

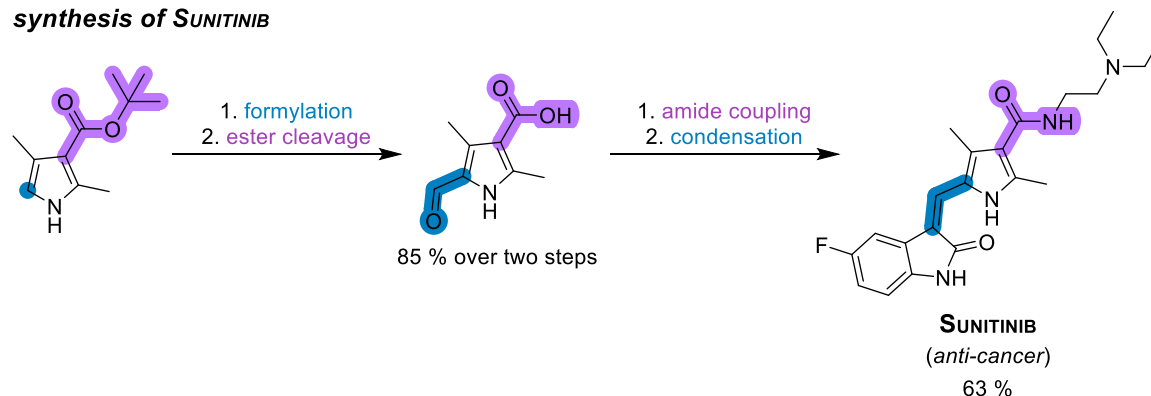


Figure 31: Large scale building block synthesis (top). Synthesis of SUNITINIB (bottom).

In the next step, various experiments were conducted to evaluate the individual reaction mechanisms including kinetic experiments, the collection of hydrogen, the isolation of potassium adducts, NMR experiments as well as different control reactions (see Figure 32). Time-resolved high-pressure NMR experiments suggested that the formation of the pyridine derivatives takes place in a two-step process. In the first catalytic cycle the dihydropyridine intermediate is formed, followed by the dehydrogenation of the polar C-N bond and formation of the desired pyridine derivative (see Figure 32 and 33).

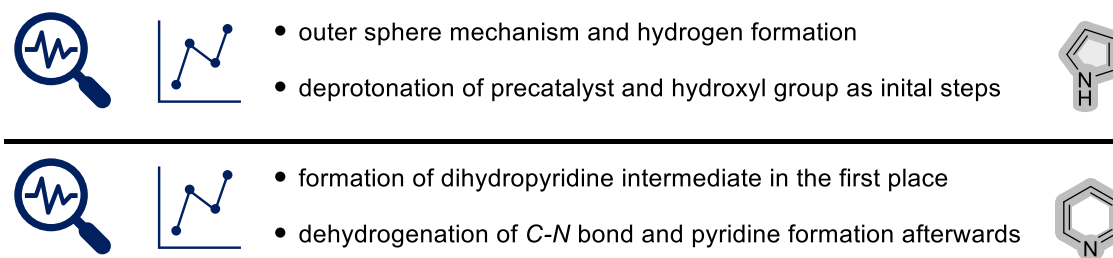


Figure 32: Mechanistic investigations for the catalytic formation of pyrroles and pyridines.

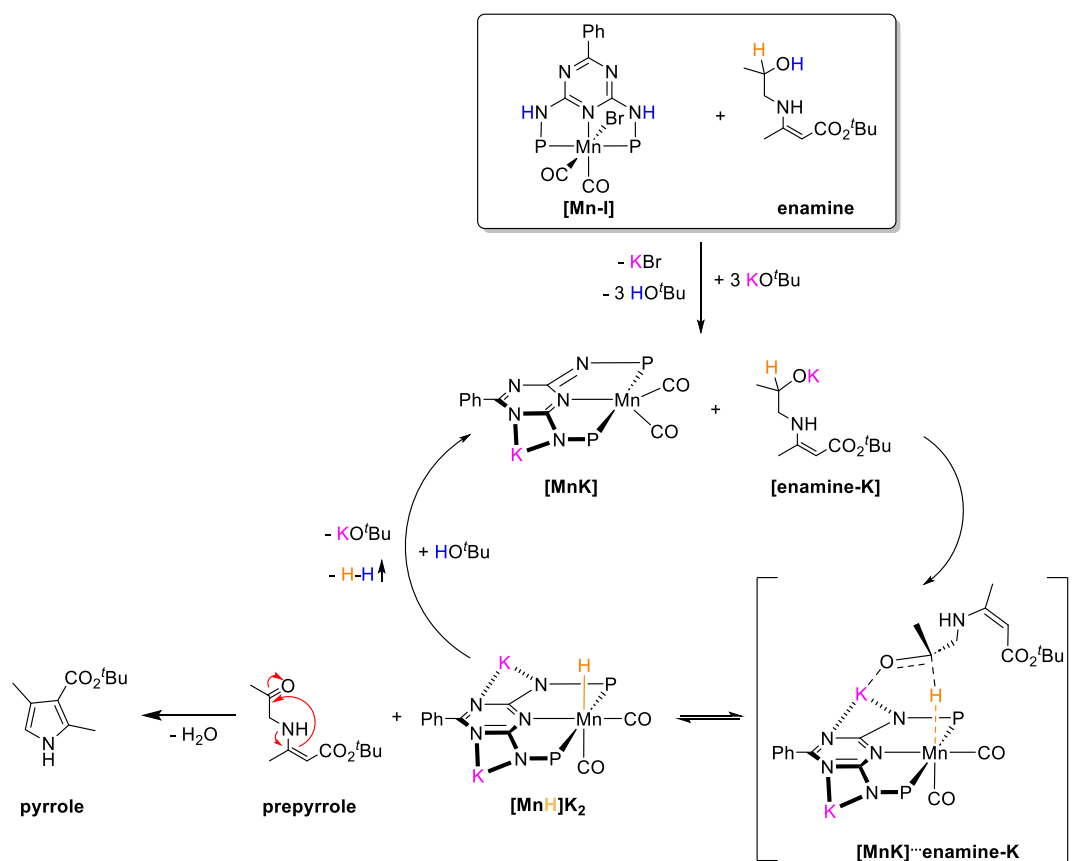


Figure 33: Proposed catalytic cycle for the formation of the corresponding pyrrole derivatives.

5.1.4 Catalytic two-step synthesis of sequence defined polyamines

Following the second project, the idea came up to establish an iterative synthesis concept integrating substituted *N*-heterocycles to form even higher functionalized compounds. Since substituted oxazoles, pyrroles and pyridines could be synthesized using the previously developed methods, these were to serve as the main building blocks.

After careful consideration and unsuccessful attempts to establish an iterative synthesis of *N*-heterocycle-containing oligomers, a revised strategy emerged that should combine iterative synthesis with complex nitrogen-containing structures without relying on oxazoles, pyrroles, or pyridines as core building blocks.

During the elongation process, the individual building block should be linked step by step in successive reaction cycles. Like a modular building block system, this approach should allow targeted control over the sequence, composition, and length of the resulting molecules. This precise controllability is of central importance for the development of customized functional materials.

One of the most promising nitrogen containing polyamines are oligo- and polyanilines. These kinds of organic materials are especially interesting because of their wide range of applications and restricted synthetic access.

A newly developed iterative synthesis concept was initially implemented as a two-step elongation process, with Pd-catalyzed aryl amination and nitroarene hydrogenation serving as the key catalytic transformations. Readily available 1-chloro-4-nitrobenzene derivatives act as the building blocks for the elongation of the conjugated substrates. Importantly, no protecting group strategy is required, as the nitro group both serves as a protecting group and activates the aryl chloride towards the amination reaction (see Figure 34).

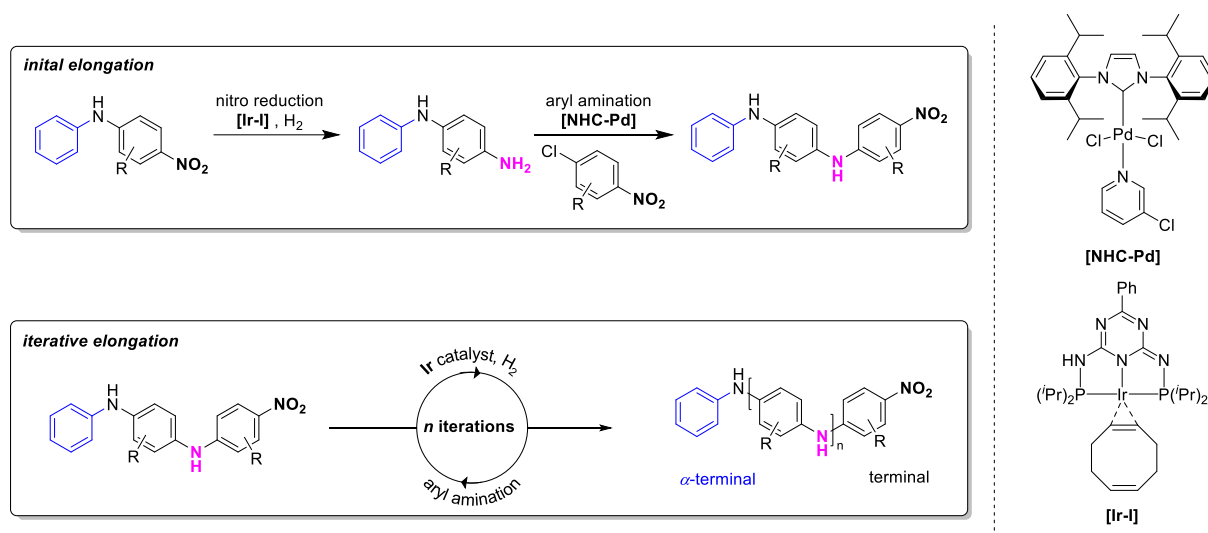


Figure 34: Iterative synthesis of sequence defined polyamines via a two-step catalytic process.

To demonstrate the general applicability and accessibility of this newly developed method, a tetraamine was synthesized without fully optimized reaction conditions (see Figure 35).

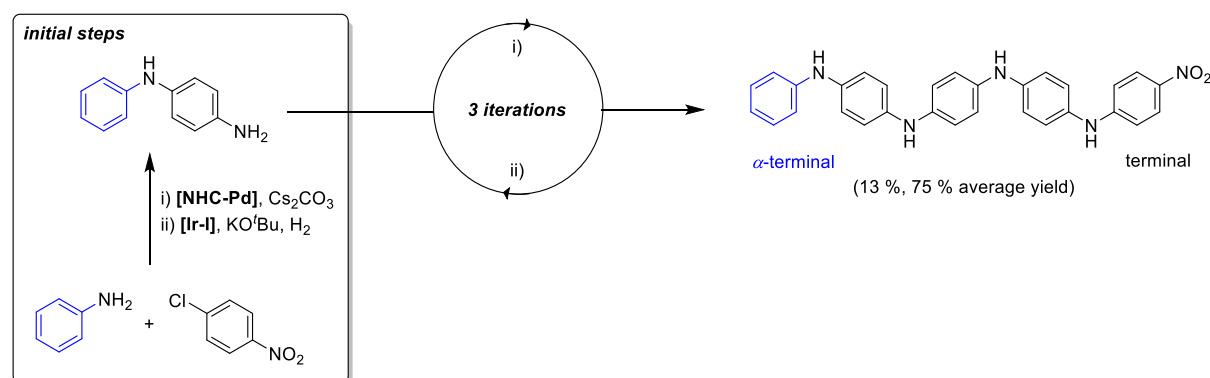


Figure 35: Iterative synthesis of a tetraamine via a catalytic two-step process.

During the elongation process, the intermediate primary amines were observed to be sensitive to oxidation, and their solubility decreased progressively with increasing chain length of the arylamine derivatives. These findings suggested that (partial) *N*-functionalization would be advantageous for the synthesis of larger derivatives, improving both solubility and oxidative stability. Additionally, this approach allows the preparation of polyamines functionalized at two anchor points, further enhancing structural diversity. Consequently, the iterative synthetic concept was expanded to incorporate an additional *N*-functionalization step (see Figure 36).

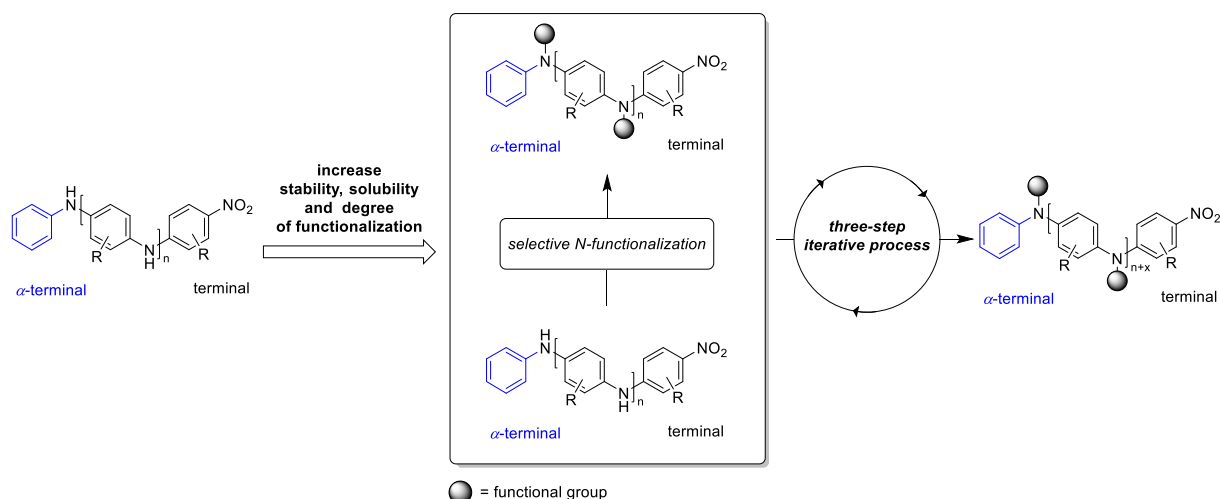


Figure 36: Development of an extended three-step synthesis process.

Initially, a substrate scope was established to identify which substituents could be introduced at the nitrogen atom. Both alkyl chains and aryl groups could be selectively incorporated. Additionally, differently substituted, and halogenated nitrobenzene derivatives were compatible, allowing further extension of the substrate scope (see Figure 37).

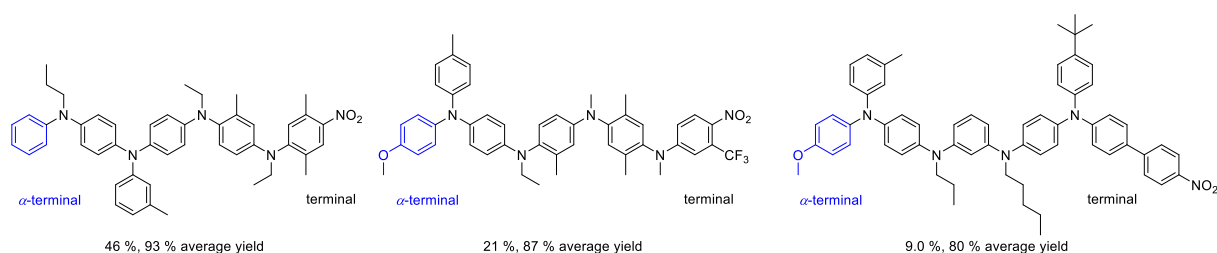


Figure 37: Selected examples of synthesized oligoamines.

Furthermore, end-group functionalization of the terminal amine was demonstrated, and a small substrate library was established. The two-dimensional functionalization and the resulting high degree of modularity allow the synthesis of a remarkable diversity of substrates, even from a limited set of different monomers (see Figure 38).

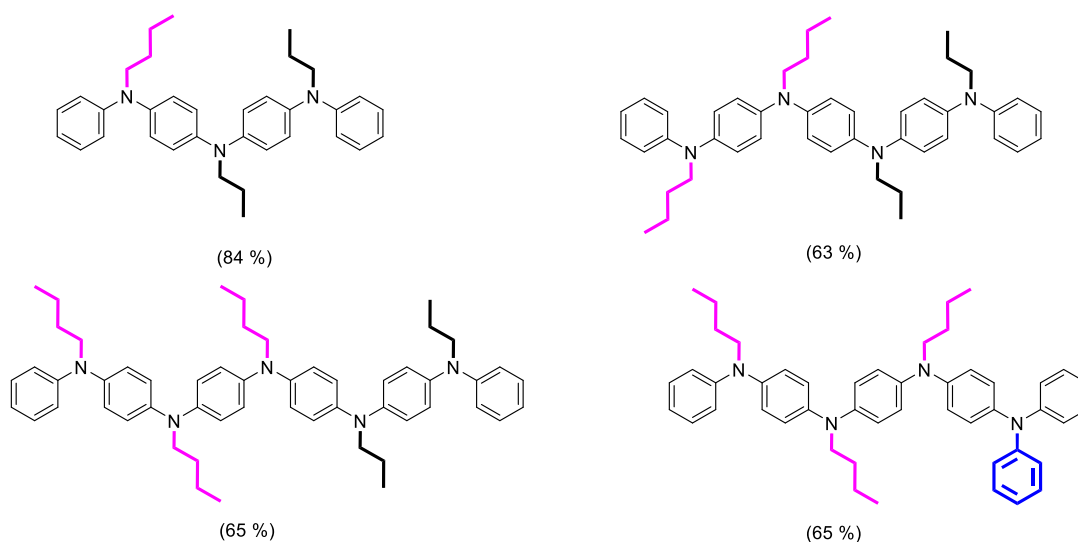
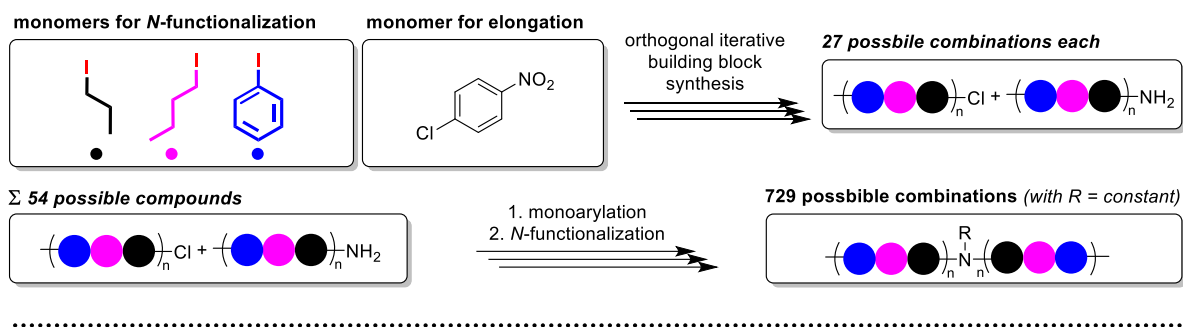


Figure 38: Schematic representation of the possibilities for the synthesis of substrate libraries.

Finally, through applying a convergent concept, complex polyamines could be synthesized via orthogonal synthesis (see Figure 39).

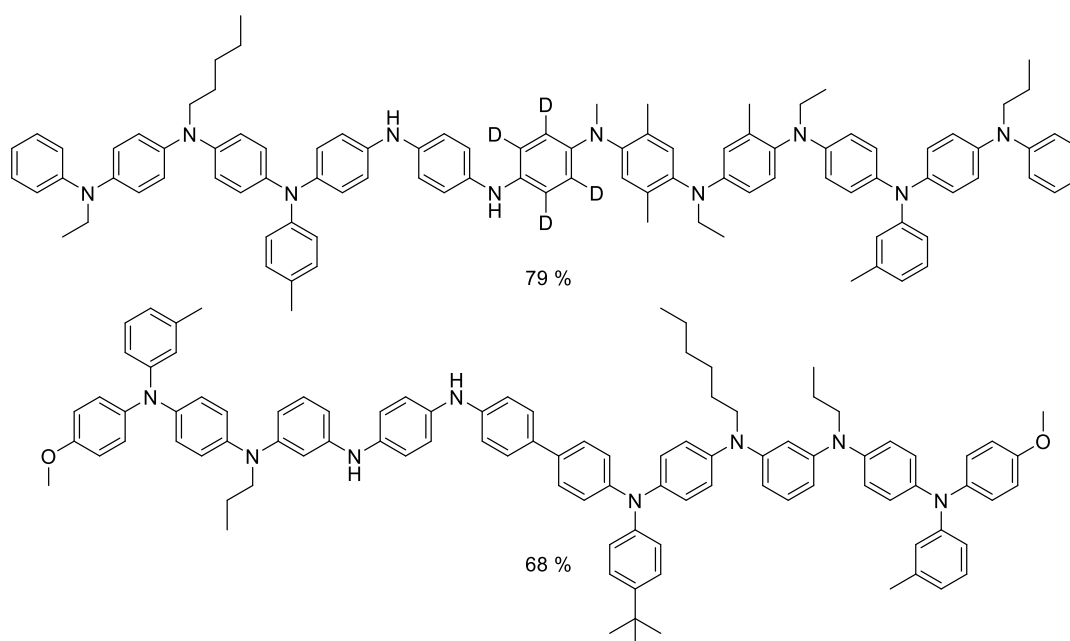


Figure 39: Two complex polyamines synthesized via orthogonal synthesis.

5.2 Report on the contributions of publications for this thesis

The results presented in this work were obtained in collaboration with others and published as indicated below. The contributions of all co-authors and contributors to the publications are listed below.

Chapter 6

This work was published in "ChemCatChem" with the title "**Manganese-catalyzed Dehydrogenation of Amido Alcohols with Liberation of Hydrogen for the Synthesis of Oxazoles**".

DOI: doi.org/10.1002/cctc.202301042

Authors: Max Leinert, Torsten Irrgang, Rhett Kempe.

I conducted the experiments, synthesized, and characterized all compounds for the final publication. Torsten Irrgang and Rhett Kempe supervised the work, participated in the scientific discussions, and co-wrote the manuscript with me.

Chapter 7

This work was published in "Journal of American Chemical Society" with the title "**A Catalytic Version of the Knorr Pyrrole Synthesis Permits Access to Pyrroles and Pyridines**".

DOI: doi.org/10.1021/jacs.4c13266

Authors: Max Leinert, Torsten Irrgang, Rhett Kempe.

I conducted the experiments, synthesized, and characterized all compounds for the final publication. Torsten Irrgang and Rhett Kempe supervised the work, participated in the scientific discussions, and co-wrote the manuscript with me.

Chapter 8

This work will be published with the title "**Catalytic two-step synthesis of sequence defined polyamines**".

Authors: Max Leinert, Elias Bandt, Torsten Irrgang, Rhett Kempe.

I conducted the experiments, synthesized, and characterized all compounds for the final publication. Elias Bandt has synthesized several final compounds and intermediates under my supervision. Torsten Irrgang and Rhett Kempe supervised the work, participated in the scientific discussions, and co-wrote the manuscript with me.

5.3 List of further publications

A list of further publications that were obtained in collaboration with others and published as indicated below.

“C-alkylation of primary amines via selective olefin hydrogenation tolerating alkynes” was resubmitted after revision to *Nature Catalysis*.

Authors: Martin Schlagbauer, Hanna Stachowiak-Dłużyńska, Frederik Freitag, Max Leinert, Matthias Knodt, Grzegorz Hreczycho, Stephan Kümmel, Torsten Irrgang and Rhett Kempe.

6. MANGANESE-CATALYZED DEHYDROGENATION OF AMIDO ALCOHOLS WITH LIBERATION OF HYDROGEN FOR THE SYNTHESIS OF OXAZOLES

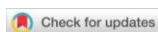
Title: Manganese-catalyzed Dehydrogenation of Amido Alcohols with Liberation of Hydrogen for the Synthesis of Oxazoles.

Authors: M. Leinert, Dr. T. Irrgang, Prof. Dr. R. Kempe

Institution: Inorganic Chemistry II – Catalyst Design, Universitätsstraße 30, NW I, 95440 Bayreuth (Germany).

DOI: doi.org/10.1002/cctc.202301042

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Manganese-catalyzed Dehydrogenation of Amido Alcohols with Liberation of Hydrogen for the Synthesis of Oxazoles

Max Leinert,^[a] Torsten Irrgang,^[a] and Rhett Kempe^{*[a]}

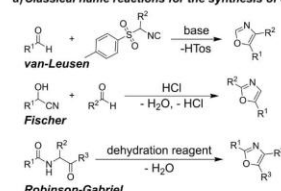
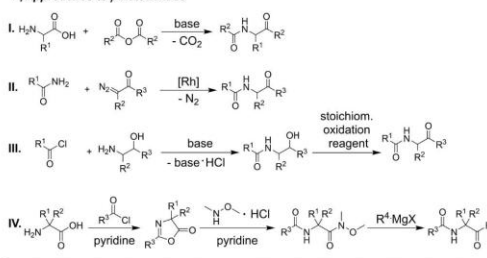
Syntheses of important classes of (heterocyclic) compounds, the sustainable generation of hydrogen, and the use of abundantly available metals are highly desirable. We introduce here a catalytic oxazole synthesis. Our reaction is a regio selective, one-pot reaction and starts from esters and amino alcohols. Both are abundantly and diversely available and inexpensive starting materials. Hydrogen is liberated during the reaction

and a molecular earth-abundant metal catalyst, a Mn(I) compound, mediates the reaction most effectively - and more efficiently than Ir and Ru catalysts. None of the oxazole derivatives synthesized, except the screening substrate and an active ingredient of a drug (an application), have been reported in literature yet.

Introduction

Reaction discovery is a central focus of chemistry and becomes especially interesting if the existing chemical space can be extended. Catalysis seems a suitable tool in this regard.^[1–4] Among the many different important compound classes known, heterocyclic compounds are especially interesting due to their numerous applications as pharmaceuticals, agro chemicals, materials, fine and bulk chemicals.^[5] Oxazoles are a prominent example, with their central structural motive seen in pharmaceuticals^[6] and in organic materials^[7] for example. Consequently, oxazole syntheses have been of great interest for more than a century (Figure 1a).^[8–11] The current liveliness of the field is expressed by numerous review articles that have appeared in very recent years.^[12] Especially interesting is the cyclization named after Robinson and Gabriel since all carbon substituents can be addressed. Here, the synthesis of the β -ketoamide starting material and its compatibility with the cyclization are the challenges. In addition, a β -ketoamide synthesis from diversely and abundantly available starting materials would be desirable. Established methods (Figure 1b) suffer from challenges to introduce different substituents (Figure 1b, I),^[13] rely on toxic and explosive diazo compounds (Figure 1b, II),^[14] need stoichiometric oxidants (Figure 1b, III)^[15] or a high chemical synthesis effort is required (Figure 1b, IV).^[16] We have contributed to catalytic dehydrogenation reactions in

a) Classical name reactions for the synthesis of oxazoles

b) Approaches to β -ketoamides

c) This work

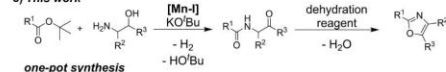


Figure 1. State of the art and work introduced here. a) Classical name reactions for the synthesis of oxazoles. b) Approaches to β -ketoamides. c) One-pot oxazole synthesis introduced here. Synthesis of 44 oxazole derivatives not yet reported. Diversely and abundantly available starting materials. Generation of hydrogen. Earth-abundant metal catalyst – a molecular Mn(I) compound, which is also superior to noble metal catalysts.

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Supporting information for this article is available on the WWW
<https://doi.org/10.1002/cctc.202301042>

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recent years,^[17–20] including *N*-heterocycle synthesis.^[21,22] The catalytic pyrrole,^[23,24,38] pyridine,^[25–27,40] and fertigine or kuenstlerine^[28] synthesis is based on a catalytic amino alcohol dehydrogenation step, and we also expected access to oxazoles via dehydrogenation catalysis (Figure 1c). Reactions that permit the generation of hydrogen and catalysts based on abundantly available metals are of general interest too. We report here on a regio selective, two-step, one-pot oxazole synthesis. Our

reaction starts from esters and amino alcohols, both of which are abundantly and diversely available starting materials, and hydrogen is liberated in the first step of our reaction (Figure 1c).^[29] The reaction has a large scope and none of the examples synthesized, except the screening substrate and an active ingredient of a drug (application), are compounds that have been disclosed in the literature so far. Our reaction has a very good functional group tolerance, including substituents sensitive to hydrogenation, despite the presence of a hydrogenation catalyst and hydrogen.^[30] A molecular manganese catalyst mediates the reaction most effectively – and more efficiently than related Ir or Ru catalysts.

Results and Discussion

Firstly, we investigated the reaction between *tert*-butyl benzoate (A1) and 1-aminopropan-2-ol (B1) to form the *N*-(2-oxopropyl)benzamide intermediate (D1). We intended to find optimal conditions for the dehydrogenation step of our oxazole synthesis (Table 1, top). The most efficient base is KO^tBu, 1,4-dioxane seemed the best solvent, and the ester to amino alcohol ratio should be 1:1. Next, PN₃5P-ligand-supported Mn carbonyl complexes were investigated (Table 1, entries 2–10). Precatalyst [Mn-I] gives rise to the most active catalyst system (Table 1, entry 2). The metal precursor [Mn(CO)₅Br] showed no catalytic activity in the benchmark dehydrogenation reaction (Table 1, entry 1). An Ir complex (Table 1, entry 11), stabilized by the same ligand as [Mn-I], showed no selective reaction. In addition, a Ru precatalyst was investigated (Table 1, entry 12), but no selective product formation was observed either. We next investigated the cyclodehydration reaction as a one-pot follow-up reaction of our dehydrogenation step. Phosphoryl chloride emerged as the most efficient and selective dehydrating agent (Robinson-Gabriel cyclization). Other reagents, such as phosphorus pentoxide or T3P (T3P = propanephosphonic acid anhydride), were not efficient enough (for details see Supplementary Table 6, entries 1–4). Heating *N*-(2-oxopropyl)benzamide D1 in 1,4-dioxane for four hours at 85 °C in the presence of phosphoryl chloride and under anaerobic conditions was sufficient to obtain 5-methyl-2-phenyloxazole (E1, Supplementary Table 6, entry 4) in a 95 % yield. With the suitable reaction conditions for a one-pot oxazole synthesis in hand, we investigated the substrate scope. The products could be isolated in yields up to 97 %. A wide range of *tert*-butyl esters and 1,2-amino alcohols can undergo our dehydrogenative oxazole synthesis (Figures 2–4). None of the compounds synthesized, except the product 5-methyl-2-phenyloxazole (E1, Supplementary Table 6) of the benchmark reaction and the commercially available oxazole Oxaprozin (O45, Figure 4, applications), have been described in the literature previously. The high number of unknown oxazole derivatives synthesized here indicate the degree of novelty of our reaction and the difficulties associated with the synthesis of selectively arylated and alkylated oxazoles.

At first, we synthesized 2,5-substituted oxazoles by using 2-amino-1-propanol and 2-amino-1-butanol as secondary amino

Table 1. Catalyst identification.^[a]

Entry	Precatalyst	Yield of D1 ^[b]
1	[Mn(CO) ₅ Br]	0
2	[Mn-I] (R = Ph)	90
3	[Mn-II] (R = Me)	46
4	[Mn-III] (R = NHC ₃ H ₇)	5
5	[Mn-IV] (R = NEt ₂)	54
6	[Mn-V] (R = <i>p</i> -OMePh)	32
7	[Mn-VI] (R = H)	0
8	[Mn-VII] (R = <i>p</i> -CF ₃ Ph)	55
9	[Mn-VIII]	66
10	[Mn-IX]	6
11	[Ir-I]	33
12	[Ru-I]	31

[a] Reaction conditions: 0.75 mmol A1, 0.75 mmol B1, 1.125 mmol (1.50 equiv.) KO^tBu, 1.50 mol% precatalyst, 1,4-dioxane (0.10 M, 7.50 mL), reflux conditions: open system under argon atmosphere. [b] Determined by GC with dodecane as an internal standard.

alcohols. Variation of the position of the methylene group at the corresponding aromatic ester derivatives had no significant impact on the yield of the oxazoles synthesized (O15–O17, Figure 2). Using *tert*-butyl 4-(*tert*-butyl)benzoate or 2-naphtoyl *tert*-butyl ester led to the isolation of O14 in a 71 % and O18 in a 83 % yield (Figure 2). In addition, O2, O4, and O6, which were synthesized from sterically demanding esters, could be isolated in yields up to 91 % (Figure 2). Using electron-poor aromatic esters resulted in yields of the corresponding oxazoles up to 96 % (O3, O10, O11, O12, O13, Figure 2). The reason for the latter might be a smooth formation of the corresponding β -hydroxyamide intermediate (C) due to an increased nucleophilicity at the carbonyl moiety of the ester derivative used. Oxazole O5, on the other hand, could be isolated in a 60 % yield due to the dehalogenation observed. Moreover, compounds O1 and O9, both containing alkoxy groups at the aromatic system, could be isolated in yields of 83 % and 64 %, respectively

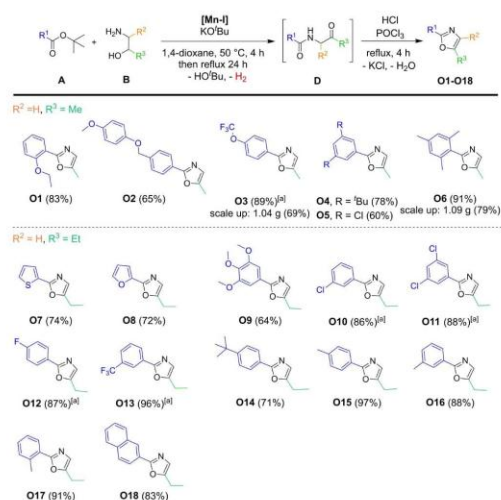


Figure 2. Synthesis of 2,5-substituted oxazoles – variation of R¹ (ester) and R² (amino alcohol). Reaction conditions: Step 1: 1.00 equiv. *tert*-butyl ester, 1.00 equiv. 1,2-amino alcohol, 1.50 equiv. KOtBu, 1.50 mol% [Mn-I], 1,4-dioxane (0.10 M), 50 °C, for 4 h, then reflux for 24 h; reflux conditions: open system under argon atmosphere. Step 2: 1.50 equiv. HCl (4.00 M in 1,4-dioxane), 3.00 equiv. POCl₃, 85 °C for 4 h; open system under argon atmosphere. Isolated yields in brackets. [a] Dehydration reaction was carried out at 80 °C for 24 h, open system under argon atmosphere.

(Figure 2). Furthermore, we were interested to see whether potentially catalyst-inhibiting heteroaromatic *tert*-butyl esters could be applied. Therefore, *tert*-butyl thiophen-2-carboxylate and *tert*-butyl furan-2-carboxylate were used and the corresponding oxazoles (**O7**, **O8**, Figure 2) were isolated in yields of 74% and 72%, respectively. Finally, two scale-up experiments were carried out. The resulting products, **O3** and **O6**, could be isolated in a 69% (1.04 g, 4.29 mmol, Figure 2) and 79% yield (1.09 g, 5.38 mmol, Figure 2), respectively. We next investigated the synthesis of a range of 2,4-substituted oxazoles by using 2-amino-2-phenylethan-1-ol, 2-amino-2-(2-chlorophenyl)ethan-1-ol, and 2-amino-2-(4-fluorophenyl)ethan-1-ol as amino alcohol starting materials. Various aliphatic *tert*-butyl esters were readily converted into the corresponding oxazoles and isolated in yields of up to 86% (**O19–O22**, **O30**, **O31**, **O38–O40**, Figure 3). The reaction of 2-naphthol *tert*-butyl ester with 2-amino-2-(2-chlorophenyl)ethan-1-ol or 2-amino-2-(4-fluorophenyl)ethan-1-ol led to the isolation of oxazoles **O34** and **O35** in yields of 93% and 96%, respectively (Figure 3). Having an electron-withdrawing group in the para position at the aromatic amino alcohol had a positive impact on the yield, combining *tert*-butyl 4-methylbenzoate with 2-amino-2-(2-chlorophenyl)ethan-1-ol or 2-amino-2-(4-fluorophenyl)ethan-1-ol. **O32** and **O36** could be isolated in yields of 56% and 84%, respectively (Figure 3). The use of aromatic *tert*-butyl esters with electron-withdrawing groups led to the isolation of the corresponding compounds in yields up to 92% (**O26–O28**, **O33**, **O37**, Figure 3). Once again, it was possible to demonstrate that a potentially catalyst-

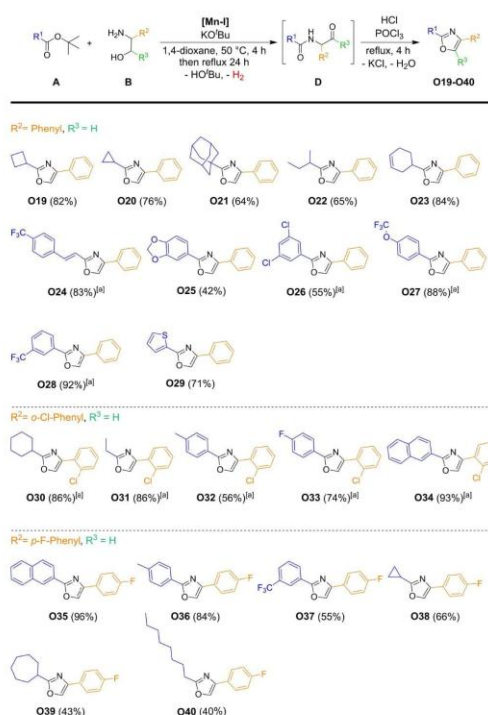


Figure 3. Synthesis of 2,5-substituted oxazoles – variation of R¹ (ester) and R² (amino alcohol). Reaction conditions: Step 1: 1.00 equiv. *tert*-butyl ester, 1.00 equiv. 1,2-amino alcohol, 1.50 equiv. KOtBu, 1.50 mol% [Mn-I], 1,4-dioxane (0.10 M), 50 °C, for 4 h, then reflux for 24 h; reflux conditions: open system under argon atmosphere. Step 2: 1.50 equiv. HCl (4.00 M in 1,4-dioxane), 3.00 equiv. POCl₃, 85 °C for 4 h; open system under argon atmosphere. Isolated yields in brackets. [a] Dehydration reaction was carried out at 80 °C for 24 h, open system under argon atmosphere.

inhibiting heteroaromatic *tert*-butyl ester could be applied in this protocol. *tert*-Butyl thiophen-2-carboxylate and 2-amino-2-phenylethan-1-ol could be converted readily into **O29** in a 71% yield (Figure 3). Interestingly, hydrogenation-sensitive functional groups, such as olefins or Michael systems, can be tolerated despite the presence of hydrogen and a (de)hydrogenation catalyst (**O23**, **O24**, Figure 3). In addition, an acetal group could be tolerated under the basic conditions. Thus, compound **O25** could be isolated in a 42% yield (Figure 3). Using cyclic 1,2-amino alcohols led to the isolation of the corresponding oxazoles **O41**, **O42** and **O43** in yields from 71 to 88% (Figure 4). Furthermore, the active component of the drug Oxaprozin could be synthesized using adjusted conditions for the dehydration reaction (**O45**, Figure 4). These reactions indicate that oxazole derivatives, where all carbon atoms are substituted, can be obtained by applying our reaction. In addition, Gemfibrozil, a commercially available lipid-lowering agent was converted in its corresponding 4-phenyl oxazole derivative in a 59% yield (**O44**, Figure 4). Finally, we became interested in the

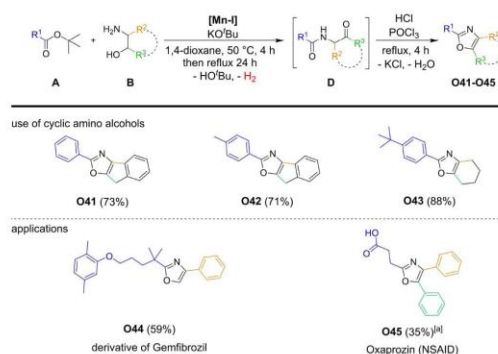


Figure 4. Synthesis of oxazoles – use of cyclic amino alcohols and applications. Reaction conditions: Step 1: 1.00 equiv. *tert*-butyl ester, 1.00 equiv. 1,2-amino alcohol, 1.50 equiv. KOtBu, 1.50 mol% [Mn-I], 1,4-dioxane (0.10 M), 50 °C, for 4 h, then reflux for 24 h, open system (anaerobic conditions). Step 2: 1.50 equiv. HCl (4.00 M in 1,4-dioxane), 3.00 equiv. POCl₃, 85 °C for 4 h; open system under argon atmosphere. Isolated yields in brackets. [a] The catalytic dehydration was carried out with 5.00 mol% [Mn-I], 3.50 equiv. KOtBu for 3 days: open system under argon atmosphere.

netic resonance experiments have shown that the hydroxyamide formed *in situ* is responsible for the protonation of the guanidine pocket of the ligand backbone and, therefore, stoichiometric amounts of base are necessary to keep the metalated Mn-catalysts alive (Supplementary Figure 20).

Conclusions

In conclusion, we introduced a catalytic oxazole synthesis. The number of compounds synthesized, which have not yet been disclosed in the literature (O1–O44), indicate the degree of novelty of our synthesis and the challenges associated with the synthesis of selectively arylated and/or alkylated oxazoles. The educts, esters, and amino alcohols used are abundantly and diversely available, inexpensive, and partially accessible from renewable resources. An earth-abundant metal catalyst, namely a molecular Mn(II) compound, mediates our reaction most efficiently, also in comparison to noble metal catalysts, and hydrogen is liberated and collectable in the first part of our two-step one-pot reaction.

Experimental Section

General reaction conditions for the synthesis of substituted oxazole derivatives: In a Schlenk tube the corresponding ester **A** (1.00 equiv.), the 1,2-amino alcohol **B** (1.00 equiv.), KOtBu (1.50 equiv.) and [Mn-I] (1.50 mol%) are dissolved in 1,4-dioxane (0.10 M). The solution is stirred at 50 °C for 4 h and then for 24 h at reflux conditions under anaerobic conditions in an open system. In case of halogenated substrates, the reaction mixture is stirred at 80 °C under identical conditions. The reaction mixture is cooled to 0 °C. HCl (4.00 M in 1,4-dioxane, 1.50 equiv.) is added. The reaction mixture is stirred at 0 °C for 5 min before POCl₃ (3.00 equiv.) is slowly added. The mixture is heated to 85 °C and stirred for another 4 h under anaerobic conditions in an open system. The reaction is quenched by adding ice. After adding Et₂O, the organic phase is washed with brine : water : NH₄Cl (1:1:1). The aqueous phase is extracted with Et₂O several times and then dried over MgSO₄. Removing the solvents under reduced pressure leads to the crude product. Column chromatography finally gives the desired product.

Supporting Information

The authors have cited additional references within the Supporting Information.^[33–41]

Acknowledgements

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mechanism of our reaction. The mechanism proposed is shown in Figure 5. All steps shown in Figure 5 are observable by spectroscopic methods, such as nuclear magnetic resonance. The formation of the β -hydroxyamide intermediate is the first step and runs base-mediated. The complete formation of the corresponding β -hydroxyamide for the benchmark substrate was accomplished after four hours at 50 °C. The catalytic active species [Mn-Ia] is formed by treatment of the precatalyst [Mn-I] with two equiv. of KOtBu.^[31,32] [Mn-Ia] abstracts hydrogen atoms from the β -hydroxyamide and forms the β -ketoamide, the doubly metallated hydride [Mn-Ib], and butanol in the presence of KOtBu. The complete formation of the corresponding β -ketoamide for the benchmark substrate was accomplished after 24 hours with 1.50 mol% catalyst loading at about 100 °C. [Mn-Ib] is able to liberate hydrogen if butanol is present. The hydrogen can be collected (obtained: 3.72 mL, calculated: 3.95 mL, Supplementary Figure 21). In addition, nuclear mag-

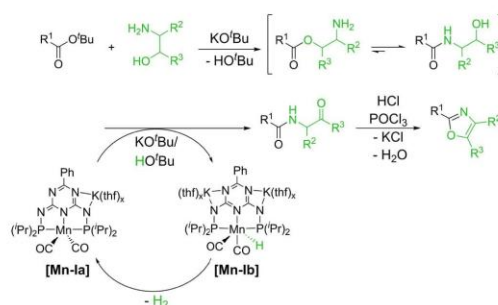


Figure 5. Mechanism proposed. All steps can be followed by spectroscopic methods.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: amino alcohols · dehydrogenation · esters · manganese · oxazoles

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Supporting Information

Manganese-catalyzed Dehydrogenation of Amido Alcohols with Liberation of Hydrogen for the Synthesis of Oxazoles

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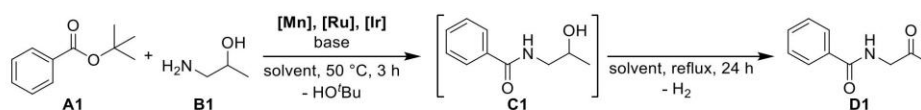
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1 Materials and methods

All reactions and manipulations with air sensitive compounds being present were performed under dry argon (Ar 5.0) or nitrogen (N₂ 5.0), using Schlenk and glove box techniques. Nonhalogenated solvents were dried over sodium benzophenone, 2-methyl tetrahydrofuran (2-Me-THF) was dried over calcium hydride, and halogenated solvents were dried over P₂O₅. Deuterated solvents were bought from Cambridge Isotope Laboratories, distilled accordingly, and stored over molecular sieves (3 Å). Other chemicals were purchased from commercial vendors and used without further purification. NMR spectra were collected on a Varian INOVA 400 MHz spectrometer or on a Bruker Avance III HD 500 MHz. Chemical shifts (δ) are reported in ppm relative to residual solvent signal CDCl₃: 7.26 ppm (¹H), 77.16 ppm (¹³C), DMSO-d₆: 2.50 ppm (¹H), 39.51 ppm (¹³C), THF-d₈: 1.72 ppm, 3.58 ppm (¹H), 67.21 ppm, 25.31 ppm (¹³C). ¹⁹F NMR spectra were collected on a Varian INOVA 400 MHz spectrometer (calibration with C₆H₅CF₃). Coupling constants (J) are given in Hz (coupling patterns: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). GC analyses were carried out using an Agilent Technologies 6890N system equipped with a Macherey-Nagel (MN) Optima 5 HT column (30 m, 320 μ m, 0.25 μ m) or an Agilent Technologies 6850 system equipped with a MN Optima 17 column (30 m, 320 μ m, 0.25 μ m). GC/MS analyses were carried out on an Agilent 7890A/MSD 5975C system equipped with a HP-5MS column (30 m, 320 μ m, 0.25 μ m). For column chromatography, MN silica gel 60 (0.040–0.063 mm particle size) was used. All organic compounds were characterized by ¹H and ¹³C NMR analysis. Unknown compounds or compounds with incomplete spectroscopic literature data were additionally analysed via LC-HRMS. Liquid chromatography-high resolution mass spectra (LC-HRMS) were obtained from a Thermo Fisher scientific Q-Exactive instrument with a hybrid quadrupole orbitrap analyser in ESI+ mode. Melting point determination was performed using a Stuart Scientific Melting Point Apparatus SMP3. The heating rate 2.50 °C per minute.

2 Screenings for the synthesis of N-(2-oxopropyl)benzamide (D1)



Supplementary Figure 1 Synthesis of **D1** starting from **A1** and **B1**.

Supplementary Table 1 Base screening.^[a]

Entry	Base	A1 [%] ^[b]	C1 [%] ^[b]	D1 [%] ^[b]
1	NaO ^t Bu	0	74	11
2	KO^tBu	0	50	46
3	LiO ^t Bu	75	25	0
4	MgO ^t Bu	>99	0	0
5	NaOH	61	33	0
6	KOH	20	46	0
7	LiOH	>99	0	0
8	NaHMDS	2	92	0
9	KHMDS	1	70	23
10	LiHMDS	95	0	0

[a] Reaction conditions: 0.75 mmol **A1**, 0.75 mmol **B1**, 1.125 mmol base (1.50 equiv.), 1.50 mol% **[Mn-I]**, THF (0.10 M, 7.50 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 2 Solvent screening.^[a]

Entry	Solvent	A1 [%] ^[b]	C1 [%] ^[b]	D1 [%] ^[b]
1	CPME	1	26	73
2	1,4-dioxane	0	6	90
3	toluene	17	28	55
4	2-Me-THF	0	40	58
5	<i>tert</i> -amyl alcohol	2	55	9
6	THF	0	50	46

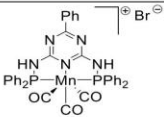
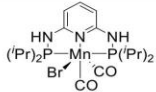
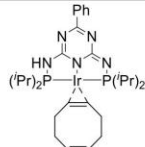
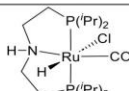
[a] Reaction conditions: 0.75 mmol **A1**, 0.75 mmol **B1**, 1.125 mmol KO^tBu (1.50 equiv.), 1.50 mol% **[Mn-I]**, solvent (0.10 M, 7.50 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 3 KO^tBu loading screening.^[a]

Entry	KO ^t Bu loading [equiv.]	A1 [%] ^[b]	C1 [%] ^[b]	D1 [%] ^[b]
1	1.00	0	33	34
2	1.30	0	22	50
3	1.50	0	6	90
4	1.80	0	4	93

[a] Reaction conditions: 0.75 mmol **A1**, 0.75 mmol **B1**, KO^tBu (1.00 - 1.80 equiv.), 1.50 mol% **[Mn-I]**, 1,4-dioxane (0.10 M, 7.50 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 4 Precatalyst screening.^[a]

Entry	Precatalyst	A1 [%] ^[b]	C1 [%] ^[b]	D1 [%] ^[b]
1	[Mn(CO) ₅ Br]	0	>99	0
2	[Mn-I] R = Ph	0	6	90
3	[Mn-II] R = Me	0	20	46
4	[Mn-III] R = NHC ₃ H ₅	0	89	5
5	[Mn-IV] R = NEt ₂	0	18	54
6	[Mn-V] R = <i>p</i> -OMePh	0	65	32
7	[Mn-VI] R = H	0	>99	0
8	[Mn-VII] R = <i>p</i> -CF ₃ Ph	0	25	55
9	 [Mn-VIII]	0	29	66
10	 [Mn-IX]	0	89	6
11	 [Ir-I]	0	3	33
12	 [Ru-I]	0	14	31

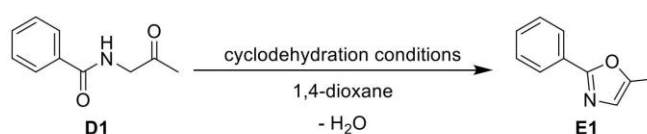
[a] Reaction conditions: 0.75 mmol **A1**, 0.75 mmol **B1**, KO^tBu 1.125 mmol (1.50 equiv.), 1.50 mol% precatalyst, 1,4-dioxane (0.10 M, 7.50 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 5 Precatalyst **[Mn-I]** loading.^[a]

Entry	Amount of [Mn-I] [mol%]	A1 [%] ^[b]	C1 [%] ^[b]	D1 [%] ^[b]
1	0.50	0	40	60
2	1.00	0	32	63
3	1.50	0	6	90
4	2.00	0	5	92

[a] Reaction conditions: 0.75 mmol **A1**, 0.75 mmol **B1**, 1.125 mmol KO^tBu (1.50 equiv.), 0.50 - 2.00 mol% **[Mn-I]**, 1,4-dioxane (0.10 M, 7.50 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

3 Screening for the synthesis of 5-methyl-2-phenyloxazole (**E1**)



Supplementary Figure 2 Synthesis of 5-methyl-2-phenyloxazole (**E1**).

Supplementary Table 6 Cyclodehydration conditions.^[a]

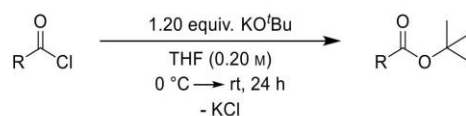
Entry	Cyclodehydration conditions	E1 [%] ^[b]
1	T3P (5.00 equiv., reflux, 24 h) ^[1]	93
2	POCl ₃ : pyridine (5:1, 3.00 equiv., 24 h, rt) ^[2]	76
3	P ₂ O ₅ (3.00 equiv., 4 h, 85 °C)	85
4	FeCl ₃ (30 mol%, reflux, 24 h)	2
5	H ₂ SO ₄ (konz., 1.00 mL, reflux, 1 h) ^[c]	0
6	POCl₃ (3.00 equiv., 4 h, 85 °C)^[3]	95

[a] Reaction conditions: 0.75 mmol **D1**, cyclodehydration conditions, 1,4-dioxane (0.10 M, 7.50 mL); [b] Determined by GC with dodecane as an internal standard. [c]: reaction conditions led to polymerization of the corresponding solvent.

4 Synthesis of ligands and / or complexes

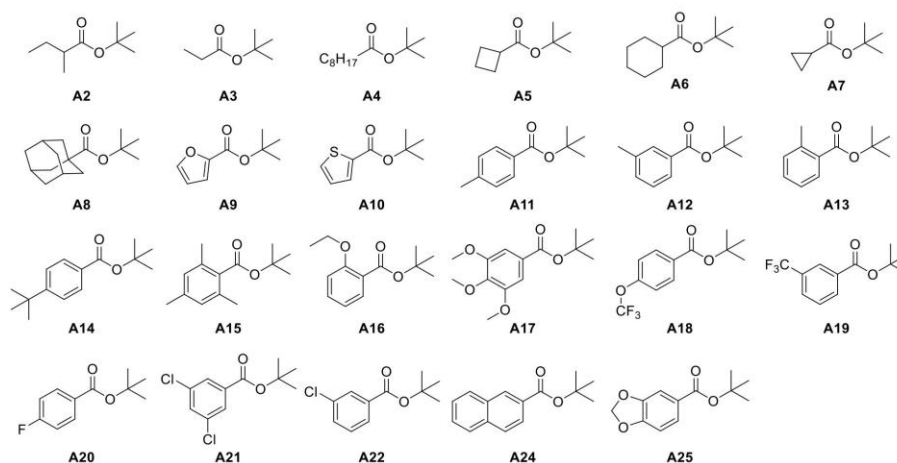
The ligands and precatalysts **[Mn-I]**-**[Mn-IX]**^[4,5,6,7], **[Ir-I]**^[8] and **[Ru-I]**^[9] were synthesized according to published procedures.

5 Synthesis of *tert*-butyl esters from carbonyl chlorides



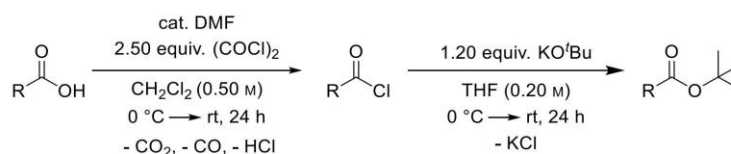
Supplementary Figure 3 General conditions for the synthesis of *tert*-butyl esters.

General reaction conditions (GP1) for the synthesis of *tert*-butyl esters from carbonyl chlorides: In a Schlenk tube the corresponding carbonyl chloride is dissolved in THF (0.20 M). The solution is cooled to 0 °C and stirred for 15 minutes at 0 °C. KO^tBu (1.20 equiv.) is slowly added to the reaction mixture. The reaction solution is slowly warmed up to rt and stirred for 24 h. After addition of water : brine (1:1) the aqueous phase is extracted with Et₂O. Drying the combined organic phases over MgSO₄ and evaporating the solvents under reduced pressure leads to the crude product. Column chromatography (*n*-pentane → *n*-pentane : EtOAc (9:1)) finally gives the desired product. All *tert*-butyl ester derivatives were checked by ¹H and ¹³C NMR spectroscopy before use.



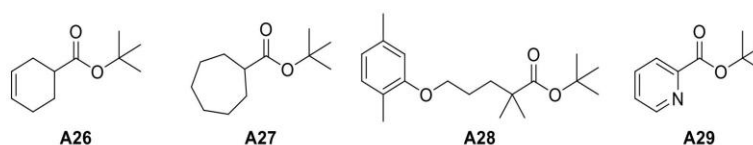
Supplementary Figure 4 Overview of the synthesized *tert*-butyl esters **A2-A25**.

6 Synthesis of *tert*-butyl esters from carboxylic acids



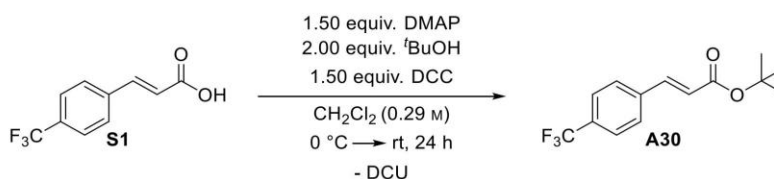
Supplementary Figure 5 Synthesis of *tert*-butyl esters starting from carboxylic acids.

General reaction conditions (GP2) for the synthesis of *tert*-butyl esters from carboxylic acids: In a Schlenk tube the corresponding carboxylic acid is dissolved in CH_2Cl_2 (0.50 M). A few drops of dry DMF are added to the mixture. The solution is cooled to 0 °C and stirred for 15 minutes at 0 °C. Oxalyl chloride ($(\text{COCl})_2$, 2.50 equiv.) is slowly added to the reaction mixture. The reaction solution is slowly warmed up to rt and stirred for 24 h. A gas bubbler is used to liberate the resulting gas. The solvent and the excess of $(\text{COCl})_2$ is removed under reduced pressure. The crude carbonyl chloride is directly used for the next step following **GP1**. All *tert*-butyl ester derivatives were checked by ^1H and ^{13}C NMR spectroscopy before use.



Supplementary Figure 6 Overview of the synthesized *tert*-butyl esters **A26-A29**.

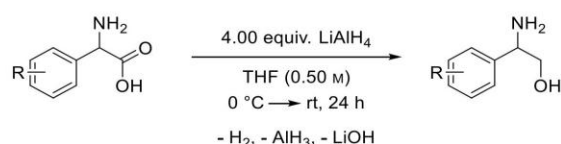
7 Synthesis of *tert*-butyl (E)-3-(4-(trifluoromethyl)phenyl)acrylate (**A30**)



Supplementary Figure 7 Synthesis of **A30** via Steglich esterification.

Synthesis of *tert*-butyl (*E*)-3-(4-(trifluoromethyl)phenyl)acrylate (A30): *N,N'*-dicyclohexylcarbodiimide (DCC) (3.59 g, 17.4 mmol, 1.50 equiv.), 4-dimethylaminopyridine (DMAP) (2.13 g, 17.4 mmol, 1.50 equiv.) and *t*BuOH (1.72 g, 23.2 mmol, 2.00 equiv.) are added to a solution of (*E*)-3-(4-(trifluoromethyl)phenyl)acrylic acid **S1** (2.50 g, 11.6 mmol, 1.00 equiv.) in anhydrous CH₂Cl₂ (0.29 M) at 0 °C.^[10] The reaction solution is slowly warmed up to rt and stirred for 24 h. The reaction mixture is filtered through Celite and the filter cake is washed with CH₂Cl₂. The organic phase is washed with brine : water (1:1). Drying the organic phase with MgSO₄ and removing the organic solvents under reduced pressure leads to the crude product. Column chromatography (*n*-pentane → *n*-pentane : EtOAc (9:1)) finally gives the desired product (1.72 g, 6.31 mmol) in 55% yield as a white crystalline solid. The *tert*-butyl ester derivative was checked by ¹H and ¹³C NMR spectroscopy before use.

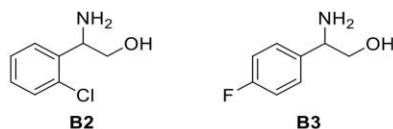
8 Synthesis of 1,2-amino alcohols from amino acids



Supplementary Figure 8 Synthesis of 1,2-amino alcohols.

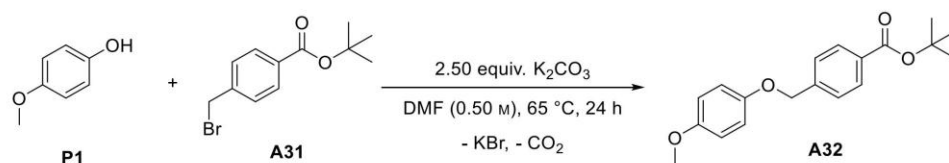
General reaction conditions (GP3) for the synthesis of 1,2-amino alcohols: In a Schlenk tube LiAlH₄ (4.00 equiv.) is suspended in THF (0.50 M). The solution is cooled to 0 °C and stirred for 15 minutes at 0 °C. The corresponding amino acid (1.00 equiv.) is slowly added to the reaction mixture. The reaction solution is slowly warmed up to rt and stirred for 24 h. A gas bubbler is used to liberate the resulting H₂. To quench the reaction, ice water is very slowly added at 0 °C to the reaction mixture until the evolution of gas can no longer be detected. The organic phase is dissolved in EtOAc and washed with water : brine (1:1) and NaOH (0.50 M). The organic phase is dried over MgSO₄ and the solvents are removed under reduced pressure.

The crude product is recrystallized from EtOAc : *n*-pentane. All 1,2-amino alcohol derivatives were checked by ^1H and ^{13}C NMR spectroscopy before use.



Supplementary Figure 9 Overview of the synthesized 1,2-amino alcohols **B2** and **B3**.

9 Synthesis of *tert*-butyl 4-((4-methoxyphenoxy)methyl)benzoate (**A32**)



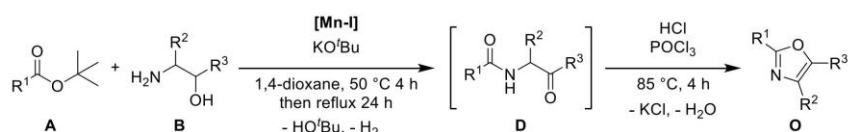
Supplementary Figure 10 Synthesis of *tert*-butyl ester **A32**.

Synthesis of *tert*-butyl 4-((4-methoxyphenoxy)methyl)benzoate (A32**):** K_2CO_3 (6.40 g, 46 mmol, 2.50 equiv.) and 4-methoxyphenol **P1** (2.74 g, 22.1 mmol, 1.20 equiv.) are added to a solution of *tert*-butyl 4-(bromomethyl)benzoate **A31** (5.00 g, 18.4 mmol, 1.00 equiv.) in dry DMF. The reaction mixture is stirred for 24 h at 65 °C. The solution is dissolved in CH_2Cl_2 and the organic phase is washed with water. The aqueous phase is extracted with CH_2Cl_2 . The combined organic phases are washed with brine. After drying the combined organic phases with MgSO_4 and removing the organic solvents under reduced pressure the crude product is obtained. Column chromatography (*n*-pentane $\rightarrow$ *n*-pentane : EtOAc (9:1)) finally gives the desired product (3.87 g, 12.3 mmol) as a white crystalline solid in 67% yield.

^1H NMR (CDCl_3 , 500 MHz, 293 K): δ = 7.99 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H), 6.91 – 6.87 (m, 2H), 6.86 – 6.80 (m, 2H), 5.07 (s, 2H), 3.76 (s, 3H), 1.59 (s, 9H) ppm.

^{13}C NMR (CDCl_3 , 125 MHz, 293 K): δ = 165.67, 154.25, 152.74, 142.12, 131.64, 129.82, 126.96, 115.99, 114.77, 81.18, 70.21, 55.86, 28.33 ppm.

10 Synthesis of oxazole derivatives



Supplementary Figure 11 Conditions for the synthesis of substituted oxazoles.

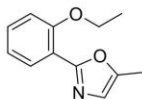
General reaction conditions for the synthesis of substituted oxazole derivatives

(GP4a): In a Schlenk tube the corresponding ester **A** (1.00 equiv.), the 1,2-amino alcohol **B** (1.00 equiv.), KO^tBu (1.50 equiv.) and [Mn-I] (1.50 mol%) are dissolved in 1,4-dioxane (0.10 M). The solution is stirred at 50 °C for 4 h and then for 24 h at reflux conditions under anaerobic conditions in an open system. In case of halogenated substrates, the reaction mixture is stirred at 80 °C under the same conditions.

(GP4b): The reaction mixture from **GP4a** is cooled to 0 °C. HCl (4.00 M in 1,4-dioxane, 1.50 equiv.) is added. The reaction mixture is stirred at 0 °C for 5 min before POCl₃ (3.00 equiv.) is slowly added. The mixture is heated to 85 °C and stirred for another 4 h under anaerobic conditions in an open system. The reaction is quenched by adding ice. After adding Et₂O, the organic phase is washed with brine : water : NH₄Cl (1:1:1). The aqueous phase is extracted with Et₂O several times and then dried over MgSO₄. Removing the solvents under reduced pressure leads to the crude product. Column chromatography finally gives the desired product.

11 Isolation and characterization of products

Synthesis of 2-(2-ethoxyphenyl)-5-methyloxazole (O1)



Chemical Formula: C₁₂H₁₃NO₂
Molecular Weight: 203.24

O1

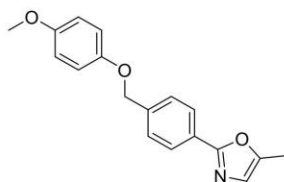
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless oil (127 mg, 623 μ mol, 83 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.96 – 7.84 (m, 1H), 7.39 – 7.33 (m, 1H), 7.01 (dd, *J* = 11.8, 4.4 Hz, 2H), 6.86 (q, *J* = 1.1 Hz, 1H), 4.17 (q, *J* = 7.0 Hz, 2H), 2.39 (d, *J* = 1.2 Hz, 3H), 1.47 (t, *J* = 7.0 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 159.46, 156.84, 148.52, 131.24, 130.22, 124.04, 120.73, 117.62, 113.55, 64.77, 14.87, 11.19 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O1]⁺: 204.10191, found: 204.10178.

Synthesis of 2-(4-((4-methoxyphenoxy)methyl)phenyl)-5-methyloxazole (O2)



Chemical Formula: C₁₈H₁₇NO₃
Molecular Weight: 295.34

O2

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (7:3)) and obtained as a white solid (144 mg, 488 μ mol, 65 %).

S12

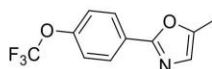
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.01 (d, J = 7.4 Hz, 2H), 7.50 (d, J = 7.0 Hz, 2H), 6.94 – 6.89 (m, 2H), 6.87 – 6.81 (m, 3H), 5.06 (s, 2H), 3.77 (s, 3H), 2.40 (s, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 154.24, 152.96, 149.27, 144.68, 139.36, 127.83, 127.44, 126.29, 116.15, 114.91, 70.37, 55.89, 11.29 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O2]⁺: 296.12812, found: 296.12801.

Melting Point: 117.2 °C.

Synthesis of 5-methyl-2-(4-(trifluoromethoxy)phenyl)oxazole (O3)



Chemical Formula: C₁₁H₈F₃NO₂
Molecular Weight: 243.19

O3

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless oil (216 mg, 890 μmol, 89 %).

A scale up experiment was performed following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) to obtain the product (1.04 g, 4.28 mmol) in 69% yield as a colourless oil.

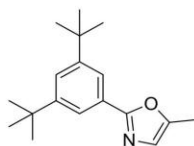
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.03 (d, J = 8.9 Hz, 2H), 7.28 (d, J = 8.3 Hz, 2H), 6.85 (s, 1H), 2.40 (s, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 159.62, 150.37, 149.49, 127.66, 126.57, 124.57, 121.22, 119.51, 11.20 ppm. CF₃ (q, J = 257,9 Hz).

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -57.84 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O3]⁺: 244.05799, found: 244.05792.

Synthesis of 2-(3,5-di-*tert*-butylphenyl)-5-methyloxazole (O4)



Chemical Formula: C₁₈H₂₅NO
Molecular Weight: 271.40

O4

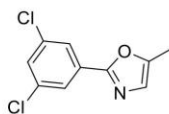
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless oil (159 mg, 585 μ mol, 78 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.86 (d, *J* = 1.8 Hz, 1H), 7.49 (t, *J* = 1.8 Hz, 1H), 6.82 (d, *J* = 1.1 Hz, 1H), 2.40 (d, *J* = 1.1 Hz, 1H), 1.37 (s, 10H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 161.72, 151.45, 151.44, 148.70, 127.24, 124.30, 124.15, 120.44, 35.12, 31.54, 11.28 ppm.

LC-HRMS (ESI⁺) *m/z* calculated for [O4]⁺: 272.20089, found: 272.20063.

Synthesis of 2-(3,5-dichlorophenyl)-5-methyloxazole (O5)



Chemical Formula: C₁₀H₇Cl₂NO
Molecular Weight: 228.07

O5

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a yellow solid (102 mg, 450 μ mol, 60 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.88 (d, *J* = 1.9 Hz, 1H), 7.39 (t, *J* = 1.9 Hz, 1H), 6.87 (d, *J* = 1.2 Hz, 1H), 2.40 (d, *J* = 1.2 Hz, 2H) ppm.

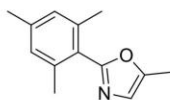
¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 158.38, 150.21, 135.71, 130.49, 129.74, 124.88, 124.34, 11.03 ppm.

S14

LC-HRMS (ESI+) m/z calculated for **[O5]⁺**: 227.99775, found: 227.99781.

Melting Point: 98.7 °C.

Synthesis of 2-mesityl-5-methyloxazole (O6)



Chemical Formula: C₁₃H₁₅NO
Molecular Weight: 201.27

O6

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless oil (184 mg, 910 μmol, 91 %).

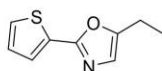
A scale up experiment was performed following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) to obtain the product (1.09 g, 5.38 mmol) in 79% yield as a colourless oil.

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 6.91 (s, 2H), 6.87 (d, *J* = 0.8 Hz, 1H), 2.37 (d, *J* = 1.1 Hz, 3H), 2.31 (s, 3H), 2.22 (s, 6H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 148.56, 139.54, 138.43, 128.55, 125.78, 123.25, 21.32, 20.36, 11.08 ppm.

LC-HRMS (ESI+) m/z calculated for **[O6]⁺**: 202.12264, found: 202.12214.

Synthesis of 5-ethyl-2-(thiophen-2-yl)oxazole (O7)



Chemical Formula: C₉H₉NOS
Molecular Weight: 179.24

O7

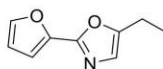
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless oil (99.0 mg, 552 μ mol, 74 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.60 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.37 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.09 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.78 (t, *J* = 1.0 Hz, 1H), 2.72 (qd, *J* = 7.5, 1.1 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 2H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 56.96, 154.11, 130.61, 127.94, 127.68, 127.00, 122.91, 19.24, 12.00 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O7]⁺: 180.04776, found: 180.04763.

Synthesis of 5-ethyl-2-(furan-2-yl)oxazole (O8)



Chemical Formula: C₉H₉NO₂
Molecular Weight: 163.18

O8

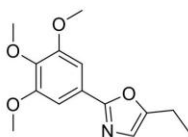
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless oil (88.0 mg, 540 μ mol, 72 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.52 (d, *J* = 1.4 Hz, 1H), 6.94 (dd, *J* = 3.4, 0.5 Hz, 1H), 6.81 (s, 1H), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1H), 2.73 (qd, *J* = 7.5, 1.0 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 154.21, 153.74, 144.13, 143.52, 122.96, 111.91, 110.64, 19.29, 12.03 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O8]⁺: 164.07061, found: 164.07047.

Synthesis of 5-ethyl-2-(3,4,5-trimethoxyphenyl)oxazole (O9)



Chemical Formula: $C_{14}H_{17}NO_4$
Molecular Weight: 263.29

O9

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (5:5)) and obtained as a white solid (169 mg, 640 μ mol, 64 %).

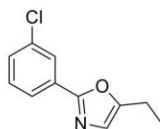
1H NMR ($CDCl_3$, 500 MHz, 293 K): δ = 7.23 (s, 2H), 6.81 (s, 1H), 3.93 (s, 6H), 3.88 (s, 3H), 2.75 (qd, J = 7.5, 0.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz, 293 K): δ = 160.55, 154.56, 153.58, 139.72, 123.38, 122.97, 103.20, 61.09, 56.36, 19.32, 11.98 ppm.

LC-HRMS (ESI+) m/z calculated for **[O9] $^+$** : 264.12303, found: 264.12285.

Melting Point: 110.5 $^{\circ}C$.

Synthesis of 2-(3-chlorophenyl)-5-ethyloxazole (O10)



Chemical Formula: $C_{11}H_{10}ClNO$
Molecular Weight: 207.66

O10

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless oil (178 mg, 860 μ mol, 86 %).

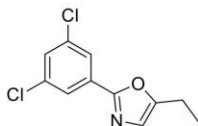
1H NMR ($CDCl_3$, 500 MHz, 293 K): δ = 7.99 (dd, J = 1.8, 0.7 Hz, 1H), 7.88 (ddd, J = 5.6, 3.0, 1.6 Hz, 1H), 7.39 – 7.36 (m, 2H), 6.85 (t, J = 1.1 Hz, 1H), 2.75 (qd, J = 7.5, 1.1 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H) ppm.

S17

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 159.51, 155.17, 135.02, 130.27, 130.05, 129.69, 126.25, 124.25, 123.44, 19.43, 12.05 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O10]⁺: 208.05237, found: 208.05244.

Synthesis of 2-(3,5-dichlorophenyl)-5-ethyloxazole (O11)



Chemical Formula: C₁₁H₉Cl₂NO
Molecular Weight: 242.10

O11

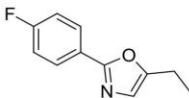
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless oil (266 mg, 1.10 mmol, 88 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.88 (d, *J* = 1.9 Hz, 2H), 7.38 (t, *J* = 1.9 Hz, 1H), 6.87 (t, *J* = 1.1 Hz, 1H), 2.75 (qd, *J* = 7.6, 1.1 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 158.23, 155.61, 135.65, 130.52, 129.74, 124.41, 123.64, 19.33, 11.90 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O11]⁺: 242.01340, found: 242.01350

Synthesis of 5-ethyl-2-(4-fluorophenyl)oxazole (O12)



Chemical Formula: C₁₁H₁₀FNO
Molecular Weight: 191.21

O12

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless oil (209 mg, 1.09 mmol, 87 %).

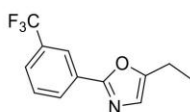
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.03 – 7.95 (m, 2H), 7.12 (t, J = 8.7 Hz, 2H), 6.82 (t, J = 1.1 Hz, 1H), 2.74 (qd, J = 7.5, 1.1 Hz, 1H), 1.30 (t, J = 7.6 Hz, 2H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 164.87, 162.89, 159.94, 154.60, 128.19, 128.12, 124.40, 124.37, 123.04, 116.07, 115.89, 19.30, 11.99 ppm. *CF* (d, J = 21,7 Hz), *o-CF* (d, J = 8.10 Hz), *m-CF* (d, J = 3.20 Hz), *p-CF* (d, J = 1.40 Hz).

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -110.48 ppm.

LC-HRMS (ESI+) m/z calculated for [O12]⁺: 192.08192, found: 192.08175.

Synthesis of 5-ethyl-2-(3-(trifluoromethyl)phenyl)oxazole (O13)



Chemical Formula: C₁₂H₁₀F₃NO
Molecular Weight: 241.21

O13

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (9:1)) and obtained as a colourless oil (290 mg, 1.20 mmol, 96 %).

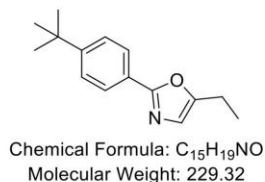
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.19 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.8 Hz, 1H), 6.88 (t, J = 1.1 Hz, 1H), 2.77 (qd, J = 7.6, 1.1 Hz, 2H), 1.33 (t, J = 7.6 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 159.24, 155.24, 131.47, 131.21, 129.35, 129.08, 128.45, 126.38, 126.06, 123.17, 122.87, 19.21, 11.81 ppm. *CF*₃ (q, J = 257,9 Hz), *o-CF*₃ (q, 32,7 Hz).

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -62.98 ppm.

LC-HRMS (ESI+) m/z calculated for [O13]⁺: 242.07873, found: 242.07859.

Synthesis of 2-(4-(*tert*-butyl)phenyl)-5-ethyloxazole (O14)



O14

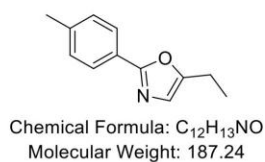
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless oil (122 mg, 533 μ mol, 71 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.93 (d, *J* = 8.6 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 6.81 (t, *J* = 1.1 Hz, 1H), 2.75 (qd, *J* = 7.5, 1.1 Hz, 2H), 1.34 (s, 9H), 1.30 (t, *J* = 7.6 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 160.92, 154.19, 153.25, 125.90, 125.78, 125.33, 122.95, 34.97, 31.37, 19.37, 12.04 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O14]⁺: 230.15394, found: 230.15377.

Synthesis of 5-ethyl-2-(*p*-tolyl)oxazole (O15)



O15

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane/ EtOAc (9:1)) and obtained as a colourless oil (136 mg, 728 μ mol, 97 %).

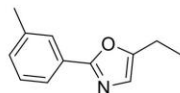
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.89 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 1.0 Hz, 1H), 2.74 (qd, *J* = 7.5, 0.9 Hz, 2H), 2.39 (s, 3H), 1.30 (t, *J* = 7.6 Hz, 3H) ppm.

S20

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 160.99, 154.21, 140.10, 129.59, 126.11, 125.36, 122.93, 21.64, 19.34, 12.03 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O15]⁺: 188.10699, found: 188.10679.

Synthesis of 5-ethyl-2-(*m*-tolyl)oxazole (O16)



Chemical Formula: C₁₂H₁₃NO
Molecular Weight: 187.24

O16

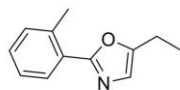
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless oil (165 mg, 880 μmol, 88 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.84 (s, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.35 – 7.30 (m, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.84 – 6.81 (m, 1H), 2.79 – 2.70 (m, 2H), 2.41 (s, 3H), 1.31 (t, *J* = 7.6 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 160.90, 154.41, 138.56, 130.79, 128.73, 127.86, 126.69, 123.23, 122.96, 21.49, 19.32, 11.99 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O16]⁺: 188.10699, found: 188.10699.

Synthesis of 5-ethyl-2-(*o*-tolyl)oxazole (O17)



Chemical Formula: C₁₂H₁₃NO
Molecular Weight: 187.24

O17

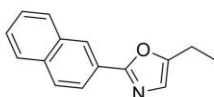
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as a colourless oil (213 mg, 1.14 mmol, 91 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.95 (dd, J = 6.8, 2.7 Hz, 4H), 7.33 – 7.26 (m, 12H), 6.88 (t, J = 1.1 Hz, 4H), 2.76 (qd, J = 7.5, 1.1 Hz, 9H), 2.68 (s, 12H), 1.31 (t, J = 7.6 Hz, 14H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 61.22, 154.14, 137.36, 131.72, 129.72, 128.82, 127.12, 126.08, 122.84, 22.22, 19.39, 12.12 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O17]⁺: 188.10699, found: 188.10708.

Synthesis of 5-ethyl-2-(naphthalen-2-yl)oxazole (O18)



Chemical Formula: C₁₅H₁₃NO
Molecular Weight: 223.28

O18

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (85:15)) and obtained as a white solid (231 mg, 1.04 mmol, 83 %).

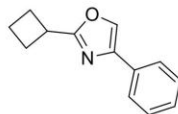
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.49 (d, J = 0.7 Hz, 1H), 8.11 (dd, J = 8.6, 1.7 Hz, 1H), 7.95 – 7.89 (m, 2H), 7.86 (dd, J = 6.0, 3.3 Hz, 1H), 7.55 – 7.49 (m, 2H), 6.90 (t, J = 1.1 Hz, 1H), 2.80 (qd, J = 7.5, 1.1 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 160.91, 154.76, 134.05, 133.23, 128.77, 128.68, 127.98, 127.12, 126.79, 125.76, 125.31, 123.36, 123.26, 19.41, 12.03 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O18]⁺: 224.10699, found: 224.10694.

Melting Point: 102.2 °C.

Synthesis of 2-cyclobutyl-4-phenyloxazole (O19)



Chemical Formula: $C_{13}H_{13}NO$
Molecular Weight: 199.25

O19

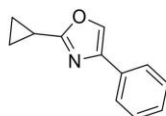
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as a red oil (122 mg, 615 μ mol, 82 %).

1H NMR ($CDCl_3$, 500 MHz, 293 K): δ = 7.82 (s, 1H), 7.74 – 7.70 (m, 2H), 7.42 – 7.36 (m, 2H), 7.32 – 7.27 (m, 1H), 3.70 (pd, J = 8.7, 1.0 Hz, 1H), 2.54 – 2.36 (m, 4H), 2.17 – 1.94 (m, 2H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz, 293 K): δ = 167.50, 140.52, 132.91, 131.34, 128.70, 127.84, 125.50, 33.29, 27.34, 18.66 ppm.

LC-HRMS (ESI+) m/z calculated for [**O19**] $^+$: 200.10699, found: 200.10706.

Synthesis of 2-cyclopropyl-4-phenyloxazole (O20)



Chemical Formula: $C_{12}H_{11}NO$
Molecular Weight: 185.23

O20

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as a red oil (105 mg, 570 μ mol, 76 %).

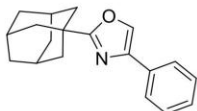
1H NMR ($CDCl_3$, 500 MHz, 293 K): δ = 7.74 (s, 1H), 7.70 (dt, J = 8.1, 1.6 Hz, 2H), 7.41 – 7.36 (m, 2H), 7.31 – 7.27 (m, 1H), 2.13 (tt, J = 8.4, 5.0 Hz, 1H), 1.15 – 1.11 (m, 2H), 1.05 (ddd, J = 7.8, 5.6, 3.8 Hz, 2H) ppm.

S23

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 166.42, 140.70, 132.43, 131.37, 128.80, 127.96, 125.57, 9.16, 8.20 ppm.

LC-HRMS (ESI+) m/z calculated for [O20]⁺: 186.09134, found: 186.09077.

Synthesis of 2-((3r,5r,7r)-adamantan-1-yl)-4-phenyloxazole (O21)



Chemical Formula: C₁₉H₂₁NO
Molecular Weight: 279.38

O21

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as an orange solid (255 mg, 800 μ mol, 64 %).

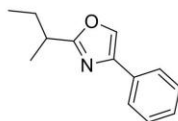
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.79 (s, 1H), 7.73 (dd, J = 8.2, 1.2 Hz, 2H), 7.41 – 7.36 (m, 2H), 7.30 – 7.26 (m, 1H), 2.10 (s, 9H), 1.80 (s, 6H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 171.43, 140.39, 132.73, 131.81, 128.87, 127.92, 125.79, 40.57, 36.75, 35.95, 28.27 ppm.

LC-HRMS (ESI+) m/z calculated for [O21]⁺: 280.16959, found: 280.16959.

Melting Point: 107.3 °C.

Synthesis of 2-(sec-butyl)-4-phenyloxazole (O22)



Chemical Formula: C₁₃H₁₅NO
Molecular Weight: 201.27

O22

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as an orange solid (164 mg, 813 μ mol, 65 %).

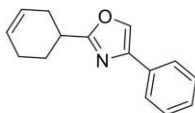
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.82 (s, 1H), 7.75 – 7.71 (m, 2H), 7.39 (dd, *J* = 10.6, 4.7 Hz, 2H), 7.32 – 7.26 (m, 1H), 3.01 – 2.93 (m, 1H), 1.91 – 1.81 (m, 1H), 1.75 – 1.64 (m, 1H), 1.37 (d, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 168.76, 140.29, 132.85, 131.41, 128.69, 127.81, 125.53, 35.51, 28.27, 18.09, 11.73 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O22]⁺: 202.12264, found: 202.12267.

Melting Point: 99.8 °C.

Synthesis of 2-(cyclohex-3-en-1-yl)-4-phenyloxazole (O23)



Chemical Formula: C₁₅H₁₅NO
Molecular Weight: 225.29

O23

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (95:5)) and obtained as a colourless oil (286 mg, 1.26 mmol, 84 %).

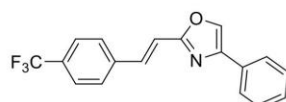
S25

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.83 (s, 1H), 7.76 – 7.71 (m, 2H), 7.43 – 7.36 (m, 2H), 7.32 – 7.27 (m, 1H), 5.76 (s, 2H), 3.17 – 3.09 (m, 1H), 2.47 (dd, J = 5.4, 2.4 Hz, 2H), 2.22 – 2.17 (m, J = 9.0, 4.8, 2.5 Hz, 3H), 1.94 – 1.83 (m, 1H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 168.22, 140.52, 133.05, 131.45, 128.82, 127.97, 126.98, 125.63, 125.41, 34.09, 29.11, 26.84, 24.81 ppm.

LC-HRMS (ESI+) m/z calculated for [O23]⁺: 226.12264, found: 226.12264.

Synthesis of (*E*)-4-phenyl-2-(4-(trifluoromethyl)styryl)oxazole (O24)



Chemical Formula: C₁₈H₁₂F₃NO
Molecular Weight: 315.30

O24

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (95:5)) and obtained as an orange solid (260 mg, 830 μ mol, 83 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.93 (s, 1H), 7.80 – 7.76 (m, 2H), 7.65 (s, 4H), 7.59 (d, J = 16.4 Hz, 1H), 7.46 – 7.42 (m, 2H), 7.37 – 7.32 (m, 1H), 7.09 (d, J = 16.4 Hz, 1H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 161.14, 142.36, 138.91, 134.62, 133.57, 130.77, 128.85, 128.31, 127.33, 125.92, 125.57, 116.21 ppm. CF₃ (q, J = 257.9 Hz), *o*-C-CF₃ (q, 32.7 Hz).

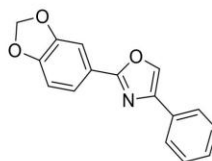
¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -62.76 ppm.

LC-HRMS (ESI+) m/z calculated for [O24]⁺: 316.09438, found: 316.09443.

Melting Point: 147,3 °C.

S26

Synthesis of 2-(benzo[d][1,3]dioxol-5-yl)-4-phenyloxazole (O25)



Chemical Formula: $C_{16}H_{11}NO_3$
Molecular Weight: 265.27

O25

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (9:1)) and obtained as a white solid (167 mg, 630 μ mol, 42 %).

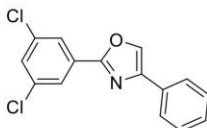
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.91 (s, 1H), 7.81 (dt, *J* = 8.1, 1.6 Hz, 2H), 7.67 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.45 – 7.40 (m, 2H), 7.37 – 7.30 (m, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.04 (s, 2H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 161.85, 149.68, 148.18, 141.95, 133.15, 131.29, 128.86, 128.19, 125.72, 121.83, 121.40, 108.72, 107.01, 101.69 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O25]⁺: 266.08117, found: 266.08127.

Melting Point: 116.5 °C.

Synthesis of 2-(3,5-dichlorophenyl)-4-phenyloxazole (O26)



Chemical Formula: $C_{15}H_9Cl_2NO$
Molecular Weight: 290.14

O26

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as an orange solid (119 mg, 413 μ mol, 55 %).

S27

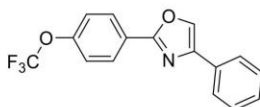
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.01 (d, J = 1.9 Hz, 2H), 7.99 (s, 1H), 7.81 (dd, J = 8.3, 1.2 Hz, 2H), 7.47 – 7.42 (m, 3H), 7.38 – 7.34 (m, 1H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 159.52, 142.64, 135.76, 134.33, 130.69, 130.33, 128.99, 128.60, 125.78, 124.94 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O26]⁺: 290.01340, found: 290.01380.

Melting Point: 114.9 °C.

Synthesis of 4-phenyl-2-(4-(trifluoromethoxy)phenyl)oxazole (O27)



Chemical Formula: C₁₆H₁₀F₃NO₂
Molecular Weight: 305.26

O27

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as an orange solid (269 mg, 880 μmol, 88 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.18 – 8.14 (m, 2H), 7.98 (s, 1H), 7.85 – 7.80 (m, 2H), 7.44 (dd, J = 10.8, 4.4 Hz, 2H), 7.37 – 7.30 (m, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 160.87, 150.79, 142.37, 133.88, 131.02, 128.95, 128.43, 128.32, 126.25, 125.78, 121.23 ppm. CF₃ (q, J = 257.9 Hz).

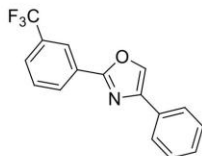
¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -57.75 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O27]⁺: 306.07364, found: 306.07351.

Melting Point: 116.6 °C.

S28

Synthesis of 4-phenyl-2-(3-(trifluoromethyl)phenyl)oxazole (O28)



Chemical Formula: $C_{16}H_{10}F_3NO$
Molecular Weight: 289.26

O28

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (9:1)) and obtained as an orange solid (399 mg, 1.38 mmol, 92 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.31 (d, *J* = 7.8 Hz, 1H), 8.01 (s, 1H), 7.86 – 7.81 (m, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.45 (dd, *J* = 10.5, 4.7 Hz, 2H), 7.40 – 7.33 (m, 1H) ppm.

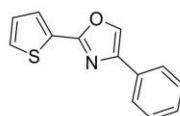
¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 160.65, 142.52, 134.09, 131.42, 130.88, 129.69, 129.53, 128.98, 128.52, 128.37, 127.02, 125.81, 123.58 ppm. CF₃ (q, *J* = 257,9 Hz), *o*-C-CF₃ (q, 32,7 Hz).

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -62.91 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O28]⁺: 290.07873, found: 290.07873.

Melting Point: 105.0 °C.

Synthesis of 4-phenyl-2-(thiophen-2-yl)oxazole (O29)



Chemical Formula: $C_{13}H_9NOS$
Molecular Weight: 227.28

O29

S29

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as an orange solid (201 mg, 888 μ mol, 71 %).

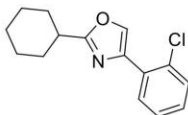
^1H NMR (CDCl_3 , 500 MHz, 293 K): δ = 7.90 (s, 1H), 7.80 (dd, J = 8.2, 1.1 Hz, 2H), 7.74 (dd, J = 3.7, 1.2 Hz, 1H), 7.48 – 7.39 (m, 3H), 7.37 – 7.31 (m, 1H), 7.14 (dd, J = 5.0, 3.7 Hz, 1H) ppm.

^{13}C NMR (CDCl_3 , 125 MHz, 293 K): δ = 158.12, 142.02, 132.87, 130.84, 129.99, 128.76, 128.42, 128.23, 127.98, 127.96, 125.71 ppm.

LC-HRMS (ESI+) m/z calculated for **[O29] $^+$** : 228.04776, found: 228.04784.

Melting Point: 102.0 $^\circ\text{C}$.

Synthesis of 4-(2-chlorophenyl)-2-cyclohexyloxazole (**O30**)



Chemical Formula: $\text{C}_{15}\text{H}_{16}\text{ClNO}$
Molecular Weight: 261.75

O30

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as an orange solid (169 mg, 645 μ mol, 86 %).

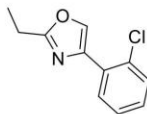
^1H NMR (CDCl_3 , 500 MHz, 293 K): δ = 8.25 (s, 2H), 8.15 (dd, J = 7.9, 1.7 Hz, 2H), 7.44 (dd, J = 8.0, 1.2 Hz, 2H), 7.36 (td, J = 7.7, 1.3 Hz, 2H), 7.26 – 7.21 (m, 2H), 2.88 (tt, J = 11.5, 3.6 Hz, 2H), 2.15 – 2.08 (m, 4H), 1.92 – 1.84 (m, 4H), 1.78 – 1.72 (m, 2H), 1.66 (ddd, J = 24.6, 12.2, 3.3 Hz, 4H), 1.51 – 1.25 (m, 7H) ppm.

^{13}C NMR (CDCl_3 , 125 MHz, 293 K): δ = 167.45, 136.74, 136.40, 131.45, 130.27, 130.23, 129.86, 128.41, 127.07, 37.64, 30.74, 25.91, 25.78 ppm.

LC-HRMS (ESI+) m/z calculated for **[O30] $^+$** : 262.09932, found: 262.09944.

Melting Point: 123.1 $^\circ\text{C}$.

Synthesis of 4-(2-chlorophenyl)-2-ethyloxazole (O31)



Chemical Formula: $C_{11}H_{10}ClNO$
Molecular Weight: 207.66

O31

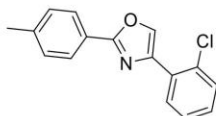
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as an orange oil (179 mg, 1.08 mmol, 86 %).

1H NMR ($CDCl_3$, 500 MHz, 293 K): δ = 8.25 (s, 1H), 8.11 (dd, J = 7.9, 1.7 Hz, 1H), 7.43 (dd, J = 8.0, 1.2 Hz, 1H), 7.34 (td, J = 7.7, 1.3 Hz, 1H), 7.25 – 7.20 (m, 1H), 2.86 (q, J = 7.6 Hz, 2H), 1.39 (t, J = 7.6 Hz, 3H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz, 293 K): δ = 165.10, 137.04, 136.64, 131.49, 130.34, 130.12, 129.81, 128.52, 127.10, 94.24, 21.81, 11.41 ppm.

LC-HRMS (ESI+) m/z calculated for [O31] $^+$: 208.05237, found: 208.05255.

Synthesis of 4-(2-chlorophenyl)-2-(*p*-tolyl)oxazole (O32)



Chemical Formula: $C_{16}H_{12}ClNO$
Molecular Weight: 269.73

O32

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (98:2)) and obtained as a white solid (113 mg, 420 μ mol, 56 %).

1H NMR ($CDCl_3$, 500 MHz, 293 K): δ = 8.38 (s, 1H), 8.27 (dd, J = 7.9, 1.7 Hz, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.46 (dd, J = 8.0, 1.1 Hz, 1H), 7.39 (td, J = 7.7, 1.2 Hz, 1H), 7.29 (d, J = 7.7 Hz, 2H), 7.28 – 7.26 (m, 1H), 2.42 (s, 3H) ppm.

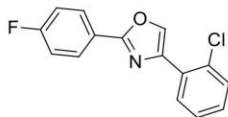
S31

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 161.12, 140.95, 138.03, 137.13, 131.63, 130.33, 130.04, 129.64, 128.71, 127.14, 126.66, 124.74, 21.71 ppm.

LC-HRMS (ESI+) m/z calculated for [O32]⁺: 270.06802, found: 270.06823.

Melting Point: 111.1 °C.

Synthesis of 4-(2-chlorophenyl)-2-(4-fluorophenyl)oxazole (O33)



Chemical Formula: C₁₅H₉ClFNO
Molecular Weight: 273.69

O33

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (98:2)) and obtained as a white solid (127 mg, 465 μ mol, 74 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.39 (s, 1H), 8.25 (dd, J = 7.9, 1.7 Hz, 1H), 8.13 (dd, J = 8.9, 5.3 Hz, 2H), 7.46 (dd, J = 8.0, 1.2 Hz, 1H), 7.39 (td, J = 7.7, 1.2 Hz, 1H), 7.28 (dd, J = 7.7, 1.6 Hz, 1H), 7.21 – 7.15 (m, 2H) ppm.

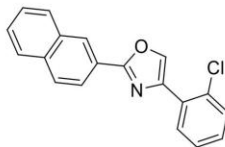
¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 165.31, 163.31, 160.10, 138.21, 137.41, 131.67, 130.38, 129.99, 129.87, 128.88, 128.86, 128.81, 127.18, 123.81, 123.78, 116.23, 116.05 ppm.

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -109.33 ppm.

LC-HRMS (ESI+) m/z calculated for [O33]⁺: 274.04295, found: 274.04325.

Melting Point: 129.2 °C.

Synthesis of 4-(2-chlorophenyl)-2-(naphthalen-2-yl)oxazole (O34)



Chemical Formula: $C_{19}H_{12}ClNO$
Molecular Weight: 305.76

O34

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a white solid (284 mg, 930 μ mol, 93 %).

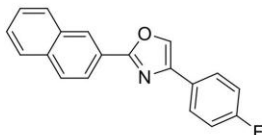
1H NMR ($CDCl_3$, 500 MHz, 293 K): δ = 8.63 (d, J = 0.8 Hz, 1H), 8.46 (s, 1H), 8.33 (dd, J = 7.9, 1.7 Hz, 1H), 8.23 (dd, J = 8.5, 1.7 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.89 (dd, J = 5.2, 4.1 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.48 (dd, J = 8.0, 1.2 Hz, 1H), 7.42 (td, J = 7.7, 1.3 Hz, 1H), 7.31 – 7.27 (m, 1H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz, 293 K): δ = 161.07, 138.35, 137.58, 134.37, 133.18, 131.69, 130.38, 130.08, 129.96, 128.91, 128.84, 128.80, 128.03, 127.47, 127.20, 126.92, 126.67, 124.70, 123.64, 18.14 ppm.

LC-HRMS (ESI+) m/z calculated for **[O34] $^+$** : 306.06802, found: 306.06808.

Melting Point: 120.1 $^{\circ}C$.

Synthesis of 4-(4-fluorophenyl)-2-(naphthalen-2-yl)oxazole (O35)



Chemical Formula: $C_{19}H_{12}FNO$
Molecular Weight: 289.31

O35

S33

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (9:1)) and obtained as a white solid (277 mg, 960 μ mol, 96 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.61 (s, 1H), 8.21 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.00 – 7.92 (m, 3H), 7.89 (dd, *J* = 8.6, 4.3 Hz, 1H), 7.88 – 7.82 (m, 2H), 7.60 – 7.53 (m, 2H), 7.18 – 7.12 (m, 2H) ppm.

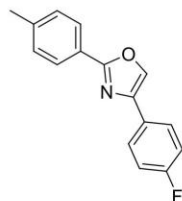
¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 141.49, 134.36, 133.37, 133.16, 128.92, 128.81, 128.03, 127.61, 127.55, 127.45, 126.92, 126.60, 124.82, 123.58, 116.00, 115.85 ppm.
CF (d, *J* = 21,7 Hz), *o-CF* (d, *J* = 8.10 Hz), *m-CF* (d, *J* = 3.20 Hz), *p-CF* (d, *J* = 1.40 Hz).

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -113.57 ppm.

LC-HRMS (ESI+) *m/z* calculated for [**O35**]⁺: 290.09757, found: 290.09681.

Melting Point: 117.5 °C.

Synthesis of 4-(4-fluorophenyl)-2-(*p*-tolyl)oxazole (**O36**)



Chemical Formula: C₁₆H₁₂FNO
Molecular Weight: 253.28

O36

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (95:5)) and obtained as a yellow solid (212 mg, 840 μ mol, 84 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.00 (d, *J* = 8.2 Hz, 2H), 7.90 (s, 1H), 7.82 – 7.77 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.16 – 7.09 (m, 2H), 2.42 (s, 3H) ppm.

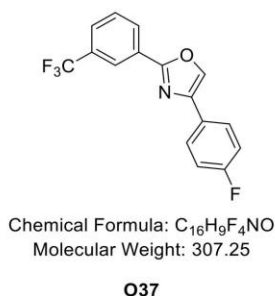
¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 141.17, 140.93, 132.89, 132.88, 129.64, 127.59, 127.56, 127.53, 127.46, 126.61, 124.84, 115.93, 115.76, 21.70 ppm. *CF* (d, *J* = 21,7 Hz), *o-CF* (d, *J* = 8.10 Hz), *m-CF* (d, *J* = 3.20 Hz), *p-CF* (d, *J* = 1.40 Hz).

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -113.78 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O36]⁺: 254.09757, found: 254.09669.

Melting Point: 134.2 °C.

Synthesis of 4-(4-fluorophenyl)-2-(3-(trifluoromethyl)phenyl)oxazole (O37)



The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (95:5)) and obtained as a yellow solid (170 mg, 550 μmol, 55 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.38 (s, 1H), 8.29 (d, *J* = 7.8 Hz, 1H), 7.96 (s, 1H), 7.84 – 7.78 (m, 2H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.17 – 7.12 (m, 2H) ppm.

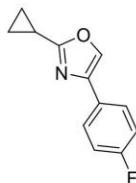
¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 141.67, 133.72, 133.70, 129.68, 129.56, 128.25, 127.61, 127.54, 127.10, 116.07, 115.90 ppm. *CF* (d, *J* = 21,7 Hz), *o-CF* (d, *J* = 8.10 Hz), *m-CF* (d, *J* = 3.20 Hz), *p-CF* (d, *J* = 1.40 Hz), CF₃ (q, *J* = 257,9 Hz), *o-C-CF₃* (q, 32,7 Hz).

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -62.92, -113.19 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O37]⁺: 308.06930, found: 308.06930.

Melting Point: 149.2 °C.

Synthesis of 2-cyclopropyl-4-(4-fluorophenyl)oxazole (O38)



Chemical Formula: C₁₂H₁₀FNO
Molecular Weight: 203.22

O38

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (9:1)) and obtained as a yellow solid (135 mg, 660 μmol, 66 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.70 – 7.63 (m, 3H), 7.06 (dd, *J* = 9.7, 7.8 Hz, 2H), 2.11 (tt, *J* = 8.4, 5.0 Hz, 1H), 1.14 – 1.01 (m, 4H) ppm.

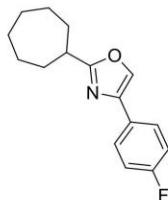
¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 166.53, 163.53, 161.57, 139.86, 132.06, 132.05, 127.59, 127.56, 127.30, 127.24, 115.84, 115.66, 9.10, 8.23 ppm. *CF* (d, *J* = 21,7 Hz), *o*-*CF* (d, *J* = 8.10 Hz), *m*-*CF* (d, *J* = 3.20 Hz), *p*-*CF* (d, *J* = 1.40 Hz).

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -114.10 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O38]⁺: 204.08192, found: 204.08139.

Melting Point: 101.4 °C.

Synthesis of 2-cycloheptyl-4-(4-fluorophenyl)oxazole (O39)



Chemical Formula: C₁₆H₁₈FNO
Molecular Weight: 259.32

O39

S36

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as an orange solid (109 mg, 430 μ mol, 43 %).

^1H NMR (CDCl_3 , 500 MHz, 293 K): δ = 139.47, 132.45, 132.44, 127.35, 127.28, 115.84, 115.67, 39.70, 32.54, 28.36, 26.40 ppm.

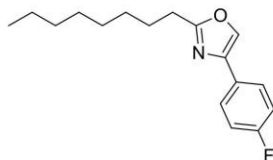
^{13}C NMR (CDCl_3 , 125 MHz, 293 K): δ = 139.47, 132.45, 132.44, 127.35, 127.28, 115.84, 115.67, 39.70, 32.54, 28.36, 26.40 ppm. *CF* (d, *J* = 21,7 Hz), *o-CF* (d, *J* = 8.10 Hz), *m-CF* (d, *J* = 3.20 Hz), *p-CF* (d, *J* = 1.40 Hz).

^{19}F NMR (CDCl_3 , 376 MHz, 293 K): δ = -114.25 ppm.

LC-HRMS (ESI+) *m/z* calculated for **[O39] $^+$** : 260.14452, found: 260.14381.

Melting Point: 72.3 $^\circ\text{C}$.

Synthesis of 4-(4-fluorophenyl)-2-octyloxazole (O40)



Chemical Formula: $\text{C}_{17}\text{H}_{22}\text{FNO}$
Molecular Weight: 275.37

O40

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a white solid (109 mg, 400 μ mol, 40 %).

^1H NMR (CDCl_3 , 500 MHz, 293 K): δ = 7.76 (s, 1H), 7.73 – 7.65 (m, 2H), 7.12 – 7.05 (m, 2H), 2.80 (t, *J* = 7.2 Hz, 1H), 1.79 (dt, *J* = 15.3, 7.6 Hz, 2H), 1.33 – 1.25 (m, 10H), 0.90 – 0.87 (m, 3H) ppm.

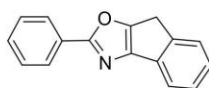
^{13}C NMR (CDCl_3 , 125 MHz, 293 K): δ = 139.78, 132.73, 132.72, 127.33, 127.27, 115.88, 115.71, 31.95, 29.32, 29.29, 29.27, 28.41, 27.27, 22.79, 14.25 ppm. *CF* (d, *J* = 21,7 Hz), *o-CF* (d, *J* = 8.10 Hz), *m-CF* (d, *J* = 3.20 Hz), *p-CF* (d, *J* = 1.40 Hz).

¹⁹F NMR (CDCl₃, 376 MHz, 293 K): δ = -114.11 ppm.

LC-HRMS (ESI+) m/z calculated for [O40]⁺: 276.17582, found: 276.17520.

Melting Point: 88.8 °C.

Synthesis of 2-phenyl-8H-indeno[1,2-d]oxazole (O41)



Chemical Formula: C₁₆H₁₁NO
Molecular Weight: 233.27

O41

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as an off-white solid (213 mg, 913 μ mol, 73 %).

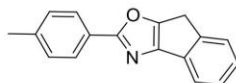
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.15 – 8.11 (m, 2H), 7.68 (d, *J* = 7.5 Hz, 1H), 7.51 – 7.45 (m, 4H), 7.40 – 7.35 (m, 1H), 7.23 (td, *J* = 7.5, 1.1 Hz, 1H), 3.77 (s, 2H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 66.01, 157.36, 146.78, 142.44, 135.06, 130.40, 128.99, 128.25, 127.50, 126.35, 125.62, 125.29, 118.87, 29.45 ppm.

LC-HRMS (ESI+) m/z calculated for [O41]⁺: 234.09134, found: 234.09144.

Melting Point: 116.1 °C.

Synthesis of 2-(*p*-tolyl)-8H-indeno[1,2-d]oxazole (O42)



Chemical Formula: C₁₇H₁₃NO
Molecular Weight: 247.30

O42

The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as an off-white solid (176 mg, 710 μ mol, 71 %).

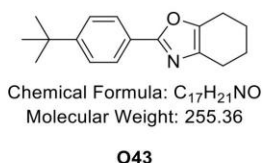
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 8.01 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 8.1 Hz, 2H), 7.22 (td, J = 7.5, 1.0 Hz, 1H), 3.75 (s, 2H), 2.42 (s, 3H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 166.29, 157.05, 146.63, 142.46, 140.72, 135.15, 129.71, 127.47, 126.32, 125.59, 125.56, 125.18, 118.80, 29.44, 21.69 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O42]⁺: 248.10699, found: 248.10698.

Melting Point: 160.9 °C.

Synthesis of 2-(4-(*tert*-butyl)phenyl)-4,5,6,7-tetrahydrobenzo[d]oxazole (O43)



The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a white solid (225 mg, 880 μmol, 88 %).

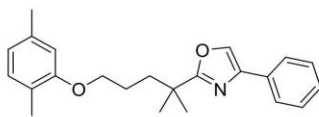
¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.94 – 7.90 (m, 2H), 7.46 – 7.41 (m, 2H), 2.69 (ddd, J = 8.1, 4.1, 2.0 Hz, 1H), 2.60 (tt, J = 5.7, 1.9 Hz, 2H), 1.94 – 1.80 (m, 4H), 1.34 (s, 9H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 159.99, 153.05, 146.64, 135.08, 125.80, 125.75, 125.48, 35.01, 31.35, 23.29, 23.15, 23.08, 22.10 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O43]⁺: 256.16959, found: 256.16952.

Melting Point: 120.5 °C.

2-(5-(2,5-dimethylphenoxy)-2-methylpentan-2-yl)-4-phenyloxazole (O44)



Chemical Formula: $C_{23}H_{27}NO_2$
Molecular Weight: 349.47

O44

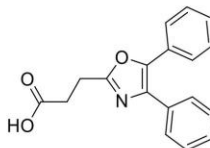
The desired product was synthesized following **GP4a** and **GP4b**. The crude product was purified via column chromatography (*n*-pentane : Et₂O (95:5)) and obtained as a colourless oil (206 mg, 590 μ mol, 59%).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.80 (s, 1H), 7.76 – 7.71 (m, 2H), 7.41 – 7.36 (m, 2H), 7.31 – 7.27 (m, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 6.58 (s, 1H), 3.89 (t, *J* = 6.3 Hz, 2H), 2.27 (s, 3H), 2.17 (s, 3H), 1.95 – 1.89 (m, 2H), 1.46 (s, 6H), 1.24 – 1.19 (m, 2H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 70.66, 157.08, 140.33, 136.58, 133.03, 131.61, 130.39, 128.79, 127.90, 125.70, 123.70, 120.74, 112.03, 67.97, 38.46, 37.13, 26.61, 21.52, 15.93 ppm.

LC-HRMS (ESI+) *m/z* calculated for [O44]⁺: 350.21146, found: 350.21146.

Synthesis of 3-(4,5-diphenyloxazol-2-yl)propanoic acid (Oxaprozin, O45)



Chemical Formula: $C_{18}H_{15}NO_3$
Molecular Weight: 293.32

O45

In a Schlenk tube the 4-(*tert*-butoxy)-4-oxobutanoic acid (263 mg, 1.50 mmol, 1.00 equiv.), 2-amino-1,2-diphenylethan-1-ol (320 mg, 1.50 mmol, 1.00 equiv.), KO^tBu (589 mg, 5.25 mmol, 3.50 equiv.) and **[Mn-I]** (5.00 mol%) are dissolved in 1,4-dioxane (0.10 M, 15.0 mL).

S40

The solution is stirred at 50 °C for 24 h and then for 72 h at reflux conditions under anaerobic conditions in an open system.

The reaction mixture is cooled to 0 °C. HCl (1.31 mL, 3.50 equiv., 4.00 M in 1,4-dioxane) is added. The reaction mixture is stirred at 0 °C for 5 min before POCl₃ (420 µL, 4.50 mmol, 3.00 equiv.) is slowly added. The mixture is heated to 85 °C and stirred for another 4 h under anaerobic conditions in an open system. The reaction is quenched by adding ice. The solution is washed with brine : water : NH₄Cl (1:1:1). The aqueous phase is extracted with Et₂O several times and then dried over MgSO₄. Removing the solvents under reduced pressure leads to the crude product. The crude product was purified via column chromatography (*n*-pentane : Et₂O (98:2)) and obtained as a white solid (154 mg, 525 µmol, 35 %).

¹H NMR (DMSO-d₆, 500 MHz, 293 K): δ = 7.71 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.62 – 7.57 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.36 – 7.29 (m, 5H), 6.67 (s, 1H), 2.76 – 2.67 (m, 2H), 2.66 – 2.58 (m, 2H) ppm.

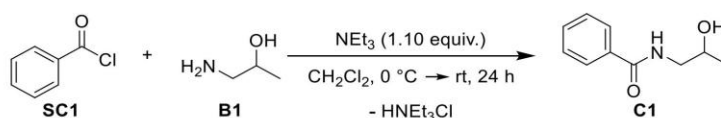
¹³C NMR (DMSO-d₆, 125 MHz, 293 K): δ = 193.70, 176.92, 135.38, 134.49, 133.13, 129.67, 128.69, 128.09, 128.02, 127.86, 59.27, 27.95 ppm.

The spectroscopic data correspond to those in the literature.^[11]

12 Mechanistic investigations

Validation of the reaction intermediates C1 and D1

To analyse for possible reaction intermediates, and to obtain spectroscopic and gas chromatographic data for reference values, the potentially as intermediate identified β -hydroxyamide *N*-(2-hydroxypropyl)benzamide (**C1**) was synthesized.

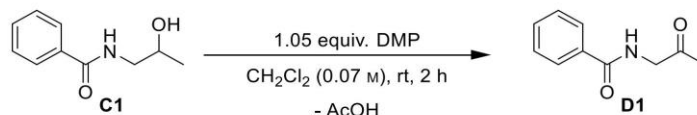


Supplementary Figure 12 Synthesis of *N*-(2-hydroxypropyl)benzamide (**C1**).

Synthesis of *N*-(2-hydroxypropyl)benzamide (C1**):** 1-Aminopropan-2-ol **B1** (3.80 g, 50.0 mmol, 1.00 equiv.) is dissolved in CH_2Cl_2 (0.42 M, 120 mL). The solution is cooled to 0 °C and benzoyl chloride **SC1** (7.73 g, 55.0 mmol, 1.10 equiv.) is slowly added to the reaction mixture. After the addition of NEt_3 (5.60 g, 55.0 mmol, 1.10 equiv.) at 0 °C, the solution is slowly warmed up to rt and stirred for 16 h. After evaporation of the solvents under reduced pressure and column chromatography (*n*-pentane : EtOAc (3:7) $\rightarrow$ THF) the desired product **C1** (7.25 g, 44.5 mmol, 89%) is obtained as a white crystalline solid.

^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ = 8.39 (t, J = 5.0 Hz, 1H), 7.87 – 7.83 (m, J = 3.7, 2.4 Hz, 2H), 7.55 – 7.42 (m, 3H), 4.75 (d, J = 4.8 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.20 (td, J = 6.0, 2.3 Hz, 2H), 1.07 (d, J = 6.2 Hz, 3H) ppm.

The spectroscopic data corresponded to those in the literature.^[12]



Supplementary Figure 13 Synthesis of *N*-(2-oxopropyl)benzamide (**D1**).

Synthesis of *N*-(2-oxopropyl)benzamide (D1**):** *N*-(2-Hydroxypropyl)benzamide **C1** (300 mg, 1.67 mmol, 1.00 equiv.) is dissolved in CH_2Cl_2 (0.07 M, 24.0 mL).

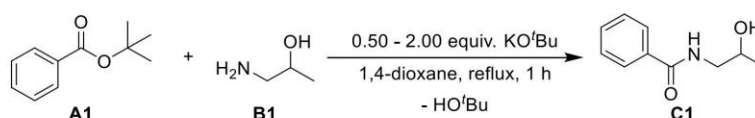
After the addition of DMP (742 mg, 1.75 mmol, 1.05 equiv.) and a few drops of H₂O the reaction is stirred for 2 h at rt. After the addition of Et₂O and NaOH (1.00 M) the reaction is stirred for further 20 min at rt. The aqueous phase is extracted with CH₂Cl₂. The combined organic phases are washed with NaHCO₃ (saturated solution in H₂O), brine and water. Finally, the organic phase is washed with Na₂S₂O₃ (10 wt% in water).

The organic phase is dried over Na₂SO₄, filtered and the solvent is evaporated under reduced pressure. Column chromatography (*n*-pentane → EtOAc (8:2)) yields the desired product **D1** (212 mg, 1.18 mmol, 72%) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.78 (t, *J* = 5.1 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.58 – 7.45 (m, 3H), 4.08 (d, *J* = 5.7 Hz, 2H), 2.13 (s, 2H) ppm.

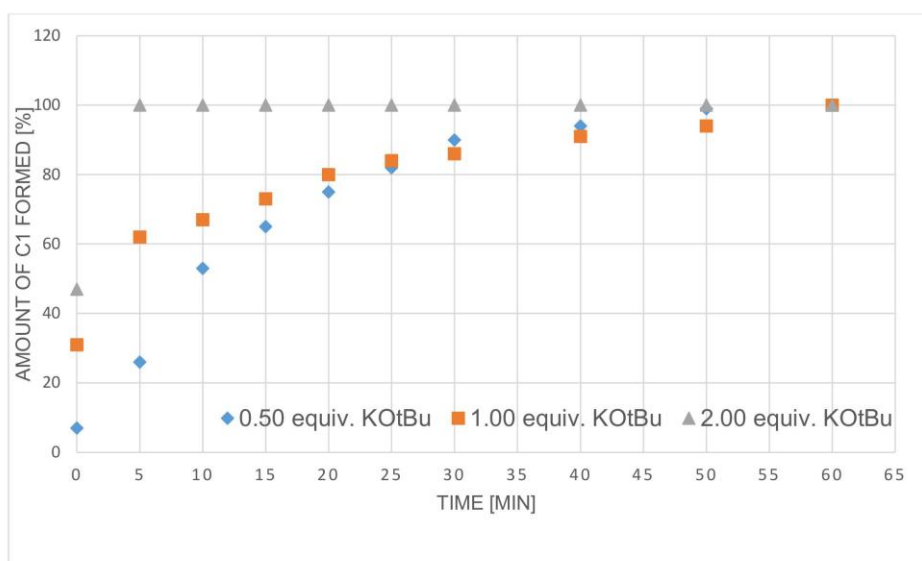
The spectroscopic data corresponds to those in the literature.^[13]

Investigation of the influence of KO^tBu on the formation of **C1**

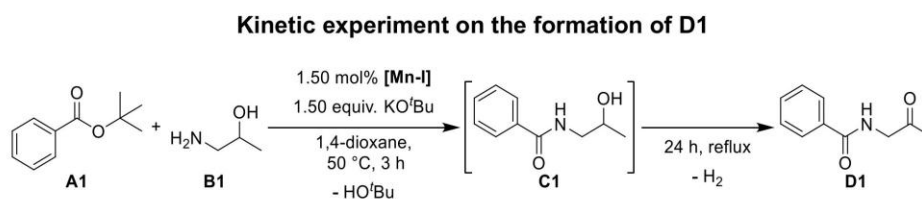


Supplementary Figure 14 Kinetic experiment for the formation of **C1**.

