DEPARTAMENT OF CHEMISTRY

PALLADIUM- AND MANGANESE-CATALYSED SYNTHESIS OF *N*-HETEROCYCLES

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Master of Science in Chemistry

DOCTORATE IN SUSTAINABLE CHEMISTRY

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Palladium- and Manganese-catalysed Synthesis of *N*-heterocycles

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Abstract

Access to a wide range of functionalized *N*-heterocyclic compounds is essential for efficient drug discovery programs. A key challenge remains the lack of simple synthetic methods using readily available starting materials. Metal-catalysed dehydrogenative coupling has proven particularly effective in providing catalytic pathways for converting alcohols and amines into valuable products, particularly in the synthesis of imines, which are crucial intermediates in the formation of nitrogen-containing compounds. Additionally, incorporating dehydrogenative coupling into multicatalytic processes offers a convenient strategy for *N*-heterocyclic synthesis.

This work explores the development of dehydrogenative coupling strategies for nitrogen-containing compounds and their implementation in multicatalytic approaches. Key findings include the conversion of primary alcohols with aniline and aminopyridines, achieving up to 99% yield of imines using only 3 mol% of a manganese-tricarbonyl complex with a bidentate triazole ligand system. For the more challenging secondary alcohols, a simple method for imine synthesis is described, utilizing $Pd(OAc)_2$ as catalyst in an acceptorless dehydrogenative coupling strategy, without any base additives. Sequential reactions with $Pd(OAc)_2$ led to the formation of indoles, representing a significant advance in the synthesis of *N*-heterocycles. Furthermore, by modifying the reaction conditions, this catalytic system enabled the selective formation of secondary amines through a borrowing hydrogen strategy. Finally, the thesis explores the dialkylation of diamines and diols using a Mn(I)-tricarbonyl complex with bis(1,2,3-triazol-5-ylidene) ligands, achieving yields of up to 99%. The catalytic activity was further demonstrated in the synthesis of 1,2,3,4-tetrahydroquinoxalines, a class of compounds with significant pharmacological activity. Additionally, an unprecedented route for the synthesis of indoline was developed using a bimetallic manganese/palladium catalytic system combining primary alcohols and amines.

Keywords: Imines, *N*-heterocycles, Dehydrogenative Coupling, Manganese, Palladium catalysis.

Resumo

O acesso a compostos *N*-heterocíclicos funcionalizados é essencial para a descoberta de fármacos. No entanto, ainda faltam métodos sintéticos simples com materiais acessíveis. O acoplamento desidrogenativo catalisado por metais tem se mostrado eficaz na conversão de álcoois e aminas em produtos valiosos, especialmente na síntese de iminas, intermediários cruciais para compostos nitrogenados. Além disso, sua incorporação em processos multicatalíticos facilita a síntese de *N*-heterocíclicos.

Este trabalho explora estratégias de acoplamento desidrogenativo e sua aplicação em abordagens multicatalíticas. Destaques incluem a conversão de álcoois primários com anilina e aminopiridinas, obtendo até 99% de iminas com 3 mol% de um complexo Mn-tricarbonila com ligante triazólico bidentado. Para álcoois secundários, um método simples com $Pd(OAc)_2$ permite a síntese de iminas sem aditivos básicos. Reações sequenciais com $Pd(OAc)_2$ levaram à formação de indóis, enquanto ajustes nas condições possibilitaram a obtenção seletiva de aminas secundárias via estratégia de transferência de hidrogênio.

Finalmente, a dialquilação de diaminas e dióis com um complexo Mn(I)-tricarbonila alcançou rendimentos de até 99%, demonstrando eficiência na síntese de 1,2,3,4-tetrahidroquinoxalinas, compostos de interesse farmacológico. Também, desenvolveu-se uma rota inédita para a síntese de indolina usando um sistema catalítico bimetálico Mn/Pd combinando álcoois primários e aminas.

Palavras-chave: Iminas, *N*-heterociclos, Acoplamento Desidrogenativo, Manganês, Catálise por Paládio.

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List of Abbreviations and Symbols

ACN	Acetonitrile
Ac	Acetyl
ADC	Acceptorless dehydrogenative coupling
aq.	Aqueous
Ar	Aromatic
bis-NHC	Bis(*N*-Heterocyclic Carbene)
BH	Borrowing Hydrogen
Bn	Benzyl
bpy	2,2-bipyridine
Bu	Butyl
Calcd.	Calculated
Cat	Catalyst
COSY	^{1}H-^{1}H Correlation Spectroscopy
d	Deuterated
dba	Dibenzylideneacetone
DC	Dehydrogenative Coupling
DCC	Dynamic Covalent Chemistry
DIPEA	*N,N*-Diisopropylethylamine
di-trz	di(1,2,3-triazolylidene)
di-tria	di(1,2,3-triazole)
DME	Dimethyl ether
DMF	*N,N*-dimetilformamida
DMSO	Dimethylsulfoxide
equiv.	Equivalents
ESI-MS	Electron-spray ionization - Mass Spectrometry
Et	Ethyl
et al.	And others
FDA	The Food and Drug Administration
GC	Gas Chromatography
h	hours
HR-MS	High Resolution - Mass Spectrometry
IBH	Interrupted borrowing hydrogen
IR	Infrared Spectroscopy
J	Coupling Constant (NMR)
L	Generalised Ligand (either neutral or anionic)
m	*metha-*
Me	Methyl
MIC	Mesoionic carbene
MS	Molecular Sieves

NHCs	N-Heterocyclic carbenes
NMR	Nuclear Magnetic Resonance
o	*ortho-*
p	*para-*
Ph	Phenyl
pH	potential of hydrogen
py	Pyridine
RT	Room temperature
rf	Retention factor
Temp.	Temperature
t	*tert*
TGA	Thermogravimetric analysis
TLC	Thin layer chromatography
trz	1,2,3-triazolylidene
triaz	1,2,3-triazole
UV	Ultraviolet
Vis	Visible
δ	Chemical Shift in ppm (NMR)
ν	Frequency (cm^{-1})

List of Publications

Publications derived from this thesis.

Chapter 2

Raydan, D., Friaes, S., Viduedo, N., Santos, A. S., Gomes, C. S., Royo, B., & Marques, M. M. B. (2022). Manganese-Catalyzed Synthesis of Imines from Primary Alcohols and (Hetero)Aromatic Amines. *Synlett*, *33*(13), 1290-1294.

Chapter 3

Raydan, D., Royo, B., & Marques, M. M. (2023). Pd-Catalyzed Switchable Access to Imines and Amines from Secondary Alcohols. *Asian Journal of Organic Chemistry*, e202300282.

Chapter 4

Garcia, B., Friaes, S., Raydan, D., Marques, M. M. B., & Royo, B., (2024). Borrowing Hydrogen Reactions Mediated by a Mn(I) Triazolylidene Complex. *In preparation*

Other publications originated from the work but not included as a complete chapter.

Santos, A. S., Raydan, D., Cunha, J. C., Viduedo, N., Silva, A. M., & Marques, M. M. B. (2021). Advances in green catalysis for the synthesis of medicinally relevant *N*-heterocycles. *Catalysts*, *11*(9), 1108.

Santos, A. S., Raydan, D., Viduedo, N., Marques, M. M. B., & Royo, B. (2022). Metal-Catalyzed Synthesis of *N*-Heterocycles via Borrowing-Hydrogen Annulation. *More Synthetic Approaches to Nonaromatic Nitrogen Heterocycles*, *1*, 281-305.

Reis, A. R., Viduedo, N., Raydan, D., & Marques, M. M. B. (2023). Bimetallic (or Multimetallic) Synthesis of *N*-Heterocycles. *Catalysts*, *13*(9), 1268.

1.

Introduction & Objectives

Part of this Chapter has been published in two **Reviews and a book Chapter: (1)** Santos, A. S., Raydan, D., Cunha, J. C., Viduedo, N., Silva, A. M., & Marques, M. M. B. (2021). Advances in green catalysis for the synthesis of medicinally relevant *N*-heterocycles. *Catalysts*, *11*(9), 1108.[1] **(2)** Reis, A. R., Viduedo, N., Raydan, D., & Marques, M. M. B. (2023). Bimetallic (or Multimetallic) Synthesis of *N*-Heterocycles. *Catalysts*, *13*(9), 1268.[2] **(3)** Santos, A. S., Raydan, D., Viduedo, N., Marques, M. M. B., & Royo, B. (2022). Metal-Catalyzed Synthesis of *N*-Heterocycles via Borrowing-Hydrogen Annulation. *More Synthetic Approaches to Nonaromatic Nitrogen Heterocycles*, *1*, 281-305.[3]

1.1 Imines Preparation & Application as Synthetic Building Blocks

Imines are nitrogen-containing analogues of aldehydes and ketones, highly valued and well-known in organic chemistry for their versatility in synthetic applications.

Hugo Schiff reported on the classical method for the synthesis of imines in 1864,[4] introducing the term "Schiff bases" to describe imines formed from the condensation of a primary amine with an aldehyde or ketone. Therefore, imines feature a double bond between carbon and nitrogen (C=N) and typically have substituents at both atoms (see Figure 1.1). This structure influences their reactivity, making imines less electrophilic than their carbonyl analogues but more reactive towards nucleophiles.

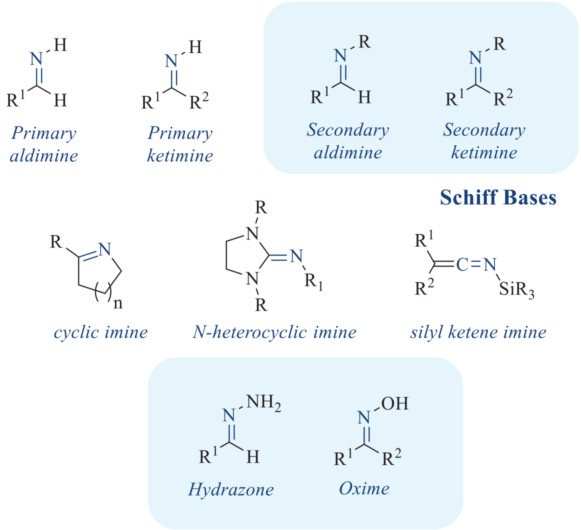
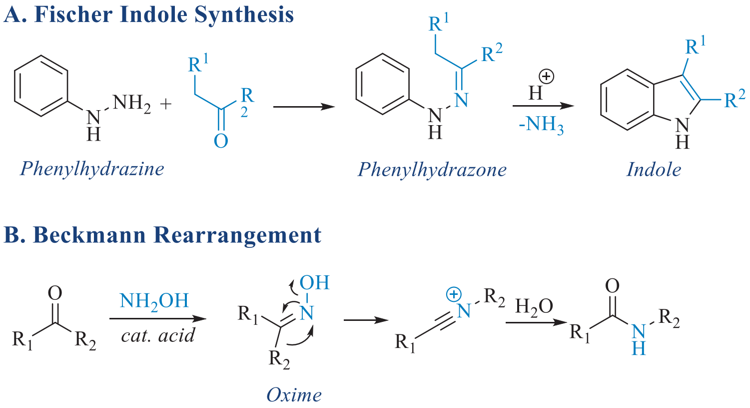


Figure 1.1. General outline of the chemical structure of imines together with analogous structures such as hydrazones and oximes.

Although imines are highly valued and well-known in organic chemistry for their versatility and reactivity,[5] other structurally similar compounds have also attracted considerable interest in various transformations. In particular, hydrazones and oximes (see Figure 1.1) have been widely studied and used in synthetic chemistry.[6,7]

Hydrazones are crucial intermediates in Fischer's synthesis of indoles, an important class of heterocyclic compounds in many natural and pharmaceutical products (see Scheme 1.1 A). On the other hand, oximes are valuable intermediates in the Beckmann rearrangement to form amides (see Scheme 1.1 B).



Scheme 1.1. Involvement of hydrazone and oxime as intermediates in reactions of **A**. Fischer Indole synthesis, and **B**. Beckmann Rearrangement.

Imines are also present in a wide range of naturally occurring and bioactive compounds (see Figure 1.2).[8] Additionally imines are found as intermediates in metabolic reactions, such as in the transamination processes involved in the biochemical transformation of amino acids.[9–11]

The classical approach to the synthesis of imines, developed by Hugo Schiff, commonly requires an acid catalyst, mineral, organic, acid resin or Lewis acid, to increase the electrophilicity of the carbonyl and to stabilise the hemiaminal intermediate. This process is reversible and thermodynamically controlled, requiring the removal of water produced as a by-product to achieve high conversion rates. Typically, removal of water can be performed through azeotropic distillation, often using a Dean-Stark apparatus, by incorporating dehydrating agents into the reaction mixture,[12,13] or through addition of dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate.[14]

In addition to these challenges, ketones are generally less reactive than aldehydes, making ketimine synthesis more difficult and less sustainable. Therefore, optimizing reaction parameters such as solvent, temperature, concentration, and pH is crucial to achieve satisfactory yields.

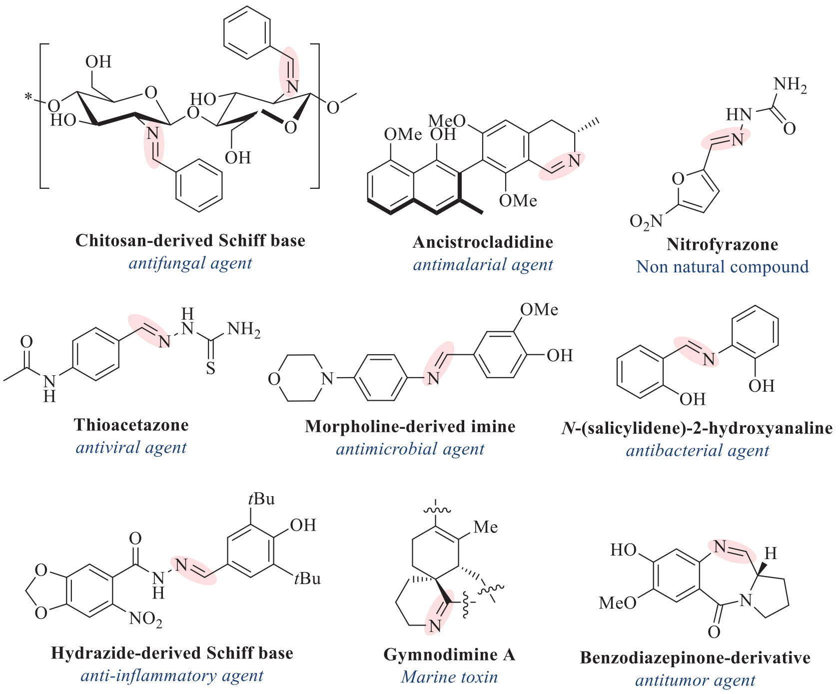
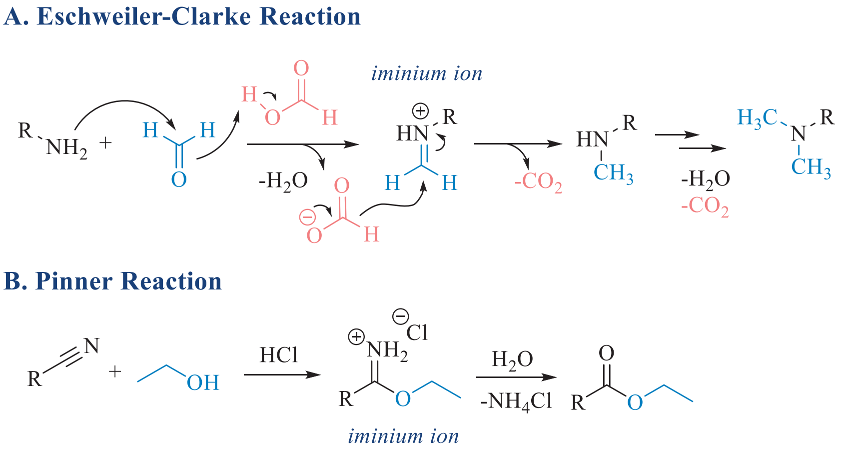


Figure 1.2. Representative examples of bioactive imine-containing compounds.

Additionally, other internal factors such as steric hindrance and electronic effects significantly influence the reaction.[15] Compounds formed with ammonia (NH_3) are generally unstable, while those formed with amines, especially when the nitrogen substituent is an aromatic ring (anilines), are more stable due to stabilization by resonance. Moreover, many aliphatic imines are less stable than their corresponding carbonyl compounds and prone to hydrolysis in water.[16]

There is another class of compounds related to imines and with important implications in several well-known transformations. These compounds are the iminium ions (or salts), derived from the reaction of aldehydes or ketones with secondary amines or the protonation of imines under acidic conditions, are more reactive towards reduction and nucleophilic attack than imines themself.[17] This increased reactivity makes iminium ions valuable intermediates in various chemical reactions such as in the Eschweiler-Clarke reaction or the Pinner reaction (see Scheme 1.2 A and B respectively).



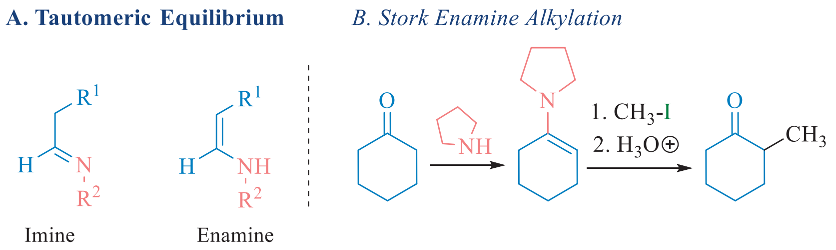
A. Eschweiler-Clarke Reaction

B. Pinner Reaction

Scheme 1.2. Implications of iminium ions in reactions such as the **A**. Eschweiler-Clarke, and **B**. Pinner reaction.

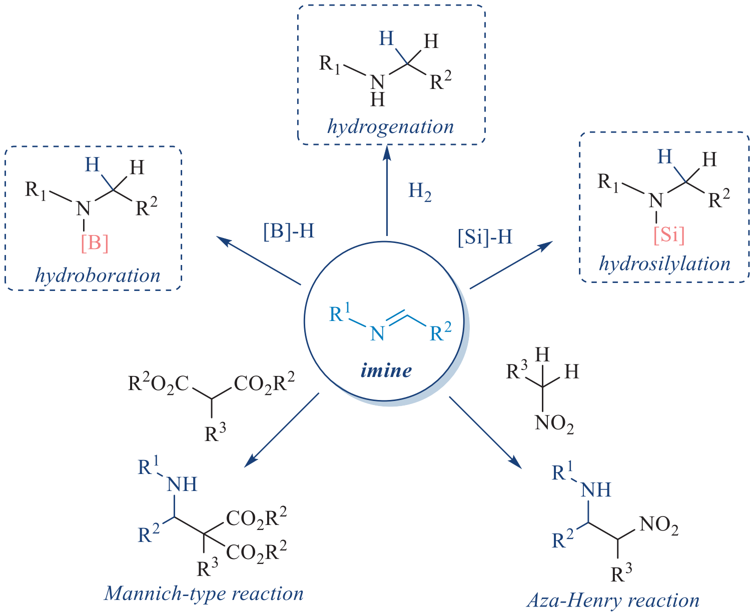
The chemistry of imines is vast and has significant implications in organic synthesis. A powerful example of the importance of imines in common synthetic transformations is their use in aldol condensation reactions, which are crucial for the formation of C-C bonds.[18] In these reactions, imines are less reactive than aldehydes or ketones, allowing better control of over-reactivity and selectivity. In addition, imines can be easily hydrolysed back to their aldehyde or ketone form, making the process very convenient.

Imines are also involved in dynamic and reversible tautomeric equilibrium, coexisting with their tautomeric enamine form (see Scheme 1.3 A). Thus, imines play a crucial role in Dynamic Covalent Chemistry (DCC), facilitating the construction of molecules and materials capable of adapting to external stimuli,[19] constituting a valuable synthetic tool in organic chemistry. Moreover, enamines are also interesting templates with high synthetic value, participating in reactions such as the Stork reaction, involving the alpha-alkylation of ketones and aldehydes (see Scheme 1.3 B). Furthermore, enamines are key intermediates in asymmetric aldol reactions, formed by the use of a catalytic amount of proline.[20,21]


A. Tautomeric Equilibrium
B. Stork Enamine Alkylation

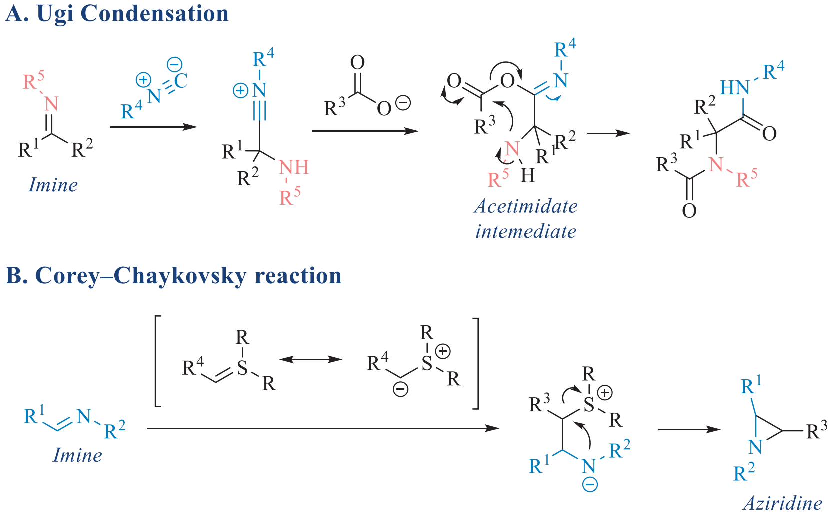
Scheme 1.3. Tautomeric equilibrium between the imine and enamine forms and the implications of the enamines in the Stork alkylation.

Imines can undergo several high-value synthetic reactions[22] such as hydrogenations, hydrosilylations, or hydroborations (see Scheme 1.4).[23,24] Moreover, imines can also serve as starting materials in classic organic reactions such as the Mannich reaction for the formation of β-aminocarbonyls, which involves the formation of an intermediate enamine, or the Aza-Henry reaction for the synthesis of β-nitroamines (see Scheme 1.4).



Scheme 1.4. Possible synthetic transformations from imines.

Imines also serve as key intermediates in organic synthesis, highlighting their versatility as building blocks in synthetic chemistry.[25] Several well-known reactions involve imines, including the multicomponent Ugi condensation or the synthesis of aziridines via the Corey-Chaykovsky reaction (or the related De Kimpe reaction) (see Scheme 1.5 A and B respectively).



A. Ugi Condensation

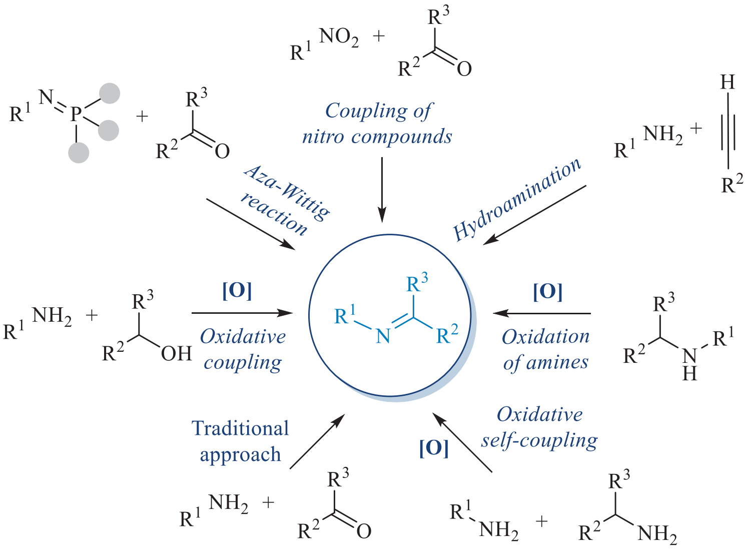
B. Corey–Chaykovsky reaction

Scheme 1.5. General routes for the **A**. Ugi reaction: Multicomponent reaction forming peptidomimetics, and **B**. Corey–Chaykovsky reaction: Epoxidation of imines.

Given the relevance of the imine intermediates, and their significant importance in organic synthesis, progress has been made in developing alternative synthetic methods for their preparation.[26,27]

Alternative methods include Aza-Wittig reaction, hydroamination of alkynes, dehydrogenation of secondary amines, coupling of aldehydes/ketones with nitro compounds, and oxidative approaches such as oxidative coupling of amines and alcohols (see Scheme 1.6).[28] However, these methods often use toxic and expensive reagents, have low atom economy and exhibit low selectivity.

Currently, catalytic routes for the sustainable synthesis of imines have gained significant attention,[29] with examples including heterogeneous catalysis, which allows for catalyst recovery and reuse; photocatalysis, which uses light energy to drive reactions; and electrosynthesis, which utilizes electricity as an environmentally friendly alternative to traditional chemical oxidants.



Scheme 1.6. Alternative approaches to imine synthesis.

1.2 Challenges in the Synthesis of *N*-heterocycles

Heterocycles are essential in modern pharmacology, constituting over 85% of biologically active compounds and playing a crucial role in the search for new drug candidates.[30,31] Nitrogen-containing heterocycles are particularly relevant, representing around 60% of FDA- small molecule approved drugs, including those studied as anticancer or antibiotic agents.[32,33]

In particular, nitrogen-based heterocycles play a crucial role in both natural ecosystems and the pharmaceutical industry, thanks to their chemical diversity and indispensable biological functions.[34] These compounds are fundamental building blocks for living organisms and represent an abundant nitrogen reservoir on Earth's surface. They can be found in many organic molecules, including proteins, nucleic acids, alkaloids, vitamins, hormones, and other biologically active compounds.[35,36] Moreover, many drugs and therapeutic agents incorporate nitrogen functional groups to provide desirable pharmacological properties such as improved bioavailability, receptor binding affinity, and metabolic stability. Therefore, the rational design of drugs, such as antibiotics, antivirals, and anticancer agents, often involves the strategic incorporation of nitrogen functionalities to optimize pharmacokinetic and pharmacodynamic properties, thereby significantly improving therapeutic outcomes and minimizing adverse effects.[37]

Some well-known bioactive *N*-heterocyclic molecules include Meriolin, Veliparib, Diazepam, Luotonin A, Robustine, Tolmetin, Chlorosulfaquinoxaline, Serotonin, Thiamine (vitamin B1), Morphine, Codeine, Caffeine, and Nicotine.[38] Some of these bioactive compounds are represented in Figure 1.3.

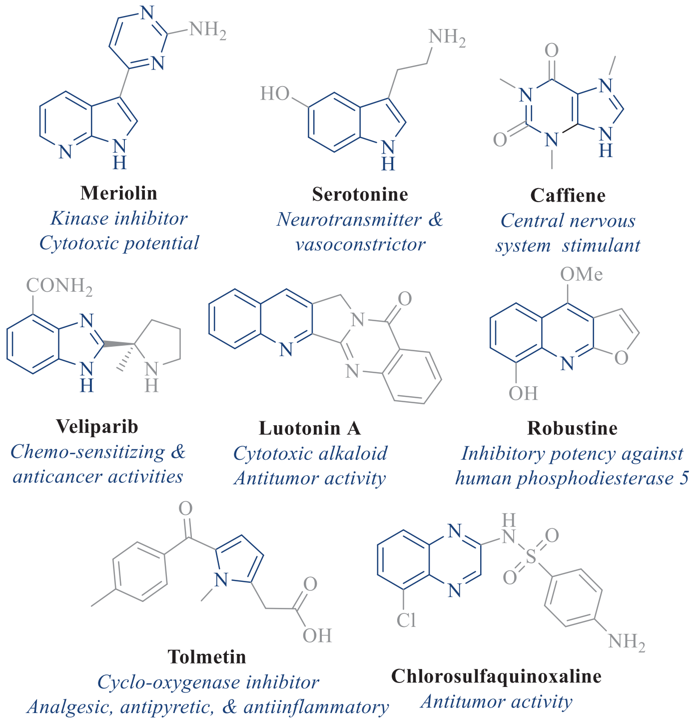


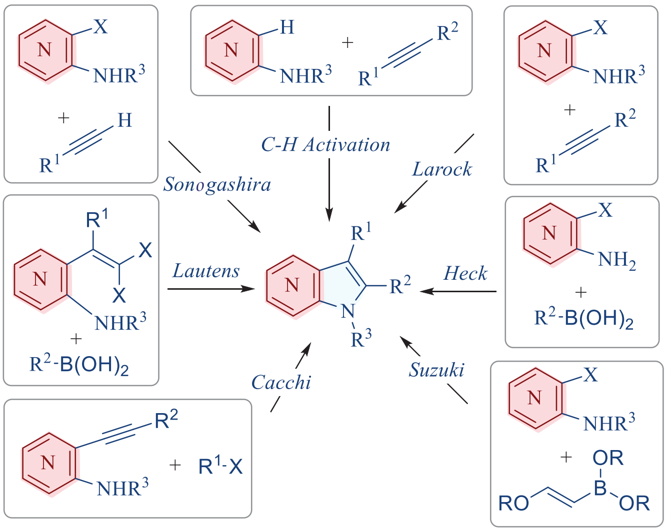
Figure 1.3. Representative examples of *N*-containing heterocycles of biological and pharmaceutical importance.

The pharmaceutical industry uses several methods to produce millions of tons of nitrogen-containing heterocycles each year.[39] These methods include the Hantzsch-Feist and the Paal-Knorr synthesis of pyrroles, the Friedländer annulation, the Skraup reaction and the Doebner von Miller for the synthesis of quinolines, among others.[40] However, several of these methods require expensive materials, harsh reaction conditions and laborious synthetic protocols, in addition to the production of toxic waste and the need to protect/deprotect functional groups.

The most commonly used synthetic routes at the laboratory level for the construction of *N*-heterocycles, particularly to the formation of C–N bond, rely on cross-coupling reactions catalysed by palladium, such as the Buchwald-Hartwig and Ullmann-Goldberg reactions.[41–43] In addition, C–H activation reactions have gained attention for building complex structures from simple compounds without prefunctionalisation.[44] However, these strategies often require pre-activated reagents, high temperatures, expensive additives and rigorous experimental conditions, which limits their applicability on an industrial scale. Therefore, it remains crucial to develop simpler and more efficient approaches for the construction of *N*-heterocycles under milder conditions and with accessible and inexpensive starting materials.

Some *N*-heterocyclic cores stand out for their importance in drug discovery programmes and their synthetic challenges. Among these molecules are the azaindoles, bioisosteres of the indoles, which contain an additional nitrogen atom in the ring (see Scheme 1.7).[45] Although rare in nature, these structures can be obtained from aminopyridines as starting materials,[46] similarly to the synthesis of indoles from anilines. However, conventional routes of indole synthesis, such as Fischer, Bartoli and Madelung synthesis, are not suitable for the synthesis of azaindoles.[47] For example, Fischer synthesis is not effective with hydrazinylpyridines, except when these possess an electrodonating group.[48–51] On the other hand, Bartoli synthesis, requires a large excess of Grignard reagent[52] and Reissert and Hemetsberger-Knittel synthesis are limited to few isomers and have low to moderate yields.[53,54]

New methodologies for the synthesis of azaindoles have been developed in response to these limitations (see Scheme 1.7).[55] These include palladium-catalysed reactions such as the Sonogashira reaction, the Larock-type reaction, the Heck reaction and the Suzuki coupling, as well as the more recent Cacchi and Lautens protocols (see Scheme 1.7). Although metal-catalysed C-H activation has also been explored for the synthesis and functionalisation of azaindoles, these strategies are still scarce.[56]



Scheme 1.7. Different metal-catalysed reactions for the synthesis of azaindoles.

Even though progress has been made, the electron deficiency of the pyridine ring still represents a significant challenge, as it alters the electronic properties of the conjugated system, limiting the efficiency of many classical methods applied to the synthesis of azaindoles. Moreover, many *N*-heterocycles with a high concentration of aromatic rings face limitations in solubility, pharmacokinetics, and bioavailability.[57,58] Due to these limitations, there is a need to also synthesise saturated nitrogen-containing heterocycles, which can offer better pharmacological properties and are crucial in the synthesis of biologically active molecules.[59]

Examples of relevant saturated *N*-heterocycles include pyrrolidine, piperidine, 1,2,3,4-tetrahydroquinolines, indolines, among others. These compounds have been used in the synthesis of several drugs (see Figure 1.4) and their synthesis presents a current challenge due to the difficulty in preparing analogues through cross-coupling reactions.[60] Conventional methods rely on lithiation and trans-metalation, followed by metal-catalysed coupling reactions, which require the use of protecting group.[60] Therefore, developing new, simpler, and more direct methods for producing these scaffolds has also become a promising area of research.

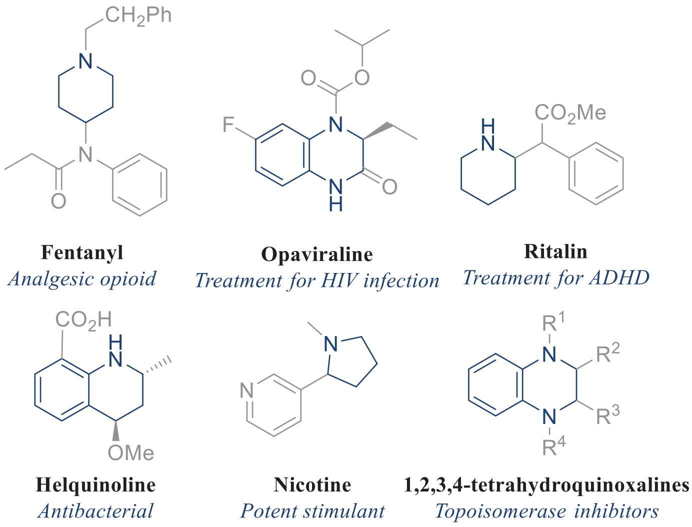


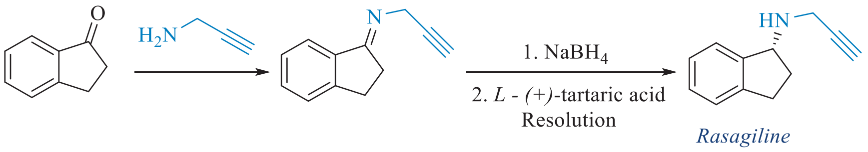
Figure 1.4. Bioactive molecules containing saturated *N*-heterocycles.

1.3 Metal-catalysed Synthesis of *N*-Heterocycles via Imines

Access to a wide range of functionalised *N*-heterocyclic compounds is crucial for improving the effectiveness of drug discovery programs. However, one of the main challenges is the lack of simple and efficient synthetic methods that use readily available materials. Imines, considered key intermediates in organic synthesis (Section 1.1), can play an essential role in the synthesis of these *N*-heterocycles.[61,62] This section will explore various synthetic strategies involving imines, highlighting the advances and limitations of these methods, and present the multi-catalytic systems as a valuable approach.

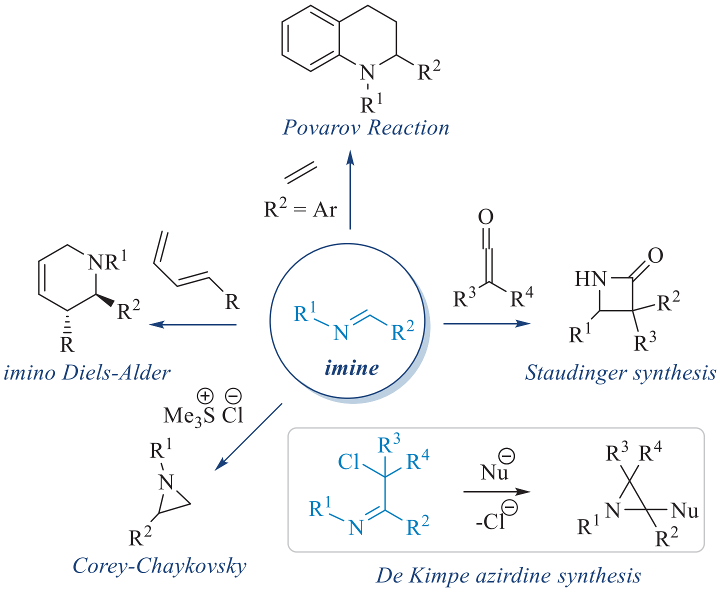
As previously mentioned, imines are powerful scaffolds for constructing complex molecules, including high-value *N*-heterocyclic molecules.[63] Numerous synthetic strategies have been reported for the generation of various *N*-heterocycles from imines or using imines as key intermediates (see Section 1.1). Unfortunately, many of these methods employ pre-formed imines, limiting the method's versatility, or requiring the isolation and purification of imine intermediates to achieve better yields.

The synthesis of high-value industrial compounds, including drugs and natural products, often involves the formation of imines as a crucial step in their synthetic route. A prominent example is the synthesis of Rasagiline, a drug used in the treatment of Parkinson's disease, which also relies on the formation of imines.[64] This intermediate is fundamental for structuring the core of the final compound (see Scheme 1.8).



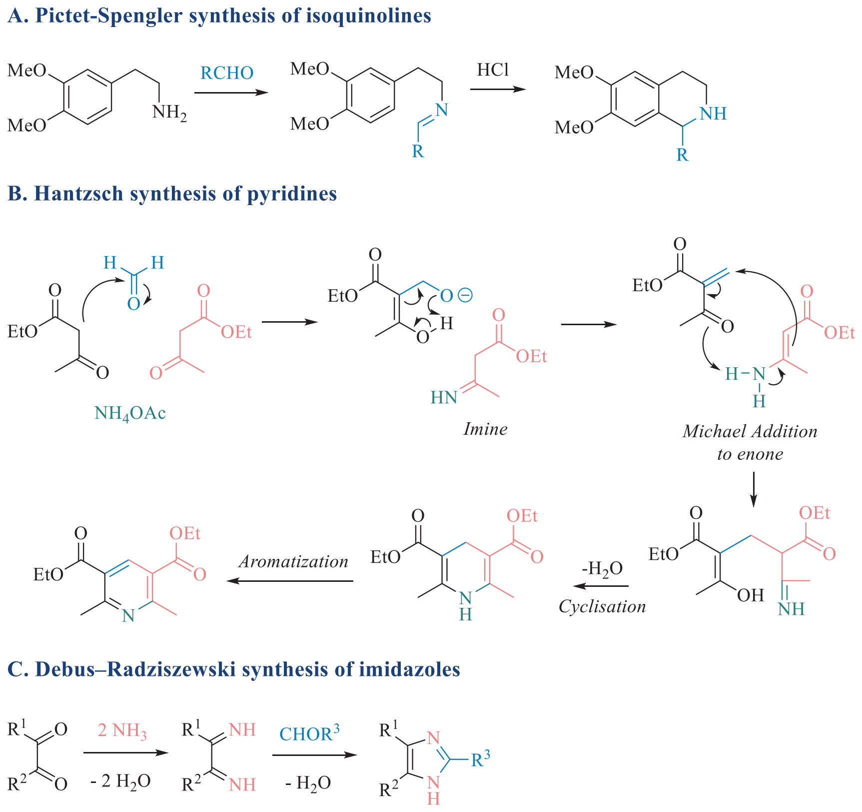
Scheme 1.8. Synthetic routes for preparation of rasagiline which involves an efficient two-step pathway to racemic *N*-propargyl-1-aminoindan and utilized a late-stage kinetic resolution with L-(+)-tartaric acid.

Other examples include pyrroles, quinazolines, isoquinolines, tetrahydroisoquinolines, aziridines, pyridines, imidazoles, among others (see Scheme 1.9).[65]



Scheme 1.9. Known transformations in organic chemistry for the synthesis of *N*-heterocycles from imines.

For example, in the Pictet-Spengler synthesis of isoquinolines, an β-arylethylamine condenses with an aldehyde to form an imine, which subsequently cyclizes under acidic conditions (see Scheme 1.10 A). Similarly, the Hantzsch synthesis of pyridines and the Debus-Radziszewski synthesis of imidazoles also involve the formation of imines as critical intermediate steps (see Scheme 1.10 B and C).


A. Pictet-Spengler synthesis of isoquinolines

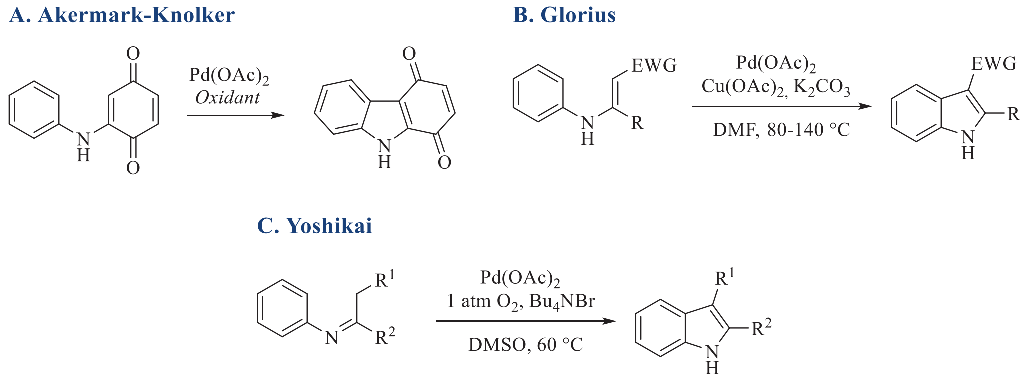
B. Hantzsch synthesis of pyridines

C. Debus–Radziszewski synthesis of imidazoles

Scheme 1.10. Synthetic routes for the construction of well-known *N*-heterocyclic scaffolds in organic chemistry.

A classic example is the already mentioned Fischer indole synthesis, where the condensation of an arylhydrazine with a ketone forms a hydrazone, which through acidic conditions forms an indole. However, this synthesis has drawbacks, such as the limited availability of commercial arylhydrazines and the use of strong acidic conditions associated with the direct condensation of an amine with aldehydes or ketones.[66,67]

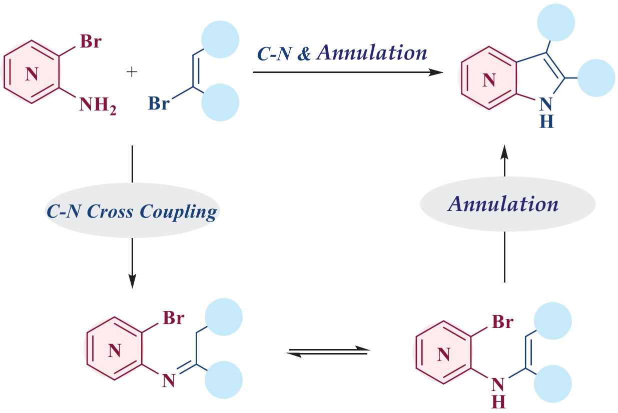
Given the prominent role of the indole scaffold in biological and medicinal chemistry, significant efforts have been made to develop alternative synthetic methods.[68] Also, due to the wide availability and low cost of commercial anilines, their use as starting materials is very attractive, although well-established methods often require modified aniline derivatives, such as arylhydrazines (Fischer indole synthesis), *o*-haloanilines (Larock, Heck, Sonogashira, and Suzuki indole synthesis), among others. In this context, Akermark and Knölker made a breakthrough by conducting seminal studies on the oxidative synthesis of carbazoloquinones and carbazoles mediated by palladium(II) (see Scheme 1.11 A).[69–72] Based on this pioneering work, Glorius and co-workers developed a copper(II)-mediated, palladium(II)-catalysed oxidative cyclisation of *N*-aryl enamines derived from anilines and *β*-dicarbonyl compounds to produce the corresponding indoles (see Scheme 1.11 B).[73,74] Subsequently, Yoshikai advanced further by developing a palladium(II)-catalysed oxidative cyclisation reaction of *N*-aryl imines to indoles, probably involving the palladation of *N*-aryl enamines formed via imine-enamine tautomerisation, notable for its operational simplicity, mild conditions and broad tolerance to various functional groups (see Scheme 1.11 C).[75] However, attempts to carry out the *one-pot* synthesis of these indoles from amines and aldehydes faced challenges, resulting in low yields and limited examples. Additionally, the few examples were restricted to the use of cyclic or activated aromatic ketones, limiting the versatility of these methods.[76–78]



Scheme 1.11. Pioneering work on the formation of indoles from imine/enamine.

The potential of multi-catalytic systems lies in their ability to exploit simple and selective catalytic cascade methods, resulting in high atomic efficiency.[79] The use of readily available materials to catalyse the formation of imine intermediates, followed by the *in situ* formation of *N*-heterocycles in a one-pot process, adds significant synthetic value. The possibility of conducting one-pot syntheses, where imine formation and subsequent cyclisation are carried out in a single vessel without the need to isolate intermediates, represents a significant improvement in terms of efficiency and practicality.

Marques research group has developed simple and direct synthetic approaches to obtain challenging indoles and azaindoles through Pd-catalysed one-pot multi-catalytic reactions.[80] To date, Marques group has explored the use of halogen-free aminopyridines to achieve azaindoles via a cascade C–N/C–H coupling route in a single step.[81] Moreover, a cascade C-N/annulation strategy of halogenated aminopyridines with vinyl bromides to access azaindoles was developed (see Scheme 1.12).[82] This method proposed a purely catalytic route under more convenient reaction conditions, offering a more elegant approach to accessing the four isomers, with yields of up to 82%. However, the limited availability of commercial vinyl bromides presents a significant drawback.



Scheme 1.12. Preparation of Azaindoles via Cascade Alkenyl Amination/annulation Reaction Involving Amino-*o*-Bromopyridines and Vinyl Bromides.

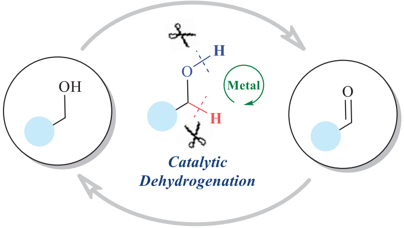
Despite significant advances in this field, there is still room for improvement taking advantage of the versatility of imines as intermediates. One promising approach is to explore multi-catalytic pathways using alcohols as substrates for the formation of imine intermediates (through dehydrogenative coupling processes) that could be subsequently employed for further derivatization.[83] As far as we know, catalysed-dehydrogenative coupling processes have not been studied in a one-pot manner combined with conventional cyclisation pathways to produce *N*-heterocycles. We believe that advances in this area would significantly improve access to *N*-heterocycles in both academic and industrial contexts.

To explore multi-catalytic approaches, it is essential to study the reaction conditions, avoiding incompatibilities between the different catalyst and intermediates formed in the different catalytic steps.

1.3.1 Dehydrogenative Coupling Reactions

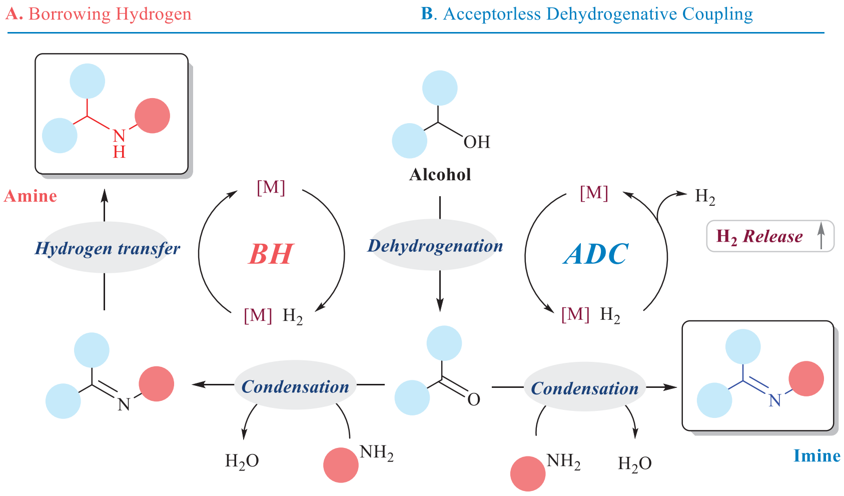
Dehydrogenative coupling (DC) reactions represent a powerful method in organic synthesis. They enable the direct formation of carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds from simple starting materials containing C-H and X-H bonds.[84] This constitutes a significant advantage, when compared to traditional synthetic methods that often require the pre-activation of substrates, involve additional synthetic steps and generate waste. Therefore, DC reactions improve synthetic routes and enhance both atom economy and sustainability.[85–87]

The DC reactions are inherently thermodynamically unfavourable, as the removal of hydrogen atoms from stable molecules is an endothermic process.[88] To overcome this challenge, catalytic systems have been developed. Metal catalysts play a crucial role in facilitating these reactions by lowering activation energies and improving reaction rates.[89–92] Additionally, alcohols are among the most common substrates for DC reactions due to their availability, stability, and green nature. The catalytic dehydrogenation of alcohols transforms them into aldehydes or ketones, which can then participate in further reactions (see Scheme 1.13).



Scheme 1.13. The general process illustrates the alcohol dehydrogenation step, which yields an electrophilic carbonyl group that can undergo further reactions.

DC reactions are highly valuable for the synthesis of nitrogen-containing compounds.[93] The dehydrogenation of alcohols to form aldehydes or ketones can be followed by reaction with amines to afford the corresponding imines (see Scheme 1.14B), which are key intermediates in the synthesis of many pharmaceuticals and agrochemicals. Further reduction of these imines can lead to a variety of amine products, demonstrating the versatility of this approach (see Scheme 1.15A). Further reduction of these imines can lead to a variety of amine products in a process referred to as "Borrowing Hydrogen", demonstrating the versatility of this approach (see Scheme 1.15A).



Scheme 1.14. A. Borrowing Hydrogen (BH) and B. Acceptorless Dehydrogenative Coupling Strategies for the reaction between alcohols and amines.

The Borrowing Hydrogen (BH) approach has garnered significant interest due to its efficiency and sustainability. This process effectively 'borrows' hydrogen from the alcohol and then returns it back, resulting in a redox neutral reaction, with high atomic efficiency and minimal by-products generation, usually only water (see Scheme 1.14A).[94–96]

Recent reports have highlighted that modifying reaction conditions can significantly influence the fate of H_2 in dehydrogenative coupling reactions.[97] Although the catalytic mechanism remains the same, the key difference is in the final step: H_2 can either be released from the system or used to reduce the imine formed. This flexibility allows for the selective favouring of either Acceptorless Dehydrogenative Coupling (ADC) for imine formation or Borrowing Hydrogen (BH) for secondary amine formation (see Scheme 1.14). Consequently, developing new strategies to control these reaction parameters is highly desirable and would significantly advance the field. Currently, there are limited strategies for the rational control of various factors in these chemical reactions, such as the use of additives like Molecular Sieves,[98-100] the choice of metals,[101] types of bases,[102,103] base loads,[104-106] ligands,[107], hydrogen sources,[108] experimental setups.[98,99]

Even though this transformation is typically achieved using expensive transition metals, recent research has focused on the use of earth-abundant metals to enhance sustainability and reduce costs. In addition to traditional catalytic methods, enabling technologies such as photocatalysis and electrochemical dehydrogenation have gained attention.[109–111] Photocatalysis leverages light energy to drive reactions, potentially offering milder conditions and greater selectivity. Electrochemical approaches use electric current to facilitate dehydrogenation, avoiding the need for chemical oxidants and allowing fine control over reaction parameters.

Dehydrogenative coupling reactions are at the forefront of green chemistry, offering efficient and sustainable routes to complex molecules. By harnessing the power of catalytic systems, these reactions can transform simple and abundant starting materials into high-value products with minimal environmental impact. Ongoing research into new catalysts and methodologies continues to expand the scope and utility of DC reactions in organic synthesis.

1.4 From Single Catalysis to Multi-catalysis

In today's chemistry, it is essential to find ways to promote chemical reactions with minimal environmental impact. Catalysis has been a fundamental concept in chemistry for over 180 years, thanks to the Swedish scientist Jöns Jacob Berzelius, enabling reactions that may not occur otherwise.[112] In simple terms, catalysts are assistants that accelerate reactions, reducing energy consumption and pollution. Catalysis also enhances selectivity, increasing the desired product yield. This is the reason why catalysis is used in more than 90% of chemical processes nowadays, being part of all sorts of industrial processes, from making medicines to producing materials we use every day.

Metals have driven significant advancements in both laboratory and industrial settings, and their use has revolutionised the field of chemistry, leading to the discovery of new reactions and processes. [113] Consequently, the impact of metal-catalysis has been widely recognised, as demonstrated by the prestigious awards given to catalysis pioneers, such as the Nobel Prize.[114,115] From metathesis to enantioselective hydrogenations, from cross-coupling reactions to click chemistry, the contributions of Chauvin, Grubbs, Schrock, Noyori, Knowles, Sharpless, Heck, Negishi, Suzuki, Sharpless, Meldal, and Bertozzi have significantly influenced the field of chemical synthesis.

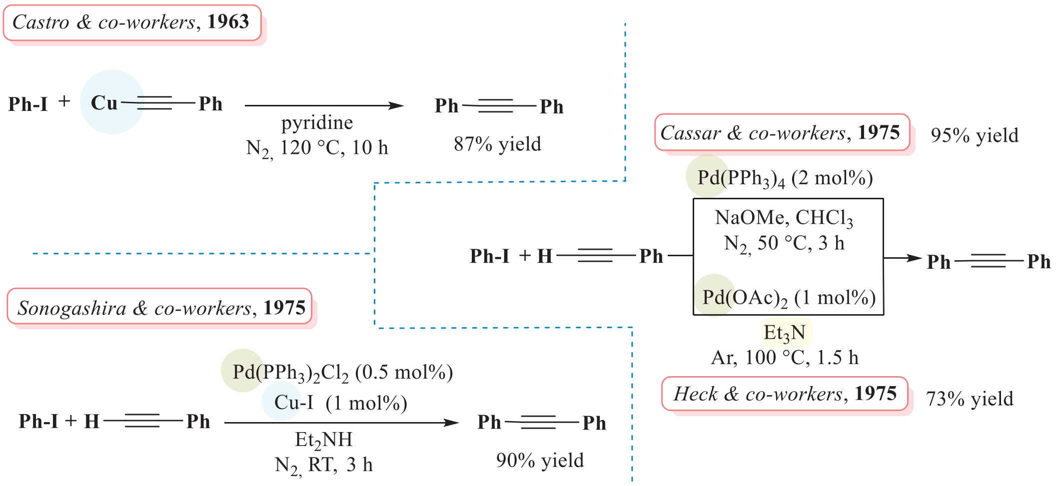
In the last years, multi-catalysis also known as cascade catalysis, which involves the use of multiple catalysts in a single reaction, or sequential multiple catalytic reactions, occurring in a single vessel, has recently attracted considerable interest.[116,117] Multi-catalytic protocols not only allow for transformations that are not possible with single metal-catalysed reactions, but they can also significantly reduce the time, waste, and cost of the synthetic process, making organic synthesis more resource-efficient.[118,119]

The concept of multi-catalysis can offer significant advantages over other types of chemical transformations. As an example, some multi-step reactions that can be achieved with a single catalyst under harsh conditions, can also be achieved with different catalysts, while reducing the severity of each step.

Multi-catalysis also allows working with unstable intermediates, being rapidly converted by successive catalytic processes, avoiding its degradation into unwanted secondary products. Moreover, in some sequential catalytic reaction processes, where one step is not thermodynamically favourable, the common process of multi-catalytic steps can lead to a globally thermodynamically favourable sequence.[120]

However, developing multi-catalytic systems requires overcoming significant challenges,[121] including i) incompatibility between multiple catalysts or reagents, i.e., the catalysts and reagents must not inhibit each other or undergo non-productive secondary reactions; ii) incompatibility of reaction conditions, i.e., all reactions must occur under the same conditions.

To better comprehend multi-catalytic phenomena, it is important to analyse well-documented examples. Pioneering studies on transition metal-catalysed cross-coupling reactions, such as *Suzuki*, *Heck*, and *Negishi* reactions, laid the foundation for bimetallic catalysis by demonstrating the selective coupling of different organic fragments.[122] For example, the well-known *Sonogashira* reaction employs two combined metal catalytic systems (see Scheme 1.15).[123]



Scheme 1.15. Previous studies that led to Sonogashira's cooperative multi-catalytic approach.

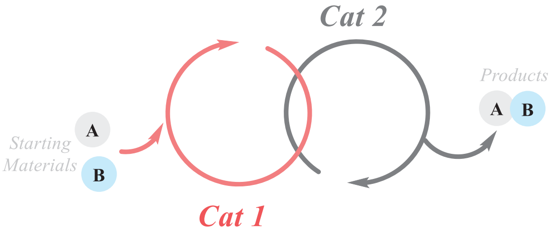
In 1963, *Castro–Stephens reaction* described the synthesis of diaryl alkynes coupling aryl halides with a stoichiometric amount of active aryl acetylenes in the presence of a stoichiometric amount of copper species, in boiling pyridine.[124] In the mid-1970s, *Heck & Cassar* reported on Pd-catalysed coupling reactions between aryl halides and terminal alkynes under relatively harsh reaction conditions,[125,126] and simultaneously, *Sonogashira & co-workers* completely combined the activation of terminal aryl alkynes and aryl halides using Cu and Pd catalysts, respectively, obtaining diaryl alkynes under low catalytic loads and mild reaction conditions (see Scheme 1.15).

1.4.1 Multi-catalytic Approaches: Classification

Given that multi-catalytic systems are less developed than their mono-catalytic analogues, it is essential to differentiate between possible scenarios. The classification of the different types of multi-catalytic processes in a single vessel is somewhat inconsistent in the chemical literature. Any system that contains multiple catalysts or catalytic reactions within the same vessel is considered as multi-catalytic, regardless of whether all reagents or catalysts are present from the beginning or added during the reaction with the possibility of changing conditions. This gives rise to the concepts of cooperative catalysis, domino catalysis, and relay catalysis.

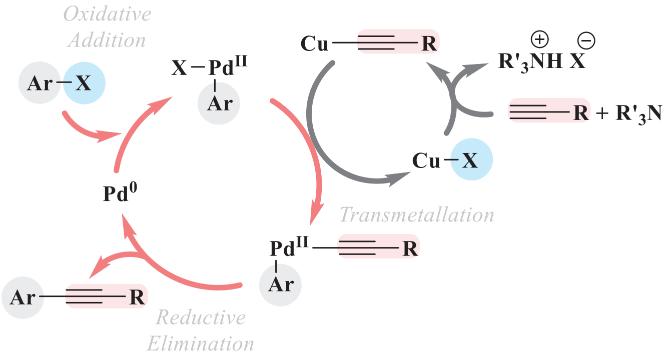
COOPERATIVE CATALYSIS

Cooperative catalysis is perhaps the style of bi(multi)metallic catalysis that involves the major interaction between catalysts and/or catalytic cycles in the reaction medium. Often referred to as ‘synergistic catalysis’, cooperative catalysis can be found, in most cases studied, as catalytic systems in which multiple catalysts operate together by sharing their individual catalytic cycles in a single reaction to create, modify or break a single bond (see Scheme 1.16).[127]



Scheme 1.16. A general outline of many of the cooperative catalysis**.**

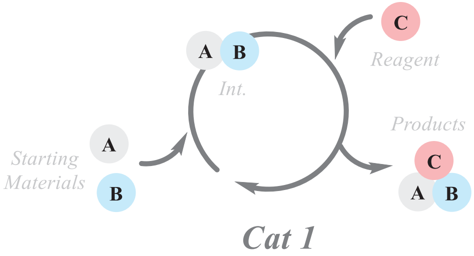
A consequence of systems of this type is that no accumulation of reaction intermediates is possible. This field of research has been extensively reviewed.[128,129] The recently mentioned example of the evolution of Cu-Pd processes in the development of the well-known *Sonogashira* reaction is a clear case of cooperative catalysis. The reaction comprises oxidative addition, trans-metallation, and reductive elimination, and proceeds along two synergistically operating catalytic cycles (see Scheme 1.17).[130]



Scheme 1.17. Cooperative Catalytic Cycles involved in the Sonogashira reaction.

