Development of Iridium Catalyst for α-Alkylation using Alcohol as Alkylating Partner and Utilization of Cobalt Catalyst for Hydrosilylative Reduction

By

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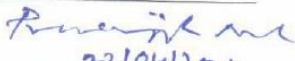## DOCTOR OF PHILOSOPHY
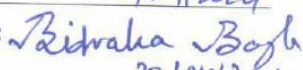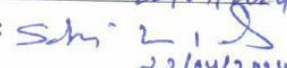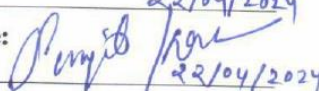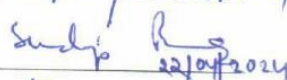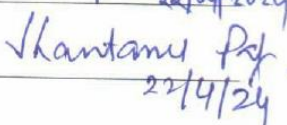*Of*

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Surajit Panda

DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

Surajit Panda

List of Publications arising from the thesis

1. Panda, S.; Saha, R.; Sethi, S.; Ghosh, R.; Bagh, B. Efficient α-Alkylation of Arylacetonitriles with Secondary Alcohols Catalyzed by a Phosphine-Free Air-Stable Iridium(III) Complex. *J. Org. Chem.* **2020**, *85*, 15610–15621.

2. Panda, S.; Nanda, A.; Behera, R. R.; Ghosh, R.; Bagh, B. Cobalt Catalyzed Chemoselective Reduction of Nitroarenes: Hydrosilylation under Thermal and Photochemical Reaction Conditions. *Chem. Commun.* **2023**, *59*, 4527–4530.

3. Panda, S.; Nanda, A.; Saha, R.; Ghosh, R.; Bagh, B. Cobalt Catalyzed Chemodivergent Synthesis of Cyclic amines and Lactams from Ketoacids and Anilines using Hydrosilylation. *J. Org. Chem.* **2023,** Accepted manuscript.

Manuscript under preparation

Panda, S.; Maharana, S.K., Saha, R., Bagh, B. Phosphine free Iridium Catalyzed C-C and C-N Bond Formation via Borrowing hydrogen and Asymmetric Dehydrogenative Coupling. (*manuscript under preparation*).

Publications not included in the thesis

1. Behera, R. R.; Ghosh, R.; Panda, S.; Khamari, S.; Bagh, B. Hydrosilylation of Esters Catalyzed by Bisphosphine Manganese(I) Complex: Selective Transformation of Esters to Alcohols. *Org. Lett.* 2020, *22*, 3642–3648.

2. Ghosh, R.; Jana, N. C.; Panda, S.; Bagh, B. Transfer Hydrogenation of Aldehydes and Ketones in Air with Methanol and Ethanol by an Air-Stable Ruthenium–Triazole Complex. *ACS Sustain. Chem. Eng.* 2021, *9*, 4903–4914.

3. Behera, R. R.; Panda, S.; Ghosh, R.; Kumar, A. A.; Bagh, B. Manganese-Catalyzed Chemoselective Hydrosilylation of Nitroarenes: Sustainable Route to Aromatic Amines. *Org. Lett.* 2022, *24*, 9179–9183.

4. Saha, R.; Panda, S.; Nanda, A.; Bagh, B. Nickel-Catalyzed α-Alkylation of Arylacetonitriles with Challenging Secondary Alcohols. *J. Org. Chem.* 2023.

5. Ghosh, R.; Behera, R. R.; Panda, S.; Behera, S. K.; Jana, N. C.; Bagh, B. Catalytic Transfer Hydrogenation of Lignocellulosic Biomass Model Compounds Furfural and Vanillin with Ethanol by an Air-stable Iron(II) Complex. *ChemCatChem* 2023, *15*, e202201062.

6. Ghosh, R.; Panda, S.; MahaKhuda, A.; Saha, R.; Bagh, B. Base Metal Iron Catalyzed Sustainable Oxidation of Vanillyl Alcohol to Vanillic Acid in Deep Eutectic Solvents and Implementation of Vanillic Acid for Fine-Chemical Synthesis. *RSC Sustain.* 2023, *1*, 1223–1232.

Conference

1. Poster(online) presentation: 2nd International Conference on "Main-group Molecules to Materials (**MMM-II),** during 13th – 15th December**,** 2021**"** at Dept. of Chemistry, NISER, Bhubaneswar. Title: Efficient α-Alkylation of Arylacetonitriles with Secondary Alcohols Catalyzed by a Phosphine-Free Air-Stable Iridium(III) Complex

2. Poster Presentation: International conference on "Modern Trends in inorganic Chemistry (**MTIC- XIX**), during 15th -17th December 2022" at the Dept. of Chemstry, BHU. Title: Manganese-Catalyzed Chemoselective Hydrosilylation of Nitroarenes: Sustainable Route to Aromatic Amines.

3. Poster Presentation: 1st KIIT-CRSI Seminar on "Modern Trends in Chemical Sciences" on 5th September 2023 at Dept. of Chemistry, KIIT, Bhubaneswar. Title: Cobalt Catalyzed Chemoselective Reduction of Nitroarenes: Hydrosilylation under Thermal and Photochemical Reaction Conditions. (*Awarded Best Poster*).

Surajit Panda

DEDICATED TO....

TO MY PARENTS

&

DR. BIDRAHA BAGH

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SYNOPSIS

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Introduction

The use of alcohol as an alkylating agent has gained prominence as a prominent source due to its lower toxicity and environmental friendliness compared to the conventional use of toxic alkyl halides.[1] While iridium-catalyzed alkylation with primary alcohols is well-established, its application with secondary alcohols has been limited.[2] Metal complexes containing pyrazole ligands can exhibit metal-ligand cooperation, and this dual activity can be tuned for alkylation reactions.[3]

Hydrosilylation proves to be a gentler reduction method compared to both metal hydrides and molecular hydrogen.[4] Over the past decades, hydrosilylation techniques have been widely employed for reducing various unsaturated bonds.[5] Cobalt, being more economical than its heavier counterparts, rhodium, and iridium, has emerged as a leading choice for highly efficient and selective hydrosilylation.[6]

Scope and organisation of present thesis

In the first part of the thesis, a complex of iridium, derived from the 2-(1H-Pyrazol-3-yl) phenol backbone, was synthesized, demonstrating pyrazole-pyrazolato metal-ligand cooperation. This iridium catalyst was employed in various alkylation reactions, introducing

alcohols as direct alkylation reagents. The iridium-catalyzed α-alkylation of aryl nitriles to produce α-alkylated nitriles using secondary alcohols was achieved. Additionally, the α-alkylation of ketones and aryl nitriles with primary alcohols was developed. Furthermore, the synthesis of quinolines from 2-aminobenzylalcohol and ketones through dehydrogenative coupling was successfully carried out. Notably, the only byproducts produced were water and/or liberated molecular hydrogen, rendering these transformations atom-economical and environmentally friendly. Each chapter of the thesis includes detailed mechanistic studies and explores the substrate scope.

In the second part, hydrosilylation purposes were addressed utilizing commercially available cobalt carbonyl catalysts. The cobalt carbonyl-catalyzed reduction of nitro compounds to amines via hydrosilylation was established. Cyclic amines and lactams play a crucial role in organic synthesis. A versatile approach for synthesizing N-substituted pyrrolidines to pyrrolidones under hydrosilylation conditions was elucidated using the commercial $Co_2(CO)_8$ catalyst. Biomass-derived levulinic acid and other ketoacids were combined with various aryl amines, demonstrating excellent tolerance to diverse functionalities. Detailed mechanistic insights and comprehensive substrate scopes are provided in the respective chapters. The thesis is organized into five chapters, and the discussions for each chapter are presented below.

Chapter 1.1 and 1.2: Introduction

The establishment of carbon-carbon bonds plays a pivotal and essential role in organic synthesis. While transition-metal-catalyzed cross-coupling reactions have significantly advanced C-C bond formation, their application is hampered by the use of harmful organometallic coupling partners and dangerous chemical compounds.[7] The borrowing hydrogen methodology emerges as a crucial strategy for functionalizing alcohols into active coupling partners, facilitating the creation of both C-C and C-N bonds.[8] This approach

involves a pair of transfer hydrogenations coupled with an intermediate reaction utilizing the in situ-generated reactive intermediate. An intriguing aspect of the borrowing hydrogen method is its alignment with thermodynamics, favouring the hydrogenation step and leading to a remarkably low E-factor, thus emphasizing its superiority in terms of synthesis, cost-efficiency, and environmental impact.[9] This approach has garnered significant attention in recent years. The metal-ligand bifunctional catalyst phenomenon involves a ligand collaboratively binding and activating the substrate through secondary interactions such as hydrogen bonding or proton transfer. Pyrazole, a five-membered N-heterocyclic compound, possesses a potentially Brønsted acidic NH group adjacent to a Schiff-base nitrogen atom. Its deprotonation ability allows the formation of pyrazolate anions, which can serve as a bridge between two metal centers, leading to the formation of di- or polynuclear complexes in specific instances.[10] The facile conversion between 16e amido and 18e amine complexes enables various catalytic reactions, including the efficient and selective reduction of carbonyl compounds, as well as the formation of C-C and C-N bonds. Section 1.1 will provide an overview of literature findings concerning alkylation reactions catalyzed by iridium, with a focus on the use of alcohol as the alkylating agent.

Silicon chemistry has recently emerged as a highly promising area in the field of chemical research. One of the notable advancements in synthetic chemistry involves the reduction of carbon-carbon multiple bonds, carbon-heteroatom bonds, and heteroatom-heteroatom bonds.[5] Catalytic hydrosilylation stands out as an advantageous method, offering advantages such as avoiding the use of highly flammable molecular hydrogen and metal hydrides that generate a large amount of salt waste.[4] Hydrosilylation procedures are often carried out under mild conditions, making them suitable for a wide range of functional groups. A novel domain in homogeneous catalysis has gained traction, focusing on harnessing abundant first-row transition metals from the Earth's crust to develop innovative catalysts. Over the last decade,

significant progress has been observed in this area.[11] Cobalt, known for its cost-effectiveness and presence in various organisms, metallozymes, and coenzymes (including B12-dependent enzymes, methionine aminopeptidase 2, and nitrile hydratase), exhibits distinct reactivity patterns compared to its counterparts in rhodium and iridium.[12] The diverse redox chemistry of cobalt opens up possibilities for creating versatile catalytic cycles. Chapter 1.2 encompasses a literature review on cobalt-catalyzed hydrosilylation reactions within organic transformations.

Chapter 2: Efficient α-Alkylation of Arylacetonitriles with Secondary Alcohols Catalyzed by a Phosphine-Free Air-Stable Iridium(III) Complex

2-(1H-Pyrazol-3-yl) phenol, upon facile coordination with [IrCp*Cl$_2$]$_2$ and subsequent dehydrochlorination in the presence of a base, forms an Ir(III) complex. This air-stable dimeric iridium(III) complex acts as a highly efficient catalyst for α-alkylation of arylacetonitriles using secondary alcohols, generating water as the sole byproduct. The α-alkylations are accomplished at 120 °C under solvent-free conditions with remarkably low (0.1−0.01 mol%) catalyst loading. Various secondary alcohols and arylacetonitriles with diverse functional groups yield α-alkylated products in good yields. The mechanistic study indicates alcohol activation through metal−ligand cooperation, forming reactive iridium-hydride species, which has been successfully separated and characterized. A maximum TOF of 10000 h^{-1} is achieved with this protocol.

Scheme 1: Iridium catalyzed α-alkylation of arylacetonitrile with secondary alcohol
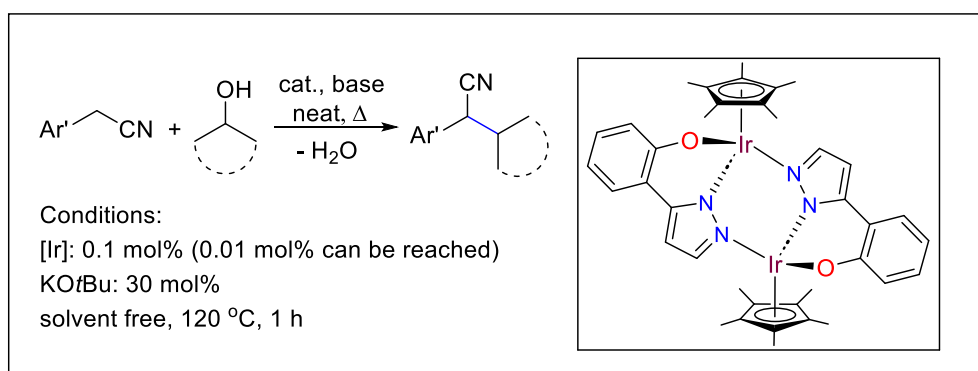
Chapter 3: Phosphine Free Iridium Catalyzed C-C and C-N Bond Formation via Borrowing Hydrogen and Asymmetric Dehydrogenative Coupling

In this chapter, we have effectively utilized the iridium-pyrazolato complex as a highly efficient catalyst for alkylating ketones and nitriles with primary alcohols. Additionally, this catalyst shows promise in generating heterocycles through acceptorless dehydrogenative reactions. Demonstrating excellence in α-alkylation reactions, the iridium catalyst achieves remarkable conversion rates in a short period, coupled with an impressively low catalyst loading (0.11 mol%). The substrate range is broad, encompassing various arylacetonitriles, ketones, and primary alcohols. Experimental evidence supports the adoption of the Borrowing Hydrogen pathway for alkylation and the dehydrogenative coupling approach for synthesizing quinolines. Thus, this catalyst operates effectively in both dimensions within the same framework.

Scheme 2: Iridium catalyzed C-C and C-N coupling reaction
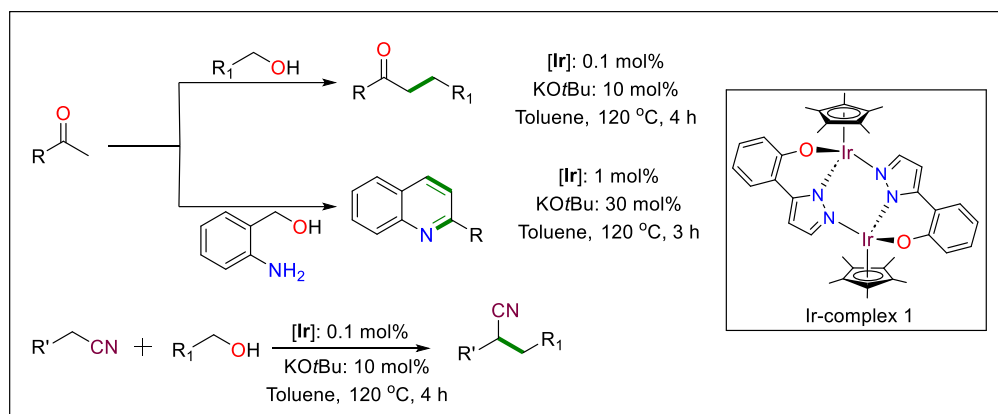
Chapter 4: Cobalt Catalyzed Chemoselective Reduction of Nitroarenes: Hydrosilylation under Thermal and Photochemical Reaction Conditions.

We have devised a highly effective Co-catalyzed hydrosilylation protocol for reducing nitroarenes to aromatic amines. $Co_2(CO)_8$, a commercially available catalyst, proves effective under both thermal and photochemical conditions. The versatility of the method is highlighted by its application to various nitroarenes with diverse electron-donating and

withdrawing functionalities. Notably, the hydrosilylation process exhibits chemoselectivity towards nitro groups, leaving other reducible groups such as ester, cyano, amide, and alkene unaffected. This catalytic hydrosilylation finds practical utility in the synthesis of crucial drug molecules and pharmaceutical intermediates. The strategy serves as a viable alternative to conventional methods that involve the use of stoichiometric quantities of toxic reducing agents for drug synthesis. Experimental evidence suggested a radical pathway.

Scheme 3: Cobalt catalayzed hydrosilylation of nitroarenes
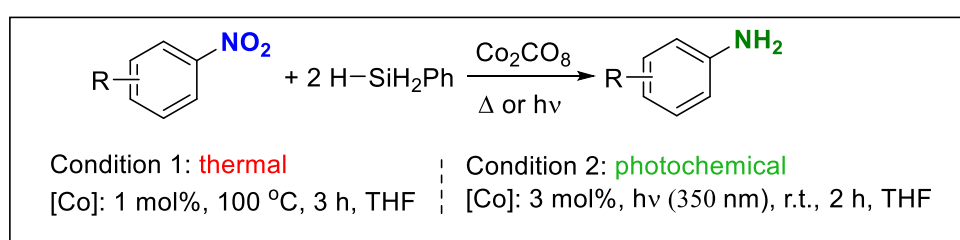
Condition 1: thermal
[Co]: 1 mol%, 100 °C, 3 h, THF

Condition 2: photochemical
[Co]: 3 mol%, hν (350 nm), r.t., 2 h, THF

Chapter 5: Cobalt Catalyzed Chemodivergent Synthesis of Cyclic amines and Lactams from Ketoacids and Anilines using Hydrosilylation.

Commercially available $Co_2(CO)_8$ was utilized as an efficient catalyst for chemodivergent synthesis of pyrrolidines and pyrrolidones from levulinic acid and aromatic amines under slightly different hydrosilylation conditions. 1.5 and 3 Equiv. of phenylsilane selectively yielded pyrrolidone and pyrrolidine, respectively. Various ketoacids and amines were successfully tested. Plausible mechanism involves the condensation of levulinic acid and amine to forms an imine which cyclizes to 3-pyrrolidin-2-one followed by reduction to pyrrolidone. Final reduction of pyrrolidone gave pyrrolidine.

Scheme 4: Cobalt catalayzed selective synthesis of pyrrolidone and pyrrolidine

Path B
$Co_2(CO)_8$ (3 mol%)
$PhSiH_3$ **(1.5 equiv.)**
120 °C, toluene, 3 h

Path A
$Co_2(CO)_8$ (3 mol%)
$PhSiH_3$ **(3 equiv.)**
120 °C, toluene, 6 h
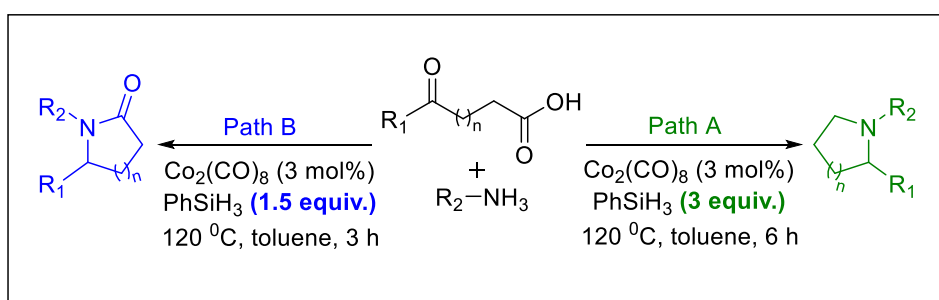
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bromophenyl)-2-phenylpiperidine (**P₉₅**) in CDCl₃ at r.t.

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List of Abbreviations Used

Å	Angstrom
Anal.	Analytically
Anhyd	Anhydrous
aq	Aqueous
bp	Boiling Point
br	Broad
°C	Degree Celcius
Calcd	Calculated
cm	Centimeter
Conc	Concentrated
conv	Conversion
d	Doublet
DCM	Dichloromethane
dd	Doublet of a Doublet
DMF	N,N-Dimethyl Formamide
eq	Equation
equiv	Equivalent

Et	Ethyl
g	Grams
h	Hours
HRMS	High-resolution Mass Spectrometry
IR	Infrared
K	Kelvin
kcal	Kilo calories
lit	Liter
m	Multiplet
M	Molar
MeCN	Acetonitrile
mp	Melting point
Me	Methyl
MHz	Mega Hertz
Min	Minutes
mL	Milliliter
mM	Millimolar
mmol	Millimole
mol	Mole
MS	Mass Spectra

N	Normal
NMR	Nuclear Magnetic Resonance
ppm	Parts per Million
rt	Room Temperature
s	Singlet, Seconds
TLC	Thin Layer Chromatography
TOF	Turn Over Frequency
TON	Turn Over Number
XRD	X-Ray Diffraction

Chapter 1.1

General Introduction of α-Alkylation Utilizing Both Primary and Secondary Alcohol

Chemists have been conscientiously working to create more eco-friendly chemical protocols. The principle of green chemistry endeavors to decrease pollution at its origin by exterminating harmful reagents, chemicals, and detrimental byproducts. Catalysis plays a crucial role within the realm of green chemistry.[1] Catalysts can enable the achievement of important chemical transformations that cause challenges when employing conventional methods, all while evading or reducing the generation of byproducts. A catalyst accelerates slow chemical reactions by lowering their activation energy. When present at catalytic quantity, it helps to execute chemical transformations without being consumed during the process.[2] Catalysis plays a critical role in contemporary industry, which produces basic chemicals, pharmaceuticals, polymers, and petrochemicals. Catalysis has been instrumental in developing sustainable and eco-friendly synthetic methods.[3]

The formation of carbon-carbon bonds represents a central and indispensable process in the field of organic synthesis. A broad range of reactions can be applied for the formation of such chemical bonds. The nucleophilic attack on electrophilic alkyl halides in C-C bond formation results not only in the alkylated product but also in a stoichiometric amount of a base.[4] Recently, transition-metal-catalyzed cross-coupling reactions have made consequential developments in C-C bond formation reactions but these coupling reactions encounter limitations due to the utilization of noxious organometallic coupling partners and perilous chemical compounds.[5] While significant strides have been made to form various alkylating compounds, the demand for readily available alkylating agents and an effective catalytic strategy remains a persistent concern within the scientific community. An ideal electrophilic agent should have a leaving group with a low molecular weight, and minimum impact on the

environment. Considering these criteria, alcohols are good alternatives, and they provide the extra benefits of being cost-effective, as well as easy to manage and store. Poor leaving ability of the OH group renders alcohols less effective as alkylating agents, as it is not easily replaced by nucleophilic attacks. Alcohols can be converted into tosylates, triflates, or sulfonates, which serve as better leaving groups but this transformation often results in poor efficiency and the generation of undesirable waste.[6] Hence borrowing hydrogen methodology plays a crucial role in functionalizing the alcohol into an active coupling partner in diverse processes for forming C-C and C-N bonds. The borrowing hydrogen approach capitalizes on the broader array of reactions accessible to carbonyl compounds. This method expands the availability of reactions that can be performed with carbonyl compounds. Carbonyl compounds are strong electrophiles and participate in a wide range of transformations such as reacting with various carbon-based nucleophiles (RLi, RMgX, etc.), formation of alkene through condensation or Wittig reaction, and generation of imines. Carbonyl compounds can function as C-nucleophiles through their corresponding enol-enolate formation which is not possible for the alcohols. A significant subset of hydrogenation reactions involves transfer hydrogenations, where hydrogen can be transferred from one molecule to another, instead of relying on gaseous hydrogen.[7] Borrowing hydrogen chemistry, also known as hydrogen auto-transfer utilizes this concept, however, it makes a fundamental distinction. In a borrowing hydrogen reaction, a pair of transfer hydrogenations is incorporated with an intermediate reaction involving the reactive intermediate generated in situ.[8] A basic outline of this idea is illustrated in Scheme 1.1.1. The hydrogen borrowing method commences with a metal-catalyzed dehydrogenation process, during which a less reactive donor molecule converts into a more reactive substrate (an alcohol can become an aldehyde or a ketone). This enhanced reactivity of the intermediate allows for subsequent reactions, leading to the formation of an unsaturated compound which is successively reduced by the metal hydrides produced during

the initial dehydrogenation step. Though metal itself does not actively participate in the condensation pathway, the electrophilic nature of the carbonyl bond can be enhanced by the

Scheme 1.1.1: General reaction mechanism of borrowing hydrogen
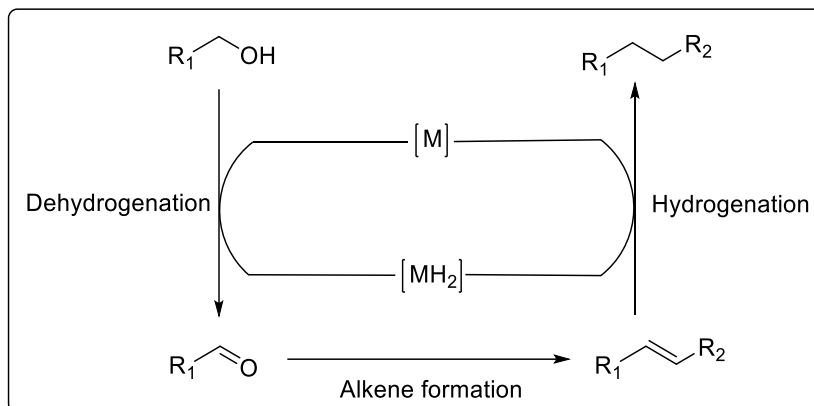
Presence of a metal. An interesting aspect of this approach is that thermodynamics typically advocates the hydrogenation step and this causes the overall process to strongly favor the formation of products, resulting in a notably low E-factor.[8b] Basically, the irreversibility of the third step in Scheme 1.1.1 steers the initial dehydrogenation step towards near completion. In this scenario, a single catalyst serves a dual purpose, firstly it aids in the dehydrogenation step and secondly, it facilitates the hydrogenation of the intermediate using metal hydrides produced during the first step. It becomes clear that the hydrogen borrowing method is a highly superior process from the perspectives of synthesis, cost-efficiency, and environmental impact and has garnered significant attention in recent years.

Enzymes in nature are known for their ability to activate normally unreactive chemical bonds through a metal-ligand cooperative interaction.[9] A similar form of metal-ligand cooperation is also evident in transition metal-catalyzed reactions. Metal-ligand bifunctional catalyst is a phenomenon where a ligand collaboratively binds and activates the substrate through secondary interactions like hydrogen bonding or proton transfer. Some of the notably successful instances include Noyori's hydrogenation catalysts and Noyori and Ikariya's

transfer-hydrogenation catalysts, which employ chelate amine ligands to introduce a protic NH group adjacent to the metal center.[10] In protonated amine form, the nitrogen ligand operates as a hydrogen-bond donor to the substrate while it works as a Brønsted base in its deprotonated amido form. This dual character enables to accomplish highly efficient catalytic reactions. The common strategy of Deprotonation-protonation was utilized in these systems such as Shvo's catalyst and Milstein's pincer complexes.[11] Pyrazole is a five-membered N-heterocyclic compound that contains a potentially Brønsted acidic NH group just next to a Schiff-base nitrogen atom. The diverse coordination chemistry displayed by pyrazoles is due to their amphiprotic nature. Pyrazole can readily undergo deprotonation and the resulting pyrazolate anion can form di- or polynuclear complexes in certain instances by serving as a bridge between two metal centers. When a pyrazole coordinates to a Lewis acidic metal center, the acidity of the NH proton increases.[12] Inter- and intramolecular hydrogen bonding as well as easy deprotonation caused by the enhanced Brønsted acidity alters the coordination mode from an L-type lone pair donation to a covalent X-type. These phenomena are expected to have an electronic influence on the complex. Deprotonation at the β-position relative to the metal occurred with ligand dissociation at the metal center (figure 1.1.1). Upon elimination of HX, β-protic pyrazole complex can yield a coordinatively unsaturated pyrazolato complex. Subsequent to that, activation of the E-H bond occurs, wherein the E element binds to the metal, and the hydrogen associates with the ligand. This occurrence is referred to as metal-ligand cooperation, highlighting the joint involvement of both the metal and the ligand in both bond activation and bond dissociation. During this hydrogen shuttle, the interconversion is linked to the alteration in the coordination mode of the pyrazole ligand, rather than the formal oxidation state of the metal.[13] Due to the easy conversion between the 16e amido and 18e amine complexes, a variety of catalytic reactions, including the reduction of carbonyl

compounds as well as the formation of C-C and C-N bonds, have been successfully achieved with exceptional efficiency and selectivity.

Figure 1.1.1 Elimination and addition in pyrazole complexes
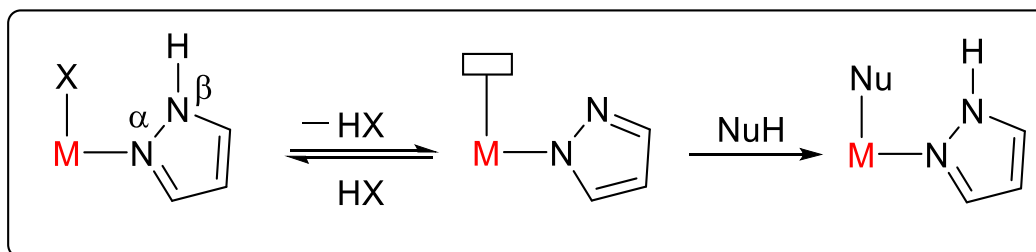
Several metal complexes were already reported with pyrazole ligands and few of them have been shown in figure 1.1.2 [13]

Figure 1.1.2 Examples of complexes containing pyrazole moiety
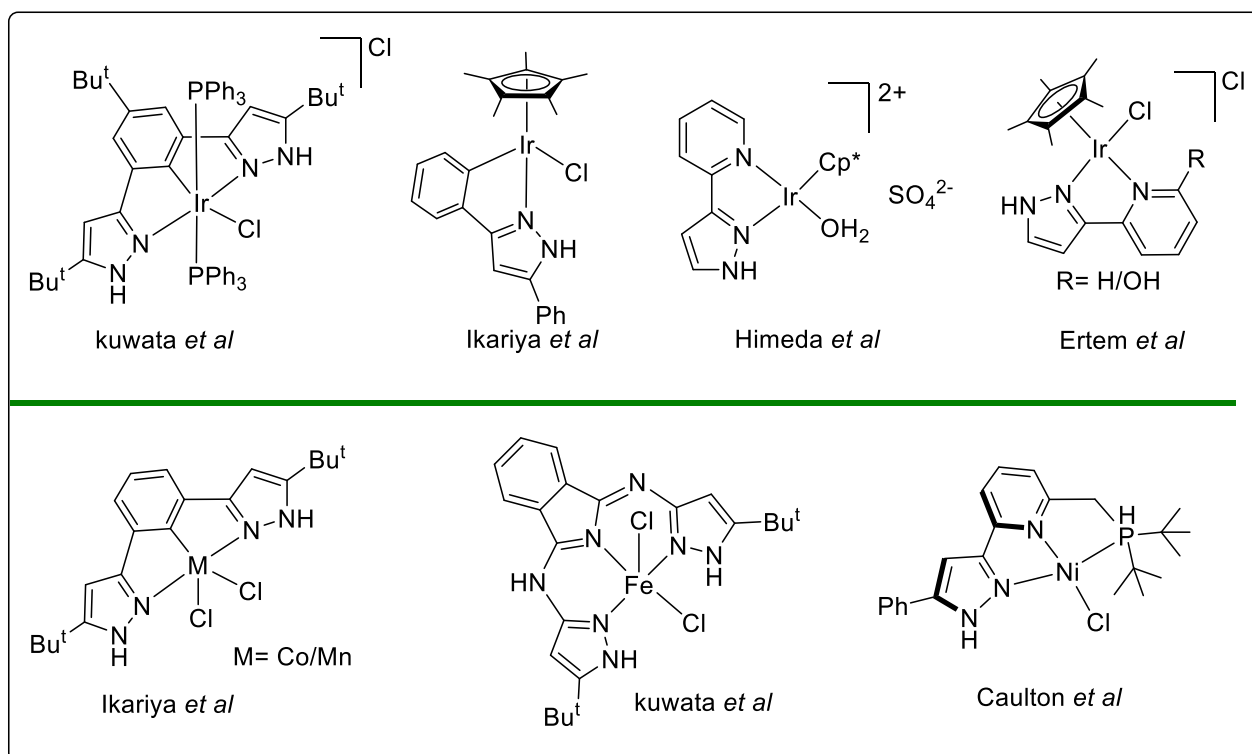
Ever since Grigg and Watanabe's teams published their findings on the transition-metal-catalyzed N-alkylation of amines using alcohols as the alkylating agents,[14] there has been a constant growth in both N-alkylation of amines and the C-alkylation of ketones and similar

compounds, using alcohols as the alkylating agents based on borrowing-hydrogen (BH) or hydrogen-auto transfer (HA) strategies. While the primary importance was directed towards N-alkylation, numerous researchers simultaneously explored C-alkylation or C-C bond formation using the borrowing hydrogen method. The classic example of this advancement is embodied by the synthesis of dihydrochalcone from acetophenone and benzyl alcohol where aldol condensation is an intermediate step. There are four different pathways that can be followed by hydrogen autotransfer processes involving the aldolic reaction subjected to the starting reagent used and those are (i) α-Alkylation of carbonyl compounds with alcohols (ii) β-Alkylation of secondary alcohols and (iii) β-Alkylation of secondary alcohols with primary alcohols.

Typically, iridium complexes exhibit greater stability compared to rhodium and cobalt complexes. This stability has been leveraged in mechanistic studies involving stoichiometric reactions. Under thermal and in highly alkaline conditions, its inherent stability makes it effective, and this distinct characteristic paves the way for numerous tandem reactions using an iridium catalyst. Thus, investigating the chemistry and applications of half-sandwich cyclometalated complexes has emerged as a highly dynamic and captivating field within the field of organometallic chemistry, primarily due to the valuable catalytic reactivity that these ligands bestow upon the complexes.[15] Over the last decade, there has been significant interest in the synthesis of cyclometalated iridium complexes for the synthesis of various C-C bond formation reactions. Hence cyclometalated iridium complexes have been a subject of considerable interest in the context of α-alkylation of ketone. An interesting contribution was made by Li *et al*., wherein they converted an alkyne into the corresponding ketone, followed by subsequent alkylation using a primary alcohol.[16] For this alkylation process, they employed [Cp*IrCl$_2$]$_2$ as an active catalyst and utilized potassium tert-butoxide as the base. This reaction detains great appeal because of the easy availability of starting materials, the

potential for achieving high yields, and its astonishing atom efficiency. Selected cyclometalated iridium complexes for this purpose are shown in Scheme-1.1.2.

Scheme 1.1.2 Iridium catalyzed α-alkylation of ketones with primary alcohol
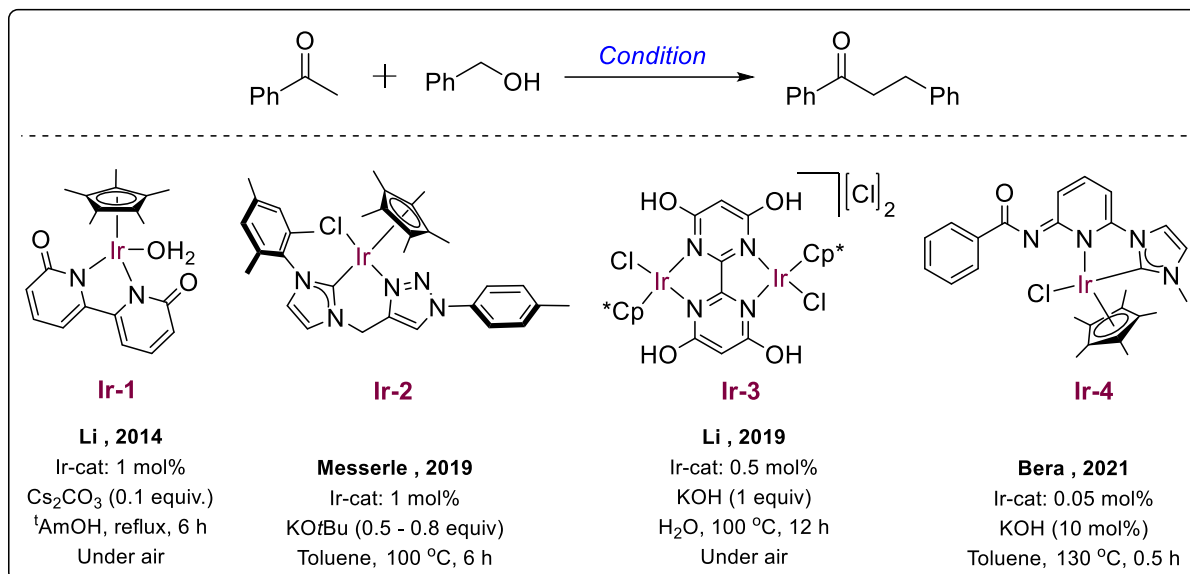
Li *et al*. synthesized a Cp*Ir-bipyridonate complex (**Ir-1**) for the alkylation of aromatic ketones with primary alcohols.[17a] This catalytic system not only showcases eco-friendliness by demanding minimal amounts of base and catalyst but also boasts the remarkable ability to operate under ambient air conditions. The efficacy of this innovative approach was particularly pronounced when employing methanol, yielding α-methylated ketones in impressively high yields. Remarkably, the versatility of this method extended its accommodating arms to ketones featuring diverse substituents, including both electron-donating and electron-withdrawing groups, as well as aliphatic ketones. In each case, the reaction delivered consistently high to excellent yields, underscoring the broad applicability of the Cp*Ir-bipyridonate complex. Delving into the intricacies of the catalytic process, a meticulous mechanistic study revealed the pivotal role of the carbonyl group present in the ligand. The reaction proceeded through an Ir-hydride intermediate (**C**) in which one carbonyl

group in the ligand converts into a hydroxy group. Subsequently, in the final step, the hydroxy and hydride proton was transferred to the unsaturated bond (Scheme 1.1.3).

Scheme 1.1.3 Proposed mechanism for iridium catalyzed α-alkylation of ketones with primary alcohol
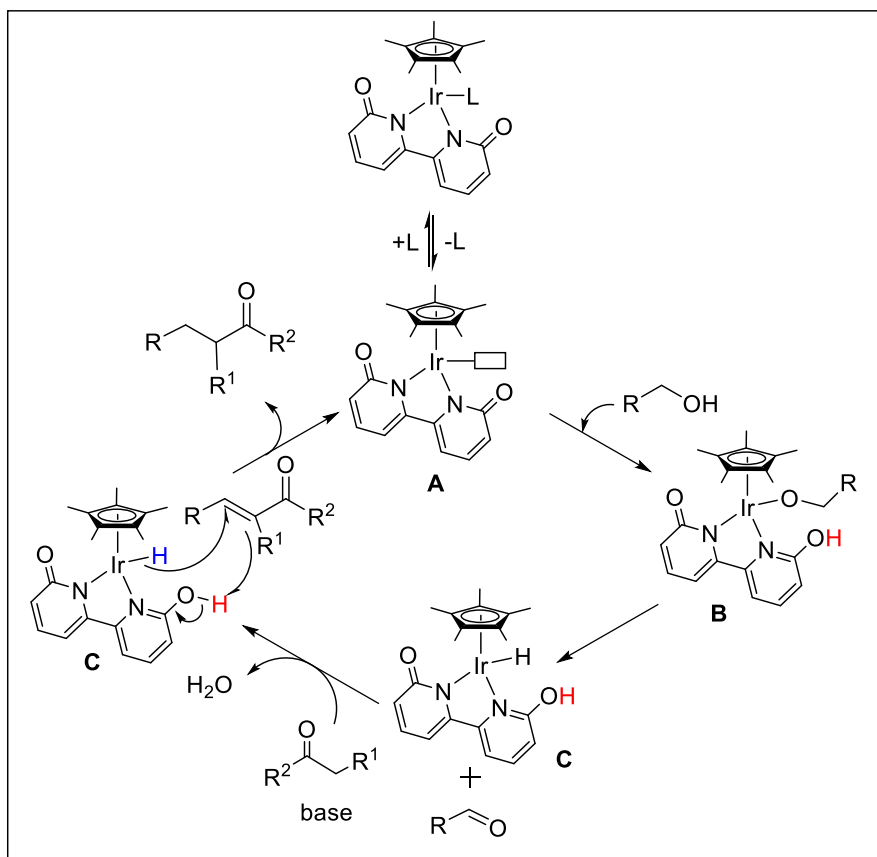
Growing environmental concerns are prompting researchers to embrace more eco-friendly reaction routes. Water medium reaction not only eliminates the need for harmful high boiling solvents but also its affordability and widespread availability contribute to its enhanced sustainability. Li *et al* have synthesized a water-soluble Ir(III) complex (**Ir-3**) using 4,4',6,6' -tetrahydroxy-2,2' -bipyrimidine as a bridging ligand.[17b] This complex has the ability to catalyze the reaction in an aqueous medium. The α-alkylation of ketones with primary alcohols was conducted using 0.5 mol% of catalyst loading in the presence of KOH as a base. Further, they have synthesized a biologically active molecule donepezil which proves the robustness of this catalytic system. Hydroxy group present in the ligand moiety has an active

role in the mechanism. Messerle and co-authors have reported a triazole-carbene ligated Ir(III) (**Ir-2**) and Rh(I) complex for the alkylation of ketones.[17c] Switching the catalyst from iridium to rhodium modifies product selectivity. The exclusive formation of α-alkylated ketone was observed when the iridium complex was used as a catalyst in the presence of KO*t*Bu (0.5 – 0.8 equiv). Changing the catalyst from iridium to rhodium as the catalyst resulted in the production of β-Alkylated alcohol using KOH (2 equiv) as the base. Mechanistic investigation revealed that the product selectivity is controlled by the mode in which enone compound co-ordinate to the metal hydride. The coordination of C=C bond to Ir-hydride was favourable while the C=O bond displayed a preference for coordinating with Rh-hydride species. Though there were various parameters that could potentially influence product selectivity, deuterated labeling studies demonstrated that the choice of transition metal catalyst is the decisive factor. Another Ir-NHC complex (**Ir-4**) was reported by Bera *et al* for the same purpose.[17d] Here they have synthesized a pyridyl(benzamide)-functionalized NHC ligand which upon reacting with [Cp*IrCl$_2$]$_2$, gave a dearomatized complex. This complex attained its aromaticity in the presence of HBF$_4$. The dearomatized complex exhibited significant activity in the alkylation of ketones and secondary alcohols using primary alcohols as reactants. The reaction can be performed with very low catalyst (0.05 mol%) and base loading (KOH, 10 mol%). This method effectively facilitated the alkylation of steroids such as pregnenolone and testosterone. The deuterium labeling experiment yielded a 95% incorporation at the β-position and a mere 2% at the α-position. This suggests that the reaction does not follow the conventional dihydride mechanism, which would typically result in similar deuterium incorporation. They expanded the scope of this system by synthesizing quinolines and lactones. Apart from cyclometalated Ir(III) complexes, there are numerous other iridium-catalyzed methods for the alkylation of ketones with primary alcohols.[18]

Various catalysts based on noble metals and different base metals have also been reported for this type of alkylating reaction.[19]

Quinolines represent a significant category of N-heterocyclic compounds that have been widely identified in various sources, including natural products, alkaloids, pharmaceuticals, and more.[20] Due to the significance of quinolines, several methods like the Skraup, Conrad-Limpach, Doebner-von Miller, and Friedlaender syntheses have been formulated to synthesize quinolines in recent decades.[21] Among these, the Friedlander synthesis stands out as the most renowned method for producing quinolines.[22] This approach involves the base or acid-catalyzed cyclization of 2-aminobenzaldehyde and a ketone to yield quinoline but the likelihood of self-condensation of the aldehyde in this reaction reduces its selectivity. Metal-catalyzed assymetric dehydrogenative coupling provides a cleaner and most traditional process compared to most conventional methods for synthesizing quinolines. Over the past decades, several noble and base metal-catalysts were employed for this purpose.[23] Ruthenium catalyst were reported for this specific purpose by Milstein and Sun.[23a-b] Kundu's group has published studies on the synthesis of quinolines using manganese, cobalt, and ruthenium catalysts.[23c-e] Srimani and coauthors have made significant contributions to this field by employing well-defined nickel and manganese catalysts.[23f-h] Darcel and coauthors have employed Knolker-type complex for this purpose.[23i] Kirchner *et al* described the utilization of a Mn-PNP complex in the synthesis of quinolines and pyrimidines.[23j] As part of our ongoing commitment to advancing iridium-catalyzed reactions, our attention will be directed towards the advancements of iridium in this particular category. The initial report regarding iridium was reported by Ishii in 2005. When 2-amino benzyl alcohol was treated with ketone in the presence of [IrCl(cod)]$_2$, PPh$_3$, and KOH at 100 °C for 3 h, they got the corresponding quinoline product at 90% yield. Their system was well tolerated with various ketones and

alcohols. Moreover, they expanded their research efforts by also synthesizing pyrrole.[24a] A significant development has occurred subsequently, which is illustrated in Scheme 1.1.4.

Scheme 1.1.4 Iridium catalyzed synthesis of quinolines from ketone
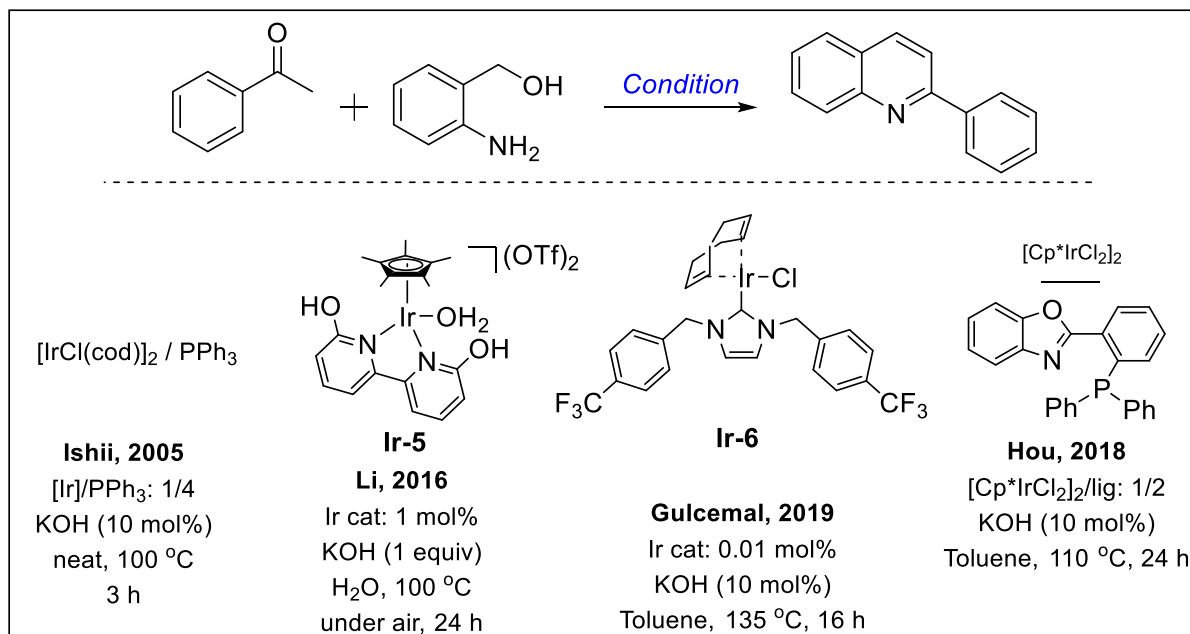
Previously, we have shown the vital role played by metal-ligand bifunctional catalysts in various transformations. Li *et al* were the first to report the synthesis of quinoline in water using the [Cp*Ir(6,6′-(OH)$_2$bpy)(H$_2$O)][OTf] complex (**Ir-5**).[24b] This catalyst was originally synthesized by Kawahara and co-workers.[25] In the presence of 1 mol% catalyst loading and 1 equiv of base, this reaction proceeded under atmospheric conditions. Several aromatic as well as aliphatic ketones were tolerated. Gulcemal's group synthesized an NHC-carbene iridium(I) complex (**Ir-6**), which they utilized in the quinoline synthesis.[24c] This catalyst possesses exceptional reactivity, achieving a turnover number of up to 9200 TON. Full conversion can be achieved with just a 0.01 mol% catalyst loading and 5 mol% of KOH at 135 °C for 16 hours under air. In addition to its effectiveness in quinoline synthesis, this catalytic system demonstrated excellent performance in the synthesis of β-alkylated alcohols. Fine-tuning was observed in product selectivity when the reaction condition was changed. By adjusting the

conditions, this method can selectively produce both β-alkylated alcohols and α-alkylated ketones from the same starting material. With this system, cholesterol derivatives were also synthesized with good yields. Hou *et al.* reported an in situ-generated benzoxazolyl iridium phosphine complex for the synthesis of quinoline.[24d] This catalytic procedure offers advantages not only in terms of its effectiveness for versatile alkylation reactions involving a wide array of ketones, alcohols, and amines but also in terms of atom-economic synthesis for quinolines and indole compounds.

Another intriguing approach for synthesizing quinoline involves employing a double dehydrogenation strategy. In this method, secondary alcohol is used which subsequently converts to ketone through metal-catalyzed dehydrogenation. Kundu *et al.* synthesized a water-soluble 2-hydroxypyridine-based Ir(III) complex (**Ir-7**, Scheme 1.1.5) to synthesize various N-heterocycles.[26a] This catalyst is also capable of transforming 2-nitrobenzyl alcohol into the corresponding quinoline structure. To check the robustness of their procedure, they synthesized (±)-galipinine, a bioactive natural compound, and conducted gram-scale syntheses of several N-heterocycles. The green chemistry metrics were assessed in the production of 2-(2-(benzo[d][1,3]dioxol-5-yl)ethyl)quinoline, demonstrating the technical advantages and environmental sustainability of the current approach. They have isolated the iridium hydride intermediate which supports their dehydrogenative mechanism. Numerous kinetic studies and DFT calculations were conducted to provide evidence for the likely reaction mechanism. These investigations revealed that this system adhered to a concerted outer-sphere mechanism for the dehydrogenation of alcohols. An innovative series of iridium catalysts, supported by P, N-ligands, has been introduced by the Kempe group (scheme 1.1.5).[26b] These ligands are derived from imidazo[1,5-b]pyridazin-7-amines and can be synthesized with a diverse range of substitution patterns. They achieved favorable results with a minimal amount of catalyst. Their findings suggested that catalysts that effectively

facilitate borrowing hydrogen reactions could also be viable options in the context of asymmetric dehydrogenative coupling reactions.

Scheme 1.1.5 Iridium catalyzed synthesis of quinoline from secondary alcohol
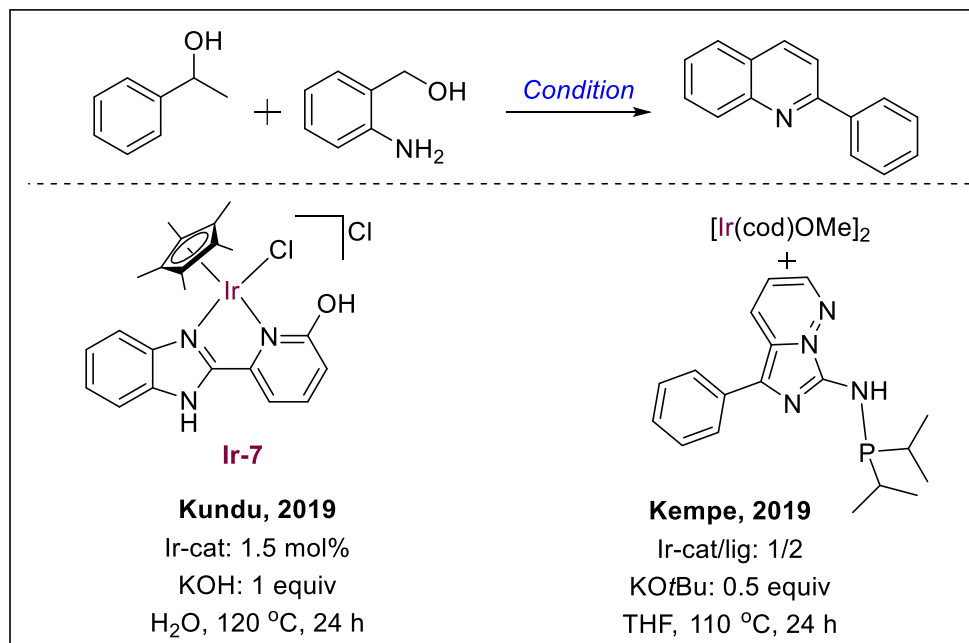
Nitriles are an important organic moiety that can be found extensively in natural products, pharmaceuticals, and pesticides. Nitriles have the capacity to undergo conversions into a range of functional groups, including carboxylic acids, amides, and amines, making them significant constituents in the construction of diverse heterocyclic compounds.[27] Therefore, there is a strong incentive to develop efficient and environmentally friendly methods for synthesizing these compounds. Hence, the concept of borrowing hydrogen emerges as a viable and eco-friendly approach for their synthesis, as it not only offers a more sustainable option but also eliminates the requirement for toxic halides traditionally used in these processes. Up to this point, numerous transition metal catalysts have been designed for this purpose.[28] Some iridium catalysts were also utilized, as depicted in Sheme 1.1.6. Grigg and his team initially introduced [IrCp*Cl$_2$]$_2$ catalyzed solvent-free elective alkylation of arylacetonitriles using primary alcohols.[29a] Only a catalyst loading of 2.5 mol% and a KOH

loading of 15 mol% were necessary to achieve complete conversion. Significantly, this catalytic system exhibited enhanced reactivity under microwave conditions, achieving complete conversion within 10 minutes at 110 °C. This process displayed excellent conversion rates for various heteroatomic arylacetonitriles and aliphatic primary alcohols. Xu and his group used terpyridine as a ligand and potassium carbonate as a base.[29b] They experimented with various iridium and ruthenium precursors using an in-situ approach, and [IrCp*Cl$_2$]$_2$ yielded the most favorable outcome among all the options. They achieved full conversion of arylacetonitriles into their respective alkylated products by employing 1 mol% [IrCp*Cl$_2$]$_2$, 2 mol% of terpyridine, and 20 mol% K$_2$CO$_3$ at 150 °C in 5 h. The catalytic system exhibits chemodivergence, as switching the base from potassium carbonate to potassium tert-butoxide leads to the production of α-alkylated acetamide products.

Scheme 1.1.6 Iridium catalyzed α-alkylation of arylnitriles with primary alcohol
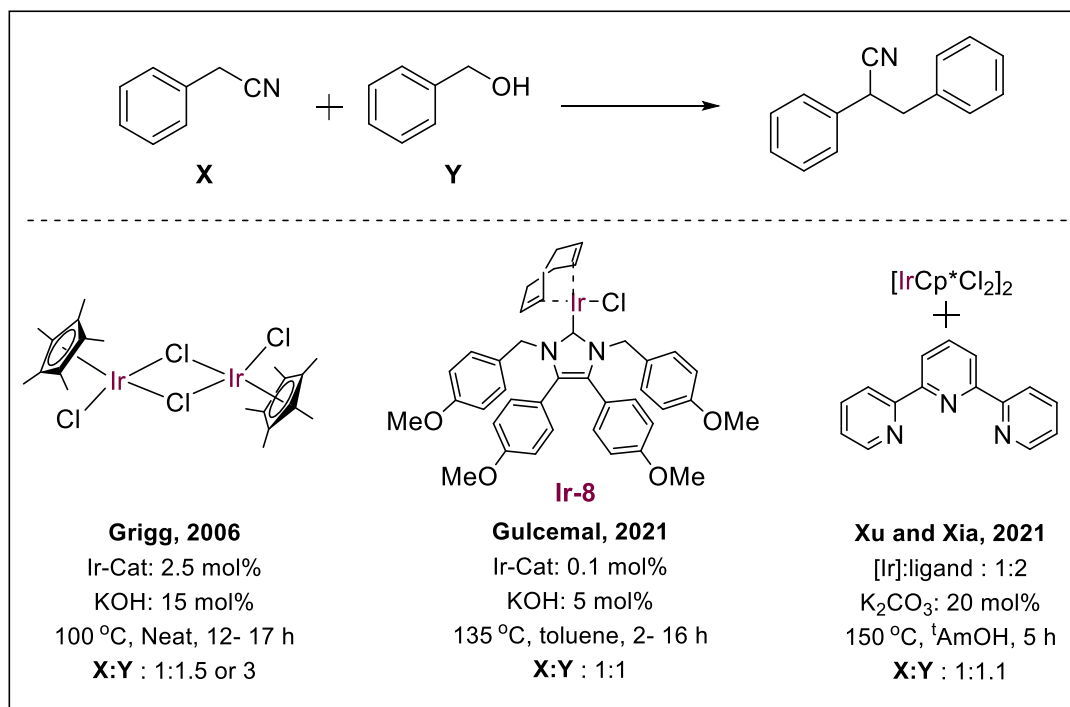
Gulcemal and his team have synthesized a range of Ir-NHC complexes by altering the ligand structure.[29c] The electronic characteristics of the NHC ligands were evaluated by comparing the IR carbonyl stretching frequencies of the [IrCl(CO)$_2$(NHC)] complexes, which were

prepared in situ in CH_2Cl_2. The alteration of benzyl groups at positions 1 and 3, as well as aryl groups at positions 4 and 5 of imidazole, impacts the electronic character of the NHC ligand and this electronic factor significantly influences the catalytic efficiency in the alkylation of arylnitriles with alcohol. Complex **Ir-8** yielded the most favorable outcome, achieving complete conversion with a mere 0.1 mol% catalyst loading, accompanied by a 5 mol% base loading within a remarkably brief duration (2 h). The calculated Turnover Number (TON) of 960 demonstrated the protocol's resilience and effectiveness. Mechanistic analysis revealed that the catalyst plays a significant role in facilitating the aldol-type Knoevenagel condensation step effectively. Iridium catalysts have been employed for the alkylation of nitriles in other substances also. Alkylation of acetonitrile with primary alcohols was reported by Obora and Cossy. Obora *et al.* employed [Ir(OH)(cod)]$_2$ as a catalyst in combination with PPh$_3$, and it demonstrated successful performance with both primary and secondary alcohols.[29d] Cossy *et al.* reported microwave-assisted alkylation of acetonitrile where they have utilized [Ir(Cl)(cod)]$_2$.[29e]

The utilization of primary alcohols for the α-alkylation of ketones stands as a well-established method renowned for generating α-alkylated ketones featuring linear carbon chains. However, the application of secondary alcohols in this context remains considerably limited, signaling a pressing need for broader exploration in this specific domain. The synthesis of β-disubstituted branched ketones, in particular, poses a greater challenge compared to their α-branched counterparts. Historically, the conventional approach to achieving β-secondary alkylation of ketones involved the use of secondary alkyl halides and robust bases. Unfortunately, this method resulted in a notable generation of waste and exhibited poor selectivity, underscoring the necessity for advancements in methodology. Consequently, secondary alcohols emerge as pivotal agents in circumventing the reliance on alkyl halides. However, it is essential to acknowledge that the dehydrogenation of secondary alcohols

presents its own set of challenges. A noteworthy breakthrough in this realm was reported by Donhoe in 2017, wherein the alkylation of ketones with secondary alcohols was successfully demonstrated (Scheme 1.1.7).[31]

Scheme 1.1.7 Iridium catalyzed α-alkylation of ketones with secondary alcohols
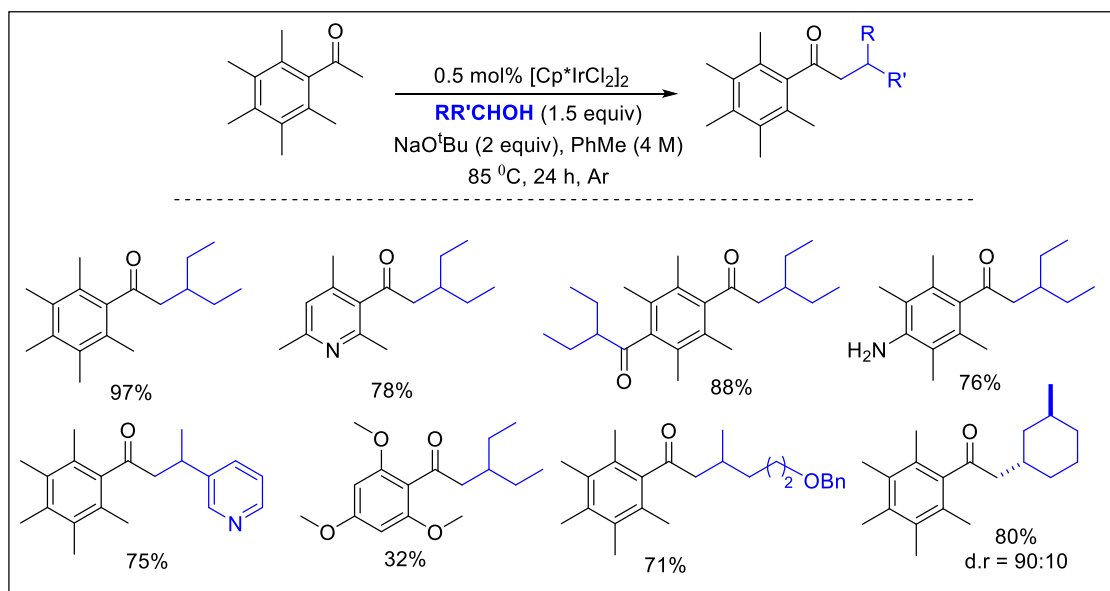
They have used pentamethylphenyl (Ph*) ketone for this purpose. There are several advantages to use this Ph* ketone for - (i) The phenyl group twists out of conjugation with the carbonyl group because of its ortho-disubstitution in the phenyl moiety,; (ii) The Ph* group inhibits the self-dimerization of the initial ketone; (iii) The alkylated ketone can undergo further functionalization by reacting it with bromine to form an acyl bromide. This process necessitated a minimal catalyst loading and relatively low temperature, even though a high base loading and 2.0 equivalents of alcohol were necessary. A variety of β-branched alkylated ketones were generated with favorable yields, and subsequently, they were modified into esters or amides through a retro-Friedel−Crafts reaction.[31] This marks the initial instance of a diastereoselective enolate hydrogen-borrowing alkylation. They have evaluated the practical applicability of this technique by synthesizing the fragrance compound (±)-3-methyl-5-phenylpentanol. A similar type of alkylation with

pentamethylphenyl (Ph*) ketone was also reported by Co, Mn, and Fe.[32] Gunanathan and coworkers employed Ru-MACHO for the same objective; however, their approach circumvented the need for hindered aryl ketones.[33] Furthermore, the low base loading of 5 mol% effectively eliminates the possibility of any aldol-based side products.