A kinetic experiment was performed to analyse the influence of KO^tBu on the formation of **C1**. Reaction conditions: 0.75 mmol **A1**, 0.75 mmol **B1**, 0.50 - 2.00 equiv. KO^tBu, 1,4-dioxane (0.10 M, 7.50 mL), reflux conditions, open system under anaerobic conditions for 1 hour. The amount of **C1** was determined by GC with dodecane as an internal standard.

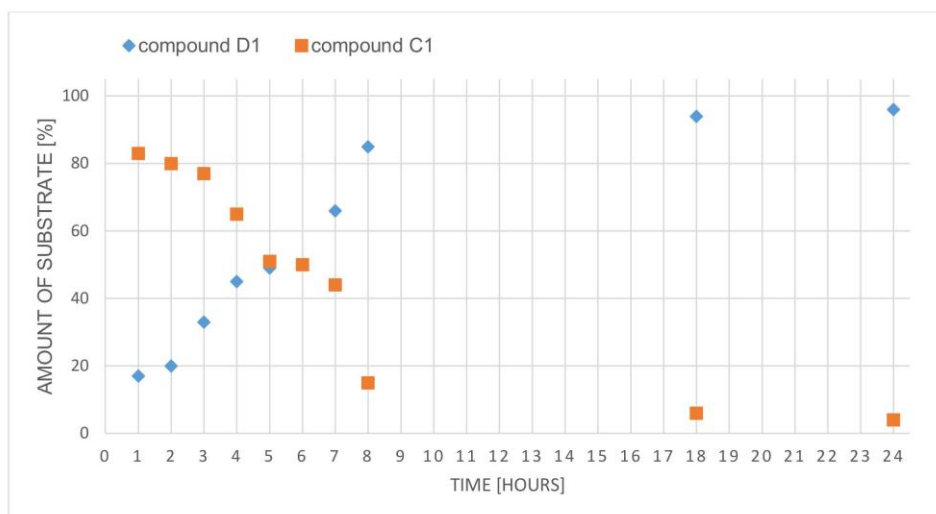


Supplementary Figure 15 Time conversion plot for the formation of **C1**.



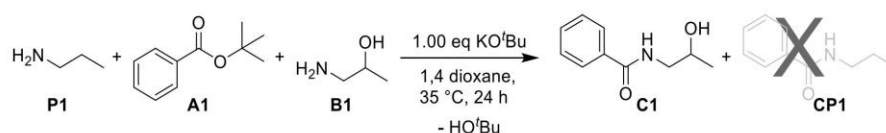
Supplementary Figure 16 Time conversion plot for the synthesis of **D1**.

A kinetic experiment was performed to analyse the formation of **D1**. Reaction conditions: 0.75 mmol **A1**, 0.75 mmol **B1**, KOtBu 1.125 mmol (1.50 equiv.), 1.50 mol% **[Mn-I]**, 1,4-dioxane (0.10 M, 7.50 mL), reflux conditions, open system. The amount of **D1** was determined by GC with dodecane as an internal standard.



Supplementary Figure 17 Time conversion plot for the synthesis of compound **D1**.

Investigations on the formation of intermediate **C1**

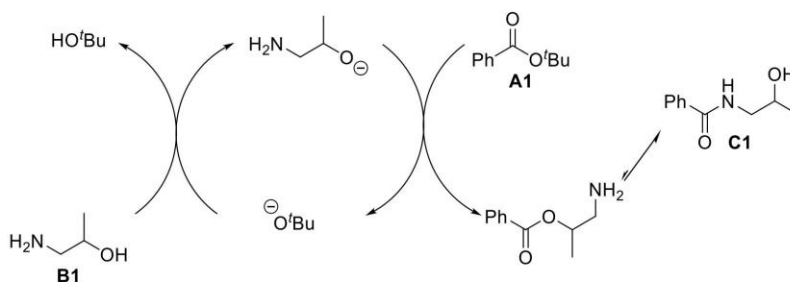


Supplementary Figure 18 Competition experiment.

A competition experiment was performed to investigate the influence of the hydroxyl group on the formation of **C1**. Reaction conditions: 0.75 mmol **P1**, 0.75 mmol **A1**, 0.75 mmol **B1**, 1.00 mmol KO^tBu (1.00 equiv.), 1,4-dioxane (0.10 M, 7.50 mL), rt, open system for 24 h. The amount of **C1** was determined by GC with dodecane as an internal standard.

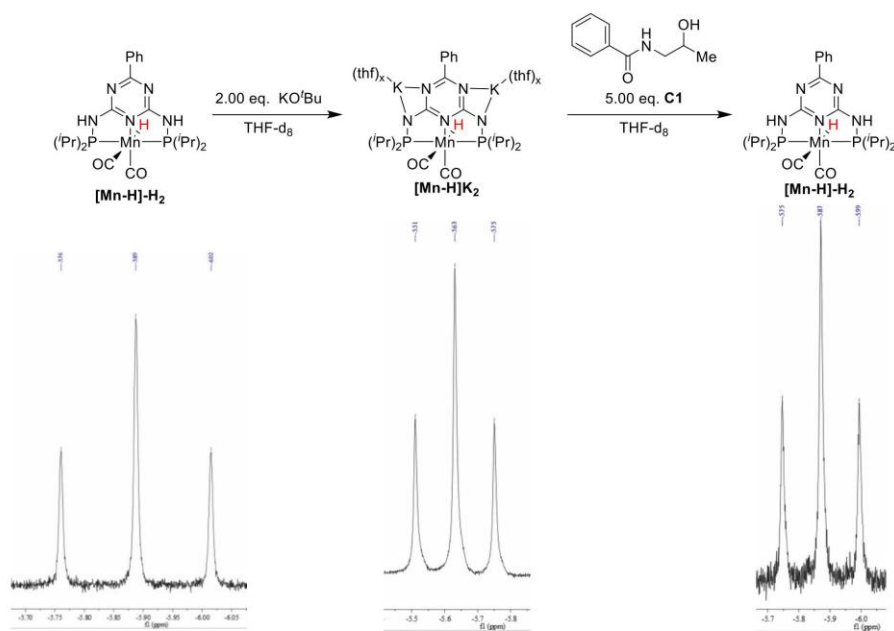
If deprotonation of the corresponding amine function would preferentially occur, the amide should form directly and compound **CP1** should be formed for the most part. In the control experiment carried out, however, only quantitative formation of intermediate **C1** was observed. This fact and that sub stoichiometric amounts of base are sufficient to form **C1**

quantitatively, indicates that the ester is formed first. After an intramolecular trans-esterification the corresponding amide is formed.



Supplementary Figure 19 Proposed mechanism for the formation of C1.

Investigations on the decomplexation of [Mn-H]K₂



Supplementary Figure 20 ¹H NMR experiment.

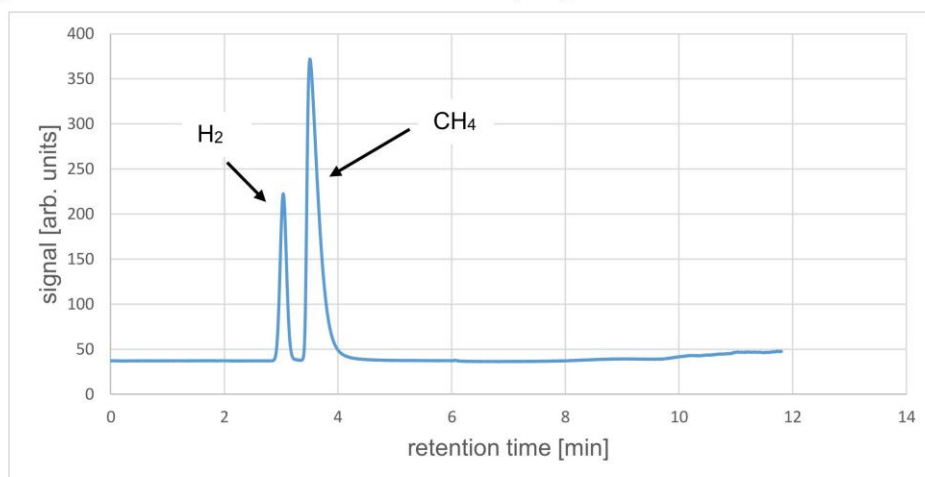
A ^1H NMR experiment was performed to investigate the decomplexation of $[\text{Mn-H}]\text{K}_2$ in presence of compound **C1**. Reaction conditions: a) 20 μmol $[\text{Mn-H}]\text{H}_2$ (stock solution in THF-d_8), 40 μmol KO^tBu (stock solution in THF-d_8). b) 100 μmol **C1**.^[14]

The comparison of the ^1H NMR spectra from the different species shows, that the addition of **C1** leads to a decomplexation of the potassium in the guanidine package from $[\text{Mn-H}]\text{K}_2$. After the addition of **C1** an insoluble precipitate formed.

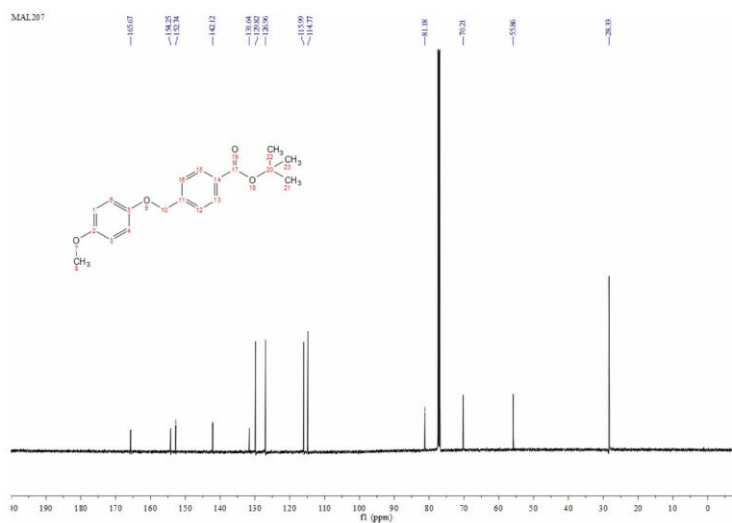
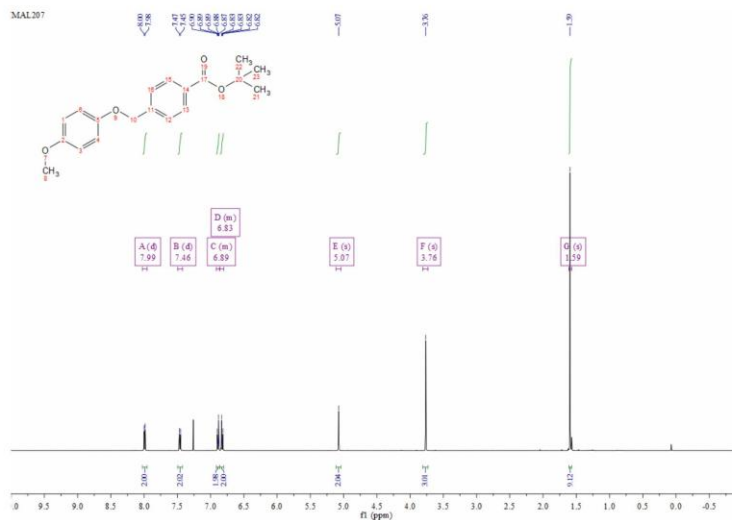
Validation of the hydrogen release during the catalytic dehydration

The release of one equivalent hydrogen was proven by analyzing the gas mixture with methane as an internal standard in the Schlenk tube after reaction. The gas mixture was analyzed using an Agilent Technologies 6890N equipped with a TCD and an Agilent special plot and molsieve capillary column (30 m, 320 μm , 0.25 μm).

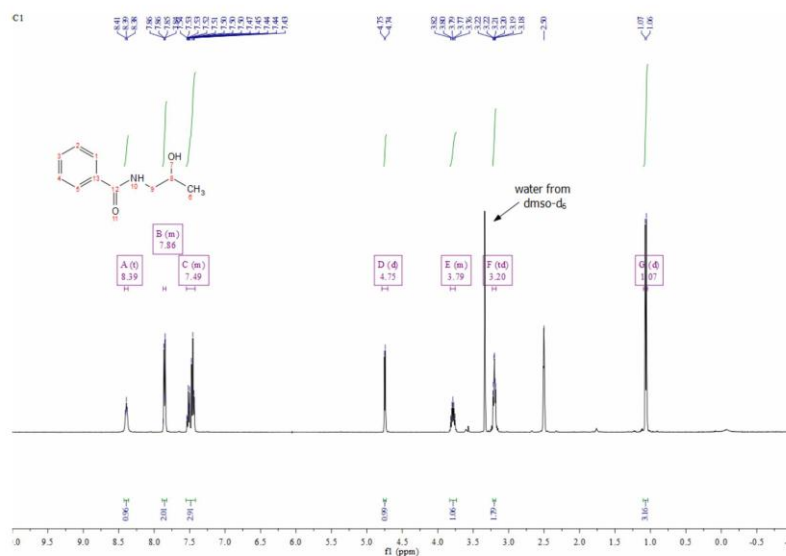
Argon was used as carrier gas. Reaction conditions: 0.2 mmol **A1**, 0.2 mmol **B1**, 1.50 mol% $[\text{Mn-I}]$, 0.30 mmol KO^tBu and 2.00 mL 1,4-dioxane were added to a Schlenk tube (100 mL) under an argon atmosphere, closed and heated at reflux conditions for 24 h. A yield of 88% of **D1** was determined and 83% of hydrogen was detected.



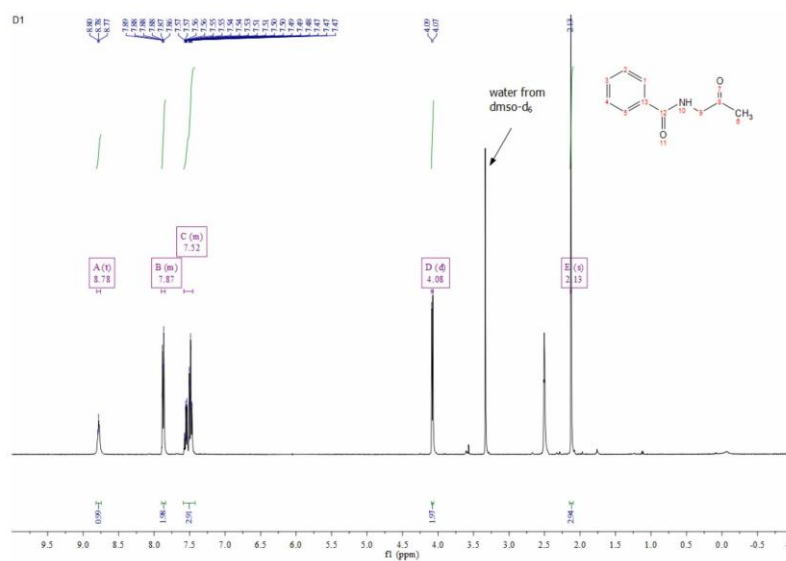
Supplementary Figure 21 Gas-chromatographic analysis from the upper gas layer.



¹H NMR spectra of C1 and D1

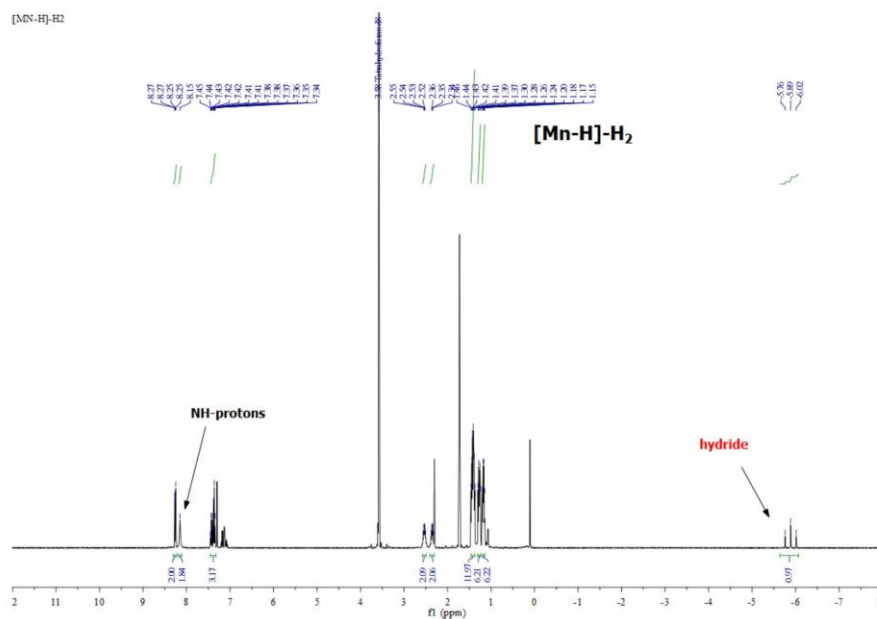


Supplementary Figure 24 ¹H NMR spectrum of **C1** (400 MHz, 293 K, DMSO-d₆).

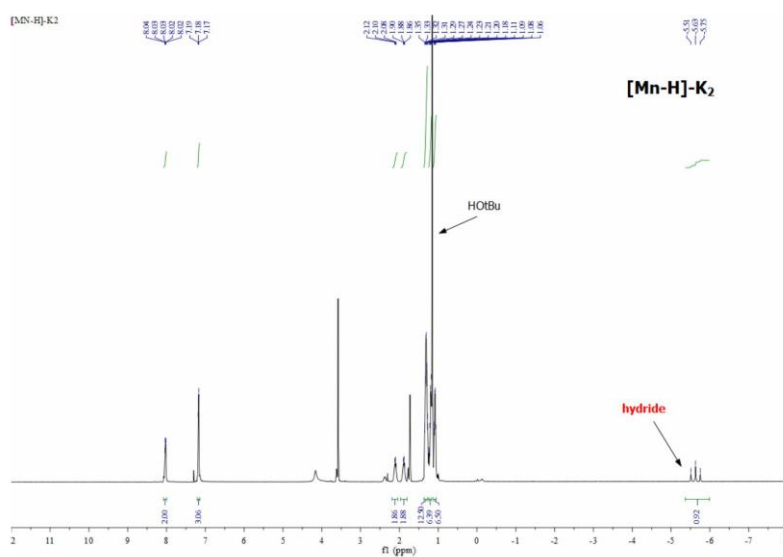


Supplementary Figure 25 ¹H NMR spectrum of **D1** (400 MHz, 293 K, DMSO-d₆).

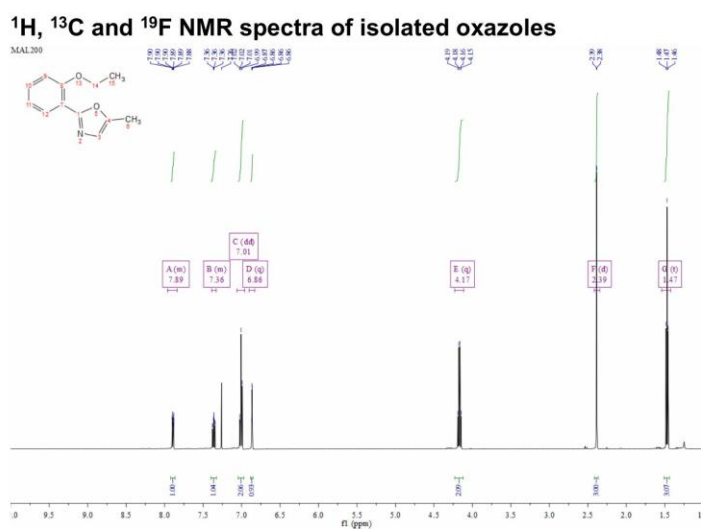
^1H NMR spectra of $[\text{Mn-H}]\text{-H}_2$, $[\text{Mn-H}]\text{-K}_2$ and $[\text{Mn-H}]\text{-K}_2 + \text{C1}$



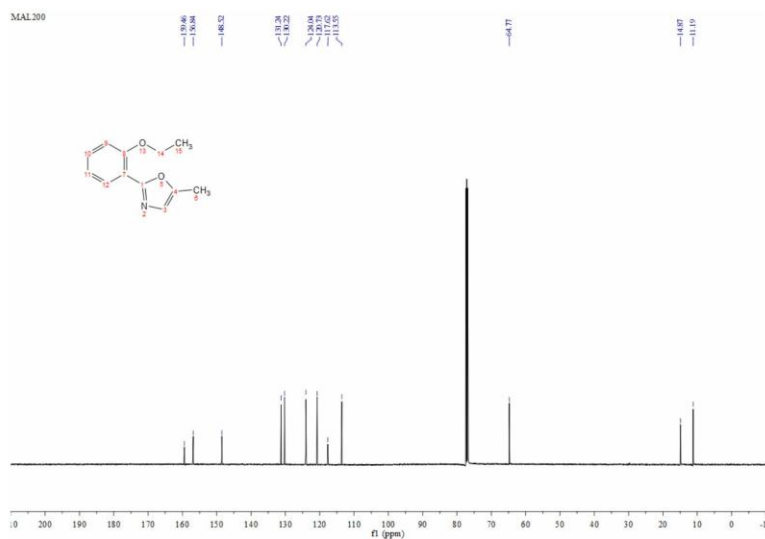
Supplementary Figure 26 ^1H NMR spectrum of $[\text{Mn-H}]\text{-H}_2$ (400 MHz, 293 K, THF-d_8).



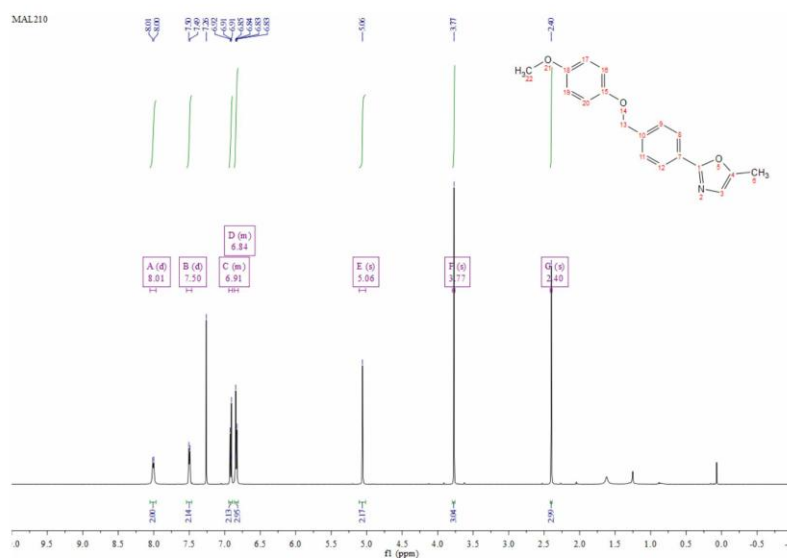
Supplementary Figure 27 ^1H NMR spectrum of $[\text{Mn-H}]\text{-K}_2$ (400 MHz, 293 K, THF-d_8).



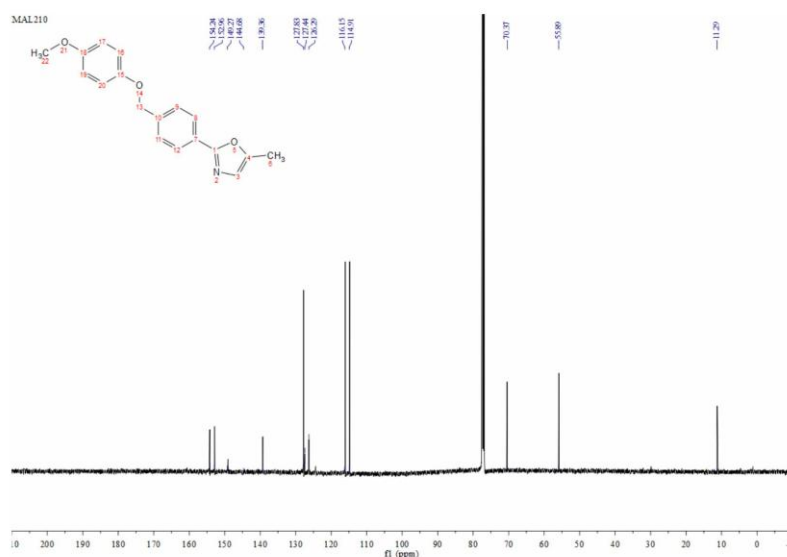
Supplementary Figure 29 ^1H NMR spectrum of **O1** (500 MHz, 293 K, CDCl_3).



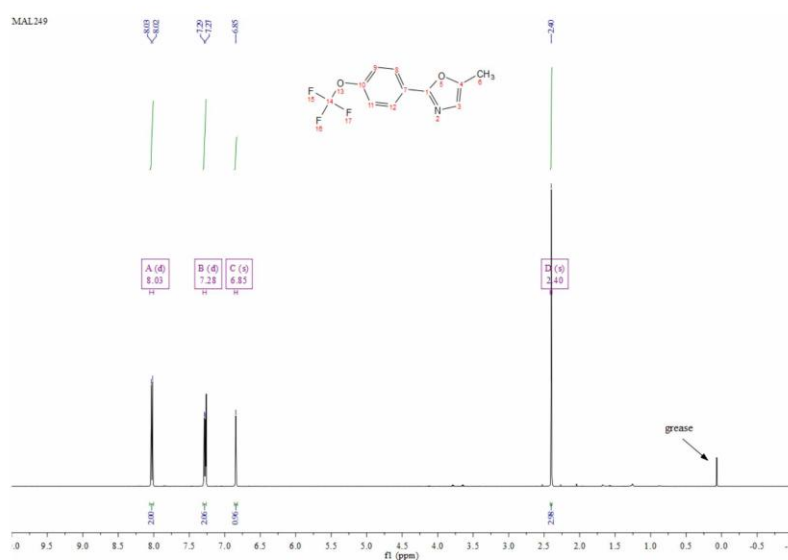
Supplementary Figure 30 ^{13}C NMR spectrum of **O1** (125 MHz, 293 K, CDCl_3).



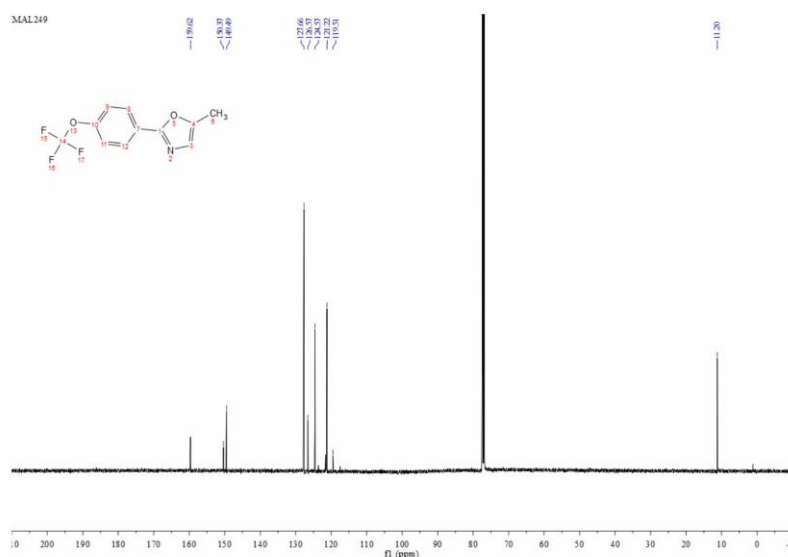
Supplementary Figure 31 ¹H NMR spectrum of **O2** (500 MHz, 293 K, CDCl₃).



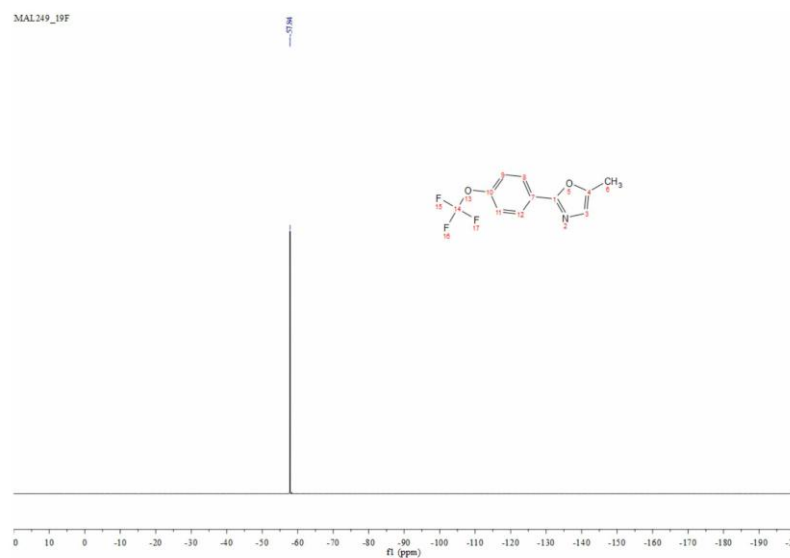
Supplementary Figure 32 ¹³C NMR spectrum of **O2** (125 MHz, 293 K, CDCl₃).



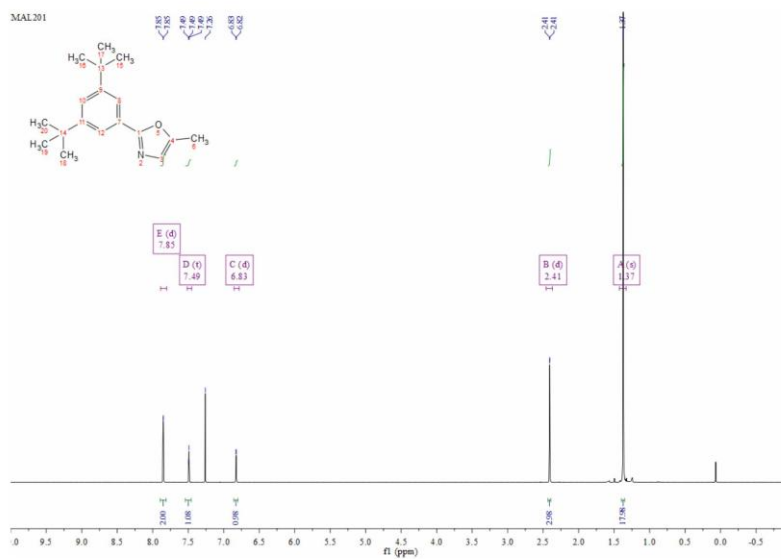
Supplementary Figure 33 ¹H NMR spectrum of **O3** (500 MHz, 293 K, CDCl₃).



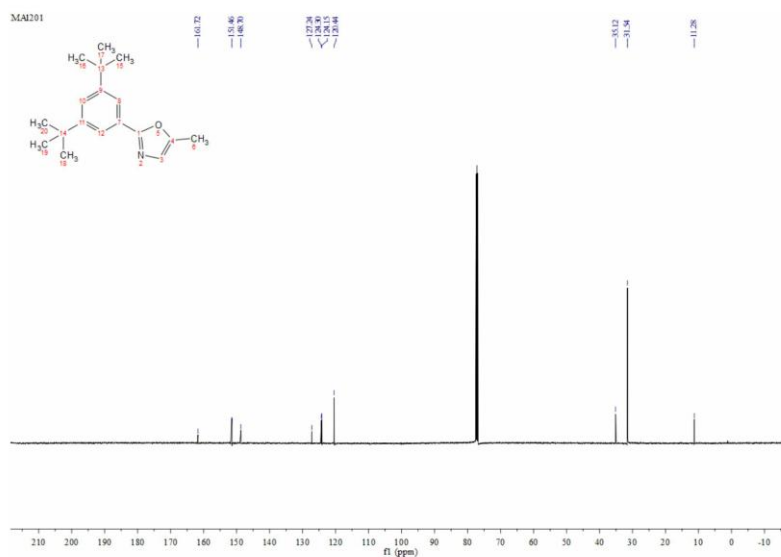
Supplementary Figure 34 ¹³C NMR spectrum of **O3** (125 MHz, 293 K, CDCl₃).



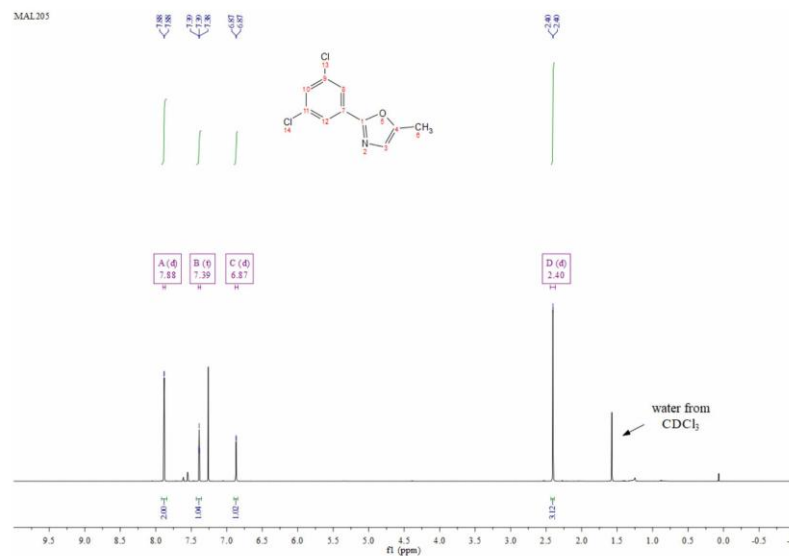
Supplementary Figure 35 ^{19}F NMR spectrum of **O3** (376 MHz, 293 K, CDCl_3).



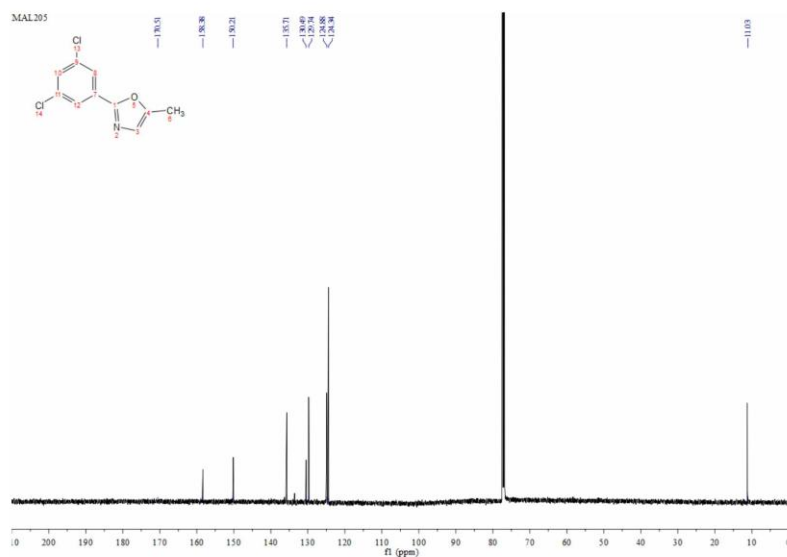
Supplementary Figure 36 ^1H NMR spectrum of **O4** (500 MHz, 293 K, CDCl_3).



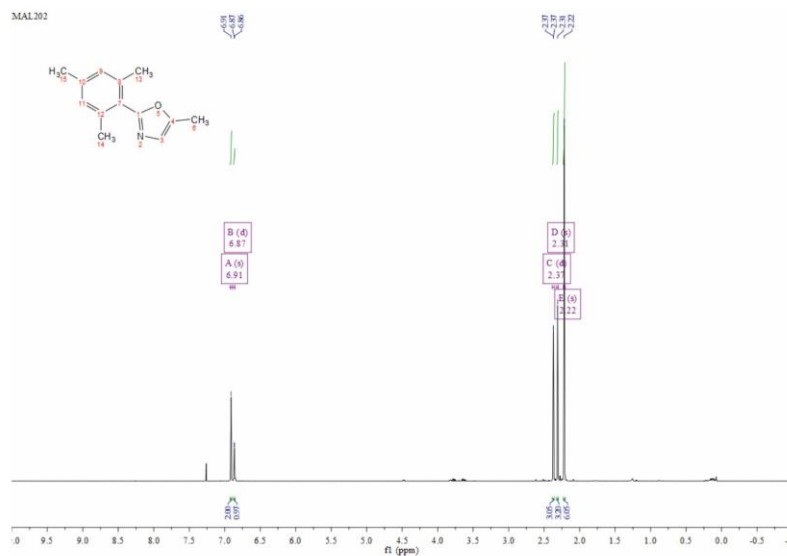
Supplementary Figure 37 ^{13}C NMR spectrum of **O4** (125 MHz, 293 K, CDCl_3).



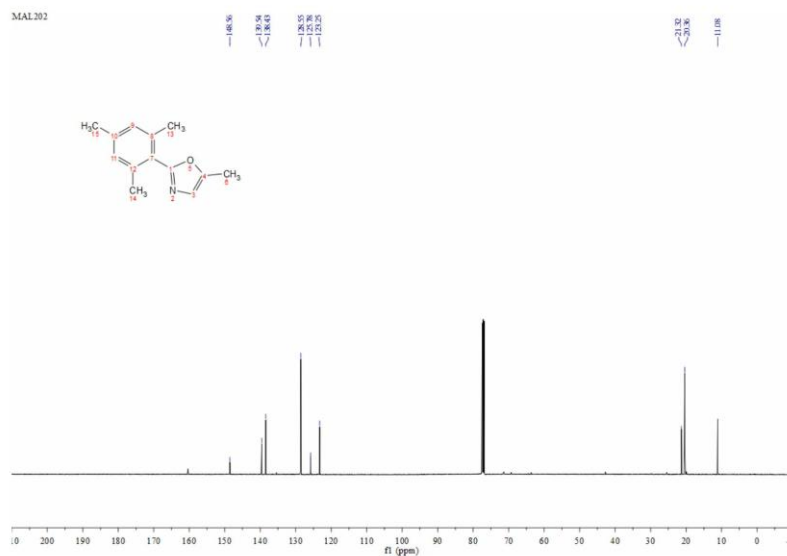
Supplementary Figure 38 ^1H NMR spectrum of **O5** (500 MHz, 293 K, CDCl_3).



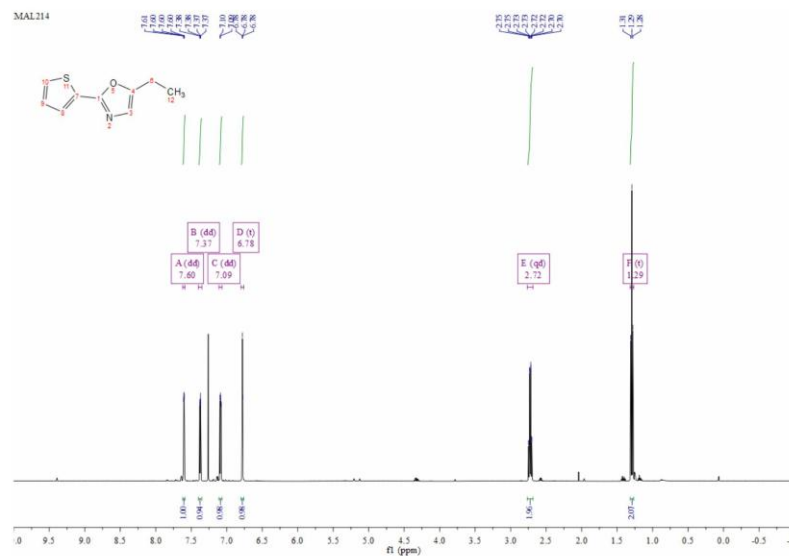
Supplementary Figure 39 ^{13}C NMR spectrum of **O5** (125 MHz, 293 K, CDCl_3).



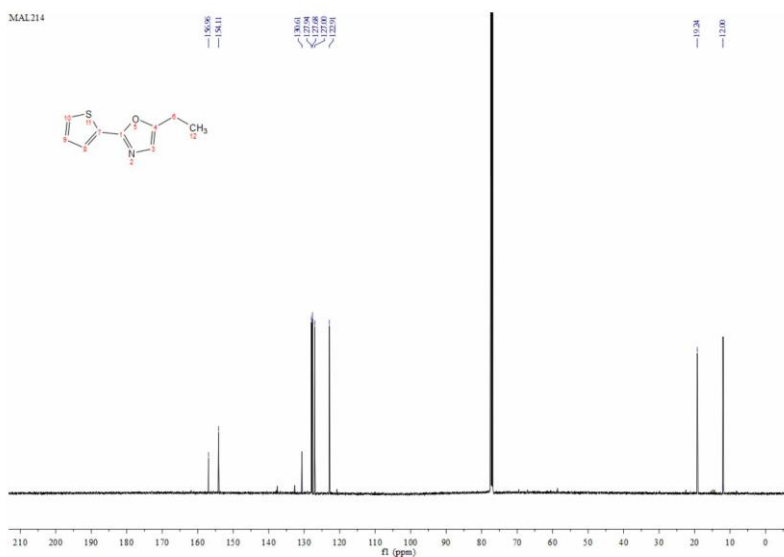
Supplementary Figure 40 ^1H NMR spectrum of **O6** (500 MHz, 293 K, CDCl_3).



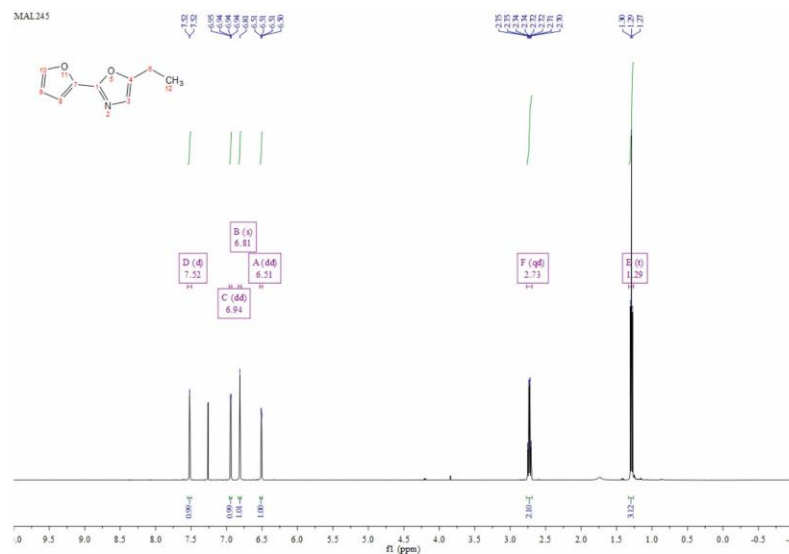
Supplementary Figure 41 ^{13}C NMR spectrum of **O6** (125 MHz, 293 K, CDCl_3).



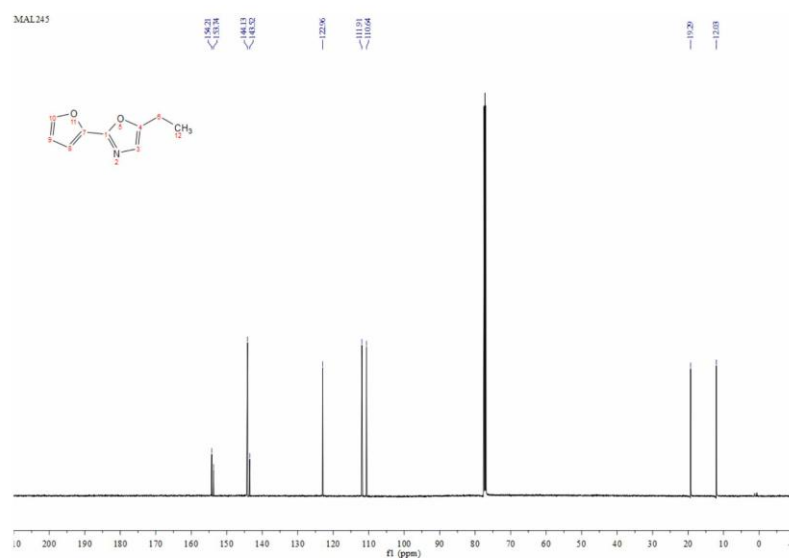
Supplementary Figure 42 ¹H NMR spectrum of **O7** (500 MHz, 293 K, CDCl₃).



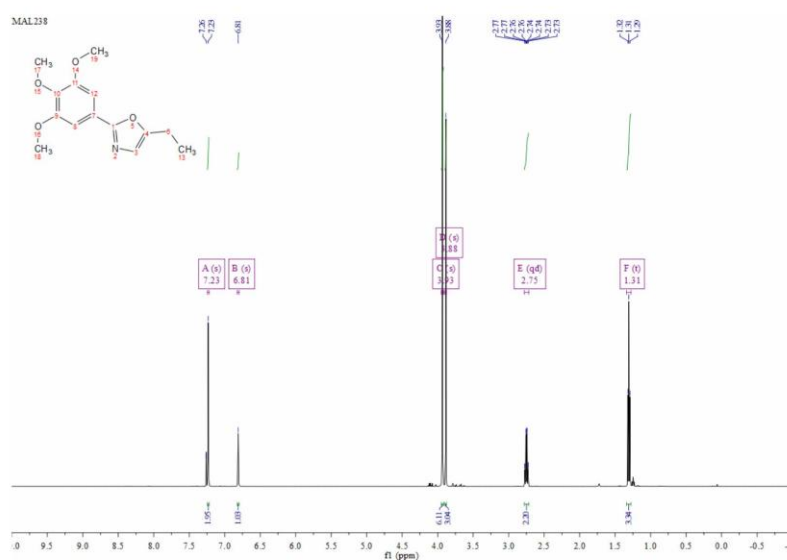
Supplementary Figure 43 ¹³C NMR spectrum of **O7** (125 MHz, 293 K, CDCl₃).



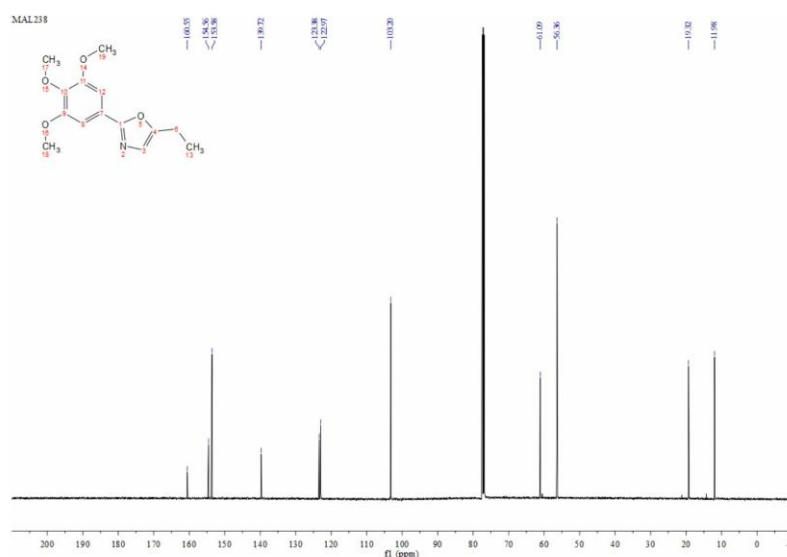
Supplementary Figure 44 ^1H NMR spectrum of **O8** (500 MHz, 293 K, CDCl_3).



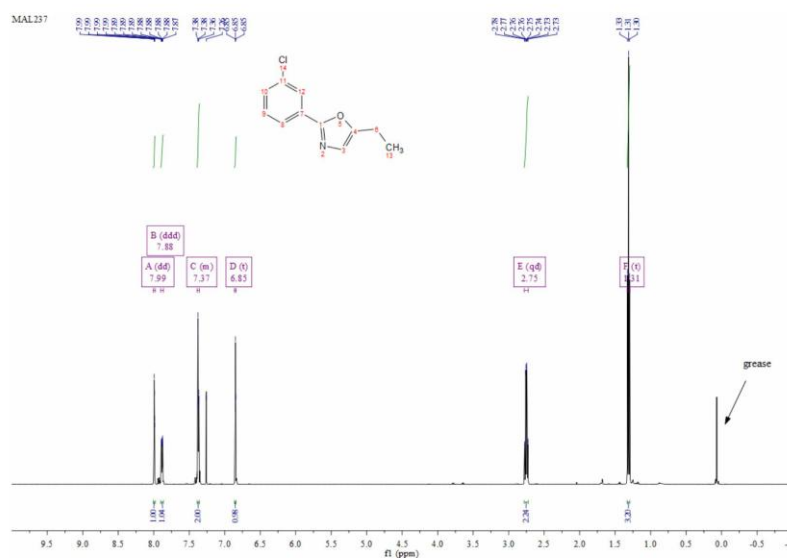
Supplementary Figure 45 ^{13}C NMR spectrum of **O8** (125 MHz, 293 K, CDCl_3).



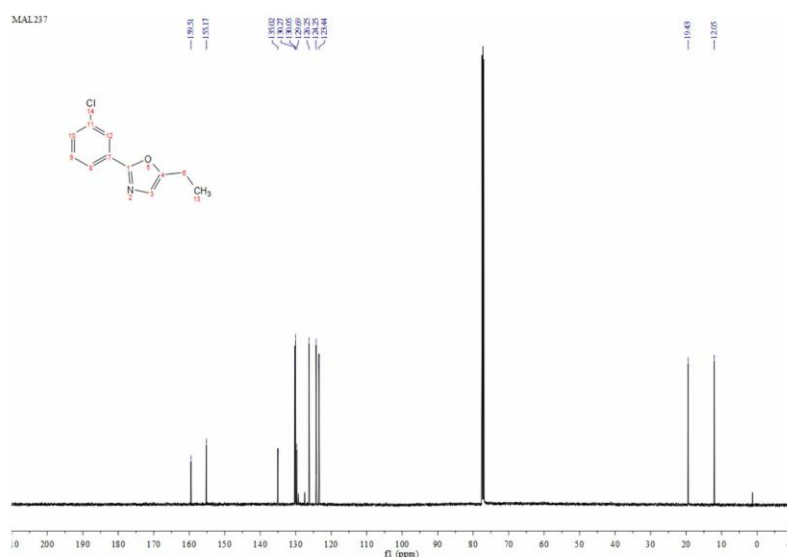
Supplementary Figure 46 ^1H NMR spectrum of **O9** (500 MHz, 293 K, CDCl_3).



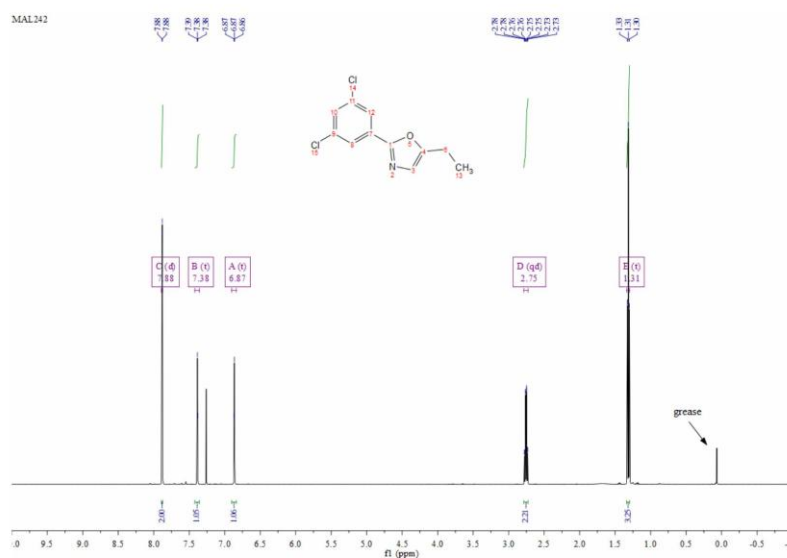
Supplementary Figure 47 ^{13}C NMR spectrum of **O9** (125 MHz, 293 K, CDCl_3).



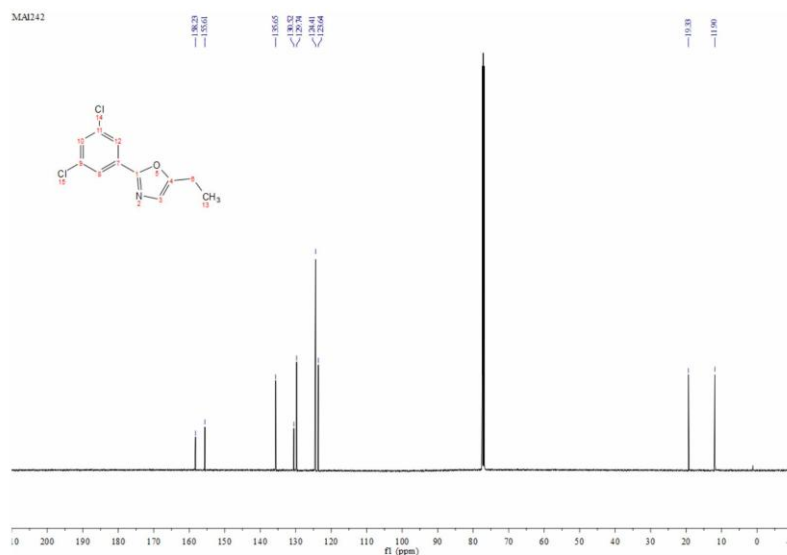
Supplementary Figure 48 ¹H NMR spectrum of **O10** (500 MHz, 293 K, CDCl₃).

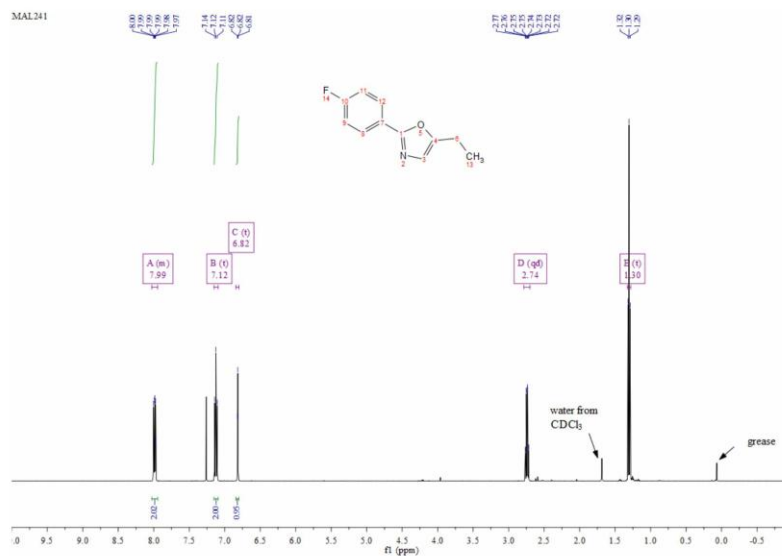


Supplementary Figure 49 ¹³C NMR spectrum of **O10** (125 MHz, 293 K, CDCl₃).

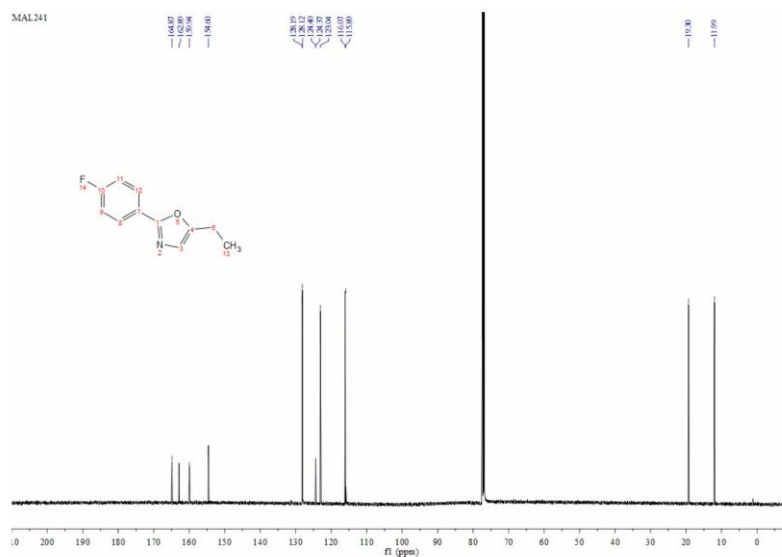


Supplementary Figure 50 ¹H NMR spectrum of **O11** (500 MHz, 293 K, CDCl₃).

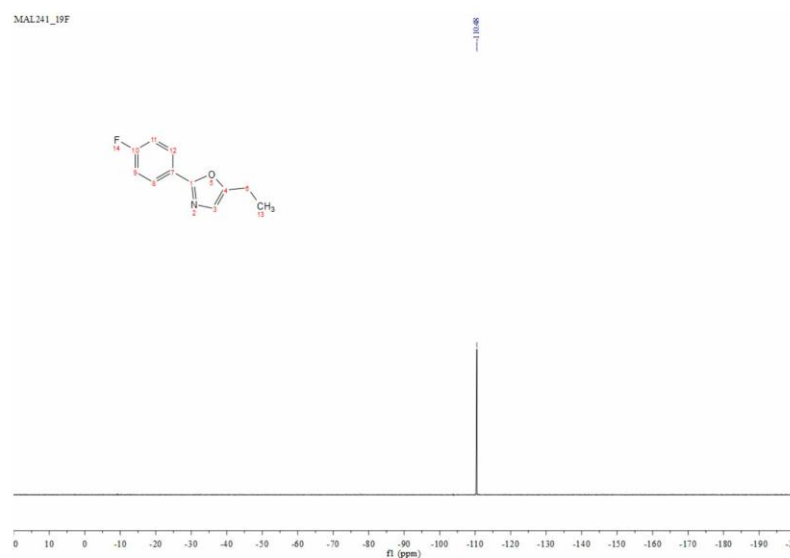




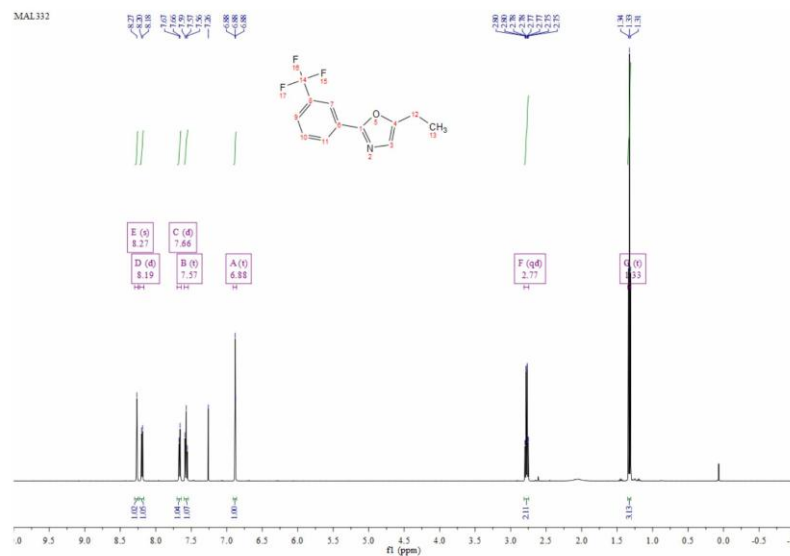
Supplementary Figure 52 ¹H NMR spectrum of **O12** (500 MHz, 293 K, CDCl₃).



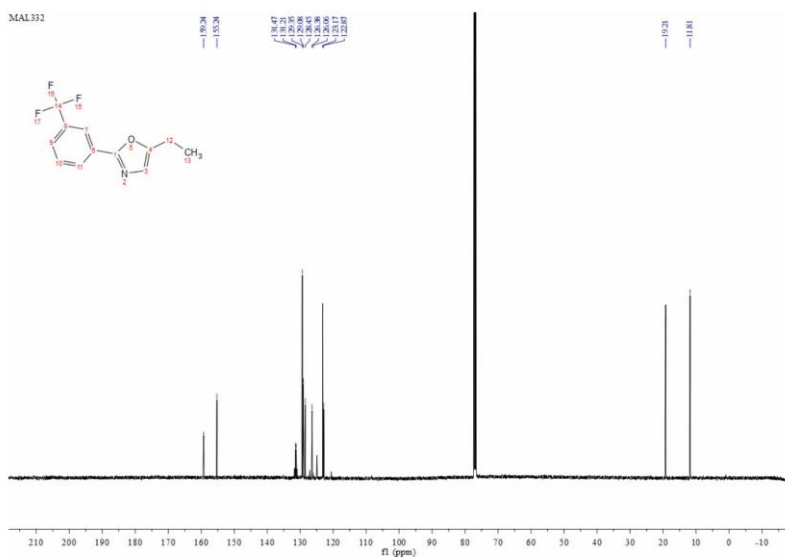
Supplementary Figure 53 ¹³C NMR spectrum of **O12** (125 MHz, 293 K, CDCl₃).



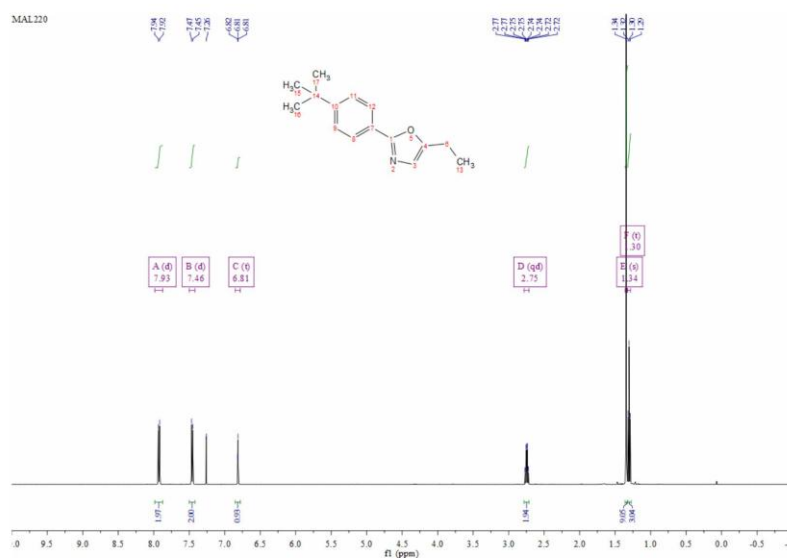
Supplementary Figure 54 ^{19}F NMR spectrum of **O12** (376 MHz, 293 K, CDCl_3).



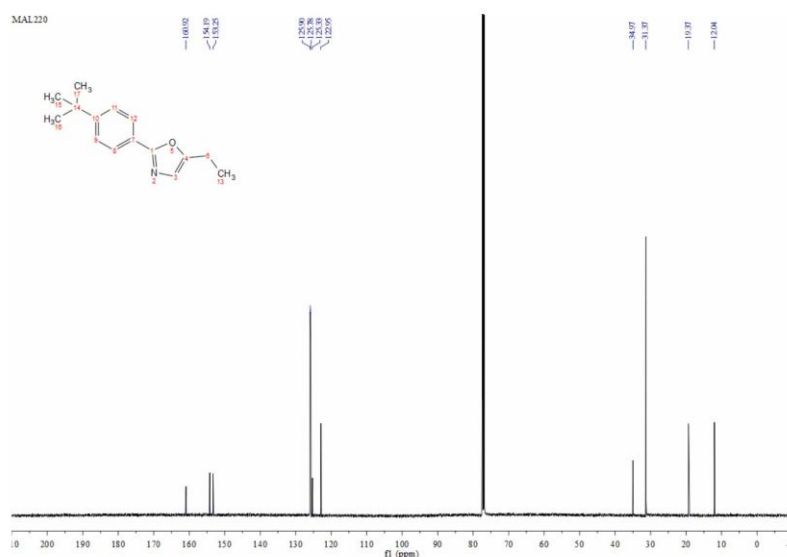
Supplementary Figure 55 ¹H NMR spectrum of **O13** (500 MHz, 293 K, CDCl₃).



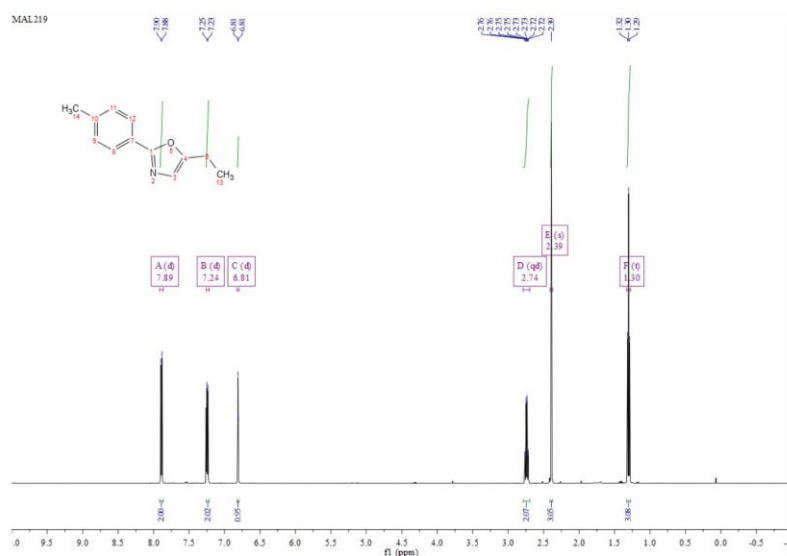
Supplementary Figure 56 ¹³C NMR spectrum of **O13** (125 MHz, 293 K, CDCl₃).



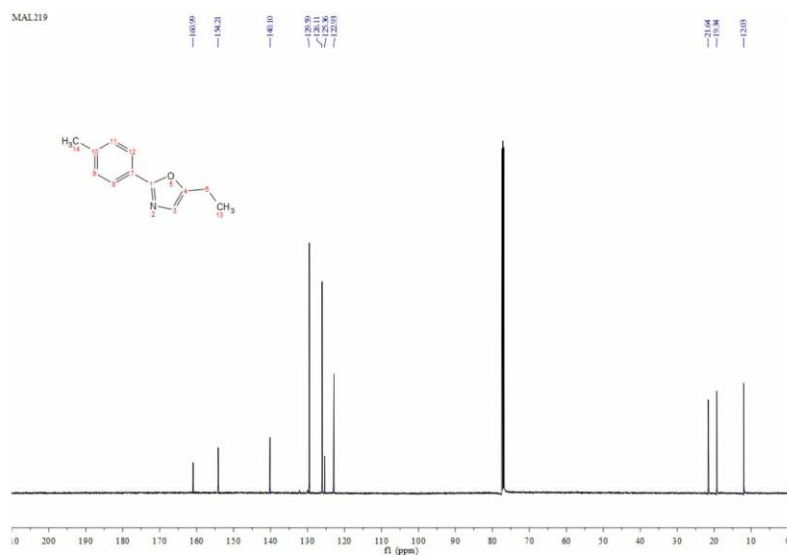
Supplementary Figure 58 ¹H NMR spectrum of **O14** (500 MHz, 293 K, CDCl₃).



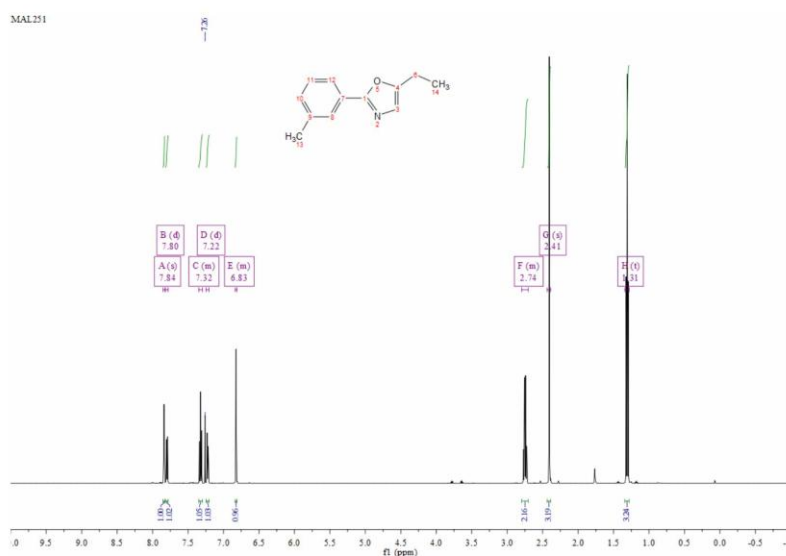
Supplementary Figure 59 ¹³C NMR spectrum of **O14** (125 MHz, 293 K, CDCl₃).



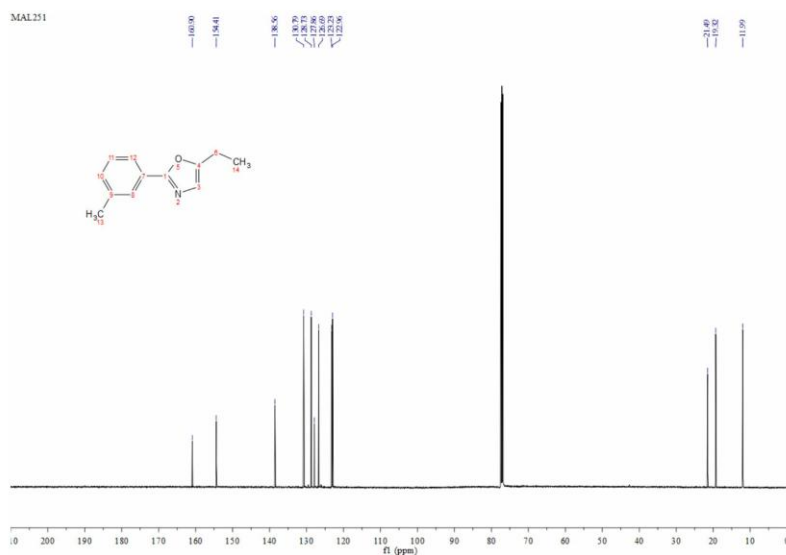
Supplementary Figure 60 ¹H NMR spectrum of **O15** (500 MHz, 293 K, CDCl₃).

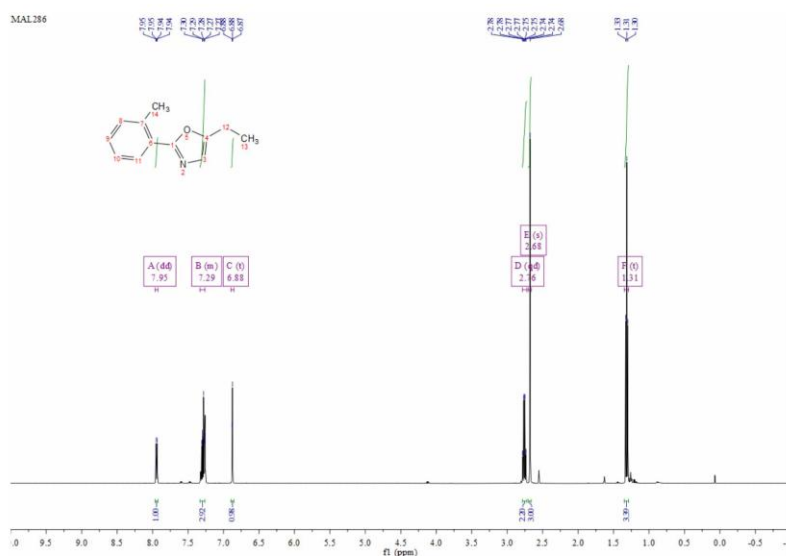


Supplementary Figure 61 ¹³C NMR spectrum of **O15** (125 MHz, 293 K, CDCl₃).

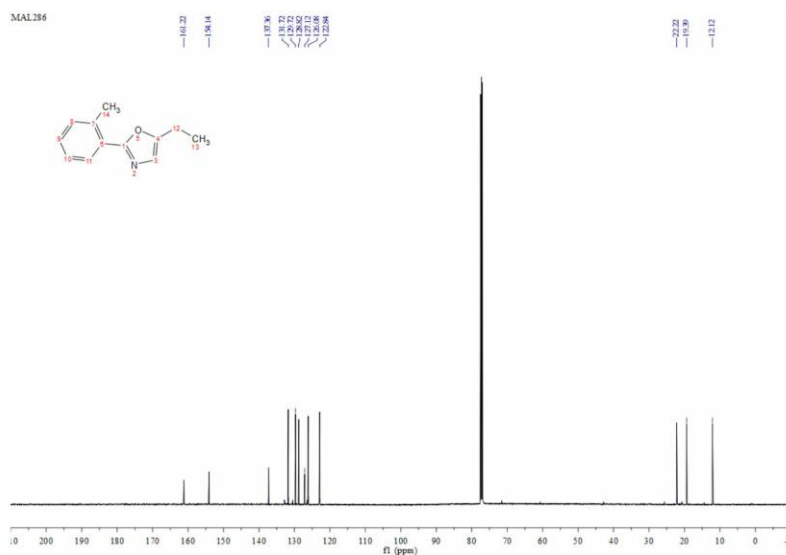


Supplementary Figure 62 ¹H NMR spectrum of **O16** (500 MHz, 293 K, CDCl₃).

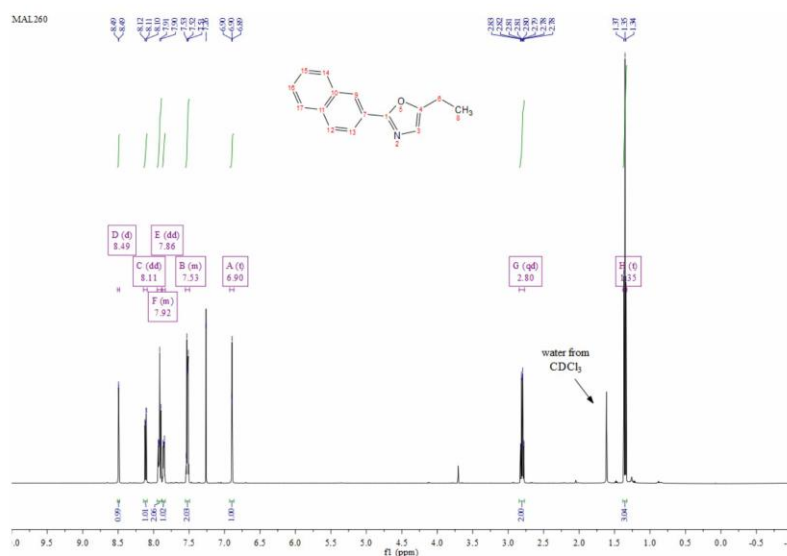




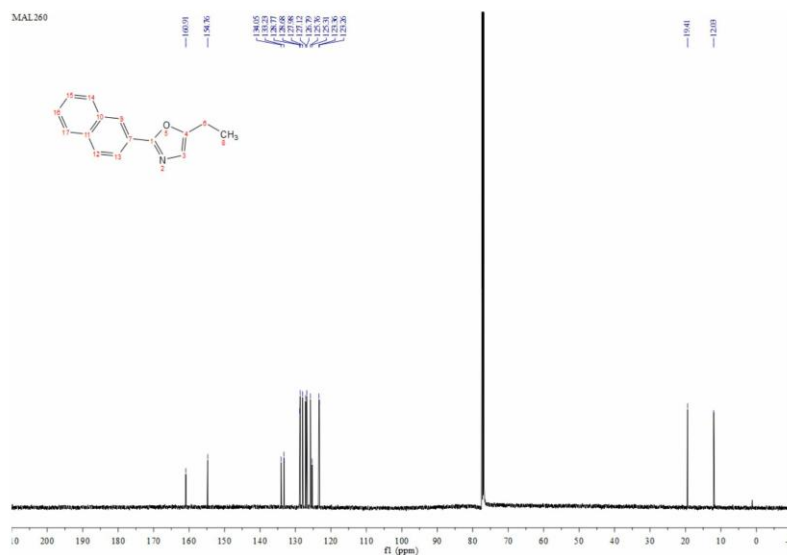
Supplementary Figure 64 ^1H NMR spectrum of **O17** (500 MHz, 293 K, CDCl_3).



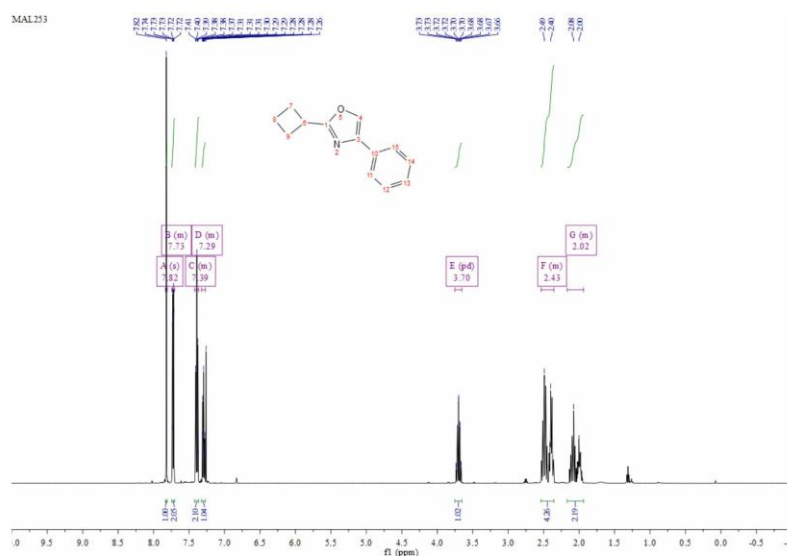
Supplementary Figure 65 ^{13}C NMR spectrum of **O17** (125 MHz, 293 K, CDCl_3).



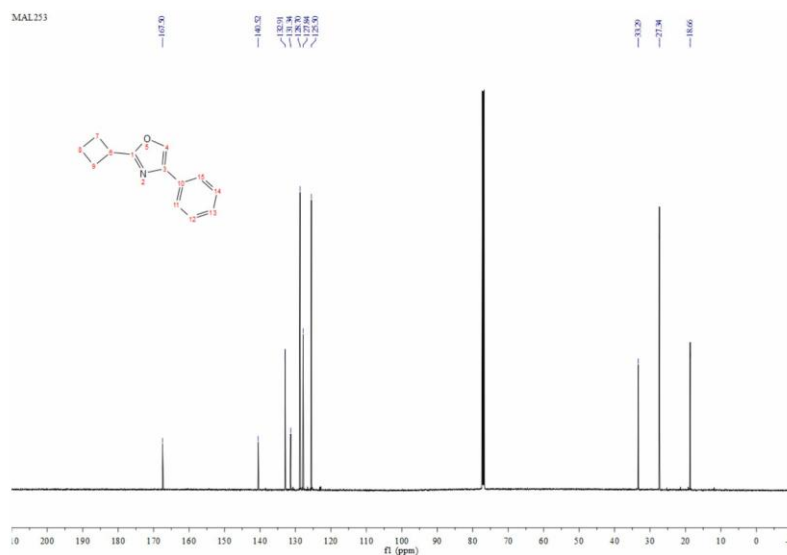
Supplementary Figure 66 ¹H NMR spectrum of **O18** (500 MHz, 293 K, CDCl₃).



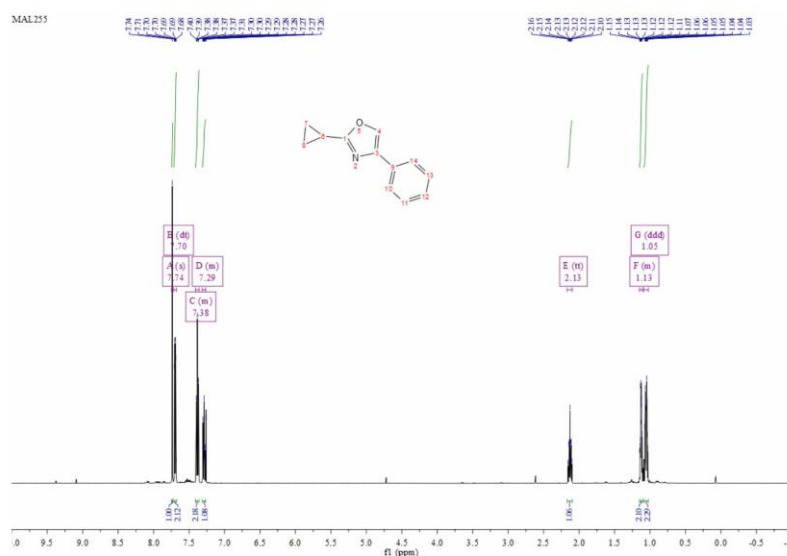
Supplementary Figure 67 ¹³C NMR spectrum of **O18** (125 MHz, 293 K, CDCl₃).



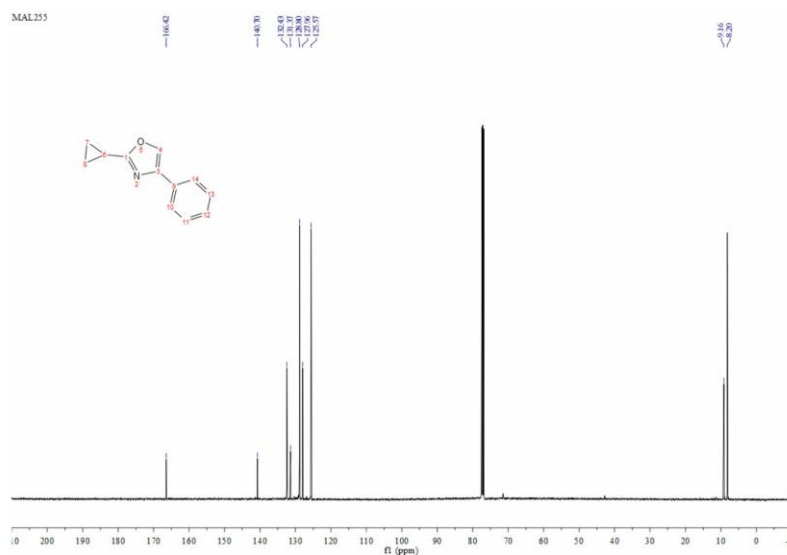
Supplementary Figure 68 ¹H NMR spectrum of **O19** (500 MHz, 293 K, CDCl₃).



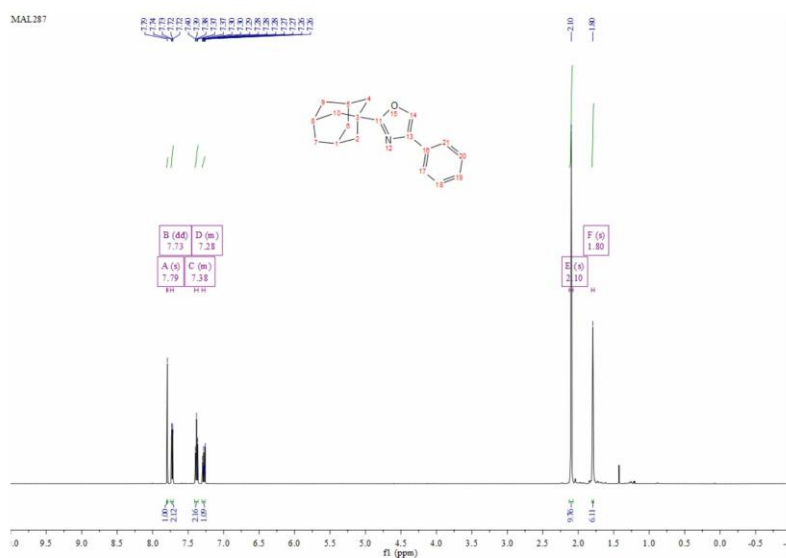
Supplementary Figure 69 ¹³C NMR spectrum of **O19** (125 MHz, 293 K, CDCl₃).



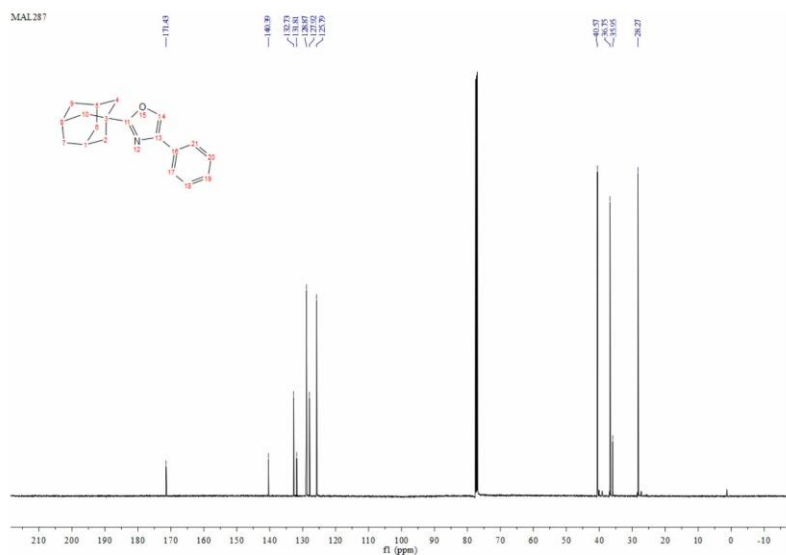
Supplementary Figure 70 ^1H NMR spectrum of **O20** (500 MHz, 293 K, CDCl_3).



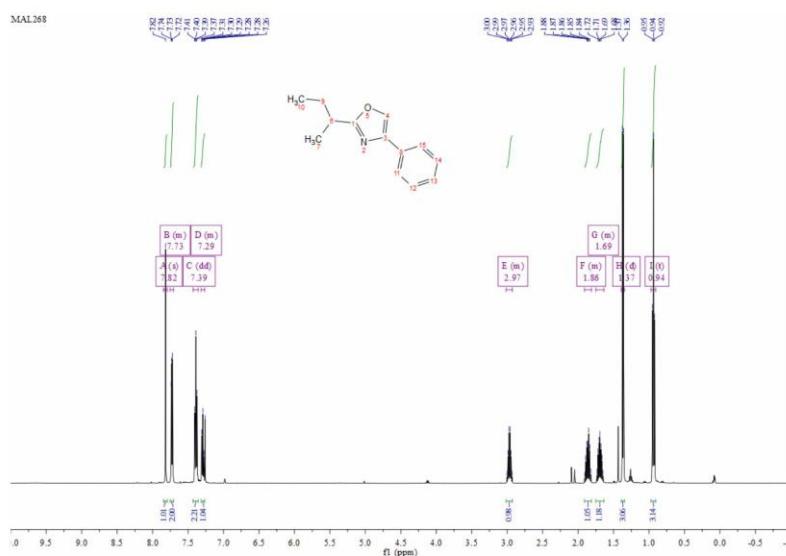
Supplementary Figure 71 ^{13}C NMR spectrum of **O20** (125 MHz, 293 K, CDCl_3).



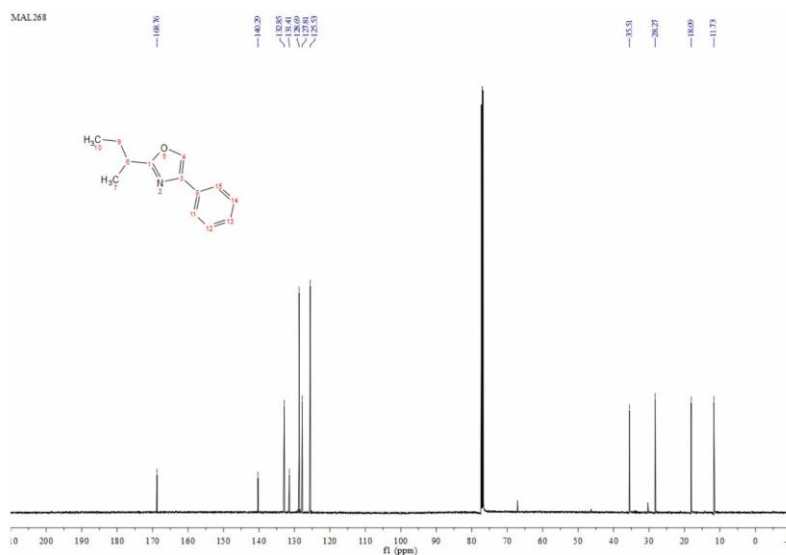
Supplementary Figure 72 ¹H NMR spectrum of **O21** (500 MHz, 293 K, CDCl₃).

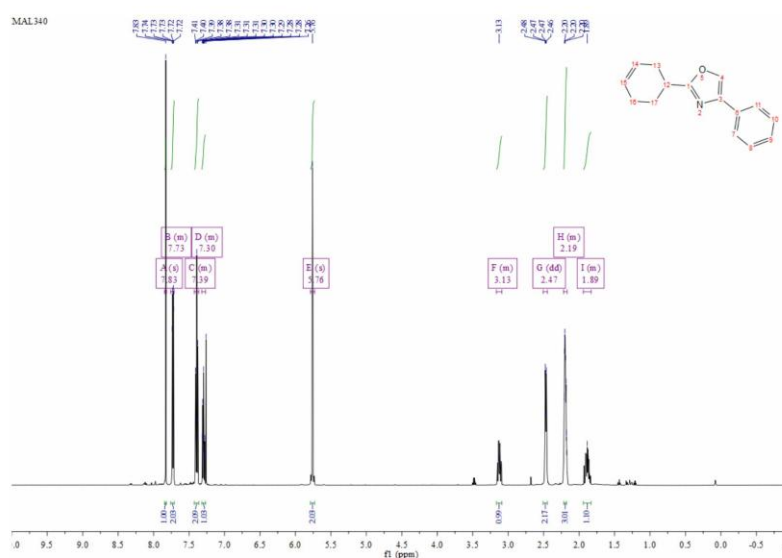


Supplementary Figure 73 ¹³C NMR spectrum of **O21** (125 MHz, 293 K, CDCl₃).

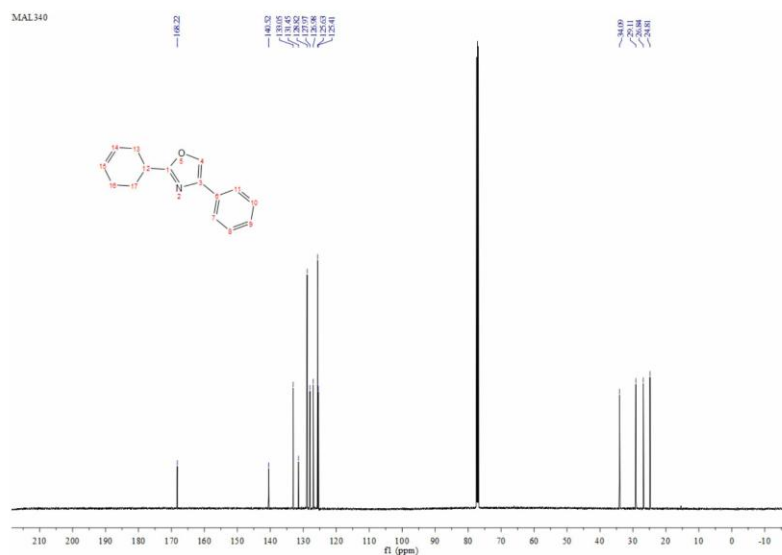


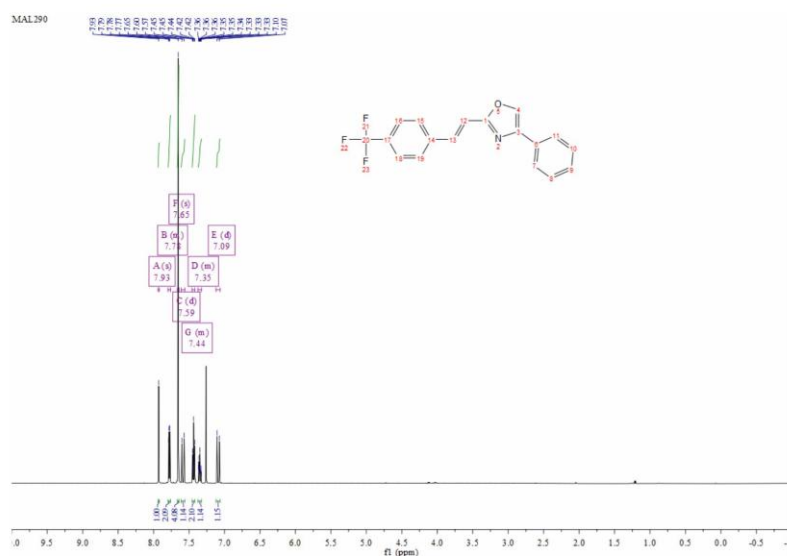
Supplementary Figure 74 ¹H NMR spectrum of **O22** (500 MHz, 293 K, CDCl₃).



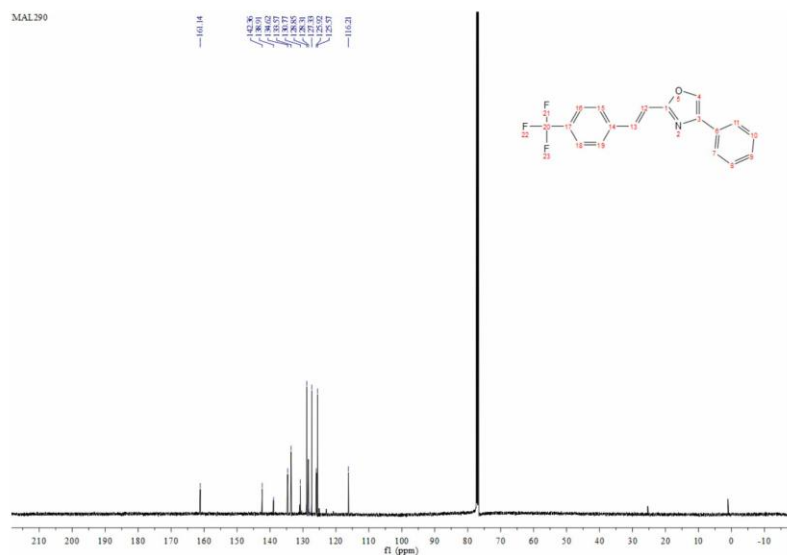


Supplementary Figure 76 ¹H NMR spectrum of **O23** (500 MHz, 293 K, CDCl₃).

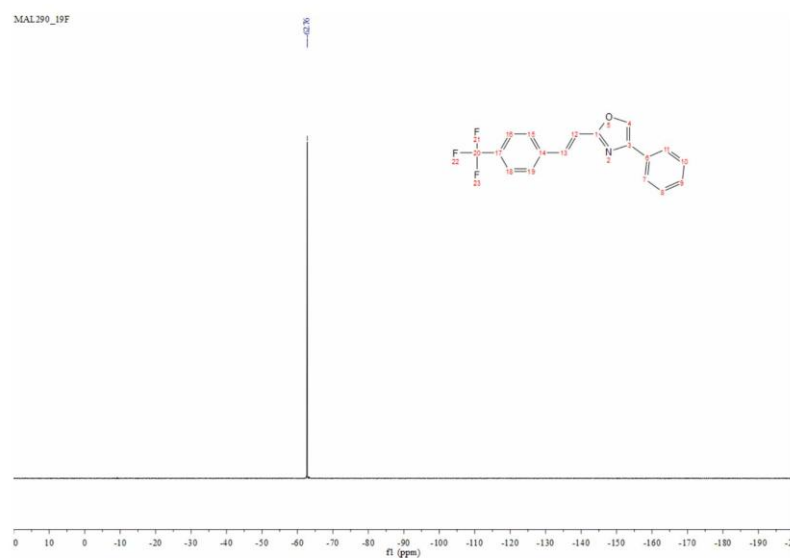




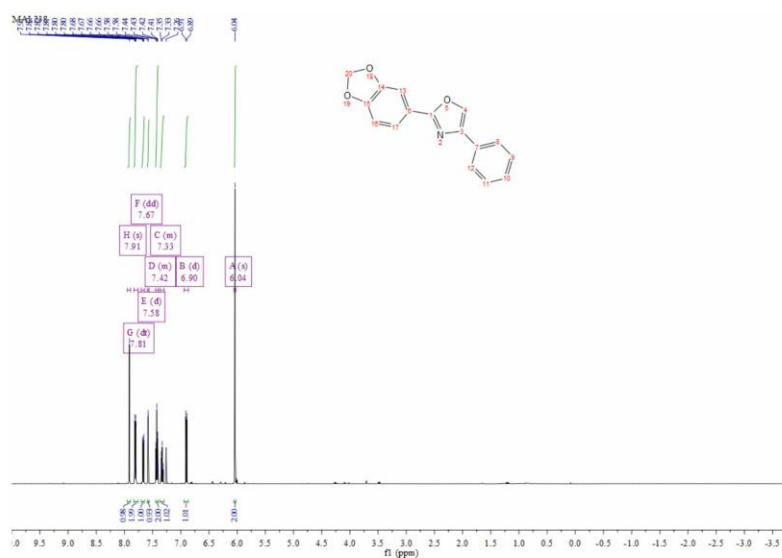
Supplementary Figure 78 ^1H NMR spectrum of **O24** (500 MHz, 293 K, CDCl_3).



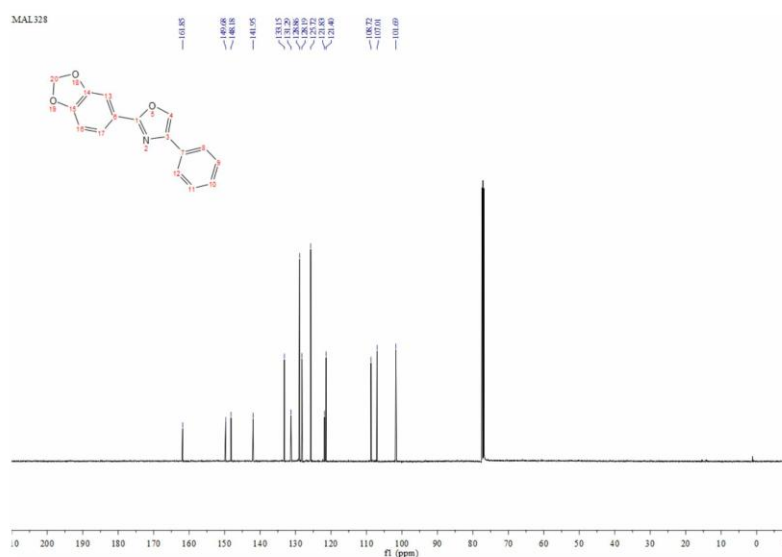
Supplementary Figure 79 ^{13}C NMR spectrum of **O24** (125 MHz, 293 K, CDCl_3).



Supplementary Figure 80 ^{19}F NMR spectrum of **O24** (376 MHz, 293 K, CDCl_3).



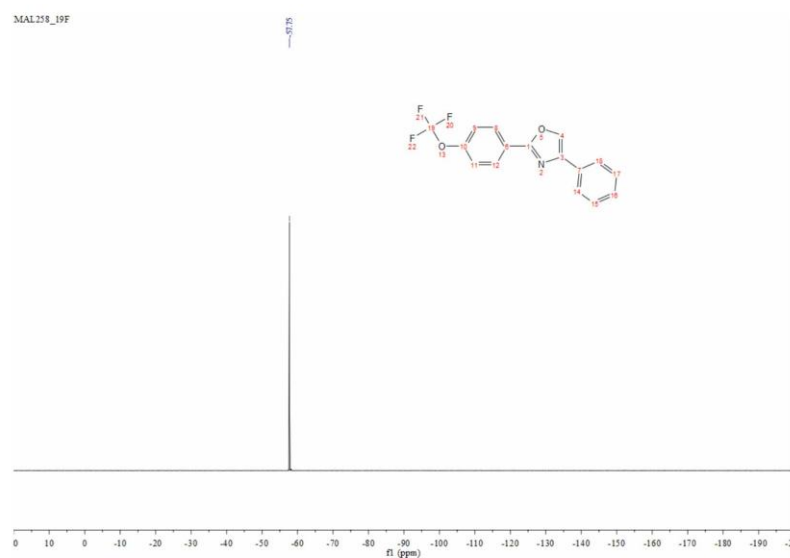
Supplementary Figure 81 ^1H NMR spectrum of **O25** (500 MHz, 293 K, CDCl_3).



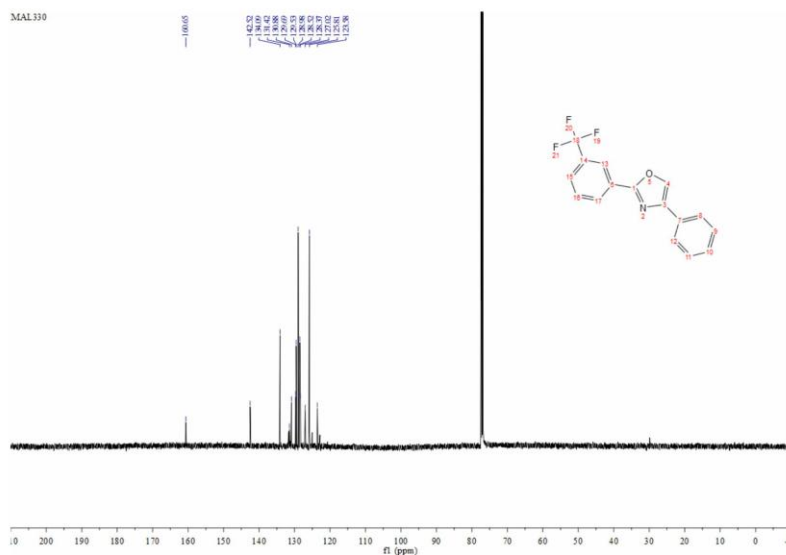
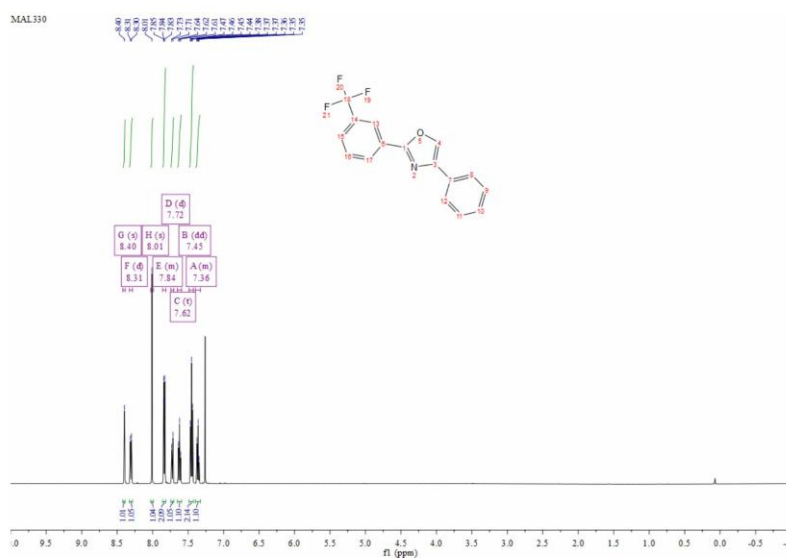
Supplementary Figure 82 ^{13}C NMR spectrum of **O25** (125 MHz, 293 K, CDCl_3).

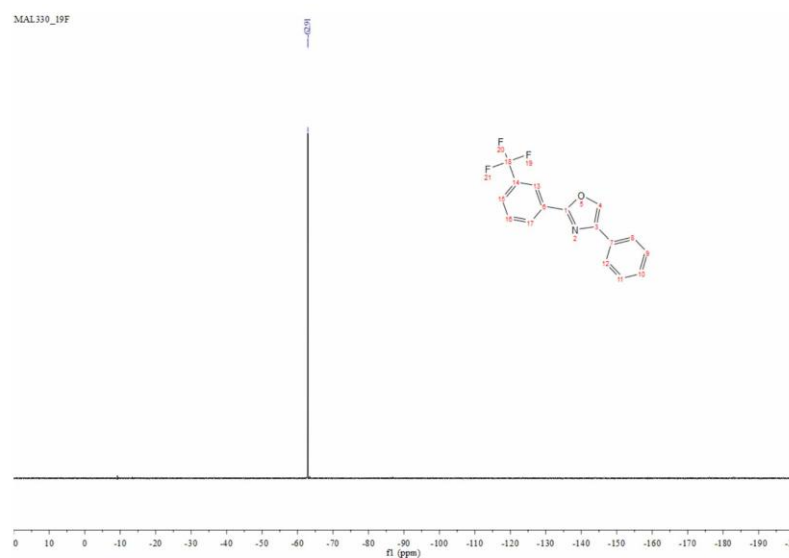


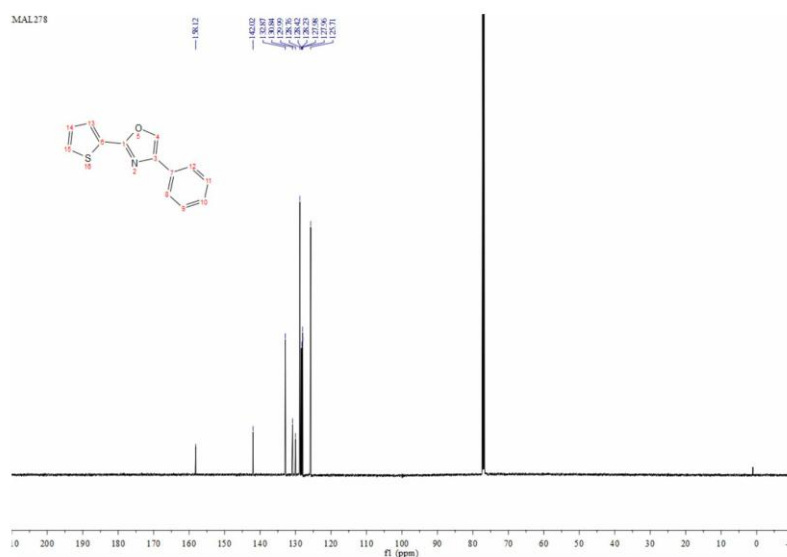
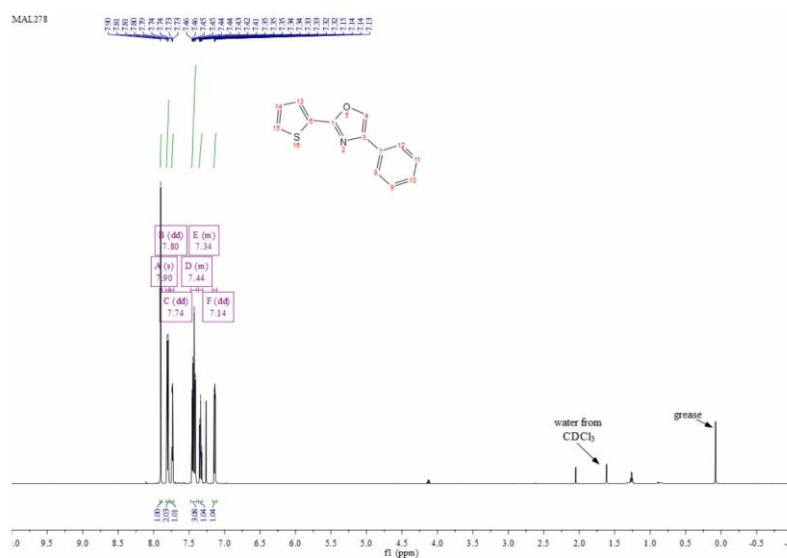


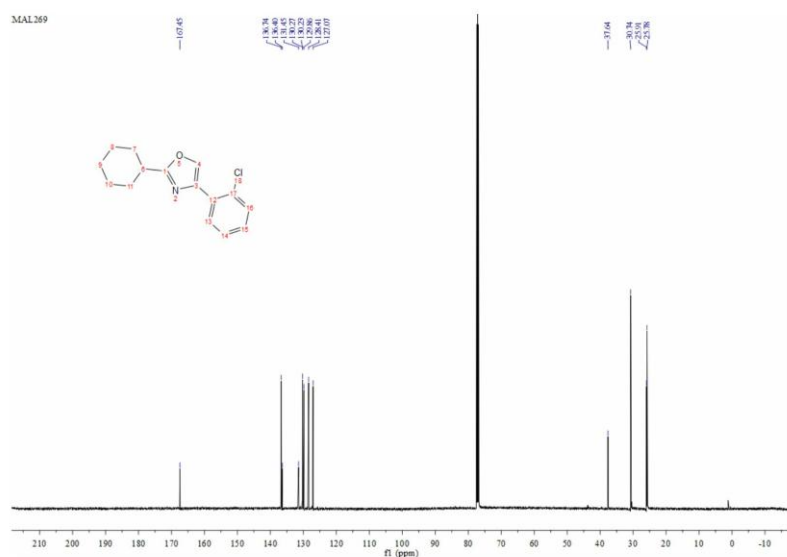
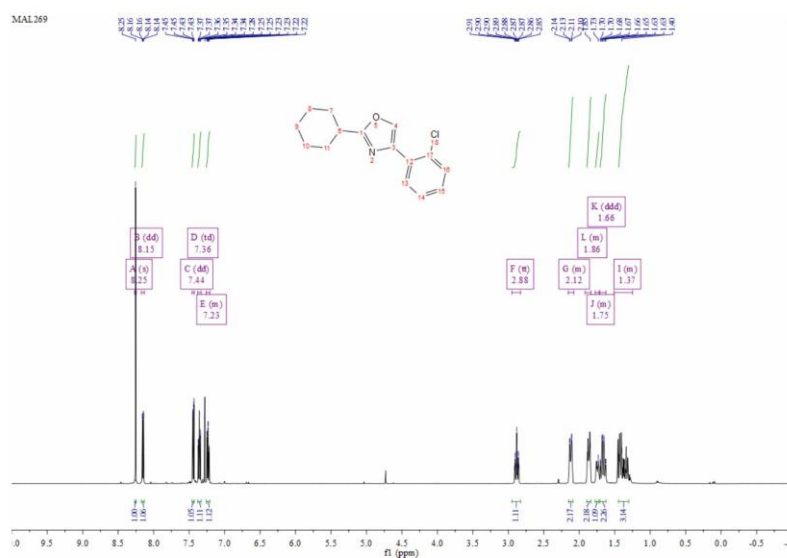


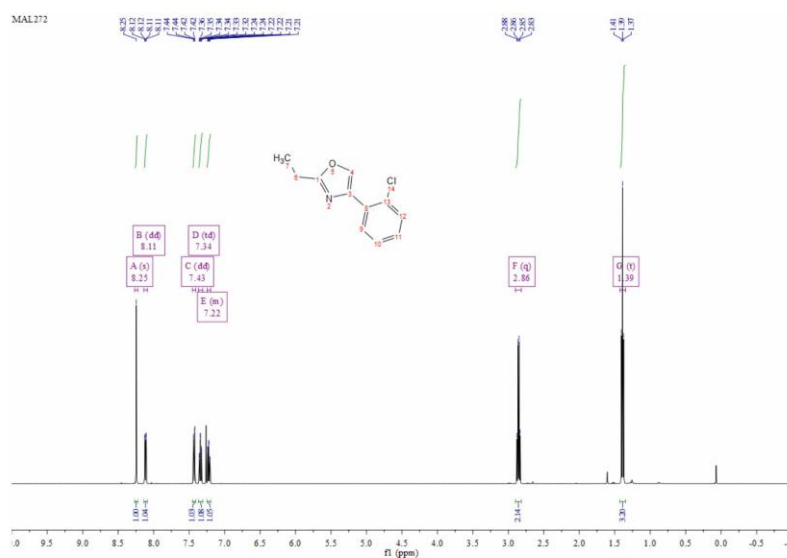
Supplementary Figure 87 ^{19}F NMR spectrum of **O27** (376 MHz, 293 K, CDCl_3).



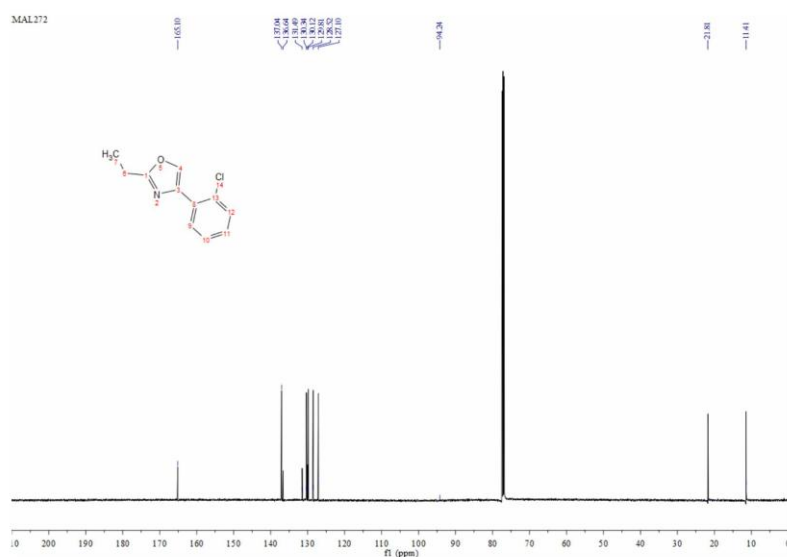


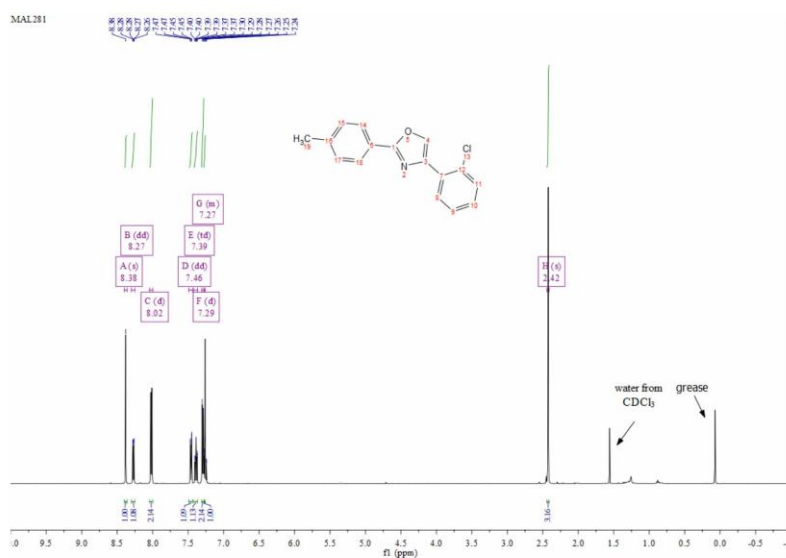




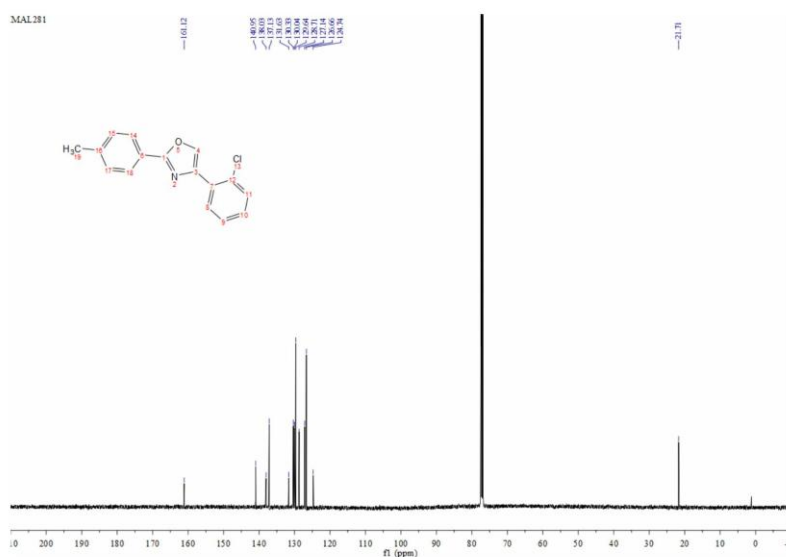


Supplementary Figure 95 ^1H NMR spectrum of **O31** (500 MHz, 293 K, CDCl_3).