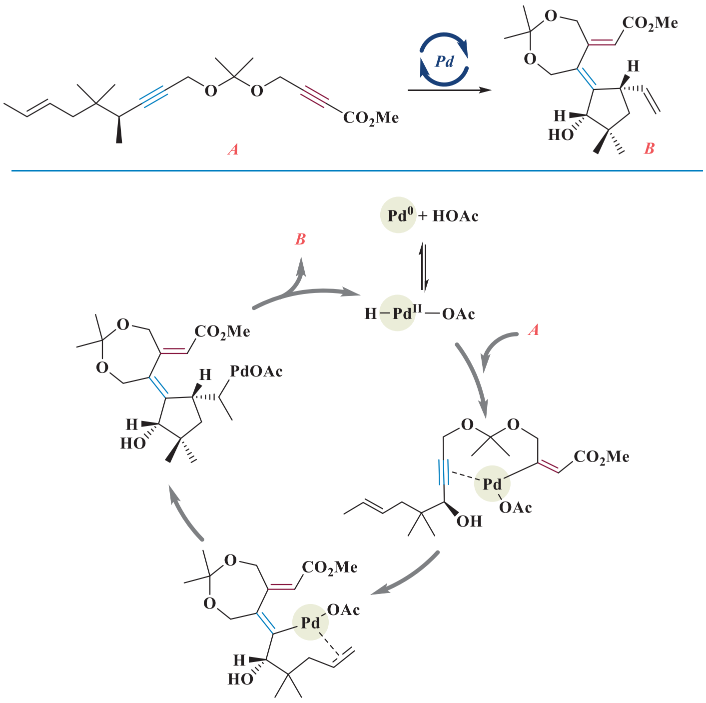
DOMINO CATALYSIS

The term domino refers to the fall of domino pieces, where the fall of the next pieces is due to the fall of the previous ones. Thus, domino catalysis refers to successive transformations on the same substrate, catalysed within the same catalytic cycle due to a single catalyst (see Scheme 1.18). Considering that a catalyst typically remains attached to the intermediates until the sequence is completed, no accumulation of reaction intermediates is possible. These reactions have been extensively reviewed in journal articles and books.[131]



Scheme 1.18. A general outline of many of the domino catalysis.

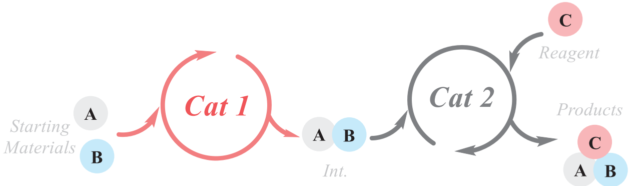
Trost & Min have demonstrated a fine example of domino reactions by employing an intramolecular Pd-catalysed polyenyne cycloisomerization from a linear polyene.[132] The starting material underwent a series of reactions during the same Pd catalytic cycle, through a sequence of hydropalladation, carbopalladation, and *β*-hydride elimination steps (see Scheme 1.19).



Scheme 1.19. The Pd catalytic cycle sequence of hydropalladation, carbopalladation, and *β*-hydride elimination steps, as an example of domino catalysis.

RELAY CATALYSIS

Sometimes referred to as ´tandem catalysis´, it is perhaps the most common form of multi-catalytic system in the literature. In its most global definition, it refers to catalytic transformations that occur in the presence of catalysts operating in isolation in distinct, non-interfering individual catalytic cycles (see Scheme 1.20).



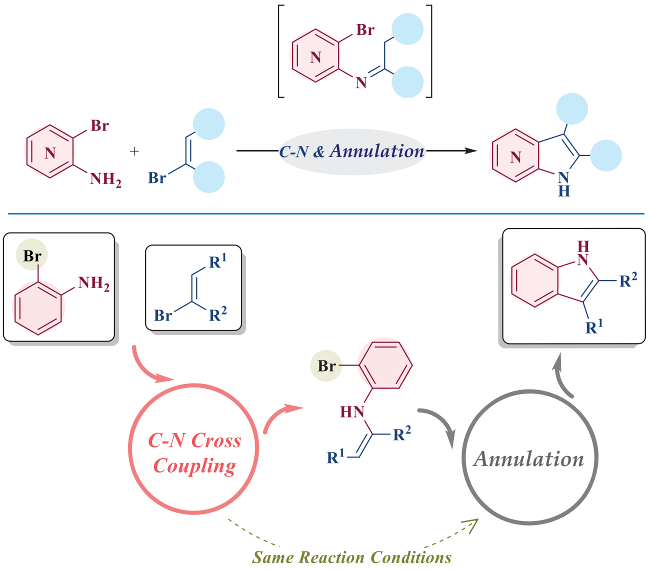
Scheme 1.20. A general outline of many of the relay catalysis.

Thus, in relay catalysis reactions, two or more catalytic transformations are performed in a sequence of independent reactions. and the accumulation of intermediates formed as a product of any catalytic cycle may be possible. Therefore, this type of multi-catalysis encompasses a larger concept and covers a variety of different systems, and it can be divided into subcategories, depending on the number of catalysts and the reaction conditions.[133]

- *AUTO-RELAY CATALYSIS*

Auto-Relay catalysis only contemplates a single (pre)catalyst (avoiding possible incompatibilities between catalysts) which catalyses multiple independent reactions within mechanistically distinct catalytic cycles, under the same reaction conditions with all reactants present from the start.

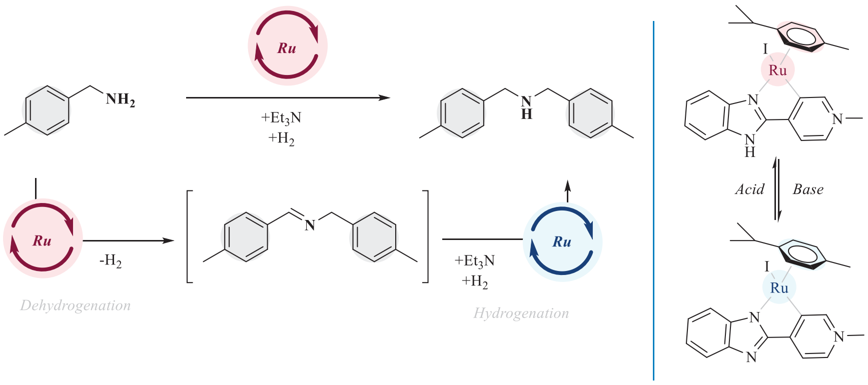
In the research group of *M.M.B. Marques & co-workers*, a reaction of this type was carried out for the challenging synthesis of substituted Azaindoles from aminopyridines. The reaction occurred via a cascade *C-N* Cross-Coupling/annulation reaction, using a $Pd_2(dba)_3$ catalyst in an XPhos/NaO^tBu system (see Scheme 1.21).[134]



Scheme 1.21. Pd catalytic cycles involving C-N cross-coupling/annulation reaction as an example of auto-relay catalysis.

- *ASSISTED-RELAY CATALYSIS*

Assisted-Relay catalysis is similar to Auto-Relay catalysis since a single catalyst operates multiple reactions within different catalytic cycles, but subsequent reactions are triggered by the addition of reagents or changes in reaction conditions. *Choudhury & co-workers* reported a Ru(II)-complex, which can adopt two different states for different catalytic functions: the first state for dehydrogenative coupling of amines and, upon addition of a base, the Ru-catalyst adapts the second state, which undergoes hydrogenation of the imine intermediate in the presence of hydrogen (Scheme 1.22). [135]

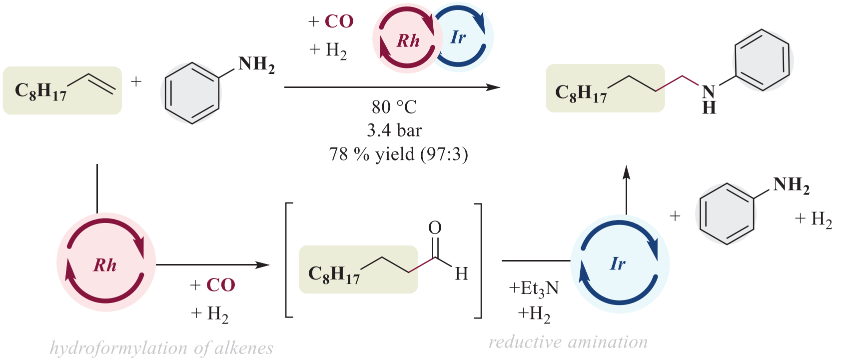


Scheme 1.22. Different modes of activation of the same Ru as an example of assisted-relay catalysis.

- *ORTHOGONAL RELAY CATALYSIS*

This is a type of catalysis where both, the catalysts and the other reagents involved, must be present at the start of the reaction. Each catalyst is designed to undergo a selective reaction sequentially, i.e. as soon as the product of one catalytic cycle is generated, it is transformed by the new catalytic cycle independently. One of the main challenges is the prospective incompatibility of the catalysts leading to inhibition of the catalytic activity.

In that context, *Hartwig & co-workers* reported an orthogonal relay protocol for hydroaminomethylation of alkenes, which connects Rh-catalysed hydroformylation of alkenes with *in situ* Ir catalysed reductive amination of aldehyde intermediates to form amines (see Scheme 1.23).[136] Although the approach requires two precious metal catalysts, the full sequence occurs under milder conditions (80 °C, 3.4 bar) with superior regioselectivity and a broader functional group tolerance when compared with the sequence in the presence of a single catalyst.

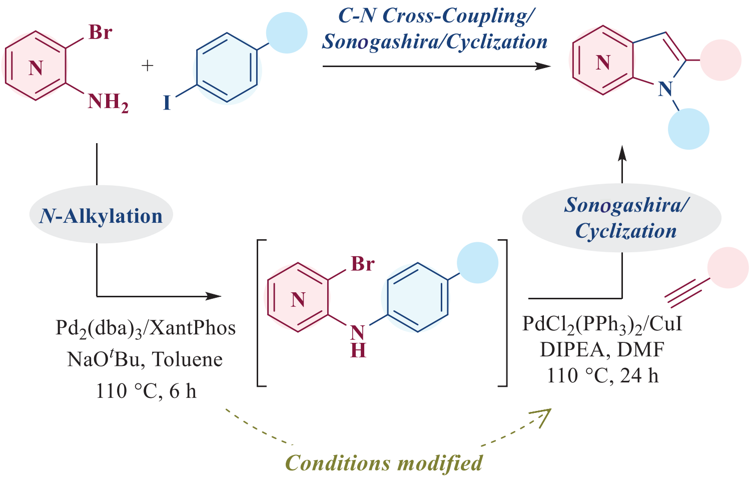


Scheme 1.23. Rh-Ir catalytic cycles involving hydroformylation/reductive amination reactions as an example of orthogonal relay catalysis.

- *SEQUENTIAL CATALYSIS*

In this scenario, the catalytic transformations are carried out by adding the catalysts or reagents for each step sequentially, i.e. the reagents for the next catalytic process are only added when the previous one is considered completed. Under this premise, it remains a one-pot reaction in which there is no need for isolation and purification of intermediates. This approach simplifies the way to deal with the problems of compatibility between catalysts and reagents, optimisation of conditions for each step, or synchronisation of reactions in the sequence.

For instance, *M.M.B. Marques & co-workers* reported a dual-catalytic palladium system for *N*-functionalized azaindole formation, in which two Pd catalysts are added sequentially, and the conditions are adapted for each step (see Scheme 1.24).[137]

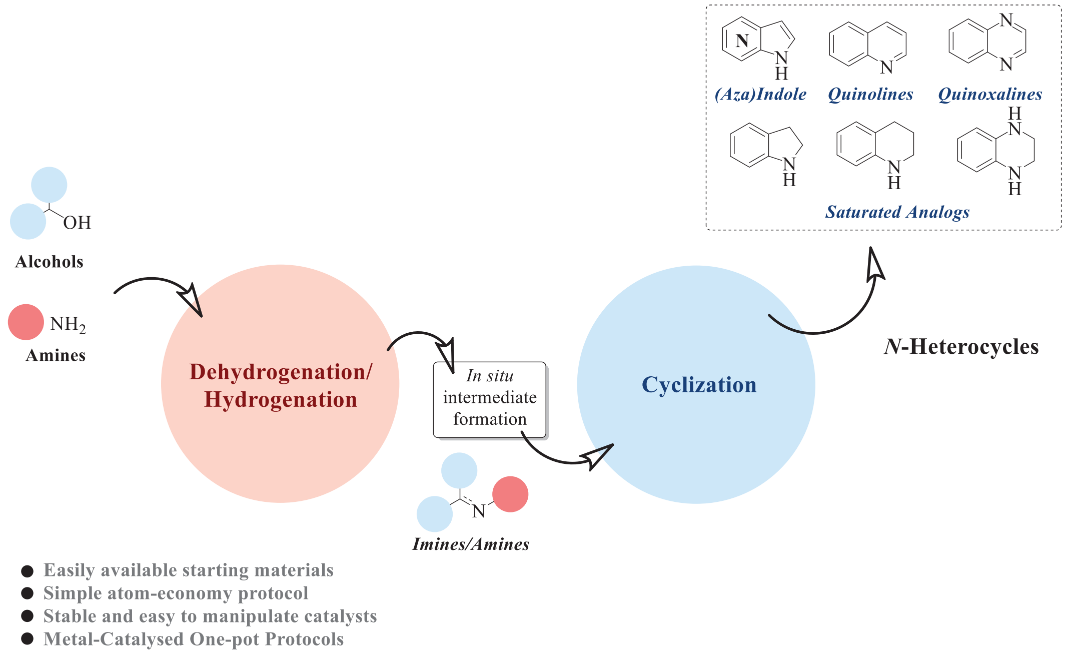


Scheme 1.24. A sequential-relay catalysis with modification of reaction conditions, involving *one-pot* *N*-Arylation/Sonogashira/Cyclization reaction from amino-*o*-bromopyridines.

1.5. Objective of the Thesis

The aim of this research is to develop and optimise metal-catalysed dehydrogenative coupling methodologies for the formation of key intermediates, such as imines, from readily available alcohols and amines. In addition, the potential of these methodologies in multi-catalytic strategies, particularly involving palladium-catalysed cyclization steps, will be explored towards the synthesis of *N*-heterocyclic compounds. Furthermore, the potential of 'borrowing hydrogen' reactions as a complementary technique for the direct formation of these *N*-heterocycles will also be investigated.

The development of these new catalytic synthetic routes aims to provide efficient and sustainable methods, maximising atom economy and minimising waste production, while expanding the synthetic possibilities using commonly available alcohol precursors and innovative multi-catalytic strategies in *N*-heterocycle synthesis.



SPECIFIC OBJECTIVES:

1. Develop and optimise a catalytic methodology to synthesise imines from primary alcohols and amines, using catalysts that are easily synthesised and functionalised, as well as stable under reaction conditions.
2. Expand the use of this methodology to more complex substrates, such as secondary alcohols, to generate imines that serve as precursors for the synthesis of *N*-heterocyclic compounds, employing multi-catalytic strategies with palladium.
3. Investigate the selective formation of secondary amines through the "borrowing hydrogen" strategy, evaluating its applicability both in the direct synthesis of saturated *N*-heterocycles and in multi-catalytic routes.

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2.

Manganese-Catalysed Synthesis of Imines from Primary Alcohols

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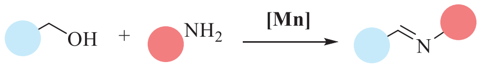
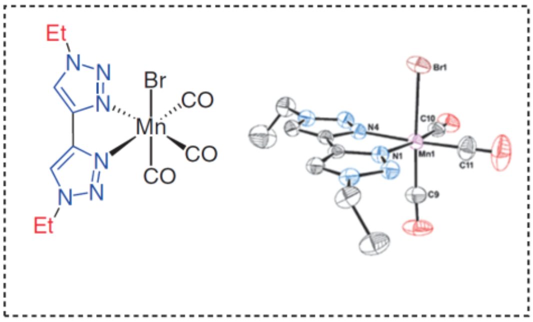
2.1 Summary



- 28 examples
- up to 99% yield
- Anilines and *N*-Heterocyclic amines
- Compatible with EWG and EDG



This Chapter describes the work developed to address the synthesis of imines from alcohols and amines, catalysed by Mn complexes. The conditions required for the formation of imines were explored by coupling alcohols and (hetero)aromatic amines through a simple and mild protocol, based on using air as the only oxidising agent. The synthetic approach employed Mn complexes bearing triazole *N^N* ligands as catalysts, which allows the preparation of a wide range of imines in excellent yields (up to 99%). In addition, the Mn-based catalysts were highly efficient and versatile, allowing for the first time the preparation of those imines containing *N*-containing heterocycles.

2.2 Introduction

Significant progress has been devoted to the synthesis of imines focused on the development of sustainable and simple protocols.[2,3] Approaches, using easily accessible starting materials, have emerged as promising in synthetic chemistry.[4,5] Particularly, the direct coupling of alcohols and amines have gained particular importance, as alcohols are cost-effective, readily available molecules, and their catalytic oxidation has been widely covered.[6,7] Moreover, carrying out one-pot alcohol-oxidation/imine-formation steps without changing the reaction conditions avoids problems during isolation, reduces energy consumption, and minimises waste. A promising strategy for the catalytic oxidation of alcohols involves the use of aerobic systems as green oxidants (O_2/air), instead of expensive and unwieldy oxidant additives, while simplifying the reaction setup.[8,9] However, one concern is that the use of mild oxidants, such as air, can lead to the formation of by-products.[10] Therefore, the development of appropriate metal catalysts and the careful optimisation of reaction conditions becomes crucial.

Major advances have been made in the field of organometallic chemistry, particularly in organometallic complexes containing phosphines.[11] Unfortunately, the use of these well-known phosphine catalysts is not always suitable for aerobic systems, since some phosphines are air-sensitive and difficult to prepare, particularly in large-scale synthesis.[12] Therefore, exploring phosphine-free ligand systems would be highly convenient. Furthermore, the development of economical, easy-to-prepare and versatile ligand catalytic systems, would have a significant impact both in academia and industry.

The substitution of phosphine ligands is not the only concern, as the choice of metal is also an important factor in modern catalysis. So far, several studies have focused on implementing alternative metallic systems to catalyse the aerobic synthesis of imines from alcohols and amines.[8] While amine-alcohol coupling chemistry has traditionally relied on precious metals like ruthenium or iridium,[13] and osmium,[14] there is now significant interest in substituting these with more abundant 3*d* options such as Mn, Fe, Co, and Ni.[15] These elements are attractive due to their low cost, availability, comparatively low toxicity, and greater sustainability.[16] Actually, earth-abundant metals have already been used in the preparation of imines, in particular, some manganese-based catalysts have been reported.[17–21] In addition, manganese (Mn) is a highly attractive option due to its abundance, representing the third most common element,[22,23] being an economical, non-toxic, and environmentally friendly option.

The organometallic chemistry of manganese began to grow rapidly in the late 1970s, and Mn sigma complexes soon became valuable tools for organic synthesis.[24] Recently, manganese catalysis has attracted intense research efforts, as evidenced by both the increasing number of publications in the literature and its growing impact on the field of catalysis. To date, commercially available and air-stable $Mn(CO)_5Br$ remains the most popular manganese(I) precursor due to its accessibility, which can be used directly in catalysis[25] or exploited for the synthesis of various Mn(I) pre-catalysts.[26,27]

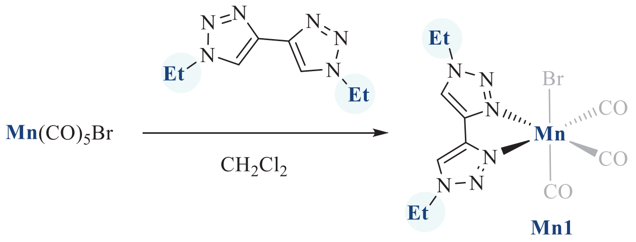
In the present study, we investigated an aerobic method for synthesising different imines by direct reaction of alcohols and (hetero)aromatic amines using newly developed Mn complexes with a synthesised phosphine-free *N^N* triazole ligand system. This Mn complex can be easily prepared from an $Mn(CO)_5Br$ precursor and the suitable triazole ligand obtained through simple click chemistry.

2.3 Results & Discussion

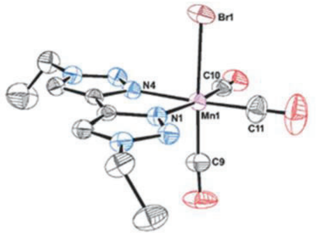
2.3.1 Synthesis & Characterization of Mn1

Mn(I) complexes with bis-triazole ligands were chosen due to their easy synthesis, stability, and ability to modulate metal reactivity. This catalyst is based on ligands accessible by 1,3-cycloadditions (click chemistry), which provides a straightforward synthesis.

A) Preparation of Mn-complex **Mn1**



B) ORTEP-3 diagram of Mn-complex **Mn1**



Scheme 2.1. A) Synthesis of complex 1; **B)** ORTEP-3 diagram of complex **Mn1** (molecule 1), using 30% probability ellipsoids. All hydrogen atoms were omitted for clarity. Selected bond lengths: Mn1–N1 2.042(3) Å, Mn1–N4 2.025(3) Å, Mn1–Br1 2.5455(6) Å, Mn1–C9 1.795(4) Å, Mn1– C10 1.807(4) Å, Mn1–C11 1.796(5) Å.

The manganese complex **Mn1** was prepared by direct reaction of $Mn(CO)_5Br$ with the corresponding triazole ligand as depicted in Scheme 2.1.[28]

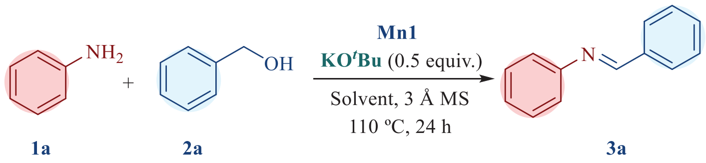
Mn(I) complexes with bis-triazole ligands were selected for their easy synthesis, stability, and ability to influence metal reactivity. These ligands, accessible through 1,3-cycloadditions (click chemistry), allow for a straightforward synthesis. With weak σ-donating and π-accepting properties, the ligands proved catalytically active in our dehydrogenation reactions. Additionally, CO co-ligands not only stabilize the complexes but also serve as effective spectroscopic probes, providing valuable electronic insights via IR spectroscopy. Ethyl groups were chosen because the complexes were stable, easy to handle, and accessible through readily available precursors like ethyl azide (EtN_3).

Additionally, the identity of **Mn1** was established by NMR, IR spectroscopy, elemental analysis, and X-ray diffraction studies. According to the IR and ^{13}C NMR spectra, the MnI center is facially coordinated by three CO ligands. Single-crystal X-ray diffraction analyses showed the octahedral structure of Mn**1** with Mn–N bond lengths of 2.042(3) and 2.025(3) Å, in accordance with previously reported complexes.[29]

2.3.2 Optimization of Reaction Conditions

Initially, the catalytic activity of **Mn1** was investigated using aniline **1a** and benzyl alcohol **2a** as the model substrates. The reaction was performed in toluene at 110 °C in the presence of a base (KO^tBu, 0.5 equiv.) and 3 mol% of **Mn1**, and leaving the reaction for 24 h. Under these conditions, the corresponding imine **3a** was obtained in a 94% yield (Table 2.1, entry 1), and was isolated by direct crystallization on toluene, providing 90% of isolated yield. Subsequently, we proceeded with the optimization of the reaction conditions.

Table 2.1. Optimization of the reaction conditions.[a]



Entry	**Cat.** (mol %)	**Solvent**	**Temp** (°C)	**Yield**[b] (%)
1	3	Toluene	110	94 (90)
2	3	MeCN	82	23
3	3	Dioxane	101	7
4	3	Toluene	50	7
5	1.5	Toluene	110	89
6[c]	3	Toluene	110	99

[a] **Reaction conditions:** aniline **1a** (0.3 mmol), benzyl alcohol **2a** (0.4 mmol), Mn catalyst **Mn1**, KO^{t}Bu (0.5 equiv.), and dry solvent (1.7 mL). [b] The yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard; [c] Addition of 260 mg 3 Å MS.

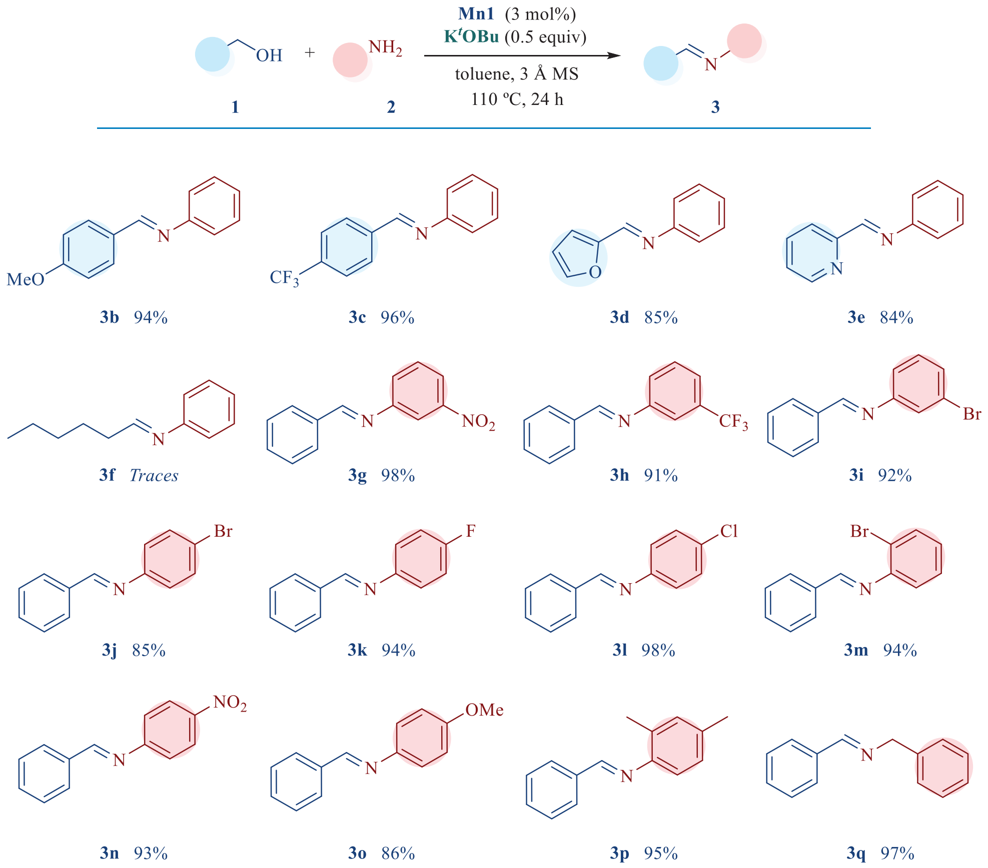
When the catalytic reaction was performed in 1,4-dioxane or acetonitrile, lower yields than those found in toluene were obtained (Table 2.1, entries 2 and 3). In addition, the temperature played an important role; when the reaction was carried at 50 °C, the yield of imine dropped drastically to 7% (Table 2.1, entry 4). Catalyst loading was also investigated. Reduction of the catalyst amount to 1.5 mmol, produced only a slight decrease of the activity (89% yield vs 99%, Table 2.1, entry 5). Interestingly, it was observed that the presence of molecular sieves (3 Å MS) and the use of dry toluene allowed to increase the yield of the imine to >99% (Table 2.1, entry 6). Noteworthy, monitoring the course of the reaction showed that the formation of the imine was completed in 3 h (Section A2.3 - Table A2.2, annexes).

2.3.3 Reaction Scope

With the optimised conditions, we proceeded with the study of the reaction scope. A variety of primary alcohols were reacted with aniline **1a**, substituted aniline **2,** and benzylamine (see Table 2.2). Aniline **1a** reacted with *p*-methoxy or *p*-CF_3 benzyl alcohol to afford imines **3b** and **3c**, respectively, in almost quantitative yield (96%). These results demonstrate that both electron withdrawing and electron donating groups at the benzyl alcohol are compatible, and do not influence the outcome of the reaction.

The reaction of **1a** with furfuryl alcohol afforded the imine **3d** in high yield (81%) In addition, pyridine-2yl methanol afforded imine **3e** in 84%. Unfortunately, the use of alkyl alcohols such as *n*-hexanol proved to be challenging, and imine **3f** was detected in only trace amount.

Table 2.2. Scope of the reaction of aniline, substituted anilines, and benzylamine with primary alcohols using Mn complex **Mn1**.[a]

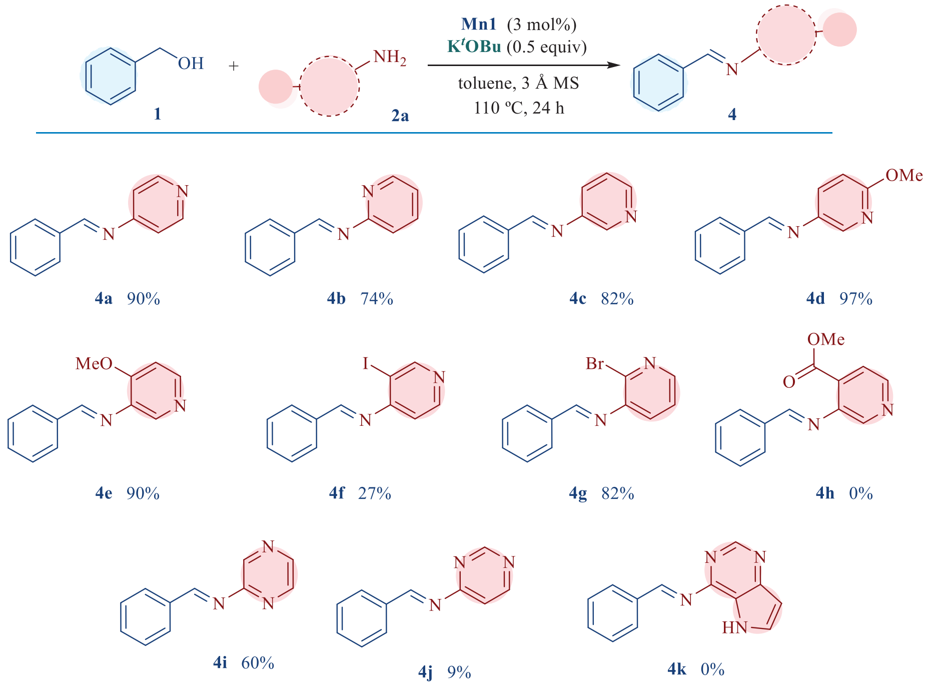


[a]**Reaction conditions:** amine **1** (0.3 mmol), alcohol **2** (0.4 mmol), Mn catalyst **Mn1** (3 mol%), KO^tBu (0.5 equiv.), 260 mg 3 Å MS, and dry solvent (1.7 mL). [b] The yield was determined by ^1H NMR using 1,3,5- trimethoxybenzene as an internal standard.

No reaction was observed using secondary alcohols, which represents a limitation of our catalytic system. Next, several aniline derivatives bearing electron-withdrawing groups, such as nitro, bromine, and trifluoromethyl groups, as well as electron-donating groups, such as methoxy and methyl groups were reacted with benzyl alcohol to afford excellent yields of the corresponding imines **3g**-3**q**. Interestingly, the formation of the imine **3g** bearing a *m*-nitro group was obtained in 68% using complex **Mn1** as the catalyst. When 2,4-dimethylaniline was used as substrate in the presence of **Mn1**, imine **3p** was obtained in 95% yield. In addition, the use of benzylamine allowed the formation of the desired imine **3q** in 94%.

Due to their electronic properties and basicity, *N*-heterocyclic amines are challenging scaffolds in oxidative coupling reactions.[30] Imines from *N*-heterocyclic amines are key intermediates in organic synthesis, although less explored than imines obtained from aromatic amines. Thus, we were interested in exploring the activity of **Mn1** in the preparation of *N*-heterocyclic-derived imines (Table 2.3). Benzyl alcohol **2a** was used as a model substrate and reacted with several *N*-heterocyclic amines.

Table 2.3. Scope of the reaction of heteroaromatic amines with benzyl alcohol using **Mn1** complex.



4a 90% **4b** 74% **4c** 82% **4d** 97%

4e 90% **4f** 27% **4g** 82% **4h** 0%

4i 60% **4j** 9% **4k** 0%

[a]**Reaction conditions:** amine **1** (0.3 mmol), alcohol **2** (0.4 mmol), Mn catalyst **Mn1** (3 mol%), KO^{t}Bu (0.5 equiv.), 260 mg 3 Å MS, and dry solvent (1.7 mL). [b] The yield was determined by ^{1}H NMR using 1,3,5- trimethoxybenzene as an internal standard.

Gratifyingly, aminopyridines reacted with benzyl alcohol **2a** to furnish the corresponding imines **4a-c** in high yields (up to 90%). The different yields are a consequence of the different reactivity of each aminopyridine.[30] The different position of the endocyclic nitrogen proved to be a key aspect in this reaction (**4a-c**), higher yield was observed for 4-aminopyridine, in which the endocyclic nitrogen is more distant from the amino group (*para*-position) (**4a**, 90%), while lower yield was obtained when 2-aminopyridine was used (**4b**, 74%). Reaction of benzyl alcohol with aminopyridines bearing electron-donating groups, afforded imines **4d** and **4e** in high yields.

2.4 Concluding Remarks and Challenges

In conclusion, simple phosphine-free Mn-triazole-based catalytic systems resulted in a highly efficient preparation of a large variety of imines through oxidative coupling of anilines and primary alcohols (yields up to 99%). The challenging *N*-heterocyclic amines also afforded the corresponding imines with moderate to high yields (up to 97% yield). For the first time, pyrimidine-2-amine and benzyl alcohol afforded the corresponding imine. Additionally, functionalized aminopyridines afforded the corresponding and difficult-to-prepare imines, opening room for further application of these intermediates in the synthesis of organic compounds.

Despite the positive results, certain limitations were observed under the catalytic conditions used, particularly with inactivated aliphatic and secondary alcohols - a problem that has been well documented in previous studies.[31] Although the use of secondary alcohols in the synthesis of complex *N*-heterocycles is a promising strategy, it remains largely unexplored.

Overcoming the challenges associated with the generation of imines from these alcohols could significantly expand the scope of these reactions. Given the lack of research in this area and the inherent difficulties in converting secondary alcohols to imines, the development of effective catalytic methods is essential.

2.5 Experimental Procedures

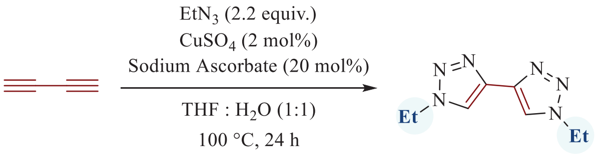
2.5.1 General Considerations

All reactions and manipulations were performed under air except when other conditions are indicated. Solvents were purified from appropriated drying agents and distilled using typical methods. All reagents were purchased from commercial suppliers and used without further purification. Analytical TLC was performed on Merck Kieselgel GF 254, 0.2 mm plates supported on aluminum with the described eluent for each case. ^{1}H and ^{13}C-NMR spectra were acquired with Bruker ARX 400 or Bruker Avance III 400 spectrometers at NOVA School of Science and Technology and ITQB NOVA. ^{1}H-NMR and ^{13}C-NMR spectra were measured at 400 and 101 MHz, respectively. The samples were prepared on 5 or 3 mm NMR tubes using $CDCl_3$ and the corresponding trace $CHCl_3$ as reference signals. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R-H) and relative intensity of signal multiplicity (nH, with n being the number of protons) of NMR signals are described as singlet (s), broad singlet (br s), doublet of doublets (dd), triplet of doublets (td), doublet (d), triplet (t) and multiplet (m) with coupling constant (*J*) being given in Hz. Electrospray mass spectra (ESI-MS) were recorded with a Micromass Quatro LC instrument; nitrogen was employed as a drying and nebulizing gas. Elemental analysis was performed in the laboratories at ITQB. The di-triazole ligand was prepared according to previously described procedures.[28]

2.5.2 Procedure for the preparation of complex Mn1

2.5.2.1 Preparation of di-triazole ligand

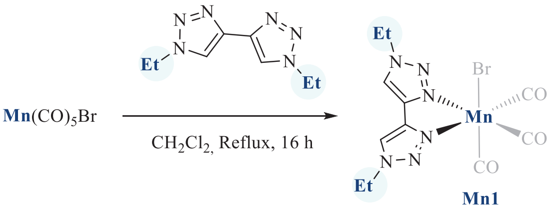
The C,C′-linked di-triazoles were synthesised in good to excellent yields (71–95%) via the ‘click’ cycloaddition of the commercially available diyne, and the corresponding azide, (Scheme 2.2).[28]



Scheme 2.2. 1,3 dipolar cycloaddition (click chemistry) towards the formation of the di-triazole ligand.

A mixture of the corresponding diyne (1 mol equiv.), azide (2.2 mol equiv.), $CuSO_4$ (2 mol%) and sodium ascorbate (20 mol%) in a 1: 1 mixture of THF : H_2O was carried out at 100 °C for 24 h. The THF was removed under reduced pressure and the organics were extracted with CH_2Cl_2 (2 × 50 mL). The combined organics were washed with dilute $(NH_4)(OH)$ (aq., 50 mL), water (2 × 50 mL) and saturated NaCl solution (aq. 1 × 40 mL), dried over anhydrous Na_2SO_4, filtered and all volatiles removed under reduced pressure yielding the di-triazole product as a white solid. Yield: 71 – 95%. ^{1}H-NMR (400 MHz, $CDCl_3$, 298 K) δ: 8.03 (s, 2H, Htrz), 4.45 (q, *J*= 7.2 Hz, 4H), 1.58 (t, J= 7.3Hz, 6H). ^{13}C{1H} NMR ($CDCl_3$, 100 MHz) δ: 140.2 (Ctrz), 120.0 (CtrzH), 45.6 (NCH_2), 15.6 (NCH_2CH_3).

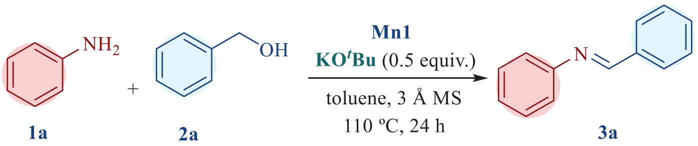
2.5.2.2 Preparation of complex Mn1



Scheme 2.3. Synthesis of the **Mn1** complex from bis-triazole ligand and Mn penta-carbonyl precursor.

Solid $MnBr(CO)_5$ (236 mg, 0.86 mmol) and di-triazole ligand (150 mg, 0.78 mmol) were dissolved in dry CH_2Cl_2 (15 mL) and the mixture was stirred at reflux during 16 h under nitrogen atmosphere. After cooling to room temperature, the solvent was removed under vacuum, and the remaining solid washed several times with ether to yield **Mn1** as a crystalline solid. Yield: 193 mg (60%). ^1H-NMR (400 MHz, DMSO-d$_6$, 298 K) δ: 8.80 (s, 2H, CH_{trz}), 4.63 (q, J = 6.8 Hz, 4H, NCH_2CH$_3$), 1.54 (t, J = 7.0 Hz, 6H, NCH$_2$CH_3). ^{13}C NMR (100 MHz, DMSO-d$_6$) δ: 222.9 (CO), 221.2 (CO), 138.6, 121.8, 46.6 (NCH$_2$CH$_3$), 14.8 (NCH$_2$CH$_3$). IR (ν, cm^{-1}): 2034 (vs), 1964 (vs), 1924 (vs). Anal. Found: C, 32.43; H, 2.80; N, 20.01. Calcd. for $C_{11}H_{12}BrMnN_6O_3$ (411.09): C, 32.14; H, 2.94; N, 20.44.

2.5.3 General procedure for the synthesis of the imine 3a



Scheme 2.4. Model reaction for the synthesis of *N*-benzylideneaniline **3a**.

The reaction of aniline **1a** (28 mg, 0.3 mmol) with benzyl alcohol **2a** (37 µL, 0.36 mmol) was carried out in dry toluene (1.7 mL) in a flask (10 mL) attached to a reflux system, in the presence of 0.5 equiv. of KO^{t}Bu (17 mg, 0.15 mmol), 3 mol% of **Mn1** (0.03 mmol, with respect to aniline **1a**), and 260 mg of molecular sieves 3Å. The reaction was stirred at 110 °C in an oil bath for 24 h. After cooling, the reaction mixture was filtered over celite, and all the volatiles were removed under vacuum. The isolated crude was dissolved in chloroform-*d* and the yield of imine **3a** was determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard (27 mg, 0.16 mmol). Moreover, possible crystallization of compound **3a** was possible in toluene at room temperature overnight. Yield after crystallization (90%) of imine **3a** (white solid); ^1H-NMR (500 MHz, CDCl$_3$): δ 8.47 (s, 1H), 7.94 – 7.92 (m, 2H), 7.49 (m, 3H), 7.40 (t, J = 7.8 Hz, 2H), 7.23 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 160.5, 152.2, 136.3, 131.5, 129.3, 128.9, 128.9, 126.0, 121.0.

The ^1H-NMR data of the imines obtained follows below:

(^{1}H NMR data were in agreement with what was previously reported)

Imine **3b** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.86 (d, J = 8.7 Hz, 2H), 7.39 (t, J = 7.9 Hz, 2H), 7.20 (m, 3H), 6.99 (d, J = 8.8 Hz, 2H), 3.89 (s, 3H).

Imine **3c** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.03 (d, J = 8.34Hz, 2H), 7.74 (d, J = 8.1 Hz, 2H), 7.46 – 7.40 (m, 2H), 7.32 – 7.22 (m, 3H).

Imine **3d** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.61–7.60 (m, 1H), 7.40–7.36 (m, 2H), 7.25–7.21 (m, 3H), 6.95 (d, J=3.5 Hz, 1H), 6.55 (d, J=3.4 Hz, 1H).

Imine **3e** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.75-8.69 (m, 1H), 8.60 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 7.7 Hz, 1H), 7.46-7.35 (m, 3H), 7.34-7.24 (m, 3H).

Imine **3g** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.09 (d, J = 7.4 Hz, 1H), 8.04 (s, 1H), 7.95 – 7.91 (m, 2H), 7.57 – 7.50 (m, 6H).

Imine **3h** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.94 – 7.88 (m, 2H), 7.56 – 7.48 (m, 5H), 7.48 – 7.45 (m, 1H), 7.40 – 7.35 (m, 1H).

Imine **3i** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.90 (d, J = 7.6 Hz, 2H), 7.55-7.45 (m, 3H), 7.40-7.33 (m, 2H), 7.30-7.22 (m, 1H), 7.14 (d, 1H).

Imine **3j** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.90 (d, J = 7.8 Hz, 2H), 7.53-7.48 (t, 5H), 7.09 (d, J = 8.2 Hz, 2H).

Imine **3k** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.92–7.90 (m, 2H), 7.50–7.48 (m, 3H), 7.26–7.20 (m, 2H), 7.09 (t, *J*=8.6 Hz, 2H).

Imine **3l** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.90 (m, 2H), 7.48 (m, 2H), 7.35 (m, 2H), 7.15 (m, 2H).

Imine **3m** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 (s,1H), 8.00 – 7.93 (m, 2H), 7.64 (d, J = 8.0, 1H), 7.55 – 7.44 (m, 3H), 7.33 (t, J = 7.6, 1H), 7.00 – 7.12 (m, 2H).

Imine **3n** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.29 (d, 2H), 7.96-7.90 (m, 2H), 7.58 – 7.40 (m, 3H), 7.25(d, 2H).

Imine **3o** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.93 – 7.86 (m, 2H), 7.50 – 7.42 (m, 3H), 7.26 – 7.20 (m, 2H), 6.96 – 6.93 (m, 2H), 3.84 (s, 3H).

Imine **3p** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H),7.92 (m, 2H), 7.49 (m, 3H), 7.07–7.03 (m, 2H), 6.86 (d,J= 9 Hz, 1H), 2.35 (s, 3H),2.34 (s, 3H).

Imine **3q** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.80 (m, 2H), 7.44-7.24 (m, 8H), 4.84 (s, 2H).

Imine **4a** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J= 4.5, 1.6 Hz, 2H), 8.38 (s, 1H), 7.92-7.89 (m, 2H), 7.51 (m, 3H), 7.0 (dd, J= 4.5, 1.6 Hz, 2H).

Imine **4b** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.50-8.49 (d, 1H), 8.00-7.99 (d, 2H), 7.78-7.75 (t, 1H), 7.53-7.47 (m, 3H), 7.45-7.42 (t, 1H), 7.34-7.33 (d, 1H).

Imine **4c** ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49-8.40 (m, 3H), 7.91 (m, 2H), 7.55-7.49 (m, 4H), 7.37-7.26 (m, 1H).

2.6 Acknowledgments

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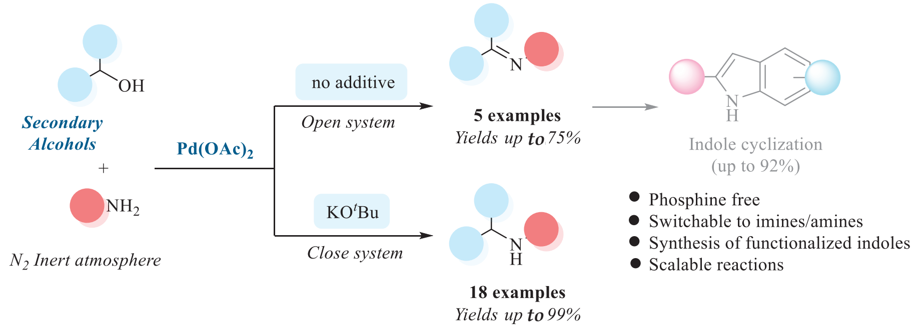
3.

Pd-Catalysed Access to Imines & Amines from Secondary Alcohols

This chapter has been published in Raydan, D., Royo, B., & Marques, M. M. B. (2023). Pd-Catalyzed Switchable Access to Imines and Amines from Secondary Alcohols. *Asian Journal of Organic Chemistry*, e202300282.[1]

3.1 Summary



This Chapter describes the investigation of commercial $Pd(OAc)_2$ as a catalyst for the challenging synthesis of imines through acceptorless alcohol dehydrogenation using secondary alcohols and amines. The reaction required low catalyst loading, showed high selectivity for the formation of the imine without the need of adding any base or additive, and can be scaled up. Moreover, to highlight the practical utility of the imine synthesis, a family of a structurally important scaffold, indole, was synthesized.

Interestingly, when the catalytic reaction was performed in a closed system, in the presence of a base, the corresponding amine was selectively obtained, giving rise to a switchable methodology for the formation of imines or amines at convenience.

4.2 Introduction

The development of new catalytic routes for the synthesis of nitrogen-containing compounds is essential in modern organic chemistry.[2,3] These compounds, such as imines and amines, play a crucial role in a variety of synthetic and industrial applications. Imines, whose synthetic advantages were explored in detail in Chapter 1, are known for their role as important synthetic intermediates in the formation of nitrogen-containing compounds. On the other hand, amines, organic compounds containing a nitrogen atom attached to one or more alkyl or aryl groups, are central to pharma and chemical industry, from the production of dyes to the manufacture of herbicides and pharmaceuticals. Moreover, amines occur naturally in a wide range of compounds, including neurotransmitters such as dopamine and serotonin, as well as vital molecules such as amino acids, peptides, proteins, and alkaloids (see Figure 3.1).[2]

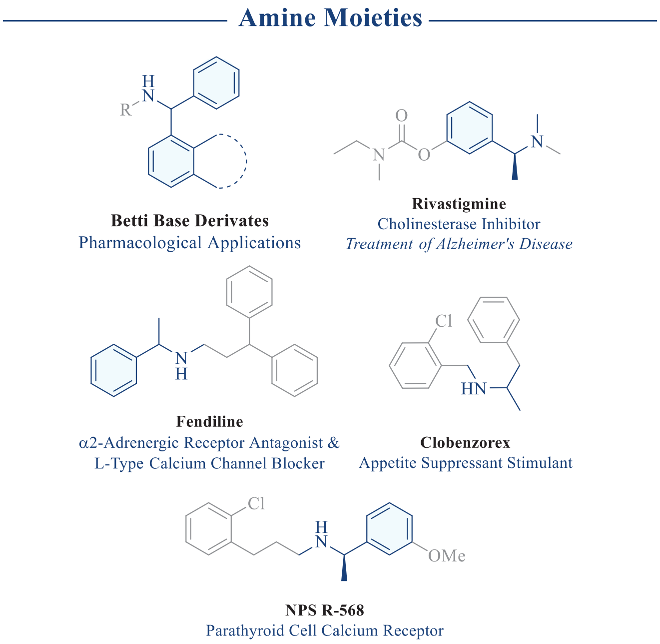
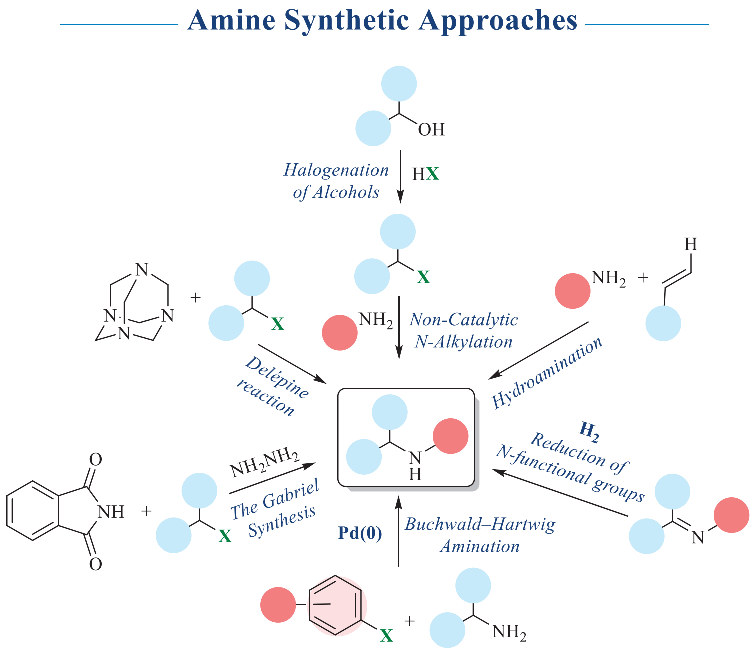


Figure 3.1. Pharmaceutically important *N*-alkylated compounds

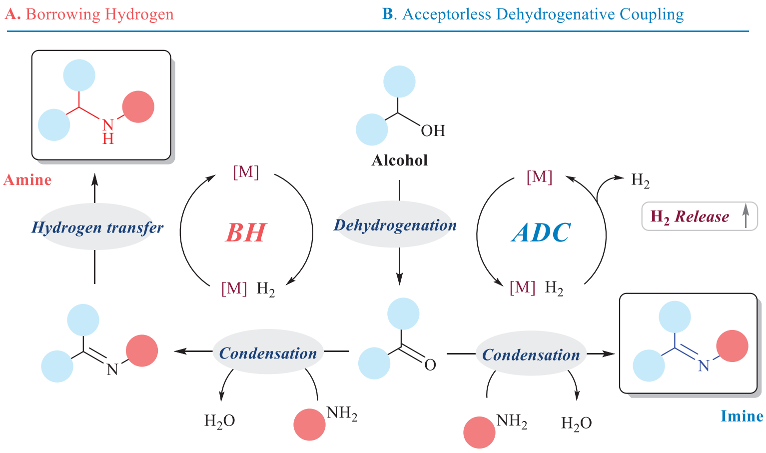
In the laboratory, the synthesis of imines is commonly performed by condensation of amines and aldehydes, as detailed in Chapter 1. On the other hand, the preparation of secondary amines also faces several challenges. Typically, their synthesis relies on direct alkylation with alkyl halides, which often results in overalkylation and generation of significant amount of waste.[4] Moreover, reduction of nitrogen-containing functional groups and hydroamination of alkenes can also face the challenges of overalkylation, harsh reactive conditions, and the need for expensive starting materials. As an alternative, some reactions such as the Delépine reaction or Gabriel synthesis can improve the selectivity of amine formation (see Scheme 3.1), but their industrial use is rare.[5,6]



Scheme 3.1. Alternative approaches to amine synthesis.

The metal-catalysed synthesis of amines has revolutionized the access to these scaffolds,[4] such as the Pd-catalysed Buchwald-Hartwig amination (see Scheme 3.1), which is used to synthesise arylamines.[7] However, many of these synthetic routes are specific to primary and/or aryl amines and may require stoichiometric additives and harsh reaction conditions, making them less efficient and applicable. Hence, there is a growing need to develop simple and efficient synthetic methodologies that can produce valuable nitrogen compounds from easily available starting materials. Alcohols can serve as a smart and sustainable alternative to amines since they are inexpensive, abundant, and environmentally friendly.[8]

In Chapter 2, we explored the used of alcohols to prepare *N*-compounds, such as imines, via an oxidative coupling. However, some catalytic systems can perform these transformations without the need of oxidizing agents, via Borrowing Hydrogen (BH, Scheme 3.2 A) and Acceptorless Dehydrogenative Coupling (ADC, Scheme 3.2 B) strategies (refer to Scheme 3.2).[9]



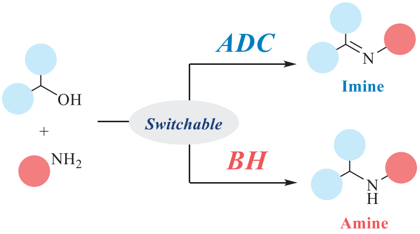
Scheme 3.2. General diagram showing the separation between a BH catalytic cycle (on the left) and an ADC catalytic cycle (on the right).

In both BH and ADC pathways, the first step involves dehydrogenation of an alcohol mediated by a metal catalyst to form a carbonyl intermediate. Subsequent reaction of the carbonyl with an amine by condensation reaction yields the corresponding imine. If the hydrogen abstracted from the starting alcohol is released from the system as hydrogen gas, then it is known as an ADC pathway, and imine is the final product. On the other hand, if the catalyst retains this hydrogen and uses it to reduce the intermediate species (the imine), then the process is named BH and the final product is the corresponding amine. In particular, the BH process has received significant attention, as it can be considered a *one-pot* dehydrogenation/hydrogenation reaction, avoiding the need for isolations or intermediate separations.[10] This process offers excellent opportunities for a wide variety of transformations by using cheap and harmless starting materials, reducing waste and by-products, and without the need for (flammable) hydrogen addition or pressurized systems. The reaction sequence results in no net oxidation or reduction.

The BH method offers numerous advantages compared to traditional alkylation techniques. For instance, it is a more efficient and less toxic option in comparison to the use of alkyl halides. Additionally, BH eliminates the need for stoichiometric oxidation and reduction steps required in various selective monoalkylation transformations, such as reductive amination. Moreover, BH eliminates the stoichiometric activation of alcohols as alkylating agents, a process seen in reactions like the Mitsunobu, or the self-alkylation of alcohols commonly found in Lewis or Brønsted acid-catalysed transformations. However, BH also has some limitations, such as the requirement for high temperatures, limited enantioselectively, and the usual need for precious metals.[11]

In the way to overcome the mentioned challenges, new catalytic systems to perform BH reactions have emerged to address the synthesis of complex molecules. Some of these alternative BH pathways take advantage of their "cascade interpretation", allowing precise manipulation of the reactive intermediates, either by interrupted borrowing hydrogen (IBH)[12] or by the addition of a second catalytic cycle that transforms the intermediates via an orthogonal multi-catalytic approach.[13]

The selective formation of imines or amines presents a major challenge due to the slightly difference in the activity of the catalysts for achieving ADC or BH pathways.[14] While recent reports have emphasized the importance of selectively targeting the synthesis of imines or amines by varying the reaction conditions, there still remains no general formula for imposing one pathway over the other, which makes selectivity a challenge (see Scheme 3.3).[14]



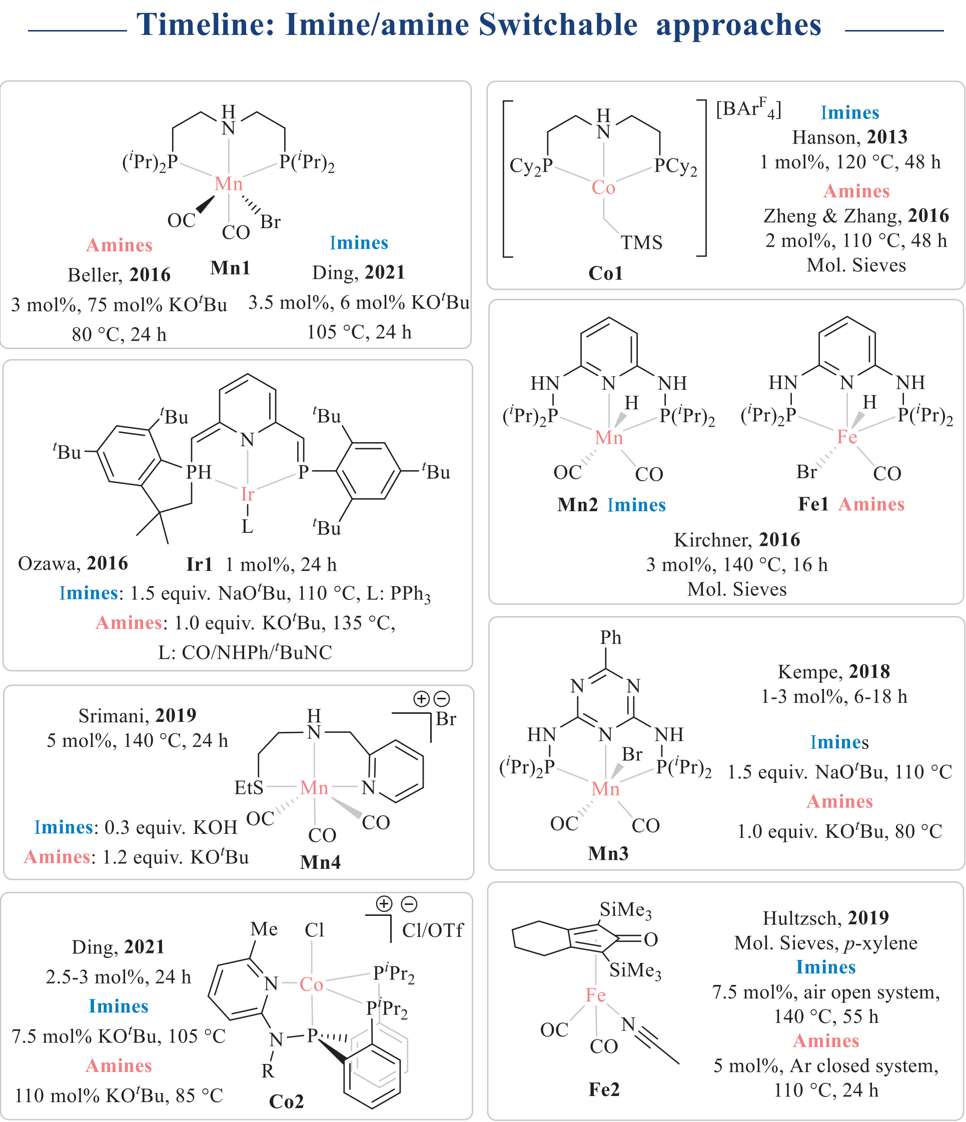
Scheme 3.3. General catalytic switchable approach towards the synthesis of BH and ADC products.