The alkylation of secondary alcohols using primary alcohols can yield two distinct compounds: a β-alkylated alcohol and an α-alkylated ketone. Both of these products are commonly obtained using an iridium catalyst (Scheme 1.1.8). Fujita and Yamaguchi documented the β-alkylation of secondary alcohols with primary alcohols employing [IrCp*Cl$_2$]$_2$ as the catalyst.[34a] Crabtree and Ryo introduced an Ir-NHC complex as a means to synthesize β-alkylated alcohols. The Ir-NHC complex (**Ir-9**), as documented by Ryo and her research team, possesses inherent chirality and has showcased outstanding catalytic efficacy in alkylation, transfer hydrogenation, and amination reactions, resulting in racemic mixtures for all synthesized compounds.[34b] Crabtree and coworkers have successfully prepared air-stable ruthenium and iridium complexes (**Ir-10**) that incorporate N-heterocyclic carbene ligands functionalized with pyrimidine groups.[34c] Both the iridium and ruthenium catalysts exhibited activity in the processes of transfer hydrogenation, β-alkylation of secondary alcohols with primary alcohols, and N-alkylation using alcohols. Selectively β-alkylated alcohols were produced by iridium and ruthenium complexes. While a low catalyst loading proved to be sufficient for the alkylation, it was notable that a relatively high amount of base was required. Regarding N-alkylation, it was observed that the iridium catalyst was compatible with the use of a mild base, such as NaHCO$_3$. Pullarkat *et al.* employed an Ir-thioether-dithiolate complex (**Ir-11**) for the β-alkylation of secondary alcohols and N-alkylation of amines.[34d] This catalyst displays remarkable activity, and the β-alkylation reaction efficiently progresses with very low catalyst loading (0.1 mol%). The predominant formation of imines, as opposed to amines, in this reaction deviates from the typical product

selectivity observed in analogous N-alkylation reactions involving organometallic catalysts.

Kundu *et al.* have made substantial advancements in this form of alkylation using ruthenium

catalysts, with loading ranging from 0.1 mol% to 0.01 mol%.[35]

Scheme 1.1.8 Iridium catalyzed α-alkylation of secondary alcohols with primary alcohols
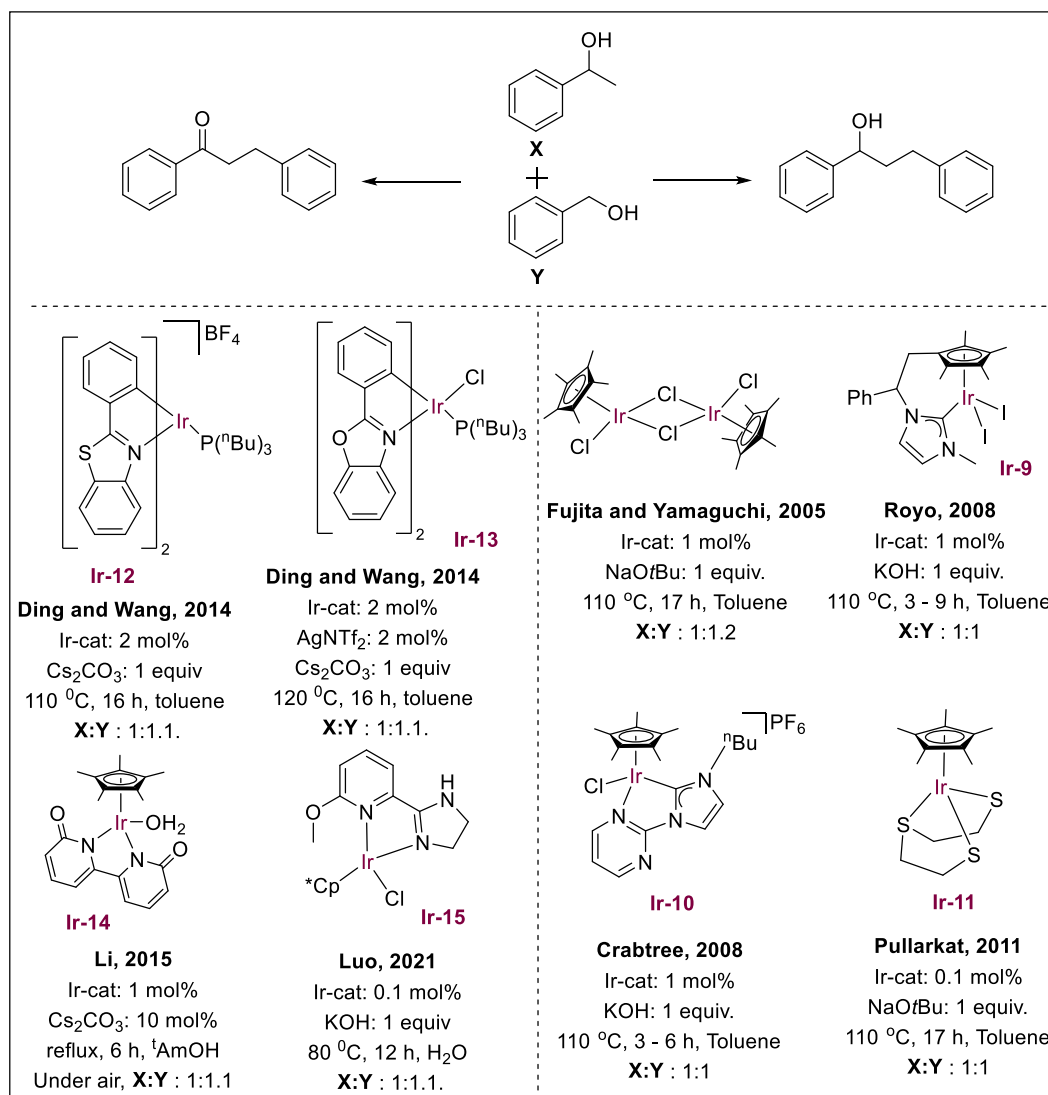
Another significant category of products that can be derived from the alkylation of secondary

and primary alcohols is α-alkylated ketones. Ding and his team successfully prepared

Iridium(III) Complexes with benzoxazolyl and benzothiazolyl ligands to facilitate reactions

involving the formation of C-C and C-N bonds.[36a,b] In case of benzoxazolyl complex (**Ir-13**),

the presence of non-coordinating anions significantly boosted the catalytic performance of these complexes, and the experiments have ruled out the likelihood of a "silver effect" as a contributing factor. Li and colleagues documented the process involving the alkylation of a secondary alcohol with a primary alcohol using a metal-ligand bifunctional iridium complex denoted as [Cp*Ir(2,2′-bpyO)(H$_2$O)] (**Ir-14**).[36c] This setup specifically generated α-alkylated ketones and reaction was carried out under air, rendering it more environmentally friendly. Numerous favorable products were generated in high quantities with only a 1 mol% catalyst loading and a 10 mol% base loading. A mechanistic investigation revealed the participation of the ligand moiety in the reaction cycle. Luo and his research team employed an iridium(III) catalyst (**Ir-15**) based on imidazole.[36d] Notably, this ligand was initially synthesized by Tang and his research group. This catalyst exhibits exceptional efficacy, necessitating only a minimal 0.1 mol% catalyst loading for the reaction. Notably, a gram-scale experiment highlights the potential practicality of this iridium-catalyzed cross-coupling method for synthesizing α-alkylated ketones.

The alkylation of arylnitriles with primary alcohols has been extensively documented, whereas the use of secondary alcohols in this context remains considerably limited to date. Gunanathan *et al*. have reported the olefination of aryl nitriles using secondary alcohols with Ru-MACHO as the catalyst.[37] Balaraman *et al*. also reported a similar reaction using a Mn-pincer complex.[38] Adhikari and coworkers documented a metal-free α-olefination of nitriles with secondary alcohol employing a photocatalyst.[39] The number of reports in this field is limited, and there is a need for continuous expansion and development in this area. Up to this point, there have been only a few reports concerning the alkylation of nitriles using secondary alcohols. The initial report on this subject was published by Sundararaju and his group, in which they utilized an in-situ generated cobalt complex for this specific purpose (Scheme 1.1.9).[40a]

Scheme 1.1.9 Iridium catalyzed α-alkylation of arylnitriles with secondary alcohols
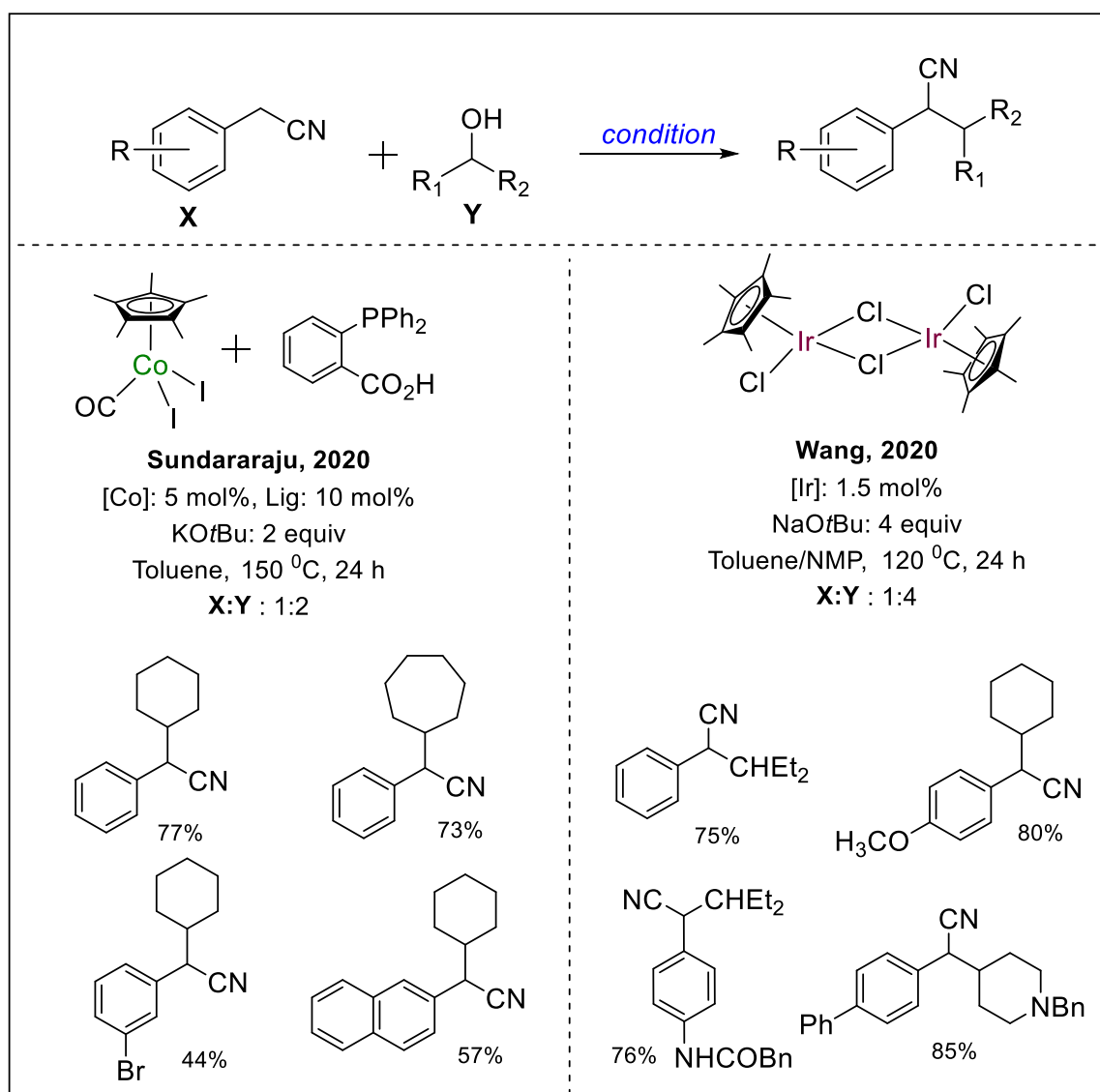
They employed a phosphine-based ligand in a 2:1 ratio with [CoCp*(CO)I$_2$]. Their use of

high temperatures and a substantial amount of base loading posed significant challenges, and

the range of substrates amenable to this approach was rather restricted. In addition to nitrile

alkylation, they have also carried out alkylation reactions on oxindoles and biologically

active N,N-dimethyl barbituric acid. A range of aryl and aliphatic secondary alcohols were

found to be compatible with various oxindoles, and a mechanistic study indicated that the

reaction follows first-order kinetics. Iridium was also employed for this purpose, and Wang

and coworkers were the pioneers in reporting the iridium-catalyzed α-alkylation of

arylacetonitriles using both primary and secondary alcohols.[40b] For this purpose, they utilized the commercially accessible compound [IrCp*(Cl)$_2$]. The significant requirement for a high amount of base, elevated time and the use of the toxic NMP solvent rendered this process less feasible. Various secondary alcohols and arylnitriles were well-tolerated, leading to good yields This process exhibits reduced selectivity, as it can also result in the hydrogenation of the double bond in allylic alcohols.

Chapter 1.2

General Introduction of Cobalt Catalyzed Hydrosilylation Reactions

Silicon chemistry has recently emerged as one of the most promising areas of chemistry research. Silicon is the eighth most plentiful element in the universe and the second most abundant in the earth's crust. The similarity between silicon and carbon has motivated scientists to investigate the possibility of substituting silicon for carbon in order to modify the biological and chemical properties of molecules.[41] In addition to the ready availability of silicon resources, organosilanes are largely environmentally friendly, and in comparison to the toxic heavier elements within Group 4, such as lead and tin, silicon compounds are generally regarded as non-toxic. The process of adding organic and inorganic silicon hydrides across various types of bonds, including carbon-carbon (C-C), carbon-heteroatom (C-O and C-N), and heteroatom-heteroatom (N-N and N-O) bonds, is commonly referred to as hydrosilylation. Seventy-five years ago, in 1947, Leo Sommer documented the inaugural instance of hydrosilylation.[42] This pioneering work involved the reaction between trichlorosilane and 1-octene, facilitated by acetyl peroxide. Nevertheless, a pivotal turning point came in 1957 when John L. Speier's discovery of hexachloroplatinic acid as an exceptionally effective precursor for the Pt catalyst emerged as a strategic breakthrough with far-reaching applications.[43] Over the next five decades, this technique is poised to gain widespread adoption as a foundational and sophisticated approach for the synthesis of organosilicon molecules and macromolecular compounds in both laboratory and industrial settings. Additionally, it will be instrumental in producing a variety of organic silyl derivatives that can be readily employed in organic synthesis. This transformation holds strong appeal for several reasons: (i) It yields alkyl- or alkenyl-silanes, which are frequently employed as foundational components for producing valuable functional hydrocarbons; (ii) The utilization of advanced procedures involving highly

effective catalysts, in conjunction with affordable and easily obtainable hydrosilane sources, enables the upscaling of hydrosilylation techniques applicable to the silicone industry; (iii) These protocols have found diverse applications in material science and even bioconjugation, further underscoring their versatility and significance.[44] Just like various other catalytic asymmetric processes, asymmetric hydrosilylation involves the use of a chiral ligand in conjunction with the metal catalyst. These optically active hydrosilylation products serve as valuable intermediates in organic synthesis and find versatile applications in various contexts.[45]

Among the most significant advancements in synthetic chemistry is the process of reducing carbon-carbon multiple bonds (such as olefins and alkynes), carbon-heteroatom bonds (including carbonyls, imines, nitriles, amides, carboxylic acids, and esters), as well as heteroatom-heteroatom bonds (like NO_2 and N_2).[46] The conventional method of employing equimolar quantities of active hydride species, such as $LiAlH_4$, $LiBH_4$, $NaBH_4$, and DIBALH, is effective but challenging, and the formation of stoichiometric byproducts is unfavorable.[47] Consequently, there is a preference for catalytic hydrogenation as an alternative, with catalytic hydrosilylation proving to be a beneficial choice that circumvents the use of highly flammable molecular hydrogen and the necessity for specialized pressure equipment.[48] The mild and easily manageable characteristics of liquid hydrosilanes make them an attractive choice over H_2. Additionally, hydrosilylation procedures are frequently conducted under gentle conditions and can accommodate a broad spectrum of functional groups. Precious metal catalysts, like Pd, Ru, Ir, and Pt, have historically been the primary choice in hydrosilylation, as they offer superior stability and activity, although their use also poses environmental concerns.[49] In response to this, researchers in the fields of chemical synthesis and catalysis are actively exploring greener alternatives, leading to the emergence of a new field in homogeneous

catalysis focused on designing novel catalysts based on abundant first-row transition metals, which has exhibited significant advancements over the past decade.[50]

In contemporary synthetic chemistry, transition metal complexes enjoy widespread popularity, serving a variety of purposes, from facilitating catalytic reactions to acting as precursors in the chemical vapor deposition of materials.[51] The emergence of a novel field in homogeneous catalysis, focused on harnessing abundant first-row transition metals from the Earth's crust to create innovative catalysts, has shown remarkable progress in the last decade. Cobalt makes up just 0.0029% of the Earth's crust by mass, and while its abundance is lower than that of iron, it surpasses its heavier counterparts, rhodium and iridium, by a factor of 40,000 and 70,000, respectively.[52] Cobalt is cost-effective and is present in various organisms, as well as in metallozymes and coenzymes, including B_{12}-dependent enzymes, methionine aminopeptidase 2, and nitrile hydratase.[53] Cobalt exhibits analogous traits to first-row transition metals in terms of electronegativity, relatively compact atomic radii, and a tendency to be classified as "hard" based on acid-base theory, when compared to 4d or 5d metals.[54] Cobalt displays reduced bond energy for Co-H and $Co-CH_3$ compared to its heavier counterparts, and it also exhibits a higher density of states than 4d or 5d metals.[55] Due to these factors, cobalt exhibits distinct reactivity patterns in comparison to its analogues in rhodium and iridium. The redox chemistry of cobalt is notably diverse. Cobalt's organometallic compounds exhibit a wide range of common oxidation states, including +3, +2, +1, 0, and -1.[56] In comparison to its neighboring metals, cobalt shows a propensity for forming low-valency complexes more readily than iron, while also demonstrating an aptitude for forming high-valency compounds more readily than nickel. In redox reactions, both one-electron and two-electron redox processes are frequently observed in cobalt complexes. Leveraging its extensive redox chemistry, one can envision the creation of versatile catalytic cycles mediated by cobalt. The primary objective of this report is to

explore the application of precisely defined cobalt complexes in hydrosilylation processes for the reduction of diverse functional groups.

The conversion of carbonyl compounds into alcohols represents a crucial category of reactions in organic chemistry, particularly in the synthesis of pharmaceuticals and natural compounds.[57] Multiple metal hydrides have been employed for this conversion, and among them, hydrosilylation stands out as a more environmentally friendly and sustainable method. Cobalt is a significant metal employed in this process, with various complexes having been developed for this specific purpose (Scheme 1.2.1). In a study by Gade *et al*., they described a chiral cobalt catalyst (**Co-1**) for the asymmetric hydrosilylation of ketones.[58a] They prepared ligands with substituents of differing steric demands, using readily available and cost-effective achiral materials as a starting point. Interestingly, the ligand's backbone did not significantly influence the catalytic performance. However, the remarkable result was that both enantiomers of a given ligand could be produced with high enantioselectivity, exceeding 99.5% ee (enantiomeric excess). Li *et al*. successfully synthesized a bidentate cobalt hydride complex (**Co-2**).[58b] This complex demonstrated high efficiency as a catalyst for the hydrosilylation of ketones and aldehydes. Remarkably, this marks the pioneering report of hydrosilylation using a cobalt hydride complex. A series of cobalt-phosphine complexes was synthesized from cobalt carbonyl by activating the corresponding ligand's C-H bond.[58c] Among these complexes, **Co-3** exhibited the highest activity when used with triethoxysilane in the hydrosilylation of aldehydes. However, these complexes did not exhibit similar activity when applied to ketones. Their mechanistic investigation revealed that the dissociation of CO is kinetically favorable, even at room temperature, but it faced a thermodynamic barrier. Notably, the reaction time can be significantly reduced by either preactivating the catalyst with an aldehyde or reintroducing more reagents to the catalytic mixture after the initial hydrosilylation reaction. Moret and coworkers have synthesized cobalt complexes, featuring a diphosphine-ketone ligand (Rdpbp),

exhibit catalytic activity in hydrosilylation reactions with phenylsilane, marking the pioneering instance of catalysis with this particular group of complexes.[58d] Among the various complexes tested, **Co-4** stood out as the most effective, demonstrating successful hydrosilylation of allylbenzene, styrene, and acetophenone. While styrene exhibited less favorable results, complete conversion was achieved with the other two substrates. Nakazawa *et al*. synthesized iron and cobalt complexes (**Co-5**) based on iminobipyridine ligands.[58e] They conducted hydrosilylation reactions with both ketones and olefins, but the metal center appeared to influence the selectivity of the reactions. For instance, when a 1:1 equimolar solution of styrene and acetophenone was present in the reaction mixture, the iron complex exhibited selectivity towards reducing the ketone group, whereas the cobalt complex preferentially reduced the styrene. Additionally, when pyridine was used as a solvent in the cobalt system, it resulted in the selective reduction of the keto group. Another bidentate cobalt complex was reported by Gosmini and coworkers.[58f] They have prepared cobalt complexes that incorporate ligands based on phosphinoquinoline. Among these complexes, the cationic bisliganded diisopropylphosphino complex, designated as **Co-6**, displayed the highest catalytic efficiency in the hydrosilylation of ketones. However, when sterically hindered ketones were used in this system, they did not yield the desired product. The deuterium study unveiled a kinetic isotope effect (KIE) of 17, signifying the involvement of hydrogen (H) in the rate-determining step. A very recent and intriguing development by Hrezycho *et al.* involves a PNP-pincer-based cobalt complex that catalyzes the hydrosilylation of ketones.[58g] This catalytic system demonstrated effectiveness with low catalyst loading and operated under mild conditions. It accommodated a wide range of aromatic and aliphatic ketones, both with electron-withdrawing and electron-donating groups. In their mechanistic investigation, they reported the formation of Co-H species using NMR spectroscopy when the complex (**Co-7**) was treated with an excess of diphenyl silane. Notably, when the same complex reacted with deuterated diphenylsilane, the

hydride peak was not observed in the NMR, confirming that the formation of the metal hydride occurs through the silane.

Scheme 1.2.1 Cobalt catalyzed hydrosilylation of ketones
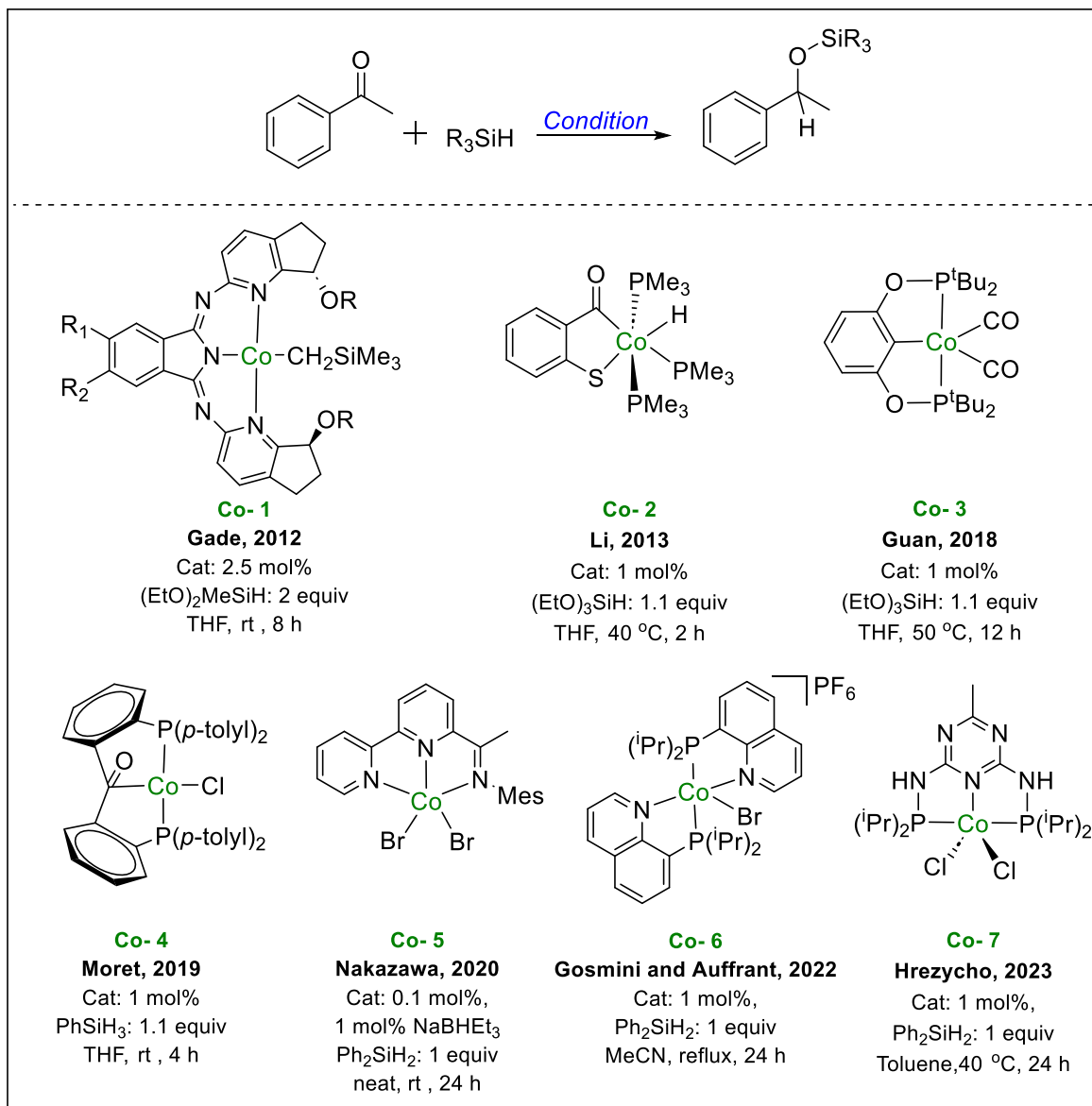
Cobalt-catalyzed hydrosilylation of alkyne is a well-established phenomenon. When alkynes undergo hydrosilylation, they generate a mixture of regio- and stereoisomeric products, including α-, β-(Z)-, and β-(E)-vinylsilanes (Scheme 1.2.2). The β-(Z)- and β-(E)-isomers are the outcomes of *anti*-Markovnikov addition of the Si-H bond to the alkyne group where as the α- isomer is the product of Markovnikov addition. Scientists have explored this chemical

transformation through various approaches to develop novel metal catalysts that enable the controlled production of vinylsilanes with specific regio- and stereochemistry.

Scheme 1.2.2 Transition metal catalyzed hydrosilylation of alkynes
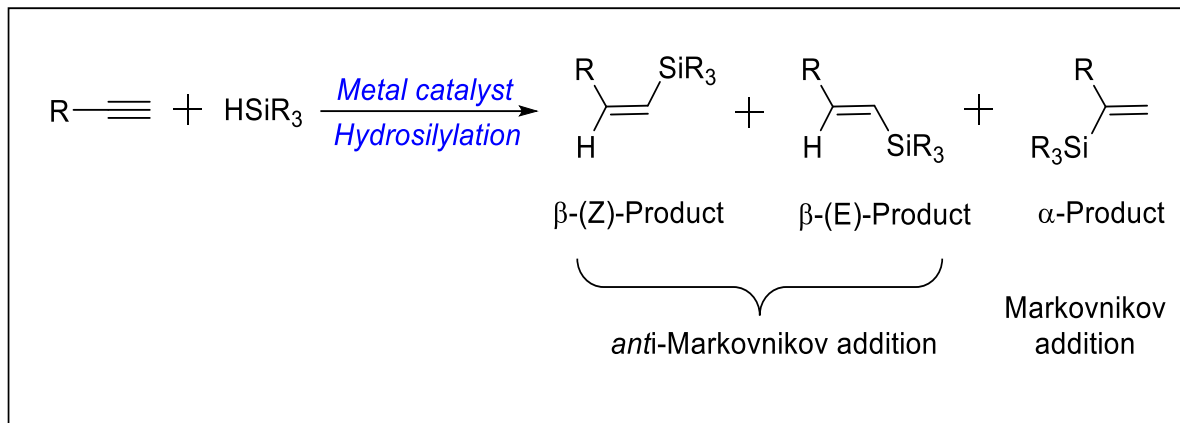
Before delving into examples of cobalt-catalyzed hydrosilylation, it's worth exploring the general mechanism to grasp the regioselectivity. Metal-catalyzed hydrosilylation typically follows two main pathways: the Chalk-Harrod and modified Chalk-Harrod pathways (Scheme 1.2.3).[59] In the Chalk-Harrod pathway, the initial step involves the oxidative addition of the Si-H bond to the metal, followed by alkyne insertion into the M-H bond, and the final step is the reductive elimination of the C-Si bond. The modified Chalk-Harrod pathway shares the same first step, but in the second step, alkyne insertion occurs into the M-Si bond, followed by the reductive elimination of the C-H bond. While both mechanistic scenarios can yield the same outcome, the chemical environment of the intermediates at the starting points of the potential mechanistic pathways ($L_nM–H$ and LnM–Si) can influence steric preferences for each scenario. This interplay of factors plays a crucial role in determining selectivity. In the realm of cobalt catalysis, the judicious selection of a ligand emerges as a parameter of significant importance. The choice of ligand not only influences but also orchestrates the chemical landscape, thereby facilitating hydrosilylation through a specific mechanistic cycle. This strategic selection of ligands, therefore, becomes a critical aspect in steering the course of the catalytic process and ultimately dictating the outcome of hydrosilylation reactions.

Scheme 1.2.3 Mechanism for transition metal catalyzed hydrosilylation of alkynes
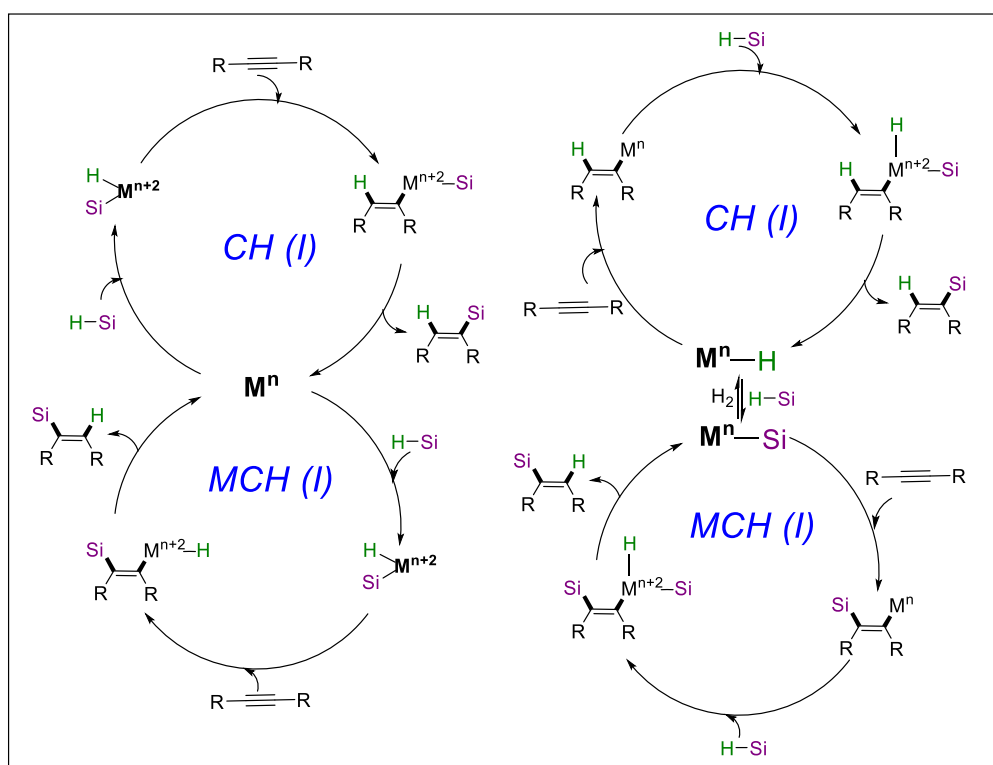
In 2016, the research teams led by Lu and Huang disclosed their findings on the cobalt-catalyzed hydrosilylation of alkynes to achieve Markovnikov-selective products (Scheme 1.2.4).[60a,b] Both groups employed NaBHEt$_3$ as an activator, which, upon interaction with the complexes, generated cobalt hydride species. The catalyst that demonstrated high efficiency for the hydrosilylation of phenylacetylene with diphenylsilane was a cobalt(II) complex denoted as **Co-8**, featuring oxazoline-iminopyridine (OIP) ligands. The most effective configuration for realizing Markovnikov addition entails the placement of a benzyl group at the α position of the oxazoline, coupled with the attachment of a dimethylphenyl group to the iminyl moiety. The Huang group recorded that the use of the pybox ligand in **Co-9** also proved to be efficient for achieving Markovnikov addition. Both protocols exhibited the advantages of minimal catalyst loading and reduced reaction time, while delivering excellent regioselectivity for a broad spectrum of aryl alkynes. Furthermore, they explored the diverse synthetic applications of the resulting vinylsilanes, unveiling a distinctive pathway to access silyl-boryl

Scheme 1.2.4 Cobalt catalyzed Markovnikov hydrosilylation of alkynes
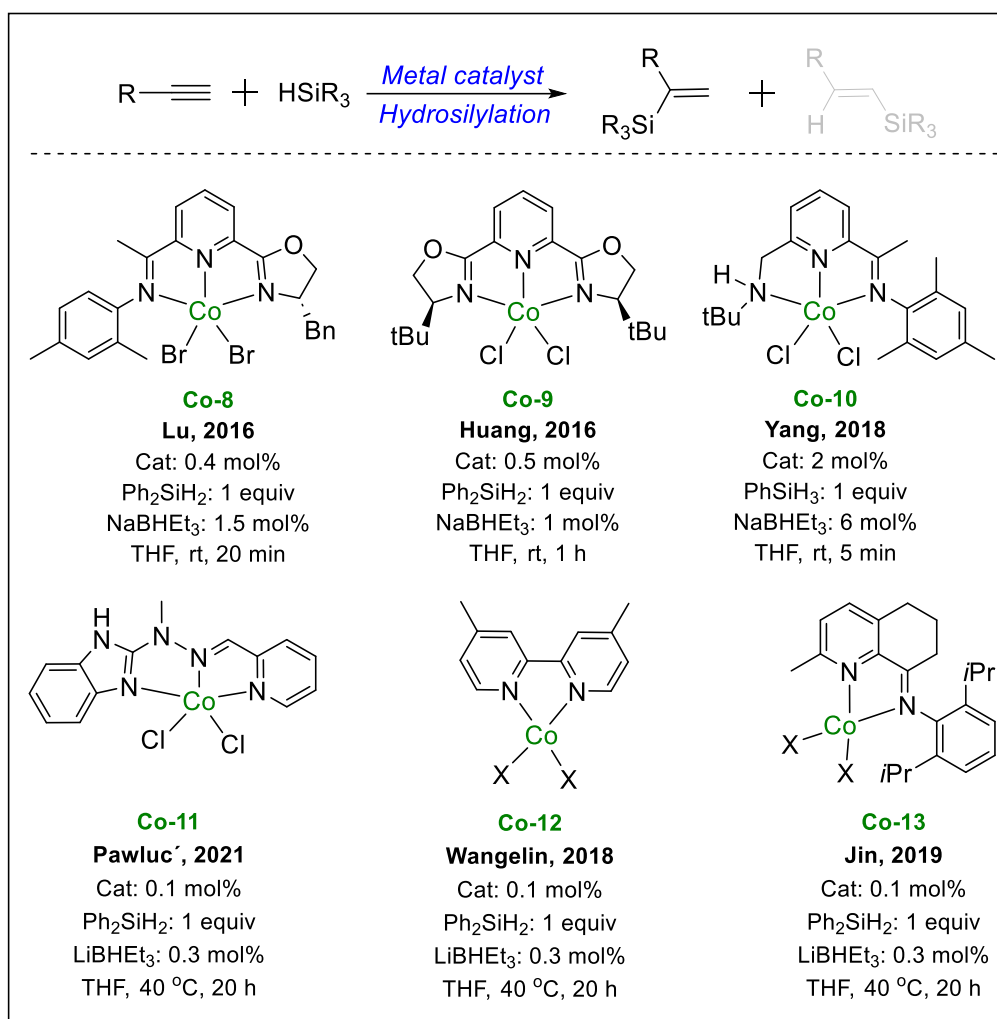
alkanes. The Huang group put forward a mechanism based on prior research, suggesting an MCH mechanism. Yang *et al.* presented another noteworthy instance of Markovnikov hydrosilylation.[60c] They utilized an amine-pyridine-imine-containing tridentate cobalt complex (**Co-10**) for this application. The presence of a sterically hindered 2,4,6-trimethylphenyl group in the imine position played a pivotal role in achieving selective Markovnikov product formation. This method exhibited high efficiency, with an impressive turnover frequency of 126,720 h-1. Importantly, it delivered excellent conversions not only with phenylsilane but also with diphenyl silane and dimethylphenyl silane. Pawluc´ made a significant contribution to this area with a cobalt complex (**Co-11**) featuring a hydrazone Schiff base ligand.[60d] They

employed LiHBEt$_3$ as an activator. This system exhibited remarkable selectivity for both terminal and internal alkynes. Deuterium labeling experiments showed that this system did not undergo Crabtree-Ojima type isomerization. Wangelin *et al.* documented the utilization of a bidentate cobalt complex (**Co-12**) for the efficient hydrosilylation of terminal alkynes, employing both phenyl silane and diphenyl silane.[60e] This system also demonstrated effectiveness with aryl alkynes and heteroaryl alkynes, albeit with reduced regioselectivity in the case of aliphatic alkynes. Jin *et al.* also reported Markovnikov-selective hydrosilylation of alkynes using cobalt complex (**Co-13**) based on ring-fused iminopyridinyl ligands.[60f] The rigidity and planar geometry of this ligand system prevented catalyst deactivation, thus stabilizing a potentially active Co(I) species. In this system, phenyl silane served as the silane substrate, achieving an outstanding turnover number of 29,700. Mechanistic studies indicated that the insights into the mechanism were consistent with those previously proposed by Liu.

For the *anti*-Markovnikov addition, there are two potential isomeric forms: one is E, and the other is Z. Ge *et al.* initially reported a cobalt-catalyzed (Z)-selective hydrosilylation of terminal alkynes using cobalt acetate and pyridine diimide ligands (as shown in Scheme 1.2.5).[61a] In their experimental investigations, the researchers noted a distinctive shift in hydrosilylation selectivity when employing the Co(acac)$_2$ with the ^{MeS}PDI ligand system. However, when they substituted the cobalt precursor with the more reactive Co(OAc)$_2$, the initially established system started favoring the formation of the thermodynamically more stable (E)-selective isomer. The addition of phenol played a crucial role in altering the isomer selectivity. In the presence of phenol, (Z)-selective hydrosilylation was observed. The in-situ generated cobalt hydride led to the isomerization of (Z)-vinylsilane to the (E)-vinylsilane. Yet, when phenol was introduced, a metal phenoxide species was formed, which did not promote isomerization. This nuanced shift in the reaction pathway emphasizes the sensitivity of

catalytic processes to the presence of specific additives, such as phenol, underscoring the importance of subtle experimental variables in influencing hydrosilylation reactions.

Scheme 1.2.5 Cobalt catalyzed *anti*-Markovnikov hydrosilylation of alkynes
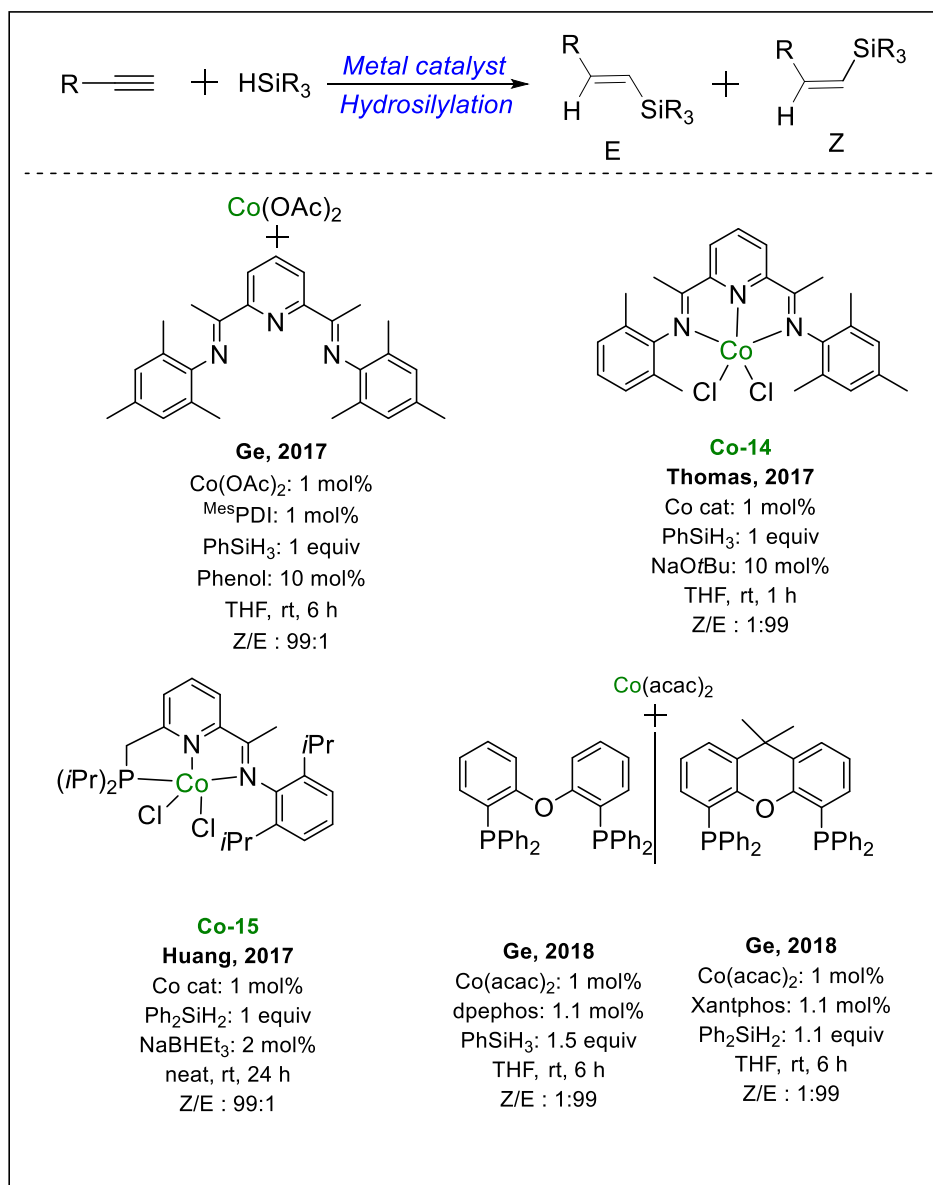
Thomas *et al*. reported a fascinating outcome when they utilized NaO*t*Bu as an activator for the hydrosilylation of alkynes with the cobalt complex **Co-14**.[61b] This base played a role in the in-situ generation of cobalt hydride. In a specific instance, when 1-octyne reacted with phenyl silane in the presence of the cobalt complex and a catalytic quantity of NaO*t*Bu, they observed the selective formation of (E)-vinylsilane. However, they did not provide an explanation for

the origin of this stereoselectivity. Huang reported the synthesis of a Cobalt complex (**Co-15**) with an NNP-pincer ligand for achieving (Z)-selective hydrosilylation.[61c] Their approach demonstrated remarkable efficiency, especially when applied to aliphatic terminal alkynes in combination with diphenyl silane, achieving selectivity ratios as high as 99:1 at room temperature. Ge *et al.* showcased a cobalt-phosphine catalyst system for achieving the anti-Markovnikov hydrosilylation of terminal alkynes.[61d] When combining Co(acac)$_2$ and dpephos, they observed the formation of (E)-vinylsilanes when reacting arylacetylenes with PhSiH$_3$. However, when employing ligands with a slightly larger bite angle, such as xantphos, dihydro silanes were necessary. It's worth noting that these systems didn't require any activators like NaBHEt$_3$. The robustness of these protocols was confirmed through gram-scale synthesis.

Petit *et al.* were the first to report a cobalt complex supported by a phosphorous-based ligand for the hydrosilylation of internal dialkynes (Scheme 1.2.6).[62]

Scheme 1.2.6 Cobalt catalyzed hydrosilylation of internal alkynes
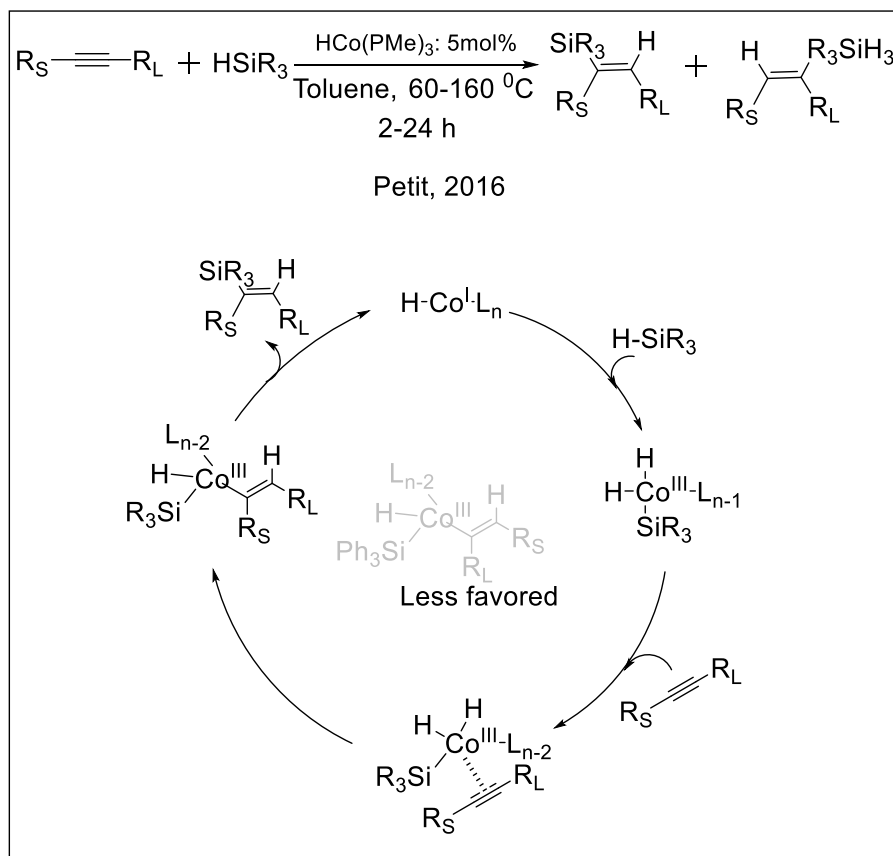
In this reaction, they achieved selective formation of (E)-vinylsilanes when a silyl group was positioned adjacent to the larger substituent. They successfully isolated a pivotal intermediate, a dihydrosilyl-cobalt(III) species, through the reaction of Co-15 with phenyl silane. Notably, the hydride within Co-15 did not engage in migratory insertion with the alkyne; instead, it formed an π-complex with the alkyne. DFT analysis revealed that this reaction followed a Chalk-Harrod-type mechanism.

Alkene hydrosilylation is a highly significant catalytic process, widely employed in the large-scale production of lubricants, adhesives, rubbers, release coatings, and chromatography stationary phases.[63] Cobalt catalysts for alkene hydrosilylation are widely recognized, and a selection of these catalysts is illustrated in Scheme 1.2.7. Deng group introduced a precisely characterized Co(II) NHC complex that incorporated a silyldonor for use in the hydrosilylation of 1-octene with phenyl silane.[64a] Complexes 16a-c exhibited catalytic efficacy in promoting *anti*-Markovnikov hydrosilylation. However, among these complexes, 16a, characterized by reduced steric hindrance, displayed superior performance. Remarkably, the desired product was obtained in a 75% yield, even with an extremely low catalyst loading of 0.005 mol%, resulting in an outstanding turnover number (TON) of 15,000. In a similar vein, the Deng research team disclosed another anti-Markovnikov-selective alkene hydrosilylation using an unsymmetrical Co(II)-amide complex (**Co-20**).[64b] This reaction involved the use of triethoxy silane and a 1 mol% catalyst loading at room temperature. Just like their earlier findings, this system exhibited remarkable chemoselectivity and accommodated a diverse range of substrates. Notably, sterically bulky silanes did not prove effective in this particular protocol. In 2015, Holland and colleagues documented their work on Co(I)-arene complexes supported by β-diketiminate ligands, which they then employed in the hydrosilylation of alkenes.[64c] Among these complexes, **Co-17** emerged as the most proficient catalyst for achieving *anti*-Markovnikov addition. The research revealed that catalysts with lower steric hindrance proved

to be more efficient, while bulkier ones were less effective. Their protocol successfully a broad

spectrum of substrates using phenyl silane, yielding isolated products in good to high yields.

Scheme 1.2.7 Cobalt catalyzed *anti*-Markovnikov hydrosilylation of alkenes
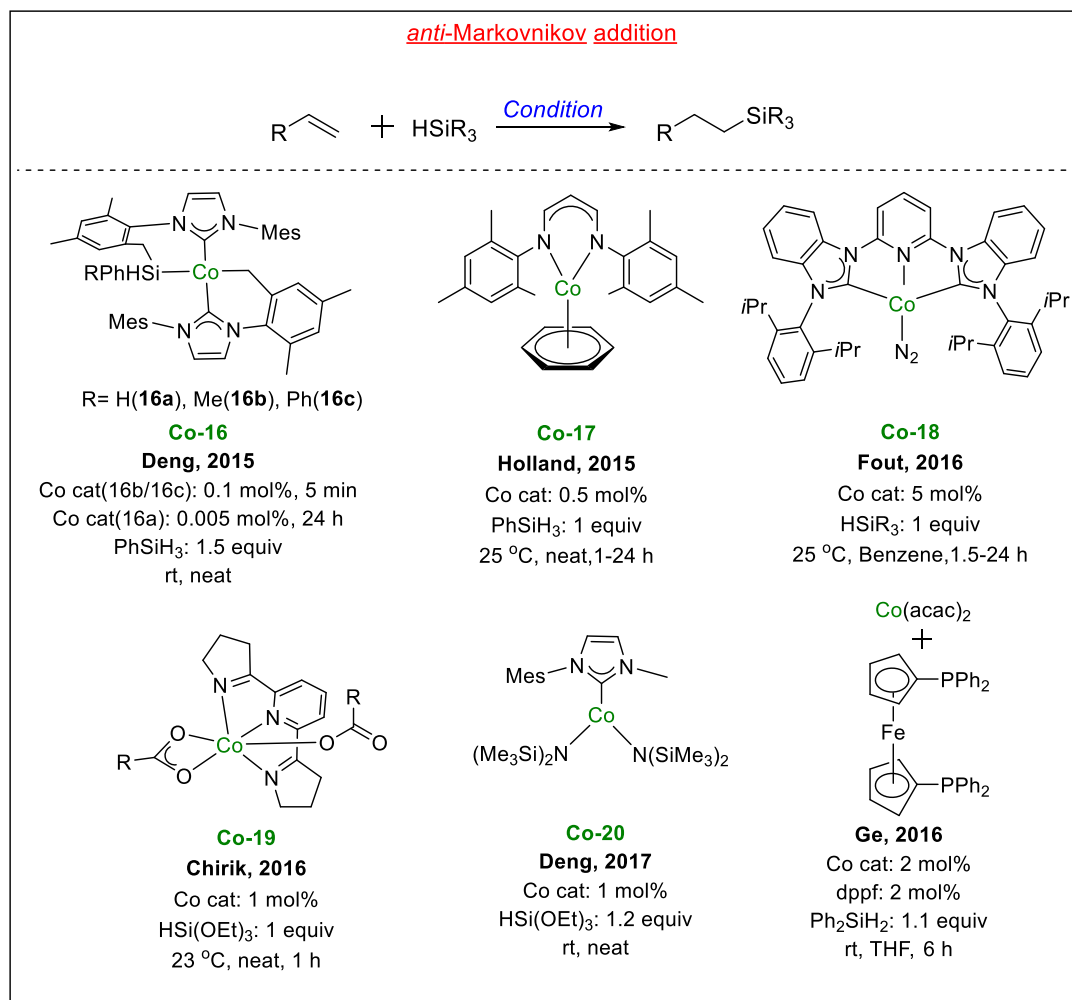
A broad spectrum of substrates using phenyl silane, yielding isolated products in good to high

yields. Notably, this method also exhibited tolerance for internal alkenes. Fout and coworkers

successfully synthesized a novel Co(I) dinitrogen complex (**Co-18**) supported by a

bis(carbene)-based pincer ligand.[64d] This complex demonstrated its utility in achieving

chemoselective *anti*-Markovnikov hydrosilylation of terminal alkenes that featured highly

reactive functional groups. The standard reaction conditions involved the use of a 5 mol%

catalyst loading, and a range of secondary and tertiary silanes were applied as hydrosilylation

reagents. In-depth mechanistic investigations unveiled the presence of a cobalt(III)-hydride

species, which was confirmed through the use of ^{1}H and ^{29}Si NMR spectroscopies. Chirik and his group made a notable contribution to *anti*-Markovnikov alkene hydrosilylation. They designed a series of cobalt(II) complexe (**Co-19**) featuring pyridine diimine ligands and bis(carboxylate) moieties for this purpose.[64e] This protocol demonstrated impressive tolerance toward various functional groups, including carbonyl, epoxide, amino, and halides. It's worth mentioning that the N-alkyl-substituted pyridine diimine (PDI) complex facilitated hydrosilylation, whereas the N-aryl-substituted variant promoted dehydrogenative silylation.