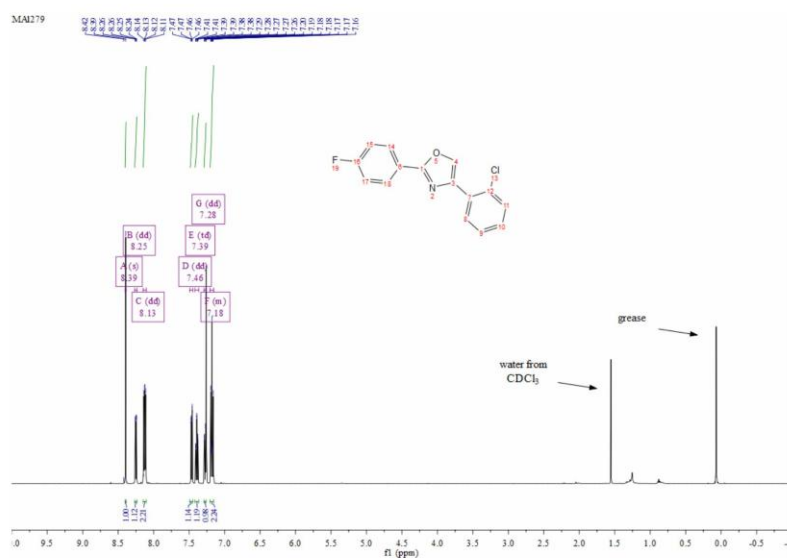




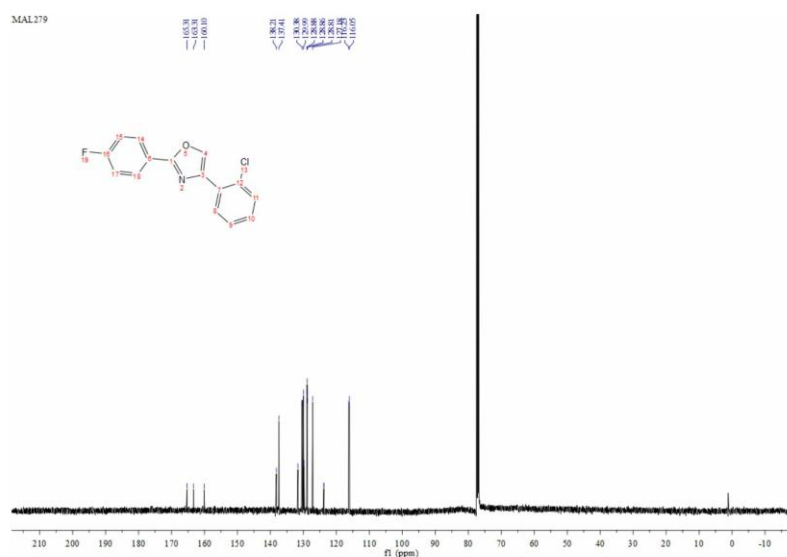
Supplementary Figure 97 ¹H NMR spectrum of **O32** (500 MHz, 293 K, CDCl₃).

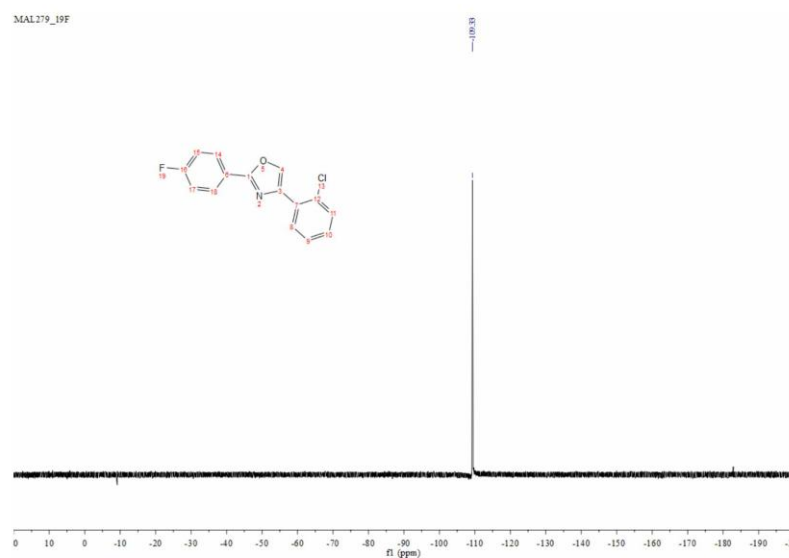


Supplementary Figure 98 ¹³C NMR spectrum of **O32** (125 MHz, 293 K, CDCl₃).

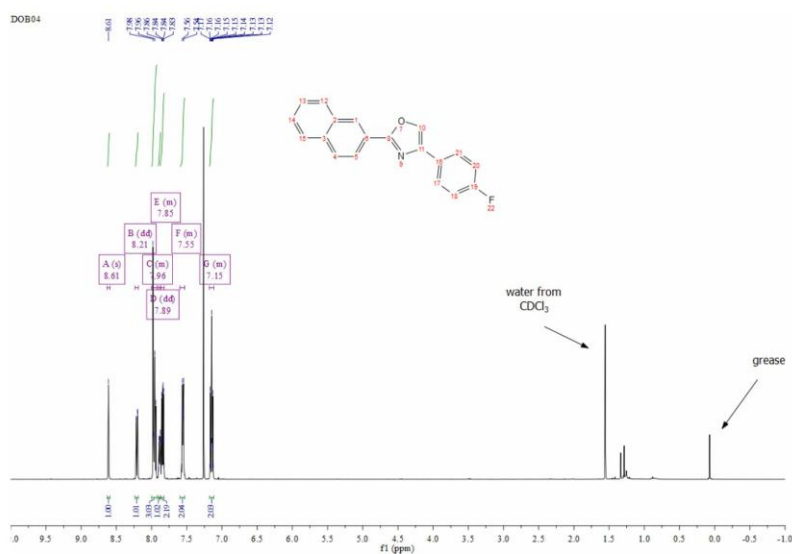


Supplementary Figure 99 ¹H NMR spectrum of O33 (500 MHz, 293 K, CDCl₃).

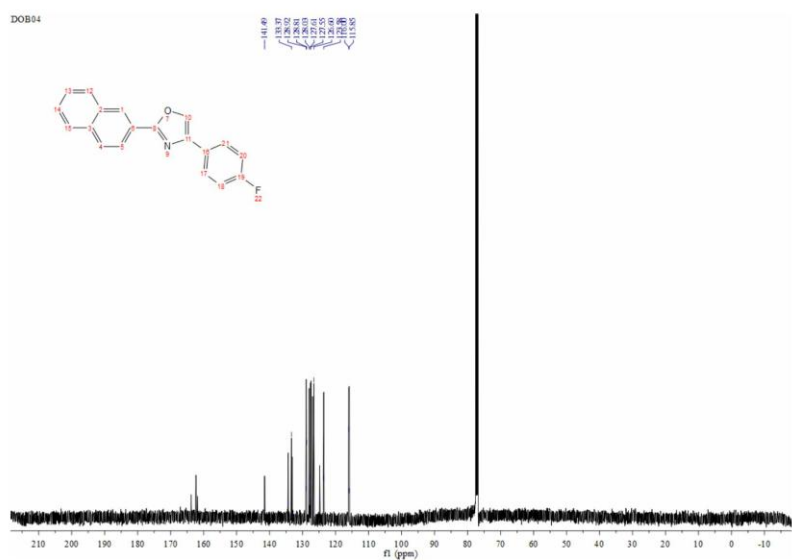




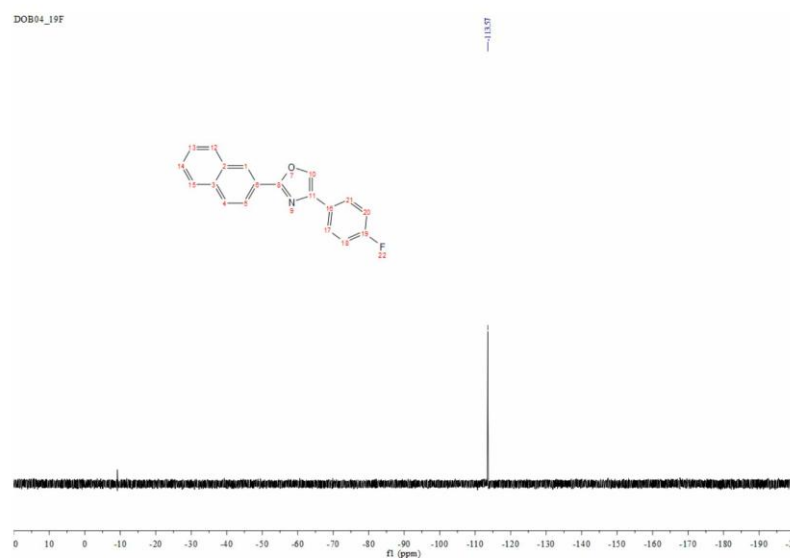
Supplementary Figure 101 ^{19}F NMR spectrum of **O33** (376 MHz, 293 K, CDCl_3).



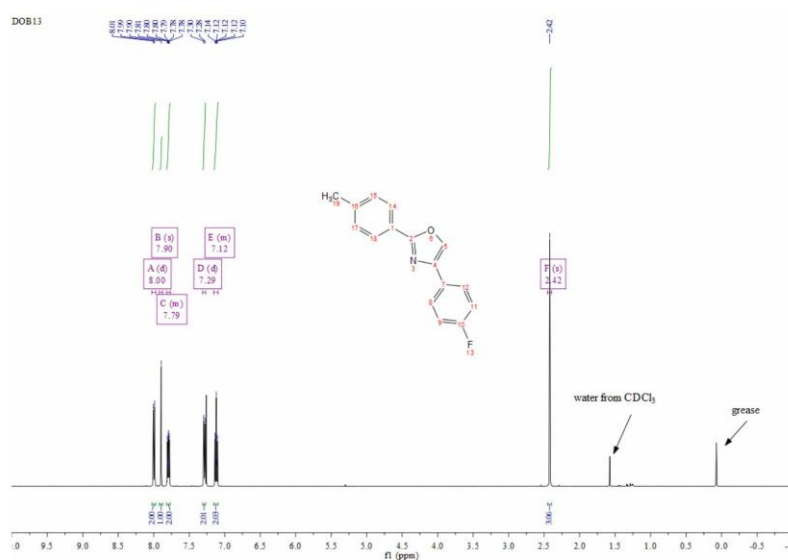
Supplementary Figure 104 ¹H NMR spectrum of **O35** (500 MHz, 293 K, CDCl₃).



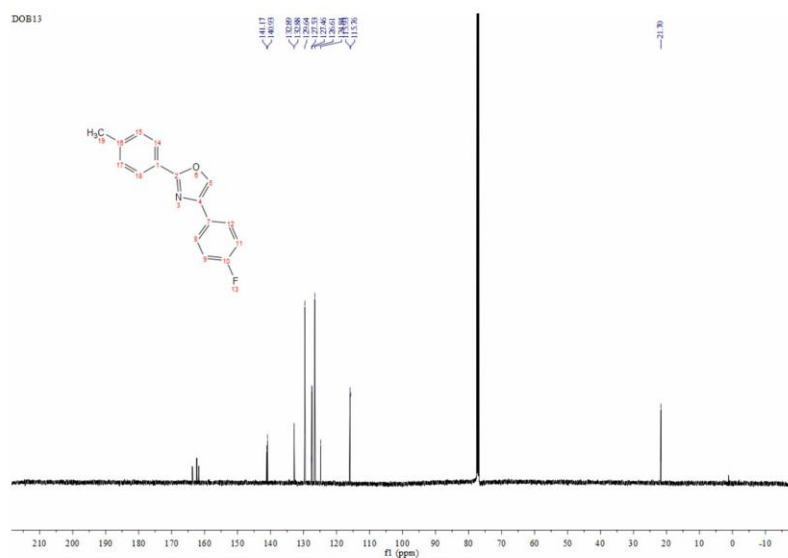
Supplementary Figure 105 ¹³C NMR spectrum of **O35** (125 MHz, 293 K, CDCl₃).

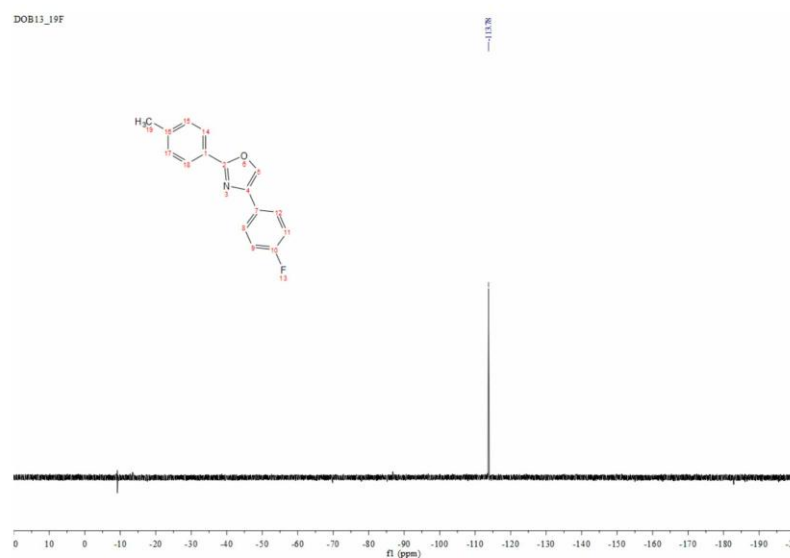


Supplementary Figure 106 ^{19}F NMR spectrum of **O35** (376 MHz, 293 K, CDCl_3).

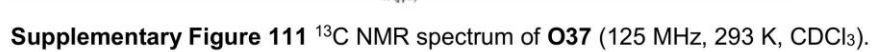


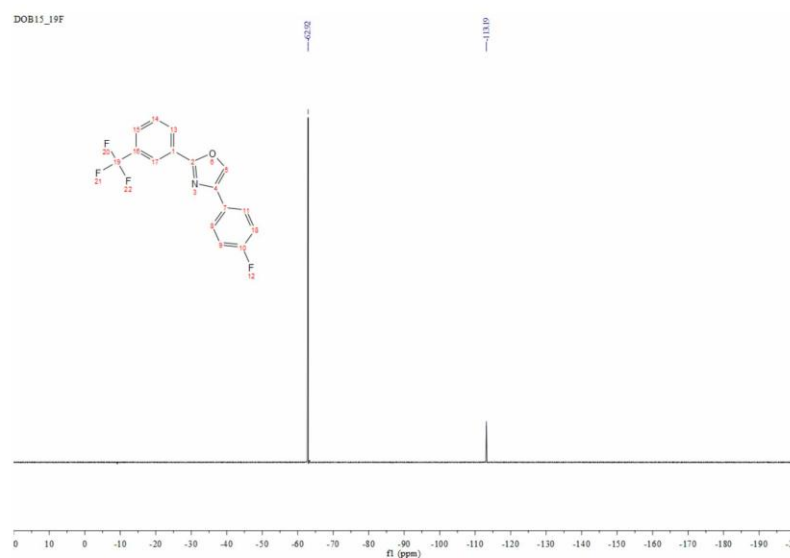
Supplementary Figure 107 ¹H NMR spectrum of **O36** (500 MHz, 293 K, CDCl₃).



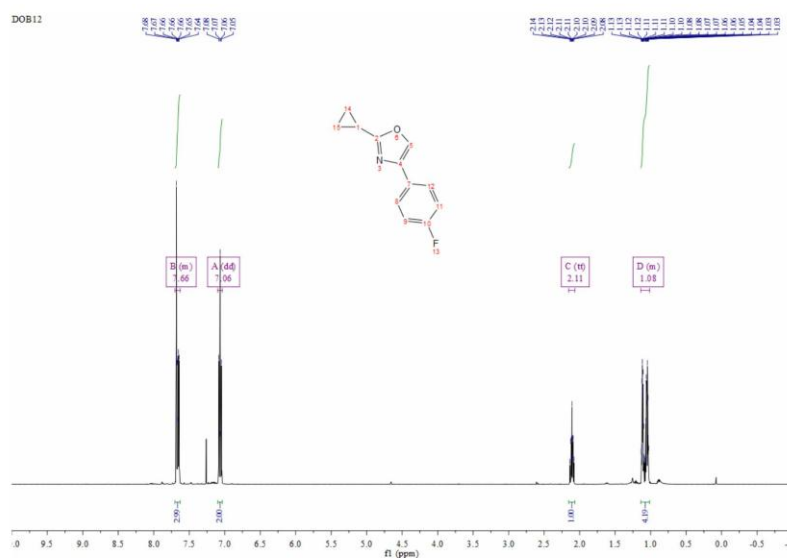


Supplementary Figure 109 ^{19}F NMR spectrum of **O36** (376 MHz, 293 K, CDCl_3).

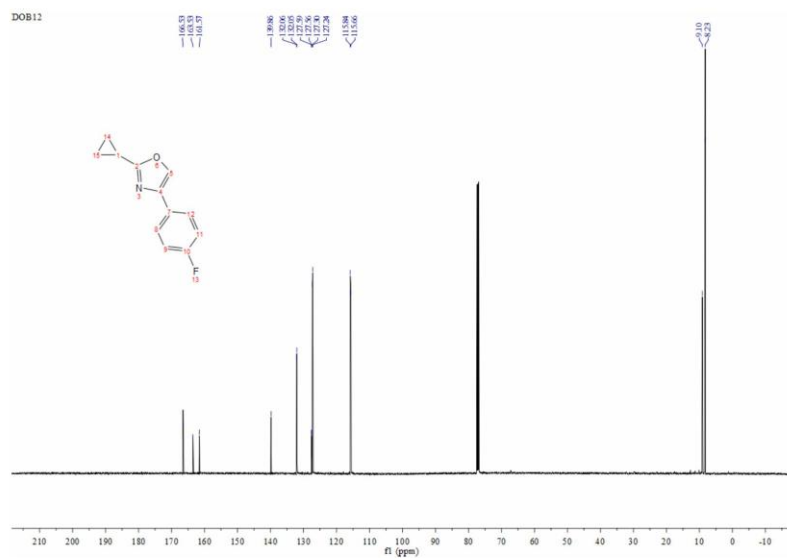




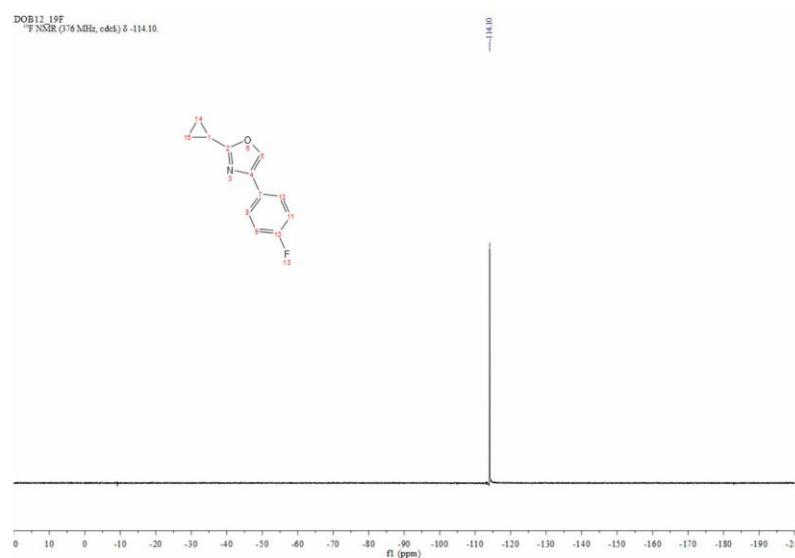
Supplementary Figure 112 ^{19}F NMR spectrum of **O37** (376 MHz, 293 K, CDCl_3).



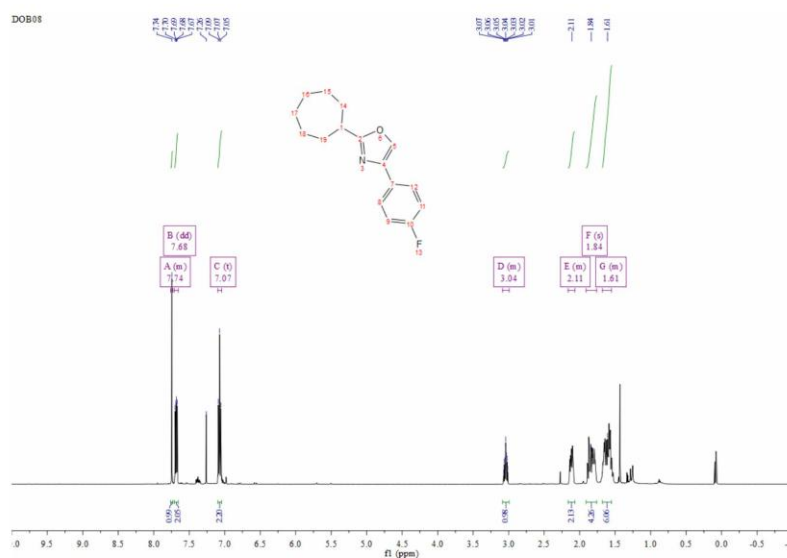
Supplementary Figure 113 ¹H NMR spectrum of **O38** (500 MHz, 293 K, CDCl₃).



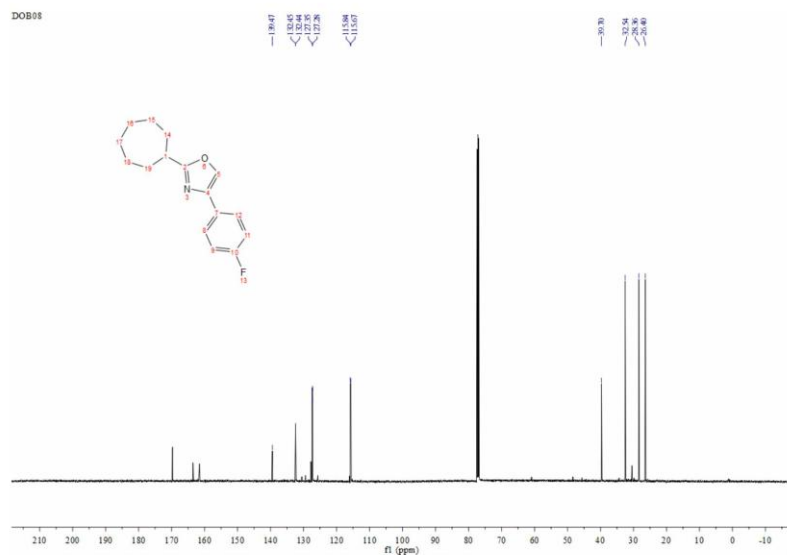
Supplementary Figure 114 ¹³C NMR spectrum of **O38** (125 MHz, 293 K, CDCl₃).



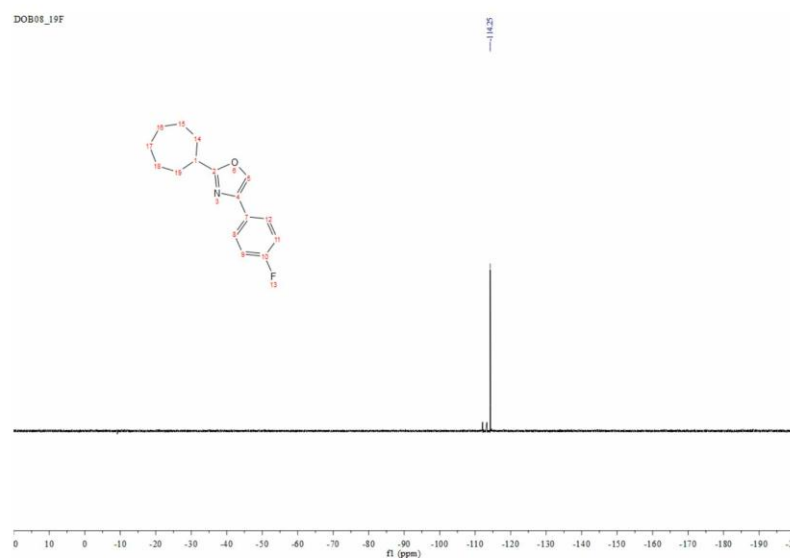
Supplementary Figure 115 ¹⁹F NMR spectrum of **O38** (376 MHz, 293 K, CDCl₃).



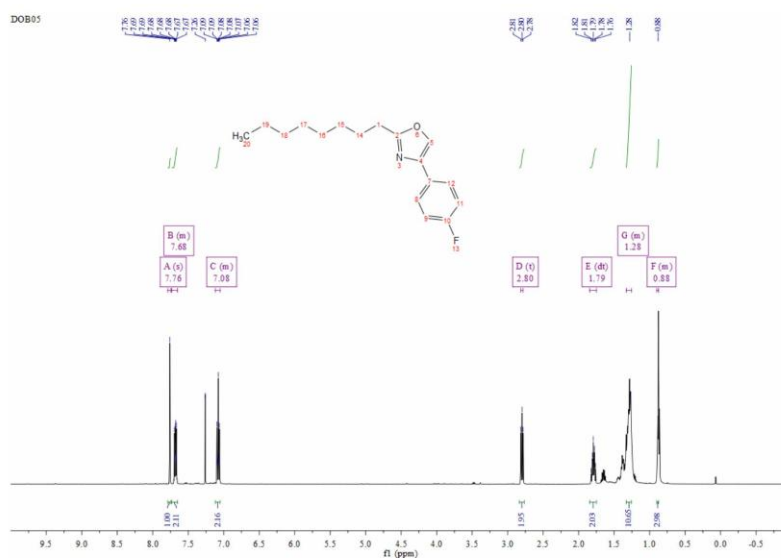
Supplementary Figure 116 ¹H NMR spectrum of **O39** (500 MHz, 293 K, CDCl₃).



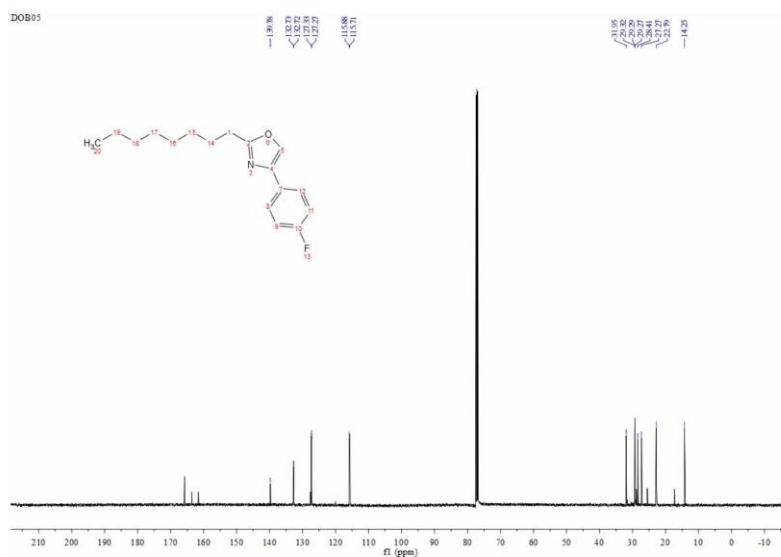
Supplementary Figure 117 ¹³C NMR spectrum of **O39** (125 MHz, 293 K, CDCl₃).



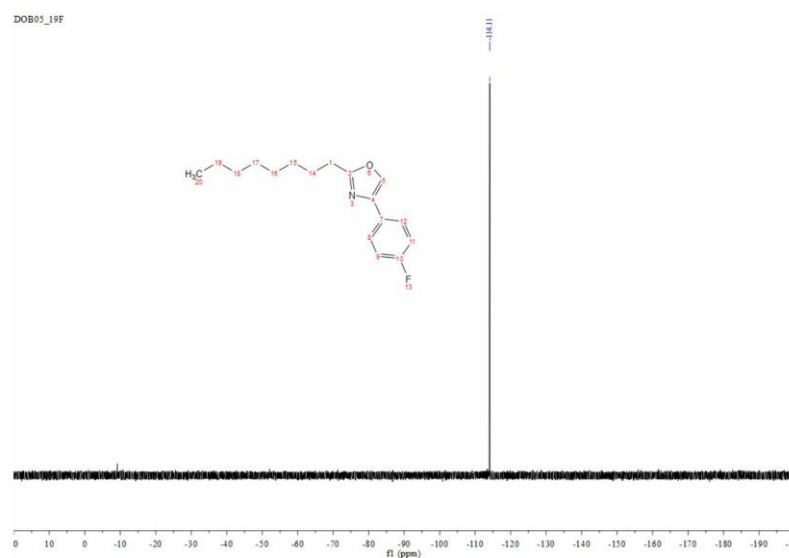
Supplementary Figure 118 ^{19}F NMR spectrum of **O39** (376 MHz, 293 K, CDCl_3).



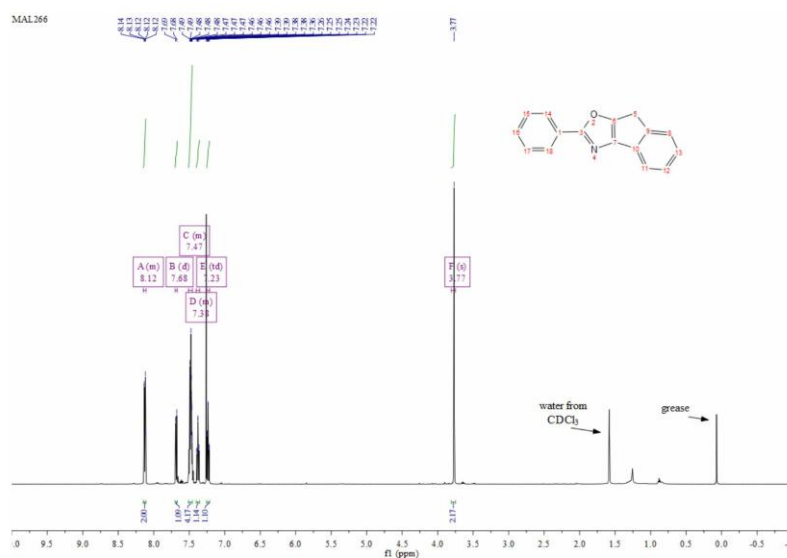
Supplementary Figure 119 ¹H NMR spectrum of **O40** (500 MHz, 293 K, CDCl₃).



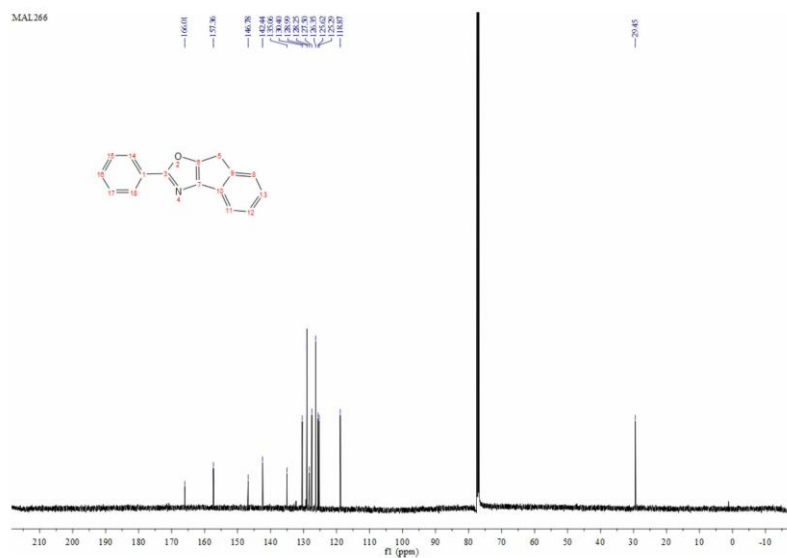
Supplementary Figure 120 ¹³C NMR spectrum of **O40** (125 MHz, 293 K, CDCl₃).



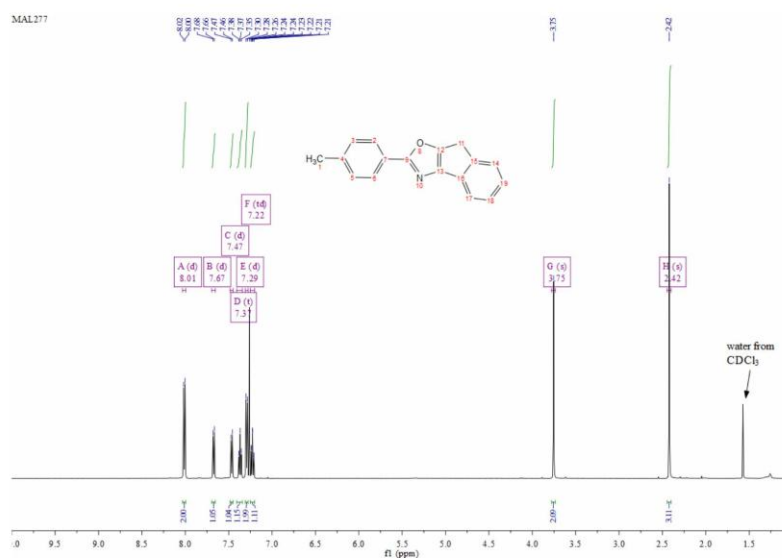
Supplementary Figure 121 ^{19}F NMR spectrum of **O40** (376 MHz, 293 K, CDCl_3).



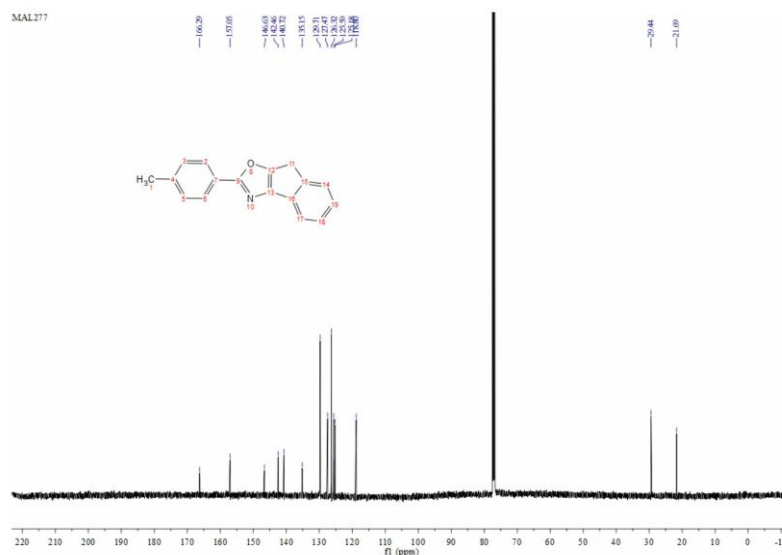
Supplementary Figure 122 ¹H NMR spectrum of **O41** (500 MHz, 293 K, CDCl₃).



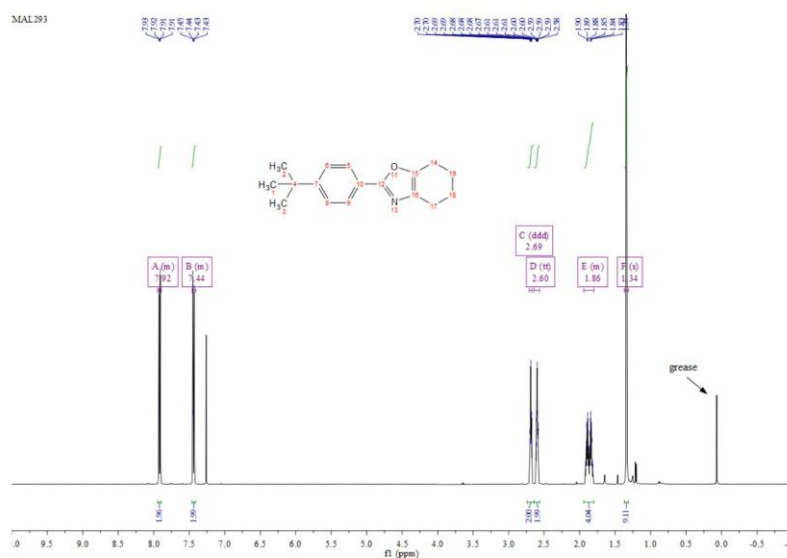
Supplementary Figure 123 ¹³C NMR spectrum of **O41** (125 MHz, 293 K, CDCl₃).



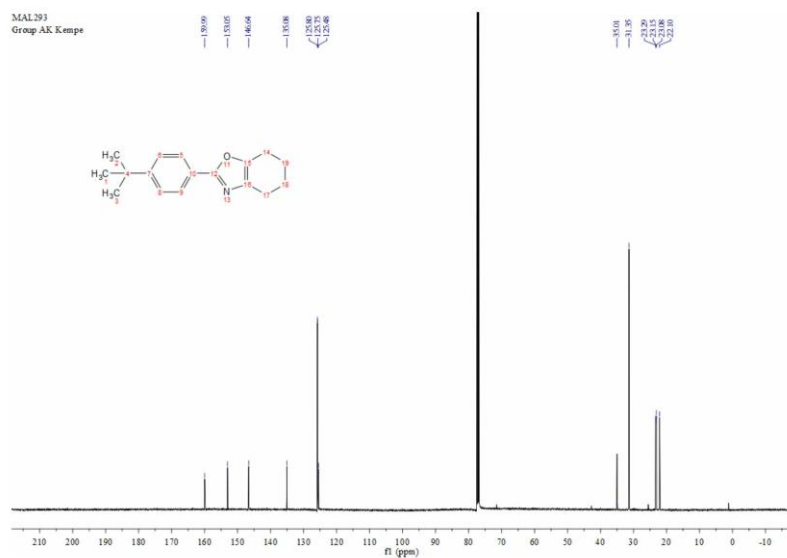
Supplementary Figure 124 ¹H NMR spectrum of **O42** (500 MHz, 293 K, CDCl₃).



Supplementary Figure 125 ¹³C NMR spectrum of **O42** (125 MHz, 293 K, CDCl₃).

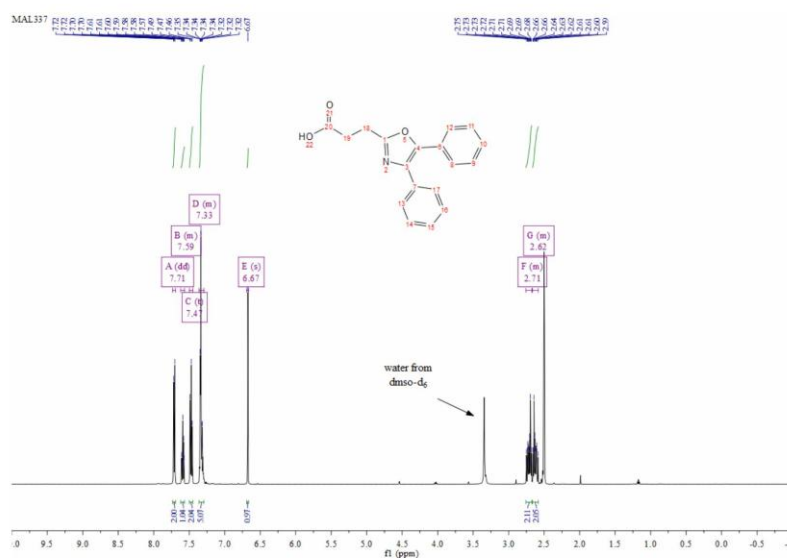


Supplementary Figure 126 ^1H NMR spectrum of **O43** (500 MHz, 293 K, CDCl_3).

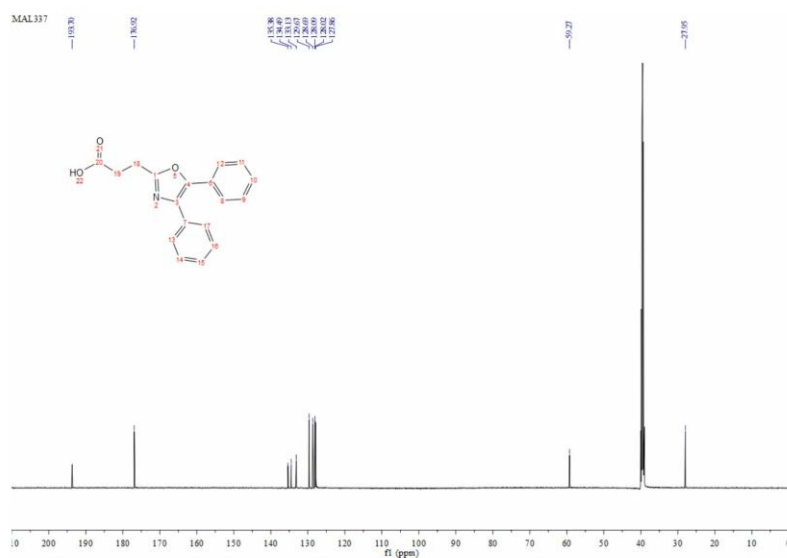


Supplementary Figure 127 ^{13}C NMR spectrum of **O43** (125 MHz, 293 K, CDCl_3).





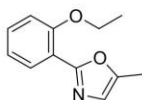
Supplementary Figure 130 ¹H NMR spectrum of O45 (500 MHz, 293 K, CDCl₃).



Supplementary Figure 131 ¹³C NMR spectrum of O45 (125 MHz, 293 K, CDCl₃).

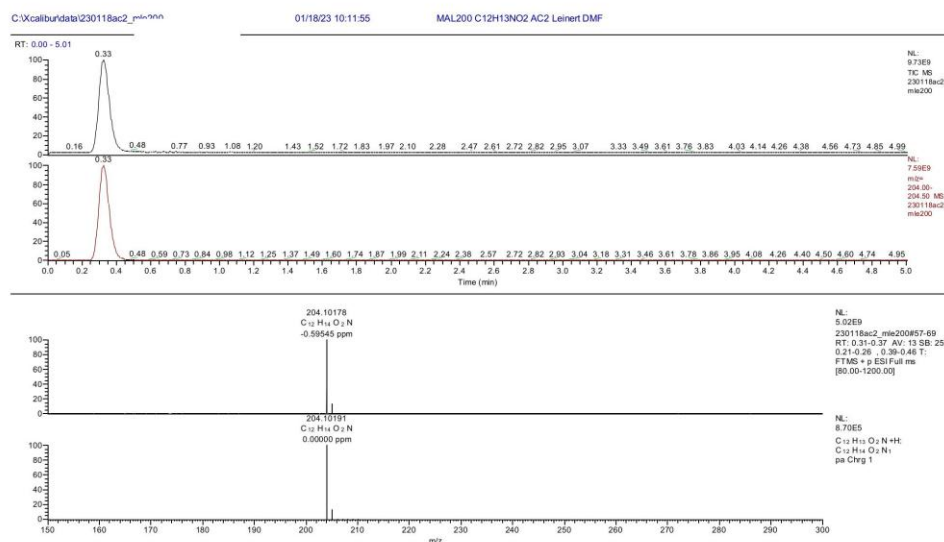
14 HRMS spectra of isolated compounds

High resolution mass spectra (HRMS) were obtained from a Thermo Fisher scientific Q-Exactive instrument with a hybrid quadrupole orbitrap analyser in ESI+ mode. Analysis was performed without HPLC column. Method – [5_MSfull_iso80 ("5" = direct connection without column, "MS_full": full scan mode 80-1200 amu, iso80: isocratic with 80% B, here MeCN)] – was used.



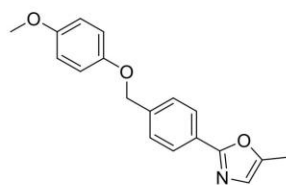
Chemical Formula: $C_{12}H_{13}NO_2$
Molecular Weight: 203.24

O1



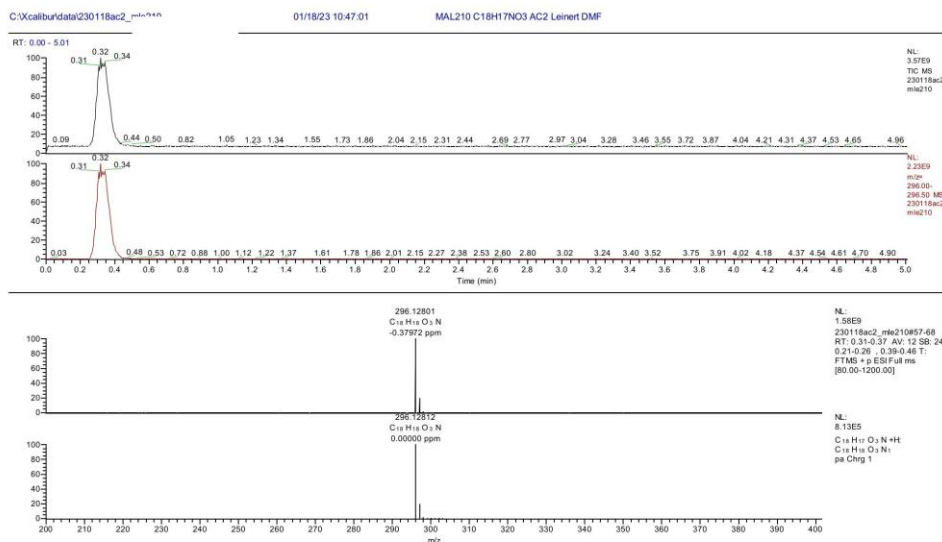
Supplementary Figure 132 HRMS spectrum of **O1**.

S110



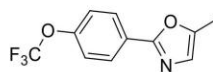
Chemical Formula: $C_{18}H_{17}NO_3$
Molecular Weight: 295.34

O2



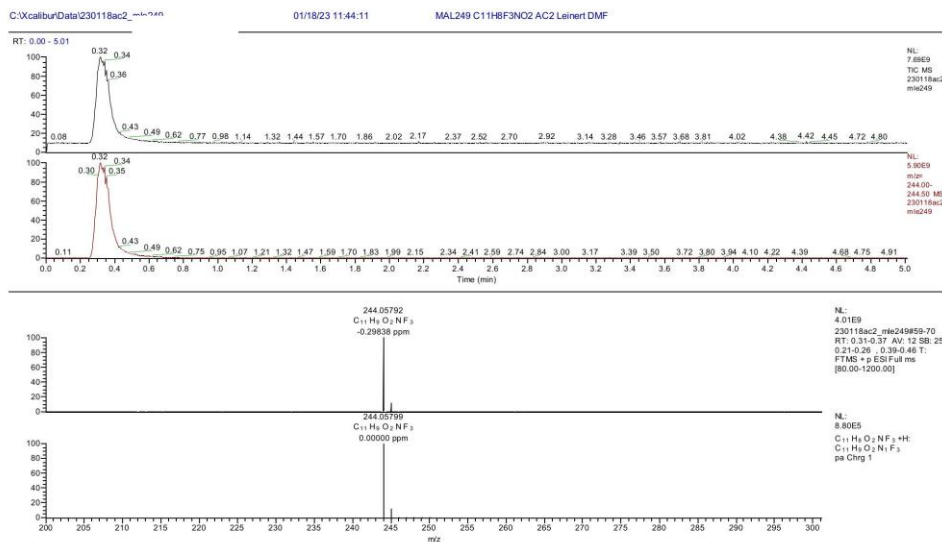
Supplementary Figure 133 HRMS spectrum of O2.

S111

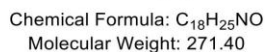


Chemical Formula: $C_{11}H_8F_3NO_2$
Molecular Weight: 243.19

O3



Supplementary Figure 134 HRMS spectrum of O3.



01/18/23 10:18:17 MAL201 C18H25NO AC2 Leinen DMF

RT: 0.00 - 5.01

0.05 0.32 0.33 0.45 0.51 0.87 1.02 1.15 1.21 1.31 1.50 1.70 1.84 2.03 2.17 2.40 2.52 2.66 2.87 2.93 3.19 3.28 3.37 3.52 3.64 3.88 4.16 4.23 4.49 4.59 4.78 5.00

100
80
60
40
20
0

0.00 0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00 3.20 3.40 3.60 3.80 4.00 4.20 4.40 4.60 4.80 5.00

Time (min)

0.22 0.33 0.49 0.61 0.72 0.87 1.00 1.15 1.24 1.36 1.50 1.62 1.76 1.93 2.03 2.20 2.26 2.40 2.52 2.76 2.84 3.01 3.08 3.22 3.46 3.62 3.71 3.84 4.11 4.22 4.42 4.49 4.63 4.85 4.98

100
80
60
40
20
0

0.00 0.20 0.40 0.60 0.80 1.00 1.20 1.40 1.60 1.80 2.00 2.20 2.40 2.60 2.80 3.00 3.20 3.40 3.60 3.80 4.00 4.20 4.40 4.60 4.80 5.00

Time (min)

272.20063
C₁₈H₂₅NO
+0.94363 ppm

272.25089
C₁₈H₂₅NO
0.00000 ppm

100
80
60
40
20
0

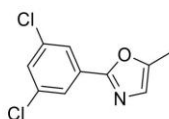
200 210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380 390 400

m/z

3.94E9
230118ac2_mba201#57-69
RT: 0.31-0.37 Av: 13 SB: 24
0.21-0.26 0.39-0.48 T:
FTMS + p ESI Full ms
[80.00-1200.00]

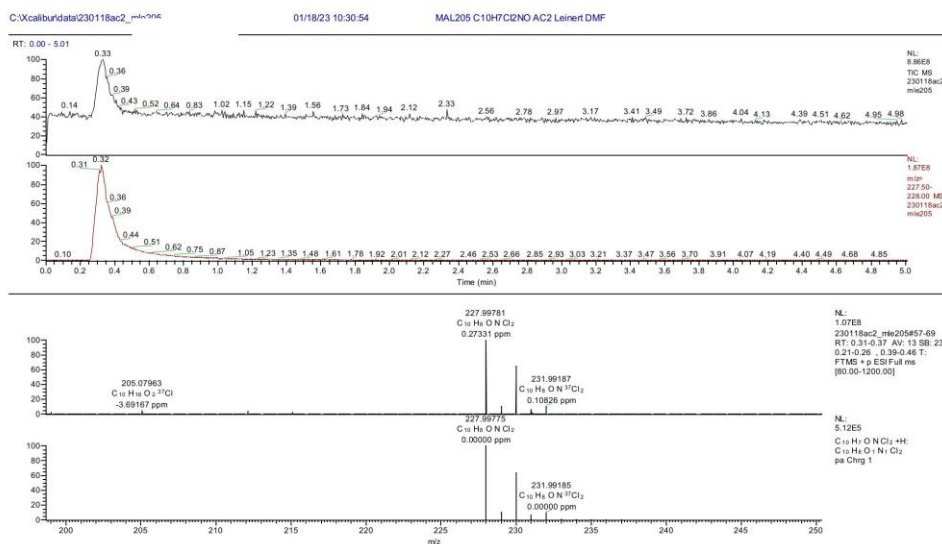
8.16E5
C₁₈H₂₅NO
C₁₈H₂₅NO
pe Chng I

Supplementary Figure 135 HRMS spectrum of **O4**.



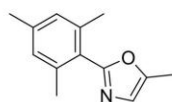
Chemical Formula: $C_{10}H_7Cl_2NO$
Molecular Weight: 228.07

05



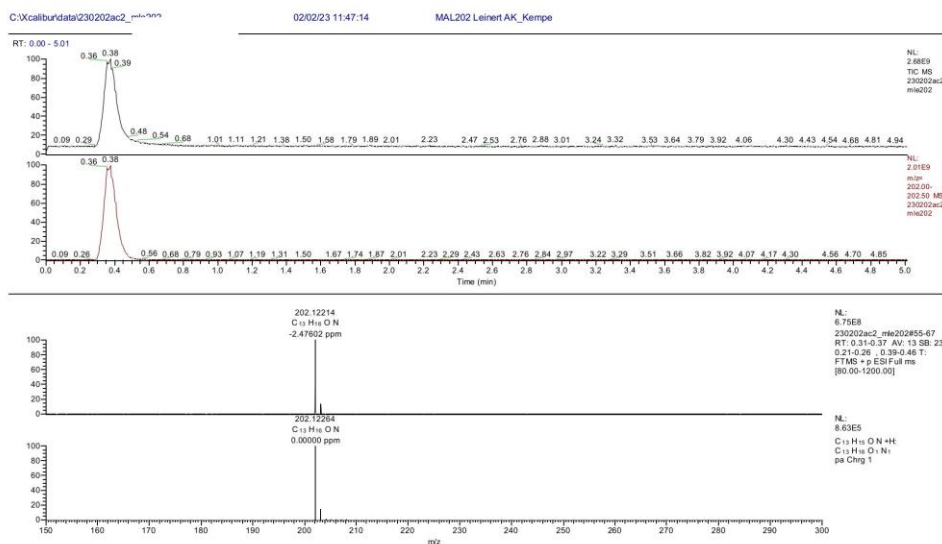
Supplementary Figure 136 HRMS spectrum of **O5**.

S114



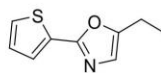
Chemical Formula: $C_{13}H_{15}NO$
Molecular Weight: 201.27

O6



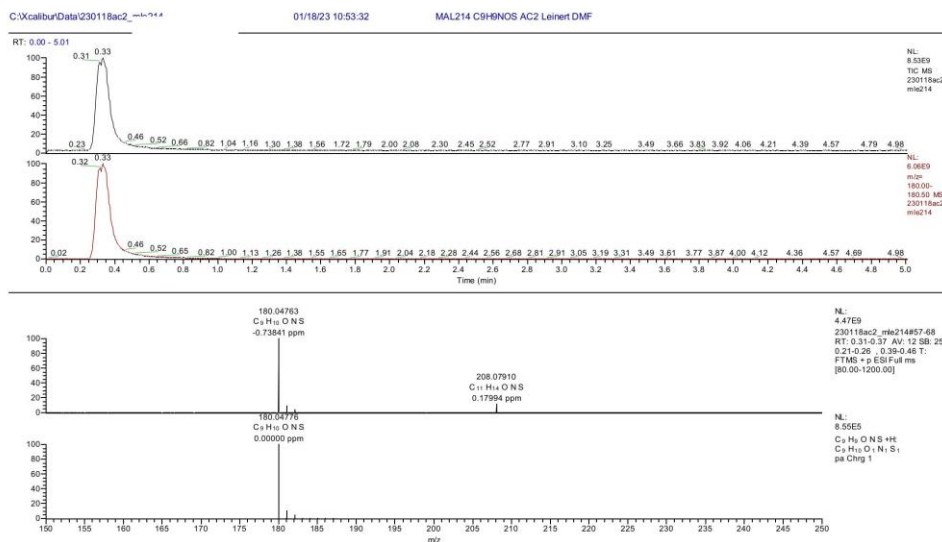
Supplementary Figure 137 HRMS spectrum of **O6**.

S115



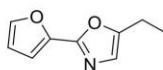
Chemical Formula: C_9H_9NOS
Molecular Weight: 179.24

O7



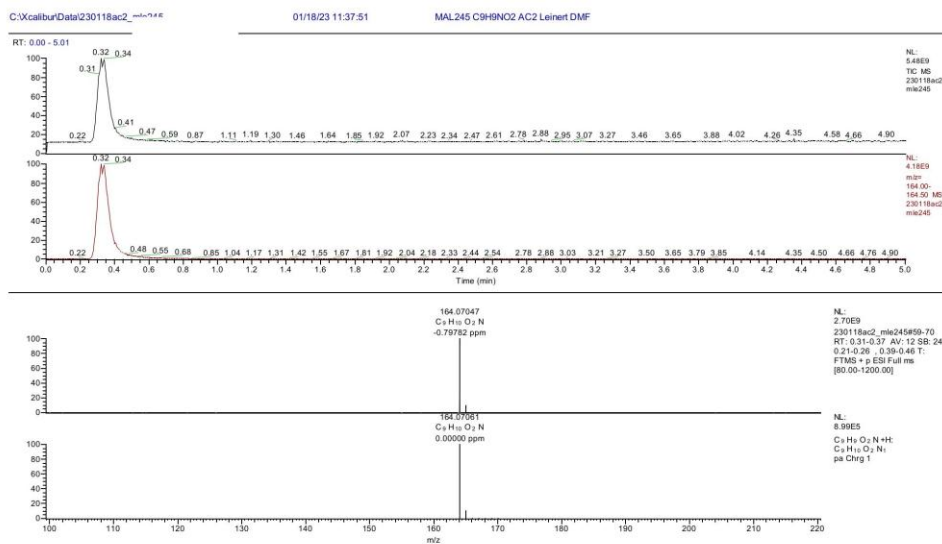
Supplementary Figure 138 HRMS spectrum of **O7**.

S116



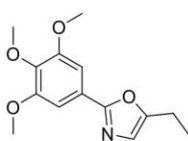
Chemical Formula: $C_9H_9NO_2$
Molecular Weight: 163.18

O8



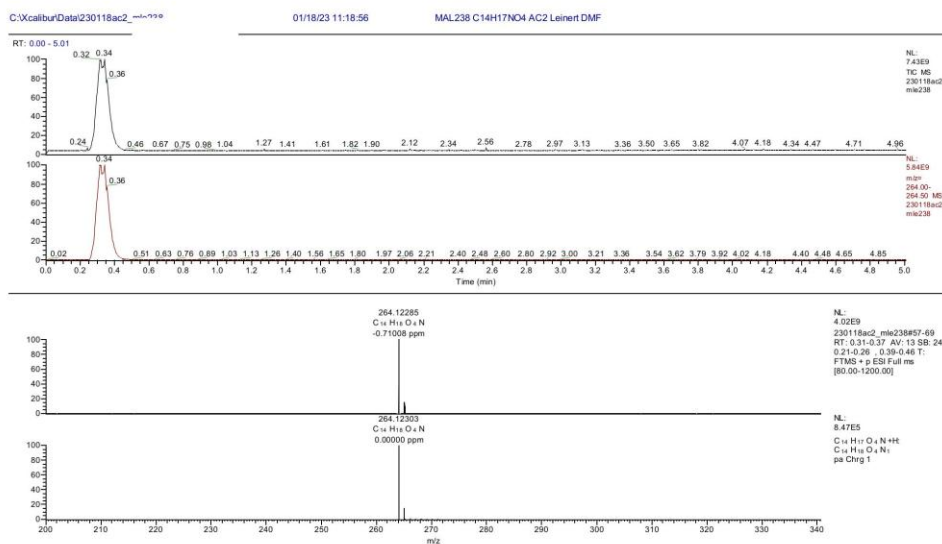
Supplementary Figure 139 HRMS spectrum of O8.

S117



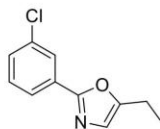
Chemical Formula: $C_{14}H_{17}NO_4$
Molecular Weight: 263.29

O9



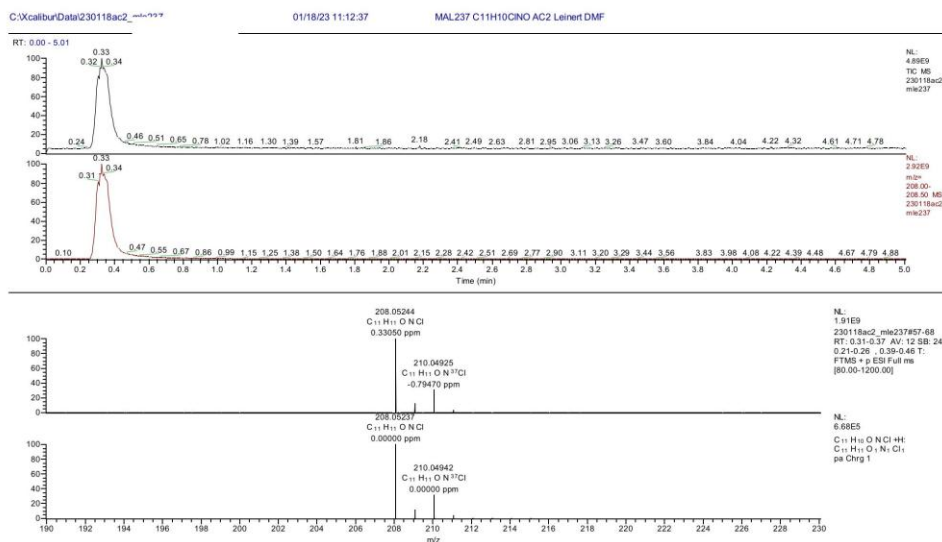
Supplementary Figure 140 HRMS spectrum of O9.

S118



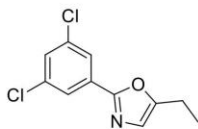
Chemical Formula: $C_{11}H_{10}ClNO$
Molecular Weight: 207.66

O10



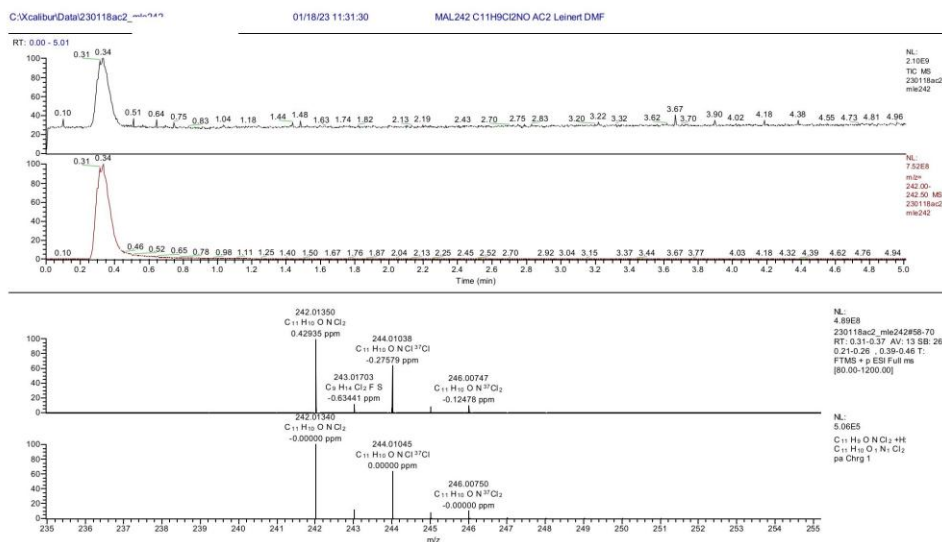
Supplementary Figure 141 HRMS spectrum of **O10**.

S119

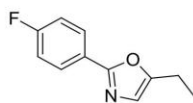


Chemical Formula: $C_{11}H_9Cl_2NO$
Molecular Weight: 242.10

O11

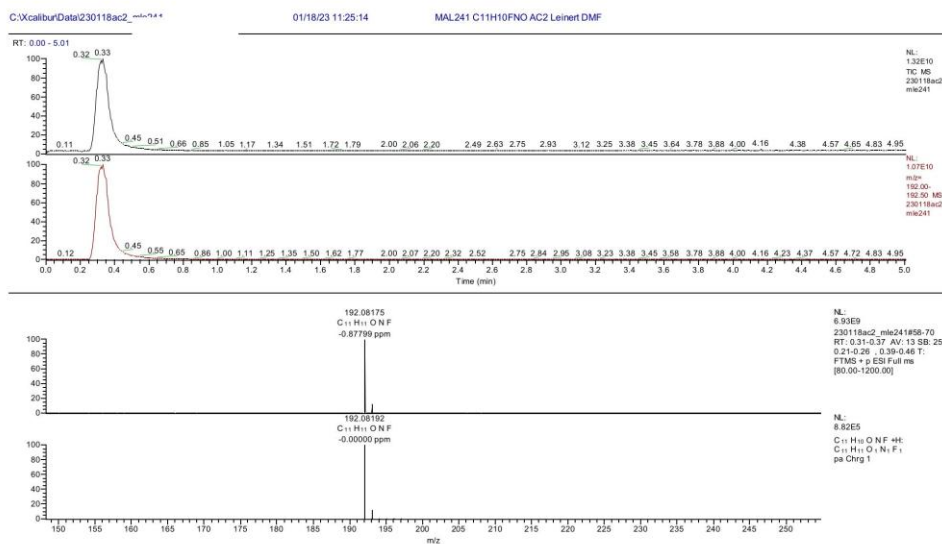


Supplementary Figure 142 HRMS spectrum of O11.



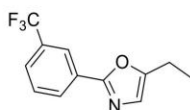
Chemical Formula: $C_{11}H_{10}FNO$
Molecular Weight: 191.21

O12



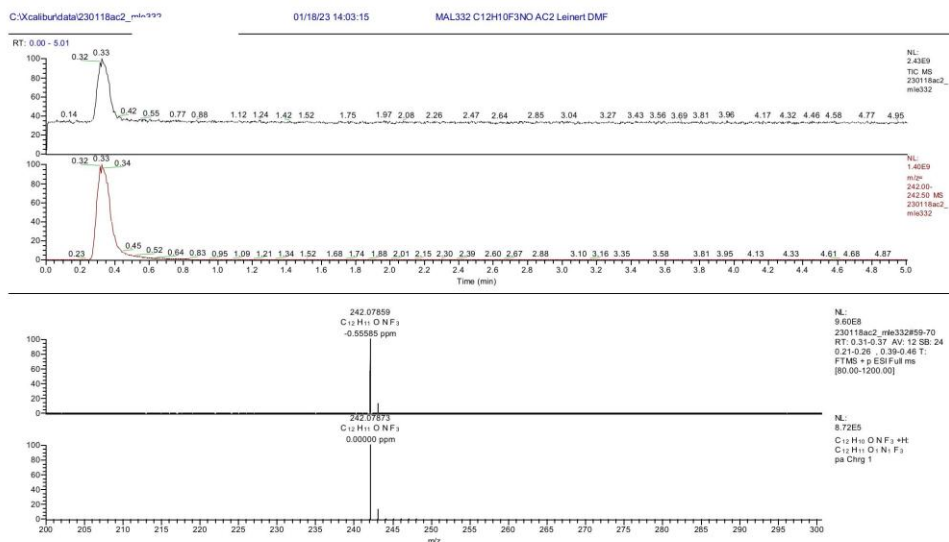
Supplementary Figure 143 HRMS spectrum of O12.

S121



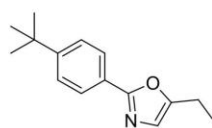
Chemical Formula: $C_{12}H_{10}F_3NO$
Molecular Weight: 241.21

O13



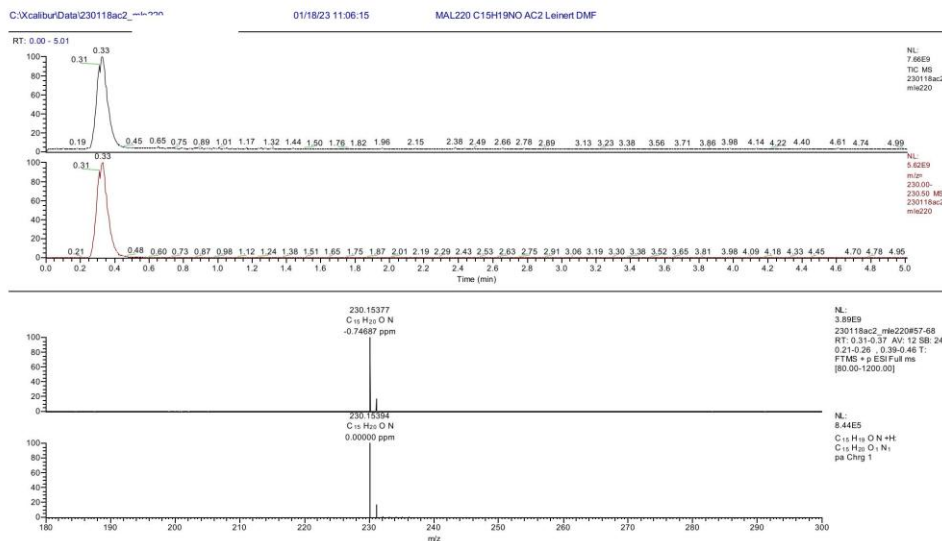
Supplementary Figure 144 HRMS spectrum of **O13**.

S122



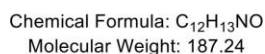
Chemical Formula: $C_{15}H_{19}NO$
Molecular Weight: 229.32

O14



Supplementary Figure 145 HRMS spectrum of **O14**.

S123



C:\Xcalibur\Data\230118ac2_mle219

01/18/23 10:59:53 MAL219 C12H13NO AC2 Leinert DMF

RT: 0.00 - 5.01

100
80
60
40
20
0

0.18 0.33 0.34 0.48 0.55 0.73 0.91 1.06 1.21 1.42 1.54 1.82 1.90 2.05 2.17 2.31 2.59 2.65 2.86 2.95 3.22 3.43 3.64 3.76 3.98 4.26 4.34 4.57 4.71 4.86

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6 3.8 4.0 4.2 4.4 4.6 4.8 5.0

Time (min)

NL:
1.46E10
YC MS
230118ac2_mle219

100
80
60
40
20
0

0.18 0.33 0.34 0.48 0.55 0.72 0.90 1.06 1.14 1.28 1.40 1.55 1.68 1.83 1.91 2.03 2.16 2.28 2.46 2.53 2.71 2.80 3.01 3.10 3.20 3.34 3.46 3.60 3.71 3.88 4.00 4.12 4.34 4.47 4.57 4.68 4.91

0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4 3.6 3.8 4.0 4.2 4.4 4.6 4.8 5.0

Time (min)

NL:
1.20E10
mle219
188.00 MS
230118ac2_mle219

100
80
60
40
20
0

188.10679
C₁₂H₁₃O N
-1.06437 ppm

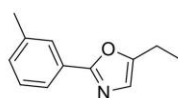
188.10699
C₁₂H₁₃O N
-0.00000 ppm

150 160 170 180 190 200 210 220 230 240 250 260 270 280 290 300

m/z

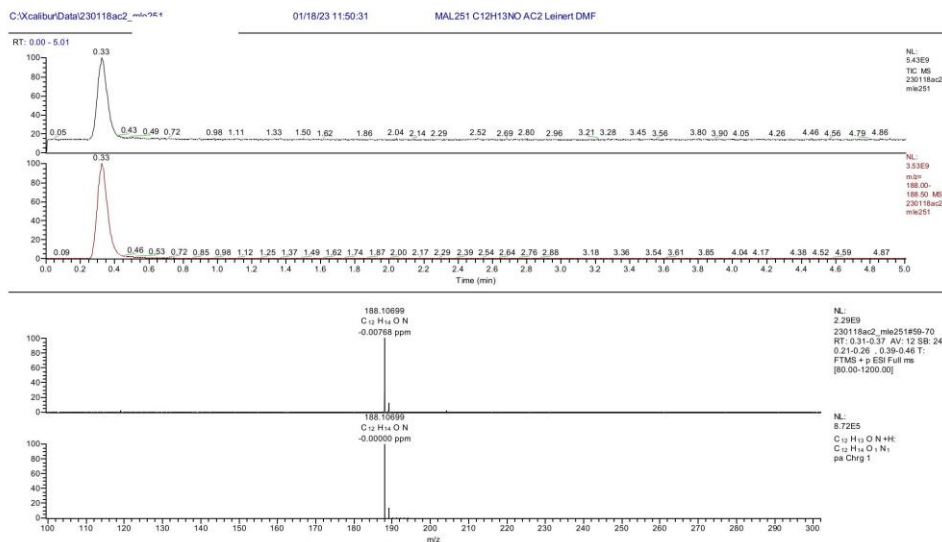
NL:
8.22E9
230118ac2_mle219S7-26
RT: 0.31-0.37 Av: 12 SB: 25
0.21-0.26 0.39-0.46 T:
FTMS + p ESI Full ms
[80.00-1200.00]

NL:
8.72E5
C₁₂H₁₃O N+H:
C₁₂H₁₃O N;
pe Chng 1



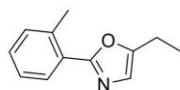
Chemical Formula: $C_{12}H_{13}NO$
Molecular Weight: 187.24

O16



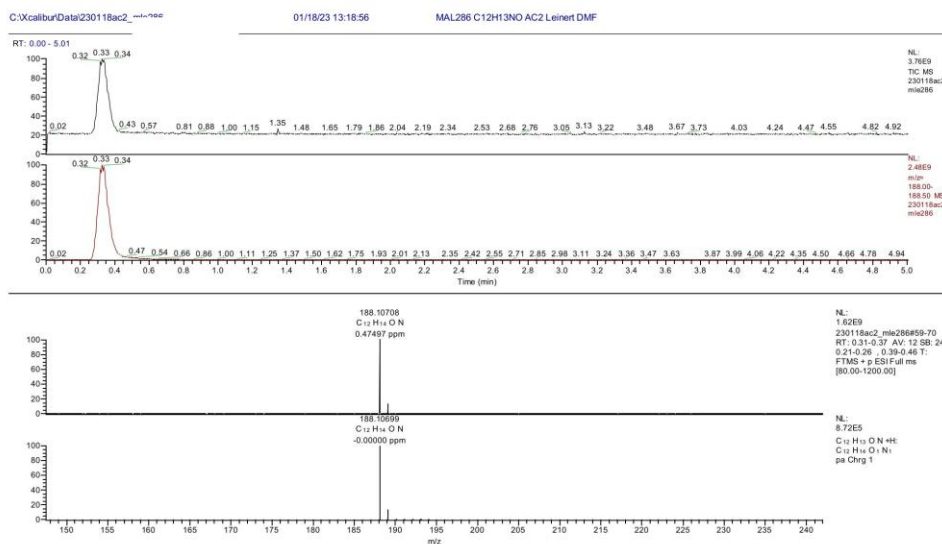
Supplementary Figure 147 HRMS spectrum of **O16**.

S125



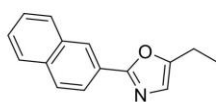
Chemical Formula: $C_{12}H_{13}NO$
Molecular Weight: 187.24

O17



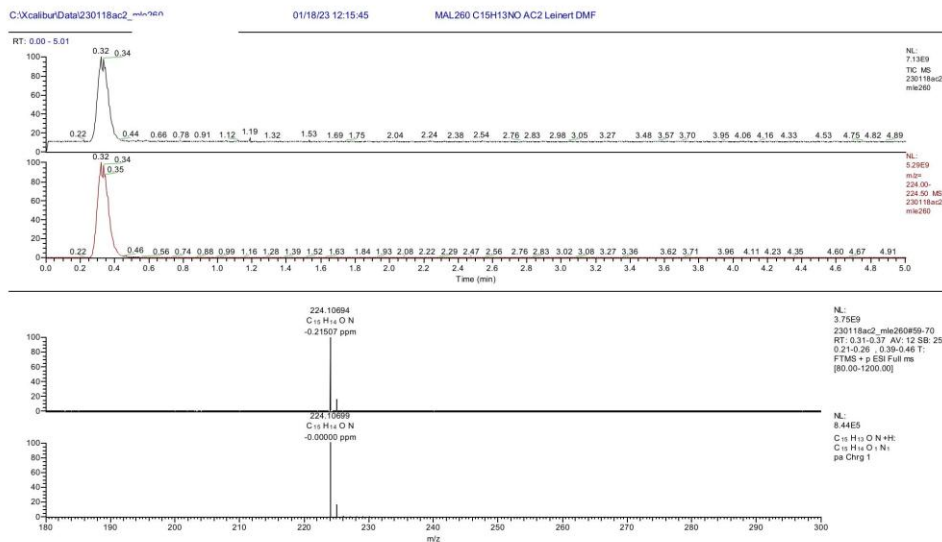
Supplementary Figure 148 HRMS spectrum of **O17**.

S126

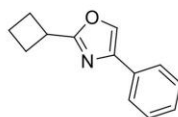


Chemical Formula: $C_{15}H_{13}NO$
Molecular Weight: 223.28

O18

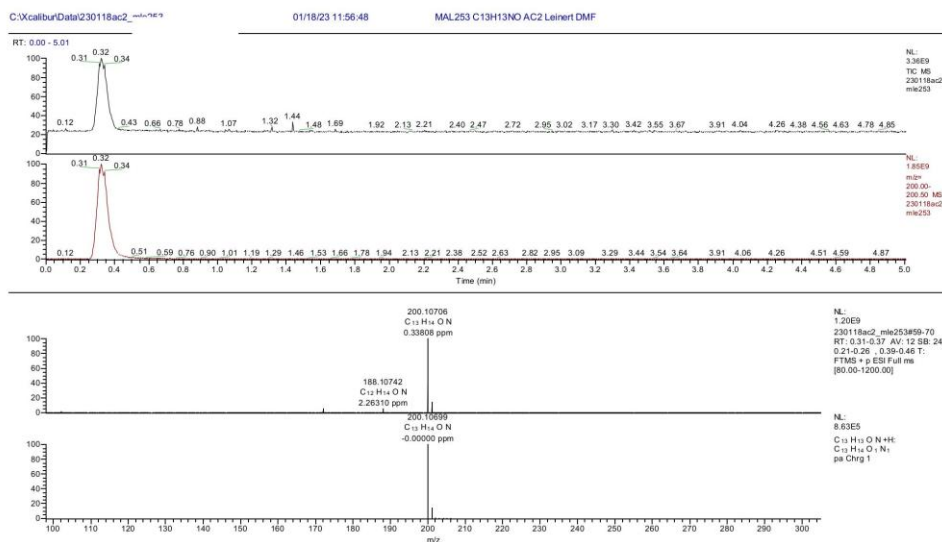


Supplementary Figure 149 HRMS spectrum of **O18**.

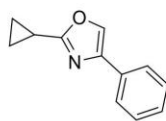


Chemical Formula: $C_{13}H_{13}NO$
Molecular Weight: 199.25

O19

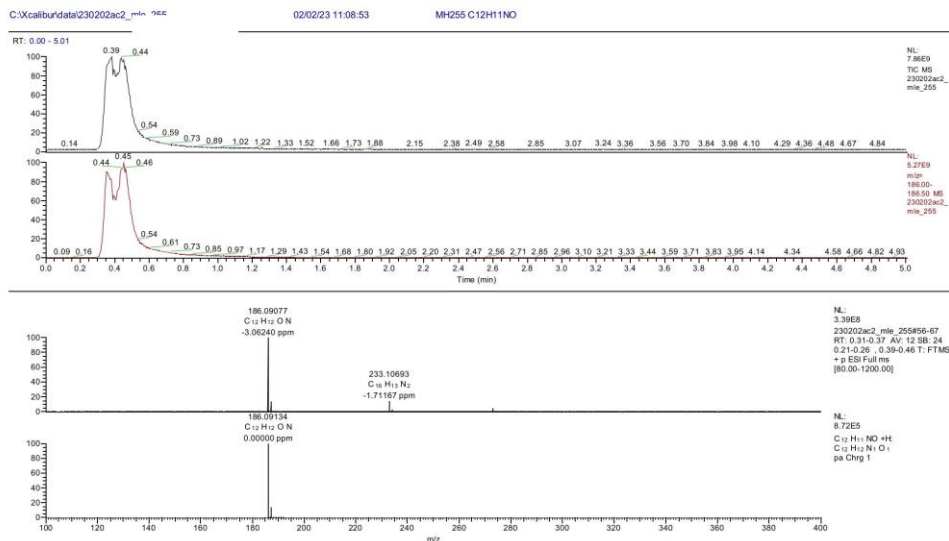


Supplementary Figure 150 HRMS spectrum of **O19**.

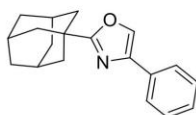


Chemical Formula: $C_{12}H_{11}NO$
Molecular Weight: 185.23

O20

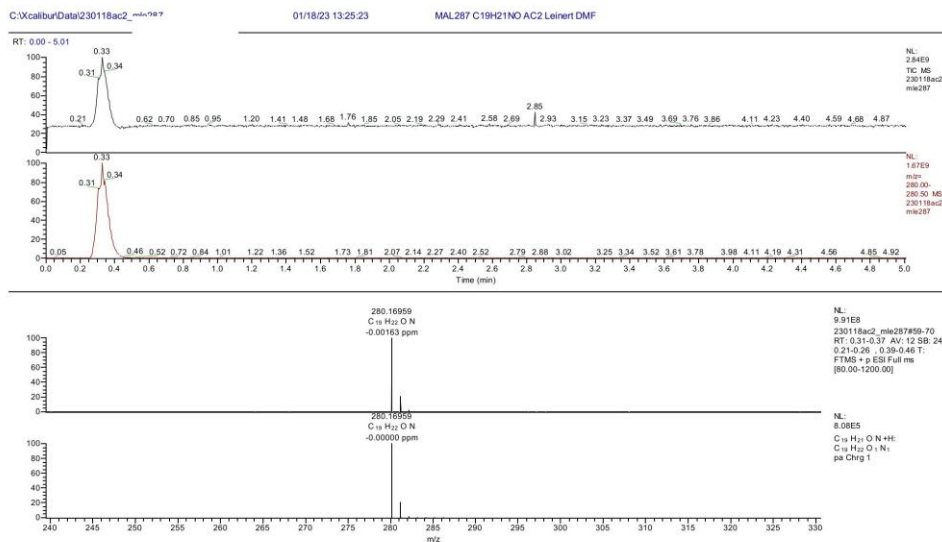


Supplementary Figure 151 HRMS spectrum of O20.



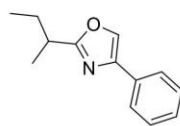
Chemical Formula: $C_{19}H_{21}NO$
Molecular Weight: 279.38

O21



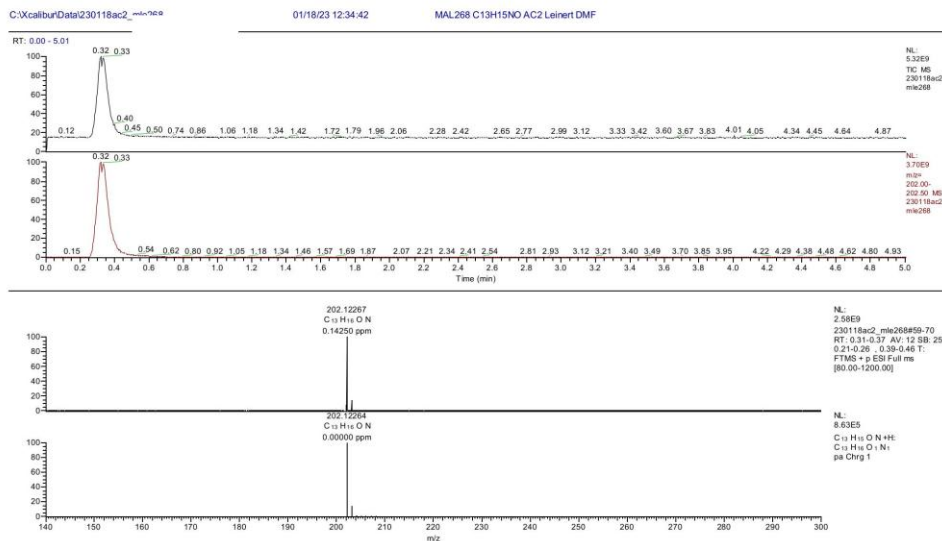
Supplementary Figure 152 HRMS spectrum of O21.

S130



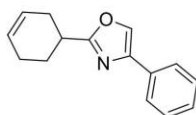
Chemical Formula: $C_{13}H_{15}NO$
Molecular Weight: 201.27

O22



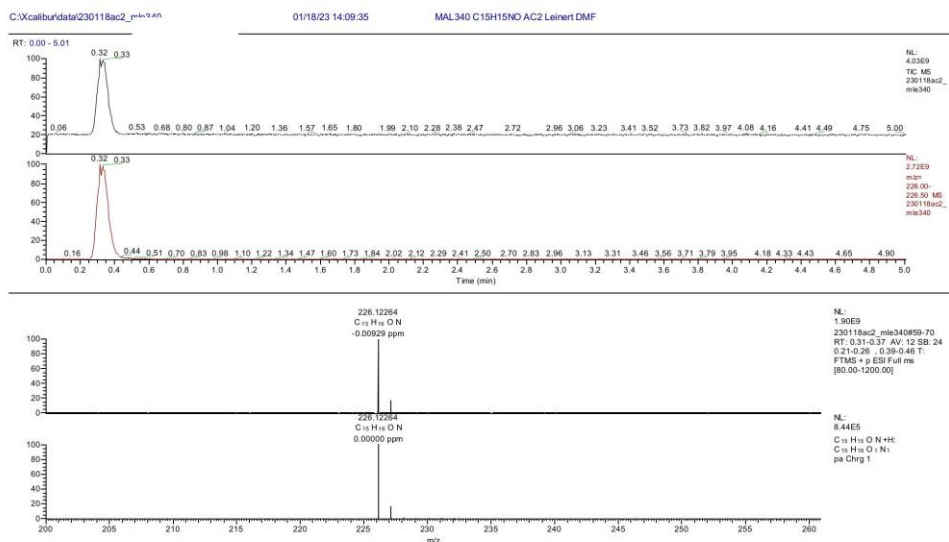
Supplementary Figure 153 HRMS spectrum of **O22**.

S131



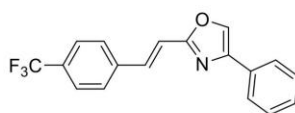
Chemical Formula: $C_{15}H_{15}NO$
Molecular Weight: 225.29

O23



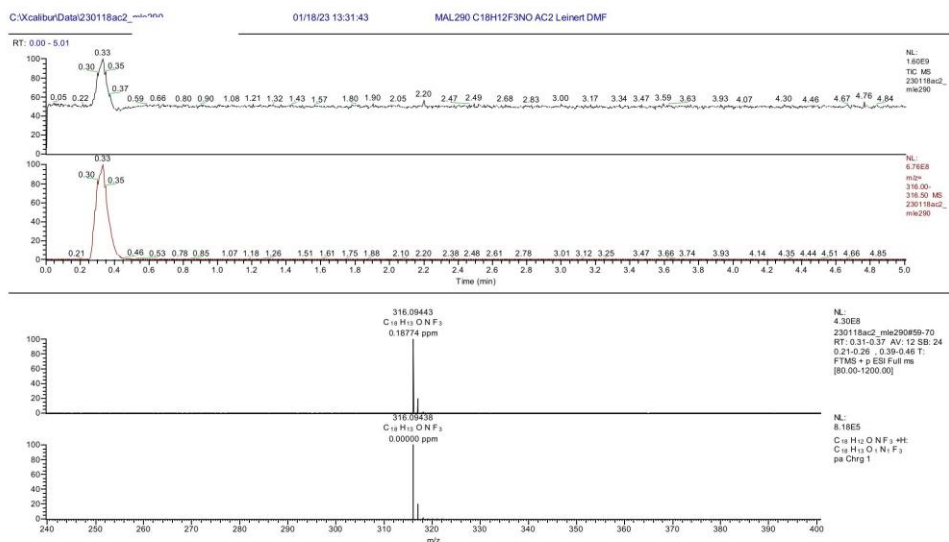
Supplementary Figure 154 HRMS spectrum of O23.

S132



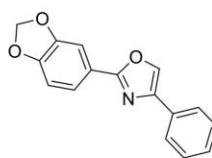
Chemical Formula: $C_{18}H_{12}F_3NO$
Molecular Weight: 315.30

O24



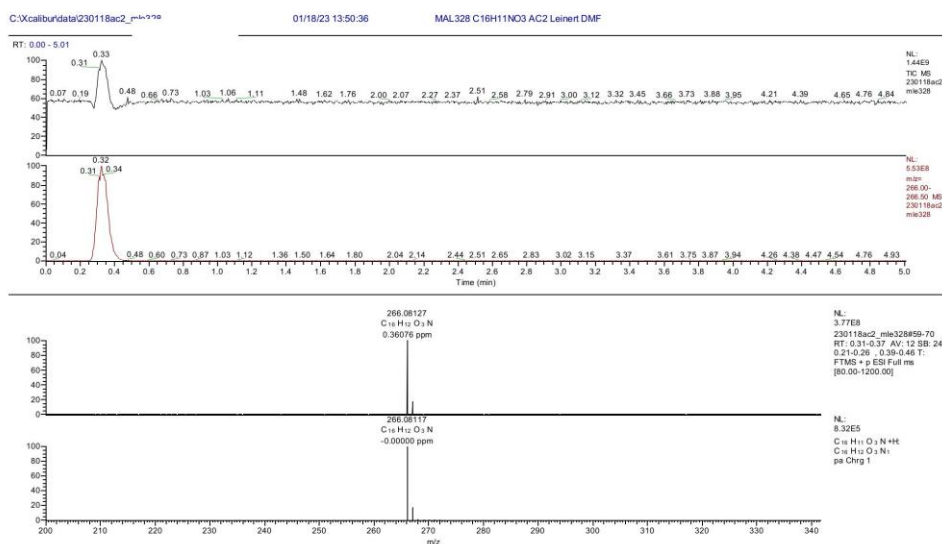
Supplementary Figure 155 HRMS spectrum of **O24**.

S133



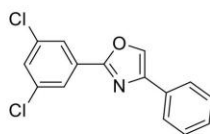
Chemical Formula: $C_{16}H_{11}NO_3$
Molecular Weight: 265.27

O25



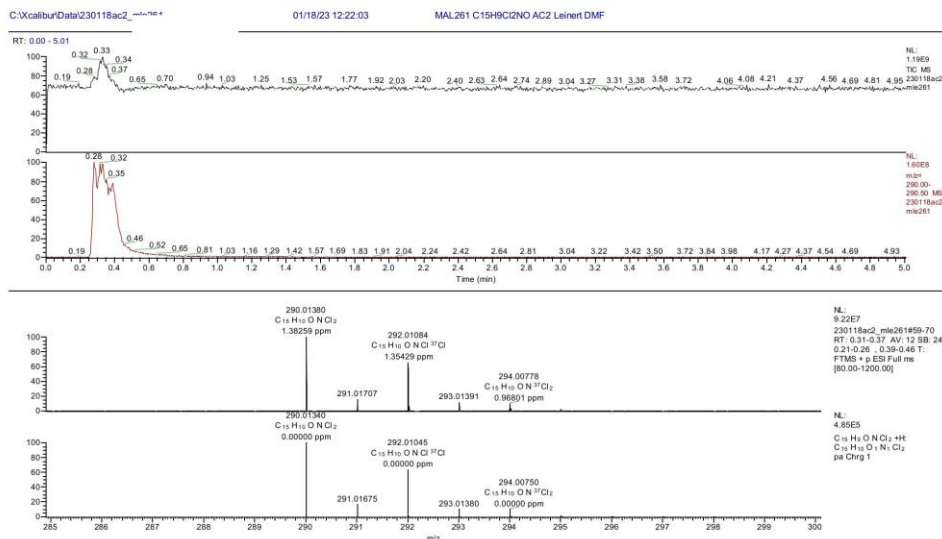
Supplementary Figure 156 HRMS spectrum of O25.

S134



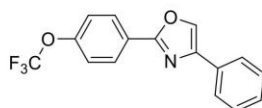
Chemical Formula: $C_{15}H_9Cl_2NO$
Molecular Weight: 290.14

O26



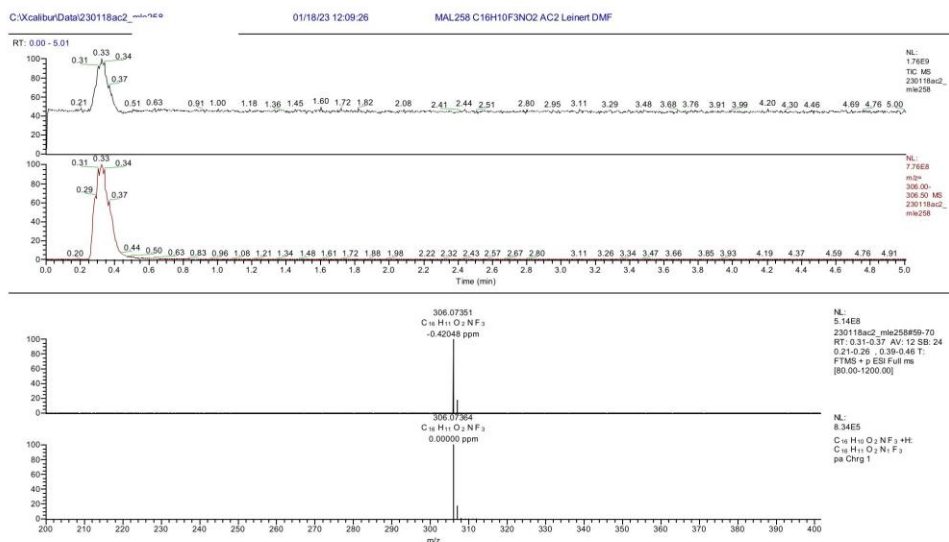
Supplementary Figure 157 HRMS spectrum of **O26**.

S135

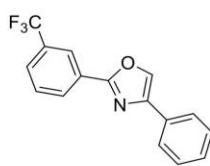


Chemical Formula: $C_{16}H_{10}F_3NO_2$
Molecular Weight: 305.26

O27

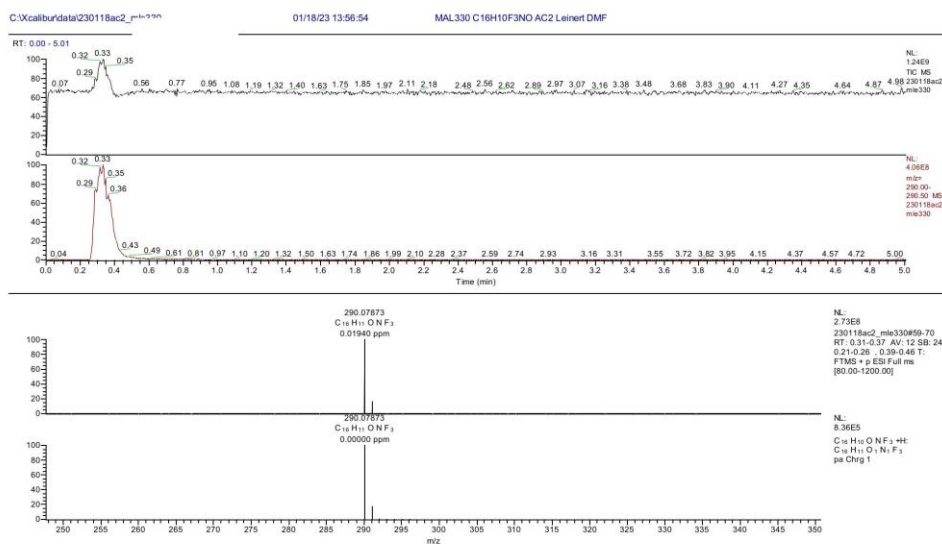


Supplementary Figure 158 HRMS spectrum of **O27**.

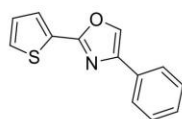


Chemical Formula: $C_{16}H_{10}F_3NO$
Molecular Weight: 289.26

O28

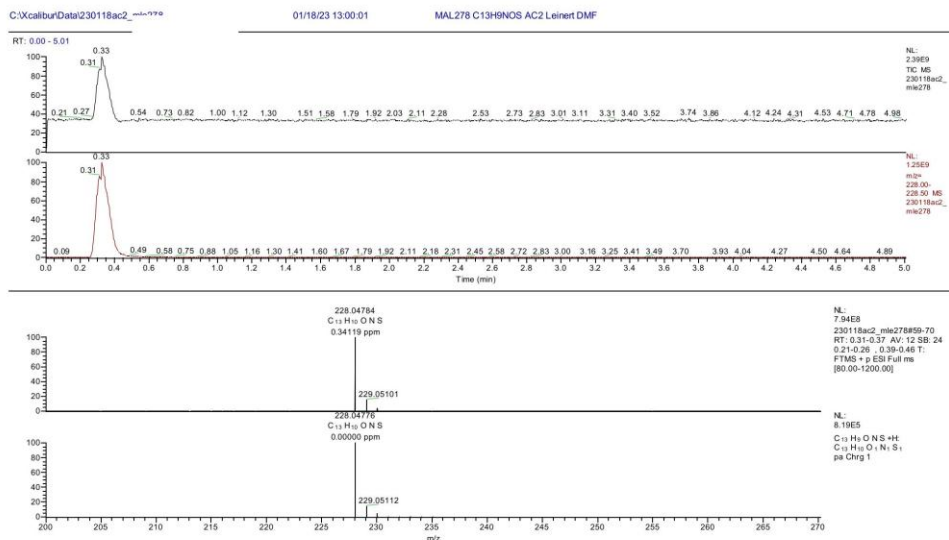


Supplementary Figure 159 HRMS spectrum of **O28**.



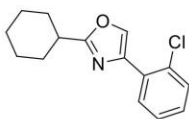
Chemical Formula: $C_{13}H_9NOS$
Molecular Weight: 227.28

O29



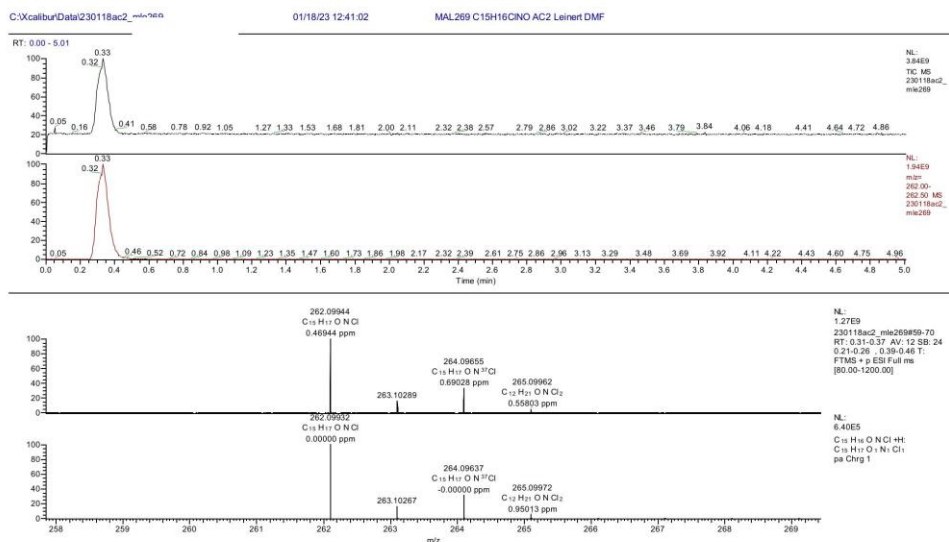
Supplementary Figure 160 HRMS spectrum of **O29**.

S138



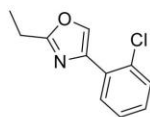
Chemical Formula: $C_{15}H_{16}ClNO$
Molecular Weight: 261.75

O30



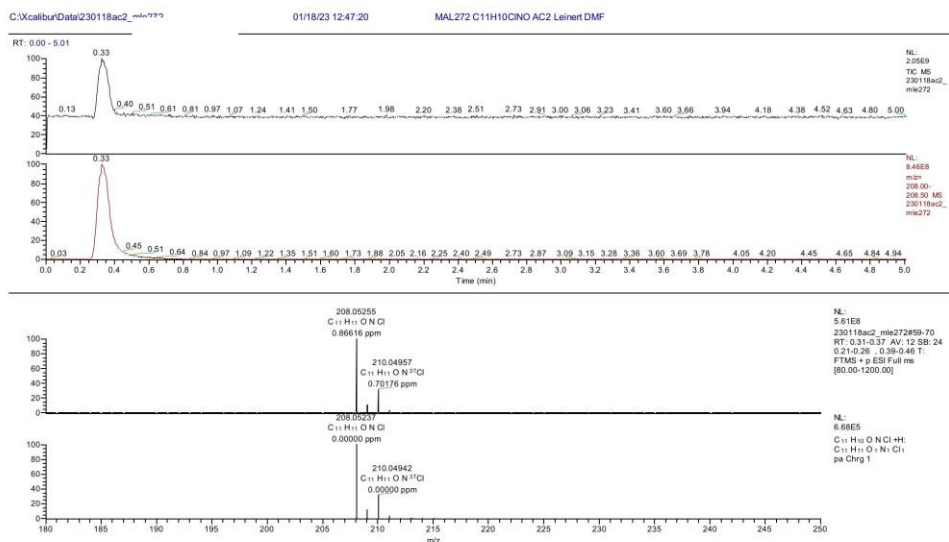
Supplementary Figure 161 HRMS spectrum of **O30**.

S139



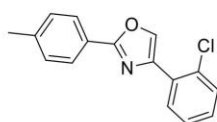
Chemical Formula: $C_{11}H_{10}ClNO$
Molecular Weight: 207.66

O31



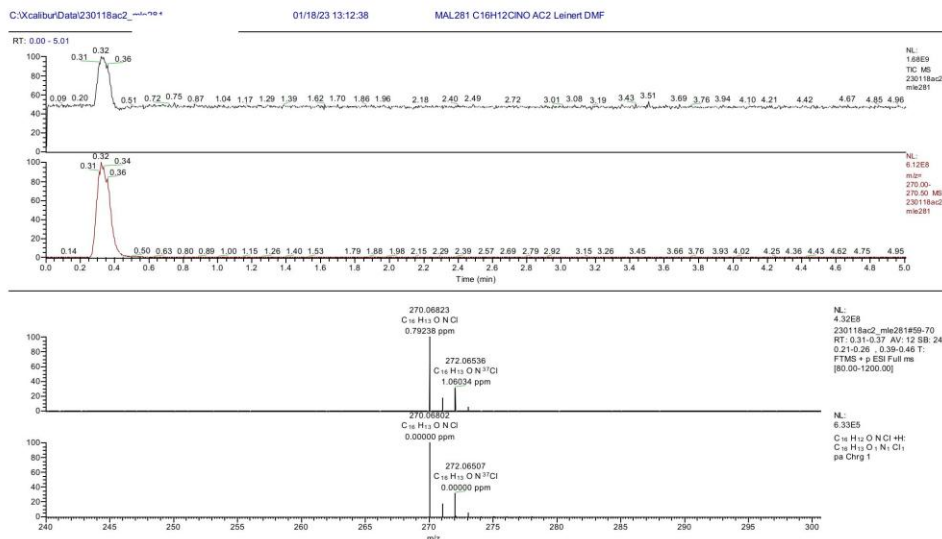
Supplementary Figure 162 HRMS spectrum of O31.

S140



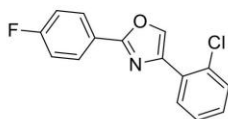
Chemical Formula: $C_{16}H_{12}ClNO$
Molecular Weight: 269.73

O32



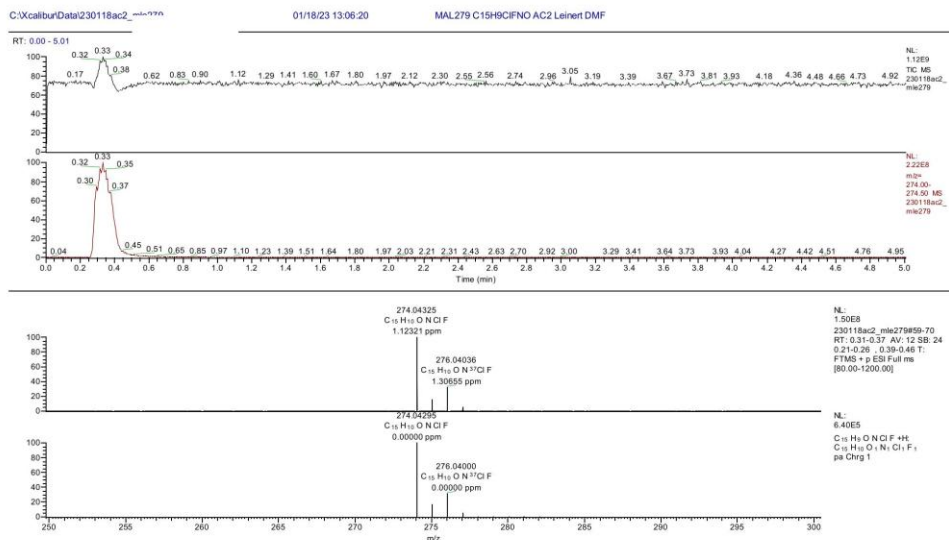
Supplementary Figure 163 HRMS spectrum of O32.

S141



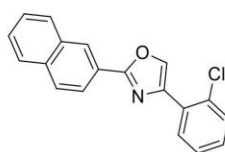
Chemical Formula: $C_{15}H_9ClFNO$
Molecular Weight: 273.69

O33



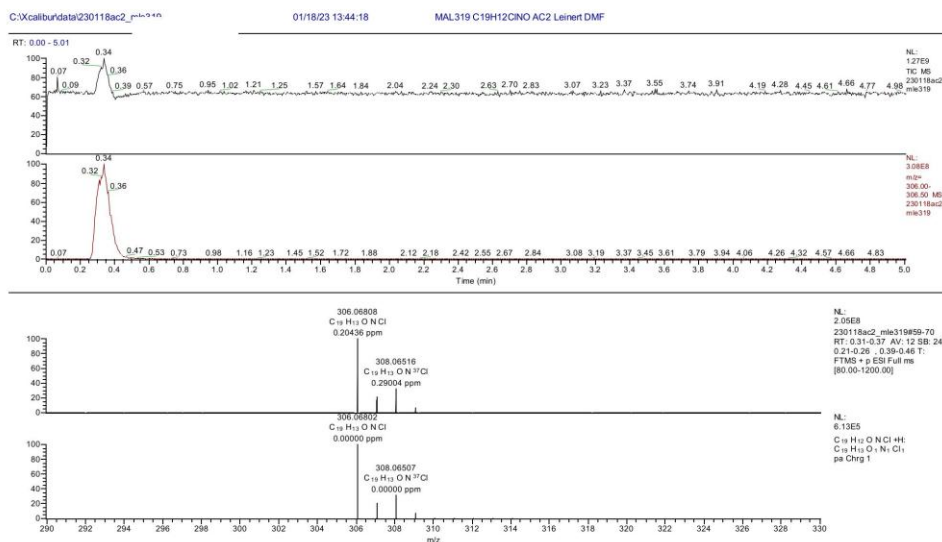
Supplementary Figure 164 HRMS spectrum of O33.

S142



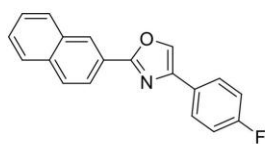
Chemical Formula: $C_{19}H_{12}ClNO$
Molecular Weight: 305.76

O34



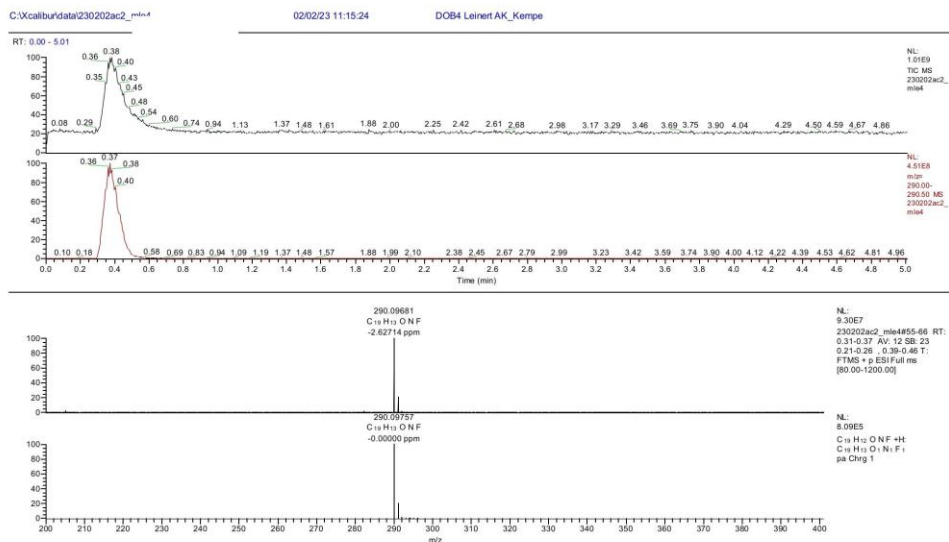
Supplementary Figure 165 HRMS spectrum of **O34**.

S143



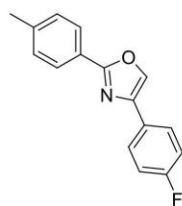
Chemical Formula: $C_{19}H_{12}FNO$
Molecular Weight: 289.31

O35



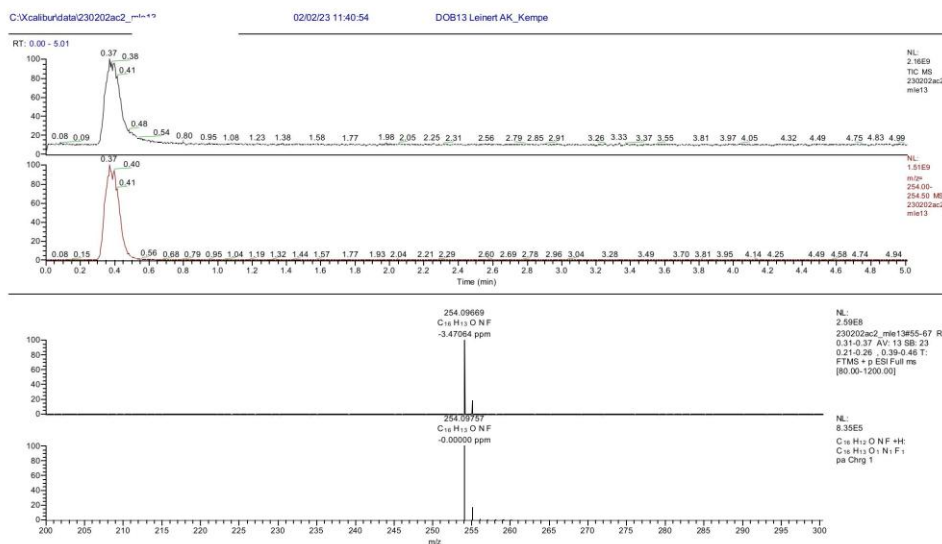
Supplementary Figure 166 HRMS spectrum of O35.

S144



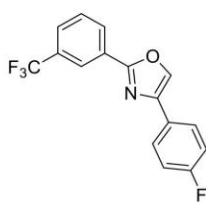
Chemical Formula: $C_{16}H_{12}FNO$
Molecular Weight: 253.28

O36



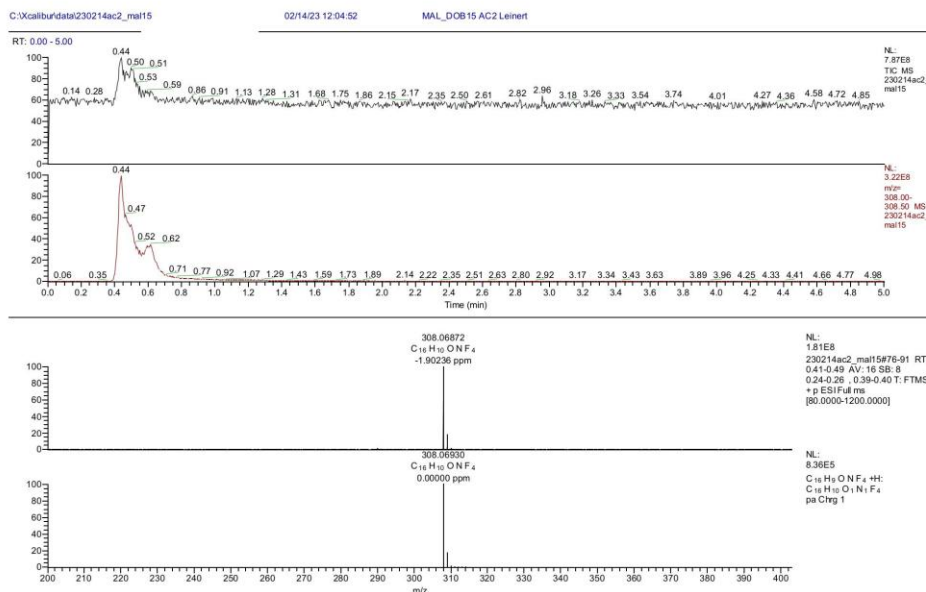
Supplementary Figure 167 HRMS spectrum of **O36**.

S145

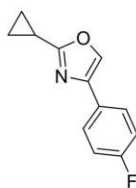


Chemical Formula: $C_{16}H_9F_4NO$
Molecular Weight: 307.25

O37

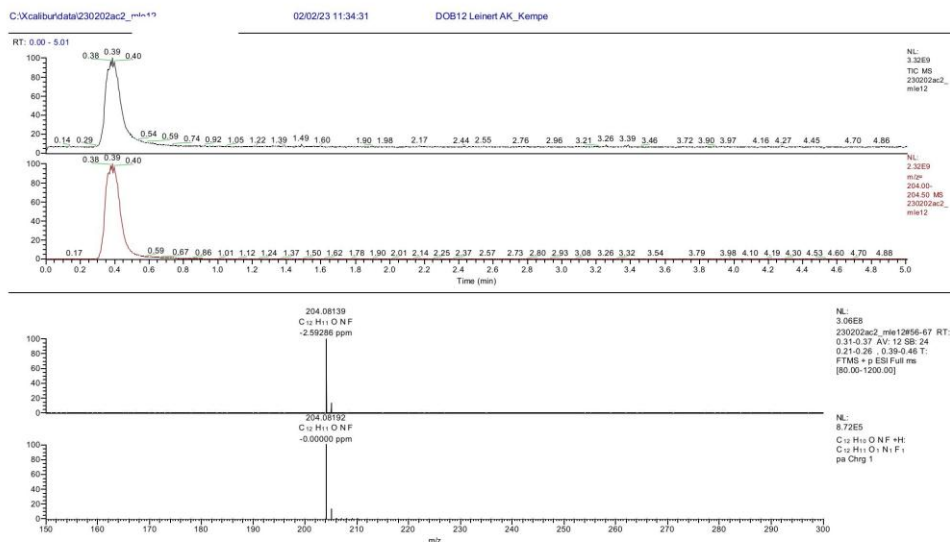


Supplementary Figure 168 HRMS spectrum of **O37**.



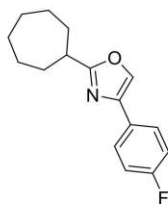
Chemical Formula: $C_{12}H_{10}FNO$
Molecular Weight: 203.22

O38



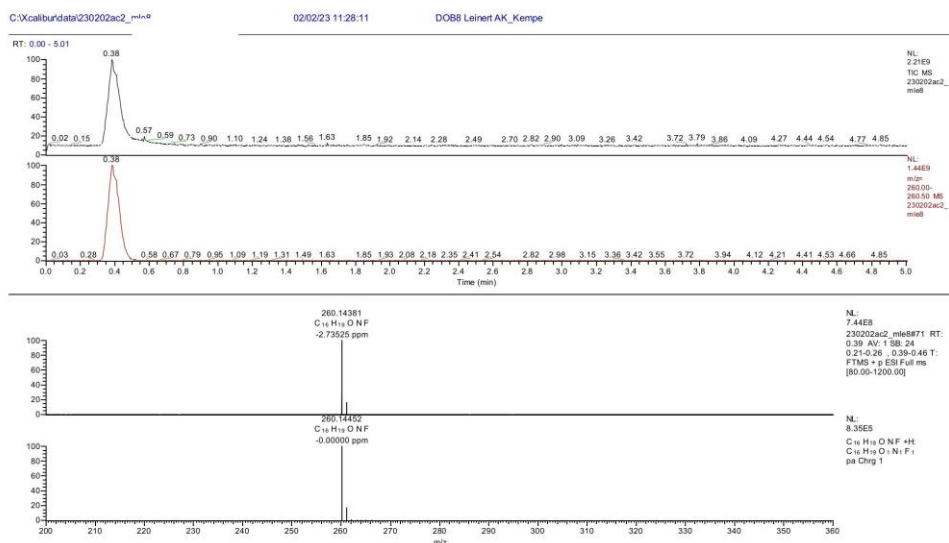
Supplementary Figure 169 HRMS spectrum of O38.