To gain a better understanding of the factors that affect the choice between BH and ADC approaches, Scheme 3.4 shows the impact of different catalysts and reaction conditions on the selectivity of the process. One important consideration is the use of molecular sieves. In 2013, *Hanson & co-workers* conducted the first synthesis of imines via Co-catalysed ADC (**Co1**).[15] Three years later, *Zheng, Zhang, & co-workers* studied the same **Co1** catalyst in the presence of molecular sieves, selectively generating amines through a BH pathway.[16] Although molecular sieves have been shown to drive the reaction selectively towards amines in some studies, other works have demonstrated their ability to promote imine formation, making their function unclear.[17] The choice of transition metals is another relevant factor in the selectivity between amines and imines, as described by *Kirchner & coworkers* with isoelectronic PNP Fe(II) (**Fe1**) and Mn(I) (**Mn2**) pincer complexes.[18]

However, the size of the reaction vessels and whether an open or closed system is used are also important parameters to consider. Research has shown that in open systems, the release of molecular hydrogen is facilitated, which can lead to stop at the imine product. Conversely, smaller vessels and/or closed systems tend to promote the hydrogenation reaction, leading to the corresponding amine via BH reaction.[15,16]

Kempe & co-workers evaluated the type of bases, particularly the type of counterions, through Mn-pincer catalysts **Mn3**. In their work they demonstrated the ability of the Mn complexes to yield imines or amines depending on the reaction conditions.[19] It is worth noting that when a closed system was used, amine was generated, while the open system facilitates the imine formation.[19]

Srivastava, Srimani, & co-workers later reported a similar strategy for amine/imine switching by changing the types of bases mediated by a phosphine-free Mn NNS pincer, **Mn4**. However, in this work, they also altered the base loads, using 30 mol% of KOH for imine formation and 1.2 equiv. of KO^{t}Bu for amine synthesis.[20] Moreover, *Ding & co-workers* examined the difference in base load and achieved amine/imine switchability using a Co catalyst, **Co2**.[21] They found that imine hydrogenation is significantly reduced with low KO^{t}Bu loads. Once again, closed and open systems were used for amine and imine formations, respectively. Another example where base loading played a crucial role was in the work of *Beller & co-workers*, who introduced the first Mn-catalysed amine formation, using **Mn1**, via BH using a high KO^{t}Bu load.[22]



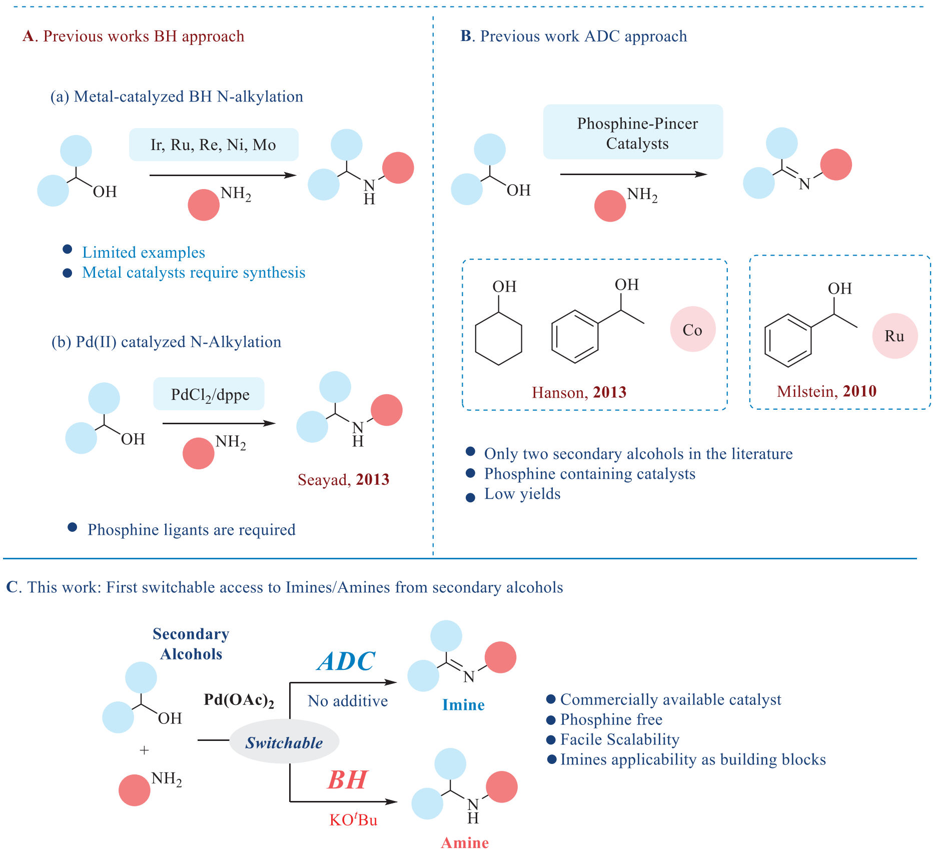
Scheme 3.4. Studies related to the phenomenon of amine/imine switchability.

In a related study, *Ding & co-workers* found that using the same **Mn1**, imines could be selectively formed in good yield using an open system by reducing the KO^{t}Bu load to 6 mol%.[23]

Previous studies have investigated the selectivity of imine/amine products by modifying the reaction conditions. *Hultzsch & co-workers* demonstrated that amine/imine switching can be achieved by quenching a **Fe2** catalyst in the presence of molecular oxygen, which inhibits the final hydrogenation step in the BH process.[24] Additionally, *Ozawa and coworkers* reported a case of amine/imine switching by changing the monodentate co-ligands in an

Ir complex, **Ir1**.[25] This switching between amines and imines has also been observed in more complex scaffolds, such as *N*-heterocyclic compounds,[26–28] showing the potential of this amine/imine selectivity towards the synthesis of more complex *N*-heterocyclic structures with saturated or unsaturated components.[29]

Despite remarkable advances in this field over the last decade, ADC and BH methodologies are generally developed using primary alcohols. The use of secondary alcohols, however, remains less common.[30] The majority of the catalytic systems capable of reacting with secondary alcohols afford the corresponding amines (via BH, Scheme 3.5A),[31–40] while synthesis of imines is limited to the use of cyclohexanol and 1-phenyl ethanol, using Co and Ru catalysts (via ADC, Scheme 3.5B).[41,42]



Scheme 3.5. Metal-catalysed BH (A) and ADC (B) with amines and secondary alcohols; previous works (A and B) and this work (C).

Additionally, the possibility of forming imines from the condensation of amines with secondary alcohols could give rise to synthetically relevant multi-catalytic scenarios.[43] Specifically, imines that coexist in equilibrium with their enamine counterparts may serve as ideal templates to promote cyclisations via catalytic cross-coupling routes, taking advantage of the well-known palladium (Pd) chemistry. Consequently, the cascade synthesis of *N*-heterocycles such as indoles, from secondary alcohols and amines, would offer a highly valuable one-pot synthetic approach.

In this work, we aimed to explore the use of a commercially available palladium $Pd(OAc)_2$ as a catalyst capable of promoting both ADC (imines) and BH (amines) processes with secondary alcohols. Intrigued by the reported reactivity of $Pd(OAc)_2$ in the synthesis of amino derivatives from primary alcohols,[44,45] we decided to further investigate its catalytic activity, not only in the formation of imines and secondary amines but also towards the formation of more complex indole templates in a cascade fashion.

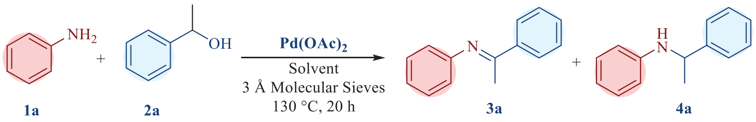
3.3 Results & Discussion

3.3.1 Optimization of Conditions Towards Imine Synthesis

We initiated our studies investigating the activity of $Pd(OAc)_2$ in a model reaction, using aniline **1a** and 1-phenylethanol **2a** as the model substrates (see Table 3.1). Satisfyingly, $Pd(OAc)_2$ (5 mol%) was capable of catalyzing this reaction to the selective formation of the imine **3a** in 66% yield when the reaction was performed in an open reflux system under nitrogen, without the addition of base, and in the presence of molecular sieves (Table 3.1, entry 1). If the reaction is performed with a lower amount of catalyst (1.5 mol% instead of 5mol%) or increasing the amount of alcohol (3 equivalents), the selectivity to the imine **3a** was poorer (Table 3.1, entries 1 and 2, respectively). In addition, increasing the catalyst loading to 10 mol% did not improve the yield of **3a**, on the contrary, produced a detrimental effect on the selectivity of the reaction; a mixture of 63% of imine **3a** and 13% of amine **4a** was obtained (Table 3.1, entry 4).

To increase the yield of **3a**, the reaction was left for longer reaction times (48 h), but unfortunately, instead of increasing the yield of **3a**, the selectivity of the reaction decreased (Table 3.1, entry 5). Likewise, the effect of other solvents such as *p*-xylene and DMF was explored, but no improvement in the yield or selectivity of the reaction was achieved (Table 3.1, entries 6 to 8). Thus, the optimized reaction conditions for the synthesis of **3a** were established using aniline **1a** and 1-phenylethanol **2a** (in a ratio 1:2, respectively), with 5 mol% of $Pd(OAc)_2$, in the presence of molecular sieves in toluene for 20 h under nitrogen atmosphere in an open reflux system.

Table 3.1. Optimization of the reaction conditions towards ADC with $Pd(OAc)_2$.[a]



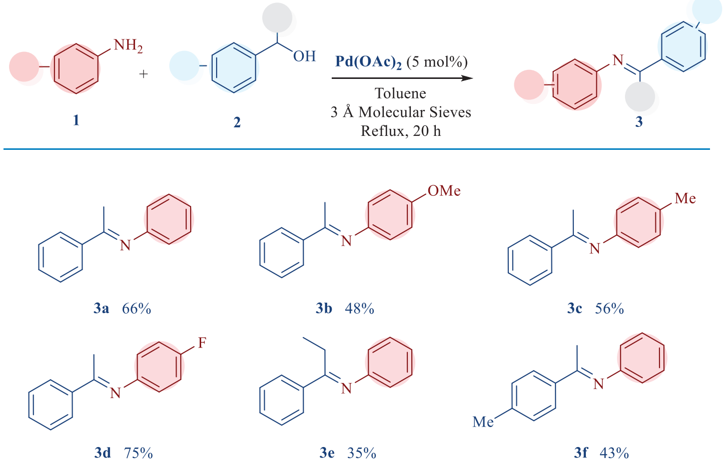
Entry	**Cat.** (mol %)	**Solvent**	**Yield**[b] **3a** (%)	**Yield**[b] **4a** (%)
1	5	Toluene	66	-
2	1.5	Toluene	57	28
3[c]	1.5	Toluene	55	35
4	10	Toluene	63	13
5[d]	5	Toluene	63	4
6	5	*p*-xylene	30	10
7[e]	5	*p*-xylene	42	39
8	5	DMF	30	10

[a] **Reaction conditions:** aniline **1a** (0.3 mmol), 1-phenyl ethanol **2a** (0.6 mmol), $Pd(OAc)_2$, 3 Å MS (1 g/mmol), Reflux, 20 h, using dry-degassed solvents (1.5 mL) under N_2 inert atmosphere in an open vessel. [b] The yield was determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Using 3 equivalents of alcohol. [d] Reaction time 48 h. [e] Reaction temperature 150 °C.

To demonstrate the utility of our catalytic system for the synthesis of imines, a scale-up experiment was performed using 10 mmol (930 mg) of aniline **1a** and 20 mmol of alcohol **2a** (2.4 g) under the optimized conditions. The pure imine **3a** was isolated by crystallization from hexane at 0 °C in 57% yield, without the need for purification by column chromatography.

A limited number of imines were synthesized by varying functionalized amines and secondary alcohols (see Table 3.2). The moderate yields indicate the involvement of these products in reversible reactions, where water sensitivity was crucial in enhancing the yields.

Table 3.2. Scope of the ADC reaction catalysed by $Pd(OAc)_2$ for imine formation.[a]

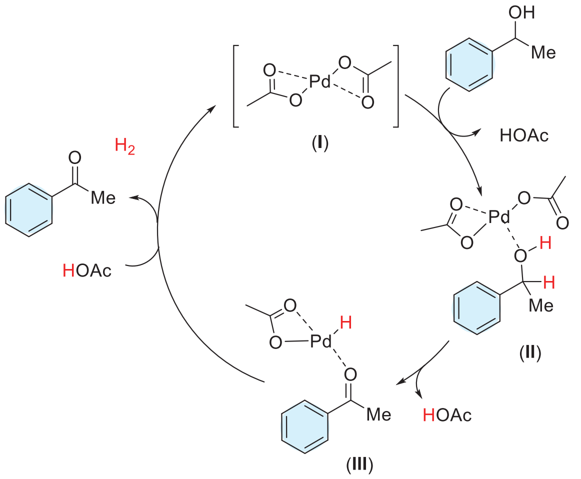


[a]**ADC Reaction conditions:** aniline (0.3 mmol), 1-phenyl ethanol (0.6 mmol), $Pd(OAc)_2$ (5 mol%), 3 Å MS (1 g/mmol), dry toluene (1.5 mL), reflux, 20 h, under N_2 inert atmosphere in an open vessel. The yields of the imine products were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

To obtain insight into the $Pd(OAc)_2$-catalysed formation of imines, we investigated the stochiometric reaction of $Pd(OAc)_2$ with 1-phenylethanol **2a**. The reaction was performed in a Young-tap NMR tube in deuterated benzene, and it was monitored by ^1H NMR spectroscopy. Formation of acetophenone (the dehydrogenated product) was observed when the NMR tube was immersed in an oil bath heated at 110°C. In addition, concomitant formation of acetic acid was detected in the ^1H NMR spectrum, indicating that initial activation of the catalysts occurs by protonation and release of the acetate ligand.

On the basis of these results, a possible catalytic cycle is proposed. As shown in Scheme 3.6, the alcohol coordinates to the Pd complex **I** to form the intermediate **II** upon β-hydride elimination. Next, a Pd-hydride (**III**) species is formed with the concomitant formation and releasing of acetic acid, which was detected by ^1H NMR

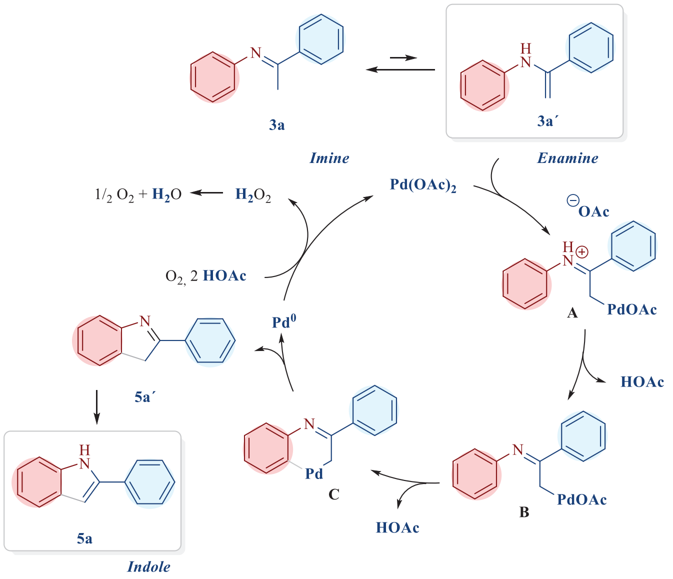
(Scheme 3.6). Finally, the ketone formed is released from the Pd complex **III**, generating **I** and releasing hydrogen.



Scheme 3.6. Proposed Catalytic Cycle for the Pd-Catalysed ADC of secondary alcohols.

3.3.2 Multi-catalytic Approach Towards Indole Synthesis

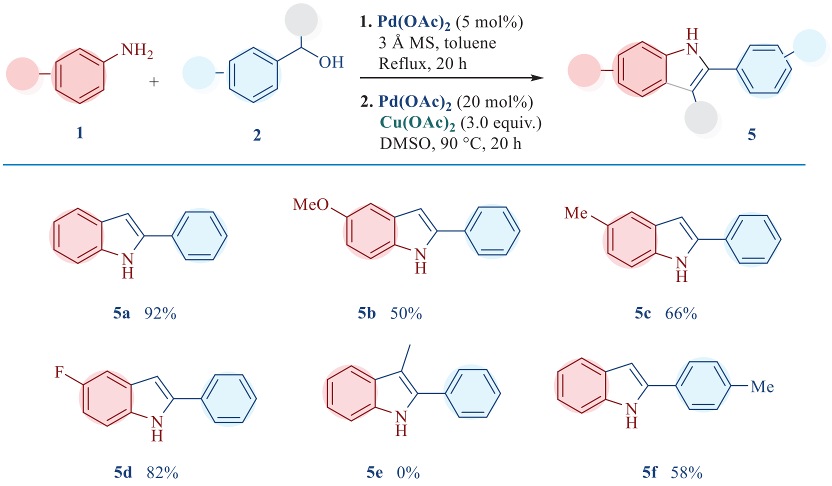
Motivated by the simplicity and selectivity of our protocol for imine formation (see Tables 3.1 and 3.2), we envisioned that the formed imines could be subsequently transformed into the corresponding indoles in an assisted-relay catalytic reaction (see Table 3.3). Recently, imine substrates have been shown to be valuable scaffolds for indole synthesis, as demonstrated by the groups of Xiao,[46] Zhang,[47] Tamariz.[48] and Yoshikai.[49] Interestingly, Yoshikai and co-workers have described a $Pd(OAc)_2$ catalysed oxidative cyclization reaction of *N*-aryl imines for the synthesis of indoles through the formation of an intermediate enamine (see Scheme 3.7).[49]



Scheme 3.7. Catalytic cycle proposed by Yoshikai *et al*. for the palladium-catalysed aerobic oxidative cyclization of *N*-aryl imines. The cycle involves a Pd(II)/Pd(0) redox process.

Inspired by this work, we explored the reaction of aniline **1a** with 1-phenyl ethanol **2a** for the formation of the imine **3a,** and the subsequent imine cyclization reaction for the formation of the corresponding indole **5a** (see Table 3.3).

Table 3.3. Scope of the multyctacalytic ADC/cyclization approach catalyzed by Pd(OAc)2 for indole formation.[a]



[a]**Aerobic oxidative cyclization reaction conditions:** new charge of Pd(OAc)2 (20 mol%), Cu(OAc)2 (0.9 mmol), dry DMSO (0.75 mL), 90 °C, 16 h, under N2 inert atmosphere in a close vessel. Indole-isolated yields are calculated with respect to aniline **1a** (two-step yields).

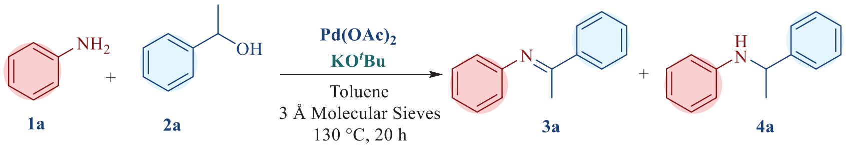
The imine cyclization reaction required the addition of $Cu(OAc)_2$ as an oxidizing agent, the increase of the Pd catalyst loading to 20 mol%, and the replacement of toluene by DMSO. The corresponding indole **5a** was obtained in 92% yield after 16 h at 90 °C. The use of DMSO for the indole formation step was crucial, as referred to in the work of Yoshikai *et al*.[49] Based on these results, we set out to evaluate a small library of functionalized imines and their subsequent cyclization to the corresponding indoles. The results are summarized in Table 3.3. Cyclization of the imines afforded the corresponding indoles in good to excellent yields (50-92%), except for the imine **3e**, probably due to steric hindrance posed by the methyl group that hampers ring-closing.

3.3.3 Optimization of Conditions Towards Amine Synthesis

Gratifyingly, when the reaction of aniline **1a** and 1-phenyl ethanol **2a** was performed in the presence of $Pd(OAc)_2$ (5 mol%) under the optimized conditions previously described, but in the presence of base (50 mol%) and in a closed vessel under nitrogen, the selectivity of the reaction shifted, and the amine **4a** was isolated as the major product in 65%, along with the corresponding imine in 13% yield (Table 3.4, entry 1). Increasing the amount of alcohol to two equivalents allowed us to obtain the corresponding *N*-alkylated amine **4a** selectively in 93% yield (Table 3.4, entry 2). The presence of molecular sieves resulted to be crucial for the performance of the catalytic reaction; no amine or imine was formed in the absence of molecular sieves (Table 3.4, entry 4). This result contrasts with some works reported in the literature in which the addition of molecular sieves shifts the product from imine to amine. [31,50,51]. Moreover, the catalyst and base loading could be reduced to 1.5 mol% of catalyst and 5 mol% of base without decreasing the selectivity of the reaction (Table 3.4, entry 8). Further reduction of the base to 2.5 mol% produced the reduction of the yield of **4a** to 74% and the formation of 13% of the imine **3a** (Table 3.4, entry 9), and in the absence of base, the selectivity decreases even further (Table 3.4, entry 10). Decreasing the temperature or the reaction time produced a detrimental in the yield of **4a** (Table 3.4, entries 3 and 5). Therefore, the optimized reaction conditions for the selective formation of the corresponding amine **4a** were established using aniline **1a** and 1-phenyl ethanol **2a** (in a 1:2 ratio), in the presence of 1.5 mol% of catalyst, KO^{t}Bu (5 mol%), and molecular sieves in toluene at 130 °C for 20 h under nitrogen atmosphere (Table 3.4, entry 8). Control experiments confirmed that no reaction takes place in the absence of a catalyst (Table 3.4, entry 11).

To demonstrate the general applicability of the catalytic system, a variety of alcohols and amines were evaluated in the *N*-alkylation of amines under previously optimized conditions. The results are summarized in Table 3.5.

Table 3.4. Optimization of the reaction conditions towards the synthesis of the amine **4a** via BH catalysed by $Pd(OAc)_2$.[a]



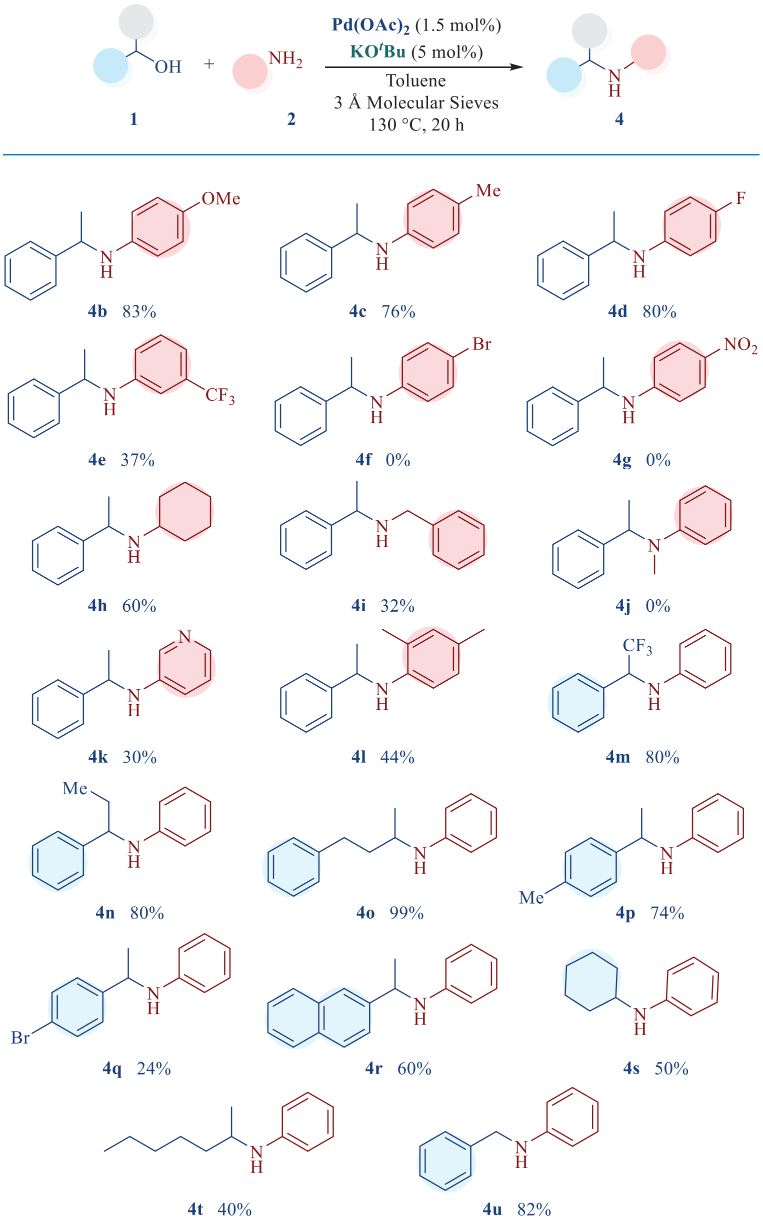
Entry	**Cat.** (mol %)	**KO^{t}Bu** (mol%)	**Yield**^{b} **3a** (%)	**Yield**^{b} **4a** (%)
1	5	50	13	65
2^c	5	50	-	93
3^d	5	50	-	<7
4^e	5	50	10	-
5^f	5	50	-	55
6	1.5	50	-	95
7	1.25	50	3	65
8	1.5	5	-	98
9	1.5	2.5	13	74
10	1.5	---	32	40
11	---	50	-	-

[a] **Reaction conditions:** aniline (0.3 mmol), 1-phenyl ethanol (0.45 mmol), $Pd(OAc)_2$, KO^{t}Bu, 3 Å MS (10 g/mmol), dry toluene (1.5 mL), 130 °C, 20 h, under N_2 inert atmosphere in a closed vessel. [b] The yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]

Using 2 equivalents of alcohol. [d] Reaction performed at 100 °C. [e] Without addition of 3 Å MS. [f] Reaction time 6 h.

Under the optimized reaction conditions, a variety of amines were obtained (see Table 3.5).

Table 3.5. Scope of the BH reaction catalysed by $Pd(OAc)_2$.[a]

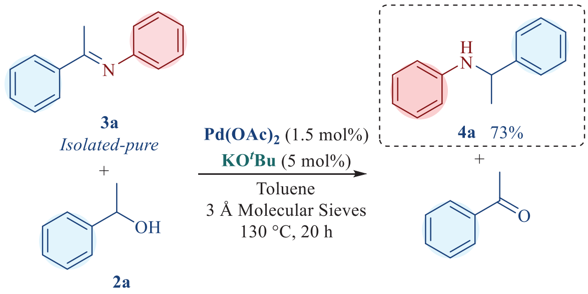


[a] **Reaction conditions:** aniline (0.3 mmol), 1-phenyl ethanol (0.6 mmol), $Pd(OAc)_2$ (1.5 mol%), KO^tBu (5 mol%), 3 Å MS (10 g/mmol), dry toluene (1.5 ml), 130 °C, 20 h, under N_2 inert atmosphere in a closed vessel. The yields were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Anilines bearing the electron-donating methoxy and methyl groups, and the electron-withdrawing F and CF_3 substituents with 1-phenyl ethanol proceeded to give the corresponding *N*-alkylated amines in moderate to excellent yields (37–83% yields, Table 3.5, amines **4b**–**4e**). When anilines substituted with -NO_2, and -Br groups were employed, no reaction was observed and the starting materials were recovered (Table 3.5, amines **4f** and **4g**).

Cyclohexyl amine, benzylamine, 3-amino pyridine, and 2,4-dimethylaniline reacted with 1-phenyl ethanol to give the corresponding amines **4h**–**4l** in moderate yields (30–60% yields, Table 3.5), while the secondary amine **4j** did not show any conversion. In addition, other secondary alcohols such as a- (trifluoromethyl)benzyl alcohol, 1-phenyl-1-propanol, and 4-phenyl-2-propanol readily afforded the corresponding amines in excellent yields (80–99%, Table 3.5, amines **4m**, **4n**, **4o**). The substituted alcohols 1-(*p*-tolyl)ethanol **4p** and 1-(4-bromophenyl)ethanol **4q** gave 74% and 24% yield respectively of the corresponding amine. Alcohol 1-(naphthalen-2-yl)ethan-1-ol **4r** afforded de product in 60% yield, while aliphatic alcohols like cyclohexanol and 2-heptanol afforded moderate yields of amines **4s** and **4t** (40–50% yields, Table 3.5). The catalytic system can also be used for the synthesis of primary alcohols (Table 3.5, **4u**).

To gain mechanistic insight into this catalytic system, a control experiment was carried out under the optimal reaction conditions. The reaction of the intermediate imine, *N*,1-diphenylethan-1-imine **3a,** with 1-phenyl ethanol **2a** gave the desired *N*-benzylaniline **4a** (73% yield), supporting a borrowing hydrogen mechanism (see Scheme 3.8).



Scheme 3.8. Hydrogen transfer between *N*,1-diphenylethan-1-imine **3a** and 1-phenyl ethanol **2a**.

3.4 Concluding Remarks and Challenges

In summary, we have reported simple and highly efficient methods for the synthesis of imines and amines using secondary alcohols. Interestingly, the ADC reaction for the selective formation of the imine **3a** (in 66% yield) can be switched to the selective formation of the amine **4a** in 98% yield, just by performing the reaction in the presence of KO^{t}Bu (5 mol%), decreasing the amount of catalyst to 1.5 mol%, and carrying out the reaction in a closed vessel under nitrogen atmosphere. It is worth highlighting that no need to add any ligands is required, and remarkably, the synthesis of the corresponding imine occurs in the absence of base. Furthermore, taking advantage of the dynamic system involved in the selective formation of the imine **3a**, it was possible to synthesize the indole **5a** with high conversion through sequential reactions using $Pd(OAc)_2$ as a catalyst.

Although a simple and efficient protocol has been developed to obtain imines and amines from secondary alcohols while utilizing direct coupling systems via ADC and BH, there are inherent limitations to consider. The formation of indoles was convenient due to the elimination of intermediate imine isolation, resulting in moderate to good yields. However, imines tend to decompose easily in the presence of water and are involved in dynamic equilibria, making it difficult to extend their scope. Additionally, fine-tuning the conditions between imine formation and cyclisation was crucial for success, with toluene being effective for imine formation and DMSO being necessary for cyclisation. This incompatibility between solvents reveals a significant challenge for optimizing reaction conditions.

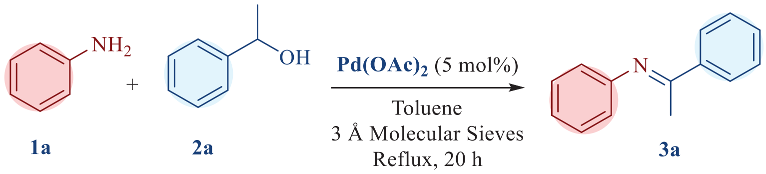
Conversely, the formation of amines through the BH pathway showed a broader scope and required minimal catalytic amounts of commercial $Pd(OAc)_2$. Directly exploring BH systems in constructing *N*-heterocycles, particularly saturated ones, is an area of significant synthetic interest.

3.5 Experimental Procedures

3.5.1 General Considerations

All reactions and manipulations were performed under nitrogen inert atmosphere except when other conditions were indicated. Solvents were purified from appropriate drying agents and distilled using typical methods. All reagents were purchased from commercial suppliers and used without further purification. All reactions were monitored by analytical TLC plates Merck Kiesel gel GF 254, 0.2 mm supported on aluminium. ^{1}H-NMR spectra were acquired with Bruker ARX 400 or Bruker Avance III 400 spectrometers at NOVA School of Science and Technology and ITQB NOVA. ^{1}H-RMN spectra were measured at 400 MHz. The samples were prepared on 5 or 3 mm NMR tubes using $CDCl_3$ as solvent. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R-H) and relative intensity of signal multiplicity (nH, with n being the number of protons) of NMR signals are described as singlet (s), broad singlet (br s), doublet of doublets (dd), triplet of doublets (td), doublet (d), triplet (t) and multiplet (m) with coupling constant (*J*) being given in Hz.

3.5.2 General procedure for the synthesis of imine 3a

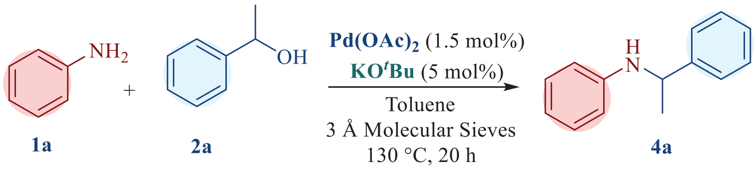


Scheme 3.9. Model reaction for the synthesis of *N*,1-diphenylethan-1-imine **3a**.

The reaction of aniline **1a** (28 mg, 0.3 mmol) with 1-phenyl ethanol **2a** (73 µl, 0.6 mmol) was carried out in 1.5 mL of dry toluene, in the presence of $Pd(OAc)_2$ (3.4 mg, 5 mol%, with respect to aniline **1a**) and activated molecular sieves 3Å (300 mg). The reaction was performed in a clean oven-dried 10 mL Schlenk equipped with a micromagnetic stir bar (2x5 mm) under a nitrogen atmosphere, heating under reflux for 20 h. After cooling, the reaction mixture was filtered over celite, and all the volatiles were removed under vacuum. The isolated crude was dissolved in chloroform-*d* and the yield of amine **3a** was determined by recording the ^{1}H-NMR spectrum using 1,3,5-trimethoxybenzene as internal standard (50.5 mg, 0.3 mmol).

The reaction was scaled up using 10 mmol of aniline and maintaining the proportions of all the other reagents. Following the procedure described above, imine **3a** was isolated in 57% as a white solid after crystallization from hexane at 0 °C. This imine **3a** could also be isolated by flash column chromatography (silica gel, hexane:ethyl acetate:Et_3N 20:2:1, v/v). Isolated imine **3a** (57% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98 (dd, *J* = 7.5, 2.1 Hz, 2H), 7.48 – 7.44 (m, 3H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.4 Hz, 2H), 2.24 (s, 3H).

3.5.3 General Procedure for the Synthesis of Amine 4a

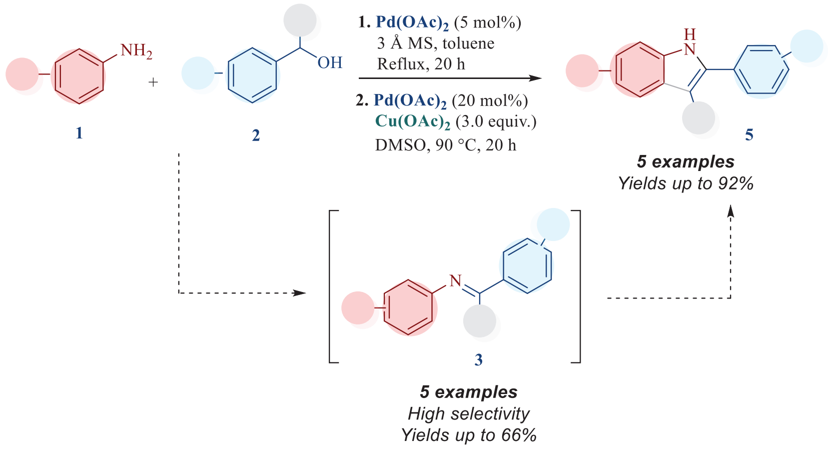


Scheme 3.10. Model reaction for the synthesis of *N*-(1-phenylethyl)aniline **4a**.

The reaction of aniline **1a** (28 mg, 0.3 mmol) with 1-phenyl ethanol **2a** (73 µl, 0.6 mmol) was carried out in 1.5 mL of dry toluene, in the presence of KO^{t}Bu (1.7 mg, 5 mol%), $Pd(OAc)_2$ (1 mg, 1.5 mol%, with respect to aniline **1a**) and activated molecular sieves 3Å (300 mg). The reaction was performed in a in a clean oven-dried 10 mL Schlenk closed with a screw cap and equipped with a micro magnetic stir bar (2x5 mm) at 130 °C in an oil bath under nitrogen inert conditions for 20 h. After cooling, the reaction mixture was filtered over celite, and all the volatiles were removed under vacuum. The isolated crude was dissolved in chloroform-*d* and the yield of amine **4a** was determined by ^{1}H-NMR spectrum using 1,3,5-trimethoxybenzene as an internal standard (50.5 mg, 0.3 mmol).

The reaction was scaled up using 10 mmol of aniline and maintaining the proportions of all the other reagents. Following the procedure described above, the amine **4a** was isolated in 89% as a yellow oil after a flash column chromatography (silica gel, Hexane:Ethyl acetate, 20:1). Isolated amine **4a** (89% yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 2H), 6.67 (t, *J* = 7.5 Hz, 1H), 6.53 (d, *J* = 7.5 Hz, 2H), 4.50 (q, *J* = 7.5 Hz, 1H), 1.53 (d, *J* = 7.5 Hz, 3H).

3.5.4 General Procedure for the Synthesis of Indoles



5 examples
Yields up to 92%

5 examples
High selectivity
Yields up to 66%

Scheme 3.11. Cascade reaction conditions for the synthesis of Indoles **5**.

The reactions were all carried out by mixing aniline derivative **1** (0.4 mmol) with 1-phenyl alcohol derivative **2** (97 µl, 0.8 mmol) with dry toluene (2 mL), in the presence of $Pd(OAc)_2$ (4.5 mg, 5 mol%) and activated molecular sieves 3Å (400 mg). The reactions were performed in a 10 mL Schlenk under a nitrogen atmosphere, heating under reflux for 20 h. After cooling, the reaction mixtures were filtered over celite, and all the volatiles were removed under vacuum. The remaining crude reaction mixtures were re-dissolved in dry DMSO (1 mL), and a new charge of $Pd(OAc)_2$ (18 mg, 20 mol%, with respect to aniline **1**) and $Cu(OAc)_2$ (218 mg, 3 equivalents with respect to aniline **1**) were added. The reaction mixtures were stirred overnight in a closed vessel at 90 °C under an air atmosphere. The reactions were monitored by TLC until completion, and the final products were isolated through column chromatography (20:1 Hexane:Ethyl acetate eluent mixture) to afford the corresponding indoles **5**.

Isolated indole **5a** (92% yield, white solid). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 12.5, 7.6 Hz, 3H), 7.51 – 7.38 (m, 3H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.21 (dd, *J* = 11.1, 4.0 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 1.2 Hz, 1H).

Isolated indole **5b** (50% yield, white solid). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.64 (d, J = 7.6 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.37 – 7.26 (m, 2H), 7.11 (d, J = 2.4 Hz, 1H), 6.87 (dd, J = 8.7, 2.5 Hz, 1H), 6.77 (s, 1H), 3.88 (s, 3H).

Isolated indole **5c** (66% yield, white solid). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.66 (d, J = 7.3 Hz, 2H), 7.44 (m, 3H), 7.34 – 7.25 (m, 2H), 7.03 (dd, J = 8.3, 1.1 Hz, 1H), 6.76 (d, J = 1.3 Hz, 1H), 2.46 (s, 3H).

Isolated indole **5d** (82% yield, pale yellow solid). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.66 (d, J = 7.3 Hz, 2H), 7.45 (t, J = 7.4 Hz, 2H), 7.35 (t, J = 7.1 Hz, 1H), 7.30 (dd, J = 8.4, 4.2 Hz, 1H), 7.27 – 7.25 (m, 1H), 6.94 (td, J = 9.1, 2.2 Hz, 1H), 6.79 (s, 1H).

Isolated indole **5e** (43% yield, pale yellow solid). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 7.5 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 7.11 (t, J = 7.4 Hz,1H), 6.78 (s, 1H), 2.40 (s, 3H).

3.6 Acknowledgements

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3.7 References

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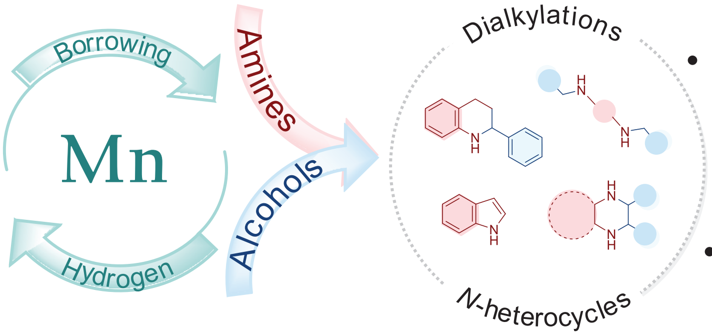
4.

Borrowing Hydrogen Reactions Mediated by a Mn(I) Triazolylidene Complex

The results described in this chapter are part of a forthcoming publication cited as: Garcia, B., Friaes, S., Raydan, D., Marques, M. M. B., & Royo, B., (2024). Borrowing Hydrogen Reactions Mediated by a Mn(I) Triazolylidene Complex.

4.1 Summary



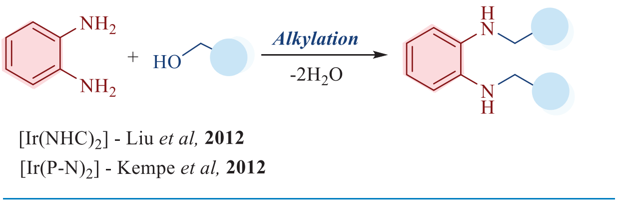
- Borrowing hydrogen dialkylations
- Phosphine free approach
- Challenging *N*-heterocycles
- 1,2,3,4-tetrahydroquinoxalines
- More than 30 examples

The Borrowing Hydrogen (BH) process has been recognised as a sustainable catalytic system converting renewable feedstocks into valuable *N*-containing compounds with water as the only by-product. While BH is known for transforming primary arylamines with benzyl alcohols, overcoming the selectivity challenge for the *N*,*N*-dialkylation of *o*-phenylenediamines with alcohols, commonly driving to benzimidazoles, is still not well-explored. At the same time, BH with *o*-phenylenediamine and vicinal diols provides an elegant way to make pharmacologically significant 1,2,3,4-tetrahydroquinoxalines. In this work we have explored the synthesis of *N*-heterocyclic compounds, namely 1,2,3,4-tetrahydroquinoxalines, through the BH process. Employing a tricarbonyl Mn(I) complex with bis(1,2,3-triazol-5-ylidene) ligands, the catalytic system exhibits excellent yields in this transformation. The study further explored the applicability of the catalytic system in the synthesis of other *N*-heterocycles, such as indoles, indolines, and tetrahydroquinolines. Notably, this manganese-catalysed BH protocol offered a sustainable approach to valuable *N*-heterocyclic compound synthesis.

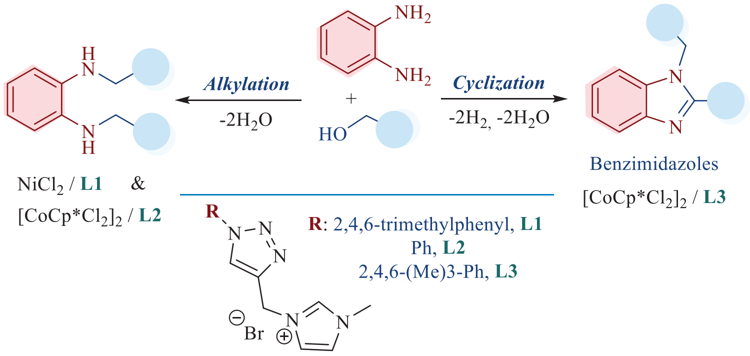
4.2 Introduction

The Borrowing Hydrogen (BH) process is considered a sustainable catalytic approach as it enables the conversion of renewable feedstocks into valuable *N*-containing compounds with water as the only by-product.[1,2] In particular, the transformation of primary arylamines with benzyl alcohols through the BH process has been extensively explored.[3] On the other hand, the dialkylation of *o*-phenylenediamines with alcohols presents a big challenge, as primary alcohols tend to form benzimidazoles instead of the dialkylated products.[4] In 2012, the groups of *Kempe & Liu* addressed this challenge by using *P*,*N*-pincer and NHC iridium catalysts to selectively synthesise symmetrically and unsymmetrically alkylated benzenediamines, avoiding selectivity issues (see Scheme 4.1).[5–7] In addition, recently the group of *Rit & co-workers* has also explored these dialkylations through the use of Ni and Co-based catalysts, showing promising results (see Scheme 4.1).[8,9] Although further studies have been conducted by other groups, limitations on substrate scope are still present.[10–16] Similarly, diol dialkylation often leads to the formation of saturated rings such as pyrroles and pyrrolidines, rather than the desired direct dialkylation products.[17,18]

(a) Previous works using Ir towards dialkylations



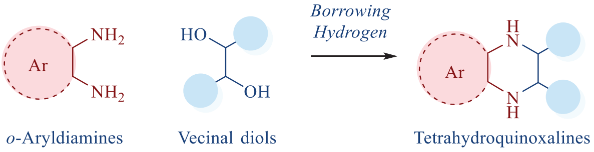
(b) Reported Ni and Co catalysts by the group of *Rit & co-workers* in 2023



Scheme 4.1. Reports using Ir, Ni, and Co in the di-alkylation process via BH strategy.

The simultaneous combination of *o*-phenylenediamine with vicinal diols through BH cycles would provide an elegant synthetic route to access rarely explored 1,2,3,4-tetrahydroquinoxalines (see

Scheme 4.2).[19–22] These tetrahydroquinoxalines are *N*-heterocyclic compounds of significant interest for their excellent pharmacological and biological activity.[23–29]

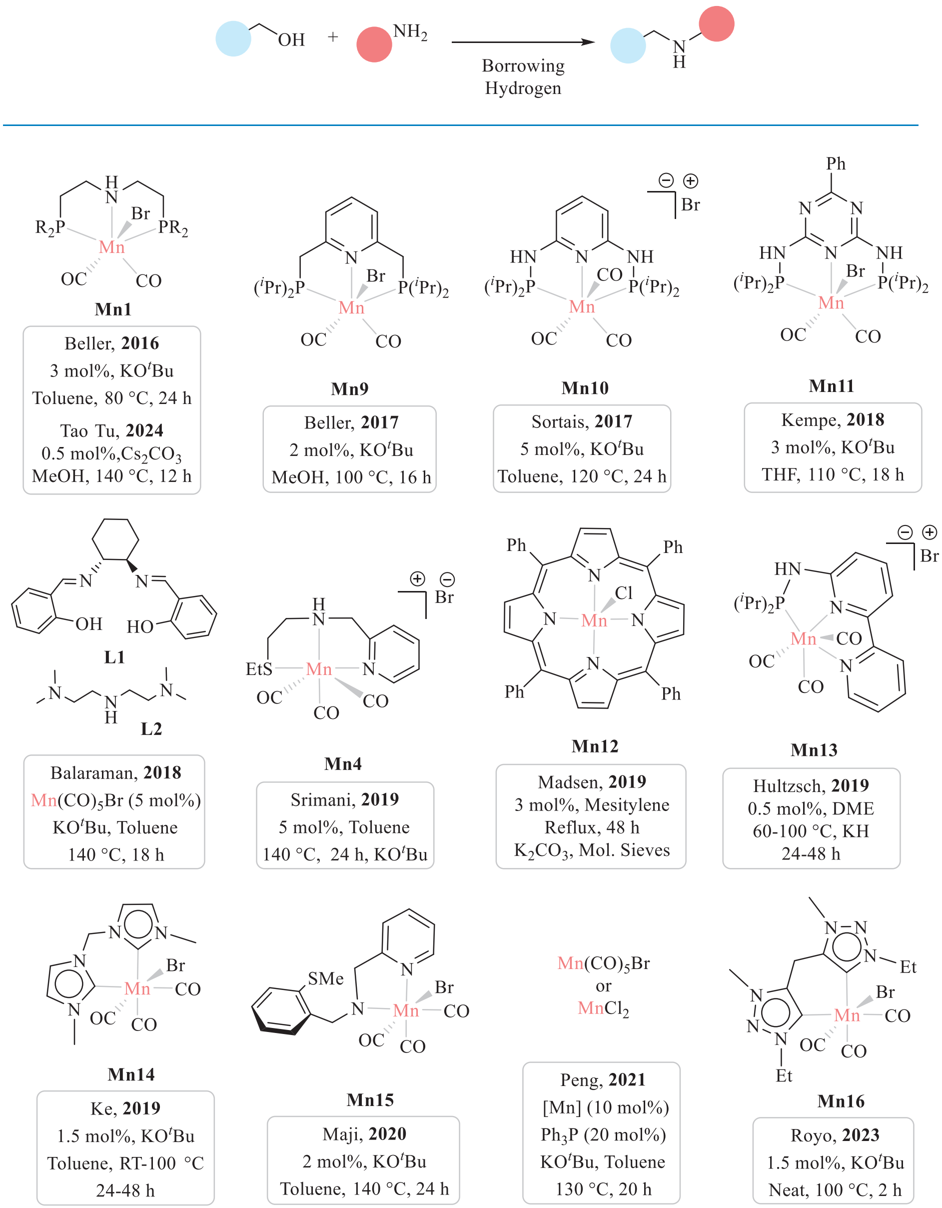


Scheme 4.2. Elegant-novel BH approach to the synthesis of 1,2,3,4-tetrahydroquinoxalines.

Regarding the metals typically found in these BH transformations, precious metals are the most commonly reported. During the last few years, these catalytic approaches have experienced a paradigm shift towards the use of earth-abundant metals. To date, only one study has successfully achieved the transformation of *o*-phenylenediamines with vicinal diols towards 1,2,3,4-tetrahydroquinoxalines, employing an earth-abundant phosphine-based nickel catalyst.[30] Hence, there is still room to explore the activity of other earth-abundant metals in these transformations.

Since the seminal works of Beller[31] and Milstein[32] in 2016, the catalytic application of Mn in BH has attracted considerable attention due to its affordability and its non-toxic properties. Nevertheless, most of the manganese systems that have been developed to date are based on phosphine ligands (see Scheme 4.3).[31,33–36]

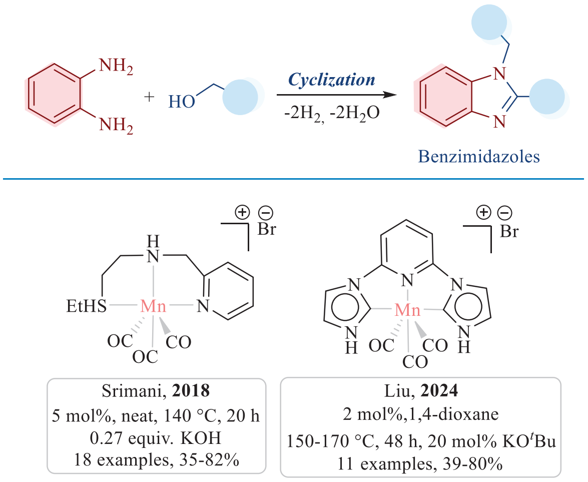
With this in mind, the group of *Royo & co-workers* has been developing manganese phosphine-free catalytic systems using *N*-heterocyclic carbene[37–40] (NHCs) and mesoionic carbene (MICs) ligands (**Mn14** and **Mn16** respectively, see Scheme 4.3).[41–45] Recently, *Royo & co-workers* demonstrated that the stronger σ-donor properties of MIC *vs* classical imidazolium-derived NHCs enhanced the catalytic activity in BH processes.[42–45] In particular, the manganese complex with the general formula [Mn(bis-trz)(CO)$_3$Br] showed to be highly efficient for the *N*-alkylation of arylamines with primary alcohols through BH process, being able to afford *N*-benzylaniline in 92% yield in the presence of low base loading (KO^{t}Bu, 0.1 equiv) (see **Mn16** in Scheme 4.3).[42]



Scheme 4.3. Well-defined manganese complexes reported in the literature for amine synthesis via BH strategy.

Motivated by these results, we decided to explore further the use of [Mn(bis-trz)$(CO)_3$Br] in BH processes to access challenging *N*-containing compounds.

To date, only a few studies based on manganese have succeeded in coupling primary alcohols with *o*-phenyldiamines. However, these studies only resulted in the formation of benzimidazoles and did not achieve selective dialkylation (see Scheme 4.4). [46,47]



Scheme 4.4. Mn-based catalytic studies towards benzimidazole synthesis from *o*-diamines and alcohols.

In Chapter 4, we describe the dialkylation of diamines and diols and the synthesis of 1,2,3,4-tetrahydroquinoxalines through BH reactions using the tricarbonyl Mn(I) complex **Mn1**, bearing a bis-1,2,3-triazol-5-ylidene ligand as a catalyst (see Figure 4.1).

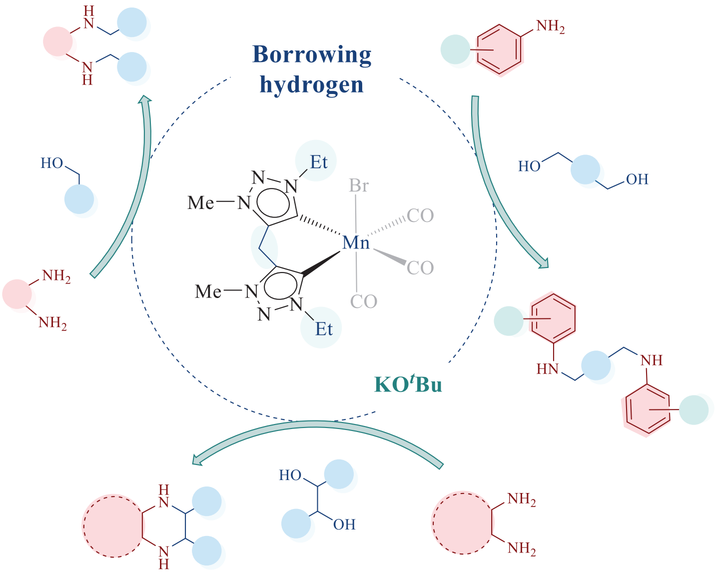
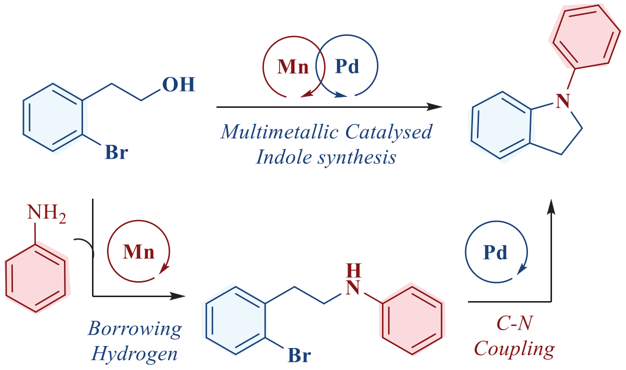


Figure 4.1. Several important Borrowing Hydrogen transformations were performed in this study using the catalyst [Mn(bis-trz)(CO)$_3$Br].

In addition, the synthesis of indolines using a bimetallic Mn/Pd one-pot catalytic system was carried out efficiently in a cascade fashion (see Scheme 4.5). This tandem reaction allows the efficient and atom-economy synthesis of an indoline, without the need of isolation of any intermediate species.

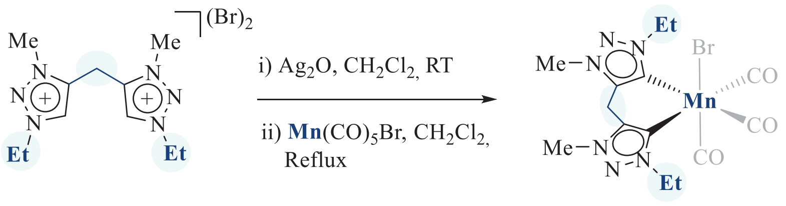


Scheme 4.5. BH/*C-N* coupling bimetallic cascade route performed in this study using **Mn1** and Pd(PPh$_3$)$_4$ as catalysts.

4.3 Results & Discussion

4.3.1 Synthesis & Characterization of Mn1 Complex

The synthesis of **Mn1** was performed following the synthetic procedure previously described by Royo´s group as depicted in Scheme 4.6.[42] First, the synthesis of C4-linked bis-triazolium salt **I** was achieved through the well-established copper-catalysed click [3 + 2] cycloaddition reaction,[48] followed by methylation with methyl triflate and subsequent anion exchange with tetra-*n*-butylammonium bromide.[42,49] Coordination of **I** to manganese was performed through the Ag transmetallation route, resulting in the isolation of **Mn1** as a pure crystalline solid.[42]



I

Mn1

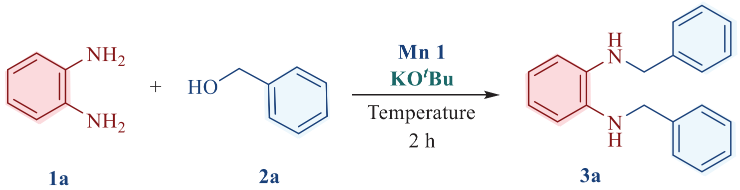
Scheme 4.6. Synthesis of **Mn1** complex from bis-triazolium salt **I**.

The thermal stability of **Mn1** was investigated through thermogravimetric analysis (TGA, Annexes – A4.1). The thermogram reveals that **Mn1** is stable up to 156 °C. From this point on, it begins to decompose at a rapid rate, rapidly losing 55% of its initial mass. Additionally, a ^{1}H-NMR analysis of **Mn1** was performed in solution (Annexes – A4.1). The experiment was made in a *J*-young NMR tube, where **Mn1** was dissolved in 0.4 mL of DMSO-d_6 and the solution was heated at 130 °C for 2h. The ^{1}H-NMR was recorded before and after 2h heating to confirm the catalyst's integrity in solution. Therefore, **Mn1** is revealed to be robust and stable at high temperatures.

4.3.2 *N*,*N*-Dialkylation of diamines with primary alcohols

We started our investigation by examining the activity of **Mn1** in the challenging *N*,*N*-dialkylation of diamines. Initially, the reaction was explored using *o*-phenylenediamine **1a** and benzyl alcohol **2a**, as a model substrates under an inert nitrogen atmosphere. Interestingly, when the reaction was performed using 4 mol% of catalyst, 0.5 equiv. of KO^{t}Bu at 130 °C, quantitative yield of the *N*,*N*-alkylated product was obtained in 2 h (Table 4.1, entry 1). The reaction was very selective to the formation of **3a** in high yield (96% yield) and with no detectable by-products formed. Furthermore, when the catalyst amount (2 mol%) and/or the temperature (100 °C) were decreased (Table 4.1, entries 2 and 3) same yields were achieved. Attempts to decrease the alcohol amount to 1 equiv. resulted in a notable 35% decrease in yield (Table 4.1, entry 4) and no formation of benzimidazole or any other side product occurred. In addition, reducing the amount of KO^{t}Bu to 0.2 equiv. produced a slight decrease in the yield to 81% (Table 4.1, entry 5). If the amount of catalyst is further reduced to a 1 mol%, the yield of **3a** decreased to 80% (Table 4.1, entry 6). Importantly, no product was observed in the absence of base or catalyst (Table 4.1, entries 7 and 8, respectively).