Ge *et al*. have documented the achievement of Markovnikov hydrosilylation of alkenes through the application of in situ generated catalysis (Scheme 1.2.8).[65a] This was accomplished using the stable $Co(acac)_2$ in conjunction with Xanthphos or [Mes]PDI. A wide range of vinyl arenes and aliphatic alkenes were found to be compatible with this method, resulting in the production of branched organosilanes in high yields. Through deuterium labeling experiments, it was elucidated that the Co/phosphine system adhered to the Chalk-Harrod mechanism with a Co-H intermediate, while the Co/[Mes]PDI system followed the Modified Chalk-Harrod mechanism with a Co-Si intermediate. Furthermore, the regioselectivity of vinylarene hydrosilylation and the chemoselectivity of aliphatic alkenes catalyzed by the Co/MesPDI system were found to be primarily influenced by the steric properties of the silanes. In addition to this, the report revealed that the Co/dppf system yielded *anti*-Markovnikov products. The Huang research group has significantly contributed to the scientific literature with their published findings, elucidating the use of phosphine-iminopyridine Co(II) complexes as catalysts for achieving the selective Markovnikov hydrosilylation of alkenes employing phenyl silane..[65b] In the comprehensive exploration of various complexes, it was revealed that among all the studied entities, **Co-21**, characterized by its minimal steric bulk, remarkably emerged as the catalyst with the highest efficiency.y. A diverse range of functionalized aliphatic 1-alkenes, featuring halide, ether, ester, acetal, and amide functional groups, were subjected to

chemoselective hydrosilyla- tion with PhSiH$_3$, resulting in the isolation of Markovnikov products in good yields. A switch from cobalt to iron as the central metal altered the selectivity

Scheme 1.2.8 Cobalt catalyzed Markovnikov hydrosilylation of alkenes
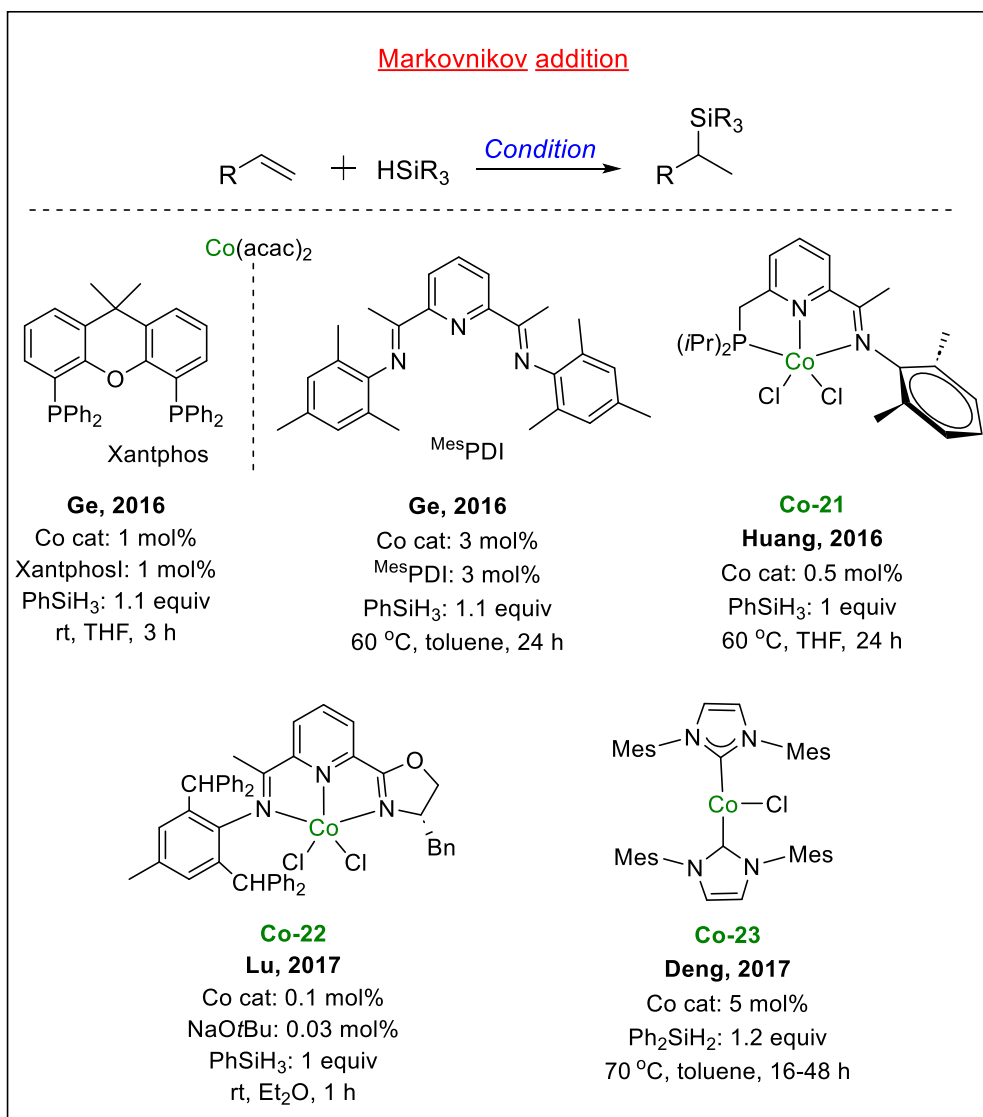
from Markovnikov to *anti*-Markovnikov. Lu *et al.* have disclosed a fascinating method for achieving both Markovnikov selectivity and enantioselectivity in the hydrosilylation of alkenes.[65c] In the pursuit of an efficient and atom-economical hydrosilylation process using phenyl silane, they utilized a cobalt complex rooted in OIP (**Co-22**), with the addition of sodium tert-butoxide as an activator. Remarkably, they were able to obtain vinylarenes with a high enantiomeric excess of 98% and aliphatic alkenes with an enantiomeric excess of 87%.

By simply employing the enantiomer of the ligand, the opposite enantiomeric outcome could be readily obtained. Moreover, this process allowed for the straightforward synthesis of compounds on a gram scale with just 0.1 mol% of the catalyst loading. Deng and his research team have documented the use of two cobalt complexes, [(IAd)(PPh$_3$)CoCl] and [(IMes)$_2$CoCl] (**Co-23**), for achieving selective anti-Markovnikov and Markovnikov hydrosilylation of alkenes.[65d] The reaction was conducted using a 5 mol% catalyst loading and diphenyl silane as the silylating agent. Aryl alkenes provided favorable yields, whereas aliphatic ones exhibited lower yields and reduced regioselectivity. Alkenes with significant steric hindrance did not participate in this particular protocol. The choice between anti-Markovnikov and Markovnikov hydrosilylation appears to be influenced by the distinct steric properties of the N-alkyl imidazolylidene, and N-aryl counterpart.

Alcohols and aldehydes serve as crucial foundations in chemical production and are fundamental raw materials in industrial processes. The focused reduction of esters to aldehydes and alcohols using silanes is gaining attention as the preferred method over ester hydrogenation because of its operational simplicity.[66] In 2018, Agbossou-Niedercorn and Michon's group introduced a system using CoCl$_2$/NaBHEt$_3$ and Co(OAc)$_2$/NaBHEt$_3$ for selectively reducing esters to alcohols and aldehydes through hydrosilylation (Scheme 1.2.9).[67a] This catalyst system offers the advantage of not requiring costly or air-sensitive ligands. The catalytically active species was presumed to be Co(0), formed by the reduction of Co(II) by NaBHEt$_3$. Catalytic characterization confirmed the partially crystalline nature of the materials, with the presence of nanoparticles also observed. The cobalt chloride salt selectively produced alcohols, while the acetate salt selectively yielded aldehyde products. Gunanathan *et al*. additionally detailed the selective reduction of esters to aldehydes using a cobalt pincer complex (**Co-24**).[67b] This singular catalyst facilitated both transformations by modifying only the silane equivalent. The process involved silylacetal or silylether intermediates, and

subsequent acid treatment resulted in aldehyde or alcohol formation. The mechanism entailed cobalt-induced activation of Si-H bonds, aided by amine-amide metal–ligand cooperation, potentially involving Co-H intermediates.

Scheme 1.2.9 Cobalt catalyzed hydrosilylation of ester
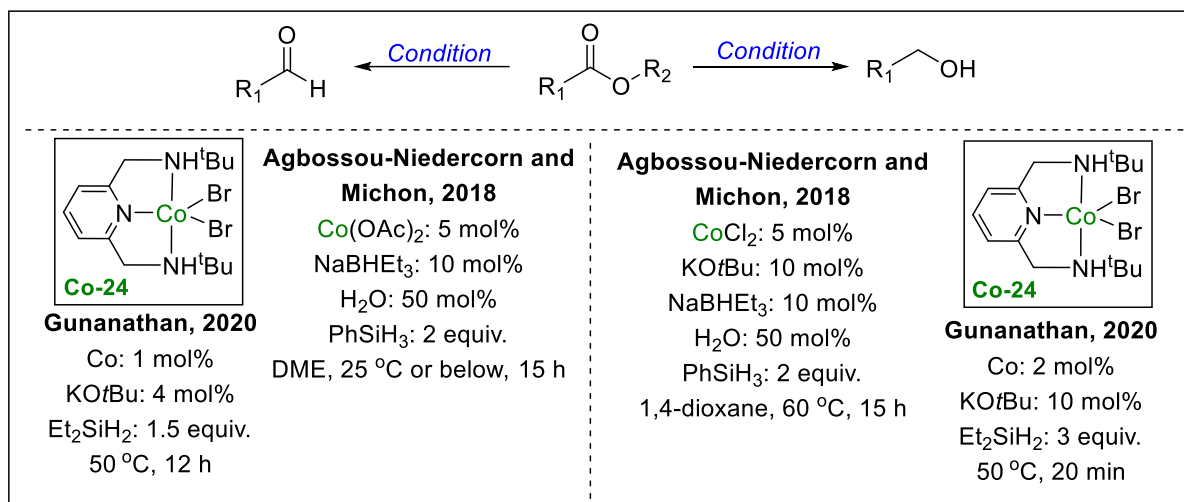
Amines, versatile organic compounds, have found widespread use as fundamental components in organic chemistry. One of the most prevalent methods for synthesizing amines involves the reduction of amides, with hydrosilylation playing a significant role in this process. Cobalt plays an crucial role in this reduction process. In 2013, Darcel and his group documented the first cobalt-catalyzed selective reduction of tertiary and secondary amides (scheme 1.2.10).[68a] Cobalt carbonyl is a renowned catalyst for hydrosilylation procedures. This method's advantage lay in employing an extremely low catalyst loading (0.5 mol%) and utilizing non-precious silane such as PMHS. The reaction was conducted under both thermal and photo-assisted conditions (UV-350 nm). In 2019, Turculet and colleagues developed a low-coordinate Fe(II) and Co(II) complex (**Co-25**) using a monoanionic P,N-ligand, N-(2-dicyclohexylphosphinophenyl)-2,6-diisopropylanilide.[68b] These complexes demonstrated efficacy in reducing tertiary amides with phenyl silane under similar reaction conditions (5 mol% catalyst, 80°C, 1–24 hours). The iron complex exhibited superior activity compared to the cobalt complex. Recently, Jin and Hu synthesized a tridentate NNN-cobalt complex (**Co-**

26) for the hydrosilylative reduction of secondary amides.[68c] They utilized an inexpensive silane (PMHS) in this method. The process accommodated various aliphatic and aromatic secondary amides, producing the corresponding amines in moderate to good yields. Mechanistic inquiries revealed a two-step process, identifying amide deoxygenation as the rate-determining step.

Scheme 1.2.10 Cobalt catalyzed hydrosilylation of amides
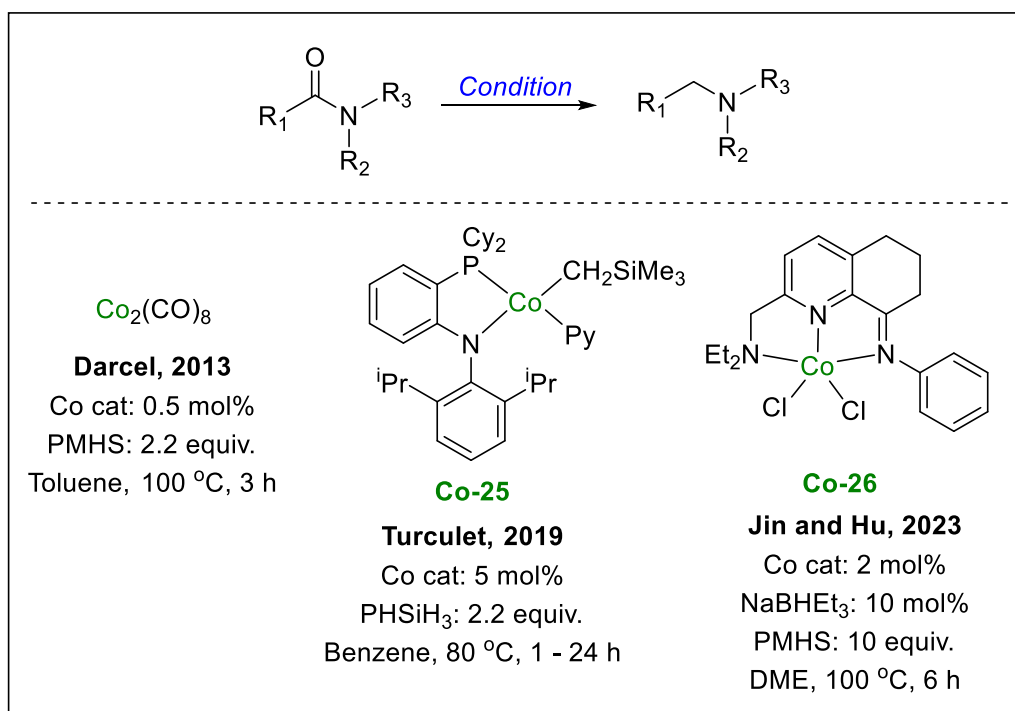
Murai *et al*. were the first to record the hydrosilylation of nitriles using a cobalt catalyst (1.2.10).[69a] They utilized cobalt carbonyl (8 mol%) as an effective catalyst with 10 equiv. of silane under a CO atmosphere at 60 °C. While electron-donating nitriles were successful, aliphatic nitriles required higher temperatures (100 °C). Propane-2-nitrile and 2-methylpropane-2-nitrile reactions were notably more efficient when PPh_3 was introduced to the reaction mixture. In 2019, Nagashima and his team employed a $Co(OPiv)_2$ and tert-butyl isocyanide system for nitrile hydrosilylation, using TMDS as the silane source.[69b] This reaction occurred under solvent-free conditions. It displayed tolerance to both aliphatic and aromatic

nitriles, even with fluoro, aldehyde, and ketone groups, resulting in the production of corresponding primary ammonium salts after acidic hydrolysis.

Scheme 1.2.11 Cobalt catalyzed hydrosilylation of nitriles

$Co_2(CO)_8$	$Co(OPiv)_2$
Murai, 1990	**Nagashima, 2019**
Co cat: 8 mol%	Co cat: 1 mol%
Me_3SiH: 10 equiv.	TMDS: 1.3 equiv.
CO atmosphere	CN-*t*-Bu: 3 mol%
Toluene, 60 - 120 °C	Neat, 80 °C
20 - 48 h	24 h
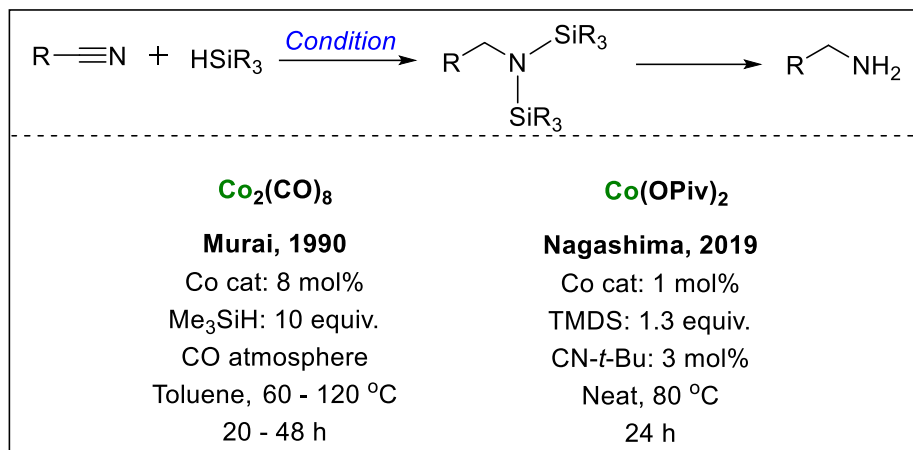
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Chapter 2

Efficient α-Alkylation of Arylacetonitriles with Secondary Alcohols Catalyzed by a Phosphine-free Air-stable Iridium(III) Complex

2.1 ABSTRACT

A well-defined and readily available air-stable dimeric iridium(III) complex catalyzed α-alkylation of arylacetonitriles using secondary alcohols with the liberation of water as the only by-product is reported. The α-alkylations were efficiently performed at 120 °C under solvent-free conditions with very low (0.1 – 0.01 mol%) catalyst loading. Various secondary alcohols including cyclic and acyclic alcohols and a wide variety of arylacetonitriles bearing different functional groups were converted into the corresponding α-alkylated products in good yields. Mechanistic study revealed that the reaction proceeds via alcohol activation by metal-ligand cooperation with the formation of reactive iridium-hydride species.

2.2 INTRODUCTION

In organic synthesis, the importance of α-alkylation of nitriles is enormous as α-alkylated nitriles are versatile building block for the synthesis of varieties of compounds such as ketones, carboxylic acids, amines, amides and heterocycles.[1] Conventional α-alkylation of nitrile involves the reaction of nitrile with stoichiometric or excess amount of base to generate nitrile anion which further reacts with toxic alkyl halide.[2] Thus, traditional α-alkylation of nitriles produce stoichiometric amount of salt waste and probable formation of dialkylated byproducts is another major disadvantage.[3] Catalytic alkylations provide a better alternative in which alcohols are utilized as alkylating reagents. Direct catalytic alkylations with alcohols are highly atom economic protocol and offer a green alternative as water is the only byproduct. Catalytic alkylation of carbonyls with alcohols is an active field of research.

A large number of metal complexes are reported with primary alcohols.[4] However, the use of secondary alcohols is limited.[5] Catalytic α-alkylation of nitriles are also gaining significant attention. In early eighties, the pioneering work on catalytic α-alkylation of arylacetonitriles by primary alcohols (methanol, ethanol and benzyl alcohol) was reported by utilizing ruthenium- and rhodium-phosphine complexes.[6] $RuH_2(PPh_3)_4$ showed highest catalytic activity. The α-alkylation of nitriles involves oxidation of alcohols to carbonyls followed by the condensation of the resultant carbonyls with nitriles to form α,β-unsaturated nitriles and finally the reduction of α,β-unsaturated nitriles by liberated hydrogen from the oxidation of alcohols. In this tandem process, metal catalysts play the key role in the first and third steps i.e. dehydrogenation and hydrogenation reactions. Catalytically generated hydrogen from the oxidation of alcohols is later utilized in the hydrogenation of unsaturated intermediates; this is often referred to as hydrogen autotransfer or borrowing hydrogen method.[7] Only first two steps i.e. dehydrogenation of alcohols followed by condensation of the resultant carbonyls with nitriles are necessary for α-olefination of nitriles with hydrogen and water as byproducts. Thus, α-olefination can be considered as less atom economic with the loss of valuable hydrogen. Utilizing the hydrogen autotransfer or borrowing hydrogen method, a varieties of transition metal catalysts were employed for α-alkylation of nitriles using mostly primary alcohols (Scheme 1). Lin and Lau et al. reported cationic aminocyclopentadienyl ruthenium complexes ($[(\eta^5$-$C_5H_4NMe_2)Ru(PPh_3)_2(MeCN)][BF_4]$ and $[(\eta^5$-$C_5H_4NEt_2)Ru(PPh_3)_2(MeCN)][BF_4]$) as weak to moderately active catalysts for α-alkylation/olefination of arylacetonitriles with primary alcohols giving a mixture of saturated (minor) and unsaturated (major) nitriles. Later α-alkylation of acetonitrile by primary alcohols was gracefully done by $[RuHCl(CO)(PPh_3)_3]$.[8b] Recently, Ru-POP,[8c] Ru-PNP[8d] and Ru-NNN[8e] pincer complexes were employed as very effective catalysts for α-alkylation of

arylacetonitriles with primary alcohols. Ru-grafted hydrotalcite[9] and palladium on MgO[10] as heterogeneous catalysts were also utilized.

Scheme 2.2.1 α-alkylation and α-olefination of nitriles.

Previous work: α-olefination and α-alkylation of arylacetonitrile with primary alcohol

Previous work: α-olefination of arylacetonitrile with secondary alcohol

Gunanathan *et al.*
[Ru]: 1 mol%
KO*t*Bu: 2 mol%
toluene, 135 °C, 10 h

Balaraman *et al.*
[Mn]: 3 mol%
KO*t*Bu: 30 mol%
toluene, 120 °C, 12 h

ACS Catal. **2018**, *8*, 2473

ACS Catal. **2020**, *10*, 947

Previous work: α-alkylation of arylacetonitrile with secondary alcohol

Wang *et al.*
[Ir]: 3 mol%
KO*t*Bu: 4 eq.
toluene, 120 °C, 24 h

Sundararaju *et al.*
[Co]: 5 mol%, **L**: 10 mol%
KO*t*Bu: 2 eq.
toluene, 150 °C, 24 h

[Cp*IrCl₂]₂
Asian J. Org. Chem
2020, *9*, 1092

Cp*Co(CO)I₂ + (**L**)

ACS Catal. **2020**, *10*, 8023

Present work: α-alkylation of arylacetonitrile with secondary alcohol

Conditions:
[Ir]: 0.1 mol% (0.01 mol% can be reached)
KO*t*Bu: 30 mol%
solvent free, 120 °C, 1 h

Cationic half-sandwich Os-NHC complex ([Os(η⁶-*p*-cymene)(OH)(IPr)][OTf])[11] and Fe-PNP pincer complexes[12] were also used effectively. Rhodium complexes were also utilized for the same purpose. By changing the reaction environment, selective α-alkylation or α-olefination of arylacetonitriles with primary alcohols was reported by using cationic binuclear Rh-species.[13] Rhodium catalysts were also employed for similar reactions such as synthesis of α-alkylated arylacetamides from arylacetonitriles and primary alcohols[14a] and allylic alkylation of allyl benzoate with α-substituted benzyl nitrile.[14b] Few iridium complexes are known to

show catalytic activity for α-alkylation of nitriles.[15] In 2006 and 2007, [IrCp*Cl$_2$]$_2$ and [IrCl(COD)]$_2$ with phosphine ligands were used for the α-alkylation of arylacetonitriles and alkyl cyanoacetates, respectively, with primary alcohols in presence of base at high temperature (100-130 °C).[15a, 15b] A few years later, two research groups independently reported Ir(I)-catalyzed ([Ir(OH)(COD)]$_2$/PPh$_3$ and [IrCl(COD)]$_2$) α-alkylation of acetonitrile using primary alcohols under microwave irradiation (130-180 °C).[15c, 15d] The α-alkylation of acetonitrile using secondary alcohols required prolonged (7-36 h) heating at 200 °C.[15c] The number of reports on α-alkylation/olefination of nitriles with secondary alcohols are extremely rare. Recently, Ru-PNP[16] and Mn-PNP[17] pincer complexes were employed as very efficient catalysts for the α-olefination of arylacetonitriles with various of secondary alcohols (Scheme 1). Manganese complexes were also used as effective catalysts for α-olefination of arylacetonitriles with primary alcohols.[18] During our study, two groups independently reported catalytic α-alkylation of arylacetonitriles with secondary alcohols.[19] Wang et al. used [Cp*IrCl$_2$]$_2$ as catalyst[19a] and Sundararaju et al. utilized Cp*Co(CO)I$_2$ in presence of 2-(diphenylphosphino)benzoic acid as ligand (Scheme 1).[19b] To the best of our knowledge, these are the only two reports on the α-alkylation of arylacetonitriles with secondary alcohols. However, the catalyst loading is rather high ([Ir]: 3 mol%; [Co]: 5 mol%, ligand: 10 mol%), as are the amount of base (2 to 4 equiv.), reaction temperature (150 °C for Co-catalyst) and reaction time (24 h). It is worth mentioning that the low substrate to catalyst (S/C) ratio (Ir: 33, Co: 20) may limit possible applications. And in recent years, developing phosphine-free stable metal catalysts is gaining significant attention for obvious reasons.[20] Herein, we address the use of a readily available phosphine-free air-stable Ir(III) complex with commercially available pyrazol-based ligand as a very effective catalyst (maximum TOF: 10000 h^{-1}) for the α-alkylation of a large number of arylacetonitriles with varieties of

secondary alcohols under solvent-free conditions and at low catalyst loading (S/C ratio of 10000 can be achieved).

2.3 RESULTS AND DISCUSSIONS

Metal-ligand bifunctional activation of substrate plays a key role in molecular catalysis. Deprotonation-protonation of the ligand attached to the metal is a common strategy employed in these systems such as Noyori-Ikariyas's catalyst,[21] Shvo's catalyst[22] and Milstein's pincer complexes.[23] Very recently Maji et. al. utilized this strategy in manganese-catalyzed α-alkylation of ketones with secondary alcohols.[24] Ligands having protic NH-group is a common feature in those complexes.[21, 22, 23, 24] On the same line of thought, we have selected a pyrazole based ligand **L₁** with a pendant phenol arm (Scheme 2.3.1).

Scheme 2.3.1 Synthesis of complex 1 and 2 with the molecular structure of 2 showing 50% ellipsoids[a]
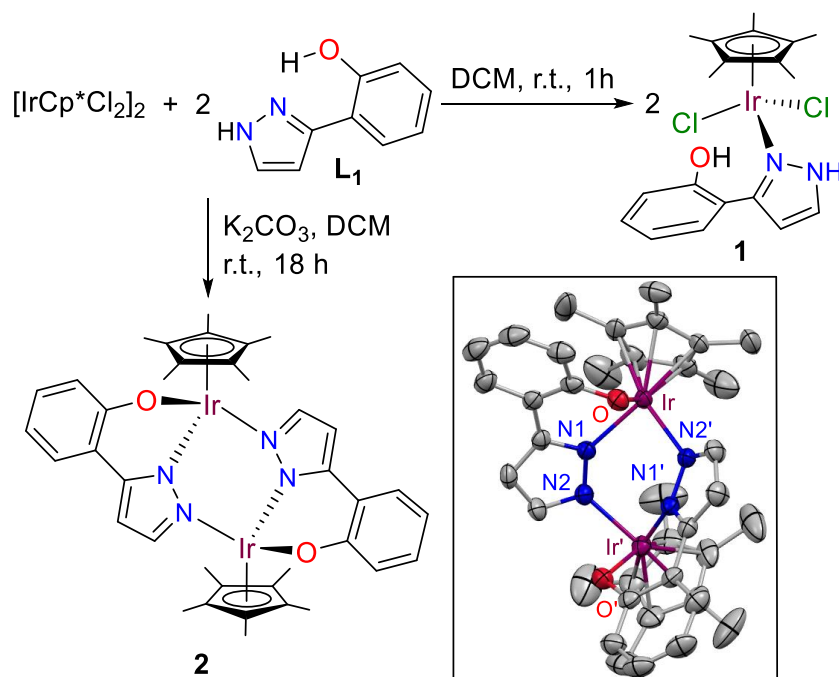
[a]Hydrogen atoms are omitted for clarity.

Facile coordination of the ligand with [IrCp*Cl₂]₂ gave complex **1** in excellent yield. The OH and NH protons appeared as broad resonances (10.97 and 13.20 ppm) in the ¹H NMR spectrum of **1**. Upon reaction of **L₁** and [IrCp*Cl₂]₂ in presence of base, smooth

dehydrochlorination resulted in the formation of complex **2** as yellow solid in almost quantitative yield (Scheme 2.3.1). Complex **2** is air-stable and was characterized by ^{1}H and ^{13}C NMR spectroscopy and mass analysis. As expected, the OH and NH resonances are absent in the ^{1}H NMR spectrum of species **2**. Complex **2** was further characterized by single crystal X-ray analysis which revealed pyrazolato-bridged dinuclear structure. The bond distances and bond angles are consistent with similar iridium complexes.[25]

With the air-stable complex **2** in hand, we set out to investigate the α-alkylation of phenylacetonitrile (**S₁**) as standard substrate with cyclohexanol (**A₁**) as a secondary alcohol (Table 2.3.1). Upon heating a mixture of **S₁** and **A₁** (2.5 equiv.) in presence of 30 mol% KO*t*Bu and 3 mol% [Ir], a complete conversion of **S₁** to 2-cyclohexyl-2-phenylacetonitrile (**P₁₁**) was observed in 24 h (entry 1). Gradually decreasing the reaction time to 6 h also gave full conversion of **S₁** to **P₁₁** (entry 1). Reducing the catalysts loading to 2 mol% yielded full conversion of **S₁** in 6 h with more than 70% isolated yield of **P₁₁** (entry 2). Further reduction of catalyst loading to 1 (entry 3), 0.5 (entry 4: 71% isolated yield of **P₁₁**) and 0.1 mol% (entry 5: 80% isolated yield of **P₁₁**) also gave full conversion of **S₁** in just 1h. Reaction did not proceed in the absence of either complex **2** (entry 6) or base (entry 7). Thereafter, we performed two reactions with less amount of base (entry 8: 20 mol% of KO*t*Bu) and at lower temperature (entry 9: 110 °C). In both cases, we observed approximately 95% yield of product. Reaction at 120 °C with 2 equiv. of **A₁** gave full conversion with 80% isolated yield (entry 10). Encouraging result was not obtained in the presence of 1 mL toluene as solvent (entry 11); unreacted starting material was observed. If the reaction is performed with 1.1 equiv. of alcohol, less than 10% unreacted starting material was observed (entry 12); however, complete conversion was observed in 1.5 h (entry 13). Thus it is not necessary to use large excess of cyclohexanol which might act as solvent.

Table 2.3.1 Catalytic performance of complex 2 for the α-alkylation of phenylacetonitrile with cyclohexanol[a]
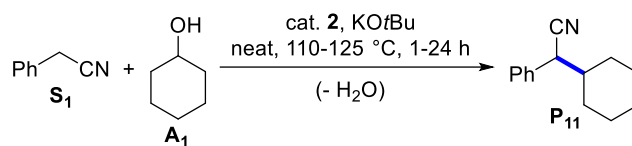
en.	[Ir]	KOtBu	A₁	temp.	time	Yield[f]
	(mol%)	(mol%)	(equiv.)	(°C)	(h)	(%)
1[a]	**3**	30	2.5	125	24/18/ 12/8/6	>99
2[a]	**2**	30	2.5	125	6	>99 (72)[g]
3[a]	**1**	30	2.5	125	6/4/2/1	>99
4[a]	**0.5**	30	2.5	125	1	>99 (71)[g]
5[b]	**0.1**	30	2.5	125	1	>99 (80)[g]
6[b]	**no**	30	2.5	125	1	0
7[b]	0.1	**no**	2.5	125	1	0
8[b]	0.1	**20**	2.5	125	1	94
9[b]	0.1	30	2.5	**110**	1	96
10[b]	0.1	30	**2.0**	120	1	>99 (80)[g]
11[b,c]	0.1	30	2.0	120	1	63
12[d]	0.1	30	**1.1**	120	1	92
13[d]	0.1	30	**1.1**	120	**1.5**	>99
14[e]	0.1	30	2.0	120	1	81[g]

[a]Reactions conducted in pressure tube (10 mL) [a]with 0.5 mmol **S₁**, 1.25 mmol of **A₁** and 3/ 2/ 1/ 0.5 mol% of [Ir]; [b]with 5.0 mmol **S₁**, 12.5/10.0 mmol of **A₁** and 0.1 mol% of [Ir]; [c]in 1 mL of toluene; [d]with 5.0 mmol **S₁**, 5.5 mmol of A1 and 0.1 mol% of [Ir]. [e]Gram-scale reaction with 10.0 mmol (1.17 g) S1, 20.0 mmol of S2 and 0.1 mol% of [Ir]. [f]Yields of **P₁** were determined by GC using p-xylene as internal standard. [g]Isolated yields of **P₁**. Key parameters for each entry are indicated in bold.

To test the robustness of the present catalytic system, a gram-scale reaction was performed with 10.0 mmol (1.17 g) of **S₁** with 2 equiv. of **A₁**, 30 mol% base, 0.1 mol% [Ir] at 120 °C for 1 h (entry 14) and 1.62 g of **P₁₁** was isolated (81%).

Having established the optimized reaction condition (0.1 mol% [Ir], 30 mol% KO*t*Bu, 2 equiv. of secondary alcohol, 120 °C, 1 h, solvent-free), we thereafter examined various other arylacetonitriles to expand the substrate scope. Catalytic α-alkylation of various arylacetonitriles using cyclohexanol as the secondary alcohol was performed (Scheme 2.3.2)

Scheme 2.3.2 α-alkylation with cyclohexanol
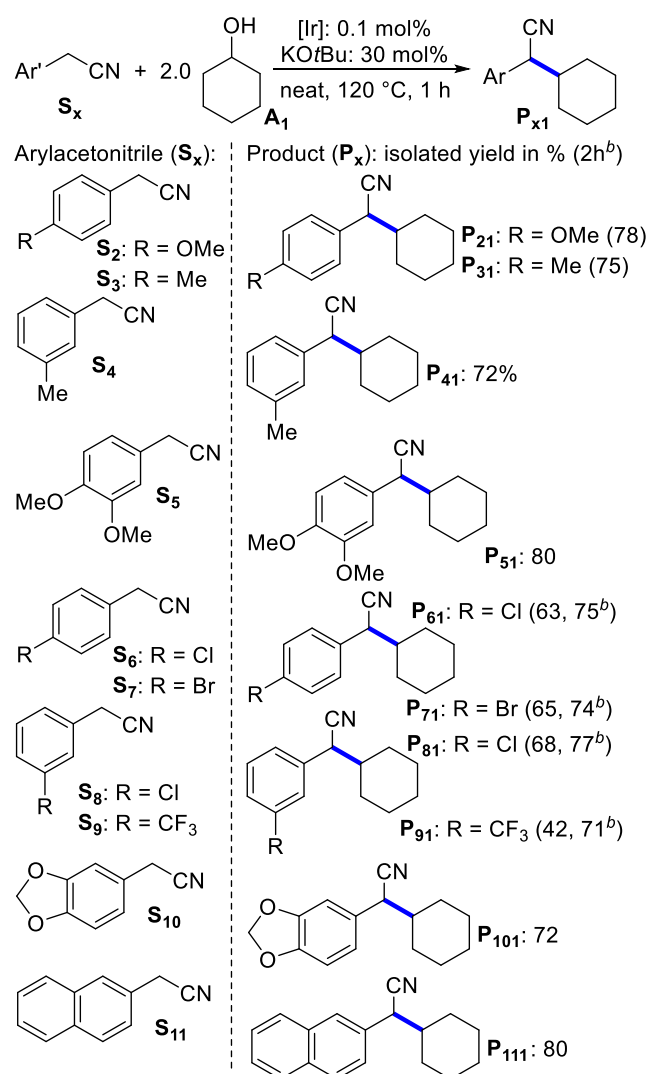
Upon reaction with cyclohexanol, 4-methoxyphenylacetonitrile (**S₂**) gave 2-cyclohexyl-2-(4-methoxyphenyl)acetonitrile (**P₂₁**) in good yield (78%). Similar result (**P₃₁**: 75%, **P₄₁**: 72%)

was obtained for electron donating methyl group at the *para* (**S₃**) and *meta* (**S₄**) position of phenylacetonitrile. Substrate with two methoxy groups (**S₅**) also gave good yield of the α-alkylated product (**P₅₁**: 80%). Substrates with mild electron withdrawing groups like halogens at either para (**S₆**, **S₇**) or meta (**S₈**) positions gave decent yields (**P₆₁**: 63%, **P₇₁**: 65%, **P₈₁**: 68%). Much diminished yield of product (**P₉₁**: 42%) was obtained for arylacetonitrile with strong electron withdrawing CF_3 group (**S₉**). In case of substrates with electron withdrawing group, we also observed acronitrile intermediates along with small amount of unreacted starting materials. However, prolonged heating for 2 h gave complete conversion with better isolated yields (**P₆₁**: 75%, **P₇₁**: 74%, **P₈₁**: 77%, **P₉₁**: 71%). Therefore, the nature of substituents on the aryl moiety has prominent effect on the outcome of the α-alkylation of arylacetonitriles. As expected, 3,4-methylenedioxy substituents on phenylacetonitrile (**S₁₀**) gave good yield of product (**P₁₀₁**: 72%). Similarly, 2-napthylacetonitrile was reacted with cyclohexanol to give the correcsponding α-branched product (**P₁₁₁**: 80%) in good yield.

Thereafter, we explored the scope of this catalytic protocol with respect to various cyclic and acyclic secondary alcohols under standard reaction conditions (Scheme 4). When cyclopentanol was reacted with phenyl acetonitrile, the corresponding α-alkylated product 2-cyclopentyl-2-phenylacetonitrile (**P₁₂**) was isolated in 84% yield. Substituted phenylacetonitrile with electron donating groups such as methyl and methoxy at *o*-, *p*- and *m*-positions gave the corresponding products in 75-80% yield. As expected, lesser yield (**P₆₂**: 65%) was obtained when cyclopentanol was reacted with 4-chlorophenylacetonitrile. Another cyclic alcohol, cycloheptanol also provided similar yields of desired products (**P₁₃**: 86%, **P₄₃**: 84%, **P₅₃**: 68%, **P₆₃**: 70%, **P₁₀₃**: 73%) with substituted phenylacetonitriles under standard reaction conditions. We also tested acyclic secondary alcohols, both symmetric and asymmetric. We were pleased to see that 3-pentanol as a symmetric acyclic secondary alcohol yielded the corresponding α-alkylated products (**P₃₄**: 76%, **P₄₄**: 73%, **P₅₄**: 54%,

Scheme 2.3.3 α-alkylation of arylacetonitriles with various secondary alcohols
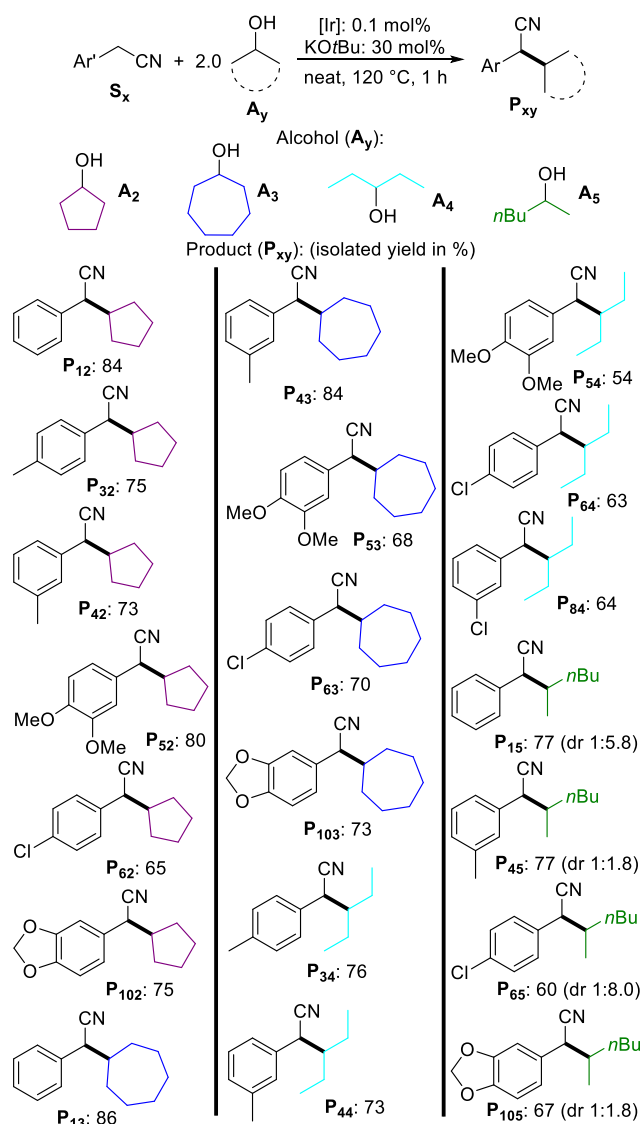
P_{64}: 63%, P_{84}: 64%) in decent to good yields upon reaction with various arylacetonitriles. Interestingly, we obtained a mixture of two diastereomers in similar yields (P_{15}: 77%, P_{45}: 77%, P_{65}: 60%, P_{105}: 67%) when substituted phenylacetonitriles were reacted with (±)-2-hexanol as an asymmetric alcohol. To test the robustness of the present catalyst, α-alkylations of phenylacetonitrile with cyclohexanol were scaled up to 25 mmol scale (multi grams) with a catalyst loading of 0.005 mol% ([Ir]: 0.01 mol%) for 1 h and we were pleased to see a complete conversion of substrate with good isolated yield of 2-cyclohexyl-2-phenylacetonitrile (4.33 g, 87%). Therefore, a maximum TOF of 10000 h^{-1} could be

achieved. Hence, a simple but highly efficient catalytic protocol is reported for the α-alkylation of a wide range of arylacetonitriles with various secondary alcohols.

Several control experiments were performed to shed light on the reaction mechanism. Complex **2** is a dimer of coordinatively unsaturated 16-electron pyrazolato complex and thus it is highly likely that it forms coordinatively saturated 18-electron mononuclear species during substrate coordination. To test this, complex **2** was reacted with DMSO and indeed DMSO-coordinated 18-electron mononuclear species **3** was isolated and fully characterized (Scheme 2.3.4). Thereafter, we performed a stoichiometric reaction of complex **2** with cyclohexanol. In the absence of KO*t*Bu, heating a mixture of complex **2** and cyclohexanol at 120 °C for 1 h resulted in the formation of iridium hydride species **4** and cyclohexanone in excellent isolated yields (Scheme 2.3.4). This clearly shows that the iridium catalyst **2** is able to dehydrogenate alcohol to ketone in the absence of a base. It is known that KO*t*Bu as a base can alone catalyze aldol-type Knoevenagel condensation and the fact is also supported by theoretical studies.[26] Hence, we performed the reaction of cyclohexanone and phenylacetonitrile in presence of 30 mol% of KO*t*Bu (Scheme 2.3.4). This indeed resulted in the formation of phenylacrylonitrile in excellent yield. Thereafter, a stoichiometric reaction of hydride species **4** with phenylacrylonitrile was carried out (Scheme 2.3.4) to test whether hydrogen could be transferred from the hydride complex **4** to the C=C of unsaturated phenylacrylonitrile. Clean formation of saturated product **P₁₁** suggested a successful hydrogen transfer from the hydride species **4**. We also tested if hydride species **4** could catalyze the hydrogenation of phenylacrylonitrile with cyclohexanol. As expected, reaction of phenylacrylonitrile with cyclohexanol in presence of 0.1 mol% of the hydride species **4** also yielded **P₁₁** (Scheme 2.3.4).

Scheme 2.3.4 Control experiments

a) Formation of mononuclear species **3**

Complex **2** + DMSO $\xrightarrow{\text{r.t., 0.5 h}}$

3 (99%)

b) Dehydrogenation of alcohol to ketone

Complex **2** + $\xrightarrow[\text{1 h}]{\text{120 °C}}$ +

4 (98%)

c) C-C bond formation by Knoevanagel condensation

Ph–CN + $\xrightarrow[\text{120 °C, 1 h}]{\text{KO}t\text{Bu (30 mol%)}}$ (88%)

d) Stoichiometric hydrogen transfer to arylacrylonitrile

Complex **4** + Ph $\xrightarrow[\text{1 h}]{\text{120 °C}}$ Complex **2** + Ph

(97%)   (85%)

e) Hydrogenation of arylacrylonitrile with cyclohexanol

Ph + $\xrightarrow[\text{120 °C, 1 h}]{\substack{\text{Complex 4} \\ \text{(0.1 mol%)}}}$ Ph

(81%)

Therefore, we proposed a plausible mechanism based on the experimental evidences and previous reports (Scheme 6).[8, 16, 17, 19] Initially alcohol interacts with the iridium dimer **2** and the O-H activation of the alcohol via proton transfer to the pyrazolato moiety yielded an alkoxy intermediate I_1. Similar instance of nitrogen atom in the pyrazolato moiety picks up the hydrogen was reported in the past; similar iridium-pyrazolato complex activated N-H bond of tosyl amine via proton transfer to the pyrazolato moiety.[25b] Thereafter, the β-hydride elimination of intermediate I_1 resulted in the formation of ketone and hydride intermediate I_2 (or complex **4**) which was isolated and fully characterized. As β-hydride elimination requires a vacant site at the metal center, this second step might also undergo a Cp ring slippage from η^5 to η^3 coordination. However, proposed β-hydride elimination in saturated complexes are also reported.[18, 19] Thereafter, ketone and arylnitrile undergo Knoevenagel condensation in

presence of base to form vinyl nitrile with the elimination of water. Finally, hydrogen transfer from the hydride intermediate **I₂** to the vinyl nitrile yielded α-alkylated arylacetonitrile with the regeneration of iridium complex **2.**

Scheme 2.3.5 Plausible mechanism for catalytic α-alkylation of arylacetonitrile
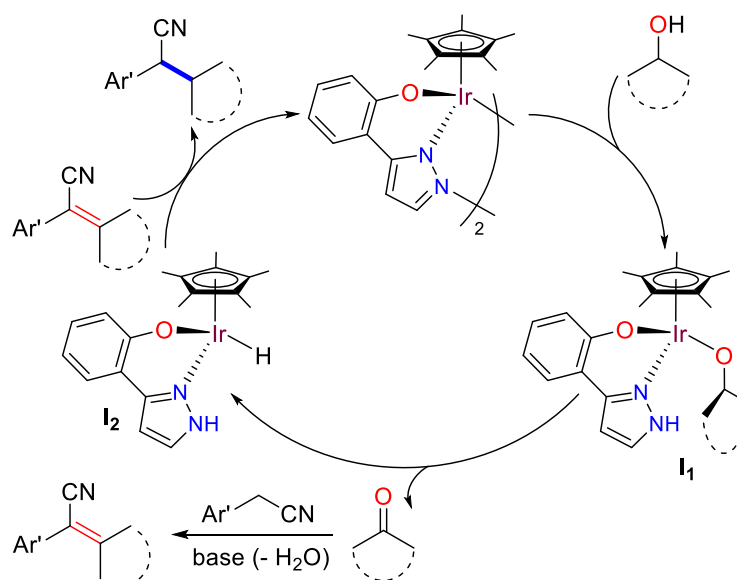
2.4 CONCLUSION

In conclusion, we have developed a readily accessible (single step synthesis) and air-stable iridium(III) catalyst which is very efficient for the α-alkylation of arylacetonitriles using challenging secondary alcohols with the liberation of water as a green byproduct. The substrate scope includes a wide range of arylacetonitriles and various secondary alcohols. Compared to the previously reported cobalt ([Co]: 5 mol%, phosphine ligand: 10 mol%) and iridium ([Ir]: 3 mol%) catalysts,[19] we can reach very low (up to 0.01 mol% of [Ir]) catalyst loading which is realistic for possible future application. Moreover, the present catalytic protocol is operative with catalytic amount of base (30 mol%) in contrast to the huge amount of base (2-4 equiv.) used in other reported catalytic systems. In addition, present catalytic system is much faster (24 h vs. 1 h; maximum TOF of 1-2 vs. 10000 h⁻¹) and another advantage of this green catalytic protocol is solvent-free α-alkylation. With the excellent

conversion in a very short period of time with attractive catalyst loading, the iridium catalyst has been proven to be an excellent catalyst for the α-alkylation reaction. Based on experimental evidences, the reaction is believed to follow the borrowing hydrogen principle which involves iridium catalyzed oxidation of alcohol to ketone followed by base catalyzed aldol-type condensation of ketone and nitrile to vinyl nitrile and finally reduction of vinyl nitrile to the α-alkylated product. Further investigations will involve the utilization of this catalyst for other catalytic reactions; particularly the isolation of iridium-hydride intermediate opens the gateway for various hydrofunctionalization reactions.

2.5 EXPREMENTAL SECTION

General experimental

Synthesis of the iridium complexes **1**, **2** and **3** were performed in air. All air and moisture sensitive experiments such as the synthesis of intermediate iridium-hydride complex **4** and catalytic α-alkylation of nitriles were performed under dry nitrogen atmosphere using standard Schlenk or glovebox (MBraun) techniques. Catalytic α-alkylation of nitriles were performed in Ace pressure tubes purchased from Sigma-Aldrich. Analysis and purification of the products were carried out in air. For the air sensitive experiments, solvents (dichloromethane (DCM) and diethylether (Et$_2$O) were distilled, degassed and stored over 3 Å molecular sieves. Solvents were purchased from Merck and Spectrochem. Deuterated solvents (CDCl$_3$ and DMSO-d6) were purchased from Sigma-Aldrich. For recording NMR spectra of air and moisture sensitive samples, CDCl$_3$ was degasses and stored over 3 Å molecular sieves. 2-(1H-Pyrazol-3-yl)phenol, [IrCp*Cl$_2$]$_2$, KO*t*Bu, *p*-xylene, all organic nitriles and all secondary alcohols were purchased from Sigma Aldrich, Alfa Aesar and TCI Chemicals and used without further purification.

^{1}H and ^{13}C{^{1}H} NMR spectra were recorded at Bruker AV-400 and JEOL-400 (^{1}H at 400 MHz and ^{13}C at 101 MHz). ^{1}H and ^{13}C{^{1}H} NMR chemical shifts are referenced in parts per

million (ppm) with respect to residual solvent peaks (CDCl$_3$: δ 7.26 and 77.16 ppm; DMSO-d6: 2.50 and 39.52 ppm). The coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to describe multiplicity: s = singlet, bs = broad signal, d = doublet, t = triplet, q = quadtrate, m = multiplate. High resolution mass spectra were recorded on a Bruker microTOF-Q II Spectrometer. Elemental analysis was carried out on a EuroEA Elemental Analyser.

Synthesis and NMR data of Complex 1,2,3,4.
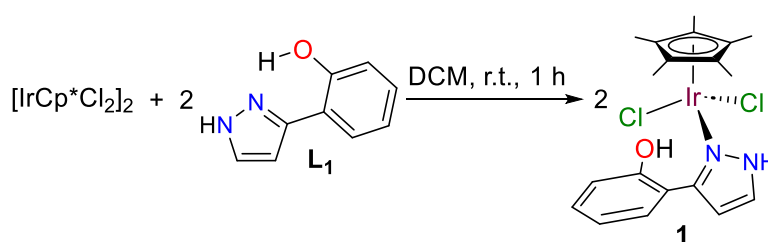
Synthesis of Complex 1. A solution of 2-(1H-Pyrazol-3-yl)phenol (0.032 g, 0.20 mmol) in DCM (2.5 mL) was added dropwise to a solution of [IrCp*Cl$_2$]$_2$ (0.080 g, 0.10 mmol) in DCM (2.5 mL) at r.t. Yellow precipitate formed instantly. The reaction mixture was stirred at r.t. for 1 h. The liquid was decanted off and the yellow solid was washed with DCM (2 x 2.5 ml). The yellow solid was dried under high vacuum to give complex 1 (0.110 g, 98%) as pure compound. ^{1}H NMR (DMSO-d6): δ 1.60 (s, 15H), 6.72-7.00 (m, 3H), 7.16 (t, J = 7 Hz, 1H), 7.71 (d, J = 7 Hz, 1H), 10.97 (bs, 1H), 13.20 (bs, 1H). ^{13}C{^{1}H} NMR (DMSO-d6): δ 8.27, 92.13, 102.10, 116.41, 117.08, 119.25, 126.84, 128.76, 155.09. HRMS (ESI) m/z for C$_{19}$H$_{23}$Cl$_2$IrN$_2$O: 558.0817, found 558.0821 [M$^+$]. Anal. Calcd for C$_{19}$H$_{23}$Cl$_2$IrN$_2$O (558.52): C, 40.86; H, 4.15; N, 5.02. Found: C, 40.83; H, 4.18; N, 5.11.
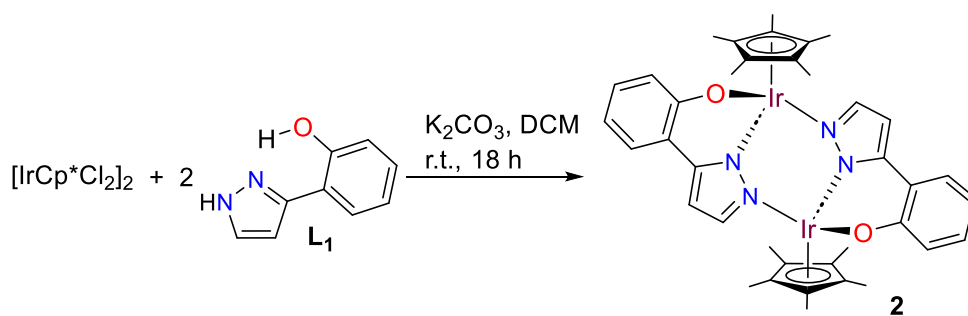
Synthesis of Complex 2. DCM (20 mL) and three to four drops of water were added to a solid mixture of 2-(1H-pyrazol-3-yl)phenol(0.032 g, 0.20 mmol), [IrCp*Cl$_2$]$_2$(0.080 g, 0.10 mmol), and K$_2$CO$_3$(0.031 g, 0.22 mmol) at r.t. The reaction mixture was stirred at r.t. for 16 h, resulting in an orange-yellow solution with a white precipitate. The solid was filtered off, and the orange-yellow solution was dried under a high vacuum. The crude product was dissolved in DCM (2 mL), and the solution was added dropwise to Et$_2$O while stirring vigorously. This resulted in an orange-yellow solid with a very pale-yellow solution. The solid was collected after filtration and dried under a high vacuum to give complex **2** (0.096 g, 99%) as a pure compound. ^{1}H NMR (CDCl$_3$): δ 1.41 (s, 15H), 6.44 (t, J = 7 Hz, 1H), 6.47 (d, J = 2 Hz, 1H), 6.69 (d, J = 7 Hz, 1H), 6.85 (t, J = 7 Hz, 1H), 7.31 (d, J = 7 Hz, 1H), 7.80 (d, J = 2 Hz, 1H). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 9.60, 84.86, 103.37, 115.76, 122.01, 126.14, 126.92, 127.17, 146.60, 150.72, 164.23. HRMS (ESI) m/z for C$_{38}$H$_{42}$Ir$_2$N$_4$O$_2$: 972.2523, found 972.2549 [M+]. Anal. Calcd for C$_{38}$H$_{42}$Ir$_2$N$_4$O$_2$ (971.21): C, 46.99; H, 4.36; N, 5.77. Found: C, 47.13; H, 4.37; N, 5.85.
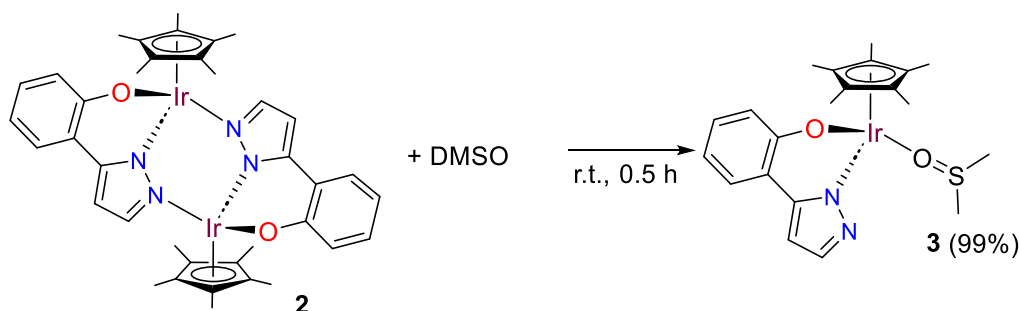
Synthesis of Complex 3. All manipulations were performed in air using commercially available solvents without further drying. DMSO (2 mL) was added to solid complex **2** (0.097 g, 0.1 mmol). The resulted yellow solution was stirred at r.t. for 30 mins. The solution was dried under high vacuum at 80 °C for 6 h to give a yellow solid as pure complex **3** (0.112 g, 99%) as pure compound. ^{1}H NMR (DMSO-d6): δ 1.49 (s, 15H), 2.54 (s, 3H), 6.42 (d, J = 2 Hz, 1H), 6.49 (t, J = 7 Hz, 1H), 6.77 (d, J = 7 Hz, 1H), 6.86 (t, J = 7 Hz, 1H), 7.30 (d, J = 7 Hz, 1H), 7.36 (d, J = 2 Hz, 1H). ^{13}C{^{1}H} NMR (DMSO-d6): δ 8.08, 40.43, 90.95, 99.18, 116.07, 121.03, 122.50, 126.36, 126.49, 141.75, 142.95, 159.59. Anal. Calcd for $C_{21}H_{27}IrN_2O_2S$ (563.74): C, 44.74; H, 4.83; N, 4.97; S, 5.69. Found: C, 44.68; H, 4.79; N, 5.01; S, 5.71.
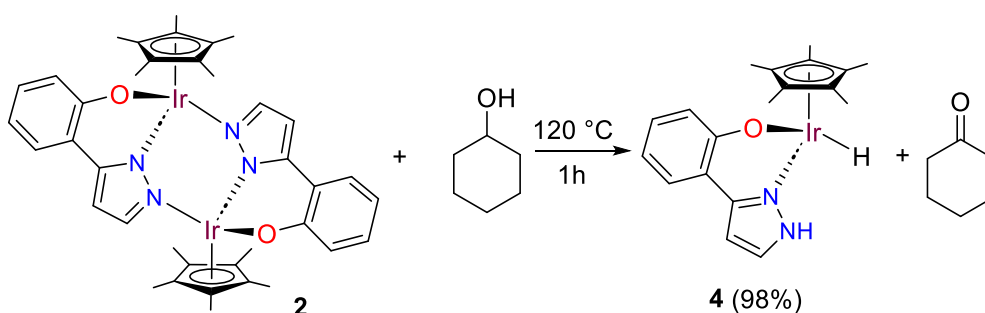
Synthesis of Complex 4. All manipulations were performed in glovebox under N_2 atmosphere using dry and degassed solvents. Excess cyclohexanol (1.0 mL, 10 mmol) was added to solid complex 2 (98 mg, 0.1 mmol). The resulted mixture was stirred at 120 °C for 1 h resulting in dark red solution. The solution was cooled down to r.t. and it was added dropwise to Et$_2$O while stirring vigorously. This resulted in a black-red precipitate and pale red solution. The liquid was decanted off (pale red was kept for further analysis) and the solid was dried to get the pure complex **4** (96 mg, 98%). ^{1}H NMR (CDCl$_3$): δ -13.20 (s, 1H), 1.83 (s, 15H), 6.26 (s, 1H), 6.76 (t, J = 7 Hz, 1H), 6.86 (s, 1H), 6.93 (d, J = 7 Hz, 1H), 7.00 (t, J = 7 Hz, 1H), 7.46 (d, J = 7 Hz, 1H), 13.76 (bs, 1H). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 11.49, 86.89, 91.64, 99.36, 116.25, 118.09, 120.13, 124.99, 126.13, 139.10, 152.13, 156.85. HRMS (ESI)

m/z for $C_{19}H_{23}IrN_2O$: 488.1522, found 488.1556 [M+]. Anal. Calcd for $C_{19}H_{23}IrN_2O$ (487.62): C, 46.88; H, 4.75; N, 5.75; S, 5.69. Found: C, 46.80; H, 4.75; N, 5.74.

General conditions for reaction optimization (Procedure A). Inside a glovebox, appropriate amount of phenylacetonitrile (S_1), cyclohexanol (A_1), KO*t*Bu, *p*-xylene (as internal standard) and complex 2 were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at appropriate temperature in a preheated oil bath for appropriate time. Thereafter, the reaction mixture was cooled down to r.t. and the product mixture was analysed by GC. Occasionally the crude product was purified by column chromatography using silica as stationary phase and a mixture of hexanes and ethylacetate (9.5:0.5) as eluent.