S147



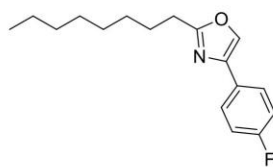
Chemical Formula: $C_{16}H_{18}FNO$
Molecular Weight: 259.32

O39



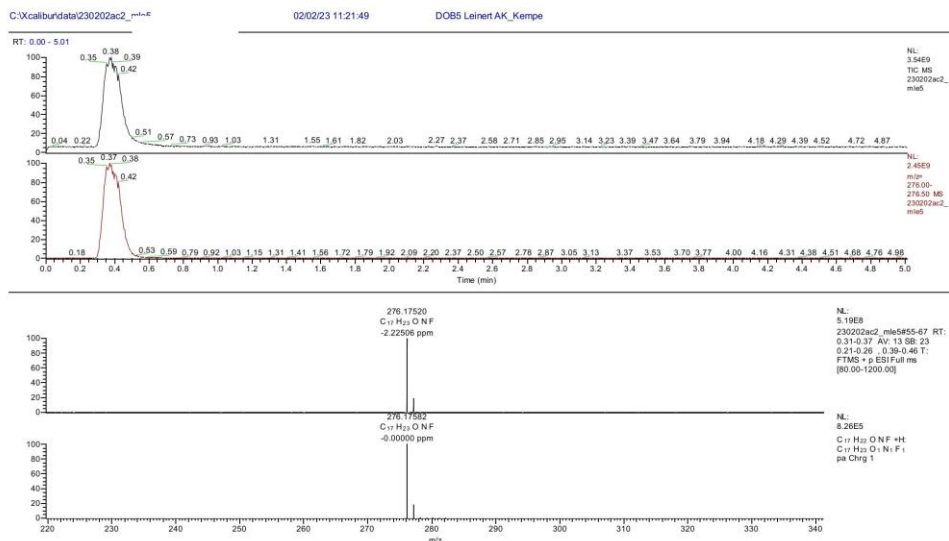
Supplementary Figure 170 HRMS spectrum of **O39**.

S148

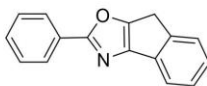


Chemical Formula: $C_{17}H_{22}FNO$
Molecular Weight: 275.37

O40

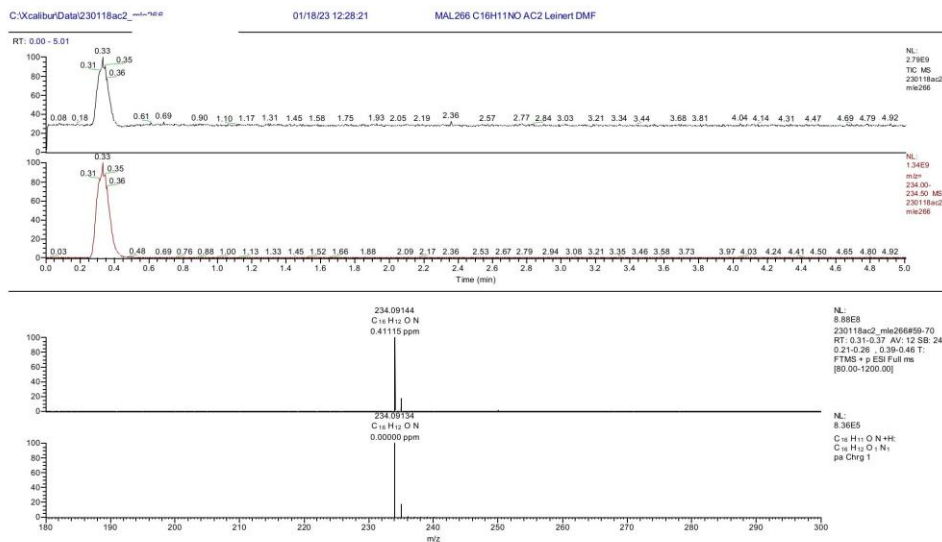


Supplementary Figure 171 HRMS spectrum of **O40**.

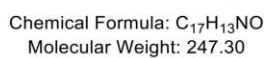


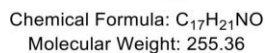
Chemical Formula: $C_{16}H_{11}NO$
Molecular Weight: 233.27

O41



S150





01/18/23 13:37:59 MAL283 C17H21NO AC2 Leinert DMF

RT: 0.00 - 5.01

100
80
60
40
20
0

0.13 0.32 0.34 0.31 0.57 0.65 0.77 1.01 1.08 1.27 1.52 1.65 1.77 1.91 2.08 2.31 2.44 2.64 2.89 2.98 3.13 3.34 3.51 3.66 3.88 4.01 4.22 4.38 4.56 4.64 4.81 4.96

NL: 3.61E9
TIC MS
230118ac2
ms293

100
80
60
40
20
0

0.09 0.31 0.34 0.51 0.63 0.78 0.90 1.01 1.15 1.29 1.47 1.58 1.81 1.89 2.01 2.20 2.41 2.53 2.77 2.83 2.90 3.12 3.42 3.49 3.61 3.70 3.96 4.05 4.24 4.30 4.59 4.83 4.97

2.33E9
m/z
256.00
256.50 MS
230118ac2
ms293

Time (min)

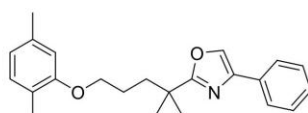
256.16952
C₁₇H₂₁O N
-0.28715 ppm

256.16958
C₁₇H₂₁O N
0.00000 ppm

NL: 1.56E9
230118ac2_ms293459-70
RT: 0.31-0.37 AV: 12 SB: 24
0.31-0.36 (-0.38-0.46) T.
FTMS + p ESI Full ms
[80.00-1200.00]

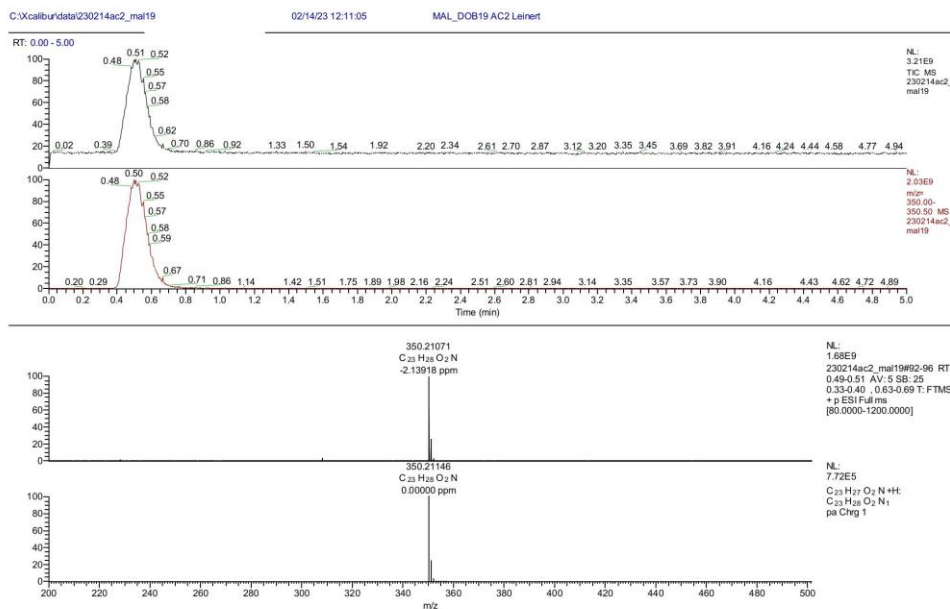
NL: 8.28E5
C₁₇H₂₁O N + H
C₁₇H₂₁O N;
pk Chng 1

Supplementary Figure 174 HRMS spectrum of **O43**.



Chemical Formula: $C_{23}H_{27}NO_2$
Molecular Weight: 349.47

O44



Supplementary Figure 175 HRMS spectrum of **O44**.

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7. A CATALYTIC VERSION OF THE KNORR PYRROLE SYNTHESIS PERMITS ACCESS TO PYRROLES AND PYRIDINES

Title: A Catalytic Version of the Knorr Pyrrole Synthesis Permits Access to Pyrroles and Pyridines.

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A Catalytic Version of the Knorr Pyrrole Synthesis Permits Access to Pyrroles and Pyridines

Max Leinert, Torsten Irrgang, and Rhett Kempe*

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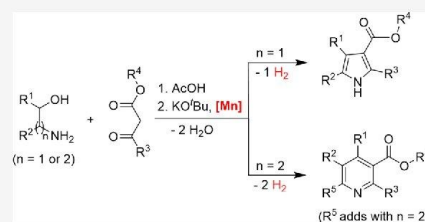
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ABSTRACT: Aromatic *N*-heterocycles, such as pyrroles and pyridines, are important natural products and bulk and fine chemicals with numerous applications as active ingredients of pharmaceuticals and agrochemicals, as catalysts, and in materials sciences. We report here a catalytic version of the Knorr pyrrole synthesis in which simple and diversely available starting materials, such as 1,2-amino alcohols or 1,3-amino alcohols and keto esters, undergo a dehydrogenative coupling to form pyrroles and pyridines, respectively. Our reaction forms hydrogen as a collectible (and usable) byproduct and is mediated by a well-defined Mn catalyst. The synthesis of highly functionalized heterocycles and applications was demonstrated, and 35 compounds, not yet reported in the literature, were introduced.



INTRODUCTION

Pyrroles and pyridines are important classes of compounds that are present in bulk and fine chemicals, important natural products, active ingredients of drugs, agrochemicals, catalysts, and materials. Pyridine itself was produced in about 7.8 megaton scale in 2022 and its production is expected to grow.¹ The photosynthesis pigment chlorophyll and the blood respiratory pigment heme are biosynthesized from the pyrrole porphobilinogen.² Atorvastatin, sunitinib, and nicotinic acid or vitamin B₃ (Figure 1A) are pyrrole or pyridine derivatives and bioactive components of pharmaceuticals. Diquat or paraquat are bipyridine-based herbicides, the Crabtree catalyst³ contains a pyridine ligand, numerous enzymes have a porphyrin core (*vide supra* chlorophyll and heme), and polypyrroles are conducting polymers used in batteries⁴ and solar cells.⁵ The importance of the two compound classes has generated unbroken interest in their synthesis. Recently published catalytic protocols for the synthesis of pyrroles^{6–14} and pyridines^{15–28} give proof of the vibrant activity in these fields. The classic Knorr pyrrole synthesis (Figure 1B) permits access to numerous active ingredients of pharmaceuticals (Figure 1A, left and middle, for instance), recognizable by the ester or amide substituent in the β -position. Unfortunately, the instability of the amino aldehyde or ketone starting material is limiting, and an extension to 1,3-amino aldehydes or ketones leading to pyridines would be highly desirable. Here, the additional dehydrogenation step, resulting from the three double bonds required per pyridine ring and only two condensation steps forming such double bonds, calls for catalysis. Dehydrogenation reactions^{29–40} where the hydrogen can be collected and used are interesting because hydrogen is a sustainable energy carrier. Methodology developments with Mn pincer catalysts are also of high interest^{41–53} since Mn

catalysts provide unique reactivity and the metal is earth-abundant. Dehydrogenative coupling or condensation has been used for the synthesis of pyrroles and pyridines employing the C–N and C–C bond formation steps shown in Figure 1C. For the synthesis of pyrroles, 1,4-dioles and amines were used as starting materials,^{54,55} a three-component reaction converting an amine, a ketone, and a diol was introduced,^{56–58} and 1,2-amino alcohols and ethanol derivatives were combined.^{59–62} In addition, 1,3-amino alcohols and ethanol derivatives were linked to form pyridines.^{63–65} We report here a catalytic version of the Knorr pyrrole synthesis (Figure 1D). Simple and diversely available starting materials, namely, 1,2-amino alcohols or 1,3-amino alcohols and keto esters, permit access to pyrroles and pyridines, respectively. Hydrogen is a byproduct of our reaction, for instance, two equiv per pyridine molecule formed, and can be collected and used subsequently. A Mn catalyst and simple acid and base catalyst mediate our reaction efficiently. The synthesis of highly functionalized compounds and applications was demonstrated, and 35 compounds, not yet reported in the literature (no CAS number), were reported. Fifteen of the 35 compounds are pyrrole derivatives carrying a different ester group.

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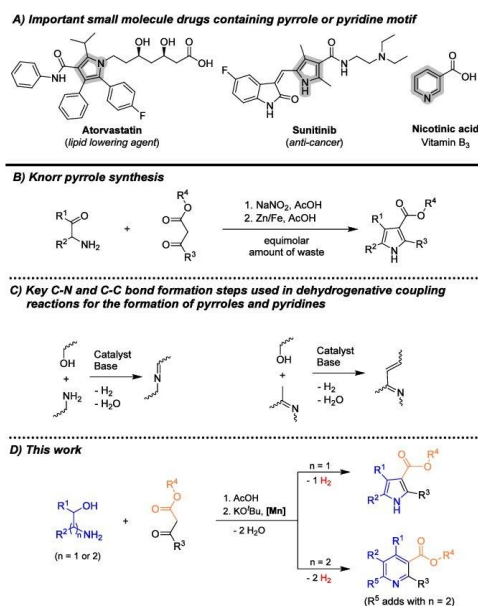


Figure 1. State of the art and work reported here. (A) Examples of active ingredients of pyrrole- or pyridine-based drugs. (B) Knorr pyrrole synthesis. (C) Dehydrogenative coupling (serpentine lines denote substituents). (D) Work reported here.

RESULTS AND DISCUSSION

Finding Optimized Reaction Conditions. We investigated the formation of *tert*-butyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**P1**, Figure 2) starting from *tert*-butyl (Z)-3-((2-hydroxypropyl)amino)but-2-enoate (**A1**, Supporting Information Tables S1–S5) to find optimal conditions for the dehydrogenation step of our pyrrole synthesis. Initially, KOtBu was determined as the most efficient base, and 1,4-dioxane seemed to be the best solvent. A base loading of 40.0 mol % showed the optimum results in this catalytic dehydrogenation reaction. PN₃P-ligand-supported Mn carbonyl complexes were investigated next (Supporting Information Table S4). Precatalyst [Mn–I] gives rise to the most active catalyst system. An Ir complex stabilized by the same ligand as [Mn–I] showed no higher activity compared to that of [Mn–I]. By increasing the amount of catalyst, the yield of the product desired could be increased to 92%.

Synthesis of Pyrrole Derivatives (Scope). With suitable reaction conditions in hand, we investigated the substrate scope. The products could be isolated in yields up to 97%. A wide range of β -hydroxy enamines **A** can undergo our dehydrogenative pyrrole synthesis (Figures 2–6). The number of substrates (35), which have not yet been reported in the literature, demonstrates the degree of novelty of our reaction. All known compounds are labeled with their corresponding CAS number in the Supporting Information. We were able to isolate compound **P1** in an 89% yield (Figure 2). Variation of the ester group showed that *tert*-butyl carboxylates gave the highest yields regardless of the transesterification steps. Compound **P2** and **P3** could be isolated in 47 and 35%

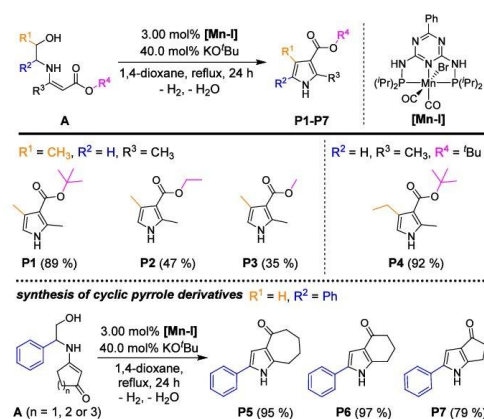


Figure 2. Synthesis of 2,3,4-substituted pyrroles including ester group variation (top, **P1–P4**) and cyclo pyrroles (bottom, **P5–P7**). Reaction conditions: 1.00 equiv β -hydroxy enamine **A**, 40.0 mol % KOtBu, 3.00 mol % [Mn–I], 1,4-dioxane (0.10 M), then reflux for 24 h; reflux conditions: open system under argon atmosphere. Isolated yields in brackets.

yield, respectively (Figure 2). We see the formation of significantly more unwanted byproducts. Product **P4** could be isolated in a 92% yield by using 1-aminopropan-2-ol as a secondary amino alcohol (Figure 2). Synthesis of cyclopyrrole derivatives was achieved by using cyclic 1,3-diketones with different ring sizes.⁶⁶ Compounds **P5–P7** could be isolated in yields up to 97% (Figure 2).

We next used β -hydroxy enamines derived from 2-amino-2-phenylethan-1-ol derivatives and *tert*-butyl acetoacetate for the formation of the associated pyrroles. Compound **P8** could be isolated in a 78% yield by using 2-amino-2-phenylethan-1-ol (Figure 3). Electron-withdrawing groups at the corresponding phenyl moiety resulted in a pyrrole formation with yields up to 95% (**P9–P11**, Figure 3). The synthesis of **P12** containing a methoxy group at the phenyl moiety led to the isolation of the corresponding product in an 84% yield (Figure 3). Several alkyl moieties, such as cyclohexyl, cyclopentyl, or *n*-alkyl groups, which are generally difficult to introduce using conventional methods, were easily tolerated under the conditions used. **P13–P16** could be isolated in yields up to 91% (Figure 3). Furthermore, we synthesized 2,3,5-substituted pyrroles by using β -hydroxy enamines that are derived from different 2-amino-3-phenylpropan-1-ol derivatives and *tert*-butyl acetoacetate (Figure 3, **P17–P22**). Compound **P17** could be isolated in a 90% yield by using 2-amino-3-phenylpropan-1-ol as the corresponding 1,2-amino alcohol (Figure 3). The usage of electron-withdrawing groups at the benzyl moiety resulted in pyrrole formations with isolated yields up to 82% (**P18** and **P19**, Figure 3). Compounds with a hydrogenation-sensitive functional group, larger π -systems, or heterocyclic moieties, known for catalyst poisoning, were isolated in yields up to 87% (**P20–P22**, Figure 3).

To demonstrate the high flexibility of the method shown here, several different 1,3-keto esters were used to synthesize 2,3,5-substituted pyrroles (Figure 4). Compound **P23**, for example, could be isolated in an 84% yield by using *tert*-butyl 3-oxo-3-phenyl propanoate (Figure 4). In addition, different

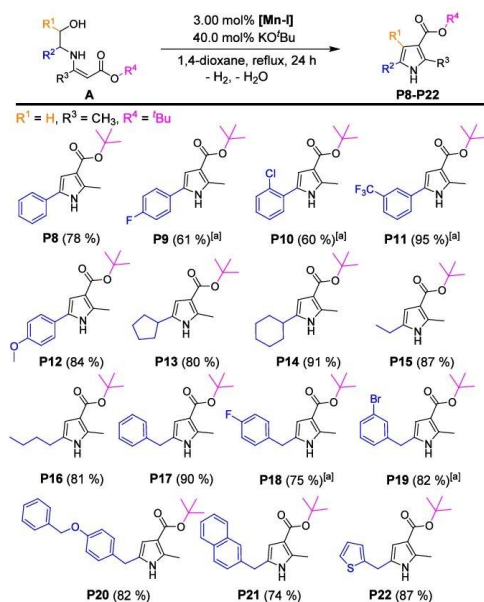


Figure 3. Synthesis of 2,3,5-substituted pyrroles—variation of R^2 . Reaction conditions: 1.00 equiv β -hydroxy enamine **A**, 40.0 mol % KO^tBu , 3.00 mol % $[\text{Mn-I}]$, 1,4-dioxane (0.10 M), then reflux for 24 h; reflux conditions: open system under argon atmosphere. [a] Dehydration reaction was carried out at 90 °C for 24 h, open system under argon atmosphere. Isolated yields in brackets.

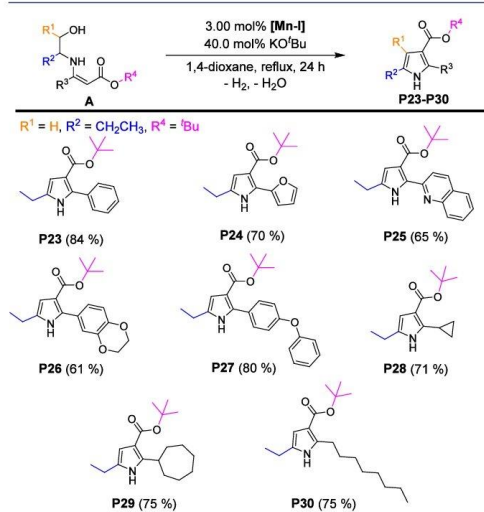


Figure 4. Synthesis of 2,3,5-substituted pyrroles—variation of R^3 . Reaction conditions: 1.00 equiv β -hydroxy enamine **A**, 40.0 mol % KO^tBu , 3.00 mol % $[\text{Mn-I}]$, 1,4-dioxane (0.10 M), then reflux for 24 h; reflux conditions: open system under argon atmosphere. Isolated yields in brackets.

sized aromatic heterocycles were introduced, and the corresponding substrates were isolated in yields up to 70% (**P24** and **P25**, Figure 4). Pyrrole derivative **P26** containing an acetal moiety could be isolated in a 61% yield (Figure 4). A phenoxy group was introduced with an 80% yield (**P27**, Figure 4). In addition, several alkyl moieties, such as a cyclopropyl, cycloheptyl, and octanoyl group could be tolerated, and the corresponding pyrroles could be isolated in yields up to 75% (**P28–P30**, Figure 4).

A catalytic two-step sequence was developed next (Figure 5). Therefore, not only the catalytic dehydrogenation step itself

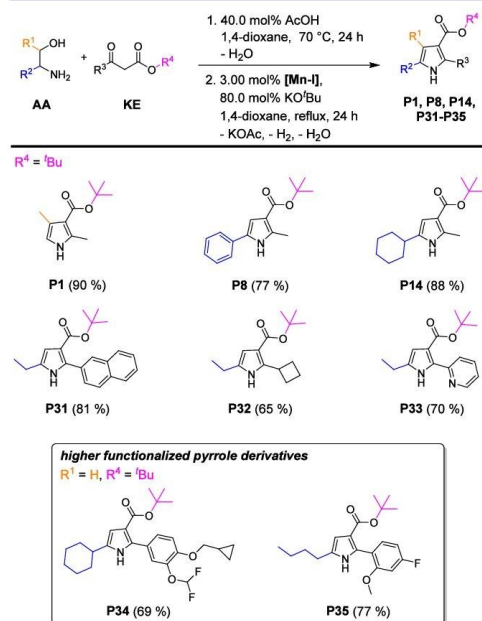


Figure 5. Catalytic one-pot sequence for the synthesis of 2,3,5-substituted pyrroles; variation of R^1 , R^2 , and R^3 . Reaction conditions: step one: 1.00 equiv 1,3-keto ester, 1.10 equiv 1,2-amino alcohol, 40.0 mol % AcOH , 1,4-dioxane (1.00 M), 70 °C, 24 h. Step two: 80.0 mol % KO^tBu , 3.00 mol % $[\text{Mn-I}]$, 1,4-dioxane (0.10 M), then reflux for 24 h; reflux conditions: open system under an argon atmosphere.

was considered, but a simplified synthesis of the intermediate products was also developed, and an additional substrate scope was prepared. Accordingly, different alkyl and aryl moieties were tested and introduced, which led to the isolation of **P1**, **P8**, and **P13** in yields up to 90% (Figure 5). Pyrrole derivative **P31** was synthesized in an 81% yield by using a 1,3-keto ester with a sterically demanding naphthoyl group (Figure 5). Introducing a cyclobutyl group or a pyridinyl moiety led to the isolation of **P32** and **P33** in a 65 and 70% yield, respectively (Figure 5). Higher functionalized compounds **P34** and **P35** could be isolated in a 69 and 77% yield, respectively (Figure 5).

Different commercially available drug molecules were converted into the corresponding *tert*-butyl, 5-phenyl-1*H*-pyrrole-3-carboxylate derivatives in the further course of this

work. Ibuprofen (NSAID) could be transferred in the desired product P36 in a 69% yield (Figure 6), naproxen (NSAID)

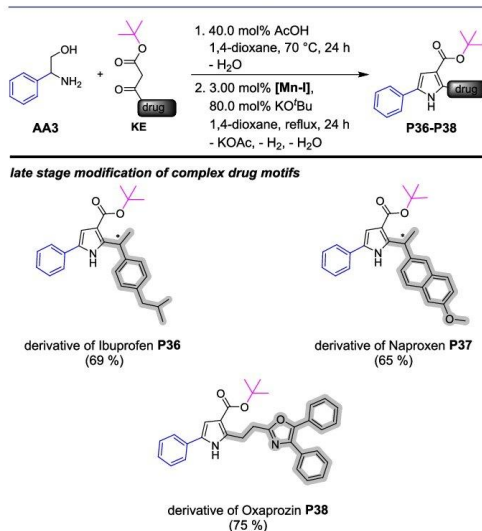


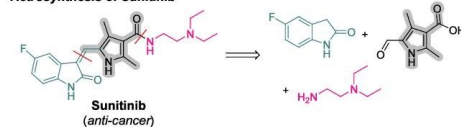
Figure 6. Catalytic one-pot sequence for the synthesis of 2,3,5-substituted pyrroles; modification of different drug molecules. Reaction conditions: step one: 1.00 equiv 1,3-keto ester, 1.10 equiv 1,2-amino alcohol, 40.0 mol % AcOH, 1,4-dioxane (1.00 M), 70 °C, 24 h. Step two: 80.0 mol % KO^tBu, 3.00 mol % [Mn-I], 1,4-dioxane (0.10 M), then reflux for 24 h; reflux conditions: open system under an argon atmosphere. Isolated yields are given in brackets.

could be isolated as the corresponding pyrrole derivative P37 in a 65% yield (Figure 6), and oxaprozin (NSAID) was modified and smoothly converted in P38 in a 75% yield (Figure 6).

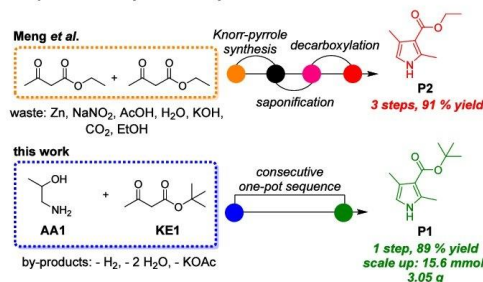
Synthesis of Sunitinib. Building block P1, which can be used to synthesize sunitinib (anticancer drug, Figure 7, top), was synthesized on a large scale. Compared to the three-step synthesis for intermediate P2 described in the literature, P1 can be produced in a single consecutive step using the newly developed method.⁶⁷ This avoids complex purification steps and the formation of equimolar amounts of waste (Figure 7, mid). The target molecule sunitinib was synthesized in four consecutive steps starting from P1 (Figure 7, bottom). The α position of intermediate P1 can be formylated under very mild conditions, thereby introducing a reactive aldehyde group (P1 $\rightarrow$ 1). The *tert*-butyl ester group can easily be transformed into the corresponding acid by using TFA (1 $\rightarrow$ 2, 85% yield over two steps). An amide coupling reaction was then carried out to form the desired amide derivative (2 $\rightarrow$ 3, 92% yield). Finally, a Knoevenagel condensation under basic conditions yielded the compound desired (3 $\rightarrow$ sunitinib, 90% yield, Figure 7, bottom).

Synthesis of Pyridine Derivatives (Scope). The synthesis of pyridine derivatives P39–P43 was accomplished by extending the methodology developed using different 1,3-amino alcohols (Figure 8). Note, two equiv of hydrogen are generated per pyridine molecule here. The substrates P39–P43 could be isolated in yields up to 87% (Figure 8). The

Retrosynthesis of Sunitinib



Comparison of the synthesis of key intermediates P1 and P2



Synthesis of Sunitinib starting from P1

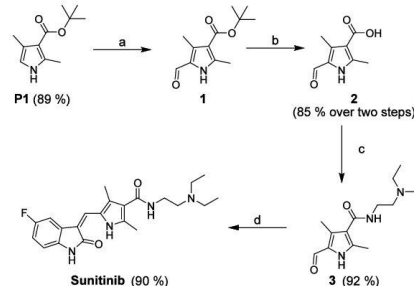


Figure 7. Retrosynthesis of sunitinib (top). Comparison of the syntheses of both key intermediates P1 and P2 (mid). Synthesis of sunitinib starting from P1 (bottom). Reaction conditions for the scale-up synthesis of P1: Step one: 17.50 mmol KE1 (1.00 equiv), 21.0 mmol AA1 (1.20 equiv), 40.0 mol % AcOH, 1,4-dioxane (1.00 M), 70 °C, 24 h. Step two: 80.0 mol % KO^tBu, 4.00 mol % [Mn-I], 1,4-dioxane (0.10 M), then reflux for 48 h; reflux conditions: open system under argon atmosphere. Reaction conditions for the synthesis of sunitinib: (a) POCl₃, DMF, CH₂Cl₂, 0 °C $\rightarrow$ reflux 90 min; (b) TFA, CH₂Cl₂, rt 24 h; (c) EDC•HCl, HOBT, NEt₃, N¹,N¹-diethylethane-1,2-diamine, DMF, rt, 24 h; (d) 5-fluorindolin-2-one, cat. piperidine, toluene, reflux, and 3 h.

methodology is flexible with respect to the introduction of aryl and alkyl substituents and can address the 2,3,5 and 6-position of the pyridine ring (Figure 8). The general synthesis of nicotinic acid derivatives via acetylation chemistry is challenging, and classic nicotinic acid synthesis, for example, requires harsh conditions such as high temperature, high pressure, and the use of HNO₃ as an oxidizing agent. This results in the release of large quantities of nitric oxides and carbon dioxide.⁶⁸

Mechanistic Studies. Finally, we became interested in the mechanism of our reaction. The proposed mechanism is shown in Figure 9. The steps for the catalytic cycle are observable by spectroscopic methods, such as nuclear magnetic resonance. First, the catalytic active species [Mn]K is formed by the reaction of precatalyst [Mn-I] with two equivalents of KO^tBu.

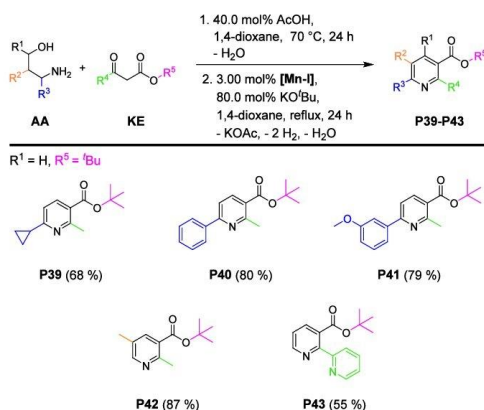


Figure 8. Catalytic one-pot sequence for the synthesis of 2,3,5,6-substituted pyridines; variation of R^2 , R^3 , and R^4 . Reaction conditions: step one: 1.00 equiv of 1,3-keto ester, 1.10 equiv of 1,3-amino alcohol, 40.0 mol % AcOH, 1,4-dioxane (1.00 M), 70 °C, 24 h. Step two: 80.0 mol % KOtBu, 3.00 mol % [Mn-I], 1,4-dioxane (0.10 M), then reflux for 24 h; reflux conditions: open system under an argon atmosphere.

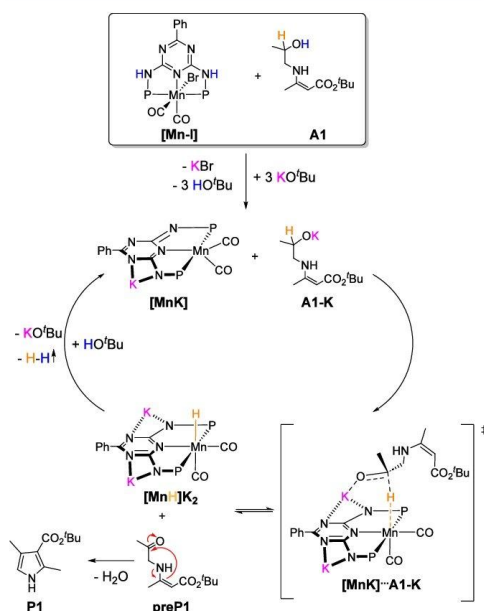


Figure 9. Proposed catalytic cycle and formation of P1. [Mn]K is simplified as a monomeric dearomatized structure, and solvent molecules are omitted for clarity. $P = P(Pr)_2$.

The third equivalent of KOtBu forms the salt A1-K.^{69,70} A1-K transfers the hydride and the potassium in an outer-sphere manner ([Mn]K⁺A1-K) to form the doubly metalated hydride [MnH]K₂ and preP1, which reacts in an intramolecular cyclodehydration to form the desired pyrrole derivative P1.

Subsequently, [MnH]K₂ reacts with HOtBu to yield dihydrogen, KOtBu, and [Mn]K, thereby closing the catalytic cycle. We collected and quantified the hydrogen formed for one of the pyrroles (P1, 80% of 1 equiv of H₂) and for one of the pyridines (P42, 78% of 2 equiv of H₂). The pyridine synthesis proceeds similarly, giving rise to dihydropyridine intermediates as concluded from NMR studies. Dehydrogenation of a polar C–N bond of the dihydropyridine intermediates leads to the final product.⁶⁹ See Supporting Information (Supplementary Figure 39) for a scheme of the mechanism proposed.

CONCLUSIONS

We report a catalytic version of the Knorr pyrrole synthesis in which simple and diversely available starting materials, such as 1,2-amino alcohols or 1,3-amino alcohols and keto esters, permit access to pyrrole or pyridine derivatives, respectively. The products are very important classes of compounds; hydrogen is generated during our reaction and can be collected, and an inexpensive and easy-to-synthesize Mn compound catalyzes the dehydrogenation step efficiently. We feel that the thermal robustness of the Mn catalysts employed here is the key to mediating the dehydrogenation steps.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.4c13266>.

Materials and experimental procedures, spectroscopic data, and mechanistic studies (PDF)

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Notes

The authors declare no competing financial interest.

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Supporting Information

A Catalytic Version of the Knorr Pyrrole Synthesis Permits Access to Pyrroles and Pyridines

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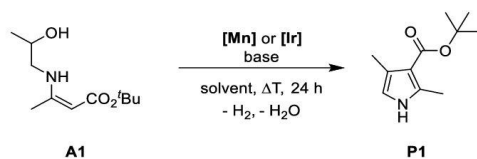
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1 Materials and methods

All reactions and manipulations with air sensitive compounds being present were performed under dry argon (Ar 5.0) or nitrogen (N₂ 5.0), using SCHLENK and glove box techniques. Non-halogenated solvents were dried over sodium benzophenone, 2-methyl tetrahydrofuran (2-Me-THF) and tetrahydrofuran (THF) were dried over calcium hydride and LiAlH₄, and halogenated solvents were dried over P₂O₅. Deuterated solvents were bought from Cambridge Isotope Laboratories, distilled accordingly, and stored over molecular sieves (3 Å). Other chemicals were purchased from commercial vendors and used without further purification. NMR spectra were collected on a Varian INOVA 300 MHz / 400 MHz spectrometer or on a Bruker Avance III HD 500 MHz. Chemical shifts (δ) are reported in ppm relative to residual solvent signal CDCl₃: 7.26 ppm (¹H), 77.16 ppm (¹³C), DMSO-d₆: 2.50 ppm (¹H), 39.51 ppm (¹³C), THF-d₈: 1.72 ppm, 3.58 ppm (¹H), 67.21 ppm, 25.31 ppm (¹³C) and CD₂Cl₂: 5.32 ppm (¹H), 53.5 ppm (¹³C). Coupling constants (*J*) are given in Hz (coupling patterns: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). GC analyses were carried out using an Agilent Technologies 6890N system equipped with a Macherey-Nagel (MN) Optima 5 HT column (30 m, 320 μ m, 0.25 μ m) or an Agilent Technologies 6850 system equipped with a MN Optima 17 column (30 m, 320 μ m, 0.25 μ m). GC/MS analyses were carried out on an Agilent 7890A/MSD 5975C system equipped with a HP-5MS column (30 m, 320 μ m, 0.25 μ m). For column chromatography, MN silica gel 60 (0.040–0.063 mm particle size) was used. All organic compounds were characterized by ¹H and ¹³C NMR analysis. Unknown compounds or compounds with incomplete spectroscopic literature data were additionally analysed via LC-HRMS. Liquid chromatography-high resolution mass spectra (LC-HRMS) were obtained from a Thermo Fisher scientific Q-Exactive instrument with a hybrid quadrupole orbitrap analyser in ESI+ mode.

2 Screenings for the Catalytic Synthesis of **P1**Supplementary Figure 1: Synthesis of **P1** starting from **A1**.Supplementary Table 1: Base screening.^[a]

Entry	Base	P1 [%] ^[b]
1	NaO ^t Bu	16
2	KO^tBu	20
3	LiO ^t Bu	0
4	NaOH	0
5	KOH	0
6	LiOH	0
7	NaHMDS	0
8	KHMDS	0
9	LiHMDS	0

[a] Reaction conditions: 0.50 mmol **A1**, 0.50 mmol base (100 mol%), 0.30 mol% **[Mn-I]**, THF (0.10 M, 5.00 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 2: Solvent screening.^[a]

Entry	Solvent	P1 [%] ^[b]
1	CPME	18
2	1,4-dioxane	32
3	toluene	0
4	2-Me-THF	21
5	THF	20

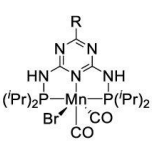
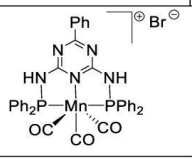
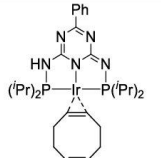
[a] Reaction conditions: 0.50 mmol **A1**, 0.50 mmol KO^tBu (100 mol%), 0.30 mol% **[Mn-I]**, solvent (0.10 M, 5.00 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 3: KO^tBu loading screening.^[a]

Entry	KO ^t Bu loading [mol%]	P1 [%] ^[b]
1	5.00	28
2	10.0	29
3	20.0	30
4	30.0	32
5	40.0	42
6	50.0	35
7	60.0	31
8	75.0	20
9	100	0

[a] Reaction conditions: 0.50 mmol **A1**, 0.025 – 0.50 mmol KO^tBu (5.00 - 100 mol%), 0.30 mol% **[Mn-I]**, 1,4-dioxane (0.10 M, 5.00 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 4: Precatalyst screening.^[a]

Entry	Precatalyst	P1 [%] ^[b]
1	[Mn(CO) ₅ Br]	0
2		42
3		30
4		0
5		32
6		0
7		40
8		36
9		40

[a] Reaction conditions: 0.50 mmol **A1**, 0.20 mmol KO^tBu (40.0 mol%), 0.30 mol% precatalyst, 1,4-dioxane (0.10 M, 5.00 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 5: Precatalyst **[Mn-I]** loading.^[a]

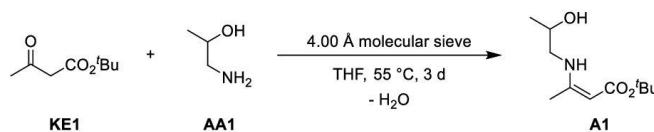
Entry	Amount of [Mn-I] [mol%]	P1 [%] ^[b]
1	0.30	42
2	0.50	39
3	1.00	55
4	2.00	83
5	2.50	84
6	3.00	92

[a] Reaction conditions: 0.50 mmol **A1**, 0.20 mmol KO^tBu (40.0 mol%), 0.30 – 3.00 mol% **[Mn-I]**, 1,4-dioxane (0.10 M, 5.00 mL), reflux conditions, open system under argon atmosphere; [b] Determined by GC with dodecane as an internal standard.

3 Synthesis of Ligands and / or Complexes

The ligands and precatalysts **[Mn-I]**–**[Mn-VII]**^{[1],[2],[3],[4]} and **[Ir-I]**^[5] were synthesized according to published procedures.

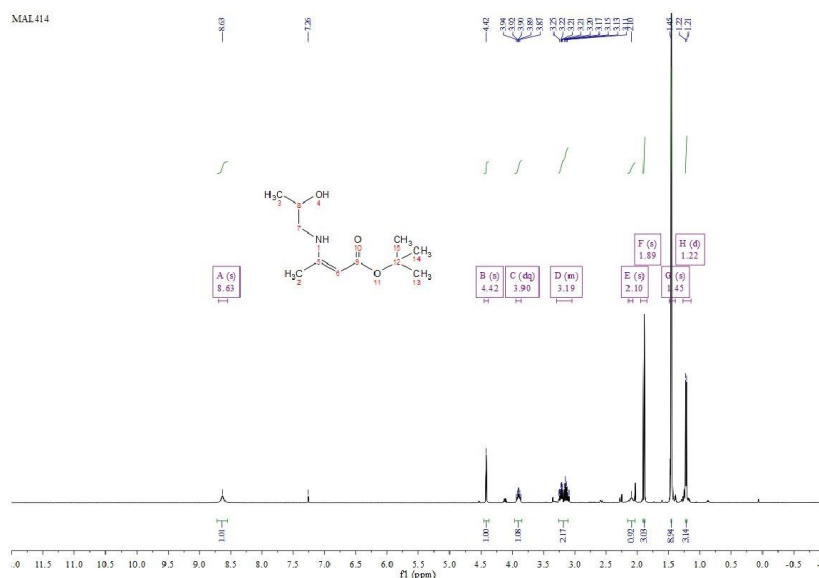
4 General Synthesis of β -Hydroxy Enamine **A1**

Supplementary Figure 2: Synthesis of β -hydroxy enamine **A1**.

General reaction conditions for the synthesis of β -hydroxy enamine **A1 (GP1):** In a SCHLENK tube *tert*-butyl acetoacetate (**KE1**, 1.00 equiv.) and 1-amino-2-propanol (**AA1**, 1.01 equiv.) are dissolved in THF (1.00 M). Molecular sieve (4.00 Å, 0.50 g / mmol) is added and the reaction mixture is heated to 55 °C for 3 days. After cooling the reaction to room temperature, the resulting molecular sieve dust is centrifuged off and the supernatant solution is decanted off and diluted with ethyl acetate. The organic phase is washed with NH₄Cl : brine : water (1:1:1) two times. The aqueous phase is extracted with ethyl acetate two times. The combined organic phases are dried over MgSO₄ and the

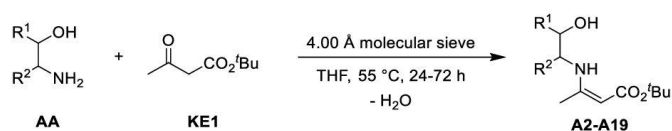
solvent is evaporated under reduced pressure. The desired product is used without further purification.

¹H NMR (CDCl₃, 400 MHz, 293 K): δ = 8.63 (s, 1H), 4.42 (s, 1H), 3.90 (dq, *J* = 12.7, 6.4 Hz, 1H), 3.25 – 3.11 (m, 2H), 2.10 (s, 1H), 1.89 (s, 3H), 1.45 (s, 9H), 1.22 (d, *J* = 6.4 Hz, 3H) ppm.



Supplementary Figure 3: ¹H NMR of **A1** in CDCl₃.

5 General Synthesis of β-Hydroxy Enamines **A2-A19**



Supplementary Figure 4: Synthesis of β-hydroxy enamines **A2-A19**.

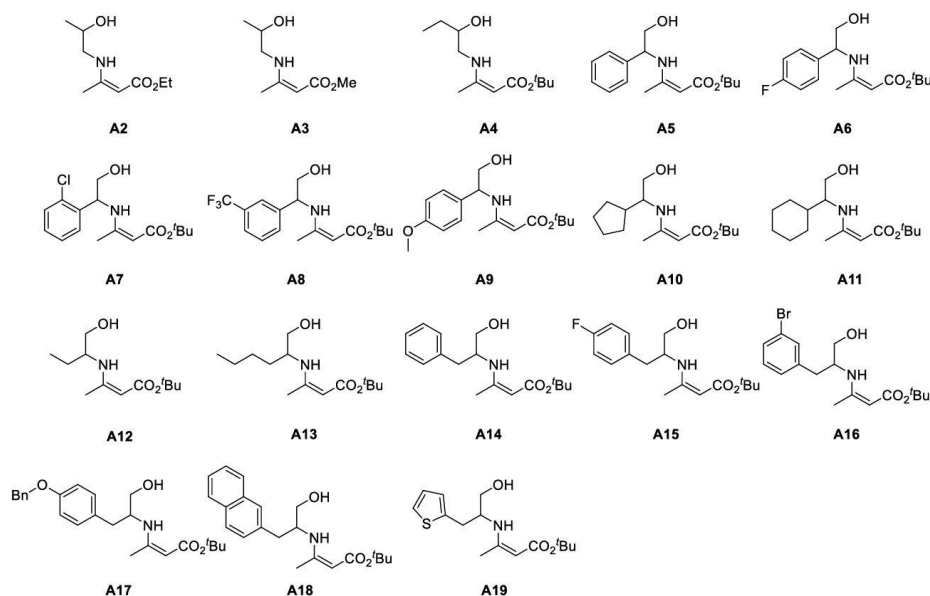
General reaction conditions for the synthesis of β-hydroxy enamines **A2-A19 (GP2):**

In a SCHLENK tube *tert*-butyl acetoacetate (**KE1**, 1.00 equiv.) and the corresponding 1,2-

amino alcohol **AA** (1.01 equiv.) are dissolved in THF (1.00 M). 4.00 Å molecular sieve (0.50 g / mmol) is added and the reaction mixture is heated to 55 °C for 24-72 h.

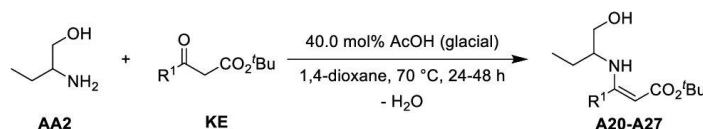
After cooling the reaction to room temperature, the resulting molecular sieve dust is centrifuged off and the supernatant solution is decanted off and diluted with ethyl acetate.

The organic phase is washed with NH₄Cl : brine : water (1:1:1) two times. The aqueous phase is extracted with ethyl acetate two times. The combined organic phases are dried over MgSO₄ and the solvent is evaporated under reduced pressure. The desired product is used without further purification. All β -hydroxy enamine derivatives were checked by ¹H and ¹³C NMR spectroscopy before use.



Supplementary Figure 5: Overview of β -hydroxy enamines **A2-A19**.

6 General Synthesis of β -Hydroxy Enamines **A20-A27**



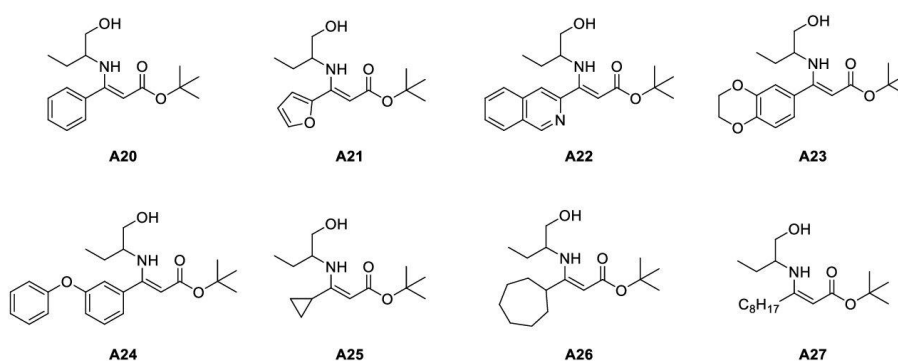
Supplementary Figure 6: Synthesis β -hydroxy enamines **A20-A27**.

General reaction condition for the synthesis of β -hydroxy enamines A20-A27 (GP3):

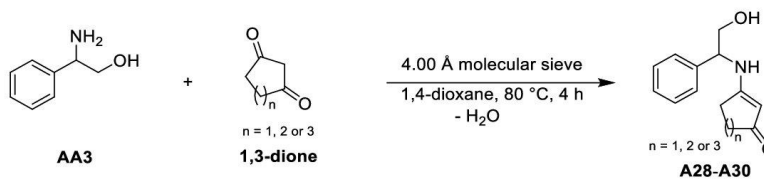
In a SCHLENK tube the acetoacetate derivative **KE** (1.00 equiv.) and 1-amino-2-butanol (**AA2**, 1.10 equiv.) are dissolved in 1,4-dioxane (1.00 M).

The mixture is cooled to 0 °C and acetic acid (40.0 mol%) is slowly added. The solution is stirred for 15 minutes at 0 °C before it is warmed to room temperature and then stirred at 70 °C for 24 - 48 h. The reaction solution is dissolved in EtOAc. The organic phase is washed with NaHCO₃ : brine : water (1:1:1) three times. The aqueous phase is extracted with EtOAc two times. The combined organic phases are dried over Na₂SO₄ and the solvent is evaporated under reduced pressure.

The desired product is used without further purification. All β -hydroxy enamine derivatives were checked by ¹H and ¹³C NMR spectroscopy before use.



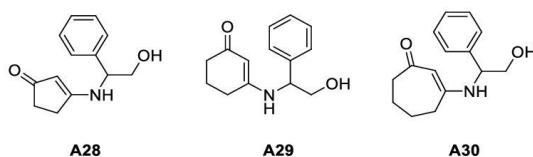
Supplementary Figure 7: Overview of β -hydroxy enamines **A20-A27**.

7 Synthesis of β -Hydroxy Enamines from 1,3-Diones

Supplementary Figure 8: Synthesis β -hydroxy enamines **A28-A30**.

Synthesis of β -hydroxy enamines from 1,3-diones (GP4): In a SCHLENK tube the corresponding 1,3-dione (5.00 mmol, 1.00 equiv.) and 1,2-amino alcohol **AA3** (693 mg, 5.05 mmol, 1.01 equiv.) are dissolved in 1,4-dioxane (7.50 mL, 0.67 M). Molecular sieve (4.00 Å, 2.50 g, 0.50 g / mmol) is added and the mixture is stirred at 80 °C for 4 h.

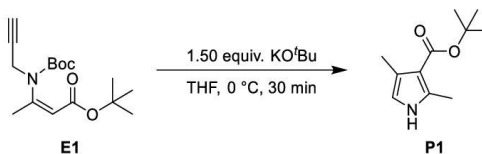
The resulting molecular sieve dust is centrifuged off and the supernatant solution is decanted off and diluted with ethyl acetate. The solvent is evaporated under reduced pressure to give the crude product. Column chromatography (ethyl acetate/methanol 99:1) finally gives the products in the desired purity (yields >99%). The ^1H NMR-analysis shows the presence of E/Z mixtures.



Supplementary Figure 9: Overview of β -hydroxy enamines **A28-A30**.

8 Synthesis of *tert*-Butyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**P1**)

To analyse for possible reaction intermediates, to obtain spectroscopic and gas chromatographic data for reference values, the screening substrate *tert*-butyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**P1**) was synthesized.



Supplementary Figure 10: Synthesis of **P1** via intramolecular cyclization.

General reaction conditions for the synthesis of *tert*-butyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate **P1 (GP5):** Referring to the literature^[6], a slightly modified synthesis protocol was used. In a SCHLENK tube the corresponding *N*-Boc-*N*-propargyl enamine **E1** (1.00 equiv.) was slowly added to a solution of KO^tBu (1.50 equiv.) in THF (0.25 M) at 0 °C. The resulting orange/brown solution is stirred at 0 °C for 30 minutes.

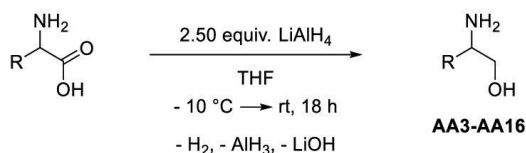
After evaporation of the solvent (**caution: some side products have an extreme powerful sweet smell!**) the remaining oily solution is diluted with ethyl acetate and washed with NH_4Cl : brine : water (1:1:1) two times. The aqueous phase is extracted with ethyl acetate two times. The combined organic phases are dried over MgSO_4 and the remaining solvent is evaporated under reduced pressure to obtain the crude product. Purification with column chromatography (*n*-pentane $\rightarrow$ ethyl acetate = 9:1 or 8:2) or recrystallization from EtOAc / *n*-pentane yields **P1** in the desired purity.

^1H NMR (CDCl_3 , 400 MHz, 293 K): δ = 8.05 (s, 1H), 6.33 (s, 1H), 2.46 (s, 3H), 2.22 (s, 3H), 1.56 (s, 9H) ppm.

^{13}C NMR (CDCl_3 , 125 MHz, 293 K): δ = 165.86, 135.47, 121.51, 114.14, 112.27, 79.34, 28.75, 14.27, 12.88 ppm.

The spectroscopic data corresponds to those in the literature.^[6]

9 Synthesis of 1,2-Amino Alcohols from Amino Acids



Supplementary Figure 11: Synthesis of 1,2-amino alcohols **AA3-AA16**.

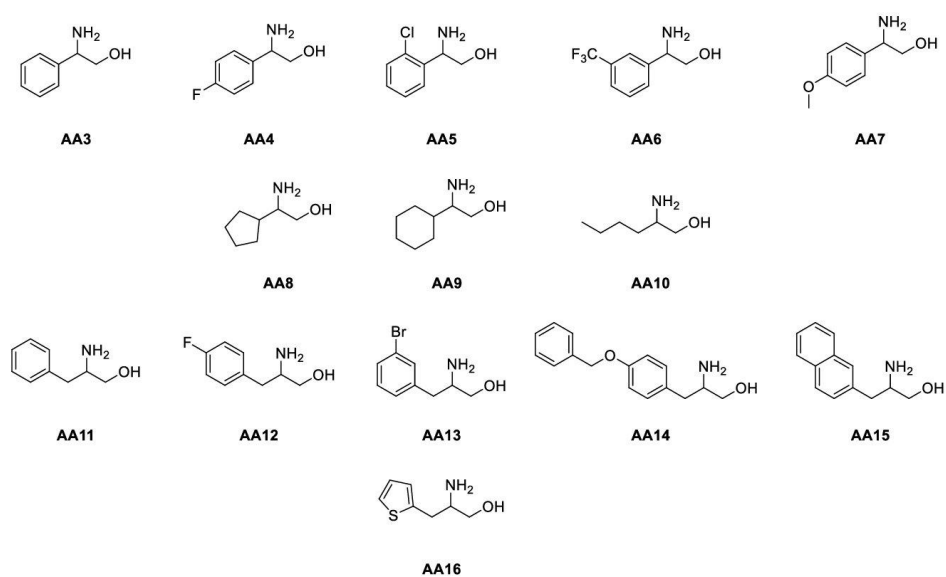
General reaction conditions for the synthesis of 1,2-amino alcohols (GP6): Referring to the literature^[7], a slightly modified synthesis protocol was used. In a SCHLENK tube the corresponding amino acid is suspended in THF (0.50 M). The solution is cooled to -10 °C and stirred for 15 minutes. LiAlH_4 (2.50 equiv.) is slowly added in portions to the reaction mixture. The reaction solution is slowly warmed up to room temperature and stirred for 24 h. A gas bubbler is used to liberate the resulting H_2 .

Work-up: Work-up for a reaction containing for example 3.00 g LiAlH_4 .

To quench the reaction, the mixture was cooled to 0 °C and diluted with diethyl ether (2.00 – 3.00 the amount of THF used for the reaction itself). A solution of water / 2-propanol (1:1, 3.00 mL) was slowly added. In addition, 1.00 M NaOH (1.50 mL) was slowly added to the solution. Water / 2-propanol (1:1, 9.00 mL) were added to the mixture before it was warmed to room temperature and MgSO_4 (15.00 g) were added.

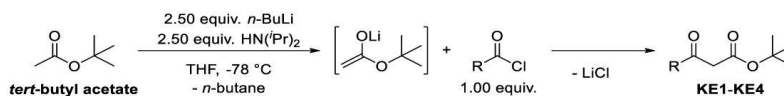
Filter the reaction mixture and wash the filter cake with EtOAc (3x).

Evaporate the solvent under reduced pressure and if the product is a solid; recrystallize the resulting 1,2-amino alcohol from EtOAc / *n*-pentane to obtain the product in the desired purity. All 1,2-amino alcohol derivatives were checked by ^1H and ^{13}C NMR spectroscopy before use.



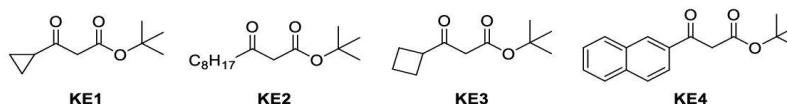
Supplementary Figure 12: Overview of 1,2-amino alcohols **AA3-AA16**.

11 Synthesis of 1,3-Keto Esters from Carbonyl Chlorides

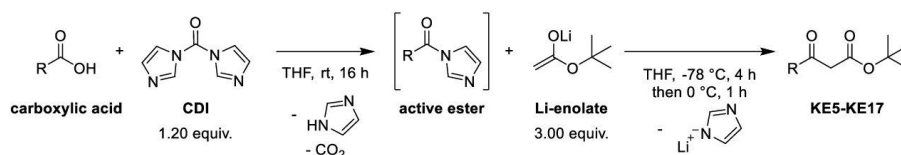
Supplementary Figure 13: Synthesis of 1,3-keto esters **KE1-KE4** from carbonyl chlorides.

General reaction conditions for the synthesis of 1,3-keto esters from carbonyl chlorides (GP7): In a SCHLENK tube diisopropylamine (2.50 equiv.) is dissolved in THF (0.50 M). The solution is cooled to -78 °C and stirred for 15 minutes before *n*-BuLi (2.50 equiv., 2.70 M in hexane) is slowly added to the mixture.

The reaction is stirred for 30 minutes. *t*BuOAc (2.50 equiv.) is added and the mixture is stirred for another hour, before the corresponding carbonyl chloride (1.00 equiv.) is slowly added. The formation of the product is monitored by TLC analysis (normally 1 - 3 h reaction time). The reaction is warmed to room temperature and quenched with saturated NH₄Cl solution. The organic phase is washed with NH₄Cl : brine : water (1:1:1) two times and with water. The aqueous phase is extracted with ethyl acetate once. The combined organic phases are washed with brine and dried over Na₂SO₄. The solvents are evaporated under reduced pressure to obtain the crude product. Column chromatography (ethyl acetate / *n*-pentane) yields the 1,3-keto ester in the desired purity. All 1,3-keto ester derivatives were checked by ¹H and ¹³C NMR spectroscopy before use.

Supplementary Figure 14: Overview of 1,3-keto esters **KE1-KE4**.

12 Synthesis of 1,3-Keto Esters from Carboxylic Acids

Supplementary Figure 15: Synthesis of 1,3-keto esters **KE5-KE17** from carboxylic acids.

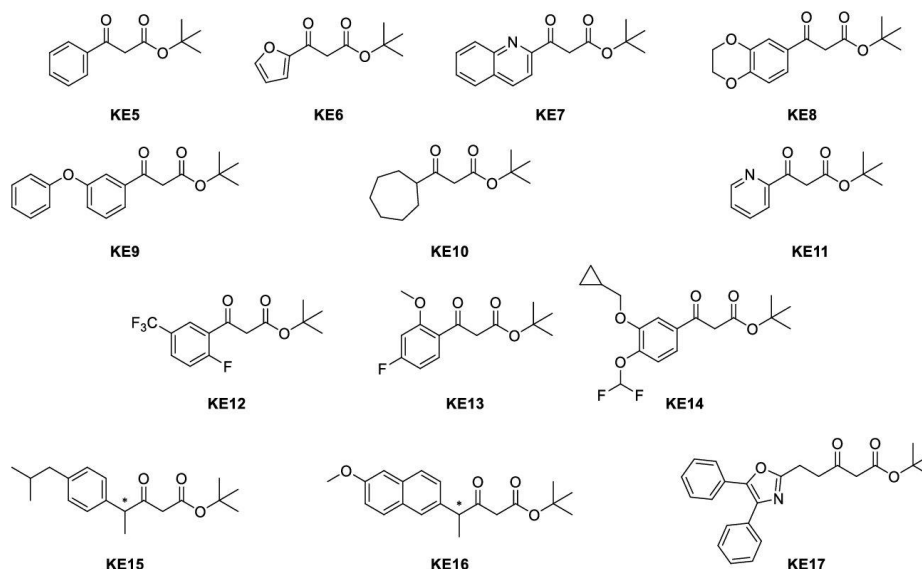
General reaction conditions for the synthesis of 1,3-keto esters from carboxylic acids (GP8): **Solution A:** In a SCHLENK tube carboxylic acid (1.00 equiv.) and *N,N'*-carbonyl diimidazole (1.20 equiv.) are dissolved in THF (0.41 M). The solution is stirred at room temperature overnight. A gas bubbler is used to remove the resulting CO₂ from the reaction solution.

Solution B: In a SCHLENK tube diisopropylamine (3.03 equiv.) is dissolved in THF (1.01 M). After the solution is cooled to -78 °C, *n*-butyllithium (3.00 equiv., 2.70 M in *n*-heptane) is added dropwise.

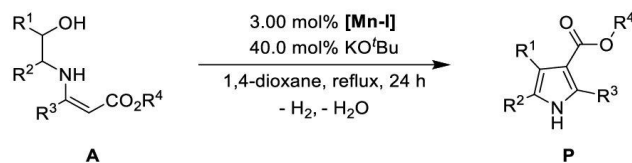
A gas bubbler is used to remove the resulting *n*-butane from the reaction mixture. The solution is stirred for 1 h at -78 °C before *tert*-butyl acetate (3.00 equiv.) is slowly added at -78 °C. The solution is stirred for 1 hour at -78 °C.

Transesterification: At -78 °C, the corresponding active ester from **Solution A** is slowly added to **Solution B**. The mixture is stirred for 4 hours at -78 °C.

Work-up: After warming the reaction mixture to room temperature, the organic phase is dissolved in EtOAc and washed with NH₄Cl : brine : water (1:1:1) two times. The aqueous phase is extracted with ethyl acetate two times. Drying the combined organic phases with Na₂SO₄ and evaporation of the solvent yields the crude product. Column chromatography (ethyl acetate / *n*-pentane) yields the 1,3-keto ester in the desired purity. All 1,3-keto ester derivatives were checked by ¹H and ¹³C NMR spectroscopy before use.

Supplementary Figure 16: Overview of 1,3-keto esters **KE5-KE17**.

13 Synthesis of Pyrrole Derivatives



Supplementary Figure 17: Catalytic synthesis of substituted pyrroles.

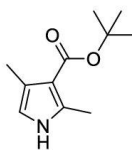
General reaction conditions for the synthesis of substituted pyrrole derivatives

(GP9): In a SCHLENK tube the corresponding β -hydroxy enamine **A** (1.00 equiv.), KO^tBu (40 mol%) and **[Mn-I]** (3.00 mol%) are dissolved in 1,4-dioxane (0.10 M). The solution is stirred at reflux conditions under anaerobic conditions in an open system for 24 h. In case of halogenated substrates, the reaction mixture is stirred at 90 °C under the same conditions. The catalytic reaction is quenched by adding water.

After adding EtOAc, the organic phase is washed with brine : water : NH₄Cl (1:1:1). The aqueous phase is extracted with EtOAc several times and then dried over Na₂SO₄. Removing the solvents under reduced pressure leads to the crude product. Column chromatography finally gives the desired product.

14 Isolation and Characterization of Pyrrole Products

tert-Butyl 2,4-dimethyl-1*H*-pyrrole-3-carboxylate (**P1**)



Chemical Formula: C₁₁H₁₇NO₂
Molecular Weight: 195.26

P1

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless solid (890 μmol, 174 mg, 89 %).

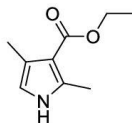
¹H NMR (CDCl₃, 400 MHz, 293 K): δ = 8.05 (s, 1H), 6.33 (s, 1H), 2.46 (s, 3H), 2.22 (s, 3H), 1.56 (s, 9H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 165.86, 135.47, 121.51, 114.14, 112.27, 79.34, 28.75, 14.27, 12.88 ppm.

The spectroscopic data corresponds to those in the literature.^[6]

LC-HRMS (ESI+) *m/z* calculated for [**P1**]⁺: 196.13 found: 196.13256.

CAS Registry Number: 2552374-08-8

Ethyl 2,4-dimethyl-1H-pyrrole-3-carboxylate (P2)

Chemical Formula: C₉H₁₃NO₂
Molecular Weight: 167.21

P2

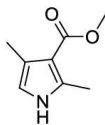
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless solid (470 μ mol, 79 mg, 47 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 10.88 (s, 1H), 6.38 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 2.11 (d, *J* = 1.0 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 165.37, 135.28, 119.51, 114.79, 109.52, 58.24, 14.45, 13.57, 12.67 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P2]⁺: 168.10 found: 168.10137.

CAS Registry Number: 2199-51-1

Methyl 2,4-dimethyl-1H-pyrrole-3-carboxylate (P3)

Chemical Formula: C₈H₁₁NO₂
Molecular Weight: 153.18

P3

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless solid (350 μ mol, 54 mg, 35 %).

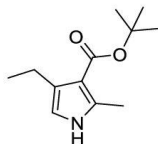
¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 10.90 (s, 1H), 6.39 (s, 1H), 3.66 (s, 3H), 2.35 (s, 3H), 2.10 (s, 3H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 165.81, 135.39, 119.50, 114.87, 109.37, 50.06, 13.57, 12.64 ppm.

LC-HRMS (ESI+) m/z calculated for $[\text{P3}]^+$: 154.08 found: 154.08575.

CAS Registry Number: 52459-90-2

***tert*-Butyl 4-ethyl-2-methyl-1*H*-pyrrole-3-carboxylate (P4)**



Chemical Formula: $\text{C}_{12}\text{H}_{19}\text{NO}_2$
Molecular Weight: 209.29

P4

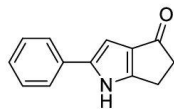
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless liquid (920 μmol , 193 mg, 92 %).

^1H NMR (DMSO- d_6 , 500 MHz, 293 K): δ = 10.81 (s, 1H), 6.38 – 6.31 (m, 1H), 2.54 (qd, J = 7.3, 0.6 Hz, 2H), 2.33 (s, 3H), 1.47 (s, 9H), 1.07 (t, J = 7.4 Hz, 3H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 164.84, 135.02, 126.57, 113.25, 110.09, 77.88, 28.23, 19.89, 15.19, 13.66 ppm.

LC-HRMS (ESI+) m/z calculated for $[\text{P4}]^+$: 210.14 found: 210.14827.

CAS Registry Number: 27172-09-4

2-Phenyl-5,6-dihydrocyclopenta[*b*]pyrrol-4(1*H*)-one (P5)

Chemical Formula: C₁₃H₁₁NO
Molecular Weight: 197.24

P5

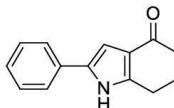
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (1:9)) and obtained as a colourless solid (790 μmol, 156 mg, 79 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 12.02 (s, 1H), 7.68 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 6.60 (s, 1H), 2.98 – 2.93 (m, 2H), 2.78 – 2.72 (m, 2H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 195.59, 160.50, 139.16, 132.13, 128.88, 126.94, 126.87, 124.03, 98.43, 40.96, 20.63 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P5]⁺: 198.09 found: 198.09074.

CAS Registry Number: 2585277-23-0

2-Phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (P6)

Chemical Formula: C₁₄H₁₃NO
Molecular Weight: 211.26

P6

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (EtOAc) and obtained as a colourless solid (970 μmol, 205 mg, 97 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.77 (s, 1H), 7.66 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 1.8 Hz, 1H), 2.83 (t, *J* = 6.2 Hz, 2H), 2.37 – 2.30 (m, 2H), 2.09 – 2.00 (m, 2H) ppm.

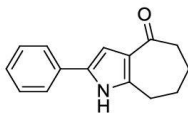
S20

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 192.80, 145.15, 132.15, 131.86, 128.83, 126.43, 123.81, 120.80, 101.60, 37.70, 23.60, 22.21 ppm.

LC-HRMS (ESI+) m/z calculated for **[P6] $^{+}$** : 212.10 found: 212.10638.

CAS Registry Number: 14006-77-0

2-Phenyl-5,6,7,8-tetrahydrocyclohepta[b]pyrrol-4(1H)-one (P7)



Chemical Formula: $\text{C}_{15}\text{H}_{15}\text{NO}$
Molecular Weight: 225.29

P7

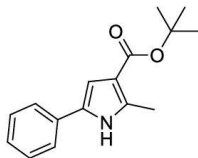
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (n -pentane : EtOAc (3:7)) and obtained as a colourless solid (950 μmol , 214 mg, 95 %).

^1H NMR (DMSO- d_6 , 500 MHz, 293 K): δ = 11.54 (s, 1H), 7.66 – 7.62 (m, 2H), 7.39 – 7.34 (m, 2H), 7.22 – 7.17 (m, 1H), 6.75 (d, J = 2.8 Hz, 1H), 3.01 – 2.96 (m, 2H), 2.60 – 2.55 (m, 2H), 1.91 – 1.85 (m, 2H), 1.83 – 1.77 (m, 2H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 195.80, 140.94, 131.79, 130.53, 128.80, 126.26, 123.70, 123.54, 105.65, 42.68, 26.95, 24.87, 22.28 ppm.

LC-HRMS (ESI+) m/z calculated for **[P7] $^{+}$** : 226.12 found: 226.12198.

R_f-Value: 0.60 (3/7 n -pentane : EtOAc)

***tert*-Butyl 2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate (P8)**

Chemical Formula: C₁₆H₁₉NO₂
Molecular Weight: 257.33

P8

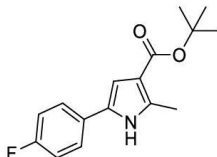
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless solid (770 μ mol, 199 mg, 77 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.51 (s, 1H), 7.61 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.20 – 7.15 (m, 1H), 6.69 (d, *J* = 2.9 Hz, 1H), 2.46 (s, 3H), 1.50 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.20, 135.86, 131.96, 129.23, 128.76, 125.93, 123.41, 113.60, 106.83, 78.38, 28.20, 12.95 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P8]⁺: 258.14 found: 258.14810.

R_f-Value: 0.75 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-(4-fluorophenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (P9)**

Chemical Formula: C₁₆H₁₈FO₂
Molecular Weight: 275.32

P9

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a yellow solid (610 μ mol, 168 mg, 61 %).

S22

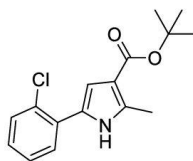
¹H NMR (DMSO-d₆, 500 MHz, 293 K): δ = 11.51 (s, 1H), 7.64 (dd, J = 8.9, 5.4 Hz, 2H), 7.19 (t, J = 8.9 Hz, 2H), 6.66 (d, J = 2.9 Hz, 1H), 2.44 (s, 3H), 1.49 (s, 9H) ppm.

¹³C NMR (DMSO-d₆, 125 MHz, 293 K): δ = 164.17, 161.61, 159.68, 135.82, 128.67, 128.64, 128.38, 125.37, 125.31, 115.69, 115.52, 113.61, 106.79, 78.41, 28.20, 12.94 ppm.

LC-HRMS (ESI+) m/z calculated for [P9]⁺: 276.13 found: 276.13867.

R_f-Value: 0.51 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-(2-chlorophenyl)-2-methyl-1H-pyrrole-3-carboxylate (P10)**



Chemical Formula: C₁₆H₁₈ClNO₂
Molecular Weight: 291.77

P10

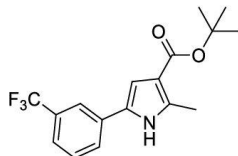
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as an orange solid (600 μ mol, 175 mg, 60 %).

¹H NMR (DMSO-d₆, 500 MHz, 293 K): δ = 11.49 (s, 1H), 7.56 (dd, J = 7.8, 1.4 Hz, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 2.8 Hz, 1H), 2.45 (s, 3H), 1.49 (s, 9H) ppm.

¹³C NMR (DMSO-d₆, 125 MHz, 293 K): δ = 164.13, 135.76, 130.62, 130.51, 129.95, 129.19, 127.92, 127.37, 125.66, 113.32, 111.46, 78.50, 28.18, 12.92 ppm.

LC-HRMS (ESI+) m/z calculated for [P10]⁺: 292.10 found: 292.10920.

R_f-Value: 0.54 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-methyl-5-(3-(trifluoromethyl)phenyl)-1*H*-pyrrole-3-carboxylate (P11)**

Chemical Formula: C₁₇H₁₈F₃NO₂
Molecular Weight: 325.33

P11

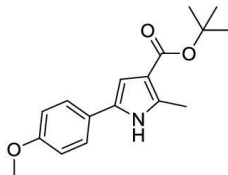
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless solid (950 μ mol, 309 mg, 95 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.74 (s, 1H), 7.98 (s, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 2.5 Hz, 1H), 2.47 (s, 3H), 1.50 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 163.99, 136.73, 132.90, 129.79, 129.53, 127.65, 127.21, 125.65, 122.94, 122.08, 119.37, 113.98, 108.40, 78.56, 28.17 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P11]⁺: 326.13 found: 326.13538.

R_f-Value: 0.63 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate (P12)**

Chemical Formula: C₁₇H₂₁NO₃
Molecular Weight: 287.36

P12

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8.5:1.5)) and obtained as a colourless solid (840 μ mol, 242 mg, 84 %).

S24

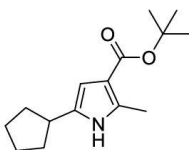
¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.38 (s, 1H), 7.53 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 6.54 (d, *J* = 2.8 Hz, 1H), 3.75 (s, 3H), 2.44 (s, 3H), 1.49 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.32, 157.72, 135.17, 129.29, 124.87, 124.83, 114.21, 113.35, 105.44, 78.28, 55.13, 28.23, 12.94 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P12]⁺: 288.15 found: 288.15847.

R_f-Value: 0.30 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-cyclopentyl-2-methyl-1*H*-pyrrole-3-carboxylate (P13)**



Chemical Formula: C₁₅H₂₃NO₂
Molecular Weight: 249.35

P13

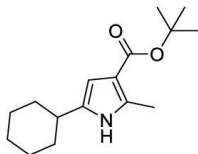
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless oil (800 μ mol, 200 mg, 80 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 10.81 (s, 1H), 5.92 (d, *J* = 2.4 Hz, 1H), 2.84 (p, *J* = 8.1 Hz, 1H), 2.33 (s, 3H), 1.93 – 1.86 (m, *J* = 16.9, 8.8, 4.1 Hz, 2H), 1.69 – 1.63 (m, *J* = 9.1, 6.4, 3.6 Hz, 2H), 1.59 – 1.53 (m, 2H), 1.51 – 1.46 (m, 2H), 1.45 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.54, 133.93, 133.28, 111.29, 104.53, 77.73, 37.74, 32.56, 28.22, 24.57, 12.86 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P13]⁺: 250.17 found: 250.17938.

R_f-Value: 0.75 (8/2 *n*-pentane : EtOAc)

tert-Butyl 5-cyclohexyl-2-methyl-1H-pyrrole-3-carboxylate (P14)

Chemical Formula: C₁₆H₂₅NO₂
Molecular Weight: 263.38

P14

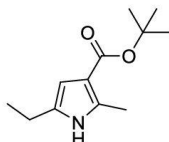
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:10)) and obtained as a colourless solid (910 μ mol, 240 mg, 91 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 10.79 (s, 1H), 5.88 (d, *J* = 2.6 Hz, 1H), 2.42 – 2.35 (m, 1H), 2.32 (s, 3H), 1.88 – 1.83 (m, 2H), 1.72 (dd, *J* = 9.0, 2.9 Hz, 2H), 1.65 (d, *J* = 12.5 Hz, 1H), 1.45 (s, 9H), 1.32 – 1.24 (m, 4H), 1.17 (ddd, *J* = 12.5, 7.8, 3.2 Hz, 1H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.56, 135.59, 132.95, 111.28, 103.93, 77.71, 35.89, 32.57, 28.22, 25.81, 25.68, 12.85 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P14]⁺: 264.19 found: 264.19480.

R_f-Value: 0.5 (8/2 *n*-pentane : EtOAc)

tert-Butyl 5-ethyl-2-methyl-1H-pyrrole-3-carboxylate (P15)

Chemical Formula: C₁₂H₁₉NO₂
Molecular Weight: 209.29

P15

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless oil (870 μ mol, 182 mg, 87 %).

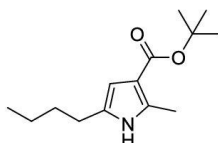
¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 10.84 (s, 1H), 5.92 (d, J = 2.8 Hz, 1H), 2.43 (q, J = 7.5 Hz, 2H), 2.33 (s, 3H), 1.45 (s, 9H), 1.12 (t, J = 7.5 Hz, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.52, 133.07, 131.58, 111.51, 105.31, 77.73, 28.23, 19.97, 13.72, 12.83 ppm.

LC-HRMS (ESI+) m/z calculated for [P15]⁺: 210.14 found: 210.14814.

R_f-Value: 0.58 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-butyl-2-methyl-1*H*-pyrrole-3-carboxylate (P16)**



Chemical Formula: C₁₄H₂₃NO₂
Molecular Weight: 237.34

P16

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless oil (810 μ mol, 193 mg, 81 %).

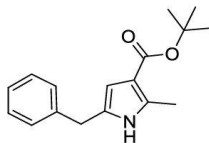
¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 10.81 (s, 1H), 5.91 (d, J = 2.8 Hz, 1H), 2.40 (t, J = 7.6 Hz, 2H), 2.32 (s, 3H), 1.52 – 1.47 (m, 2H), 1.45 (s, 9H), 1.27 (dd, J = 14.9, 7.6 Hz, 2H), 0.87 (t, J = 7.6 Hz, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.52, 133.00, 130.06, 111.57, 106.02, 77.75, 31.21, 28.24, 26.38, 21.71, 13.75, 12.86 ppm.

LC-HRMS (ESI+) m/z calculated for [P16]⁺: 238.17 found: 238.17940.

R_f-Value: 0.60 (8/2 *n*-pentane : EtOAc)

S27

***tert*-Butyl 5-benzyl-2-methyl-1*H*-pyrrole-3-carboxylate (P17)**

Chemical Formula: C₁₇H₂₁NO₂
Molecular Weight: 271.36

P17

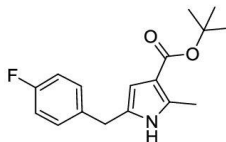
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless solid (900 μmol, 244 mg, 90 %).

¹H NMR (CDCl₃, 500 MHz, 293 K): δ = 7.75 (s, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.20 (d, *J* = 7.4 Hz, 2H), 6.29 (d, *J* = 2.9 Hz, 1H), 3.88 (s, 2H), 2.41 (s, 3H), 1.54 (s, 9H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 165.37, 139.09, 134.33, 128.83, 128.77, 128.42, 126.73, 113.34, 108.56, 79.30, 33.90, 28.63, 13.48 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P17]⁺: 272.16 found: 272.16363.

R_f-Value: 0.64 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-(4-fluorobenzyl)-2-methyl-1*H*-pyrrole-3-carboxylate (P18)**

Chemical Formula: C₁₇H₂₀FO₂
Molecular Weight: 289.35

P18

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a yellow solid (750 μmol, 217 mg, 75 %).

S28

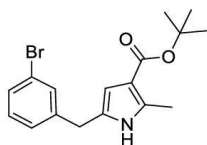
^1H NMR (DMSO- d_6 , 500 MHz, 293 K): δ = 10.97 (s, 1H), 7.26 – 7.17 (m, 2H), 7.16 – 7.05 (m, 2H), 5.94 (d, J = 2.8 Hz, 1H), 3.76 (s, 2H), 2.32 (s, 3H), 1.44 (s, 9H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 164.40, 161.73, 159.81, 136.25, 136.23, 133.81, 130.20, 130.14, 128.79, 115.07, 114.91, 111.85, 107.33, 77.91, 32.11, 28.20, 12.85 ppm.

LC-HRMS (ESI+) m/z calculated for **[P18] $^+$** : 290.15 found: 290.15407.

CAS Registry Number: 1625659-73-5

***tert*-Butyl 5-(3-bromobenzyl)-2-methyl-1H-pyrrole-3-carboxylate (P19)**



Chemical Formula: $\text{C}_{17}\text{H}_{20}\text{BrNO}_2$
Molecular Weight: 350.26

P19

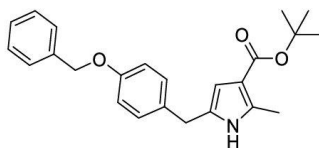
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as an orange solid (820 μmol , 288 mg, 82 %).

^1H NMR (DMSO- d_6 , 500 MHz, 293 K): δ = 7.39 (ddd, J = 7.7, 3.3, 1.6 Hz, 1H), 7.30 – 7.20 (m, 3H), 6.00 (d, J = 2.7 Hz, 1H), 3.77 (d, J = 4.7 Hz, 2H), 2.32 (s, 3H), 1.44 (s, 9H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 164.43, 164.38, 143.06, 140.11, 133.97, 131.08, 128.95, 128.42, 127.58, 126.05, 121.62, 111.82, 107.59, 77.97, 28.21 ppm.

LC-HRMS (ESI+) m/z calculated for **[P19] $^+$** : 349.06 found: 349.06176.

R_f-Value: 0.61 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-(4-(benzyloxy)benzyl)-2-methyl-1*H*-pyrrole-3-carboxylate (P20)**

Chemical Formula: C₂₄H₂₇NO₃
Molecular Weight: 377.48

P20

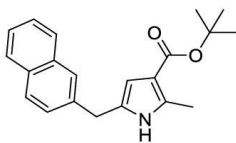
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless solid (820 μ mol, 310 mg, 82 %, contains 1.74 wt% 1,4-dioxane).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 10.93 (s, 1H), 7.44 – 7.42 (m, 2H), 7.38 (dd, *J* = 8.6, 6.8 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 2H), 6.94 – 6.91 (m, 2H), 5.92 (d, *J* = 2.7 Hz, 1H), 5.06 (s, 2H), 3.70 (s, 2H), 2.33 (s, 3H), 1.45 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.45, 156.71, 137.25, 133.68, 132.25, 129.42, 129.34, 128.43, 127.77, 127.61, 114.65, 111.77, 107.11, 77.85, 69.15, 32.16, 28.21, 12.85 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P20]⁺: 378.20 found: 378.20510.

R_r-Value: 0.69 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-methyl-5-(naphthalen-2-ylmethyl)-1*H*-pyrrole-3-carboxylate (P21)**

Chemical Formula: C₂₁H₂₃NO₂
Molecular Weight: 321.42

P21

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless solid (740 μ mol, 238 mg, 74 %).

S30

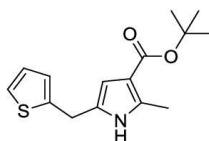
¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.03 (s, 1H), 7.87 – 7.82 (m, 3H), 7.70 (s, 1H), 7.46 (tdd, *J* = 8.4, 6.8, 3.4 Hz, 2H), 7.38 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.01 (d, *J* = 2.8 Hz, 1H), 3.95 (s, 2H), 2.33 (s, 3H), 1.44 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.43, 137.69, 133.87, 133.12, 131.70, 128.77, 127.81, 127.52, 127.38, 126.33, 126.10, 125.42, 111.88, 107.49, 77.91, 33.24, 28.21, 12.87 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P21]⁺: 322.17 found: 322.17896.

R_f-Value: 0.34 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-methyl-5-(thiophen-2-ylmethyl)-1*H*-pyrrole-3-carboxylate (P22)**



Chemical Formula: C₁₅H₁₉NO₂S
Molecular Weight: 277.38

P22

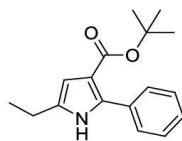
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless solid (870 μ mol, 242 mg, 87 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.04 (s, 1H), 7.32 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.88 – 6.86 (m, 1H), 6.02 (d, *J* = 2.6 Hz, 1H), 3.99 (s, 2H), 2.33 (s, 3H), 1.45 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.38, 142.94, 133.83, 128.23, 126.88, 125.06, 124.23, 111.83, 107.35, 77.96, 28.21, 12.85 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P22]⁺: 278.11 found: 278.11139.

R_f-Value: 0.46 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-ethyl-2-phenyl-1*H*-pyrrole-3-carboxylate (P23)**

Chemical Formula: C₁₇H₂₁NO₂
Molecular Weight: 271.36

P23

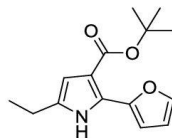
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8.1:1.5)) and obtained as a colourless solid (840 μ mol, 228 mg, 84 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.23 (s, 1H), 7.52 (dt, *J* = 8.2, 1.7 Hz, 2H), 7.40 – 7.36 (m, 2H), 7.33 – 7.28 (m, 1H), 6.16 (d, *J* = 2.8 Hz, 1H), 2.53 (q, *J* = 7.6 Hz, 2H), 1.37 (s, 9H), 1.18 (t, *J* = 7.6 Hz, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 163.98, 134.70, 134.16, 132.61, 129.17, 127.60, 127.20, 112.38, 107.57, 78.27, 28.01, 19.97, 13.73 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P23]⁺: 272.16 found: 272.16365.

R_f-Value: 0.56 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-ethyl-2-(furan-2-yl)-1*H*-pyrrole-3-carboxylate (P24)**

Chemical Formula: C₁₅H₁₉NO₃
Molecular Weight: 261.32

P24

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless solid (700 μ mol, 183 mg, 70 %).

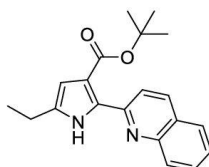
^1H NMR (DMSO- d_6 , 500 MHz, 293 K): δ = 11.49 (s, 1H), 11.49 (s, 1H), 7.70 (dd, J = 1.7, 0.7 Hz, 1H), 7.70 (dd, J = 1.7, 0.7 Hz, 1H), 7.17 (dd, J = 3.4, 0.7 Hz, 1H), 7.17 (dd, J = 3.4, 0.7 Hz, 1H), 6.57 (dd, J = 3.4, 1.8 Hz, 1H), 6.57 (dd, J = 3.4, 1.8 Hz, 1H), 6.14 (d, J = 2.8 Hz, 1H), 6.14 (d, J = 2.8 Hz, 1H), 2.54 (q, J = 7.6 Hz, 2H), 1.47 (s, 9H), 1.16 (t, J = 7.6 Hz, 3H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 163.47, 146.36, 141.59, 134.80, 124.98, 112.03, 111.80, 109.05, 107.61, 78.59, 28.12, 19.85, 13.75 ppm.

LC-HRMS (ESI+) m/z calculated for **[P24] $^+$** : 262.14 found: 262.14343.

R_f-Value: 0.65 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-ethyl-2-(quinolin-2-yl)-1*H*-pyrrole-3-carboxylate (P25)**



Chemical Formula: $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$
Molecular Weight: 322.41

P25

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless oil (650 μmol , 210 mg, 65 %).

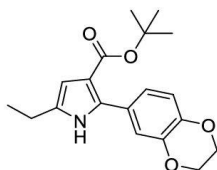
^1H NMR (DMSO- d_6 , 500 MHz, 293 K): δ = 11.66 (s, 1H), 9.35 (s, 1H), 8.66 (s, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.77 (t, J = 7.3 Hz, 1H), 7.65 (t, J = 7.3 Hz, 1H), 6.27 (d, J = 2.6 Hz, 1H), 2.61 (q, J = 7.5 Hz, 2H), 1.47 (s, 9H), 1.20 (t, J = 7.5 Hz, 3H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 164.31, 151.35, 143.59, 135.55, 135.17, 132.90, 127.66, 127.23, 126.94, 126.90, 118.94, 113.68, 109.09, 78.82, 28.08, 19.88, 13.86 ppm.

LC-HRMS (ESI+) m/z calculated for **[P25] $^+$** : 323.17 found: 323.17440.

R_f-Value: 0.48 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-5-ethyl-1*H*-pyrrole-3-carboxylate (P26)**



Chemical Formula: C₁₉H₂₃NO₄
Molecular Weight: 329.40

P26

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (7.5:2.5)) and obtained as a colourless oil (610 µmol, 201 mg, 61 %).

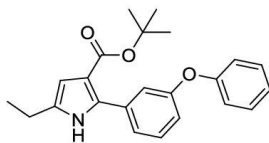
¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.11 (s, 1H), 7.07 (d, *J* = 2.1 Hz, 1H), 7.01 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.11 (d, *J* = 2.7 Hz, 1H), 4.25 (s, 4H), 2.52 (q, *J* = 7.5 Hz, 2H), 1.39 (s, 9H), 1.16 (t, *J* = 7.5 Hz, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.00, 142.80, 142.41, 134.33, 133.69, 125.67, 122.14, 117.87, 116.18, 111.83, 107.49, 78.18, 64.24, 64.10, 28.04, 19.94, 13.71 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P26]⁺: 330.16 found: 330.16935.

R_f-Value: 0.27 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-ethyl-2-(3-phenoxyphenyl)-1*H*-pyrrole-3-carboxylate (P27)**



Chemical Formula: C₂₃H₂₅NO₃
Molecular Weight: 363.46

P27

S34

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless oil (800 μ mol, 291 mg, 80 %).

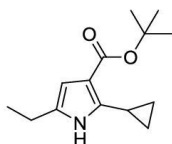
^1H NMR (DMSO- d_6 , 500 MHz, 293 K): δ = 8.34 (d, J = 10.5 Hz, 1H), 7.46 – 7.39 (m, 3H), 7.20 – 7.15 (m, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.08 (ddd, J = 8.4, 2.6, 0.8 Hz, 1H), 7.07 – 7.03 (m, 2H), 6.90 – 6.87 (m, 1H), 3.30 (ddd, J = 16.1, 9.6, 5.2 Hz, 2H), 1.40 (s, 9H), 0.72 (t, J = 7.4 Hz, 3H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 169.14, 163.29, 156.85, 156.14, 138.10, 130.34, 130.20, 123.98, 122.57, 119.14, 119.07, 117.23, 86.25, 77.78, 66.38, 63.52, 56.85, 28.31, 25.41, 10.23 ppm.

LC-HRMS (ESI+) m/z calculated for **[P27] $^+$** : 364.18 found: 364.38139.

R_f-Value: 0.44 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-cyclopropyl-5-ethyl-1H-pyrrole-3-carboxylate (P28)**



Chemical Formula: $\text{C}_{14}\text{H}_{21}\text{NO}_2$
Molecular Weight: 235.33

P28

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless oil (710 μ mol, 167 mg, 71 %).

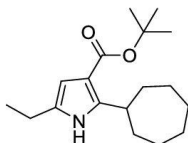
^1H NMR (DMSO- d_6 , 500 MHz, 293 K): δ = 10.29 (s, 1H), 5.90 (d, J = 2.6 Hz, 1H), 2.57 (tt, J = 8.6, 5.5 Hz, 1H), 2.40 (q, J = 7.5 Hz, 2H), 1.46 (s, 9H), 1.09 (t, J = 7.5 Hz, 3H), 0.86 (ddd, J = 8.6, 5.5, 4.1 Hz, 2H), 0.76 – 0.70 (m, 2H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 164.64, 138.94, 131.64, 112.34, 105.42, 77.78, 28.26, 19.89, 13.67, 8.34, 8.04 ppm.

LC-HRMS (ESI+) m/z calculated for [P28]⁺: 236.16 found: 236.16376.

R_r-Value: 0.72 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-cycloheptyl-5-ethyl-1*H*-pyrrole-3-carboxylate (P29)**



Chemical Formula: C₁₈H₂₉NO₂
Molecular Weight: 291.43

P29

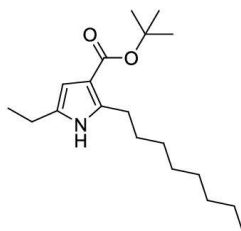
The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless solid (820 μmol, 239 mg, 82 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 10.60 (s, 1H), 5.89 (d, *J* = 2.7 Hz, 1H), 3.52 – 3.46 (m, 1H), 2.44 (q, *J* = 7.5 Hz, 2H), 1.79 – 1.50 (m, 12H), 1.45 (s, 9H), 1.11 (t, *J* = 7.5 Hz, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.47, 143.74, 131.83, 109.29, 105.00, 77.73, 37.46, 34.29, 28.27, 27.24, 26.58, 19.92, 13.57 ppm.

LC-HRMS (ESI+) m/z calculated for [P29]⁺: 292.22 found: 292.22620.

R_r-Value: 0.83 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-ethyl-2-octyl-1*H*-pyrrole-3-carboxylate (P30)**

Chemical Formula: C₁₉H₃₃NO₂
Molecular Weight: 307.48

P30

The desired product was synthesized following **GP9**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless solid (750 μ mol, 231 mg, 75 %).

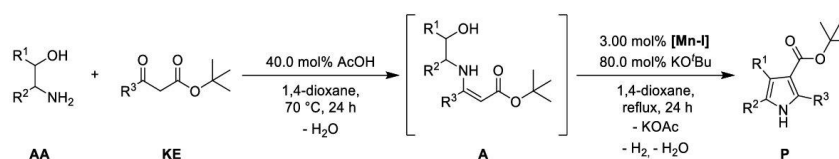
¹H NMR (CD₂Cl₂, 500 MHz, 293 K): δ = 7.38 (s, 1H), 5.51 (d, *J* = 3.0 Hz, 1H), 2.23 – 2.20 (m, 2H), 1.95 – 1.85 (m, 2H), 1.07 – 0.96 (m, 2H), 0.90 (s, 9H), 0.71 – 0.67 (m, 10H), 0.60 – 0.57 (m, 3H), 0.27 (s, 3H) ppm.

¹³C NMR (CD₂Cl₂, 125 MHz, 293 K): δ = 165.42, 138.39, 132.36, 113.03, 106.53, 79.21, 32.42, 30.45, 30.07, 30.01, 29.83, 28.91, 28.75, 27.97, 23.23, 20.98, 14.43, 13.75 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P30]⁺: 308.25 found: 308.25736.

R_f-Value: 0.69 (8/2 *n*-pentane : EtOAc)

15 Catalytic One-pot Synthesis of Pyrrole Derivatives



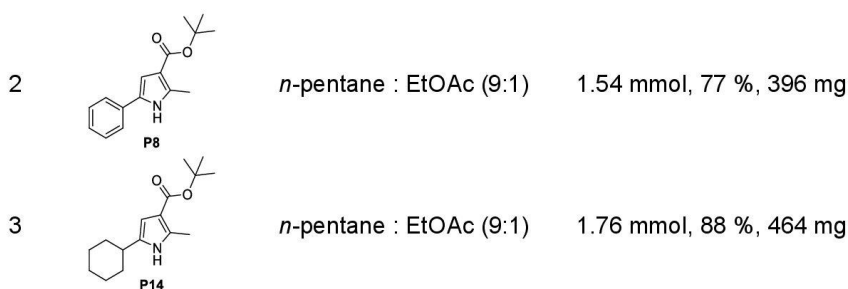
Supplementary Figure 18: Catalytic one-pot synthesis of pyrrole derivatives.

General reaction conditions for the catalytic one-pot synthesis of substituted pyrrole derivatives (GP10): In a SCHLENK tube the corresponding 1,3-keto ester **KE** (2.00 mmol, 1.00 equiv.), 1,2-amino alcohol **AA** (2.20 mmol, 1.10 equiv.) and AcOH (glacial, 0.80 mmol, 40.0 mol%) are dissolved in 1,4-dioxane (2.00 mL, 1.00 M). The mixture is stirred at 70 °C for 24 h.

KOtBu (1.60 mmol, 180 mg, 80.0 mol%) is dissolved in 1,4-dioxane (10.0 mL, 0.16 M). **[Mn-I]** (0.06 mmol, 37.0 mg, 3.00 mol%) is dissolved in 1,4-dioxane (8.00 mL, 7.50×10^{-3} M). The reaction mixture is cooled to room temperature before the KOtBu solution is slowly added. After stirring for 5 minutes the **[Mn-I]**-solution is added. The mixture is stirred at reflux conditions under anaerobic conditions in an open system for 24 h. The catalytic reaction is quenched by adding water. After adding EtOAc, the organic phase is washed with brine : water : NH₄Cl (1:1:1). The aqueous phase is extracted with EtOAc several times. The combined organic phases are dried over Na₂SO₄. Removing the solvents under reduced pressure leads to the crude product. Column chromatography finally gives the desired product.

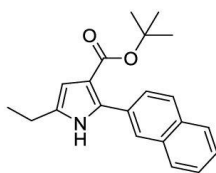
Supplementary Table 6: pyrroles **P1**, **P8** and **P14** synthesized following **GP10**.

Entry	pyrrole	column chromatography	yield ^[a]
1	P1	<i>n</i> -pentane : EtOAc (8:2)	1.80 mmol, 90 %, 352 mg



[a] Isolated yield after following **GP10** and column chromatography.

***tert*-Butyl 5-ethyl-2-(naphthalen-2-yl)-1*H*-pyrrole-3-carboxylate (P31)**



Chemical Formula: C₂₁H₂₃NO₂
Molecular Weight: 321.42

P31

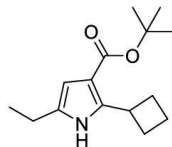
The desired product was synthesized following **GP10**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as a colourless solid (1.62 mmol, 521 mg, 81 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.40 (s, 1H), 8.03 (s, 1H), 7.94 – 7.89 (m, 3H), 7.70 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.54 – 7.48 (m, 2H), 6.23 (d, *J* = 2.7 Hz, 1H), 2.58 (q, *J* = 7.5 Hz, 2H), 1.36 (s, 9H), 1.21 (t, *J* = 7.5 Hz, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.05, 134.56, 134.47, 132.51, 132.09, 130.24, 127.93, 127.91, 127.51, 127.38, 126.72, 126.23, 126.03, 112.86, 107.84, 78.41, 28.01, 20.04, 13.78 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P31]⁺: 322.17 found: 322.17925.

R_f-Value: 0.67 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-cyclobutyl-5-ethyl-1*H*-pyrrole-3-carboxylate (P32)**

Chemical Formula: C₁₅H₂₃NO₂
Molecular Weight: 249.35

P32

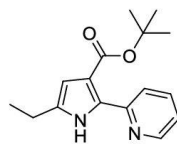
The desired product was synthesized following **GP10**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless liquid (1.30 mmol, 325 mg, 65 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 10.85 (s, 1H), 5.91 (d, *J* = 2.6 Hz, 1H), 4.20 – 4.07 (m, 1H), 2.48 (dd, *J* = 12.7, 5.2 Hz, 2H), 2.21 – 2.13 (m, 4H), 1.91 – 1.84 (m, 1H), 1.78 – 1.71 (m, 1H), 1.45 (s, 9H), 1.13 (t, *J* = 7.5 Hz, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.38, 140.10, 132.39, 110.69, 105.45, 77.79, 31.90, 28.85, 28.19, 19.97, 17.71, 13.73 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P32]⁺: 250.17 found: 250.17943.

R_f-Value: 0.71 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-ethyl-2-(pyridin-2-yl)-1*H*-pyrrole-3-carboxylate (P33)**Chemical Formula: C₁₆H₂₀N₂O₂

Molecular Weight: 272.35

P33

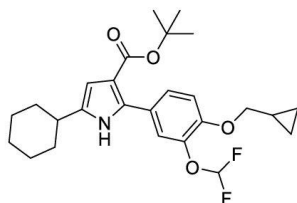
The desired product was synthesized following **GP10**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless liquid (1.40 mmol, 382 mg, 70 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.58 (s, 1H), 8.58 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.21 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.84 – 7.78 (m, 1H), 7.26 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.23 (d, *J* = 2.9 Hz, 1H), 2.57 (q, *J* = 7.5 Hz, 2H), 1.46 (s, 9H), 1.17 (t, *J* = 7.5 Hz, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 164.17, 149.96, 148.54, 136.20, 135.41, 132.69, 123.46, 121.87, 114.02, 108.90, 78.90, 28.03, 19.84, 13.85 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P33]⁺: 273.15 found: 273.15892.

R_f-Value: 0.50 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-cyclohexyl-2-(4-(cyclopropylmethoxy)-3-(difluoromethoxy)phenyl)-1*H*-pyrrole-3-carboxylate (P34)**

Chemical Formula: C₂₆H₃₃F₂NO₄
Molecular Weight: 461.55

P34

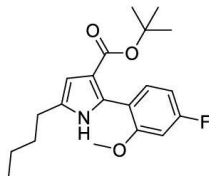
The desired product was synthesized following **GP10**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless solid (1.38 mmol, 637 mg, 69 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.16 (s, 1H), 7.25 (d, *J* = 1.8 Hz, 1H), 7.11 (ddd, *J* = 84.1, 53.6, 41.6 Hz, 3H, ¹⁹F coupling), 6.11 (d, *J* = 2.4 Hz, 1H), 3.92 (d, *J* = 7.0 Hz, 2H), 2.54 – 2.51 (m, 1H), 1.93 (d, *J* = 8.5 Hz, 2H), 1.75 (dd, *J* = 8.7, 2.7 Hz, 2H), 1.38 (s, 9H), 1.37 – 1.22 (m, 6H), 1.19 (dd, *J* = 11.1, 7.9 Hz, 1H), 0.59 – 0.56 (m, 2H), 0.36 – 0.32 (m, 2H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 163.96, 149.00, 138.21, 133.60, 130.81, 121.74, 120.43, 116.72, 115.43, 112.41, 106.16, 78.35, 73.05, 35.96, 32.60, 27.99, 25.89, 10.01, 3.10, 3.05 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P34]⁺: 462.24 found: 462.24362.

R_f-Value: 0.52 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 5-butyl-2-(4-fluoro-2-methoxyphenyl)-1*H*-pyrrole-3-carboxylate (P35)**

Chemical Formula: C₂₀H₂₆FO₃
Molecular Weight: 347.43

P35

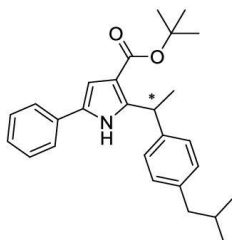
The desired product was synthesized following **GP10**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless oil (1.54 mmol, 535 mg, 77 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 8.52 (dd, *J* = 66.4, 8.2 Hz, 1H, ¹⁹F coupling), 7.19 (t, *J* = 7.4 Hz, 1H), 6.98 (dd, *J* = 11.4, 2.2 Hz, 1H), 6.80 (t, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 1.40 (s, 9H), 1.34 – 0.90 (m, 6H), 0.80 (m, 3H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 169.40, 160.08, 157.20, 130.82, 121.32, 106.81, 106.65, 99.62, 99.41, 85.18, 84.59, 77.33, 55.82, 32.34, 28.39, 21.85, 13.80 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P35]⁺: 348.19 found: 348.19884.

R_f-Value: 0.50 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-(1-(4-isobutylphenyl)ethyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (P36)**

Chemical Formula: C₂₇H₃₃NO₂
Molecular Weight: 403.57

P36

S43

The desired product was synthesized following **GP10**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (95:5)) and obtained as a colourless oil (1.38 mmol, 736 mg, 69 %).

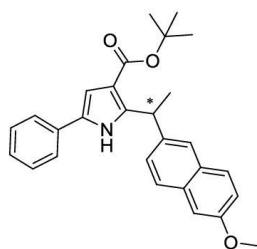
¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.23 (d, *J* = 2.1 Hz, 1H), 7.68 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.68 (d, *J* = 2.7 Hz, 1H), 5.09 (q, *J* = 7.4 Hz, 1H), 2.37 (d, *J* = 7.1 Hz, 2H), 1.98 (d, *J* = 4.3 Hz, 1H), 1.77 (dt, *J* = 13.5, 6.8 Hz, 1H), 1.67 (d, *J* = 7.5 Hz, 3H), 1.46 (s, 9H), 0.83 (d, *J* = 6.6 Hz, 6H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 142.92, 142.29, 138.64, 131.91, 130.42, 129.36, 128.72, 128.60, 127.50, 126.78, 126.22, 124.27, 113.09, 107.29, 78.69, 44.23, 34.87, 29.67, 28.14, 22.19, 22.18, 19.56 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P36]⁺: 404.25 found: 404.25731.

R_f-Value: 0.56 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-(1-(6-methoxynaphthalen-2-yl)ethyl)-5-phenyl-1*H*-pyrrole-3-carboxylate (P37)**



Chemical Formula: C₂₈H₂₉NO₃
Molecular Weight: 427.54

P37

The desired product was synthesized following **GP10**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8.5:1.5)) and obtained as a colourless solid (1.30 mmol, 556 mg, 65 %).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 11.29 (d, *J* = 2.0 Hz, 1H), 7.82 – 7.77 (m, 1H), 7.74 – 7.71 (m, 2H), 7.69 – 7.67 (m, 2H), 7.45 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.36 (t, *J* = 7.8

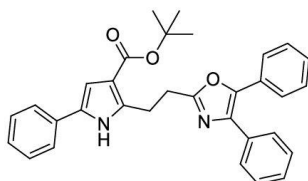
Hz, 2H), 7.33 – 7.29 (m, 1H), 7.20 (t, $J = 7.4$ Hz, 1H), 7.12 (dd, $J = 8.9, 2.5$ Hz, 1H), 6.71 (d, $J = 2.7$ Hz, 1H), 5.25 (q, $J = 7.3$ Hz, 1H), 3.84 (s, 3H), 1.77 (d, $J = 7.4$ Hz, 3H), 1.48 (s, 9H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): $\delta = 164.22, 156.90, 142.83, 139.99, 132.79, 131.89, 130.54, 129.10, 128.60, 128.37, 127.28, 126.76, 126.57, 124.57, 124.29, 118.55, 113.19, 107.35, 105.74, 105.67, 78.78, 55.12, 35.15, 28.17, 19.44$ ppm.

LC-HRMS (ESI+) m/z calculated for $[\text{P37}]^+$: 428.22 found: 428.22101.

R_f-Value: 0.66 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-(2-(4,5-diphenyloxazol-2-yl)ethyl)-5-phenyl-1H-pyrrole-3-carboxylate
(P38)**



Chemical Formula: $\text{C}_{32}\text{H}_{30}\text{N}_2\text{O}_3$
Molecular Weight: 490.60

P38

The desired product was synthesized following **GP10**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8.5:1.5)) and obtained as a colourless solid (1.50 mmol, 736 mg, 75 %).

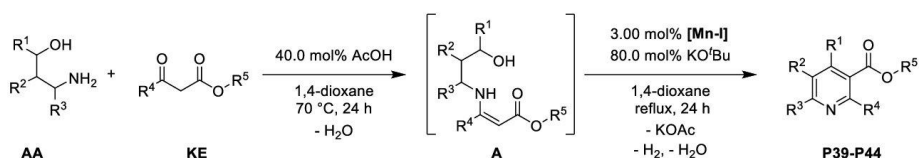
^1H NMR (DMSO- d_6 , 500 MHz, 293 K): $\delta = 11.68$ (d, $J = 2.1$ Hz, 1H), 7.65 (d, $J = 7.3$ Hz, 2H), 7.57 (dd, $J = 5.2, 3.3$ Hz, 2H), 7.51 – 7.48 (m, 2H), 7.42 – 7.34 (m, 9H), 7.20 (t, $J = 7.3$ Hz, 1H), 6.76 (d, $J = 2.8$ Hz, 1H), 3.40 – 3.36 (m, 2H), 3.18 (t, $J = 7.8$ Hz, 2H), 1.50 (s, 9H) ppm.

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): $\delta = 163.93, 162.43, 144.73, 137.90, 134.30, 132.09, 131.85, 129.88, 128.90, 128.82, 128.79, 128.67, 128.51, 128.15, 127.33, 126.43, 126.16, 123.62, 113.94, 107.12, 78.80, 28.17, 28.11, 24.56$ ppm.

LC-HRMS (ESI+) m/z calculated for [P38]⁺: 491.23 found: 491.23163.

R_f-Value: 0.49 (8/2 *n*-pentane : EtOAc)

16 Catalytic One-pot Synthesis of Pyridine Derivatives

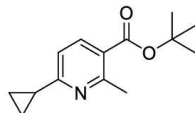


Supplementary Figure 19: General synthesis of pyridine derivatives

General reaction conditions for the catalytic one-pot synthesis of substituted pyridine derivatives (GP11): In a SCHLENK tube the corresponding 1,3-keto ester **KE** (2.00 mmol, 1.00 equiv.), 1,3-amino alcohol **AA** (2.20 mmol, 1.10 equiv.) and AcOH (glacial, 0.80 mmol, 40.0 mol%) are dissolved in 1,4-dioxane (2.00 mL, 1.00 M). The mixture is stirred at 70 °C for 24 h.

KOtBu (1.60 mmol, 180 mg, 80.0 mol%) is dissolved in 1,4-dioxane (10.0 mL, 0.16 M). **[Mn-I]** (0.06 mmol, 37.0 mg, 3.00 mol%) is dissolved in 1,4-dioxane (8.00 mL, 7.50 × 10⁻³ M). The reaction mixture is cooled to room temperature before the KOtBu solution is slowly added. After stirring for 5 minutes the **[Mn-I]**-solution is added. The mixture is stirred at reflux conditions under anaerobic conditions in an open system for 24 h. The catalytic reaction is quenched by adding water. After adding EtOAc, the organic phase is washed with brine : water : NH₄Cl (1:1:1). The aqueous phase is extracted with EtOAc several times. The combined organic phases are dried over Na₂SO₄. Removing the solvents under reduced pressure leads to the crude product. Column chromatography finally gives the desired product.

17 Isolation and Characterization of Pyridine Products

***tert*-Butyl 6-cyclopropyl-2-methylnicotinate (P39)**

Chemical Formula: C₁₄H₁₉NO₂
Molecular Weight: 233.31

P39

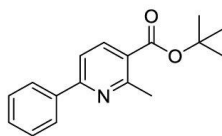
The desired product was synthesized following **GP11**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8:2)) and obtained as a colourless liquid (318 mg, 68 %, 1.36 mmol).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 7.94 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 8.1 Hz, 1H), 2.60 (s, 3H), 2.11 (tt, *J* = 8.0, 4.9 Hz, 1H), 1.53 (s, 9H), 1.01 – 0.94 (m, 4H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 165.59, 164.83, 157.87, 138.00, 123.41, 118.70, 81.12, 27.81, 24.81, 16.88, 10.44 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P39]⁺: 234.14 found: 234.14798.

R_f-Value: 0.81 (8/2 *n*-pentane : EtOAc)

***tert*-Butyl 2-methyl-6-phenylnicotinate (P40)**

Chemical Formula: C₁₇H₁₉NO₂
Molecular Weight: 269.34

P40

The desired product was synthesized following **GP11**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (93:7)) and obtained as a colourless liquid (216 mg, 80 %, 800 μmol).

S47

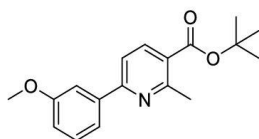
¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 8.17 (d, *J* = 8.4 Hz, 1H), 8.14 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.51 (ddd, *J* = 8.4, 7.6, 3.6 Hz, 3H), 2.77 (s, 3H), 1.57 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 165.44, 158.04, 157.35, 139.21, 137.59, 129.85, 128.85, 126.98, 125.15, 117.48, 81.55, 27.81, 24.86 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P40]⁺: 270.14 found: 270.14799.

CAS Registry Number: 627881-42-9

***tert*-Butyl 6-(3-methoxyphenyl)-2-methylnicotinate (P41)**



Chemical Formula: C₁₈H₂₁NO₃
Molecular Weight: 299.37

P41

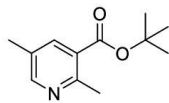
The desired product was synthesized following **GP11**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (9:1)) and obtained as a colourless liquid (473 mg, 79 %, 1.58 mmol).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 8.16 (d, *J* = 8.2 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.06 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.84 (s, 3H), 2.76 (s, 3H), 1.57 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 165.43, 159.72, 157.95, 157.09, 139.15, 139.06, 129.95, 125.29, 119.33, 117.68, 115.46, 112.26, 81.57, 55.23, 27.80, 24.88 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P41]⁺: 300.15 found: 300.15827.

R_f-Value: 0.75 (8/2 *n*-pentane : EtOAc)

tert-Butyl 2,5-dimethylnicotinate (P42)

Chemical Formula: C₁₂H₁₇NO₂
Molecular Weight: 207.27

P42

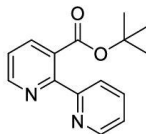
The desired product was synthesized following **GP11**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (8.5:1.5)) and obtained as a colourless liquid (361 mg, 87 %, 1.74 mmol).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 8.41 (s, 1H), 7.88 (s, 1H), 2.61 (s, 3H), 2.29 (s, 3H), 1.54 (s, 9H) ppm.

¹³C NMR (DMSO-*d*₆, 125 MHz, 293 K): δ = 165.77, 154.74, 151.60, 137.78, 130.41, 126.28, 81.50, 27.74, 23.85, 17.18 ppm.

LC-HRMS (ESI+) *m/z* calculated for [P42]⁺: 208.13 found: 208.13239.

R_r-Value: 0.40 (8/2 *n*-pentane : EtOAc)

tert-Butyl [2,2'-bipyridine]-3-carboxylate (P43)

Chemical Formula: C₁₅H₁₆N₂O₂
Molecular Weight: 256.31

The desired product was synthesized following **GP11**. The crude product was purified via column chromatography (*n*-pentane : EtOAc (2:8)) and obtained as a yellow crystalline solid (282 mg, 55 %, 1.10 mmol).

¹H NMR (DMSO-*d*₆, 500 MHz, 293 K): δ = 8.75 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.60 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.03 (dt, *J* = 7.8, 0.9 Hz, 1H), 8.00 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.97 (td, *J* = 7.7, 1.7 Hz, 1H), 7.54 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.47 (ddd, *J* = 7.4, 4.8, 1.2 Hz, 1H), 1.35 (s, 9H) ppm.

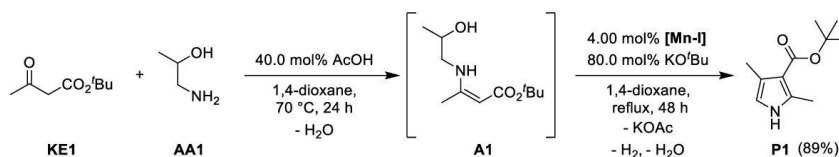
S49

^{13}C NMR (DMSO- d_6 , 125 MHz, 293 K): δ = 167.05, 156.23, 154.73, 150.09, 148.29, 137.08, 136.96, 129.69, 123.83, 123.32, 122.44, 81.17, 27.44 ppm.

LC-HRMS (ESI+) m/z calculated for [**P43**] $^+$: 257.12 found: 257.12766.

R_f-Value: 0.50 (2/8 *n*-pentane : EtOAc)

18 Synthesis of Sunitinib

Supplementary Figure 20: Synthesis of **P1** via consecutive one-pot reaction.

Scale-up synthesis of P1: In a SCHLENK tube the corresponding 1,3-keto ester **KE1** (2.77 g, 2.90 mL, 17.5 mmol, 1.00 equiv.), 1,2-amino alcohol **AA1** (1.58 g, 21.0 mmol, 1.62 mL, 1.20 equiv.) and AcOH (glacial, 420 mg, 400 μL, 7.00 mmol, 40.0 mol%) are dissolved in 1,4-dioxane (17.5 mL, 1.00 M). The mixture is stirred at 70 °C for 24 h.

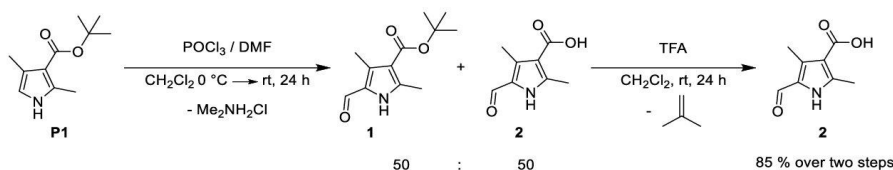
KO^tBu (1.57g, 14.0 mmol, 80.0 mol%) is dissolved in 1,4-dioxane (78.8 mL, 0.18 M). **[Mn-I]** (427 mg, 0.7 mmol, 4.00 mol%) is dissolved in 1,4-dioxane (78.8 mL, 8.88 × 10⁻³ M).

The reaction mixture is cooled to room temperature before the KO^tBu solution is slowly added. After stirring for 5 minutes the **[Mn-I]** solution is added. The mixture is stirred at reflux conditions under anaerobic conditions in an open system for 48 h. The catalytic reaction is quenched by adding water. The solvent is evaporated under vacuum. EtOAc is added to dissolve the residues. The organic phase is washed with brine : water : NH₄Cl (1:1:1). The aqueous phase is extracted with EtOAc several times. The combined organic phases are dried over Na₂SO₄. Removing the solvents under reduced pressure leads to the crude product. Column chromatography (8.5 / 1.5 *n*-pentane/EtOAc) finally yields the desired product **P1** (3.05 g, 15.6 mmol, 89%) as a colourless solid.

¹H NMR (CDCl₃, 400 MHz, 293 K): δ = 8.05 (s, 1H), 6.33 (s, 1H), 2.46 (s, 3H), 2.22 (s, 3H), 1.56 (s, 9H) ppm.