Table 4.1. Optimization studies for the dialkylation of *o*-phenylenediamine with benzyl alcohol[a]



1a **2a** **3a**

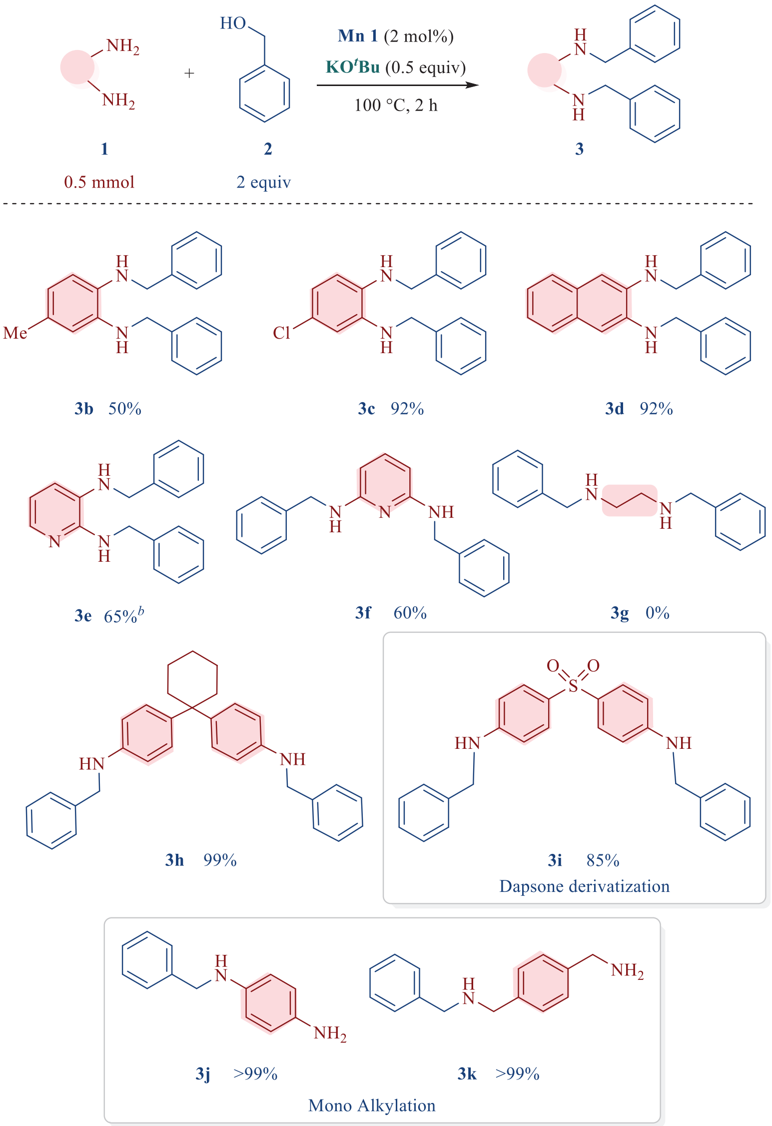
o-phenylenediamine Benzyl alcohol

Entry	Cat. Loading (mol%)	KO^{t}Bu (equiv.)	Alcohol (equiv.)	Temp. (°C)	**3a** (%)[b]
1	4	0.5	2	130	98
2	2	0.5	2	130	96
3	2	0.5	2	100	96
4	2	0.5	1	100	35
5	2	0.2	2	100	81
6	1	0.5	2	100	80
7	2	-	2	130	-
8	-	0.5	2	130	-

[a]**Reaction conditions:** *o*-phenylenediamine (0.5 mmol), benzyl alcohol, KO^{t}Bu, catalyst, neat conditions, 2 h, in a closed Schlenk under N_2. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

Encouraged by these results, we decided to explore the scope of the reaction using the optimized conditions presented in Table 4.1, entry 3 (2 mol% of **Mn1** and 0.5 equiv. of KO^{t}Bu, at 100°C for 2 hours). Various diamines were examined, revealing different reactivity depending on the aromatic ring functionalization, e.g., *p*-Me **3b** (50% of yield) and *p*-Cl **3c** (92% of yield) (see Table 4.2). 2,3-Diaminonaphthalene yielded the N,N-dialkylated product **3d** in high yield (92%), and pyridine ring-substituted diamines like 2,3-diaminopyridine and 2,5-diaminopyridine produced the corresponding products **3e** (65%) and **3f** (60%), respectively, in moderate yields (65% and 60%), contrasting with other catalytic systems reported in the literature that have a limitation in the *N*-alkylation of aromatic amines containing heteroatoms.[9]

Table 4.2. Substrate scope for the *N*,*N*-dialkylation of diamines with benzyl alcohol.[a]

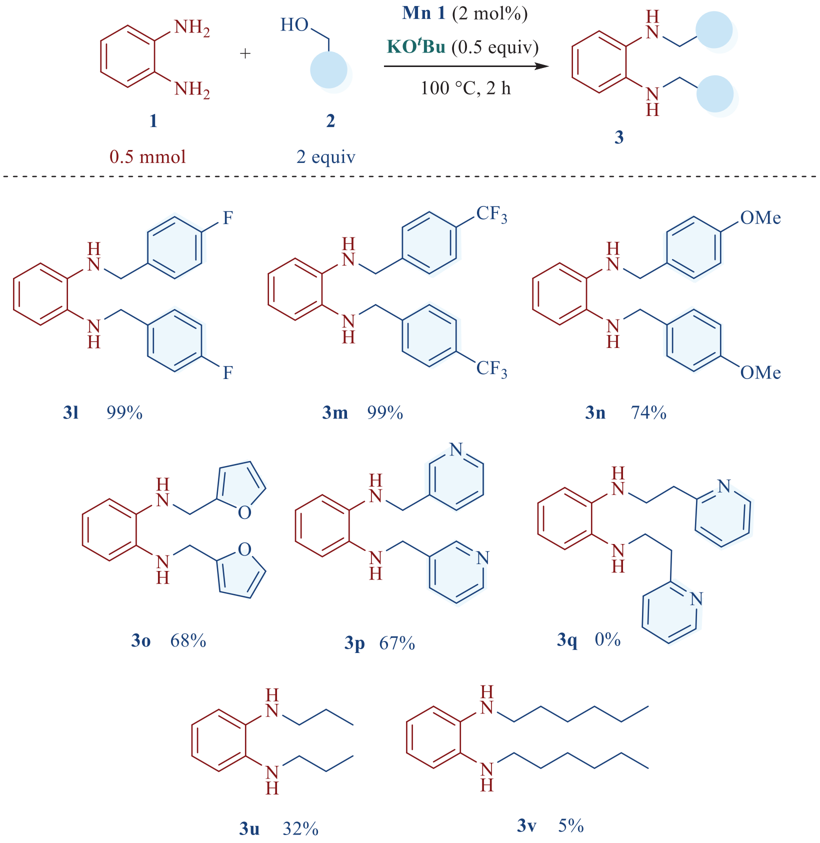


[a] **Reaction conditions:** diamine (0.5 mmol), benzyl alcohol (1 mmol), KO^{t}Bu (0.5 equiv.), catalyst (2 mol %), neat conditions, 100 °C, 2 h, in a closed schlenk under N_2. [b] Reaction with 4 mol% of catalyst loading. [c] Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

A limitation of the catalytic system was observed when the aliphatic diamine **3g** was used. Other challenging substrates, such as 4,4'-(cyclohexane-1,1-diyl)dianiline and 4,4'-sulfonyldianiline, yielded the corresponding dialkylated amines in high yields (99% for **3h** and 85% for **3i**, Table 4.2). Interestingly, using this catalytic system the -diphenyl sulfone **3i** (Dapsone), a pharmacologically valuable antibiotic, was efficiently obtained. Under the same reaction conditions, the alkylation of 1,4-benzenediamine and 1,4-bis(aminomethyl)benzene afforded the monoalkylated products **3j** and **3k**, respectively, in quantitative yield. Hence, it is noteworthy that the catalytic activity of the current protocol for the dialkylation of *N*,*N*-diamines is competitive compared to reported systems with limited substrate scope.[10–16,50]

The use of a variety of primary alcohols was also explored. Initially, benzylic alcohols bearing various electron-donating and -withdrawing substituents were investigated. As shown in Table 4.3, the desired products **3l–n** were obtained in good to high yields (74-99%).

Table 4.3. Substrate scope for the *N*,*N*-dialkylation of *o*-phenylenediamine with primary alcohols.[a]



[a]**Reaction conditions:** Diamine (0.5 mmol), alcohol (1 mmol), KO*ᵗ*Bu (0.5 equiv.), catalyst (2 mol %), neat conditions, 100 °C, 2 h, in a closed schlenk under N_2. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

It was observed that the methoxy-substituted benzyl alcohol yielded the alkylated product **3n** in a relatively lower yield, while the F and CF_3 substituted benzyl alcohols allowed to obtain the corresponding alkylated products in high yields. Furthermore, various aromatic rings were explored, such as furfuryl alcohol, which led to the formation of the dialkylated compound **3o** in 68%, and 3-pyridinemethanol, which was converted into **3p** in 67% yield. On the other hand, 3-pyridineethanol failed to react with *o*-phenylenediamine, and aliphatic alcohols gave low yields of the target compounds (32% for **3u** and 5% for **3v**, respectively, Table 4.3).

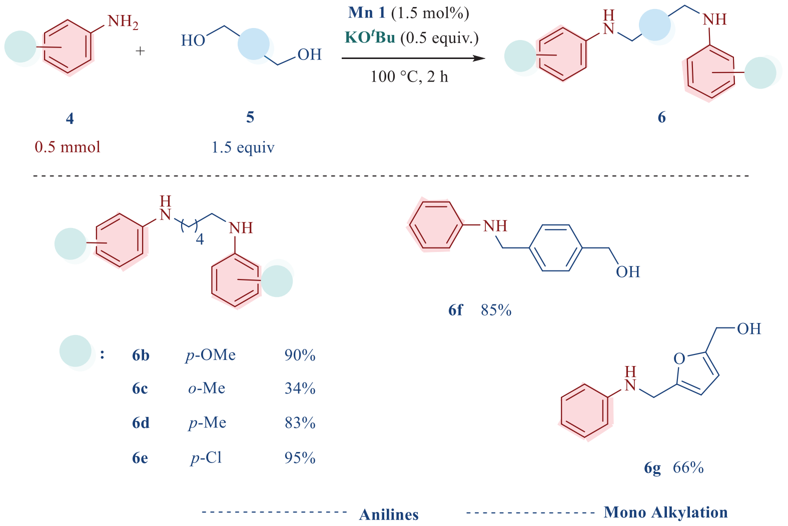
4.3.3 Direct Reaction of primary diols with anilines

Encouraged by the results obtained in the dialkylation of diamines, we decided to explore the direct reaction of anilines with diols. For this purpose, the model reaction of aniline **4a** with 1,5-pentanediol **5a** was investigated. Under the reaction conditions reported in entry 3, Table 4.1 (2 mol% **Mn1** and 0.5 equiv. of KO^{t}Bu, using 2 equiv. of alcohol at 100 °C for 2 hours), quantitative yield to the corresponding diamine **6a** was obtained. Reducing the alcohol amount to 1.5 equiv. also resulted in quantitative conversion (entry 2, Table 4.7 experimental procedures). but attempts to reduce the alcohol further to achieve a 1:1 or 1:0.5 stoichiometry of aniline **4a** and 1,5-pentanediol **5a** provided significantly lower yields (37-39%, entries 3 and 4, Table 4.7 experimental procedures). The presence of an excess of alcohol seems crucial for attaining high yields in this transformation. With the optimal conditions found (1.5 mol% of **Mn1** and 0.5 equiv. of KO^{t}Bu, at 100 °C for 2 hours), the scope of the reaction was explored using different anilines and diols.

Starting from 1,5-pentanediol **5a**, it was proven that **Mn1** is highly effective in the dialkylation process of *p*-substituted amines with various electron-donating (Me, OMe) and electron-withdrawing (Cl) substituents (see Table 4.4). It was possible to produce the corresponding alkylated amines in very good yields (90% for **6b**, 83 % for **6d** and 95 % for **6e**, Table 4.4), showing the great tolerance to the different substituents. However, when the aniline has the substituent in *para*-position, the yield decreases drastically (**6c** vs **6d**, Table 4.4).

Interestingly, using this approach it was possible to obtain monoalkylated products in moderate to higher yields (85% for **6f** and 66% for **6g**, Table 4.4), which open space to asymmetric dialkylation processes. Our approach provides an efficient alternative synthetic route for the synthesis of dialkylated amines and diamines, which are valuable molecules in organic synthesis and material science.[51–53]

Table 4.4. Substrate scope for the direct reaction of diols with functionalized anilines[a]

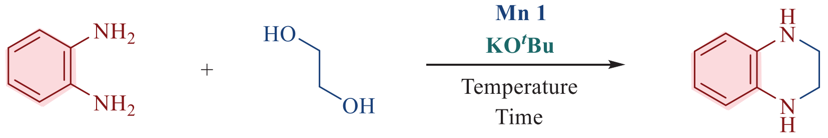


[a]**Reaction conditions:** functionalized aniline (0.5 mmol), diol (0.75 mmol), KO^tBu (0.5 equiv.), catalyst (1.5 mol %), neat conditions, 100 °C, 2 h, in a closed schlenk under N_2. [b]Yields determined by quantitative ^1H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

4.3.4 Synthesis of tetrahydroquinoxalines

To the best of our knowledge, there have been no studies of manganese-catalysed BH reactions for the synthesis of 1,2,3,4-tetrahydroquinoxalines. In this work, we proposed to explore the model reaction of *o*-phenylenediamines **1a** and ethyleneglycol **5b** for the synthesis of 1,2,3,4-tetrahydroquinoxaline **7a** (refer to Table 4.5). Using 4 mol% of catalyst, 0.5 equiv. of KO^tBu, and an excess of 2 equiv. of ethyleneglycol **5b**, the 1,2,3,4-tetrahydroquinoxaline **7a** was isolated in 75% yield after 16 hours at 130 °C (entry 1, Table 4.5). The reaction time was reduced to just 2 hours without noting any detrimental effect in the yield (entry 2, Table 4.5). However, if the temperature is reduced from 130 to 100 °C, a significant reduction of the product yield (entries 3 and 4, Table 4.5) is observed. Furthermore, increasing the alcohol amount to 4 equiv. resulted in a significant 41% decrease in yield (entry 5, Table 4.5). The influence of the base was also examined by varying the amount of $\mathrm{KO}^t\mathrm{Bu}$ between 0.4 and 0.6 equiv., yielding slightly lower conversions in both cases (entries 6 and 7, Table 4.5). A complete screening of various bases and solvents did not allowed to improve the yield (see Tables 4.10 and 4.11, experimental procedures). Moreover, control experiments demonstrated that the presence of both base and catalyst is essential for the success of the reaction (entries 8 and 9, Table 4.5).

Table 4.5. Optimization studies for the synthesis of 1,2,3,4-tetrahydroquinoxaline from *o*-phenylenediamine and ethyleneglycol[a]



1a *o*-phenylenediamine

5b Ethyleneglycol

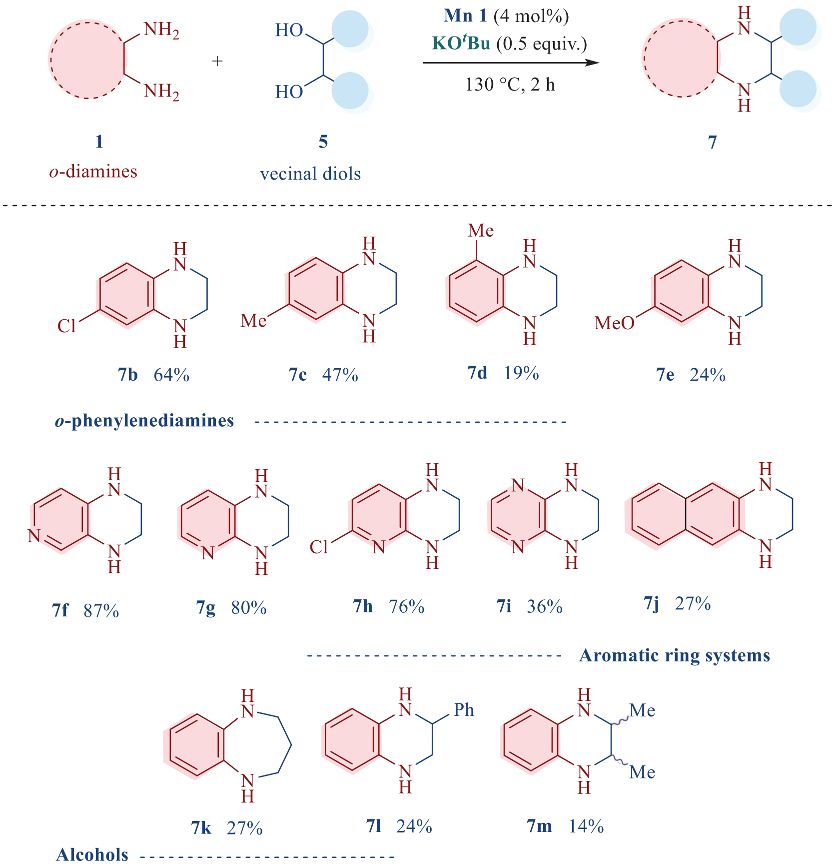
7a

Entry	Cat. Loading (mol%)	$\mathrm{KO}^t\mathrm{Bu}$ (equiv.)	Alcohol (equiv.)	Temp. (°C)	Time (h)	**7a** (%)b
1	4	0.5	2	130	16	75
2	4	0.5	2	130	2	75
3	4	0.5	2	100	2	50
4	4	0.5	2	150	2	59
5	4	0.5	4	130	2	41
6	4	0.6	2	130	2	67
7	4	0.4	2	130	2	61
8	-	0.5	2	130	2	-
9	4	-	2	130	2	-

[a]**Reaction conditions:** functionalized aniline (0.5 mmol), ethyleneglycol, $\mathrm{KO}^t\mathrm{Bu}$, catalyst, neat conditions, in a closed schlenk under N_2. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

Next, under the optimized conditions, the scope of the reaction was explored. As shown in Table 4.6, both electron-donating (*p*-OMe, *p*-Me, or *o*-Me) and electron-withdrawing (*p*-Cl) substituents on the benzene ring of 1,2-arylenediamines were well tolerated, yielding moderate conversions for *p*-Cl and *p*-Me substituents (64% for **7b** and 47% for **7c**, respectively in Table 4.6). The substitution at the aromatic ring with a Me group in *o*-position (**7d**) as well as the introduction of a OMe substituent in *p*-position (**7e**) leads to lower yields (19% and 24%, respectively in Table 4.6).

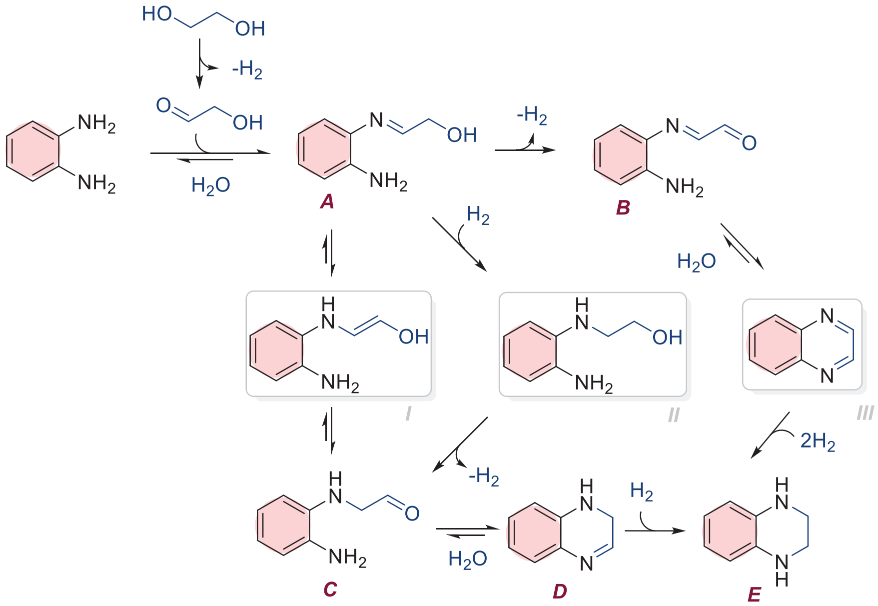
Table 4.6. Substrate scope for the synthesis of tetrahydroquinolines through *N*,*N*-dialkylation of *o*-diamines with 1,2-diols[a]



[a]**Reaction conditions:** *o*-diamine (0.5 mmol), vicinal diol (1 mmol), KO^{t}Bu (0.5 equiv.), catalyst (4 mol %), neat conditions, 130 °C, 2 h, in a closed schlenk under N_2. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

Interestingly, when a nitrogen heteroatom is present in the aromatic ring, high yields of the corresponding products are obtained (86% for **7f**, 80% for **7g**, and 76% for **7h**, Table 4.6). A limitation of the system is observed when the reaction was performed with an electronrich diamine substrate, the yield **7j** drastically decreased to 27%. In addition, very low yields were isolated when secondary diols were used (24% for **7l** and 14% for **7m**, Table 4.6).

We propose that, in the presence of our catalyst, o-phenylenediamine undergoes double alkylation with the vicinal diol via the borrowing hydrogen strategy, efficiently yielding the tetrahydroquinoxaline scaffold (*E*) with water as the only by-product (Scheme 4.7, three possible pathways considered). Although not explicitly shown in Scheme 4.7, the active catalytic intermediate in this borrowing hydrogen strategy is likely a metal hydride species.



Scheme 4.7. Proposed Pathways for the Synthesis of 1,2,3,4-Tetrahydroquinoxaline via Borrowing Hydrogen Strategy.

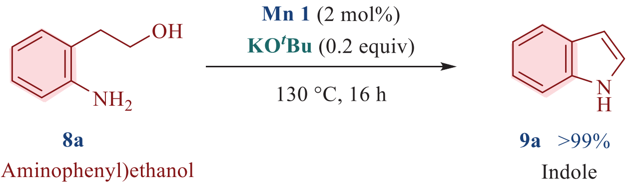
On the other hand, we consider the concentration of glyoxal, which could form through double dehydrogenation of the diol, to be too low under catalytic conditions to represent a significant pathway.

A particularly appealing alternative involves tautomeric equilibria starting from imine *A*, leading to compound *C*. This route is synthetically attractive as it bypasses the formation of aromatic quinoxaline *III*. The same reasoning applies to the formation of compound *II* after a full borrowing hydrogen cycle, which also leads to compound C while avoiding quinoxaline *III*.

Nevertheless, without detailed mechanistic studies, we cannot rule out the possibility that imine ***A*** undergoes dehydrogenation to form compound ***B*** and its corresponding quinoxaline *III*, which would then be hydrogenated to afford product ***E***.

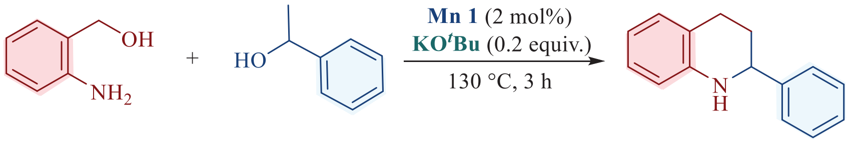
4.3.5 Synthesis of other *N*-heterocycles

Encouraged by the results obtained for the intermolecular cyclization to form 1,2,3,4-tetrahydroquinoxalines, we decided to extend our study to evaluate the synthetic potential of **Mn1** for the synthesis of other *N*-heterocycles, such as indoles. The intramolecular cyclization of 2(2-aminophenyl)ethanol was attempted using 2 mol% of catalyst in the presence of 0.5 equiv. of KO^{t}Bu, in 16 hours at 130 °C (entry 5, Table 4.12 experimental procedures). Under these conditions, the corresponding indole **9a** was obtained in 75% yield. Gratifyingly, a quantitative conversion of the intramolecular cyclization of 2(2-aminophenyl)ethanol was achieved by reducing the amount of KO^{t}Bu to 0.2 equiv. (Scheme 4.8 and entry 6, Table 4.11 experimental procedures).



Scheme 4.8. Catalytic borrowing hydrogen approach towards the synthesis of an indole from the 2-(2-Aminophenyl)ethanol.

Furthermore, complex **Mn1** was applied as catalyst for the synthesis of the 1,2,3,4-tetrahydroquinoline **10a**, by direct reaction of (2-aminophenyl)methanol and 1-phenylethanol. Using the catalytic conditions optimized for the synthesis of **9a**, **Mn1** was capable to form the 1,2,3,4-tetrahydroquinoline in 40 % of yield, in 3h (see Scheme 4.9).



8b
(2-aminophenyl)methanol

2b
1-phenyl ethanol

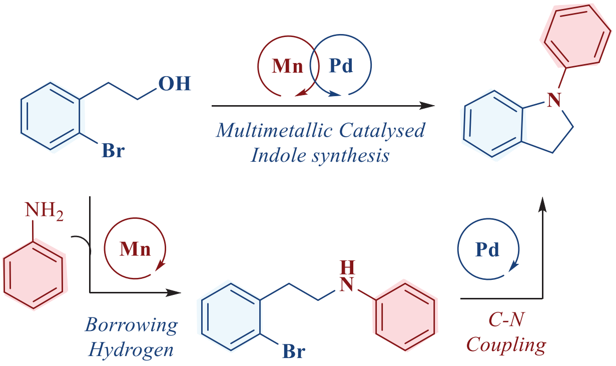
10a
1,2,3,4-tetrahydroquinoline

Scheme 4.9. Catalytic borrowing hydrogen approach towards the synthesis of an 1,2,3,4-tetrahydroquinoline (**10a**) from (2-aminophenyl)methanol (**8b**) and 1-phenyl ethanol (**2b**).

Further attempts to improve the yield and selectivity of this reaction were performed. Starting with 2 mol% of **Mn1** and increasing the amount of KO^{t}Bu to 0.5 equiv., resulted in 36% of the desired tetrahydroquinoline **10a**, along with the by-product corresponding quinoline (**10b)** (entry 2, Table 4.13 experimental procedures). Increasing the reaction time to 16 h does not seem to affect the yield of tetrahydroquinoline, indeed a higher amount (33% vs 15%) of the by-product **10b** was observed (entry 3, Table 4.13 experimental procedures). Despite the use of a secondary alcohol as alkylation agent could be a limitation of our system, we demonstrate that our catalyst is very efficient to do the borrowing hydrogen procedure as the tetrahydroquinoline is the major product observed.

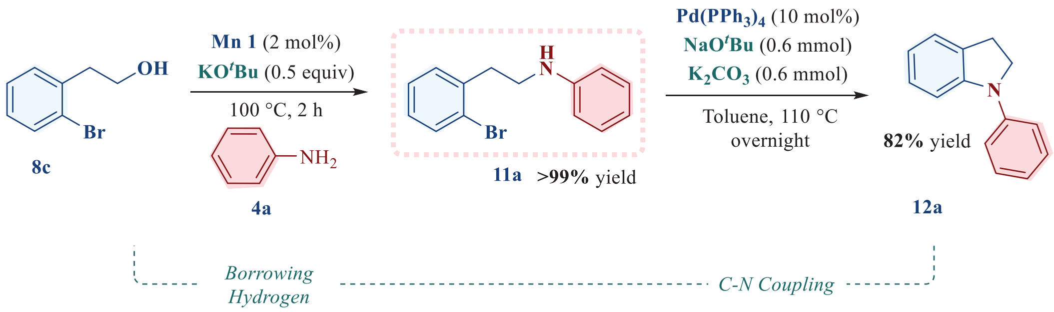
4.3.6 One-pot Bimetallic Synthesis of Indoline

Indolines are commonly found in heterocyclic substructures in natural products and drug-like molecules.[54] To synthesise indoline derivatives, several protocols have been developed, including Pictet-Spengler (*P-S*) and Bischler-Napieralski (*B-N*) reactions, as well as other catalytic approaches.[55] Recently, significant progress has been made in developing novel cascade processes using two distinct metal catalysts.[56] However, compatibility issues between catalytic systems can make the development of such processes challenging. While reactions promoted by two sequential relay metal-catalytic systems are rare, we present our investigations on the one-pot cascade reaction catalysed by manganese and palladium complexes with the aim of achieving the synthesis of indoline through a pathway involving *C–N* coupling via BH between aniline and ethylene glycol, and subsequent intramolecular C–N-cross-coupling reaction to generate a saturated 5-member ring (see Scheme 4.10).



Scheme 4.10. Bimetallic Mn-Pd catalysed synthesis of indoline in one-pot fashion.

The first reaction step involves the BH catalysis between an amine and alcohol with the possibility of forming 5-membered rings. For the model reaction, we used aniline **4a** and 2-(2-bromophenyl)ethanol **8a**. The conditions used to obtain a quantitative yield of product **11a** consisted of 2 mol% **Mn1**, 0.5 equiv. KO^{t}Bu, at 100 °C under neat conditions for 2 hours of reaction (see Scheme 4.11). An optimisation table of this reaction step can be found in the experimental section (see Table 4.14 experimental procedures).



Scheme 4.11. Two cascade steps for the reaction between aniline **4a** and alcohol **8c** towards the formation of indoline **12a** in 82% yield and without the need to isolate the reaction intermediate **11a**.

After 2 hours of reaction, and without the need to isolate or remove any reagents from the previous step, 10 mol% Pd(PPh_3)$_4$ was added together with a mixture of NaO^{t}Bu and K_2CO_3 in a 1:1 ratio, following the protocol already reported in the literature.[57] The reaction was left to stand overnight in toluene at 110 °C, resulting in a yield of 82% (see Scheme 4.11). An optimisation table of this cyclisation step can also be found in the experimental section (see Table 4.15 experimental procedures).

4.4 Conclusions

In summary, our study focused on the Borrowing Hydrogen (BH) process using an earth-abundant Mn(I) tricarbonyl complex featuring bis(1,2,3-triazol-5-ylidene) ligands for the dialkylation of diamines and diols has been presented. The catalytic activity of [Mn(bis-trz)$(CO)_3$Br] **Mn1** was explored, and its remarkable efficiency in the *N*,*N*-dialkylation of diamines with primary alcohols was demonstrated. Notably, the catalytic system exhibited competitive performance compared to reported systems.

Moreover, the catalytic system was extended to the synthesis of 1,2,3,4-tetrahydroquinoxalines, a class of *N*-heterocyclic compounds with significant pharmacological and biological activity. Furthermore, our studies demonstrated the catalytic system's applicability in the synthesis of other *N*-heterocycles, such as indoles and tetrahydroquinolines, providing additional insights into the versatility of the BH process.

While our system exhibited promising results, certain limitations were identified, particularly in the synthesis of 1,2,3,4-tetrahydroquinoxalines which efficiency was affected by the choice of secondary alcohols, indicating a need for further improvement of the catalytic system. The present study demonstrated the catalytic potential of **Mn1** in a variety of BH transformations, offering a sustainable and economically viable alternative for the synthesis of valuable *N*-heterocyclic compounds.

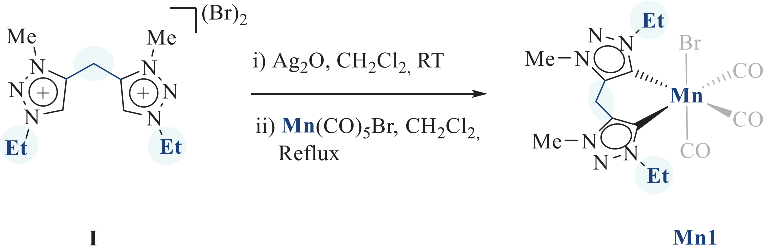
4.5 Experimental Procedures

4.5.1 General Considerations

Syntheses of ligands and metal complex were performed under a nitrogen atmosphere in dried and degassed solvents using standard Schlenk techniques. Solvents were purified using appropriate drying agents. Deuterated solvents were degassed and stored over molecular sieves. Aniline was distilled and *o*-phenylenediamine was recrystallized from hot $CHCl_3$ before used. All other reagents were purchased from commercial suppliers and used without further purification. Catalytic experiments were carried out under a nitrogen atmosphere. Elemental analysis was performed in our laboratories at ITQB-NOVA by C. Almeida. ESI-HRMS data were provided by the Mass Spectrometry Unit (UniMS), ITQB/IBET. Infrared spectra were recorded on samples as KBr pellets using a Bruker IFS 66/S ATR-FTIR spectrometer. The preparation of compounds **I**[1,2] and **Mn1**[1], was performed following the procedures described in the literature. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer. The samples were prepared on 5 or 3 mm NMR tubes using $CDCl_3$ as solvent. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R-H) and relative intensity of signal multiplicity (nH, with n being the number of protons) of NMR signals are described as singlet (s), broad singlet (br s), doublet of doublets (dd), triplet of doublets (td), doublet (d), triplet (t) and multiplet (m) with coupling constant (*J*) being given in Hz.

4.5.2 Synthesis of Mn1 complex

4.5.2.1 Procedure for the synthesis of complex Mn1



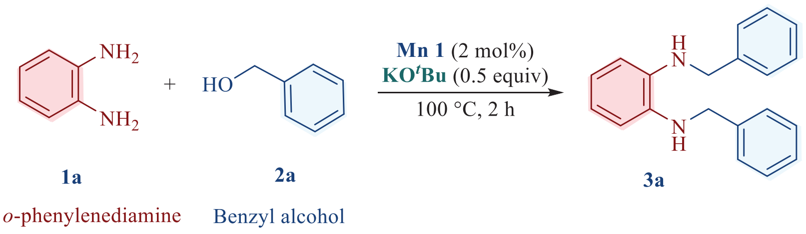
Scheme 4.12. Synthesis of complex **Mn1**.

The appropriate bis-triazolium bromide **I** (1 mmol) salt was dissolved in dry dichloromethane, Ag_2O (1.2 mmol) was added at room temperature, and the mixture was stirred for 4 h. Then, $Mn(CO)_5Br$ (1 mmol) was added, and the mixture was heated under reflux for 72 h. After cooling to room temperature, the solution was filtered through a pad of Celite and concentrated to dryness. The residue was washed with Et_2O (3 × 15 mL) to yield the corresponding Mn complex as yellow solids.

Characterization of Mn1: Yellow crystalline solid was isolated from CH_2Cl_2/hexane recrystallization. Isolated yield of **Mn1**: (0.122 g, 54% yield). ^{1}H-NMR (400MHz, DMSO-d$_6$): δ_H 4.78–4.72 (q, $3J_{H-H}$= 7.3 Hz, 4H, NCH_2CH_3), 4.32 (d, $2J_{H-H}$ = 18.0Hz, 1H, $CH_{2\ linker}$), 4.22 (s, 3H, NCH_3), 4.17 (s, 3H, NCH_3), 4.10 (d, $2J_{H-H}$=18.4 Hz, 1H, $CH_{2\ linker}$), 1.59 (t, $3J_{H-H}$ = 7.2 Hz, 3H, NCH_2CH_3), 1.54 (t, $3J_{H-H}$ = 7.2 Hz, 3H, NCH_2CH_3). ^{13}C{1H} NMR (100MHz, DMSO-d6): δ C 221.36 (CO), 217.51 (CO), 165.31 ($C_{carbene}$-Mn), 142.10 (C_{trz}-NCH_3), 48.89 and 47.77 (C_{trz}-NCH_2CH_3), 36.11 (C_{trz}-NCH_3), 21.10 (C_{trz}-$CH_{2linker}$), 15.79 (C_{trz}-NCH_2CH_3). Selected IR data (KBr): ν (CO) 1995 s, 1908 s, 1884 s cm−1. Anal. Calcd for $C_{14}H_{18}BrMnN_6O_3$: C, 37.11; H, 4.00; N, 18.54. Found: C, 37.00; H, 4.25; N, 18.50.

4.5.3 Catalytic reactions of diamines and diols

4.5.3.1 General procedure for the *N,N*-dialkylation of diamines with primary alcohols



Scheme 4.13. *N,N*-dialkylation of *o*-phenylenediamine with benzyl alcohol, catalysed by **Mn1**.

The reaction of *o*-phenylenediamine **1a** (54 mg, 0.5 mmol) with benzyl alcohol **2a** (104 µl, 1.0 mmol) was carried out in neat conditions, in the presence of **Mn1** (4.5 mg, 2 mol%, with respect to *o*-phenylenediamine **1a**) and KO^{t}Bu (28 mg, 0.25 mmol). The reaction was performed in a 10 mL screw-caped schlenk equipped with a micro magnetic stir bar (2x5 mm) under nitrogen atmosphere, heating at 100 °C during 2 h. After cooling, the reaction mixture was dissolved in chloroform and filtered through a pad of celite, and all the volatiles were removed under vacuum. The resulting crude was analyzed in chloroform-d_3 and the yield of diamine **3a** was determined by recording the ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard (42 mg, 0.25 mmol).

^{1}H-NMR of **3a** (400 MHz, $CDCl_3$): δ 7.45–7.20 (m, 10H), 6.85–6.70 (m, 4H), 4.32 (s, 4H) ppm. In accordance with the literature.[50]

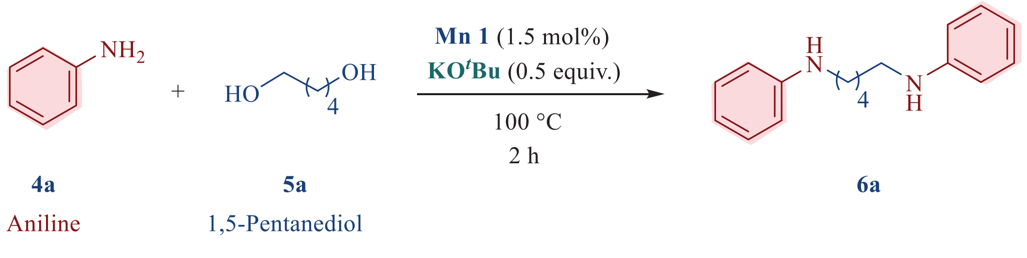
4.5.3.2 Optimization studies for the *N,N*-dialkylation of *o*-phenylenediamine 1a with benzyl alcohol 2a

Table 4.7. Optimization of the reaction conditions for the dialkylation of *o*-phenylenediamine **1a** with benzyl alcohol **2a** [a]

Entry	Cat. Loading (mol%)	KO^{t}Bu (equiv.)	Alcohol (equiv.)	Temp. (°C)	3a (%)[b]
1	4	0.5	2	130	98
2	2	0.5	2	130	96
3	2	0.5	2	100	96
4	2	0.5	1	100	35
5	2	0.2	2	100	81
6	2	0.2	2.5	100	85
7	1	0.5	2	100	80
8	1	0.5	2.5	100	81
9	2	-	2	130	-
10	-	0.5	2	130	-

[a]**Reaction conditions:** *o*-phenylenediamine (0.5 mmol), benzyl alcohol, KO^{t}Bu, catalyst, neat conditions, 2 h, in a closed Schlenk under N_2. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

4.5.3.3 General procedure for the direct reaction of primary anilines with diols



Scheme 4.14. Dialkylation of 1,5-pentanediol with aniline, catalysed by **Mn1**.

The reaction of aniline **4a** (45 µl, 0.5 mmol) with 1,5-pentanediol **5a** (79 µl, 0.75 mmol) was carried out in neat conditions, in the presence of **Mn1** (3.9 mg, 1.5 mol%, with respect to aniline **4a**) and KO^{t}Bu (28 mg, 0.25 mmol). The reaction was performed in a 10 mL screw-caped schlenk equipped with a micro magnetic stir bar (2x5 mm) under nitrogen atmosphere, heating at 100 °C during 2 h. After cooling, the reaction mixture was dissolved in chloroform, filtered over celite, and all the volatiles were removed under vacuum. An aliquot of crude was analyzed in chloroform-d_3 and the yield of diamine **6a** was determined by recording the ^{1}H-NMR spectrum using 1,3,5-trimethoxybenzene as internal standard (42 mg, 0.25 mmol).

^{1}H-NMR of **6a** (400 MHz, $CDCl_3$): δ 7.18 (t, J = 7.8 Hz, 4H), 6.70 (t, J = 7.4 Hz, 2H), 6.60 (d, J = 7.8 Hz, 4H), 3.13 (t, 2H) ppm. In accordance with the literature.[17]

4.5.3.4 Optimization studies for the direct reaction of aniline with 1,5-pentanediol

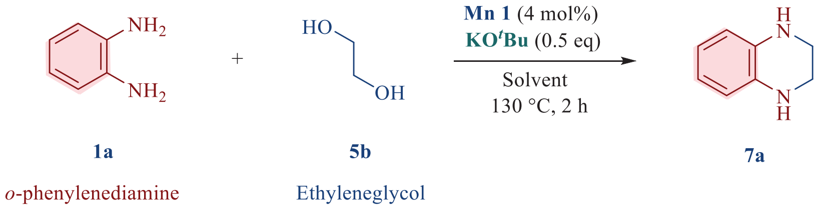
Table 4.8. Screening of the reaction conditions for the dialkylation of 1,5-pentanediol with aniline[a]

Entry	Aniline **4a** (mmol)	Alcohol **5a** (equiv.)	**6a** (%)[b]
1	0.5	2	>99
2	0.5	1.5	>99
3	0.5	0.5	39
4	1	0.5	37

[a] **Reaction conditions:** Aniline, 1,5-pentanediol, catalyst (1.5 mol%), KO^tBu (0.5 equiv), neat conditions, 100 °C, 2 h, in a closed Schlenk under N_2. [b] Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

4.5.4 Catalytic synthesis of tetrahydroquinoxalines

4.5.4.1 General procedure for the synthesis of tetrahydroquinoxalines



Scheme 4.15. Synthesis of 1,2,3,4-tetrahydroquinoxaline **7a**, catalysed by **Mn1.**

The reaction of *o*-phenylenediamine **1a** (54 mg, 0.5 mmol) with ethyleneglycol **5b** (56 µl, 1.0 mmol) was carried out in neat conditions, in the presence of **Mn1** (9 mg, 4 mol%, with respect to *o*-phenylenediamine **1a**) and *t*-BuOK (28 mg, 0.25 mmol). The reaction was performed in a 10 mL screw-caped schlenk equipped with a micro magnetic stir bar (2x5 mm) under nitrogen atmosphere, heating at 100 °C during 2 h. After cooling, the reaction mixture was dissolved in chloroform, filtered over celite, and all the volatiles were removed under vacuum. An aliquot of crude was analyzed in chloroform-d_3 and the yield of diamine **6a** was determined by recording the ^{1}H-NMR spectrum using 1,3,5-trimethoxybenzene as internal standard (42 mg, 0.25 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.60-6.45 (m, 4H), 3.60 (br s, 2H), 3.42 (s, 4H) ppm. In accordance to literature.[58]

4.5.4.2 Optimization studies for the synthesis of tetrahydroquinoxaline 7a from *o*-phenylenediamine and ethyleneglycol

Table 4.9. Optimization of the reaction conditions for the synthesis of 1,2,3,4-tetrahydroquinoxaline from *o*-phenylenediamine and ethyleneglycol[a]

Entry	Cat. Loading (mol%)	KO^{t}Bu (equiv.)	Alcohol (equiv.)	Temp. (°C)	Time (h)	**7a** (%)[b]
1	1.5	0.5	2	100	2	27
2	2	0.5	2	100	2	39
3	2	0.5	1	100	2	20
4	4	0.5	2	100	2	50
5	4	0.5	2	130	2	75
6	4	0.5	2	130	16	75
7	5	0.5	2	130	2	73
8	4	0.5	2	150	2	59
9	4	0.5	4	130	2	41
10	4	1	2	130	2	44
11	4	0.6	2	130	2	67
12	4	0.4	2	130	2	61
13	4	0.2	2	130	2	56
14	-	0.5	2	130	2	-
15	4	-	2	130	2	-

[a]**Reaction conditions:** functionalized aniline (0.5 mmol), ethyleneglycol, KO^{t}Bu, catalyst, neat conditions, in a closed schlenk under N_2. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

Table 4.10. Screening of bases for the synthesis of tetrahydroquinoxalines

Entry	Base	**7a** (%)[b]
1	$CsCO_3$	44
2	K_2CO_3	30
3	KO^{t}Bu	75
4	NaO^{t}Bu	41
5	KOH	66
6	NaOH	55
7	NaH	52

[a]**Reaction conditions:** *o*-phenylenediamine (0.5 mmol), ethyleneglycol (1 mmol), base (0.5 equiv), catalyst (4 mol %), neat conditions, 130 °C, 2 h, in a closed schlenk under N_2. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

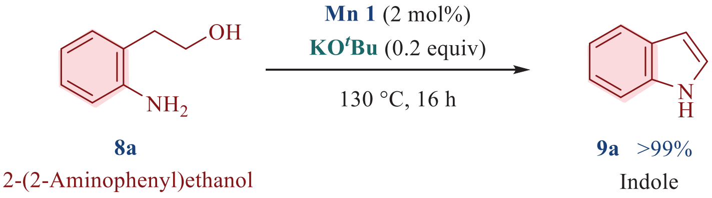
Table 4.11. Screening of solvents for the synthesis of tetrahydroquinoxalines

Entry	Solvent	**7a** (%)[b]
1	Toluene	28
2[c]	Toluene	28
3	CH_3CN	34
4	*tert*-butanol	44
5	*tert*-AmOH	47
6[d]	H_2O	15
7	neat	75
8[c]	neat	42

[a]**Reaction conditions:** *o*-phenylenediamine (0.5 mmol), ethyleneglycol (1 mmol), KO^tBu (0.5 equiv.), catalyst (4 mol %), solvent, 130 °C, 2 h, in a closed schlenk under N_2. [b]Yields determined by quantitative ^1H-NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]With 100 mg of 3 Å Molecular Sieves. [d]Using 0.5 equiv. of KOH instead of KO^tBu.

4.5.5 Catalytic synthesis of other *N*-heterocycles

4.5.5.1 Procedure for the synthesis of indole 9a



Scheme 4.16. Synthesis of the indole **9a**, catalysed by **Mn1**.

The reaction of 2-(2-aminophenyl)ethanol **8a** (69 mg, 0.5 mmol) to form the indole **9a** was carried out in neat conditions, in the presence of **Mn1** (4.5 mg, 2 mol%, with respect to **8a**) and KO^tBu (11 mg, 0.1 mmol). The reaction was performed in 10 mL screw-caped schlenk equipped with a micro magnetic stir bar (2x5 mm) under nitrogen atmosphere, heating at 130 °C during 16 h. After cooling, the reaction mixture was dissolved in chloroform, filtered over celite, and all the volatiles were removed under vacuum. An aliquot of crude was analyzed in chloroform-d_3 and the yield of diamine **9a** was determined by recording the ^{1}H-NMR spectrum using 1,3,5-trimethoxybenzene as internal standard (42 mg, 0.25 mmol).

^{1}H-NMR (400 MHz, CDCl$_3$) δ 8.2 (br, 1H), 7.65 (dd, J = 7.8 Hz, 1H), 7.40 (dd, J = 8.4, 1H), 7.30-7.27 (m, 1H), 7.21-7.19 (m, 2H), 6.56 (s, 1H) ppm. In accordance to literature.[59]

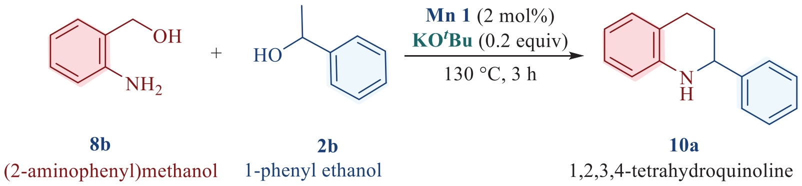
4.5.5.2 Optimization studies for the synthesis of indole 9a from 2-(2-aminophenyl)ethanol

Table 4.12. Screening of the reaction conditions for the synthesis of indole 9a from 2-(2-aminophenyl)ethanol[a]

Entry	KO^{t}Bu (equiv.)	Temp. (°C)	Time (h)	**9a** (%)[b]
1	0.5	100	16	28
2	0.5	100	3	26
3	0.5	130	3	51
4	1	130	16	44
5	0.5	130	16	75
6	0.2	130	16	>99
7	0.2	130	2	64

[a]**Reaction conditions:** 2-(2-Aminophenyl)ethanol (0.5 mmol), KO^{t}Bu, catalyst (2 mol %), neat conditions, 2 h, in a closed Schlenk under N$_2$. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

4.5.5.3 Procedure for the synthesis of 1,2,3,4-tetrahydroquinoline 10a



Scheme 4.17. Synthesis of 1,2,3,4-tetrahydroquinoline **10a**, catalysed by **Mn1.**

The reaction of (2-aminophenyl)methanol **8b** (62 mg, 0.5 mmol) with 1-phenylethanol (**2b**) (63 µl, 1.0 mmol) was carried out in neat conditions, in the presence of **Mn1** (4.5 mg, 2 mol%, with respect to **8b**) and KO^{t}Bu (11 mg, 0.1 mmol). The reaction was performed in a 10 mL screw-caped schlenk equipped with a micro magnetic stir bar (2x5 mm) under nitrogen atmosphere, heating at 130 °C during 3 h. After cooling, the reaction mixture was dissolved in chloroform, filtered over celite, and all the volatiles were removed under vacuum. An aliquot of crude was analyzed in chloroform-d_3 and the yield of diamine **10a** was determined by recording the ^{1}H-NMR spectrum using 1,3,5-trimethoxybenzene as internal standard (42 mg, 0.25 mmol).

4.5.5.4 Optimization studies for the synthesis of 10a from (2-aminophenyl)methanol and 1-phenylethanol

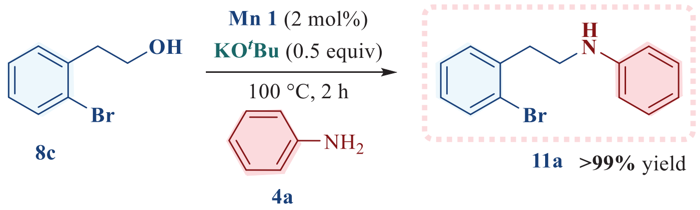
Table 4.13. Optimization studies for the synthesis of 1,2,3,4-tetrahydroquinoline from (2-aminophenyl)methanol and 1-phenylethanol[a]

Entry	Cat. loading (mol%)	KO^{t}Bu (equiv.)	Temp. (°C)	Time (h)	**10a** (%)[b]	**10b** (%)[b]
1	2	0.5	100	3	-	-
2	2	0.5	130	3	36	15
3	2	0.5	130	16	35	33
4	4	0.5	130	3	26	14
5	2	0.2	130	3	40	20
6	2	0.2	150	16	40	20

[a] **Reaction conditions:** (2-Aminophenyl)methanol (0.5 mmol), KO^{t}Bu, catalyst, neat conditions, in a closed Schlenk under N_2. [b] Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

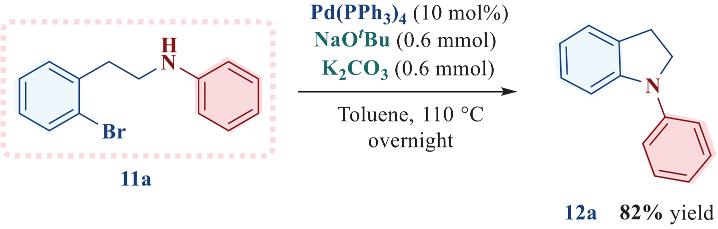
4.5.6 Bimetallic approach towards an indoline

4.5.6.1 Procedure for the synthesis of indoline 12a



Scheme 4.18. Alkylation of aniline **4a** with 2-(2-Bromophenyl)ethanol **8c**, catalysed by **Mn1**.

The reaction of aniline **4a** (46 µl, 0.5 mmol) with 2-(2-bromophenyl)etanol **8c** (136 µl, 1.0 mmol) was carried out in neat conditions, in the presence of **Mn1** (4.5 mg, 2 mol%, with respect to aniline **4a**) and KO^{t}Bu (28 mg, 0.5 mmol). The reaction was performed in a clean oven-dried 10 mL screw-caped schlenk equipped with a micro magnetic stir bar (2x5 mm) under nitrogen atmosphere, heating at 100 °C during 2 h. An aliquot of the crude was then analysed in chloroform-d$_3$, and the yield of compound **11a** was determined by recording the ^{1}H-NMR spectrum using 1,3,5-trimethoxybenzene as an internal standard (42 mg, 0.25 mmol).



Scheme 4.19. Cyclization of **11a** towards indoline **12a**, catalysed by **Mn1**.

After cooling, the reaction mixture was opened under a nitrogen pressure system to introduce Pd(PPh$_3$)$_4$ (10 mol%), NaO^{t}Bu (0.6 mmol), and K$_2$CO$_3$ (0.6 mmol), along with dry toluene at 110 °C. The reaction was left to stir overnight, after which the solvent was evaporated. The resulting crude product was dissolved in chloroform, filtered through celite, and all volatiles were removed under vacuum.

Flash column chromatography was carried out in order to obtain compound **12a**.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.25 – 7.22 (m, 2H), 7.25 – 7.14 (m, 2H), 7.10-6.95 (m, 1H), 6.94 (t, J = 7.2 Hz, 1H), 6.76 (t, J = 7.3 Hz, 1H), 3.95 (t, J = 8.4 Hz, 2H), 3.13 (t, J = 8.3 Hz, 2H) ppm. In accordance to literature.[60]

4.5.6.2 Optimization studies for the synthesis of 11a and 12a

Table 4.14. Optimization studies for the synthesis of **11a** from aniline **4a** and 2-(2-Bromophenyl)etanol **8c** [a]

Entry	Cat. loading (mol%)	**8c** (equiv.)	**11a** (%)[b]
1	1.5	1.5	76
2	2	1.5	88
3	1.5	2	92
4	2	2	>99

[a]**Reaction conditions:** Aniline **4a** (0.5 mmol), KO^{t}Bu (0.5 equiv), **Mn1**, neat conditions, in a closed Schlenk under N_2. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

Table 4.15. Optimization studies for the synthesis of *N*-phenyl indoline **12a** from aniline **4a** and 2-(2-Bromophenyl)etanol **8c** [a]

Entry	Cat. loading (mol%)	**8c** (equiv.)	**11a** (%)[b]	**12a** (%)
1	1.5	1.5	76	62
2	2	1.5	88	72
3	1.5	2	92	75
4	2	2	>99	82

[a]**Reaction conditions:** Aniline **4a** (0.5 mmol), KO^{t}Bu (0.5 equiv), **Mn1**, neat conditions, in a closed Schlenk under N_2. [b]Yields determined by quantitative ^{1}H-NMR using 1,3,5-trimethoxybenzene as the internal standard.

4.6 Acknowledgments

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5.

Conclusions and outlook

This research focused on optimising the selective synthesis of imines through the dehydrogenative condensation of anilines and alcohols, exploring different catalytic systems to develop one-pot cascade reactions towards the synthesis of high-value molecules. Imines, as key building blocks, enabled the generation of *N*-alkylated products and *N*-heterocycles of interest, highlighting their importance as intermediates in synthesising complex compounds.

In the first part of the project, imines were synthesised from anilines and primary benzylic alcohols, evaluating a novel manganese complex with N^N triazole ligands. This system allowed for the first time the efficient synthesis of imines with nitrogen-containing heterocycles, demonstrating air stability and efficient utilisation of atmospheric oxygen. Exceptional yields of up to 99% were obtained under optimised conditions (3 mol% Mn catalyst, 0.5 equiv. KOtBu in toluene at 110 °C with molecular sieves). However, limitations in reactivity with unactivated aliphatic alcohols and secondary alcohols were identified, suggesting areas for improvement in future research.

In the second part of the work, commercial catalysts were investigated, highlighting the activity of $Pd(OAc)_2$ for the transformation of anilines with secondary alcohols. This system achieved imine yields of up to 75% without the need for additional bases. The resulting imines showed the ability to form enamines, which in turn serve as valuable resources for the construction of more complex *N*-heterocycles. A family of indoles was therefore synthesised from these imines, eliminating the need to isolate intermediates, thereby simplifying the process and improving overall efficiency. In addition, by adjusting the reaction conditions (including catalytic amounts of KOtBu in a closed inert system), the reaction was selectively driven towards secondary amine formation with yields up to 98%. However, working with imines as intermediates posed significant challenges, limiting the effective implementation of cascade systems. In contrast, the "borrowing hydrogen" principle proved more efficient for the formation of secondary amines, which can also serve as valuable building blocks for *N*-heterocycle synthesis.

The third part of the study focused mainly on BH transformations with emphasis on the construction of *N*-heterocycles such as 1,2,3,4-tetrahydroquinoxalines. To this end, a Mn(I) tricarbonyl complex with bis(1,2,3-triazol-5-ylidene) ligands was investigated for the dialkylation of diamines and diols. This catalytic system was found to be highly efficient, with yields of up to 99% achieved using catalytic amounts of the precatalyst [Mn(bis-trz)(CO)3Br] (2.0 mol%) and KOtBu (0.5 equiv) as the base at 130 °C under inert conditions and without the use of solvents, in only 2 hours. In addition, an innovative Mn/Pd bimetallic cascade route was implemented for the synthesis of indolines, further expanding the scope and applicability of this approach.

Overall, this study not only demonstrated the efficacy of the investigated catalytic systems for the synthesis of imines and *N*-heterocycles, but also opened new avenues for the development of sustainable and efficient synthetic methods in modern chemistry.

Annexes

Chapter 2 - Annexes

Manganese-Catalysed Synthesis of Imines from Primary Alcohols

A2.1 Characterisation of the complexe **Mn1**

(The ditriazole ligand was prepared according to previously described procedures).[1]

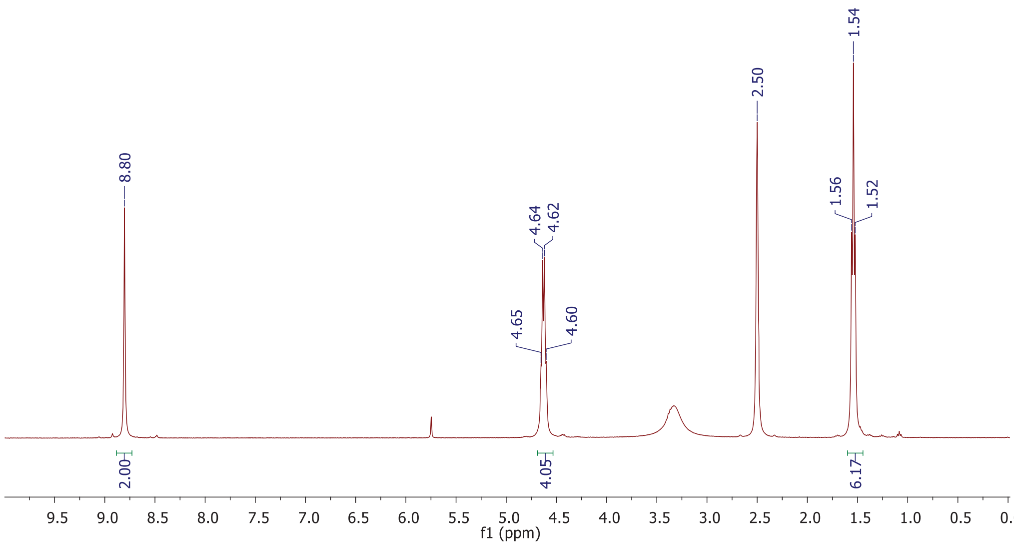

Figure A2.1. ^{1}H-NMR spectrum of complex **Mn1** (DMSO-d$_6$, 400 MHz, 23 °C).

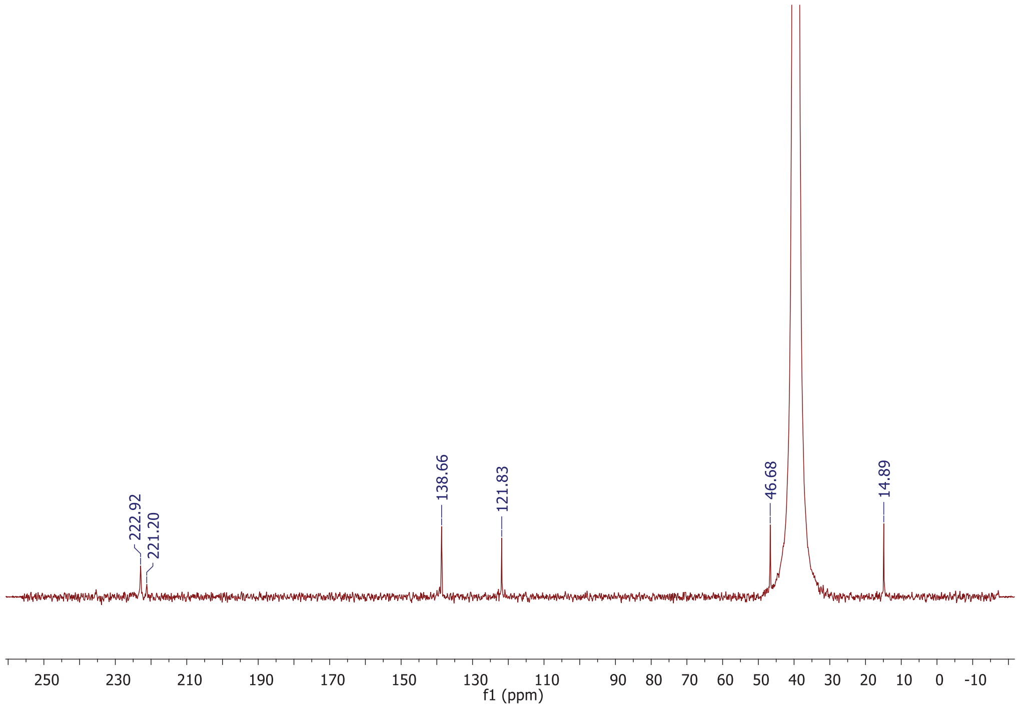

Figure A2.2. ^{13}C-NMR spectrum of complex **Mn1** (DMSO-d$_6$, 400 MHz, 23 °C).