General condition for gram scale synthesis of P_{11} (Procedure B). Inside a glovebox, a mixture of phenylacetonitrile (1.17 g, 10.0 mmol), cyclohexanol (2.00 g, 20.0 mmol), KO*t*Bu (0.34 g, 0.30 mmol) and complex **2** (4.8 mg, 5 x 10^{-3} mmol) were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at 120 °C in a preheated oil bath for 1 h. Thereafter, the reaction mixture was cooled down to r.t. and the crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.5:0.5) as eluent) to give a colorless oil as product (1.62 g, 81%).

4.33 g of P_{11} (87%) was obtained by heating a mixture of phenylacetonitrile (2.93 g, 25.0 mmol), cyclohexanol (5.00 g, 50.0 mmol), KO*t*Bu (0.85 g, 0.75 mmol) and complex **2** (1.2 mg, 1.25 x 10^{-3} mmol).

General condition for substrate screening (Procedure C). Inside a glovebox, a mixture of organic nitrile (5.0 mmol), secondary alcohol (1.00 g, 10.0 mmol), KO*t*Bu (0.17 g, 0.15 mmol) and complex **2** (2.4 mg, 2.5 x 10^{-3} mmol) were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at 120 °C in a preheated oil bath for 1 h (occasionally 2 h). Thereafter, the reaction mixture was cooled down to r.t. and the

crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate or hexane and Et_2O as eluent) to give pure product.

Synthesis of 2-cyclohexylidene-2-phenylacetonitrile (P_{11}'). A mixture of 2-phenylacetonitrile (0.586 g, 5.0 mmol), cyclohexanone (0.491 g, 5.0 mmol) and KO*t*Bu (0.168 g, 1.5 mmol) was stirred in a pressure tube at 120 °C for 1 h under N_2 atmosphere. The mixture was cooled down to r.t. and the following work up was performed in air. From the reaction mixture, 2-cyclohexylidene-2-phenylacetonitrile (0.868 g, 88%) was purified by column chromatography (using silica as stationary phase and a mixture of hexanes and ethylacetate (9.5:0.5) as eluent). ^1H NMR ($CDCl_3$): δ 1.53-1.69 (m, 4H), 1.70-1.82 (m, 2H), 2.27-2.36 (m, 2H), 2.63-2.73 (m, 4H), 7.25-7.43 (m, 5H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 25.91, 27.94, 28.13, 31.30, 35.37, 107.75, 118.70, 128.21, 128.66, 129.26, 133.90, 161.93.

Synthesis of P_{11} by stoichiometric reaction of complex 4 and 2-cyclohexylidene-2-phenylacetonitrile. A mixture of complex **4** (49 mg, 0.1 mmol) and 2-cyclohexylidene-2-phenylacetonitrile (20 mg, 0.1 mmol) was stirred in a narrow pressure tube (2 mL) at 120 °C for 1 h under N_2 atmosphere. The mixture was cooled down to r.t. and the following work up was performed in air. From the reaction mixture, P_{11} (17 mg, 85%) was extracted in Et_2O (2 x 5 mL) and it was purified by column chromatography using silica as stationary phase and a mixture of hexanes and ethylacetate (9.5:0.5) as eluent. The yellow solid insoluble in Et_2O was found to be complex **2** (47 mg, 97%).

Synthesis of P_{11} by reaction of 2-cyclohexylidene-2-phenylacetonitrile and A_1 catalysed by complex 4. A mixture of complex **4** (2.4 mg, 0.005 mmol), 2-cyclohexylidene-2-phenylacetonitrile (99 mg, 0.50 mmol) and A_1 (56 mg, 0.55 mmol) was stirred in a pressure tube at 120 °C for 1 h under N_2 atmosphere. The mixture was cooled down to r.t. and the following work up was performed in air. From the reaction mixture, P_{11} (82 mg, 82%) was

purified by column chromatography using silica as stationary phase and a mixture of hexanes and ethylacetate (9.5:0.5) as eluent.

NMR data

Following known compounds are characterized by ^{1}H and ^{13}C{^{1}H} NMR spectroscopies and new compounds are characterized by ^{1}H and ^{13}C{^{1}H} NMR spectroscopies and HRMS:

2-cyclohexyl-2-phenylacetonitrile (P$_{11}$):[27] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.5:0.5) as eluent) to give pure product P$_{11}$ as colorless oil (0.798 g, 80%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.04-1.35 (m, 5H), 1.56-1.95 (m, 6H), 3.63 (d, J = 7 Hz, 1H), 7.27-7.42 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 25.81, 25.85, 25.95, 29.59, 31.23, 42.78, 44.35, 120.14, 127.91, 127.99, 128.80, 134.72.

2-cyclohexyl-2-(4-methoxylphenyl)acetonitrile (P$_{21}$):[19a] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.5:0.5) as eluent) to give pure product P$_{21}$ as colorless oil (0.894 g, 78%). ^{1}H NMR (400 MHz, CDCl$_3$): δ1.00-1.26 (m, 5H), 1.53-1.90 (m, 6H), 3.56 (d, J = 7 Hz, 1H), 3.81 (s, 3H), 6.89 (d, J = 8 Hz, 2H), 7.20 (d, J = 8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 25.94, 26.00, 26.06, 29.79, 31.22, 42.94, 43.65, 55.45, 114.27, 120.54, 126.79, 129.18, 159.33.

2-cyclohexyl-2-(4-methylphenyl)acetonitrile (P$_{31}$):[27] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.5:0.5) as eluent) to give pure product P$_{31}$ as colorless oil (0.798 g, 75%). ^{1}H NMR (400 MHz, CDCl$_3$): δ1.05-1.27 (m, 5H), 1.58-1.92 (m, 6H), 2.34 (s, 3H), 3.59 (d, J = 7 Hz, 1H), 7.12-7.21 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 21.00, 25.81, 25.86, 25.94, 29.60, 31.15, 42.74, 43.89, 120.25, 127.84, 129.42, 131.70, 137.60.

2-cyclohexyl-2-(3-methylphenyl)acetonitrile (P$_{41}$):[27] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as

eluent) to give pure product P_{41} as a colorless oil (0.724 g, 68%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.06-1.34 (m, 5H), 1.60-1.97 (m, 6H), 2.39 (s, 3H), 3.63 (d, *J* = 7 Hz, 1H), 7.03-7.16 (m, 3H), 7.23-7.31 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 21.32, 25.77, 25.83, 25.91, 29.56, 31.20, 42.67, 44.17, 120.16, 125.04, 128.56, 134.62, 138.48.

2-cyclohexyl-2-(3,4-dimethoxyphenyl)acetonitrile (P_{51}):[19a] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as eluent) to give pure product P_{51} as a colorless oil (1.011 g, 78%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.06-1.31 (m, 5H), 1.56-1.88 (m, 6H), 3.55 (d, *J* = 7 Hz, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 6.71-6.89 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 14.22, 22.76, 25.97, 29.84, 31.28, 42.93, 44.06, 56.11, 111.02, 111.27, 120.47, 127.20, 148.82, 149.26.

2-cyclohexyl-2-(4-chlorophenyl)acetonitrile (P_{61}):[27] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as eluent) to give pure product P_{61} as colorless oil (0.733 g, 63%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.96-1.29 (m, 5H), 1.49-1.84 (m, 6H), 3.54 (d, *J* = 7 Hz, 1H), 7.15 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 25.83, 25.86, 25.97, 29.58, 31.22, 42.84, 43.83, 119.79, 129.09, 129.41, 133.29, 134.02.

2-cyclohexyl-2-(4-bromophenyl)acetonitrile (P_{71}): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as eluent) to give pure product P_{71} as colorless oil (0.750 g, 54%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.98-1.30 (m, 5H), 1.49-1.85 (m, 6H), 3.59 (d, *J* = 7 Hz, 1H), 7.16 (d, *J* = 8 Hz, 2H), 7.50 (d, *J* = 8 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 25.90, 25.92, 26.04, 29.68, 29.83, 31.30, 42.88, 43.99, 119.68, 122.16, 129.78, 131.03, 132.04, 132.12, 133.91. HRMS (ESI) m/z for $C_{14}H_{16}BrNNa$: 300.0358, found 300.0309 [(M + Na)$^+$].

2-cyclohexyl-2-(3-chlorophenyl)acetonitrile (P_{81}):[27] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as

eluent) to give pure product P$_{81}$ as white solid (0.699 g, 60%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.97-1.28 (m, 5H), 1.48-1.84 (m, 6H), 3.54 (d, *J* = 7 Hz, 1H), 7.04-7.15 (m, 1H), 7.17-7.27 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 25.79, 25.82, 25.94, 29.53, 31.26, 42.75, 44.03, 119.56, 126.26, 128.29, 130.14, 134.81, 136.73.

2-cyclohexyl-2-(3-trifluromethylphenyl)acetonitrile (P$_{91}$):[27] Compound P91 was synthesized according to the general procedure C. Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.5:0.5) as eluent) to give pure product as colorless oil (0.560 g, 42%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.05-1.27 (m, 5H), 1.60-1.91 (m, 6H), 3.71 (d, *J* = 7 Hz, 1H), 7.37-7.71 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 25.79, 25.82, 25.95, 29.51, 31.31, 42.86, 44.29, 119.45, 124.86, 125.03, 129.52, 131.45, 135.90.

2-cyclohexyl-2-(3,4-methylenedioxyphenyl)acetonitrile (P$_{101}$): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.5:0.5) as eluent) to give pure product P$_{101}$ as colorless oil (0.876 g, 72%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.00-1.28 (m, 5H), 1.56-1.92 (m, 6H), 3.51 (d, *J* = 7 Hz, 1H), 5.98 (s, 2H), 6.67-6.81 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 25.85, 25.91, 25.96, 29.79, 31.13, 42.86, 44.01, 101.42, 108.32, 108.40, 120.28, 121.49, 128.40, 147.38, 148.11. HRMS (ESI) m/z for C$_{15}$H$_{17}$NNaO$_2$: 266.1157, found 266.1165 [(M + Na)$^+$].

2-cyclohexyl-2-(2-napthyl)acetonitrile (P$_{111}$):[19a] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.8:0.2) as eluent) to give pure product P$_{111}$ a white solid (0.994 g, 80%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.00-1.28 (m, 5H), 1.59-1.97 (m, 6H), 3.81 (d, *J* = 7 Hz, 1H), 7.34-7.41 (m, 1H), 7.46-7.56 (m, 2H), 7.75-7.90 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 25.94, 25.96, 26.09, 29.72, 29.85, 31.48, 42.87, 44.62, 120.28, 125.60, 126.53, 126.78, 127.22, 127.83, 127.99, 128.83, 132.15, 132.88, 133.27**.**

2-cyclopentyl-2-phenylacetonitrile (P$_{12}$):[28] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.0:1.0) as eluent) to give pure product P$_{12}$ as colorless oil (0.778 g, 84%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.29-1.40 (m, 1H), 1.48-1.78 (m, 6H), 1.80-1.91 (m, 1H), 2.24-2.38 (m, 1H), 3.72 (d, J = 7 Hz, 1H), 7.27-7.40 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 24.91, 24.98, 30.32, 31.05, 42.56, 45.35, 120.64, 127.69, 128.01, 129.00, 135.96.

2-cyclopentyl-2-(4-methylphenyl)acetonitrile (P$_{32}$): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.7:0.3) as eluent) to give pure product P$_{32}$ as colorless oil (0.747 g, 75%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.28-1.40 (m, 1H), 1.47-1.77 (m, 6H), 1.79-1.90 (m, 1H), 2.24-2.39 (m, 4H), 3.67 (d, J = 7 Hz, 1H), 7.11-7.27 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 21.17, 24.96, 25.01, 30.36, 31.05, 42.42, 45.37, 120.85, 127.60, 129.67, 132.98, 137.80. HRMS (ESI) m/z for C$_{14}$H$_{17}$NNa: 222.1253, found 222.1250 [(M + Na)$^+$].

2-cyclopentyl-2-(3-methylphenyl)acetonitrile (P$_{42}$): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.8:0.2) as eluent) to give pure product P$_{42}$ as colorless oil (0.727 g, 73%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.28-1.40 (m, 1H), 1.48-1.75 (m, 6H), 1.79-1.90 (m, 1H), 2.21-2.43 (m, 4H), 3.67 (d, J = 7 Hz, 1H), 7.07-7.16 (m, 3H), 7.20-7.25 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 21.52, 24.95, 25.01, 30.38, 31.11, 42.54, 45.35, 120.80, 124.81, 128.37, 128.87, 135.90, 138.82. HRMS (ESI) m/z for C$_{14}$H$_{17}$NNa: 222.1253, found 222.1249 [(M + Na)$^+$].

2-cyclopentyl-2-(3,4-dimethoxyphenyl)acetonitrile (P$_{52}$):[28] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (8.5:1.5) as eluent) to give pure product P$_{52}$ as colorless oil (0.981 g, 80%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.28-1.40 (m, 1H), 1.47-1.77 (m, 6H), 1.79-1.90 (m, 1H), 2.22-2.37 (m, 1H), 3.63 (d, J = 7 Hz, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 6.74-6.88 (m, 3H). ^{13}C{^{1}H} NMR (101

MHz, CDCl$_3$): δ 24.97, 25.01, 30.43, 31.04, 42.21, 45.39, 110.66, 111.36, 120.04, 120.86, 128.42, 148.82, 149.33.

2-cyclopentyl-2-(4-chlorophenyl)acetonitrile (P$_{62}$):[29] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et2O (9.8:0.2) as eluent) to give pure product **P$_{62}$** as colorless oil (0.714 g, 65%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.25-1.38 (m, 1H), 1.48-1.77 (m, 6H), 1.78-1.89 (m, 1H), 2.21-2.36 (m, 1H), 3.70 (d, *J* = 7 Hz, 1H), 7.22-7.30 (m, 2H), 7.31-7.38 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 24.91, 25.00, 30.28, 31.04, 42.01, 45.30, 120.20, 129.05, 129.23, 134.04, 134.48.

2-cyclopentyl-2-(3,4-methylenedioxyphenyl)acetonitrile (P$_{102}$): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.8:0.2) as eluent) to give pure product **P$_{102}$** as colorless oil (0.858 g, 75%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.22-1.35 (m, 1H), 1.45-1.75 (m, 6H), 1.78-1.90 (m, 1H), 2.18-2.32 (m, 1H), 3.59 (d, *J* = 7 Hz, 1H), 5.95 (s, 2H), 6.72-6.82 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 24.85, 24.89, 30.32, 30.87, 42.14, 45.32, 101.37, 107.95, 108.45, 120.66, 121.05, 129.59, 147.33, 148.12. HRMS (ESI) m/z for C$_{14}$H$_{15}$NNaO$_2$: 252.0995, found 252.0988 [(M + Na)$^+$].

2-cycloheptyl-2-phenylacetonitrile (P$_{13}$): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.8:0.2) as eluent) to give pure product **P$_{13}$** as colorless oil (0.916 g, 86%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.35-1.61 (m, 8H), 1.63-1.84 (m, 4H), 1.90-2.03 (m, 1H), 3.74 (d, *J* = 7 Hz, 1H), 7.27-7.40 (m, 5H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ25.94, 26.09, 27.67, 27.73, 30.55, 33.05, 44.41, 44.64, 120.26, 127.78, 127.87, 128.73, 135.11. HRMS (ESI) m/z for C$_{15}$H$_{19}$NNa: 236.1410, found 236.1414 [(M + Na)$^+$].

2-cycloheptyl-2-(3-methylphenyl)acetonitrile (P$_{43}$): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate

(9.8:0.2) as eluent) to give pure product **P₄₃** as a colorless oil (0.954 g, 84%). ^{1}H NMR (400 MHz, CDCl₃): δ1.30-1.65 (m, 8H), 1.66-1.86 (m, 4H), 1.88-2.05 (m, 1H), 3.70 (d, J = 7 Hz, 1H), 7.05-7.15 (m, 3H), 7.17-7.32 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl₃): δ 21.44, 26.05, 26.20, 27.78, 27.84, 30.66, 33.21, 44.51, 44.73, 120.50, 125.06, 128.62, 128.67, 135.10, 138.59. HRMS (ESI) m/z for $C_{16}H_{21}NNa$: 250.1566, found 250.1566 [(M + Na)$^+$].

2-cycloheptyl-2-(3,4-dimethoxyphenyl)acetonitrile (P₅₃): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (7.5:2.5) as eluent) to give pure product **P₅₃** as colorless oil (0.930 g, 68%). ^{1}H NMR (400 MHz, CDCl₃): δ 1.34-1.61 (m, 8H), 1.65-1.85 (m, 4H), 1.86-1.97 (m, 1H), 3.64 (d, J = 7 Hz, 1H), 3.87 (s, 3H), 3.89 (s, 3H), 6.75-6.88 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl₃): δ 26.26, 26.29, 27.88, 27.95, 30.92, 33.11, 44.48, 44.67, 56.05, 56.13, 111.02, 111.30, 120.47, 120.69, 127.69, 148.79, 149.26. HRMS (ESI) m/z for $C_{17}H_{23}NNaO_2$: 296.1621, found 296.1627 [(M + Na)$^+$].

2-cycloheptyl-2-(4-chlorophenyl)acetonitrile (P₆₃): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.8:0.2) as eluent) to give pure product **P₆₃** as colorless oil (0.867 g, 70%). ^{1}H NMR (400 MHz, CDCl₃): δ 1.32-1.61 (m, 8H), 1.63-1.81 (m, 4H), 1.87-1.99 (m, 1H), 3.70 (d, J = 7 Hz, 1H), 7.22-7.28 (m, 2H), 7.31-7.38 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl₃): δ 26.17, 26.32, 27.85, 27.92, 30.81, 33.25, 44.38, 44.67, 119.99, 129.28, 129.44, 133.86, 134.10. HRMS (ESI) m/z for $C_{15}H_{18}ClNNa$: 270.1020, found 270.1023 [(M + Na)$^+$].

2-cycloheptyl-2-(3,4-methylenedioxyphenyl)acetonitrile (P₁₀₃): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and ethylacetate (9.0:1.0) as eluent) to give pure product **P₁₀₃** as a pale yellow oil (0.940 g, 73%). ^{1}H NMR (400 MHz, CDCl₃): δ 1.30-1.60 (m, 8H), 1.61-1.83 (m, 4H), 1.83-1.96 (m, 1H), 3.60 (d, J = 7 Hz, 1H), 5.95 (s, 2H), 6.68-6.80 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl₃): δ

26.03, 26.15, 27.76, 27.82, 30.80, 32.92, 44.37, 44.55, 101.38, 108.22, 108.34, 120.45, 121.44, 128.86, 147.29, 148.08. HRMS (ESI) m/z for $C_{16}H_{19}NNaO_2$: 2801306, found 280.1311 [(M + Na)$^+$].

3-ethyl-2-(4-methylphenyl)pentanenitrile (P$_{34}$):[19a] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as eluent) to give pure product **P$_{34}$** as colorless oil (0.764 g, 76%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.87 (t, *J* = 8 Hz, 3H), 0.95 (t, *J* = 8 Hz, 3H), 1.34-1.57 (m, 5H), 2.35 (s, 3H), 3.87 (d, *J* = 7 Hz, 1H), 7.10-7.25 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 11.09, 11.20, 21.16, 22.63, 23.25, 40.43, 46.31, 120.33, 127.92, 129.61, 132.14, 137.71.

3-ethyl-2-(3-methylphenyl)pentanenitrile (P$_{44}$):[27] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as eluent) to give pure product **P$_{44}$** as colorless oil (0.734 g, 73%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.87 (t, *J* = 8 Hz, 3H), 0.97 (t, *J* = 8 Hz, 3H), 1.36-1.58 (m, 4H), 1.64-1.73 (m, 1H), 2.37 (s, 3H), 3.88 (d, *J* = 7 Hz, 1H), 7.06-7.17 (m, 3H), 7.22-7.29 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 11.06, 11.20, 21.52, 22.63, 23.27, 40.73, 46.28, 120.23, 125.12, 128.68, 128.78, 135.10, 138.72.

3-ethyl-2-(3,4-dimethoxyphenyl)pentanenitrile (P$_{54}$):[19a] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.0:1.0) as eluent) to give pure product **P$_{54}$** as colorless oil (0.667 g, 54%). ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.87 (t, *J* = 8 Hz, 3H), 0.94 (t, *J* = 8 Hz, 3H), 1.34-1.59 (m, 5H), 3.63 (d, *J* = 7 Hz, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 6.72-6.89 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 11.05, 11.16, 22.71, 23.19, 29.83, 40.49, 46.27, 56.07, 56.15, 111.01, 111.36, 120.45, 127.55, 148.40, 149.32.

3-ethyl-2-(4-chlorophenyl)pentanenitrile (P$_{64}$):[19a] Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as

eluent) to give pure product **P_{64}** as colorless oil (0.698 g, 63%). ^{1}H NMR (400 MHz, CDCl$_3$):

δ 0.86 (t, J = 8 Hz, 3H), 0.96 (t, J = 8 Hz, 3H), 1.34-1.54 (m, 4H), 1.60-1.71 (m, 1H), 3.89 (d,

J = 7 Hz, 1H), 7.17-7.42 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ 11.11, 11.23, 22.64,

23.34, 40.31, 46.42, 119.69, 129.20, 129.39, 133.74, 134.01.

3-ethyl-2-(3-chlorophenyl)pentanenitrile (P_{84}): Crude product was purified by column

chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.0:1.0) as

eluent) to give pure product **P_{84}** as colorless oil (0.709 g, 64%). ^{1}H NMR (400 MHz, CDCl$_3$):

δ 0.87 (t, J = 8 Hz, 3H), 0.97 (t, J = 8 Hz, 3H), 1.35-1.57 (m, 4H), 1.62-1.72 (m, 1H), 3.89 (d,

J = 7 Hz, 1H), 7.18-7.25 (m, 1H), 7.28-7.35 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$): δ

11.08, 11.24, 22.65, 23.36, 40.55, 46.36, 119.46, 126.27, 128.32, 130.25, 134.97, 137.23.

HRMS (ESI) m/z for C$_{13}$H$_{16}$ClNNa: 244.0863, found 244.0861 [(M + Na)$^+$].

3-methyl-2-phenylheptanenitrile (P_{15}): Crude product was purified by column

chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as

eluent) to give pure product P$_{15}$ (mixture of two diastereomers) as colorless oil (0.775 g,

77%). ^{1}H NMR (400 MHz, CDCl$_3$) (m$_j$: major isomer, m$_n$: minor isomer): δ 0.84 (m$_n$), 0.91

(m$_j$) (two t, J = 8 Hz, 3H), 0.96 (m$_j$), 1.00 (m$_n$) (two d, J = 8 Hz, 3H), 1.25-1.57 (m, 6H),

1.85-2.01 (m, 1H), 3.69 (m$_n$), 3.86 (m$_j$) (two d, J = 8 Hz, 1H), 7.27-7.60 (m, 5H). ^{13}C{^{1}H}

NMR (101 MHz, CDCl$_3$): δ 14.10, 15.83, 17.58, 22.73, 29.32, 34.81, 38.76, 43.57, 44.32,

119.62, 127.88, 127.94, 128.19, 128.92, 134.78, 135.19. HRMS (ESI) m/z for C$_{14}$H$_{19}$NNa:

224.1410, found 224.1416 [(M + Na)$^+$].

3-methyl-2-(3-methylphenyl)heptanenitrile (P_{45}): Crude product was purified by column

chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as

eluent) to give pure product P$_{45}$ (mixture of two diastereomers) as colorless oil (0.829 g,

77%). ^{1}H NMR (400 MHz, CDCl$_3$) (m$_j$: major isomer, m$_n$: minor isomer): δ 0.90 (mn), 0.95

(m$_j$) (two t, J = 8 Hz, 3H), 0.99 (m$_j$), 1.02 (m$_n$) (two d, J = 8 Hz, 3H), 1.26-1.59 (m, 6H),

1.88-2.04 (m, 1H), 3.67 (m_n), 3.84 (m_j) (two d, J = 8 Hz, 1H), 7.05-7.33 (m, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$): δ 14.07, 14.10, 15.83, 17.51, 21.12, 22.73, 29.31, 32.67, 34.76, 38.29, 38.71, 43.19, 43.90, 119.80, 120.57, 127.74, 128.04, 129.15, 129.27, 129.53, 129.55, 131.70, 132.13, 137.66, 137.77. HRMS (ESI) m/z for C$_{15}$H$_{21}$NNa: 238.1566, found 238.1575 [(M + Na)$^+$].

3-methyl-2-(4-chlorophenyl)heptanenitrile (P$_{65}$): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as eluent) to give pure product P$_{65}$ (mixture of two diastereomers) as colorless oil (0.707 g, 60%). ^1H NMR (400 MHz, CDCl$_3$) (m$_j$: major isomer, m$_n$: minor isomer): δ 0.86 (m$_j$), 0.90 (m$_n$) (two t, J = 8 Hz, 3H), 0.95 (m$_n$), 0.99 (m$_j$) (two d, J = 8 Hz, 3H), 1.15-1.40 (m, 6H), 1.83-2.01 (m, 1H), 3.67 (m$_j$), 3.83 (m$_n$) (two d, J = 8 Hz, 1H), 7.11-7.28 (m, 2H), 7.29-7.47 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$): δ 14.08, 15.80, 17.55, 22.73, 29.10, 29.32, 29.84, 32.61, 34.77, 38.36, 38.80, 43.06, 43.77, 119.97, 129.14, 129.24, 129.53, 133.29, 134.13. HRMS (ESI) m/z for C$_{14}$H$_{18}$ClNNa: 258.1025, found 258.1020 [(M + Na)$^+$].

3-methyl-2-(3,4-methylenedioxyphenyl)heptanenitrile (P$_{105}$): Crude product was purified by column chromatography (silica as stationary phase and a mixture of hexanes and Et$_2$O (9.8:0.2) as eluent) to give pure product P$_{105}$ (mixture of two diastereomers) as colorless oil (0.821 g, 67%). ^1H NMR (400 MHz, CDCl$_3$) (m$_j$: major isomer, m$_n$: minor isomer): δ 0.86 (m$_n$), 0.89 (m$_j$) (two t, J = 8 Hz, 3H), 0.95 (two d, J = 8 Hz, 3H), 1.16-1.40 (m, 6H), 1.78-1.95 (m, 1H), 3.57 (m$_n$), 3.73 (m$_j$) (two d, J = 8 Hz, 1H), 5.95 (m$_j$), 6.01 (m$_n$) (two s, 1H), 7.11-7.28 (m, 2H), 7.29-7.47 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$): δ 14.02, 15.83, 17.35, 22.65, 29.02, 29.19, 32.67, 34.54, 38.32, 38.70, 43.19, 43.86, 101.39, 108.14, 108.35, 108.38, 119.66, 120.39, 121.21, 121.56, 128.37, 128.77, 129.53, 147.28, 147.36, 148.10. HRMS (ESI) m/z for C$_{15}$H$_{19}$NNaO$_2$: 268.1313, found 268.1310 [(M + Na)$^+$].