¹³C NMR (CDCl₃, 125 MHz, 293 K): δ = 165.86, 135.47, 121.51, 114.14, 112.27, 79.34, 28.75, 14.27, 12.88 ppm.

The spectroscopic data corresponds to those in the literature.^[6]



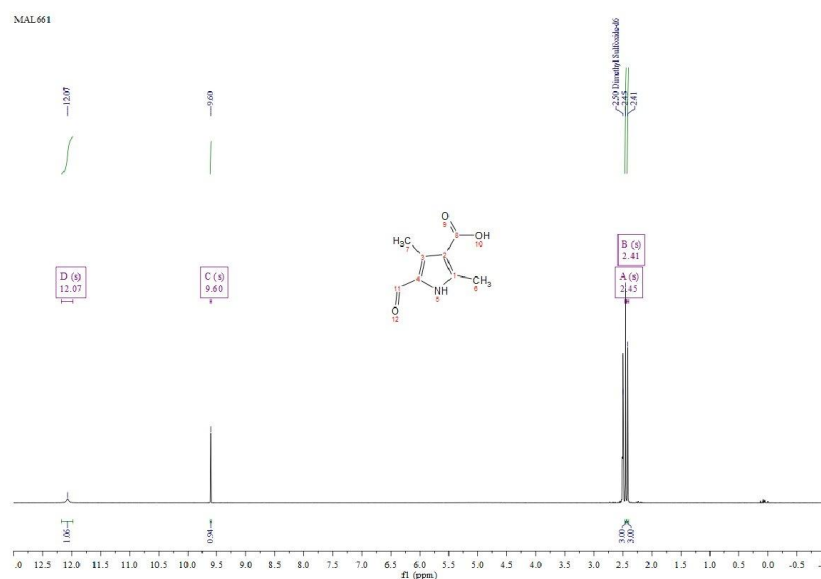
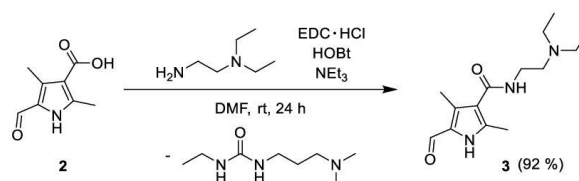
Supplementary Figure 21: Synthesis of carboxylic acid **2** via VILSMEIER-HAACK formylation and cleavage of the *tert*-butyl ester **1** with TFA.

VILSMEIER-HAACK-formylation for the synthesis of 1: Referring to the literature^[8], a slightly modified synthesis protocol was used. DMF (439 mg, 6.00 mmol, 465 μL , 1.12 equiv.) is cooled with a salt-ice bath. POCl_3 (1.45 g, 9.50 mmol, 866 μL , 1.75 equiv.) is dissolved in CH_2Cl_2 (2.00 mL, 4.75 M). The POCl_3 -solution is slowly added to the DMF. The reaction is cooled with an ice bath and stirred for 30 minutes. Pyrrole **P1** (1.06 g, 5.42 mmol, 1.00 equiv.) is dissolved in CH_2Cl_2 (2.50 mL, 2.17 M) and added to the POCl_3 /DMF-solution while cooling. The solution is stirred under reflux conditions for 90 minutes before the solvent is evaporated under reduced pressure. To the bright yellow residues is added KOH (1.96 g, 35.0 mmol, 6.44 equiv.) in H_2O (12.5 mL, 2.80 M). The suspension is refluxed for 30 minutes before cooling to room temperature. The precipitating pale grey solid is filtrated and washed with cold water several times. The solvents were evaporated under reduced pressure to give a 50:50 mixture (determined via UPLC-MS analysis) of compound **1** and **2**.

Ester cleavage with TFA: A 50:50 mixture of compound **1** and **2** (2.71 mmol : 2.71 mmol) is suspended in CH_2Cl_2 : TFA (8.00 mL : 1.00 mL). The resulting dark brown solution is stirred for 24 h at room temperature. A gas bubbler is used to liberate the resulting isobutene. The solvents are evaporated under reduced pressure to yield the desired product **2** (771 mg, 4.61 mmol, 85 %) as a pale grey solid.

^1H NMR (DMSO-d_6 , 300 MHz, 293 K): δ = 12.07 (s, 1H), 9.60 (s, 1H), 2.45 (s, 3H), 2.41 (s, 3H) ppm.

The spectroscopic data corresponds to those in the literature.^[9]

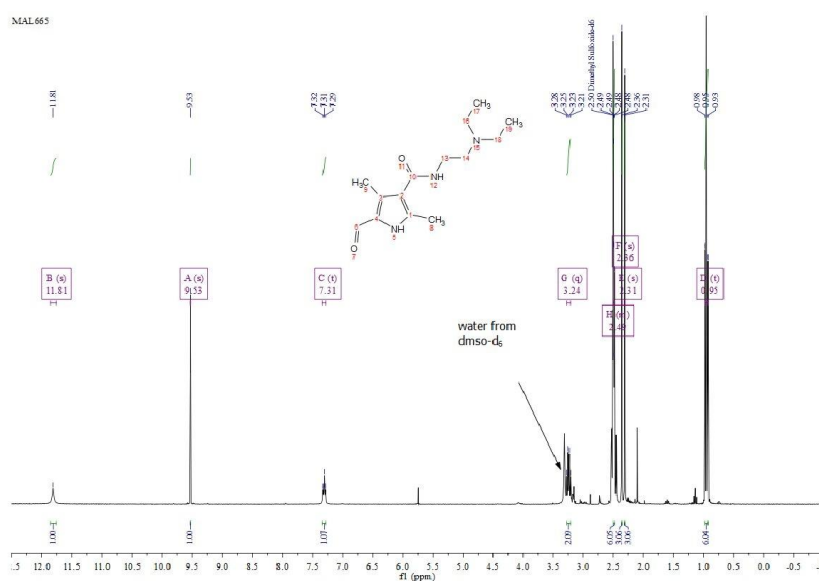
Supplementary Figure 22: ^1H NMR spectrum of carboxylic acid **2** in DMSO-d_6 .Supplementary Figure 23: Synthesis of compound **3** via amide-coupling.

Synthesis of compound 3 through amide coupling: Referring to the literature^[10], a slightly modified synthesis protocol was used. Carboxylic acid **2** (500 mg, 3.00 mmol, 1.00 equiv.) is dissolved in DMF (15.0 mL, 0.20 M). NEt_3 (456 mg, 4.50 mmol; 624 μL , 1.50 equiv.), EDC·HCl (978 mg, 5.10 mmol, 1.70 equiv.), HOBT (608 mg, 4.50 mmol, 1.50 equiv.) and N,N' -diethylethane-1,2-diamine (397 mg, 4.50 mmol, 484 μL , 1.50 equiv.) are added to the solution. The reaction is stirred at room temperature for 24 h before the solvents are evaporated under reduced pressure. The residues are dissolved in EtOAc. The organic phase is washed with sat. NaHCO_3 -solution : 2 N NaOH (1:1) two times.

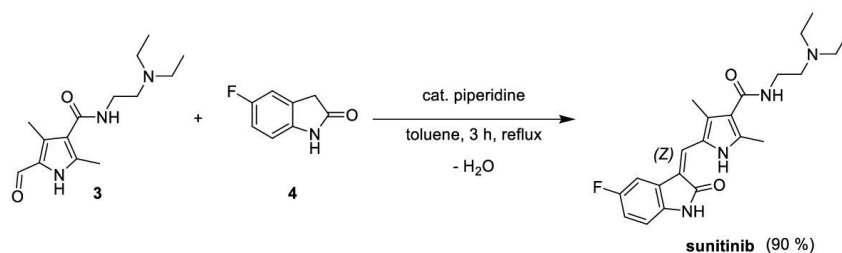
The combined aqueous layers are extracted with EtOAc several times. The combined organic layers are dried over Na₂SO₄. The solvents are evaporated under reduced pressure to obtain the crude product **3**. Column chromatography (9:1 CH₂Cl₂ / MeOH) finally gives the product **3** (733 mg, 2.76 mmol, 92%) as a light-yellow solid.

¹H NMR (DMSO-d₆, 300 MHz, 293 K): δ = 11.81 (s, 1H), 9.53 (s, 1H), 7.31 (t, *J* = 5.5 Hz, 1H), 3.24 (q, *J* = 7.1 Hz, 2H), 2.50 – 2.47 (m, 6H), 2.36 (s, 3H), 2.31 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 6H) ppm.

The spectroscopic data corresponds to those in the literature.^[9]



Supplementary Figure 24: ¹H NMR spectrum of amide **3** in DMSO-d₆.

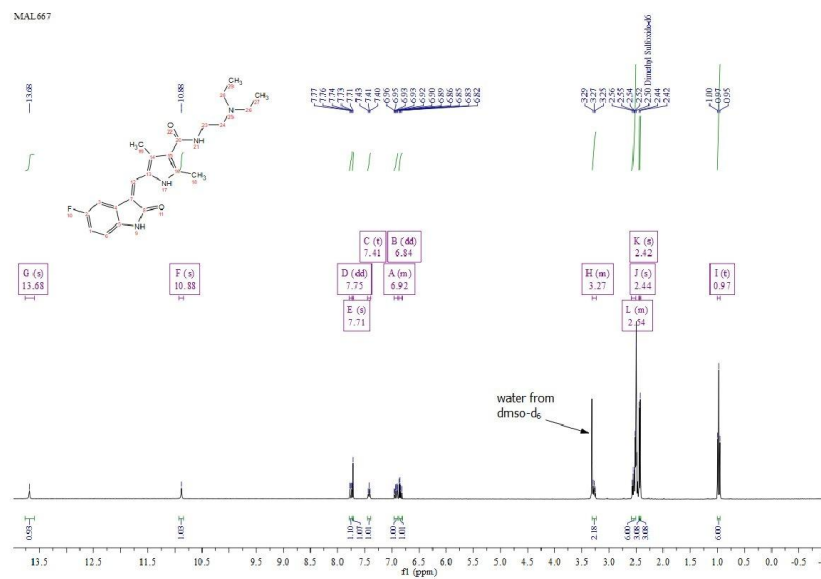


Supplementary Figure 25: Synthesis of sunitinib via KNOEVENAGEL-condensation.

KNOEVENAGEL-condensation for the synthesis of sunitinib: Referring to the literature^[8], a slightly modified synthesis protocol was used. Aldehyde **3** (556 mg, 2.10 mmol, 1.00 equiv.) and compound **4** (348 mg, 2.30 mmol, 1.10 equiv.) are suspended in toluene (9.00 mL, 0.23 M). Three drops of piperidine are added via a PASTEUR-pipette and the reaction is refluxed for 3 h. The resulting precipitate is filtered and washed with cold Et₂O several times. The solvents are removed under reduced pressure to give **sunitinib** (754 mg, 1.89 mmol, 90 %) as a bright orange solid.

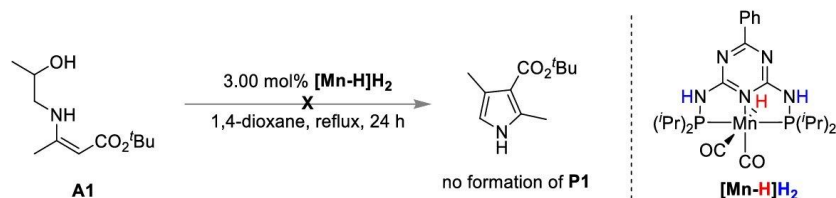
¹H NMR (DMSO-d₆, 300 MHz, 293 K): δ = 13.68 (s, 1H), 10.88 (s, 1H), 7.75 (dd, J = 9.5, 2.5 Hz, 1H), 7.71 (s, 1H), 7.41 (t, J = 5.6 Hz, 1H), 6.96 – 6.89 (m, 1H), 6.84 (dd, J = 8.5, 4.6 Hz, 1H), 3.31 – 3.23 (m, 2H), 2.58 – 2.51 (m, J = 7.0, 5.6 Hz, 6H), 2.44 (s, 3H), 2.42 (s, 3H), 0.97 (t, J = 7.1 Hz, 6H) ppm.

The spectroscopic data corresponds to those in the literature.^[9]

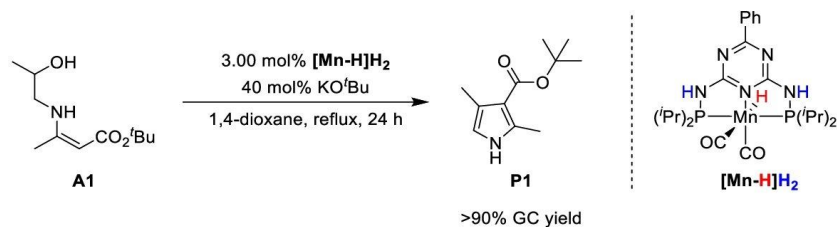


Supplementary Figure 26: ¹H NMR spectrum of **sunitinib** in DMSO-d₆.

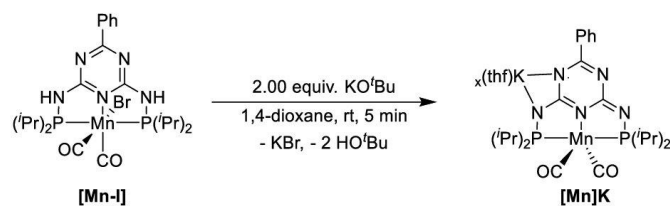
19 Mechanistic Studies and Control Experiments

Validation of the Catalytic Cycle for the Formation of **P1** starting from **A1**Supplementary Figure 27: Attempted formation of **P1** with $[\text{MnH}]_2$ without KO^tBu .

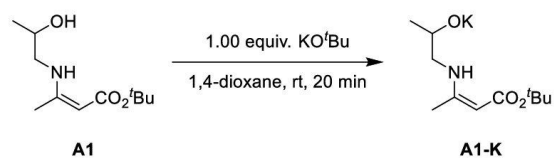
Hydride complex $[\text{MnH}]_2$ without any potassium source was used in the reaction shown. No formation of **P1** could be detected.

Supplementary Figure 28: Formation of **P1** using $[\text{MnH}]_2$ with KO^tBu .

Using KO^tBu as a potassium source in the reaction shown, an almost quantitative formation of **P1** could be detected via GC analysis.

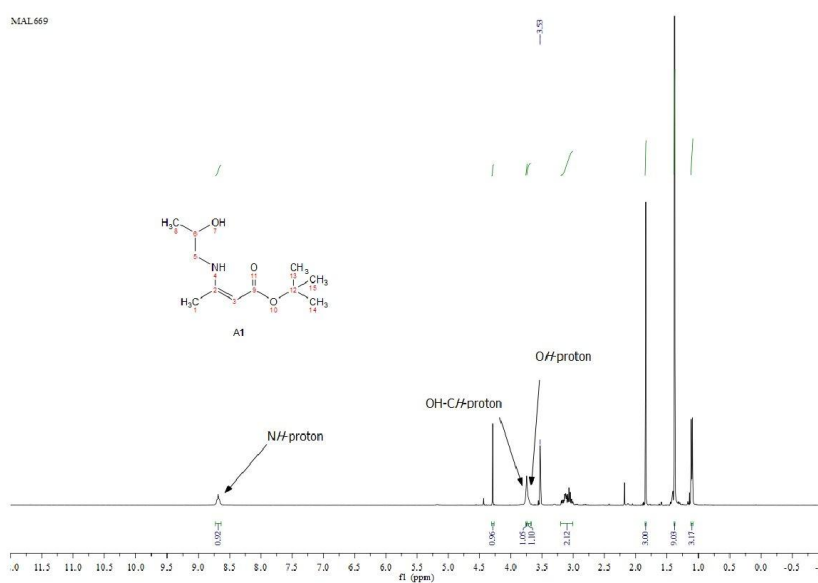
Supplementary Figure 29: Preparation of $[\text{Mn}]\text{K}$ with KO^tBu .

[Mn]K was prepared by treating **[Mn-I]** with two equivalents of KO^tBu.

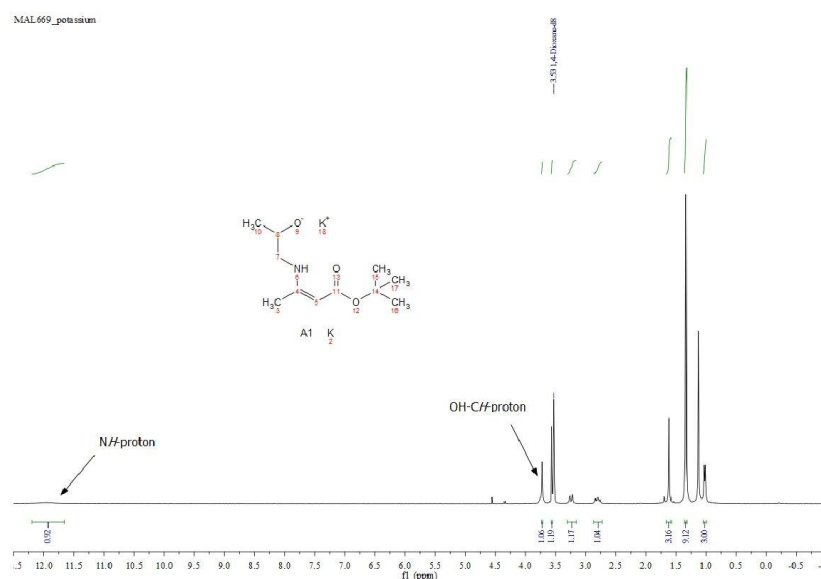


Supplementary Figure 30: Formation of **A1-K**.

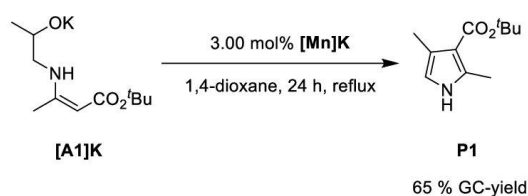
Compound **A1** was treated with 1.00 equiv. of KO^tBu to form **A1-K**.



Supplementary Figure 31: ¹H NMR spectrum of **A1** in 1,4-dioxane-d₈.



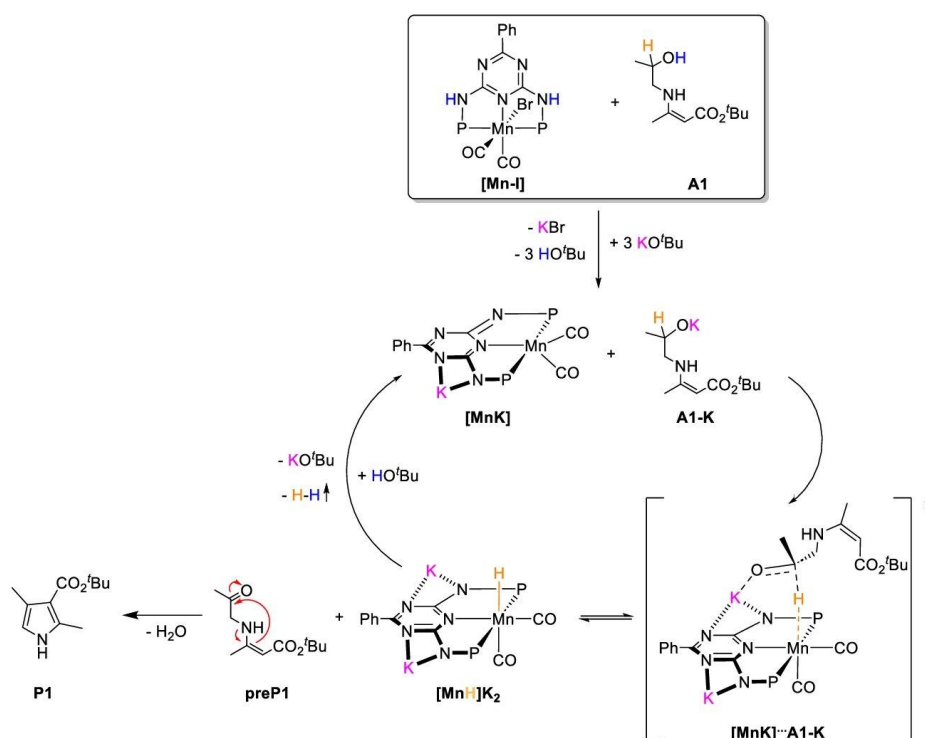
Supplementary Figure 32: ^1H NMR spectrum of **A1-K** in 1,4-dioxane- d_8 .



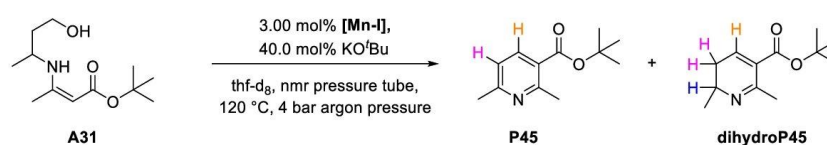
Supplementary Figure 33: Synthesis of **P1** with **[Mn]K** starting from **[A1]K**.

After the addition of **[Mn]K** to **A1-K**, the reaction mixture was stirred at reflux conditions for 24 h. 65 % yield of **P1** could be detected via GC-analysis.

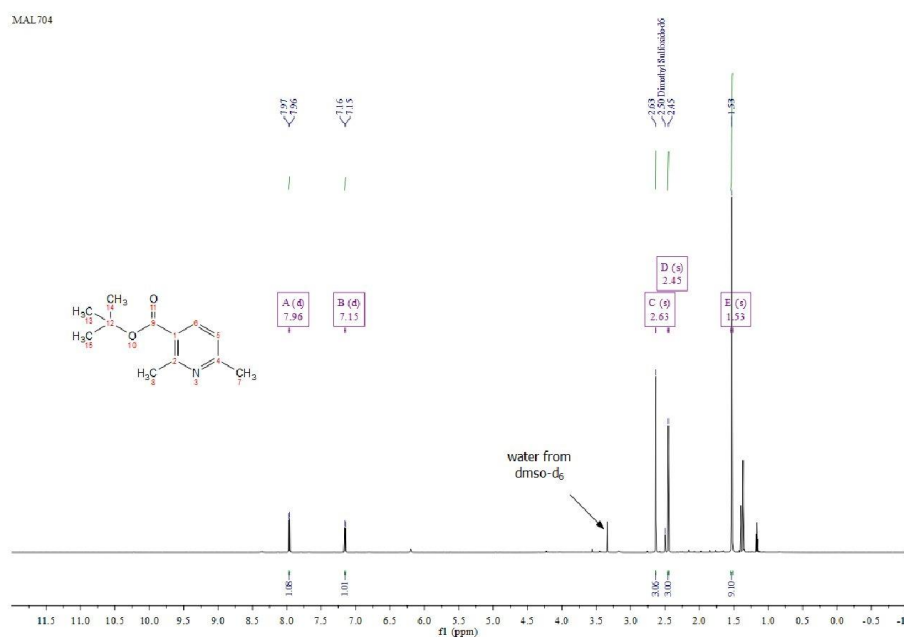
20 Proposed Catalytic Cycle for the Formation of P1

Supplementary Figure 34: Proposed catalytic cycle for the formation of **P1**.

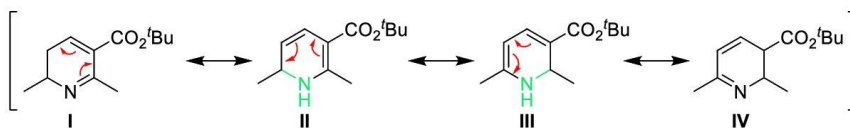
Validation of the Catalytic Cycle for the Formation of P45

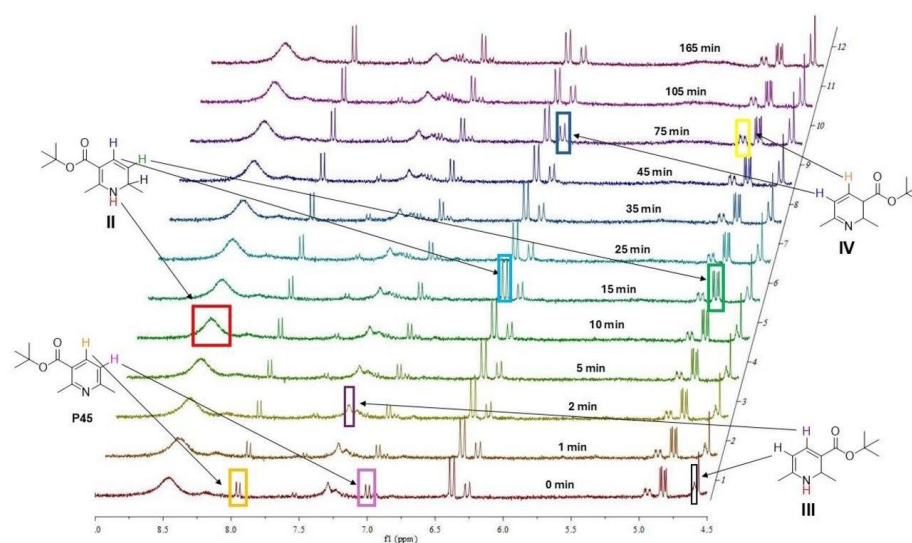
Supplementary Figure 35: NMR experiment to investigate possible intermediate **dihydroP45** and its isomers.

Compound **P45** was synthesized according to **GP11** in a 2.50 mmol scale.

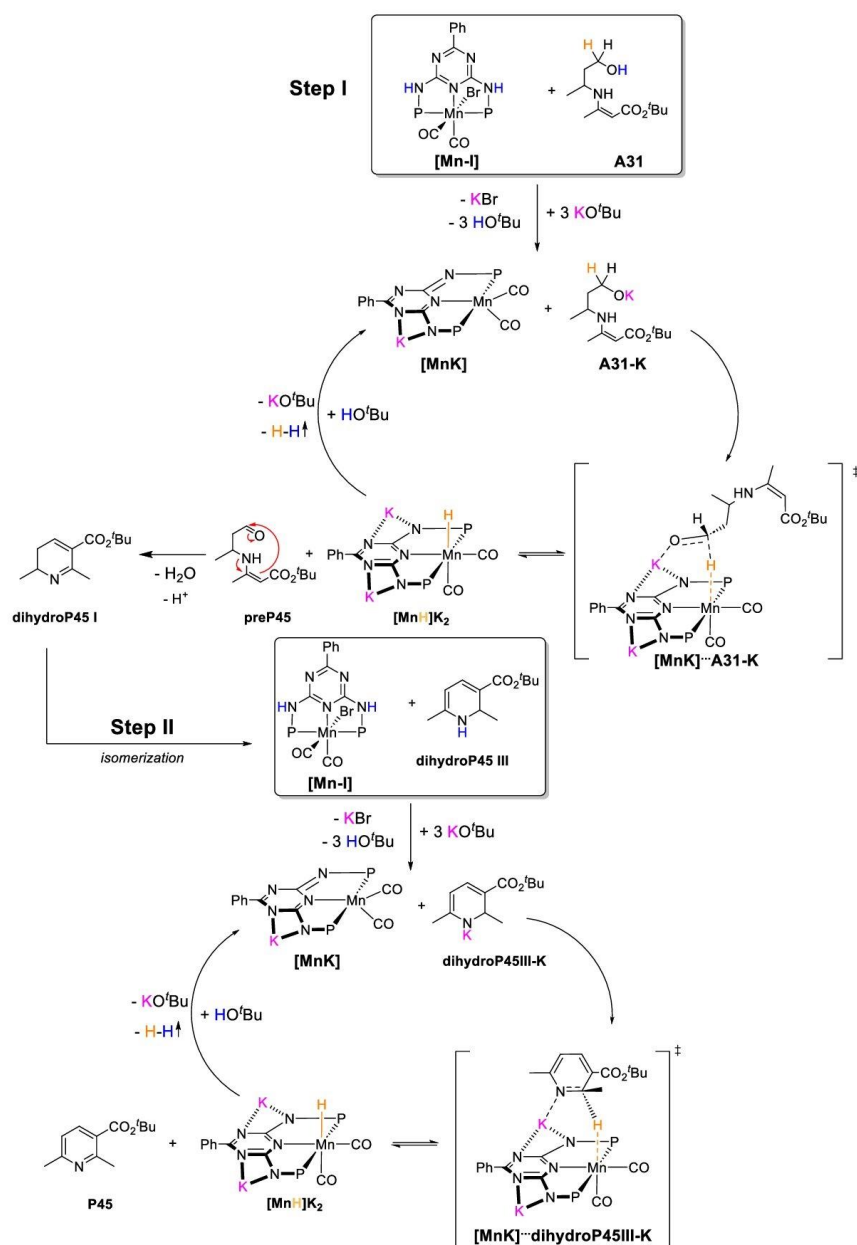
Supplementary Figure 36: ^1H NMR of compound **P45**.

Compound **A31** was synthesized according to **GP2**. 0.50 mmol of compound **A31** was dissolved in THF- d_8 (4.00 mL, 0.125 M). 3.00 mol% **[Mn-I]** (9.16 mg) and 40.0 mol% KO^tBu (22.4 mg) were added, and the mixture was stirred for 5.00 minutes at rt. 0.50 mL (0.06 mmol substrate) of the resulting solution was transferred into an NMR high pressure tube. The tube was placed under 4 bar argon pressure and heated up until 120 °C during the ^1H measurements.

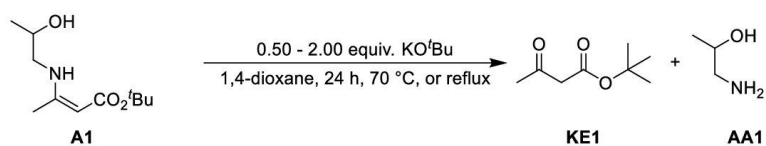
Supplementary Figure 37: Proposed mesomeric structures with consisting MICHAEL system for dihydro**P45**.



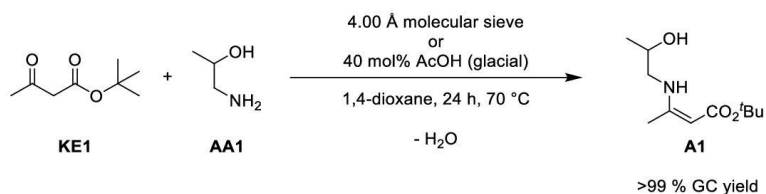
Supplementary Figure 38: NMR spectra measured at 120 °C in a period of 2 h 45 min showing the formation of pyridine **P45** and the presence of the isomers of dihydro**P45** **II-IV**.

Supplementary Figure 39: Proposed two step catalytic cycle for formation of **P45**.

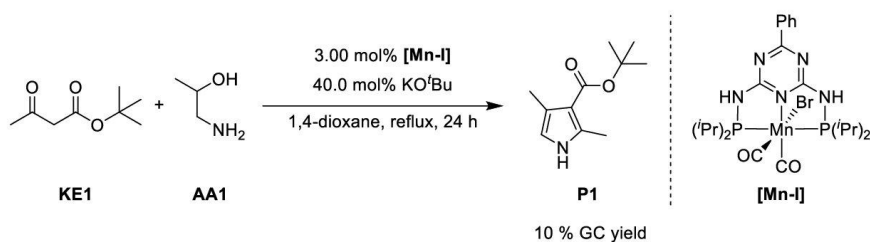
Determination of the Consecutive One-Pot Reaction

Supplementary Figure 40: Decomposition of **A1** under the influence of KO^tBu.

The usage of a strong potassium enolate led to the decomposition of **A1** under several reaction conditions tested. With high amounts of base, less formation of **P1** could be detected and rapid decomposition of **A1** was observed.

Supplementary Figure 41: The formation and stability of **A1** under mild acidic conditions.

On the other hand, compound **A1** was very stable under mild acidic conditions without any decomposition.

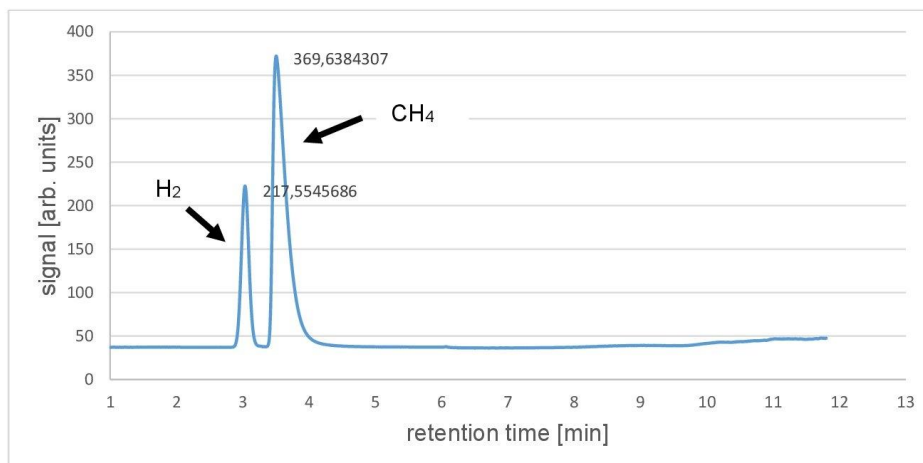
Supplementary Figure 42: Attempted one-step synthesis of **P1** from **KE1** and **AA1**.

An attempt to synthesize **P1** via a catalytic one-step synthesis without any preformation of **A1** only led to the formation of **P1** in 10 % GC yield.

Determination of Hydrogen Release During the Catalytic Dehydrogenation for **P1**

The release of one equivalent hydrogen was proven by analyzing the gas mixture with methane as an internal standard in the SCHLENK tube after reaction. The gas mixture was analyzed using an Agilent Technologies 6890N equipped with a TCD and an Agilent special plot and molsieve capillary column (30 m, 320 μ m, 0.25 μ m).

Argon was used as carrier gas. Reaction conditions: 0.5 mmol **A1**, 3.00 mol% **[Mn-I]**, 40 mol% KO^tBu and 5.00 mL 1,4-dioxane were added to a SCHLENK tube (250 mL) under an argon atmosphere, closed and heated at reflux conditions for 24 h. A yield of 85 % of **P1** was determined and 80 % of hydrogen was detected. Therefore 0.34 mmol (7.62 mL calculated: 9.52 mL) H₂ (*ideal gas equation*) was detected.

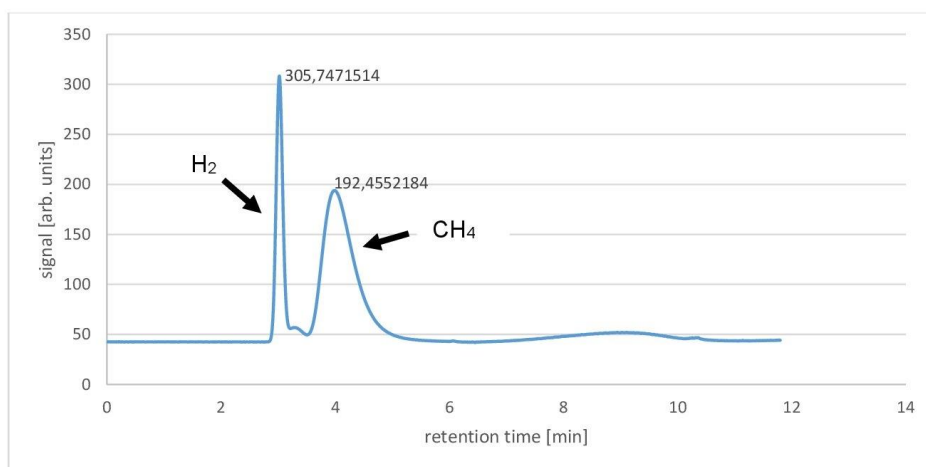


Supplementary Figure 43: Validation of the hydrogen release via GC with CH₄ as an internal standard. 80 % (0.34 mmol, 7.62 mL) of the released hydrogen was detected.

Determination of Hydrogen Release During the Catalytic Dehydrogenation for P42

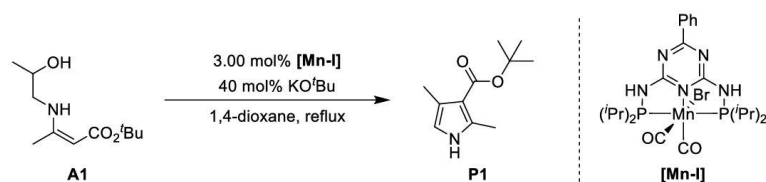
The release of one equivalent hydrogen was proven by analyzing the gas mixture with methane as an internal standard in the SCHLENK tube after reaction. The gas mixture was analyzed using an Agilent Technologies 6890N equipped with a TCD and an Agilent special plot and molsieve capillary column (30 m, 320 μm , 0.25 μm).

Argon was used as carrier gas. Reaction conditions: 0.5 mmol **A31**, 3.00 mol% **[Mn-I]**, 40 mol% KO^tBu and 5.00 mL 1,4-dioxane were added to a SCHLENK tube (300 mL) under an argon atmosphere, closed and heated at reflux conditions for 24 h. A yield of 82 % of **P42** was determined and 78 % of hydrogen was detected. Therefore 0.64 mmol (0.32 mmol x 2, 14.3 mL, calculated: 18.4 mL) H₂ (*ideal gas equation*) was detected.



Supplementary Figure 44: Validation of the hydrogen release via GC with CH₄ as an internal standard. 80 % (0.64 mmol, 14.3 mL) of the released hydrogen was detected.

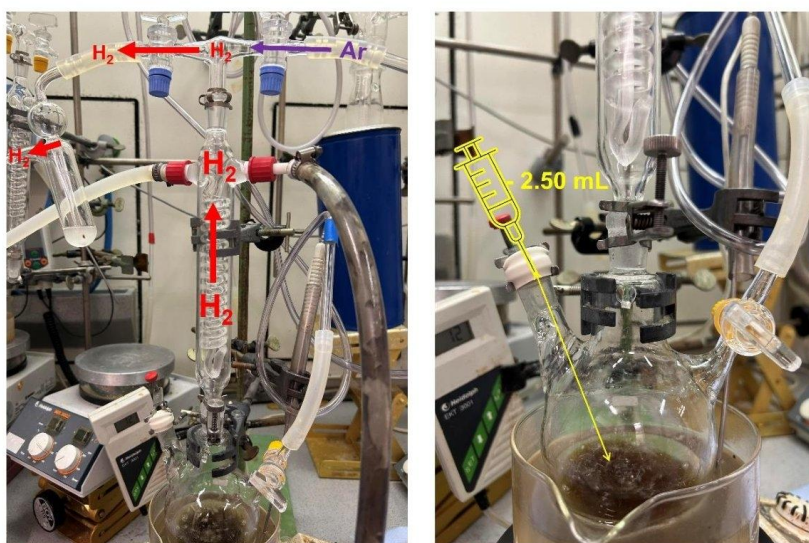
Time Conversion Plots for the Formation of P1



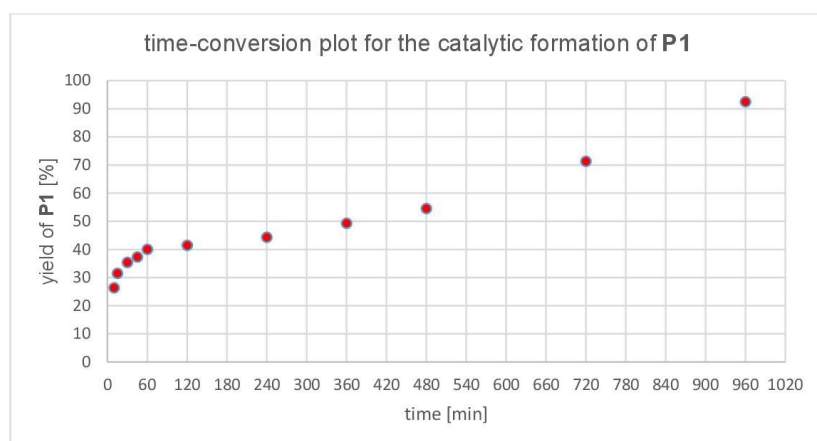
Supplementary Figure 45: Reaction conditions for the time conversion plot.

Reaction conditions for the kinetic measurements: In a round bottom SCHLENK tube **A1** (810 mg, 3.75 mmol, 1.00 equiv.), KO^tBu (170 mg, 1.50 mmol, 40.0 mol%) and **[Mn-I]** are dissolved in 1,4-dioxane (37.5.0 mL, 0.10 M). The mixture is stirred at reflux conditions under anaerobic conditions in an open system.

Taking samples for the GC measurements: At each defined time point, 2.50 mL (250 μmol) of the reaction solution is removed, quenched with 1.00 mL sat. Na₂SO₄-solution and diluted with 5.00 mL EtOAc. Dodecane (50.0 μL, 100 μL / 0.50 mmol) is added. 750 μL of the supernatant organic phase is used for the GC analysis.

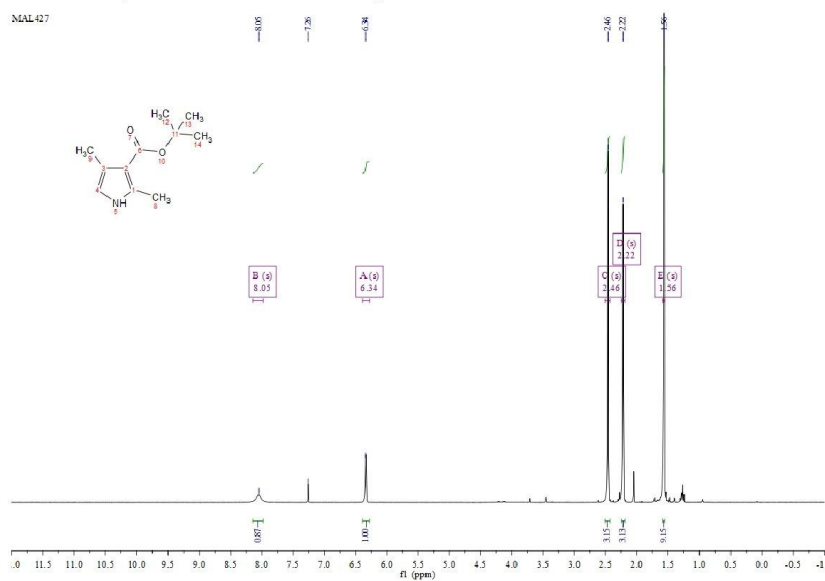


Supplementary Figure 46: Pictures with schematic representation of the process.

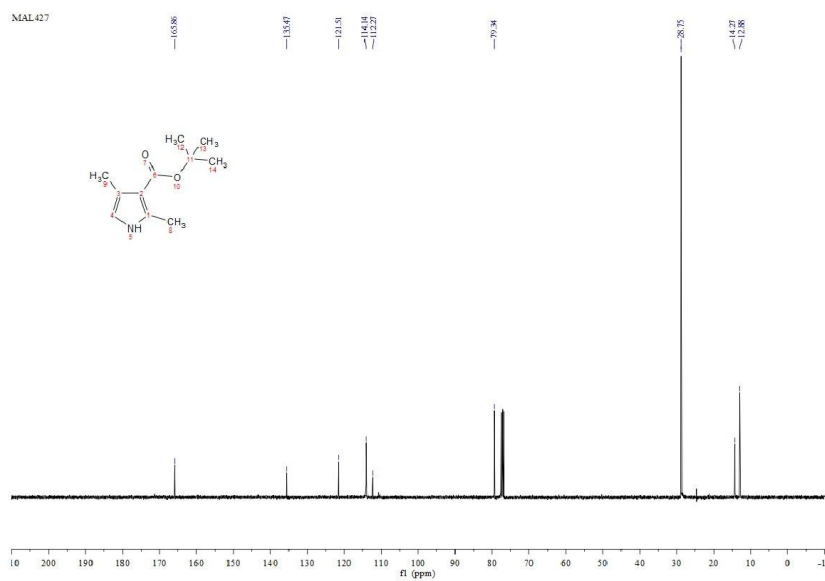


Supplementary Figure 47: Time Conversion plot for the catalytic formation of **P1**.

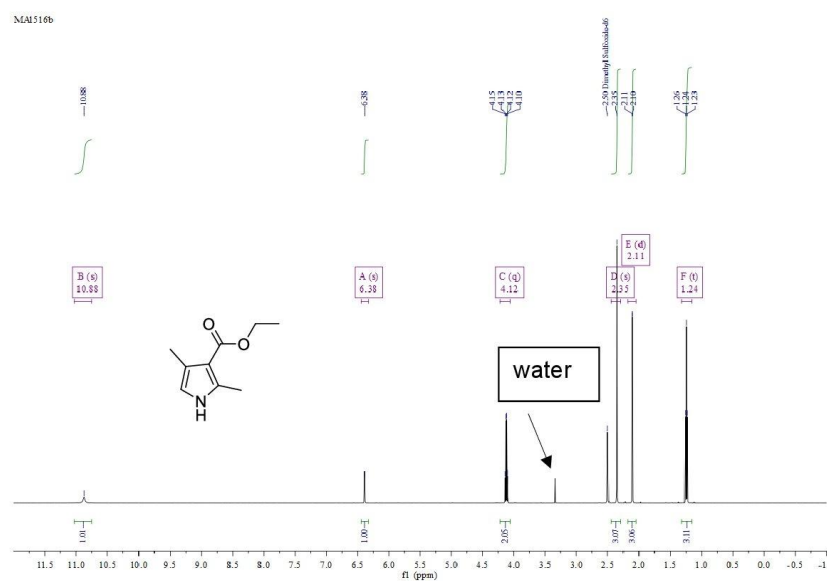
21 NMR-spectra of isolated compounds



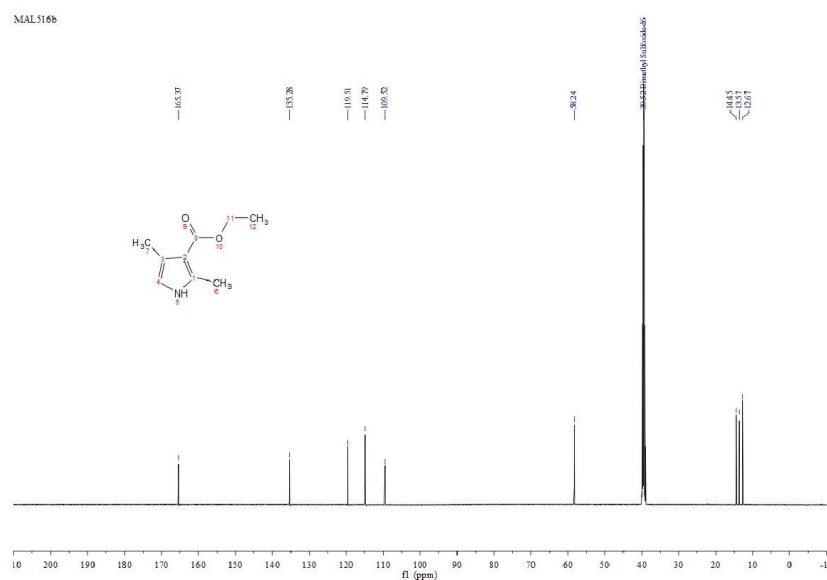
Supplementary Figure 48: ^1H NMR spectrum of **P1** in CDCl_3 .



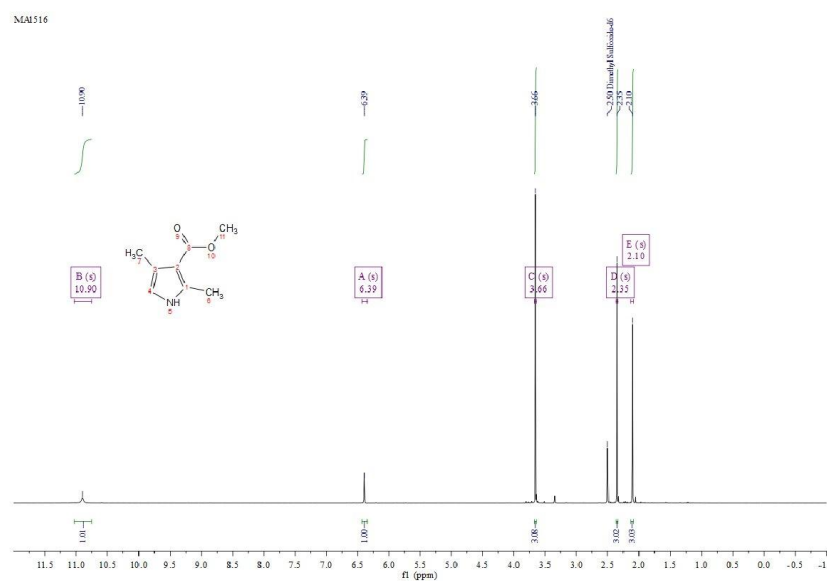
Supplementary Figure 49: ^{13}C NMR spectrum of **P1** in CDCl_3 .



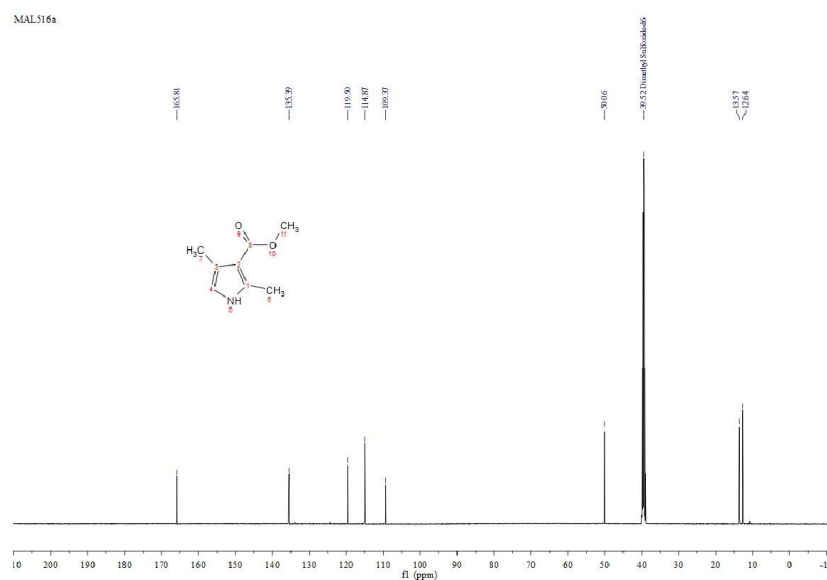
Supplementary Figure 50: ^1H NMR spectrum of **P2** in DMSO-d_6 .



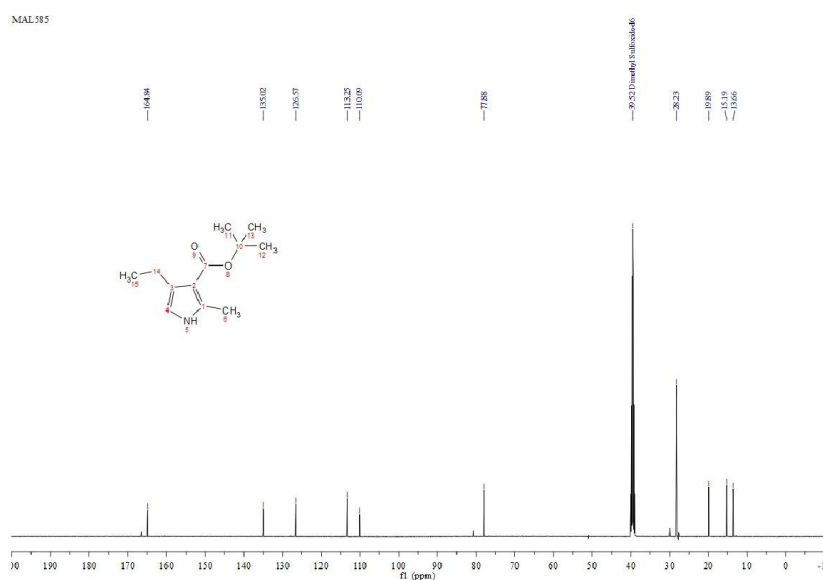
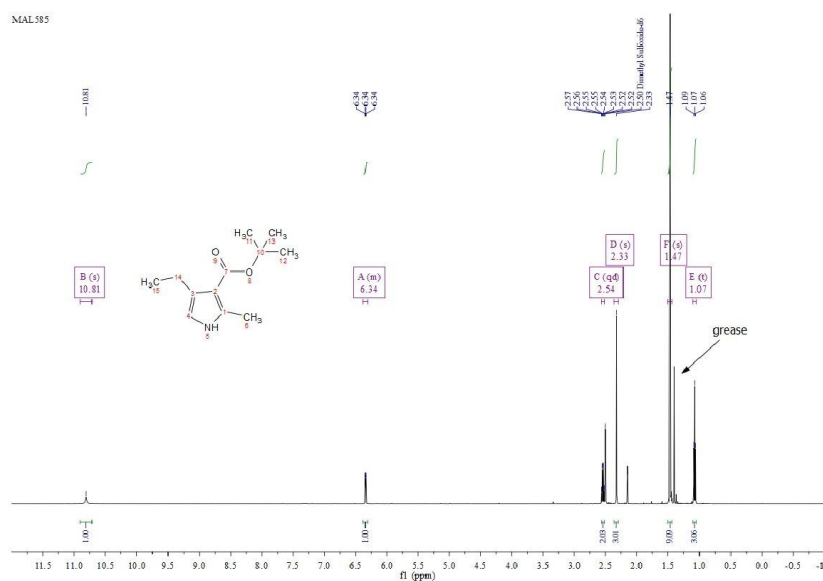
Supplementary Figure 51: ^{13}C NMR spectrum of **P2** in DMSO-d_6 .

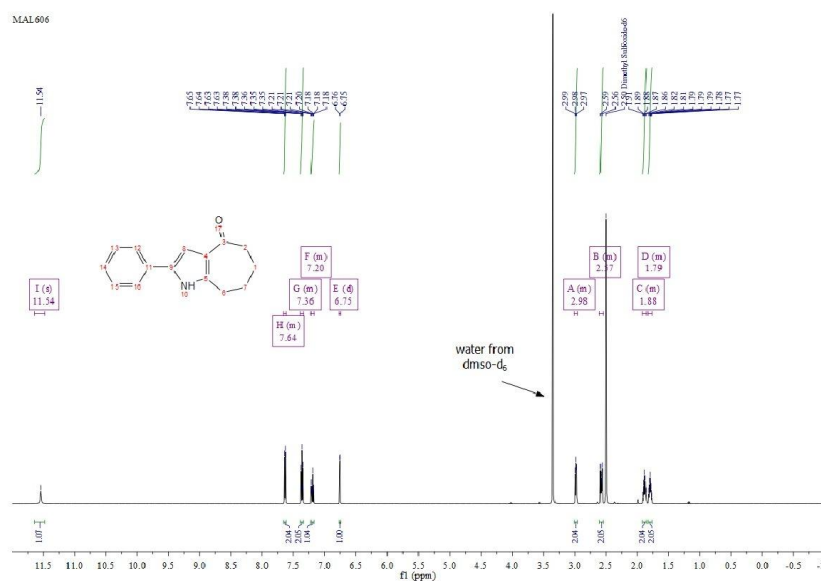


Supplementary Figure 52: ¹H NMR spectrum of **P3** in DMSO-d₆.

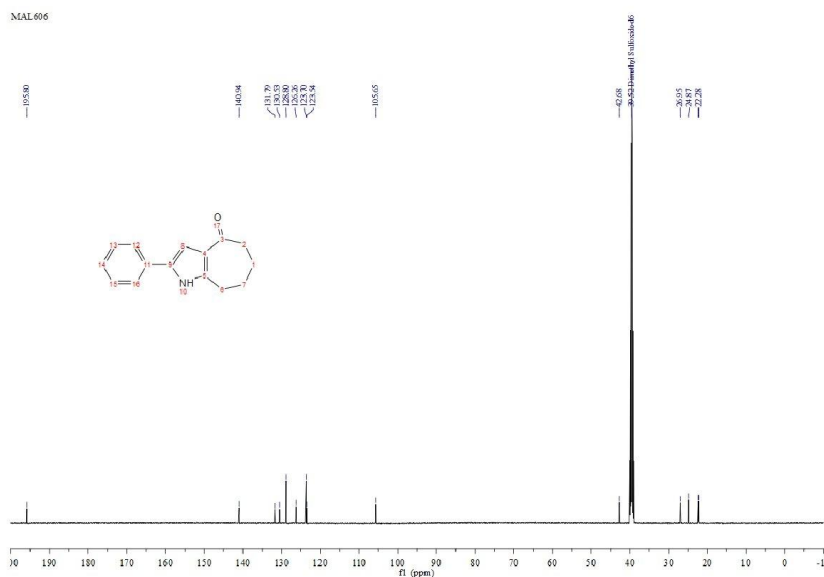


Supplementary Figure 53: ¹³C NMR spectrum of **P3** in DMSO-d₆.

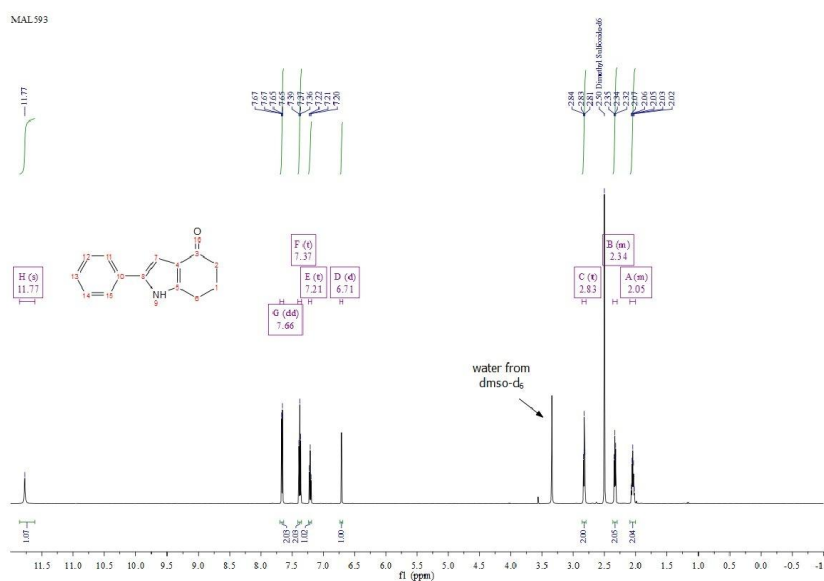




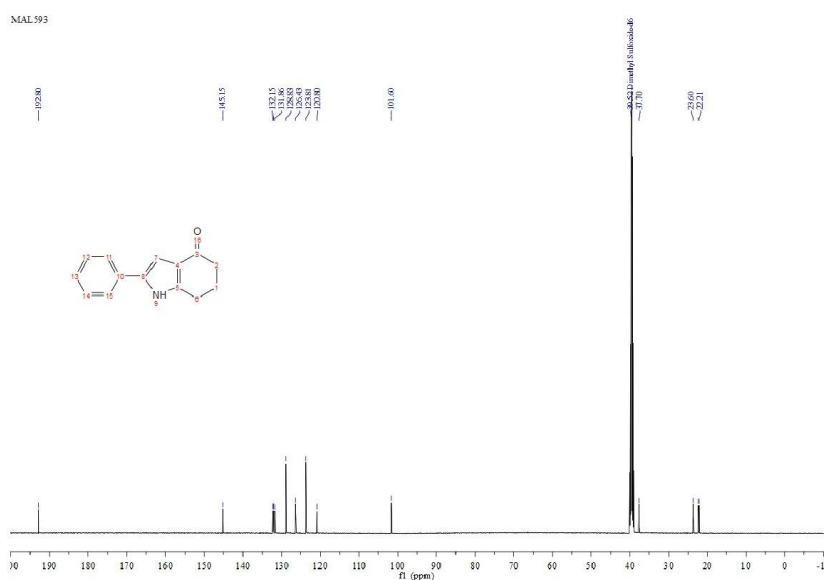
Supplementary Figure S6: ^1H NMR spectrum of **P5** in $\text{DMSO-}d_6$.



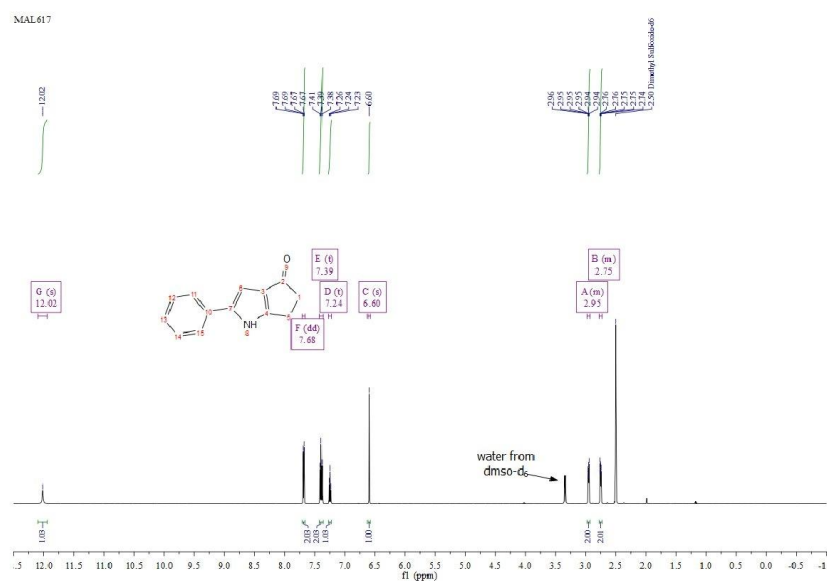
Supplementary Figure S7: ^{13}C NMR spectrum of **P5** in $\text{DMSO-}d_6$.



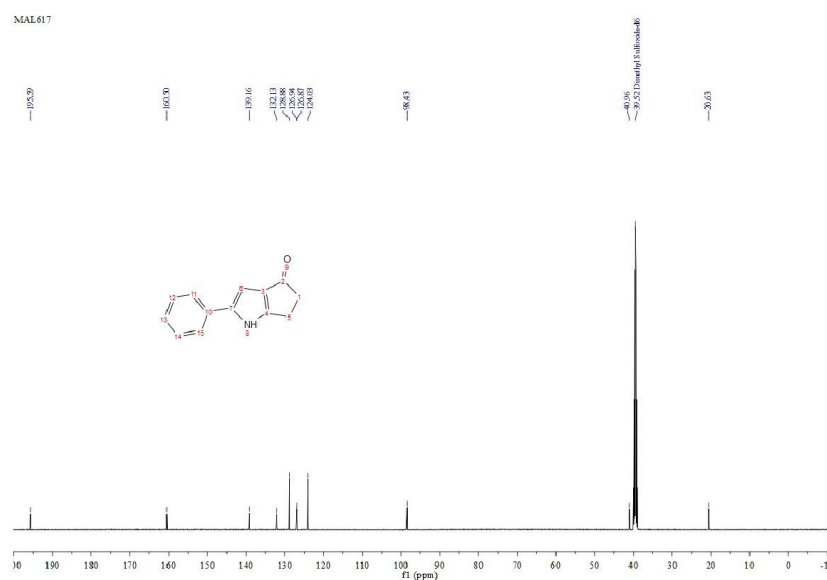
Supplementary Figure 58: ¹H NMR spectrum of **P6** in DMSO-d₆.



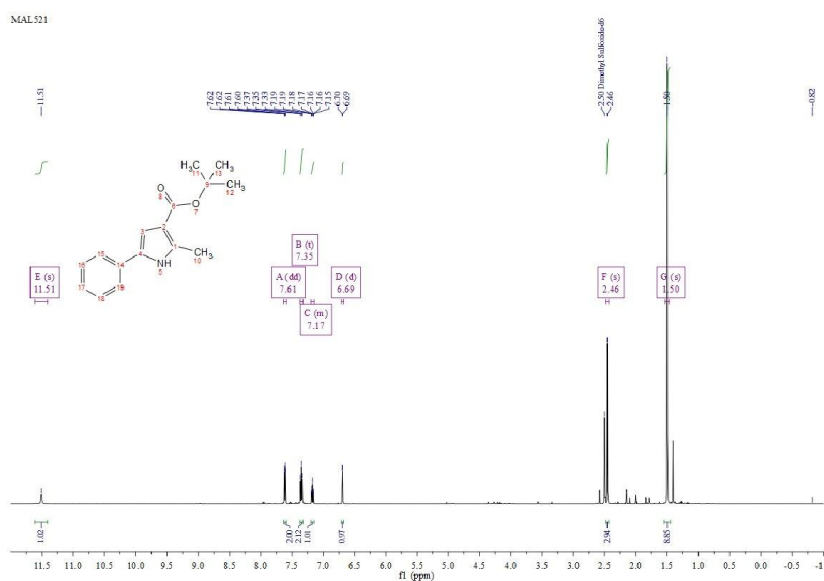
Supplementary Figure 59: ¹³C NMR spectrum of **P6** in DMSO-d₆.



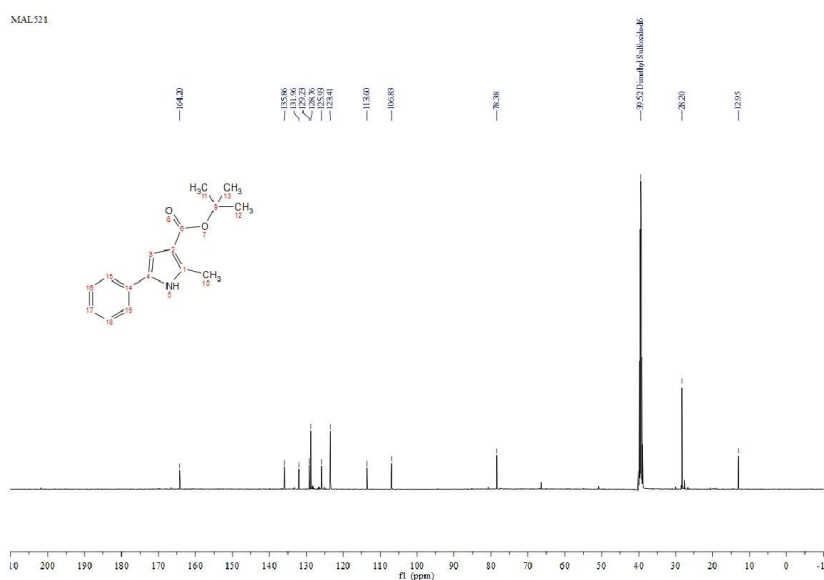
Supplementary Figure 60: ^1H NMR spectrum of **P7** in DMSO- d_6 .



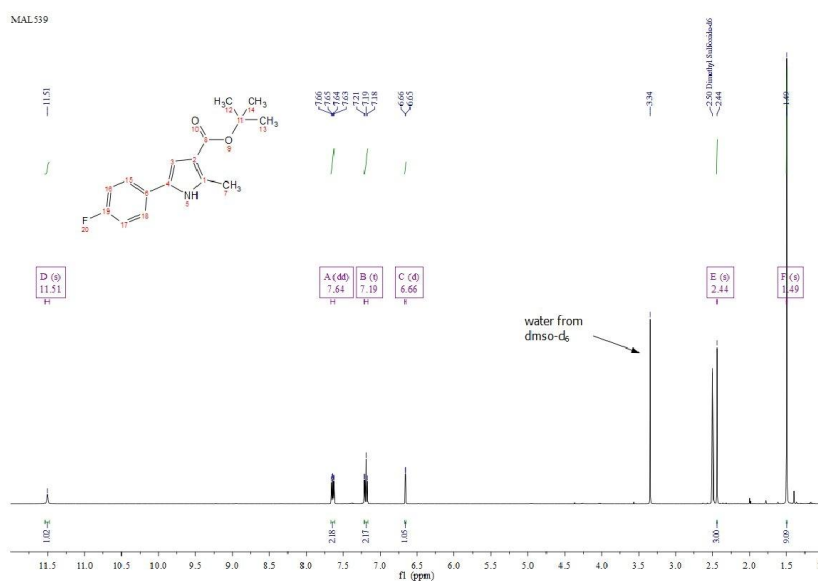
Supplementary Figure 61: ^{13}C NMR spectrum of **P7** in DMSO- d_6 .



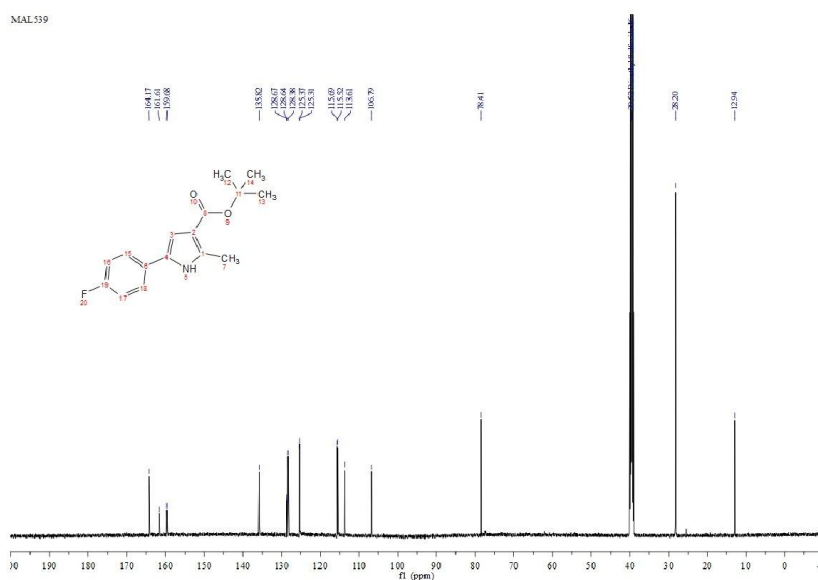
Supplementary Figure 62: ^1H NMR spectrum of **P8** in DMSO-d_6 .



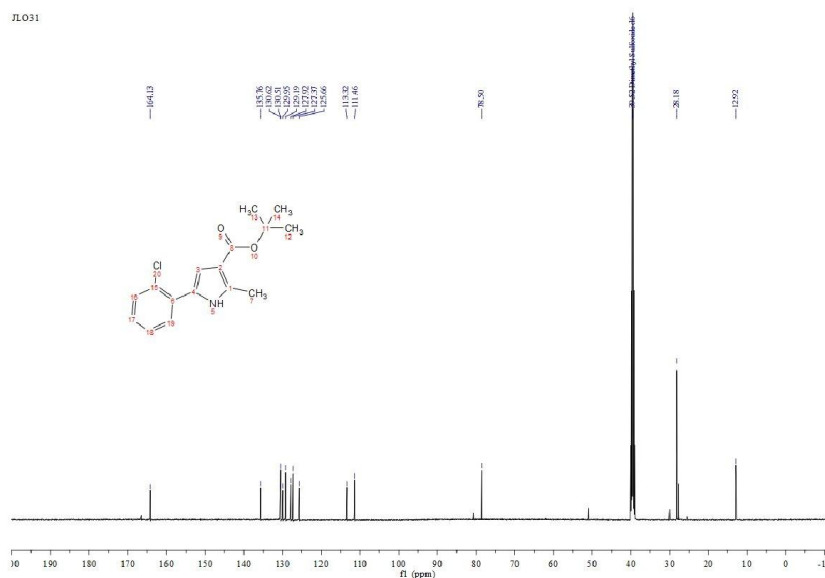
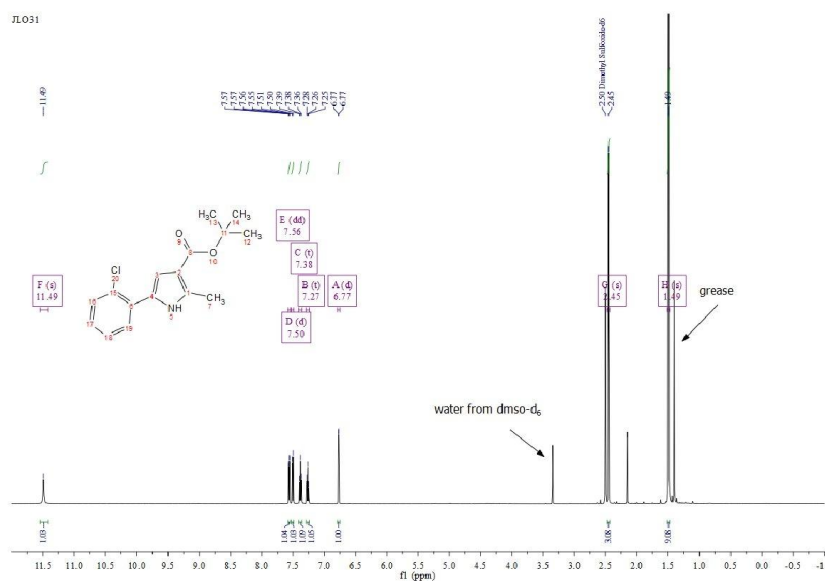
Supplementary Figure 63: ^{13}C NMR spectrum of **P8** in DMSO-d_6 .

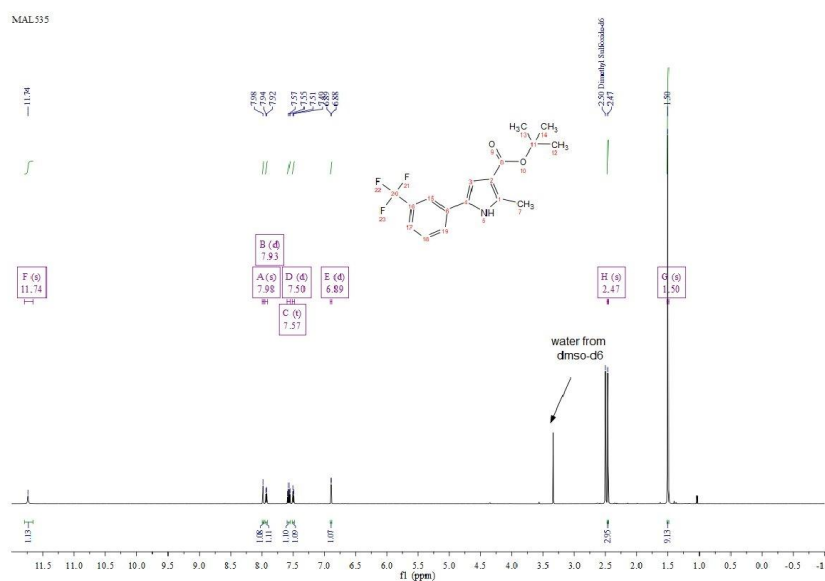


Supplementary Figure 64: ^1H NMR spectrum of **P9** in DMSO- d_6 .

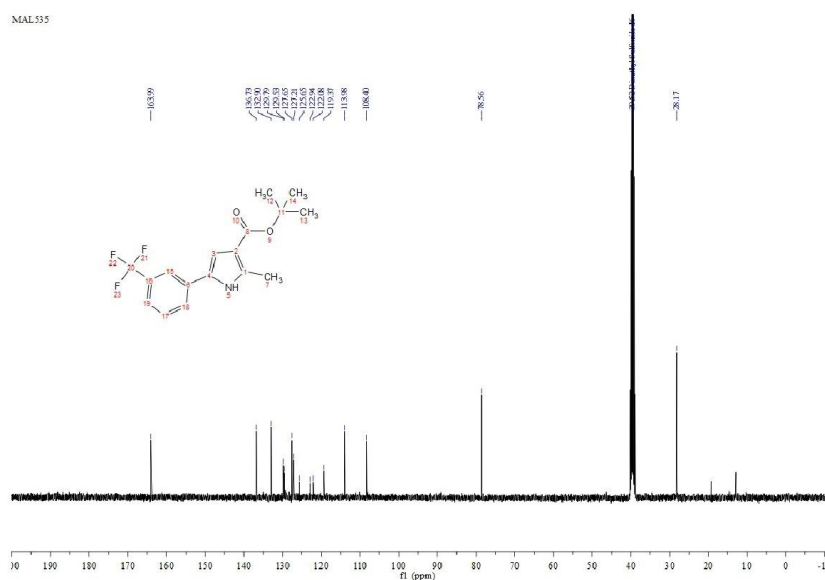


Supplementary Figure 65: ^{13}C NMR spectrum of **P9** in DMSO- d_6 .

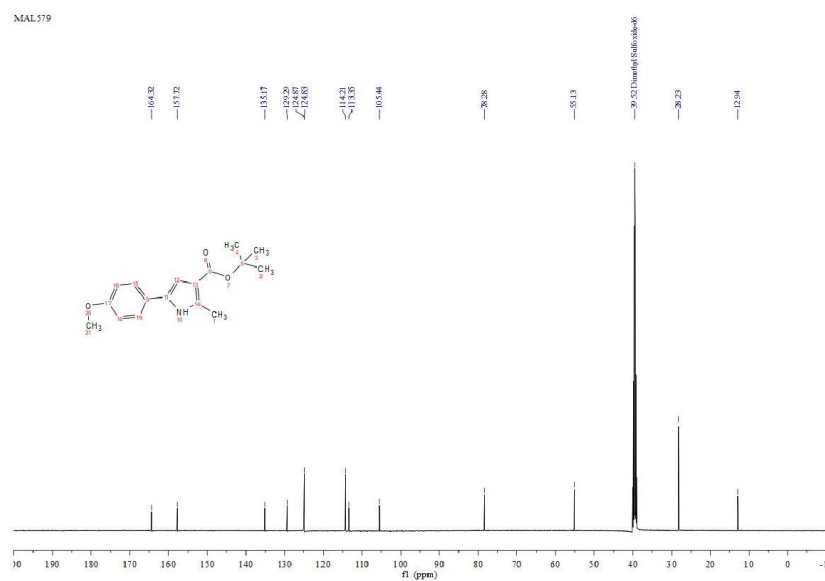
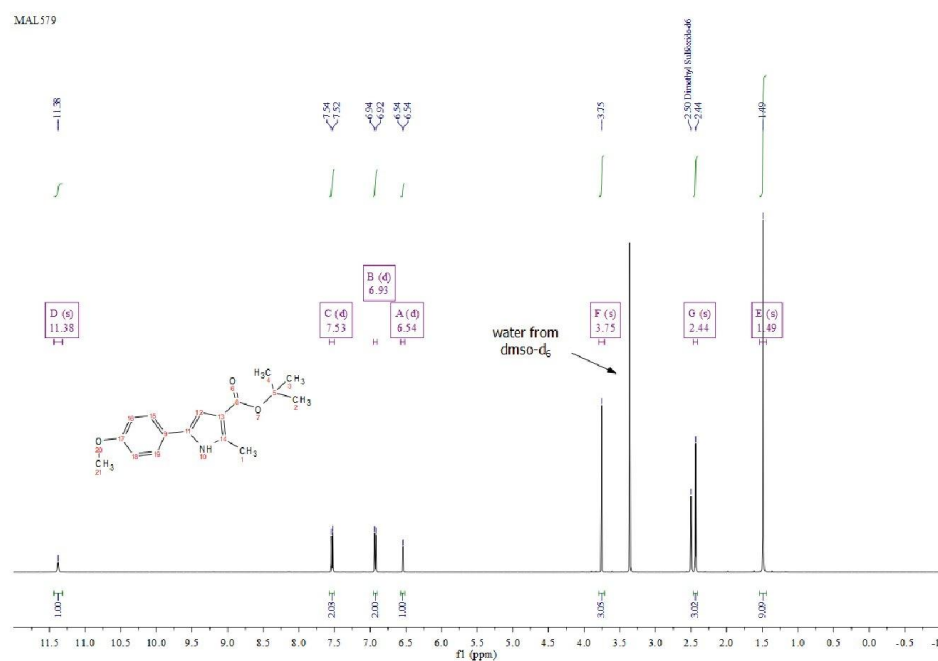


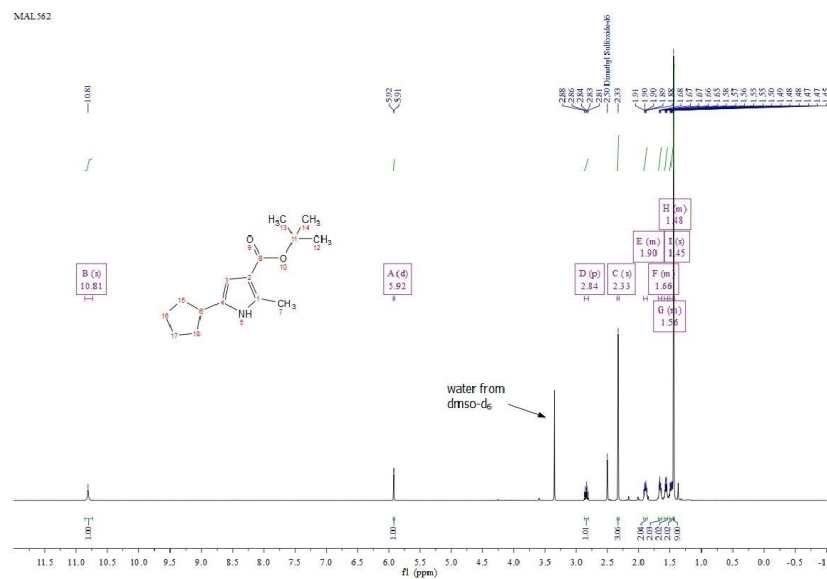


Supplementary Figure 68: ^1H NMR spectrum of **P11** in DMSO-d_6 .

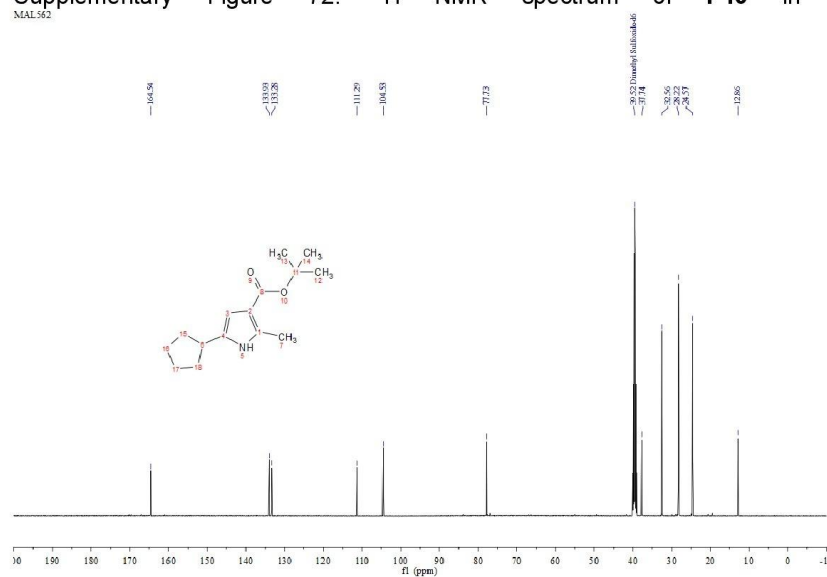


Supplementary Figure 69: ^{13}C NMR spectrum of **P11** in DMSO-d_6 .

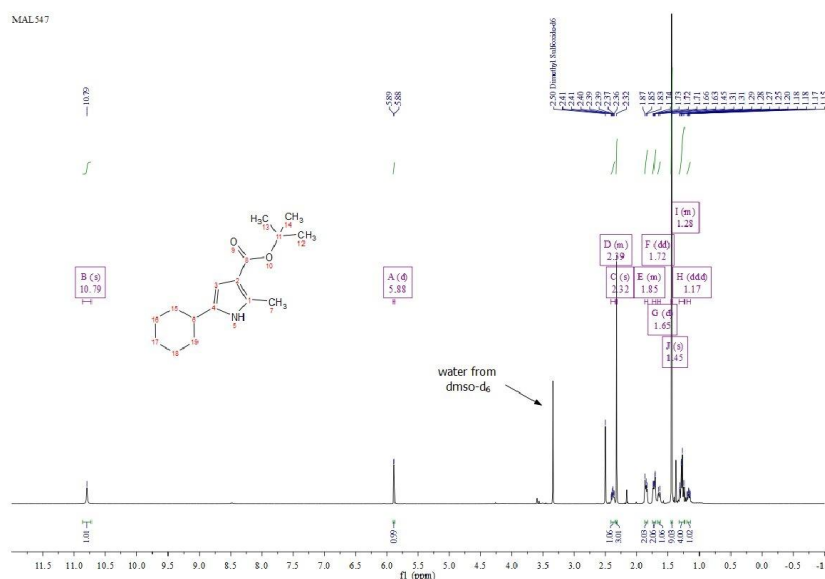




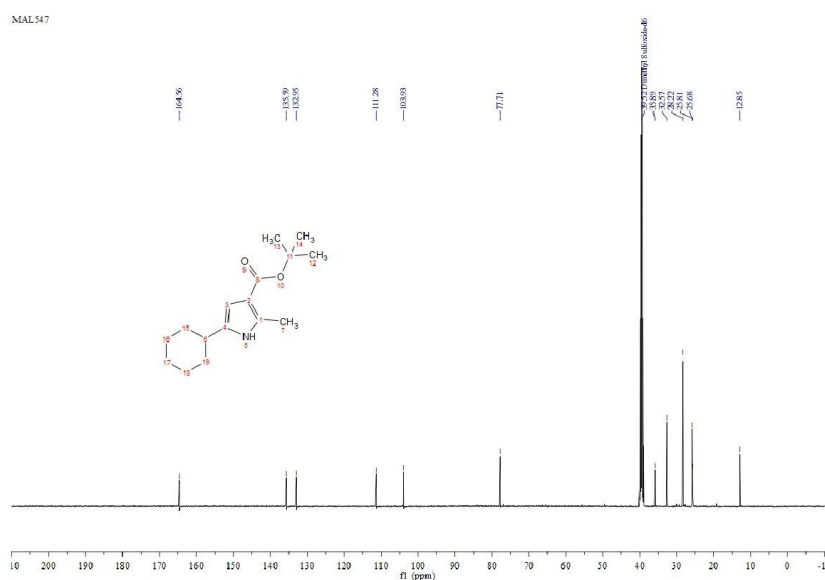
Supplementary Figure 72: ^1H NMR spectrum of **P13** in DMSO-d_6 .



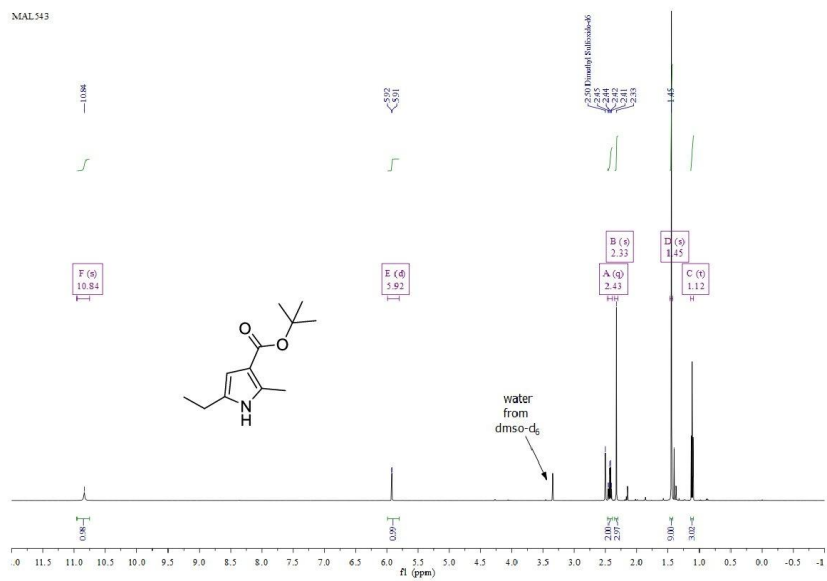
Supplementary Figure 73: ^{13}C NMR spectrum of **P13** in DMSO-d_6 .



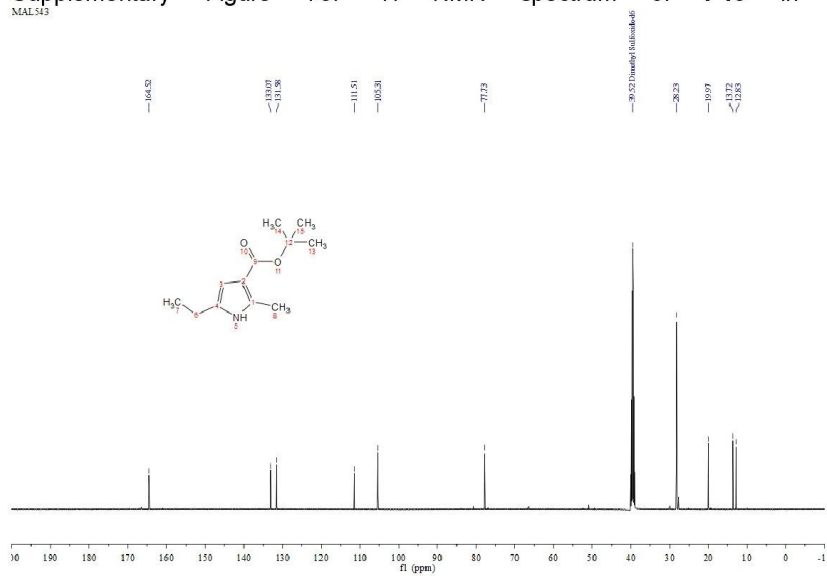
Supplementary Figure 74: ^1H NMR spectrum of **P14** in DMSO- d_6 .

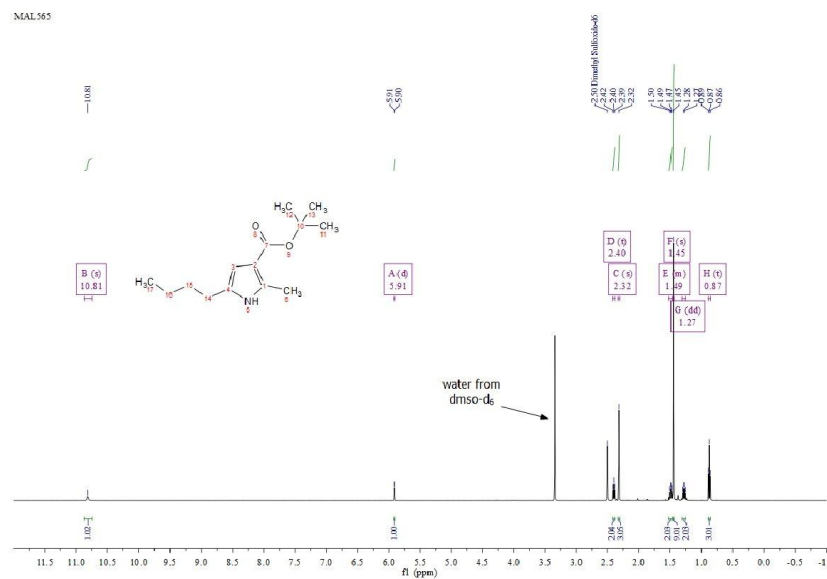


Supplementary Figure 75: ^{13}C NMR spectrum of **P14** in DMSO- d_6 .

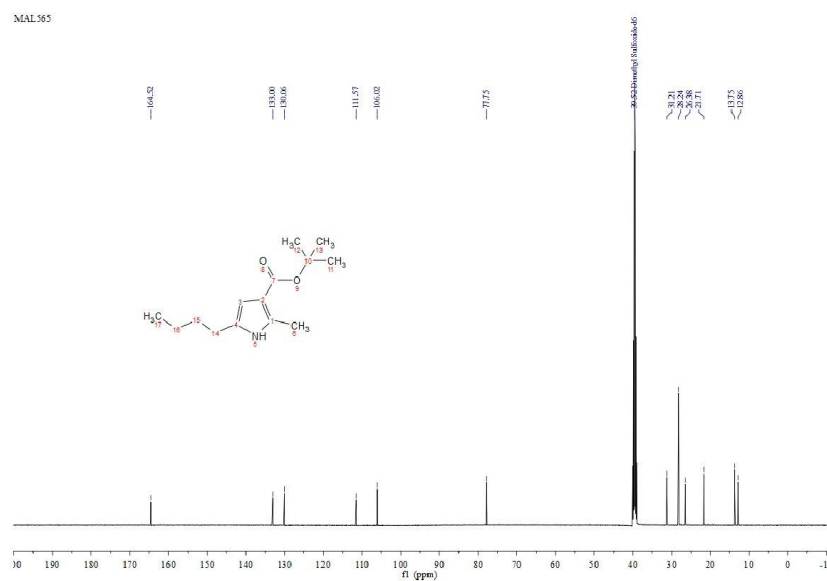


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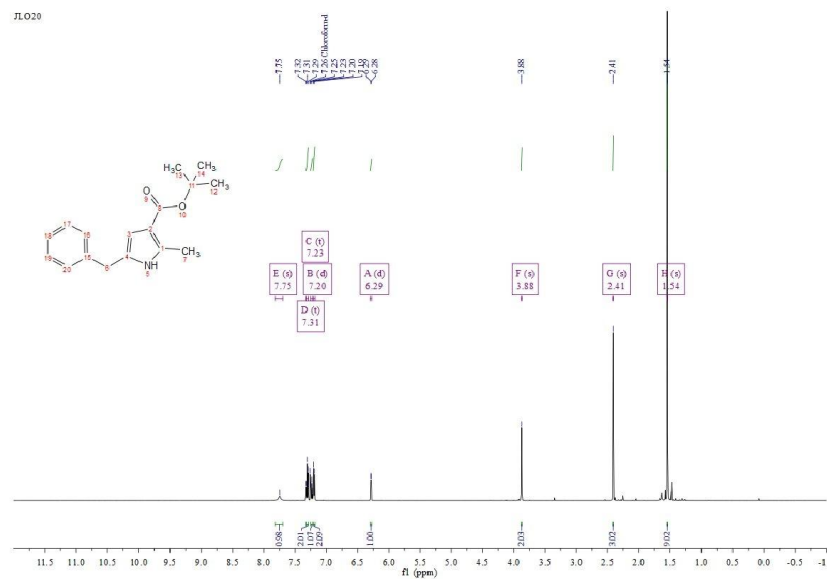




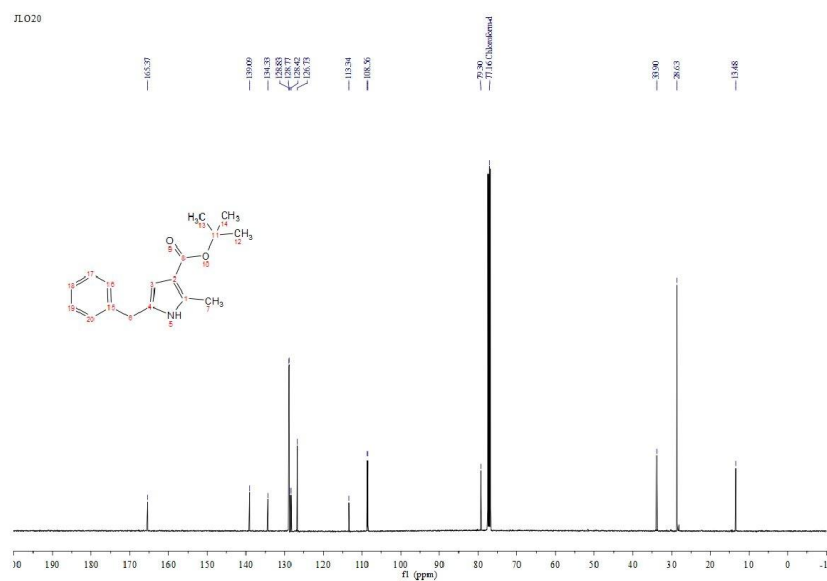
Supplementary Figure 78: ^1H NMR spectrum of **P16** in $\text{DMSO-}d_6$.



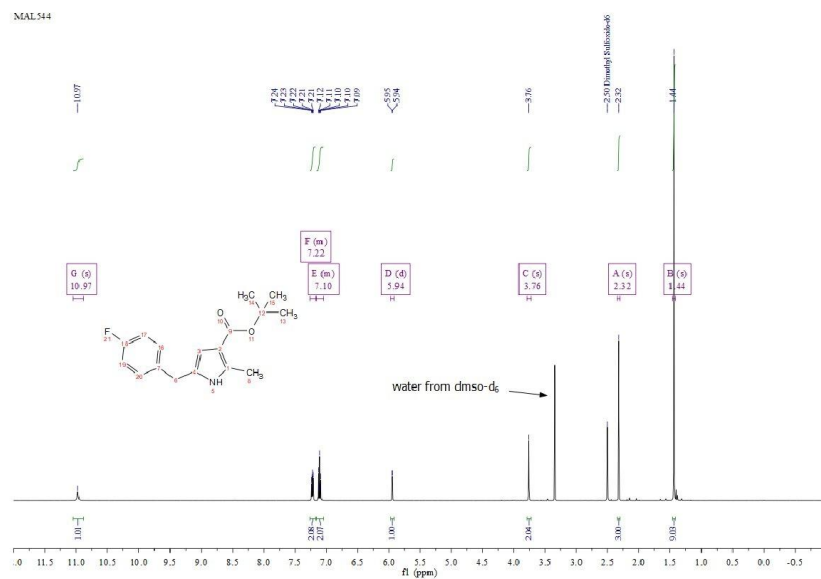
Supplementary Figure 79: ^{13}C NMR spectrum of **P16** in $\text{DMSO-}d_6$.



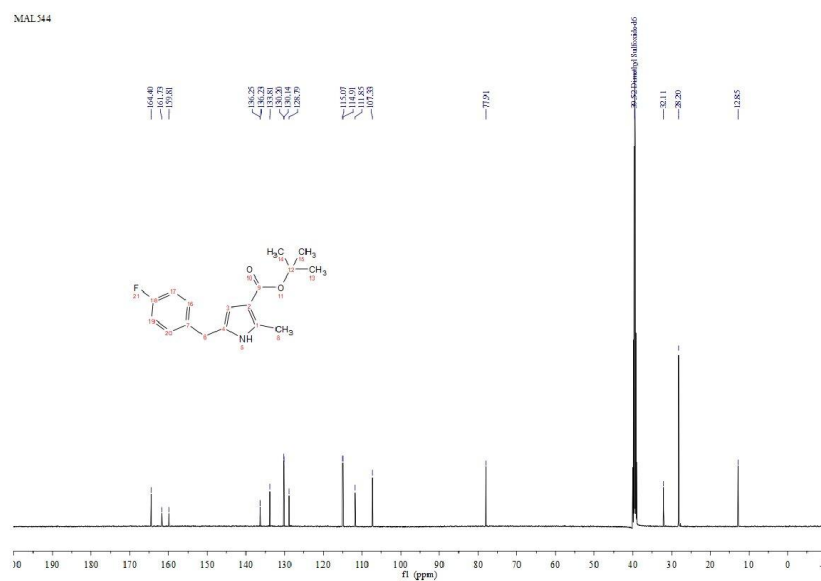
Supplementary Figure 80: ^1H NMR spectrum of **P17** in CD_2Cl_2 .



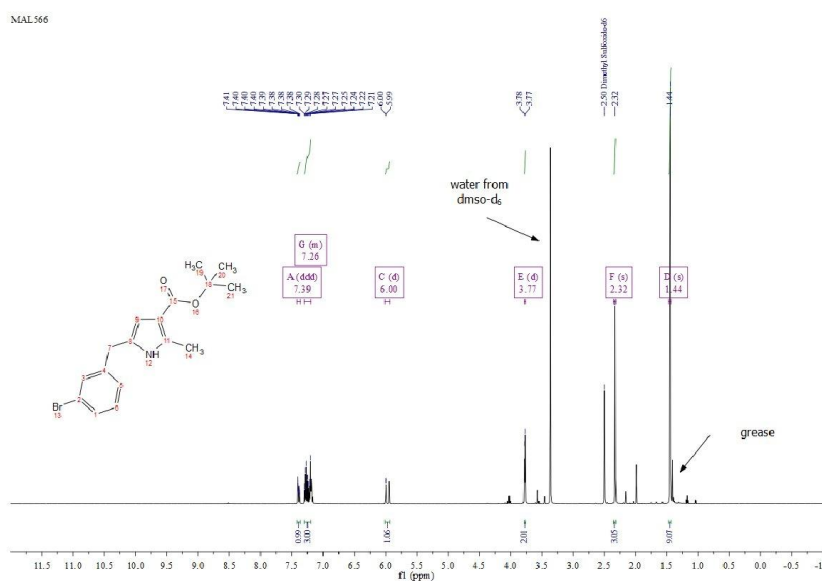
Supplementary Figure 81: ^{13}C NMR spectrum of **P17** in CD_2Cl_2 .



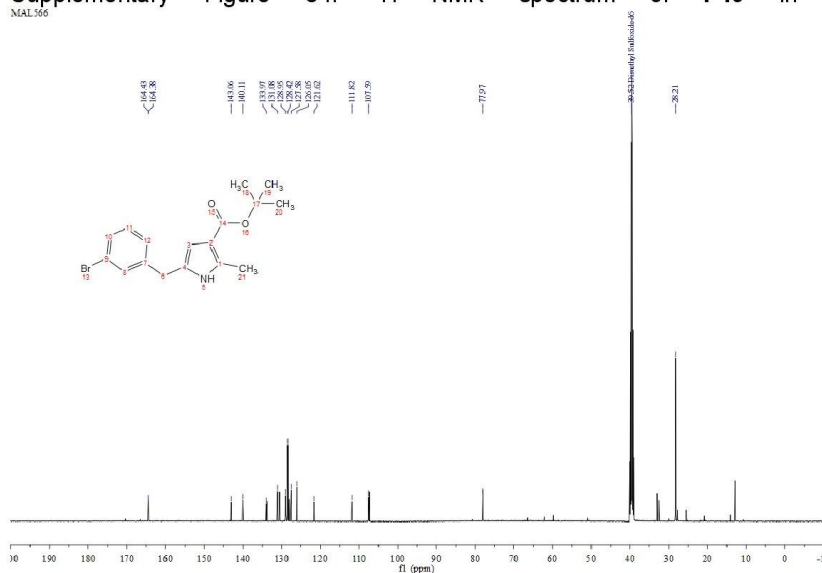
Supplementary Figure 82: ^1H NMR spectrum of **P18** in DMSO-d_6 .



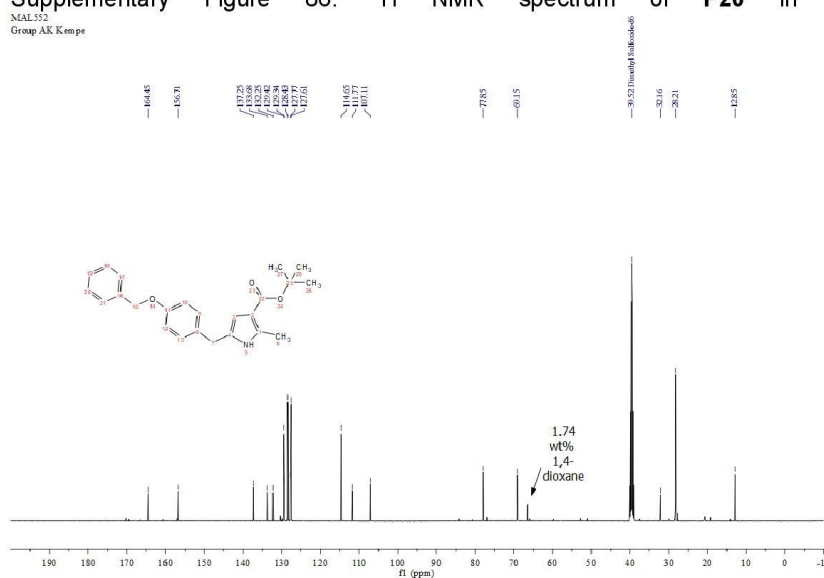
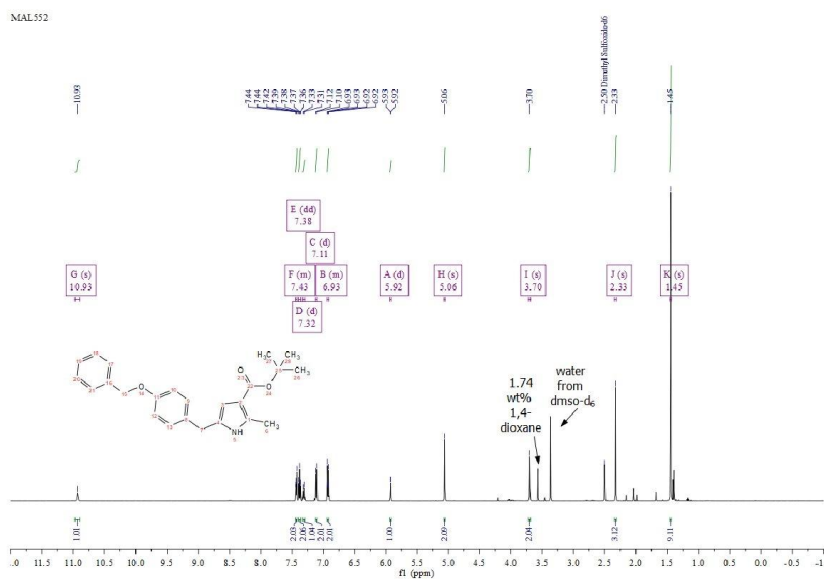
Supplementary Figure 83: ^{13}C NMR spectrum of **P18** in DMSO-d_6 .

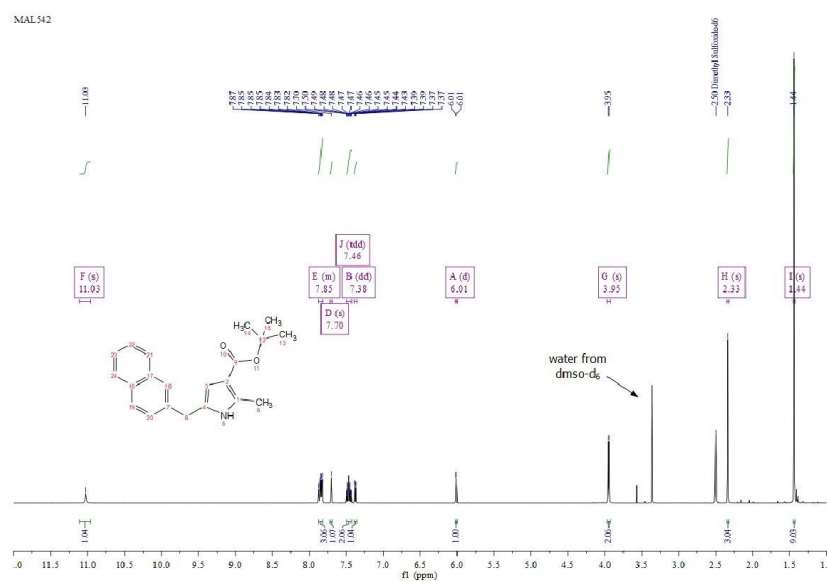


Supplementary Figure 84: ^1H NMR spectrum of **P19** in DMSO-d_6 .

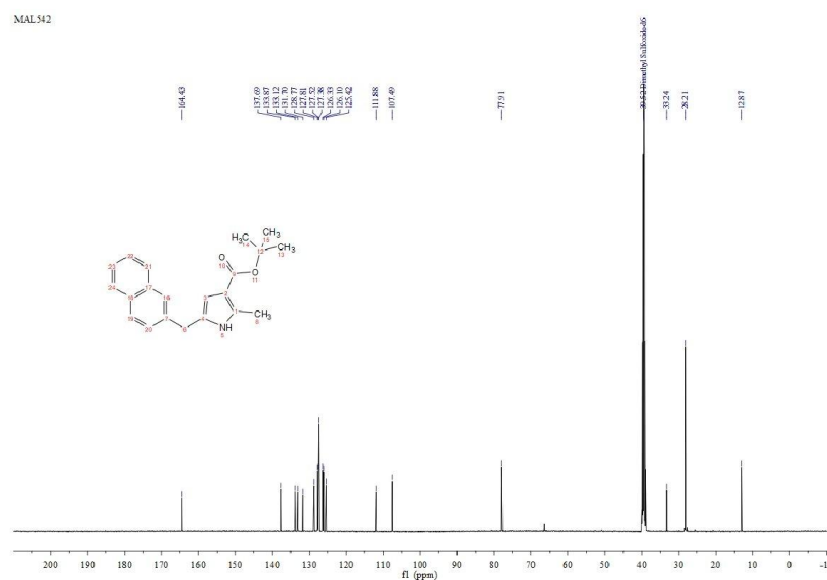


Supplementary Figure 85: ^{13}C NMR spectrum of **P19** in DMSO- d_6 .

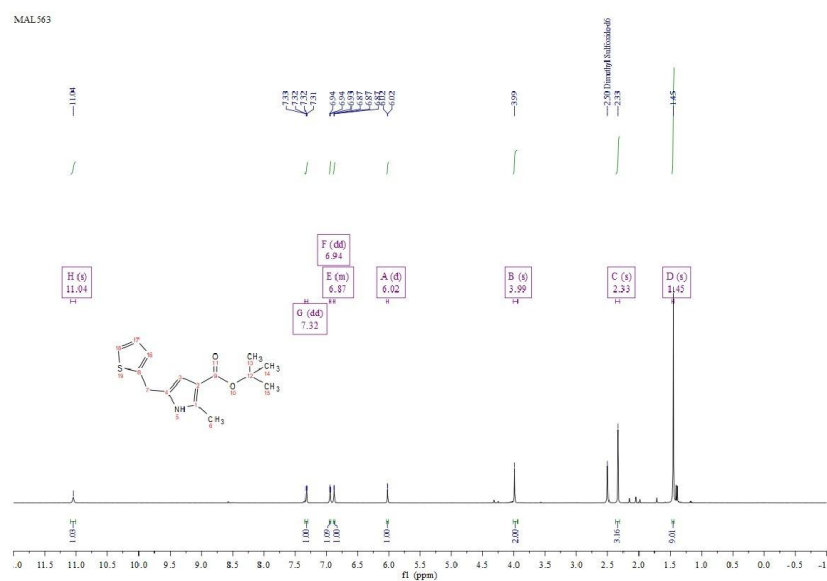




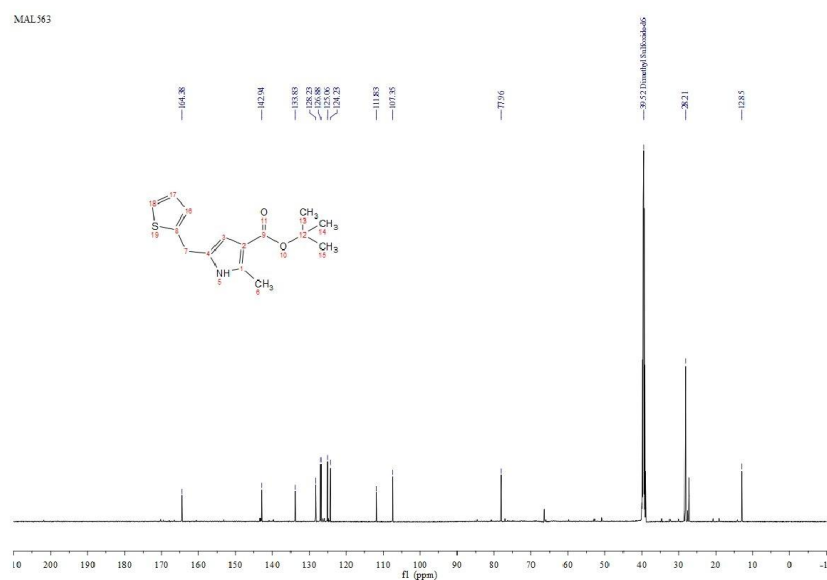
Supplementary Figure 88: ¹H NMR spectrum of **P21** in DMSO-d₆.



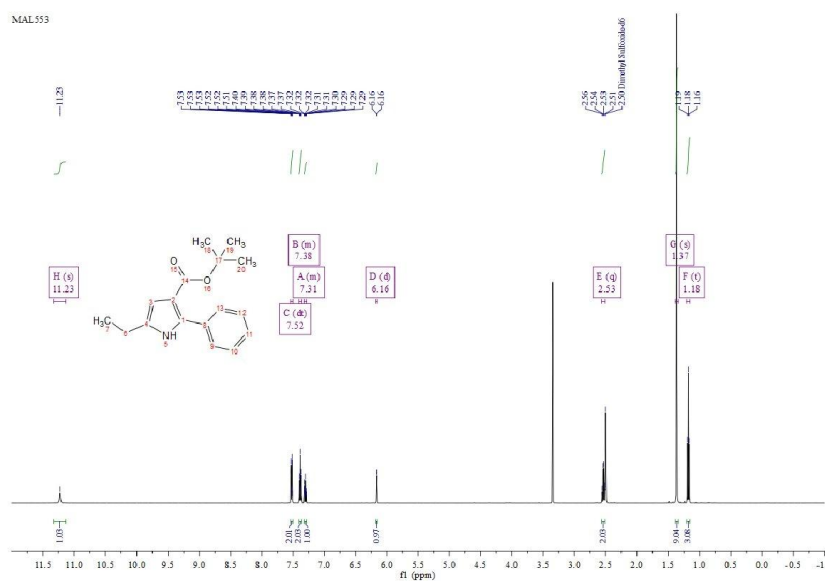
Supplementary Figure 89: ¹³C NMR spectrum of **P21** in DMSO-d₆.



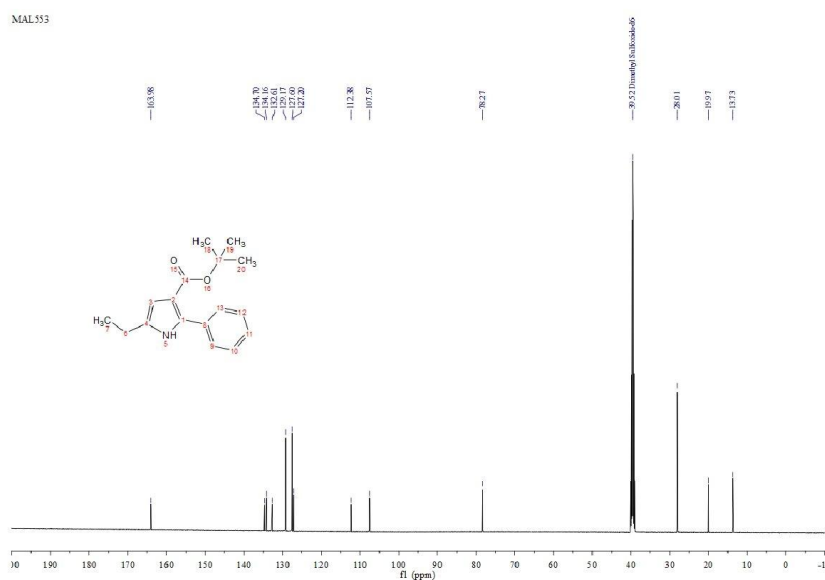
Supplementary Figure 90: ^1H NMR spectrum of **P22** in DMSO-d_6 .



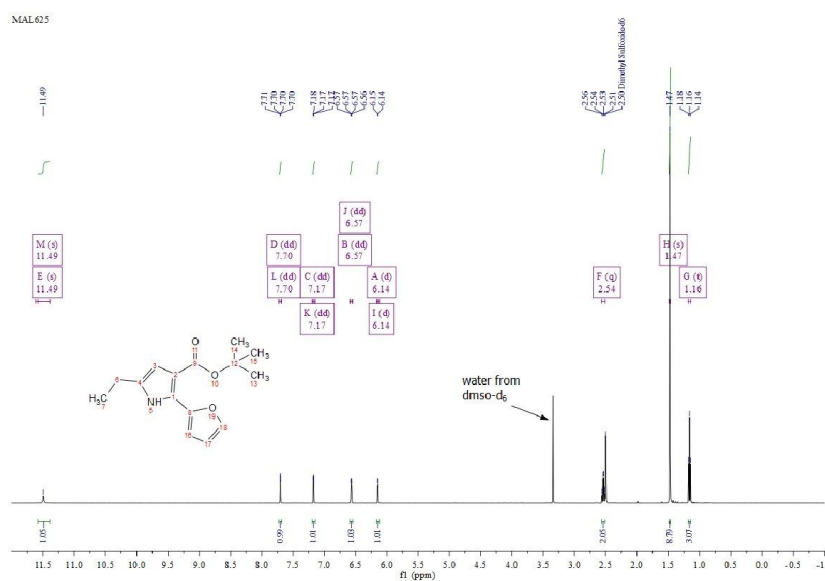
Supplementary Figure 91: ^{13}C NMR spectrum of **P22** in DMSO-d_6 .