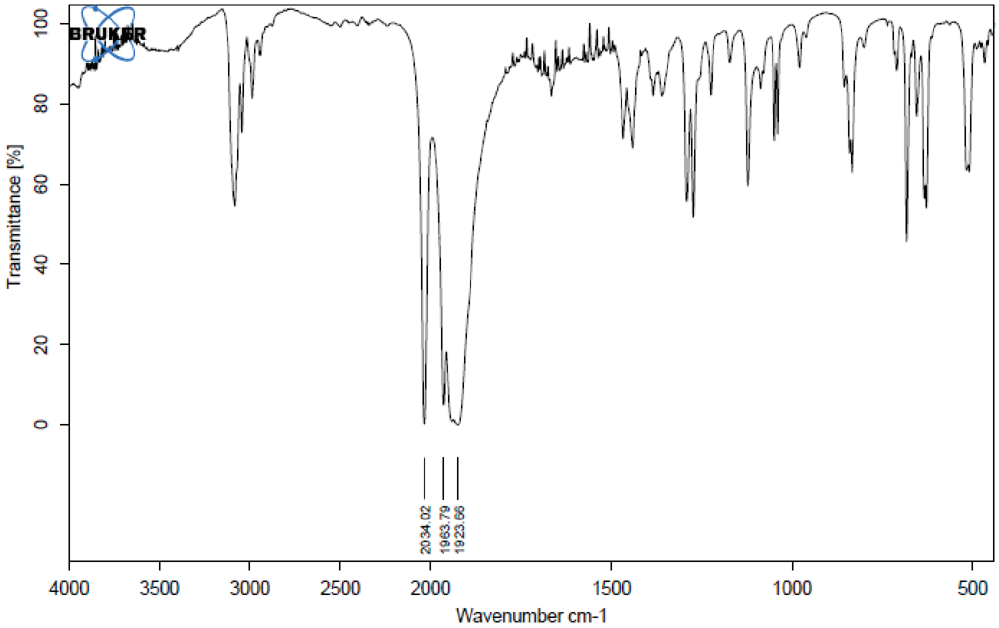

Figure A2.3. IR spectrum of complex **Mn1** (KBr, cm^{-1}).

A2.2 X-Ray crystallographic studies of **Mn1**

A crystal suitable for single-crystal X-ray analysis of complex **Mn1** was selected, covered with Fomblin (polyfluoro ether oil), and mounted on a nylon loop. The data was collected at room temperature on a Bruker D8 Venture diffractometer equipped with a Photon 100 CMOS detector, using graphite monochromated Mo-Kα radiation (λ=0.71073 Å). The data was processed using the APEX3 suite software package, which includes integration and scaling (SAINT), absorption corrections (SADABS)[2] and space group determination (XPREP). Structure solution and refinement were done using direct methods with the programs SHELXT 2014/5 and SHELXL (version 2018/3)[3,4] inbuilt in APEX, and WinGX-Version 2021.3[5] software packages. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted in idealised positions and allowed to refine riding on the parent carbon or oxygen atom with C–H distances of 0.93 Å, 0.96 Å, and 0.97 Å for aromatic, methyl, and methylene H atoms, respectively. The molecular diagrams were drawn with ORTEP-3 (version 2020.1),[3] included in the software package. Crystal data for **Mn1**:

C11H12BrMnN6O3, FW = 411.09, triclinic, space group P-1 (no.2), Dc = 1.659 g cm-3, Z = 4, a = 10.4780(6), b = 12.2656(8), c = 13.4843(8) Å, α = 74.007(3), β = 89.407(2), γ = 81.390(2) °, V = 1646.27(17) Å3, T = 296(2) K, Bruker D8 Venture diffractometer with Photon 100 CMOS area detector, λ (MoKα) = 0.71073 Å, μ = 3.248 mm-1. Of 70351 reflections measured, 8188 were unique. Refinement on F2 concluded with the values R1 = 0.0490 and wR2 = 0.0986 for 401 parameters and 5055 data with I > 2σI. The data was deposited in the CCDC under deposit number 2102122.

Table A2.1. Bond lengths [Å] and angles [°] for **Mn1**.

Bond lengths	
C(1)-N(1)	1.363(4)
C(1)-C(2)	1.370(5)
C(1)-C(5)	1.438(5)
C(2)-N(3)	1.328(5)
C(2)-H(2)	0.9300
C(3)-C(4)	1.472(5)
C(3)-N(3)	1.476(5)
C(3)-H(3A)	0.9700
C(3)-H(3B)	0.9700
C(4)-H(4A)	0.9600
C(4)-H(4B)	0.9600
C(4)-H(4C)	0.9600
C(5)-C(6)	1.351(5)
C(5)-N(4)	1.368(4)
C(6)-N(6)	1.343(5)
C(6)-H(6)	0.9300
C(7)-C(8)	1.451(7)
C(7)-N(6)	1.464(5)
C(7)-H(7A)	0.9700
C(7)-H(7B)	0.9700
C(8)-H(8A)	0.9600
C(8)-H(8B)	0.9600
C(8)-H(8C)	0.9600
C(9)-O(1)	1.124(5)
C(9)-Mn(1)	1.795(4)
C(10)-O(2)	1.140(4)
C(10)-Mn(1)	1.807(4)
C(11)-O(3)	1.141(5)
C(11)-Mn(1)	1.796(5)
C(12)-C(13)	1.355(5)
C(12)-N(7)	1.370(4)
C(12)-C(16)	1.438(5)
C(13)-N(9)	1.347(4)
C(13)-H(13)	0.9300
C(14)-C(15)	1.459(7)
C(14)-N(9)	1.479(5)
C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700
C(15)-H(15A)	0.9600
C(15)-H(15B)	0.9600
C(15)-H(15C)	0.9600
C(16)-C(17)	1.361(5)
C(16)-N(10)	1.366(4)
C(17)-N(12)	1.347(4)
C(17)-H(17)	0.9300
C(18)-N(12)	1.463(4)
C(18)-C(19)	1.481(6)
C(18)-H(18A)	0.9700
C(18)-H(18B)	0.9700
C(19)-H(19A)	0.9600
C(19)-H(19B)	0.9600
C(19)-H(19C)	0.9600
C(20)-O(4)	1.134(4)
C(20)-Mn(2)	1.787(4)
C(21)-O(5)	1.133(4)
C(21)-Mn(2)	1.812(4)
C(22)-O(6)	1.151(4)
C(22)-Mn(2)	1.785(4)
N(1)-N(2)	1.315(4)
N(1)-Mn(1)	2.042(3)
N(2)-N(3)	1.344(4)
N(4)-N(5)	1.316(4)
N(4)-Mn(1)	2.025(3)
N(5)-N(6)	1.333(4)
N(7)-N(8)	1.307(4)
N(7)-Mn(2)	2.047(3)
N(8)-N(9)	1.341(4)
N(10)-N(11)	1.311(4)
N(10)-Mn(2)	2.051(3)

N(11)-N(12)	1.336(4)
Mn(1)-Br(1)	2.5455(6)
Mn(2)-Br(2)	2.5390(6)

Bond angles

N(1)-C(1)-C(2)	107.2(3)
N(1)-C(1)-C(5)	113.9(3)
C(2)-C(1)-C(5)	138.9(4)
N(3)-C(2)-C(1)	104.7(3)
N(3)-C(2)-H(2)	127.6
C(1)-C(2)-H(2)	127.6
C(4)-C(3)-N(3)	113.1(3)
C(4)-C(3)-H(3A)	109.0
N(3)-C(3)-H(3A)	109.0
C(4)-C(3)-H(3B)	109.0
N(3)-C(3)-H(3B)	109.0
H(3A)-C(3)-H(3B)	107.8
C(3)-C(4)-H(4A)	109.5
C(3)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	109.5
C(3)-C(4)-H(4C)	109.5
H(4A)-C(4)-H(4C)	109.5
H(4B)-C(4)-H(4C)	109.5
C(6)-C(5)-N(4)	107.2(3)
C(6)-C(5)-C(1)	139.0(3)
N(4)-C(5)-C(1)	113.8(3)
N(6)-C(6)-C(5)	105.4(3)
N(6)-C(6)-H(6)	127.3
C(5)-C(6)-H(6)	127.3
C(8)-C(7)-N(6)	112.8(4)
C(8)-C(7)-H(7A)	109.0
N(6)-C(7)-H(7A)	109.0
C(8)-C(7)-H(7B)	109.0
N(6)-C(7)-H(7B)	109.0
H(7A)-C(7)-H(7B)	107.8
C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5
H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5
H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5
O(1)-C(9)-Mn(1)	177.4(5)
O(2)-C(10)-Mn(1)	178.7(4)
O(3)-C(11)-Mn(1)	178.4(5)
C(13)-C(12)-N(7)	107.5(3)
C(13)-C(12)-C(16)	137.8(3)
N(7)-C(12)-C(16)	114.7(3)
N(9)-C(13)-C(12)	104.5(3)
N(9)-C(13)-H(13)	127.7
C(12)-C(13)-H(13)	127.7
C(15)-C(14)-N(9)	111.7(4)
C(15)-C(14)-H(14A)	109.3
N(9)-C(14)-H(14A)	109.3
C(15)-C(14)-H(14B)	109.3
N(9)-C(14)-H(14B)	109.3
H(14A)-C(14)-H(14B)	107.9
C(14)-C(15)-H(15A)	109.5
C(14)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
C(14)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
C(17)-C(16)-N(10)	107.4(3)
C(17)-C(16)-C(12)	138.1(3)
N(10)-C(16)-C(12)	114.4(3)
N(12)-C(17)-C(16)	104.9(3)
N(12)-C(17)-H(17)	127.6
C(16)-C(17)-H(17)	127.6
N(12)-C(18)-C(19)	111.3(4)
N(12)-C(18)-H(18A)	109.4
C(19)-C(18)-H(18A)	109.4
N(12)-C(18)-H(18B)	109.4
C(19)-C(18)-H(18B)	109.4
H(18A)-C(18)-H(18B)	108.0
C(18)-C(19)-H(19A)	109.5
C(18)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(18)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
O(4)-C(20)-Mn(2)	176.6(3)
O(5)-C(21)-Mn(2)	177.3(3)
O(6)-C(22)-Mn(2)	176.3(3)
N(2)-N(1)-C(1)	110.3(3)
N(2)-N(1)-Mn(1)	132.2(2)
C(1)-N(1)-Mn(1)	117.2(2)
N(1)-N(2)-N(3)	105.0(3)
C(2)-N(3)-N(2)	112.8(3)
C(2)-N(3)-C(3)	129.3(3)
N(2)-N(3)-C(3)	117.9(3)
N(5)-N(4)-C(5)	109.8(3)
N(5)-N(4)-Mn(1)	132.5(2)
C(5)-N(4)-Mn(1)	117.7(2)
N(4)-N(5)-N(6)	105.8(3)
N(5)-N(6)-C(6)	111.7(3)
N(5)-N(6)-C(7)	119.6(3)
C(6)-N(6)-C(7)	128.7(4)
N(8)-N(7)-C(12)	110.3(3)
N(8)-N(7)-Mn(2)	133.2(2)
C(12)-N(7)-Mn(2)	116.4(2)
N(7)-N(8)-N(9)	105.3(3)
N(8)-N(9)-C(13)	112.3(3)
N(8)-N(9)-C(14)	119.9(3)
C(13)-N(9)-C(14)	127.7(3)

N(11)-N(10)-C(16)	109.9(3)
N(11)-N(10)-Mn(2)	133.5(2)
C(16)-N(10)-Mn(2)	116.6(2)
N(10)-N(11)-N(12)	106.1(3)
N(11)-N(12)-C(17)	111.7(3)
N(11)-N(12)-C(18)	119.9(3)
C(17)-N(12)-C(18)	128.4(3)
C(9)-Mn(1)-C(11)	88.7(2)
C(9)-Mn(1)-C(10)	90.55(16)
C(11)-Mn(1)-C(10)	92.36(19)
C(9)-Mn(1)-N(4)	95.69(18)
C(11)-Mn(1)-N(4)	172.64(17)
C(10)-Mn(1)-N(4)	93.50(15)
C(9)-Mn(1)-N(1)	90.67(14)
C(11)-Mn(1)-N(1)	96.73(16)
C(10)-Mn(1)-N(1)	170.85(16)
N(4)-Mn(1)-N(1)	77.36(12)
C(9)-Mn(1)-Br(1)	175.92(16)
C(11)-Mn(1)-Br(1)	87.57(17)
C(10)-Mn(1)-Br(1)	91.25(11)
N(4)-Mn(1)-Br(1)	87.86(8)
N(1)-Mn(1)-Br(1)	88.13(8)
C(22)-Mn(2)-C(20)	88.58(17)
C(22)-Mn(2)-C(21)	89.75(16)
C(20)-Mn(2)-C(21)	90.76(16)
C(22)-Mn(2)-N(7)	175.05(13)
C(20)-Mn(2)-N(7)	93.50(13)
C(21)-Mn(2)-N(7)	94.71(14)
C(22)-Mn(2)-N(10)	97.64(13)
C(20)-Mn(2)-N(10)	91.28(13)
C(21)-Mn(2)-N(10)	172.37(14)
N(7)-Mn(2)-N(10)	77.83(11)
C(22)-Mn(2)-Br(2)	89.80(12)
C(20)-Mn(2)-Br(2)	177.79(12)
C(21)-Mn(2)-Br(2)	90.74(10)
N(7)-Mn(2)-Br(2)	88.00(7)
N(10)-Mn(2)-Br(2)	87.44(7)

Table S2. Torsion angles [°] for 1.

N(1)-C(1)-C(2)-N(3)	0.1(4)
C(5)-C(1)-C(2)-N(3)	178.5(4)
N(1)-C(1)-C(5)-C(6)	-176.9(4)
C(2)-C(1)-C(5)-C(6)	4.8(8)
N(1)-C(1)-C(5)-N(4)	2.8(4)
C(2)-C(1)-C(5)-N(4)	-175.5(4)
N(4)-C(5)-C(6)-N(6)	0.5(4)
C(1)-C(5)-C(6)-N(6)	-179.8(4)
N(7)-C(12)-C(13)-N(9)	0.3(3)
C(16)-C(12)-C(13)-N(9)	179.8(4)
C(13)-C(12)-C(16)-C(17)	-2.9(7)
N(7)-C(12)-C(16)-C(17)	176.6(4)
C(13)-C(12)-C(16)-N(10)	-180.0(4)
N(7)-C(12)-C(16)-N(10)	-0.6(4)
N(10)-C(16)-C(17)-N(12)	-0.1(4)
C(12)-C(16)-C(17)-N(12)	-177.4(4)
C(2)-C(1)-N(1)-N(2)	-0.2(4)
C(5)-C(1)-N(1)-N(2)	-179.0(3)
C(2)-C(1)-N(1)-Mn(1)	174.9(2)
C(5)-C(1)-N(1)-Mn(1)	-3.9(3)
C(1)-N(1)-N(2)-N(3)	0.1(3)
Mn(1)-N(1)-N(2)-N(3)	-174.0(2)
C(1)-C(2)-N(3)-N(2)	-0.1(4)
C(1)-C(2)-N(3)-C(3)	-179.6(3)
N(1)-N(2)-N(3)-C(2)	0.0(4)
N(1)-N(2)-N(3)-C(3)	179.5(3)
C(4)-C(3)-N(3)-C(2)	123.5(4)
C(4)-C(3)-N(3)-N(2)	-56.0(5)
C(6)-C(5)-N(4)-N(5)	-0.3(4)
C(1)-C(5)-N(4)-N(5)	179.9(3)
C(6)-C(5)-N(4)-Mn(1)	179.3(2)
C(1)-C(5)-N(4)-Mn(1)	-0.6(4)
C(5)-N(4)-N(5)-N(6)	0.0(4)
Mn(1)-N(4)-N(5)-N(6)	-179.5(2)
N(4)-N(5)-N(6)-C(6)	0.3(4)
N(4)-N(5)-N(6)-C(7)	179.7(3)
C(5)-C(6)-N(6)-N(5)	-0.5(4)
C(5)-C(6)-N(6)-C(7)	-179.9(4)
C(8)-C(7)-N(6)-N(5)	115.4(5)
C(8)-C(7)-N(6)-C(6)	-65.3(6)
C(13)-C(12)-N(7)-N(8)	0.2(3)
C(16)-C(12)-N(7)-N(8)	-179.4(3)
C(13)-C(12)-N(7)-Mn(2)	-177.6(2)
C(16)-C(12)-N(7)-Mn(2)	2.8(3)
C(12)-N(7)-N(8)-N(9)	-0.5(3)
Mn(2)-N(7)-N(8)-N(9)	176.7(2)
N(7)-N(8)-N(9)-C(13)	0.7(4)
N(7)-N(8)-N(9)-C(14)	178.2(3)
C(12)-C(13)-N(9)-N(8)	-0.6(4)
C(12)-C(13)-N(9)-C(14)	-177.8(3)
C(15)-C(14)-N(9)-N(8)	54.7(5)
C(15)-C(14)-N(9)-C(13)	-128.3(5)
C(17)-C(16)-N(10)-N(11)	0.1(4)
C(12)-C(16)-N(10)-N(11)	178.1(3)
C(17)-C(16)-N(10)-Mn(2)	-179.9(2)
C(12)-C(16)-N(10)-Mn(2)	-1.9(3)
C(16)-N(10)-N(11)-N(12)	0.0(3)
Mn(2)-N(10)-N(11)-N(12)	180.0(2)
N(10)-N(11)-N(12)-C(17)	-0.1(4)
N(10)-N(11)-N(12)-C(18)	-179.0(3)
C(16)-C(17)-N(12)-N(11)	0.1(4)
C(16)-C(17)-N(12)-C(18)	179.0(3)
C(19)-C(18)-N(12)-N(11)	-104.7(4)
C(19)-C(18)-N(12)-C(17)	76.6(5)

A2.3 ^{1}H-NMR spectra and kinetic profile of the model reaction catalysed by **Mn1**

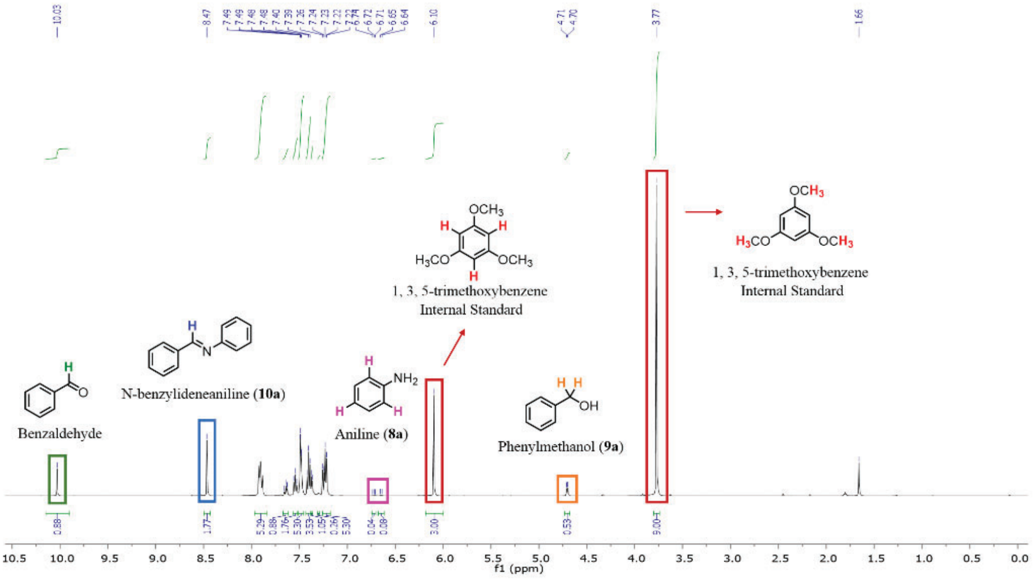

Figure A2.4. ^{1}H-NMR spectrum of the crude model reaction with **Mn1** ($CDCl_3$, 500 MHz, 23 °C). The yield of the imine **4a** was determined by ^{1}H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard.

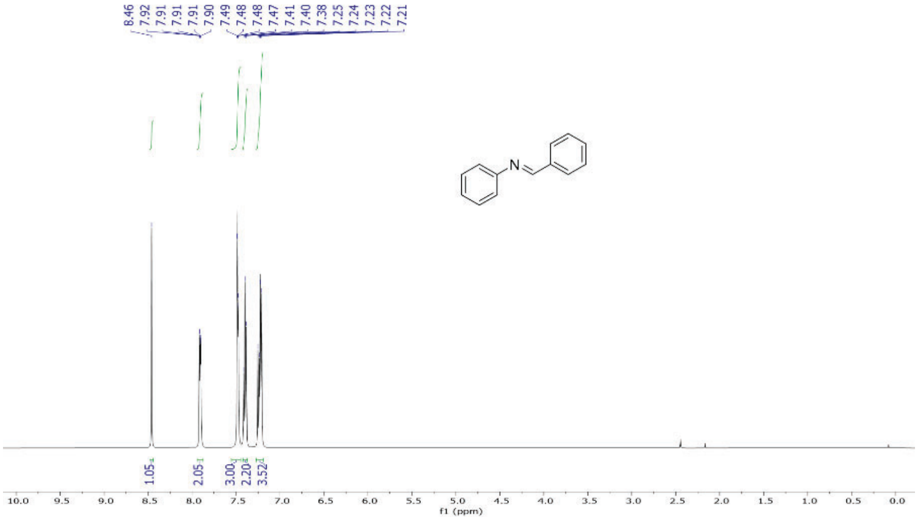

Figure A2.5. ^{1}H-NMR spectrum of the isolated imine **4a**, model reaction with **Mn1** ($CDCl_3$, 500 MHz, 23 °C).

Table A2.2. Data obtained for the synthesis of *N*-benzylideneaniline (**4a**) from aniline (0.3 mmol) and benzyl alcohol (0.36 mmol), using catalyst **Mn1** (3 mol%), KO^{t}Bu (0.5 equiv.), 260 mg of molecular sieves 3Å, in dry toluene at 110 ^{0}C.

Entry	Time (h)	Yield[a] (%)
1	1	0
2	2.5	77
3	3	85
4	5	92
5	16	96
6	24	99

[a] The yield was determined by ^{1}H NMR using 1,3,5- trimethoxybenzene as an internal standard.

A2.4 ^{1}H NMR spectra of the catalytic reactions

In all cases the yield of the corresponding imine was determined using 1,3,5-trimethoxybenzene (0.16mmol) as an internal standard.

(*E*)-1-(4-methoxyphenyl)-*N*-phenylmethanimine **3b** (94% yield)

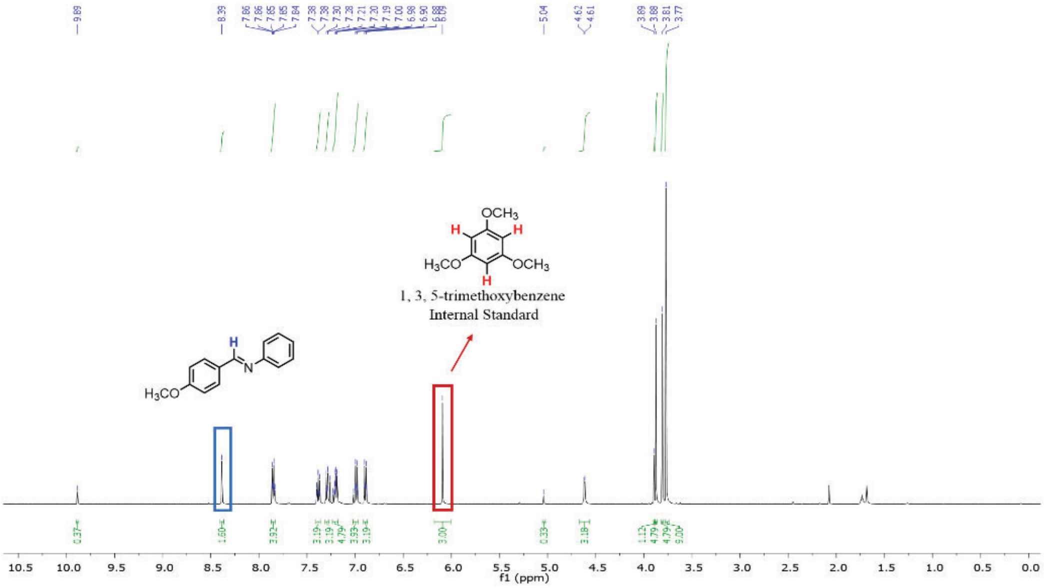

Figure A2.6. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-phenyl-1-(4-(trifluoromethyl)phenyl)methanimine **3c** (96% yield)

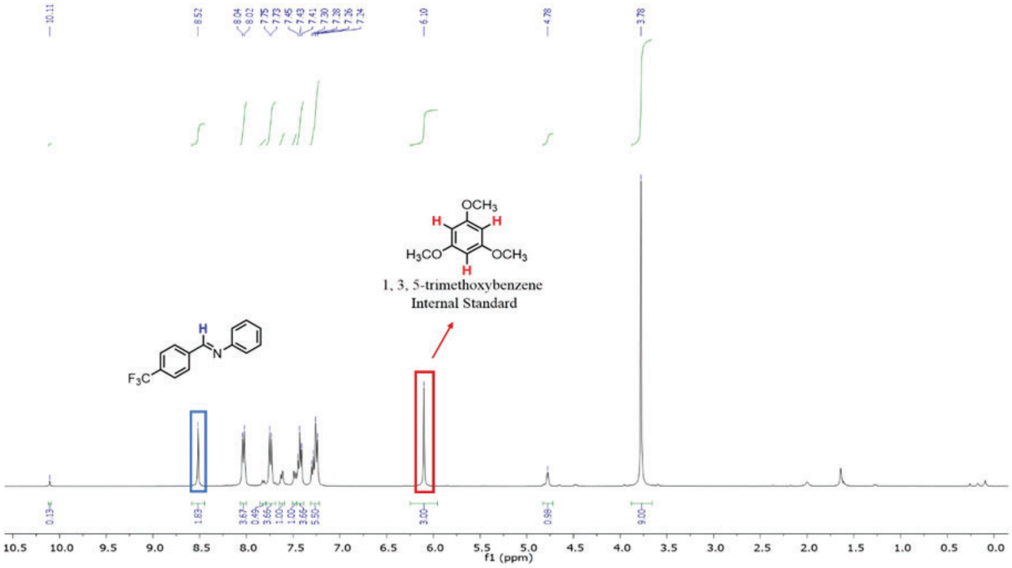

Figure A2.7. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-1-(furan-2-yl)-*N*-phenylmethanimine **3d** (81%)

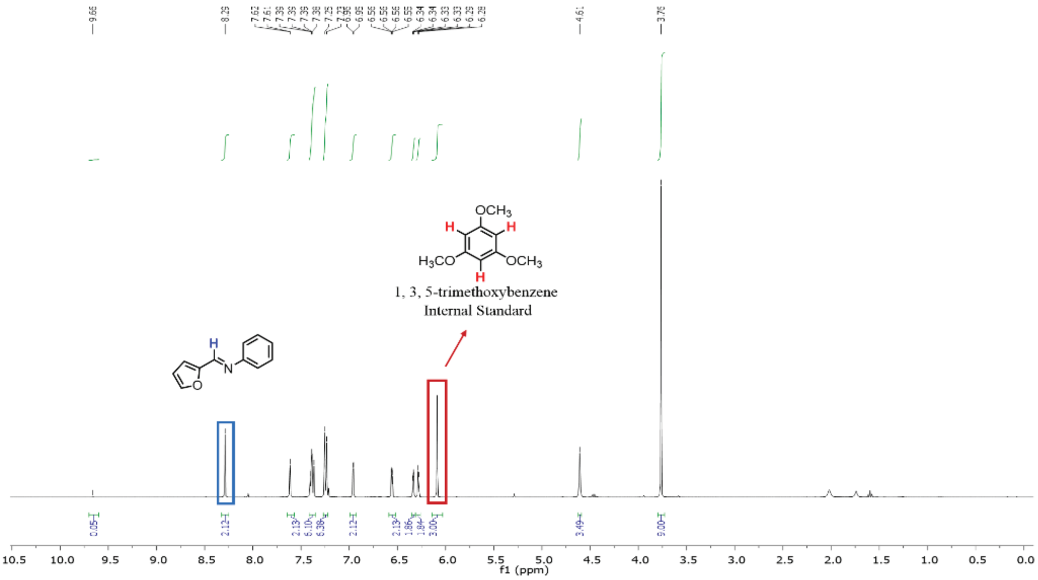

Figure A2.8. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-phenyl-1-(pyridin-2-yl)methanimine **3e** (84%).

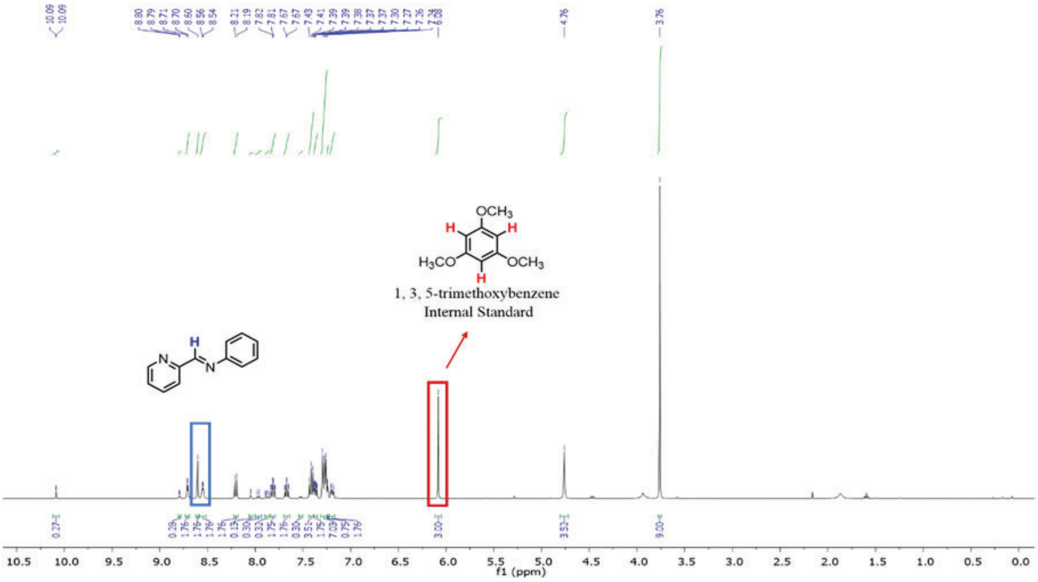

Figure A2.9. ¹H-NMR spectrum of the crude reaction (CDCl3, 500 MHz, 23 °C).

(*E*)-*N*-(3-nitrophenyl)-1-phenylmethanimine **3g** (68%)

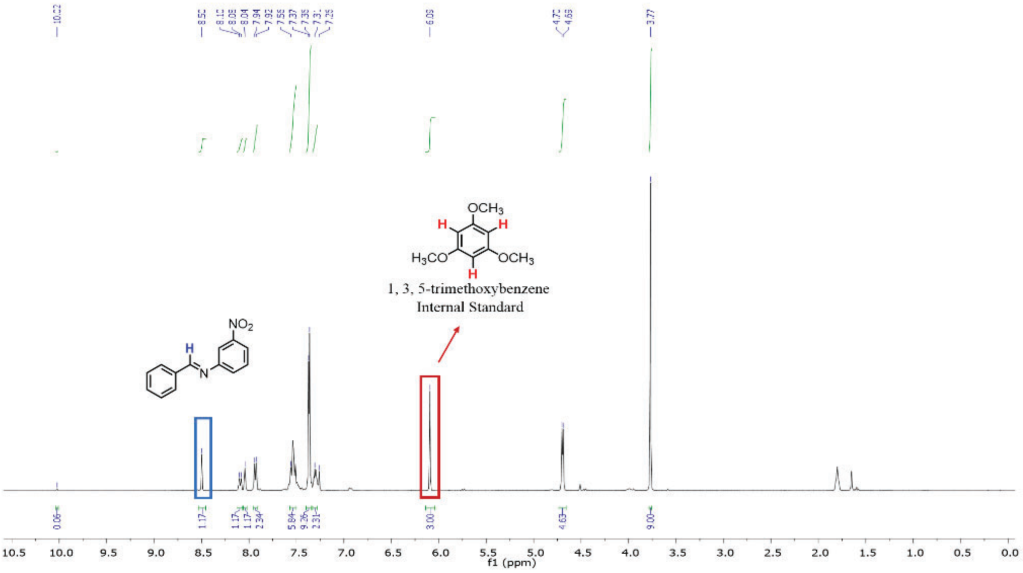

Figure A2.10. ¹H-NMR spectrum of the crude reaction (CDCl3, 500 MHz, 23 °C).

(*E*)-1-phenyl-*N*-(3-(trifluoromethyl)phenyl)methanimine **3h** (91%)

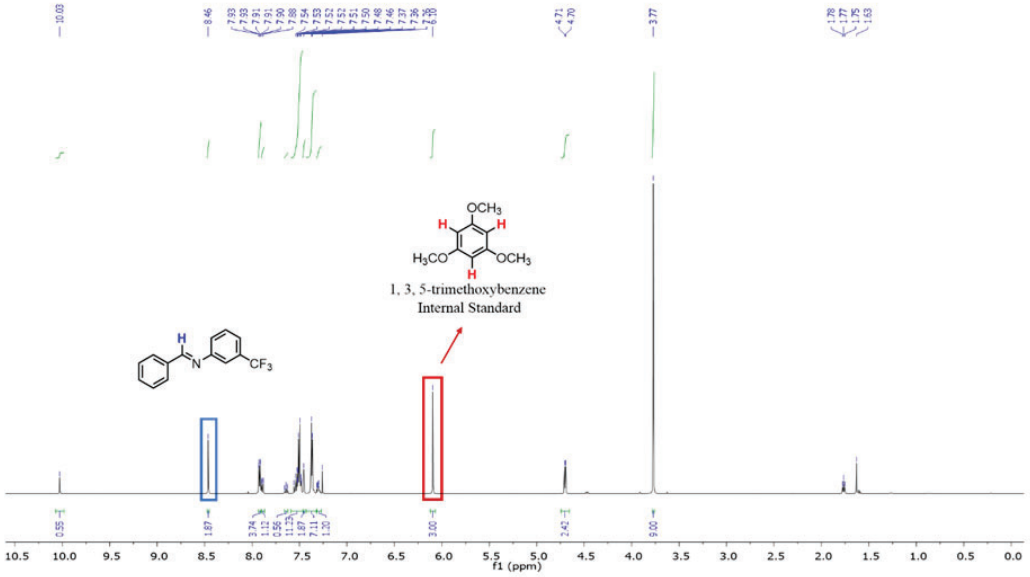

Figure A2.11. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C)

(*E*)-*N*-(3-bromophenyl)-1-phenylmethanimine **3i** (92%)

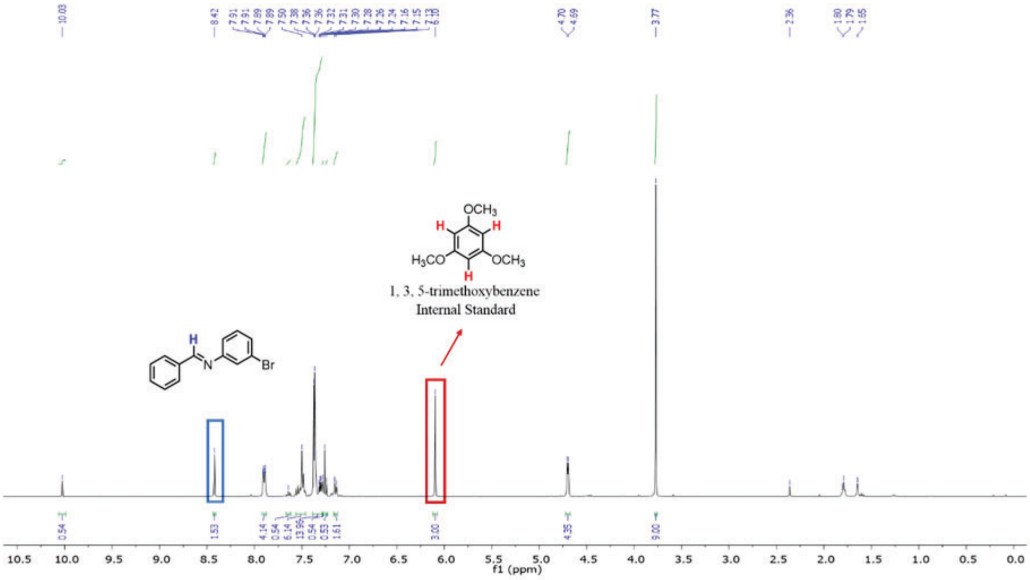

Figure A2.12. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(4-bromophenyl)-1-phenylmethanimine **3j** (85%)

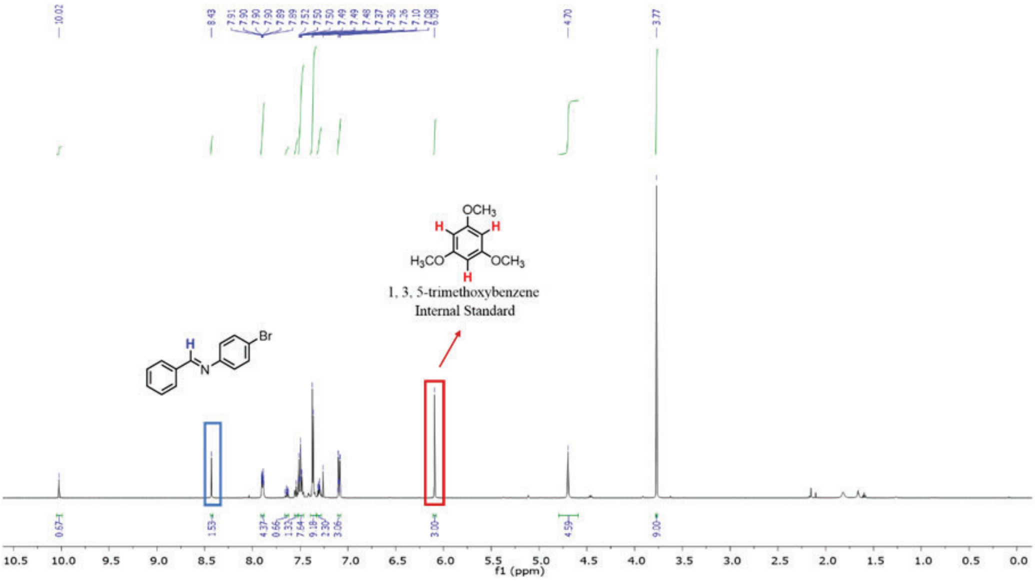

Figure A2.13. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(4-fluorophenyl)-1-phenylmethanimine **3k** (94%)

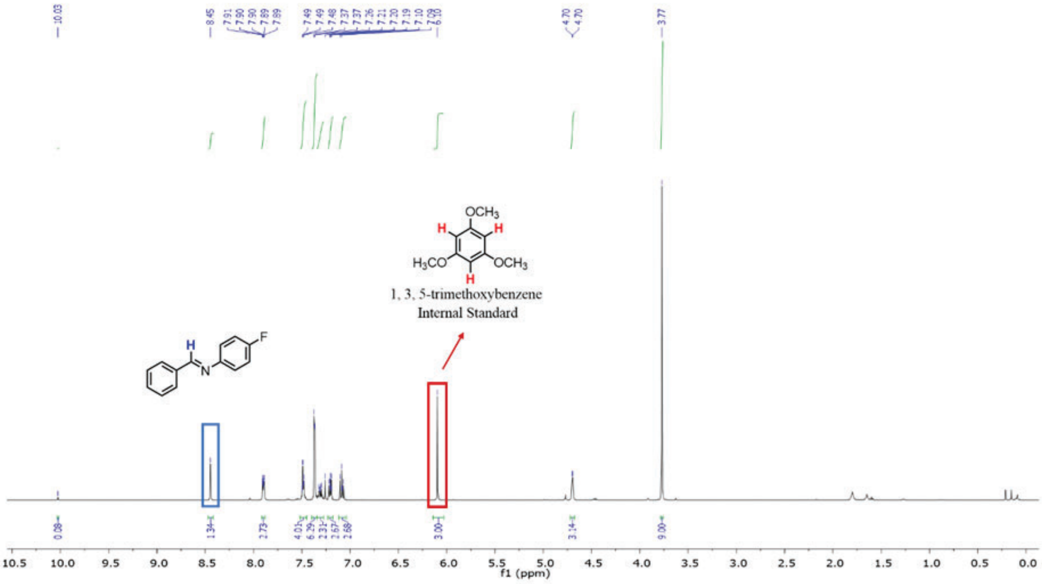

Figure A2.14. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(4-chlorophenyl)-1-phenylmethanimine **3l** (98%)

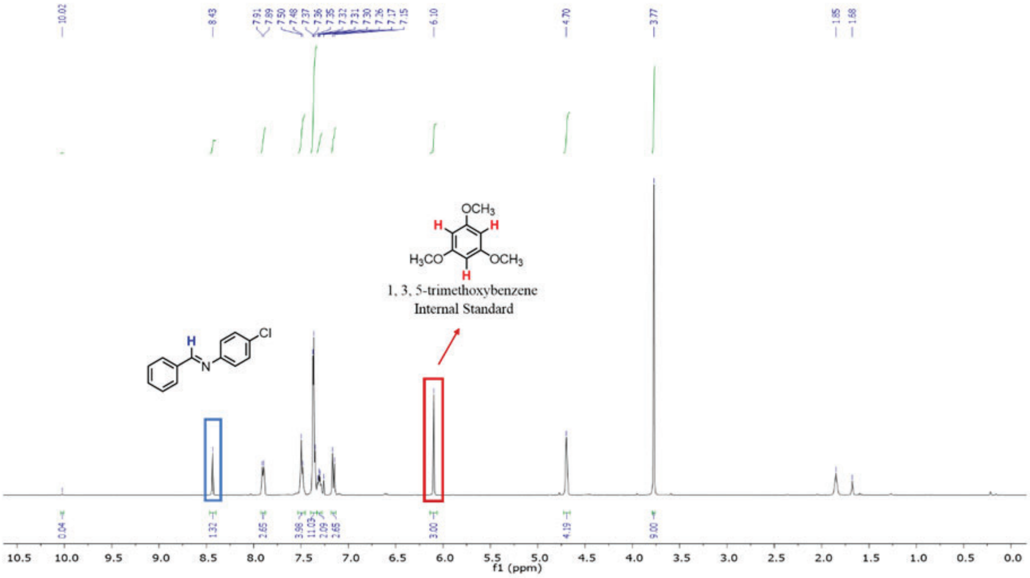

Figure A2.15. ¹H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(2-bromophenyl)-1-phenylmethanimine **3m** (94%)

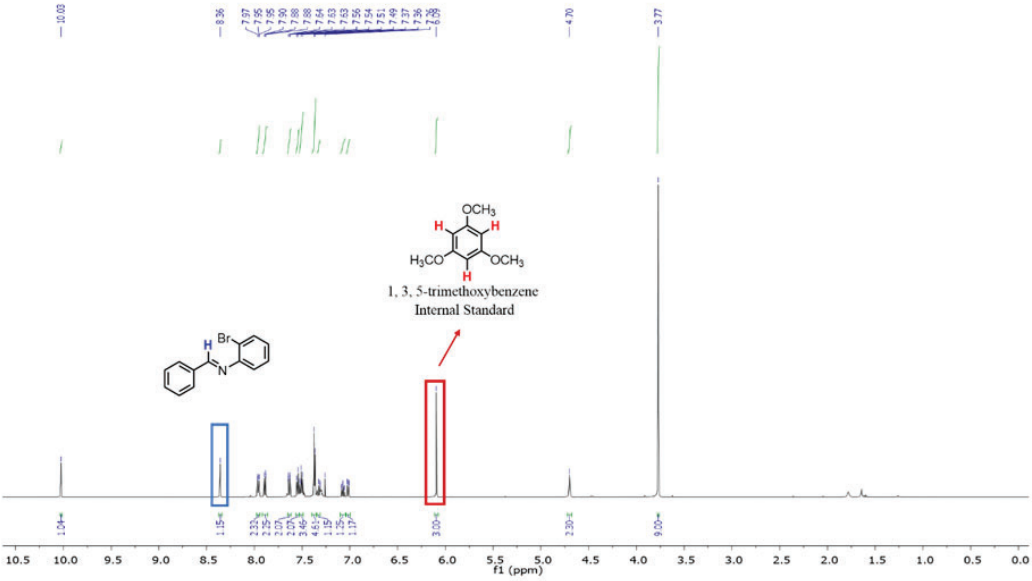

Figure A2.16. ¹H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(4-nitrophenyl)-1-phenylmethanimine **3n** (93%)

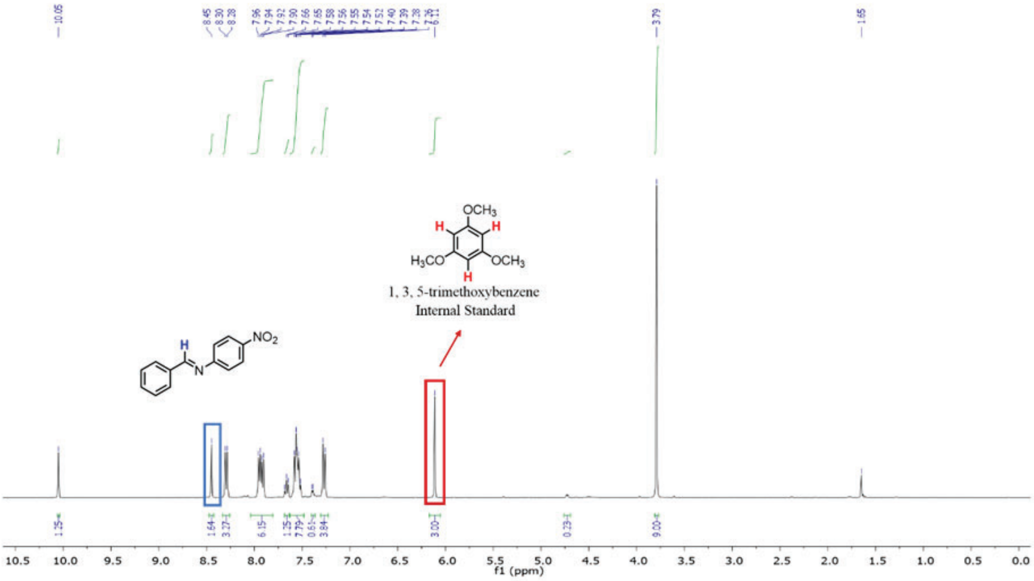

Figure A2.17. ¹H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(4-methoxyphenyl)-1-phenylmethanimine **3o** (86%)

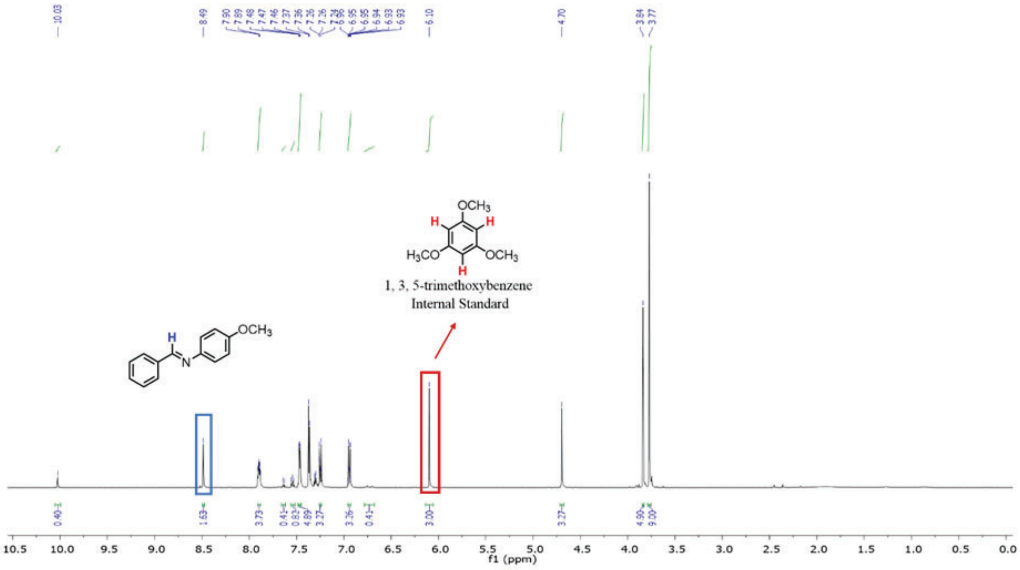

Figure A2.18. ¹H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(2,4-dimethylphenyl)-1-phenylmethanimine **3p** (95%)

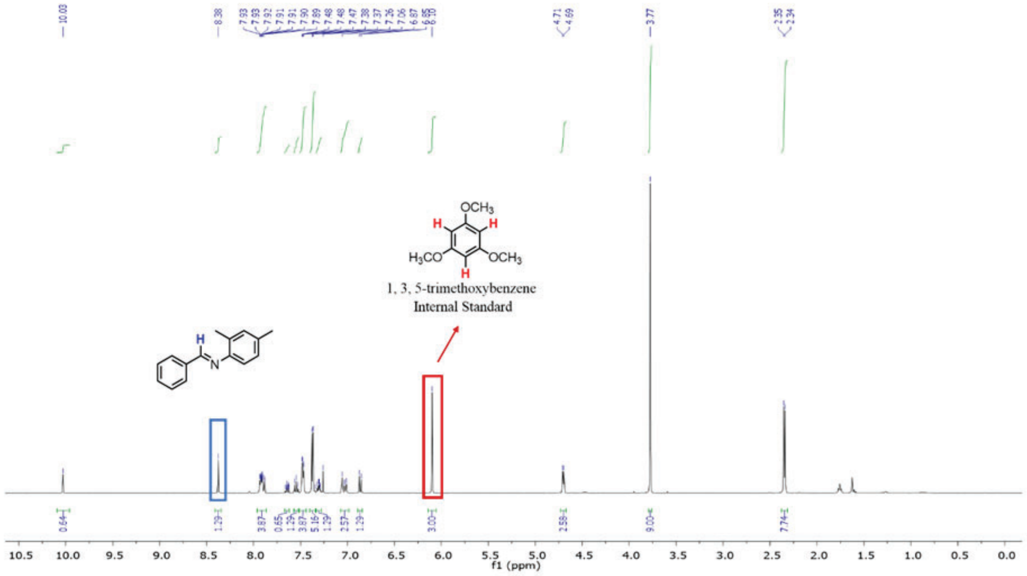

Figure A2.19. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-benzyl-1-phenylmethanimine **3q** (97%)

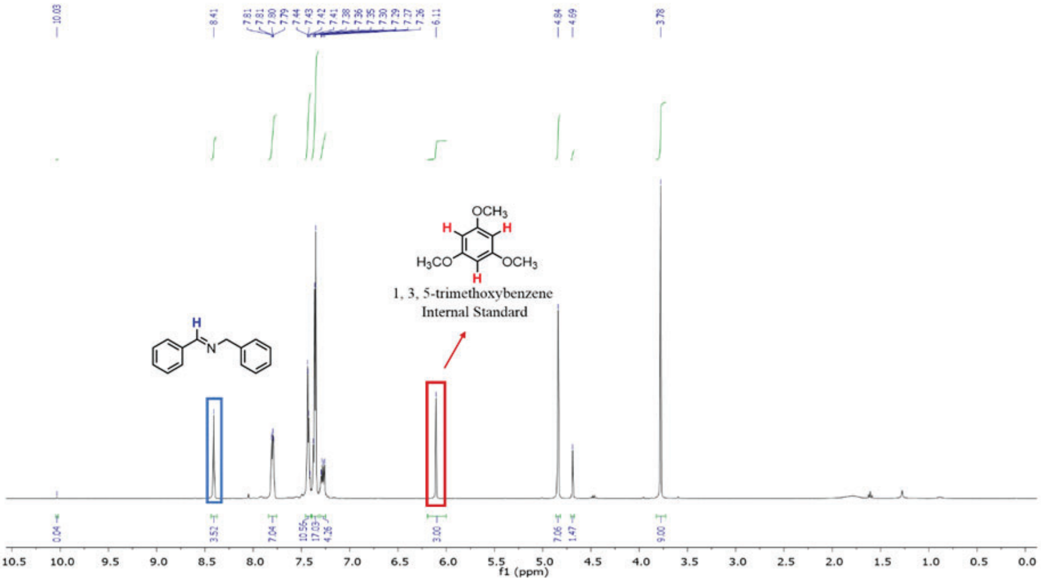

Figure A2.20. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-propyl-1-phenylmethanimine **3r** (41%)

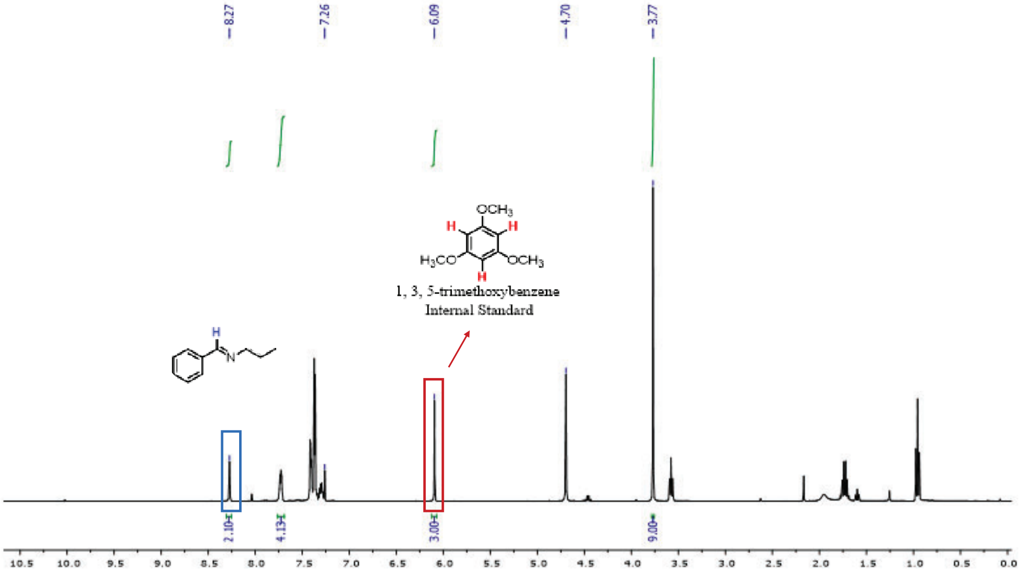

Figure A2.21. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(5-methoxypyridin-2-yl)-1-phenylmethanimine **4d** (97%)

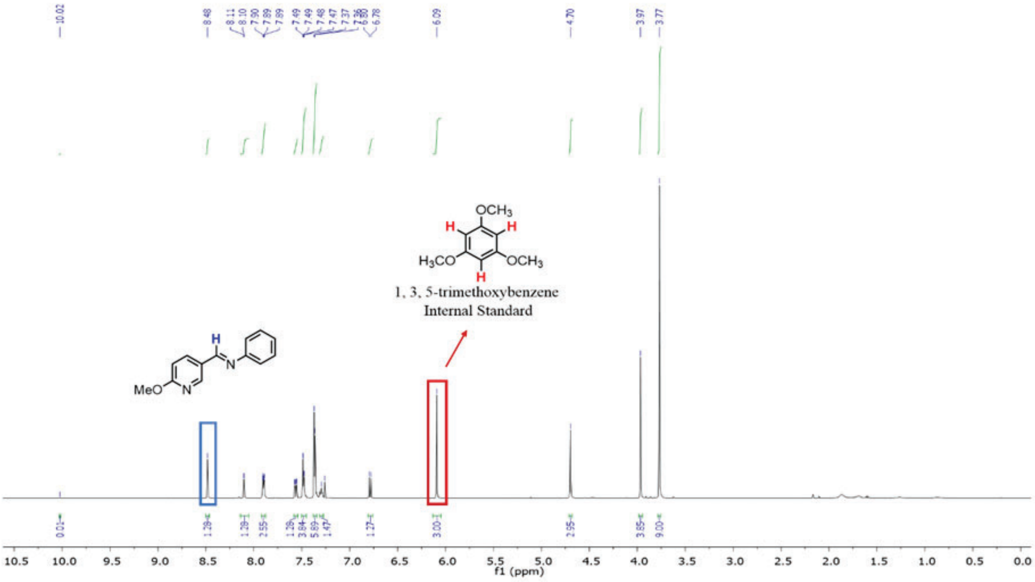

Figure A2.22. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-1-phenyl-*N*-(pyridin-4-yl)methanimine **4a** (90%)

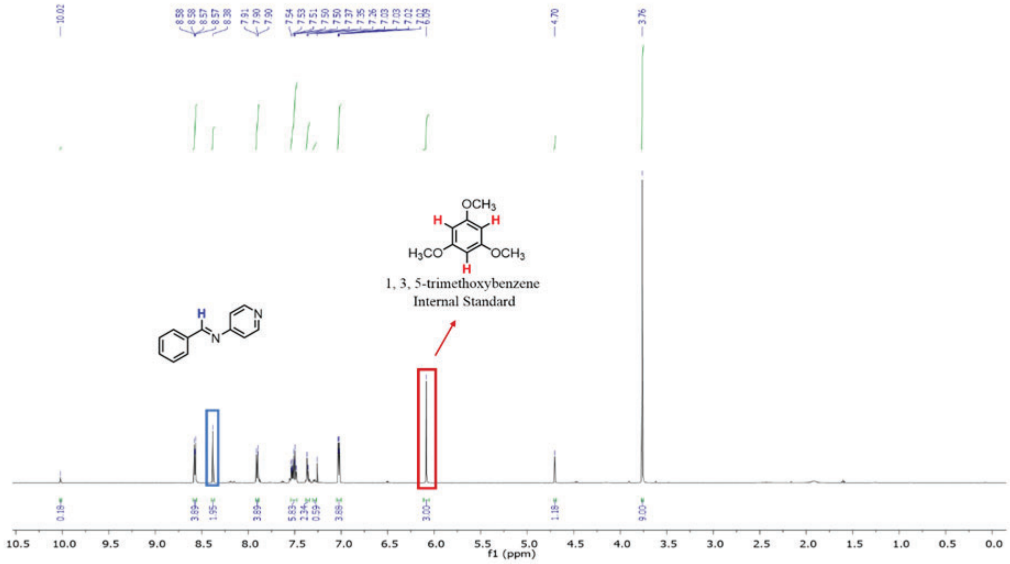

Figure A2.23. ¹H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-1-phenyl-*N*-(pyridin-2-yl)methanimine **4b** (74%)

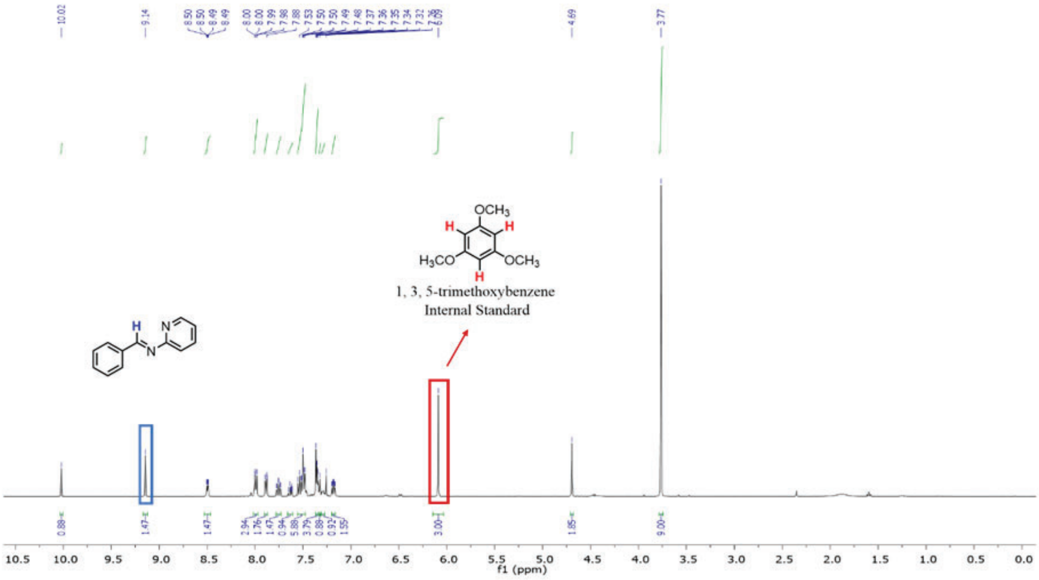

Figure A2.24. ¹H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-1-phenyl-*N*-(pyridin-3-yl)methanimine **4c** (82%)

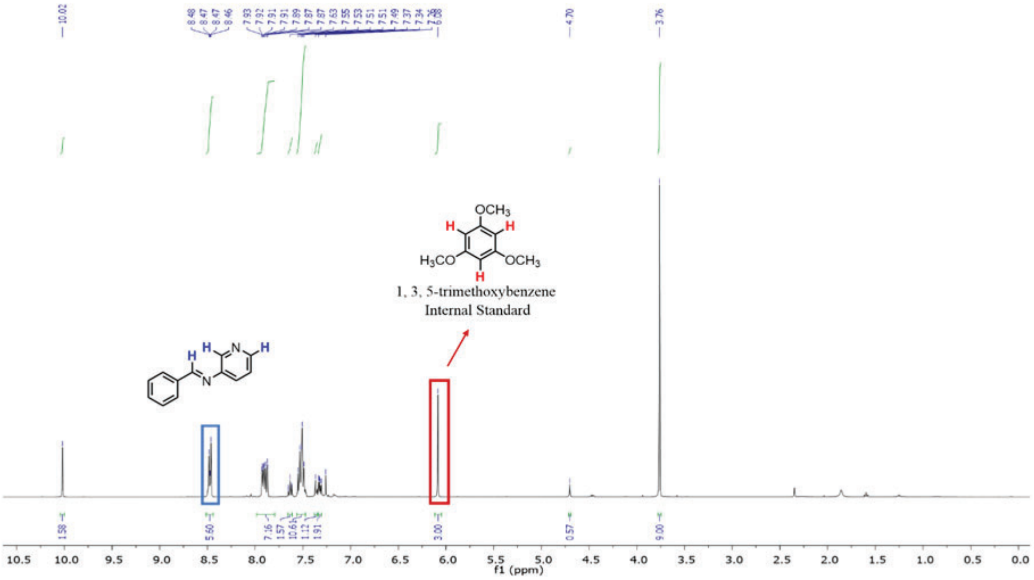

Figure A2.25. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(4-methoxypyridin-3-yl)-1-phenylmethanimine **4e** (90%)

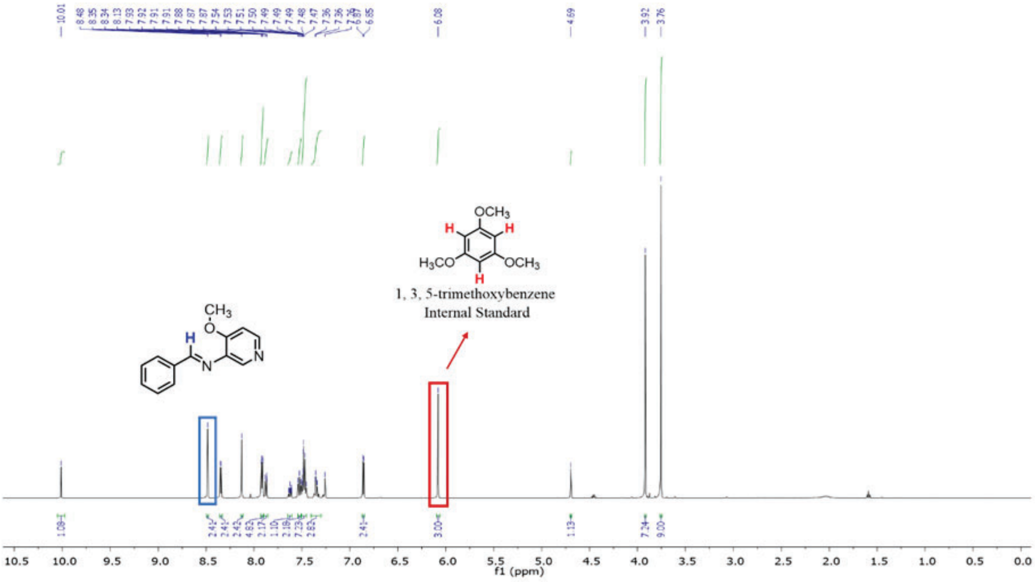

Figure A2.26. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 500 MHz, 23 °C).