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NMR spectra of complexes and some products:
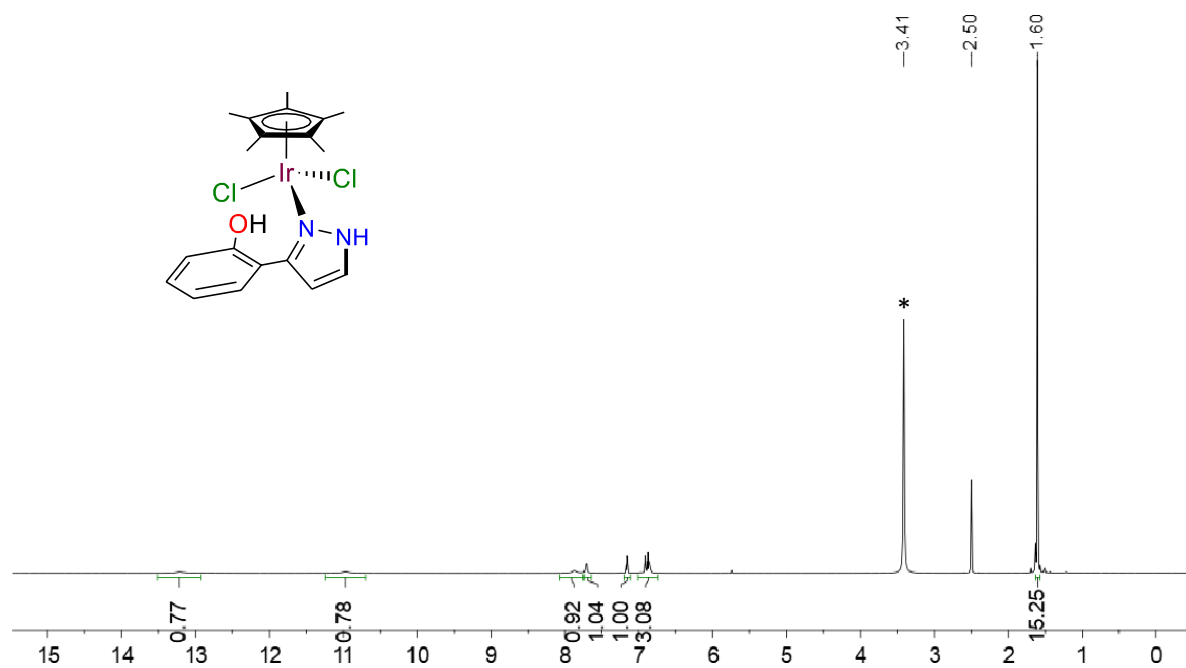
Figure 2.1 ^{1}H NMR (400 MHz) spectrum of complex **1** in DMSO-d6 at r.t.
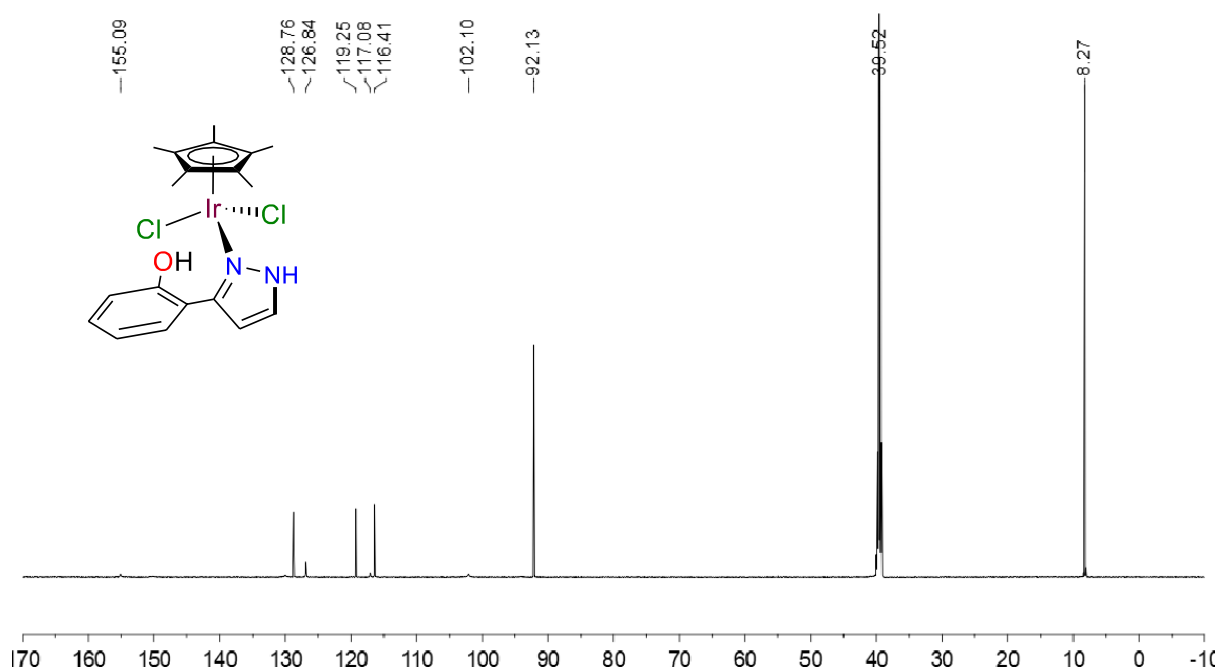
Figure 2.2 ^{13}C{^{1}H} NMR (101 MHz) spectrum of complex **1** in DMSO-d6 at r.t.
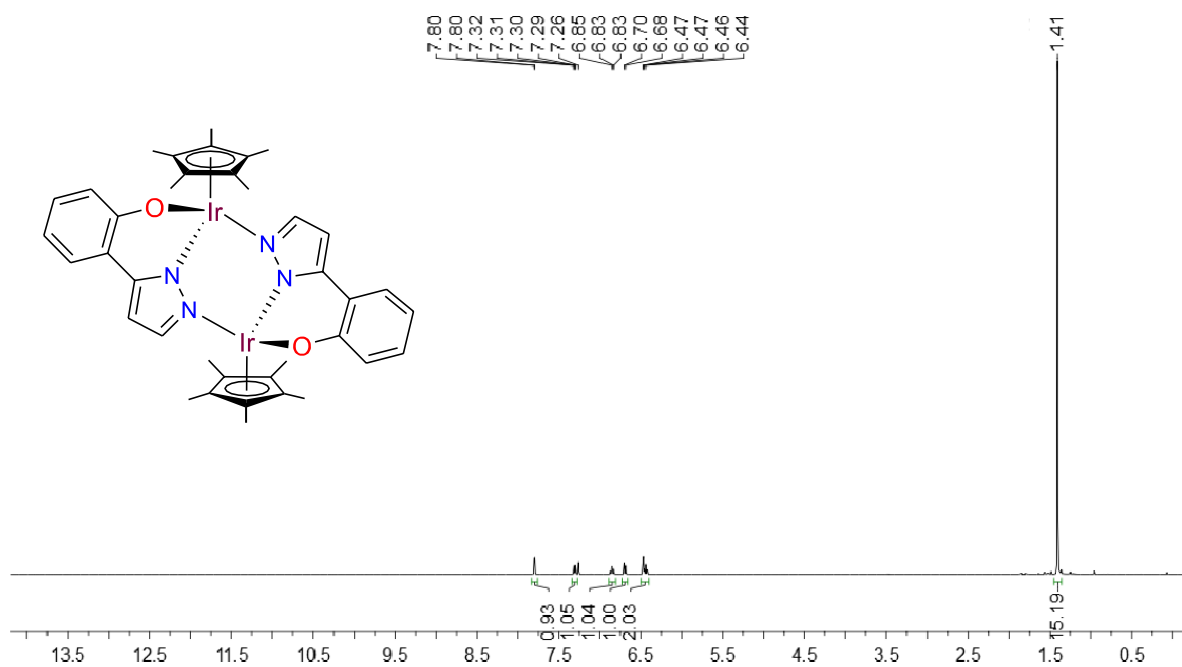
Figure 2.3 ^{1}H NMR (400 MHz) spectrum of complex **2** in CDCl$_3$ at r.t.
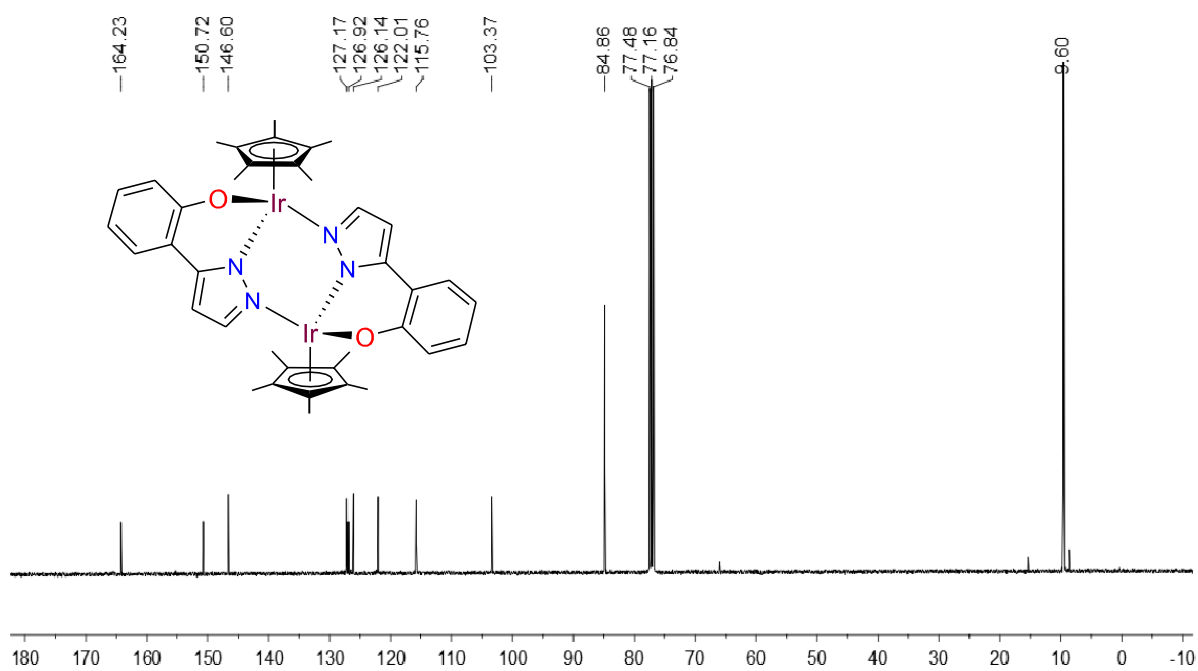
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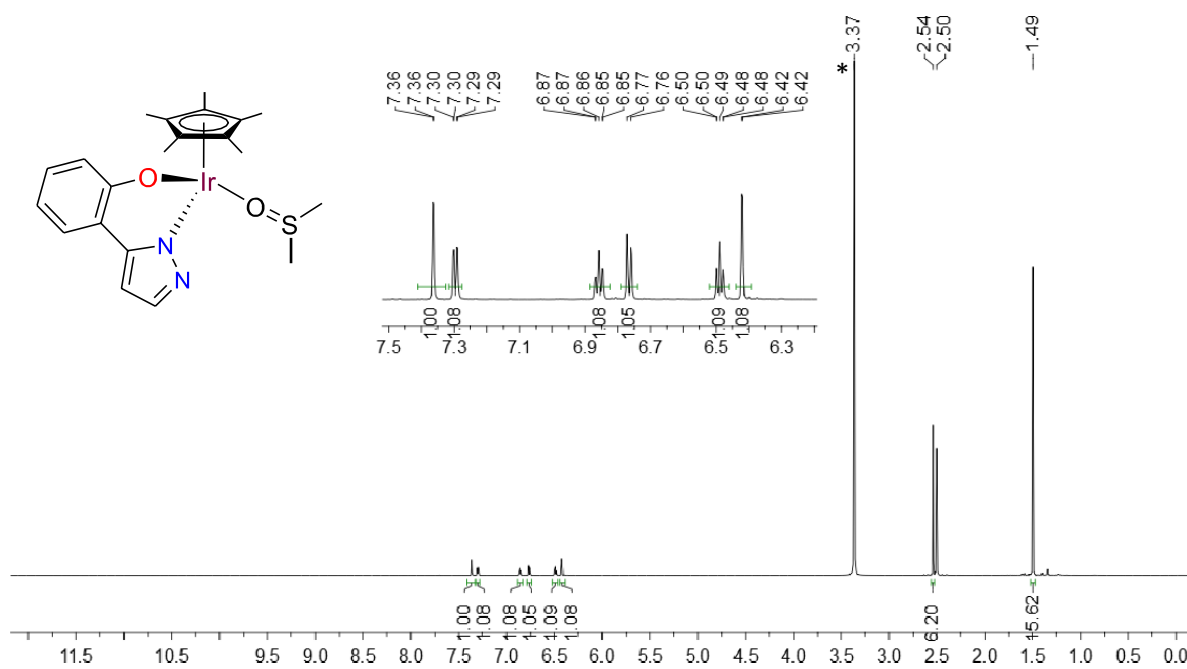
Figure 2.5 ^{1}H NMR (400 MHz) spectrum of complex **3** in DMSO-d6 at r.t. (* indicates H₂O).
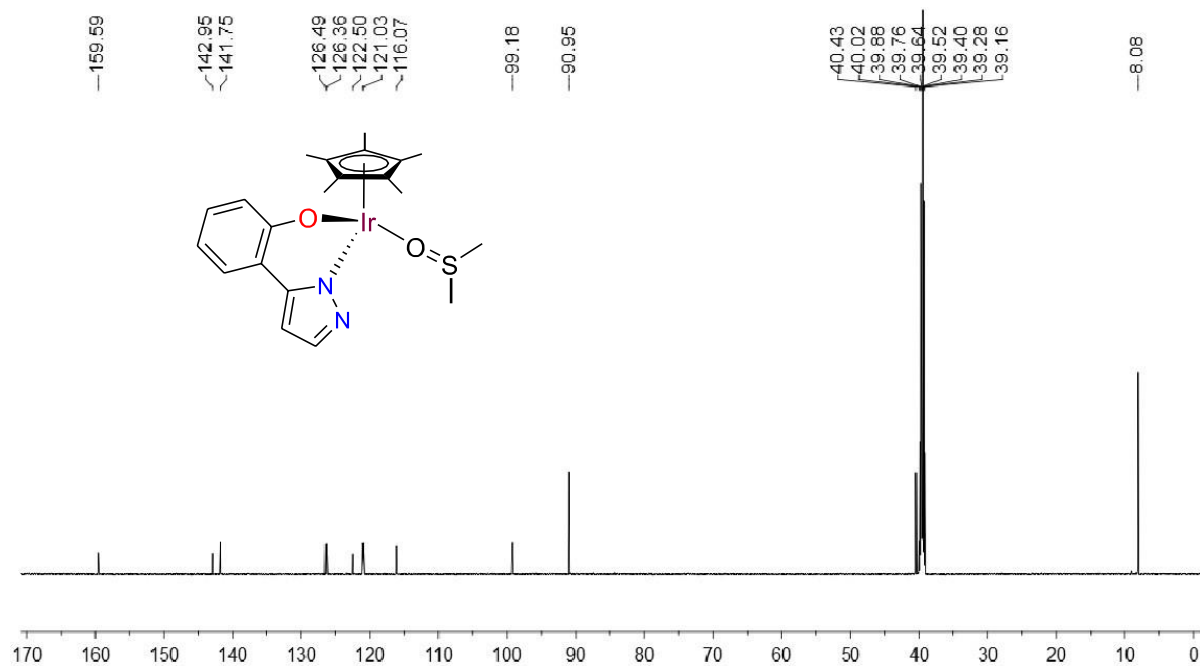
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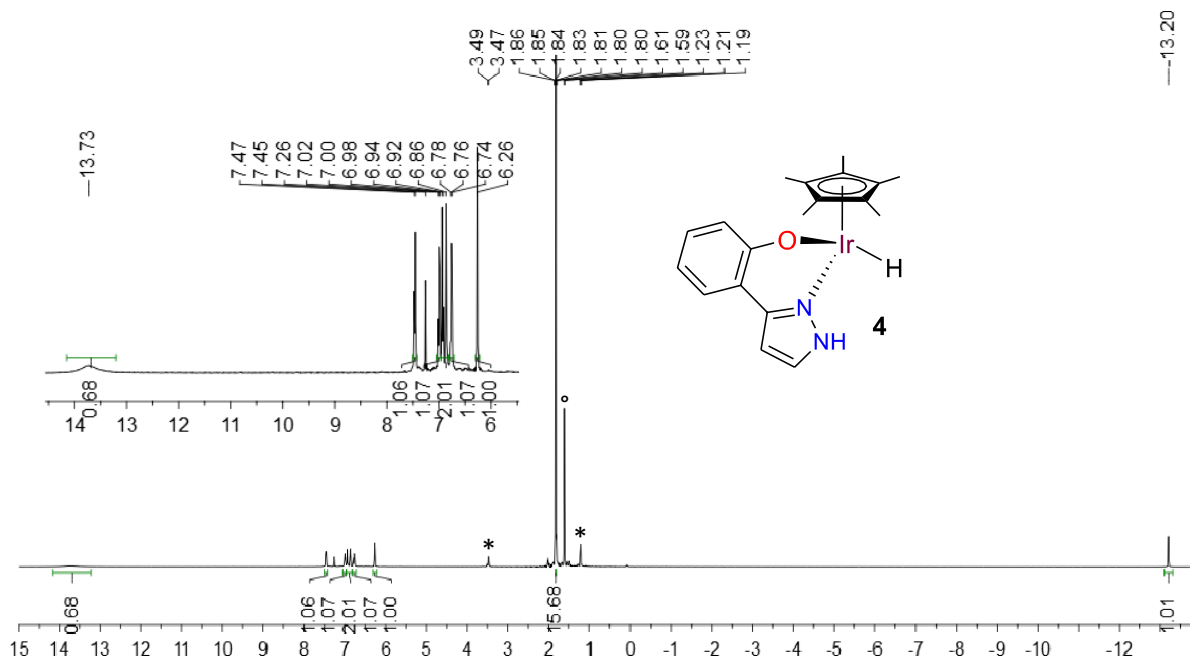
Figure 2.7 ^{1}H NMR (400 MHz) spectrum of complex **4** in CDCl$_3$ at r.t.
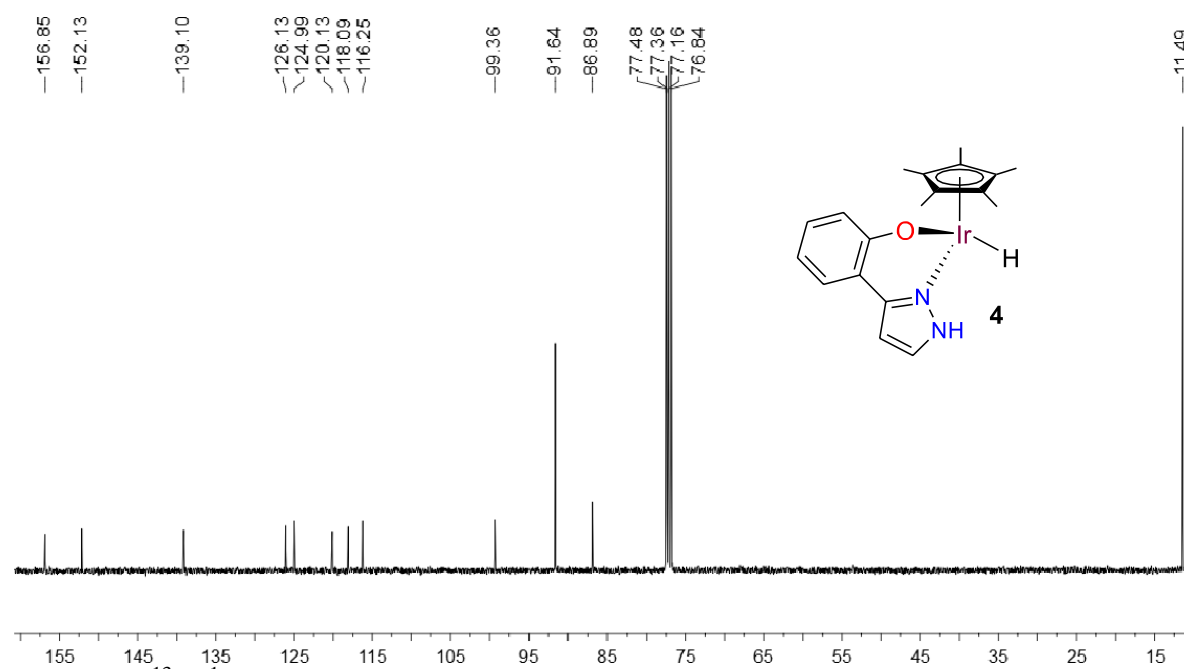
Figure 2.8 ^{13}C{^{1}H} NMR (101 MHz) spectrum of complex **4** in CDCl$_3$ at r.t.
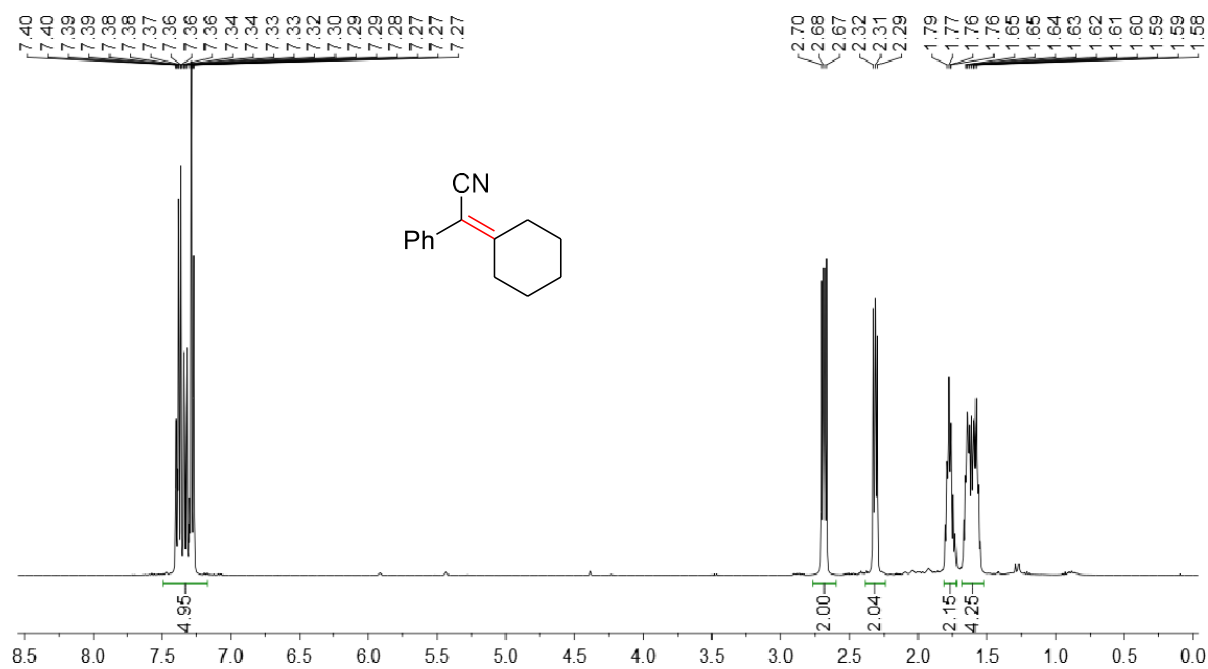
Figure 2.9 ^{1}H NMR (400 MHz) spectrum of **2**-cyclohexylidene-2-phenylacetonitrile (**P$_{11'}$**) in CDCl$_3$ at r.t.
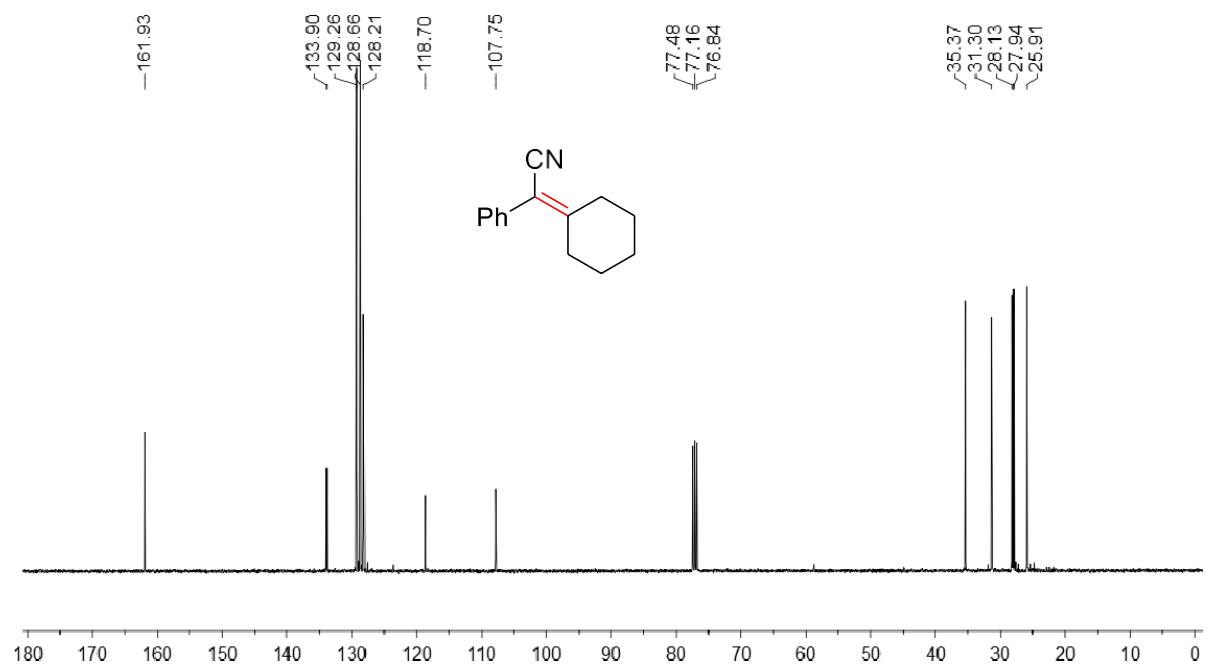
Figure 2.10 ^{13}C{^{1}H} NMR spectrum of 2-cyclohexylidene-2-phenylacetonitrile (**P$_{11'}$**) in CDCl$_3$ at r.t.
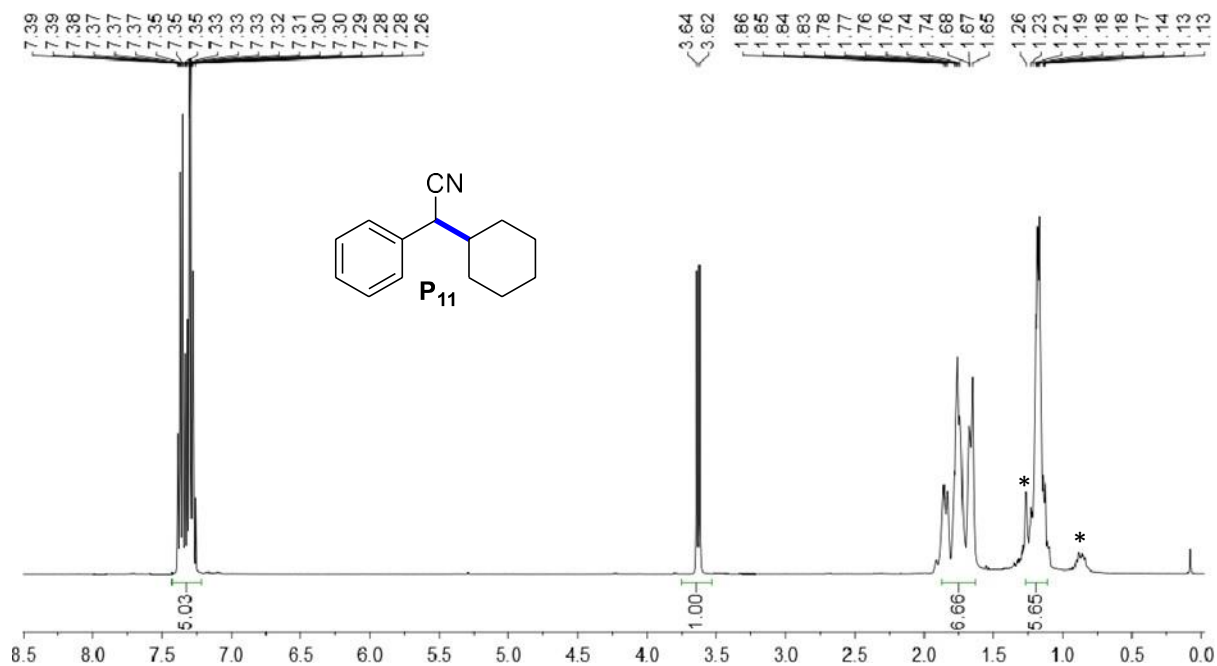
Figure 2.11 ^{1}H NMR (400 MHz) spectrum of 2-cyclohexyl-2-phenylacetonitrile (**P$_{11}$**) in CDCl$_3$ at r.t. (* indicates H-grease).
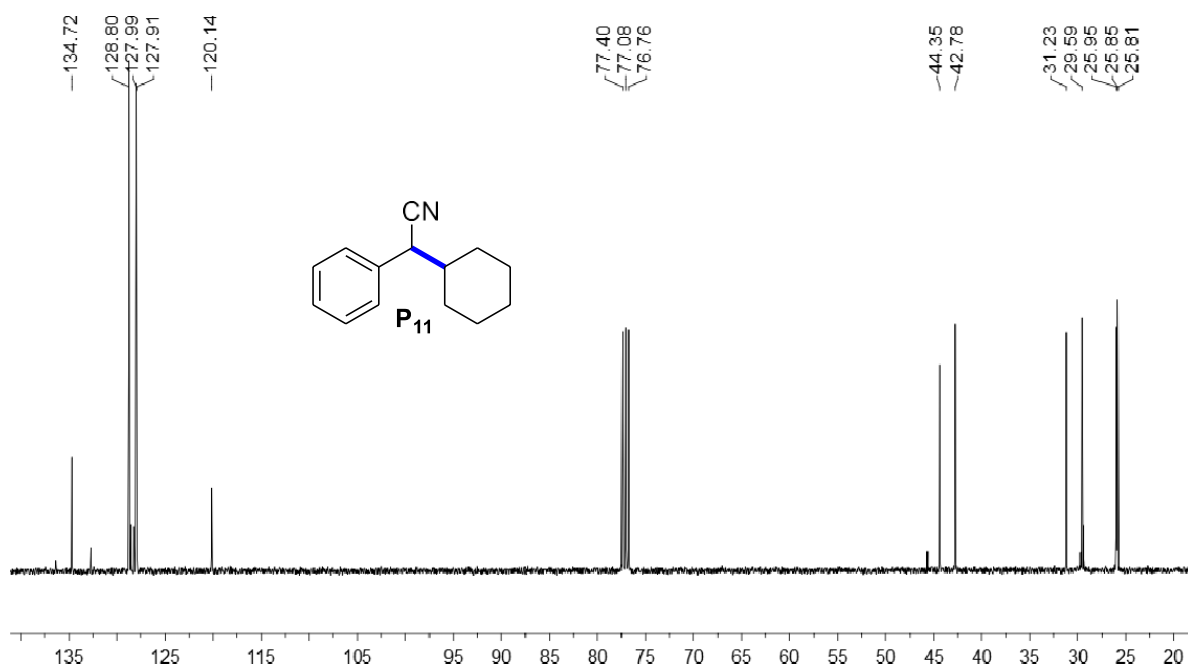
Figure 2.12 ^{13}C{^{1}H} NMR spectrum of 2-cyclohexyl-2-phenylacetonitrile (**P$_{11}$**) in CDCl$_3$ at r.t.
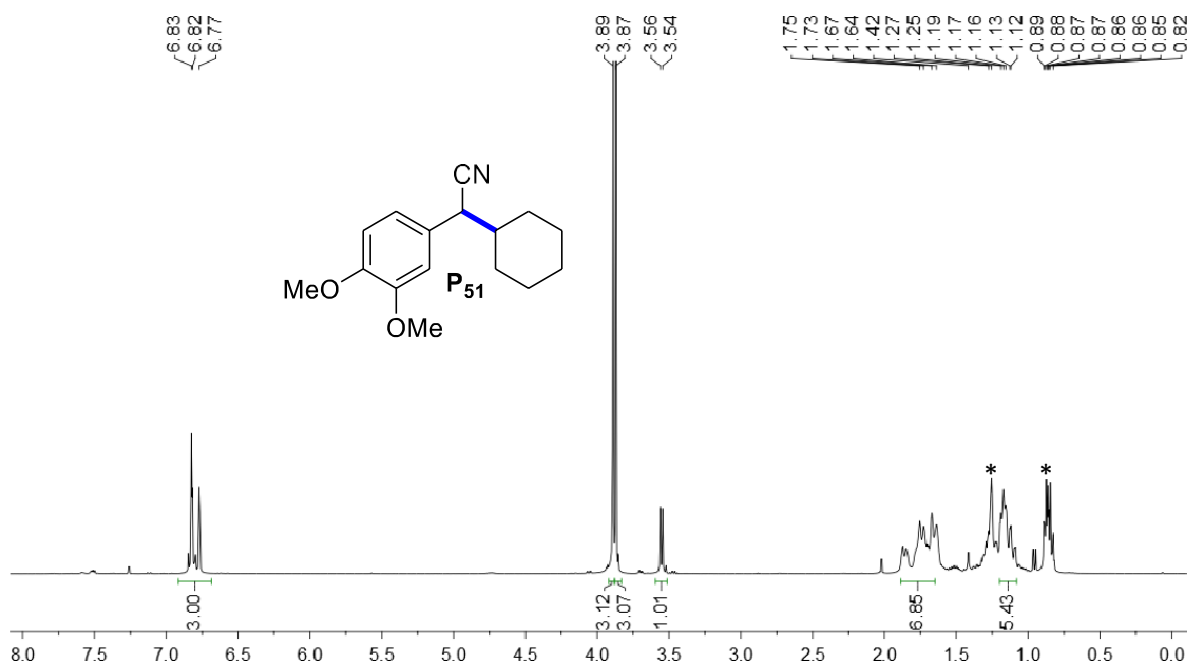
Figure 2.13 ^{1}H NMR (400 MHz) spectrum of 2-cyclohexyl-2-(3,4-dimethoxyphenyl) acetonitrile (**P$_{51}$**) in CDCl$_3$ at r.t.. (* indicates H-grease).
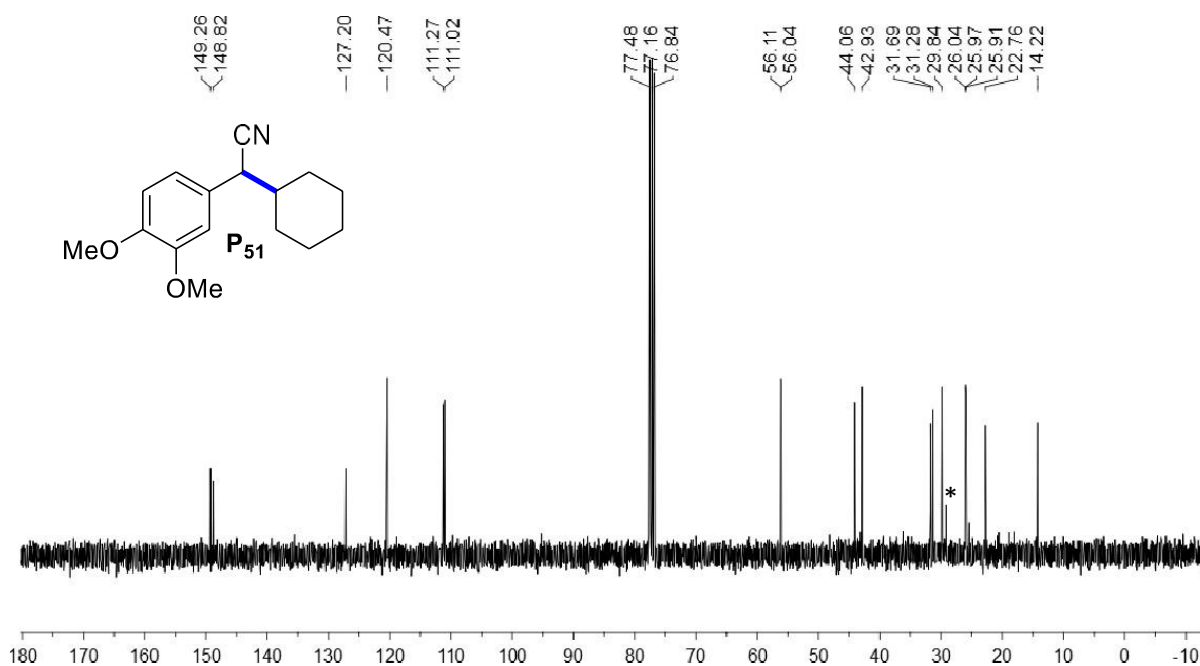
Figure 2.14 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 2-cyclohexyl-2-(3,4-dimethoxyphenyl) acetonitrile (**P$_{51}$**) in CDCl$_3$ at r.t. (* indicates H-grease).
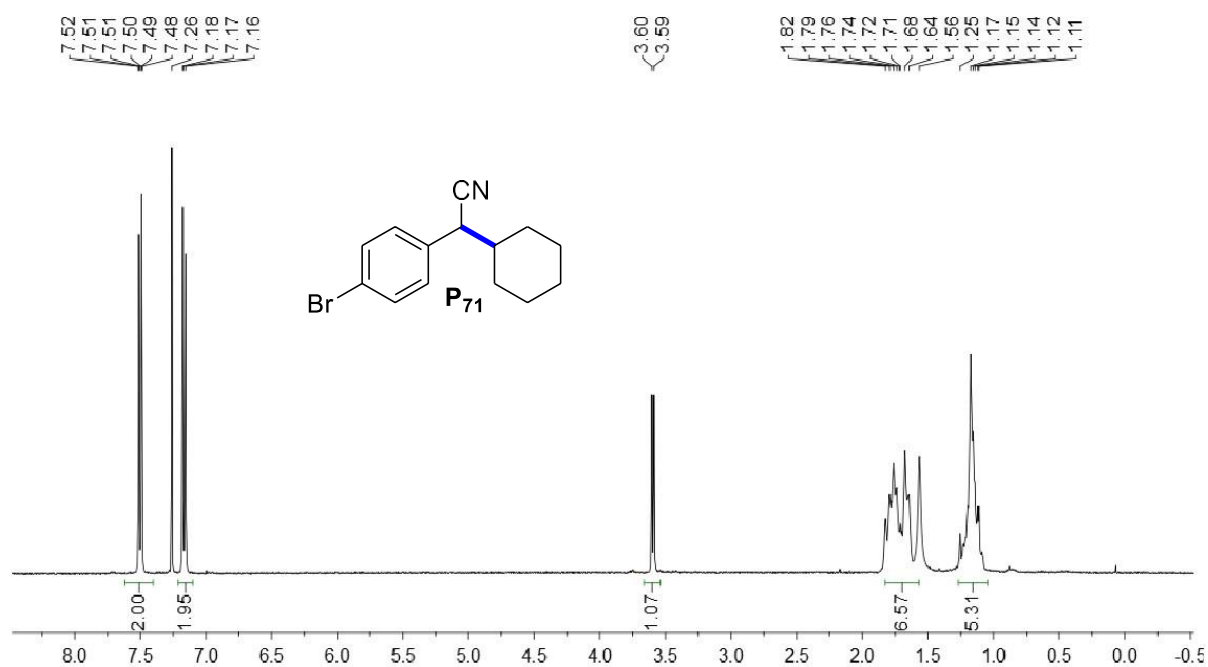
Figure 2.15 ^{1}H NMR (400 MHz) spectrum of 2-cyclohexyl-2-(4-bromophenyl)acetonitrile (**P$_{71}$**) in CDCl$_3$ at r.t.
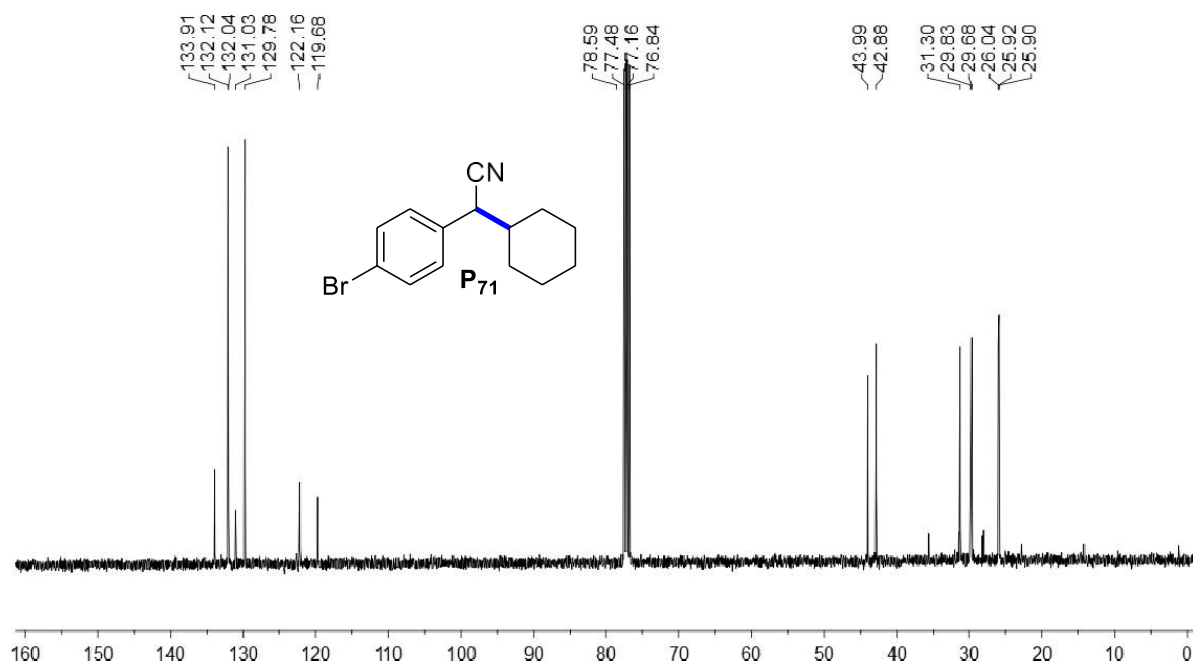
Figure 2.16 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 2-cyclohexyl-2-(4-bromophenyl)acetonitrile (**P$_{71}$**) in CDCl$_3$ at r.t.
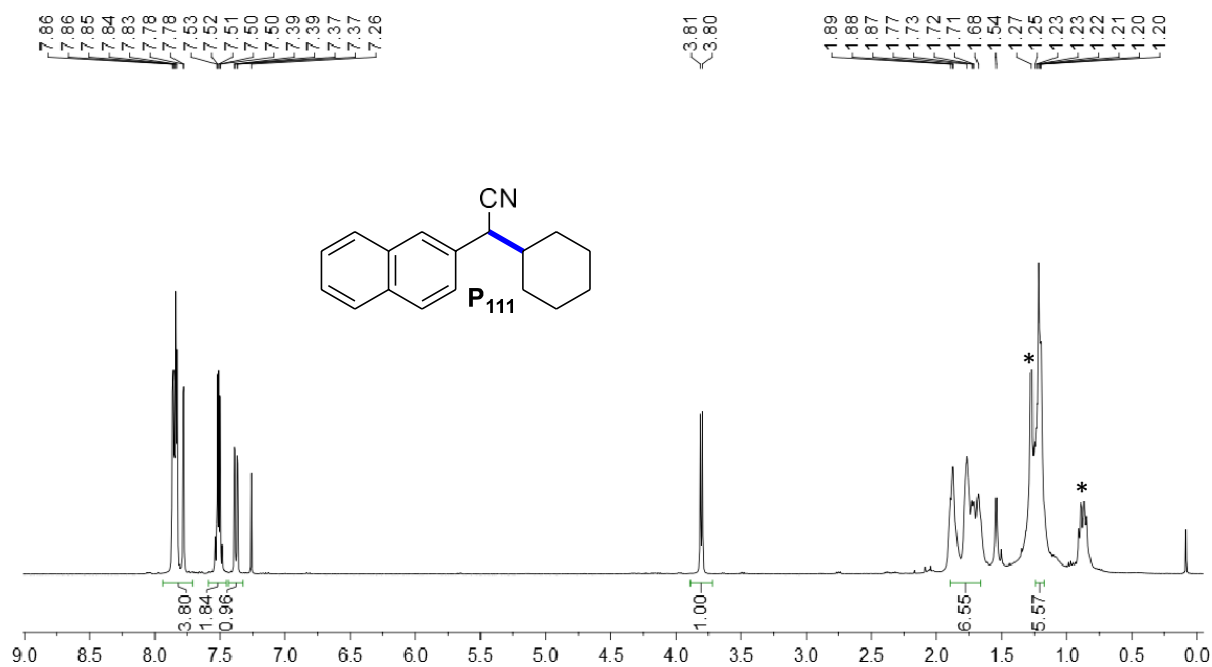
Figure 2.17 ^{1}H NMR (400 MHz) spectrum of 2-cyclohexyl-2-(2-napthyl)acetonitrile (**P$_{111}$**) in CDCl$_3$ at r.t. (* indicates H-grease).
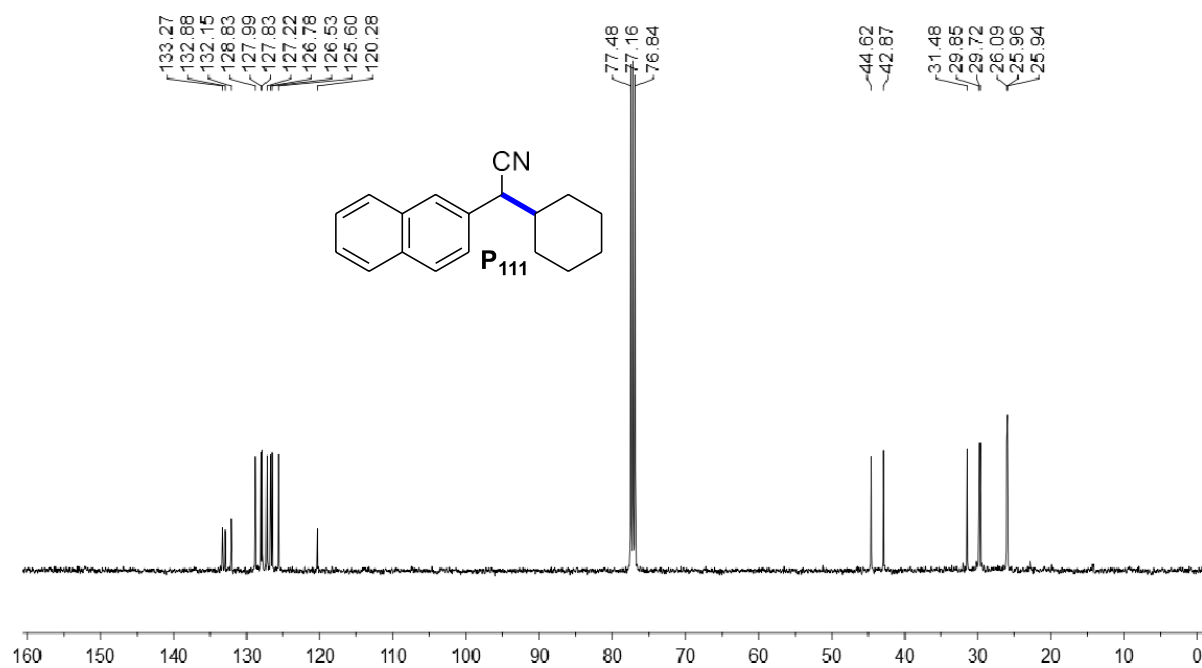
Figure 2.18 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 2-cyclohexyl-2-(2-napthyl)acetonitrile (**P$_{111}$**) in CDCl$_3$ at r.t.
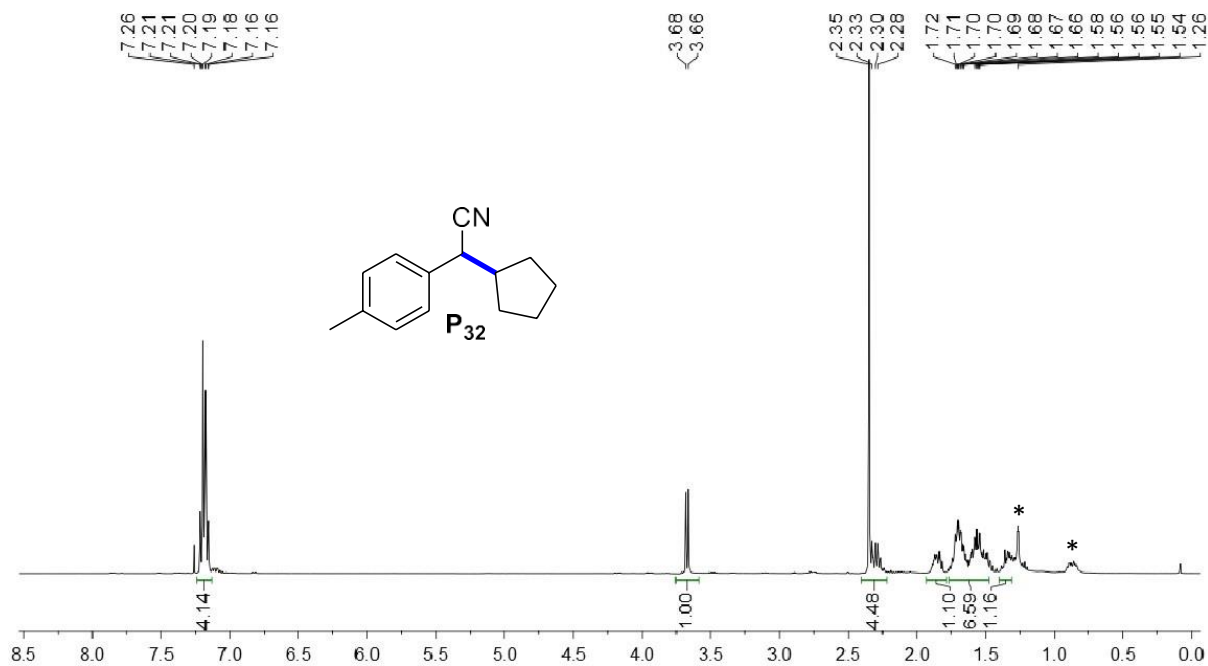
Figure 2.19 ^{1}H NMR (400 MHz) spectrum of -cyclopentyl-2-(4-methylphenyl)acetonitrile (**P32**) in CDCl3 at r.t. (* indicates H-grease).
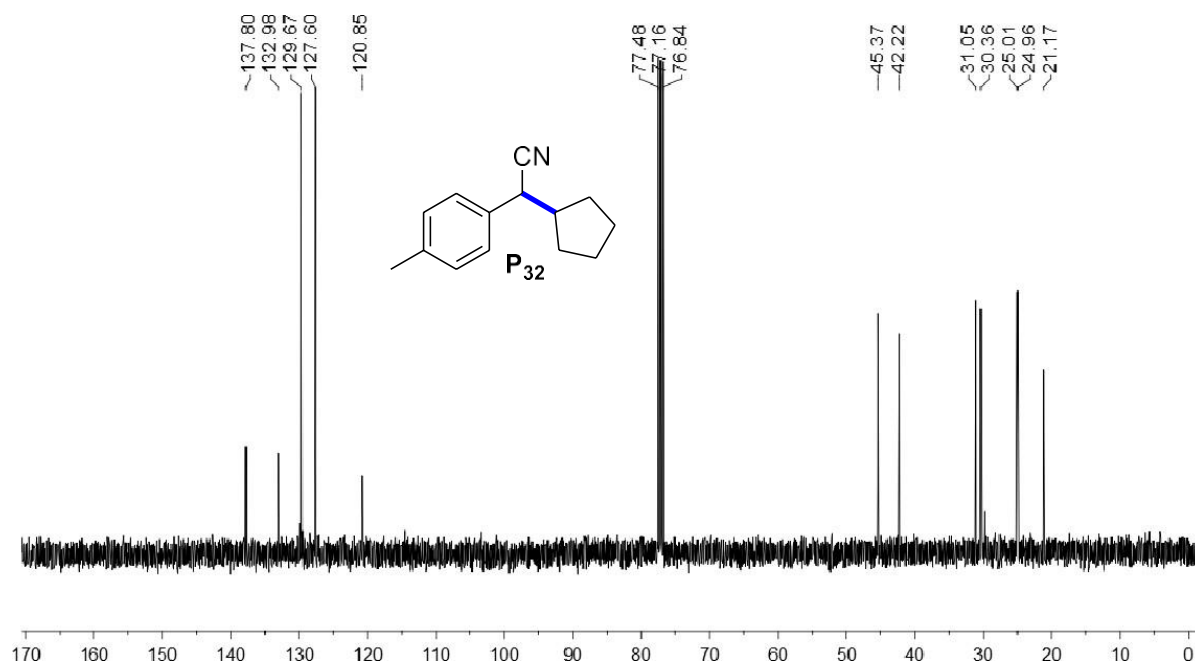
Figure 2.20 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 2-cyclopentyl-2-(4-methylphenyl)acetonitrile (**P32**) in CDCl3 at r.t.
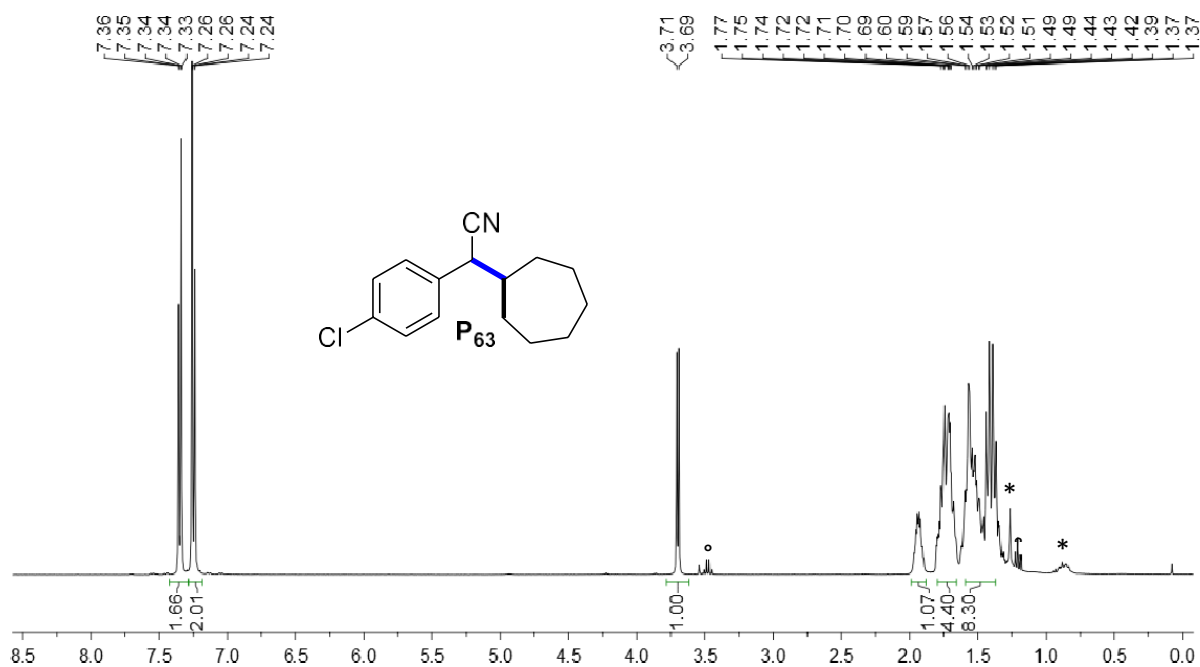
Figure 2.21 ^{1}H NMR (400 MHz) spectrum of 2-cycloheptyl-2-(4-chlorophenyl)acetonitrile (**P$_{63}$**) in CDCl$_3$ at r.t. (* indicates H-grease, ° indicates Et$_2$O).
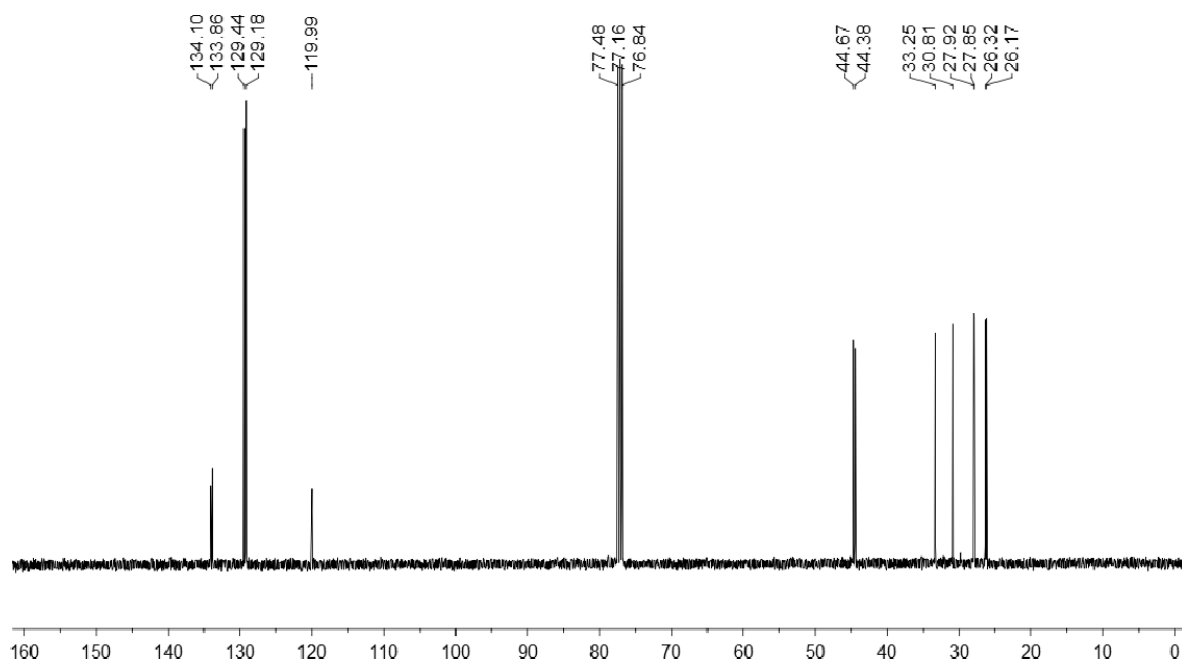
Figure 2.22 ^{13}C{^{1}H} NMR (400 MHz) spectrum of 2-cycloheptyl-2-(4-chlorophenyl)acetonitrile (**P$_{63}$**) in CDCl$_3$ at r.t.
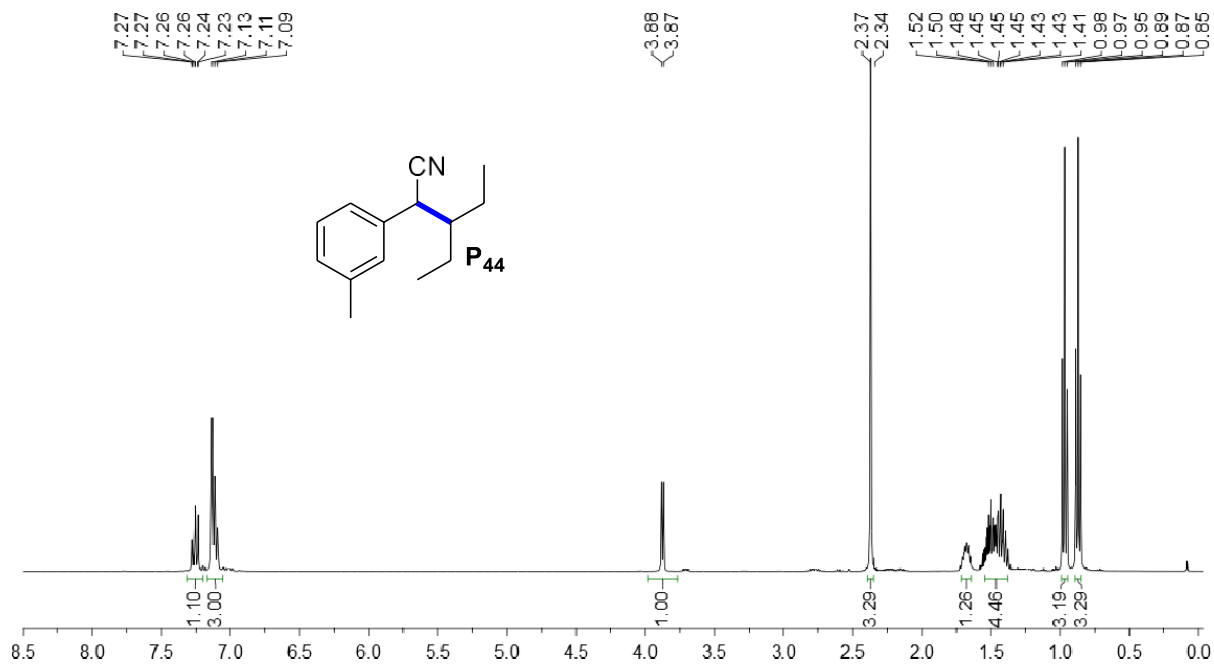
Figure 2.23 ^{1}H NMR (400 MHz) spectrum of 3-ethyl-2-(3-methylphenyl)pentanenitrile (**P₄₄**) in CDCl₃ at r.t.
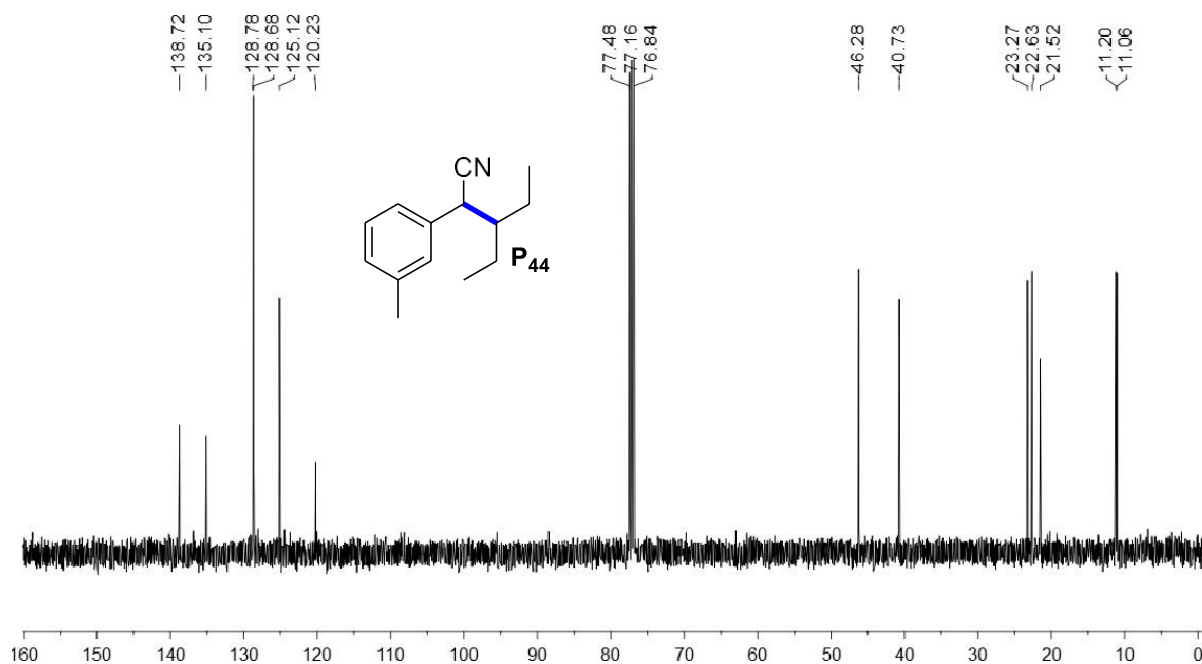
Figure 2.24 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 3-ethyl-2-(3-methylphenyl)pentanenitrile (**P₄₄**) in CDCl₃ at r.t.
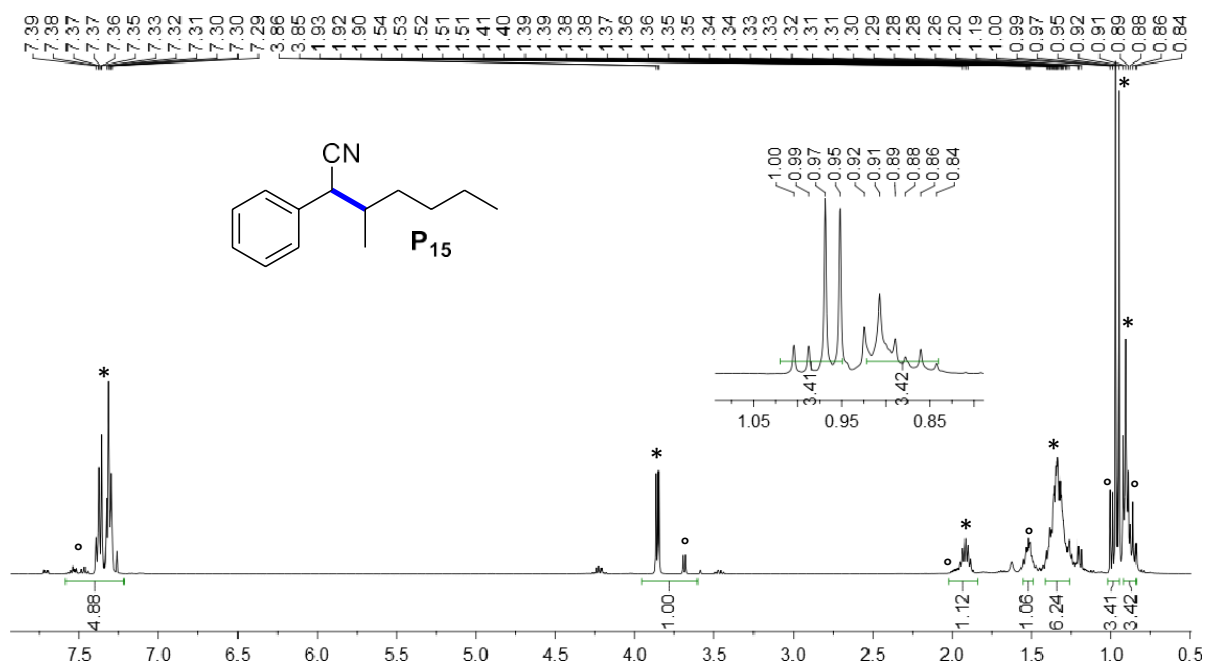
Figure 2.25 ^{1}H NMR (400 MHz) spectrum of 3-methyl-2-phenylheptanenitrile (**P$_{15}$**) in CDCl$_3$ at r.t. (two diastereomers are indicated by * and °).
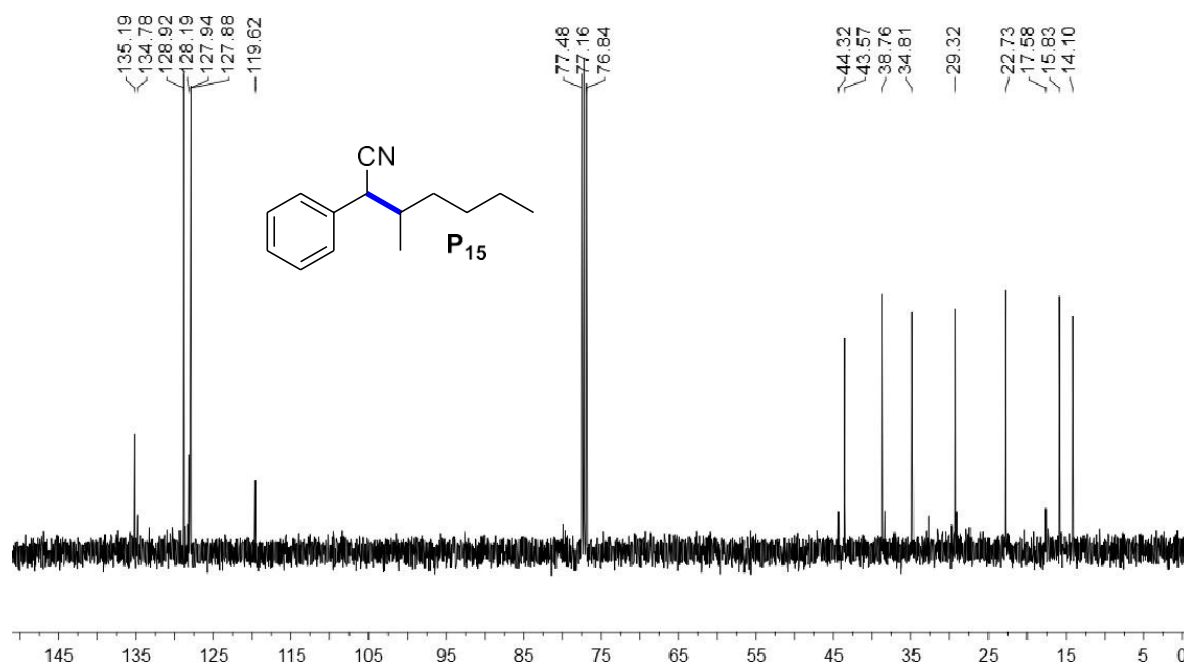
Figure 2.26 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 3-methyl-2-phenylheptanenitrile (**P$_{15}$**) in CDCl$_3$ at r.t.

X-ray structure determination

Crystallographic data and structure determinations details are compiled in Table S1. The crystals were obtained by slow evaporation of a DCM solution at r.t. The crystals were coated with silicon oil on a glass slide and a suitable single crystal was mounted on a glass fibre. Crystal data were collected with a Rigaku Oxford diffractometer and with an INCOATEC micro source (Mo-Kα radiation, λ = 0.71073 Å, multilayer optics) at 293 K. The structure was determined using direct methods employed in ShelXT,[S1] OleX,[S2] and refinement was carried out using least-square minimization implemented in ShelXL.[S3] All nonhydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom positions were fixed geometrically in idealized positions and were refined using a riding model. CCDC 2025918 (for complex 2) contains the supplementary crystallographic data for this paper.

Table 2.2 Crystallographic Data and Refinement Parameters for complex **2**

Empirical formula	$C_{140}H_{192}Ir_8N_{32}O_{16}$
CCDC	2025918
Formula weight (g mol^{-1})	4116.84
Temperature	293(2)
Wavelength	0.71073
Crystal system	Monoclinic
Space group	P 1 21/c 1
a (Å)	12.9319(4)
b (Å)	20.6645(6)
c (Å)	14.6864(5)
α (deg)	90
β (deg)	108.374(4)
γ (deg)	90
volume (Å^3)	3724.6(2)
Z	1
D_{calc} (g cm^{-3})	1.835
μ (mm^{-1})	0.7187
$F(000)$	2000
Crystal Size	0.25 x 0.24 x 0.20 mm^3
θ Range (deg)	3.211−26.733
Index Ranges	−16≤ h ≤16, −26≤ k ≤25, −18≤ l ≤18
Reflections collected	66050
Independent reflections (R$_{int}$)	7824 (0.0390)
Completeness to theta = 25.07^0	99.71
Refinement method	Full-matrix least-squares on F^2

Data/Restraints/parameters	7824/0/425
Goodness-of-fit on $F2$	1.014
Final R indices [I>2σ(I)]	$R_1 = 0.0204$, wR_2 =0.0454
R indices (all data)	$R_1 = 0.0250$, wR_2 =0.0463
Largest diff. peak/hole (e Å^{-3})	1.151/ −0.696

Figure 2.27 Molecular Structure of complex **2** showing 50% ellipsoids[a]
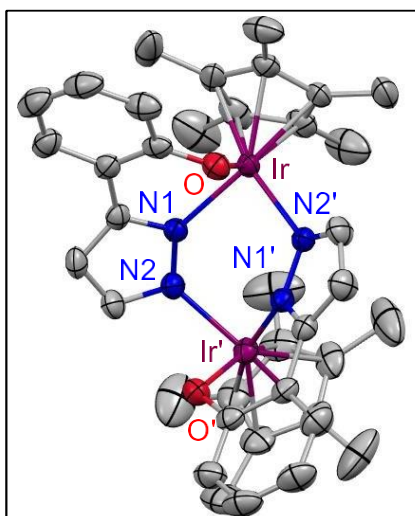
[a]Hydrogen atoms are omitted for clarity. Selected bond distances (Å) and angles (deg): Ir1-O1 2.097(2), Ir1-N1 2.084(3), Ir1-N2′ 2.101(3), Ir1-Cpcentroid 1.801, Ir1′-O1′ 2.087(2), Ir1′-N1′ 2.052(3), Ir1′-N2 2.091(3), Ir1′-Cpcentroid 1.778, N1-N2 1.367(4), N1′-N2′ 1.372(4) and O1-Ir1-N1 78.51(9), O1-Ir1-N2′ 81.41(10), N1-Ir1-N2′ 86.18(10), O1′-Ir1′-N1′ 80.84(10), O1′-Ir1′-N2 84.14(10), N1′-Ir1′-N2 85.81(10).

Chapter 3

Phosphine Free Iridium Catalyzed C-C and C-N Bond Formation via Borrowing Hydrogen and Asymmetric Dehydrogenative Coupling

3.1 ABSTRACT

Here, we report the use of a previously synthesized iridium pyrazolato complex as a catalyst for the α-alkylation of ketones and arylnitriles with primary alcohols, employing a borrowing hydrogen strategy. The alkylation reactions were efficiently conducted at 120 °C, utilizing a very low catalyst loading (0.1 mol%). A broad range of aromatic and aliphatic primary alcohols, in combination with various arylnitriles and ketones, were successfully transformed into their respective alkylated products. Additionally, quinoline derivatives were synthesized from 2-aminobenzylalcohol and ketones through dehydrogenative coupling. A mechanistic investigation unveiled that the key step involves metal-ligand cooperation through alcohol activation.

3.2 INTRODUCTION

The advancement of catalytic methodologies for creating carbon-carbon bonds is of utmost importance in organic synthesis as these processes are essential in creating the complex structures found in a wide array of agrochemical, medicinal, and bio-active compounds.[1] Traditionally, the α-alkylation of ketones and nitriles involved the use of electrophilic halides as alkylating agents alongside a stoichiometric quantity of base.[2] Furthermore, there have been several reports on transition metal-catalyzed cross-coupling reactions for the formation of C-C bonds.[3] Nonetheless, conventional methods usually meet up with multistep procedures, environmentally harmful organometallic coupling agents, and a considerable amount of bases, resulting in the production of vast quantities of waste.[4] Hence scientists would consistently favour the development of more efficient and green alkylation methods that utilize readily available and non-toxic starting materials. The increasing environmental concerns and fast depletion of petroleum-based resources have propelled the demand to seek

superior, sustainable, and renewable alternatives for producing fine chemicals.[5] In this regard, any innovative process should make use of cheap and easily accessible starting materials while also considering the generation of environmentally friendly reaction by-products as a crucial aspect.[6] Alcohols can be readily produced from lignocellulosic biomass through fermentation or catalytic conversion processes and serve as exceptionally valuable counterparts for C-C bond-forming reactions.[7] Utilizing alcohol in a C-C bond formation reaction is attractive due to its ease of maintenance and storage, and provide an endless array of option. Hence the concept of borrowing hydrogen has emerged as a favourable approach for the formation of C-C bond.[8] The initial step of borrowing hydrogen is the dehydrogenation of alcohol to the corresponding ketone followed by base-assisted aldol/Knoevenagel-type condensation with substrate to result α,β-unsaturated product upon elimination of H_2O. In the final step, the α,β-unsaturated product is subjected to reduction by a metal catalyst to form an alkylated product. Metal catalyst plays a significant role in facilitating hydrogen shuttling in the first step and is also crucial for the dehydrogenation of alcohol which is an energetically demanding process.[9] Thus this concept has gained considerable attention and recognition within the catalyst community in recent decades mainly because of its emphasis on atom economy and its advocacy for a more greener and environmentally friendly process.[10] This immensely valuable process has arisen as a compelling method for constructing various types of C-C and C-N bonds in a single step.[8a,11] Various heterogeneous catalysts were used for the same objective but with elevated temperature, extended reaction time, and requirement of excess amount of alcohol.[12] For usage in hydrogen auto-transfer, several ruthenium[13], iridium[14], and other transition metal-based homogeneous complexes[15] have evolved over the past ten years. In particular, Ir(III)-half sandwich complexes that contain pentamethylcyclopentadienyl ligands such as Cp*Ir(III), have surfaced as highly efficient and promising catalysts. Illustrative instances

encompass [Cp*IrCl$_2$]$_2$, N-heterocyclic carbene ligands based Cp*Ir(III) complexes, and diverse complexes relying on other ligands.[14a-h] More recently we have shown that Cp*Ir(III)-pyrazolato complex serves as a catalyst with dual metal-ligand functionality in the alkylation of arylnitriles with secondary alcohols.[16] Metal-ligand cooperation assumes a significant role in catalytic processes. It has the capability to considerably enhance the catalytic activity when applied in BH with ligands that assimilate functional groups like NH and OH. Several noteworthy catalysts, including Noyori-Ikariya's catalyst, Shvo's catalyst, and Milstein's pincer complexes, have effectively employed deprotonation-protonation of the coordinated ligand as a highly advantageous approach.[17]

Scheme 3.2.1. Iridium catalyzed C-C and C-N coupling reaction.
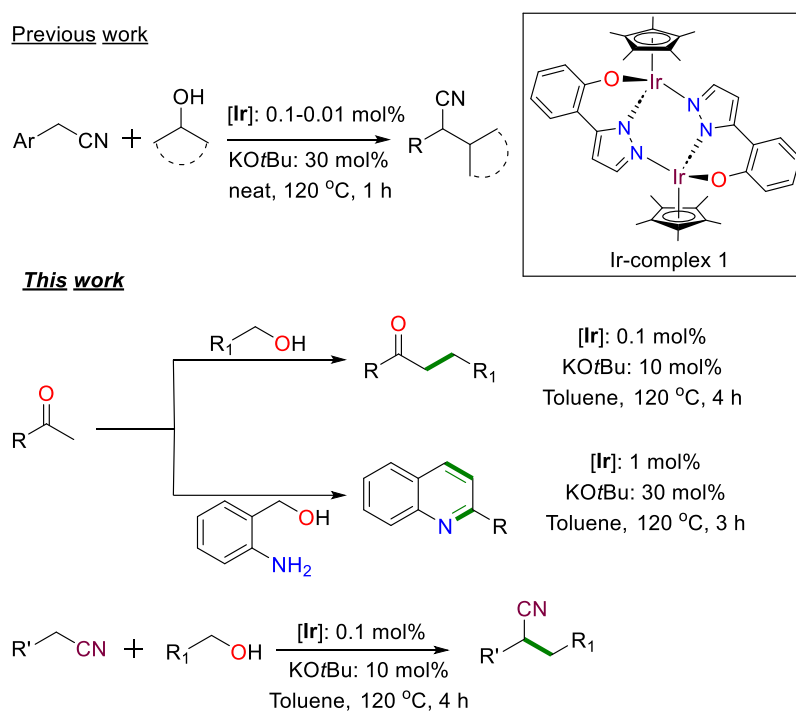
Thus, Despite the exciting results we had with secondary alcohols, we aim to further explore the performance of the same complex with primary alcohols (Scheme 3.2.1).

3.3 RESULTS AND DISCUSSIONS

Ketones play a vital role as essential intermediates in the synthesis of polymers, drugs, and natural products.[18] The α-alkylation of ketones using primary alcohols via the BH method involves the utilization of diverse transition-metal complexes like Mn, Re, Fe, Ru, Co, Rh, Ir, and Pd.[19] One of the primary challenges encountered in this type of alkylation reaction is achieving the product selectivity between two distinct alkylated products: alkylated alcohols and alkylated ketones. Apart from the transition metal-mediated BH processes, the formation of alkylated ketones and alcohols can also be triggered by the presence of an alkali base alone.[20] The inclusion of base in the reaction mixture can activate the Oppenauer route, which incorporates the oxidation of alcohols to carbonyls as well as the MPV reduction pathway which eventually leads to the reduction of carbonyls to their corresponding alcohols.[20b,21] These side reactions can have a notable influence on the product selectivity.[22] Hence there is a necessity to develop a catalyst that can effectively regulate product selectivity even when base is present in the reaction mixture. Several iridium catalysts have been previously reported for this alkylation to manifest alkylated ketones. Li *et al.* reported α-alkylation of ketones with primary alcohols using [Cp*Ir(2,2′-bpyO)(H$_2$O)] catalyst under air.[19i] The same group has also used a cyclometalated Ir(III) complex for this purpose.[19j] In their study, Gulcemal and co-workers presented an iridium-based system that enables a low catalyst loading to serve the alkylation of ketones.[19k] Glorious *et al.* reported this type of alkylation in water using [Cp*IrCl$_2$]$_2$, but their system requires 2 equiv. of alcohols and cationic surfactant.[19l] Recently NHC-based iridium complexes were utilized by Bera *et al.* for the alkylation of ketones.[19m] Nonetheless, some of these methods continue to encounter issues such as high temperature, high catalyst or base loading, and subpar product selectivity.

We embarked on a study to investigate the α-alkylation of acetophenone as a standard substrate with benzyl alcohol. After heating a mixture of S$_1$ and A$_1$ (1.5 equiv) at 120 °C in the presence of 20 mol% KO*t*Bu and 3 mol% [Ir] for 24 h, we observed complete conversion of acetophenone to the corresponding alkylated product 1,3-diphenylpropan-1-one (entry 1). Gradually decreasing the time to 3 h also led to the full conversion (entry 1).

Table 3.3.1 Reaction optimization of acetophenone with benzyl alcohol catalyzed by Iridium complex. [a]
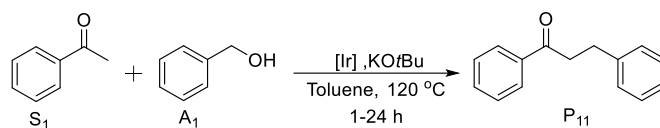
en	[Ir] mol%	KOtBu mol%	A_1 (equiv)	temp. (°C)	time (h)	Yield(%)[b]
1	3	20	1.5	120	24/12/6/3	>99
2	2	20	1.5	120	3	>99 (89)[c]
3	1	20	1.5	120	3/2/1	>99 (95)[c]
4	1	20	1.5	120	0.5	84
5	1	20	1.0	120	1	>99
6	1	15	1.0	120	1	>99
7	1	10	1.0	120	1	>99
8	0.5	10	1.0	120	2	>99
9[d]	0.1	10	1.0	120	4	>99 (93)[c]
10[d]	0.1	10	1.0	100	4	89

[a]Reaction conditions: S_1 (0.5 mmol), A_1 (0.5 mmol), [Ir] (3/2/1/0.5 mol%), KO^{t}Bu (20-10 mol%), solvent (1.0 mL) at 120 °C for 1-24 h. [b]Yields determined by GC using p-xylene (0.25 mmol) as an internal standard. [c]Isolated yield. [d]Reaction conditions: S_1 (5 mmol), A_1 (5 mmol), [Ir] (0.1 mol%), KO^{t}Bu (10 mol%), solvent (3.0 mL) at 100/120 °C for 4h.

Thereafter catalyst loading was reduced to 2 mol% and we achieved complete conversion of S_1 in 3 h with more than 89% of isolated yield (entry 2). Complete conversion was observed when catalyst loading was decreased to 1 mol% in 3 h and 2 h, an isolated yield of 93% was noted in 1 h (entry 3). Further reducing the time to 0.5 h, we failed to achieve complete conversion of acetophenone (entry 4). We performed the alkylation with 1.0 equiv of alcohol and we observed full conversion of S_1 (entry 5). The complete conversion was obtained by reducing base loading to 15 and 10 mol% (entries 6, 7). Additionally, we aimed to decrease the catalyst loading to 0.5 and 0.1 mol% (entries 8, 9). We achieved full conversion of S_1 in 4

h with an isolated yield of 93% (entries 10). Decreasing the temperature failed to give complete conversion.

Once we got the optimized condition (Table 1, entry 9), we proceeded to investigate the substrate scope. Initially, our focus was directed toward various aromatic primary alcohols. The reaction of acetophenone with different benzyl alcohols including those with electron-donating and electron-withdrawing groups such as methyl, tertbutyl, methoxy, chloro and

Scheme 3.3.1 α-alkylation of ketones with primary alcohols
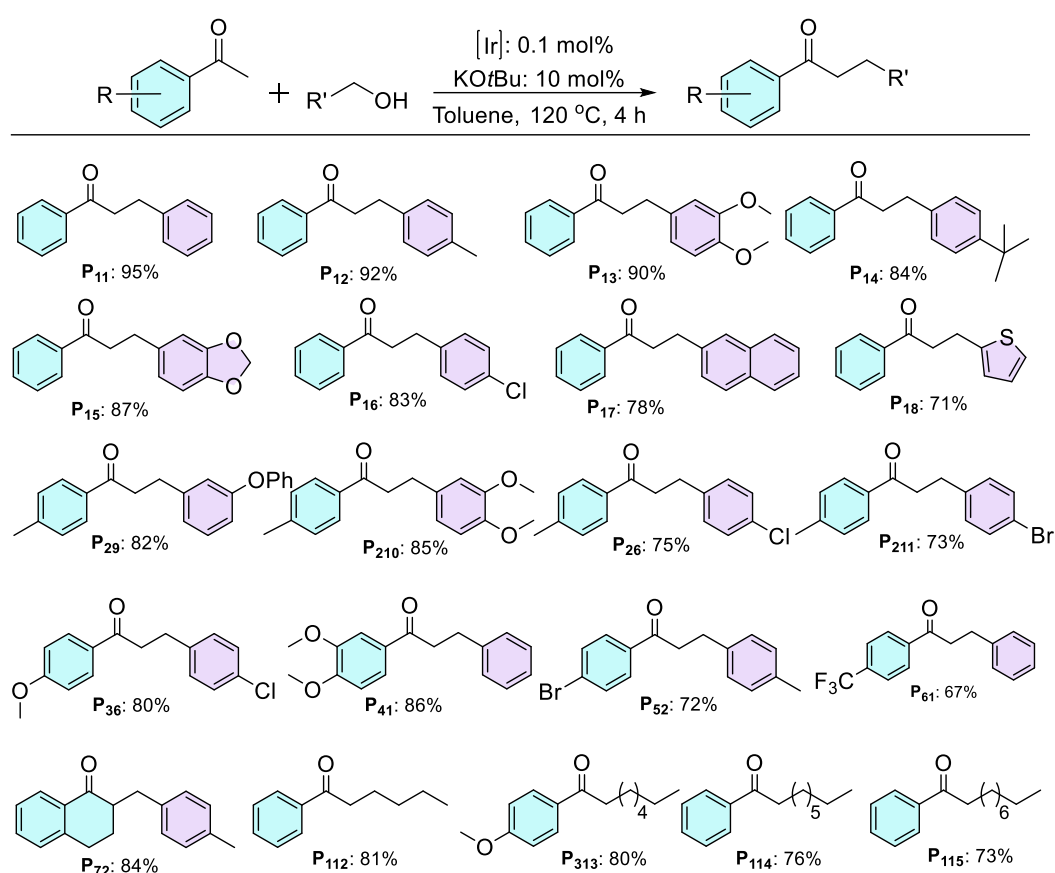
methylenedioxy was well tolerated and gave satisfactory yield (**P₁₂**: 92%, **P₁₃**: 90%, **P₁₄**: 84%, **P₁₅**: 87%, **P₁₆**: 83%). The conversion of 1-naphthyl methanol and 2-thiophene methanol resulted in the formation of the corresponding product in good yield (**P₁₇**: 78%, **P₁₈**: 71%). Subsequently, different electron donating groups containing acetophenones engaged with various substituted benzyl alcohols to produce the alkylated product in good to excellent yield (**P₂₉**: 82%, **P₂₁₀**: 85%, **P₂₆**: 75%, **P₂₁₁**: 73%, **P₃₆**: 80%, **P₄₁**: 86%). 4-bromoacetophenone

and 4'-(trifluoromethyl)-acetophenone also tolerated well with this protocol and gave satisfactory yield (**P$_{52}$**: 72%, **P$_{61}$**: 67%). 1-Tetralone serves as a crucial starting material for the synthesis of agricultural and pharmaceutical agents. 1-tetralone gave the corresponding alkylated ketone(**P$_{72}$**) in 84% yield. Aliphatic primary alcohols like 1-butanol, 1-hexanol, 1-heptanol, 1-octanol were also effectively converted with good yield (**P$_{112}$**: 81%, **P$_{313}$**: 80%, **P$_{114}$**: 76%, **P$_{115}$**: 73%).

The α-alkylation of nitriles emerges as a fundamentally significant transformation routinely applied over various chemical synthesis and biological procedures.[23] Alkylation of nitriles presents greater difficulties as the cyano group is sensitive towards activated hydrogen and water. Metal catalyst has the ability to shuttle hydrogen from alcohol to nitrile to produce aldehydes and amines[24] which subsequently can be transformed into secondary amines.[25] Grigg *et al.* first explored iridium catalyzed α-alkylation of nitriles with primary alcohols through the BH method.[26] Afterwards, numerous noble metal catalysts like Ru, Os, Rh, etc. have been engineered for this purpose.[27] Obora *et al.* employed the [Ir(OH)(cod)]$_2$ / PPh$_3$ system for the alkylation of acetonitrile with alcohol.[28] Cossy *et al.* also conducted a similar type of alkylation using [Ir(Cl)(cod)]$_2$ under microwave conditions.[29a] The same group also reported iridium-catalyzed intramolecular alkylation of nitriles.[29b] Recently Wang *et al.* reported iridium-catalyzed alkylation of nitriles with primary and secondary alcohol.[30] This transformation has also experienced the development of several base metals such as Fe, Mn, Ni, and Co.[31] Many of these catalysts are plagued by issues such as elevated temperature and time, high catalyst loading, and requirement of excess amount of alcohol.