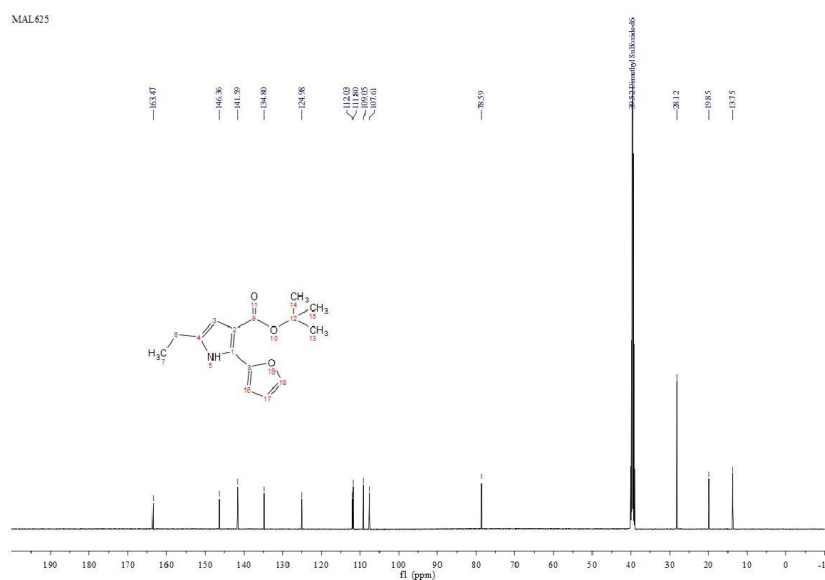
Supplementary Figure 92: ^1H NMR spectrum of **P23** in DMSO- d_6 .



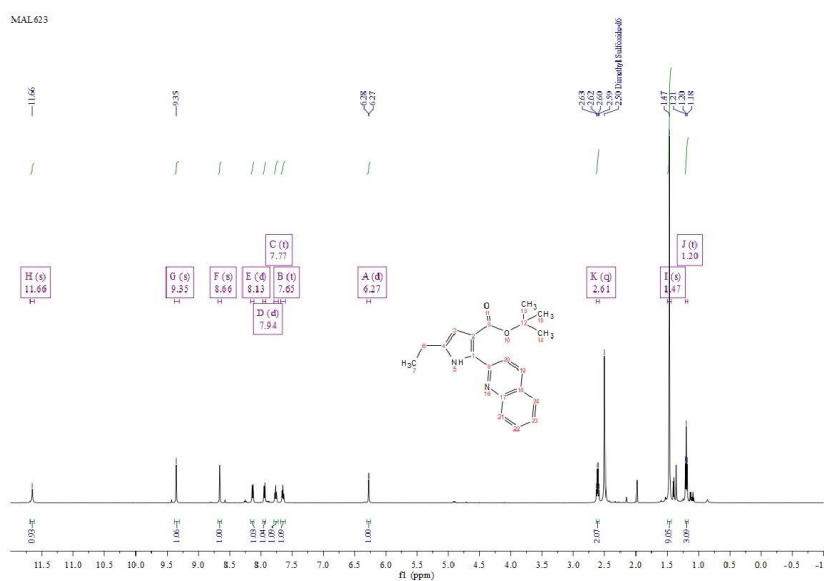
Supplementary Figure 93: ^{13}C NMR spectrum of **P23** in DMSO- d_6 .



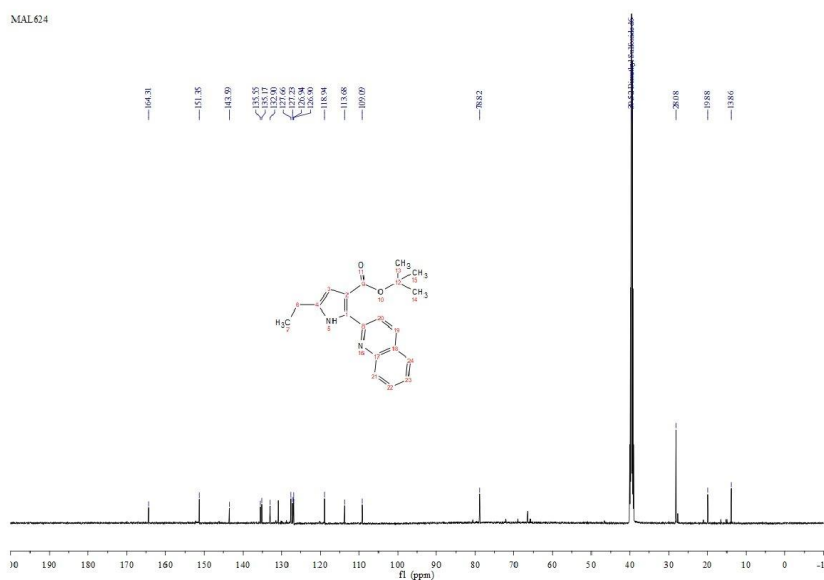
Supplementary Figure 94: ¹H NMR spectrum of **P24** in DMSO-d₆.



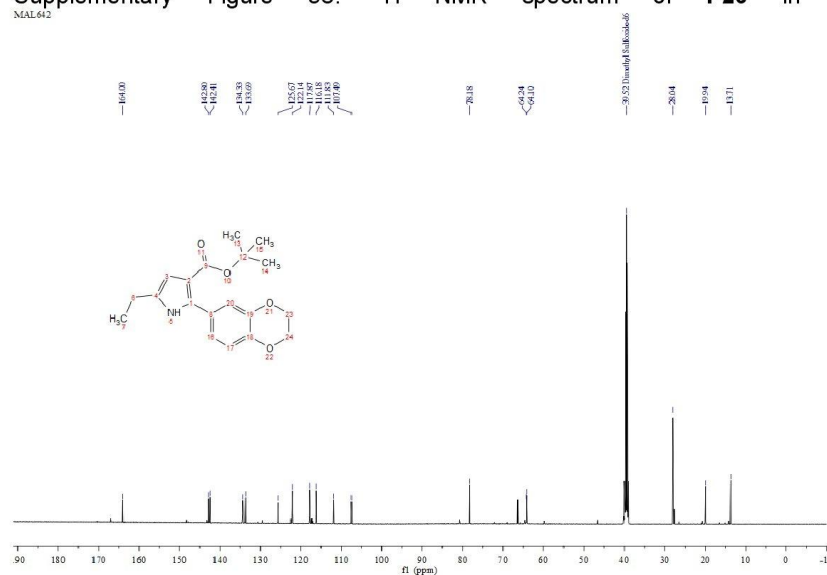
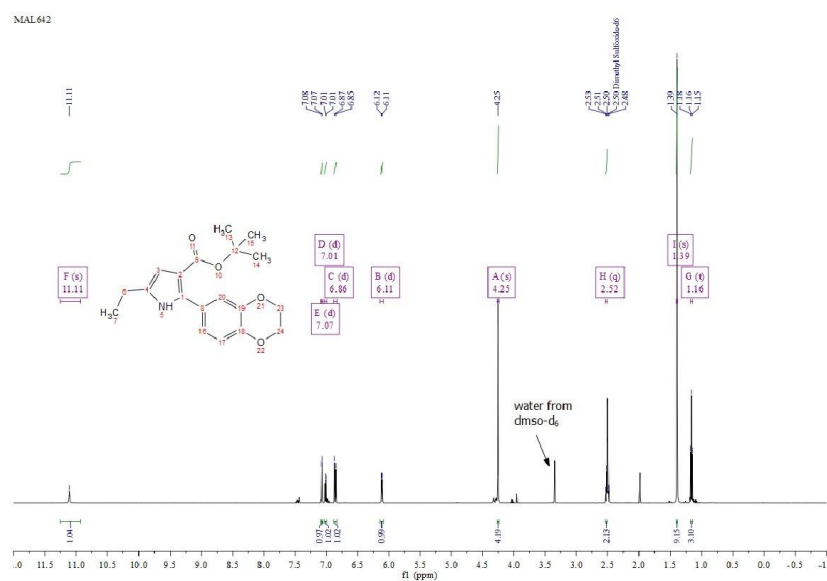
Supplementary Figure 95: ¹³C NMR spectrum of **P24** in DMSO-d₆.



Supplementary Figure 96: ^1H NMR spectrum of **P25** in DMSO-d_6 .

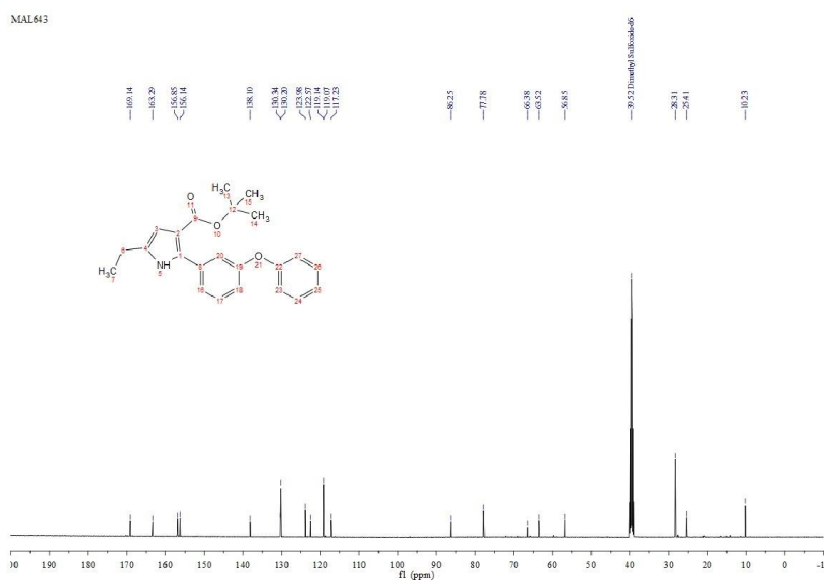


Supplementary Figure 97: ^{13}C NMR spectrum of **P25** in DMSO-d_6 .

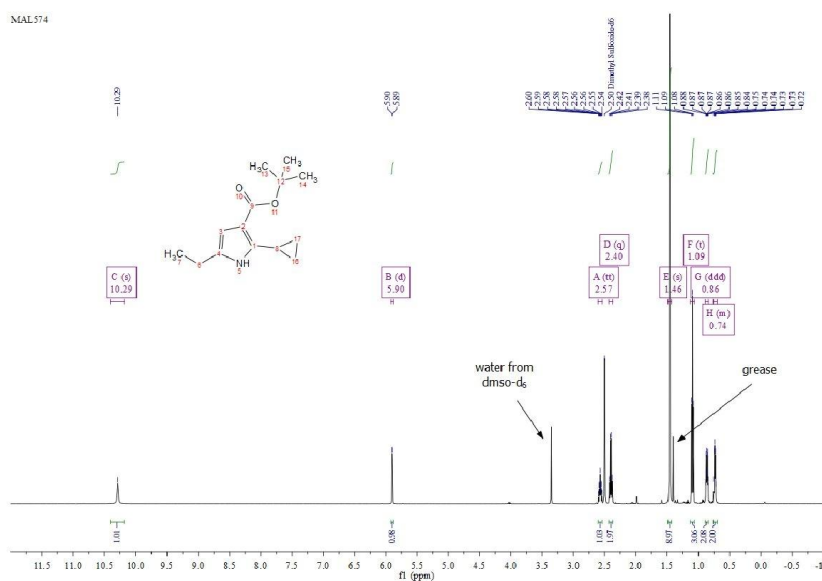




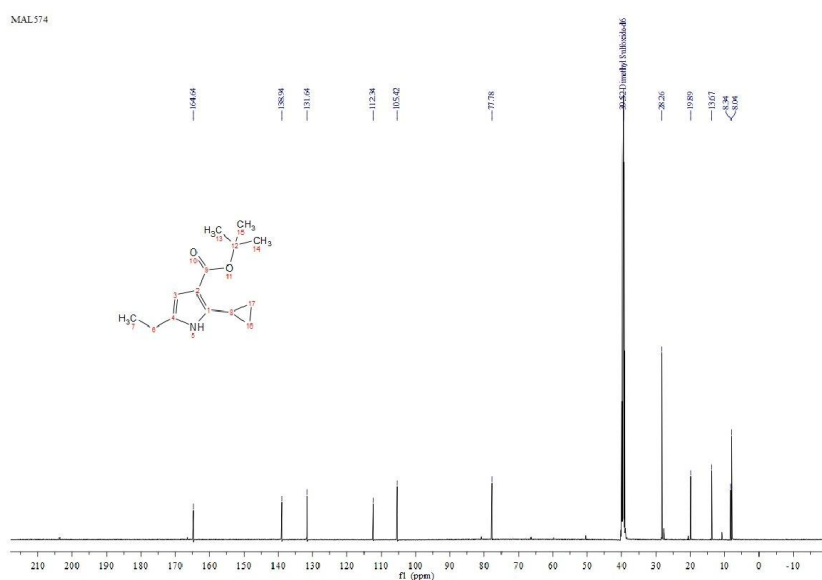
Supplementary Figure 100: ^1H NMR spectrum of **P27** in DMSO-d_6 .



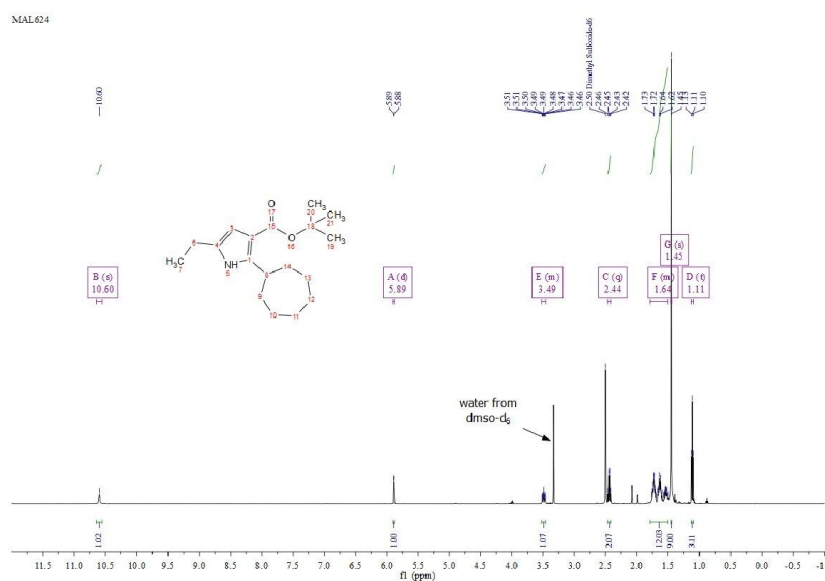
Supplementary Figure 101: ^{13}C NMR spectrum of **P27** in DMSO-d_6 .



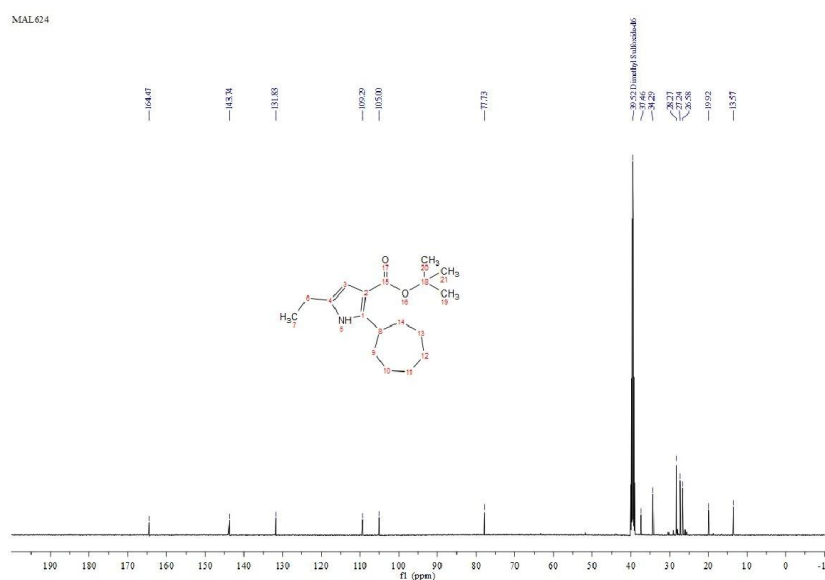
Supplementary Figure 102: ^1H NMR spectrum of **P28** in DMSO-d_6 .



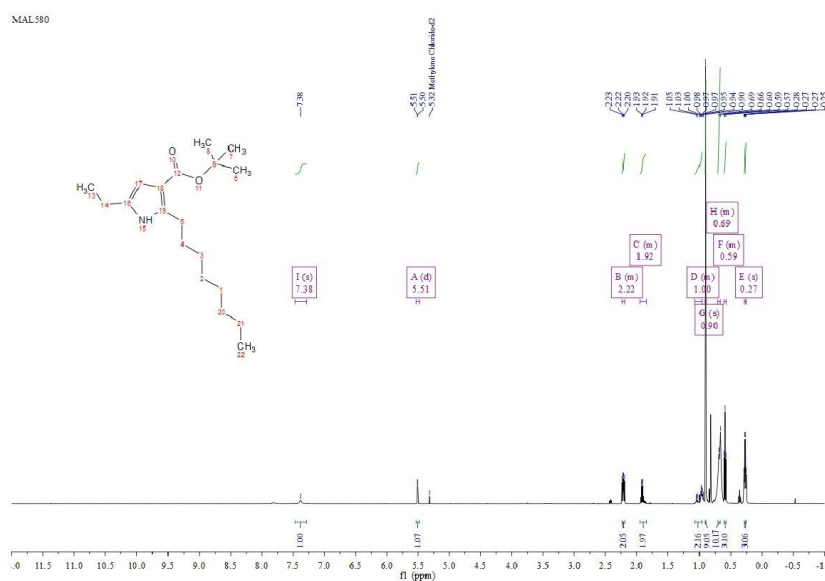
Supplementary Figure 103: ^{13}C NMR spectrum of **P28** in DMSO-d_6 .



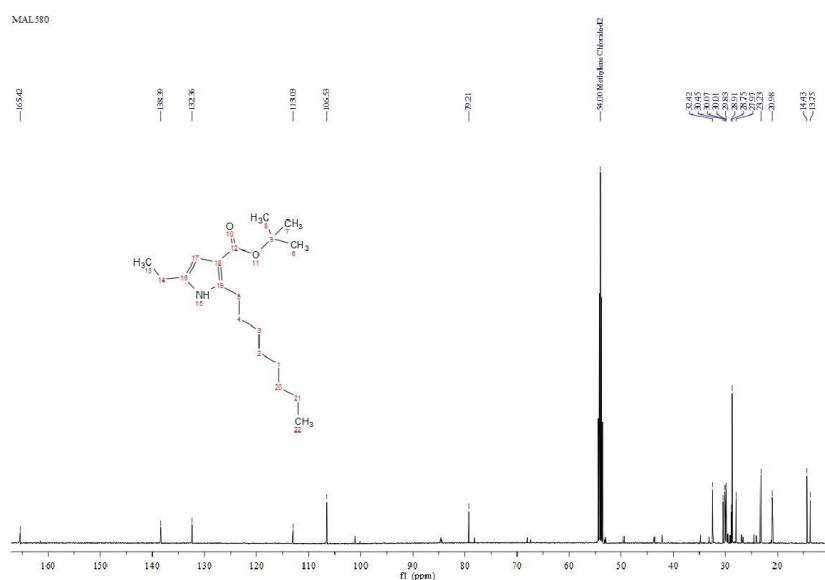
Supplementary Figure 104: ¹H NMR spectrum of **P29** in DMSO-d₆.



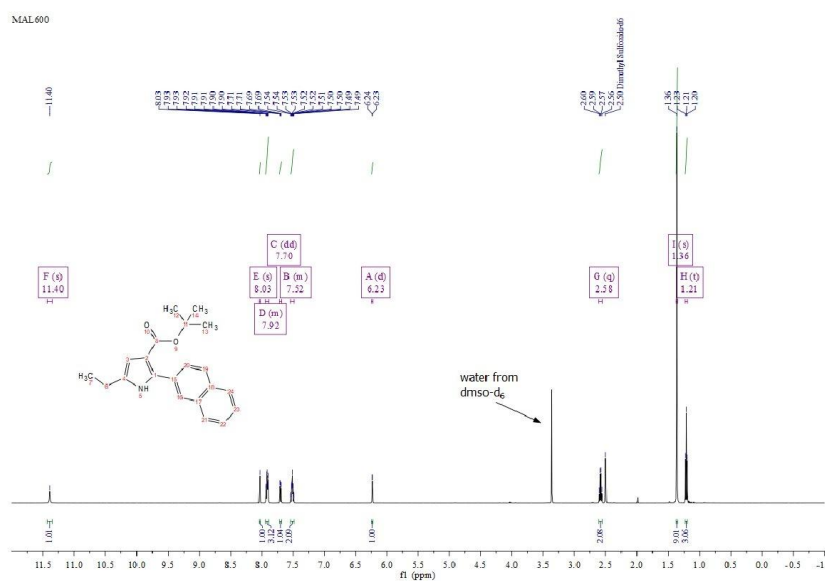
Supplementary Figure 105: ¹³C NMR spectrum of **P29** in DMSO-d₆.



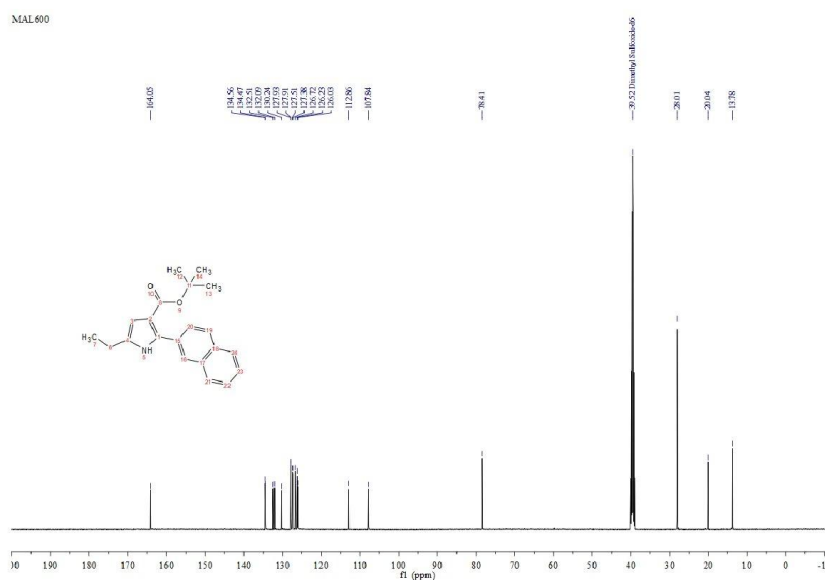
Supplementary Figure 106: ¹H NMR spectrum of **P30** in CD₂Cl₂.



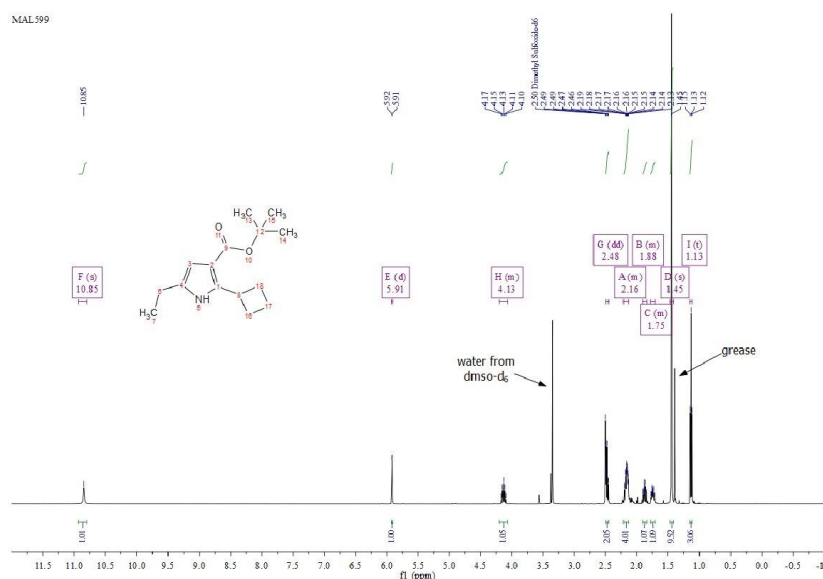
Supplementary Figure 107: ¹³C NMR spectrum of **P30** in CD₂Cl₂.



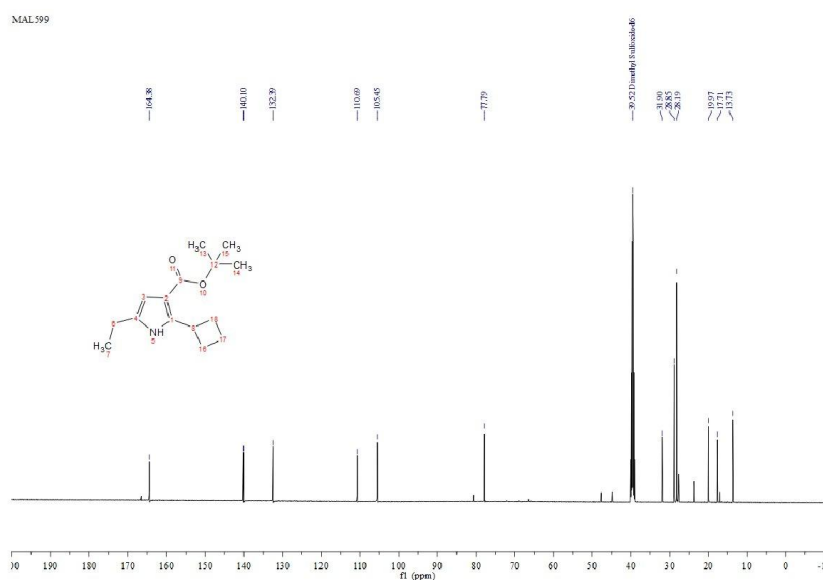
Supplementary Figure 108: ¹H NMR spectrum of **P31** in DMSO-d₆.



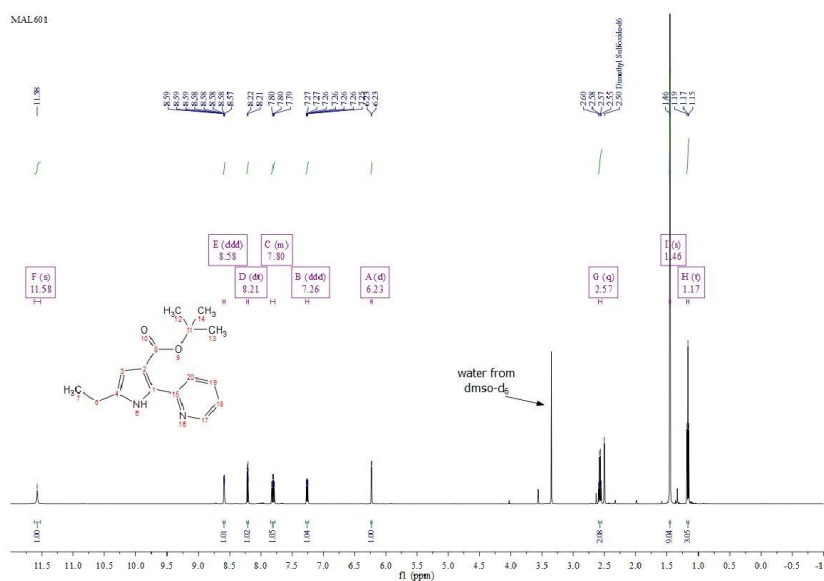
Supplementary Figure 109: ¹³C NMR spectrum of **P31** in DMSO-d₆.



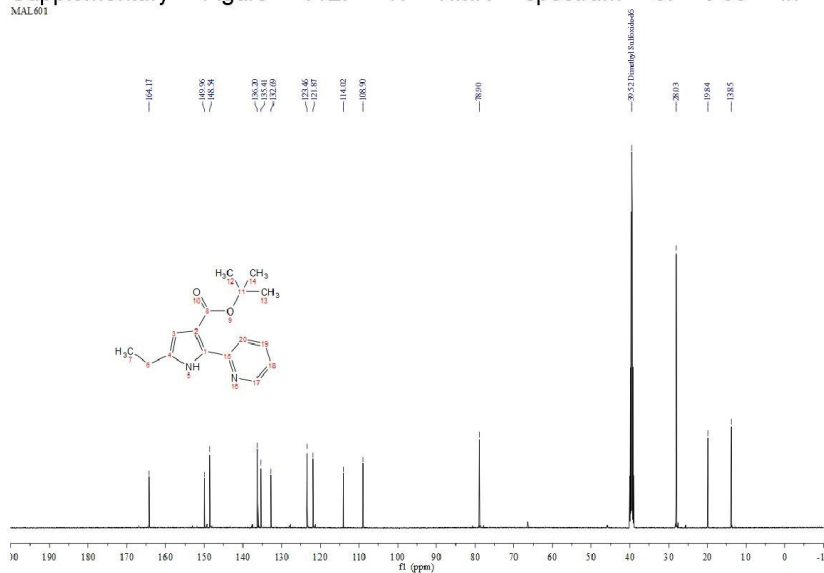
Supplementary Figure 110: ^1H NMR spectrum of **P32** in DMSO- d_6 .



Supplementary Figure 111: ^{13}C NMR spectrum of **P32** in DMSO- d_6 .

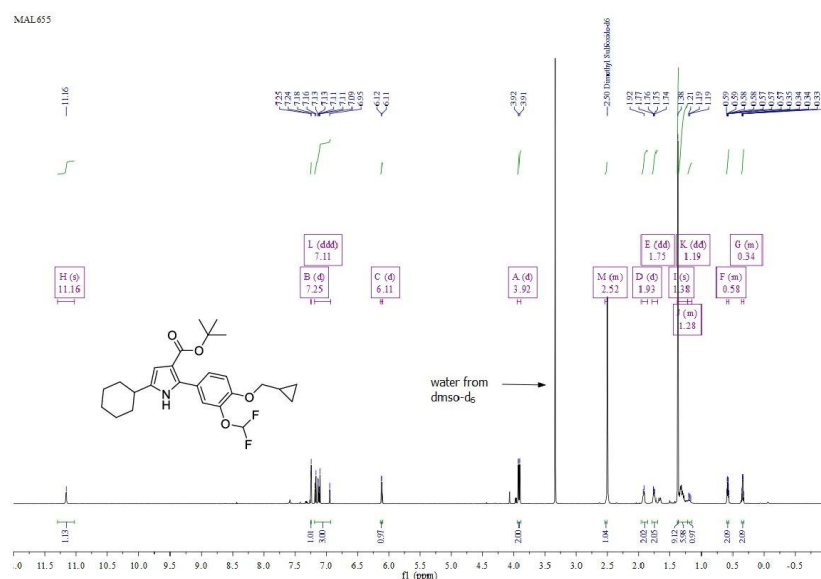


Supplementary Figure 112: ^1H NMR spectrum of **P33** in DMSO- d_6 .

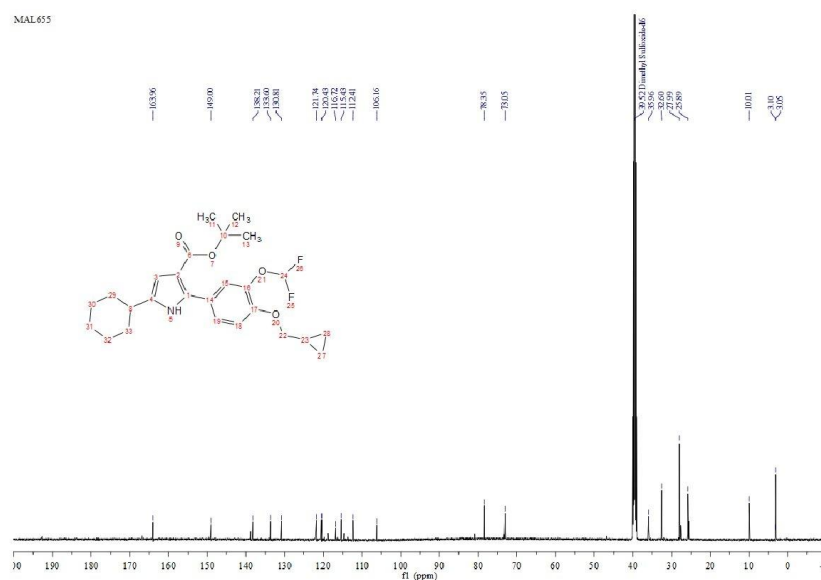


Supplementary Figure 113: ^{13}C NMR spectrum of **P33** in DMSO- d_6 .

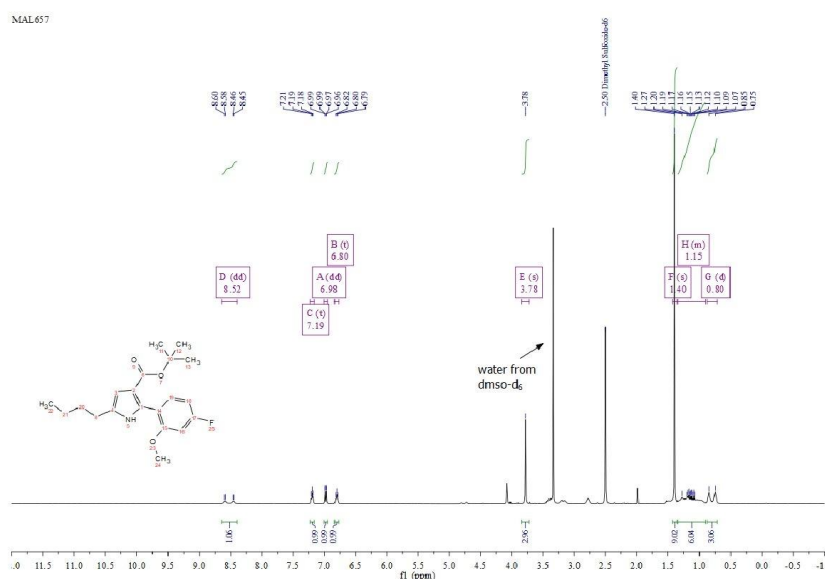
S101



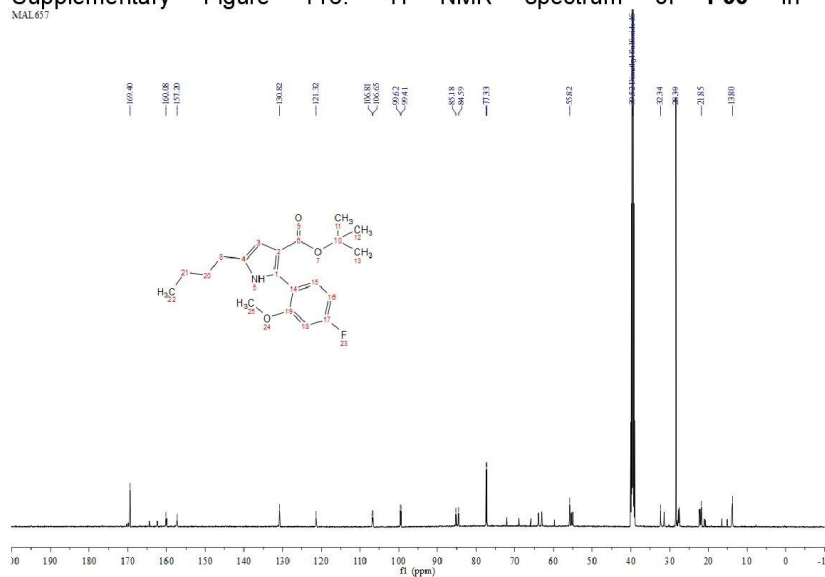
Supplementary Figure 114: ¹H NMR spectrum of **P34** in DMSO-d₆.



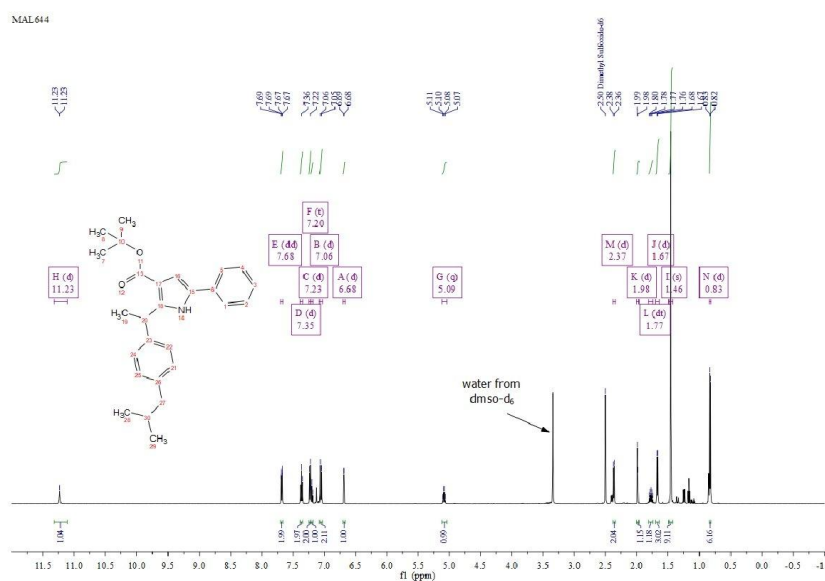
Supplementary Figure 115: ¹³C NMR spectrum of **P34** in DMSO-d₆.



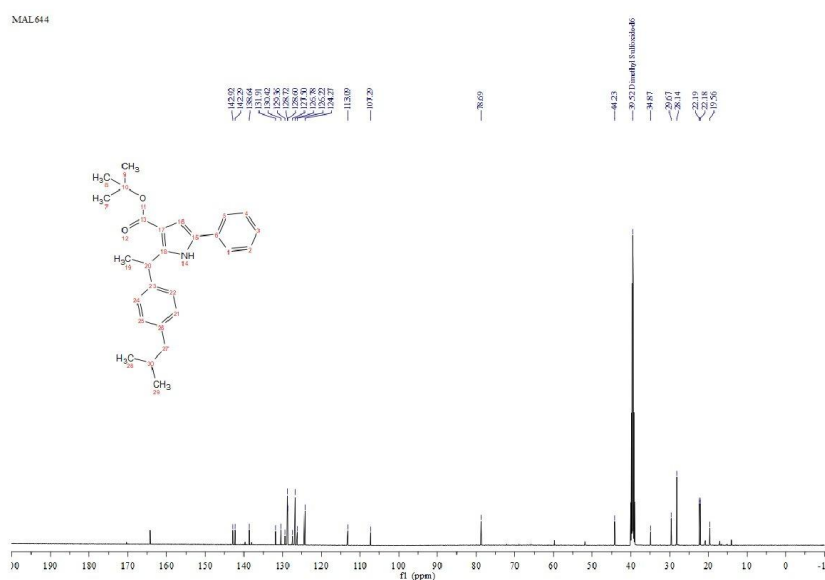
Supplementary Figure 116: ^1H NMR spectrum of **P35** in DMSO-d_6 .



Supplementary Figure 117: ^{13}C NMR spectrum of **P35** in DMSO-d_6 .

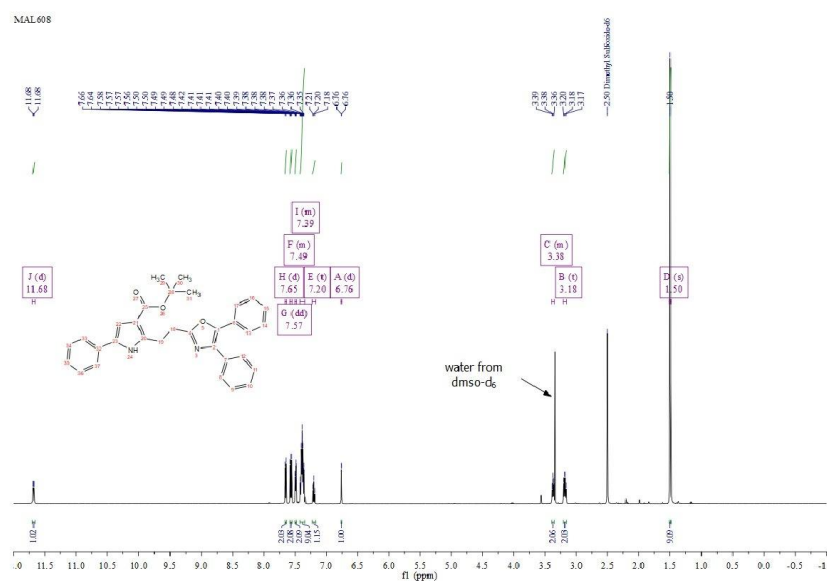


Supplementary Figure 118: ^1H NMR spectrum of **P36** in DMSO- d_6 .

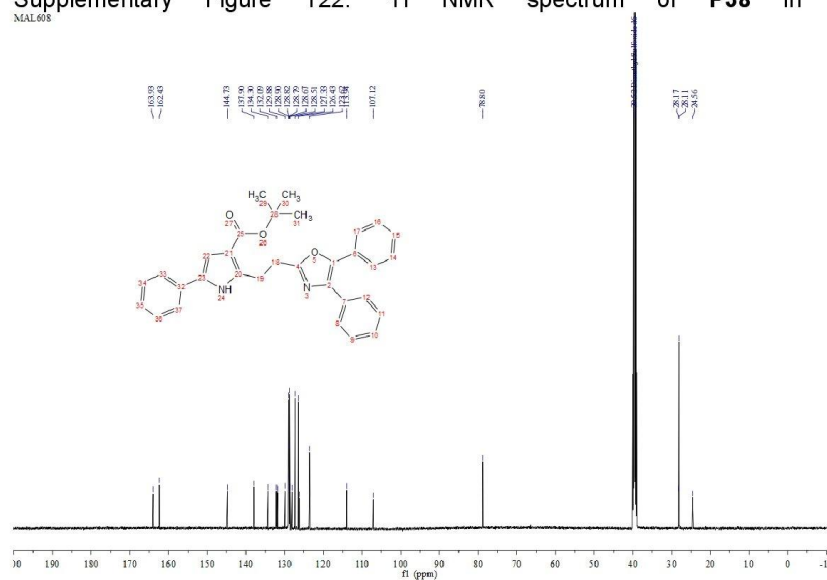


Supplementary Figure 119: ^{13}C NMR spectrum of **P36** in DMSO- d_6 .

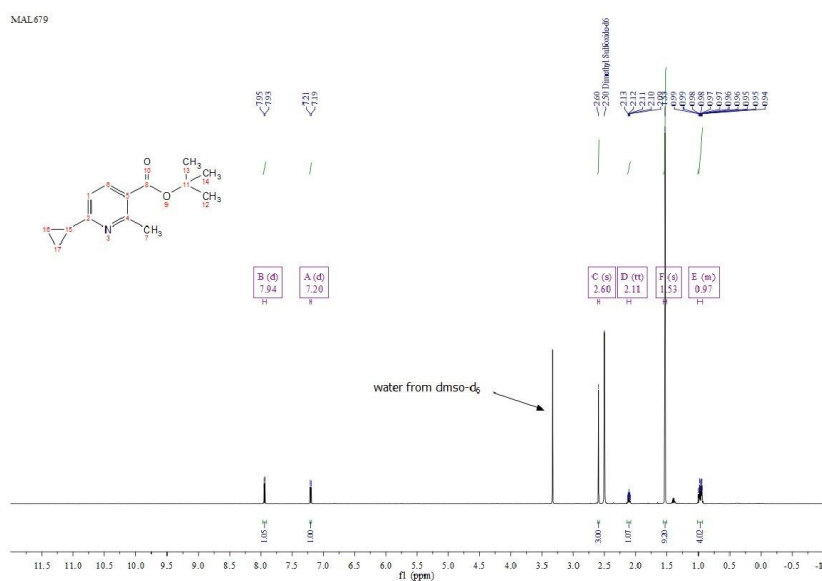




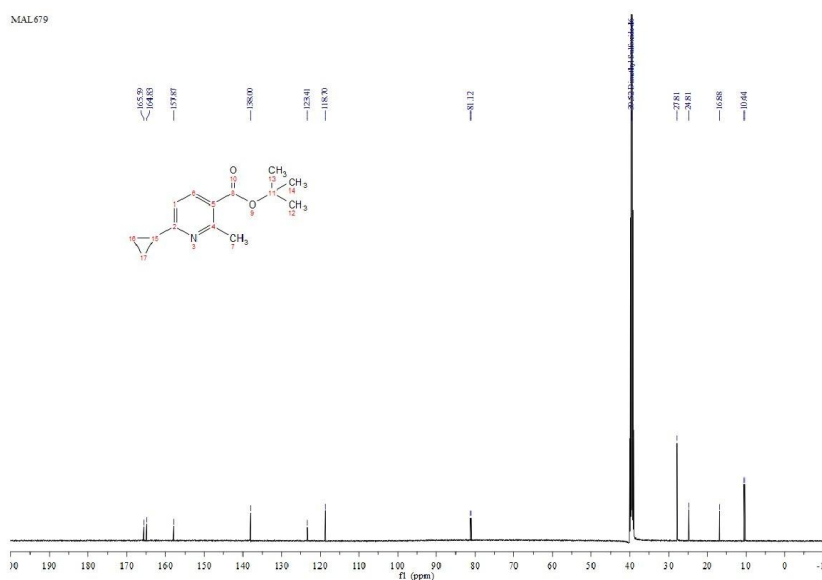
Supplementary Figure 122: ^1H NMR spectrum of **P38** in DMSO- d_6 .



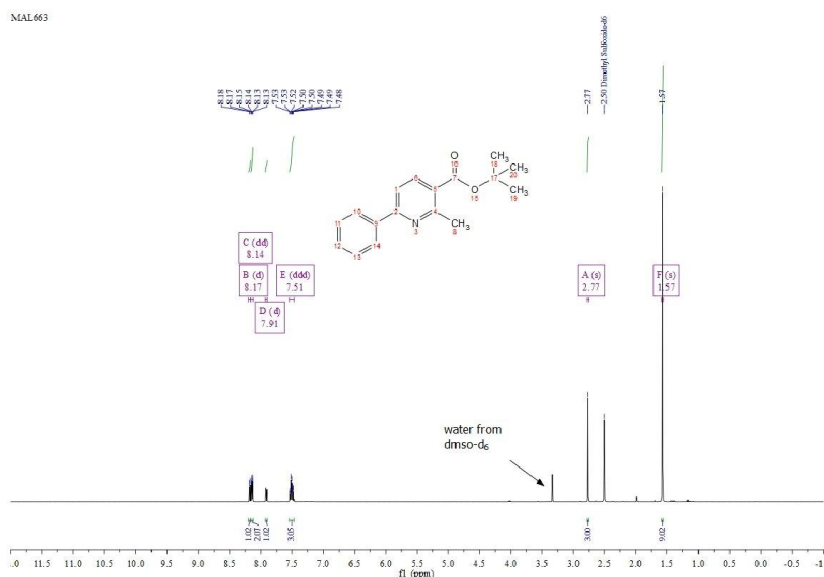
Supplementary Figure 123: ^{13}C NMR spectrum of **P38** in DMSO- d_6 .



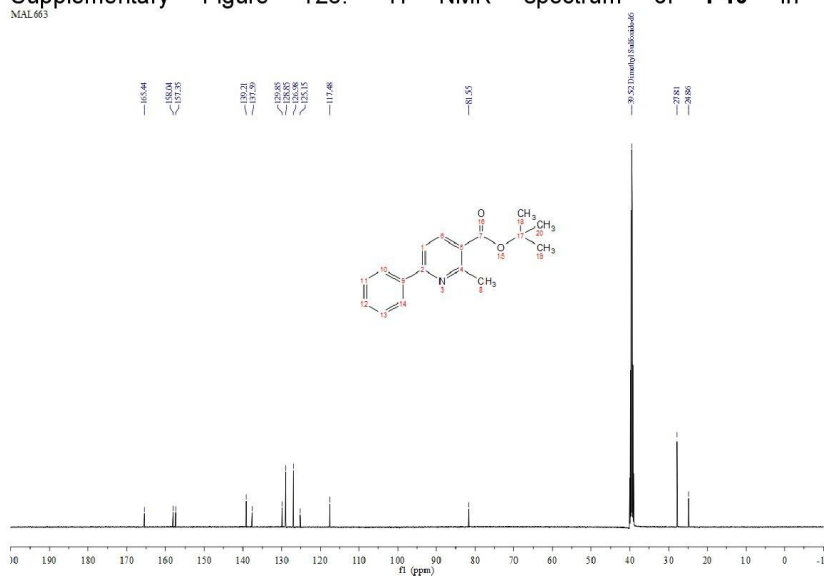
Supplementary Figure 124: ¹H NMR spectrum of **P39** in DMSO-d₆.



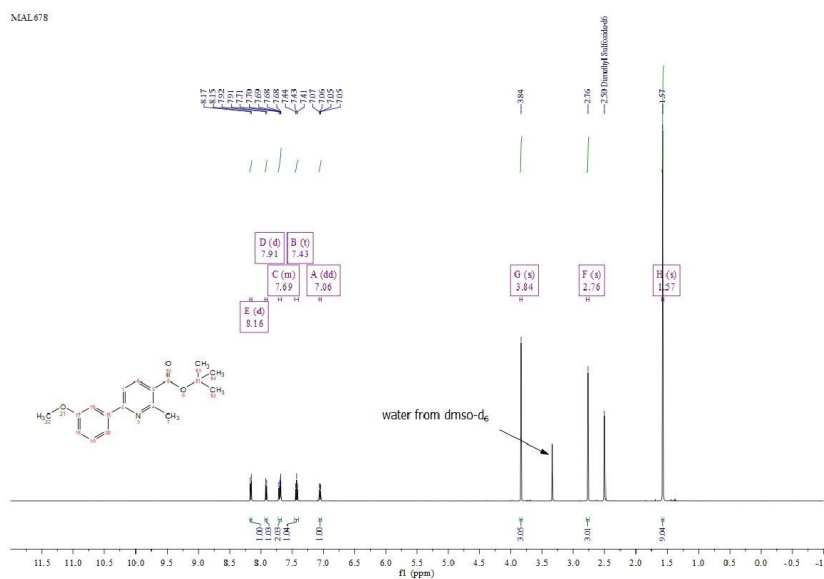
Supplementary Figure 125: ¹³C NMR spectrum of **P39** in DMSO-d₆.



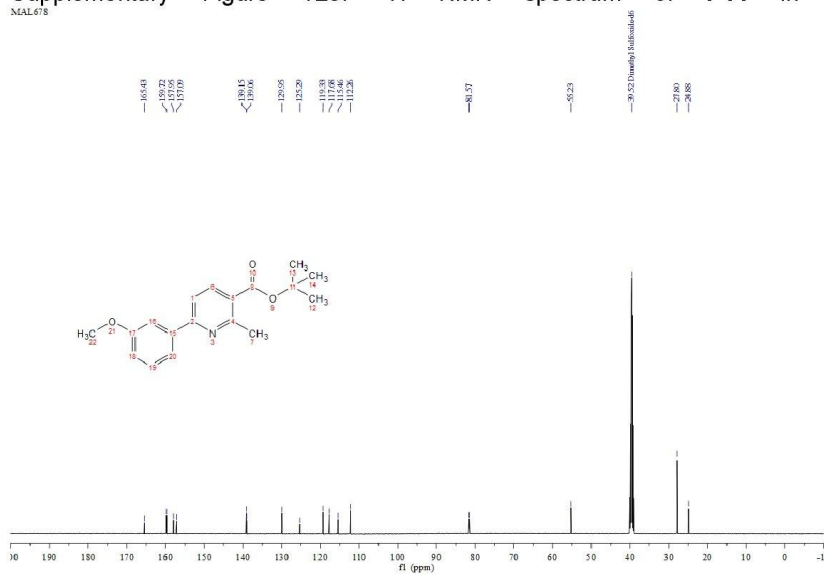
Supplementary Figure 126: ¹H NMR spectrum of **P40** in DMSO-d₆.



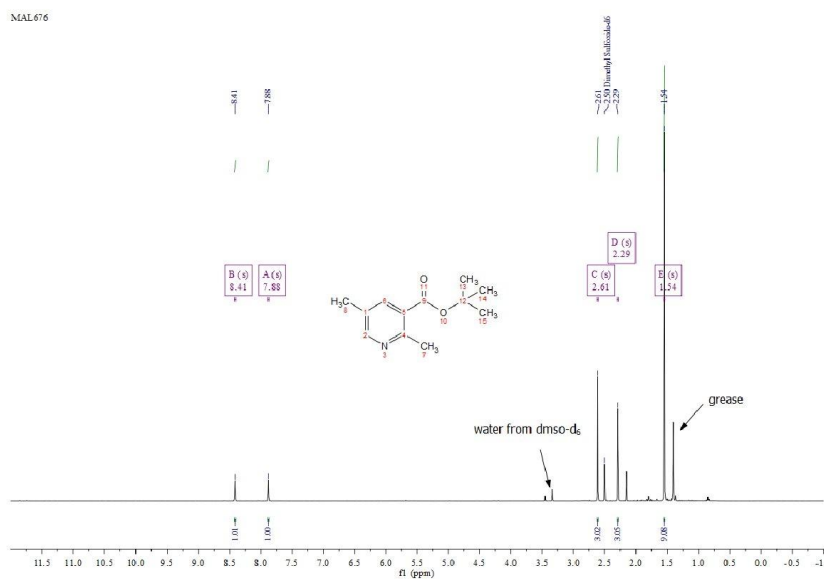
Supplementary Figure 127: ¹³C NMR spectrum of **P40** in DMSO-d₆.



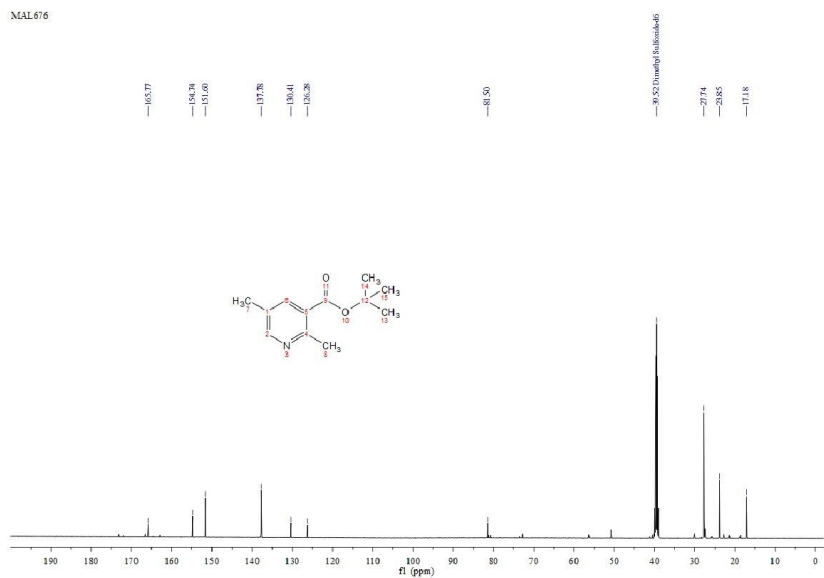
Supplementary Figure 128: ¹H NMR spectrum of **P41** in DMSO-d₆.



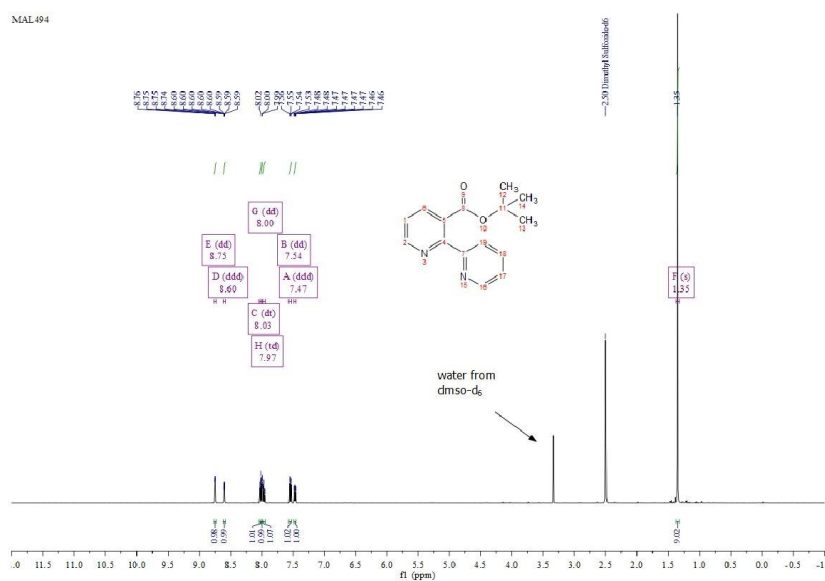
Supplementary Figure 129: ¹³C NMR spectrum of **P41** in DMSO-d₆.



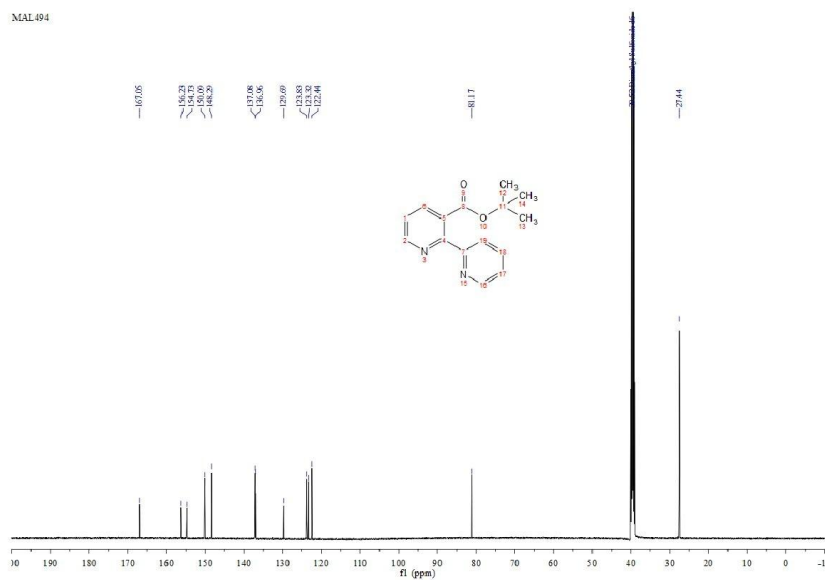
Supplementary Figure 130: ^1H NMR spectrum of **P42** in $\text{DMSO-}d_6$.



Supplementary Figure 131: ^{13}C NMR spectrum of **P42** in $\text{DMSO-}d_6$.



Supplementary Figure 132: ¹H NMR spectrum of **P43** in DMSO-d₆.



Supplementary Figure 133: ¹³C NMR spectrum of **P43** in DMSO-d₆.

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8. CATALYTIC TWO-STEP SYNTHESIS OF SEQUENCE DEFINED POLYAMINES

Title: Catalytic two-step synthesis of sequence defined polyamines.

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To be submitted

RESEARCH ARTICLE

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Supporting information for this article is given via a link at the end of the document.

Abstract:

Monodisperse and sequence-defined polymers are abundant and of fundamental importance in nature. Polypeptides and DNA are examples, but rare in artificial chemical synthesis. We report here the synthesis of monodisperse, sequence-defined and flexible macromolecules containing an arylamine main chain. Palladium-catalyzed cross-coupling and nitroarene hydrogenation were used to form the new amine end group enabling further chain growth. Readily available 1-chloro-4-nitrobenzenes were used as building blocks mostly to avoid protecting group chemistry and activate the aryl chloride for the amination step. Alkylation of the secondary arylamines increases the stability and solubility of the macromolecules, and the synthesis, for instance, of a decamer without solubility problems under catalytic conditions was demonstrated. Alteration of the arene and/or the alkyl substituent permits a two-dimensional structure variation and the synthesis of even more complex molecules. The amine end group is accessible for functionalization chemistry, and pyrrole synthesis and cross-linking have been demonstrated.

Introduction

Monodisperse and sequence-defined and flexible oligomers and polymers are abundant in nature but rare in chemical synthesis.[1,2,3] Polypeptides or DNA are typical examples and the basis of the complex structures enabling life.[4,5,6,7] Amines play a fundamentally important role in chemistry and the life sciences. [8,9,10,11] Many bulk and fine chemicals are amines and the amine motive figures prominently among pharmaceuticals and other bioactive small molecules. [12,13,14] Polyanilines (Figure 1a) are conducting polymers used in electronics, [15,16] organic light-emitting diodes materials, [17] biosensors [18,19,20] and electrode materials. [21,22] Oligoaniline composites (Figure 1a) are used in drug delivery, [23,24] bioimaging, [25,26] tissue engineering [27] and antimicrobial therapy [28,29], and Fedratinib® and Imatinib® are anticancer drugs containing a di(arylamine) structure (Figure 1a). [30] Monodisperse oligoanilines have been synthesized (Figure 1b) iteratively [31,32,33,34], but sequence flexibility has not been demonstrated. We have reported recently on iterative olefin [35,36] and N-heterocyclic syntheses [37], and report here on the synthesis of monodisperse, sequence-defined and flexible oligo- and polyamines that contain an arylamine main chain. We used Pd-catalyzed aryl amination of 1-halogeno-3-or-4-nitrobenzenes followed by nitro group hydrogenation to form the new amine end group enabling the next chain growth step. Readily available 1-chloro-4-nitrobenzenes were mostly used to avoid a protecting group approach and activate the aryl chloride for the amination step. Alkylation of the secondary arylamines obtained after each chain growth step increases the stability and solubility of the macromolecules, and the synthesis, for instance, of a decamer without solubility problems under catalytic conditions has been demonstrated. Alteration of the arene and/or the alkyl substituent permits a two-dimensional structure variation leading to more structural flexibility and complexity. The amine end group is accessible for diverse functionalization chemistry, and pyrrole synthesis and cross-linking have been demonstrated. The cross-coupling of oligoamine sequences can simplify macromolecule synthesis.

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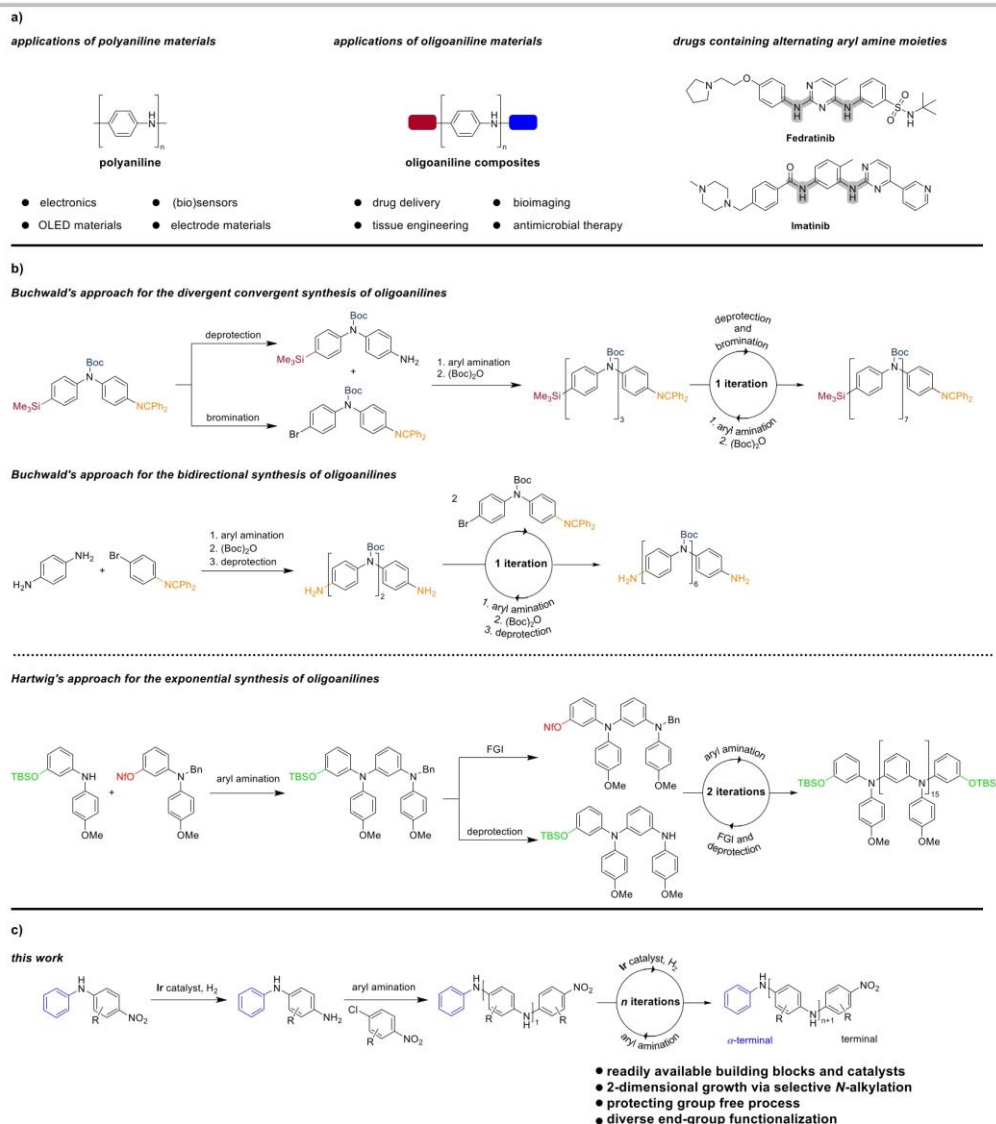


Figure 2. Applications, state of the art of synthesis and work reported here. a) Important areas of application for oligo- and oligoanilines and examples of the key structural motif appearing in active ingredients of marketed drugs. b) Buchwald's approaches to oligoanilines via a divergent convergent or bidirectional synthesis protocol and Hartwig's exponential synthesis of oligo(*m*)-anilines. c) Iterative synthesis of sequence-defined oligoamines via a two-step elongation process. FGI = functional group interconversion.

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Results and Discussion

Optimization of reaction conditions and synthesis of tetraamine 1 and nonaamine 2

The initial phase of the project focused on finding suitable reactions, catalysts and reaction conditions for an iterative catalytic two-step synthesis of oligo- and polyamines. We define oligoamines here as compounds with fewer than eight amine functionalities based on observations that oligoanilines with eight amine functionalities behave like polyanilines.[38],[39],[40] Tetraamine **1** was the initial target molecule and was synthesized by a catalytic two-step sequence combining the Pd-catalyzed aryl amination of anilines and 1-chloro-4-nitrobenzene[41], and Ir-catalyzed nitroarene hydrogenation over seven individual steps (Figure 2, 75 % average yield). During the synthesis, the intermediate secondary amines were found to be sensitive to oxidation, and solubility decreased drastically with increasing chain length. We concluded that *N*-functionalization of the intermediate secondary amine, such as *N*-alkylation, would be beneficial for the synthesis of higher molecular weight derivatives, ensuring both enhanced stability and improved solubility. Moreover, it enables the preparation of polyamines differently functionalized at the main chain and the amine (two-dimensional functionalization), providing a higher degree of structural diversity. We next optimized the three individual reaction steps in detail. The catalytic hydrogenation of *N*-butyl-4-nitro-*N*-phenylaniline was examined using a series of Ir- and Mn-based pincer complexes in combination with various organic and inorganic bases, enabling the identification of suitable conditions for the hydrogenation of the nitro group of the terminal arene. Potassium *tert*-butoxide (KO^tBu) was determined as the most effective base, with 1,4-dioxane emerging as the most efficient solvent. A base loading of 5.0 mol% afforded the best results in the catalytic hydrogenation. Increasing the temperature to 60 °C and the H₂ pressure to 30 bars further improved the yield of the hydrogenation product. PN₅P-ligand-supported Ir precatalysts were investigated, with [Ir-I] providing the most active catalyst system (Figure 2). A manganese complex stabilized by the same ligand as [Ir-I] showed a lower selectivity and activity. Increasing the precatalyst loading from 0.10 to 0.50 mol% enabled the yield of the hydrogenation product to exceed 99 % (see Supporting Information, Tables S1–S7 for details). A straightforward alkylation protocol was employed from literature, using 1.50 equivalents of sodium hydride and the corresponding *n*-iodoalkane.[42] The commercially available Pd-PEPPSI-*i*Pr (Δ [NHC-Pd], Figure 2) catalyst was used for the aryl amination step. This catalyst has been extensively studied in the literature,[41],[43] and the cross-coupling conditions employed here were adapted from methods reported previously.[41],[43] In contrast to the procedures reported, an equimolar ratio of amine to halogenated nitrobenzene derivative was used and the reaction mixture was diluted to 0.25 M to suppress double arylation of the primary amine, which had been observed in preliminary test reactions. Reducing the Pd catalyst loading from 4.0 to 3.0 mol% and extending the reaction time resulted in lower yields of the product desired without improving the selectivity toward the mono-arylated species. The general use of 1-chloro-4-nitrobenzene derivatives can be rationalized by their better (commercial) availability compared to the corresponding bromo or iodo nitrobenzene analogs.[44] Nonaamine **2** was synthesized to demonstrate the accessibility of polyamines as defined (*vide supra*) and applicability of the optimized reaction conditions. Nonaamine **2** could be isolated in an 0.8 % yield over 26 steps (Figure 2, 83 % average yield). The introduction of *N*-butyl groups ensured sufficient solubility in organic solvents and guaranteed chemical stability.

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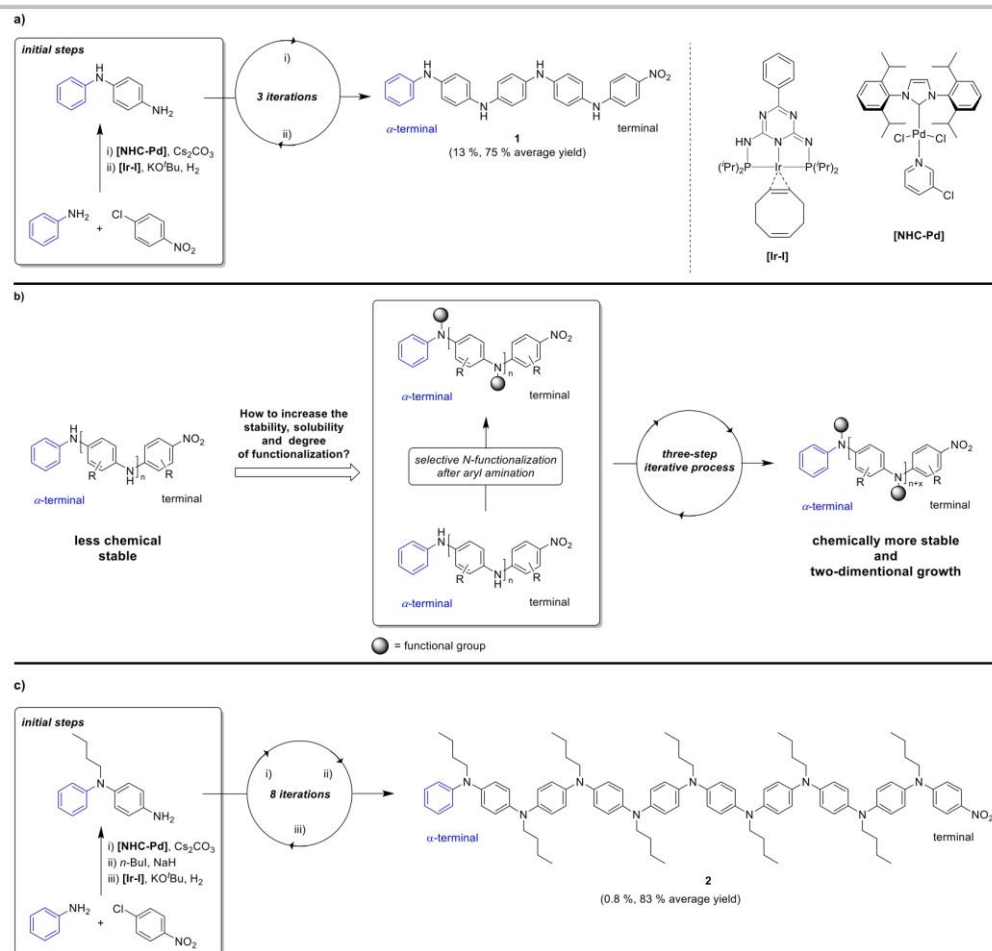


Figure 2. Development of the iterative synthesis approach of oligo- and polyamines. a) The synthesis of the tetraamine **1** (seven sequential steps) should demonstrate the general feasibility of the iterative synthesis protocol developed. Reaction conditions: i) **[NHC-Pd]**, Cs_2CO_3 , DME, 80 °C, 24 h; ii) **[Ir-I]**, KOtBu, 1,4-dioxane : DME : toluene (1:2:1), 80 °C, 60 bar H_2 , 24 h. b) Extension of the synthesis concept to include a selective *N*-functionalization step. c) Synthesis of the nonaamine **2** (26 sequential steps). Amine alkylation with 1-iodobutane increases both chemical stability and solubility. Reaction conditions: i) **[NHC-Pd]**, Cs_2CO_3 , DME, 80 °C, 24 h; ii) NaH, *n*-BuLi, THF, reflux, 4–18 h; iii) **[Ir-I]**, KOtBu, 1,4-dioxane, 60 °C, 30 bar H_2 , 24 h / 80 °C, 50 bar H_2 , 72 h.

Optimization of reaction conditions and synthesis of tetraamine **1** and nonaamine **2**

Different linkage patterns were introduced next into the oligoamine main chain. We used either 1-chloro-4-nitrobenzene or 1-bromo-3-nitrobenzene for the synthesis of tetraamine **3** (Figure 3, 80 % average yield). The aryl amination with the meta-substituted nitrobenzene derivative did not give any significantly lower yields compared to the amination with *para*-substituted building blocks, but lower yields were obtained in the hydrogenation of the nitro group when *meta*-substituted nitrobenzene was employed.

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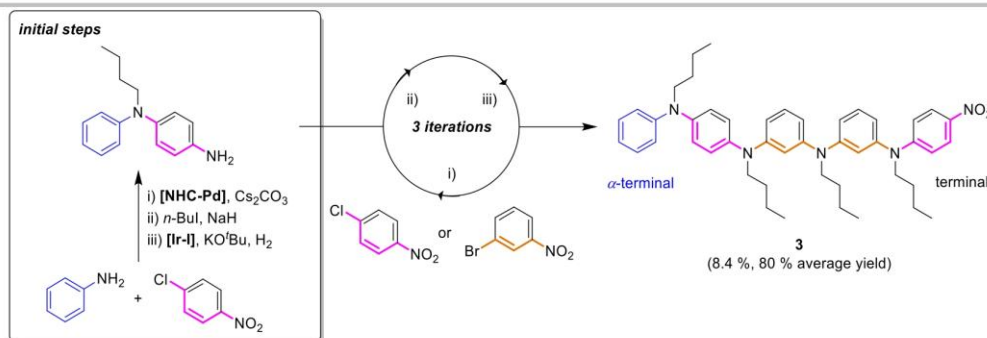
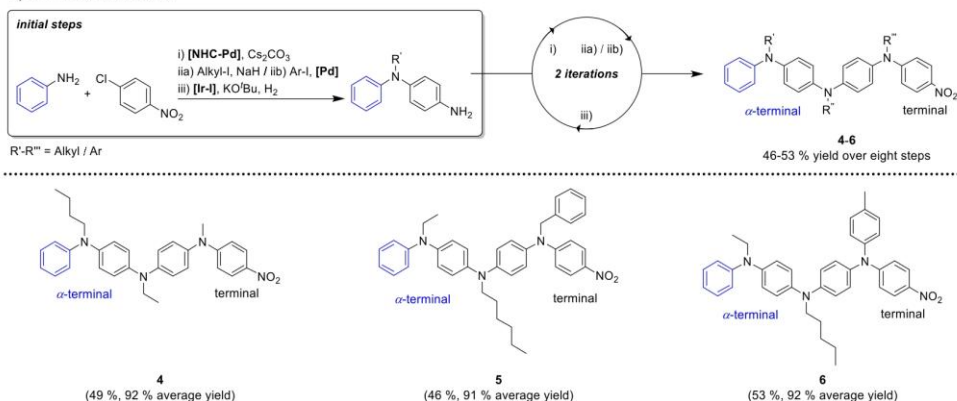


Figure 3. Variation of chain-linking. Synthesis of the tetraamine **3** (11 sequential steps) by using 4- and 3-nitro-substituted aryl benzenes. Reaction conditions: i) **[NHC-Pd]**, Cs_2CO_3 , DME, 80 °C, 24 h; ii) NaH, *n*-BuI, THF, reflux, 4–18 h; iii) **[Ir-I]**, KO^tBu, 1,4-dioxane, 60 °C, 30 bar H_2 , 24 h / 80 °C, 50 bar H_2 , 72 h.

Different *N*-functionalizations were explored to synthesize the triarylamine **4–6**. Methyl or *n*-hexyl moieties were readily introduced (Figure 4, tetraamine **4** and **5**). A sterically more demanding benzyl group could also be introduced without additional effort using benzyl bromide. **4** could be isolated in a 49 % yield over eight steps (Figure 4, 92 % average yield) and compound **5** could be isolated in a 46 % yield over eight steps (Figure 4, 91 % average yield). Compound **6** was synthesized to demonstrate the feasibility of introducing an aryl substituent at the nitrogen atom. The arylation of the secondary amine group proceeded smoothly with 1.50 equivalents of the corresponding aryl iodide and 5.00 mol% Pd precatalyst.[45],[46] **6** was isolated in a 53 % yield over eight steps (Figure 4, 92 % average yield). The use of various *p*-chloronitrobenzene derivatives was examined next. An *n*-butyl group was initially introduced to increase solubility. Compound **7** could be isolated in a 36 % yield over eight steps (Figure 4, 88 % average yield). Sterically demanding derivatives were employed and, after the introduction of a naphthyl moiety, compound **8** could be isolated in a 28 % yield over eight steps (Figure 4, 85 % average yield). Introducing a biaryl bridge and a doubly substituted nitroaryl moiety led to the isolation of compound **9** in a 13 % yield over eight steps (Figure 4, 76 % average yield). Particular care was taken to prevent oxidation during the synthesis and isolation of the primary amine intermediates leading to compounds **7–9** by performing all steps and purification under an inert atmosphere.

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a) N-Functionalization



b) Variation of different nitrobenzene derivatives

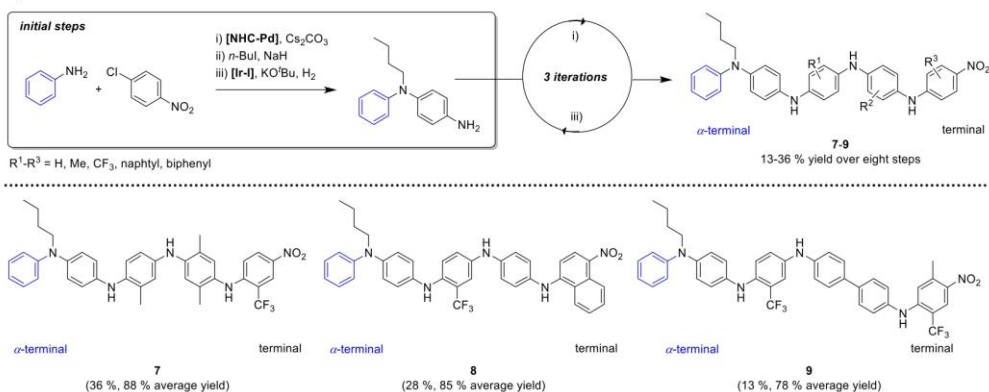


Figure 1: Variation of the N-functionalization (a) and the main chain (b). a) Synthesis of triamines **4-6** (eight sequential steps). Alkyl chains can be readily introduced. Additionally, it is also possible to incorporate aryl residues by using aryl iodide derivatives. i) $[\text{NHC-Pd}]$, Cs_2CO_3 , DME, 80°C , 24 h; ii) NaH, n -alkyl iodide, THF, reflux, 4–18 h; iib) $[\text{Pd}_2(\text{dba})_3]$, DavePhos, NaO^tBu , aryl iodide, 1,4-dioxane, reflux, 36 h; iii) $[\text{Ir-I}]$, KO^tBu , 1,4-dioxane, 60°C , 30 bar H_2 , 24 h / 80°C , 50 bar H_2 , 72 h. b) Synthesis of tetraamines **7-9** (eight sequential steps). Both electron-rich and -poor nitro aryl compounds can be used for chain extension. Reaction conditions: i) $[\text{NHC-Pd}]$, Cs_2CO_3 , DME, 80°C , 24 h then NaH, n -BuI, THF, reflux, 4–18 h; ii) $[\text{Ir-I}]$, KO^tBu , 1,4-dioxane, 60°C , 30 bar H_2 , 24 h / 80°C , 50 bar H_2 , 72 h.

The catalytic three-step synthesis enables the synthesis of complex amines by combining different *p*-chloronitrobenzene derivatives with varied *N*-functionalization steps (Figure 5). The introduction of electron-rich nitrobenzene derivatives and substituents in the ortho position relative to chlorine leads to improved yields in the Pd-catalyzed monoarylation. Sterically demanding aryl substituents prevented alkylation of the secondary amine under the previously established conditions, and the alkylation protocol had to be modified. Employing an excess of the corresponding *n*-alkyl iodide and higher reaction temperatures up to 90°C accelerated the alkylation, enabling yields of over 95 % (see Supporting Information for details). Tetraamine **10** could be isolated in a 46 % yield over 11 steps (Figure 5, 93 % average yield), compound **11** could be isolated in a 21 % yield over 11 steps (Figure 5, 87 % average yield) and substrate **12** was isolated in a 9.0 % yield over 11 steps (Figure 5, 80 % average yield).

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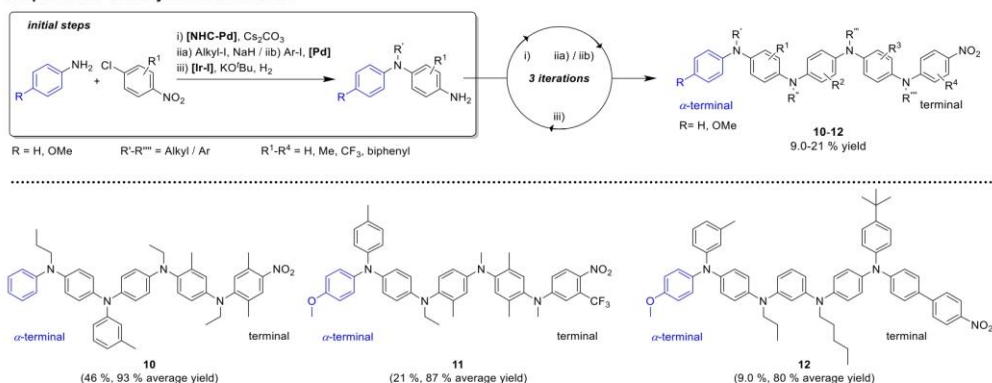
Sequential *N*- and aryl functionalization

Figure 2: Variation of both the main chain and the *N*-functionalization for the synthesis of oligoamines. Synthesis of tetraamines **10-12** (11 sequential steps) by using different *p*-halogen-nitrobenzene derivatives and different alkyl or aryl iodides for *N*-functionalization. Reaction conditions: i) [NHC-Pd], Cs₂CO₃, DME, 80 °C, 24 h; ii) NaH, *n*-alkyl iodide, THF, reflux, 4–18 h or NaH, excess *n*-alkyl iodide, THF, 90 °C, pressure tube; ii) [Pd₂(dba)₃], DavePhos, NaO^tBu, aryl iodide, 1,4-dioxane, reflux, 36 h; iii) [Ir-I], KO^tBu, 1,4-dioxane, 60 °C, 30 bar H₂, 24 h / 80 °C, 50 bar H₂, 72 h.

Functionalization of the terminal amine group

We next demonstrated the functionalization of the terminal primary amine generated via hydrogenation (Figure 6). **13** was obtained from diamine **2c** via an acylation protocol,[47] affording the product in a quantitative yield after aqueous workup and flash chromatography (Figure 6). In addition, diamine **2c** was transformed into the triarylamine derivative **14** through aryl amination. The unsymmetrical coupling of chlorobenzene and 4-bromotoluene was accomplished in a one-pot sequence using a published procedure and a highly active Pd precatalyst ([Pd-BrettPhos]) developed by Fors et al. (Figure 6, 89 % yield; see the Supporting Information for further information).[48],[49] The selectivity arises from the faster oxidative addition of aryl bromides relative to the aryl chloride. Condensation of primary amine **2c** with hexane-2,5-dione under mild acidic conditions using 10 mol% sulfamic acid afforded the pyrrole derivative **15** in a quantitative yield (Figure 6).[50] Terephthaloyl dichloride was reacted with amine **2c**, affording the corresponding diamide **16** in a 97 % yield after recrystallization (Figure 6) indicating that simple linker molecules permit a rapid assembly of larger oligomers.

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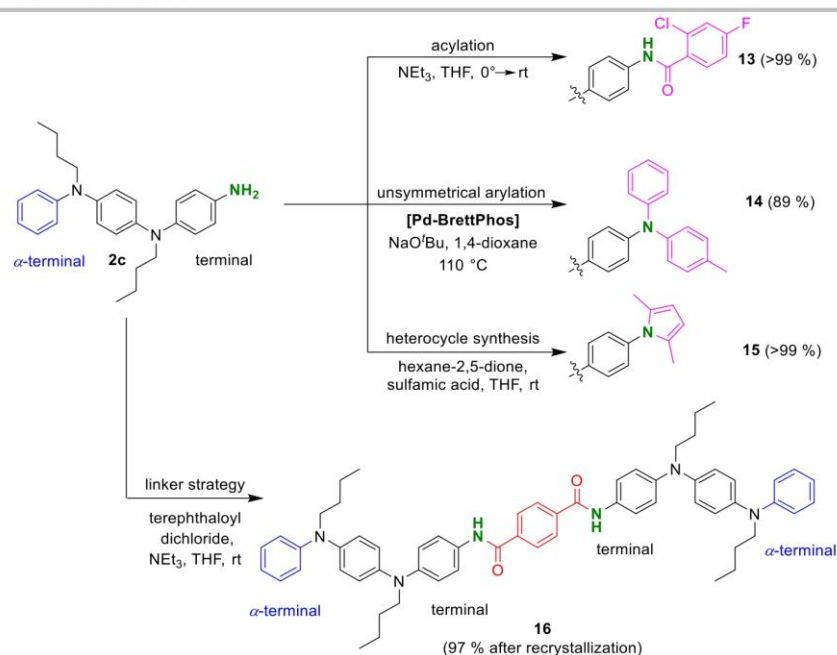


Figure 3: Functionalization of the terminal amine group. Various end-group functionalizations of compound **2c**.

Orthogonal iterative synthesis

We next synthesized oligoamines via orthogonal iterative synthesis by the selective aryl amination of terminal primary amines with 1-chloro-4-iodobenzene, followed by the aryl amination of the original terminal primary amines and the chloroarene terminus generated from them. The NHC-based Pd precatalyst used for the iterative extension sequence shows a high selectivity for nonactivated aryl halides, but low selectivity regarding the monoarylation of primary amines with fewer nonactivated or activated aryl halides. Therefore, we again used the Pd precatalyst **[Pd-BrettPhos]** developed by Fors et al. for the orthogonal iterative synthesis steps (Figure 7).^{[48],[49]} The resulting secondary amine moiety offers a site for functionalization. Many products can be generated from a comparably small number of oligoamines educts. Substrates **17–20** were synthesized accordingly (Figure 7c).

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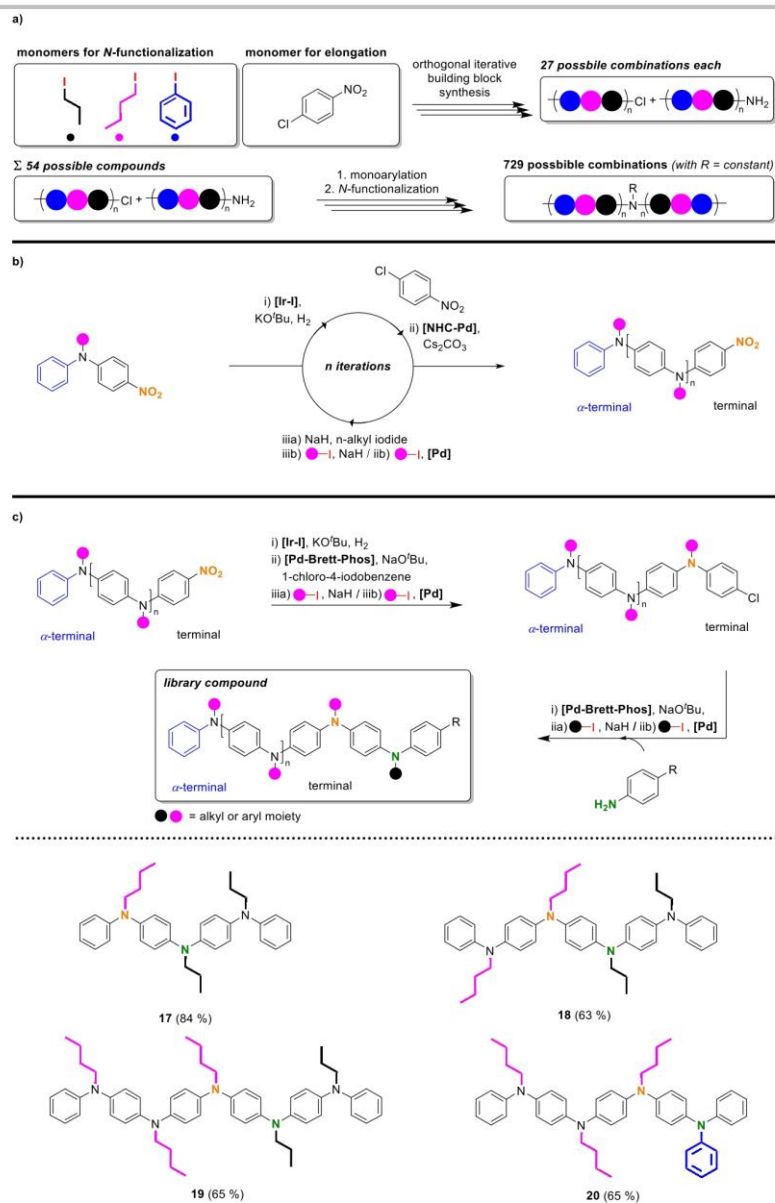


Figure 4: Orthogonal iterative synthesis of oligoamines. Development of a substrate library from individual building blocks. a) Schematic representation of the possibilities for the synthesis of large substrate libraries. b) Iterative synthesis of building blocks using optimized conditions. Reaction conditions: i) [Ir-I], KOtBu, 1,4-dioxane, 60 °C, 30 bar H₂, 24 h / 80 °C, 50 bar H₂, 72 h; ii) [NHC-Pd], Cs₂CO₃, DME, 80 °C, 24 h; iii) NaH, n-alkyl iodide, THF, reflux, 4–18 h; iiiib) [Pd₂(dba)₃], DavePhos, NaOtBu, aryl iodide, 1,4-dioxane, reflux, 36 h. c) Orthogonal synthesis of building blocks 17–20 by selective aryl amination using 1-chloro-4-iodobenzene followed by N-alkylation or N-arylation. Reaction conditions: i) [Ir-I], KOtBu, 1,4-dioxane, 60 °C, 30 bar H₂, 24 h / 80 °C, 50 bar H₂, 72 h; ii) [Pd-Brett-Phos], NaOtBu, 1-chloro-4-iodobenzene, toluene, 60 °C, 18 h; iii) NaH, n-alkyl iodide, THF, reflux, 4–18 h; iiiib) [Pd₂(dba)₃], DavePhos, NaOtBu, aryl iodide, 1,4-dioxane, reflux, 36 h

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Finally, we synthesized polyamines (Figure 8) employing the orthogonal iterative synthesis approach described in Figure 7. Decaamine **21** and octaamine **22** were isolated in 79 % and 68 % yields, respectively (Figure 8).

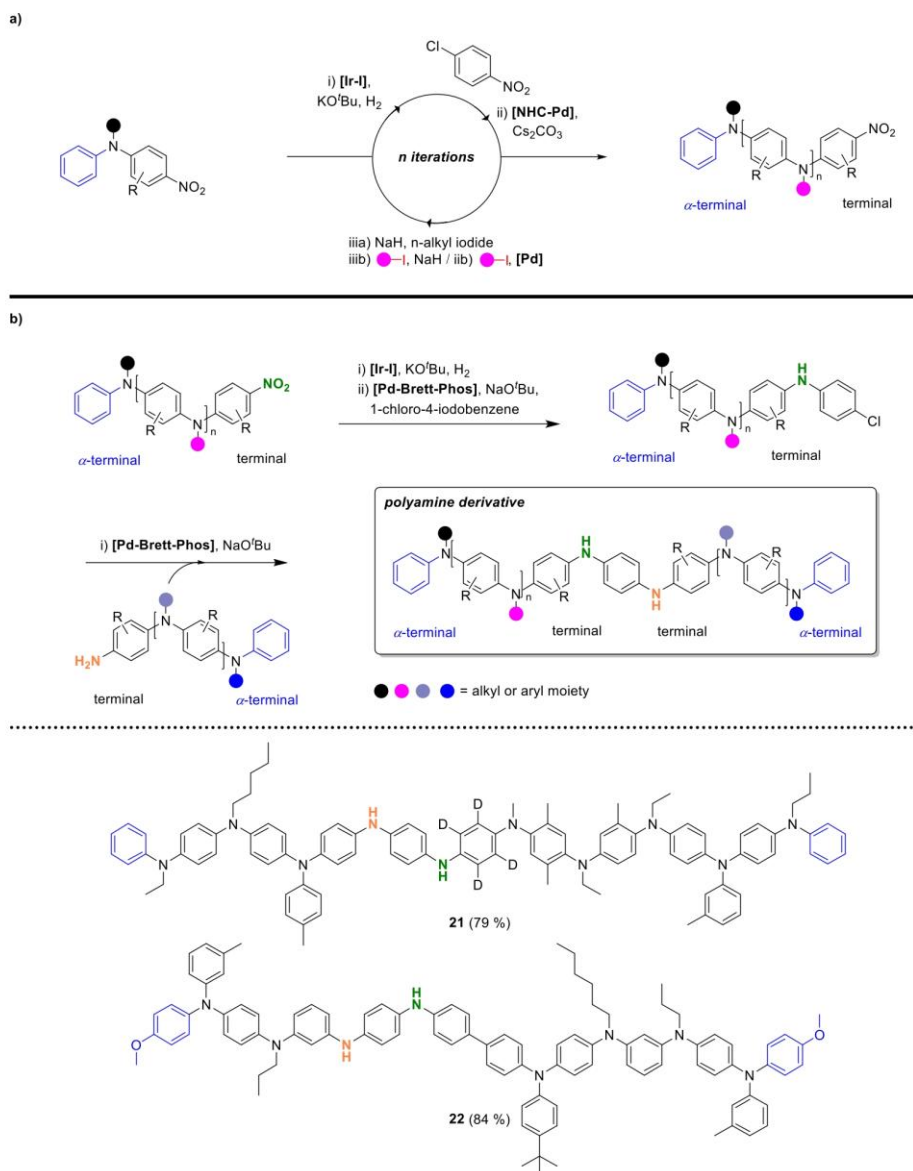


Figure 5: Synthesis of complex oligoamines via orthogonal synthesis. Polyamines can be synthesized from functionalized building blocks in two steps using the previously developed linker strategy. a) Iterative synthesis of building blocks using optimized conditions. Reaction conditions: i) **[Ir-I]**, KOtBu, 1,4-dioxane, 60 °C, 30 bar H₂, 24 h / 80 °C, 50 bar H₂, 72 h; ii) **[NHC-Pd]**, Cs₂CO₃, DME, 80 °C, 24 h; iii) NaH, *n*-alkyl iodide, THF, reflux, 4–18 h; iiiib) **[Pd₂(dba)₃]**, DavePhos, NaOtBu, aryl iodide, 1,4-dioxane, reflux, 36 h. b) Synthesis of polyamines **21** and **22**. Reaction conditions: i) **[Ir-I]**, KOtBu, 1,4-dioxane, 60 °C, 30 bar H₂, 24 h / 80 °C, 50 bar H₂, 72 h; ii) **[Pd-Brett-Phos]**, NaOtBu, 1-chloro-4-iodobenzene, toluene, 60 °C, 18 h or **[Pd-Brett-Phos]**, NaOtBu, toluene, 70 °C, 24 h.

Conclusion

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In conclusion, we demonstrated the synthesis of monodisperse, sequence-defined and flexible macromolecules containing an arylamin main chain. Palladium-catalyzed cross-coupling and nitroarene hydrogenation were used to form the new amine end group enabling further chain growth. Readily available 1-chloro-4-nitrobenzenes were used as building blocks mostly to avoid protecting group chemistry and activate the aryl chloride for the amination step. Alkylation of the secondary arylamines increases the stability and solubility of the macromolecules and the synthesis, for instance, of a decamer without solubility problems under catalytic conditions was demonstrated. Alteration of the arene and/or the alkyl substituent permits a two-dimensional structure variation and the synthesis of even more complex molecules. The amine end group is accessible for functionalization chemistry and pyrrole synthesis, and cross-linking has also been demonstrated. Furthermore, polyamines were synthesized using an orthogonal iterative synthesis approach.

Supporting Information

The authors have cited additional references within the Supporting Information.[51-58]

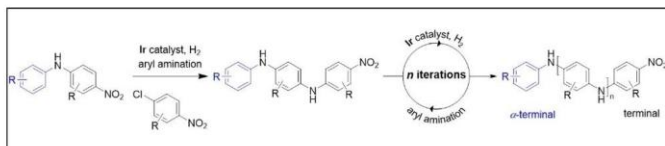
Acknowledgements

We declare no conflict of interests. The authors would like to acknowledge Dr. Ulrike Lacher for the measurements of the HRMS spectra. We thank Dr. Winfried Kretschmer for help with NMR measurements.

Keywords: iterative synthesis • catalysis • polyamines • aryl amination • hydrogenation

RESEARCH ARTICLE

Entry for the Table of Contents



Monodisperse and sequence-defined polymers are abundant and of fundamental importance in nature; polypeptides and DNA are examples, but rare in artificial chemical synthesis. We report here the synthesis of monodisperse, sequence-defined and flexible macromolecules containing an arylamin main chain. Palladium-catalyzed cross-coupling and nitroarene hydrogenation were used to form the new amine end group enabling further chain growth. Readily available 1-chloro-4-nitrobenzenes were used as building blocks mostly to avoid protecting group chemistry and activate the aryl chloride for the amination step. Alkylation of the secondary arylamines increases the stability and solubility of the macromolecules and synthesis, for instance, of a decamer without solubility problems under catalytic conditions was demonstrated. Alteration of the arene and/or the alkyl substituent permits a two-dimensional structure variation and the synthesis of even more complex molecules. The amine end group is accessible for functionalization chemistry and pyrrole synthesis, and crosslinking have been demonstrated for instance.

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Supplementary Information

Catalytic two-step synthesis of sequence defined polyamines

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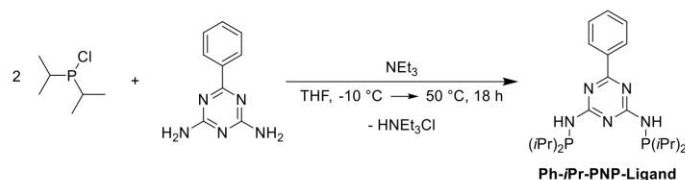
1 Materials and methods

All reactions and manipulations with air sensitive compounds being present were performed under dry argon (Ar 5.0) or nitrogen (N₂ 5.0), using Schlenk and glove box techniques. Nonhalogenated solvents were dried over sodium benzophenone, 2-methyl tetrahydrofuran (2-Me-THF) was dried over calcium hydride, and halogenated solvents were dried over P₂O₅. THF and DME were dried over LiAlH₄ several times. Deuterated solvents were bought from Cambridge Isotope Laboratories, distilled accordingly, and stored over molecular sieves (3 Å). Other chemicals were purchased from commercial vendors and used without further purification. Hydrogenation reactions were conducted in PARR Instrument stainless steel autoclaves 300 or 600 mL equipped with heating mantles and temperature controllers. NMR spectra were collected on a Varian INOVA 300 MHz spectrometer or on a Bruker Avance III HD 500 MHz. Chemical shifts (δ) are reported in ppm relative to residual solvent signal CDCl₃: 7.26 ppm (¹H), 77.16 ppm (¹³C), DMSO-d₆: 2.50 ppm (¹H), 39.51 ppm (¹³C), THF-d₈: 1.72 ppm, 3.58 ppm (¹H), 67.21 ppm, 25.31 ppm (¹³C). Coupling constants (J) are given in Hz (coupling patterns: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet). GC analyses were carried out using an Agilent Technologies 6890N system equipped with a Macherey-Nagel (MN) Optima 5 HT column (30 m, 320 μ m, 0.25 μ m) or an Agilent Technologies 6850 system equipped with a MN Optima 17 column (30 m, 320 μ m, 0.25 μ m). For column chromatography, MN silica gel 60 (0.040– 0.063 mm particle size) was used. All organic compounds were characterized by ¹H and ¹³C NMR analysis. Unknown compounds or compounds with incomplete spectroscopic literature data were additionally analysed via LC-HRMS. Liquid chromatography-high resolution mass spectra (LC-HRMS) were obtained from a Thermo Fisher scientific Q-Exactive instrument with a hybrid quadrupole orbitrap analyser in ESI+ mode.

2 Synthesis of ligands and complexes

The ligands and (pre)catalysts were synthesized according to published procedures.^{[51],[52],[53],[54],[55]}

Synthesis of Ph-*i*Pr-PNP-ligand



Supplementary Figure 1: Synthesis of **Ph-*i*Pr-PNP-Ligand**.

Reaction conditions for the synthesis of Ph-*i*Pr-PNP-Ligand: In a Schlenk tube, the corresponding diamine (20.0 mmol, 1.00 equiv.) is dissolved in THF (80.0 mL, 0.25 M). The solution is cooled to -10 °C before chlorodiisopropylphosphane (6.71 g, 7.00 mL, 44.0 mmol, 2.20 equiv.) is slowly added. NEt₃ (80.0 mmol, 8.10 g, 11.1 mL, 4.00 equiv.) is slowly added over 10 minutes to the reaction mixture. After stirring for 1 h at -10 °C, the solution is warmed to RT and heated to 50 °C for 18 h.

The solution is filtered, and the precipitate is washed with THF two times. The solvent and excess NEt₃ is removed under reduced pressure. The residue is completely dissolved in 10-15 mL toluene at 70 °C.

The clear mixture is cooled to RT and the corresponding product is recrystallized at -30 °C over three days. The toluene is removed via filtration, and the white precipitate is washed with hexane 3 times. The remaining solvent is removed under reduced pressure to obtain the Ph-*i*Pr-PNP-Ligand (yields between 45-80%) in the desired purity. The product is analysed via ¹H NMR and ³¹P NMR before use.

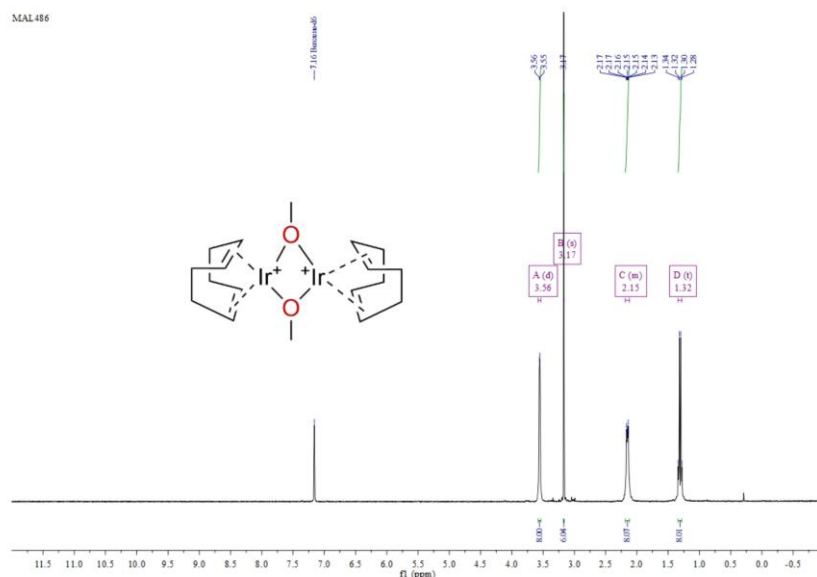
Synthesis of $[\text{Ir}(\mu^2\text{-OMe})(\text{COD})]_2$ 

Supplementary Figure 2: Synthesis of $[\text{Ir}(\mu^2\text{-OMe})(\text{COD})]_2$.

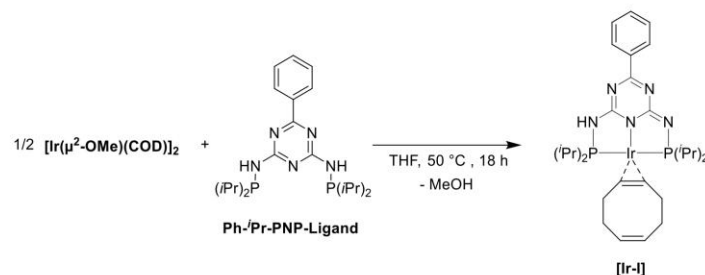
Reaction conditions for the synthesis of $[\text{Ir}(\mu^2\text{-OMe})(\text{COD})]_2$: $[\text{Ir}(\mu^2\text{-Cl})(\text{COD})]_2$ (1.00 g, 1.49 mmol, 1.00 equiv.) and KOH (184 mg, 3.28 mmol, 2.20 equiv.) are dissolved in MeOH (degassed, 45.0 mL, 0.033 M).

The solution is stirred at RT for 18 h under exclusion of light. The supernatant solution is removed, and the remaining precipitate is washed with degassed water 3 times before the remaining solvent is removed under reduced pressure to obtain $[\text{Ir}(\mu^2\text{-OMe})(\text{COD})]_2$ (988 mg, 1.06 mmol, 71%) in the desired purity. The precursor is analysed via ^1H NMR before use.

^1H NMR (C_6D_6 , 300 MHz, 293 K): δ = 3.56 (d, J = 2.8 Hz, 4H), 3.17 (s, 3H), 2.19 – 2.12 (m, 4H), 1.32 (t, J = 7.8 Hz, 4H) ppm.

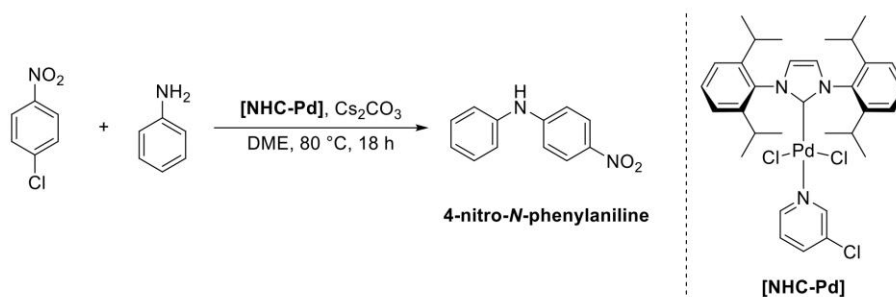


Supplementary Figure 3: ^1H NMR spectrum of $[\text{Ir}(\mu^2\text{-OMe})(\text{COD})]_2$.

Synthesis of (pre)catalyst [Ir-I]

Supplementary Figure 4: Synthesis of (pre)catalyst [Ir-I].

Reaction conditions for the synthesis of (pre)catalyst [Ir-I]: $[\text{Ir}(\mu^2\text{-OMe})(\text{COD})]_2$ (1.00 mmol, 663 mg, 1.00 equiv.) and Ph-*i*Pr-PNP-Ligand (2.00 mmol, 839 mg, 2.00 equiv.) are dissolved in THF (20.0 mL, 0.20 M). The mixture is stirred at 50 °C for 18 h. The solvent is removed under reduced pressure to give complex [Ir-I] (yields between 90->99%) in the desired purity. The complex is analysed via ^1H NMR and ^{31}P NMR before use.

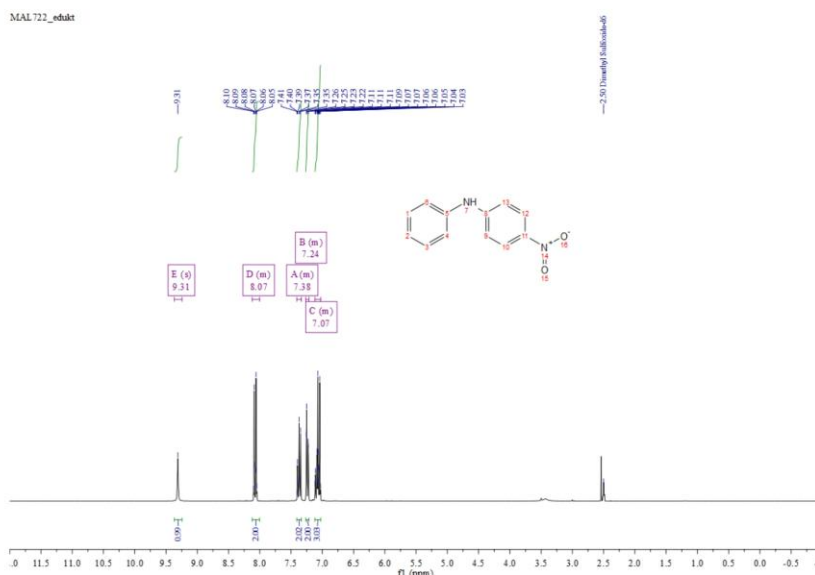
3 Synthesis of 4-nitro-*N*-phenylanilineSupplementary Figure 5: Synthesis of 4-nitro-*N*-phenylaniline.

General reaction conditions for the synthesis of 4-nitro-*N*-phenylaniline (GP1): Referring to the literature^[56], a slightly modified synthesis protocol is used. In a Schlenk tube, 1-chloro-4-nitrobenzene (1.00 equiv.) and aniline (1.00 equiv.) are dissolved in DME (0.25 M). [NHC-Pd] (4.00 mol%) and Cs_2CO_3 (3.00 equiv.) are added, and the reaction mixture is stirred at 80 °C for 24 h in an open system under argon atmosphere.

The reaction is cooled to RT and quenched by adding saturated NaCl-solution (brine). The organic phase is diluted with EtOAc and washed with water two times. The combined

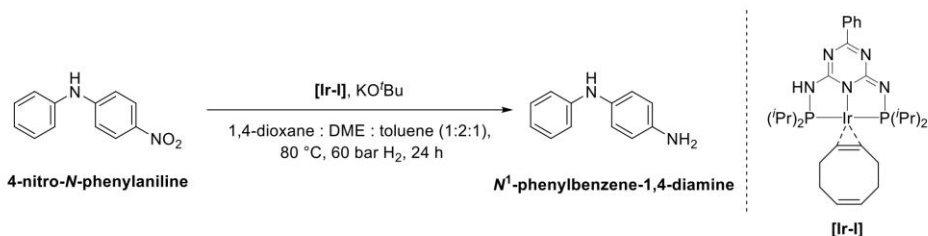
aqueous phases are washed with EtOAc one time. The combined organic phases are dried with MgSO_4 or Na_2SO_4 and the solvents are removed under reduced pressure. Column chromatography (*n*-pentane / EtOAc 9:1) affords 4-nitro-*N*-phenylaniline (yields between 90-98%) as a yellow solid.

^1H NMR (dmso- d_6 , 300 MHz, 293 K): δ = 9.31 (s, 1H), 8.12 – 8.00 (m, 2H), 7.41 – 7.34 (m, 2H), 7.27 – 7.21 (m, J = 8.5, 1.1 Hz, 2H), 7.12 – 7.03 (m, 3H) ppm.



Supplementary Figure 6: ^1H NMR spectrum of 4-nitro-*N*-phenylaniline.

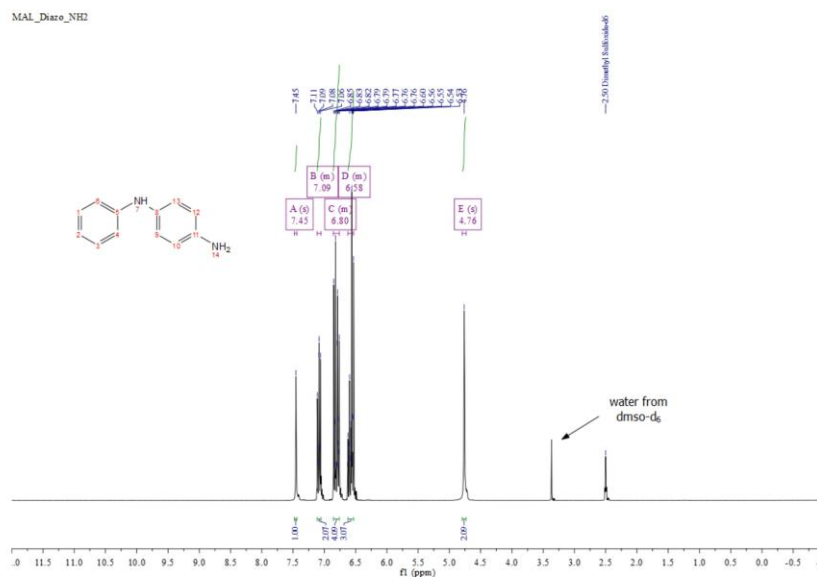
4 Synthesis of *N*¹-phenylbenzene-1,4-diamine



Supplementary Figure 7: Synthesis of *N*¹-phenylbenzene-1,4-diamine.

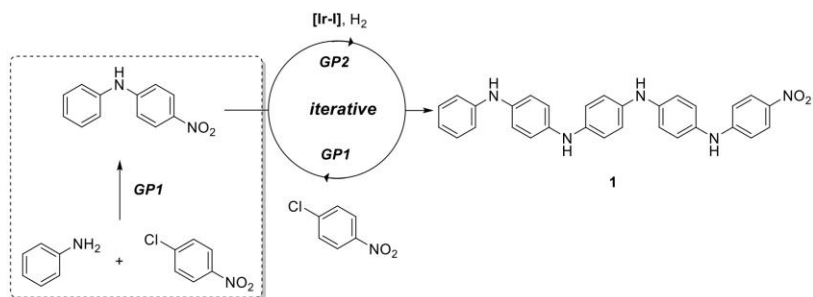
General reaction conditions for the synthesis of *N*¹-phenylbenzene-1,4-diamine (GP2): 4-Nitro-*N*-phenylaniline (1.00 equiv.), [Ir-I] (5.00 mol%) and KO^tBu (10.0 mol%) are dissolved in a mixture of 1,4-dioxane : DME : toluene (1:2:1, 0.31 M). The reaction mixture is placed in an autoclave, and the vessel is pressurized to 60 bar H₂. The reaction is stirred for 24 h at 80 °C. The reaction is concentrated under vacuum and directly used for chromatography (*n*-pentane / EtOAc 4:6) to afford *N*¹-phenylbenzene-1,4-diamine (yields between 90-99%) as a light-yellow solid.

¹H NMR (dmsO-d₆, 300 MHz, 293 K): δ = 7.45 (s, 1H), 7.11 – 7.05 (m, 2H), 6.85 – 6.76 (m, 4H), 6.62 – 6.53 (m, 3H), 4.76 (s, 2H) ppm.



Supplementary Figure 8: ¹H NMR spectrum of *N*¹-phenylbenzene-1,4-diamine.

5 Synthesis of compound 1

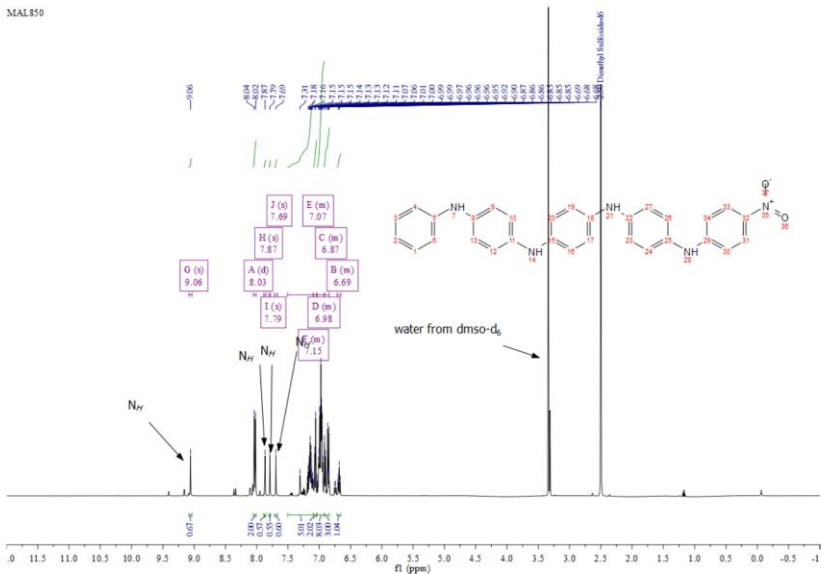
Supplementary Figure 9: Synthesis of compound **1**.