(*E*)-*N*-(3-iodopyridin-4-yl)-1-phenylmethanimine **4f** (27%)

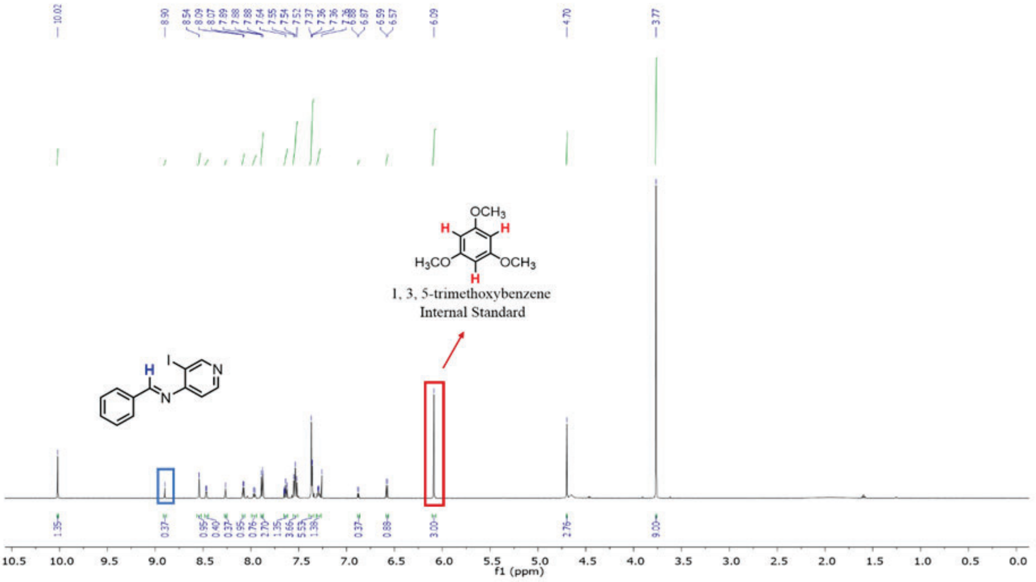

Figure A2.27. ^{1}H-NMR spectrum of the crude reaction (CDCl$_3$, 500 MHz, 23 °C).

(*E*)-*N*-(2-bromopyridin-3-yl)-1-phenylmethanimine **4g** (82%)

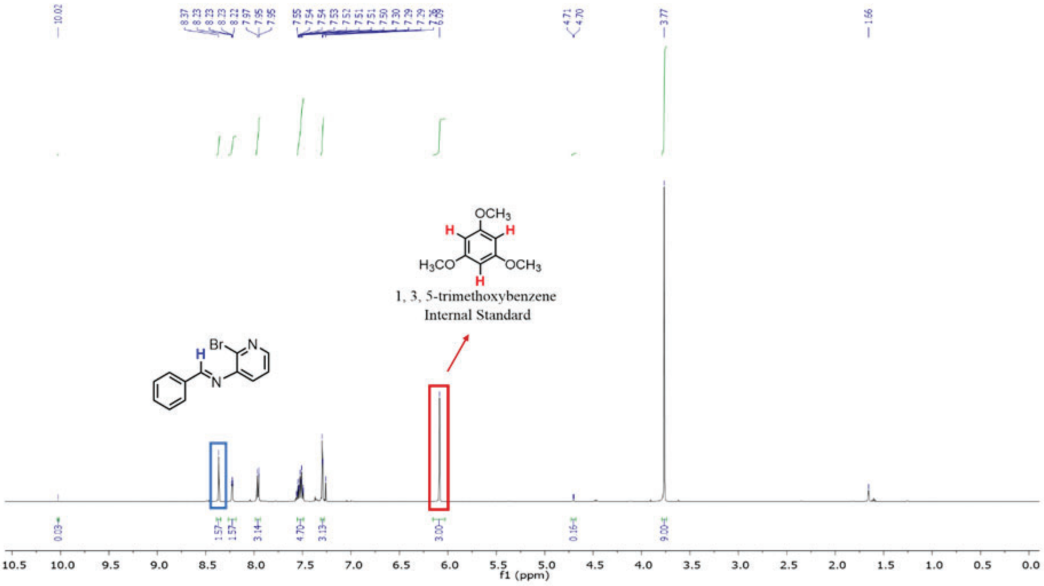

Figure A2.28. ^{1}H-NMR spectrum of the crude reaction (CDCl$_3$, 500 MHz, 23 °C).

(*E*)-1-phenyl-*N*-(pyrazin-2-yl)methanimine **4i** (60%)

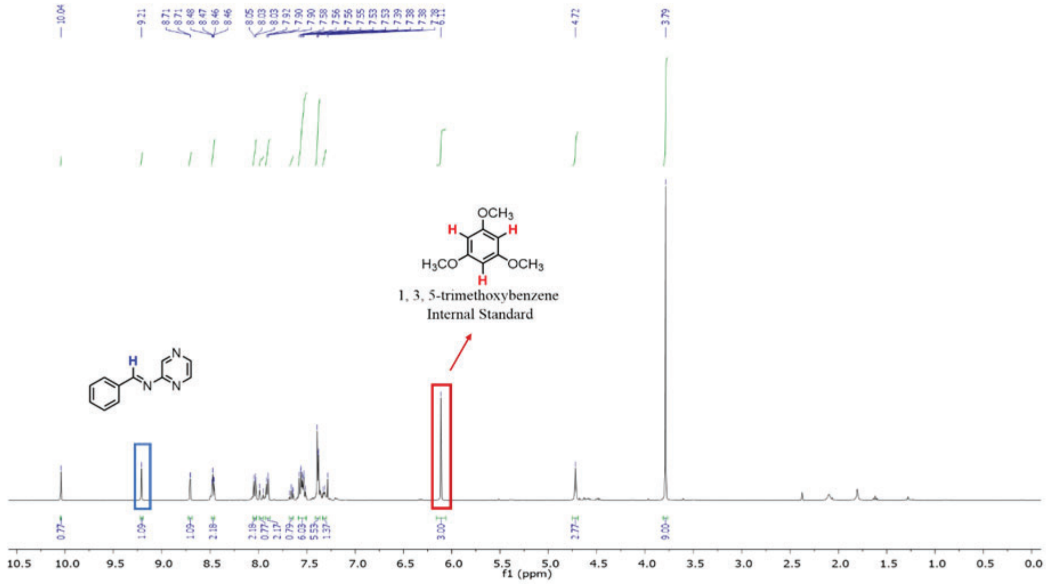

Figure A2.29. ^{1}H-NMR spectrum of the crude reaction (CDCl$_3$, 500 MHz, 23 °C).

A2.5 References

1. Á. Vivancos and M. Albrecht, *Organometallics* 2017, **36**, 1580–1590.

2. L. Krause, R. Herbst-Irmer, G. M. Sheldrick & D. Stalke, *J. Appl. Crystallogr.*, 2015, **48**, 3–10.

3. G. M. Sheldrick, *Acta Crystallogr. Sect. C Struct. Chem.*, 2015, **71**, 3–8.

4. C. B. Hübschle, G. M. Sheldrick and B. Dittrich, *J. Appl. Crystallogr.*, 2011, **44**, 1281–1284.

5. L. J. Farrugia, *J. Appl. Crystallogr.*, 2012, **45**, 849–854.

Chapter 3 - Annexes

Pd-Catalysed Access to Imines & Amines from Secondary Alcohols

A3.1 ^{1}H-NMR of imine **3a** and q^{1}H-NMR of imine **3a** reaction crude

A3.2 ^{1}H-NMR of amine **4a** and q^{1}H-NMR of amine **4a** reaction crude

A3.3 Pd(OAc)$_2$-catalysed stochiometric reaction of 1-phenylethanol **2a**

A3.4 ^{1}H-NMR spectra of indoles

A3.5 ^{1}H-NMR spectra of the BH reactions

A3.6 Control reaction of 1-phenyl ethanol and *N*,1-diphenylethan-1-imine

A3.1 ^{1}H-NMR of imine **3a** and q^{1}H-NMR of imine **3a** reaction crude

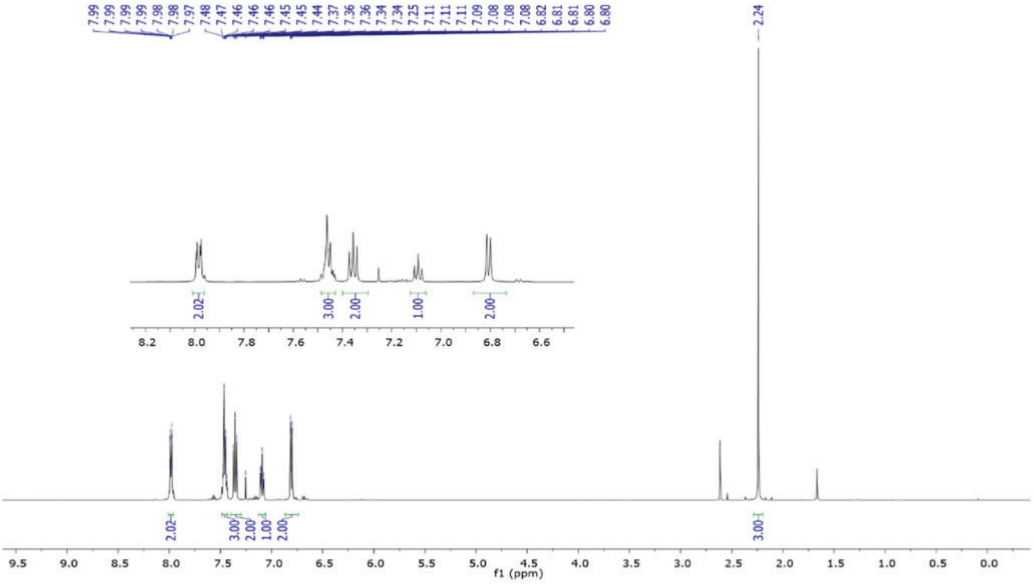

Figure A3.1. ^{1}H-NMR spectrum of the isolated product **3a** ($CDCl_3$, 400 MHz, 23 ºC).

The NMR analysis of *N*,1-diphenylethan-1-imine **3a** in the reaction crude gave 66% yield and it is shown below in Figure A3.2, together with the assignment of spectrum signals.

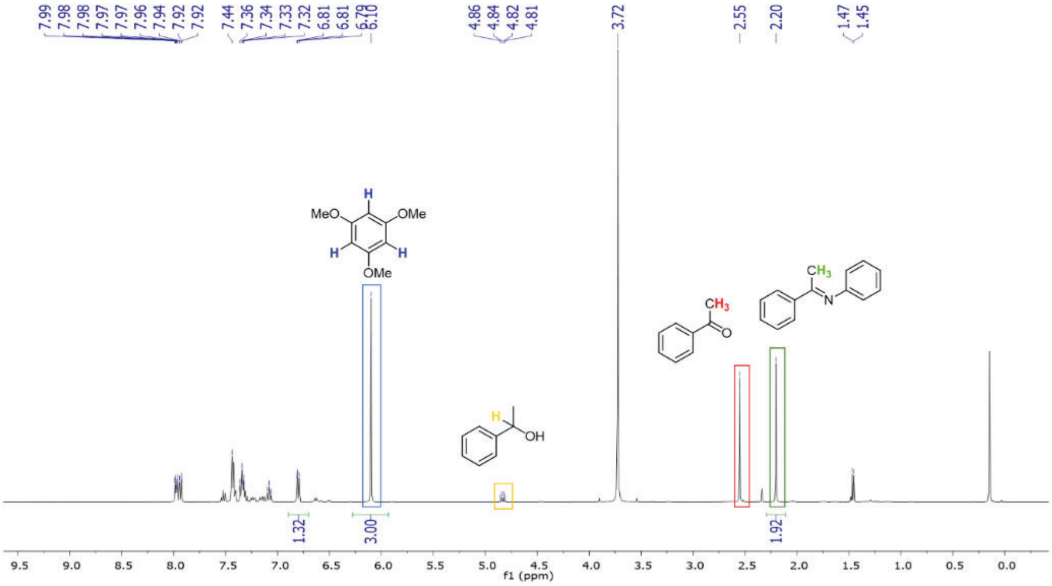

Figure A3.2. ^{1}H-NMR spectrum of the crude model reaction ($CDCl_3$, 400 MHz, 23 ºC). The yield of the amine **3a** was determined by ^{1}H NMR analysis of the crude product using 0.3 mmol of 1,3,5-trimethoxybenzene as an internal standard with respect to the 0.3 mmol of aniline used as starting material.

A3.2 ^{1}H-NMR of amine **4a** and q^{1}H-NMR of amine **4a** reaction crude

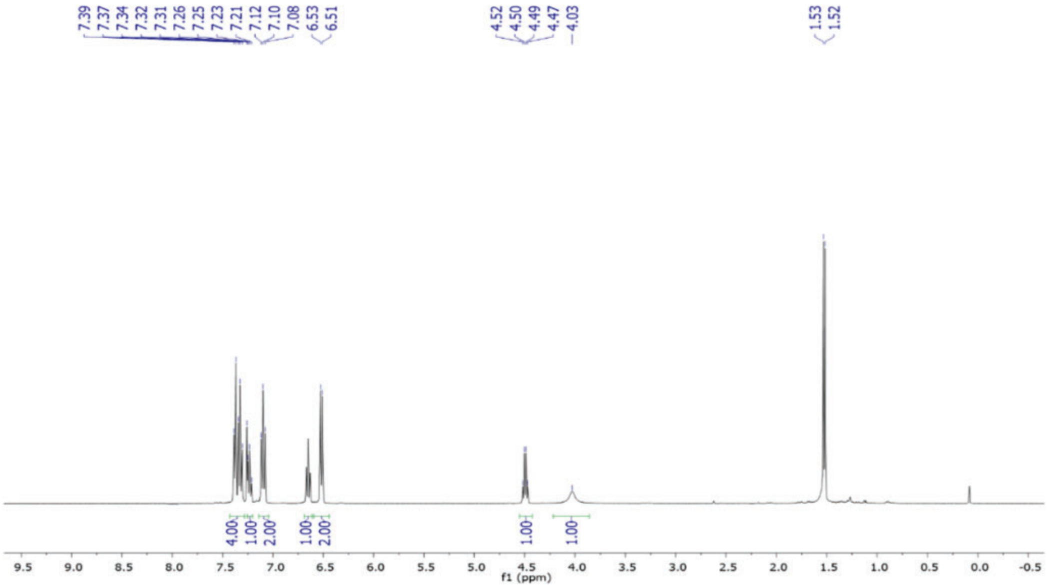

Figure A3.3. ^{1}H-NMR spectrum of the isolated product **4a** (CDCl$_3$, 400 MHz, 23 ºC).

The ^{1}H NMR analysis of *N*-(1-phenylethyl)aniline **4a** in the reaction crude gave 98% yield and it is shown below in Figure A3.4, together with the assignment of spectrum signals.

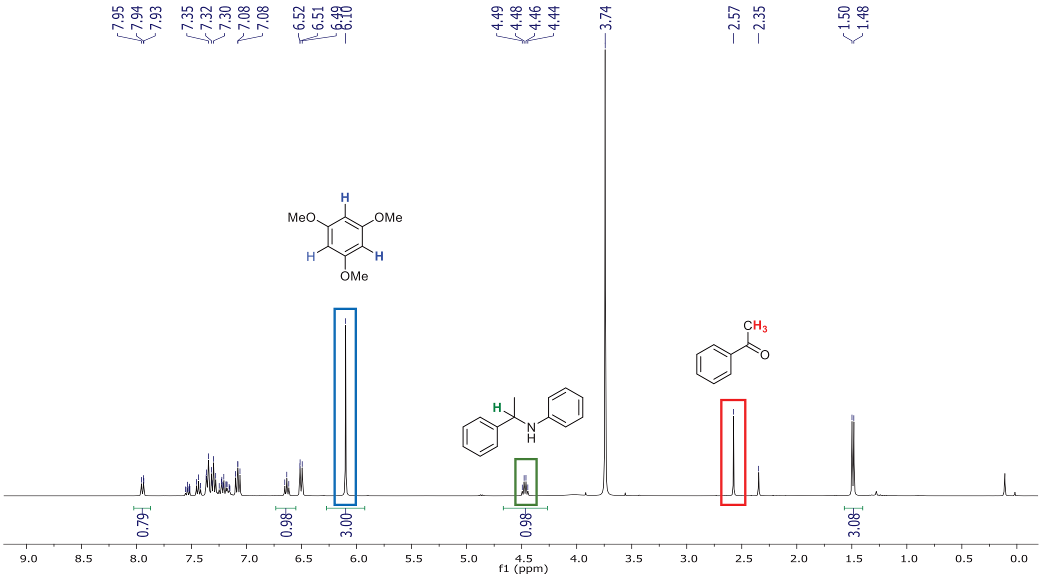

Figure A3.4. ^{1}H-NMR spectrum of the crude model reaction with (CDCl$_3$, 400 MHz, 23 ºC). The yield of the amine **4a** was determined by ^{1}H NMR analysis of the crude product using 0.3 mmol of 1,3,5-trimethoxybenzene as an internal standard with respect to the 0.3 mmol of aniline used as starting material.

A3.3 Pd(OAc)$_2$-catalysed stochiometric reaction of 1-phenylethanol **2a**

The stochiometric reaction of Pd(OAc)$_2$ (0.2 mmol) with 1-phenylethanol **2a** (0.2 mmol) was monitored by ^{1}H NMR spectroscopy in a Young-tap close NMR tube, using dry deuterated benzene (1 mL) (see Figure A3.5).

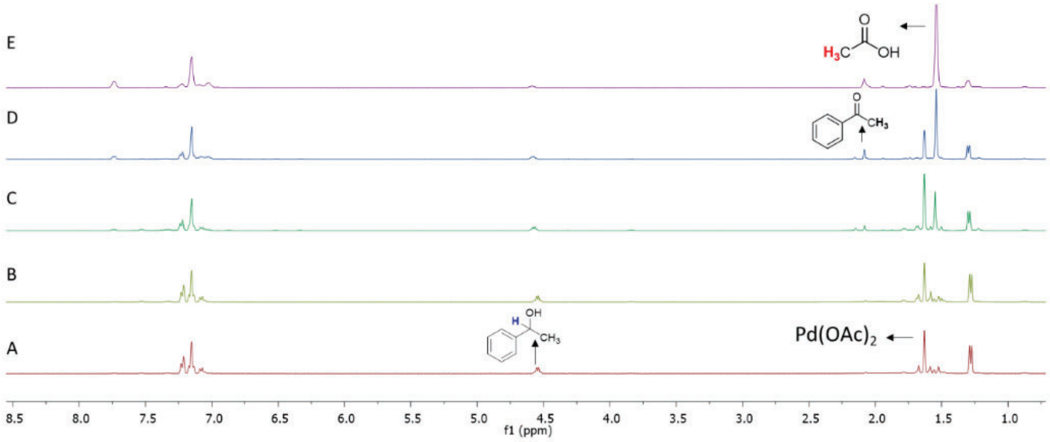

Figure A3.5. ^{1}H-NMR spectra of the stochiometric reaction of 1-phenylethanol **2a** and Pd(OAc)$_2$ in benzene-*d6* under the following conditions: (A) spectrum recorded just after adding the reagents at room temperature; (B) spectrum recorded after 1 h of reaction at room temperature; (C) spectrum recorded after 1 h at 110 °C; (D) spectrum recorded after 3 h at 110 °C; (E) spectrum recorded after 5 h at 110 °C.

A3.4 ^{1}H-NMR spectra of indoles

(All the yields were obtained from pure isolated samples of the corresponding indoles after column chromatography)

2-Phenylindole **5a** (92% yield, white solid)

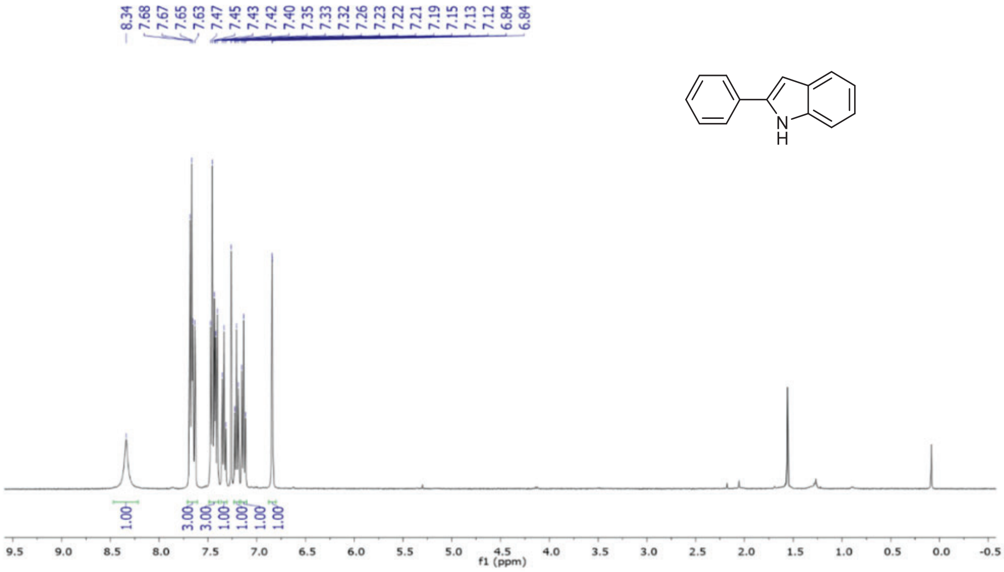

Figure A3.6. ^{1}H-NMR spectrum of the indole **5a** ($CDCl_3$, 400 MHz, 23 °C).

5-methoxy-2-phenyl-1H-indole **5b** (50% yield, white solid)

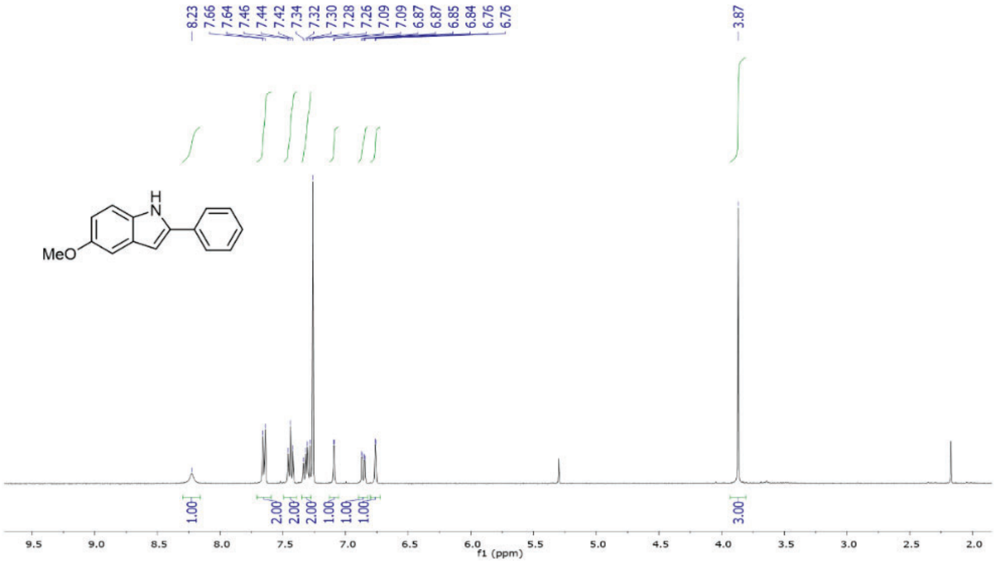

Figure A3.7. ^{1}H-NMR spectrum of the indole **5b** ($CDCl_3$, 400 MHz, 23 °C).

5-methyl-2-phenyl-1H-indole **5c** (66% yield, white solid)

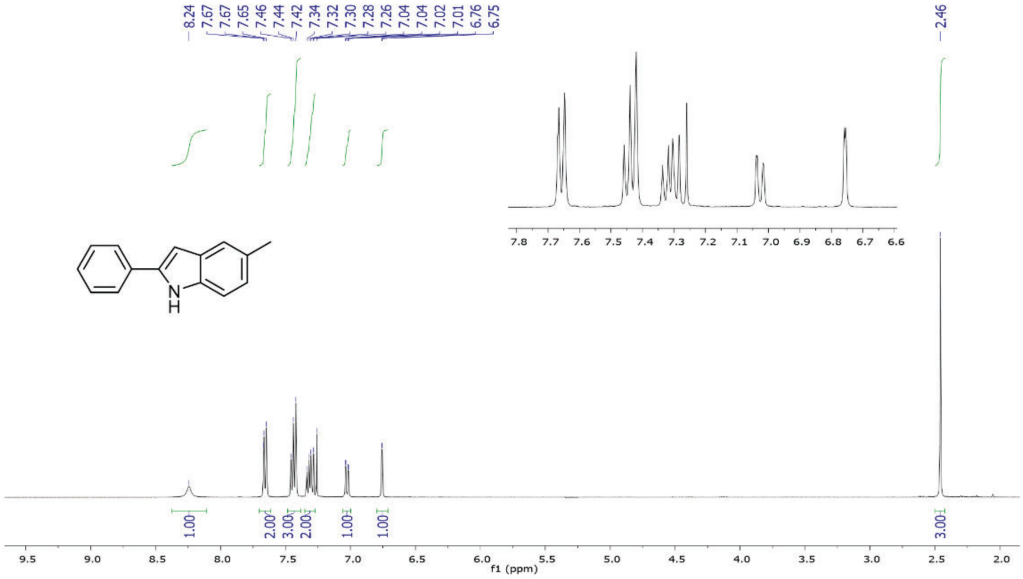

Figure A3.8. ^{1}H-NMR spectrum of the indole **5c** ($CDCl_3$, 400 MHz, 23 °C).

5-fluoro-2-phenyl-1H-indole **5d** (82% yield, pale yellow solid)

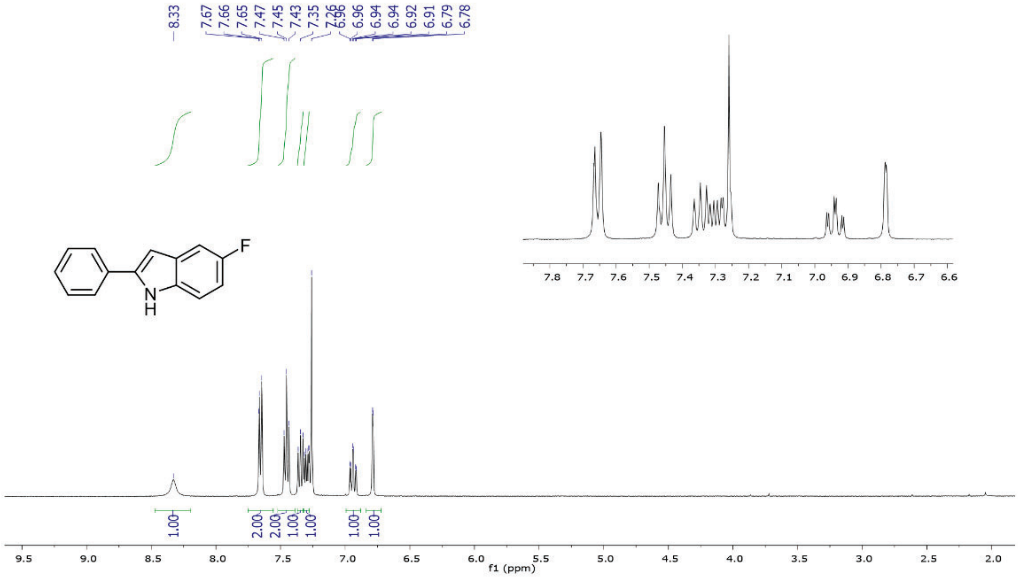

Figure A3.9. ^{1}H-NMR spectrum of the indole **5d** ($CDCl_3$, 400 MHz, 23 °C).

2-(p-tolyl)-1H-indole **5e** (43% yield, pale yellow solid)

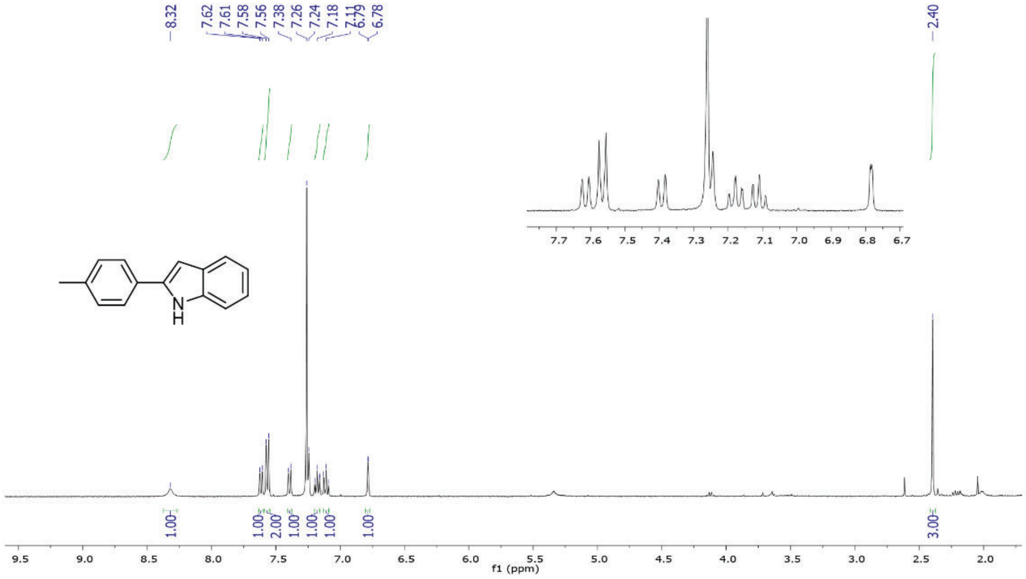

Figure A3.10. ^{1}H-NMR spectrum of the indole **5e** ($CDCl_3$, 400 MHz, 23 °C).

A3.5 ^{1}H-NMR spectra of the BH reactions

(in all cases the yield of the corresponding amine was determined using 1,3,5-trimethoxybenzene (0.3mmol) as an internal standard)

4-methoxy-*N*-(1-phenylethyl)aniline **4b** (83% Amine and 15% Imine)

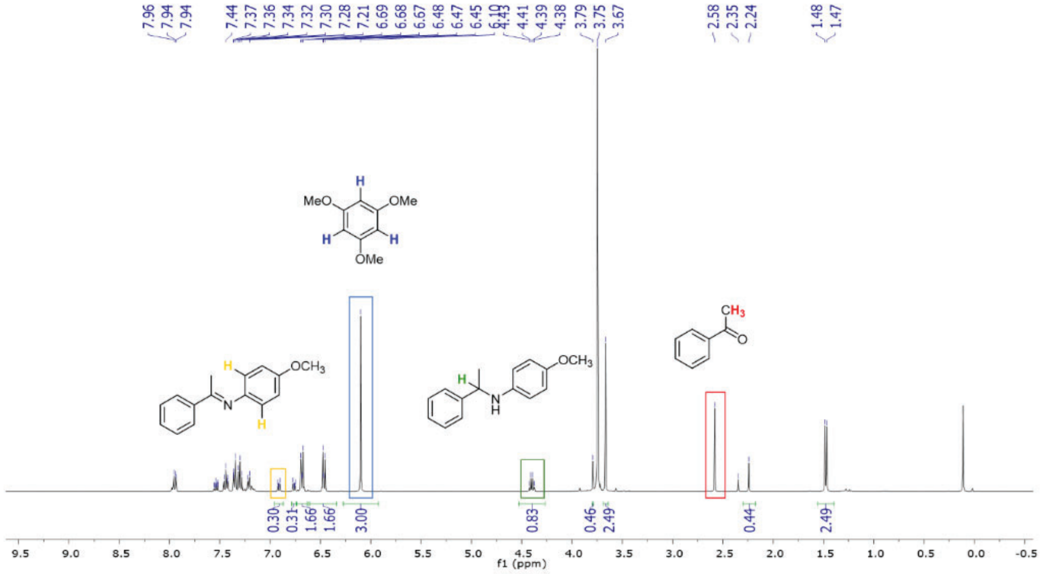

Figure A3.11. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 400 MHz, 23 °C).

4-methyl-*N*-(1-phenylethyl)aniline **4c** (76% Amine and 21% Imine)

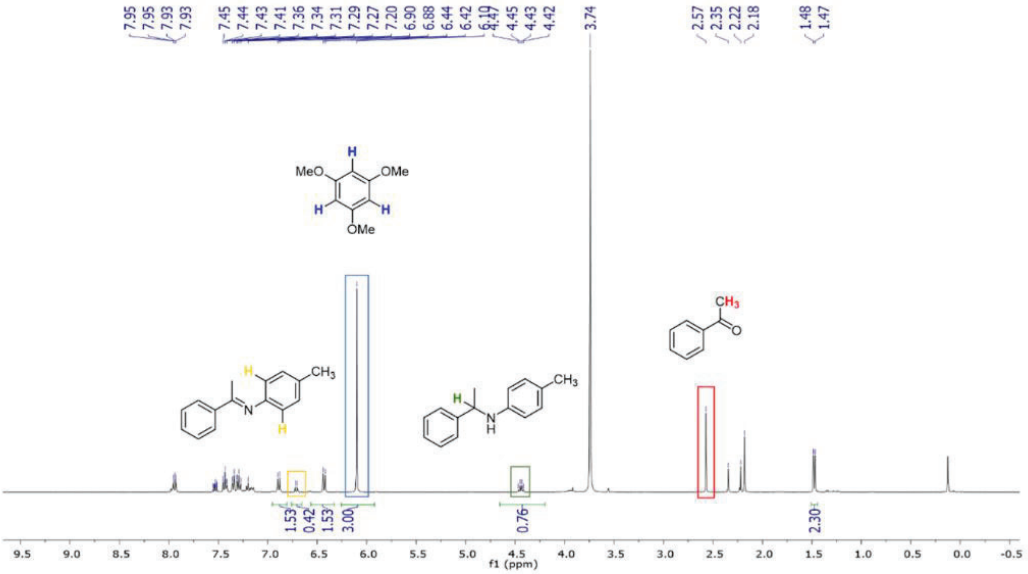

Figure A3.12. ¹H-NMR spectrum of the crude reaction (CDCl3, 400 MHz, 23 °C).

4-fluoro-*N*-(1-phenylethyl)aniline **4d** (80% Amine and 10% Imine)

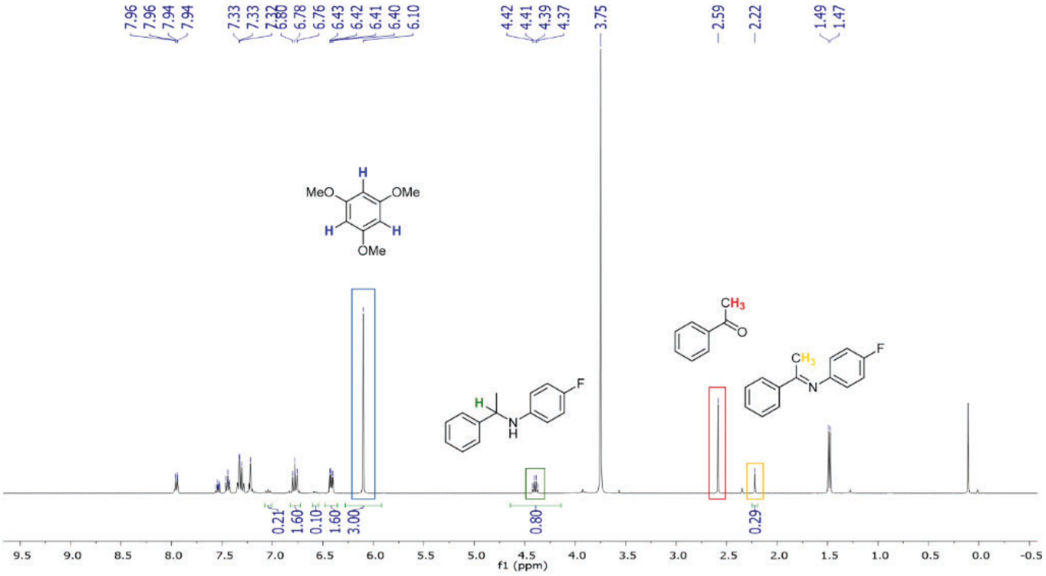

Figure A3.13. ¹H-NMR spectrum of the crude reaction (CDCl3, 400 MHz, 23 °C).

N-(1-phenylethyl)-3-(trifluoromethyl)aniline **4e** (37% Amine and 25% Imine)

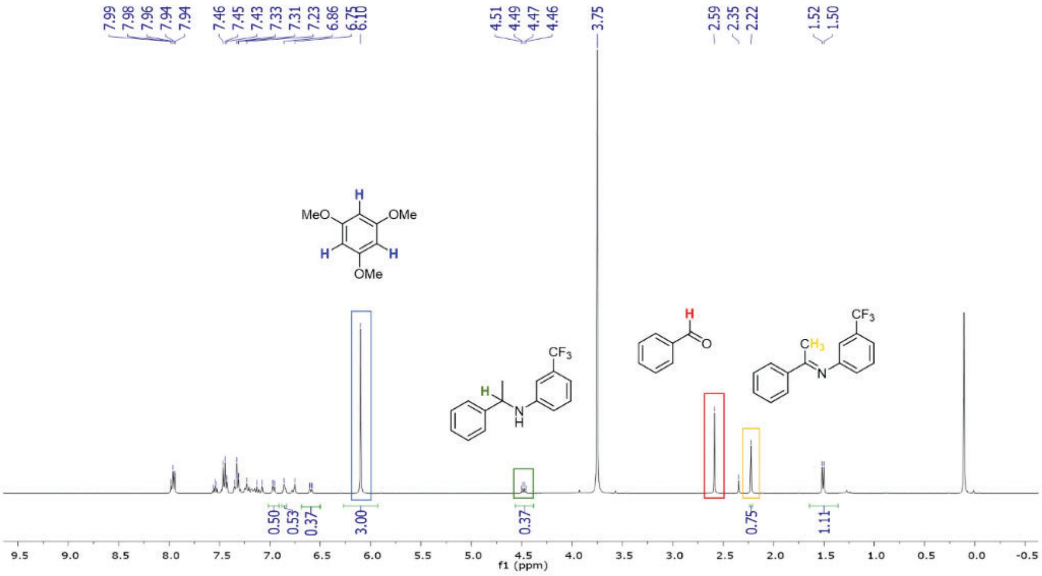

Figure A3.14. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 400 MHz, 23 °C).

N-(1-phenylethyl)cyclohexanamine **4h** (60%)

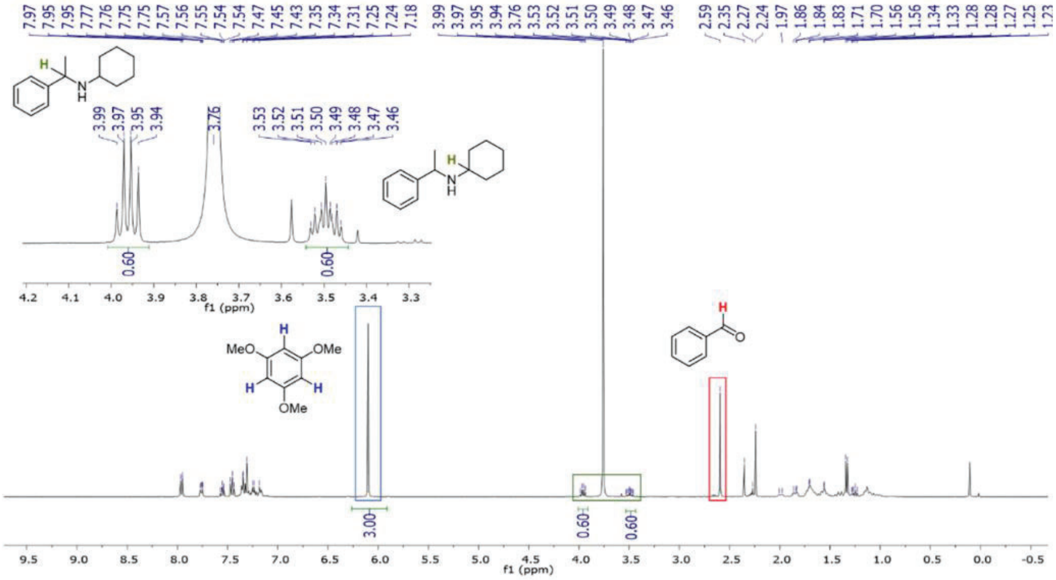

Figure A3.15. ^{1}H-NMR spectrum of the crude reaction with **4** ($CDCl_3$, 500 MHz, 23 °C).

N-benzyl-1-phenylethan-1-amine **4i** (32%)

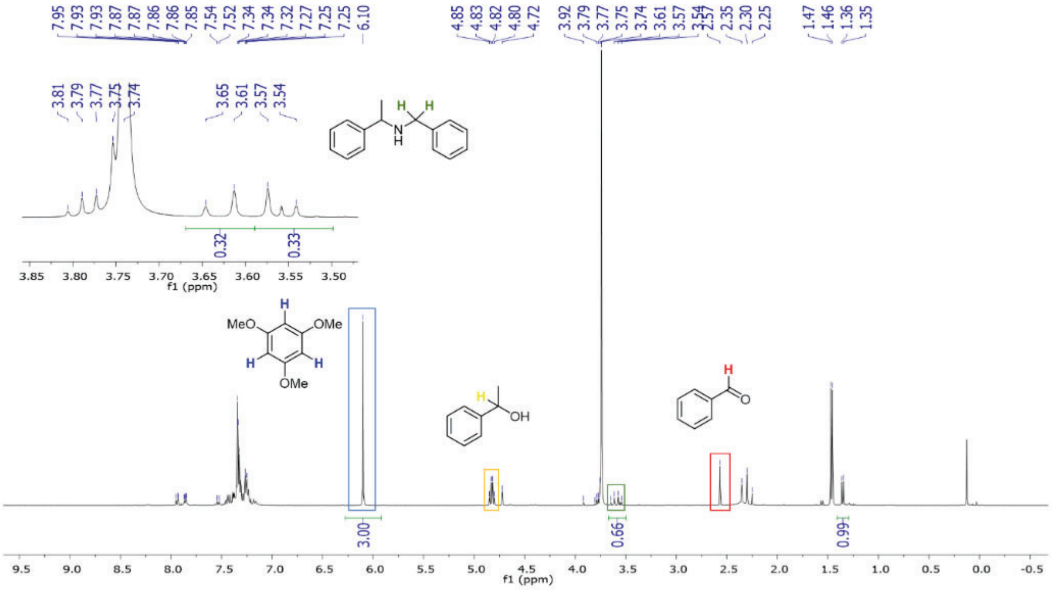

Figure A3.16. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 400 MHz, 23 °C).

N-(1-phenylethyl)pyridin-3-amine **4j** (30%)

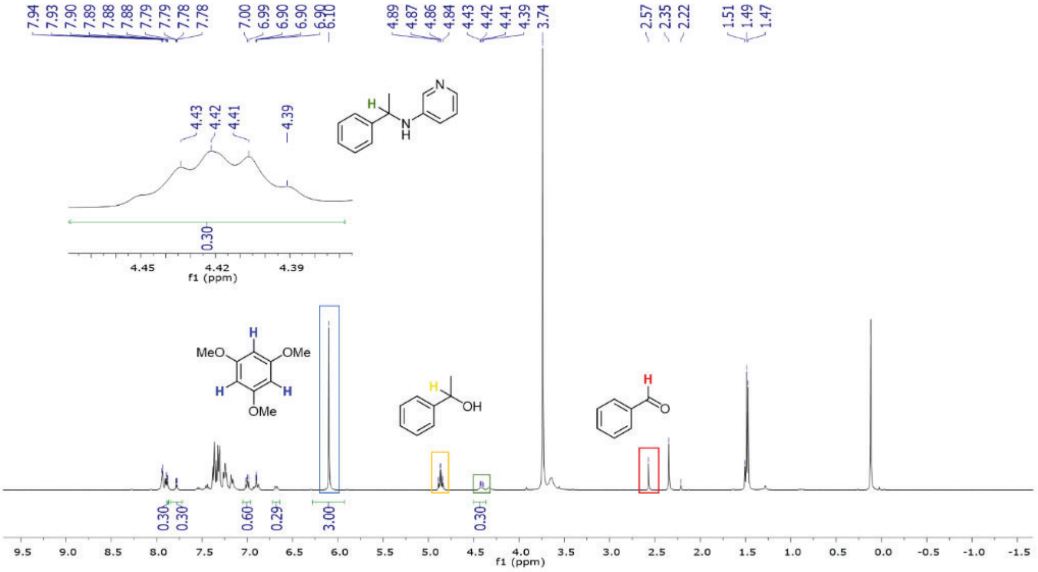

Figure A3.17. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 400 MHz, 23 °C).

2,4-dimethyl-*N*-(1-phenylethyl)aniline **4k** (44% Amine and 52% Imine)

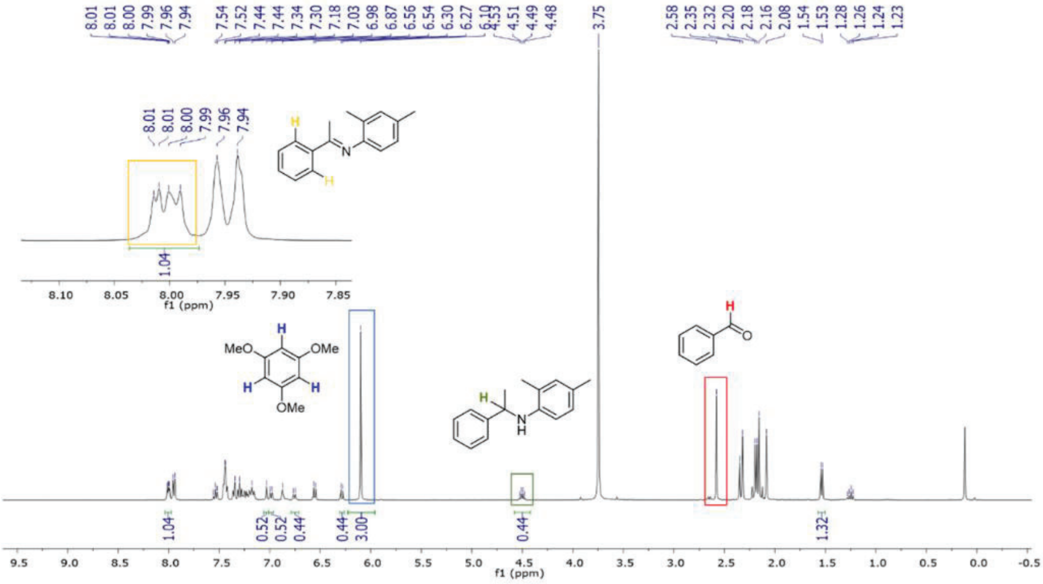

Figure A3.18. ^{1}H-NMR spectrum of the crude reaction (CDCl$_3$, 400 MHz, 23 °C).

N-(2,2,2-trifluoro-1-phenylethyl)aniline **4l** (80%).

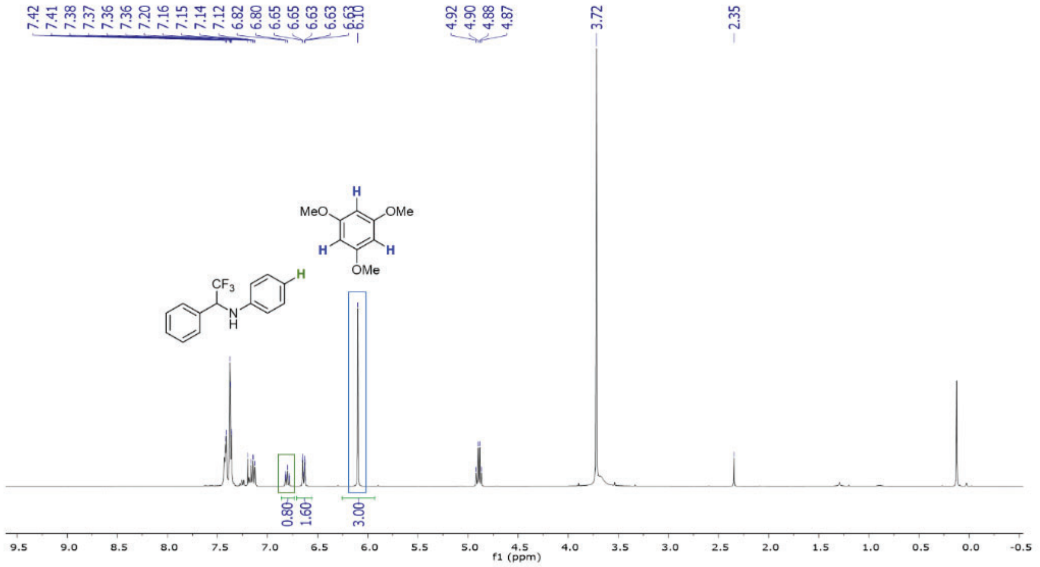

Figure A3.19. ^{1}H-NMR spectrum of the crude reaction (CDCl$_3$, 400 MHz, 23 °C).

N-(1-phenylpropyl)aniline **4m** (80%)

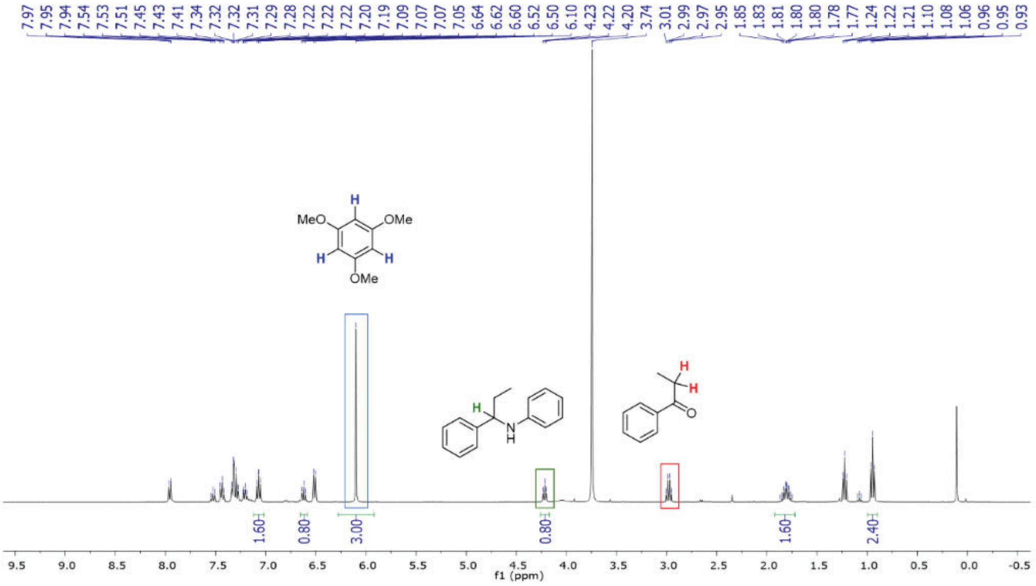

Figure A3.20. ¹H-NMR spectrum of the crude reaction (CDCl₃, 400 MHz, 23 °C)

N-(4-phenylbutan-2-yl)aniline **4n** (99%)

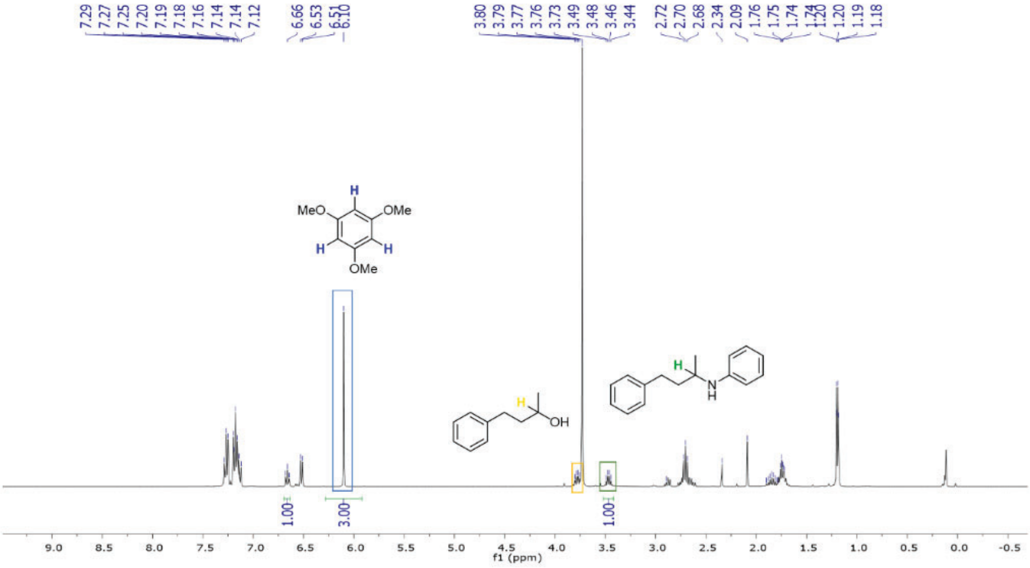

Figure A3.21. ¹H-NMR spectrum of the crude reaction (CDCl₃, 400 MHz, 23 °C).

N-(1-(p-tolyl)ethyl)aniline **4o** (74% yield)

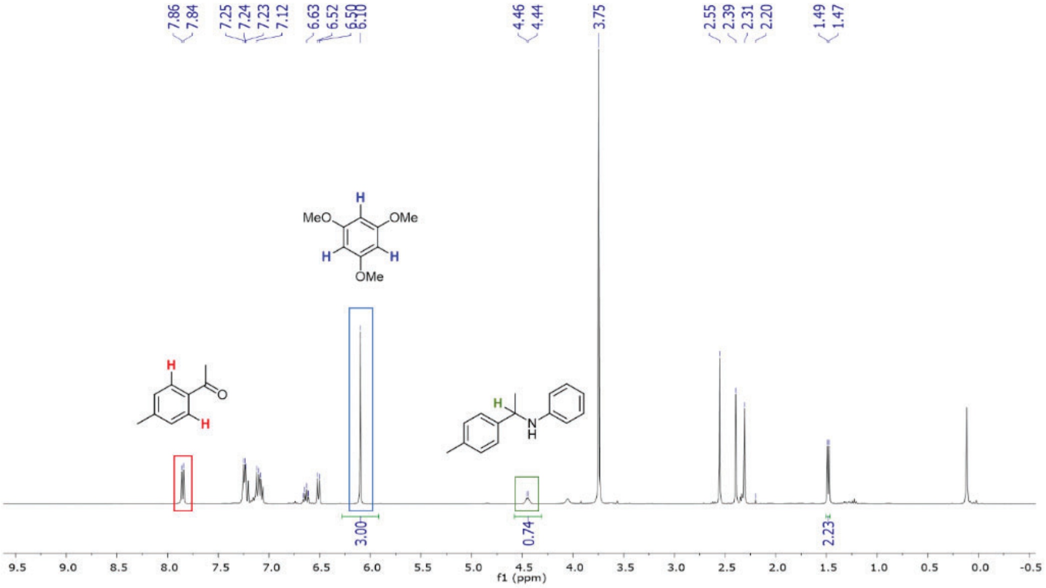

Figure A3.22. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 400 MHz, 23 °C).

N-(1-(4-bromophenyl)ethyl)aniline **4p** (24%)

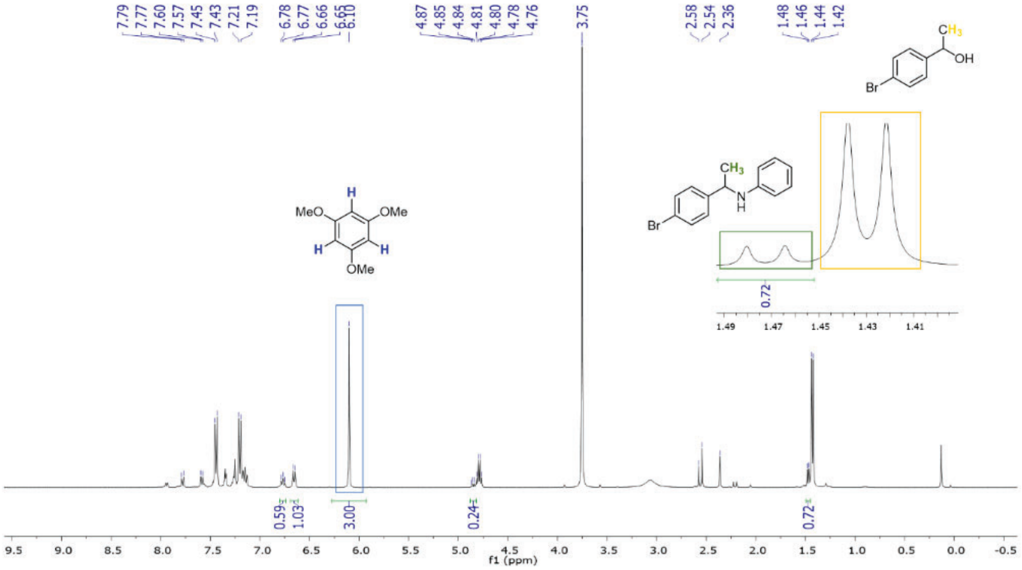

Figure A3.23. ^{1}H-NMR spectrum of the crude reaction ($CDCl_3$, 400 MHz, 23 °C).