We have utilized our iridium catalysis for this purpose, implementing it under the same optimized condition as those utilized for ketone alkylation. Next, we explored the range of substrates by using nitriles as well as aromatic and aliphatic primary alcohols. Phenyl acetonitrile reacting with benzyl alcohol gave the corresponding alkylated product 2,3-

diphenylpropanenitrile (**N$_{11}$**) in 93% yield. Aromatic alcohol featuring electron-donating as well as electron-withdrawing groups gave good to excellent yield using this protocol (**N$_{12}$:** 91%**, N$_{14}$:** 85%**, N$_{15}$:** 89%**, N$_{19}$:** 83%**, N$_{16}$:** 81%). Polycyclic alcohol 1-naphthyl methanol underwent a successful transformation to the corresponding product (**N$_{17}$**) in 85% yield.

Scheme 3.3.2 α-alkylation of arylnitriles with primary alcohols
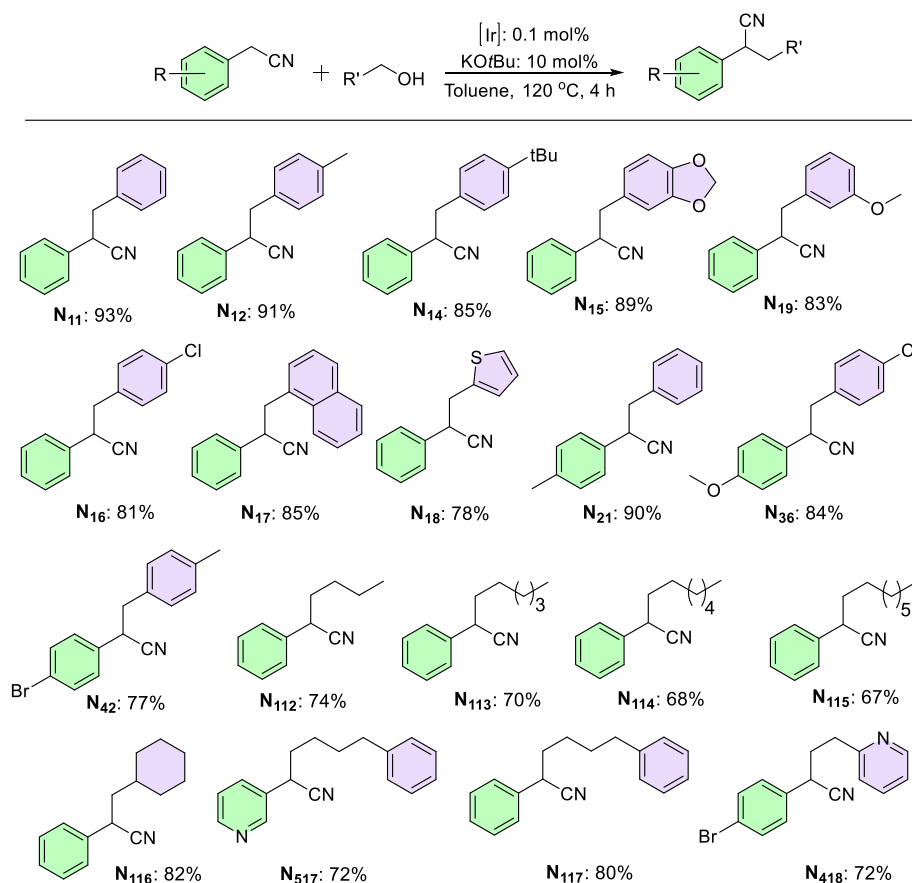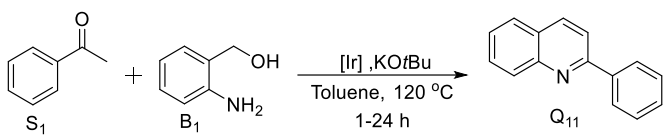
Heteroatom-containing alcohol such as 2-thiophene-methanol provided the alkylated product in good yield (**N$_{18}$:** 78%). Arylacetonitriles bearing electron-donating and withdrawing groups were effectively reacted with different aromatic primary alcohols, resulting in successful conversion to their corresponding alkylated products with excellent yield (**N$_{21}$:** 90%**, N$_{36}$:** 84%**, N$_{42}$:** 77%, **N$_{418}$:** 72%). Afterward, we were eager to check the reactivity of highly challenging nonactivated primary and cyclic alcohols. 1-butanol, 1-hexanol, 1-heptanol, 1-octanol and cyclohexyl methanol were successfully converted with moderate yield (**N$_{112}$:** 74%**, N$_{113}$:** 70%**, N$_{114}$:** 68%, **N$_{115}$:** 67%, **N$_{116}$:** 82%). Arylnitrile containing

heteroatom like 2-pyridyl acetonitrile reacted with unactivated aromatic alcohol 4-phenyl-1-butanol to yield the corresponding alkylated product (**N₅₁₇**) in 72% yield.

Polycyclic N-heterocycles are regularly found in natural products as well as in active pharmaceutical ingredients (APIs). Around 59% of the drug molecules approved by the US Food and Drug Administration contained a nitrogen heterocycle.[32] Quinolines have a well-established history of manifesting antimalarial, anti-cancer, and enzyme-inhibiting characteristics.[33] The Friedländer cyclization has emerged as a particularly useful and straightforward technique for the preparation of quinoline among the several reported practical methods.[34] This process involves carbonyl compounds that possess an active α-methylene group condensing with 2-amino benzaldehyde or ketones to give quinoline. 2-amino benzyl alcohols can easily be replaced with 2-amino benzaldehydes as the latter tend to be relatively unstable and can undergo self-condensation. Recently, there has been a remarkable growth in transition-metal-catalyzed acceptorless dehydrogenative coupling (ADC).[1c,8g,35] Employing readily available alcohols as alternative substrates amplifies the eco-friendliness and sustainability of the reaction because this process only deals with H_2 and H_2O as byproducts. ADC method proves highly effective for the synthesis of various heterocycles and has been considered as an atom-economy and green methodology.[5a,36] Noble metal catalysts particularly Ru, Ir, Re, and Pd have been thoroughly explored for the synthesis of quinolines through dehydrogenative annulation reactions.[37] Ishii *et al.* first reported Ir(I) catalyzed snthesis of quinolines from amino alcohol and ketones using PPh₃ as a ligand.[37g] An NHC-Ir(I) complex was used by Gulcemal *et al.* for a similar objective.[37h] Li *et al.* used a water-soluble metal−ligand bifunctional Ir(III) catalyst for the synthesis of quinoline under air.[37i] Kundu *et al.* also demonstrated an Ir(III) catalyzed modified Friedlander synthesis of quinolines.[37j] Several base metal complexes were also reported for the synthesis of quinolines through dehydrogenative coupling.[38]

We commenced the optimization process by selecting acetophenone and 2-amino benzyl alcohol as model substrates. Complete conversion of S_1 was observed after heating a mixture of S_1, B_1 (1.5 equivalents), 50 mol% KOtBu in toluene at 140 °C for 24 h (entry 1).

Table 3.3.2 Reaction optimization for the synthesis of quinoline catalyzed by Iridium complex. [a]

| en	[Ir] (mol%)	KO*t*Bu (mol%)	B_1 (equiv)	temp. (°C)	time (h)	Yield (%)[b]
1	3	50	1.5	140	24/12/6/3	>99
2	2	50	1.5	140	3	>99(89)[c]
3	1	50	1.5	140	3	>99
4	1	50	1.5	140	2	86
5	1	30	1.5	140	3	>99
6	1	20	1.5	140	3	88
7	1	30	1.5	120	3	>99 (94)[c]
8	1	30	1.5	100	3	79
9	1	30	1.0	120	3	84

[a]Reaction conditions: S_1 (0.5 mmol), B_1 (0.5 mmol), [Ir] (3/2/1 mol%), KO^{t}Bu (20-50 mol%), solvent (1.0 mL) at 140/120 °C for 2-24 h. [b]Yields determined by GC using p-xylene (0.25 mmol) as an internal standard. [c]Isolated yield

Reducing the duration to 3 h resulted in the same outcome with an isolated yield of Q_{11} in 89% (entry 2). Achieving full conversion was still possible when reducing the catalyst loading to 1 mol% while keeping all other parameters unchanged but reducing the time to 2 h resulted in a small amount of unreacted starting material (entry 3,4). Reducing the base loading resulted in complete conversion, but further decreasing the base loading did not lead to full conversion(entry 5,6). By lowering the temperature to 120 °C, we achieved complete

conversion with an isolated yield of 94% (entry 7). We did not witness the full conversion of S1 when we reduced both the amount of alcohol and the temperature (entry 8,9).

After getting the optimized condition (Table 2, entry 7) in hand, we performed the substrate scope of different ketones with 2-amino benzyl alcohol. Both electron-donating, as well as electron-withdrawing groups containing ketones, yielded the corresponding quinolines in good yield (**Q13:** 85%, **Q14:** 82%, **Q16:** 66%, **Q18:** 88%). Tetralone and 2-naphthyl acetophenone also gave the corresponding quinoline in good yield (**Q17:** 91%, **Q19:** 83%). A favourable yield was obtained for a heteroatom-containing ketone and an aliphatic cyclic ketone (**Q110:** 73%, **Q111:** 76%).

Scheme 3.3.3 synthesis of quinolines
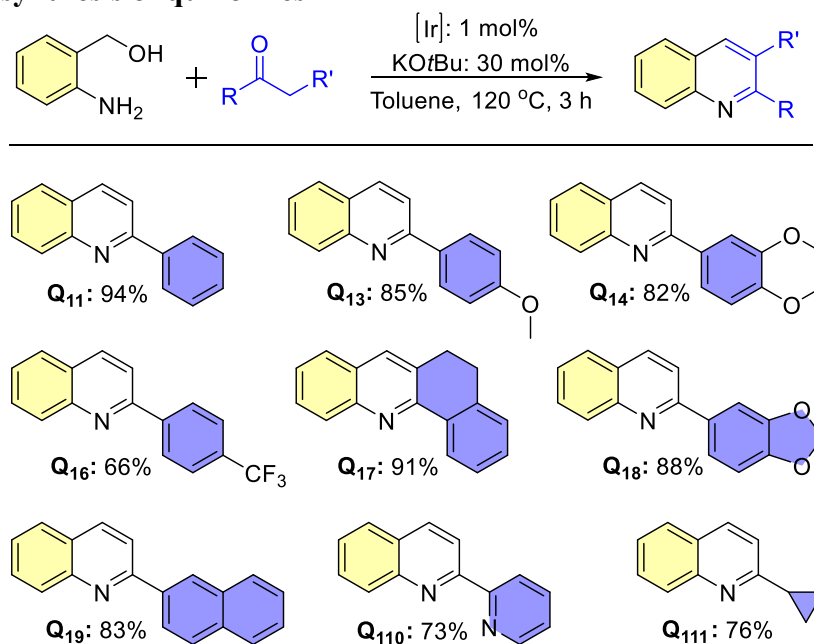
Subsequently, we shifted our focus towards exploring a feasible reaction pathway, and we conducted several control experiments to gain insight into the reaction's underlying mechanism. In order to assess the homogeneity of the reaction, we conducted a mercury drop test. This involved introducing a single drop of mercury into the reaction mixture while operating under optimized conditions. An isolated 87% yield of the corresponding alkylated product implied the presence of a homogeneous catalytic pathway. Subsequently, we

Scheme 3.3.4 control experiments

a) Mercury poisoning test

87%
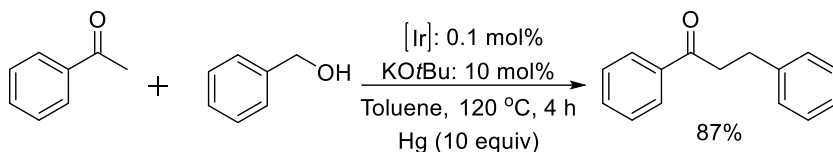
b) Radical scavenging test

TEMPO: 82%
BHT: 86%
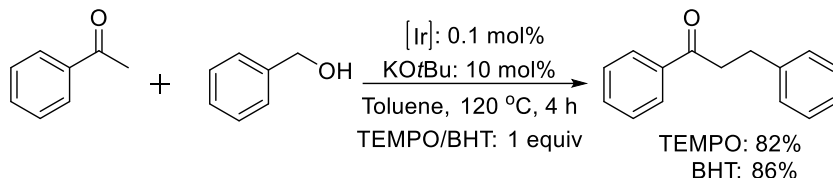
c) C=C bond formation by aldol condensation

D₁ (90%)
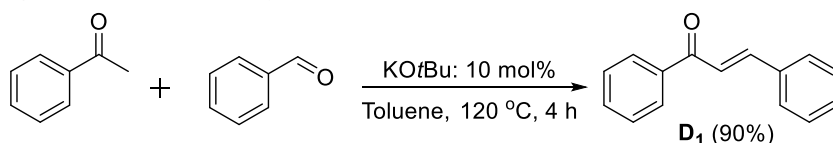
d) Hydrogenation of a,b-unsaturated compound

D₁   **P₁₁** (92 %)
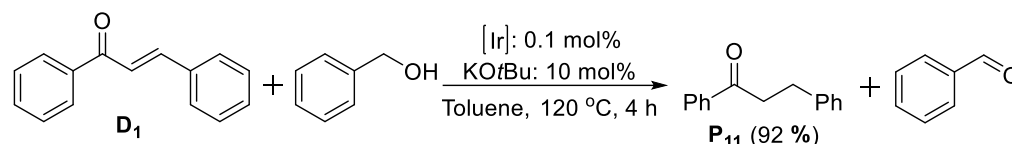
e) Hydrogen evolution test

72%
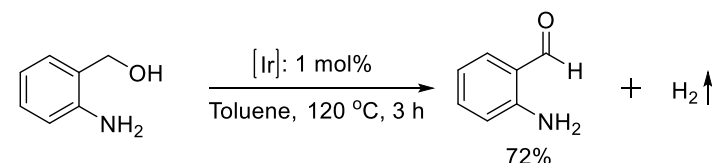
conducted radical scavenging tests in the presence of various established radical scavengers, including 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) radical, and dibutylhydroxytoluene (BHT). The presence of radical scavengers during the alkylations resulted in the expected product in satisfactory yields. As a result, it is plausible to exclude the possibility of a radical reaction pathway. In this particular reaction, it is recognized that the corresponding olefinated product serves as a significant intermediate. To achieve this, we conducted a reaction involving acetophenone and benzyl alcohol in the presence of solely a base. We were delighted to observe the production of the corresponding olefinated product (**D₁**) in a satisfactory yield, demonstrating that this pathway is independent of the metal catalyst. Following that, we carried out a reaction involving the olefinated product (**D₁**) and benzyl

alcohol under the optimized conditions. The successful formation of the alkylated product in a substantial yield with benzaldehyde as a dehydrogenated product confirmed the transfer of the benzylic C-H and alcoholic O-H hydrogen of benzyl alcohol to the C=C bond. Dehydrogenative coupling reactions encompass the liberation of hydrogen. In this context, a reaction was conducted using 2-amino benzylalcohol in the presence of a catalyst, resulting in the isolation of the corresponding dehydrogenative product with a yield of 72%. The confirmation of hydrogen evolution was achieved through Gas Chromatography.

Subsequently, we put forth a mechanism rooted in control experiments and prior research findings.[16,39] We presented two distinct mechanisms: one involving hydrogen borrowing and the other encompassing dehydrogenative coupling. In both scenarios, the process begins with alcohol's interaction with complex **1**, leading to O-H activation through proton transfer to the pyrazolato moiety, ultimately yielding an alkoxy intermediate (I_1 and I_1'). Thereafter, the β-hydride elimination of both intermediate I_1 and I_1' results in the generation of the aldehyde and the respective Ir-H intermediate (I_2). The Ir-H intermediate (I_2) had been previously isolated by our research group.[16] Subsequently, the corresponding aldehyde participates in an aldol condensation reaction with the ketone, yielding a chalcone (D_1) while eliminating water. This chalcone (D_1) is then subject to reduction by the Ir-hydride, resulting in the formation of the corresponding α-alkylated ketone. In the dehydrogenative coupling pathway, a cross-aldol condensation catalyzed by a base takes place between the resultant o-amino benzaldehyde (D_2) and ketones, leading to the formation of quinolines. The resulting hydride intermediate assumes a crucial role, culminating in the regeneration of iridium complex 1. This regenerative step is achieved through the elimination of dihydrogen (H_2), underscoring the intricacy and self-sustaining nature of the catalytic cycle.

Scheme 3.3.5 proposed reaction mechanism
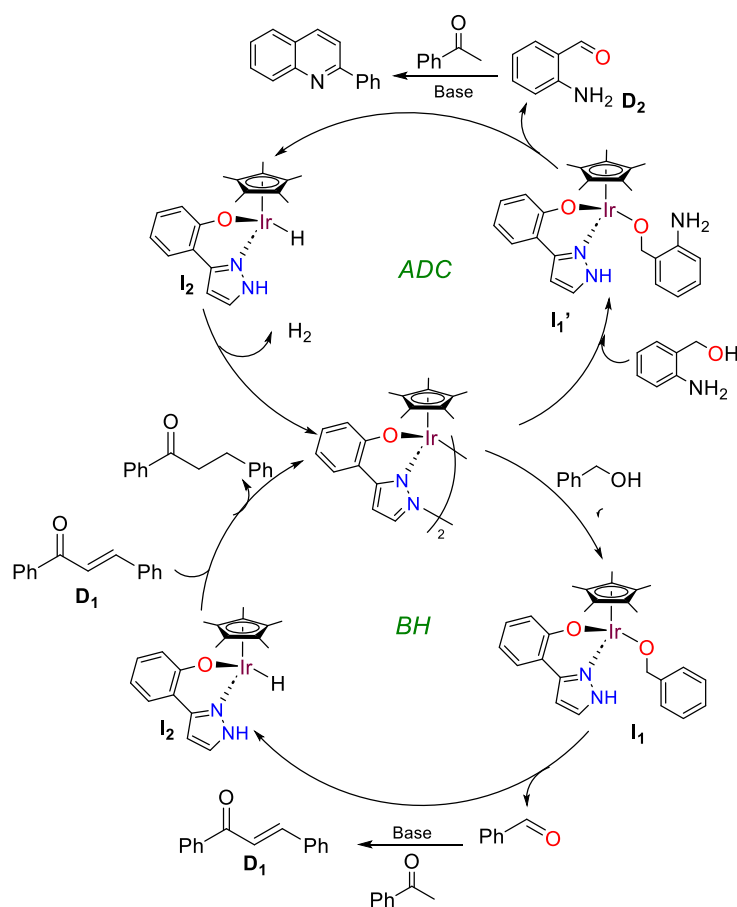
3.4 CONCLUSION

In summary, we harnessed the iridium-pyrazolato complex as a potent catalyst for the alkylation of ketones and nitriles using primary alcohols. Furthermore, this catalyst exhibits promise in the creation of heterocycles through acceptorless dehydrogenative reactions. The iridium catalyst has demonstrated its excellence as a catalyst for α-alkylation reactions, achieving remarkable conversion rates within a brief timeframe and exhibiting an appealingly low catalyst loading (0.1/1 mol%). The substrate range encompasses an extensive array of arylacetonitriles, ketones, and diverse primary alcohols. Experimental evidence substantiates the employment of the Borrowing Hydrogen pathway for alkylation and the dehydrogenative coupling approach for synthesizing quinolines. Therefore, this catalyst operates in both dimensions within the same framework.

3.5 EXPERIMENTAL SECTION

General experimental. All air and moisture sensitive experiments were performed under dry nitrogen atmosphere using standard Schlenk or glovebox (MBraun) techniques. Catalytic α-alkylation of nitriles, ketones and quinolines were performed in Ace pressure tubes purchased from Sigma-Aldrich. Analysis and purification of the products were carried out in air. For the air sensitive experiments, solvents toluene and diethylether (Et_2O) were distilled, degassed and stored over 3 Å molecular sieves. Solvents were purchased from Merck and Spectrochem. Deuterated solvents ($CDCl_3$ and DMSO-d6) were purchased from Sigma-Aldrich. 2-(1H-Pyrazol-3-yl)phenol, [IrCp*Cl$_2$]$_2$, KO*t*Bu, *p*-xylene, all organic nitriles and all primary alcohols were purchased from Sigma Aldrich, Alfa Aesar and TCI Chemicals and used without further purification.

^{1}H and ^{13}C{^{1}H} NMR spectra were recorded at Bruker AV-400 and JEOL-400 (^{1}H at 400 MHz and ^{13}C at 101 MHz). ^{1}H and ^{13}C{^{1}H} NMR chemical shifts are referenced in parts per million (ppm) with respect to residual solvent peaks ($CDCl_3$: δ 7.26 and 77.16 ppm; DMSO-d6: 2.50 and 39.52 ppm). The coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to describe multiplicity: s = singlet, bs = broad signal, d = doublet, t = triplet, q = quadtrate, m = multiplate. High resolution mass spectra were recorded on a Bruker microTOF-Q II Spectrometer.

General conditions for reaction optimization for the alkylation of ketones: Inside a glovebox, appropriate amount of acetophenone (S$_1$), benzyl alcohol (A$_1$), KO*t*Bu, *p*-xylene (as internal standard), Ir-complex **1** and toluene (1.5-3mL) were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at appropriate temperature in a preheated oil bath for appropriate time. Thereafter, the reaction mixture was cooled down to r.t. and the product mixture was analysed by GC. Occasionally the crude

product was purified by column chromatography using silica as stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as eluent.

General conditions for reaction optimization of quinoline: Inside a glovebox, appropriate amount of acetophenone (S_1), 2-amino benzyl alcohol (B_1), KOtBu, p-xylene (as internal standard), Ir-complex **1** and toluene (1.5mL) were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at appropriate temperature in a preheated oil bath for appropriate time. Thereafter, the reaction mixture was cooled down to r.t. and the product mixture was analysed by GC. Occasionally the crude product was purified by column chromatography using silica as stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as eluent.

General condition for substrate screening for the alkylation of ketones: Inside a glovebox, a mixture of ketone (5.0 mmol), primary alcohol (5 mmol), KOtBu (0.56 g, 0.5 mmol), Ir-complex **1** (2.4 mg, 2.5×10^{-3} mmol) and toluene (3 mL) were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at 120 °C in a preheated oil bath for 4 h. Thereafter, the reaction mixture was cooled down to r.t. and the crude product was purified by column chromatography (silica as stationary phase and a mixture of petroleum ether and ethylacetate) to give the pure product.

General condition for substrate screening for the alkylation of nitriles: Inside a glovebox, a mixture of nitrile (5.0 mmol), primary alcohol (5 mmol), KOtBu (0.56 g, 0.5 mmol), Ir-complex **1** (2.4 mg, 2.5×10^{-3} mmol) and toluene (3 mL) were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at 120 °C in a preheated oil bath for 4 h. Thereafter, the reaction mixture was cooled down to r.t. and the crude product was purified by column chromatography (silica as stationary phase and a mixture of petroleum ether and ethylacetate) to give the pure product.

General condition for substrate screening of quinoline moieties: Inside a glovebox, a mixture of ketone (0.5 mmol), 2-amino benzylalcohol (0.092 g, 0.75 mmol), KO*t*Bu (0.017 g, 0.15 mmol), Ir-complex **1** (2.4 mg) and toluene (1.5 mL) were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at 120 °C in a preheated oil bath for 3 h. Thereafter, the reaction mixture was cooled down to r.t. and the crude product was purified by column chromatography (silica as stationary phase and a mixture of petroleum ether and ethylacetate) to give a pure product.

Catalyst poisoning test: Inside a glovebox, a mixture of ketone (5.0 mmol), primary alcohol (5 mmol), KO*t*Bu (0.56 g, 0.5 mmol), Ir-complex (2.4 mg, 2.5×10^{-3} mmol), a drop of Hg and toluene (3 mL) were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at 120 °C in a preheated oil bath for 4 h. Thereafter, the reaction mixture was cooled down to r.t. and the mixture was then analyzed by GC to determine the yield of the corresponding alkylated product.

Radical trapping test: Inside a glovebox, a mixture of ketone (5.0 mmol), primary alcohol (5 mmol), KO*t*Bu (0.56 g, 0.5 mmol), Ir-complex (2.4 mg, 2.5×10^{-3} mmol), TEMPO (0.781 g, 5 mmol) or BHT (1.101 g, 5 mmol) and toluene (3 mL) were transferred into a pressure tube fitted with a magnetic stir-bar. The reaction mixture was heated at 120 °C in a preheated oil bath for 4 h. Thereafter, the reaction mixture was cooled down to r.t. and the mixture was then analyzed by GC to determine the yield of the corresponding alkylated product

Synthesis of 1,3-diphenylprop-2-en-1-one (D$_1$): A mixture of acetophenone (0.586 g, 5.0 mmol), benzaldehyde (0.491 g, 5.0 mmol) and KO*t*Bu (0.056 g, 0.5 mmol) was stirred in a pressure tube at 120 °C for 4 h under N$_2$ atmosphere. The mixture was cooled down to r.t. and the following workup was performed in air. From the reaction mixture, 1,3-diphenylprop-2-en-1-one (0.937 g, 90%) was purified by column chromatography (using silica as stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as eluent).

^{1}H NMR (400 MHz, CDCl$_3$): δ NMR (400 MHz) δ 8.06 – 8.00 (m, 2H), 7.82 (d, *J* = 15.7 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.63 – 7.48 (m, 4H), 7.46 – 7.38 (m, 3H). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 190.6, 144.9, 138.3, 135.0, 132.9, 130.66, 129.1, 128.7, 128.6, 128.6, 122.2.

Reduction of 1,3-diphenylprop-2-en-1-one (D$_1$): A mixture of 1,3-diphenylprop-2-en-1-one (01.040 g, 5.0 mmol), benzylalcohol (0.525 g, 5.0 mmol) and KO*t*Bu (0.056 g, 0.5 mmol) was stirred in a pressure tube at 120 °C for 4 h under N$_2$ atmosphere. The mixture was cooled down to r.t. and the following workup was performed in air. From the reaction mixture, 1,3-diphenylpropan-1-one (P$_{11}$) (0.956 g, 91%) was purified by column chromatography (using silica as stationary phase and a mixture of petroleum ether and ethylacetate (9.8:0.2) as eluent).

Dehydrogenation of 2-aminobenzylalcohol: Inside a glovebox, 2-aminobenzylalcohol (0.123 g, 1 mmol), Ir-complex (4.8 mg) and toluene (3 mL) were transferred into a seal capped vial fitted with a magnetic stir-bar. The reaction mixture was heated at 120 °C in a preheated oil bath for 3 h. Thereafter, the reaction mixture was cooled down to r.t. and hydrogen evaluation determined by gas chromatography. From the reaction mixture, 2-aminobenzaldehyde (0.087 g, 72%) was purified by column chromatography (using silica as stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as eluent).

NMR data of products

1,3-diphenylpropan-1-one (P$_{11}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent] to give pure product P$_{11}$ as a white solid (0.998 g, 95%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 – 7.95 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.38 – 7.25 (m, 4H), 7.21 (t, *J* = 7.4 Hz, 1H), 3.30 (t, *J* = 7.3 Hz, 2H), 3.07 (t, *J* = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 199.3, 141.4, 136.9, 133.2, 128.7, 128.6, 128.5, 128.1, 126.2, 40.5, 30.2.

1-phenyl-3-(p-tolyl)propan-1-one (P$_{12}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent] to give pure product P$_{12}$ as a white solid (1.031 g, 92%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97 – 7.95 (m, 2H), 7.58 – 7.54 (m, 1H), 7.47 – 7.44 (m, 2H), 7.17 – 7.11(m, 4H), 3.31 – 3.27 (m, 2H), 3.06 – 3.02 (m, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 199.6, 138.4, 137.1, 135.8, 133.2, 129.4, 128.8, 128.5, 128.2, 40.8, 29.9, 21.2.

2-(3,4-dimethoxyphenyl)-1-phenylpropan-1-one (P$_{13}$): The crude product was purified by column chromatography (silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent) to give pure product P$_{13}$ as a white solid (1.216 g, 90%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.82 – 6.78 (m, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.29 (t, *J* = 7.6 Hz, 2H), 3.02 (t, *J* = 7.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 199.5, 149.0, 147.4, 137.0, 134.0, 133.2, 128.7, 128.1, 120.2, 111.9, 111.4, 56.0, 55.9, 40.8, 29.9.

3-(4-(tert-butyl)phenyl)-1-phenylpropan-1-one (P$_{14}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.5:0.5) as the eluent] to give pure product P$_{14}$ as a white solid (1.118 g, 84%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 – 7.99 (m, 2H), 7.60 – 7.56 (m, 1H), 7.50 – 7.46 (m, 2H), 7.38 – 7.35 (m, 2H), 7.25 – 7.22 (m, 2H), 3.35 – 3.32 (m, 2H), 3.10 – 3.06 (m, 2H), 1.35 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 199.5, 149.1, 138.3, 137.0, 133.2, 128.7, 128.2, 128.2, 125.5, 40.6, 34.5, 31.5, 29.7.

3-(benzo[d][1,3]dioxol-5-yl)-1-phenylpropan-1-one (P$_{15}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.5:0.5) as the eluent] to give pure product P$_{15}$ as a white solid (1.106 g, 87%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45

(t, J = 7.6 Hz, 2H), 6.75 – 6.69 (m, 3H), 5.91 (s, 2H), 3.26 (t, J = 7.6 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 199.3, 147.7, 145.9, 136.9, 135.1, 133.2, 128.7, 128.1, 121.2, 109.0, 108.3, 100.9, 40.7, 29.9.

3-(4-chlorophenyl)-1-phenylpropan-1-one (P$_{16}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent)] to give pure product P$_{16}$ as a white solid (1.015 g, 83%); ^1H NMR (400 MHz, CDCl$_3$) δ 7.97 – 7.95 (m, 2H), 7.58 – 7.54 (m, 1H), 7.48 – 7.44 (m, 2H), 7.27 – 7.25 (m, 2H), 7.19 (d, J = 8.0 Hz, 2H), 3.30 – 3.27 (m, 2H), 3.05 (t, J = 7.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 198.9, 139.8, 136.8, 133.2, 131.9, 129.9, 128.7, 128.7, 128.1, 40.2, 29.4.

1-(naphthalen-2-yl)-1-phenylpropan-1-one (P$_{17}$): The crude product was purified by column chromatography [(silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent)] to give pure product P$_{17}$ as a white solid (1.015 g, 78%); ^1H NMR (400 MHz, CDCl$_3$) δ 8.09 (d, J = 8.1 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.94 – 7.88 (m, 1H), 7.79 – 7.76 (m, 1H), 7.59 – 7.50 (m, 3H), 7.47 – 7.43 (m, 4H), 3.53 (t, J = 7.4 Hz, 2H), 3.39 (t, J = 7.3 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 199.4, 137.4, 136.8, 134.0, 133.2, 131.8, 129.0, 128.7, 128.1, 127.1, 126.2, 126.2, 125.7, 125.7, 123.6, 39.8, 27.2.

1-phenyl-3-(thiophen-2-yl)propan-1-one (P$_{18}$): The crude product was purified by column chromatography [(silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent) as the eluent] to give pure product P$_{18}$ as a yellow oil (0.767 g, 71%); ^1H NMR (400 MHz, CDCl$_3$) δ 7.98 – 7.96 (m, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.14 – 7.12 (m, 1H), 6.94 – 6.92 (m, 1H), 6.87 – 8.86 (m, 1H), 3.39 – 3.35 (m, 2H), 3.32 – 3.28 (m, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 198.7, 143.0, 136.8, 133.3, 128.8, 128.2, 127.0, 124.8, 123.5, 40.6, 24.3.

3-(3-phenoxyphenyl)-1-(p-tolyl)propan-1-one (P$_{29}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent] to give pure product P$_{29}$ as a yellow oil (1.297 g, 82%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79 (d, J = 8.2 Hz, 2H), 7.28 – 7.23 (m, 2H), 7.18 (t, J = 7.6 Hz, 3H), 7.03 (t, J = 7.6 Hz, 1H), 6.95 – 6.93 (m, 3H), 6.86 – 6.82 (m, 1H), 6.79 – 6.75 (m, 1H), 3.19 (t, J = 7.6 Hz, 2H), 3.01 – 2.95 (m, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 198.7, 157.4, 157.2, 143.9, 143.5, 134.4, 129.8, 129.4, 128.2, 123.4, 123.3, 118.9, 116.5, 40.1, 30.1, 21.7. HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for C$_{22}$H$_{21}$O$_2$ 317.1534; Found 317.1527.

2-**(3,4-dimethoxyphenyl)-1-(p-tolyl)propan-1-one (P$_{210}$):** The crude product was purified by column chromatography [(silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.5:0.5) as the eluent)] to give pure product P$_{210}$ as a white solid (1.200 g, 85%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 6.81 – 6.77 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.25 (t, J = 7.7 Hz, 2H), 3.00 (t, J = 7.7 Hz, 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 199.2, 149.0, 147.4, 144.0, 134.5, 134.1, 129.4, 128.3, 120.3, 111.9, 111.4, 56.0, 55.9, 40.7, 30.0, 21.8.

3-**(4-chlorophenyl)-1-(p-tolyl)propan-1-one (P$_{26}$):** The crude product was purified by column chromatography [silica as the stationary phase and a mixture of mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent] to give pure product P$_{26}$ as a white solid (0.970 g, 75%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.1 Hz, 4H), 7.10 (d, J = 8.2 Hz, 2H), 3.17 (t, J = 7.5 Hz, 2H), 2.95 (t, J = 7.6 Hz, 2H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 198.5, 144.0, 139.9, 134.3, 131.8, 130.0, 129.4, 128.6, 128.2, 40.0, 29.5, 21.7.

4-(4-bromophenyl)-1-(p-tolyl)propan-1-one (P$_{211}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and

ethyl acetate (9.8:0.2) as the eluent] to give pure product P_{211} as a white solid (1.106 g, 73%).

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.41 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 3.27 (t, *J* = 7.6 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 198.6, 144.1, 140.5, 134.4, 131.6, 130.4, 129.4, 128.2, 120.0, 40.1, 29.6, 21.8.

4-(4-chlorophenyl)-1-(4-methoxyphenyl)propan-1-one (P$_{36}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.5:0.5) as the eluent] to give pure product P_{36} as a white solid (1.098 g, 80%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 3.89 (s, 3H), 3.25 (t, *J* = 7.6 Hz, 1H), 3.05 (t, *J* = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 197.6, 163.6, 140.0, 131.9, 130.4, 130.0, 128.7, 113.9, 55.6, 39.9, 29.7.

1-(3,4-dimethoxyphenyl)-3-phenylpropan-1-one (P$_{41}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.5:0.5) as the eluent] to give pure product P_{41} as a white solid (1.162 g, 86%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 – 7.53 (m, 2H), 7.32 – 7.19 (m, 5H), 6.87 (d, *J* = 8.4 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H) 3.27 (t, *J* = 7.7 Hz, 2H), 3.06 (t, *J* = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 198.0, 153.3, 149.1, 141.5, 130.2, 128.6, 128.5, 126.2, 122.7, 110.2, 110.1, 56.2, 56.1, 40.1, 30.5.

1-**(4-bromophenyl)-3-(p-tolyl)propan-1-one (P$_{52}$):** The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent] to give pure product P_{52} as a white solid (1.091 g, 72%). ^{1}H NMR (400 MHz, CDCl$_3$) δ ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.42 – 7.30 (m, 2H), 3.48 (m, 1H), 3.27 (t, *J* = 7.6 Hz, 1H), 2.57 (s, 3H).

$^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 198.3, 138.0, 135.8, 135.6, 132.0, 129.6, 129.3, 128.4, 128.2, 40.6, 29.6, 21.1.

2-phenyl-1-(4-(trifluoromethyl)phenyl)propan-1-one (P$_{61}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9:1) as the eluent] to give pure product P$_{61}$ as a colorless oil (0.932 g, 67%). ^1H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.23 – 7.10 (m, 5H), 3.23 (t, *J* = 7.6 Hz, 1H), 2.99 (t, *J* = 7.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 198.3, 141.0, 139.6, 134.4 (q, *J* = 32.7 Hz), 128.7, 128.5, 128.5, 126.4, 125.8 (q, *J* = 3.7 Hz), 122.4 (q, *J* = 273.6 Hz), 40.8, 30.0.

2-(4-methylbenzyl)-3,4-dihydronaphthalen-1(2H)-one (P$_{72}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent] to give pure product P$_{72}$ as a white solid (1.051 g, 84%); ^1H NMR (400 MHz, CDCl$_3$) δ NMR (400 MHz,) δ 8.08 (d, *J* = 8.0, 1H), 7.49 – 7.45 (m, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.13 (s, 4H), 3.46 (dd, *J* = 13.7, 4.0 Hz), 2.99 – 2.85 (m, 2H), 2.76 –2.68 (m, 1H), 2.66 – 2.60 (m, 1H), 2.33 (s, 3H), 2.14 – 2.08 (m, 1H), 1.83 – 1.73 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 199.6, 144.2, 137.0, 135.7, 133.5, 132.6, 129.3, 129.2, 128.8, 127.6, 126.7, 49.6, 35.3, 28.7, 27.7, 21.1.

1-phenylhexan-1-one (P$_{112}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as the eluent] to give pure product P$_{112}$ as a colorless oil (0.713 g, 81%). ^1H NMR (400 MHz, CDCl$_3$) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.78 – 1.73 (m, 2H), 1.41 – 1.33 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 200.8, 137.2, 133.0, 128.7, 18.2, 38.7, 31.7, 24.2, 22.7, 14.1.

1-(4-methoxyphenyl)octan-1-one (P$_{313}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethyl

acetate (9.8:0.2) as the eluent] to give pure product P_{313} as a colorless oil (0.936 g, 80%). ^{1}H

NMR (400 MHz, CDCl$_3$) δ 7.94 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H),

2.90 (t, J = 7.4 Hz, 2H), 1.75 – 1.67 (m, 2H), 1.36 – 1.26 (m, 8H), 0.87 (t, J = 7.4 Hz, 3H).

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 199.4, 163.4, 130.4, 130.3, 113.8, 55.6, 38.4, 31.8, 29.5,

24.8, 22.8, 14.2.

1-phenylnonan-1-one (P_{114}): The crude product was purified by column chromatography

[silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as

the eluent] to give pure product P_{114} as a colorless oil (0.829 g, 76%). ^{1}H NMR (400 MHz,

CDCl$_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 2.97 (t, J

= 7.4 Hz, 2H), 1.78 – 1.71 (m, 2H), 1.40 – 1.28 (m, 10H), 0.89 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H}

NMR (101 MHz, CDCl$_3$) δ 200.7, 137.2, 133.0, 128.6, 128.2, 38.7, 32.0, 29.6, 29.5, 29.4,

24.5, 22.8, 14.2.

1-phenyldecan-1-one (P_{115}): The crude product was purified by column chromatography

[silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9.8:0.2) as

the eluent] to give pure product P_{81} as a colorless oil (0.848 g, 73%). ^{1}H NMR (400 MHz,

CDCl$_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 2.97 (t, J

= 7.5 Hz, 2H), 1.78 – 1.71 (m, 2H), 1.36 – 1.24 (m, 8H), 0.89 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H}

NMR (101 MHz, CDCl$_3$) δ 200.8, 137.2, 133.0, 128.7, 128.2, 38.8, 32.0, 29.6, 29.5, 29.3,

27.7, 24.5, 22.8, 14.2.

2,3-Diphenylpropanenitrile (N_{11}): The crude product was purified by column

chromatography [silica as the stationary phase and a mixture of petroleum ether and

ethylacetate (9.5:0.5) as the eluent] to give pure product N_{11} as a colorless oil (0.964 g, 93%);

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 – 7.17 8H), 7.07 – 7.04 (m, 2H), 3.92 (dd, J = 8.2, 6.6

Hz, 1H), 3.14 – 3.02 (m, 1H). ^{13}C{^{1}H} NMR (101MHz, CDCl$_3$) δ 136.4, 135.3, 129.3, 129.1,

128.7, 128.3, 127.6, 127.5, 120.5, 42.3, 39.9.

2-Phenyl-3-(p-tolyl)propanenitrile (N$_{12}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product N$_{12}$ as a white solid (1.000 g, 91%); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.39 – 7.24 (m, 5H), 7.11 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 1H), 3.97 (dd, J = 8.2, 6.6 Hz, 1H), 3.17 – 3.04 (m, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ = 137.1, 135.4, 133.3, 129.4, 129.2, 129.1, 128.2, 127.6, 120.6, 41.9, 40.0, 21.2.

3-3-(4-(tert-butyl)phenyl)-2-phenylpropanenitrile (N$_{14}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product N$_{14}$ as a white solid (1.112 g, 85%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 – 7.05 (m, 7H), 7.06 (d, J = 8.0 Hz, 2H), 3.92 (dd, J = 8.2, 6.6 Hz, 1H), 3.12 – 3.01 (m, 2H), 1.25 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 150.4, 135.6, 133.4, 129.1, 128.9, 128.3, 127.5, 125.7, 120.6, 41.9, 40.0, 34.6, 31.4.

3-(Benzo[d][1,3]dioxol-4-yl)-2-phenylpropanenitrile (N$_{15}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as the eluent] to give pure product N$_{15}$ as a colorless oil (1.118 g, 89%); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.38 – 7.25 (m, 5H), 6.73 (d, J = 8.0 Hz, 1H), 6.62 – 6.58 (m, 2H), 5.92 (s, 2H), 3.96 (dd, J = 8.2, 6.6 Hz, 1H), 3.12 – 3.02 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ = 147.8, 146.9, 135.2, 130.0, 129.1, 128.3, 127.5, 122.5, 120.4, 109.5, 108.4, 101.1, 41.9, 40.0.

3-phenoxy-3-(2-phenylpropyl)benzene (N$_{19}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as the eluent] to give pure product N$_{19}$ as a colorless oil (1.242 g, 83%); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.33 – 7.26 (m, 5H), 7.24 – 7.18 (m, 3H), 7.06 (t, J = 7.4 Hz, 1H), 6.92 – 6.86 (m, 4H), 6.70 (s, 1H), 3.94 (dd, J = 8.2, 6.6 Hz, 1H), 3.07 (m, 2H). ^{13}C{^{1}H}

NMR (101 MHz, CDCl$_3$) δ = 157.3, 157.0, 138.2, 135.0, 130.0, 129.8, 129.1, 128.3, 127.5, 124.1, 123.4 120.3, 119.6, 118.9, 117.9, 41.9, 39.5.

3-(4-Chlorophenyl)-2-phenylpropanenitrile (N$_{16}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product N$_{16}$ as a white solid (0.979 g, 81%), ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.41 – 7.34 (m, 3H), 7.29 – 7.24 (m, 4H), 7.06 (d, J = 8.4 Hz, 2H), 4.0 (dd, J = 8.1, 6.6 Hz, 1H), 3.20 – 3.10 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ = 134.8, 134.7, 133.4, 130.7, 129.2, 128.8, 128.4, 127.6, 120.2, 41.5, 39.6.

3-(Naphthalen-1-yl)-2-phenylpropanenitrile (N$_{17}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product N$_{17}$ as a white solid (1.093 g, 85%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.96 – 7.91 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.44 – 7.30 (m, 7H), 4.18 (dd, J = 8.2, 6.6 Hz, 1H), 3.68 – 3.57 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 135.6, 134.0, 132.3, 131.3, 129.3, 129.2, 128.4, 128.3, 128.1, 127.4, 126.6, 125.8, 125.5, 122.7, 120.6, 39.6, 38.8.

2-Phenyl-3-(thiophen-2-yl)propanenitrile(N$_{18}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as the eluent] to give pure product **N$_{18}$** as a colorless oil (0.831 g, 78%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.30 (m, 5H), 7.19 (dd, J = 5.1, 1.1 Hz, 1H), 6.95 - 6.93 (m, 1H), 6.90 – 6.83 (m, 1H), 4.06 (dd, J = 8.2, 6.6 Hz, 1H), 3.48 – 3.33 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 138.0, 134.8, 129.2, 128.5, 127.5, 127.2, 127.1, 125.0, 120.2, 40.1, 36.2.

1-Phenyl-2-(p-tolyl)propanenitrile(N$_{21}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product **N$_{21}$** as a white solid (0.995 g, 90%);

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.34 – 7.25 (m, 3H), 7.20 – 7.13 (m, 6H), 3.98 (dd, J = 8.3, 6.6 Hz, 1H), 3.21 – 3.11 (m, 2H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 138.1, 136.5, 132.3, 129.9, 129.7, 129.3, 128.7, 127.4, 120.7, 42.3, 39.5, 21.2.

2-(4-chlorophenyl)-2-(4-methoxyphenyl)propanenitrile(N$_{36}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as the eluent] to give pure product **N$_{36}$** as a white solid (1.141 g, 84%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.16 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 3.84 (t, J = 7.2 Hz, 1H), 3.71 (s, 3H), 3.08 – 2.93 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 159.5, 134.8, 133.3, 130.7, 128.8, 128.7, 126.7, 120.4, 114.4, 55.4, 41.5, 38.7.

2-(4-bromophenyl)-3-(p-tolyl)propanenitrile(N$_{42}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as the eluent] to give pure product **N$_{42}$** as a white solid (1.155 g, 77%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 (d, J = 8.0 Hz, 2H), 7.11 – 6.98 (m, 4H), 6.99 (d, J = 8.0 Hz, 2H), 3.94 (t, J = 7.3 Hz 1H), 3.15 – 3.03 (m, 2H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 137.2, 134.3, 132.8, 132.2, 129.4, 129.3, 129.2, 122.3, 120.1, 41.6, 39.4, 21.2.

2-phenylhexanenitrile(N$_{112}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product **N$_{112}$** as colorless oil (0.641 g, 74%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27 – 7.17 (m, 5H), 3.80 (dd, J = 8.2, 6.6 Hz, 1H), 1.68 – 1.84 (m, 2H), 1.39 - 1.19 (m, 4H), 0.94 (t, J = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 136.2, 129.1, 128.0, 127.3, 121.1, 37.5, 35.7, 29.2, 22.2, 13.9.

2-phenyloctanenitrile(N$_{113}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product **N$_{113}$** as colorless oil (0.704 g, 70%); ^{1}H NMR (400 MHz,

CDCl$_3$) δ 7.39 – 7.29 (m, 5H), 3.77 (dd, *J* = 8.2, 6.6 Hz, 1H), 1.97 – 1.80 (m, 2H), 1.54 – 1.38 (m, 2H), 1.36 – 1.22 (m, 6H), 0.88 (t, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 136.1, 129.0, 128.0, 127.2, 121.0, 37.4, 36.0, 31.5, 28.6, 27.0, 22.6, 14.0.

2-phenylnonanenitrile(N$_{114}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product **N$_{114}$** as colorless oil (0.732 g, 68%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.31 – 7.22 (m, 5H), 3.68 (dd, *J* = 8.4, 6.4 Hz, 1H), 1.983 – 1.77 (m, 2H), 1.41 – 1,37 (m, 2H), 1.22 – 1.18 (m, 8H), 0.79 (t, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 136.2, 129.2, 128.1, 127.4, 121.1, 37.5, 36.0, 31.8, 29.1, 29.0, 27.2, 22.7, 14.2.

3-phenyldecanenitrile(N$_{115}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product **N$_{115}$** as colorless oil (0.768 g, 67%); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.40 – 7.30 (m, 5H), 3.77 (dd, *J* = 8.2, 6.6 Hz, 1H), 1.97 – 1.80 (m, 2H), 1.54 – 1.25 (m, 13H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ = 136.2, 129.2, 128.1, 127.4, 121.1, 37.6, 36.1, 31.9, 29,3, 29.1, 27.2, 22.8, 14.2.

3-cyclohexyl-2-phenylpropanenitrile(N$_{116}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product **N$_{116}$** as colorless oil (0.768 g, 67%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.31 (m, 5H), 3.85 (dd, *J* = 8.2, 6.6 Hz, 1H), 1.92 – 1.82 (m, 2H), 1.77 – 1.63 (m, 5H), 1.58 – 1.51 (m, 1H), 1.30 – 1.23 (m, 2H), 1.22 – 1.15 (m, 1H), 1.03 – 0.91 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 136.5, 129.1, 128.9, 128.8, 127.9, 127.2, 125.6, 121.1, 43.7, 35.3, 34.8, 33.2, 32.3, 26.3, 25.9, 25.8.

6-phenyl-2-(pyridin-2-yl)hexanenitrile(N$_{517}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as the eluent] to give pure product **N$_{517}$** as colorless oil (0.850 g, 72%); ^{1}H

NMR (400 MHz, CDCl$_3$) δ 8.48 – 8.46 (m, 1H), 7.61 – 7.57 (m, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.17 – 7.11 (m, 3H), 7.08 – 7.03 (m, 3H), 3.85 (t, J = 7.3 Hz, 1H), 2.50 (t, J = 7.4 Hz, 2H), 1.96 – 1.90 (m, 2H), 1.61 – 1.40 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ = 149.9, 142.0, 137.4, 128.4, 125.8, 123.0, 121.7, 120.2, 39.8, 35.6, 34.0, 30.8, 26.7.

2,6-diphenylhexanenitrile(N$_{117}$): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as the eluent] to give pure product **N$_{117}$** as colorless oil (0.941 g, 80%); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.32 – 7.18 (m, 7H), 7.14 – 7.06 (m, 3H), 3.67 (dd, J = 8.2, 6.6 Hz, 1H), 2.53 (t, J = 7.3 Hz, 2H), 1.93 – 1.77 (m, 2H), 1.60 – 1.42 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ = 142.1, 136.0, 129.2, 128.5, 128.4, 128.1, 127.3, 126.0, 121.0, 37.4, 35.9, 35.7, 30.9, 26.8.

2-phenylquinoline (**Q$_{11}$**): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as the eluent] to give pure product **Q$_{11}$** as white solid (0.096 g, 94%) ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.22 (d, J = 8.0 Hz, 1H), 8.20 – 8.15 (m, 3H), 7.88 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.0, 1H), 7.75 – 7.71 (m, 1H), 7.55 – 7.51 (m, 3H), 7.50 – 7.43 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 157.4, 148.4, 139.8, 129.9, 129.5, 129.0, 127.7, 127.6, 126.4, 119.2.

2-(4-methoxyphenyl)quinoline (**Q$_{13}$**): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9:1) as the eluent] to give pure product **Q$_{13}$** as white solid (0.100 g, 85%) ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.19 – 8.12 (m, 4H), 7.85 – 7.79 (m, 2H), 7.73 – 7.69 (m, 1H), 7.52 – 7.48 (m, 1H), 7.05 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 161.0, 157.1, 148.4, 136.8, 132.4, 129.7, 129.0, 127.6, 127.1, 126.0, 118.7, 114.4, 55.5.

2-(3,4-dimethoxyphenyl)quinoline (**Q$_{14}$**): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and

ethylacetate (9:1) as the eluent] to give pure product **Q₁₄** as white solid (0.109 g, 82%); ^{1}H

NMR (400 MHz, CDCl₃) δ 8.17 – 8.13 (m, 2H), 7.88 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.80 –

7.77 (m, 1H), 7.72 – 7.68 (m, 1H), 7.65 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.51 – 7.47 (m, 1H), 6.97

(d, *J* = 8.0 Hz, 1H), 4.04 (s, 3H), 3.94 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl₃) δ 157.2,

150.8, 149.8, 148.6, 137.0, 132.9, 130.0, 129.9, 127.8, 127.4, 126.4, 120.6, 119.0, 111.4,

110.8, 56.4, 56.3.

2-(4-(trifluoromethyl)phenyl)naphthalene (**Q₁₆**): The crude product was purified by

column chromatography [silica as the stationary phase and a mixture of petroleum ether and

ethylacetate (9:1) as the eluent] to give pure product **Q₁₆** as white solid (0.089 g, 66%); ^{1}H

NMR (400 MHz, CDCl₃) δ 8.33 – 8.16 (m, 4H), 7.87 – 7.83 (m, 2H), 7.80 – 7.73 (m, 3H),

7.58 – 7.54 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl₃) δ 155.8, 148.4, 143.1, 137.2, 131.2

(q, *J* = 32.5 Hz), 130.1, 130.0, 128.0, 127.6, 127.0, 125.8 (q, $^3J_{C-F}$ = 3.0 Hz), 123.0 (q, $^1J_{C-F}$ =

271.0 Hz), 118.9.

5,6-dihydrobenzo[*c*]acridine (**Q₁₇**): The crude product was purified by column

chromatography [silica as the stationary phase and a mixture of petroleum ether and

ethylacetate (9:1) as the eluent] to give pure product **Q₁₇** as white solid (0.105 g, 91%); ^{1}H

NMR (400 MHz, CDCl₃) δ 8.62 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.89 (s, 1H),

7.74 (*J* = 8.1, 1H), 7.69 – 7.65 (m, 1H), 7.50 – 7.44 (m, 2H), 7.41 – 7.37 (m, 1H), 7.29 (d, *J* =

8.0 Hz, 1H), 3.13 – 3.08 (m, 2H), 3.03 – 2.99 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl₃) δ

153.4, 147.7, 139.5, 134.8, 133.8, 130.6, 129.8, 129.4, 128.7, 128.0, 127.4, 127.0, 126.1,

28.9, 28.4.

2-(benzo[*d*][1,3]dioxol-5-yl)quinoline (**Q₁₈**): The crude product was purified by column

chromatography [silica as the stationary phase and a mixture of petroleum ether and

ethylacetate (9:1) as the eluent] to give pure product **Q₁₈** as white solid (0.110 g, 88%); ^{1}H

NMR (400 MHz, CDCl₃) δ 8.20 – 8.11 (m, 2H), 7.81 – 7.78 (m, 2H), 7.75 – 7.69 (m, 2H),

7.66 (dd, J = 8.1, 1.8 Hz, 1H), 7.52 – 7.48 (m, 1H), 6.95 (d, J = 8.1 Hz, 1H), 6.04 (s, 2H).

^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 156.8, 149.0, 148.5, 148.3, 136.8, 134.3, 129.8, 129.7, 127.5, 127.1, 126.2, 121.9, 118.7, 108.6, 108.1, 101.5.

2-(naphthalen-2-yl)quinoline (**Q$_{19}$**): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product **Q$_{19}$** as white solid (0.106 g, 83%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.63 (s, 1H), 8.39 (dd, J = 8.1, 1.8 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 8.04 – 8.02 (m, 3H), 7.92 – 7.84 (m, 2H), 7.78 – 7.74 (m, 1H), 7.59 – 7.51 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 157.3,148.5,137.1,136.9, 134.0, 133.6, 129.9, 129.0, 128.7, 127.8, 127.6, 127.4,127.3, 126.8, 126.5,125.2, 119.3.

2-(pyridin-2-yl)quinoline (**Q$_{110}$**): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product **Q$_{110}$** as white solid (0.075 g, 73%); ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.33 (d, J = 2.2 Hz, 1H), 8.67 (dd, J = 4.8, 1.6 Hz, 1H), 8.55 – 8.44 (m, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.18 – 8.14 (m, 1H), 7.86 – 7.82 (m, 2H), 7.76 – 7.72 (m, 1H), 7.54 (t, J = 7.4 Hz, 1H), 7.45 – 7.41 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 154.7, 150.2, 148.8, 148.4, 137.3, 135.2, 135.11, 130.1, 129.8, 127.7, 127.4, 126.9, 123.8, 118.6.

2-cyclopropylquinoline (**Q$_{111}$**): The crude product was purified by column chromatography [silica as the stationary phase and a mixture of petroleum ether and ethylacetate (9.5:0.5) as the eluent] to give pure product **Q$_{111}$** as white solid (0.064 g, 76%);^{1}H NMR (400 MHz, CDCl$_3$) δ 8.0 – 7.96 (m, 2H), 7.73 (dd, J = 8.1, 1.2 Hz, 1H), 7.66 – 7.62 (m, 1H,), 7.44 – 7.40 (m, 1H), 7.16 (d, J = 8.0 Hz, 1H), 2.28 – 2.21 (m, 1H), 1.18 – 1.15 (m, 2H), 1.12 – 1.07 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 163.5, 148.1, 136.0, 129.3, 128.8, 127.6, 126.9, 125.3, 119.4, 18.2, 10.4.