Compound **1** is synthesized following **GP1** and **GP2** (260 mg, 533 μ mol, 13% yield, 75% average yield) over 7 steps and isolated as a red solid.

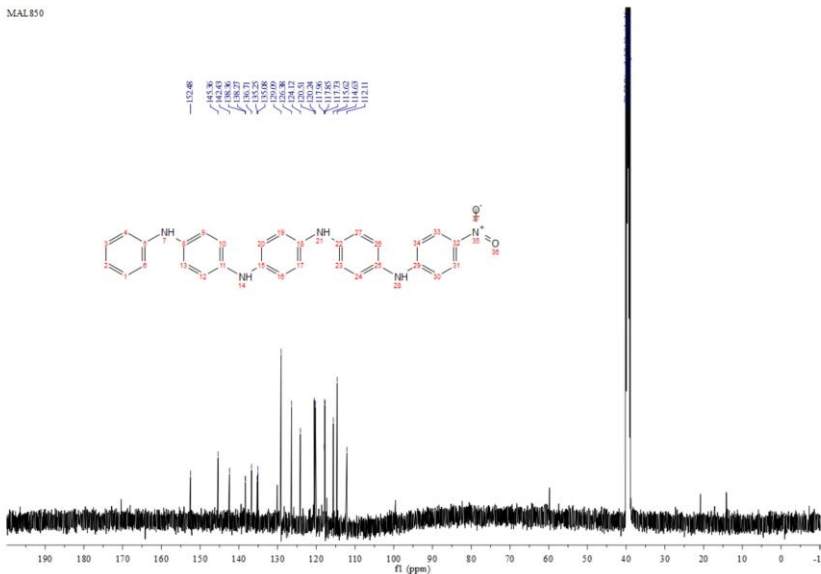
¹H NMR (dmso-d₆, 300 MHz, 293 K): δ = 9.06 (s, 1H), 8.03 (d, J = 9.3 Hz, 2H), 7.87 (s, 1H), 7.79 (s, 1H), 7.69 (s, 1H), 7.51 – 7.10 (m, 5H), 7.09 – 7.04 (m, 2H), 7.03 – 6.92 (m, 8H), 6.92 – 6.84 (m, 3H), 6.72 – 6.66 (m, 1H) ppm.

¹³C NMR (dmso-d₆, 75 MHz, 293 K): δ = 152.48, 145.36, 142.43, 138.36, 138.27, 136.71, 135.25, 135.08, 129.09, 126.38, 124.12, 120.51, 120.24, 117.96, 117.85, 117.73, 115.62, 114.63, 112.11 ppm.

LC-HRMS (ESI+) m/z calculated for [**1**]⁺: 488.20810 found: 488.20833.

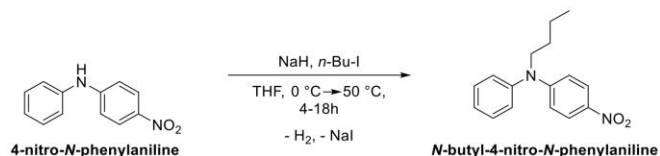


Supplementary Figure 10: ^1H NMR spectrum of compound **1**.



Supplementary Figure 11: ^{13}C NMR spectrum of compound **1**.

6 Synthesis of *N*-butyl-4-nitro-*N*-phenylaniline



Supplementary Figure 12: Synthesis of *N*-butyl-4-nitro-*N*-phenylaniline.

Reaction conditions for the synthesis of N-butyl-4-nitro-N-phenylaniline (GP3): 4-

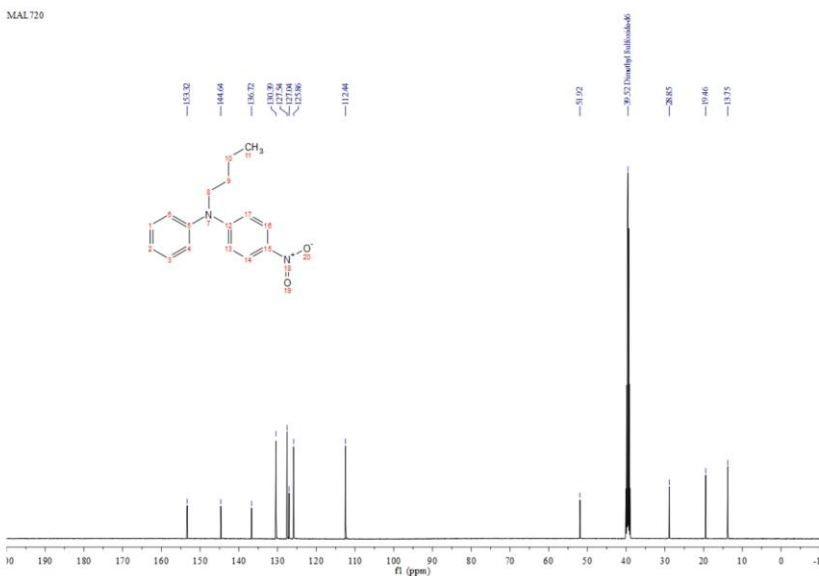
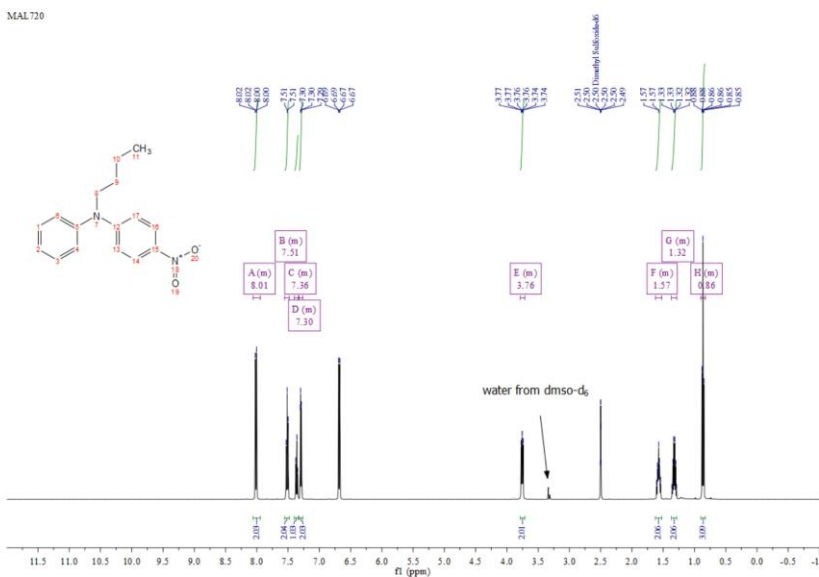
Nitro-*N*-phenylaniline (1.00 g, 4.67 mmol, 1.00 equiv.) gets dissolved in THF (36.0 mL, 0.13 M). At 0 °C NaH (235 mg, 7.00 mmol, 60% on mineral oil, ~1.50 equiv.) is added in portions to the solution. The solution is stirred at 0 °C for 5 minutes and additional 15 minutes at RT. A gas bubbler is used to adjust the pressure. 1-Iodobutane (*n*-Bu-I, 1.30 g, 803 µL, 7.00 mmol, 1.50 equiv.) is slowly added and the mixture is refluxed for 4-18 hours. The mixture is cooled to RT. The reaction is quenched by adding H₂O.

The organic phase is dissolved in EtOAc and washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times.

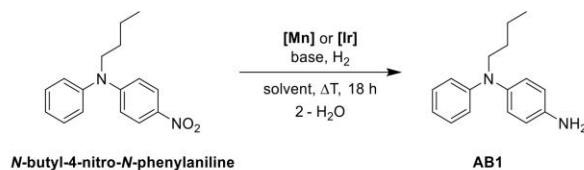
The combined organic phases are dried over MgSO_4 or Na_2SO_4 and the solvent is removed under reduced pressure. Column chromatography (*n*-pentane / EtOAc 9:1) affords *N*-butyl-4-nitro-*N*-phenylaniline (1.26 g, 4.67 mmol, >99%) as a yellow brown oil.

¹H NMR (dms_o-d₆, 500 MHz, 293 K): δ = 8.06 – 7.95 (m, 2H), 7.56 – 7.48 (m, 2H), 7.40 – 7.34 (m, 1H), 7.33 – 7.27 (m, 2H), 3.79 – 3.72 (m, 2H), 1.62 – 1.53 (m, 2H), 1.37 – 1.28 (m, 2H), 0.90 – 0.83 (m, 3H) ppm.

¹³C NMR (dms_o-d₆, 126 MHz, 293 K): δ = 153.32, 144.64, 136.72, 130.39, 127.54, 127.04, 125.86, 112.44, 51.92, 28.85, 19.46, 13.75 ppm.



7 Screening for the catalytic reduction of *N*-butyl-4-nitro-*N*-phenylaniline

Supplementary Figure 15: Screening for the synthesis of **AB1**.Supplementary Table 1: Base screening.^[a]

Entry	Base	AB1 [%] ^[b]
1	NaO ^t Bu	22
2	KO^tBu	48
3	LiO ^t Bu	0
4	Mg(O ^t Bu) ₂	0
5	NaOH	0
6	KOH	0
7	LiOH	0
8	NaHMDS	12
9	KHMDS	17
10	LiHMDS	0
11	PhCOOK	0

[a] Reaction conditions: 0.25 mmol *N*-butyl-4-nitro-*N*-phenylaniline, 125 μmol base (5.00 mol%), 0.10 mol% **[Ir-I]**, 1,4-dioxane (0.25 M, 1.00 mL), 50 °C; 10 bar H₂, 18 h; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 2: Solvent screening.^[a]

Entry	Solvent	AB1 [%] ^[b]
1	tetrahydrofuran (THF)	15
2	1,2-dimethoxyethane (DME)	22
3	1,4-dioxane	48
4	cylopentyl methyl ether (CPOMe)	11
5	toluene	8

[a] Reaction conditions: 0.25 mmol *N*-butyl-4-nitro-*N*-phenylaniline, 125 μmol KO^tBu (5.00 mol%), 0.10 mol% **[Ir-I]**, solvent (0.25 M, 1.00 mL), 50 °C; 10 bar H₂, 18 h; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 3: KO^tBu loading screening.^[a]

Entry	KO ^t Bu loading [mol%]	AB1 [%] ^[b]
1	5.00	48
2	10.0	40
3	15.0	33
4	20.0	31
5	25.0	26
6	50.0	11

[a] Reaction conditions: 0.25 mmol *N*-butyl-4-nitro-*N*-phenylaniline, 12.5 μ mol – 125 μ mol KO^tBu (5.00 – 50.0 mol%), 0.10 mol% **[Ir-I]**, 1,4-dioxane (0.25 M, 1.00 mL), 50 °C; 10 bar H₂, 18 h; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 4: Temperature screening.^[a]

Entry	Temperature [°C]	AB1 [%] ^[b]
1	50	39
2	60	48
3	70	37
4	80	35
5	90	20

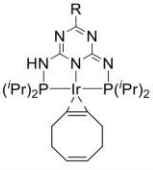
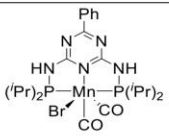
[a] Reaction conditions: 0.25 mmol *N*-butyl-4-nitro-*N*-phenylaniline, 12.5 μ mol KO^tBu (5.00 mol%), 0.10 mol% **[Ir-I]**, 1,4-dioxane (0.25 M, 1.00 mL), Δ T; 10 bar H₂, 18 h; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 5: H₂ pressure screening.^[a]

Entry	H ₂ pressure [bar]	AB1 [%] ^[b]
1	10.0	48
2	20.0	58
3	30.0	67

[a] Reaction conditions: 0.25 mmol *N*-butyl-4-nitro-*N*-phenylaniline, 12.5 μ mol KO^tBu (5.00 mol%), 0.10 mol% **[Ir-I]**, 1,4-dioxane (0.25 M), 60 °C; 10.0-30.0 bar H₂, 18 h; [b] Determined by GC with dodecane as an internal standard.

Supplementary Table 6: (Pre)catalyst screening.

Entry	Precatalyst			AB1 [%] ^[b]
1		[Ir-I]	R = Ph	67
2		[Ir-II]	R = Me	33
3		[Ir-III]	R = <i>p</i> CF ₃ -Ph	50
4				17

[a] Reaction conditions: 0.25 mmol *N*-butyl-4-nitro-*N*-phenylaniline, 12.5 μmol KO^tBu (5.00 mol%), 0.10 mol% (pre)catalyst, 1,4-dioxane (0.25 M, 1.00 mL), 60 °C; 30 bar H₂, 18 h; [b] Determined by GC with dodecane as an internal standard.

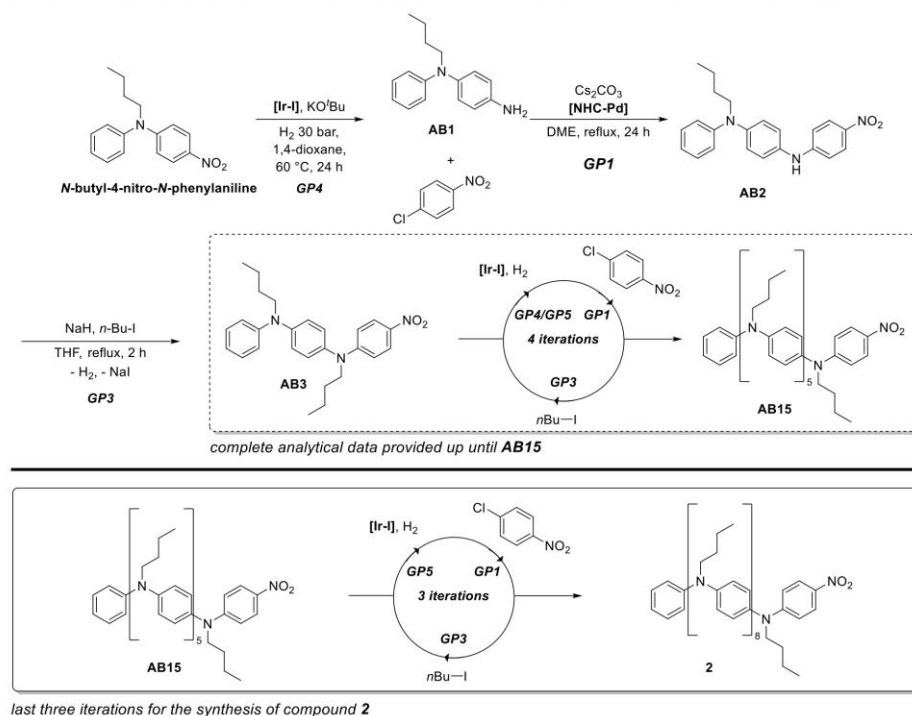
Supplementary Table 7: (Pre)catalyst loading.^[a]

Entry	Amount of [Ir-I] [mol%]	AB1 [%] ^[b]
1	0.10	67
2	0.25	85
3	0.50	>99
4	1.00	>99

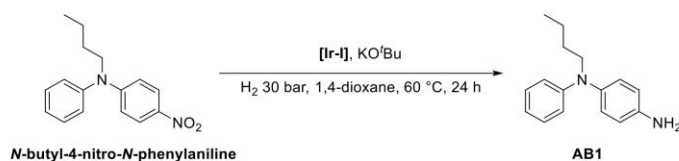
[a] Reaction conditions: 0.25 mmol *N*-butyl-4-nitro-*N*-phenylaniline, 12.5 μmol KO^tBu (5.00 mol%), 0.10 - 0.50 mol% [Ir-I], 1,4-dioxane (0.25 M, 1.00 mL), 60 °C; 30 bar H₂, 18 h; [b] Determined by GC with dodecane as an internal standard.

8 Synthesis of compound 2

To demonstrate the general feasibility of this newly developed synthetic concept, compound **2** was prepared. For improved evaluation and traceability, complete analytical data are provided for most individual intermediates from **AB2** through **AB15**.



Supplementary Figure 16: Overview of the synthesis of compound **2** starting from *N*-butyl-4-nitro-*N*-phenylaniline.

Supplementary Figure 17: Synthesis of compound **AB1**.

General reaction conditions for the synthesis of AB1 (GP4): In a glass vial *N*-butyl-4-nitro-*N*-phenylaniline (1.00 equiv.) gets dissolved in 1,4-dioxane (0.25 M). **[Ir-I]** (0.50 mol%) and KO^tBu (5.00 mol%) are added. The vial is placed in an autoclave, and the vessel is pressurized to 30 bar H₂. The reaction is stirred for 24 h at 60 °C.

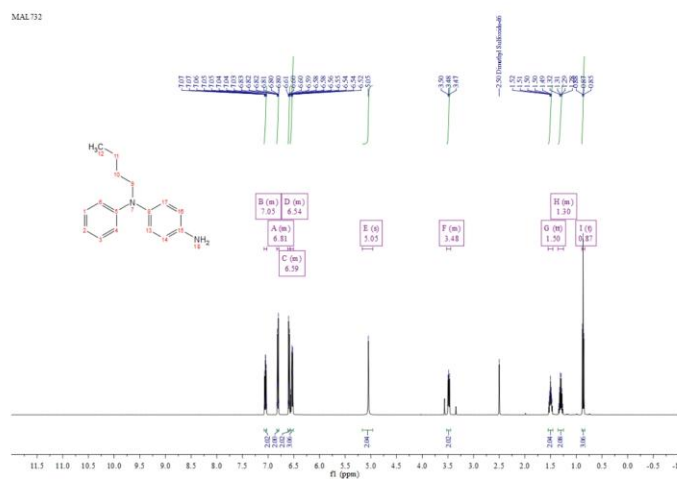
The reaction is quenched by adding H₂O. The organic phase gets dissolved in EtOAc washed with water : brine (1:1) two times.

The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na₂SO₄ and the solvent gets removed under reduced pressure. Column chromatography (*n*-pentane / EtOAc 7.5:2.5) affords **AB1** (>99%) as a dark green oil.

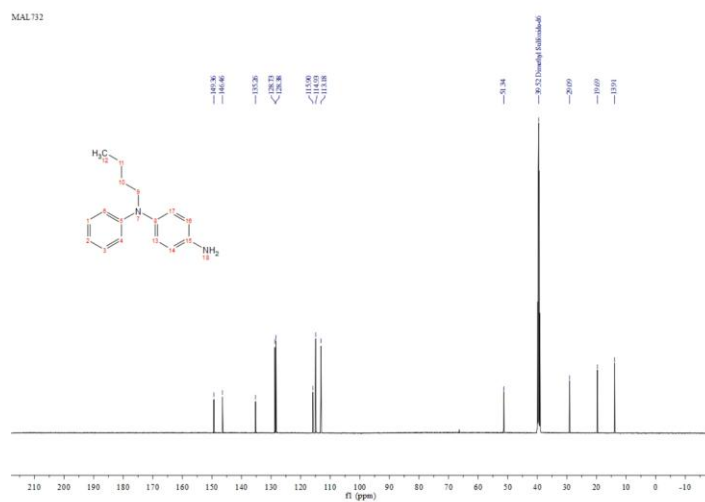
Reaction conditions for the scale up synthesis of AB1: In 5 different glass vials each *N*-butyl-4-nitro-*N*-phenylaniline (0.75 mmol, 203 mg, 1.00 equiv.) gets dissolved in 1,4-dioxane (3.00 mL, 0.25 M). **[Ir-I]** (3.75 μmol, 2.70 mg, 0.50 mol%) and KO^tBu (37.5 μmol, 4.20 mg, 5.00 mol%) are added. The vials are placed in an autoclave, and the vessel is pressurized to 30 bar H₂. The reaction is stirred for 24 h at 60 °C. All reaction solutions are combined and quenched by adding H₂O. The organic phase gets dissolved in EtOAc washed with water : brine (1:1) two times. The combined aqueous phases get extracted with EtOAc one time. The combined organic phases are dried over Na₂SO₄ and the solvent is removed under reduced pressure. Column chromatography (*n*-pentane / EtOAc 7:3) affords **AB1** (634 mg, 2.64 mmol, 70%) as a dark green oil.

¹H NMR (dms^o-d₆, 500 MHz, 293 K): δ = 7.08 – 7.02 (m, 2H), 6.83 – 6.79 (m, 2H), 6.62 – 6.57 (m, 2H), 6.57 – 6.51 (m, 3H), 5.05 (s, 2H), 3.52 – 3.45 (m, 2H), 1.50 (tt, *J* = 7.4, 6.6 Hz, 2H), 1.36 – 1.25 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H) ppm.

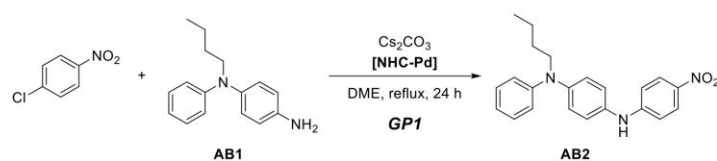
¹³C NMR (dms^o-d₆, 126 MHz, 293 K): δ = 149.36, 146.46, 135.26, 128.73, 128.38, 115.90, 114.93, 113.18, 51.34, 29.09, 19.69, 13.91 ppm.



Supplementary Figure 18: ^1H NMR spectrum of compound **AB1**.



Supplementary Figure 19: ^{13}C NMR spectrum of compound **AB1**.

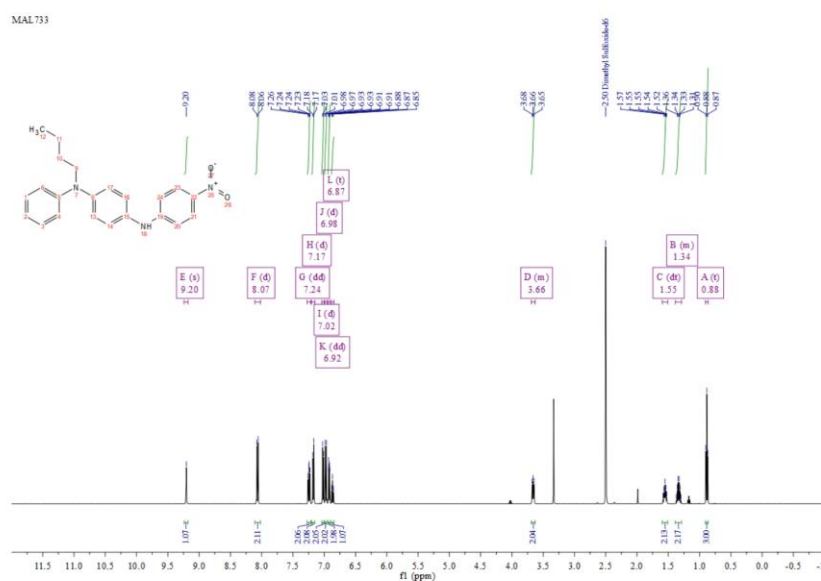
Supplementary Figure 20: Synthesis of compound **AB2**.

Reaction conditions for the synthesis of compound AB2: Following **GP1**, in a Schlenk tube, **N1** (570 mg, 2.37 mmol, 1.00 equiv.) Cs_2CO_3 (2.32 g, 7.11 mmol, 3.00 equiv.), **[NHC-Pd]** (64.4 mg, 94.8 μmol , 4.00 mol%) and 1-chloro-4-nitrobenzene (373 mg, 2.37 mmol, 1.00 equiv.) are dissolved in 9.50 mL DME (0.25 M). The reaction is stirred under reflux conditions for 20 h in an open system under argon. The reaction cooled to RT and the organic phase is dissolved in EtOAc. The organic phase is washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na_2SO_4 and the solvent is removed under reduced pressure. Column chromatography (8.5/1.5 *n*-pentane / EtOAc) affords **AB2** (787 mg, 2.18 mmol, 92%) as a dark red solid.

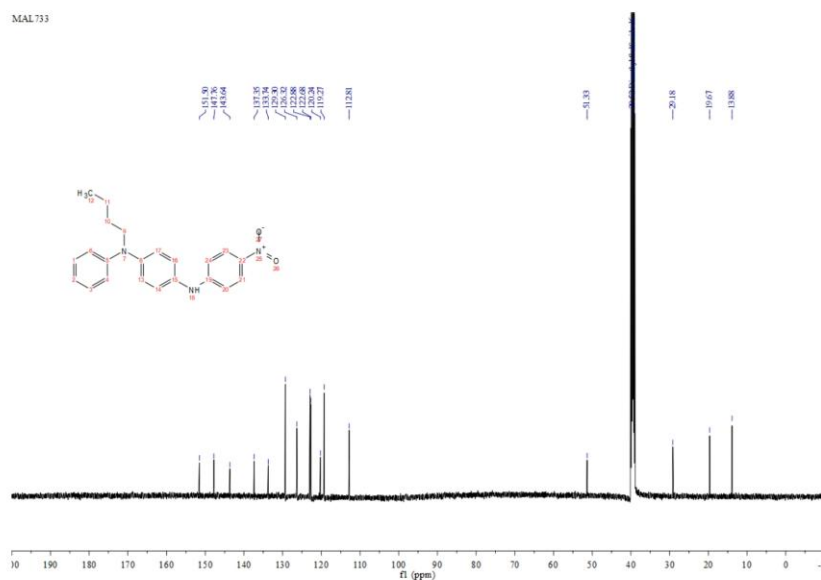
^1H NMR ($\text{dms}\text{-d}_6$, 500 MHz, 293 K): δ = 9.20 (s, 1H), 8.07 (d, J = 9.3 Hz, 2H), 7.24 (dd, J = 8.6, 7.3 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 7.02 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 9.3 Hz, 2H), 6.92 (dd, J = 8.6, 0.9 Hz, 2H), 6.87 (t, J = 7.4 Hz, 1H), 3.69 – 3.63 (m, 2H), 1.55 (dt, J = 12.3, 7.4 Hz, 2H), 1.39 – 1.29 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H) ppm.

^{13}C NMR ($\text{dms}\text{-d}_6$, 126 MHz, 293 K): δ = 151.50, 147.76, 143.64, 137.35, 133.74, 129.30, 126.32, 122.88, 122.68, 120.24, 119.27, 112.81, 51.33, 29.18, 19.67, 13.88 ppm.

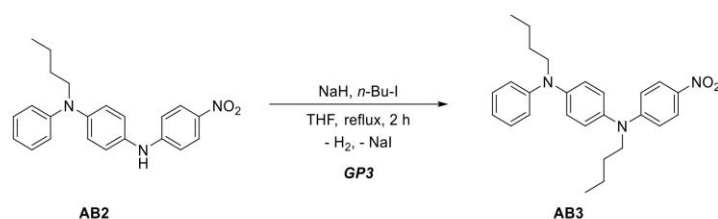
LC-HRMS (ESI+) m/z calculated for $[\text{AB2}]^+$: 362.18630 found: 362.18619.



Supplementary Figure 21: ^1H NMR spectrum of compound AB2.



Supplementary Figure 22: ^{13}C NMR spectrum of compound AB2.

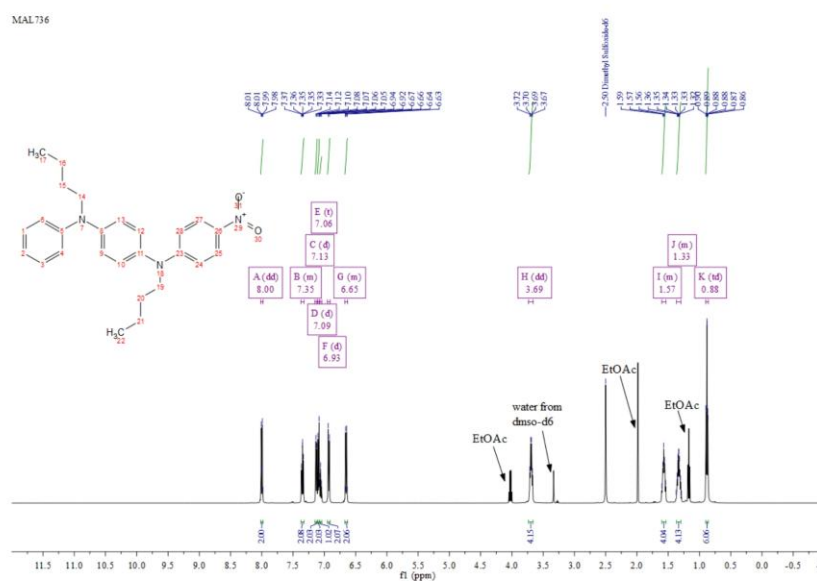
Supplementary Figure 23: Synthesis of compound **AB3**.

Reaction conditions for the synthesis of AB3: Following **GP3**, compound **AB2** (1.17 g, 3.22 mmol, 1.00 equiv.) gets dissolved in THF (24.8 mL, 0.13 M). NaH (162 mg, 4.84 mmol, 60% on mineral oil, ~1.50 equiv.) is added in portions to the solution. The solution is stirred for 15 minutes at RT. A gas bubbler is used to adjust the pressure. 1-Iodobutane (*n*-Bu-I, 891mg, 550 μ L, 4.84 mmol, 1.50 equiv.) is slowly added and the mixture is refluxed for 2 hours. The mixture is cooled to RT. The reaction is quenched by adding H₂O. The organic phase is dissolved in EtOAc and washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na₂SO₄ and the solvent is removed under reduced pressure. Column chromatography (*n*-pentane / EtOAc 9:1) affords **AB3** (1.35 g, 3.22 mmol, >99%) as a dark red oil.

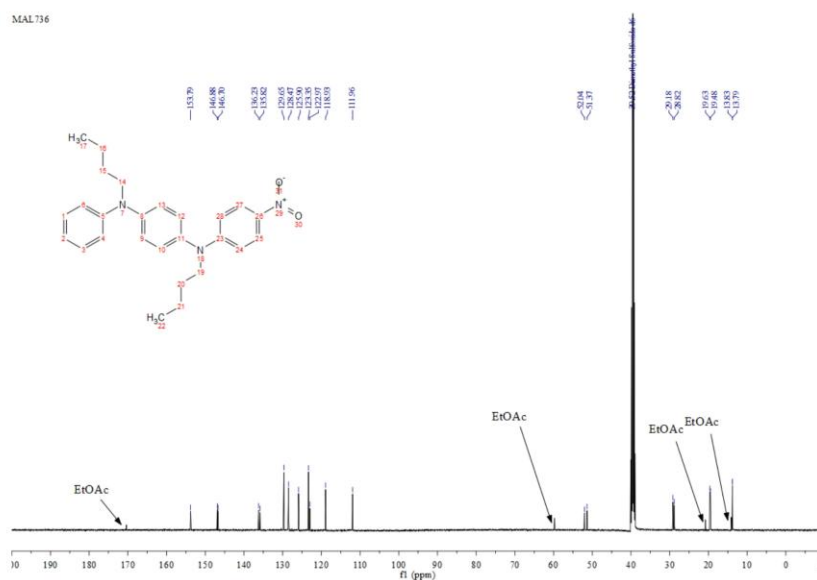
¹H NMR (dmso-d₆, 500 MHz, 293 K): δ = 8.00 (d, *J* = 9.5 Hz, 2H), 7.35 (dd, *J* = 8.3, 7.5 Hz, 2H), 7.13 (d, *J* = 7.5 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.06 (dd, *J* = 11.6, 4.2 Hz, 1H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.65 (d, *J* = 9.5 Hz, 2H), 3.69 (dd, *J* = 15.1, 7.3 Hz, 4H), 1.62 – 1.52 (m, 4H), 1.39 – 1.28 (m, 4H), 0.88 (td, *J* = 7.3, 1.3 Hz, 6H) ppm.

¹³C NMR (dmso-d₆, 126 MHz, 293 K): δ = 153.79, 146.88, 146.70, 136.23, 135.82, 129.65, 128.47, 125.90, 123.35, 122.97, 118.93, 111.96, 52.04, 51.37, 29.18, 28.82, 19.63, 19.48, 13.83, 13.79 ppm.

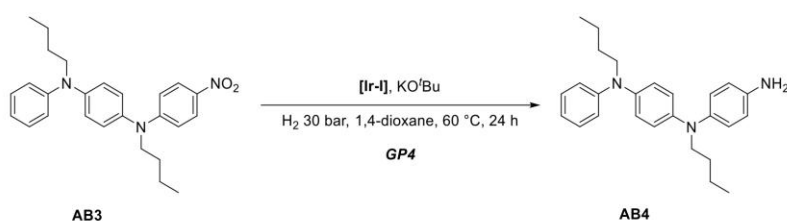
LC-HRMS (ESI+) *m/z* calculated for [**AB3**]⁺: 418.24890 found: 418.24688.



Supplementary Figure 24: ^1H NMR spectrum of compound **AB3**.



Supplementary Figure 25: ^{13}C NMR spectrum of compound **AB3**.

Supplementary Figure 26: Synthesis of compound **AB4**.

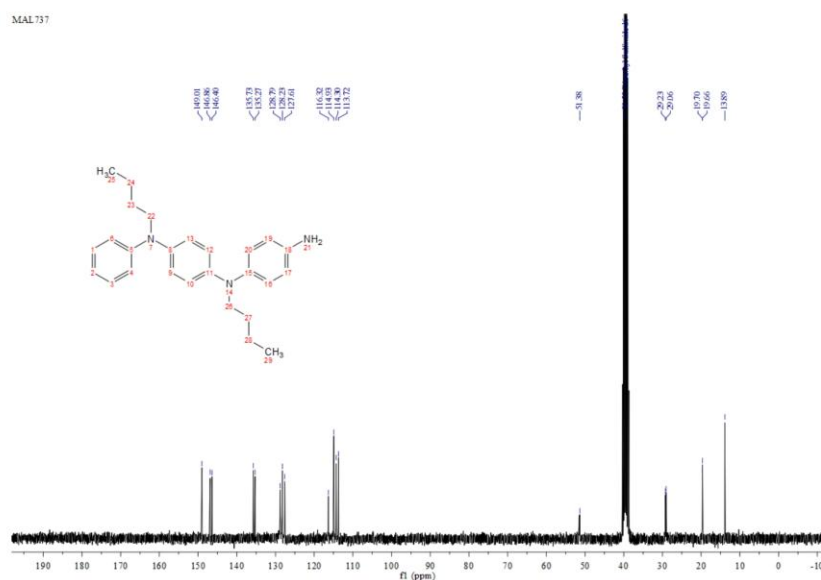
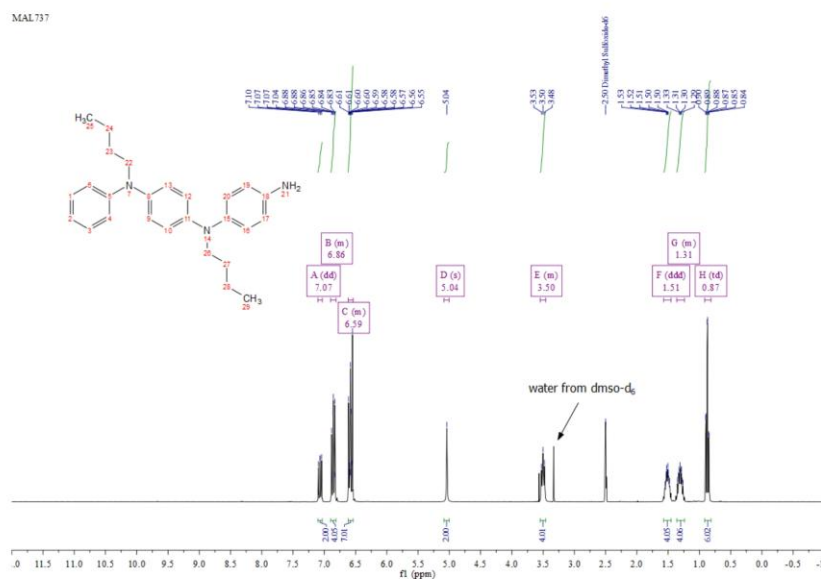
Reaction conditions for the synthesis of AB4: Following **GP4**, compound **AB3** (1.35 g, 3.22 mmol, 1.00 equiv.) KO^tBu (18.1 mg, 161 μmol, 5.00 mol%) and **[Ir-I]** (11.5 mg, 32.2 μmol, 0.50 mol%) are dissolved in 1,4-dioxane (13.0 mL, 0.25 M). The vial is placed in an autoclave and the vessel is pressurized to 30 bar H₂. The reaction is stirred for 24 h at 60 °C. The reaction is quenched by adding H₂O. The organic phase gets dissolved in EtOAc washed with water : brine (1:1) two times.

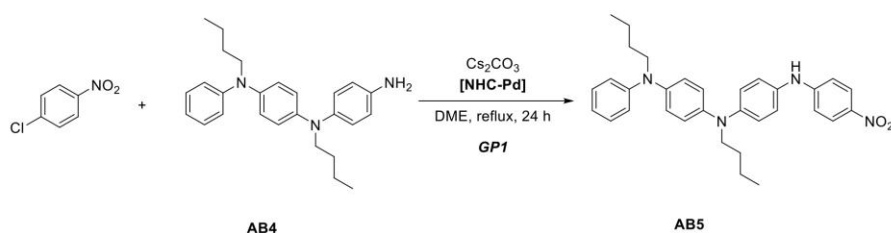
The combined aqueous phases get extracted with EtOAc one time. The combined organic phases are dried over Na₂SO₄ and the solvent gets removed under reduced pressure. Column chromatography (*n*-pentane / EtOAc 8:2) affords **AB4** (624 mg, 1.61 mmol, 50%) as a dark green oil. **AB3** (624 mg, 1.61 mmol) is recovered.

¹H NMR (dmsO-d₆, 300 MHz, 293 K): δ = 7.07 (m, 2H), 6.90 – 6.81 (m, 4H), 6.62 – 6.54 (m, 7H), 5.04 (s, 2H), 3.55 – 3.46 (m, 4H), 1.51 (m, 4H), 1.36 – 1.24 (m, 4H), 0.87 (m, 6H) ppm.

¹³C NMR (dmsO-d₆, 75 MHz, 293 K): δ = 149.01, 146.86, 146.40, 135.73, 135.27, 128.79, 128.23, 127.61, 116.32, 114.93, 114.30, 113.72, 51.38, 29.23, 29.06, 19.70, 19.66, 13.89 ppm.

LC-HRMS (ESI+) *m/z* calculated for [**AB4**]⁺: 388.27472 found: 388.27429.



Supplementary Figure 29: Synthesis of compound **AB5**.

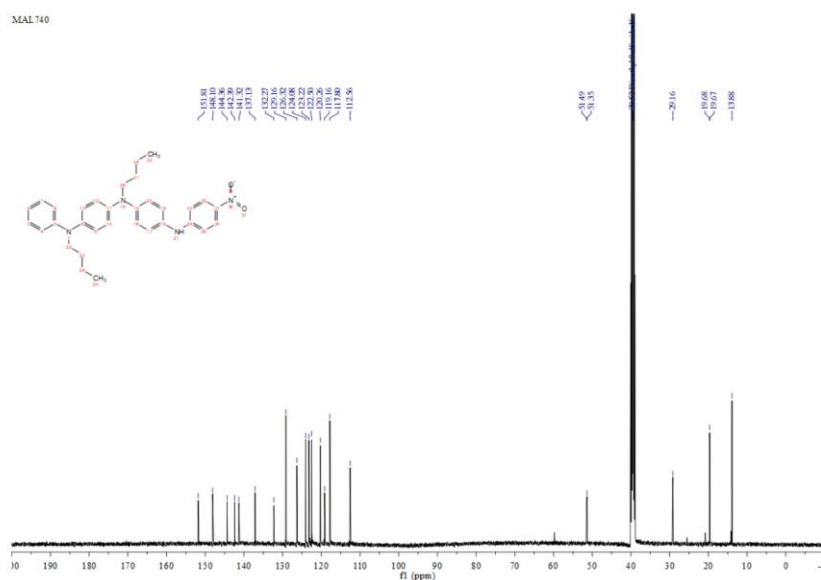
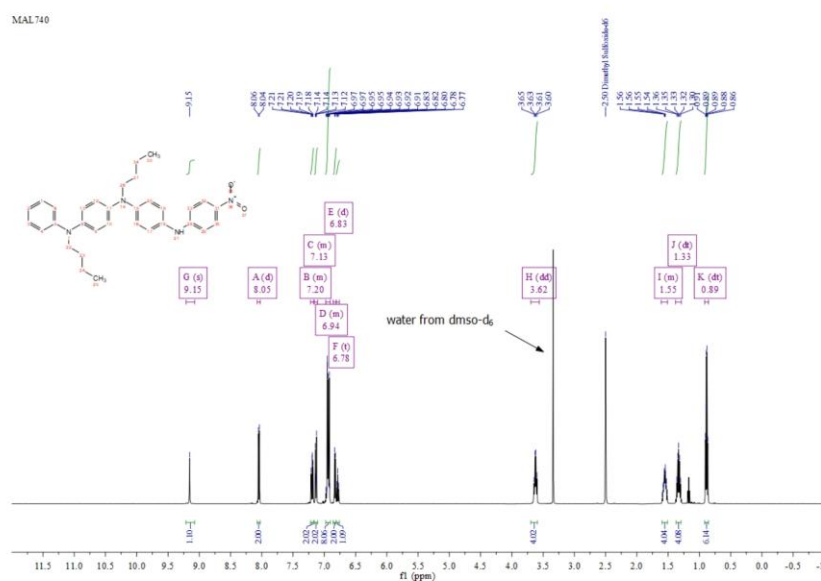
Reaction conditions for the synthesis of AB5: Following **GP1**, in a Schlenk tube **AB4** (520 mg, 1.34 mmol, 1.00 equiv.) Cs_2CO_3 (1.31 g, 4.03 mmol, 3.00 equiv.), **[NHC-Pd]** (46.0 mg, 67.0 μmol , 5.00 mol%) and 1-chloro-4-nitrobenzene (214 mg, 1.36 mmol, 1.01 equiv.) are dissolved in 5.36 mL DME (0.25 M). The reaction is stirred under reflux conditions for 24 h in an open system under argon. The reaction cooled to RT and the organic phase is dissolved in EtOAc. The organic phase is washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na_2SO_4 and the solvent is removed under reduced pressure.

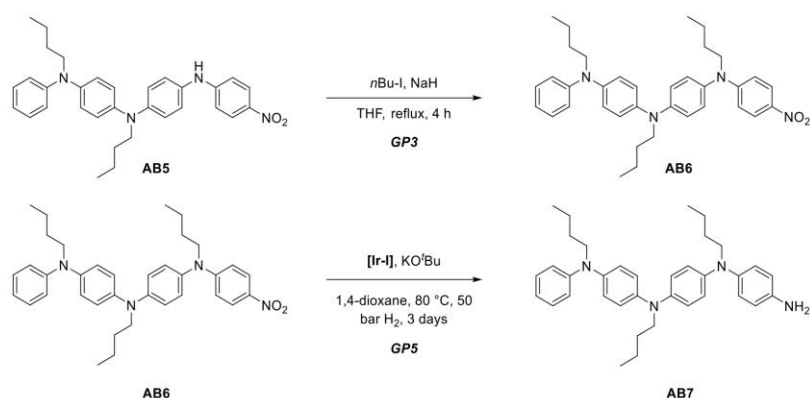
Column chromatography (9/1 *n*-pentane / EtOAc) affords **AB5** (614 mg, 1.20 mmol, 90%) as a dark red solid.

^1H NMR ($\text{dms}\text{-d}_6$, 500 MHz, 293 K): δ = 9.15 (s, 1H), 8.05 (d, J = 9.3 Hz, 2H), 7.22 – 7.17 (m, 2H), 7.16 – 7.11 (m, 2H), 6.98 – 6.90 (m, 8H), 6.83 (d, J = 7.3 Hz, 2H), 6.78 (t, J = 7.3 Hz, 1H), 3.62 (dd, J = 14.9, 7.5 Hz, 4H), 1.61 – 1.51 (m, 4H), 1.33 (dt, J = 14.9, 7.5 Hz, 4H), 0.89 (dt, J = 14.9, 7.5 Hz, 6H) ppm.

^{13}C NMR ($\text{dms}\text{-d}_6$, 126 MHz, 293 K): δ = 151.81, 148.10, 144.36, 142.39, 141.32, 137.13, 132.27, 129.16, 126.32, 124.08, 123.22, 122.50, 120.26, 119.16, 117.80, 112.56, 51.49, 51.35, 29.16, 19.68, 19.67, 13.88 ppm.

LC-HRMS (ESI+) m/z calculated for **[AB5] $^+$** : 509.29110 found: 509.29120.



Supplementary Figure 32: Synthesis of compound **AB7**.

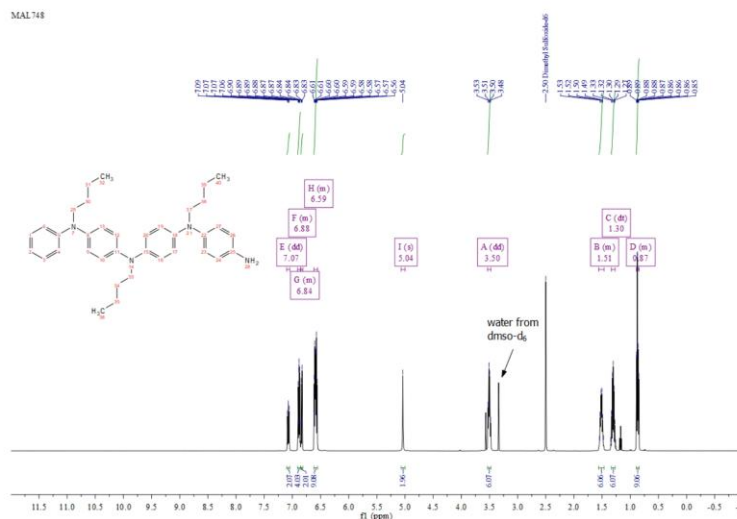
1. Reaction conditions for the synthesis of AB6: Following **GP3**, compound **AB5** (950 mg, 1.87 mmol, 1.00 equiv.) gets dissolved in THF (15.0 mL, 0.13 M). NaH (95.0 mg, 2.81 mmol, 60% on mineral oil, 1.50 equiv.) is added in portions to the solution. The solution is stirred for 5 minutes at RT. A gas bubbler is used to adjust the pressure. 1-Iodobutane (*n*-Bu-I, 516 mg, 319 μ L, 2.81 mmol, 1.50 equiv.) is slowly added and the mixture is refluxed for 4 hours. The mixture is cooled to RT. The reaction is quenched by adding H₂O. The organic phase is dissolved in EtOAc and washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na₂SO₄ and the solvent is removed under reduced pressure. The crude product is directly used for the next step.

2. Adjusted reaction conditions for the hydrogenation (GP5): **AB6** (1.06 g, 1.87 mmol, 1.00 equiv.), KO^tBu (21.0 mg, 187 μ mol, 10.0 mol%) and **[Ir-I]** (47.0 mg, 65.5 μ mol, 3.50 mol%) are dissolved in 1,4-dioxane (2.50 mL, 0.75 M). The vial is placed in an autoclave and the vessel is pressurized to 50 bar H₂. The reaction is stirred for 72 h at 80 °C. The reaction is quenched by adding H₂O. The organic phase gets dissolved in EtOAc washed with water : brine (1:1) two times. The combined aqueous phases get extracted with EtOAc one time. The combined organic phases are dried over Na₂SO₄ and the solvent gets removed under reduced pressure. Column chromatography (*n*-pentane / EtOAc 8:2) affords **AB7** (852 mg, 1.59 mmol, 85% over two steps) as a greenish oil.

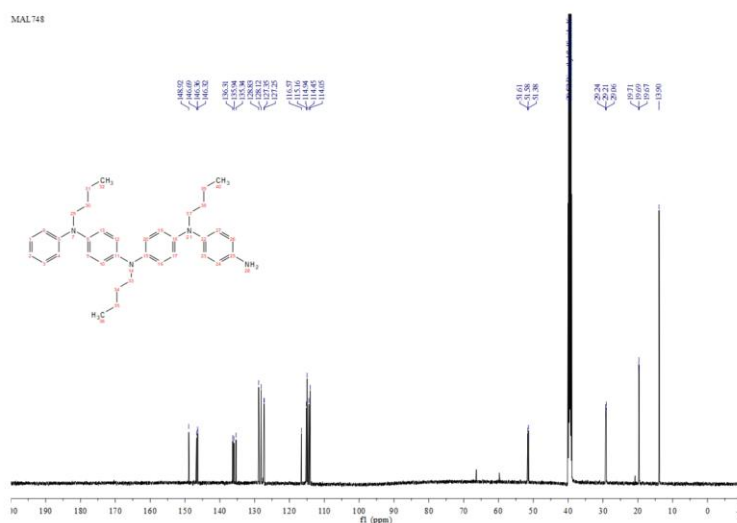
^1H NMR (dms o -d $_6$, 500 MHz, 293 K): δ = 7.07 (dd, J = 8.4, 7.6 Hz, 2H), 6.91 – 6.86 (m, 4H), 6.85 – 6.82 (m, 2H), 6.62 – 6.55 (m, 9H), 5.04 (s, 2H), 3.50 (dd, J = 15.2, 7.7 Hz, 6H), 1.56 – 1.47 (m, 6H), 1.30 (dt, J = 15.2, 7.7 Hz, 6H), 0.89 – 0.84 (m, 9H) ppm.

^{13}C NMR (dms o -d $_6$, 126 MHz, 293 K): δ = 148.92, 146.69, 146.36, 146.32, 136.31, 135.94, 135.34, 128.83, 128.12, 127.35, 127.25, 116.57, 115.16, 114.94, 114.45, 114.05, 51.61, 51.58, 51.38, 29.24, 29.21, 29.06, 19.71, 19.69, 19.67, 13.90 ppm.

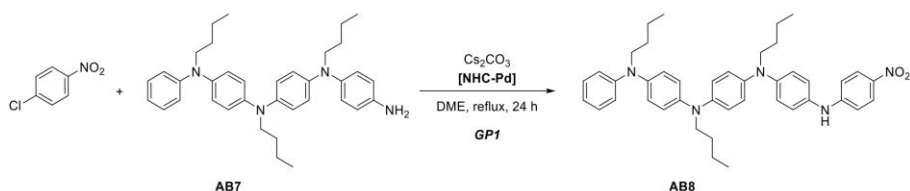
LC-HRMS (ESI $^+$) m/z calculated for **[AB7] $^+$** : 535.37952 found: 535.37892.



Supplementary Figure 33: ^1H NMR spectrum of compound **AB7**.



Supplementary Figure 34: ^{13}C NMR spectrum of compound **AB7**.



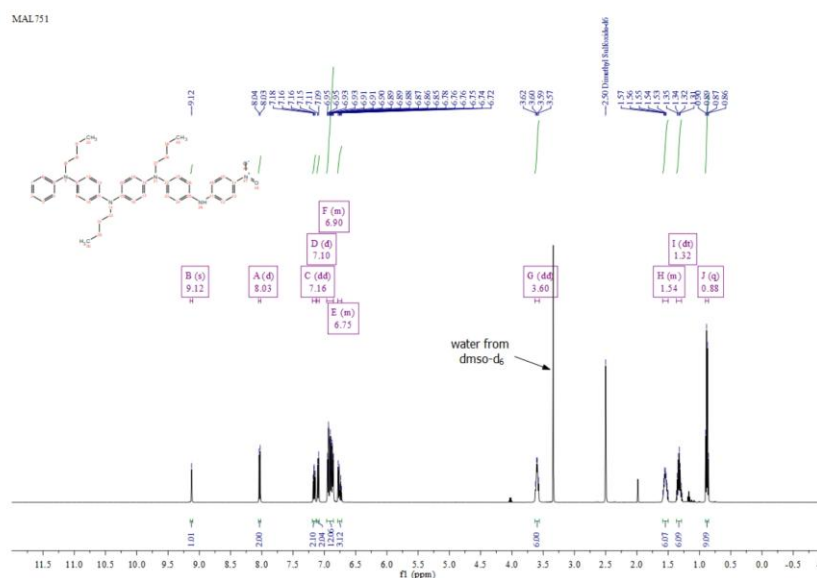
Supplementary Figure 35: Synthesis of compound **AB8**.

Reaction conditions for the synthesis of AB8: Following **GP1**, in a Schlenk tube, **AB7** (770 mg, 1.44 mmol, 1.00 equiv.), Cs₂CO₃ (1.40 g, 4.32 mmol, 3.00 equiv.), **[NHC-Pd]** (49.0 mg, 72.0 μmol, 5.00 mol%) and 1-chloro-4-nitrobenzene (227 mg, 1.44 mmol, 1.00 equiv.) are dissolved in 5.76 mL DME (0.25 M). The reaction is stirred under reflux conditions for 24 h in an open system under argon. The reaction cooled to RT and the organic phase is dissolved in EtOAc. The organic phase is washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na₂SO₄ and the solvent is removed under reduced pressure. Column chromatography (8.5/1.5 *n*-pentane / EtOAc) affords **AB8** (841 mg, 1.28 mmol, 89%) as a dark red solid.

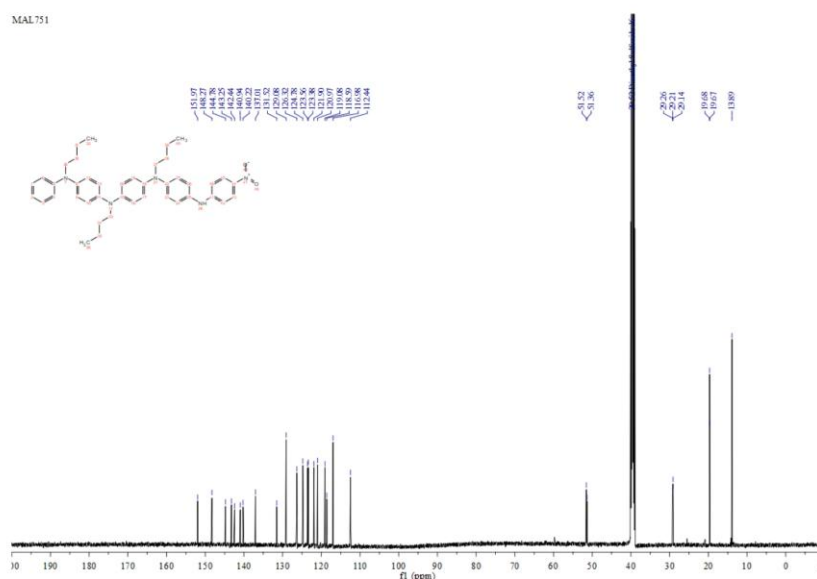
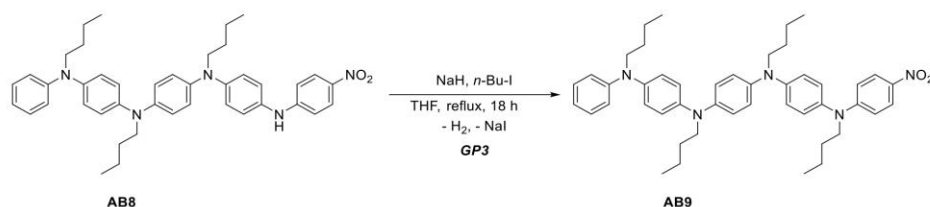
^1H NMR (dms o -d $_6$, 500 MHz, 293 K): δ = 9.12 (s, 1H), 8.03 (d, J = 8.6 Hz, 2H), 7.16 (dd, J = 8.6, 7.3 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 6.96 – 6.85 (m, 12H), 6.79 – 6.72 (m, 3H), 3.60 (dd, J = 15.8, 8.9 Hz, 6H), 1.59 – 1.50 (m, 6H), 1.32 (dt, J = 15.8, 8.9 Hz, 6H), 0.88 (q, J = 8.9 Hz, 9H) ppm.

^{13}C NMR (dms o -d $_6$, 126 MHz, 293 K): δ = 151.97, 148.27, 144.78, 143.25, 142.44, 140.94, 140.22, 137.01, 131.52, 129.08, 126.32, 124.78, 123.56, 123.38, 121.90, 120.97, 119.08, 118.59, 116.98, 112.44, 51.52, 51.36, 29.26, 29.21, 29.14, 19.68, 19.67, 13.89 ppm.

LC-HRMS (ESI $^+$) m/z calculated for [AB8] $^+$: 656.39590 found: 656.39221.



Supplementary Figure 36: ^1H NMR spectrum of compound AB8.

Supplementary Figure 37: ^{13}C NMR spectrum of compound **AB8**.Supplementary Figure 38: Synthesis of compound **AB9**.

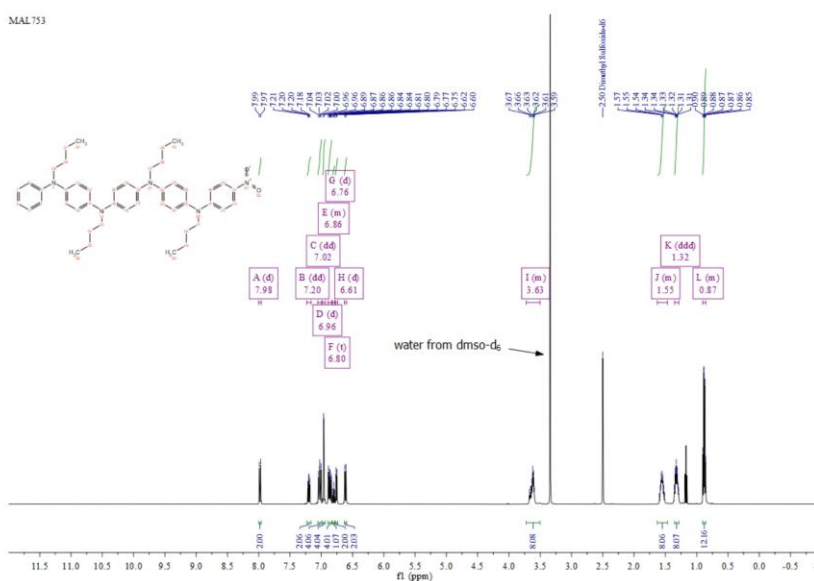
Reaction conditions for the synthesis of AB9: Following **GP3**, compound **AB8** (693 mg, 1.06 mmol, 1.00 equiv.) gets dissolved in THF (~8.00 mL, 0.13 M). NaH (54.0 mg, 1.59 mmol, 60% on mineral oil, ~1.50 equiv.) is added in portions to the solution. The solution is stirred for 15 minutes at RT. A gas bubbler is used to adjust the pressure. 1-Iodobutane (*n*-Bu-I, 294 mg, 182 μL , 1.59 mmol, 1.50 equiv.) is slowly added and the mixture is refluxed for 18 hours. The mixture is cooled to RT. The reaction is quenched by adding H_2O . The organic phase is dissolved in EtOAc and washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na_2SO_4 and the solvent is removed under

reduced pressure. Column chromatography (*n*-pentane / EtOAc 9:1) affords **AB9** (755 mg, 1.06 mmol, >99%) as a dark red oil.

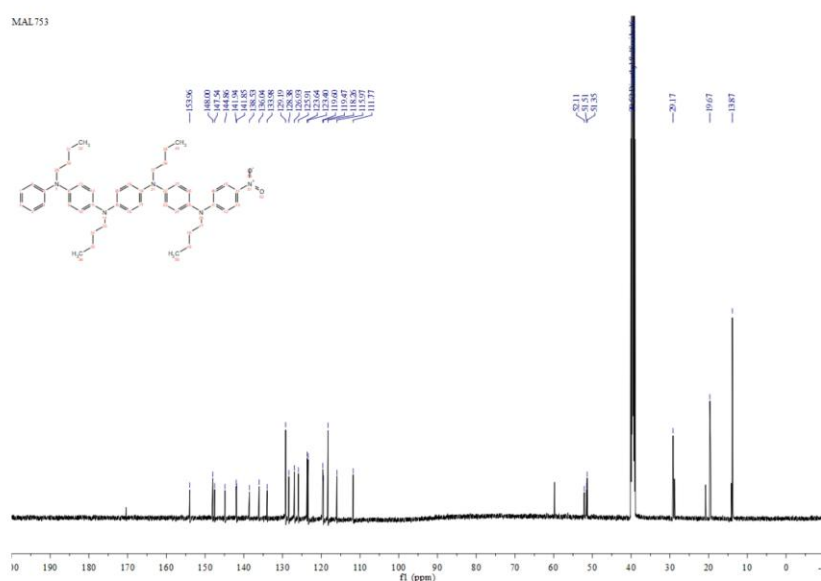
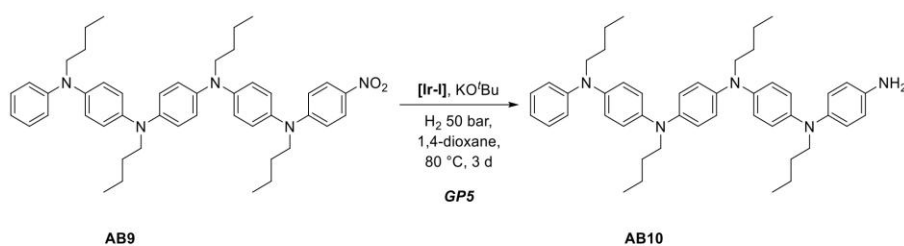
¹H NMR (dms_o-d₆, 500 MHz, 293 K): δ = 7.98 (d, *J* = 8.9 Hz, 2H), 7.20 (dd, *J* = 8.9, 7.3 Hz, 2H), 7.02 (dd, *J* = 10.9, 8.9 Hz, 4H), 6.96 (d, *J* = 10.9 Hz, 4H), 6.89 – 6.84 (m, 4H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 8.9 Hz, 2H), 3.72 – 3.50 (m, 8H), 1.63 – 1.47 (m, 8H), 1.32 (m, 8H), 0.90 – 0.85 (m, 12H) ppm.

¹³C NMR (dms_o-d₆, 126 MHz, 293 K): δ = 153.96, 148.00, 147.54, 144.86, 141.94, 141.85, 138.53, 136.04, 133.98, 129.19, 128.38, 126.93, 125.91, 123.64, 123.40, 119.60, 119.47, 118.26, 115.97, 111.77, 52.11, 51.51, 51.35, 29.17, 19.67, 13.87 ppm.

LC-HRMS (ESI+) *m/z* calculated for [**AB9**]⁺: 712.45850 found: 712.45506.



Supplementary Figure 39: ¹H NMR spectrum of compound **AB9**.

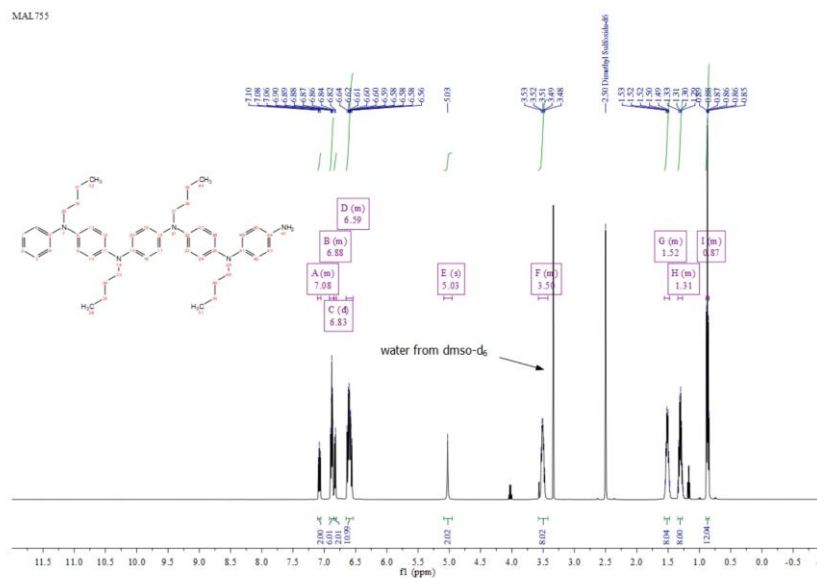
Supplementary Figure 40: ^{13}C NMR spectrum of compound **AB9**.Supplementary Figure 41: Synthesis of compound **AB10**.

Reaction conditions for the synthesis of AB10: Following **GP5**, **AB9** (680 mg, 955 μmol , 1.00 equiv.), KOtBu (10.7 mg, 95.5 μmol , 10.0 mol%) and **[Ir-I]** (24.0 mg, 33.4 μmol , 3.50 mol%) are dissolved in 1,4-dioxane (4.00 mL, 0.24 M). The vial is placed in an autoclave and the vessel is pressurized to 50 bar H_2 . The reaction is stirred for 72 h at 80 $^\circ\text{C}$. The reaction is quenched by adding H_2O . The organic phase gets dissolved in EtOAc washed with water : brine (1:1) two times. The combined aqueous phases get extracted with EtOAc one time. The combined organic phases are dried over Na_2SO_4 and the solvent gets removed under reduced pressure. Column chromatography (*n*-pentane / EtOAc 7:3) affords **AB10** (590 mg, 869 μmol , 91%) as a greenish oil.

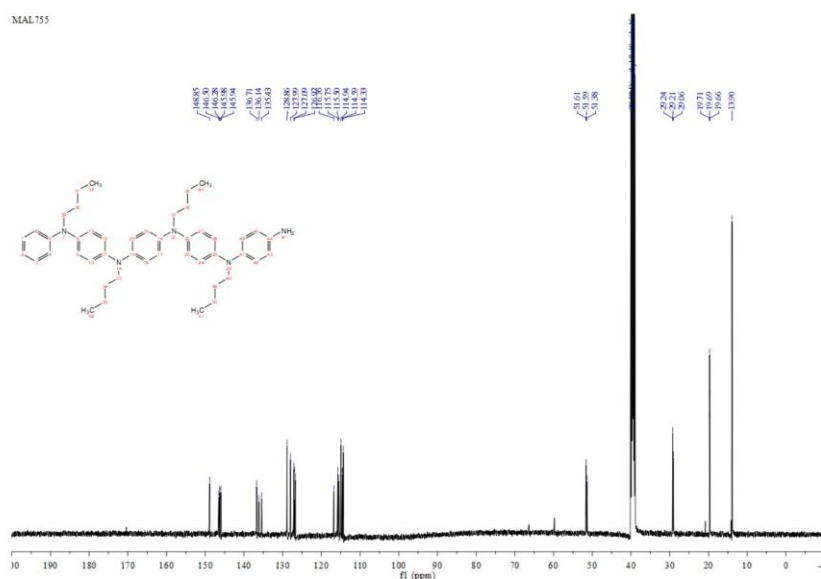
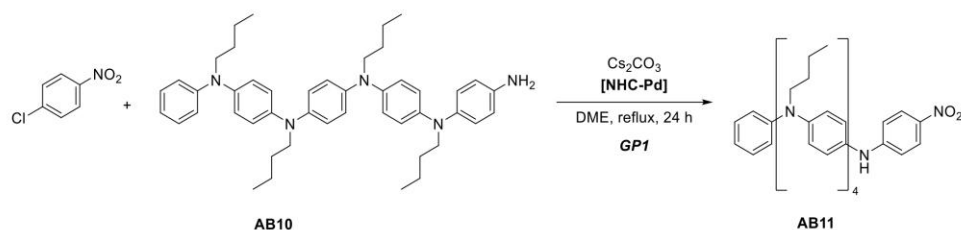
^1H NMR (dms o -d $_6$, 500 MHz, 293 K): δ = 7.11 – 7.05 (m, 2H), 6.92 – 6.85 (m, 6H), 6.83 (d, J = 8.5 Hz, 2H), 6.65 – 6.54 (m, 11H), 5.03 (s, 2H), 3.57 – 3.42 (m, 8H), 1.56 – 1.48 (m, 8H), 1.34 – 1.27 (m, 8H), 0.90 – 0.84 (m, 12H) ppm.

^{13}C NMR (dms o -d $_6$, 126 MHz, 293 K): δ = 148.85, 146.50, 146.28, 145.98, 145.94, 136.71, 136.14, 135.43, 128.86, 127.99, 127.09, 126.92, 126.70, 116.76, 115.75, 115.50, 114.94, 114.59, 114.33, 51.61, 51.59, 51.38, 29.24, 29.21, 29.06, 19.71, 19.69, 19.66, 13.90 ppm.

LC-HRMS (ESI $^+$) m/z calculated for [AB10] $^+$: 682.48432 found: 682.48353.



Supplementary Figure 42: ^1H NMR spectrum of compound AB10.

Supplementary Figure 43: ^{13}C NMR spectrum of compound **AB10**.Supplementary Figure 44: Synthesis of compound **AB11**.

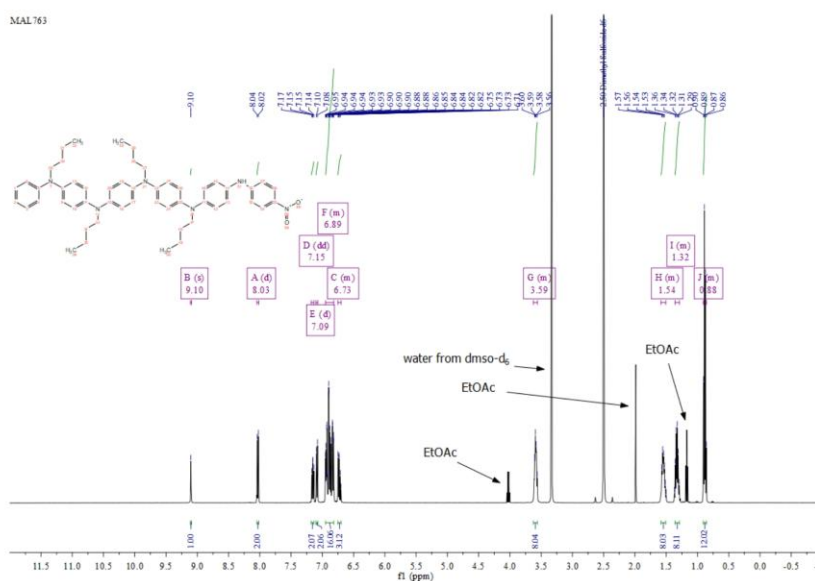
Reaction conditions for the synthesis of AB11: Following **GP1**, in a Schlenk tube, **AB10** (519 mg, 761 μmol , 1.00 equiv.), Cs_2CO_3 (744 mg, 2.28 mmol, 3.00 equiv.), **[NHC-Pd]** (26.0 mg, 38.1 μmol , 5.00 mol%) and 1-chloro-4-nitrobenzene (120 mg, 761 μmol , 1.00 equiv.) are dissolved in 3.04 mL DME (0.25 M). The reaction is stirred under reflux conditions for 24 h in an open system under argon. The reaction cooled to RT and the organic phase is dissolved in EtOAc. The organic phase is washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na_2SO_4 and the solvent is removed under

reduced pressure. Column chromatography (9/1 *n*-pentane / EtOAc) affords **AB11** (520 mg, 647 μ mol, 85%) as a dark red solid.

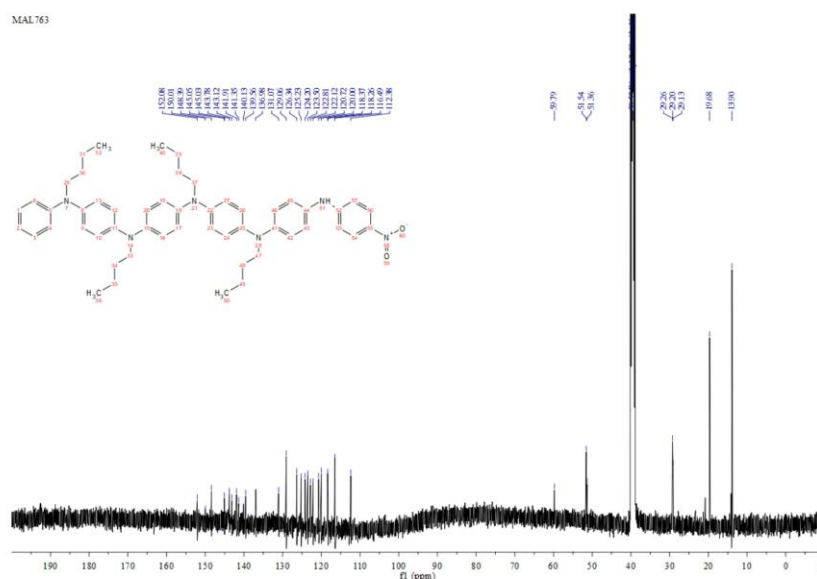
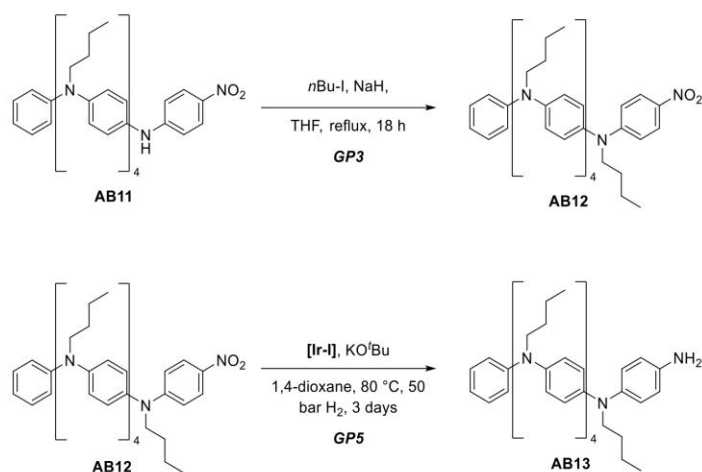
^1H NMR (dms- d_6 , 300 MHz, 293 K): δ = 9.10 (s, 1H), 8.03 (d, J = 8.9 Hz, 2H), 7.15 (dd, J = 8.9, 7.3 Hz, 2H), 7.09 (d, J = 8.9 Hz, 2H), 6.95 – 6.82 (m, 16H), 6.75 – 6.70 (m, 3H), 3.62 – 3.56 (m, 8H), 1.58 – 1.51 (m, 8H), 1.36 – 1.29 (m, 8H), 0.91 – 0.86 (m, 12H) ppm.

^{13}C NMR (dms- d_6 , 75 MHz, 293 K): δ = 152.08, 150.01, 148.39, 145.05, 145.03, 143.78, 143.12, 141.91, 141.35, 140.13, 139.56, 136.98, 131.07, 129.06, 126.34, 125.23, 124.20, 123.50, 122.81, 122.12, 120.72, 120.00, 118.37, 118.26, 116.49, 112.38, 59.79, 51.54, 51.36, 29.26, 29.20, 29.13, 19.68, 13.90 ppm.

LC-HRMS (ESI+) m/z calculated for [**AB11**] $^+$: 803.50070 found: 803.49637.



Supplementary Figure 45: ^1H NMR spectrum of compound **AB11**.

Supplementary Figure 46: ^{13}C NMR spectrum of compound **AB11**.Supplementary Figure 47: Synthesis of compound **AB13**.

1. Reaction conditions for the synthesis of AB12: Following **GP3**, compound **AB11** (454 mg, 565 μmol , 1.00 equiv.) gets dissolved in THF (4.35 mL, 0.13 M). NaH (28.5 mg, 848 μmol , 60% on mineral oil, ~ 1.50 equiv.) is added in portions to the solution. The

solution is stirred for 5 minutes at RT. A gas bubbler is used to adjust the pressure. 1-iodobutane (*n*-Bu-I, 156 mg, 96.3 μ L, 848 μ mol, 1.50 equiv.) is slowly added and the mixture is refluxed for 18 hours. The mixture is cooled to RT. The reaction is quenched by adding H₂O.

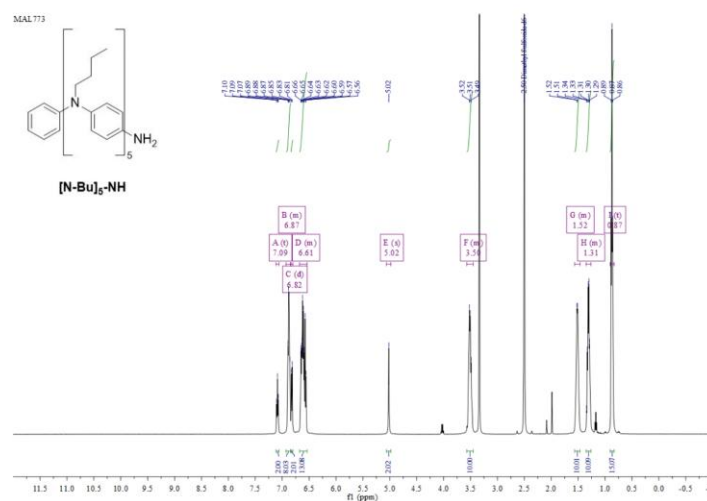
The organic phase is dissolved in EtOAc and washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na₂SO₄ and the solvent is removed under reduced pressure. The crude product is directly used for the next step.

2. Reaction conditions for the synthesis of AB13: Following **GP5**, **AB12** (486 mg, 565 μ mol, 1.00 equiv.), KO^tBu (6.34 mg, 56.5 μ mol, 10.0 mol%) and **[Ir-I]** (20.3 mg, 19.8 μ mol, 3.50 mol%) are dissolved in 1,4-dioxane (4.00 mL, 0.14 M). The vial is placed in an autoclave, and the vessel is pressurized to 50 bar H₂. The reaction is stirred for 72 h at 80 °C. The reaction is quenched by adding H₂O. The organic phase gets dissolved in EtOAc washed with water : brine (1:1) two times. The combined aqueous phases get extracted with EtOAc one time. The combined organic phases are dried over Na₂SO₄ and the solvent gets removed under reduced pressure. Column chromatography (*n*-pentane / EtOAc 7:3) affords **AB13** (403 mg, 486 μ mol, 86% over two steps) as a greenish oil.

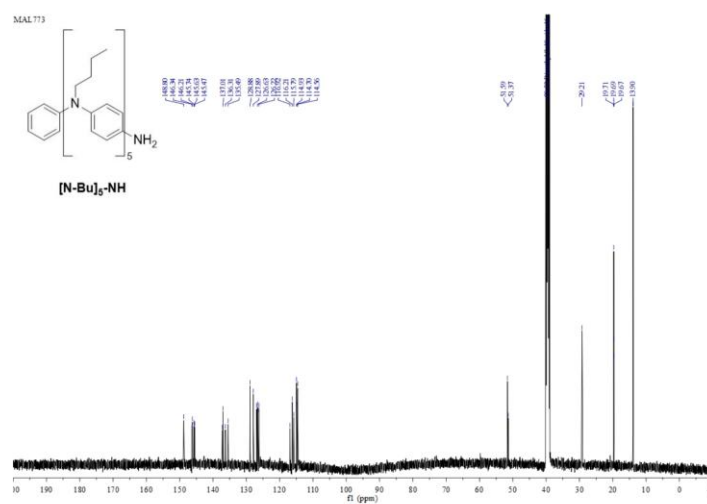
¹H NMR (dmso-d₆, 500 MHz, 293 K): δ = 7.09 (t, *J* = 7.8 Hz, 2H), 6.93 – 6.84 (m, 8H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.68 – 6.54 (m, 13H), 5.02 (s, 2H), 3.57 – 3.45 (m, 10H), 1.57 – 1.46 (m, 10H), 1.35 – 1.26 (m 10H), 0.87 (t, *J* = 7.2 Hz, 15H) ppm.

¹³C NMR (dmso-d₆, 126 MHz, 293 K): δ = 148.80, 146.34, 146.21, 145.74, 145.63, 145.47, 137.21, 137.01, 136.31, 135.49, 128.88, 127.89, 126.89, 126.63, 126.28, 126.22, 116.92, 116.21, 115.79, 114.93, 114.70, 114.56, 51.59, 51.37, 29.21, 19.71, 19.69, 19.67, 13.90 ppm.

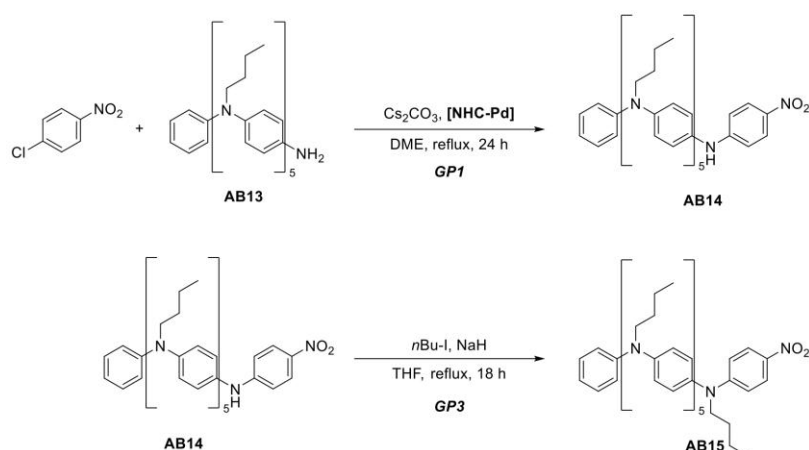
LC-HRMS (ESI+) *m/z* calculated for **[AB13]⁺**: 829.58912 found: 829.58727.



Supplementary Figure 48: ^1H NMR spectrum of compound **AB13**.



Supplementary Figure 49: ^{13}C NMR spectrum of compound **AB13**.

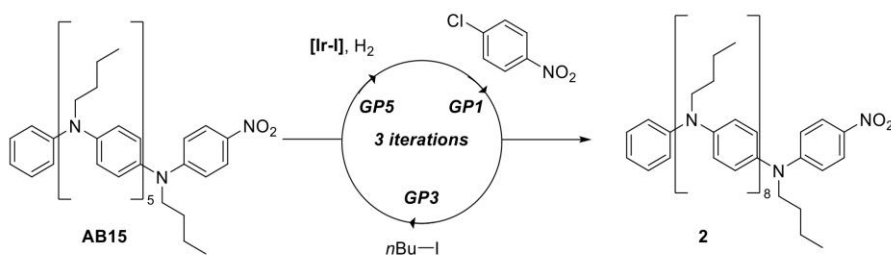
Supplementary Figure 50: Synthesis of compound **AB15**.

1. Reaction conditions for the synthesis of AB14: Following **GP1**, **AB13** (338 mg, 407 μmol , 1.00 equiv.), 1-chloro-4-nitrobenzene (64.2 mg, 407 μmol , 1.00 equiv.), **[NHC-Pd]** (13.9 mg, 20.4 μmol , 5.00 mol%) and Cs_2CO_3 (398 mg, 1.22 mmol, 3.00 equiv.) are dissolved in DME (2.50 mL, 0.16 M). The reaction is stirred under reflux conditions for 24 h in an open system under argon. The reaction cooled to RT and the organic phase is dissolved in EtOAc. The organic phase is washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times.

The combined organic phases are dried over Na_2SO_4 and the solvent is removed under reduced pressure. Column chromatography (8.5/1.5 *n*-pentane / EtOAc) affords **AB14** (300 mg, 318 μmol , 78%) as a dark red solid.

2. Reaction conditions for the synthesis of AB15: Following **GP3**, **AB14** (250 mg, 237 μmol , 1.00 equiv.) gets dissolved in THF (1.50 mL, 0.16 M). NaH (12.0 mg, 356 μmol , 60% on mineral oil, ~1.50 equiv.) is added. The reaction is stirred for 5 minutes at RT. A gas bubbler is used to adjust the pressure. *n*-BuI (65.5 mg, 40.4 μl , 356 μmol , 1.50 equiv.) is added and the solution is stirred under reflux conditions in an open system under argon atmosphere for 18 h. The reaction solution is directly used for column chromatography (9/1 *n*-pentane / EtOAc). Compound **AB15** is isolated (239 mg, 237 μmol , >99%) as a dark red oil.

The compound was used directly for the next steps without complete characterization.



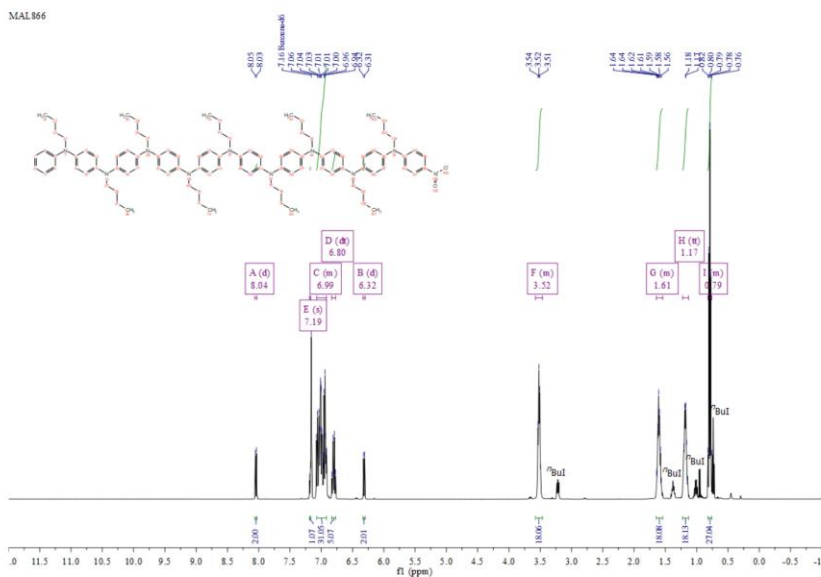
Supplementary Figure 51: Synthesis of compound 2.

Compound **2** is synthesized following **GP1**, **GP3**, and **GP5** (51.0 mg, 35.2 μ mol, 0.8% yield, 83% average yield) over 26 steps as an orange solid.

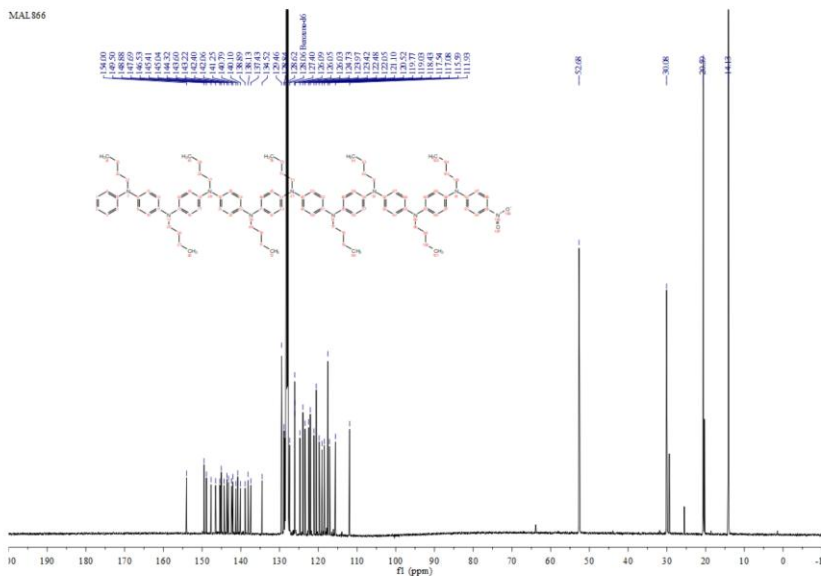
1H NMR (C_6D_6 , 500 MHz, 293 K): δ = 8.04 (d, J = 9.4 Hz, 2H), 7.19 (s, 1H), 7.07 – 6.92 (m, 31H), 6.80 (dt, J = 9.4, 5.6 Hz, 5H), 6.32 (d, J = 9.4 Hz, 2H), 3.58 – 3.47 (m, 18H), 1.64 – 1.54 (m, 18H), 1.17 (tt, J = 9.2, 4.4 Hz, 18H), 0.82 – 0.76 (m, 27H) ppm.

^{13}C NMR (C_6D_6 , 126 MHz, 293 K): δ = 154.00, 149.50, 148.88, 147.69, 146.53, 145.41, 145.04, 144.32, 143.60, 143.22, 142.40, 142.06, 141.25, 140.79, 140.10, 138.89, 138.13, 137.43, 134.52, 129.46, 128.84, 128.62, 127.40, 126.09, 126.05, 126.03, 124.73, 123.97, 123.42, 122.48, 122.05, 121.10, 120.52, 119.77, 119.03, 118.43, 117.54, 117.08, 115.59, 111.93, 52.68, 30.08, 20.59, 14.13 ppm.

LC-HRMS (ESI+) m/z calculated for $[2]^+$: 1447.98250 found: 1447.97368.

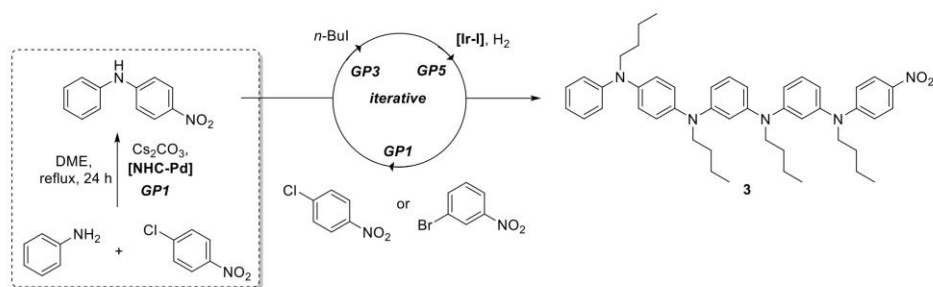


Supplementary Figure 52: ^1H NMR spectrum of compound **2**.



Supplementary Figure 53: ^{13}C NMR spectrum of compound 2.

9 Synthesis of compound 3



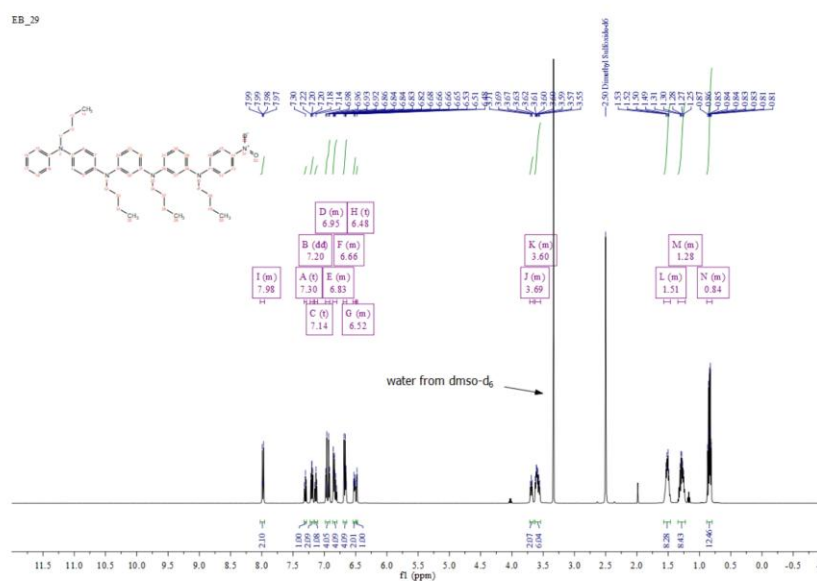
Supplementary Figure 54: Synthesis of compound 3.

Compound **3** is synthesized following **GP1**, **GP3** and **GP5** (248 mg, 348 μ mol, 8.42% yield, 80% average yield) over 11 steps as a red oil.

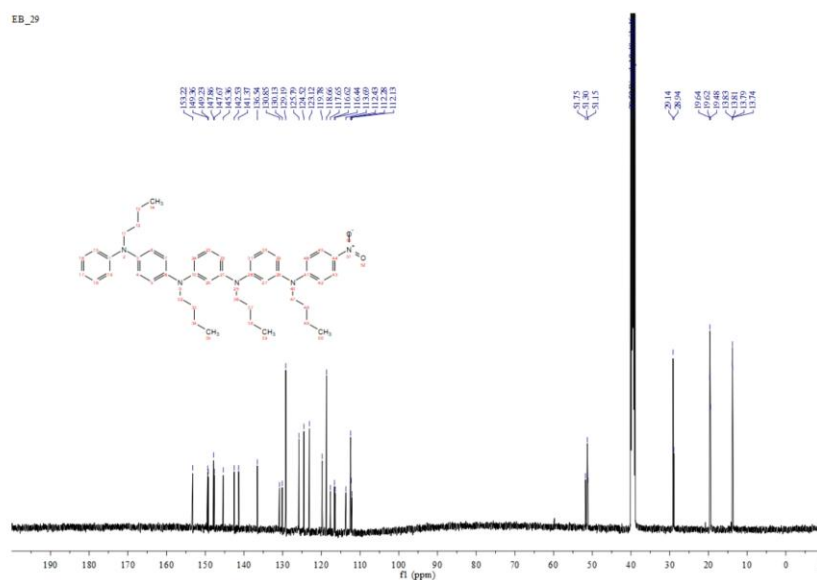
^1H NMR (dmso- d_6 , 500 MHz, 293 K): δ = 8.02 – 7.96 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.20 (dd, J = 8.6, 7.4 Hz, 2H), 7.14 (t, J = 8.1 Hz, 1H), 6.98 – 6.91 (m, 4H), 6.86 – 6.80 (m, 4H), 6.70 – 6.64 (m, 4H), 6.54 – 6.50 (m, 2H), 6.48 (t, J = 2.0 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.63 – 3.54 (m, 6H), 1.57 – 1.47 (m, 8H), 1.35 – 1.23 (m, 8H), 0.88 – 0.80 (m, 12H) ppm.

^{13}C NMR (dmso- d_6 , 126 MHz, 293 K): δ = 153.22, 149.36, 149.23, 147.86, 147.67, 145.36, 142.53, 141.37, 136.54, 130.85, 130.13, 129.19, 125.79, 124.52, 123.12, 119.78, 118.66, 117.65, 116.62, 116.44, 113.69, 112.43, 112.28, 112.13, 51.75, 51.30, 51.15, 29.14, 28.94, 19.64, 19.62, 19.48, 13.83, 13.81, 13.79, 13.74 ppm.

LC-HRMS (ESI+) m/z calculated for $[\mathbf{3}]^+$: 712.45850 found: 712.45432.

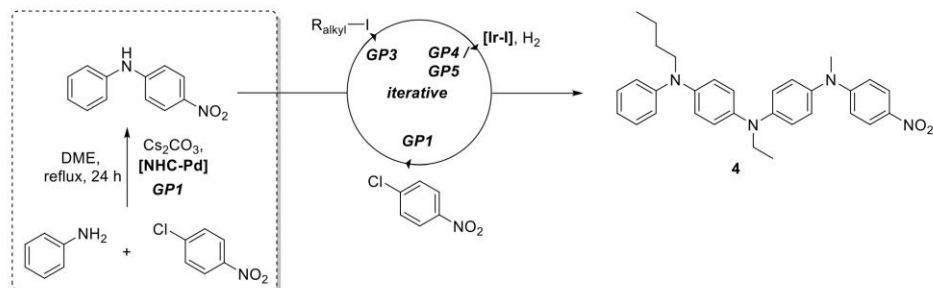


Supplementary Figure 55: ¹H NMR spectrum of compound **3**.



Supplementary Figure 56: ¹³C NMR spectrum of compound **3**.

10 Synthesis of compound 4



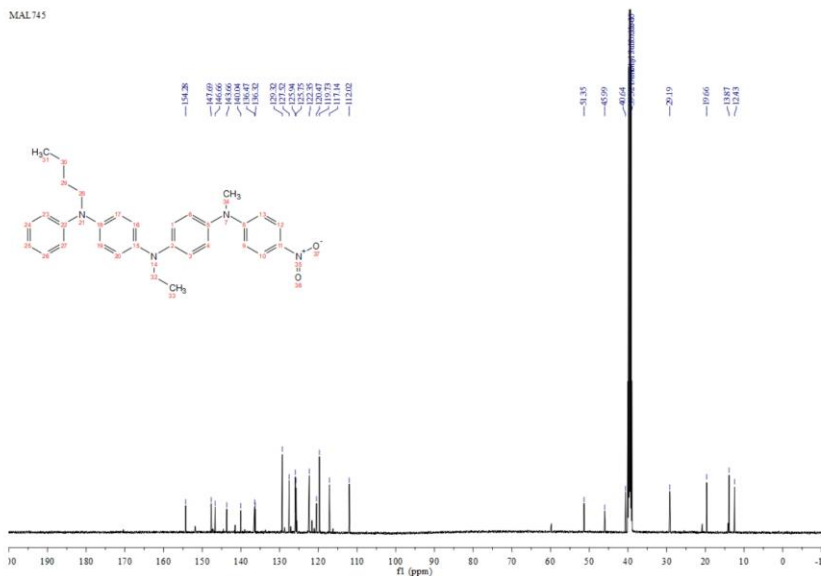
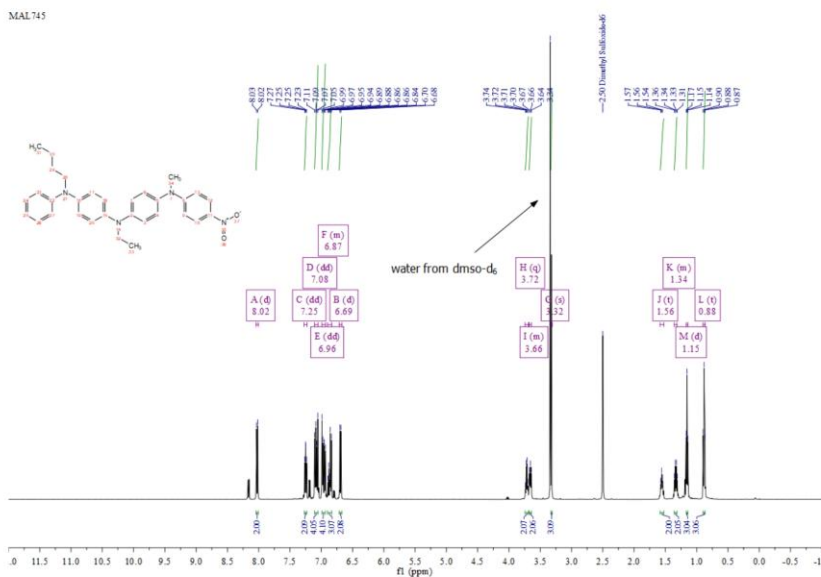
Supplementary Figure 57: Synthesis of compound 4.

Compound **4** is synthesized following **GP1**, **GP3** and **GP4/GP5** (245 mg, 495 μ mol, 49% yield, 92% average yield) over 8 steps as a dark red oil.

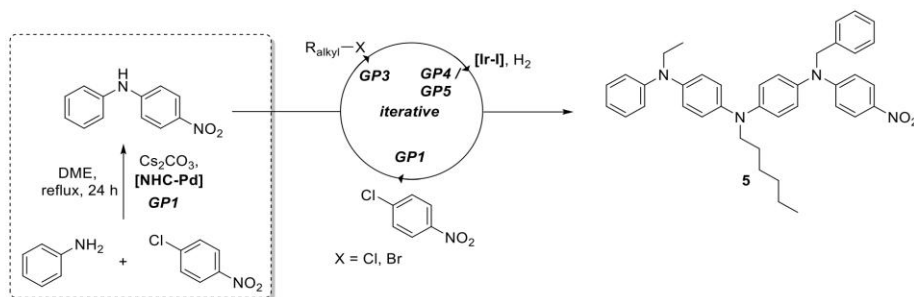
^1H NMR (dms o -d $_6$, 500 MHz, 293 K): δ = 8.02 (d, J = 9.5 Hz, 2H), 7.25 (dd, J = 8.4, 7.4 Hz, 2H), 7.08 (dd, J = 18.2, 8.4 Hz, 4H), 6.96 (dd, J = 18.2, 8.4 Hz, 4H), 6.90 – 6.84 (m, 3H), 6.69 (d, J = 9.5 Hz, 2H), 3.72 (q, J = 7.0 Hz, 2H), 3.68 – 3.64 (m, 2H), 3.32 (s, 3H), 1.56 (t, J = 7.6 Hz, 2H), 1.36 – 1.32 (m, 2H), 1.15 (d, J = 7.0 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H) ppm.

^{13}C NMR (dms o -d $_6$, 126 MHz, 293 K): δ = 154.28, 147.69, 146.66, 143.66, 140.04, 136.47, 136.32, 129.32, 127.52, 125.94, 125.75, 122.35, 120.47, 119.73, 117.14, 112.02, 51.35, 45.99, 40.64, 29.19, 19.66, 13.87, 12.43 ppm.

LC-HRMS (ESI+) m/z calculated for [**4**] $^+$: 495.27545 found: 495.27550.



11 Synthesis of compound 5



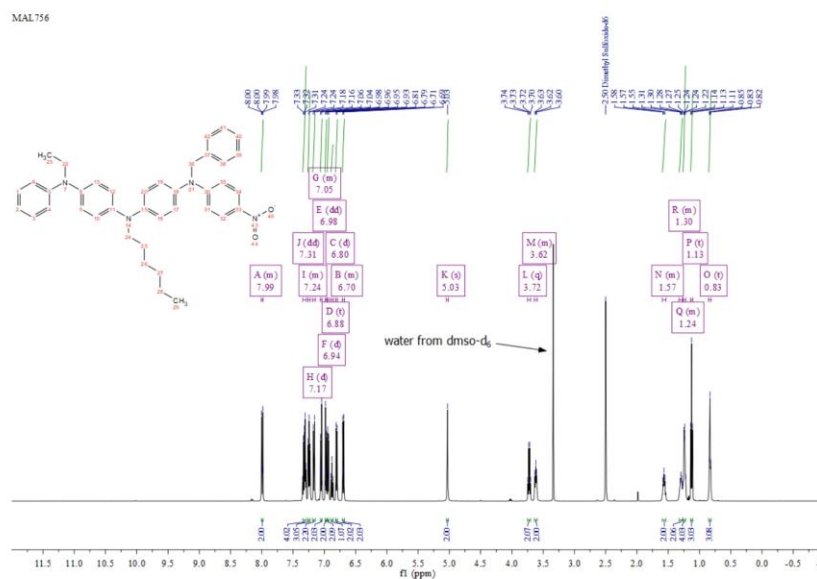
Supplementary Figure 60: Synthesis of compound 5.

Compound **5** is synthesized following **GP1**, **GP3** and **GP4/GP5** (413 mg, 690 μmol , 46% yield, 91% average yield) over 8 steps as a dark red oil.

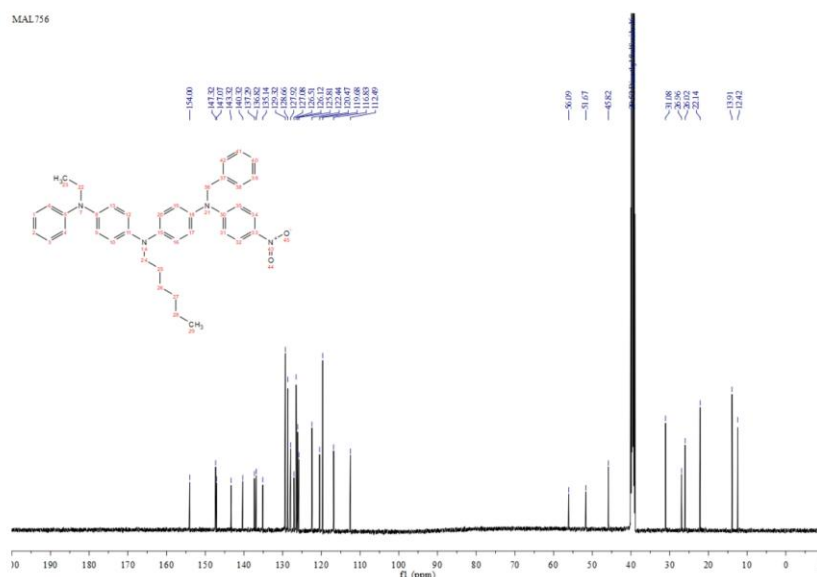
^1H NMR ($\text{dms}\text{-d}_6$, 500 MHz, 293 K): δ = 8.01 – 7.98 (m, 2H), 7.31 (dd, J = 13.2, 8.9 Hz, 4H), 7.26 – 7.23 (m, 3H), 7.17 (d, J = 8.9 Hz, 2H), 7.06 – 7.04 (m, 2H), 6.98 (dd, J = 8.9, 2.5 Hz, 2H), 6.94 (d, J = 7.7 Hz, 2H), 6.88 (t, J = 7.7 Hz, 1H), 6.80 (d, J = 8.9 Hz, 2H), 6.71 – 6.68 (m, 2H), 5.03 (s, 2H), 3.72 (q, J = 7.0 Hz, 2H), 3.64 – 3.60 (m, 2H), 1.59 – 1.54 (m, 2H), 1.33 – 1.27 (m, 2H), 1.26 – 1.22 (m, 4H), 1.13 (t, J = 7.0 Hz, 3H), 0.83 (t, J = 7.0 Hz, 3H) ppm.

^{13}C NMR ($\text{dms}\text{-d}_6$, 126 MHz, 293 K): δ = 154.00, 147.32, 147.07, 143.32, 140.32, 137.29, 136.82, 135.14, 129.32, 128.66, 127.92, 127.08, 126.51, 126.12, 125.81, 122.44, 120.47, 119.68, 116.83, 112.49, 56.09, 51.67, 45.82, 31.08, 26.96, 26.02, 22.14, 13.91, 12.42 ppm.

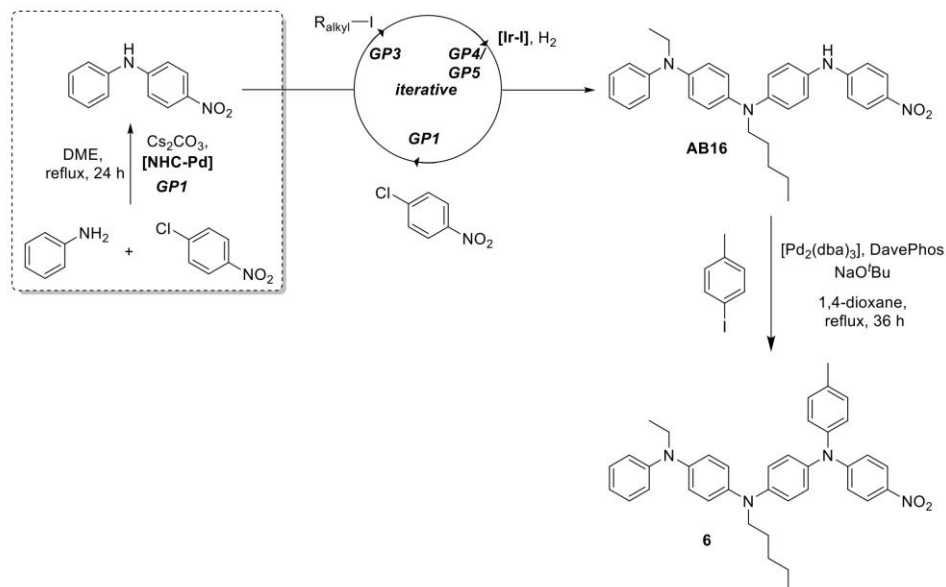
LC-HRMS (ESI+) m/z calculated for $[\mathbf{5}]^+$: 599.33805 found: 599.33717.



Supplementary Figure 61: ^1H NMR spectrum of compound **5**.



12 Synthesis of compound 6



Supplementary Figure 63: Synthesis of compound 6.

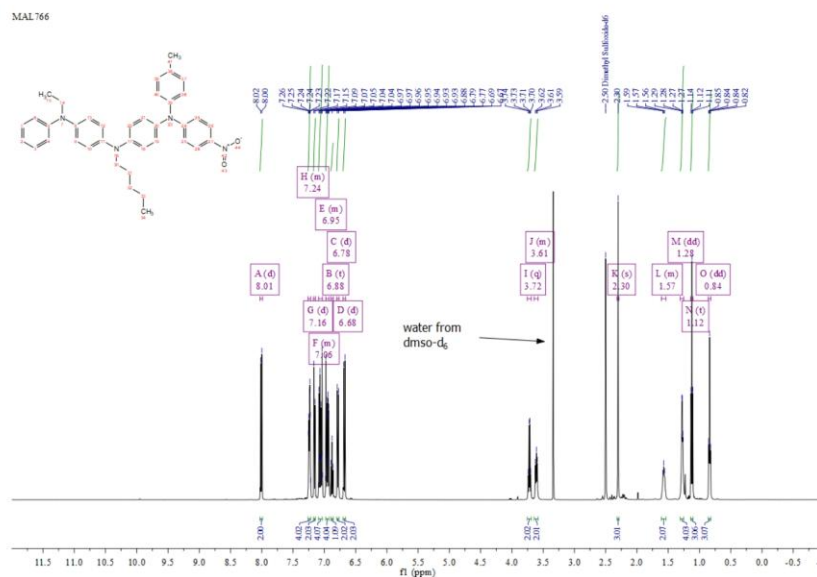
Compound **AB16** is synthesized following **GP1**, **GP3** and **GP4/GP5** (405 mg, 820 μmol , 55% yield, 93% average yield) over 7 steps as a dark red oil. The compound was directly used for the next step without complete characterization.

Reaction conditions for the synthesis of 6 (GP6): Referring to the literature^[57], a slightly modified synthesis protocol is used. **AB16** (405 mg, 820 μmol , 1.00 equiv.), $[\text{Pd}_2(\text{dba})_3]$ (37.5 mg, 41.0 μmol , 5.00 mol%), 2'-(dicyclohexylphosphaneyl)-*N,N*-dimethyl-[1,1'-biphenyl]-2-amine (DavePhos, 36.1 mg, 91.6 μmol , 10.0 mol%), NaO^tBu (118 mg, 1.23 mmol, 1.50 equiv.) and 1-iodo-4-methylbenzene (268 mg, 1.23 mmol, 1.50 equiv.) are dissolved in 1,4-dioxane (4.00 mL, 0.21 M). The reaction is stirred under reflux conditions for 36 h in an open system under argon. The reaction cooled to RT and the organic phase is dissolved in EtOAc. The organic phase is washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na_2SO_4 and the solvent is removed under reduced pressure. Column chromatography (95:5 *n*-pentane / EtOAc) affords **6** (461 mg, 787 μmol , 96%) as a dark red oil.

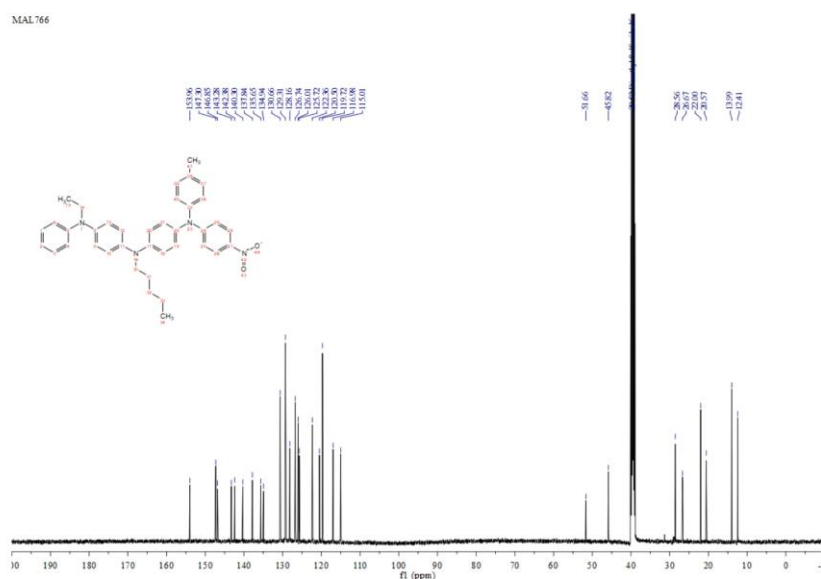
^1H NMR (dms o - d_6 , 500 MHz, 293 K): δ = 8.01 (d, J = 9.4 Hz, 2H), 7.26 – 7.22 (m, 4H), 7.16 (d, J = 8.3 Hz, 2H), 7.09 – 7.03 (m, 4H), 6.95 (m, 4H), 6.88 (t, J = 7.3 Hz, 1H), 6.78 (d, J = 9.4 Hz, 2H), 6.68 (d, J = 9.4 Hz, 2H), 3.72 (q, J = 7.0 Hz, 2H), 3.64 – 3.58 (m, 2H), 2.30 (s, 3H), 1.61 – 1.54 (m, 2H), 1.28 (dd, J = 7.0, 3.3 Hz, 4H), 1.12 (t, J = 7.0 Hz, 3H), 0.84 (dd, J = 8.6, 5.4 Hz, 3H) ppm.

^{13}C NMR (dms o - d_6 , 126 MHz, 293 K): δ = 153.96, 147.30, 146.85, 143.28, 142.38, 140.30, 137.84, 135.65, 134.94, 130.66, 129.31, 128.16, 126.74, 126.01, 125.72, 122.36, 120.50, 119.72, 116.98, 115.01, 51.66, 45.82, 28.56, 26.67, 22.00, 20.57, 13.99, 12.41 ppm.

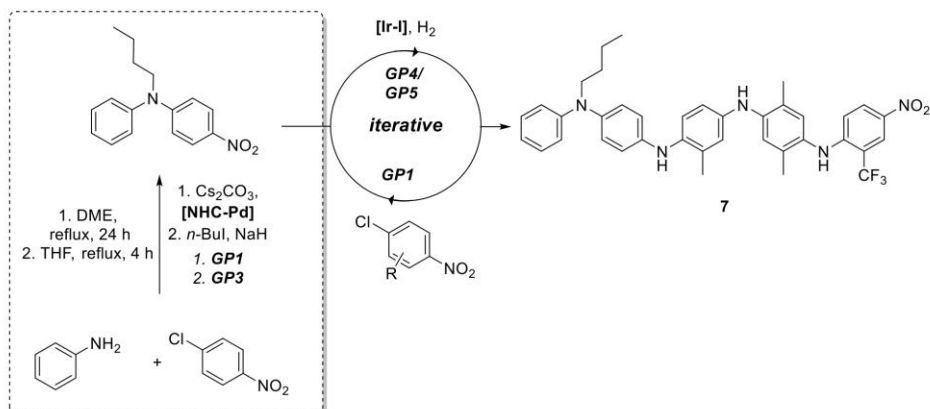
LC-HRMS (ESI $^+$) m/z calculated for $[\mathbf{6}]^+$: 585.32240 found: 585.32088.



Supplementary Figure 64: ^1H NMR spectrum of compound **6**.

Supplementary Figure 65: ^{13}C NMR spectrum of compound **6**.

13 Synthesis of compound **7**

Supplementary Figure 66: Synthesis of compound **7**.

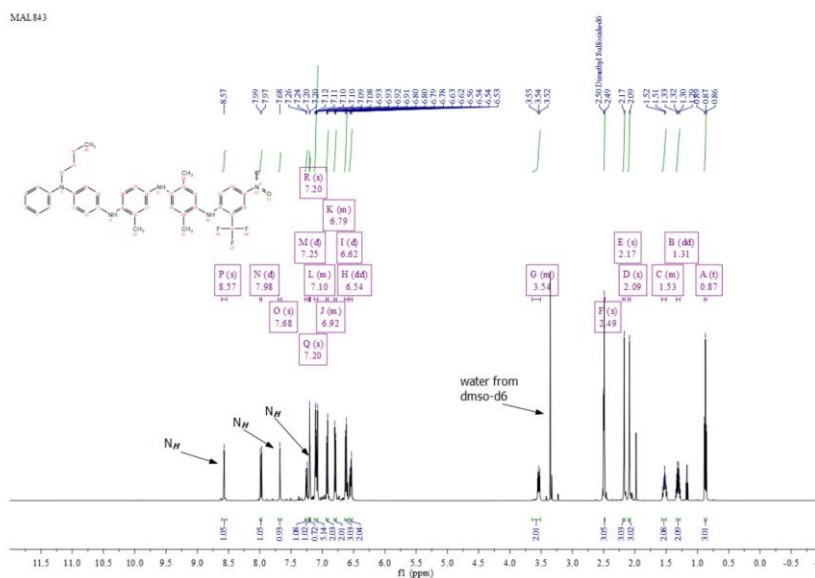
Compound **7** is synthesized following **GP1**, **GP3** and **GP4/GP5** (331 mg, 506 μmol , 36% yield, 88% average yield) over 8 steps as an orange solid.