N-cyclohexylaniline **4q** (50%)

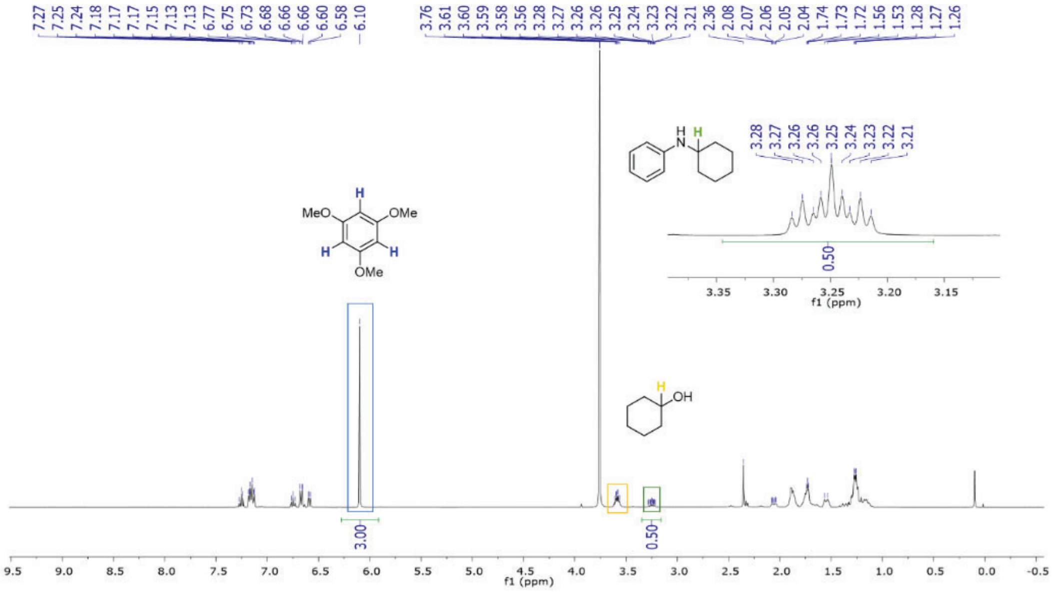

Figure A3.25. ^{1}H-NMR spectrum of the crude reaction (CDCl$_3$, 400 MHz, 23 °C).

N-(heptan-2-yl)aniline **4r** (40%)

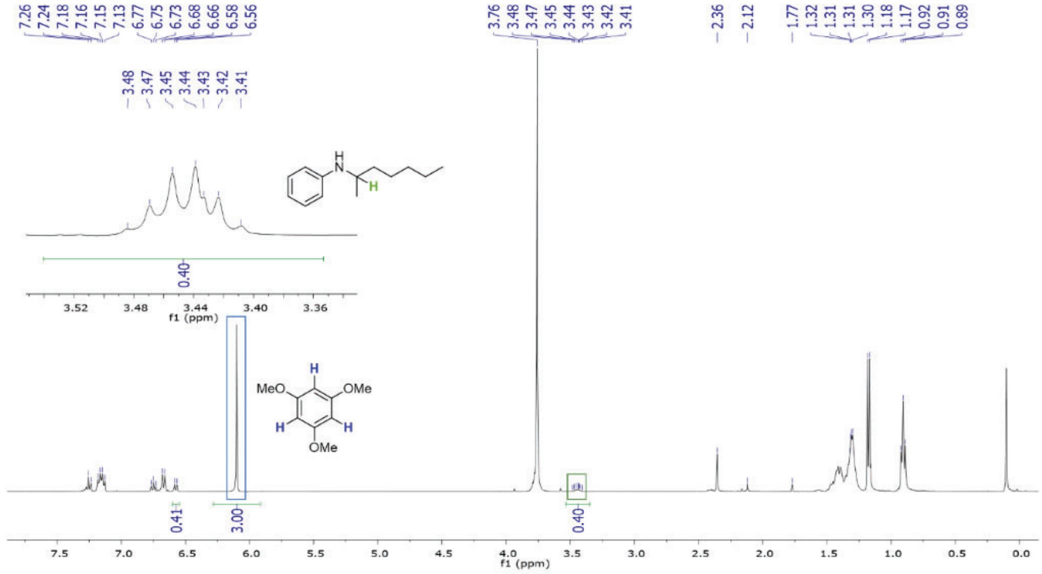

Figure A3.26. ^{1}H-NMR spectrum of the crude reaction (CDCl$_3$, 400 MHz, 23 °C)

A3.6 Control reaction of 1-phenyl ethanol and *N*,1-diphenylethan-1-imine

Reaction of 1-phenyl ethanol (0.4 mmol), and *N*,1-diphenylethan-1-imine (0.2 mmol) under the optimized conditions afforded the expected product *N*-(1-phenylethyl)aniline in 73% yield (Figure A3.27).

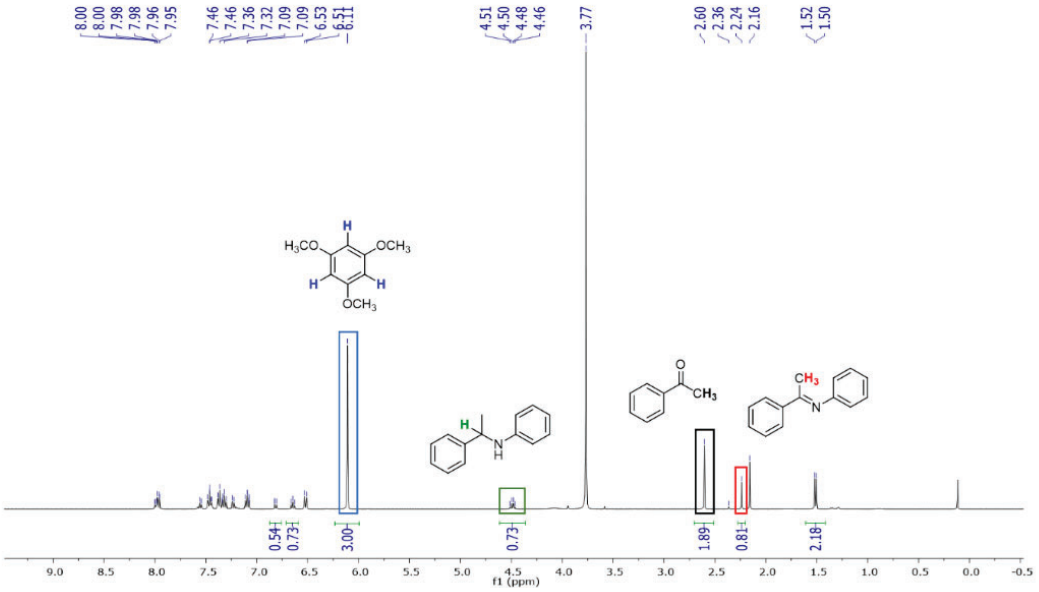

Figure A3.27. Reaction of *N*,1-diphenylethan-1-imine and 1-phenyl ethanol (**2a)** to yield the corresponding amine. The yields of the amine and imine were determined using 1,3,5-trimethoxybenzene (0.2 mmol) as an internal standard.

Chapter 4 - Annexes

Mn(I) Borrowing Hydrogen Dialkylations: Expanding Catalytic Frontiers for Challenging *N*-Heterocyclic Compounds

(The preparation of compounds **I**[1,2] and **Mn1**[1] *was performed following the procedures described in the literature).*

A4.1 Thermal stability of **Mn1**

A4.1.1 Thermogravimetric analysis

The experiment was made with a TGA7 apparatus from Perkin Elmer. A sample with an initial mass of 4 mg was placed in an open platinum crucible and transferred to the balance. It was then heated at 5 °C min^{-1} from 35 °C to 500 °C. The mass of sample was monitored with a sensitivity of 0.1 μg throughout the experiment. Nitrogen (Praxair 5.0) was used as purge gas of the sample (flow rate: 22.5 cm^3×min^{-1}) and balance (flow rate: 38 cm^3×min^{-1}) chambers. The mass scale was calibrated with a standard 100 mg weight. The temperature calibration was based on the Curie points (T_C) of alumel alloy (Perkin-Elmer, T_C = 427.35 K) and nickel (Perkin-Elmer, 99.99%, T_C = 628.45 K) standard reference materials.

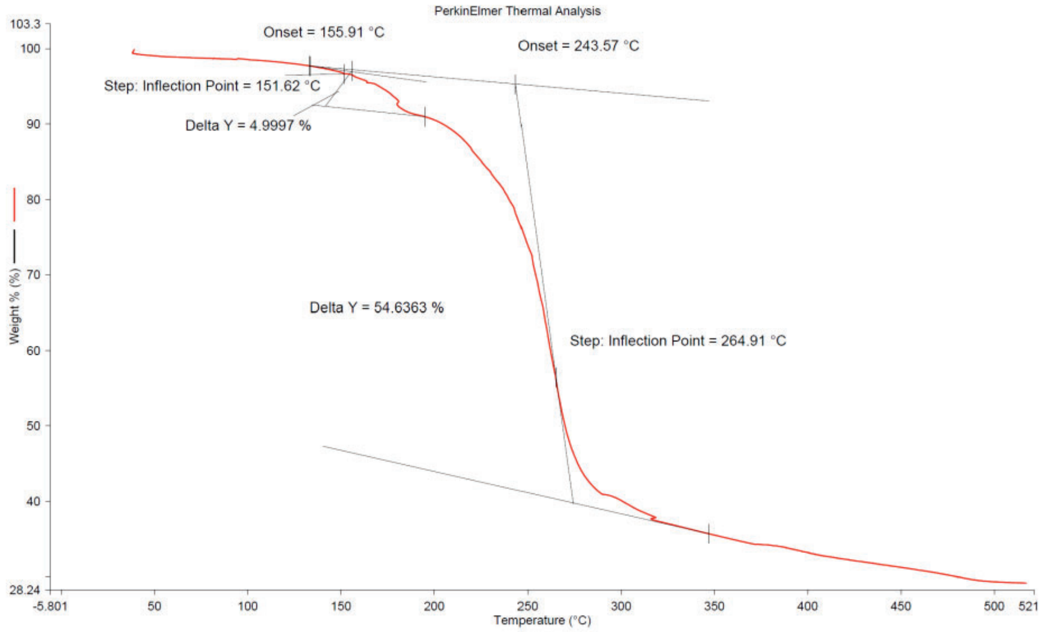

Figure A4.1. Thermogram of **Mn1**.

A4.1.2 Thermal stability in solution

The experiment was performed in a J-young NMR tube with 10 mg of **Mn1** and 0.5 mL of DMSO-d$_6$. It was performed a ^{1}H-NMR before starting to heat the sample (Figure A4.11 a). The tube was heated at 130 °C, for 2h and analysed again by ^{1}H-NMR (Figure A4.2 b).

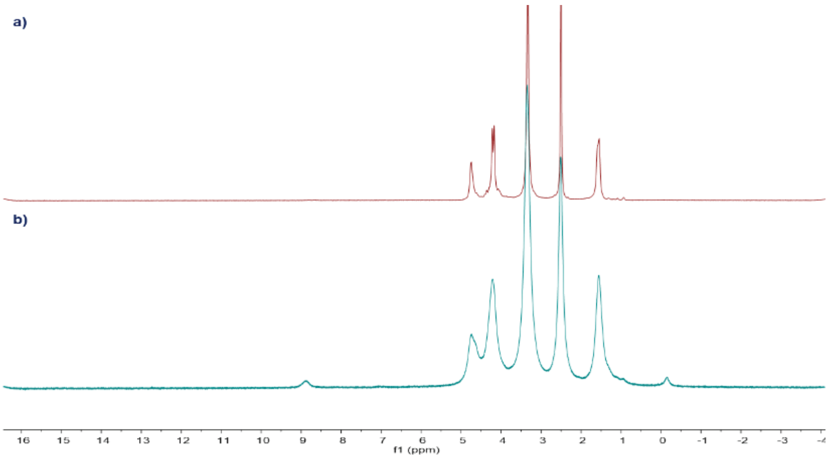

Figure A4.2. ^{1}H NMR spectrum (DMSO-d6, 400 MHz) of the thermal stability of **Mn1**, at 130 °C.

A4.2 determination of yields via q^{1}H-NMR analysis of model reactions

The NMR analysis of the corresponding compounds in the reaction crude is shown below, together with the assignment of spectrum signals. The yields were determined by ^{1}H-NMR analysis of the crude product using 0.25 mmol of 1,3,5-trimethoxybenzene as an internal standard with respect to the 0.5 mmol of the corresponding starting material used.

A4.2.1 Determination of the yield of **3a** by ¹H-NMR

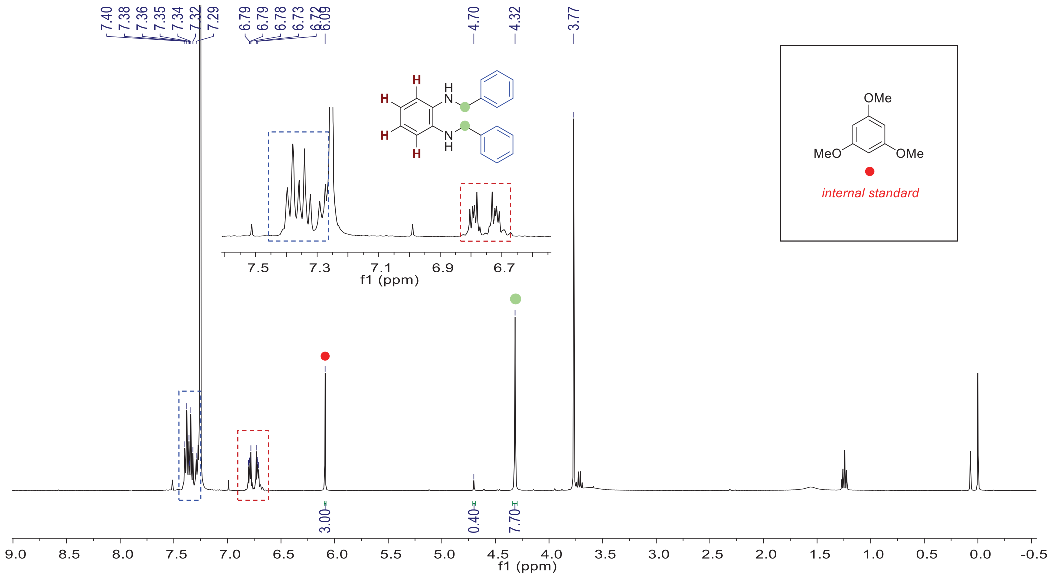

Figure A4.3. ¹H-NMR spectrum ($CDCl_3$, 400 MHz) of **3a**.

A4.2.2 Determination of the yield of **6a** by ¹H NMR

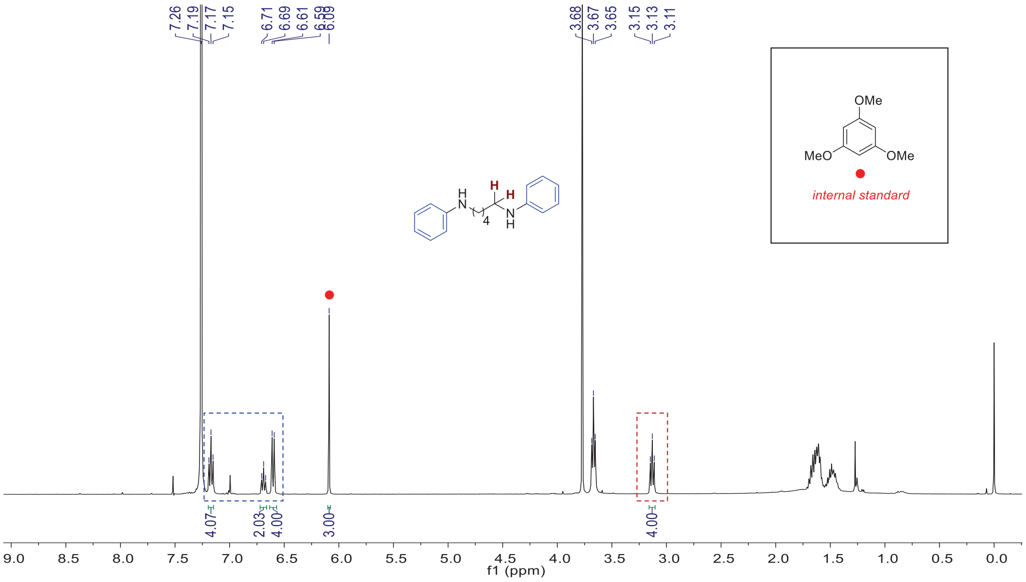

Figure A4.4. ¹H-NMR spectrum ($CDCl_3$, 400 MHz) of **6a**.

A4.2.3 Determination of the yield of **7a** by ^{1}H-NMR

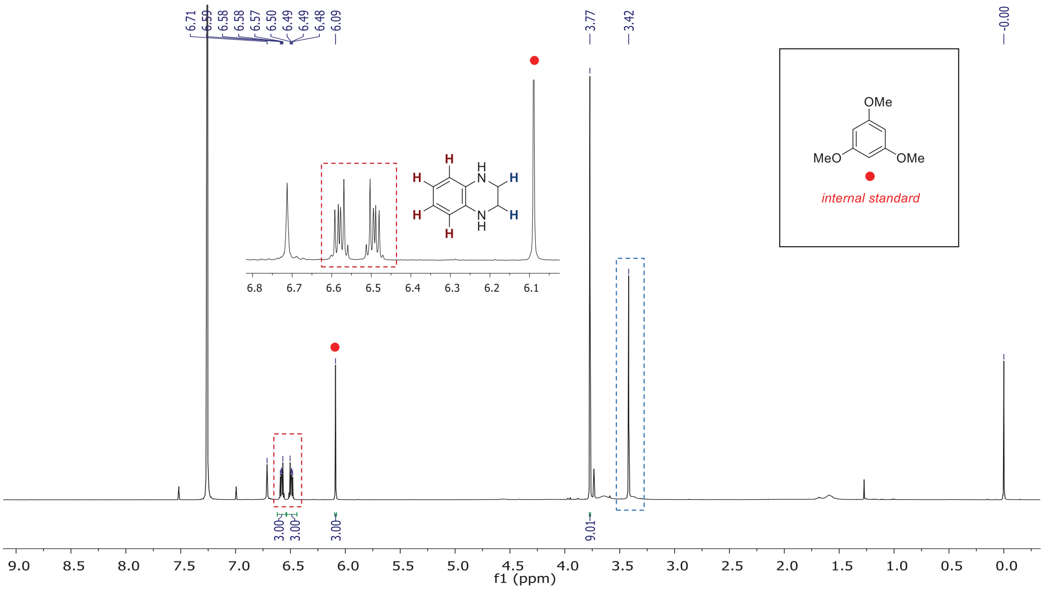

Figure A4.5. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of **7a**.

A4.2.4 Determination of the yield of **9a** by ^{1}H-NMR

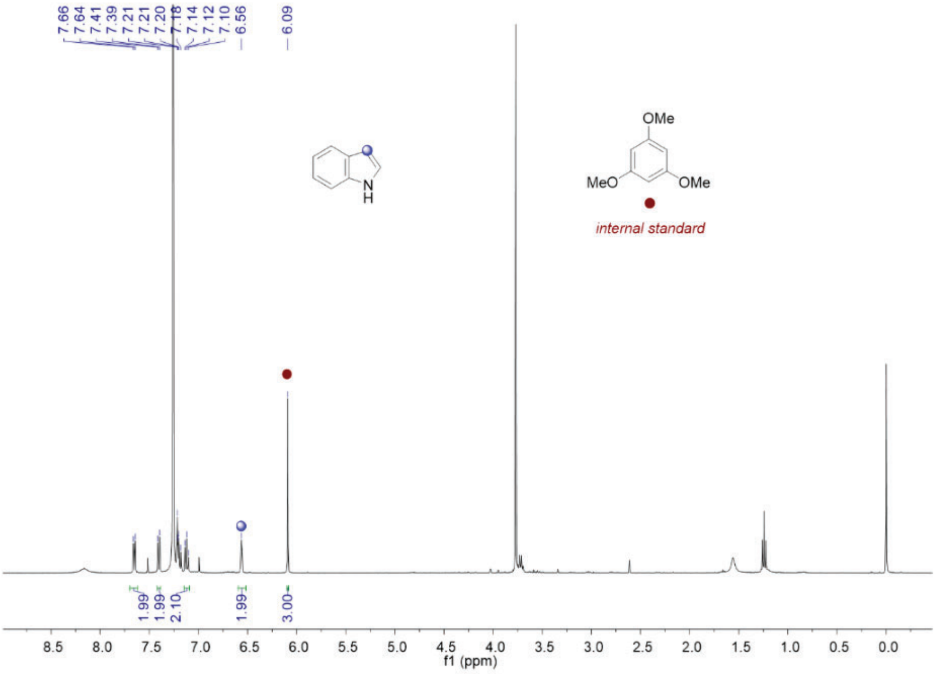

Figure A4.6. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of **9a**.

A4.2.5 Determination of the yield of **10a** by ^{1}H-NMR

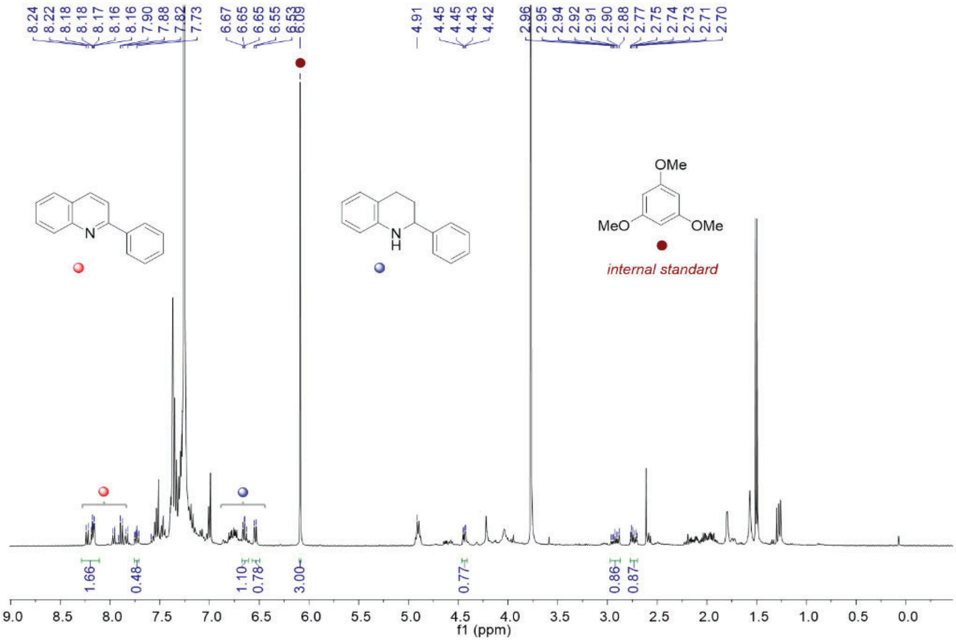

Figure A4.7. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction from the catalytic synthesis of **10a**.

A4.3 *N,N*-dialkylation scope of diamines with primary alcohols

^{1}H-NMR spectra were recorded with a Bruker Avance III 400 MHz. Yields of the final products were calculated using 1,3,5-trimethoxybenzene (0.25 mmol) as internal standard.

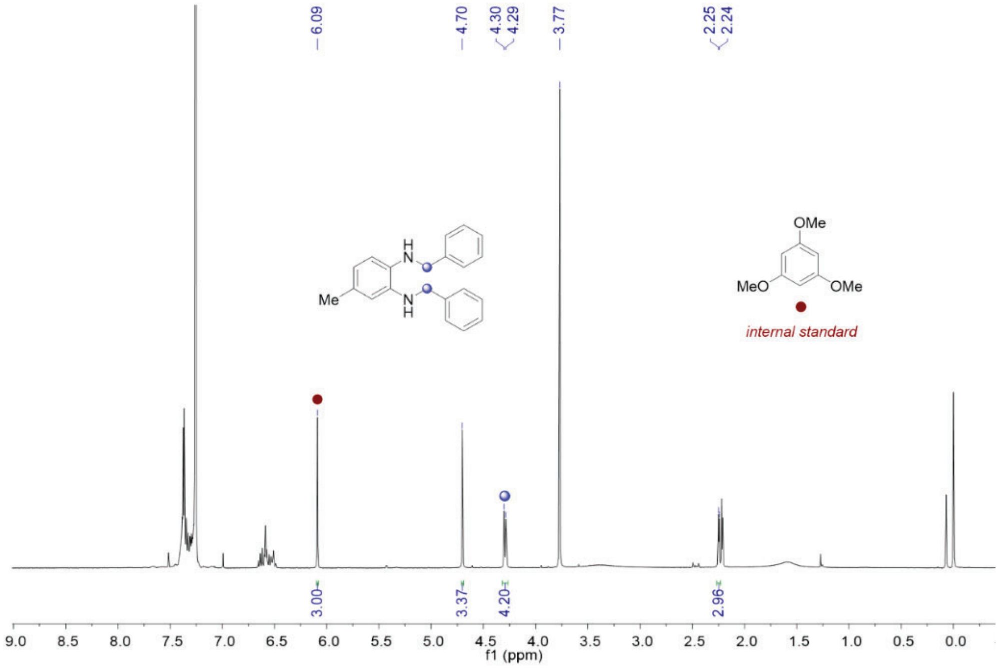

Figure A4.8. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **3b** (50%).

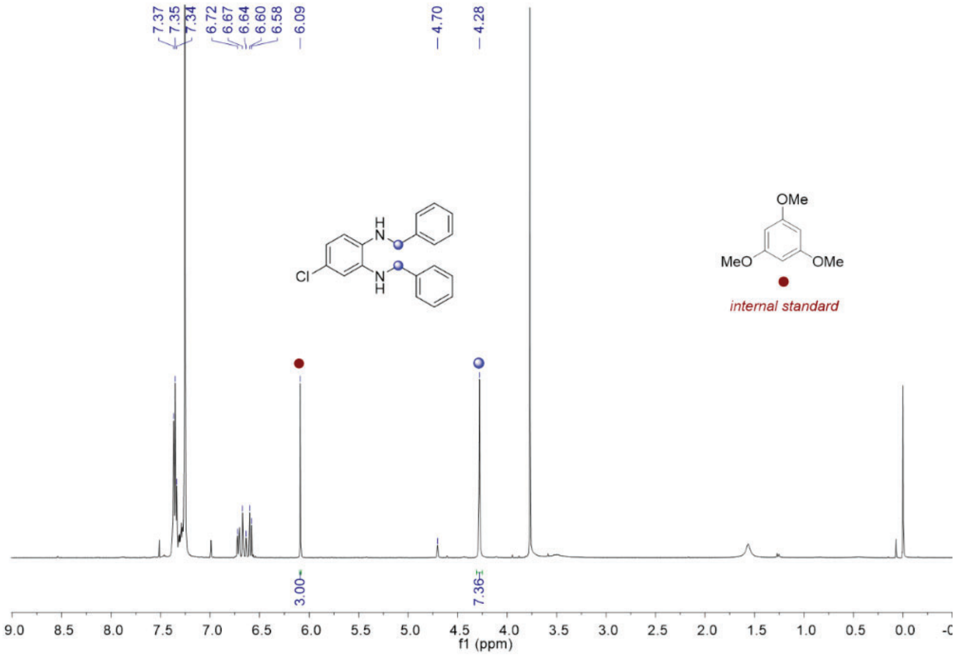

Figure A4.9. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **3c** (92%).

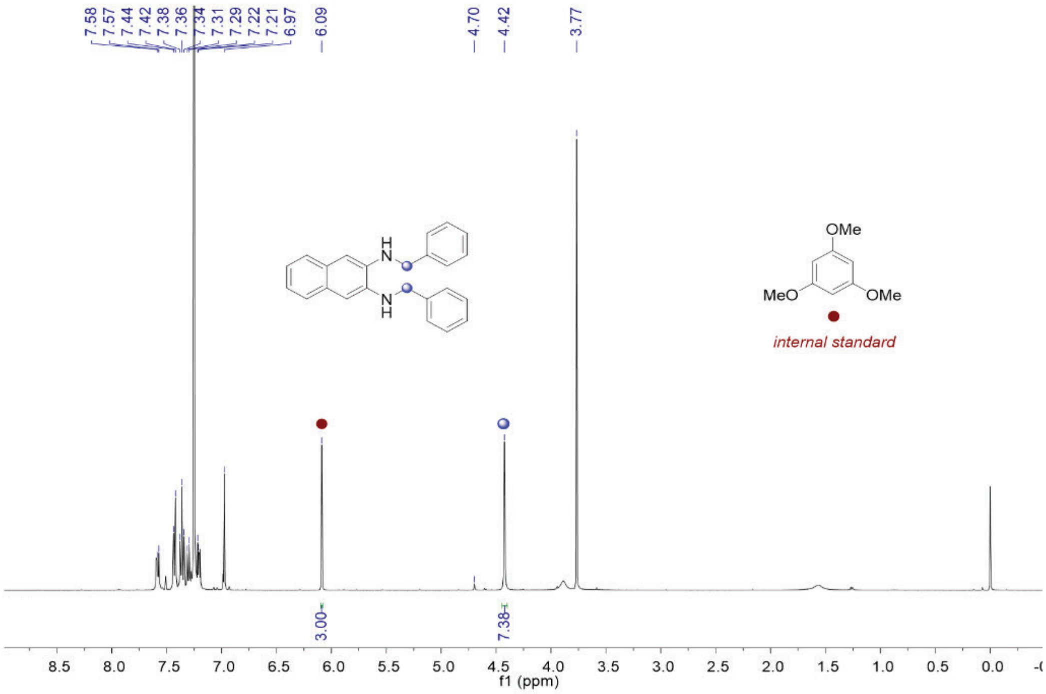

Figure A4.10. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of the crude of the reaction of **3d** (92%).

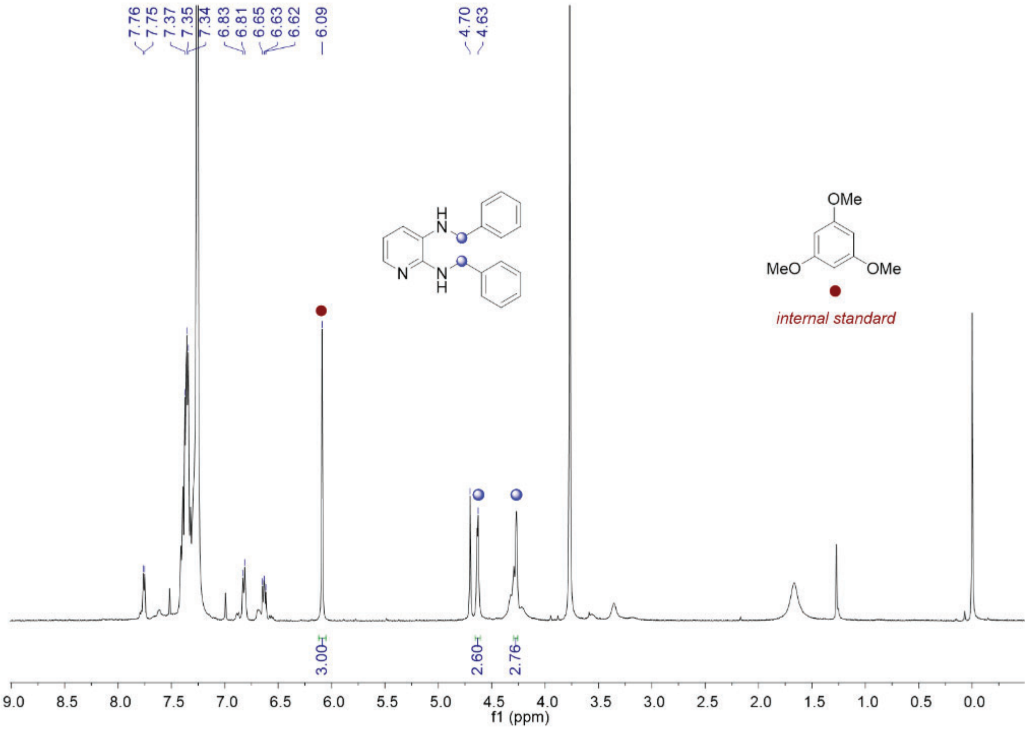

Figure A4.11. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of the crude of the reaction of **3e** (65%).

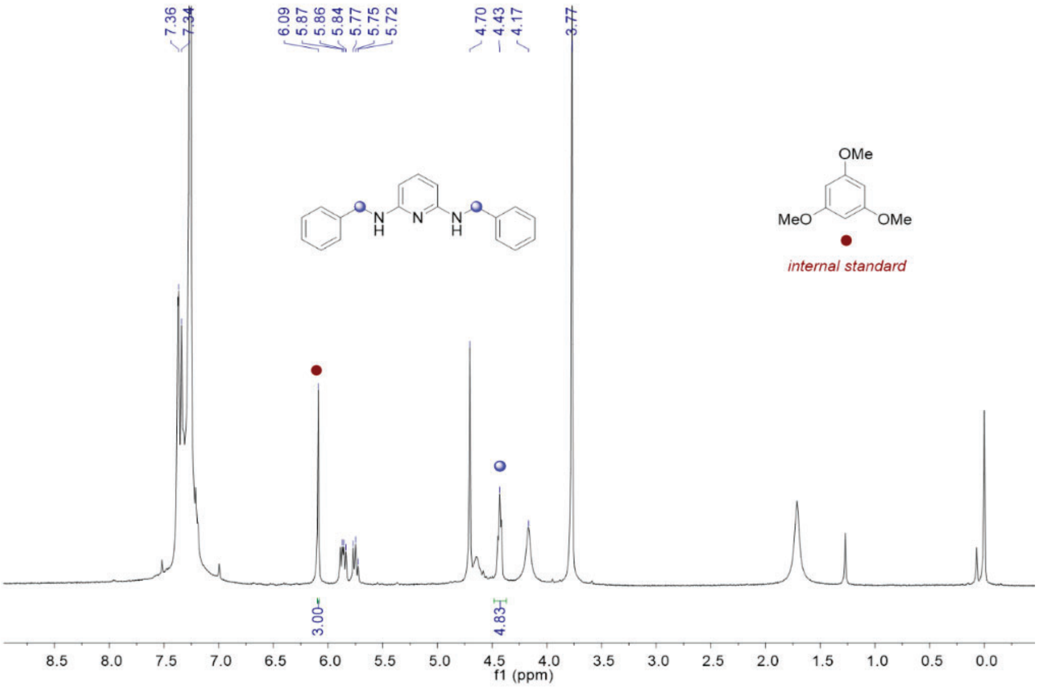

Figure A4.12. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **3f** (60%).

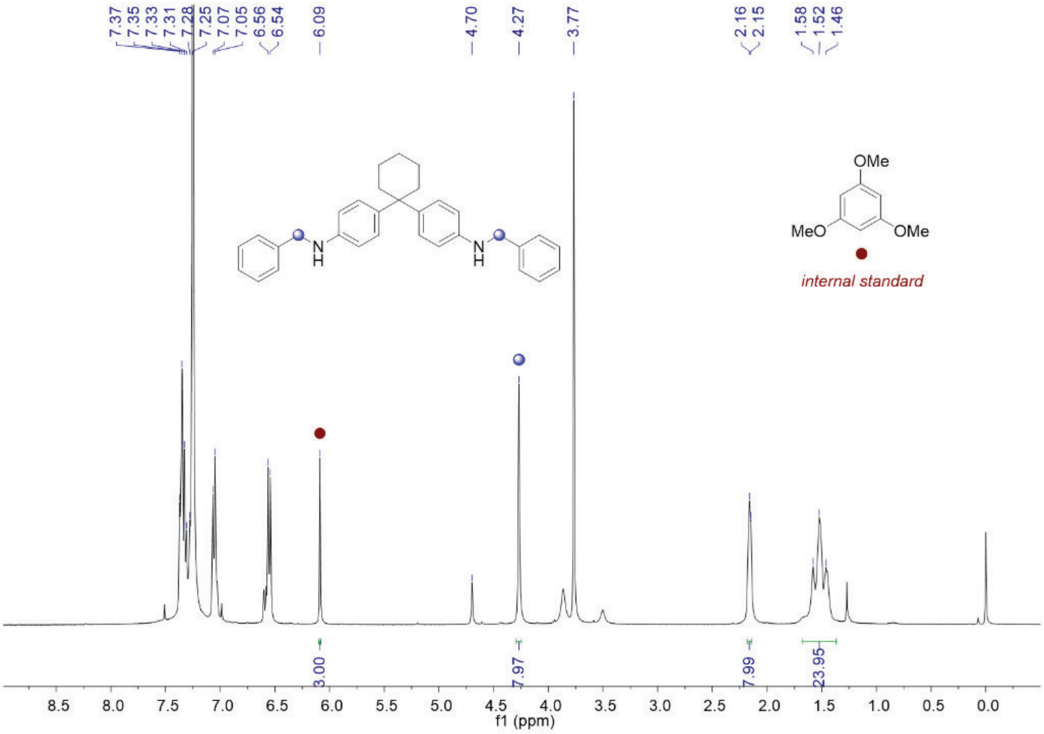

Figure A4.13. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **3h** (99%).

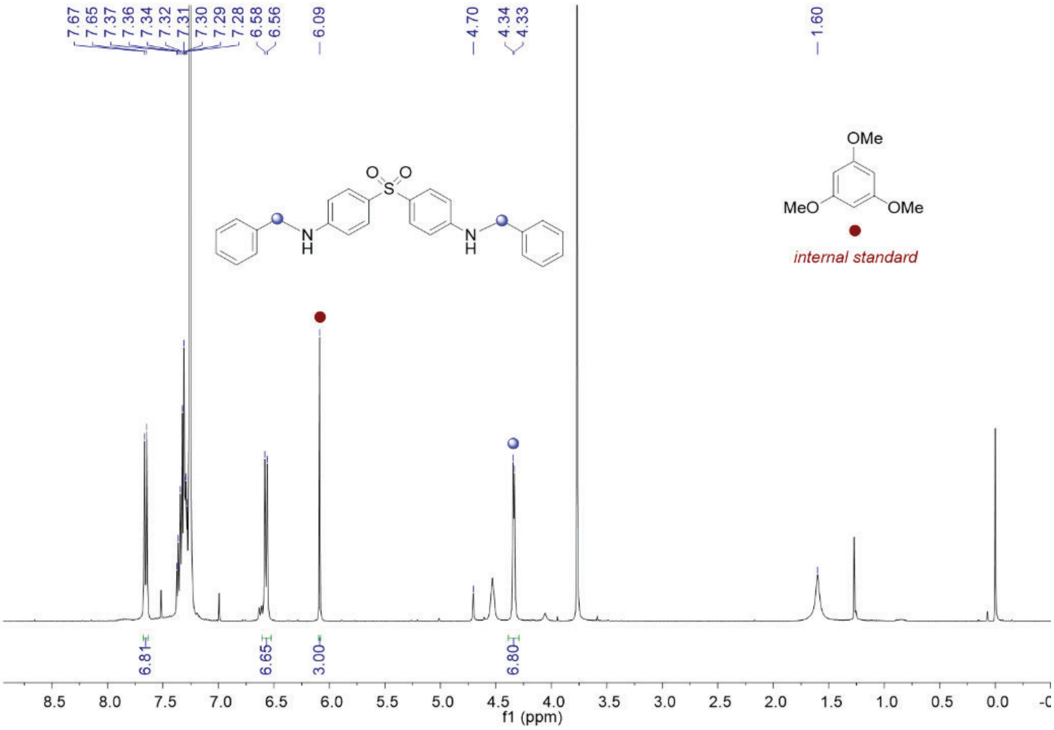

Figure A4.14. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of the crude of the reaction of **3i** (85%).

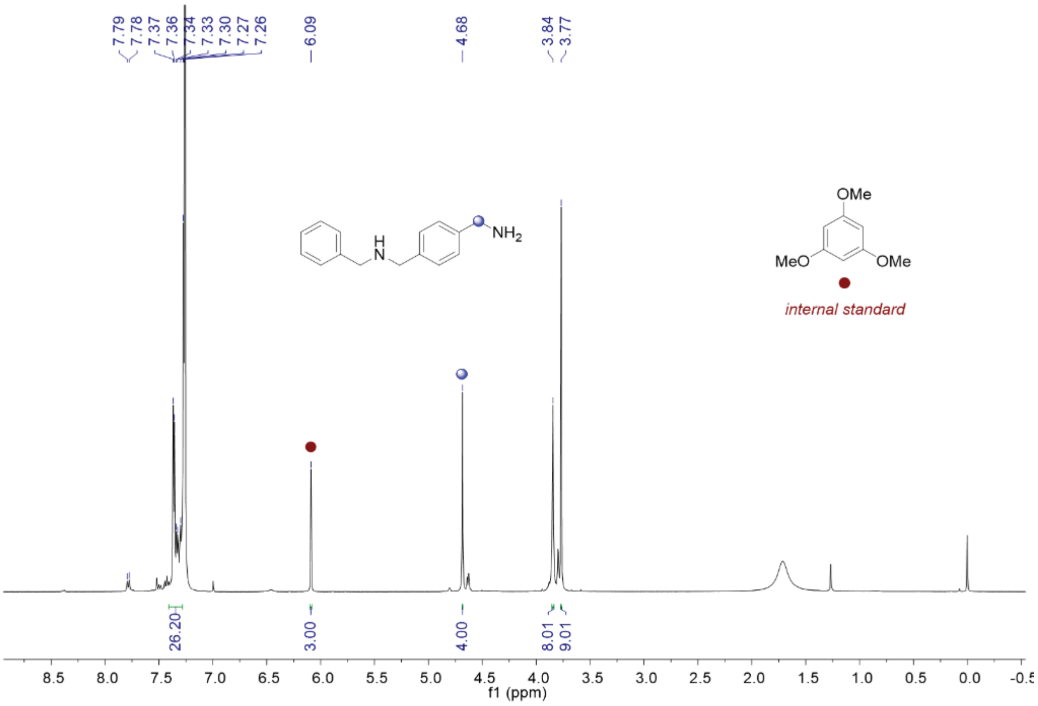

Figure A4.15. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of the crude of the reaction of **3j** (>99%).

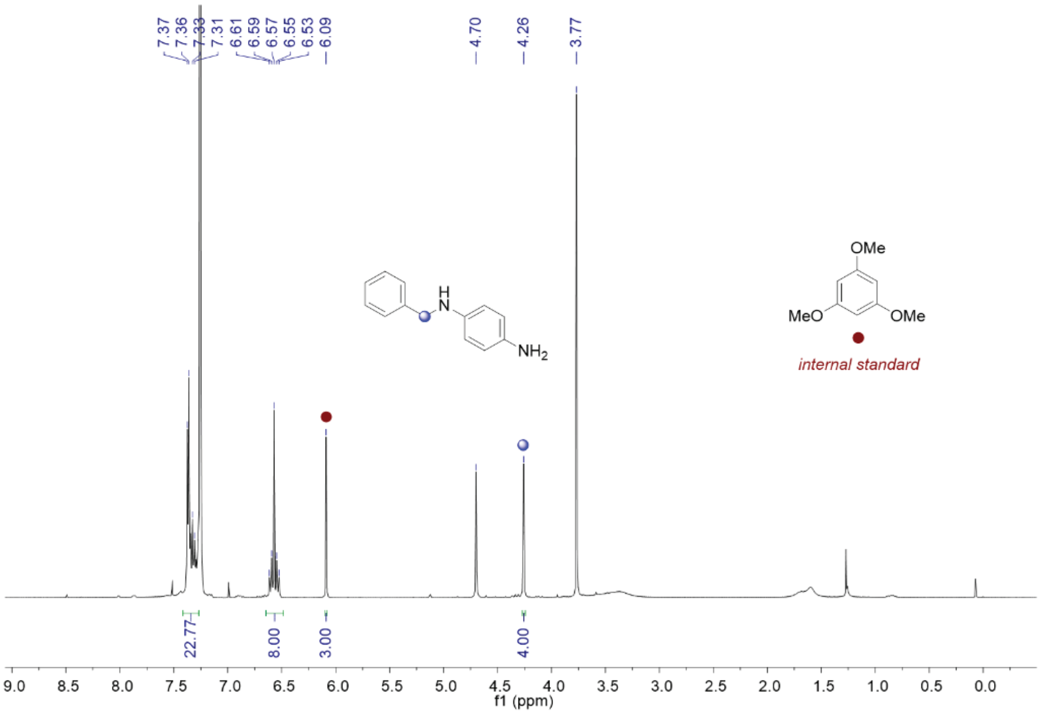

Figure A4.16. ¹H-NMR spectrum (CDCl3, 400 MHz) of the crude of the reaction of **3k** (>99%).

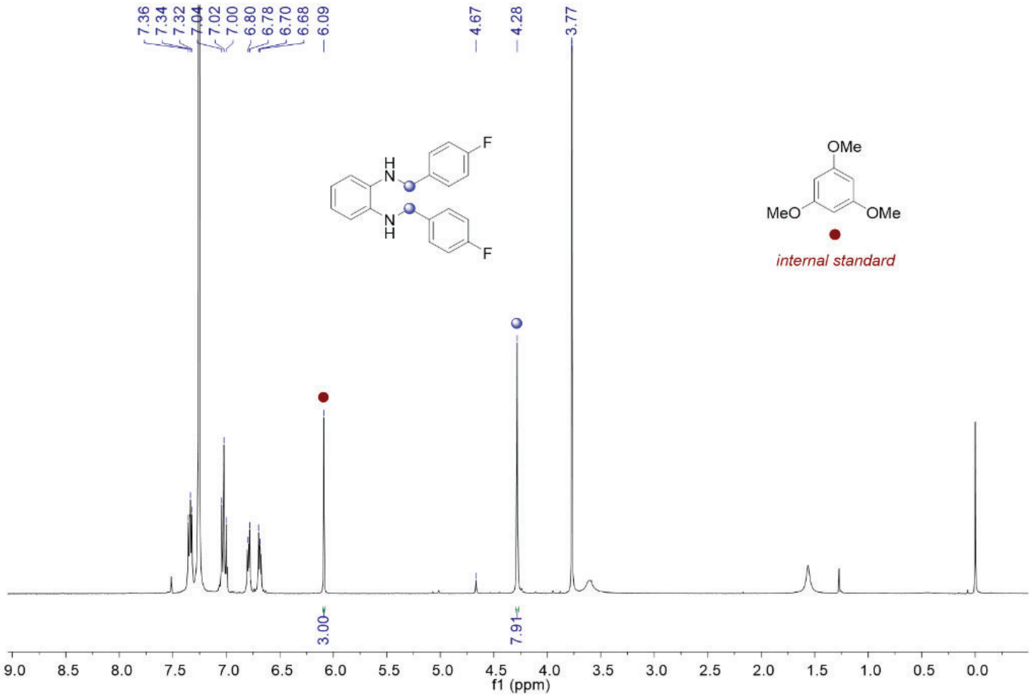

Figure A4.17. ¹H-NMR spectrum (CDCl3, 400 MHz) of the crude of the reaction of **3l** (99%).

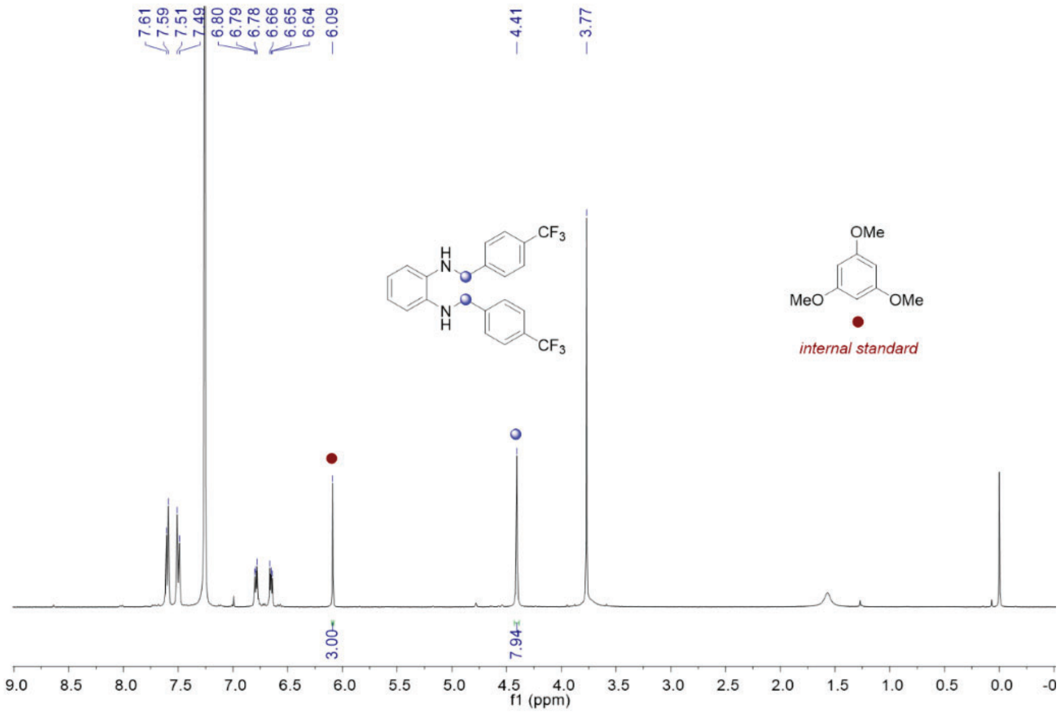

Figure A4.18. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **3m** (99%).

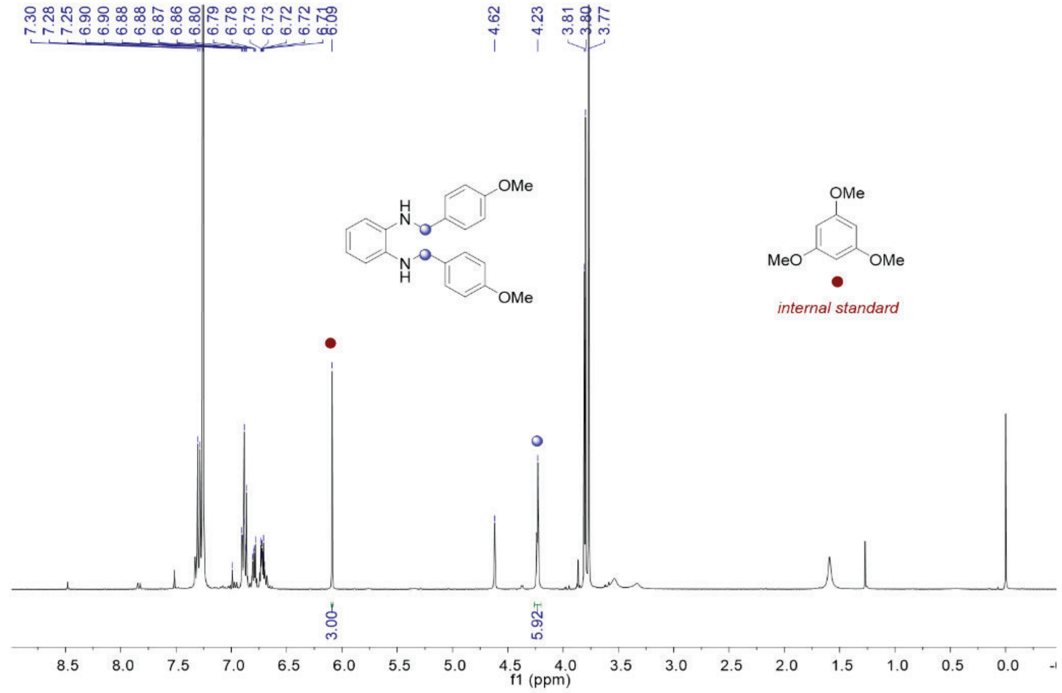

Figure A4.19. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **3n** (74%).

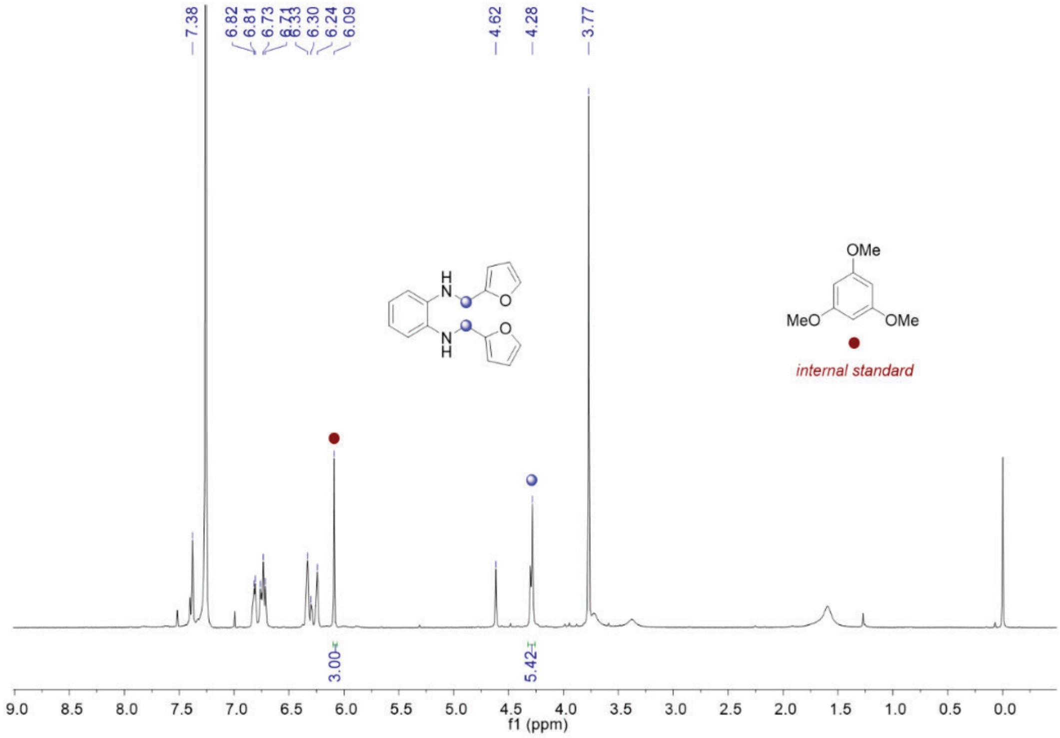

Figure A4.20. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **3o** (68%).

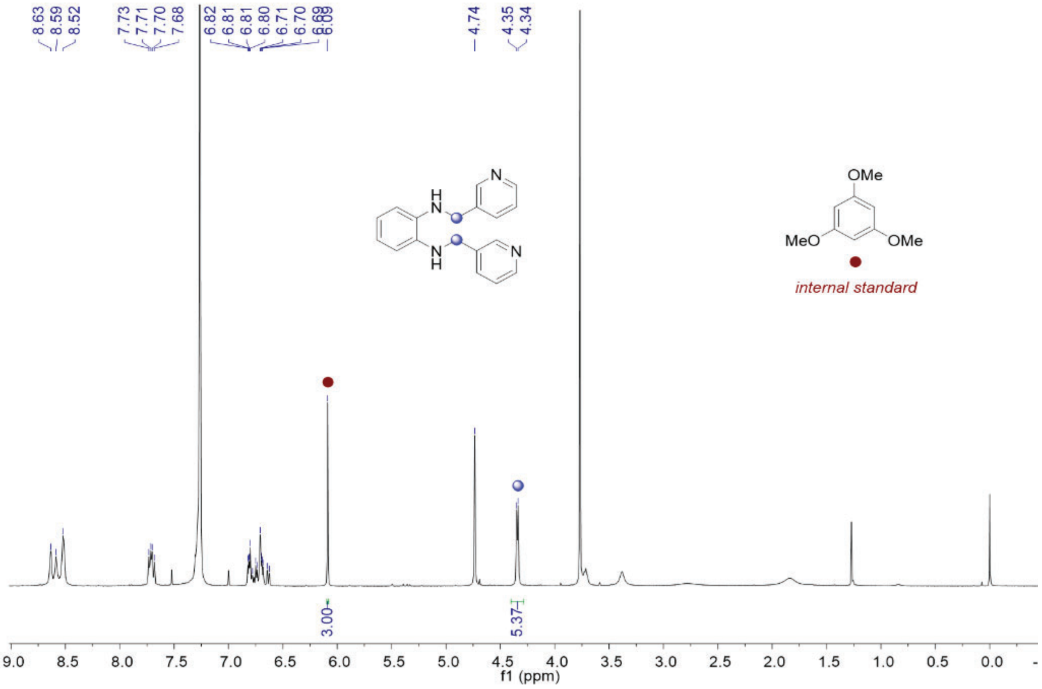

Figure A4.21. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **3p** (67%).

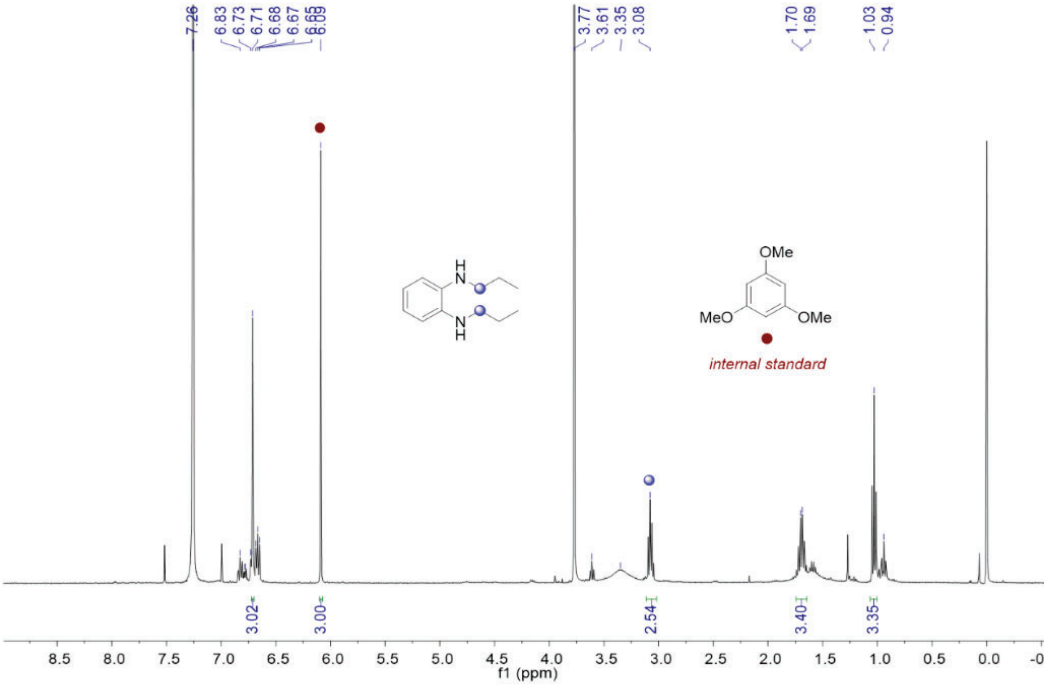

Figure A4.22. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of the crude of the reaction of **3u** (32%).