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NMR spectra of compounds
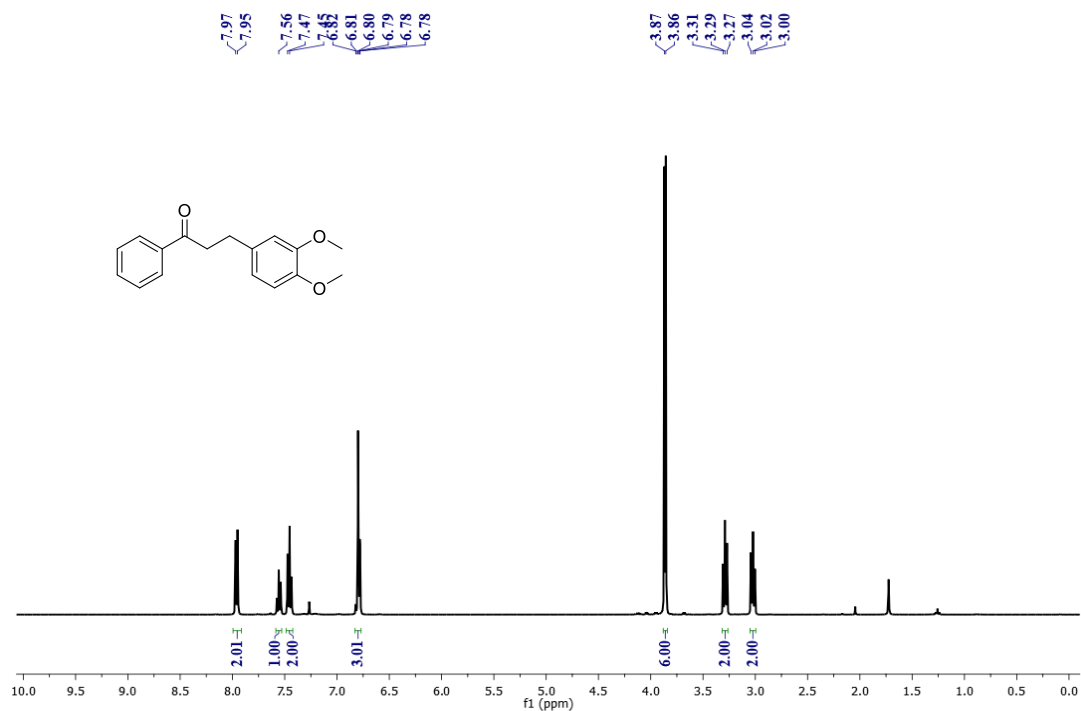
Figure 3.1 ^{1}H NMR (400 MHz) of 2-(3,4-dimethoxyphenyl)-1-phenylpropan-1-one **(P$_{13}$)**
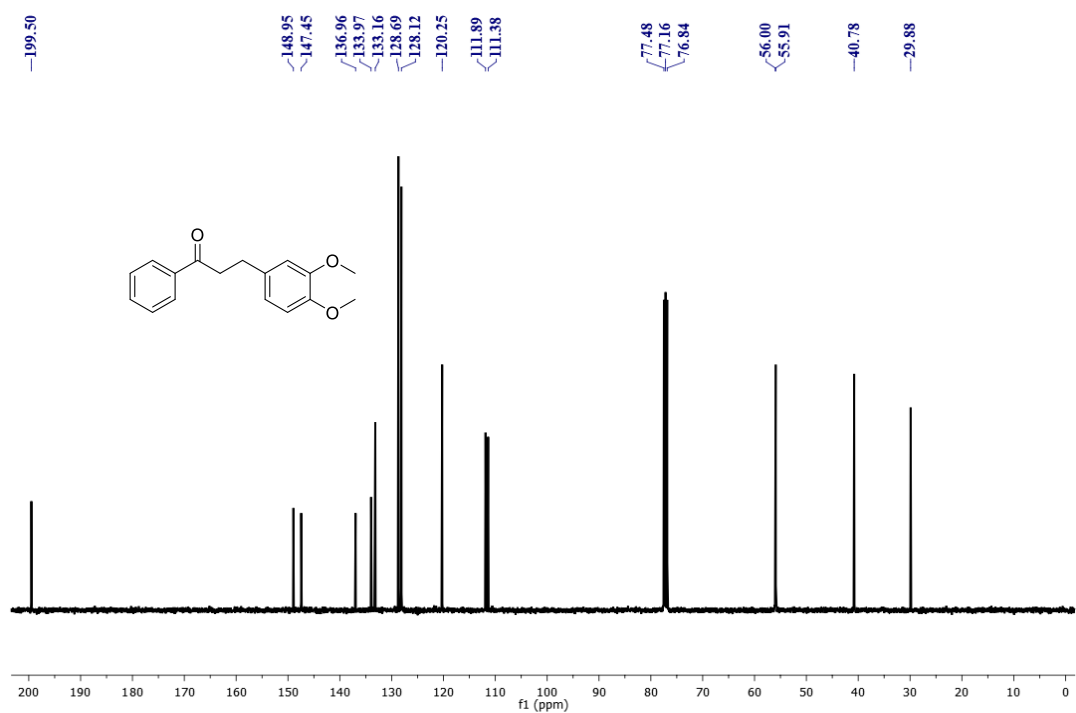
Figure 3.2 ^{13}C{^{1}H} NMR (101 MHz) of 2-(3,4-dimethoxyphenyl)-1-phenylpropan-1-one **(P$_{13}$)**.
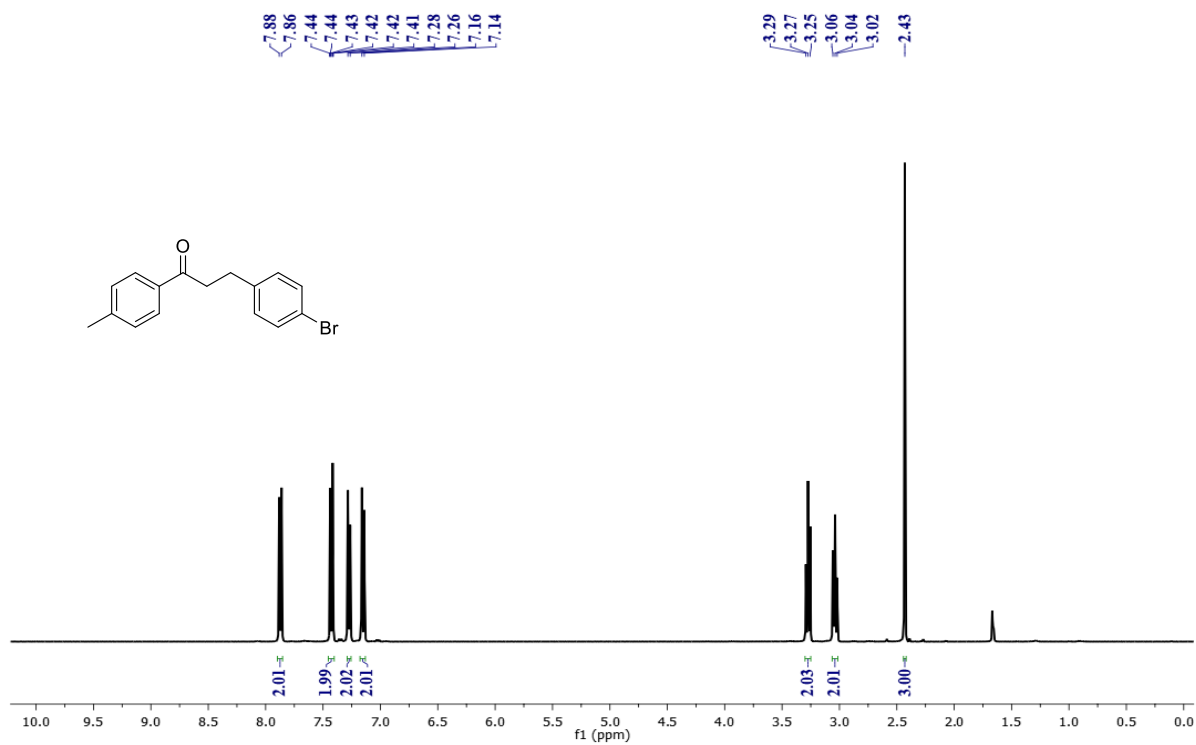
Figure 3.3 ^{1}H NMR of 3-(4-bromophenyl)-1-(p-tolyl)propan-1-one (**P$_{211}$**).
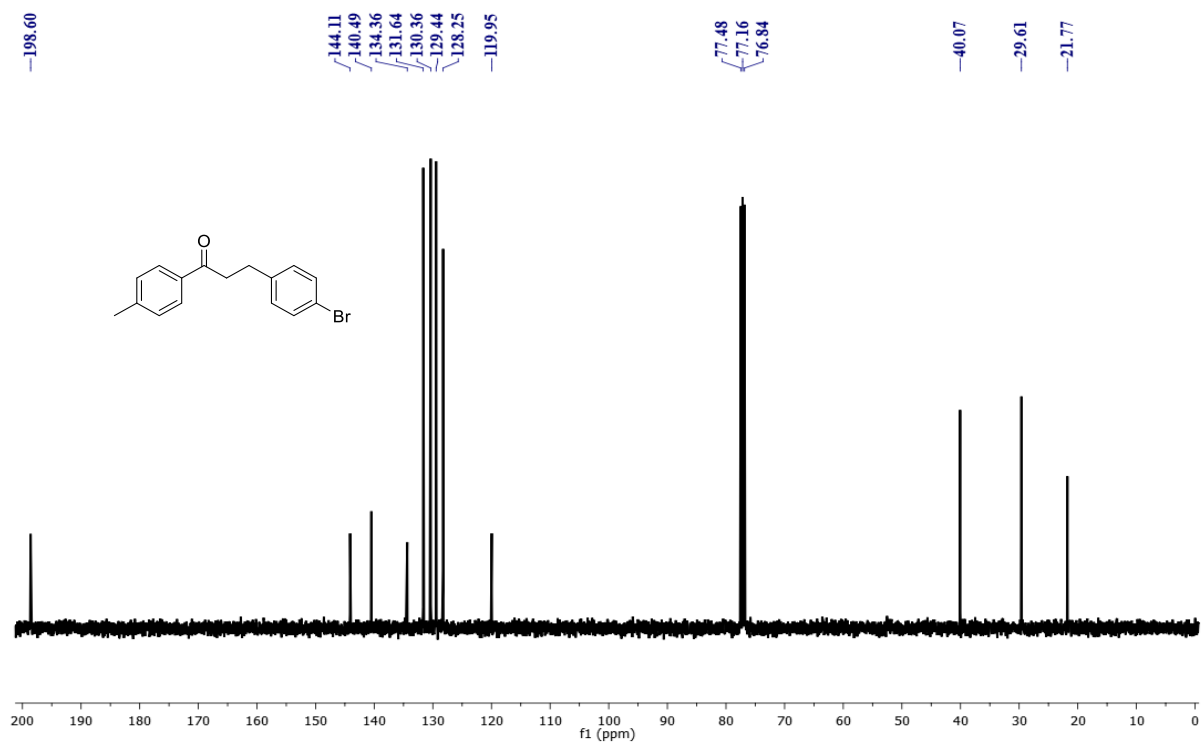
Figure 3.4 ^{13}C{^{1}H} NMR of 3-(4-bromophenyl)-1-(p-tolyl)propan-1-one (**P$_{211}$**).
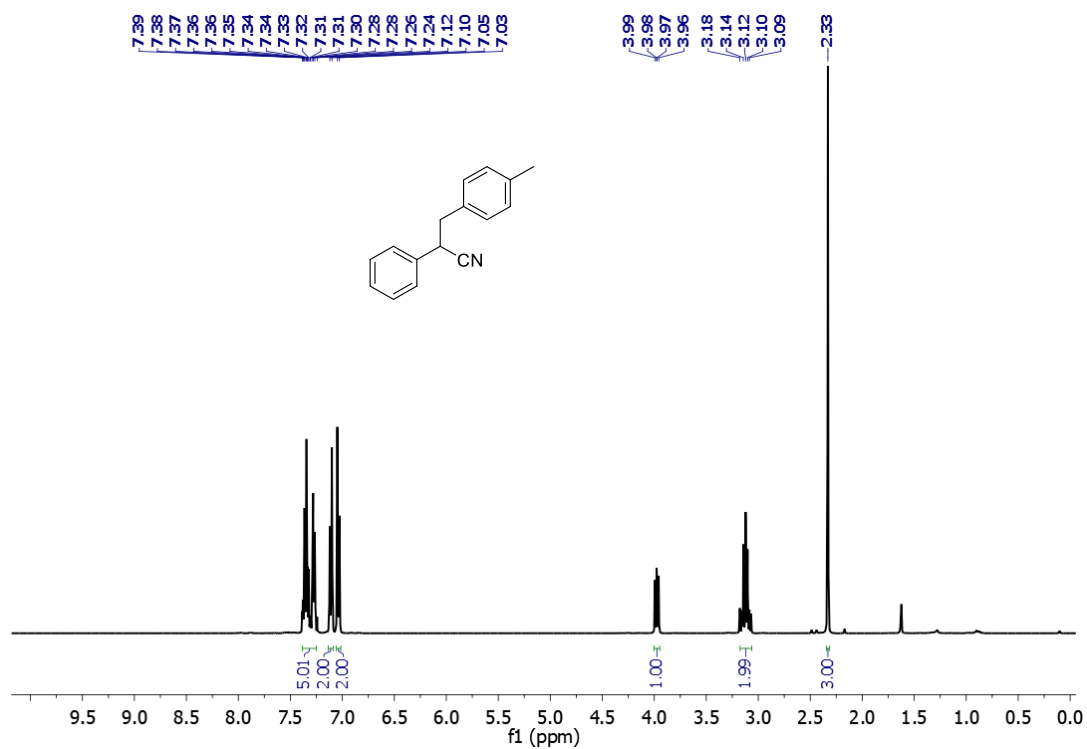
Figure 3.5 ^{1}H NMR (400 MHz) of 2-Phenyl-3-(p-tolyl) propanenitrile (**N$_{12}$**)
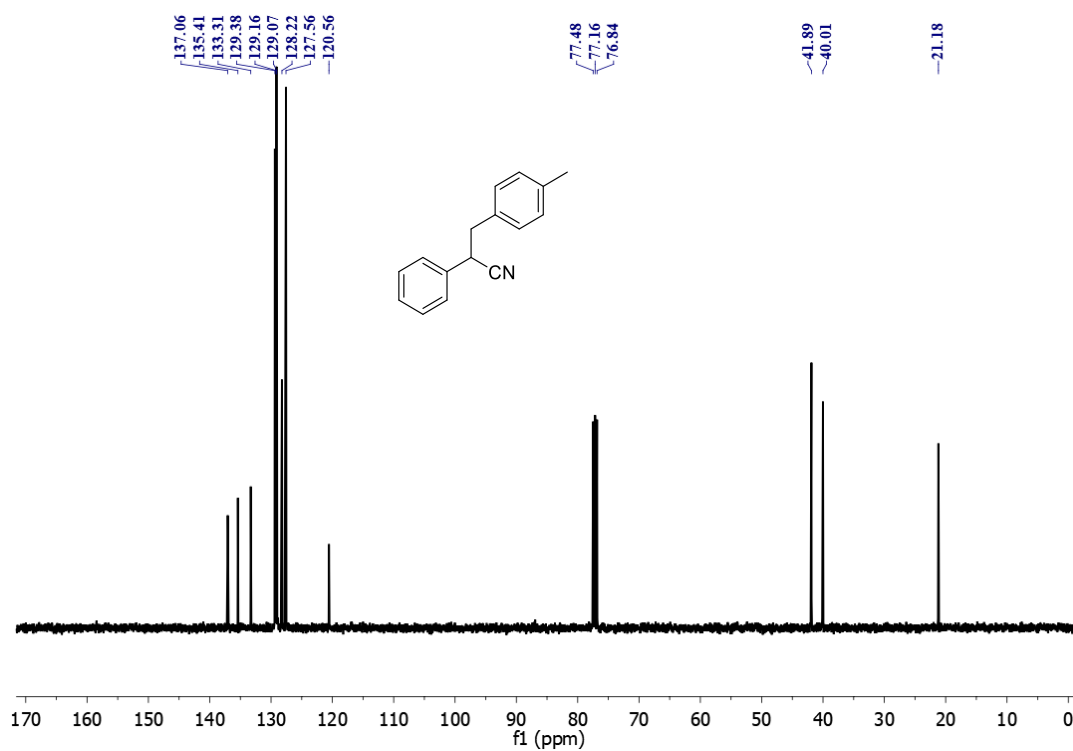
Figure 3.6 ^{13}C{^{1}H} NMR (101 MHz) of 2-Phenyl-3-(p-tolyl) propanenitrile (**N$_{12}$**)
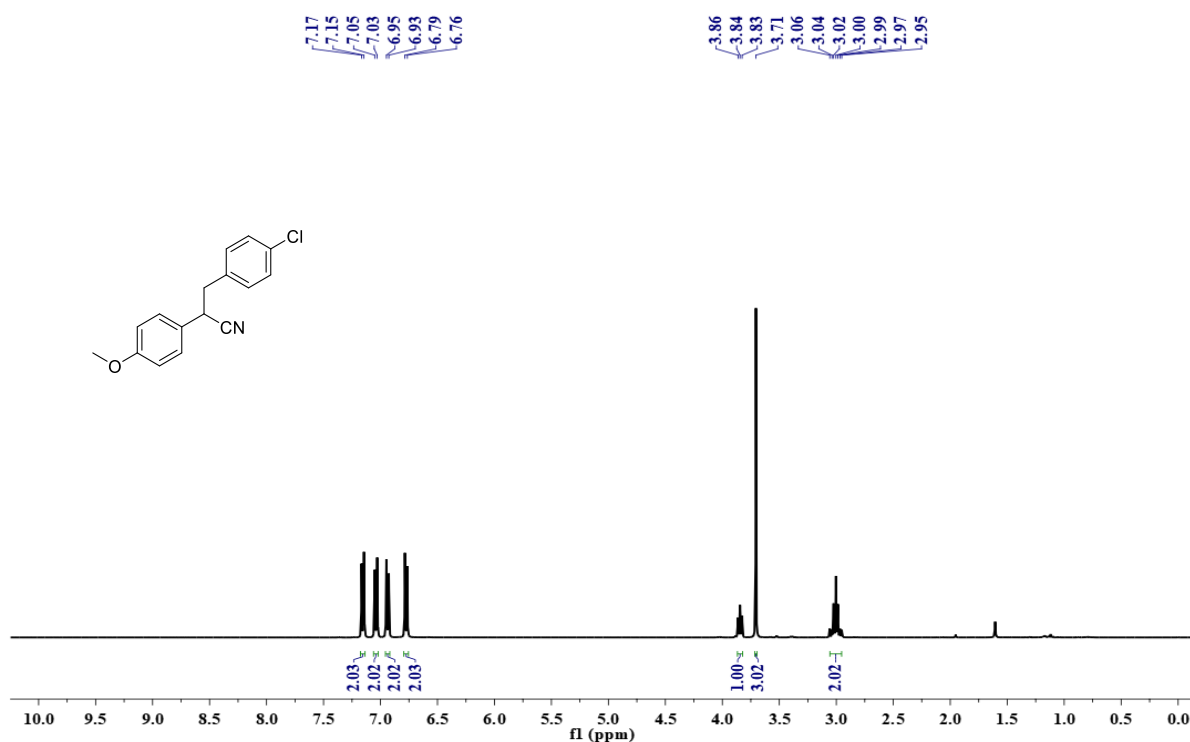
Figure 3.7 ^{1}H NMR (400 MHz) of 3-(4-chlorophenyl)-2-(4-methoxyphenyl) propanenitrile (**N$_{36}$**).
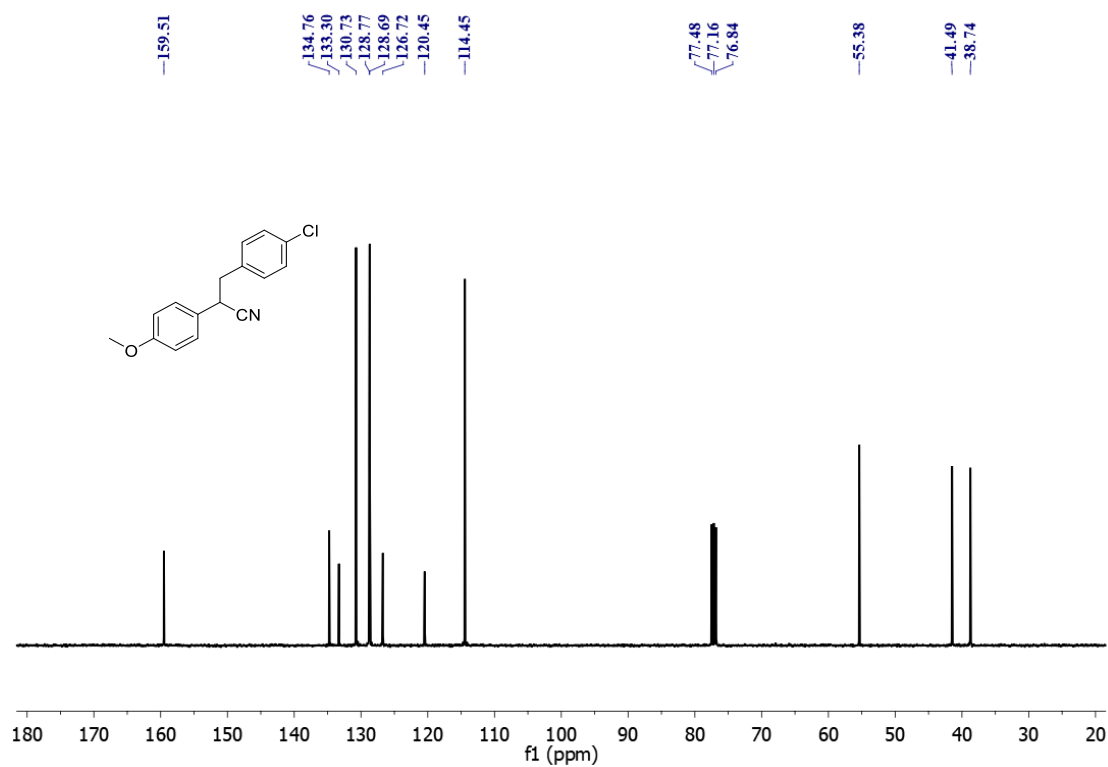
Figure 3.8 ^{13}C{^{1}H} NMR (101 MHz) of 3-(4-chlorophenyl)-2-(4-methoxyphenyl) propanenitrile (**N$_{36}$**).
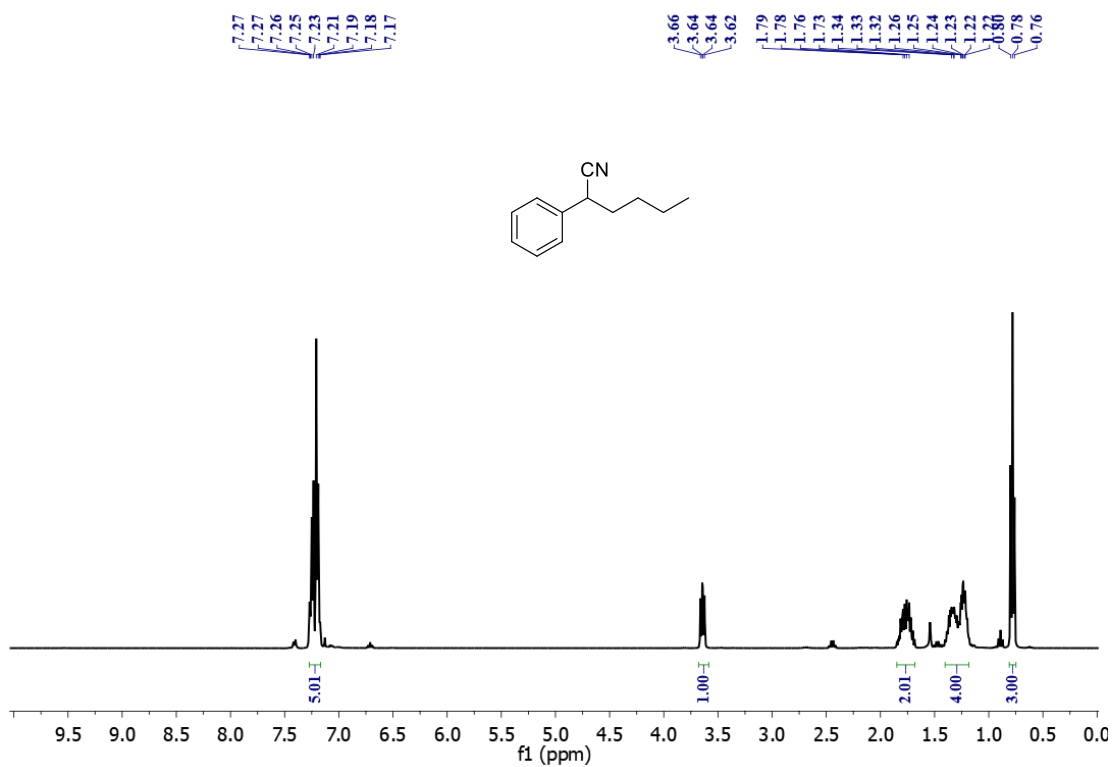
Figure 3.9 ^{1}H NMR (400 MHz) of 2-phenylhexanenitrile (**N$_{112}$**).
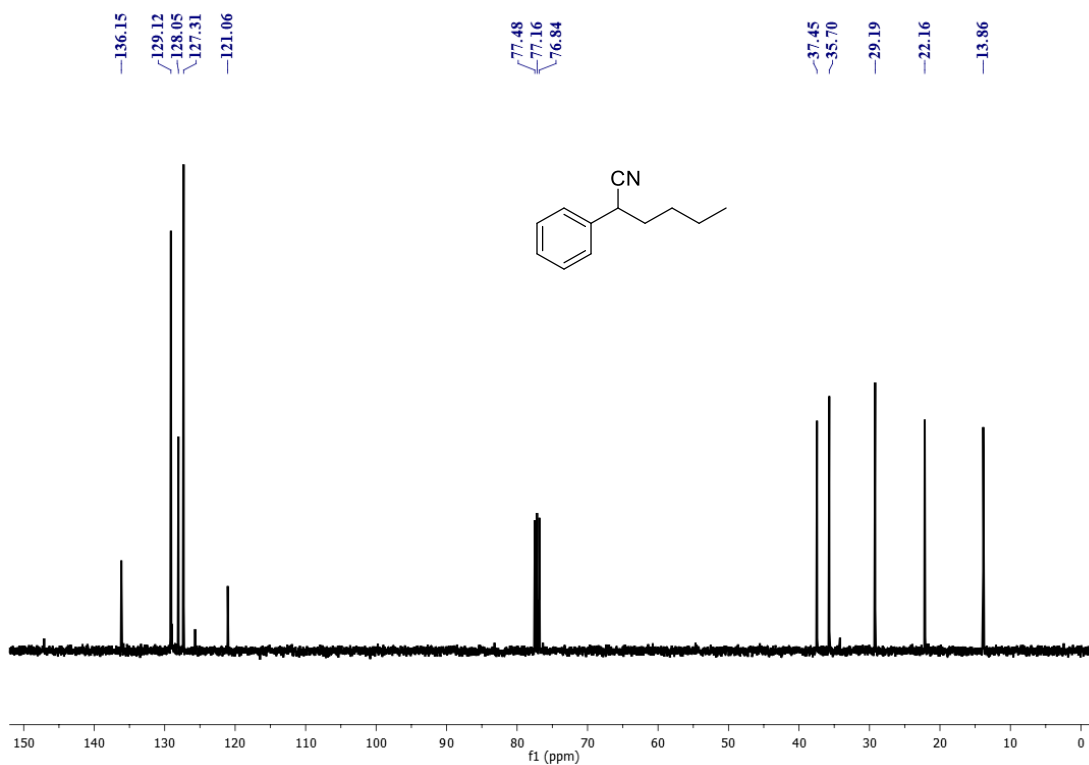
Figure 3.10 ^{13}C{^{1}H} NMR (101 MHz) of 2-phenylhexanenitrile (**N$_{112}$**)
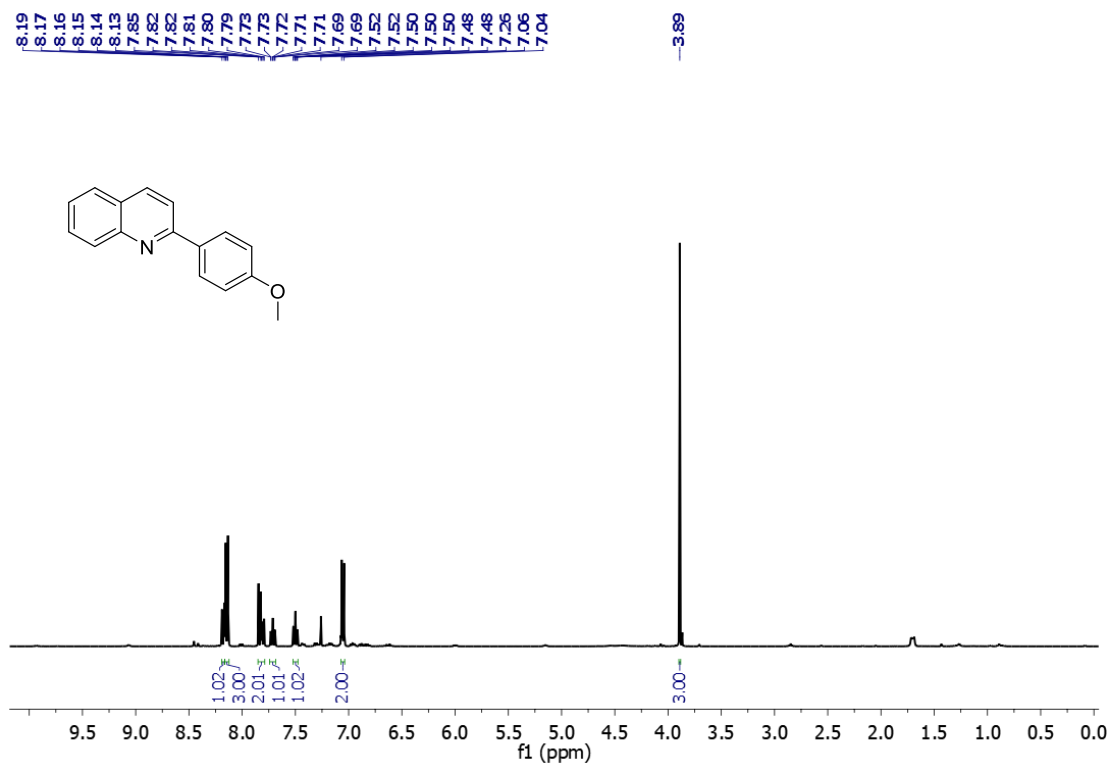
Figure 3.11 ¹H NMR (400 MHz) of 2-(4-methoxyphenyl) quinoline (**Q₁₃**).
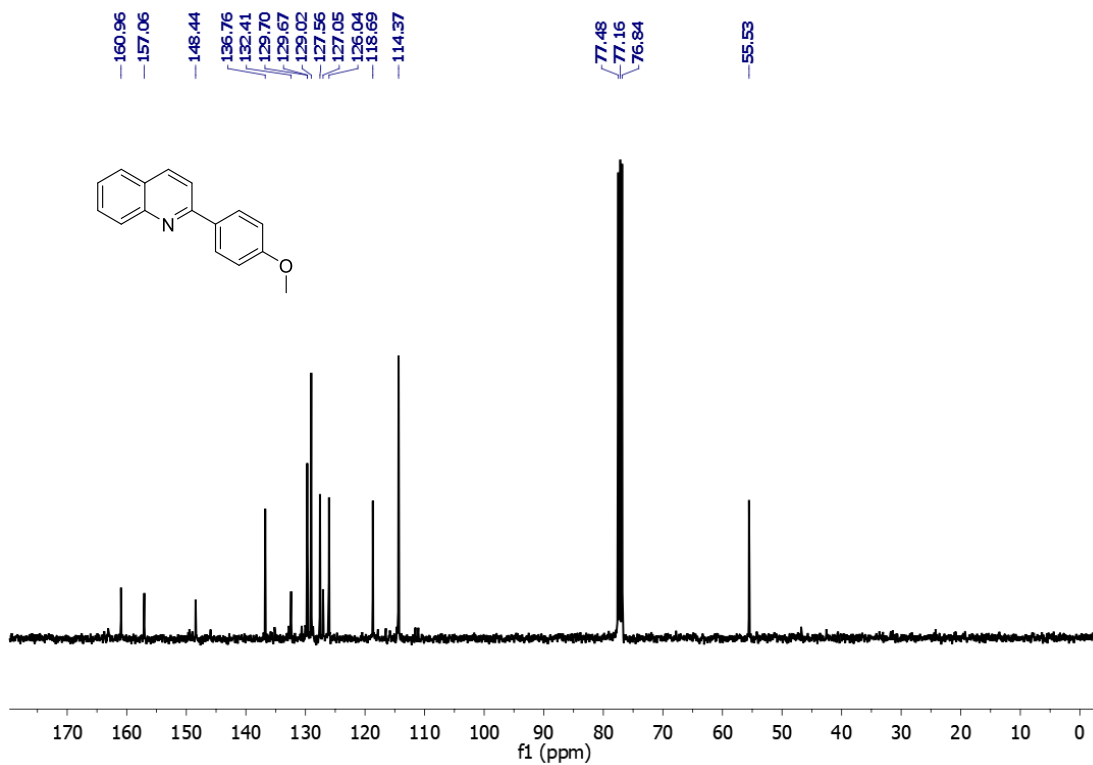
Figure: 3.12 ¹³C{¹H} NMR (101 MHz) of 2-(4-methoxyphenyl) quinoline (**Q₁₃**).

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Figure 3.13 ¹H NMR (400 MHz) of 2-cyclopropylquinoline (**Q₁₁₁**).

Figure: 3.14 ¹³C{¹H} NMR (101 MHz) of 2-cyclopropylquinoline (**Q₁₁₁**).

Chapter 4

Cobalt Catalyzed Chemoselective Reduction of Nitroarenes: Hydrosilylation under Thermal and Photochemical Reaction Conditions

4.1 ABSTRACT

Commercially available $Co_2(CO)_8$ was used as an effective catalyst for the hydrosilylation of nitroarenes under both thermal and photochemical conditions. A wide variety of nitroarenes with various functionalities were selectively reduced to aromatic amines. Syntheses of drug molecules expand the potential utility of this protocol. Experimental evidence suggested a radical pathway.

4.2 INTRODUCTION

Aromatic amines are essential building blocks that are heavily used in the production of dyes, agrochemicals, drugs, polymers, pigments, and other industrially and biologically important molecules.[1] Moreover, the amino group can be easily converted to diazonium salts which can be readily functionalized with various groups such as fluoro, chloro, bromo, iodo and hydroxo. Among several methods for amine syntheses, the reduction of nitro compounds to the corresponding amines is one of the foremost and straightforward techniques. Béchamp reduction, an early non-catalytic method to synthesize aniline derivatives from nitroarenes, required a stoichiometric or excess amount of Fe dust or ferrous salt.[2] In addition, the requirement of corrosive hydrochloric acid and generation of a huge amount of waste are other major drawbacks. Besides Béchamp reduction, several reducing agents such as CO/H_2O, hydroiodic acid, tin chloride, sodium hydrosulfite, and ammonia borane have also been employed. Although hydride reducing agents such as $LiAlH_4$, $NaBH_4$, and NaH are commonly used for the reduction of various functionalities, these hydride reagents tend to

produce azo compounds in the reduction of the nitro group.[3] However, Ni-catalyzed reduction of nitroarenes with NaBH4 is reported.[4] In addition to the use of stoichiometric reducing agents including metal hydride, transfer hydrogenation and classical hydrogenation of nitroarenes to aromatic amines have been well-explored. Hydrazines were also used as a hydrogen source and several catalysts have been reported.[5] Formic acid has also been used for the catalytic transfer hydrogenation of nitroarenes.[6] Catalytic hydrogenation can be considered as the most effective and green protocol as compared to other reduction methods with stoichiometric reducing reagents. Classical hydrogenation of nitroarenes is well established with costly Pd/C or Pt/C and highly pyrophoric RANEY[s] Ni catalysts, along with various other heterogeneous catalysts.[7] A significant setback in dealing with heterogeneous catalysts is poor chemoselectivity of nitroarenes bearing other reducible groups. Many heterogeneous catalysts are also associated with toxic impurities or by-products.[8] Due to the use of mild reaction conditions and better selectivity, homogeneous hydrogenation has gained momentum. Several homogeneous noble metals (Ru, Ir, Pt, Pd and Au) and a few base metal catalysts (Fe and Mn) have been developed for the hydrogenation of nitroarenes.[9] Catalytic hydrosilylation is another effective route for nitroarene reduction. Hydrosilylation provides a good alternative to avoid the use of flammable and pressurized hydrogen gas and a costly experimental set up in classical hydrogenation. In the last two decades, silanes have been extensively used for the reduction of various functionalities; for example, ketones, esters, carboxylic acids, alkenes, and imines have been heavily studied,[10] but reports on hydrosilylation of the nitro group are limited. A few reports have been published on the hydrosilylation of nitroarenes using noble metal catalysts (Ru, Rh, Pd, Pt and Au),[11] but noble metals are scarce, expensive and often toxic. In contrast, the use of earth-abundant, inexpensive and often environmentally benign base metals is sustainable. A few research groups have already made some advances in this field (Scheme 1). More than a decade ago, Beller *et al.* reported

Fe-catalyzed hydrosilylation of nitroarenes using $FeBr_2$ (10 mol%) in the presence of PPh_3 (12 mol%).[12] A few groups reported Fe-catalyzed hydrosilylation of nitroarenes to anilines, which were directly utilized for further reactions.[13] In 2021, Darcel *et al.* reported a Fe-NHC catalyst for nitroarene hydrosilylation under visible light irradiation; however, high reaction temperature (90 °C) was required.[14] Apart from Fe, there are three reports on Ni-catalyzed hydrosilylation of nitroarenes.[15] Quan and Wang *et al.* used $Ni(acac)_2$ (10 mol%) as catalyst.[15a] Recently, Mandal *et al.* reported a Ni-NHC complex (5 mol%) as an efficient catalyst.[15b] Royo *et al.* also utilized Ni-NHC complex for the same purpose.[15c] Very recently, we reported the first example of Mn-catalyzed hydrosilylation of nitroarenes.[16] In the above reports, hydrosilylations were performed at elevated temperatures. However, there is no report on the Co-catalyzed hydrosilylation of nitroarene (to the best of our knowledge).

Scheme 4.2.1 Base metal catalyzed hydrosilylation of nitroarenes to aromatic amines

Previous work: Base-metal catalyzed hydrosilylation of nitroarenes to anilines

Present work: Cobalt catalyzed hydrosilylation of nitroarenes to anilines

Condition 1: thermal
[Co]: 1 mol%, 100 °C, 3 h, THF

Condition 2: photochemical
[Co]: 3 mol%, hν (350 nm), r.t., 2 h, THF
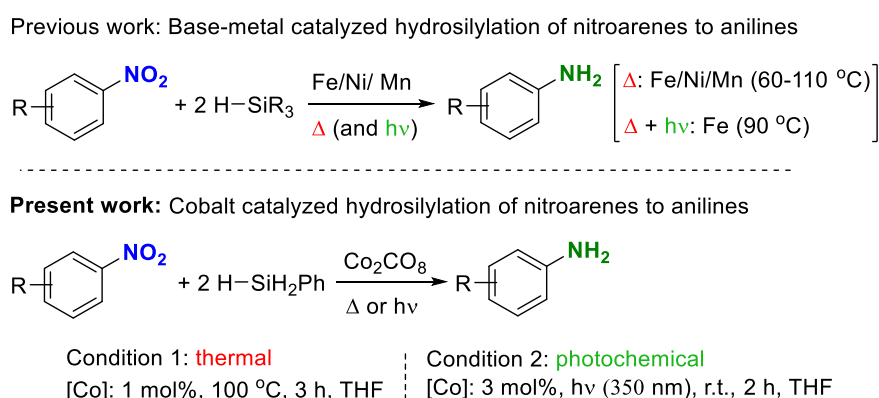
In addition to Fe-, Ni- and Mn-catalyzed hydrosilylation of nitroarenes, other base metal catalysts need to be developed. One important example is Co, which is much cheaper and less toxic than its heavier counterparts (Rh and Ir). In fact, Co catalysts have emerged as one of the premier candidates in the hydrosilylation of a plethora of substrates such as alkynes, alkenes, allenes, aldehydes, ketones, amides and nitriles.[17] Surprisingly, cobalt-catalyzed hydrosilylation of nitro compounds to the corresponding amines has not been reported so far. $Co_2(CO)_8$ has long been used in various hydrosilylations; mostly thermal activation has been

reported. It emerges as an excellent hydrosilylation catalyst due to the lower bond energy of the Co–H bond in the generated intermediate H–Co(CO)$_4$ as compared to its heavier analogues.[18] Photochemical activation of Co$_2$(CO)$_8$ is equally feasible. Employing photochemical methods for hydrosilylation at r.t. adds more value in this catalytic protocol. Herein, we report commercially available Co$_2$(CO)$_8$ as an efficient catalyst for chemoselective hydrosilylation of nitroarenes to aromatic amines under both thermal as well as photochemical conditions (Scheme 4.2.1).

4.3 RESULTS AND DISCUSSIONS

The use of Co$_2$(CO)$_8$ as a catalyst in the hydrosilylation of various organic substrates is not uncommon.[19] Sonoda *et al.* reported Co$_2$(CO)$_8$ catalyzed hydrosilylation of methyl acrylates in 1983.[19a] Kato *et al.* reported Co$_2$(CO)$_8$ catalyzed hydrosilylation of nitriles to access *N,N*-dislylamines in 1990.[19b] Since then, the applicability of Co$_2$(CO)$_8$ in hydrosilylations has been extended to several other substrates such as alkenes, alkynes and α,β-unsaturated esters.[19c–e] Keeping a note of the previous use, we set out to evaluate the catalytic performance of Co$_2$(CO)$_8$ in the hydrosilylation of nitroarenes using *p*-nitroanisole as the standard substrate (Table 4.2.1). The reduction conditions for the hydrosilylation of *p*-nitroanisole were optimized by changing various catalyst loadings in the presence of several silanes at different reaction temperatures (Table 4.2.1)

To our delight, we observed that 4-nitroanisole was completely reduced to 4-methoxyaniline in the presence of 5 mol% Co$_2$(CO)$_8$ loading and 2 equiv. of phenylsilane at 90 °C in 10 h (entry 1). With 2 mol% catalyst loading, complete reduction of *p*-nitroanisole was also noted in 10 h at 90, 80 and 70 °C (entries 1 and 2). However, the product yield was significantly reduced if the reaction temperature was further reduced to 60 °C (entry 3). Thereafter, we increased the reaction temperature to 100 °C and complete conversion to 4-methoxyaniline was observed

Table 4.3.1 Catalytic performance under thermal conditions.[a]
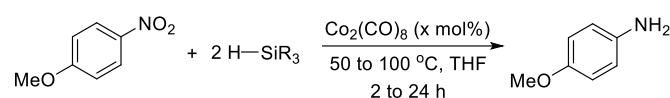
en	catalyst (mol%)	silane (2 eq)	L	temp (°C)	time (h)	yield[b] (%)
1	5/3/2	$PhSiH_3$	-	90	24/10	>99 (96[c])
2	2	$PhSiH_3$	-	80/70	10	>99
3	2	$PhSiH_3$	-	60	10	72
4	2	$PhSiH_3$	-	100	10/6	>99
5	**1**	**$PhSiH_3$**	**-**	**100**	**6/3**	**>99 (95[c])**
6	1	$PhSiH_3$	-	100	2	88
7	1	$PhSiH_3$	-	100	3	<5[d]
8	no	$PhSiH_3$	-	100	3	<3
9	1	Et_2SiH_2	-	100	3	45
10	1	Et_3SiH	-	100	3	<10
11	1	Ph_2SiH_2	-	100	3	38
12	1	silane[e]	-	100	3	<5
13	1	$PhSiH_3$	**L**[f]	100	3	<5

[a]Reactions conducted in an ace pressure tube (15 ml) with 0.5 mmol of *p*-nitroanisole, 1.0 mmol of silane, 3/2/1 mol% of **1**, and 1.5 mL of THF. [b]Yields were determined by GC using *p*-xylene (0.5 mmol) as standard. [c]Isolated yields. [d]Solvent-free condition. [e]Silane: Ph_3SiH, *i*Pr_3SiH, Me_2PhSiH, PMHS, TMDS. [f]**L** (ligand): 1,10-phenanthroline, TMEDA, DPPE

in just 6 h (entry 4). The catalyst loading was further reduced to 1 mol%, and to our delight, we observed complete reduction of the nitroarene in 3 h at 100 °C (entry 5). Further lowering the time to 2 h resulted in a small amount of unreacted substrate (entry 6). The reaction failed to proceed under solvent-free conditions (entry 7) and in the absence of $Co_2(CO)_8$ (entry 8). Thereafter, we tested various secondary and tertiary silanes such as diethylsilane, triethylsilane, diphenylsilane, triphenylsilane, dimethylphenylsilane, triisopropylsilane, TMDS and PMHS (entries 9 to 12). However, little to no conversion was observed in all cases. In addition, the reaction was carried out in the presence of three commercially available ligands *N,N*, *N′,N′*-tetramethylethylenediamine, 1,10-phenanthroline and 1,2-

bis(diphenylphosphino)ethane (entry 13). However, very poor reduction of the nitroarene was observed in all cases. Thus, the optimum conditions for the hydrosilylation of nitroarene were fixated at 1 mol% $Co_2(CO)_8$, 2 equiv. of $PhSiH_3$, 100 °C and 3 h (entry 5, depicted in bold).

The UV-vis spectrum of $Co_2(CO)_8$ exhibits λ_{max} at 350 nm. In addition to the reaction optimization under thermal conditions, the performance of the catalyst was evaluated under photo irradiation using *p*-nitroanisole as the standard substrate (Table 4.3.2).

Table 4.3.2 Catalytic performance under photochemical conditions at r.t.[a]

en	catalyst (mol%)	silane (2 eq)	temp (°C)	time (h)	yield[b] (%)
1	5	$PhSiH_3$	r.t.	0.5	>99 (93)[c]
2	5	$PhSiH_3$	r.t.	0.5	<5[d]
3	**3**	**$PhSiH_3$**	**r.t.**	**2**	**>99 (92)[c]**
4	3	$PhSiH_3$	r.t.	1	90
5	2	$PhSiH_3$	r.t.	9	>99 (94)[c]
6	1	$PhSiH_3$	r.t.	24	58

[a]Reactions conducted in a quartz tube (15 ml) with 0.5 mmol *p*-nitroanisole, 1.0 mmol silane, 5/3/2/1 mol% $Co_2(CO)_8$, in THF (1.5 mL) using 350 nm light. [b]Yields of product were determined by GC using *p*-xylene (0.50 mmol) as standard. [c]Isolated yields. [d]Reaction conducted under solvent-free conditions.

Irradiation with light of 350 nm wavelength, we observed that the *p*-nitroanisole was completely reduced to *p*-methoxyaniline in the presence of 5 mol% $Co_2(CO)_8$ and 2 equiv. phenylsilane in 0.5 h at r.t. (entry 1). The hydrosilylation did not proceed under solvent-free condition (entry 2). The catalyst loading was reduced to 3 mol% and we achieved complete reduction of the nitroarene in 2 h (entry 3). Complete reduction of *p*-nitroanisole could not be achieved in 1 h (entry 4). The catalyst loading was then reduced to 2 mol% and complete reduction of substrate was observed in 9 h (entry 5). If the catalyst loading is further reduced to 1 mol%, complete conversion of *p*-nitroanisole to *p*-methoxyaniline could not be achieved even in 24 h (entry 6). Therefore, following condition was considered as optimized reaction condition: 3 mol% $Co_2(CO)_8$, 2 equiv. of $PhSiH_3$, r.t. and 2 h (entry 3, depicted in bold).

With the optimized hydrosilylation condition in hand, the versatility and the tolerance of various functional groups were investigated by expanding the substrate scope (Scheme 4.3.1) to various substituted nitroarenes (0.5 mmol scale). A wide range of nitroarenes substituted with electron-donating groups such as amine, alkyl, halogen and thioalkyl groups were successfully reduced to the corresponding aniline derivatives with good to excellent isolated yields (A_{2a}: 90%, A_{2b}: 80%, A_{2c}: 82%, A_{2d}: 85%, A_{2e}: 84%, A_{2f}: 85%, A_{3b}: 77%, A_{4a}: 90%, A_{4b}: 81%, A_{4c}: 70%, A_{4d}: 80%, A_{4e}: 75%, A_{4F}: 80%, A_{4g}: 89%, A_6: 78%). In addition, nitroarenes substituted with electron withdrawing groups such as hydroxymethyl, amides, esters and trifluoromethyl also adhered to the protocol and good yields of products were achieved (A_{3a}: 87%, A_{4h}: 80%, A_{4i}: 84%, A_{4j}: 75%, A_{4k}: 85%). The electronic nature of substituents has no effect on this nitroarene reduction. These reductions were specific to the nitro group only and other functionalities susceptible to reduction such as alkenes, esters, amides and nitrile were left unaltered. Thus, present catalytic protocol exhibited excellent chemoselectivity. Halogen-substituted nitroarenes do not show any dehalogenated product. 4-nitrostilbene (N_5) was also reduced to 4-styrylaniline (A_5: 88%). This hydrosilylation protocol was further applied to various heteroaromatic nitro compounds such as 5-nitroindole (N_{11}) and 2-chloro-3-nitropyridine (N_{12}) which were successfully reduced to 2-chloro-3-aminopyridine (A_{11}: 65%) and 5-aminoindole (A_{12}: 75%), respectively. Not only heteroaromatic nitro compounds, hydrosilylation of some polycyclic aromatic nitro compounds such as 1-nitronapthalene (N_7) and 2-nitrofluorene (N_{10}) was successfully reduced to 1-napthylamine (A_7: 90%) and 2-aminofluorene (A_{10}: 60%) as well. Finally, the procedure proved to be effective for various nitroquinolines (N_8 and N_9) and excellent isolated yields of corresponding aminoquinolines were noted (A_8: 85% and A_9: 70%). Various nitroarenes with sterically protected nitro groups (N_{13}, N_{14} and N_{15}) could be easily reduced to the corresponding aromatic amines. Nitroarene (N_{16}) having both fluoro and

Scheme 4.3.1 Hydrosilylation of various nitroarenes.
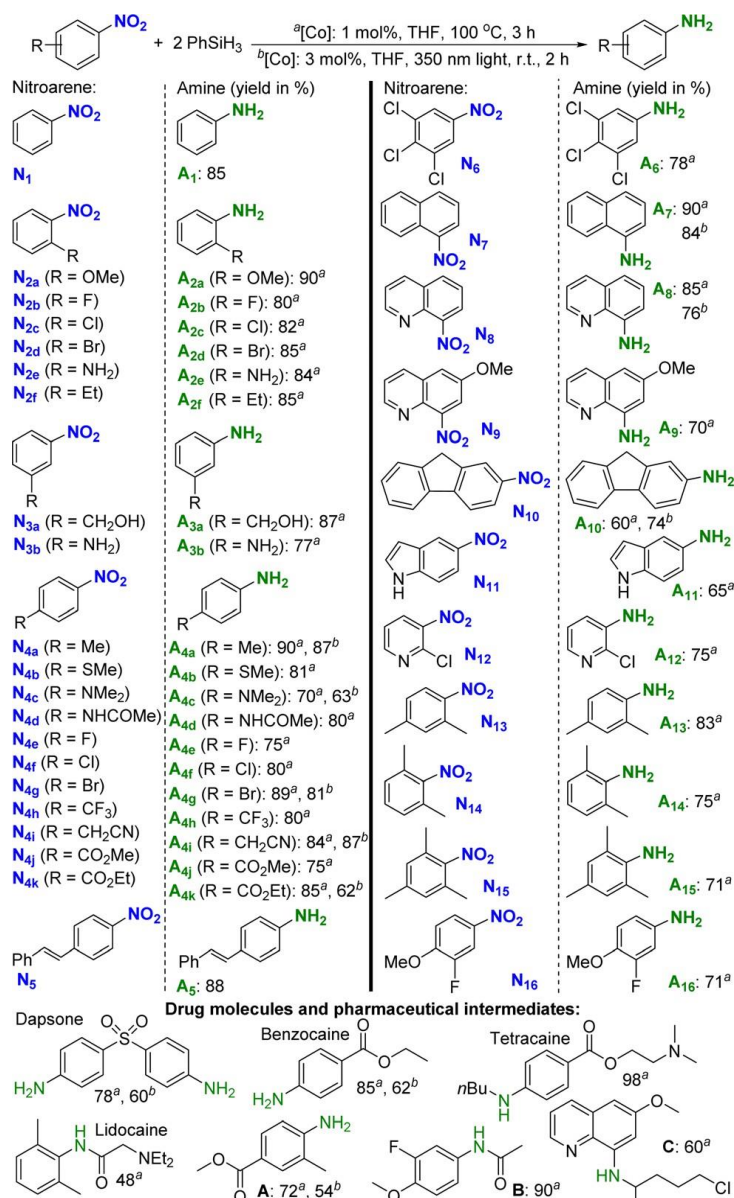
methoxy groups was also successfully tested (**A$_{16}$**: 71%). It should be noted that nitroarenes

with carboxylic acid, hydroxyl and amides groups failed to give the corresponding amines.

Finally, gram-scale reductions of **N$_{4i}$** (80%) and **N$_9$** (70%) were also successfully done.

Subsequently, the hydrosilylation of various nitroarenes was carried out using optimized

photochemical conditions to check the efficacy of that protocol. To our delight, the process

exhibited good tolerance to substituted nitroarenes having a wide range of functional groups

such as halogen, ester, heterocycles, benzyl cyanide, and heteroaromatics (**N$_{4a}$, N$_{4c}$, N$_{4d}$, N$_{4g}$,**

N$_{4i}$, N$_{4k}$, N$_7$, N$_8$, N$_{10}$) with good to excellent yields (**A$_{4a}$:** 87%, **A$_{4c}$:** 63%, **A$_{4d}$:** 82%, **A$_{4g}$:** 81%, **A$_{4i}$:** 87%, **A$_{4k}$:** 62%, **A$_7$:** 84%, **A$_8$:** 76%, **A$_{10}$:** 74%). Needless to say, this established the competency of the photochemical hydrosilylation as a viable alternative to its thermal counterpart.

Finally, the scope of optimized hydrosilylation protocols was extended in real-world applications. The robustness of these protocols against diverse nitro substrates inspired us to test its applicability in synthesizing various important drug molecules and pharmaceutical intermediates (Scheme 2). Using both thermal and photochemical hydrosilylation protocols, we synthesized benzocaine, a topical pain reliever. Dapsone, an antibiotic in the treatment of leprosy, was also synthesized by using thermal and photochemical hydrosilylation of dinitrodiphenyl sulfone. The syntheses of these drugs using catalytic hydrosilylation represented a significantly better procedure as compared to conventional methods of using toxic $SnCl_2$/HCl. Other important local anesthetics such as lidocaine and tetracaine were also synthesized utilizing the thermal protocol. In addition, three pharmaceutical intermediates A, B and C were also synthesized. Compound A is a starting material for telmisartan used to treat high blood pressure. Compounds B and C are precursors to drugs used for the treatment of malaria. As $Co_2(CO)_8$ is associated with acute toxicity, we performed ICP analysis of a couple of products to check the cobalt content. We were pleased to find very low cobalt contents in *p*-methoxyaniline (0.012 ppm) and benzocaine (0.003 ppm).

At first, the homogeneity of this catalytic hydrosilylation was established through the mercury drop experiment where the nitroarene was successfully reduced to the corresponding aromatic amine (equation-a in the above scheme). Thereafter, the catalytic hydrosilylation of nitroarene was carried out in presence of radical-scavengers such as TEMPO and BHT (equation-b in the above scheme). The progress of the reaction was hindered and very low yields of the corresponding aromatic amine were obtained, hence indicating a radical

Scheme 4.3.2 Control Experiments

a) Mercury drop test:
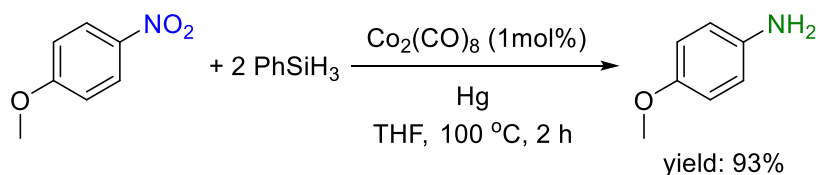
b) Radical trapping test:
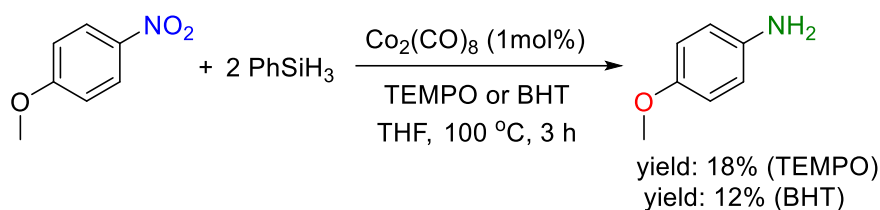
c) Catalytic hydrosilylation of N-hydroxyaniline:
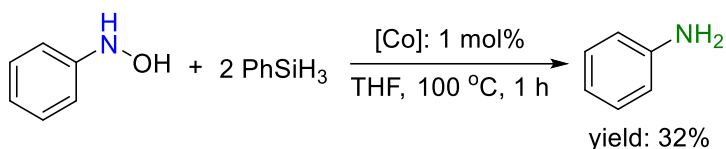
d) Catalytic hydrosilylation of diazobenzene:
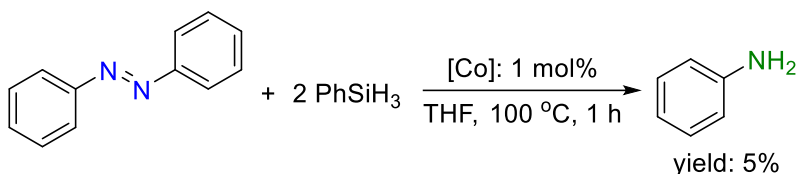
e) Catalytic hydrosilylation of 1,2-diphenylhydrazine:
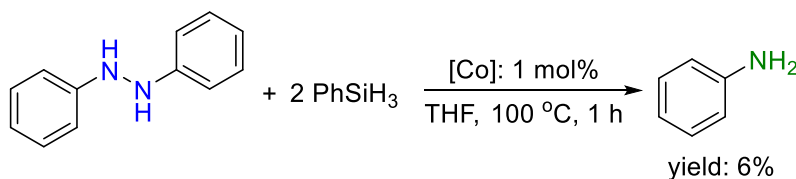
pathway is in action. Several experiments were conducted to identify the plausible intermediates. HRMS analysis of the reaction mixture revealed the presence of the diazoarene intermediate [HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$, 243.1134; found, 243.1177], however, we were unable to detect the presence of the N-hydroxylamine intermediate. This advocates that the reaction might proceed through condensation route. However, Rueping *et al.* previously suggested the direct route for manganese catalysed

catalytic hydrogenation of nitroarenes. To obtain more clarity, we performed the catalytic hydrosilylation of N-hydroxyaniline, diazobenzene and 1,2-diphenylhydrazine. While hydrosilylation of N-Phenylhydorxylamine gave corresponding amine in 32% yield, the hydrosilylation of diazobenzene and 1,2-diphenylhydrazine produced roughly 5% of yield of amine. This clearly suggests that direct route is the favourable path for this cobalt carbonyl catalyzed hydrosilylation of nitroarene; however, the condensation route cannot be ruled out.