¹H NMR (dms_o-d₆, 500 MHz, 293 K): δ = 8.57 (s, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.68 (s, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.20 (s, 1H), 7.20 (s, 1H), 7.13 – 7.07 (m, 5H), 6.94 – 6.90 (m, 2H), 6.81 – 6.78 (m, 2H), 6.62 (d, *J* = 8.5 Hz, 3H), 6.54 (dd, *J* = 9.0, 5.6 Hz, 2H), 3.64 – 3.51 (m, 2H), 2.49 (s, 3H), 2.17 (s, 3H), 2.09 (s, 3H), 1.57 – 1.50 (m, 2H), 1.31 (dd, *J* = 15.0, 7.5 Hz, 2H), 0.87 (t, *J* = 7.5 Hz, 3H) ppm.

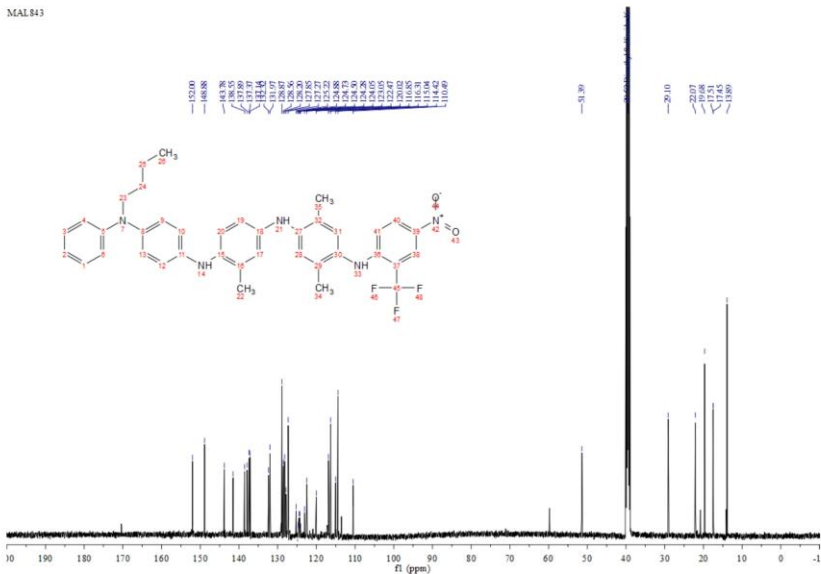
¹³C NMR (dms_o-d₆, 126 MHz, 293 K): δ = 152.00, 148.88, 143.78, 141.53, 138.55, 137.89, 137.37, 137.14, 132.32, 131.97, 128.87, 128.56, 128.20, 127.85, 127.27, 125.22, 124.88, 124.73, 124.50, 124.28, 124.05, 123.05, 122.47, 120.02, 116.85, 116.31, 115.04, 114.42, 110.49, 51.39, 29.10, 22.07, 19.68, 17.51, 17.45, 13.89 ppm.

¹⁹F NMR (dms_o-d₆, 471 MHz, 293 K): δ = -59.72 ppm.

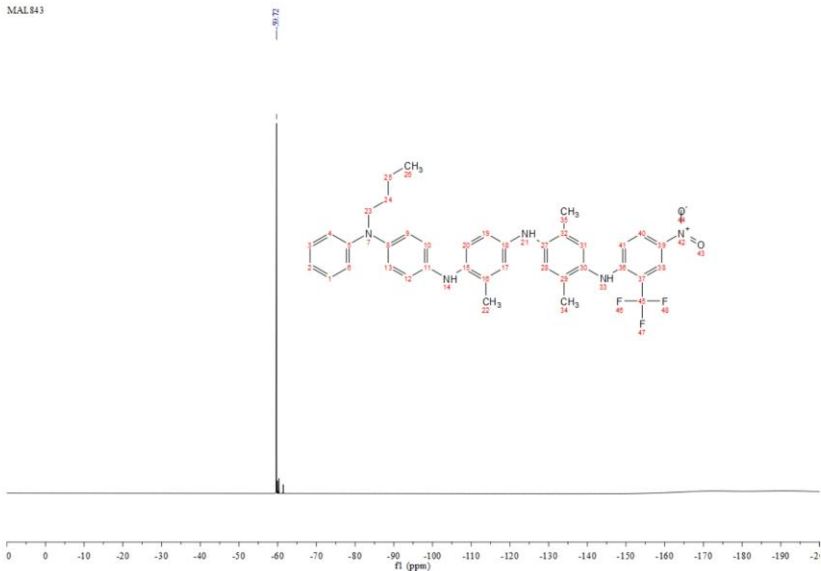
LC-HRMS (ESI⁺) *m/z* calculated for [7]⁺: 654.30504 found: 654.30117.



Supplementary Figure 67: ¹H NMR spectrum of compound **7**.

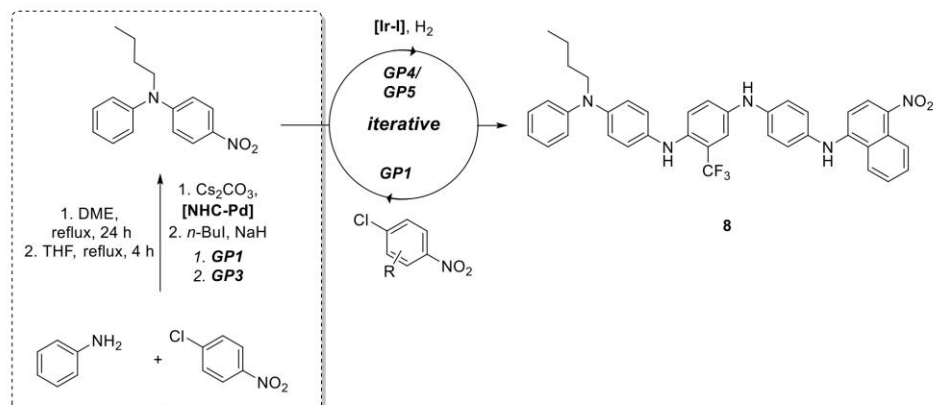


Supplementary Figure 68: ^{13}C NMR spectrum of compound 7.



Supplementary Figure 69: ^{19}F NMR spectrum of compound 7.

14 Synthesis of compound 8



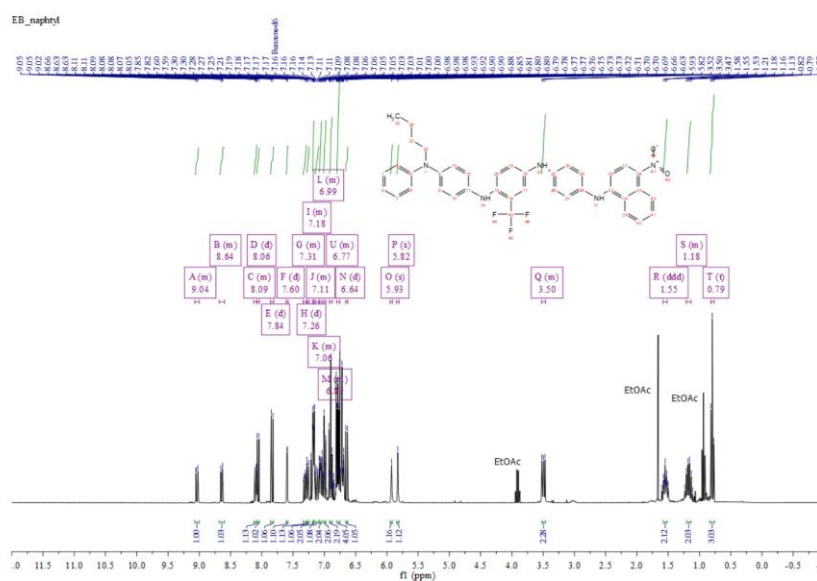
Supplementary Figure 70: Synthesis of compound 8.

Compound **8** is synthesized following **GP1**, **GP3** and **GP4/GP5** (193 mg, 292 μmol , 28% yield, 85% average yield) over 8 steps as dark red solid.

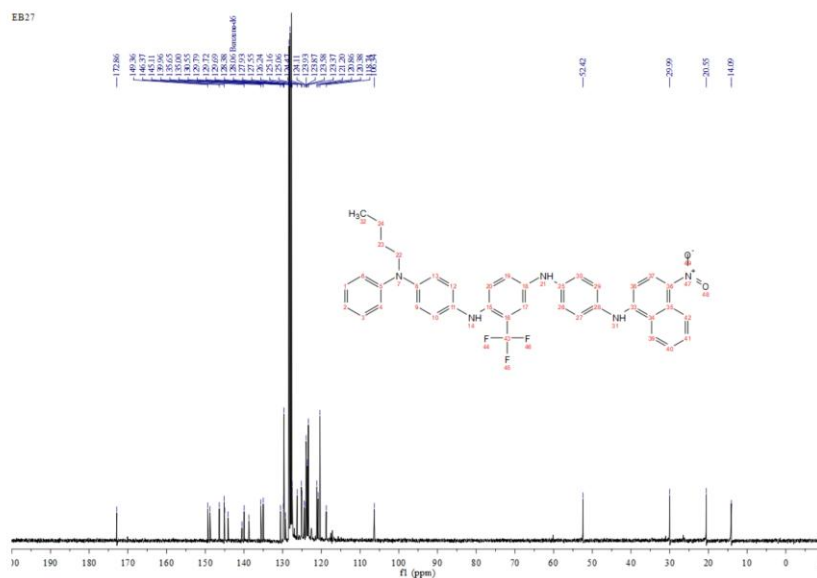
^1H NMR (C_6D_6 , 300 MHz, 293 K): δ = 9.07 – 9.00 (m, 1H), 8.68 – 8.60 (m, 1H), 8.13 – 8.08 (m, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 2.6 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.26 (d, J = 6.4 Hz, 1H), 7.19 – 7.17 (m, 2H), 7.15 – 7.09 (m, 1H), 7.08 – 7.04 (m, 2H), 7.01 – 6.97 (m, 2H), 6.92 – 6.87 (m, 2H), 6.80 – 6.75 (m, 4H), 6.64 (d, J = 8.7 Hz, 1H), 5.93 (s, 1H), 5.82 (s, 1H), 3.52 – 3.46 (m, 2H), 1.58 – 1.52 (m, 2H), 1.21 – 1.14 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H) ppm.

^{13}C NMR (C_6D_6 , 75 MHz, 293 K): δ = 172.86, 149.36, 148.78, 146.37, 145.11, 145.00, 144.11, 140.54, 139.96, 138.70, 135.65, 135.00, 130.55, 129.79, 129.72, 129.69, 129.27, 127.93, 127.55, 126.24, 125.16, 125.06, 124.47, 124.11, 123.93, 123.87, 123.58, 123.37, 121.20, 120.86, 120.38, 118.74, 106.34, 52.42, 29.99, 20.55, 14.09 ppm.

LC-HRMS (ESI+) m/z calculated for $[\mathbf{8}]^+$: 662.27374 found: 662.26867.

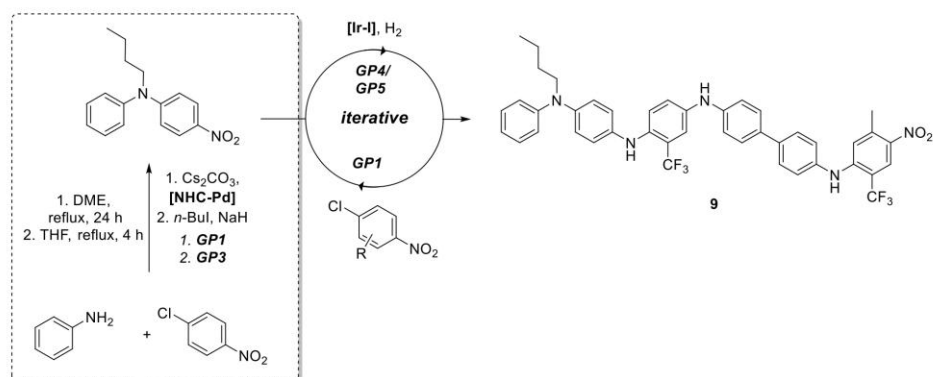


Supplementary Figure 71: ^1H NMR spectrum of compound **8**.



Supplementary Figure 72: ^{13}C NMR spectrum of compound **8**.

15 Synthesis of compound 9



Supplementary Figure 73: Synthesis of compound 9.

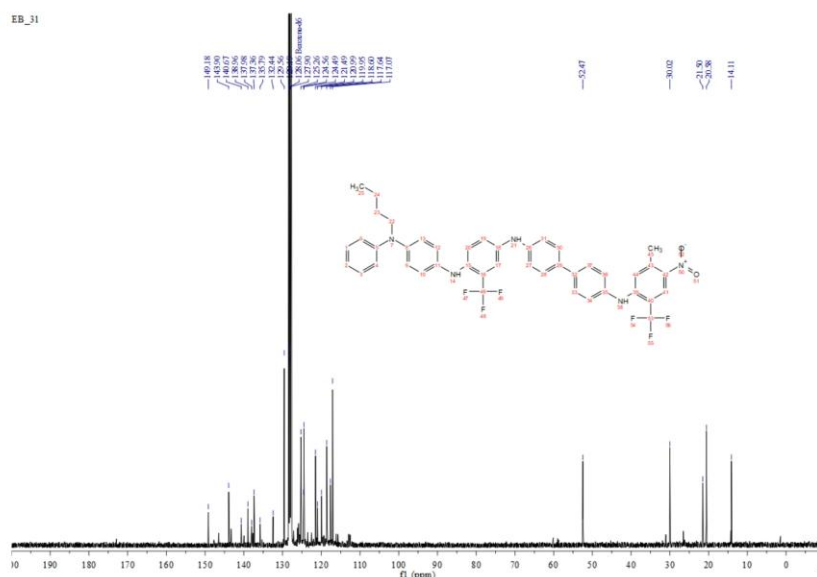
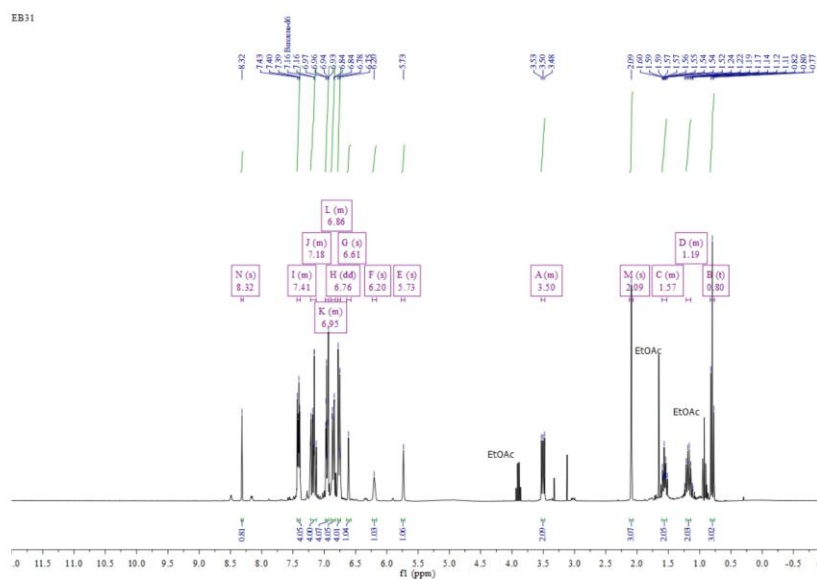
Compound **9** is isolated (140 mg, 181 μ mol, 13% yield, 78% average yield) over 8 steps as dark red solid.

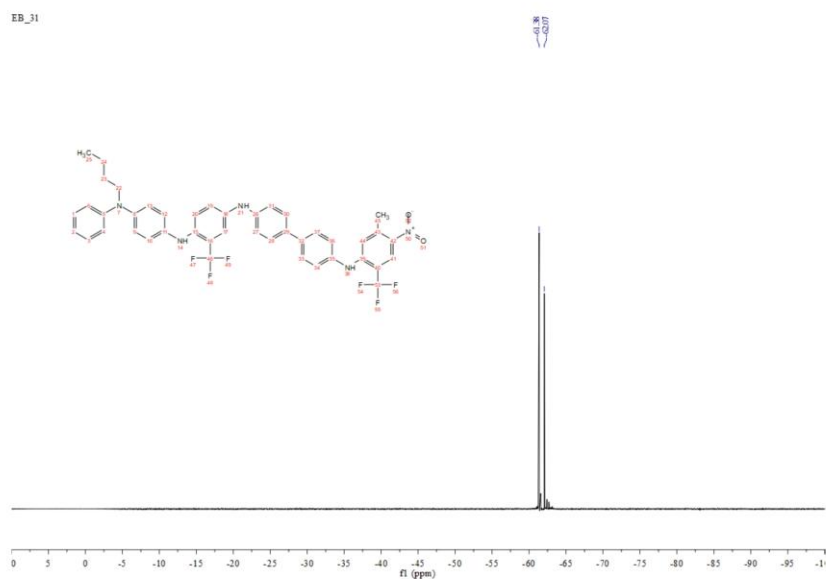
¹H NMR (C₆D₆, 300 MHz, 293 K): δ = 8.32 (s, 1H), 7.44 – 7.38 (m, 4H), 7.22 – 7.13 (m, 4H), 6.98 – 6.93 (m, 4H), 6.89 – 6.82 (m, 4H), 6.76 (dd, J = 6.6, 4.7 Hz, 4H), 6.61 (s, 1H), 6.20 (s, 1H), 5.73 (s, 1H), 3.53 – 3.47 (m, 2H), 2.09 (s, 3H), 1.60 – 1.53 (m, 2H), 1.22 – 1.14 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H) ppm.

¹³C NMR (C₆D₆, 75 MHz, 293 K): δ = 149.18, 143.90, 140.67, 138.96, 137.98, 137.36, 135.79, 132.44, 129.56, 128.19, 127.90, 125.26, 124.56, 124.49, 121.49, 120.99, 119.95, 118.60, 117.64, 117.07, 52.47, 30.02, 21.50, 20.58, 14.11 ppm.

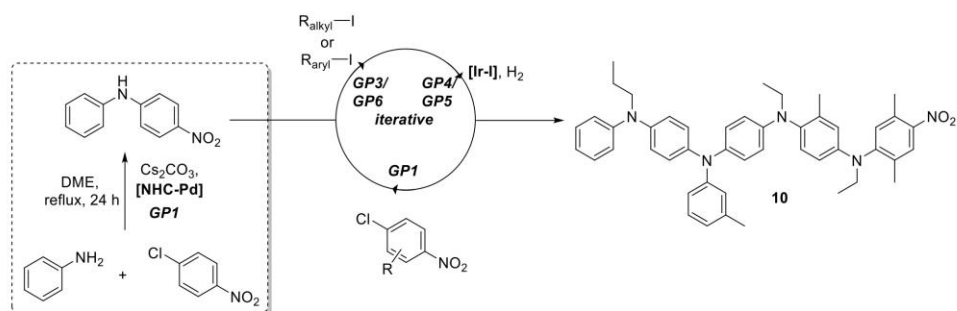
¹⁹F NMR (C₆D₆, 282 MHz, 293 K): δ = -61.38, -62.07 ppm.

LC-HRMS (ESI+) m/z calculated for [9]⁺: 770.29242 found: 770.28866.



Supplementary Figure 76: ^{19}F NMR spectrum of compound **9**.

16 Synthesis of compound **10**

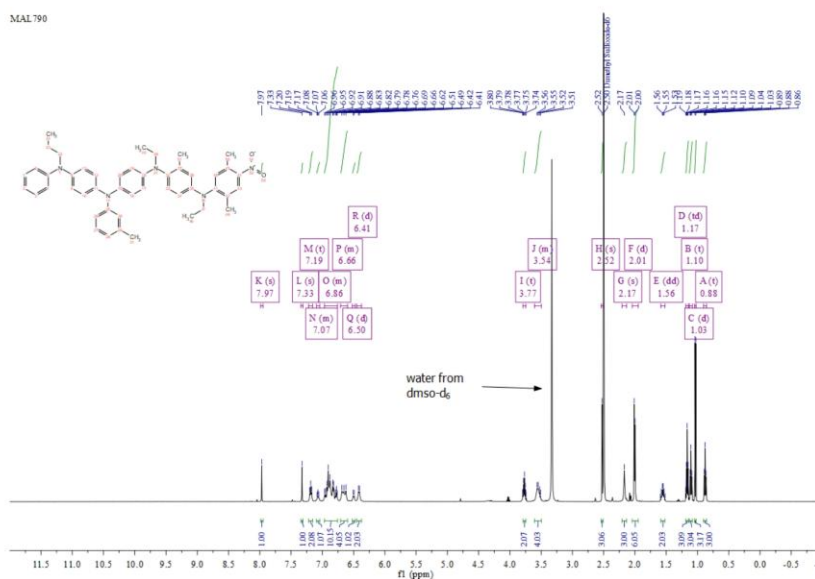
Supplementary Figure 77: Synthesis of compound **10**.

Compound **10** is synthesized following **GP1**, **GP3/GP6** and **GP4/GP5** (375 mg, 522 μmol , 46% yield, 93% average yield) over 11 steps as an orange solid.

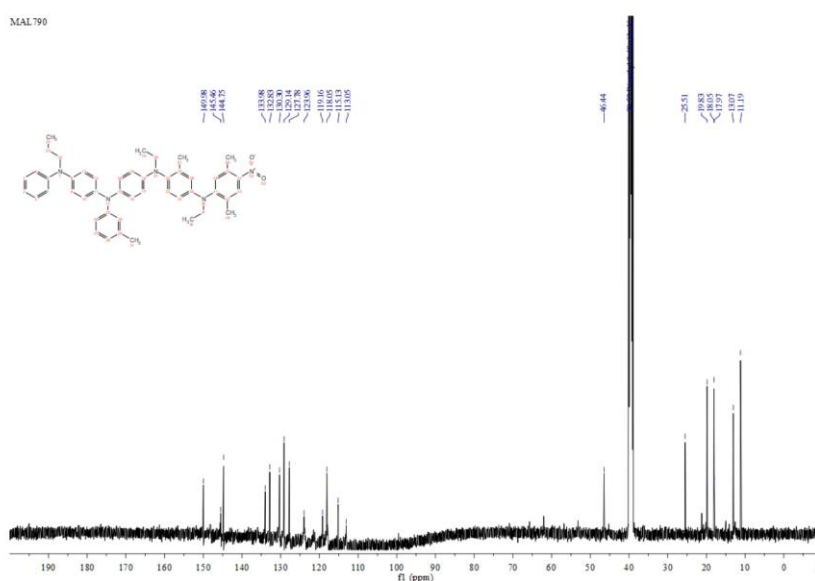
^1H NMR (dms o - d_6 , 500 MHz, 293 K): δ = 7.97 (s, 1H), 7.33 (s, 1H), 7.19 (t, J = 7.5 Hz, 2H), 7.09 – 7.04 (m, 1H), 6.97 – 6.76 (m, 10H), 6.71 – 6.60 (m, 4H), 6.50 (d, J = 7.0 Hz, 1H), 6.41 (d, J = 7.5 Hz, 2H), 3.77 (t, J = 7.4 Hz, 2H), 3.61 – 3.50 (m, 4H), 2.52 (s, 3H), 2.17 (s, 3H), 2.01 (d, J = 6.3 Hz, 6H), 1.56 (dd, J = 14.9, 7.4 Hz, 2H), 1.17 (td, J = 7.4, 3.7 Hz, 3H), 1.10 (t, J = 7.4 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H) ppm.

^{13}C NMR (dms o - d_6 , 126 MHz, 293 K): δ = 149.98, 145.46, 144.75, 133.98, 132.83, 130.30, 129.14, 127.78, 123.96, 119.16, 118.05, 115.13, 113.05, 46.44, 25.51, 19.83, 18.05, 17.97, 13.07, 11.19 ppm.

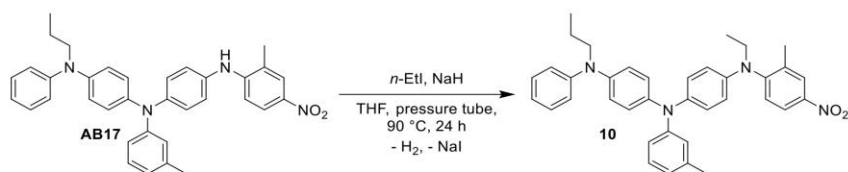
LC-HRMS (ESI $^{+}$) m/z calculated for $[\mathbf{10}]^{+}$: 718.41155 found: 718.41627.



Supplementary Figure 78: ^1H NMR spectrum of compound **10**.

Supplementary Figure 79: ¹³C NMR spectrum of compound **10**.

Due to the slow reaction speed for the alkylation of the secondary amines next to a functionalized aryl moiety, a new approach is introduced.

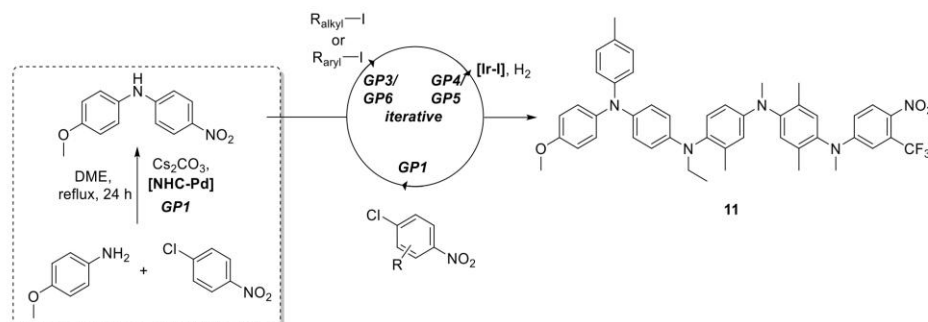
Supplementary Figure 80: Synthesis of compound **10** from **AB17**.

Reaction conditions for the synthesis of 10 (GP7): **AB17** (1.34 g, 2.47 mmol, 1.00 equiv.) is dissolved in THF (10.0 mL, 0.25 M) and transferred into a pressure tube. NaH (166 mg, 4.94 mmol, 60% on mineral oil, 2.00 equiv.) is added at RT in portions. The reaction mixture is stirred for 5 minutes at RT. $n\text{-EtI}$ (3.85 g, 2.00 mL, 24.7 mmol, 10.0 equiv.) is added. The reaction is stirred at 90 °C oil bath temperature for 24 h. The mixture is cooled to RT. The reaction is quenched by adding H_2O . The organic phase is dissolved in EtOAc and washed with water : brine (1:1) two times. The combined aqueous phases are extracted with EtOAc two times. The combined organic phases are dried over Na_2SO_4 .

The solvent and not reacted *n*-EtI is carefully removed under reduced pressure. Column chromatography (9/1 *n*-pentane / EtOAc) yields **10** (1.34 g, 2.35 mmol, 95%) as a dark red oil.

The compound was directly used for the next steps without complete characterization.

17 Synthesis of compound 11



Supplementary Figure 81: Synthesis of compound **11**.

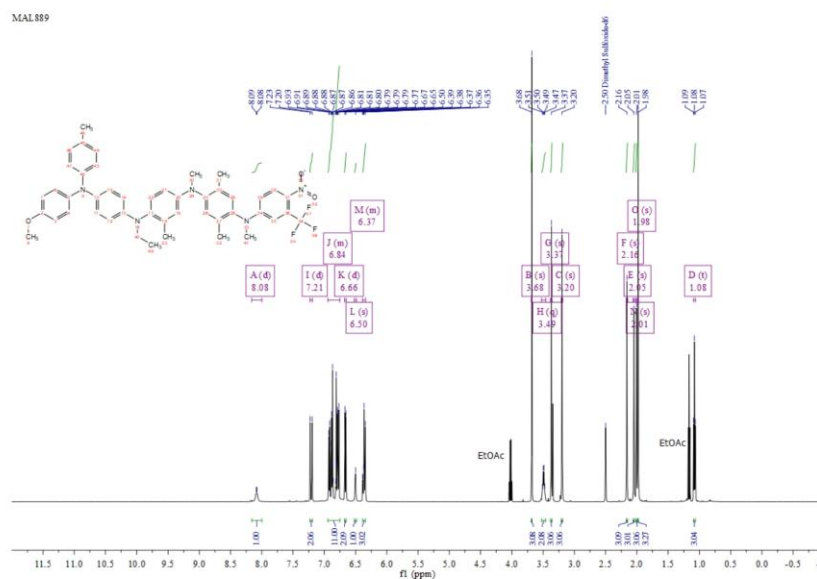
Compound **11** is synthesized following **GP1**, **GP3/GP6** and **GP4/GP5** (84.3 mg, 109 μ mol, 21% yield, 87% average yield) over 11 steps as an orange film.

^1H NMR (dmso- d_6 , 500 MHz, 293 K): δ = 8.08 (d, J = 7.0 Hz, 1H), 7.21 (d, J = 15.1 Hz, 2H), 6.94 – 6.75 (m, 11H), 6.66 (d, J = 8.5 Hz, 2H), 6.50 (s, 1H), 6.39 – 6.34 (m, 3H), 3.68 (s, 3H), 3.49 (q, J = 6.8 Hz, 2H), 3.37 (s, 3H), 3.20 (s, 3H), 2.16 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H) ppm.

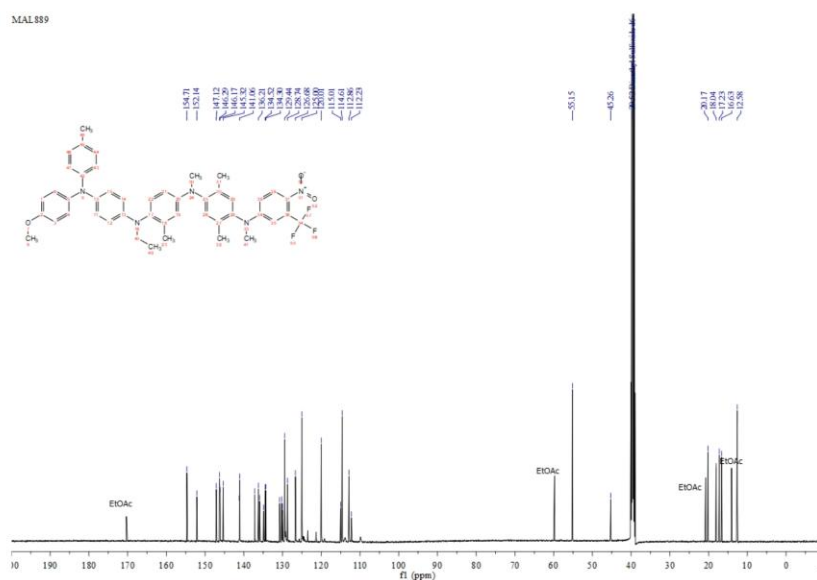
^{13}C NMR (dmso- d_6 , 126 MHz, 293 K): δ = 154.71, 152.14, 147.12, 146.29, 146.17, 145.32, 141.17, 141.06, 137.18, 136.21, 135.91, 134.91, 134.52, 134.30, 130.76, 130.20, 130.01, 129.44, 128.74, 126.68, 125.00, 120.01, 115.01, 114.61, 112.86, 112.23, 55.15, 45.26, 20.17, 18.04, 17.23, 16.63, 12.58 ppm.

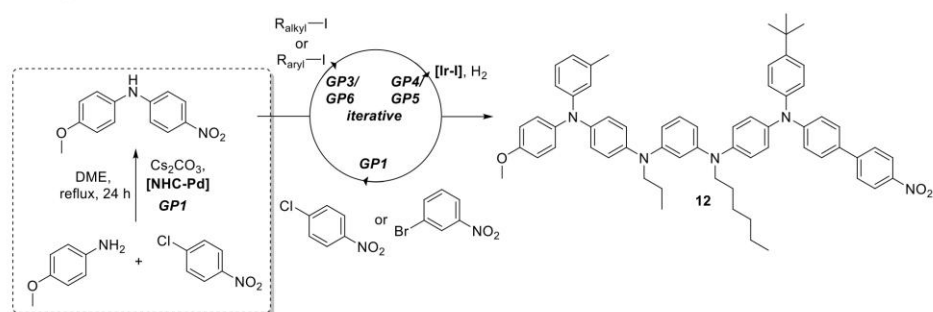
^{19}F NMR (dmso- d_6 , 471 MHz, 293 K): δ = -59.08 ppm.

LC-HRMS (ESI+) m/z calculated for $[\mathbf{11}]^+$: 774.36255 found: 774.35641.



Supplementary Figure 82: ¹H NMR of compound 11.



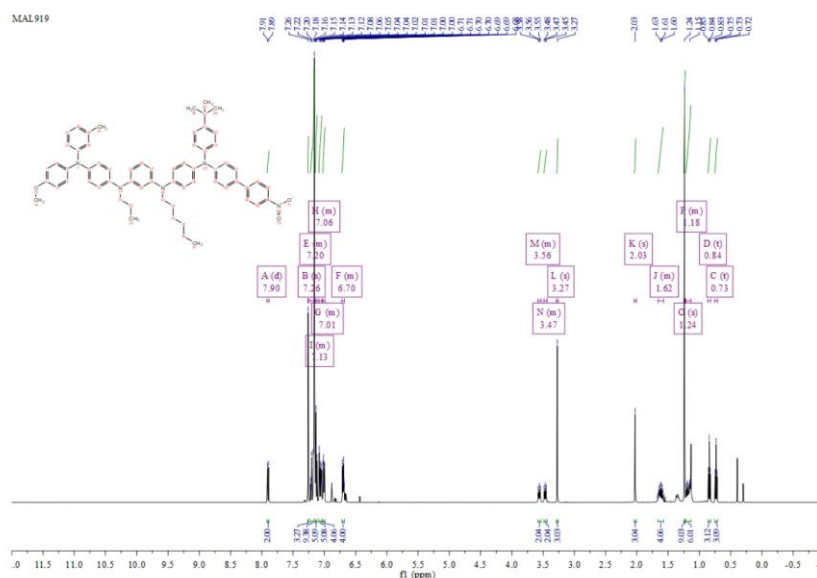
Supplementary Figure 84: ^{19}F NMR of compound **11**.18 Synthesis of compound **12**Supplementary Figure 85: Synthesis of compound **12**.

Compound **12** is synthesized following **GP1**, **GP3/GP6** and **GP4/GP5** (178 mg, 189 μmol , 9.0% yield, 80% average yield) over 11 steps as a deep red solid.

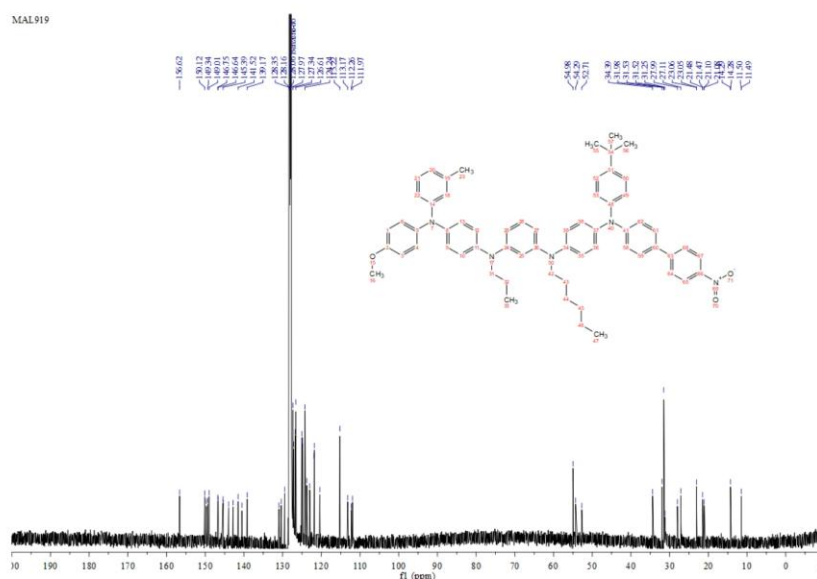
^1H NMR (C_6D_6 , 500 MHz, 293 K): δ = 7.90 (d, J = 8.9 Hz, 2H), 7.26 (s, 3H), 7.22 – 7.16 (m, 9H), 7.14 – 7.11 (m, 5H), 7.09 – 7.04 (m, 5H), 7.02 – 6.99 (m, 4H), 6.72 – 6.68 (m, 4H), 3.58 – 3.53 (m, 2H), 3.49 – 3.44 (m, 2H), 3.27 (s, 3H), 2.03 (s, 3H), 1.66 – 1.57 (m, 4H), 1.24 (s, 9H), 1.22 – 1.14 (m, 6H), 0.84 (t, J = 7.4 Hz, 3H), 0.73 (t, J = 7.4 Hz, 3H) ppm.

^{13}C NMR (C_6D_6 , 126 MHz, 293 K): δ = 156.62, 150.12, 149.69, 149.34, 149.01, 146.75, 146.64, 145.39, 145.37, 143.97, 142.80, 141.52, 140.54, 139.17, 130.95, 130.36, 129.47, 128.35, 128.16, 127.97, 127.34, 127.15, 126.78, 126.61, 125.05, 124.87, 124.80, 124.24, 123.77, 123.01, 121.85, 121.81, 120.41, 115.22, 113.17, 112.26, 111.97, 54.98, 54.29, 52.71, 34.41, 34.39, 32.00, 31.98, 31.53, 31.52, 31.25, 28.01, 27.99, 27.13, 27.11, 23.06, 23.05, 21.48, 21.47, 21.10, 21.08, 14.29, 14.28, 11.50, 11.49 ppm.

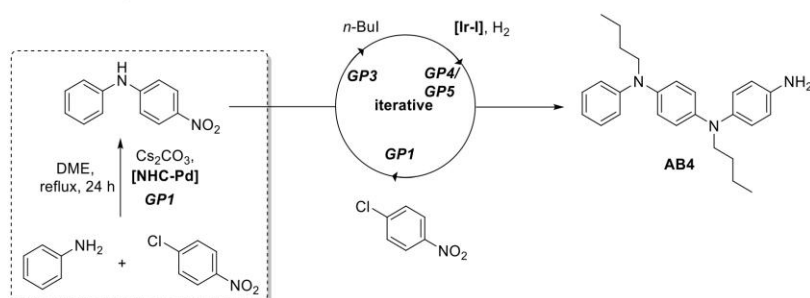
LC-HRMS (ESI+) m/z calculated for $[\mathbf{12}]^+$: 942.53167 found: 942.52650.



Supplementary Figure 86: ^1H NMR spectrum of compound **12**.

Supplementary Figure 87: ^{13}C NMR spectrum of compound 12.

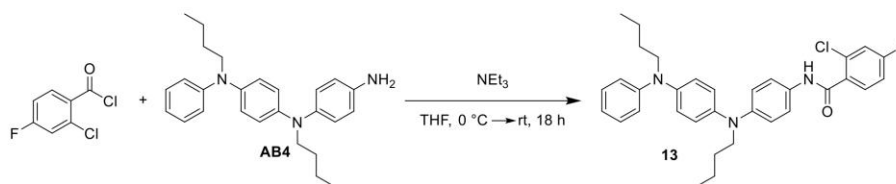
19 Scale-up synthesis of compound AB4



Supplementary Figure 88: Iterative synthesis of AB4.

Compound **AB4** is synthesized following GP1, GP3 and GP4/GP5 (1.26 g 3.25 mmol, 65%, 93% average yield) over 6 steps as a colourless oil.

20 Synthesis of compound 13

Supplementary Figure 89: Synthesis of compound **13**.

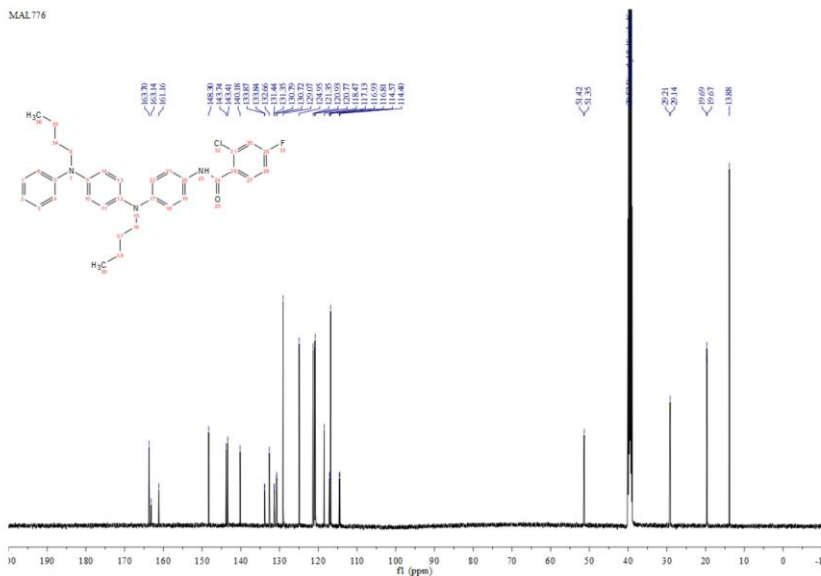
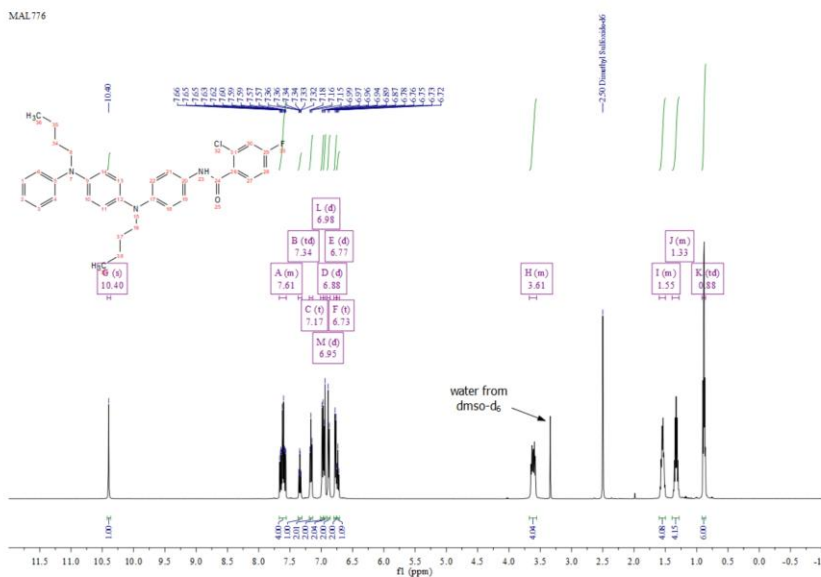
Reaction conditions for the synthesis of 13: **AB4** (164 mg, 423 μ mol, 1.00 equiv.) gets dissolved in THF (5.00 mL, 0.085 M). The solution is cooled to 0 °C. NEt_3 (55.7 mg, 76.2 μ L, 550 μ mol, 1.30 equiv.) is slowly added to the reaction mixture. The solution is stirred for 15 minutes at 0 °C. 2-Chloro-4-fluorobenzoyl chloride (89.9 mg, 62.2 μ L, 446 μ mol, 1.10 equiv.) is added dropwise to the cooled reaction mixture. The reaction mixture is stirred at 0 °C for 2 hours before warming to RT. The solution is stirred for 16 hours at RT. The organic phase is dissolved in EtOAc and washed with water two times. The combined aqueous phases are extracted with EtOAc one time.

The combined organic phases are dried over Na_2SO_4 and the solvent is evaporated under reduced pressure. Column chromatography (*n*-pentane / EtOAc 9:1) affords **13** (231 mg, 423 μ mol, >99%) as an orange solid.

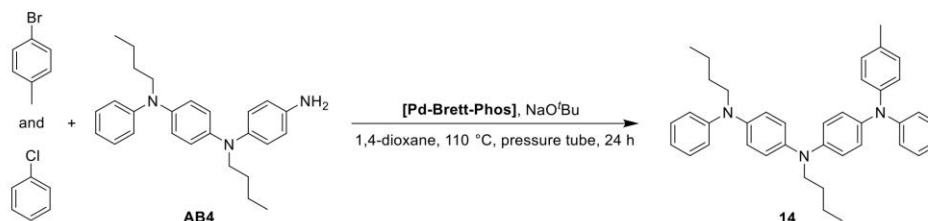
^1H NMR (dmsol-d_6 , 500 MHz, 293 K): δ = 10.40 (s, 1H), 7.67 – 7.56 (m, 4H), 7.34 (td, J = 8.5, 2.5 Hz, 1H), 7.17 (t, J = 7.9 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.77 (d, J = 8.5 Hz, 2H), 6.73 (t, J = 7.9 Hz, 1H), 3.67 – 3.56 (m, 4H), 1.60 – 1.50 (m, 4H), 1.39 – 1.28 (m, 4H), 0.88 (td, J = 7.3, 4.0 Hz, 6H) ppm.

^{13}C NMR (dmsol-d_6 , 126 MHz, 293 K): δ = 163.70, 163.14, 161.16, 148.30, 143.74, 143.41, 140.18, 133.87, 133.84, 132.66, 131.44, 131.35, 130.79, 130.72, 129.07, 124.95, 121.35, 120.93, 120.77, 118.47, 117.13, 116.93, 116.81, 114.57, 114.40, 51.42, 51.35, 29.21, 29.14, 19.69, 19.67, 13.88 ppm.

LC-HRMS (ESI+) m/z calculated for $[\mathbf{13}]^+$: 544.25255 found: 544.24958.



21 Synthesis of compound 14

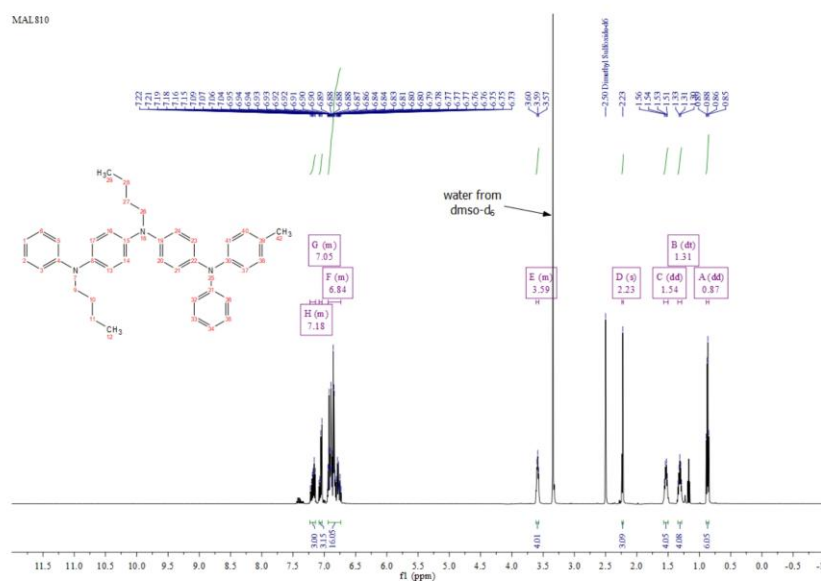
Supplementary Figure 92: Synthesis of compound **14**.

Reaction conditions for the synthesis of 14: **AB4** (224 mg, 578 μ mol, 1.00 equiv.) is dissolved in 1,4-dioxane (1.20 mL, 0.50 M) and transferred into a pressure tube. NaO^tBu (133 mg, 1.39 mmol, 2.40 equiv.), chlorobenzene (65.0 mg, 578 μ mol, ~ 60.0 μ L, 1.00 equiv.), 4-bromo toluene (99.0 mg, 578 μ mol, 71.0 μ L, 1.00 equiv.) and **[Pd-Brett-Phos]** (2.30 mg, 2.89 μ mol, 0.50 mol%) are added. The reaction is stirred at 110 °C for 24 h. The reaction solution is directly used for column chromatography (*n*-pentane / EtOAc 9:1). Compound **14** is isolated (285 mg, 514 μ mol, 89%) as a greenish oil.

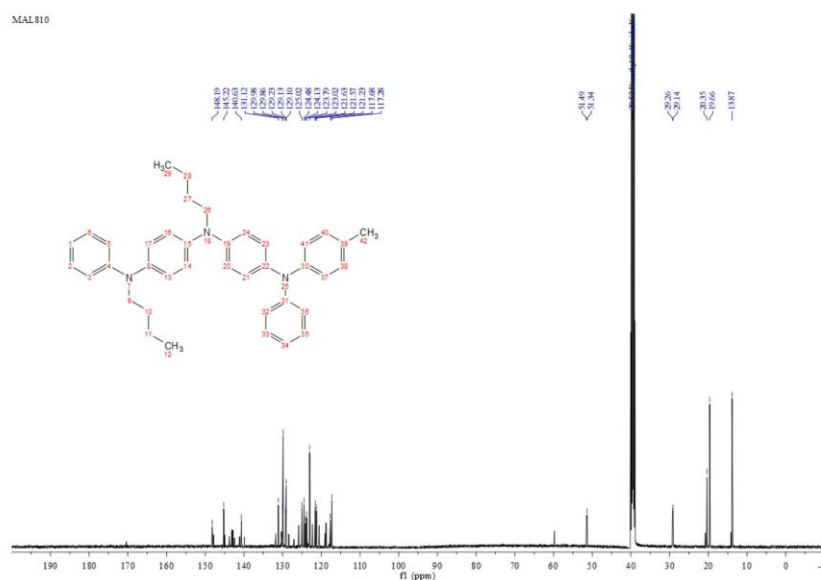
¹H NMR (dms-*d*₆, 500 MHz, 293 K): δ = 7.23 – 7.14 (m, 3H), 7.08 – 7.03 (m, 3H), 6.94 – 6.73 (m, 16H), 3.61 – 3.57 (m, 4H), 2.23 (s, 3H), 1.54 (dd, *J* = 15.2, 7.3 Hz, 4H), 1.31 (dt, *J* = 15.2, 7.3 Hz, 4H), 0.87 (dd, *J* = 13.0, 7.3 Hz, 6H) ppm.

¹³C NMR (dms-*d*₆, 126 MHz, 293 K): δ = 148.19, 145.22, 140.63, 131.12, 129.98, 129.86, 129.23, 129.13, 129.10, 125.02, 124.48, 124.13, 123.79, 123.02, 121.63, 121.57, 121.23, 117.68, 117.28, 51.49, 51.34, 29.26, 29.14, 20.35, 19.66, 13.87 ppm.

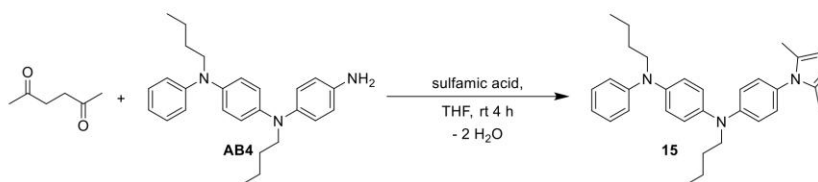
LC-HRMS (ESI⁺) *m/z* calculated for [**14**]⁺: 554.35297 found: 544.34471.



Supplementary Figure 93: ^1H NMR spectrum of compound 14.



Supplementary Figure 94: ^{13}C NMR spectrum of compound 14.

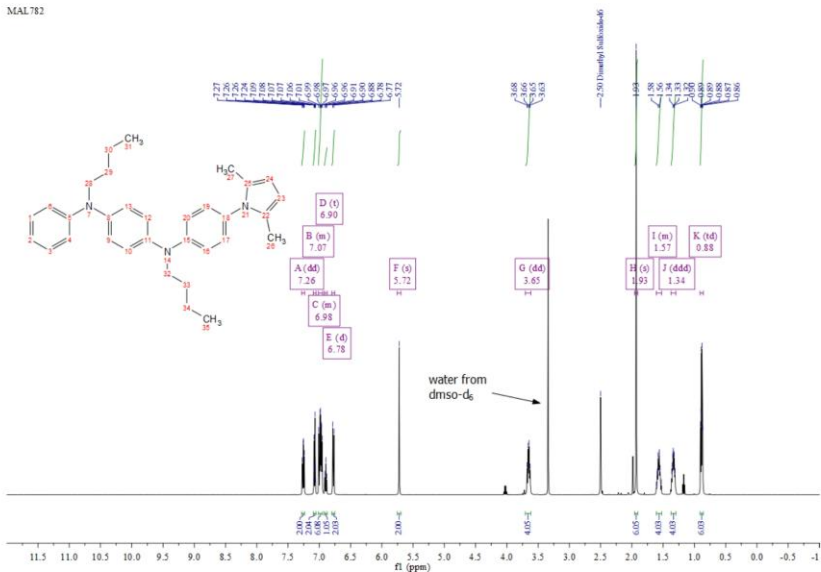
22 Synthesis of compound 15Supplementary Figure 95: Synthesis of compound **15**.

Reaction conditions for the synthesis of 15: AB4 (125 mg, 323 μmol , 1.00 equiv.), hexane-2,5-dione (44.3 mg, 45.5 μL , 388 μmol , 1.20 equiv.) and sulfamic acid (3.14 mg, 32.3 μmol , 10.0 mol%) are dissolved in THF (250 μL , 1.29 M). The reaction is stirred at RT for 4 h. The reaction solution is directly used for column chromatography (*n*-pentane / EtOAc 92:8). **15** is isolated (150 mg, 323 μmol , >99%) as an orange oil.

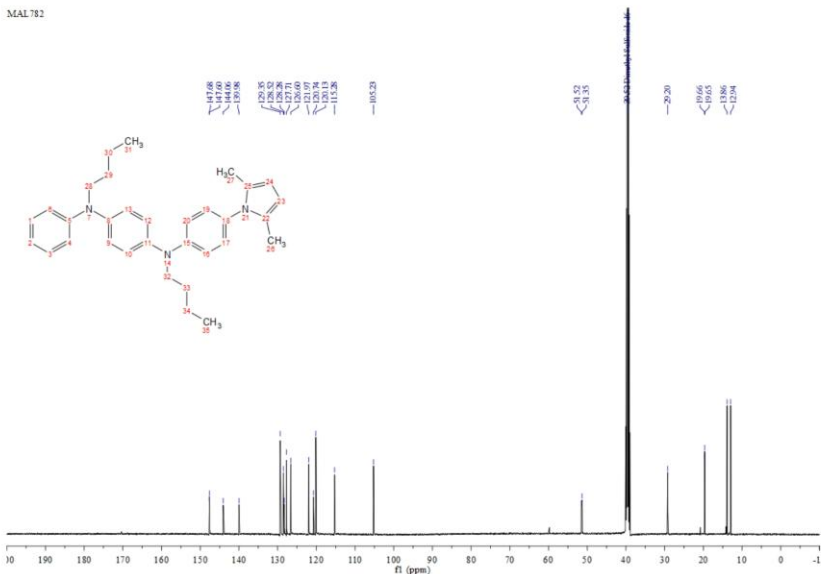
^1H NMR (dmso- d_6 , 500 MHz, 293 K): δ = 7.26 (dd, J = 8.4, 7.4 Hz, 2H), 7.10 – 7.05 (m, 2H), 7.02 – 6.95 (m, 6H), 6.90 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 8.4 Hz, 2H), 5.72 (s, 2H), 3.65 (dd, J = 14.8, 9.2 Hz, 4H), 1.93 (s, 6H), 1.61 – 1.52 (m, 4H), 1.34 (ddd, J = 14.8, 7.4, 4.4 Hz, 4H), 0.88 (td, J = 7.4, 4.4 Hz, 6H) ppm.

^{13}C NMR (dmso- d_6 , 126 MHz, 293 K): δ = 147.68, 147.60, 144.06, 139.98, 129.35, 128.52, 128.28, 127.71, 126.60, 121.97, 120.74, 120.13, 115.28, 105.23, 51.52, 51.35, 29.20, 19.66, 19.65, 13.86, 12.94 ppm.

LC-HRMS (ESI $^+$) m/z calculated for [**15**] $^+$: 466.32167 found: 466.32100.

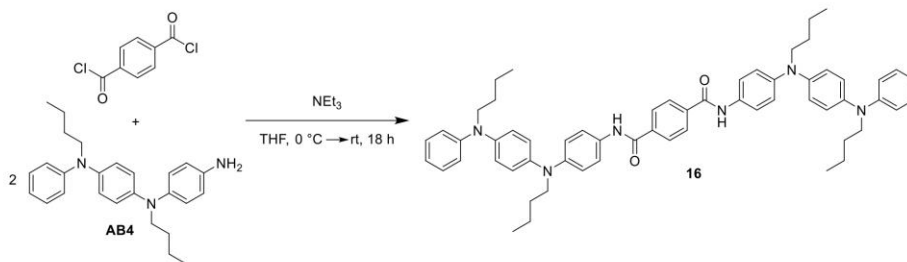


Supplementary Figure 96: ^1H NMR spectrum of compound **15**.



Supplementary Figure 97: ^{13}C NMR spectrum of compound **15**.

23 Synthesis of compound 16

Supplementary Figure 98: Synthesis of compound **16**.

Reaction conditions for the synthesis of 16: **AB4** (150 mg, 387 μmol , 2.00 equiv.) gets dissolved in THF (7.00 mL, 0.055 M). The solution is cooled to 0 $^{\circ}\text{C}$. NEt_3 (50.9 mg, 69.7 μL , 503 μmol , 2.30 equiv.) is carefully added at 0 $^{\circ}\text{C}$. The reaction mixture is stirred for 15 minutes at 0 $^{\circ}\text{C}$. Terephthaloyl dichloride (43.2 mg, 213 μmol , 1.10 equiv.) is slowly added to the reaction mixture at 0 $^{\circ}\text{C}$. The reaction is stirred for 2 hours at 0 $^{\circ}\text{C}$ and then for 16 hours at RT. The corresponding suspension is cooled to 0 $^{\circ}\text{C}$ again and *n*-pentane is slowly added.

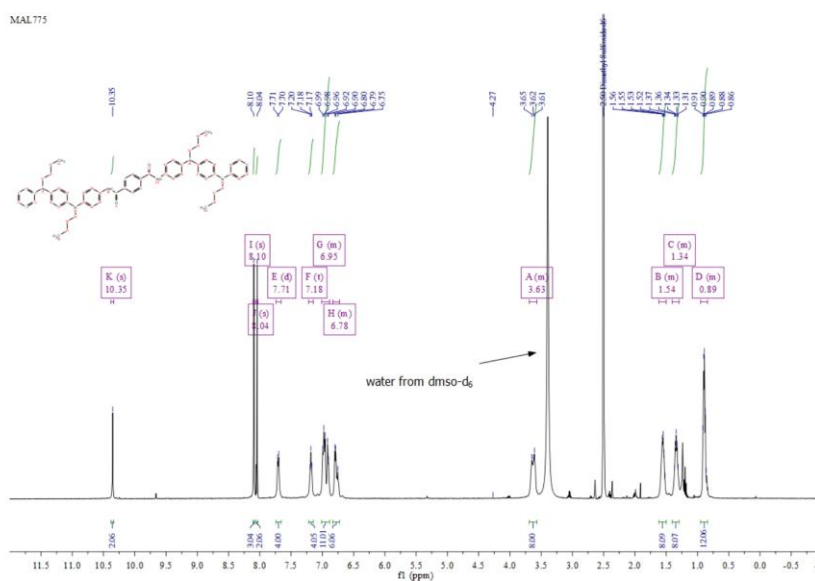
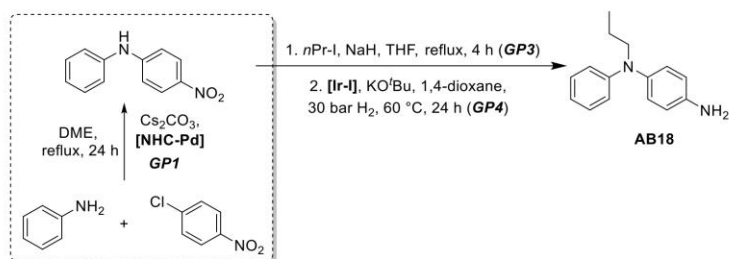
The precipitate is filtered and washed with cold water and cold *n*-pentane two times. The desired product **16** is isolated without further purification (340 mg, 376 μmol , 97%) as a yellow crystalline solid.

^1H NMR (dms- d_6 , 500 MHz, 293 K): δ = 10.35 (s, 2H), 8.10 (s, 3H), 8.04 (s, 2H), 7.71 (d, J = 7.7 Hz, 4H), 7.18 (t, J = 7.7 Hz, 4H), 7.01 – 6.88 (m, 11H), 6.83 – 6.72 (m, 6H), 3.69 – 3.57 (m, 8H), 1.62 – 1.50 (m, J = 14.6, 7.3 Hz, 8H), 1.40 – 1.29 (m, 8H), 0.95 – 0.84 (m, J = 14.0, 7.0 Hz, 12H) ppm.

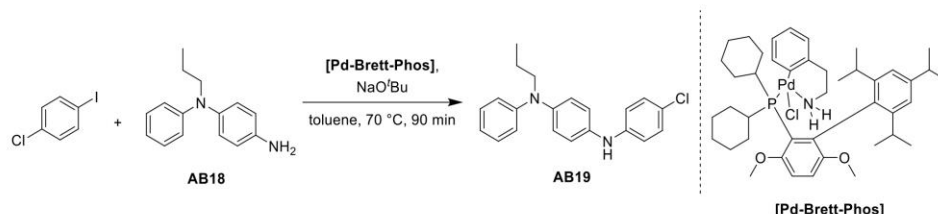
Due to the insolubility of the compound in most organic solvents (CDCl_3 , $\text{C}_2\text{D}_2\text{Cl}_4$, C_6D_6 , DMF- d_7) and only poor solubility in dms- d_6 no proper ^{13}C NMR spectrum could be measured.

LC-HRMS (ESI+) m/z calculated for [**16**] $^+$: 905.54765 found: 905.54155.

Elemental Analysis calculated for [**16**] $^+$: C: 79.61; H: 7.57; N: 9.28; O: 3.53. found: C 80.01, H: 7.59, N: 9.34, O: 3.51.

Supplementary Figure 99: ^1H NMR spectrum of compound **16**.**24 Scale-up synthesis of compound AB18**Supplementary Figure 100: Synthesis of compound **AB19**.

Compound **AB18** is synthesized following **GP1**, **GP3** and **GP4** (1.32 g, 5.85 mmol, 70% yield, 89% average yield) over 3 steps as a green oil. It was directly used without further characterization.

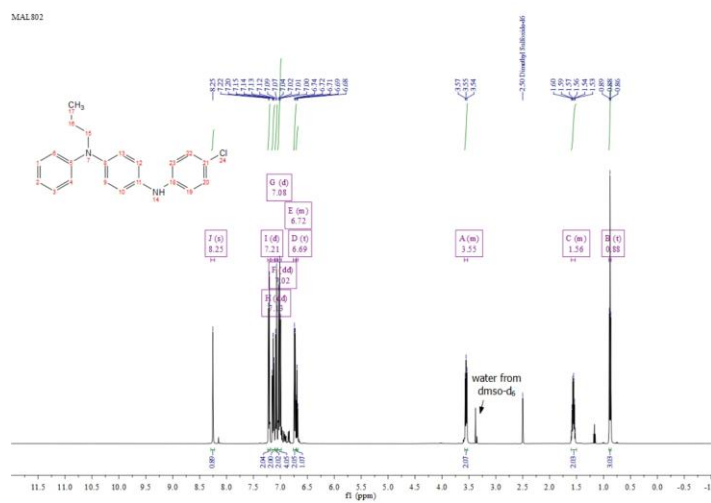
25 Synthesis of compound **AB19**Supplementary Figure 101: Synthesis of compound **AB19**.

Reaction conditions for the synthesis of **AB19:** Referring to the literature,^[58] a slightly modified synthesis protocol is used. **AB18** (1.32 g, 5.85 mmol, 1.00 equiv.), NaO^tBu (787 mg, 8.19 mmol, 1.40 equiv.), 1-chloro-4-iodobenzene (1.40 g, 5.85 mmol, 1.00 equiv.) and **[Pd-Brett-Phos]** (46.7 mg, 58.5 μ mol, 1.00 mol%) are dissolved in toluene (11.7 mL, 0.50 M). The reaction mixture is stirred for 90 min at 70 °C. The reaction is cooled to RT and directly used for column chromatography (*n*-pentane / EtOAc 9:1). **AB19** is isolated (1.85 g, 5.50 mmol, 94%) as a dark greenish oil.

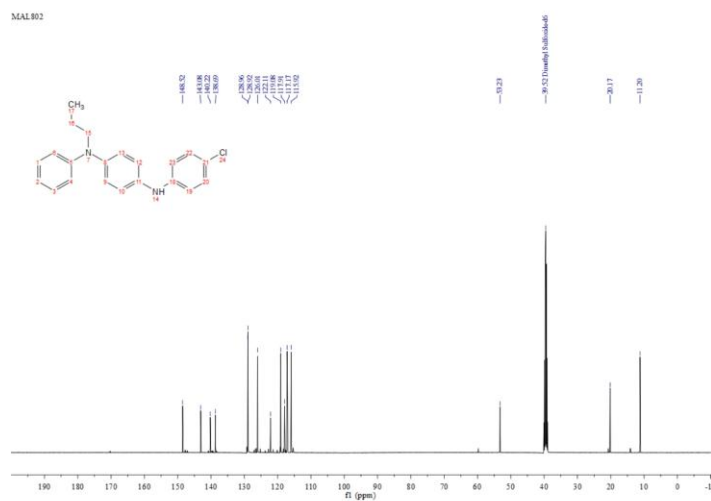
¹H NMR (dmso-*d*₆, 500 MHz, 293 K): δ = 8.25 (s, 1H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.13 (dd, *J* = 8.8, 7.5 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.02 (dd, *J* = 11.2, 8.8 Hz, 4H), 6.76 – 6.71 (m, 2H), 6.69 (t, *J* = 7.5 Hz, 1H), 3.58 – 3.52 (m, 2H), 1.60 – 1.53 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H) ppm.

¹³C NMR (dmso-*d*₆, 126 MHz, 293 K): δ = 148.52, 143.08, 140.22, 138.69, 128.96, 128.92, 126.01, 122.11, 119.08, 117.91, 117.17, 115.92, 53.23, 20.17, 11.20 ppm.

LC-HRMS (ESI+) *m/z* calculated for [**AB19**]⁺: 337.14660 found: 337.14609.

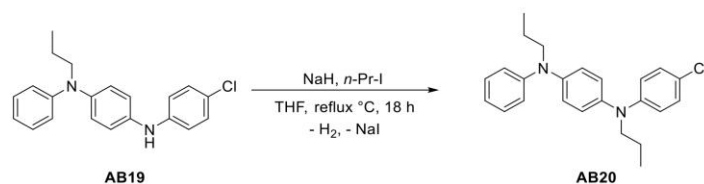


Supplementary Figure 102: ^1H NMR spectrum of compound **AB19**.



Supplementary Figure 103: ^{13}C NMR spectrum of compound **AB19**.

26 Synthesis of compound AB20



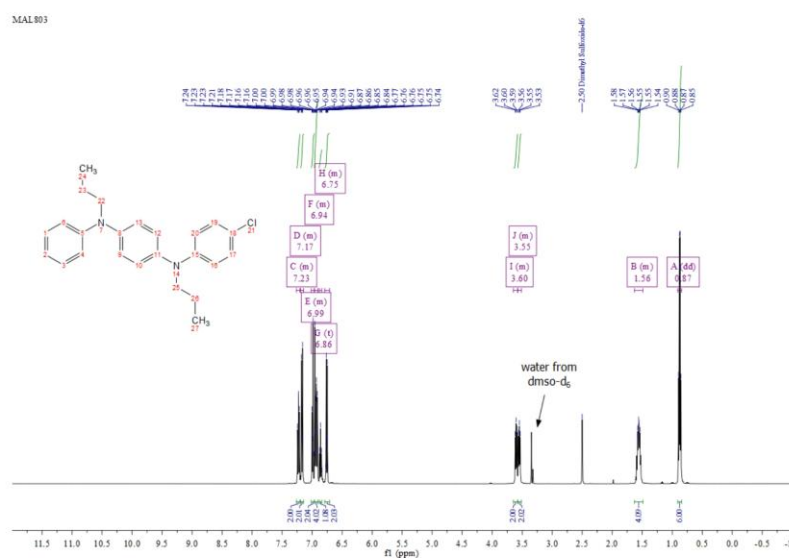
Supplementary Figure 104: Synthesis of compound **AB20**.

Reaction conditions for the synthesis of AB20: **AB19** (1.36 g, 4.04 mmol, 1.00 equiv.), NaH (149 mg, 4.44 mmol, 60% on mineral oil, 1.10 equiv.) is dissolved in THF (0.25 M, 16.2 mL) at RT. The reaction is stirred for 5 minutes at RT. A gas bubbler is used to adjust the pressure. *n*-Propyl iodide (3.43 g, 1.96 mL, 20.2 mmol, 5.00 equiv.) are added and the mixture is stirred at 18 h under reflux conditions in an open system under argon atmosphere. The reaction is cooled to RT and directly used for column chromatography (n-pentane / EtOAc 97:3). **AB20** is isolated (1.50 g, 3.95 mmol, 98%) as a dark greenish oil.

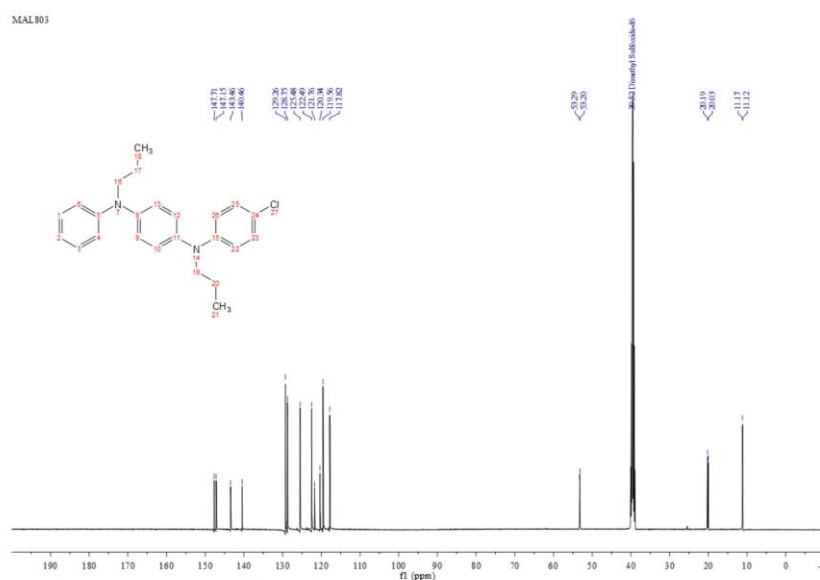
¹H NMR (dmso-*d*₆, 500 MHz, 293 K): δ = 7.26 – 7.20 (m, 2H), 7.19 – 7.14 (m, 2H), 7.02 – 6.96 (m, 2H), 6.96 – 6.91 (m, 4H), 6.86 (t, *J* = 7.3 Hz, 1H), 6.79 – 6.71 (m, 2H), 3.65 – 3.57 (m, 2H), 3.57 – 3.51 (m, 2H), 1.63 – 1.49 (m, 4H), 0.87 (dd, *J* = 13.4, 7.3 Hz, 6H) ppm.

¹³C NMR (dmso-*d*₆, 126 MHz, 293 K): δ = 147.71, 147.15, 143.46, 140.46, 129.26, 128.75, 125.48, 122.49, 121.76, 120.34, 119.56, 117.82, 53.29, 53.20, 20.19, 20.03, 11.17, 11.12 ppm.

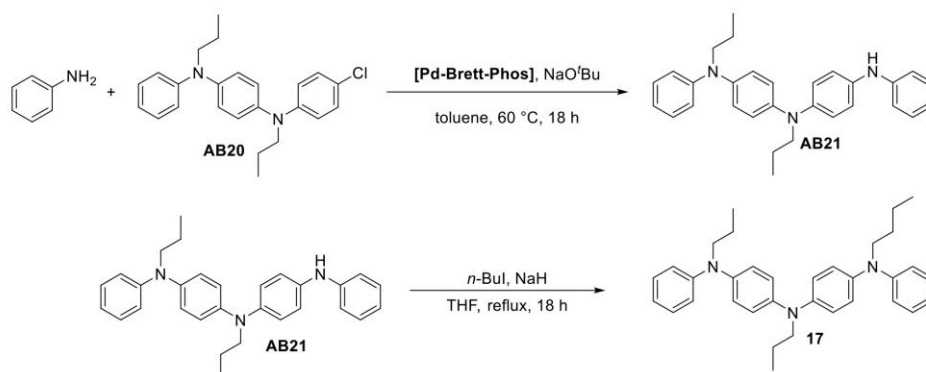
LC-HRMS (ESI+) *m/z* calculated for [**AB20**]⁺: 379.19355 found: 379.19274.



Supplementary Figure 105: ^1H NMR spectrum of compound AB20.



Supplementary Figure 106: ^{13}C NMR spectrum of compound AB20.

27 Synthesis of compound 17Supplementary Figure 107: Synthesis of compound **17**.

1. Reaction conditions for the synthesis of AB21: In a Schlenk tube, **AB20** (543 mg, 1.43 mmol, 1.00 equiv.), aniline (133 mg, 1.43 mmol, 1.00 equiv.), NaO^tBu (193 mg, 131 μ L, 1.43 mmol, 1.00 equiv.) and **[Pd-Brett-Phos]** (28.6 mg, 35.6 μ mol, 2.50 mol%) are dissolved in toluene (4.20 mL, 0.32 M). The reaction is stirred at 60 °C for 18 hours.

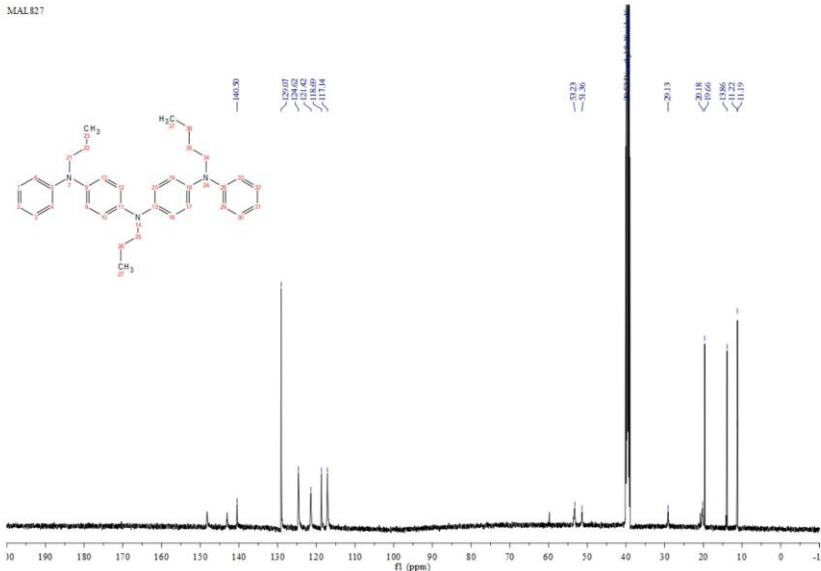
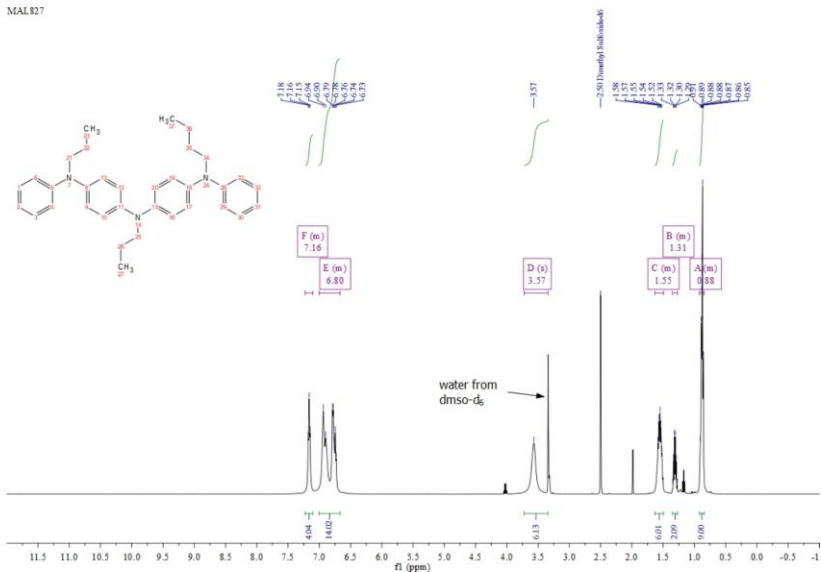
The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 9:1) to yield **AB21** (558 mg, 1.28 mmol, 90%) as a greenish oil.

2. Reaction conditions for the synthesis of 17: **AB21** (558 mg, 1.28 mmol, 1.00 equiv.), NaH (64.5 mg, 1.92 mmol, 60% on mineral oil, ~1.50 equiv.) and *n*-BuLi (353 mg, 218 μ L, 1.92 mmol, 1.50 equiv.) are dissolved in THF (5.12 mL, 0.25 M). The mixture is stirred under reflux conditions for 18 h. The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 95:5 $\rightarrow$ 9/1) to yield **17** (287 mg, 1.19 mmol, 93%) as a greenish transparent oil.

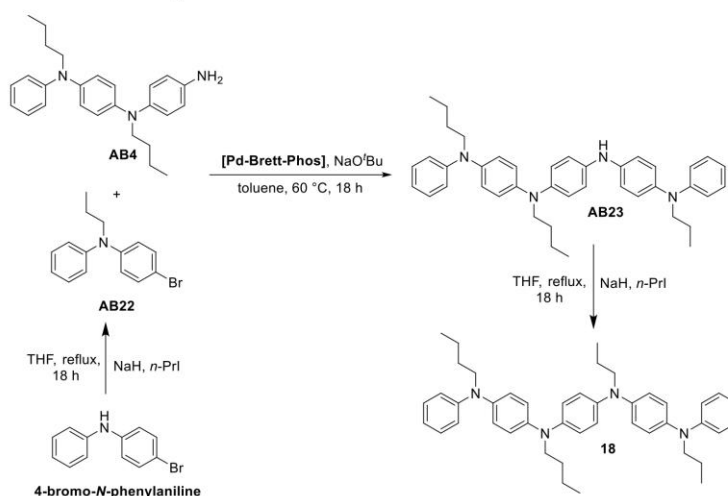
¹H NMR (dms-*d*₆, 500 MHz, 293 K): δ = 7.22 – 7.10 (m, *J* = 7.2 Hz, 4H), 7.00 – 6.67 (m, 14H), 3.57 (s, 6H), 1.63 – 1.49 (m, *J* = 15.7, 7.7 Hz, 6H), 1.35 – 1.27 (m, 2H), 0.92 – 0.84 (m, 9H) ppm.

¹³C NMR (dms-*d*₆, 126 MHz, 293 K): δ = 140.50, 129.07, 124.62, 121.42, 118.69, 117.14, 53.23, 51.36, 29.13, 20.18, 19.66, 13.86, 11.22, 11.19 ppm.

LC-HRMS (ESI⁺) *m/z* calculated for [**17**]⁺: 492.33732 found: 492.33313.



28 Synthesis of compound 18



Supplementary Figure 110: Synthesis of compound 18.

Reaction conditions for the synthesis of AB22: 4-Bromo-*N*-phenylaniline (868 mg, 3.50 mmol, 1.00 equiv.), NaH (176 mg, 5.25 mmol, 60% on mineral oil, ~1.50 equiv.) and *n*-PrI (893 mg, 510 μ L, 5.25 mmol, 1.50 equiv.) are dissolved in THF (14.0 mL, 0.25 M). The mixture is stirred under reflux conditions for 18 h. The reaction mixture is cooled to RT, diluted in EtOAc and washed with sat NH₄Cl / water / brine 1:1:1 two times. The combined aqueous phases are extracted with EtOAc one time. The combined organic phases are dried over Na₂SO₄. The solvent and the excess alkyl iodide are removed under reduced pressure to obtain AB22 in the desired purity.

1. Reaction conditions for the synthesis of AB23: In a Schlenk tube, AB4 (405 mg, 1.05 mmol, 1.00 equiv.), AB22 (381 mg, 1.31 mmol, 1.25 equiv.), NaOtBu (141 mg, 1.47 mmol, 1.40 equiv.) and [Pd-Brett-Phos] (21.0 mg, 26.3 μ mol, 2.50 mol%) are dissolved in toluene (3.28 mL, 0.32 M). The reaction is stirred at 60 °C for 18 hours. The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 9:1) to yield AB23 (453 mg, 760 μ mol, 72%) as a greenish oil.

2. Reaction conditions for the synthesis of 18: AB23 (453 mg, 760 μ mol, 1.00 equiv.), NaH (27.4 mg, 1.14 mmol, 60% on mineral oil, ~1.50 equiv.) and *n*-PrI (194 mg, 111 μ L,

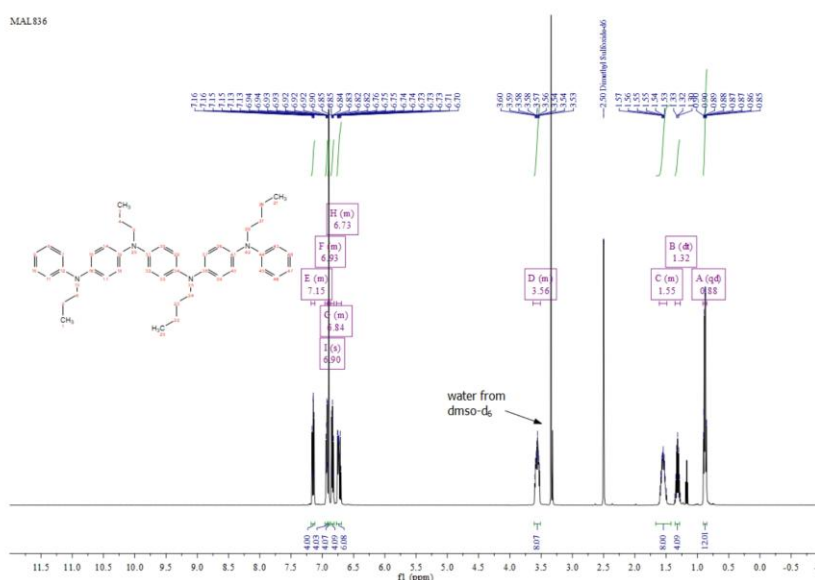
1.14 mmol, 1.50 equiv.) are dissolved in THF (1.50 mL, 0.50 M). The mixture is stirred under reflux conditions for 18 h.

The reaction mixture is directly used for column chromatography (n-pentane / EtOAc 95:5) to yield **18** (426 mg, 667 μ mol, 88%) as a greenish transparent oil.

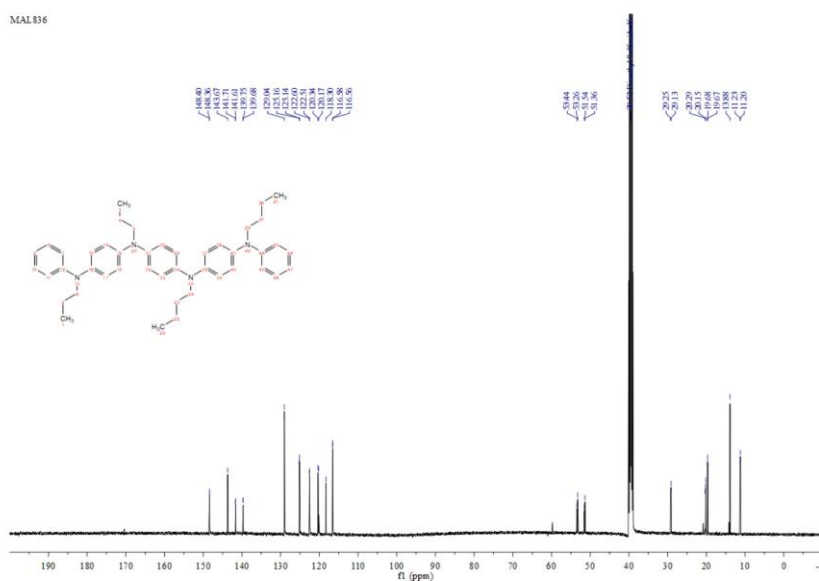
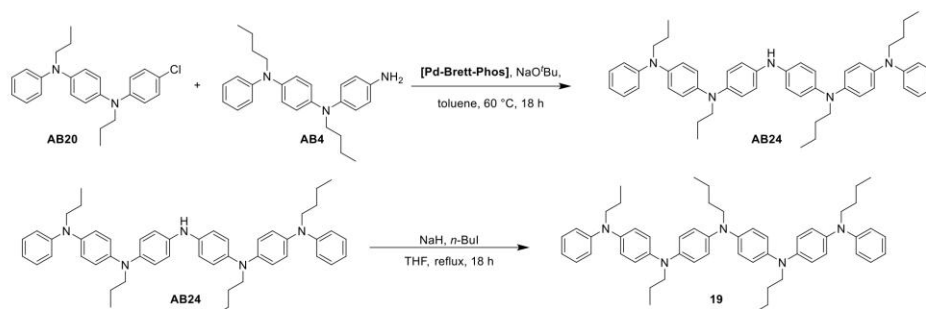
^1H NMR (dms- d_6 , 500 MHz, 293 K): δ = 7.18 – 7.12 (m, 2H), 6.96 – 6.91 (m, 2H), 6.90 (s, 2H), 6.86 – 6.81 (m, 2H), 6.77 – 6.69 (m, 3H), 3.63 – 3.51 (m, 4H), 1.61 – 1.49 (m, 4H), 1.32 (dt, J = 15.0, 7.4 Hz, 2H), 0.88 (qd, J = 7.4, 3.7 Hz, 6H) ppm.

^{13}C NMR (dms- d_6 , 126 MHz, 293 K): δ = 148.40, 148.36, 143.67, 141.71, 141.61, 139.75, 139.68, 129.04, 125.16, 125.14, 122.60, 122.51, 120.34, 120.17, 118.30, 116.58, 116.56, 53.44, 53.26, 51.54, 51.36, 29.25, 29.13, 20.29, 20.15, 19.68, 19.67, 13.88, 11.23, 11.20 ppm.

LC-HRMS (ESI+) m/z calculated for $[\mathbf{18}]^+$: 639.44212 found: 639.43711.



Supplementary Figure 111: ^1H NMR spectrum of compound **18**.

Supplementary Figure 112: ^{13}C NMR spectrum of compound **18**.**29 Synthesis of compound 19**Supplementary Figure 113: Synthesis of compound **19**.

1. Reaction conditions for the synthesis of AB24: In a Schlenk tube, **AB4** (250 mg, 645 μ mol, 1.00 equiv.), **AB20** (245 mg, 645 μ mol, 1.00 equiv.), NaO^tBu (87.0 mg, 903 μ mol, 1.40 equiv.) and **[Pd-Brett-Phos]** (15.5 mg, 19.4 μ mol, 3.00 mol%) are dissolved in toluene (2.00 mL, 0.32 M).

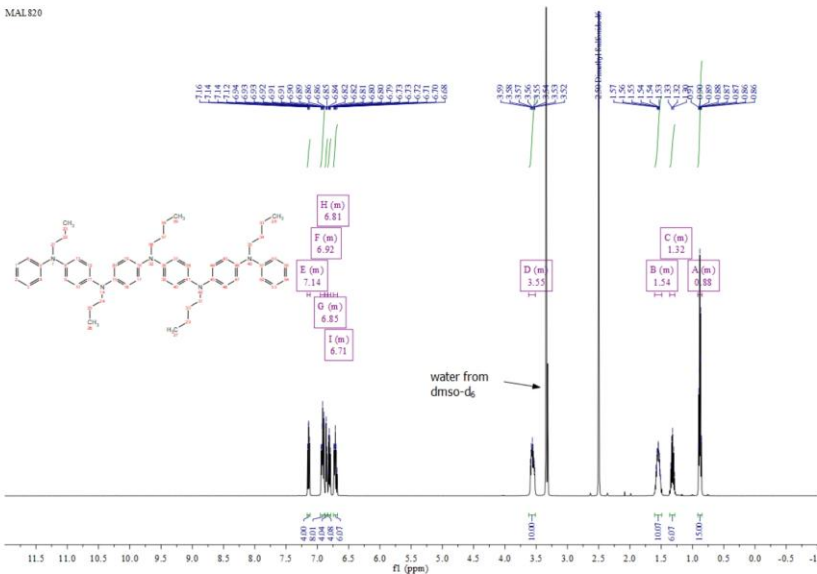
The reaction is stirred at 60 °C for 18 hours. The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 95:5) to yield **AB24** (343 mg, 470 μ mol, 73%) as a greenish oil.

2. Reaction conditions for the synthesis of 19: **AB24** (343 mg, 470 μ mol, 1.00 equiv.), NaH (24.0 mg, 705 μ mol, 60% on mineral oil, ~1.50 equiv.) and *n*-BuI (130 mg, 80.0 μ L, 705 μ mol, 1.50 equiv.) are dissolved in THF (1.88 mL, 0.25 M). The mixture is stirred under reflux conditions for 18 h. The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 95:5) to yield **19** (329 mg, 418 μ mol, 89%) as a greenish oil.

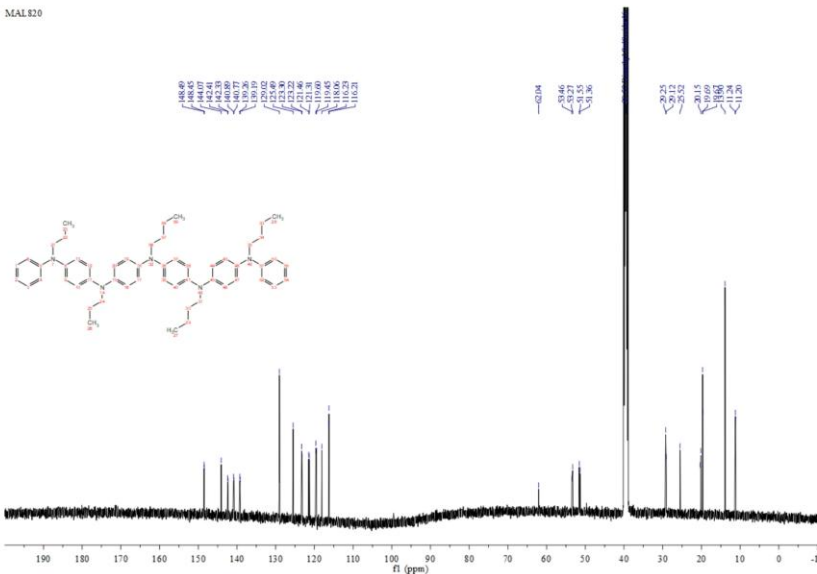
¹H NMR (dmso-*d*₆, 500 MHz, 293 K): δ = 7.16 – 7.12 (m, *J* = 8.5, 7.4 Hz, 4H), 6.95 – 6.89 (m, *J* = 14.9, 7.8, 3.2 Hz, 8H), 6.88 – 6.84 (m, 4H), 6.83 – 6.78 (m, 4H), 6.74 – 6.68 (m, 6H), 3.62 – 3.51 (m, *J* = 20.4, 9.1, 6.3 Hz, 10H), 1.60 – 1.49 (m, 10H), 1.36 – 1.28 (m, *J* = 15.0, 7.6 Hz, 6H), 0.92 – 0.85 (m, *J* = 7.3, 2.8 Hz, 15H) ppm.

¹³C NMR (dmso-*d*₆, 126 MHz, 293 K): δ = 148.49, 148.45, 144.07, 142.41, 142.33, 140.89, 140.77, 139.26, 139.19, 129.02, 125.49, 123.30, 123.22, 121.46, 121.31, 119.60, 119.45, 118.06, 116.23, 116.21, 62.04, 53.46, 53.27, 51.55, 51.36, 29.25, 29.12, 25.52, 20.29, 20.15, 19.69, 19.67, 13.90, 11.24, 11.20 ppm.

LC-HRMS (ESI⁺) *m/z* calculated for [**19**]⁺: 786.54692 found: 786.54133.

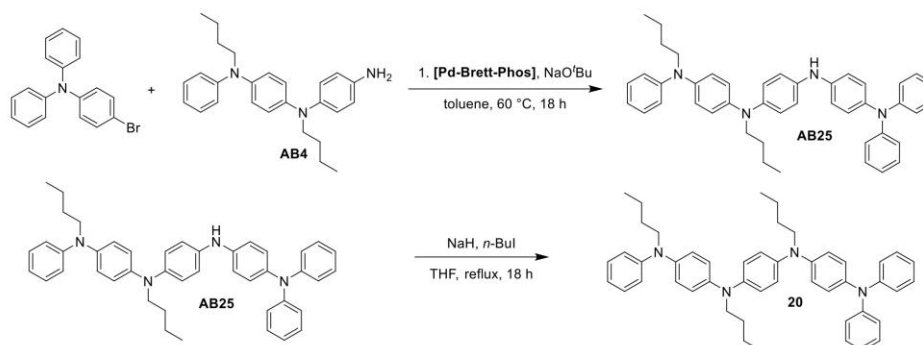


Supplementary Figure 114: ¹H NMR spectrum of compound **19**.



Supplementary Figure 115: ^{13}C NMR spectrum of compound **19**.

30 Synthesis of compound 20



Supplementary Figure 116: Synthesis of compound 20.

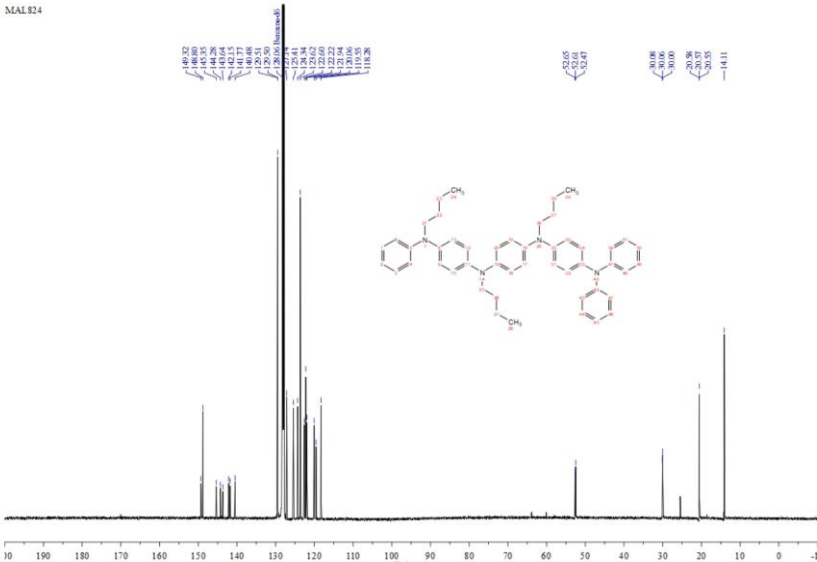
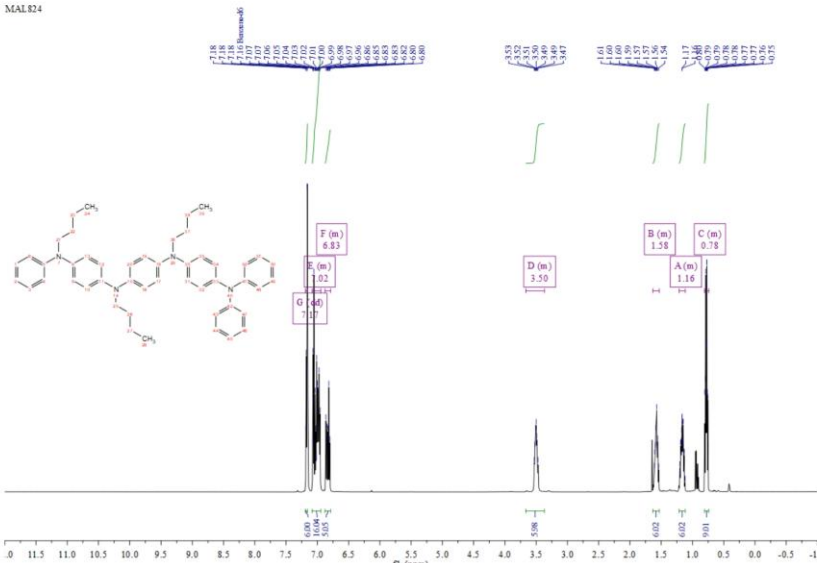
1. Reaction conditions for the synthesis of AB25: In a Schlenk tube, **AB4** (250 mg, 645 μmol , 1.00 equiv.), 4-bromo-*N,N*-diphenylaniline (209 mg, 645 μmol , 1.00 equiv.), NaOtBu (87.0 mg, 903 μmol , 1.40 equiv.) and **[Pd-Brett-Phos]** (15.5 mg, 19.4 μmol , 3.00 mol%) are dissolved in toluene (2.00 mL, 0.32 M). The reaction is stirred at 60 °C for 18 hours. The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 95:5) to yield **AB25** (327 mg, 516 μmol , 80%) as a greenish oil.

2. Reaction conditions for the synthesis of 20: **AB25** (327 mg, 516 μmol , 1.00 equiv.), NaH (26.1 mg, 777 μmol , 60% on mineral oil, ~1.50 equiv.) and *n*-BuLi (143 mg, 88.0 μL , 777 μmol , 1.50 equiv.) are dissolved in THF (2.00 mL, 0.25 M). The mixture is stirred under reflux conditions for 18 h. The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 95:5) to yield **20** (287 mg, 418 μmol , 81%) as a greenish transparent solid.

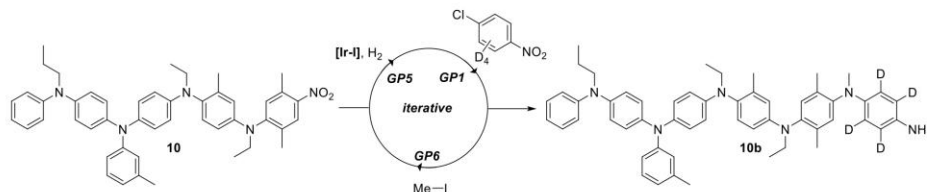
^1H NMR (C_6D_6 , 500 MHz, 293 K): δ = 7.17 (dd, J = 6.2, 5.2 Hz, 6H), 7.08 – 6.95 (m, 16H), 6.88 – 6.79 (m, 5H), 3.67 – 3.37 (m, 6H), 1.63 – 1.53 (m, 6H), 1.21 – 1.11 (m, 6H), 0.81 – 0.74 (m, 9H) ppm.

^{13}C NMR (C_6D_6 , 126 MHz, 293 K): δ = 149.32, 148.80, 145.35, 144.28, 143.64, 142.15, 141.77, 140.48, 129.51, 129.50, 127.14, 125.41, 124.34, 123.62, 122.60, 122.22, 121.94, 120.06, 119.55, 118.28, 52.65, 52.61, 52.47, 30.08, 30.06, 30.00, 20.58, 20.57, 20.55, 14.11 ppm.

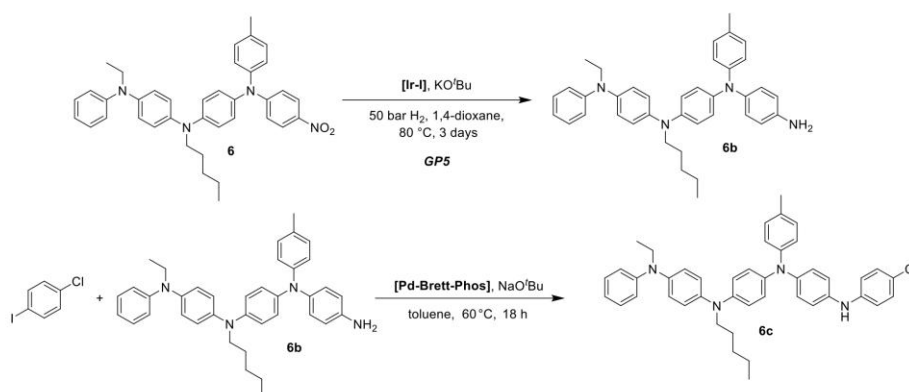
LC-HRMS (ESI+) m/z calculated for **[20] $^+$** : 687.44212 found: 687.44769.



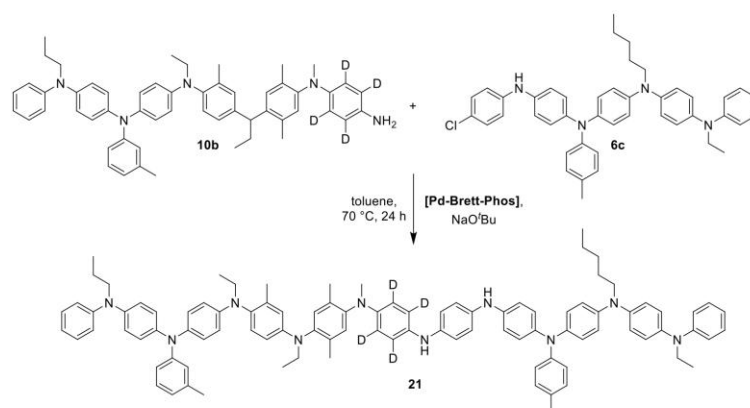
31 Synthesis of compound 21

Supplementary Figure 119: Synthesis of compound **10b**.

Compound **10b** is synthesized following **GP1**, **GP6** and **GP5** (62.0 mg, 77.8 μmol , 15% yield, 62% average yield) over 4 steps as a reddish film. Compound **10b** was directly used for the synthesis of **21**.

Supplementary Figure 120: Synthesis of compound **6c**.

Compound **6c** is synthesized following **GP6** and standardized conditions for the monoarylation (160 mg, 246 μmol , 32% yield, 57% average yield) over 2 steps as a blue film. Compound **6c** was directly used for the synthesis of **21**.

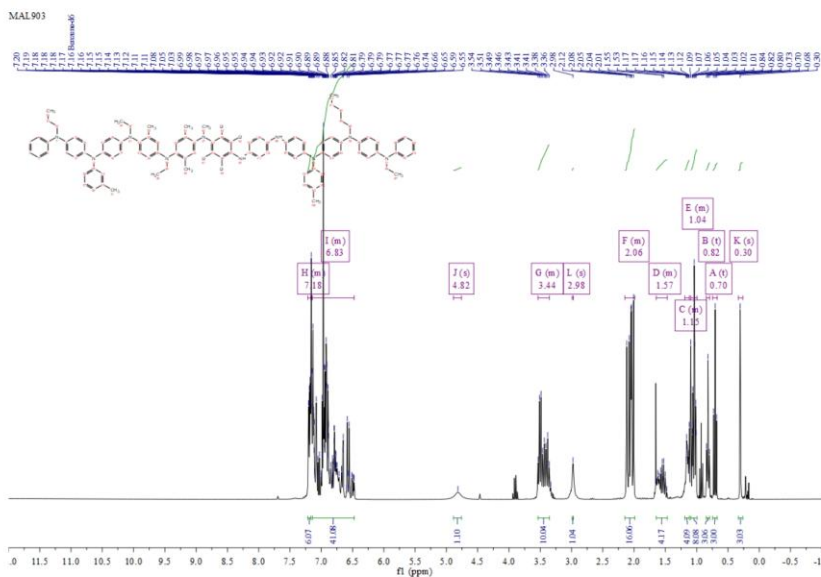
Supplementary Figure 121: Synthesis of compound **21**.

Reaction conditions for the synthesis of compound 21: In a Schlenk tube, amine **10b** (62.0 mg, 77.8 μmol , 1.00 equiv.), compound **6b** (52.0 mg, 78.0 μmol , 1.01 equiv.), NaOtBu (10.5 mg, 109 μmol , 1.40 equiv.) and [Pd-Brett-Phos] (1.87 mg, 2.34 μmol , 3.00 mol%) are dissolved in toluene (1.00 mL, 0.078 M). The reaction is stirred at 70 °C for 24 h. The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 8.5:1.5). Compound **21** is finally isolated (87.8 mg, 61.6 μmol , 79% yield) as a colourless solid.

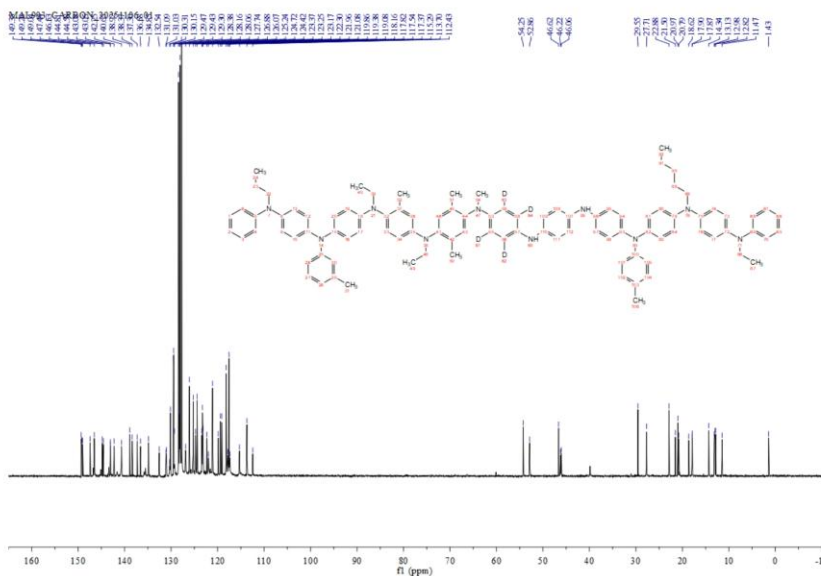
^1H NMR (C_6D_6 , 300 MHz, 293 K): δ = 7.22 – 7.17 (m, 6H), 7.14 – 6.47 (m, 41H), 4.82 (s, 1H), 3.54 – 3.35 (m, 10H), 2.98 (s, 1H), 2.15 – 1.99 (m, 16H), 1.65 – 1.47 (m, 4H), 1.19 – 1.12 (m, 4H), 1.09 – 0.99 (m, 8H), 0.82 (t, J = 6.7 Hz, 3H), 0.70 (t, J = 7.4 Hz, 3H), 0.30 (s, 3H) ppm.

^{13}C NMR (C_6D_6 , 75 MHz, 293 K): δ = 149.35, 149.20, 149.04, 147.44, 146.53, 144.81, 144.58, 143.08, 143.05, 142.25, 140.65, 138.92, 138.37, 137.30, 136.58, 134.85, 132.54, 131.09, 131.03, 130.31, 130.15, 129.47, 129.43, 129.30, 128.38, 128.16, 127.74, 126.88, 126.07, 125.24, 124.72, 124.42, 123.37, 123.25, 123.17, 122.30, 121.96, 121.08, 119.86, 119.38, 119.08, 118.16, 117.82, 117.54, 117.37, 115.29, 113.70, 112.43, 54.25, 52.86, 46.62, 46.22, 46.06, 29.55, 27.71, 22.88, 21.50, 20.97, 20.79, 18.62, 17.90, 17.87, 14.34, 13.13, 12.98, 12.82, 11.47, 1.43 ppm.

LC-HRMS (ESI⁺) m/z calculated for [**21**]⁺: 1427.01186 found: 1426.87396.

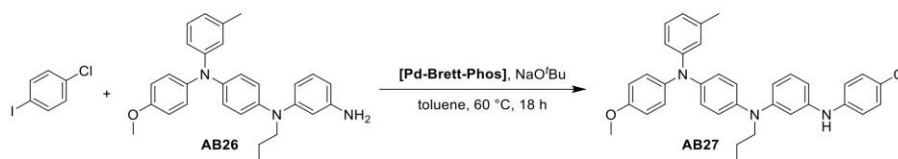


Supplementary Figure 122: ^1H NMR spectrum of compound **21**.

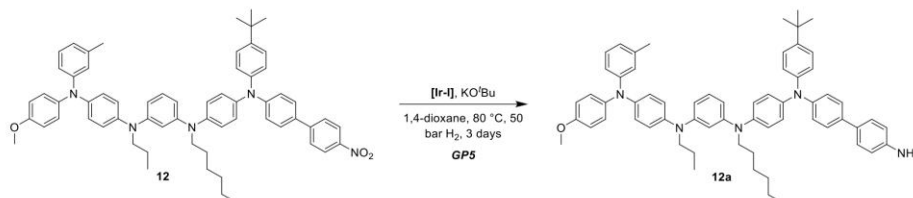


Supplementary Figure 123: ^{13}C NMR spectrum of compound **21**.

32 Synthesis of compound 22

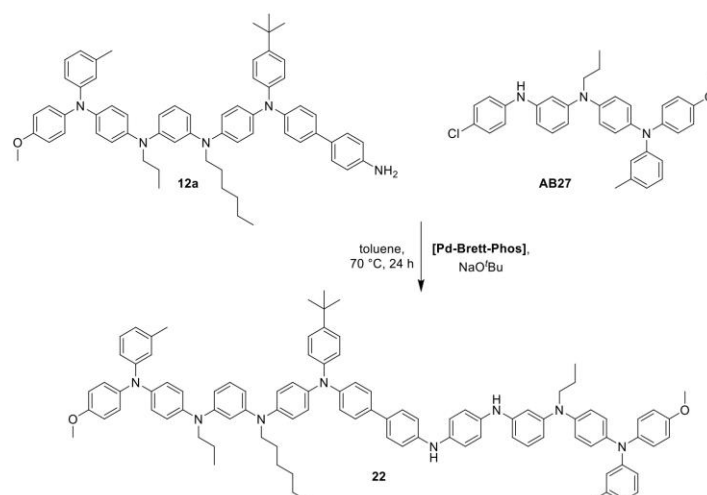
Supplementary Figure 124: Synthesis of compound **AB27**.

Reaction conditions for the synthesis of compound AB27: In a Schlenk tube, amine **AB26** (162 mg, 370 μmol , 1.00 equiv.), NaOtBu (50.0 mg, 518 μmol , 1.40 equiv.), 1-chloro-4-iodo-benzene (88.2 mg, 370 μmol , 1.00 equiv.) and **[Pd-Brett-Phos]** (7.40 mg, 9.25 μmol , 2.50 mol%) are dissolved in 1 mL toluene and 0.50 mL DME (0.25 M). The reaction is stirred at 60 $^{\circ}\text{C}$ for 18 h. The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 9:1). Compound **AB27** is finally isolated (170 mg, 310 μmol , 84%) as a colourless solid. Compound **AB27** was directly used for the synthesis of **22**.

Supplementary Figure 125: Synthesis of compound **12a**.

Reaction conditions for the synthesis of compound 12a: **12** (544 mg, 577 μmol , 1.00 equiv.), KOtBu (4.86 mg, 43.3 μmol , 7.50 mol%) and **[Ir-I]** (14.5 mg, 20.2 μmol , 3.50 mol%) are dissolved in 1,4-dioxane (3.00 mL, 0.19 M). The vial is placed in an autoclave, and the vessel is pressurized to 50 bar H_2 . The reaction is stirred for 72 h at 80 $^{\circ}\text{C}$. The reaction is quenched by adding H_2O . The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 7:3) to afford compound **12a** (484 mg, 531 μmol , 92% yield) as a colourless crystalline solid.

Compound **12a** was directly used for the synthesis of **22**.

Supplementary Figure 126: Synthesis of compound **22**.

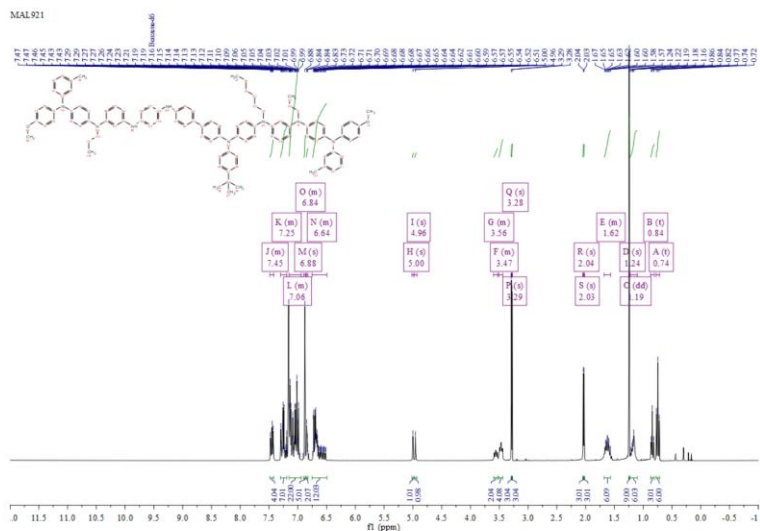
Reaction conditions for the synthesis of compound **22:** In a Schlenk tube, amine **12a** (145 mg, 159 μ mol, 1.00 equiv.), compound **AB27** (87.2 mg, 159 μ mol, 1.00 equiv.), NaOtBu (21.4 mg, 223 μ mol, 1.40 equiv.) and [Pd-Brett-Phos] (4.50 mg, 5.60 μ mol, 3.50 mol%) are dissolved in toluene (2.00 mL, 0.08 M). The reaction is stirred at 70 °C for 24 h. The reaction mixture is directly used for column chromatography (*n*-pentane / EtOAc 8:2). Compound **22** is finally isolated (143 mg, 100 μ mol, 63% yield) as a colourless crystalline solid.

^1H NMR (C_6D_6 , 300 MHz, 293 K): δ = 7.48 – 7.42 (m, 4H), 7.30 – 7.19 (m, 7H), 7.15 – 6.94 (m, 22H), 6.88 (s, 5H), 6.85 – 6.83 (m, 2H), 6.75 – 6.49 (m, 12H), 5.00 (s, 1H), 4.96 (s, 1H), 3.60 – 3.53 (m, 2H), 3.51 – 3.44 (m, 4H), 3.29 (s, 3H), 3.28 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.68 – 1.57 (m, 6H), 1.24 (s, 9H), 1.19 (dd, J = 10.7, 5.8 Hz, 6H), 0.84 (t, J = 7.4 Hz, 3H), 0.74 (t, J = 7.4 Hz, 6H) ppm.

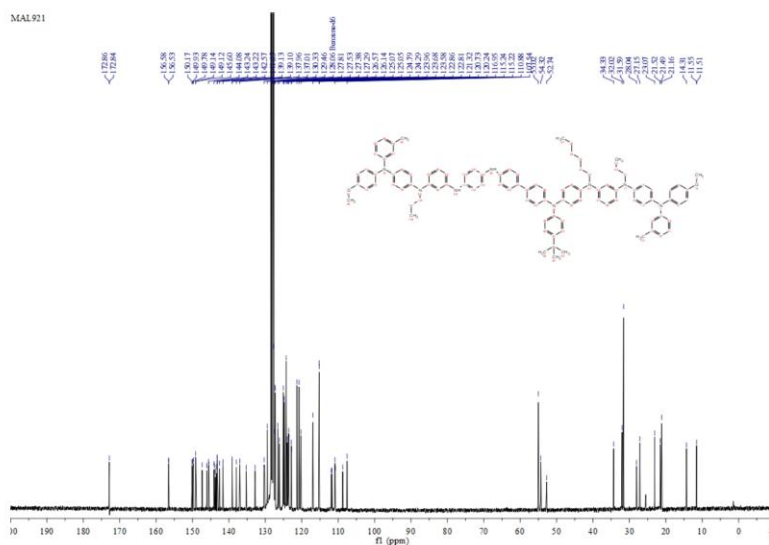
^{13}C NMR (C_6D_6 , 75 MHz, 293 K): δ = 172.86, 172.84, 156.58, 156.53, 150.17, 149.93, 149.78, 149.14, 149.12, 147.35, 146.10, 145.60, 145.49, 144.08, 144.00, 143.76, 143.47, 143.24, 143.22, 142.57, 141.65, 141.62, 139.13, 139.10, 137.96, 137.01, 135.26, 132.82, 130.33, 130.21, 129.46, 127.81, 127.53, 127.38, 127.29, 126.57, 126.14, 125.07, 125.05, 124.79, 124.29, 123.96, 123.68, 123.58, 122.86, 122.81, 121.32, 120.73, 120.24, 116.95,

115.24, 115.22, 111.87, 111.70, 110.88, 110.79, 108.73, 107.54, 55.02, 54.32, 52.74, 34.33, 32.02, 31.59, 28.04, 27.15, 23.07, 21.52, 21.49, 21.16, 14.31, 11.55, 11.51 ppm.

LC-HRMS (ESI+) m/z calculated for $[22]^+$: 1423.81985 found: 1423.81148.



Supplementary Figure 127: ^1H NMR spectrum of compound **22**.



Supplementary Figure 128: ^{13}C NMR spectrum of compound **22**.

33 Supplementary references

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