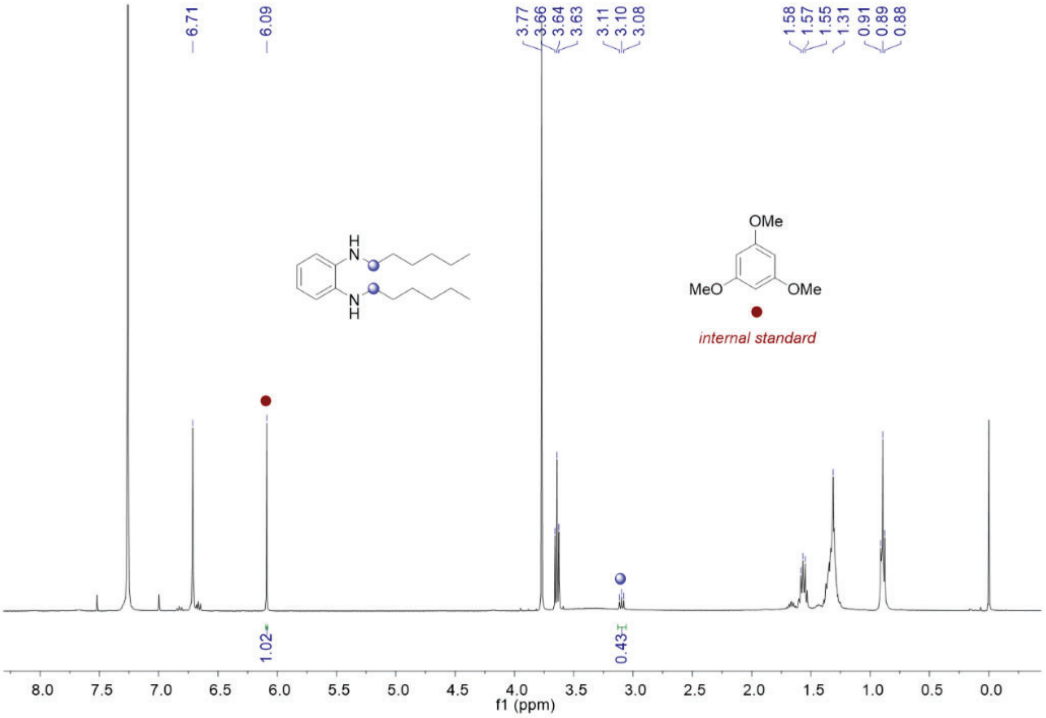

Figure A4.23. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of the crude of the reaction of **3v** (5%).

A4.4 Direct reaction of diols with anilines

^{1}H-NMR spectra were recorded with a Bruker Avance III 400 MHz. Yields of the final products were calculated using 1,3,5-trimethoxybenzene (0.25 mmol) as internal standard.

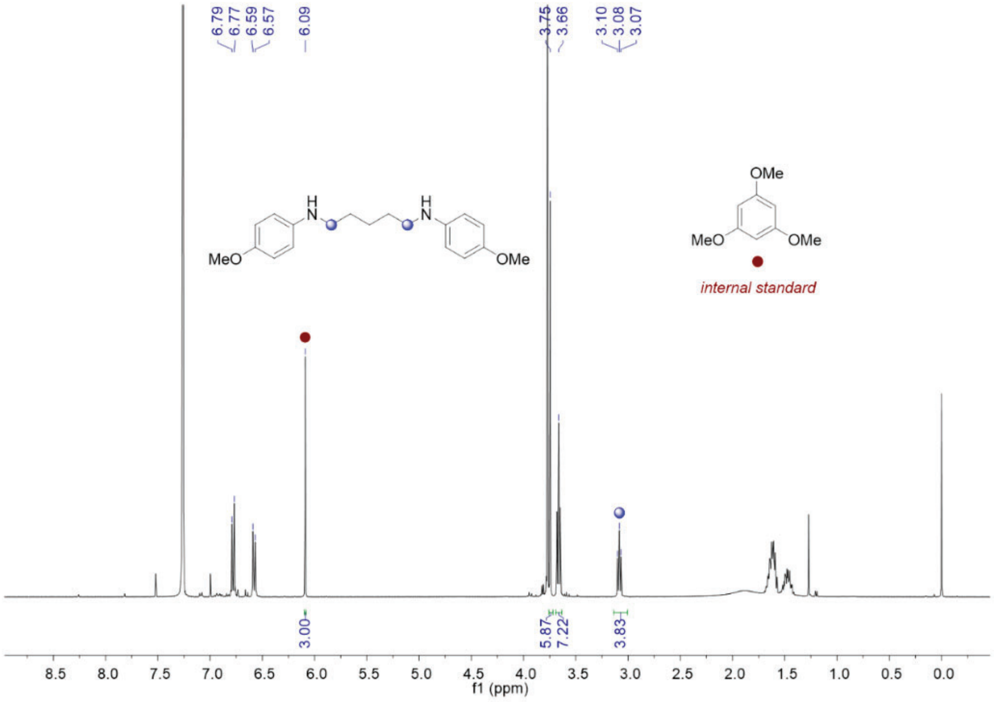

Figure A4.24. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **6b** (90%).

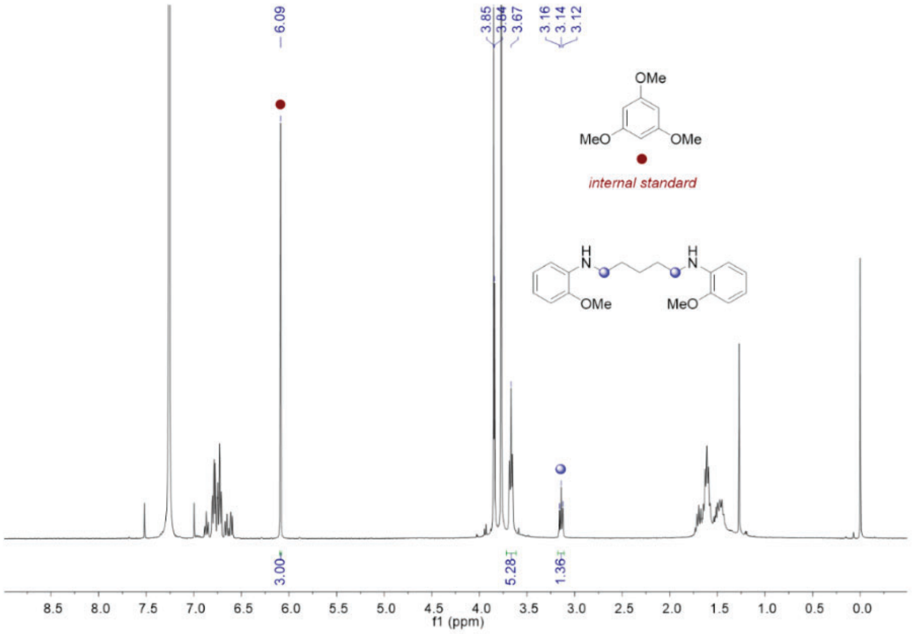

Figure A4.25. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **6c** (34%).

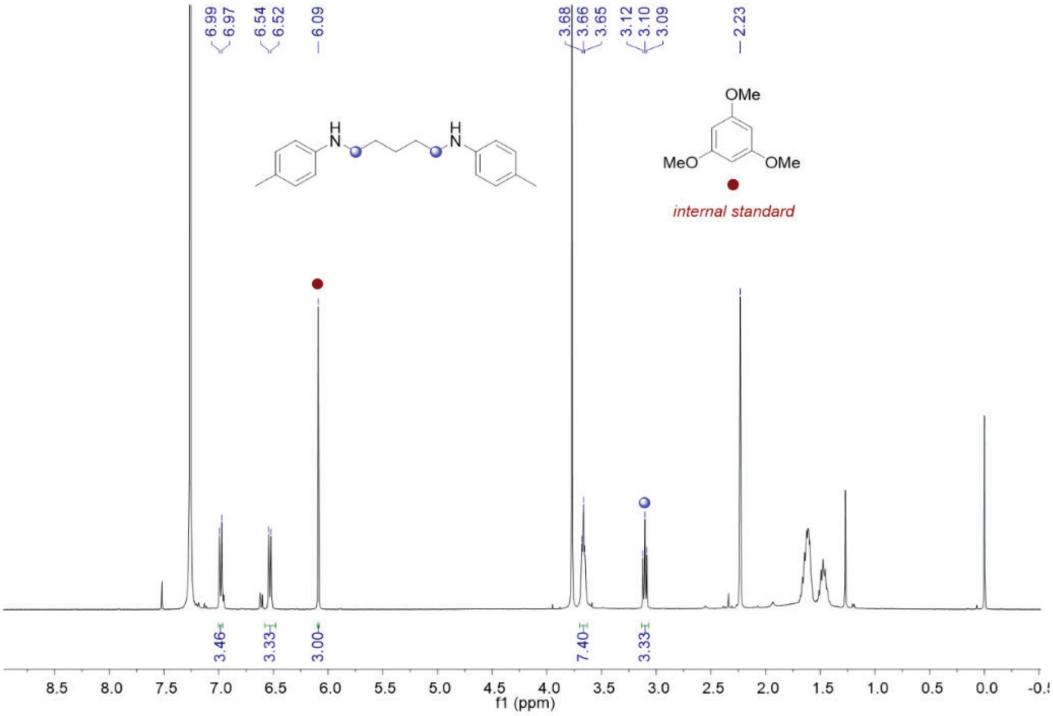

Figure A4.26. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of the crude of the reaction of **6d** (83%).

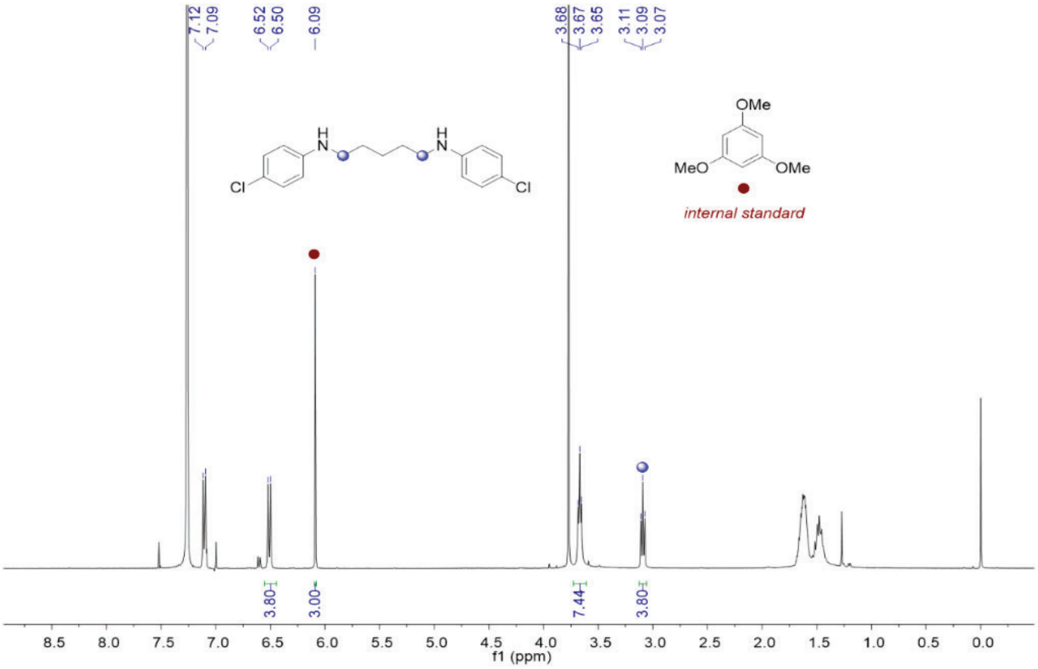

Figure A4.27. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of the crude of the reaction of **6e** (95%).

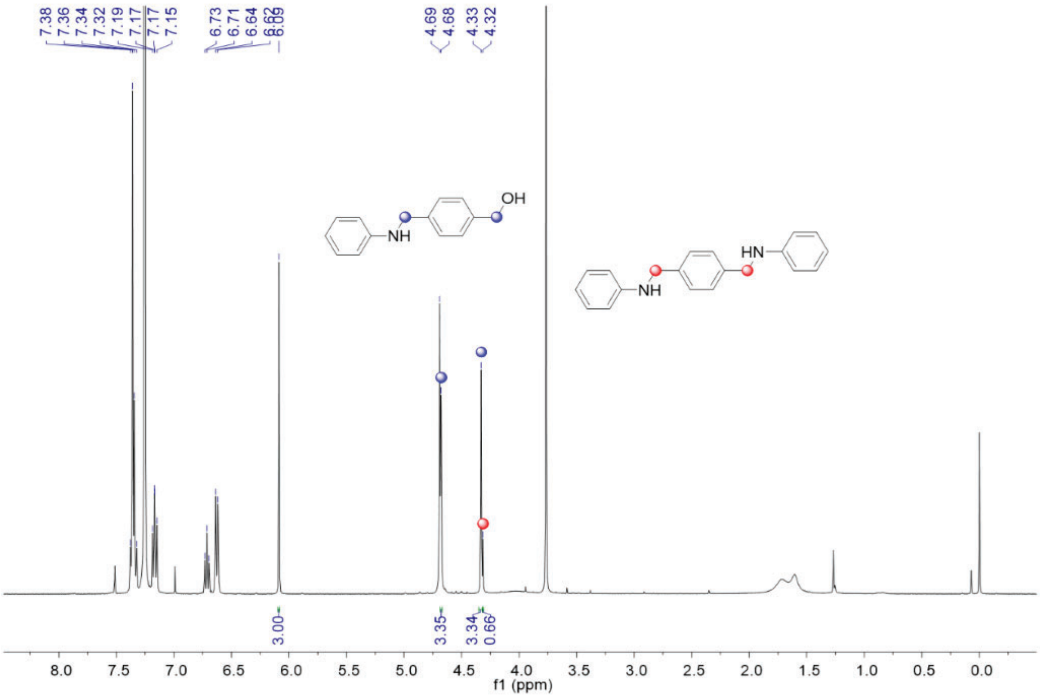

Figure A4.28. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **6f** (84%). It was observed the formation of the dialkylated product with 17% of yield.

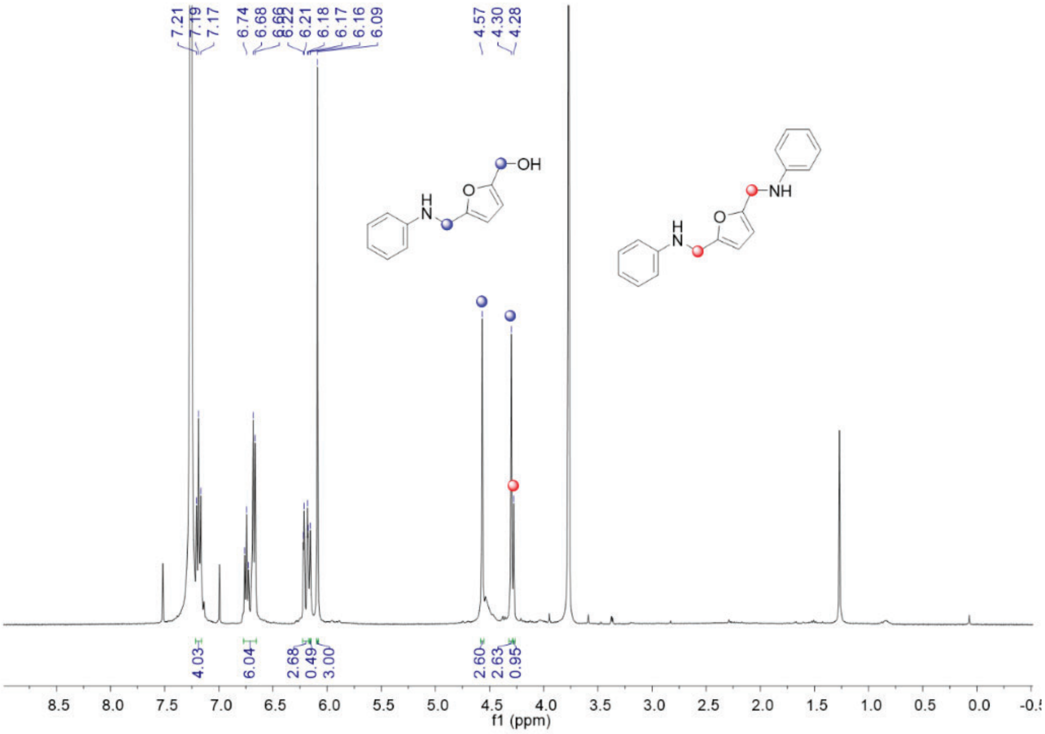

Figure A4.29. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **6g** (66%). It was observed the formation of the dialkylated product with 24% of yield.

A4.5 Scope of tetrahydroquinoxalines

^{1}H NMR spectra were recorded with a Bruker Avance III 400 MHz. Yields of the final products were calculated using 1,3,5-trimethoxybenzene (0.25 mmol) as internal standard.

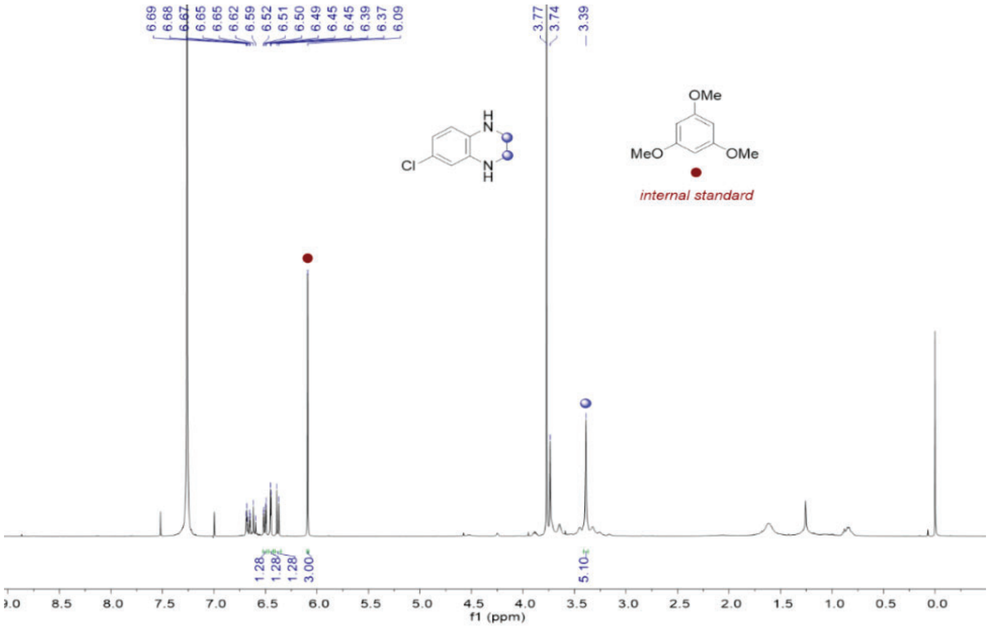

Figure A4.30. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7b** (64%).

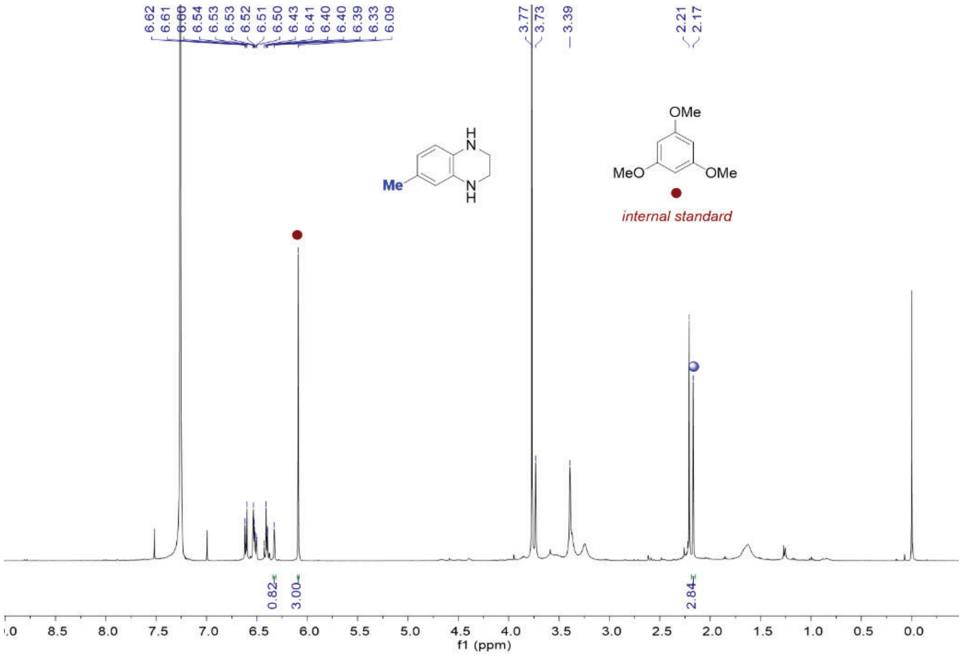

Figure A4.31. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7c** (47%).

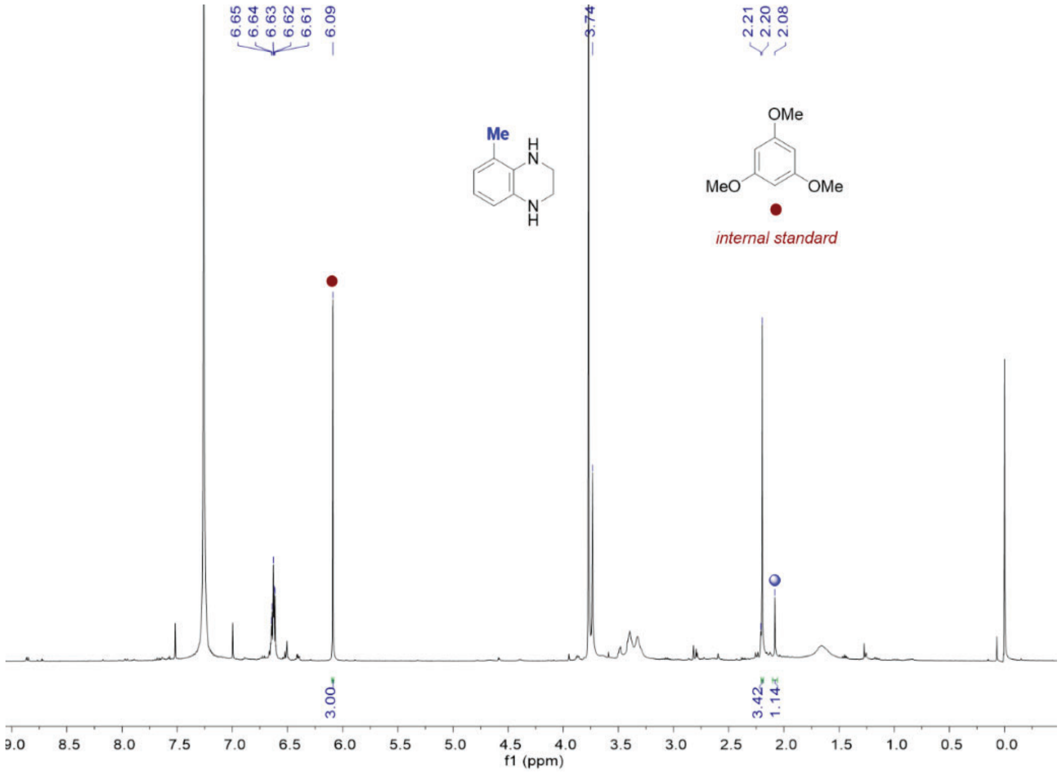

Figure A4.32. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7d** (19%).

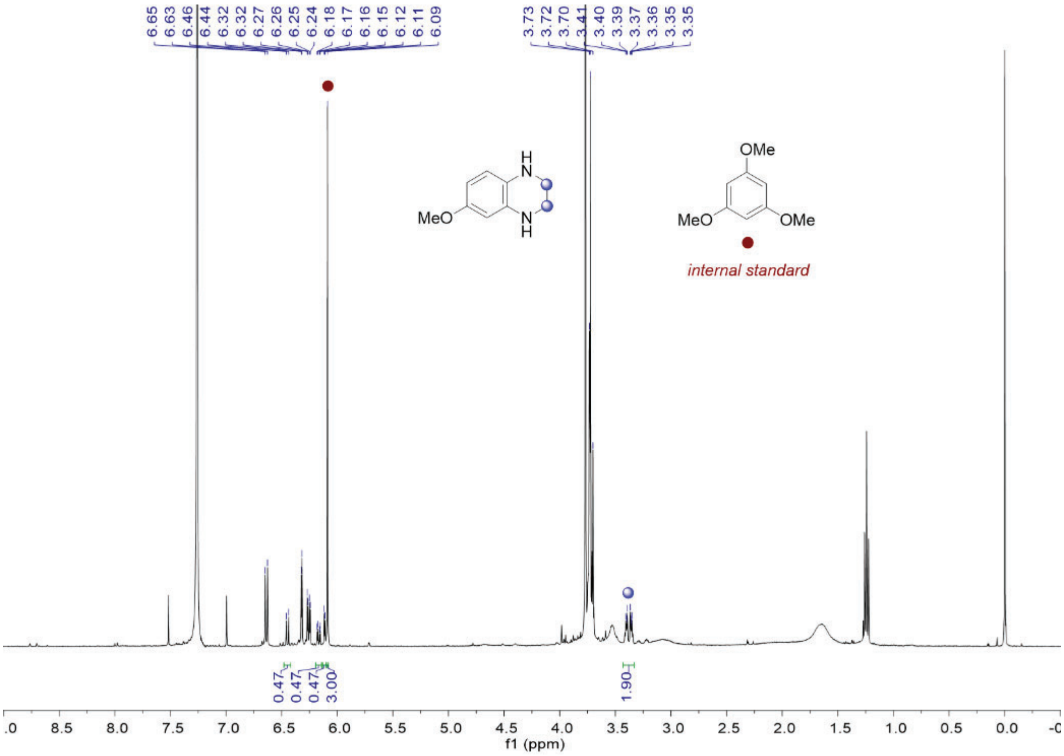

Figure A4.33. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7e** (24%).

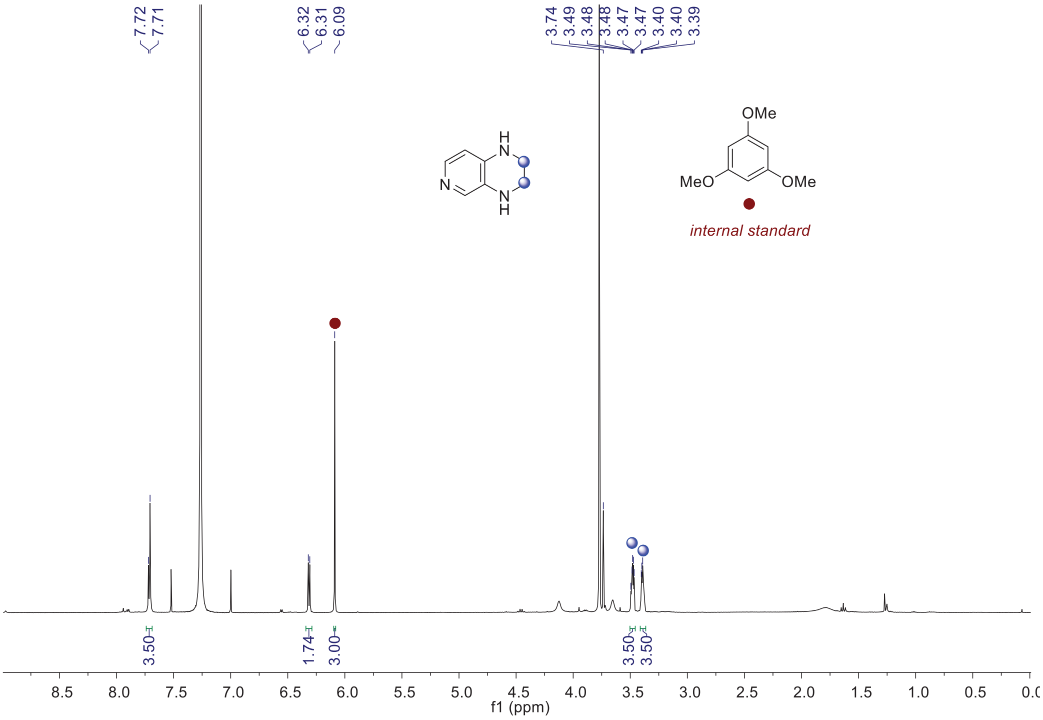

Figure A4.34. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7f** (86%).

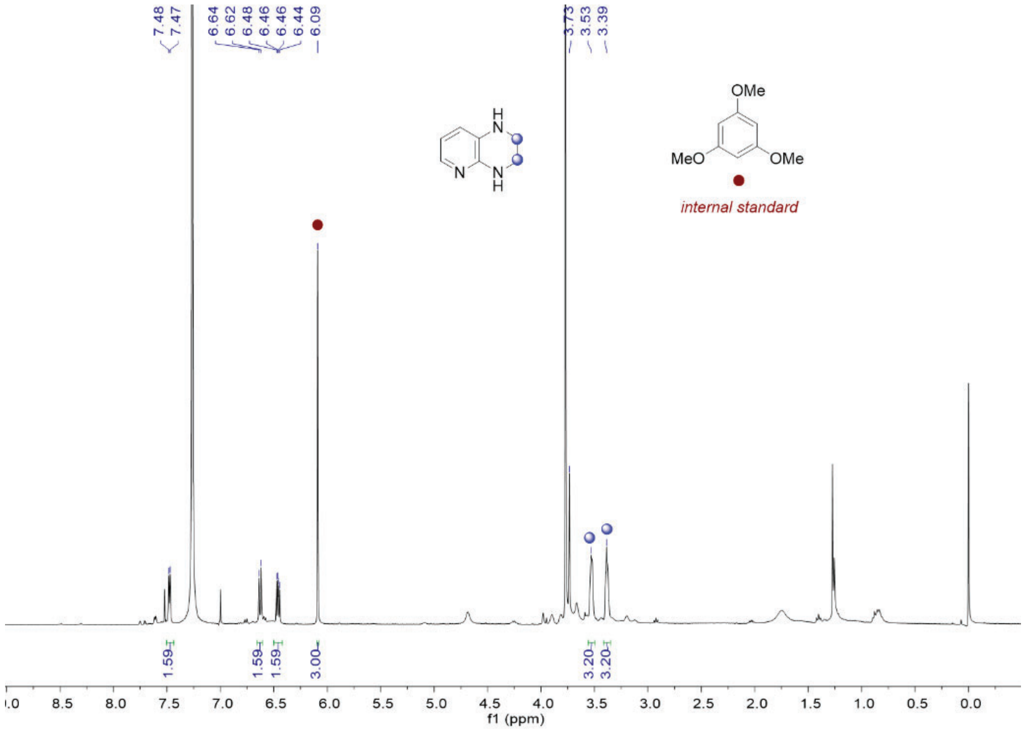

Figure A4.35. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7g** (80%).

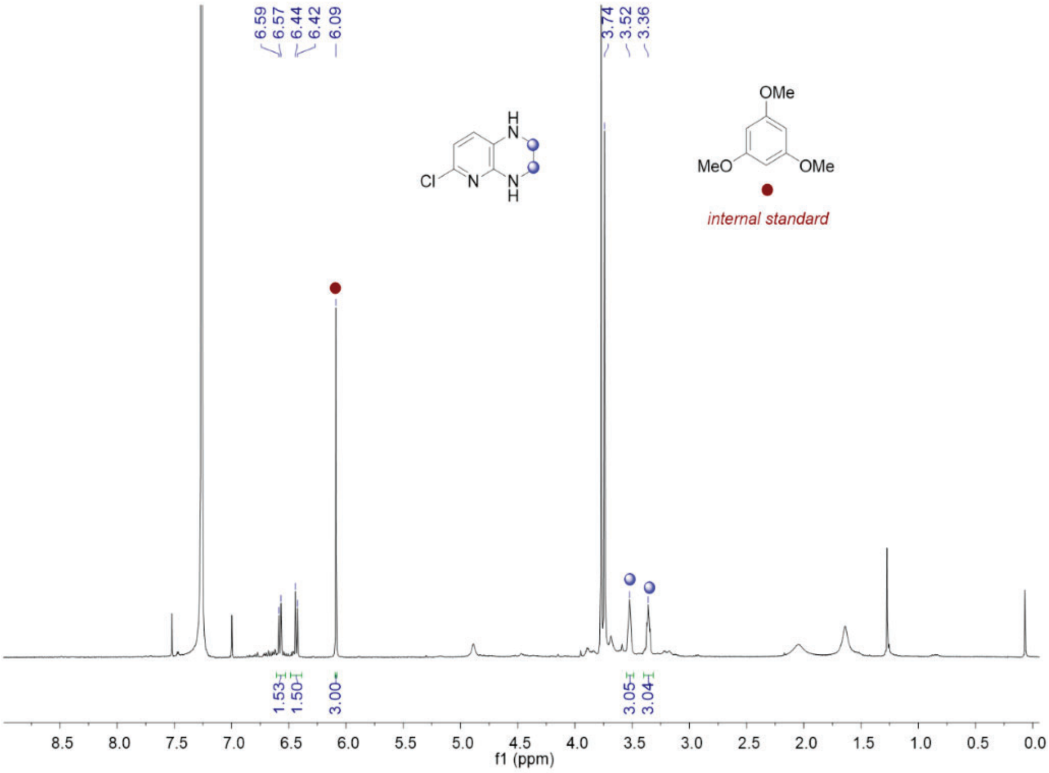

Figure A4.36. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7h** (76%).

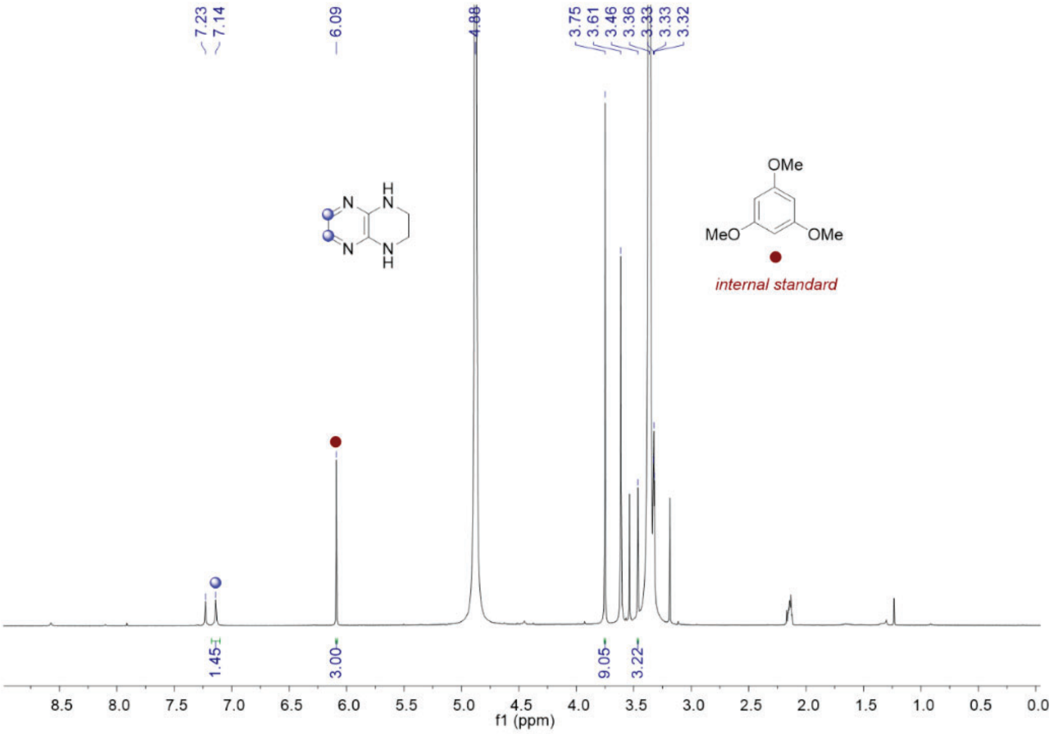

Figure A4.37. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7i** (36%).

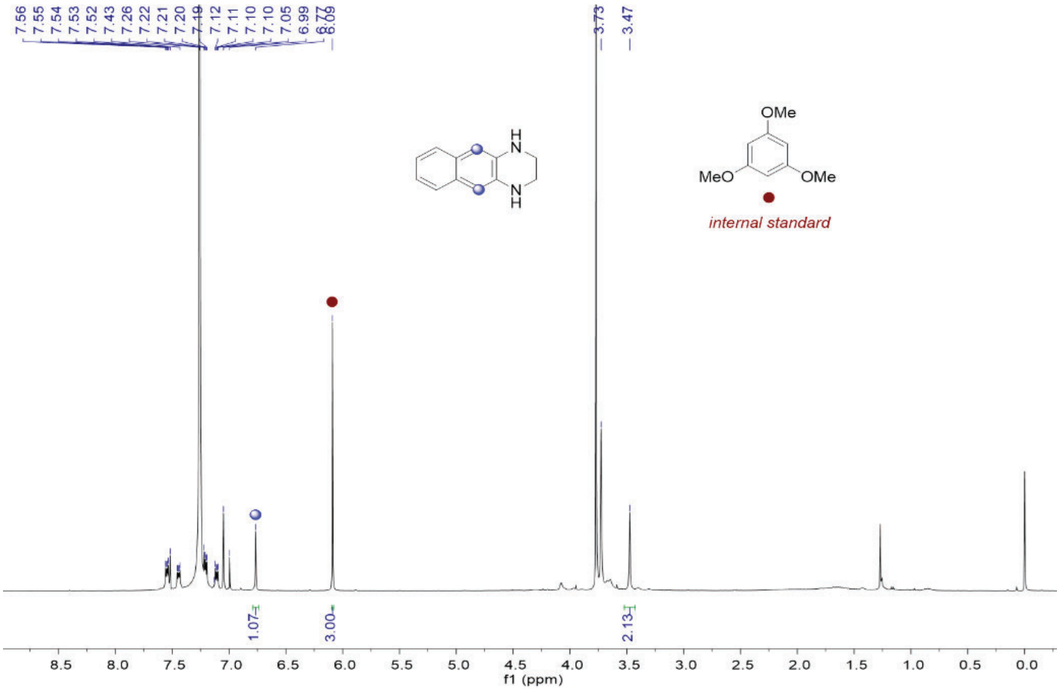

Figure A4.38. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7j** (27%).

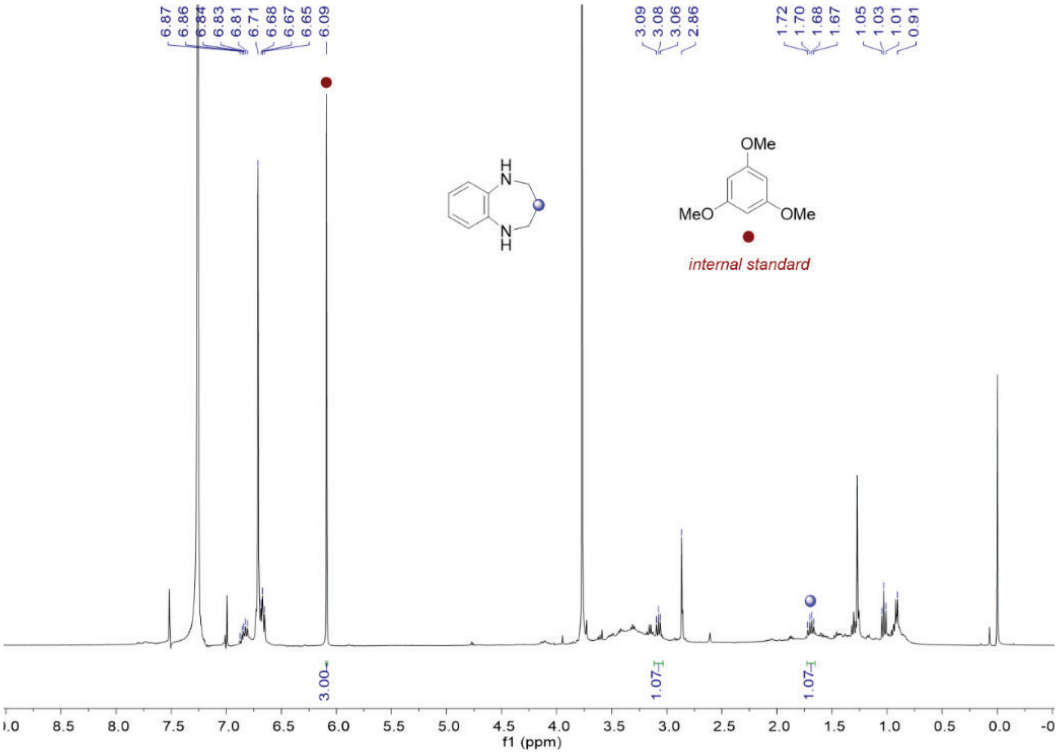

Figure A4.39. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7k** (27%).

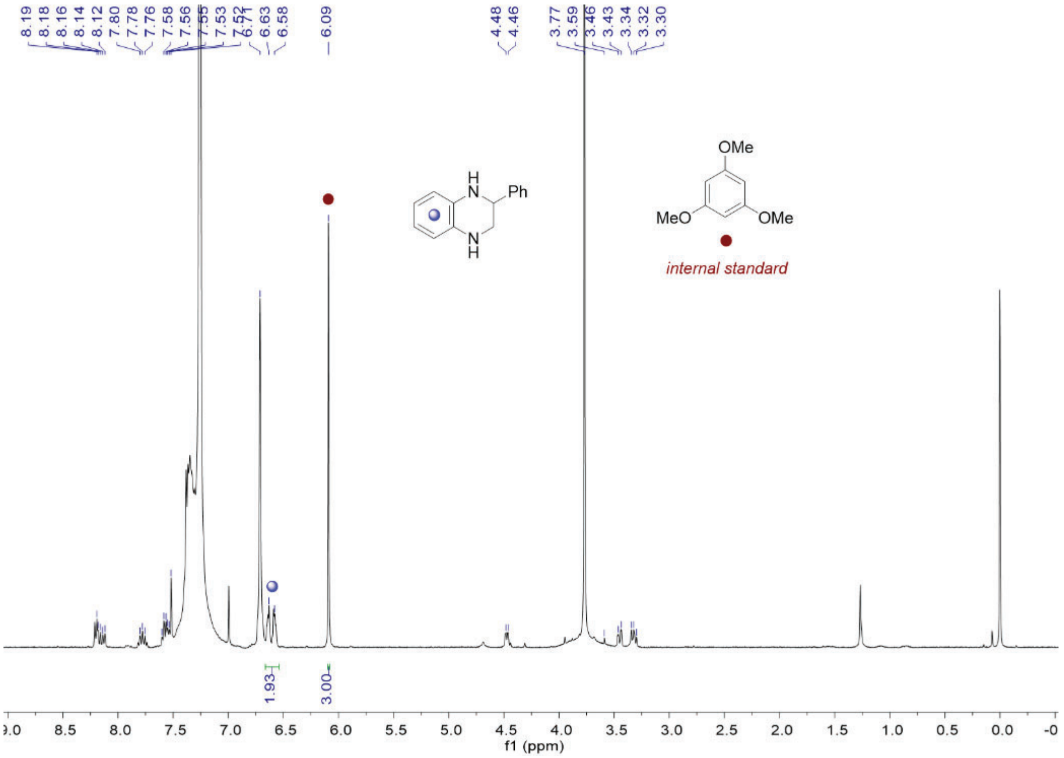

Figure A4.40. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7l** (24%).

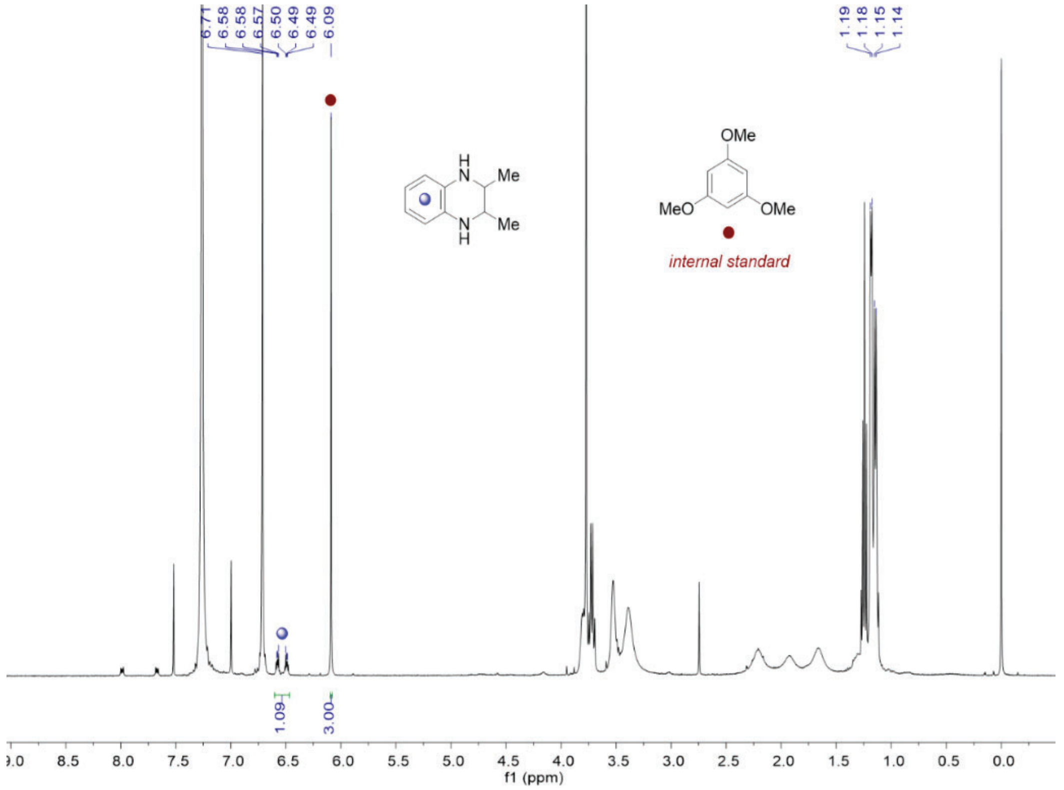

Figure A4.41. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **7m** (14%).

A4.6 NMR spectra of the isolated compounds

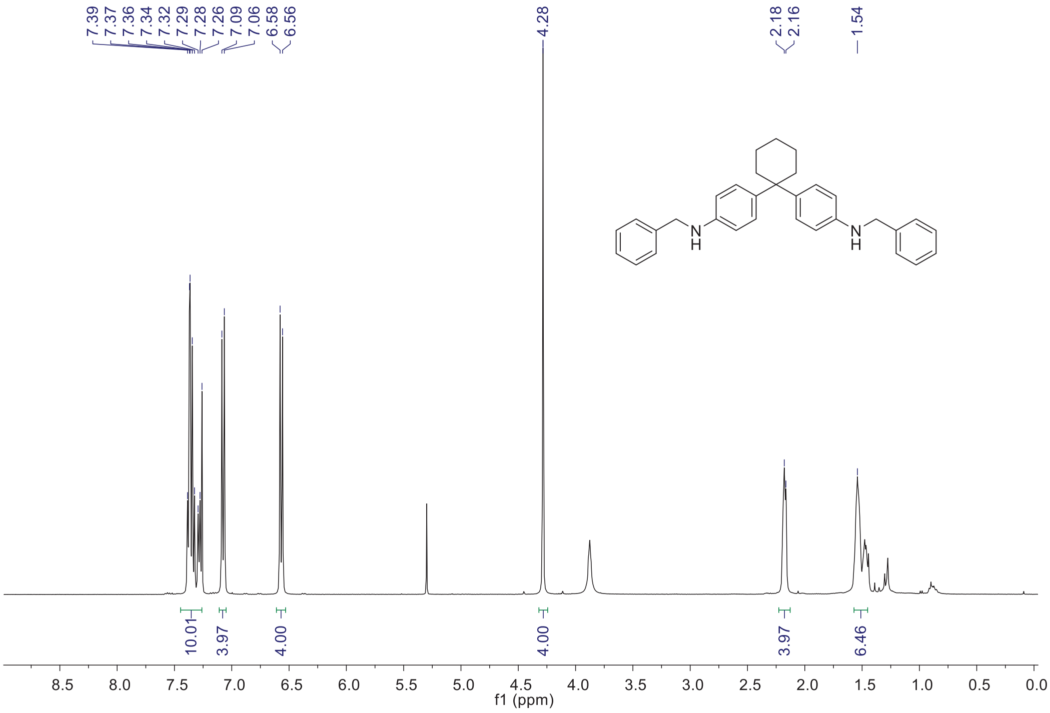

Figure A4.42. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of **3h**.

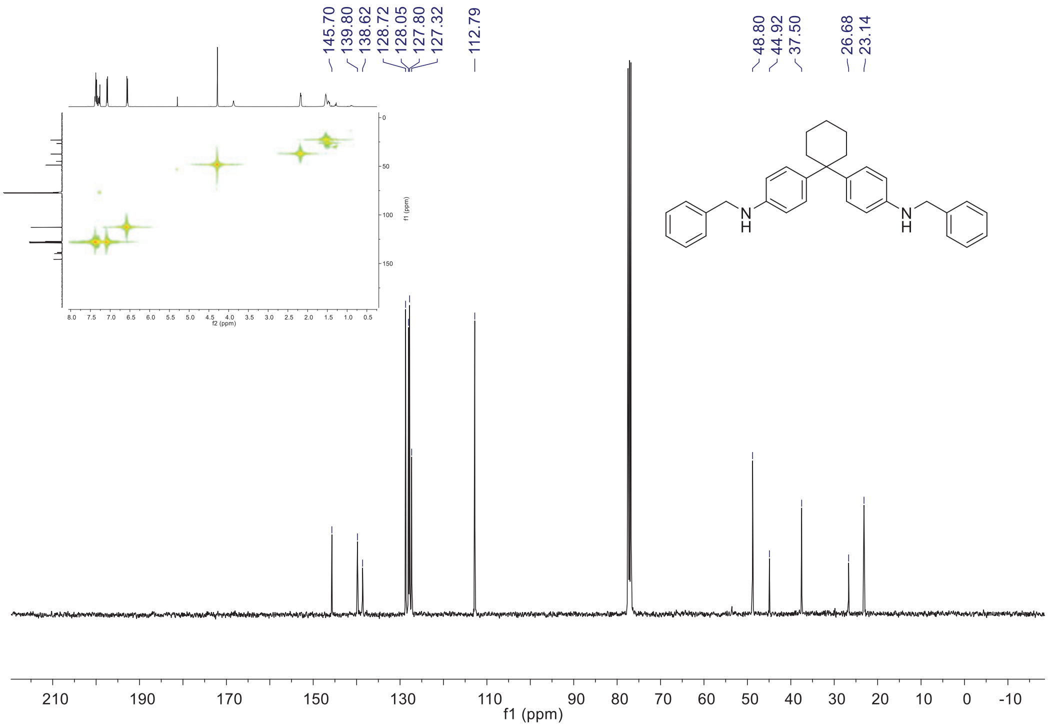

Figure A4.43. ^{13}C-NMR spectrum (CDCl$_3$, 400 MHz) of **3h**.

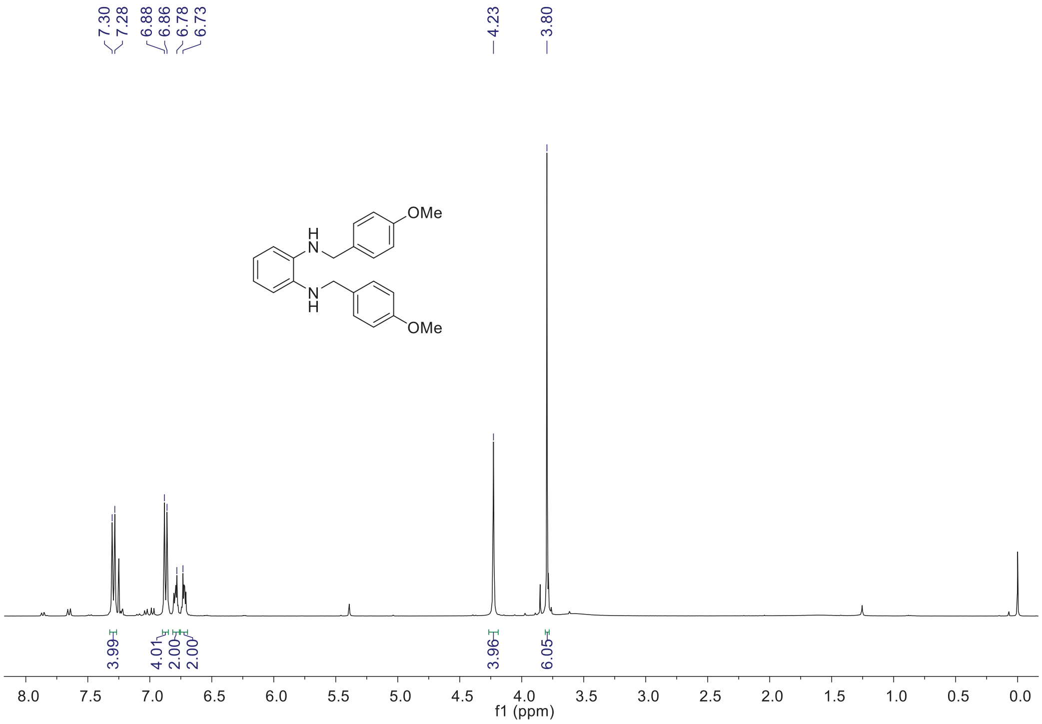

Figure A4.44. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of **3n**.

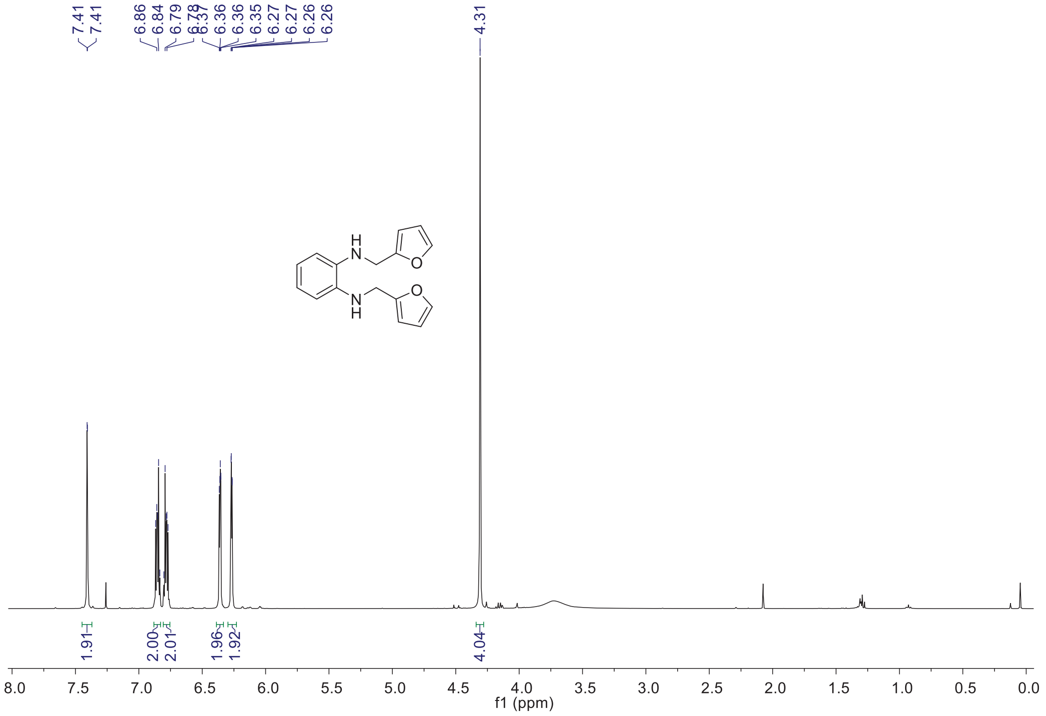

Figure A4.45. ^{1}H-NMR spectrum (CDCl$_3$, 400 MHz) of **3o**.

A4.7 Bimetallic approach: ^{1}H NMR analysis of **11a** and indoline **12a**

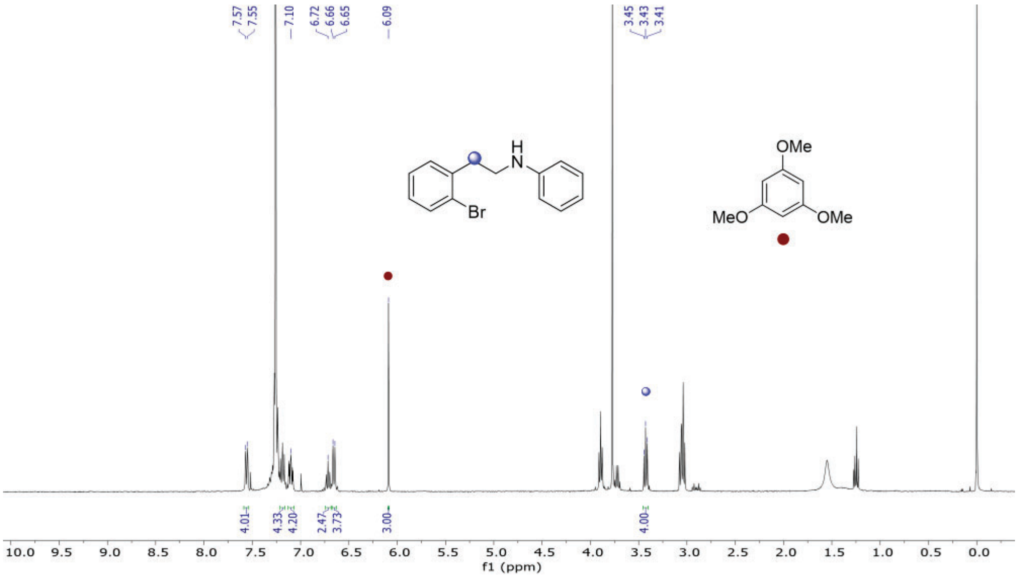

Figure A4.46. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of the crude of the reaction of **11a** (>99%).

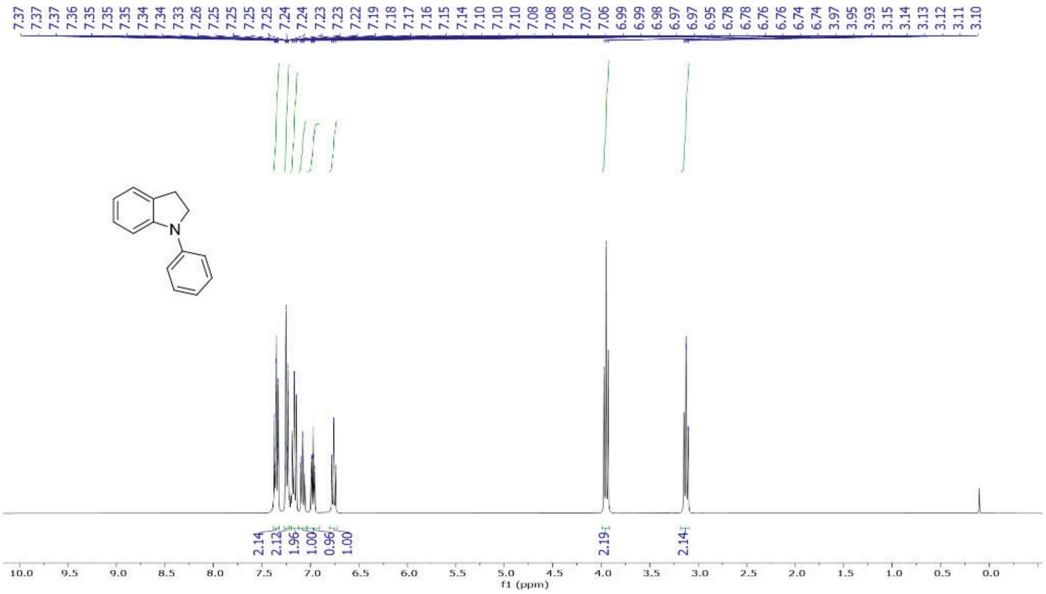

Figure A4.47. ^{1}H-NMR spectrum ($CDCl_3$, 400 MHz) of **12a**.

A4.8 References

1. S. Friães, C. S. B. Gomes, B. Royo, *Organometallics* **2023**, *42*, 1803–1809.

2. B. Garcia, B. Royo, *ChemCatChem* **2024**, DOI 10.1002/cctc.202400024.

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PALLADIUM- AND MANGANESE-CATALYSED SYNTHESIS OF *N*-HETEROCYCLES

DANIEL ALEJANDRO RAYDAN

2024