Scheme 4.3.3 Plausible reaction mechanism
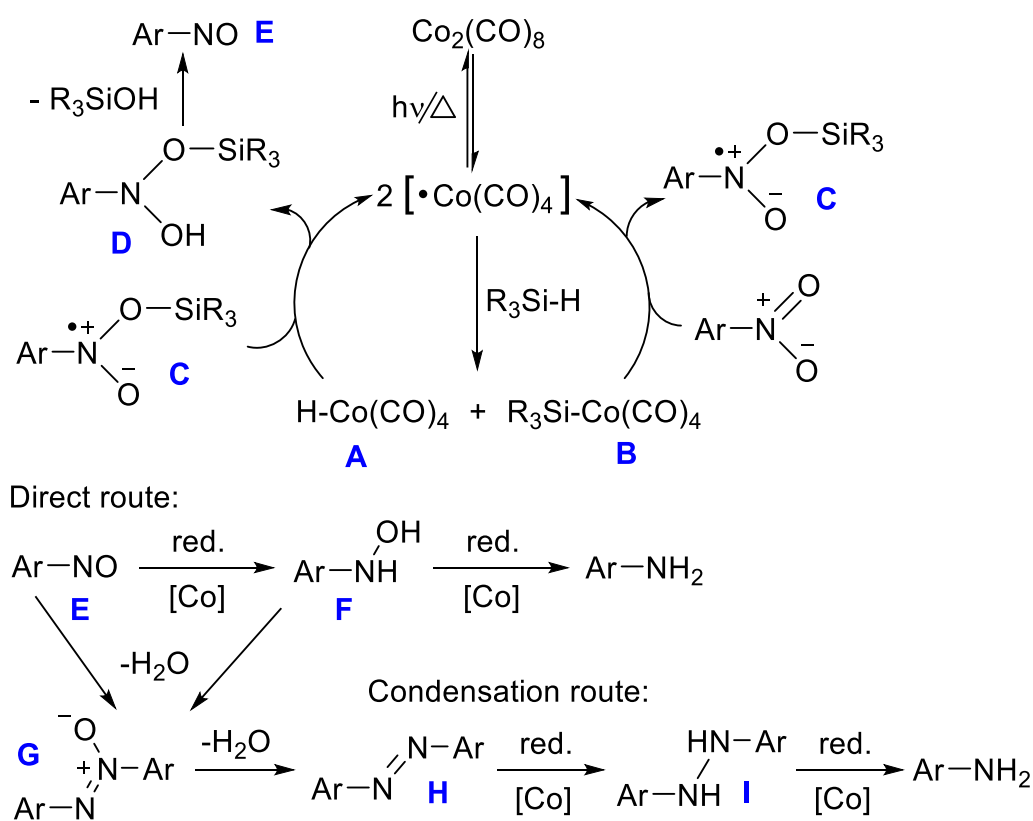
A plausible catalytic pathway involves the homoleptic cleavage of the metal-metal bond in $Co_2(CO)_8$ under photochemical or thermal reaction condition to generate two 17-electron radical species $(CO)_4Co^\bullet$. Thereafter, two $(CO)_4Co^\bullet$ species react with phenyl silane to give highly reactive tetracarbonyl cobalt hydride (A) and tetracarbonyl(silyl) cobalt(I) (B) intermediate. It is believed that tetracarbonyl cobalt hydride species decomposes to give hydrogen and dicobalt octacarbonyl in absence of any substrate[S16]. However, in presence of

nitroarene, tetracarbonyl(silyl) cobalt(I) (B) reacts with nitroarene and leads to the formation of C and regenerate one $(CO)_4Co^{\bullet}$. Thereafter, tetracarbonyl cobalt hydride (A) reacts with C to produce $Ar-N(OSiR_3)OH$ (D) and regenerate another $(CO)_4Co^{\bullet}$. Finally, elimination of silanol results in the formation of nitrosoarene (E). At this stage, there are two available pathways towards the formation of the corresponding aromatic amine from nitrosoarene.[S4] The direct route involves the stepwise reduction of nitrosoarene to N-hydroxylamine (F) and finally aromatic amine. The condensation route involvess the formation of azoxyarene (G) by the condensation of arylnitroso and N-hydroxylamine. Azoxyarene forms azo compound (H) which further reduce to amine through hydrazine intermediate (I).

4.4 CONCLUSION

In conclusion, we have developed an efficient Co-catalyzed hydrosilylation protocol for the reduction of nitroarenes to aromatic amines. This work represents the first report on cobalt-catalyzed hydrosilylation of nitroarenes. Commercially available $Co_2(CO)_8$ proved to be an efficient catalyst for the reduction of nitroarenes under both thermal as well as photochemical conditions. Substrate scope was expanded with various nitroarenes with different electron donating and withdrawing functionalities. Present hydrosilylation is chemoselective to nitro group and various reducible groups such as ester, cyano, amide and alkene were unaltered. Present catalytic hydrosilylation was applied in the syntheses of several important drug molecules and pharmaceutical intermediates. We successfully utilized this hydrosilylation strategy as a replacement for the conventional methods involving stoichiometric amounts of toxic reducing agents to synthesize the drug molecules. Based on experimental evidences, we propose a catalytic path which involve a radical mechanism. Further investigation will involve the use of $Co_2(CO)_8$ in different hydrofuntionalization reactions under photochemical conditions.

4.5 EXPERIMENTAL SECTION

General experimental. All air and moisture-sensitive experiments such as catalytic hydrosilylation of nitroarenes were performed under dry nitrogen atmosphere using standard Schlenk or glovebox (MBraun) techniques. Hydrosilylation of nitroarenes was performed in Ace pressure tubes purchased from Sigma-Aldrich. For the air-sensitive experiments, solvents (petroleum ether, diethyl ether, *n*-pentane and THF) were distilled, degassed and stored over 3 Å molecular sieves. Solvents (acetonitrile, hexanes, pentane, ethyl acetate, DCM, MeOH and THF) were purchased from Merck, Finar and Rankem. For recording NMR spectra of air and moisture-sensitive samples, $CDCl_3$ was degasses and stored over 3 Å molecular sieves. $CDCl_3$ was purchased from Sigma Aldrich. Co_2CO_8, $PhSiH_3$, Ph_2SiH_2, Ph_3SiH, *i*Pr_3SiH, Me_2PhSiH, Et_3SiH, PMHS, TMDS and all nitroarenes as substrates for hydrosilylation were purchased from Sigma Aldrich, Alfa Aesar and TCI Chemicals and used without further purification.

^1H and ^{13}C NMR spectra were recorded using Bruker AV-400 , AV-700 and JEOL-400 (^1H at 400 MHz and ^{13}C at 101 MHz). ^1H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethylsilane (δ 0.00 ppm) and $^{13}C\{^1H\}$ NMR chemical shifts are referenced in ppm with respect to $CDCl_3$ (δ 77.16 ppm). The coupling constants (*J*) are reported in hertz (Hz). The following abbreviations are used to describe multiplicity: s = singlet, bs = broad signal, d = doublet, t = triplet, q = quartet, m = multiplate. High resolution mass spectra were recorded on a Bruker micrOTOF-Q II Spectrometer. All the gas chromatography data were collected on Shimadzu GC-2010 Plus. All the photochemical reactions were done in Luzchem Photoreactor Model - LZC-4X. Metal impurity was determined by using an inductively coupled plasmaoptical emission spectrophotometer (iCAP 7000 ICP-OES).

General procedure for reaction optimization (Thermal): In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1/2/3/4/5 mol%), *p*-nitroanisole (0.077 g, 0.5 mmol), phenylsilane (0.109 g, 1.0 mmol,) and THF (2 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (60-100 °C) in a preheated oil bath for 2 to 24 h. After cooling to r.t., MeOH (1 mL) and *p*-xylene (0.053 g, 0.5 mmol) was added to the resultant mixture. The mixture was then analyzed by GC to determine the conversion of the nitroarene to the amine. Thereafter, water (3 mL) was added to the previous mixture and the mixture was extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. All volatiles were removed under high vacuum to give crude product. Occasionally, the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

General procedure for reaction optimization (Photochemical): In a dried quartz glass tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1/2/3/4/5 mol%), *p*-nitroanisole (0.077 g, 0.5 mmol), phenylsilane (0.109 g, 1.0 mmol) and THF (2 mL) were added successively under a nitrogen atmosphere. The reaction mixture was exposed to 350 nm UV light irradiation for 1 to 24 h at r.t.. After completion of reaction, MeOH (1 mL) and *p*-xylene (0.053 g, 0.5 mmol) was added to the resultant mixture. The mixture was then analyzed by GC to determine the conversion of the nitroarene to the amine. Thereafter, water (3 mL) was added to the previous mixture and the mixture was extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. All volatiles were removed under high vacuum to give crude product. Occasionally, the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

General conditions for substrate screening (Thermal)[a]: In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1 mol%, 0.0017 g), corresponding nitroarene (0.077 g, 0.5 mmol), phenylsilane (0.109 g, 1.0 mmol) and THF (2 mL) were added successively under nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After cooling to r.t., MeOH (1 mL) and water (3 mL) (occasionally 10 wt% of NaOH solution (3 mL)) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

General conditions for substrate screening (Photochemical)[b]: In a dried quartz glass tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (3 mol%, 0.0051 g), corresponding nitroarene (0.077 g, 0.5 mmol), phenylsilane (0.109 g, 1.0 mmol) and THF (2 mL) were added successively under nitrogen atmosphere. The reaction mixture was exposed to 350 nm UV light irradiation for 2 h. After completion of reaction, MeOH (1 mL) and water (3 mL) (occasionally 10 wt% of NaOH solution (3 mL)) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

Gram Scale synthesis of 2-(4-aminophenyl)acetonitrile (A_{4i}): In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1 mol%, 0.034 g), corresponding nitroarene (1.62 g, 10 mmol), phenylsilane (2.16 g, 20 mmol) and THF (10 mL) were added successively under nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After cooling to r.t., MeOH (10 mL) and 10 wt% of NaOH

solution (30 mL) were added to the resultant mixture. The mixture was then extracted with Et$_2$O (3 x 15 mL). The organic layer was collected and dried over anhydrous Na$_2$SO$_4$. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9:1) as eluent. (1.05 g, 80%).

Gram Scale synthesis of 6-Methoxy-Quinolin-8-amine (A$_9$): In a dried pressure tube fitted with a magnetic stir bar, Co$_2$(CO)$_8$ (1 mol%, 0.034 g), corresponding nitroarene (2.04 g, 10 mmol), phenylsilane (2.16 g, 20 mmol) and THF (10 mL) were added successively under nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After cooling to r.t., MeOH (10 mL) and 10 wt% of NaOH solution (30 mL) were added to the resultant mixture. The mixture was then extracted with Et$_2$O (3 x 15 mL). The organic layer was collected and dried over anhydrous Na$_2$SO$_4$. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9:1) as eluent. (1.22 g, 70%).

Mercury drop test: In a dried pressure tube fitted with a magnetic stir bar, Co$_2$(CO)$_8$ (1 mol%), *p*-nitroanisole (0.077 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol), mercury (100 equiv.) and THF (2 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 100 °C in a preheated oil bath for 3 h. After cooling to r.t., MeOH (1 mL) and *p*-xylene (0.053 g, 0.5 mmol) was added to the resultant mixture. The mixture was filtered and the filtrate was analyzed by GC to determine the conversion of the nitroarene to the amine.

Radical trapping test: In a dried pressure tube fitted with a magnetic stir bar, Co$_2$(CO)$_8$ (1 mol%), *p*-nitroanisole (0.077 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol,), TEMPO (0.078 g, 0.5 mmol) or BHT (0.110 g, 0.5 mmol) and THF (2 mL) were added successively

under a nitrogen atmosphere. The reaction mixture was heated at 100 °C in a preheated oil bath for 3 h. After cooling to r.t., MeOH (1 mL) and *p*-xylene (0.053 g, 0.5 mmol) was added to the resultant mixture. The mixture was then analyzed by GC to determine the conversion of the nitroarene to the amine.

Catalytic hydrosilylation of N-hydroxyaniline: In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1.7 mg, 1 mol%), N-hydroxyaniline (0.054 g, 0.5 mmol) (0.077 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol and THF (2 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 100 °C in a preheated oil bath for 1 h. After cooling to r.t., MeOH (1 mL) and *p*-xylene (0.053 g, 0.5 mmol) as standard was added to the resultant mixture. The mixture was then analyzed by GC to determine the conversion of the nitroarene to the amine.

Catalytic hydrosilylation of diazobenzene: In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1.7 mg, 1 mol%), diazobenzene (0.091 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol and THF (2 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 100 °C in a preheated oil bath for 1 h. After cooling to r.t., MeOH (1 mL) and *p*-xylene (0.053 g, 0.5 mmol) as standard was added to the resultant mixture. The mixture was then analyzed by GC to determine the conversion of the nitroarene to the amine.

Catalytic hydrosilylation of 1,2-diphenylhydrazine: In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1.7 mg, 1 mol%), 1,2-diphenylhydrazine (0.092 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol and THF (2 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 100 °C in a preheated oil bath for 1 h. After cooling to r.t., MeOH (1 mL) and *p*-xylene (0.053 g, 0.5 mmol) as standard was added to the resultant mixture. The mixture was then analyzed by GC to determine the conversion of the nitroarene to the amine.

Following anilines (obtained by hydrosilylation of nitroarenes purified by column chromatography) are known compounds and they are characterized by ^{1}H and ^{13}C NMR spectroscopy.

***p*-Anisidine (A_0):** A mixture of petroleum ether, ethyl acetate, and methanol (8:1.5:0.5) was used as eluent for column chromatography. Isolated as a brown liquid [A_0: (0.058 g, 95%)[a]; (0.056 g, 92%)[b]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.78 – 6.72 (m, 2H), 6.67 – 6.63 (m, 2H), 3.75 (s, 3H), 3.29 (brs, 2H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 152.90, 140.01, 116.52, 114.90, 55.81.

Aniline (A_1): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a yellow liquid (A_1: 0.039 g, 85%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.18 (t, *J* = 7.7 Hz, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 2H), 3.42 (brs, 2H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 146.42, 129.39, 118.70, 115.24.

***o*-Anisidine (A_{2a}):** A mixture of petroleum ether, ethyl acetate, and methanol (7:2.5:0.5) was used as eluent for column chromatography. Isolated as a brown liquid (A_{2a}: 0.055 g, 90%) ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.83 – 6.78 (m, 2H), 6.74 (dt, *J* = 7.6, 1.7 Hz, 2H), 3.86 (s, 3H), 3.50 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 147.47, 136.16, 121.18, 118.67, 115.20, 110.54, 77.48, 77.16, 76.84, 55.54.

2-Fluoroaniline (A_{2b}): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a colorless oil (A_{2b}: 0.044 g, 80%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 6.99 (dd, *J* = 10.5, 8.8 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.77 (t, *J* = 8.1 Hz, 1H), 6.69 (d, *J* = 4.7 Hz, 1H), 3.67 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 153.09, 150.72, 134.46 (d, *J* = 12.9 Hz), 124.52 (d, *J* = 3.3 Hz), 118.80 (d, *J* = 6.7 Hz), 117.12, 115.40, 115.22.

2-Chloroaniline (A_{2c}): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a brown liquid (A_{2c}: 0.052 g, 82%).^{1}H

NMR (700 MHz, CDCl$_3$) δ 7.28 (d, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 11.4, 3.9 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.74 – 6.71 (m, 1H), 4.07 (brs, 2H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 143.01, 129.50, 127.72, 119.37, 119.11, 115.98.

2-Bromoaniline (**A$_{2d}$**): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a brown liquid (**A$_{2d}$**: 0.073 g, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.11 (td, *J* = 8.0, 1.4 Hz, 1H), 6.77 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.62 (td, *J* = 7.9, 1.5 Hz, 1H), 3.92 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 144.18, 132.71, 128.47, 119.55, 115.88, 109.46.

o-Phenylenediamine (**A$_{2e}$**): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a grey solid (**A$_{2e}$**: 0.045 g, 84%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.75 – 6.69 (m, 4H), 3.25 (brs, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 134.83, 120.39, 116.85.

2-Ethylaniline (**A$_{2f}$**): A mixture of petroleum ether and ethyl acetate (6:4) was used as eluent for column chromatography. Isolated as a colorless oil (**A$_{2f}$**: 0.051 g, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.07 (dd, *J* = 17.3, 7.8 Hz, 2H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 3.63 (brs, 2H), 2.54 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 144.09, 128.47, 128.20, 126.92, 118.94, 115.49, 24.10, 13.10.

(3-Aminophenyl)methanol (**A$_{3a}$**): A mixture of petroleum ether and ethyl acetate (6:4) was used as eluent for column chromatography. Isolated as a yellow oil (**A$_{3a}$**: 0.053g, 87%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.14 (t, *J* = 7.7 Hz, 1H), 6.76 – 6.72 (m, 1H), 6.70 (s, 1H), 6.61 (dd, *J* = 7.8, 1.8 Hz, 1H), 4.60 (s, 2H), 3.64 (brs, 2H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 146.76, 142.37, 129.65, 117.25, 114.54, 113.72, 65.46.

Benzene-1,3-diamine (**A$_{3b}$**): A mixture of petroleum ether and ethyl acetate (6:4) was used as eluent for column chromatography. Isolated as a brown solid (**A$_{3b}$**: 0.042 g, 77%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.94 (t, *J* = 7.9 Hz, 1H), 6.12 (dd, *J* = 7.9, 2.2 Hz, 2H), 6.04 (t,

J = 2.1 Hz, 1H), 3.54 (brs, 4H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 147.62, 130.34, 106.12, 102.05.

p-Toluidine (**A$_{4a}$**): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a brown liquid [**A$_{4a}$**: (0.048 g, 90%)[a]; (0.046 g, 87%)[b]]. ^1H NMR (400 MHz, CDCl$_3$) δ 6.99 (d, J = 7.9 Hz, 2H), 6.63 (d, J = 8.3 Hz, 2H), 3.43 (brs, 2H), 2.27 (s, 3H). $^{13}C\{^1H\}$ NMR (176 MHz, CDCl$_3$) δ 143.89, 129.84, 127.87, 115.37, 20.53.

4-(Methylthio)aniline (**A$_{4b}$**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a brown solid (**A$_{4b}$**: 0.056 g, 81%). ^1H NMR (400 MHz, CDCl$_3$) δ 7.18 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.5 Hz, 2H), 3.64 (brs, 2H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 145.23, 131.20, 125.93, 115.87, 18.92.

N^1,N^1-Dimethylbenzene-1,4-diamine (**A$_{4c}$**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a purple solid [**A$_{4c}$**: (0.048 g, 70%)[a]; (0.043 g, 67%)[b]]. ^1H NMR (400 MHz, CDCl$_3$) δ 6.68 (d, J = 9.2Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 2.85 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 145.01, 138.02, 116.74, 115.73, 42.25.

N-(4-Aminophenyl)acetamide (**A$_{4d}$**): A mixture of petroleum ether and ethyl acetate (7:3) was used as eluent for column chromatography. Isolated as a pale yellow solid [**A$_{4d}$**: (0.060 g, 80%)[a]; (0.061 g, 82%)[b]]. ^1H NMR (700 MHz, DMSO-d$_6$) δ 9.44 (brs, 1H), 7.19 (d, J = 8.4 Hz, 2H), 6.50 (d, J = 8.4 Hz, 2H), 4.80 (brs, 2H), 1.96 (s, 3H). $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d$_6$) δ 167.21, 144.47, 128.63, 120.87, 113.83, 23.60.

4-Fluoroaniline (**A$_{4e}$**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a brown solid (**A$_{4e}$**: 0.042g, 75%). ^1H NMR (700 MHz, CDCl$_3$) δ 6.86 (t, J = 8.4 Hz, 2H), 6.60 (s, 2H), 3.37 (brs, 1H). $^{13}C\{^1H\}$ NMR

(176 MHz, CDCl$_3$) δ 157.23, 155.90, 142.38, 116.25, 115.67 (d, J = 22.3 Hz).

4-Chloroaniline (**A$_{4f}$**): A mixture of petroleum ether and ethyl acetate (8.5:1.5) was used as eluent for column chromatography. Isolated as a pale yellow solid (**A$_{4f}$**: 0.051 g, 80%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.11 (d, J = 8.4 Hz, 2H), 6.58 (d, J = 8.4 Hz, 2H), 3.44 (brs, 2H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 144.91, 129.09, 123.28, 116.45.

4-Bromoaniline (**A$_{4g}$**): A mixture of petroleum ether and ethyl acetate (8.5:1.5) was used as eluent for column chromatography. Isolated as a white solid [**A$_{4g}$**: (0.077 g, 89%)[a]; (0.070 g, 81%)[b]]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25 – 7.22 (m, 2H), 6.69 – 6.50 (m, 2H), 3.63 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 132.14, 116.84, 111.89.

4-(trifluoromethyl)aniline (**A$_{4h}$**): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a yellow liquid (**A$_{4h}$**: 0.064 g, 80%).^{1}H NMR (700 MHz, CDCl$_3$) δ 7.39 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 3.93 (brs, 2H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 149.47, 126.82 (q, J = 3.7 Hz), 125.72, 124.18, 120.30 (q, J = 32.8 Hz), 114.32.

2-(4-aminophenyl)acetonitrile (**A$_{4i}$**): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a yellow liquid [**A$_{4i}$**: (0.055 g, 84%)[a]; (0.057 g, 87%)[b]]. ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.08 (d, J = 6.7 Hz, 2H), 6.66 (d, J = 6.5 Hz, 2H), 3.72 (brs, 2H), 3.62 (s, 2H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 146.34, 129.05, 119.45, 118.63, 115.59, 22.92.

Methyl 4-aminobenzoate (**A$_{4j}$**): A mixture of hexanes and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as an off-white solid (**A$_{4j}$**: 0.057 g, 75%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.85 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 3.85 (s, 3H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 167.32, 150.94, 131.74, 119.88, 113.94, 51.75.

Ethyl 4-aminobenzoate (**A$_{4k}$**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a pale yellow solid [**A$_{4k}$**: (0.070 g,

85%)[a]; (0.051 g, 62%)[b]]. ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.85 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.00 (brs, 2H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 166.86, 150.87, 131.67, 120.20, 113.90, 60.43, 14.54.

(E)-4-Styrylaniline (**A$_5$**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a pale yellow solid (**A$_5$**: 0.086 g, 88%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (d, J = 7.3 Hz, 2H), 7.34 (dd, J = 8.2, 6.7 Hz, 4H), 7.22 (t, J = 7.3 Hz, 1H), 7.04 (d, J = 16.3 Hz, 1H), 6.93 (d, J = 16.3 Hz, 1H), 6.71 – 6.66 (m, 2H), 3.74 (brs, 2H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 146.27, 138.08, 128.81, 128.73, 128.17, 127.88, 127.02, 126.23, 125.25, 115.34.

3,4,5-Trichloroaniline (**A$_6$**): A mixture of petroleum ether and ethyl acetate (6:4) was used as eluent for column chromatography. Isolated as a brown solid (**P$_8$**: 0.077 g, 78%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 6.68 (s, 2H), 3.73 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 145.72, 134.30, 119.97, 115.21.

Naphthalen-1-amine (**A$_7$**): A mixture of petroleum ether and ethyl acetate (8.5:1.5) was used as eluent for column chromatography. Isolated as a purple solid [**A$_7$**: (0.064g, 90%)[a]; (0.060g, 84%)[b]]. ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.83 (dd, J = 9.0, 6.0 Hz, 2H), 7.50 – 7.45 (m, 2H), 7.35 – 7.29 (m, 2H), 6.79 (d, J = 7.1 Hz, 1H), 4.14 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 142.17, 134.51, 128.67, 126.45, 125.96, 124.98, 123.78, 120.91, 119.11, 109.82.

Quinolin-8-amine (**A$_8$**): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a reddish solid [**A$_8$**: (0.061 g, 85%)[a]; (0.055 g, 76%)[b]]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.76 (dd, J = 4.2, 1.7 Hz, 1H), 8.07 (dd, J = 8.3, 1.7 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.15 (dd, J = 8.2, 1.1 Hz, 1H), 6.93 (dd, J = 7.5, 1.2 Hz, 1H), 4.81 (brs, 2H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 147.52, 144.04, 138.49, 136.16, 128.98, 127.51, 121.45, 116.16, 110.21.

6-Methoxy-Quinolin-8-amine (**A₉**): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a brown oil (**A₉**: 0.061 g, 70%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.59 (dd, J = 4.2, 1.6 Hz, 1H), 7.95 (dd, J = 8.3, 1.6 Hz, 1H), 7.31 (dd, J = 8.3, 4.2 Hz, 1H), 6.58 (d, J = 2.6 Hz, 1H), 6.48 (d, J = 2.6 Hz, 1H), 4.93 (brs, 2H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 145.11, 134.97, 121.94, 101.78, 94.73, 55.41.

9H-Fluoren-2-amine (**A₁₀**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a brown yellow solid [**A₁₀**: (0.054 g, 60%)[a]; (0.067 g, 74%)[b]]. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (d, J = 7.5 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.20 (td, J = 7.4, 1.0 Hz, 1H), 6.89 – 6.87 (m, 1H), 6.71 (dd, J = 8.0, 2.2 Hz, 1H), 3.81 (s, 2H), 3.72 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 145.86, 145.27, 142.38, 142.26, 133.12, 126.77, 125.20, 124.87, 120.77, 118.70, 114.10, 111.93, 36.94.

1H-Indol-5-amine (**A₁₁**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a yellow solid (**A₁₀**: 0.043 g, 65%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.02 (brs, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.12 (t, J = 2.8 Hz, 1H), 6.96 (d, J = 2.2 Hz, 1H), 6.67 (dd, J = 8.5, 2.2 Hz, 1H), 6.38 (ddd, J = 3.0, 2.0, 0.9 Hz, 1H), 3.00 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 139.56, 130.84, 128.90, 124.86, 113.10, 111.65, 105.73, 101.65.

2-Chloropyridin-3-amine (**A₁₂**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a light yellow solid (**A₁₂**: 0.048 g, 75%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 – 7.78 (m, 1H), 7.05 – 7.01 (m, 2H), 4.08 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 139.77, 138.79, 137.11, 123.48, 122.52.

2,4-Dimethylaniline (**A₁₃**): A mixture of petroleum ether and ethyl acetate (9:1) was used as eluent for column chromatography. Isolated as a grey brown oil (**A₁₃**: 0.050 g, 83%). ^{1}H

NMR (700 MHz, CDCl$_3$) δ 6.99 – 6.94 (m, 2H), 6.66 (d, *J* = 7.9 Hz, 1H), 3.50 (brs, 2H), 2.34 (s, 3H), 2.23 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 141.99, 131.08, 127.75, 127.30, 122.44, 115.12, 20.40, 17.27.

2,6-Dimethylaniline (**A₁₄**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a yellow oil (**A₁₄**: 0.045 g, 75%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.01 (d, *J* = 7.6 Hz, 2H), 6.71 (t, *J* = 7.5 Hz, 1H), 3.52 (brs, 2H), 2.24 (s, 6H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 142.75, 128.33, 121.79, 118.10, 17.68.

2,4,6-Dimethylaniline (**A₁₅**): A mixture of petroleum ether and ethyl acetate (8:2) was used as eluent for column chromatography. Isolated as a yellow oil (**A₁₅**: 0.048 g, 71%) ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.78 (s, 2H), 3.14 (brs, 2H), 2.22 (s, 3H), 2.17 (s, 6H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 140.12, 128.97, 127.39, 122.08, 20.49, 17.73.

3-fluoro-4-methoxyaniline (**A₁₆**): A mixture of petroleum ether, ethyl acetate, and methanol (8:1.5:0.5) was used as eluent for column chromatography. Isolated as a brown oil (**A₁₆**: 0.051 g, 71%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.79 (t, *J* = 9.0 Hz, 1H), 6.47 (dd, *J* = 12.7, 2.7 Hz, 1H), 6.38 (ddd, *J* = 8.6, 2.7, 1.4 Hz, 1H), 3.81 (s, 3H), 3.45 (brs, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 154.59, 152.16, 141.13, 140.48, 115.88 (d, *J* = 3.1 Hz), 110.42 (d, *J* = 3.1 Hz), 104.47, 104.26, 57.53.

Synthesis of drug molecules:

Synthesis of Dapsone:
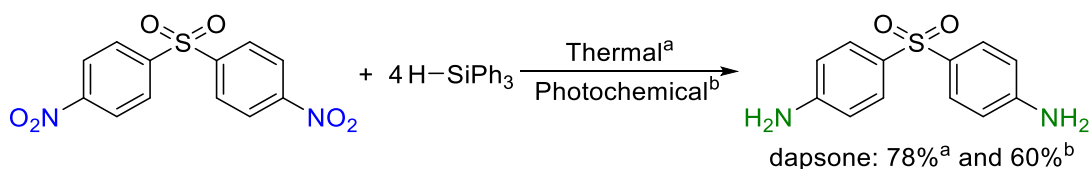
dapsone: 78%[a] and 60%[b]

Thermal protocol: In a dried pressure tube fitted with a magnetic stir bar, Co$_2$(CO)$_8$ (1

mol%, 0.0017 g), corresponding nitroarene (0.154 g, 0.5 mmol), phenylsilane (0.218 g, 1.05 mmol) and THF (2 mL) were added successively under nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After cooling to r.t., MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (8:2) as eluent to afford yellow hygroscopic solid as pure product (0.096 g, 78%).

Photochemical protocol: In a dried quartz glass tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (3 mol%, 0.0051g), corresponding nitroarene (0.154 g, 0.5 mmol), phenylsilane (0.218 g, 1.05 mmol) were added successively under nitrogen atmosphere. The reaction mixture was exposed to 350 nm UV light irradiation for 2 h. After completion of the reaction, MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (8:2) as eluent to afford yellow hygroscopic solid as pure product (0.075 g, 60%). ^{1}H NMR (700 MHz, DMSO-d_6) δ 7.44 (d, *J* = 8.6 Hz, 4H), 6.58 (d, *J* = 8.6 Hz, 4H), 5.93 (brs, 4H). ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6) δ 152.63, 128.42, 128.13, 112.77.

Synthesis of benzocaine:
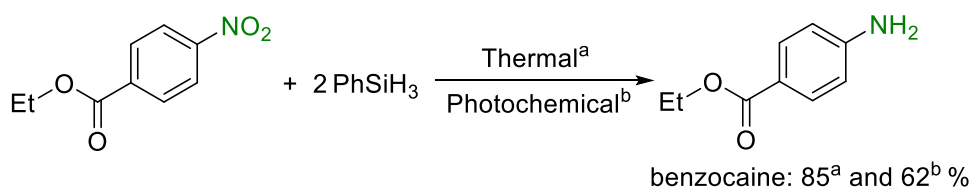

benzocaine: 85[a] and 62[b] %

Thermal protocol: In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1 mol%, 0.0017 g), corresponding nitroarene (0.092 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol) and THF (2 mL) were added successively under nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After cooling to r.t., MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (8:2) as eluent to afford yellow hygroscopic solid as pure product (0.070 g, 85%).

Photochemical protocol: In a dried quartz glass tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (3 mol%, 0.0051g), corresponding nitroarene (0.092 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol) were added successively under nitrogen atmosphere. The reaction mixture was exposed to 350 nm UV light irradiation for 2 h. After completion of the reaction, MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (8:2) as eluent to afford yellow hygroscopic solid as pure product (0.051 g, 62%).
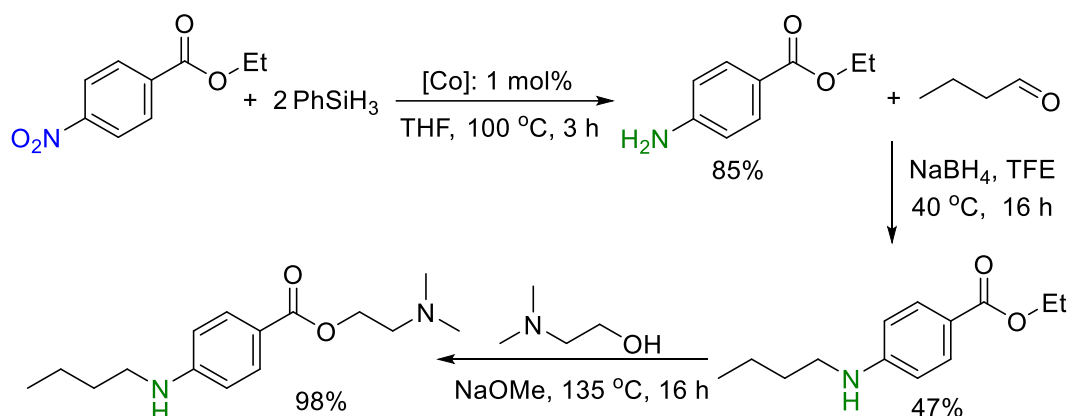
Synthesis of Tetracaine:

Synthesis of ethyl 4-aminobenzoate (step 1): In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1 mol%, 0.0017 g), corresponding nitroarene (0.092 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol) and THF (2 mL) were added successively under nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After cooling to r.t., MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent to afford yellow hygroscopic solid as pure product (0.070 g, 85%).

Synthesis of ethyl 4-(butylamino)benzoate (step 2): The Synthetic process was previously reported. This is a modified procedure. In a round bottom flask, a solution of the appropriate carbonyl compound (0.036 g, 0.5 mmol) and TFE (2 mL) was magnetically stirred at 40 °C. After 5 min, the ethyl 4-aminobenzoate (0.083 g, 0.5 mmol) was added, and the mixture vigorously stirred. After stirring for 5 min, NaBH₄ (0.023 g, 0.6 mmol) was added and the progress of the reaction conversion was followed by TLC (hexane–EtOAc, 8:2). After completion of the reaction, the mixture was filtered and the residue was washed with TFE (2 mL). The solvent was distilled off (to recover for the next run) and the pure product was obtained. the crude product was further purified by silica gel column chromatography with petroleum ether and ethyl acetate (8:2) as eluent. (0.052

g; 47%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 8.8 Hz, 2H), 4.31 (q,

J = 7.1 Hz, 2H), 4.11 (brs, 1H), 3.15 (t, *J* = 7.1 Hz, 2H), 1.60 (dd, *J* = 14.8, 7.4 Hz, 2H), 1.43 (dt, *J*

= 14.9, 7.3 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz,

CDCl$_3$) δ 167.05, 152.22, 131.61, 118.44, 111.38, 60.24, 43.18, 31.51, 20.32, 14.57, 13.95.

Synthesis of tetracaine (step 3): The Synthetic process was previously reported. This is a

modified procedure. In a round bottom flask a solution of ethyl 4-(butylamino)benzoate (0.110 g,

0.5 mmol) in 2-(dimethylamino)ethan-1-ol (1.5 mL) was treated with NaOMe (5 mg, 0.1 mmol),

heated to 135 ºC and stirred at the same temperature for 16 h. The mixture was cooled to room

temperature and diluted with H$_2$O (10 mL) and CH$_2$Cl$_2$ (10 mL). The layers were separated and the

aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were washed

with brine, dried (MgSO$_4$) and evaporated. Purification by column chromatography on silica gel

eluting with petroleum ether and ethyl acetate (7:3) gave pure product (0.129 g; 98%). ^{1}H NMR

(700 MHz, CDCl$_3$) δ 7.84 (d, *J* = 6.4 Hz, 2H), 6.51 (d, *J* = 6.7 Hz, 2H), 4.36 (s, 2H), 4.14 (s, 1H),

3.14 (d, *J* = 4.7 Hz, 2H), 2.69 (s, 2H), 2.33 (s, 6H), 1.63 – 1.56 (m, 2H), 1.42 (dt, *J* = 14.8, 7.4 Hz,

2H), 0.94 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 131.73, 117.97, 111.36, 62.33,

58.03, 45.89, 43.12, 31.46, 20.28, 13.92.

Synthesis of lidocaine:

Synthesis of 2,6-dimethylaniline (step 1): In a dried pressure tube fitted with a magnetic stir bar,

Co$_2$(CO)$_8$ (1 mol%, 0.0017 g), corresponding nitroarene (0.092 g, 0.5 mmol), phenylsilane (0.109

g, 1.05 mmol) and THF (2 mL) were added successively under nitrogen atmosphere. The reaction

mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After

cooling to r.t., MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et$_2$O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na$_2$SO$_4$. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (8:2) as eluent to afford yellow hygroscopic solid as pure product (0.045 g, 75%).
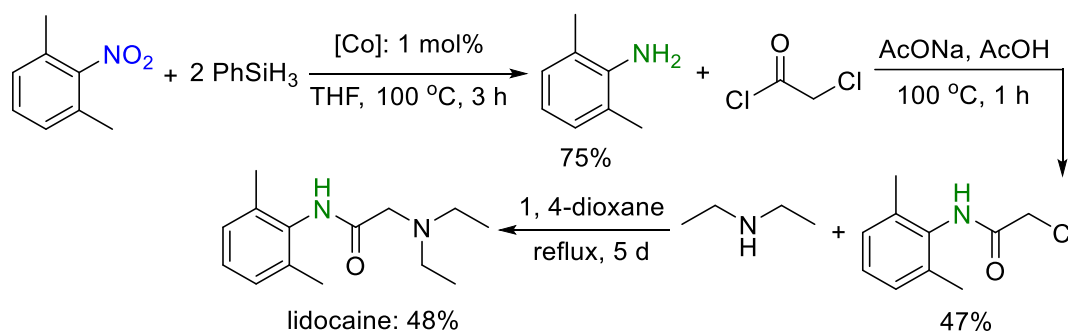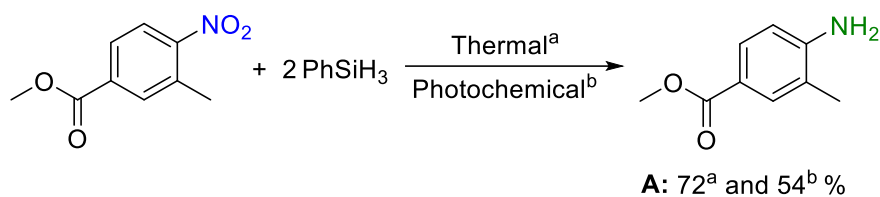
Synthesis of 2-chloro-N-(2,6-dimethylphenyl)acetamide (step 2): The Synthetic process was previously reported. This is a modified procedure. In a dried round-bottom flask fitted with a magnetic stirring bar, chloroacetyl chloride (0.169 g, 1.5 mmol) and 2, 6-dimethylaniline (0.121 g, 0.5 mmol) were added and the mixture was stirred until slurry was observed. Sodium acetate (0.164 g, 2 mmol) was added into the mixture and it was allowed to run at reflux condition for 1 h. After completion of the reaction, it was cooled to 0 °C for 20 minutes. The solid material was filtered off and washed with cold water to obtain the crude. The crude was dried under vacuum to get white crystalline solid as pure compound (0.046 g, 47%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.85 (brs, 1H), 7.16 – 7.09 (m, 3H), 4.25 (d, J = 3.6 Hz, 2H), 2.24 (s, 6H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 164.48, 135.48, 132.81, 128.51, 128.03, 42.92, 18.42.

Synthesis of lidocaine (step 3): The Synthetic process was previously reported. This is a modified procedure. In a dried pressure tube fitted with magnetic stirring bar, 2-chloro-N-(2,6-dimethylphenyl)-acetamide (0.197 g, 1 mmol), diethyl amine (310 µl, 3 mmol) and triethyl amine (834 µl, 6 mmol) were taken and 1,4 dioxane (4 ml) was added into it. Then the reaction mixture was allowed to run for five days in reflux condition. After completion of the reaction, the resultant mixture was dried under high vacuum to remove all the volatiles. After drying a dark red solid was isolated as crude product. The crude product was purified by column chromatography (silica gel as stationary phase and 1:1 mixture of ethyl acetate and hexanes as eluent) to give red solid as pure product (0.113 g, 48%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 9.02 (s, 1H), 7.07 (s, 3H), 3.29 (s, 2H), 2.74 (d, J = 5.3 Hz, 4H), 2.22 (s, 6H), 1.15 (s, 6H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 170.05, 135.22, 133.96, 128.33, 127.26, 57.12, 49.06, 18.67, 12.56.

Synthesis of intermediate A:

A: 72[a] and 54[b] %

Thermal protocol: In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1 mol%, 0.0017 g), corresponding nitroarene (0.083 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol) and THF (2 mL) were added successively under nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After cooling to r.t., MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (8:2) as eluent to afford yellow hygroscopic solid as pure product (0.059 g, 72%).
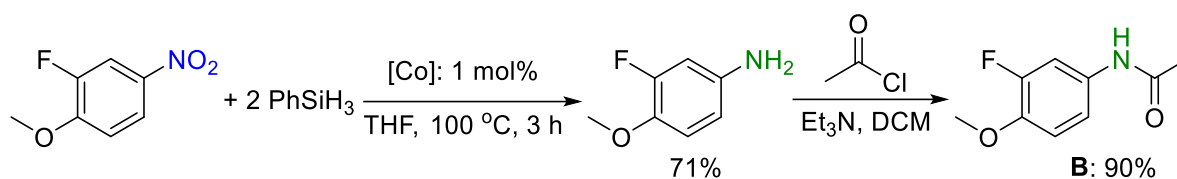
Photochemical protocol: In a dried quartz glass tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (3 mol%, 0.0051g), corresponding nitroarene (0.083 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol) were added successively under nitrogen atmosphere. The reaction mixture was exposed to 350 nm UV light irradiation for 2 h. After completion of the reaction, MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (8:2) as eluent to afford yellow hygroscopic solid as pure product (0.044 g, 54%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 10.9, 2.6 Hz, 2H), 6.63 (d, J = 8.2 Hz, 1H), 3.99 (brs, 2H), 3.85 (s, 3H), 2.17 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.52, 149.27, 132.37, 129.43, 121.16, 119.76, 113.80, 51.70, 17.25.

Synthesis of intermediate B:

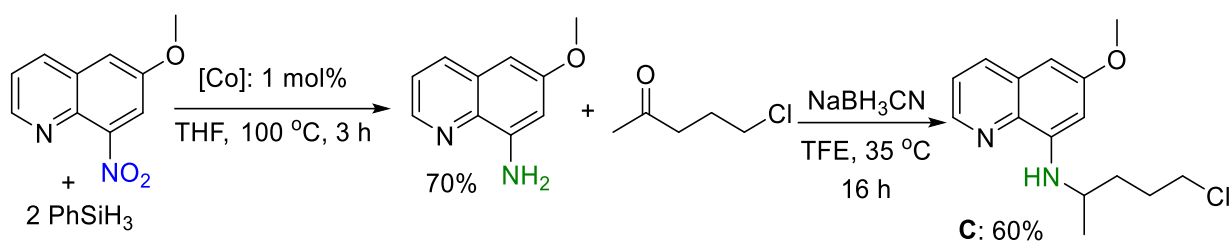**Synthesis of 3-fluoro-5-methoxyaniline:** In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1 mol%, 0.0017 g), corresponding nitroarene (0.086 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol) and THF (2 mL) were added successively under nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After cooling to r.t., MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether, ethyl acetate and methanol (8:1.5:0.5) as eluent to afford yellow hygroscopic solid as pure product (0.050 g, 71%).

Synthesis of N-(3-fluoro-5-methoxyphenyl)acetamide (B): The Synthetic process was previously reported. In a 50 mL round-bottom flask aniline (0.070 g, 0.5 mmol), 5 mL dry DCM and dry Et_3N (0.075 g, 1.5 equiv.) added. The reaction mixture cooled to 0 °C and stir for 15 minute. Then, CH_3COCl (0.046 g, 1.2 equiv.) added dropwise to the reaction mixture and stirred at room temperature for 12 h. After completion (judged by TLC), the resulting reaction mixture was extracted with DCM (3 x 5 mL) and dried over Na_2SO_4. Solvent evaporated and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (8:2) as eluent to afford pure product (0.082g, 90%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.38 (dd, J = 12.8, 2.5 Hz, 1H), 7.14 – 7.09 (m, 1H), 6.87 (t, J = 9.0 Hz, 1H), 3.84 (s, 3H), 2.13 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 168.70, 153.37, 150.93, 144.54 (d, J = 11.1 Hz), 131.50 (d, J = 9.3 Hz), 115.94 (d, J = 3.1 Hz), 113.79 (d, J = 2.3 Hz), 109.62, 109.50 (d, J = 22.6 Hz), 56.70, 24.40.

Synthesis of intermediate C:

Synthesis of 6-Methoxyquinolin-8-amine: In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (1 mol%, 0.0017 g), corresponding nitroarene (0.102 g, 0.5 mmol), phenylsilane (0.109 g, 1.05 mmol) and THF (2 mL) were added successively under nitrogen atmosphere. The reaction mixture was heated at an appropriate temperature (100 °C) in a preheated oil bath for 3 h. After cooling to r.t., MeOH (1 mL) and 10 wt% of NaOH solution (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (9:1) as eluent to afford yellow hygroscopic solid as pure product (0.060 g, 70%).

Synthesis of N-(5-Chloropentan-2-yl)-6-methoxyquinolin-8-amine (C): The Synthetic process was previously reported. This is a modified procedure. In a round bottom flask, a solution of the appropriate carbonyl compound (0.060 g, 0.5 mmol) and TFE (2 mL) was magnetically stirred at 40 °C. After 5 min, the 6-Methoxyquinolin-8-amine (0.087 g, 0.5 mmol) was added, and the mixture vigorously stirred. After stirring for 5 min, $NaBH_3CN$ (0.063 g, 1 mmol) was added and the progress of the reaction conversion was followed by TLC (Pet ether–EtOAc, 8:2). After completion of the reaction, the mixture was filtered and the residue was washed with TFE (2 mL). The solvent was distilled off (to recover for the next run) and the pure product was obtained. the crude product was further purified by silica gel column chromatography with petroleum ether and ethyl acetate(8:2) as eluent to get pure product (0.083 g, 60%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 8.64 (d, J = 2.6 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.30 – 7.25 (m, 1H), 6.54 (s, 2H), 4.62 (dd, J = 12.7,

6.3 Hz, 1H), 4.04 (dd, J = 17.2, 8.6 Hz, 1H), 3.90 (s, 3H), 3.36 (t, J = 7.1 Hz, 1H), 2.26 (dt, J = 11.7, 9.6 Hz, 1H), 2.06 – 1.69 (m, 4H), 1.09 (d, J = 6.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 158.31, 144.32, 134.92, 130.75, 121.13, 105.58, 95.72, 55.38, 52.81, 33.90, 23.92, 19.22.

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GC Experiment

<Chromatogram>

<Peak Table>
FID1

Peak#	Name	Ret. Time	Area	Area%
1	p-xylene	2.685	4835183	63.436
2	p-anisidine	4.981	2787017	36.564
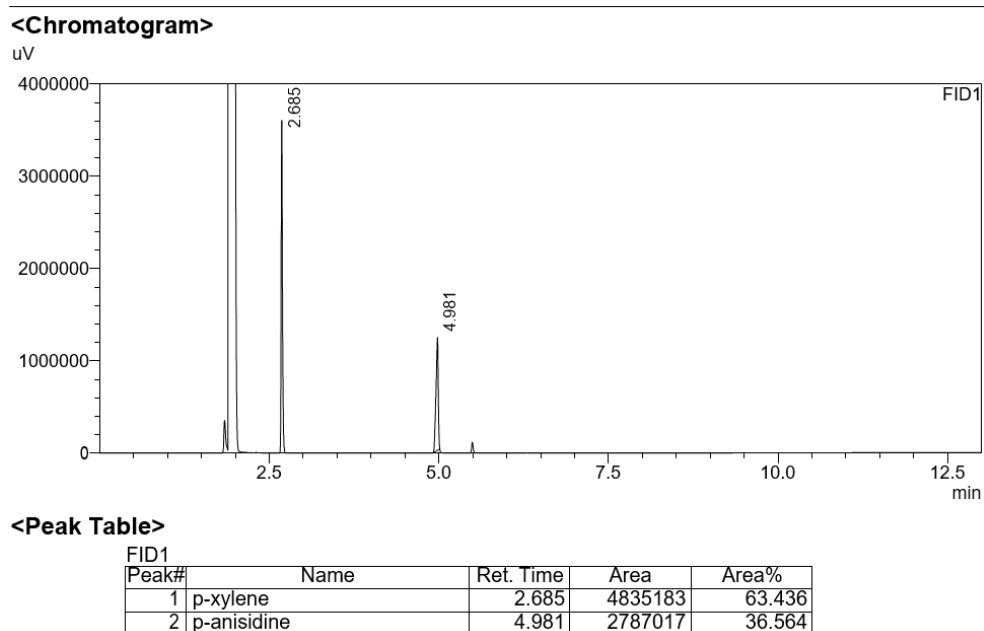
Figure 4.1 Representative GCMS spectrum of the crude reaction mixture from catalytic hydrosilylation of p-nitroanisole performed in presence of 2.1 equiv. of $PhSiH_3$, 1 mol% of catalyst and 1.5ml of THF at 100 ^{0}C for 3 h.

<Chromatogram>

<Peak Table>
FID1

Peak#	Name	Ret. Time	Area	Area%
1	p-xylene	2.686	4795966	63.457
2	p-anisidine	4.981	2761893	36.543
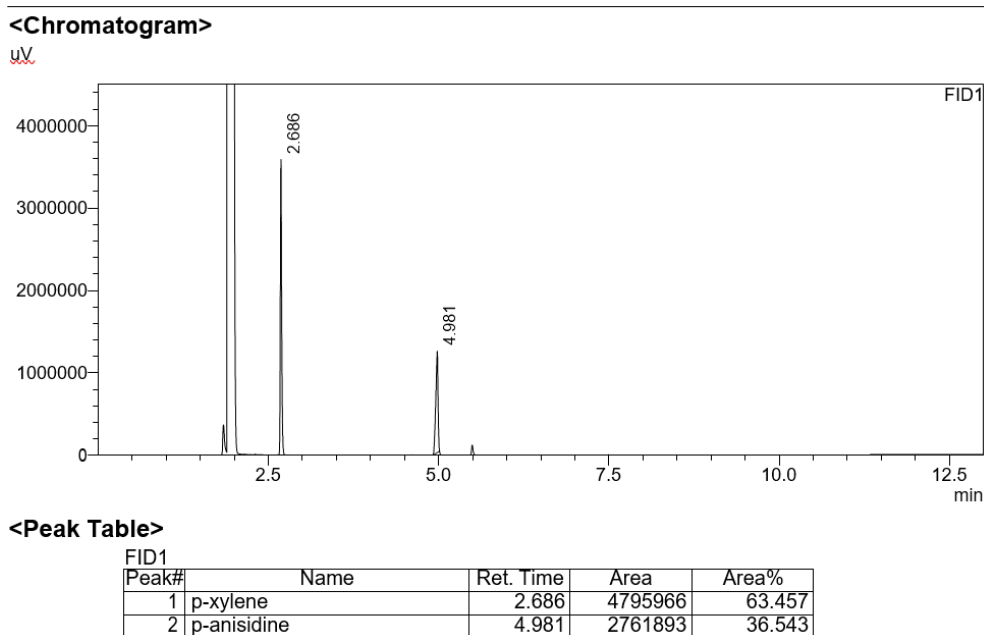
Figure 4.2 Representative GCMS spectrum of the crude reaction mixture from catalytic hydrosilylation of p-nitroanisole performed in presence of 2.1 equiv. of $PhSiH_3$, 3 mol% of catalyst and 1.5ml of THF for 3 h at r.t. (350 nm).

Following are the ¹H and ¹³C{¹H} NMR spectra of aromatic amines:
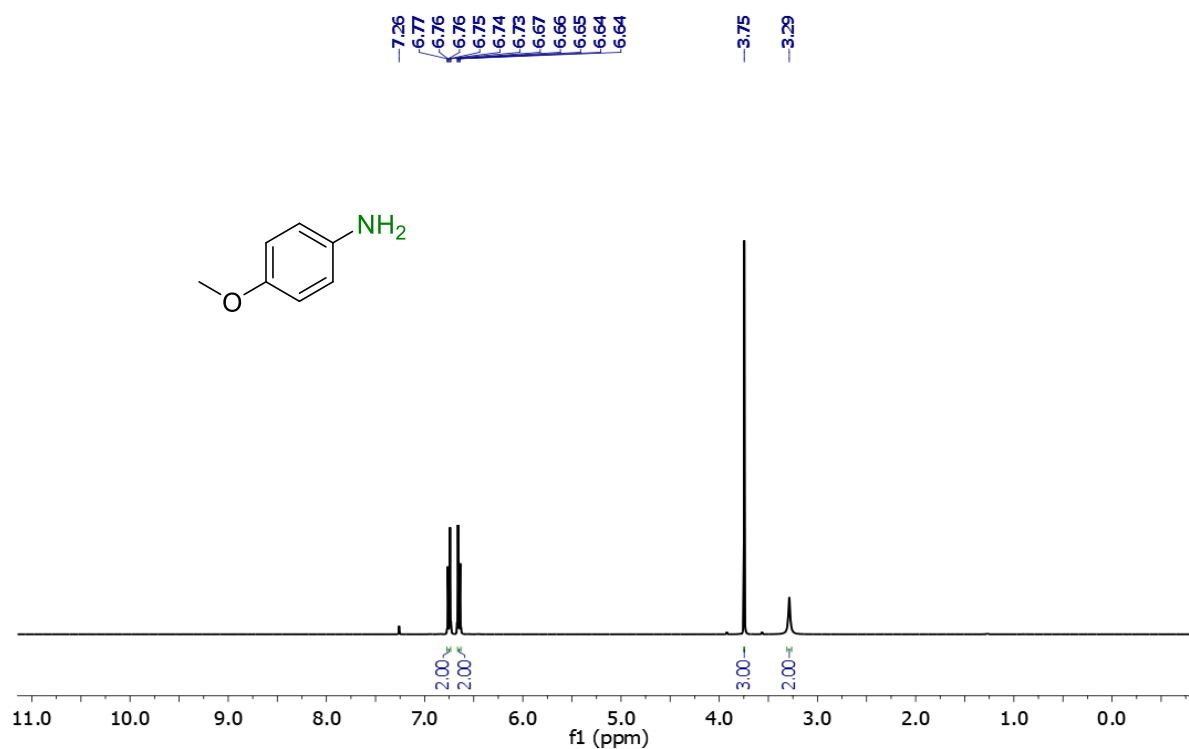
Figure 4.3 ¹H NMR (400 MHz) spectrum of *p*-Anisidine (A₀) in CDCl₃ at r.t.
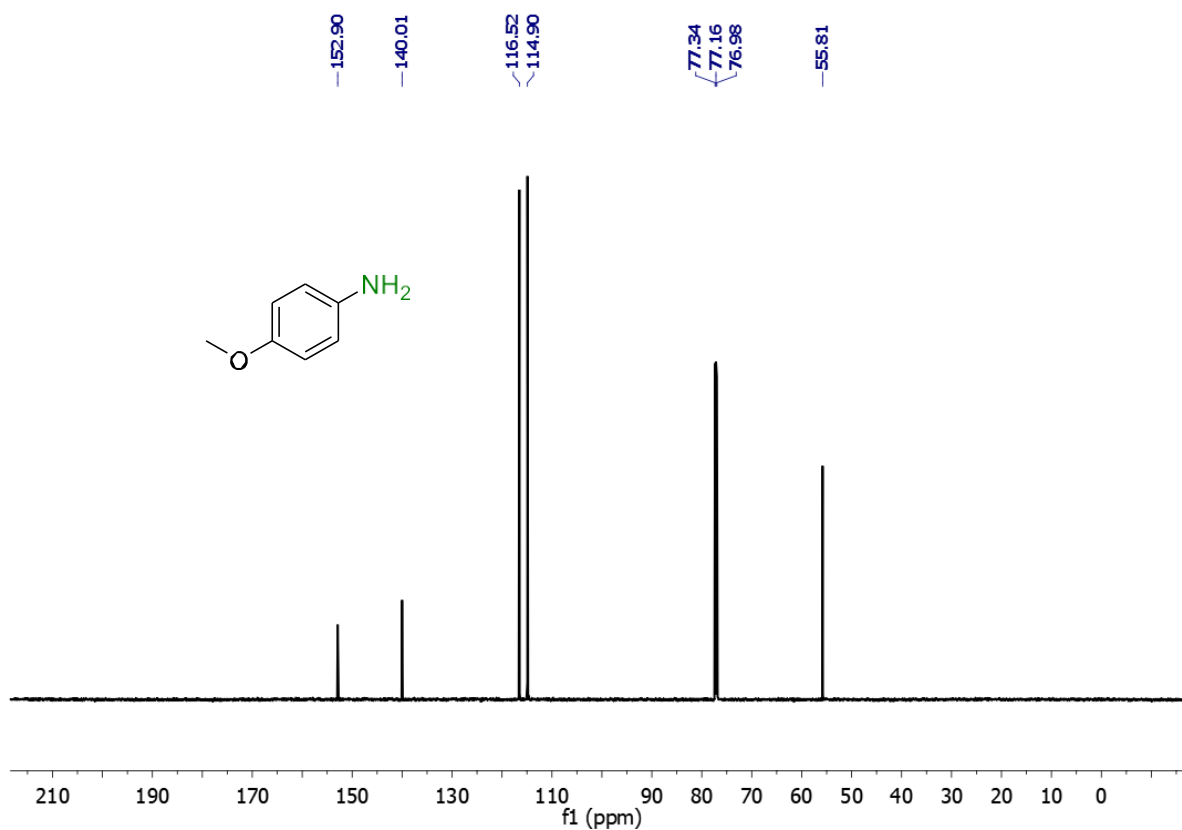
Figure 4.4 ¹³C{¹H} NMR (400 MHz) spectrum of *p*-Anisidine (A₀) in CDCl₃ at r.t.
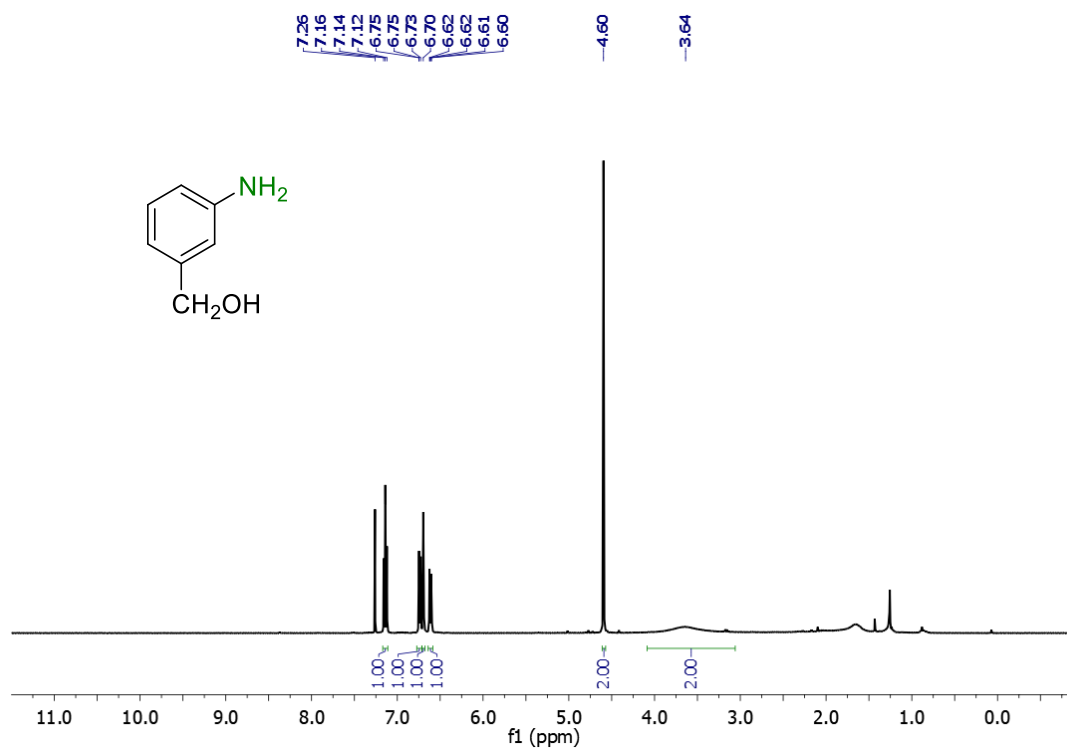
Figure 4.5 ^{1}H NMR (400 MHz) spectrum of (3-aminophenyl)methanol (**A$_{3a}$**) in CDCl$_3$ at r.t.
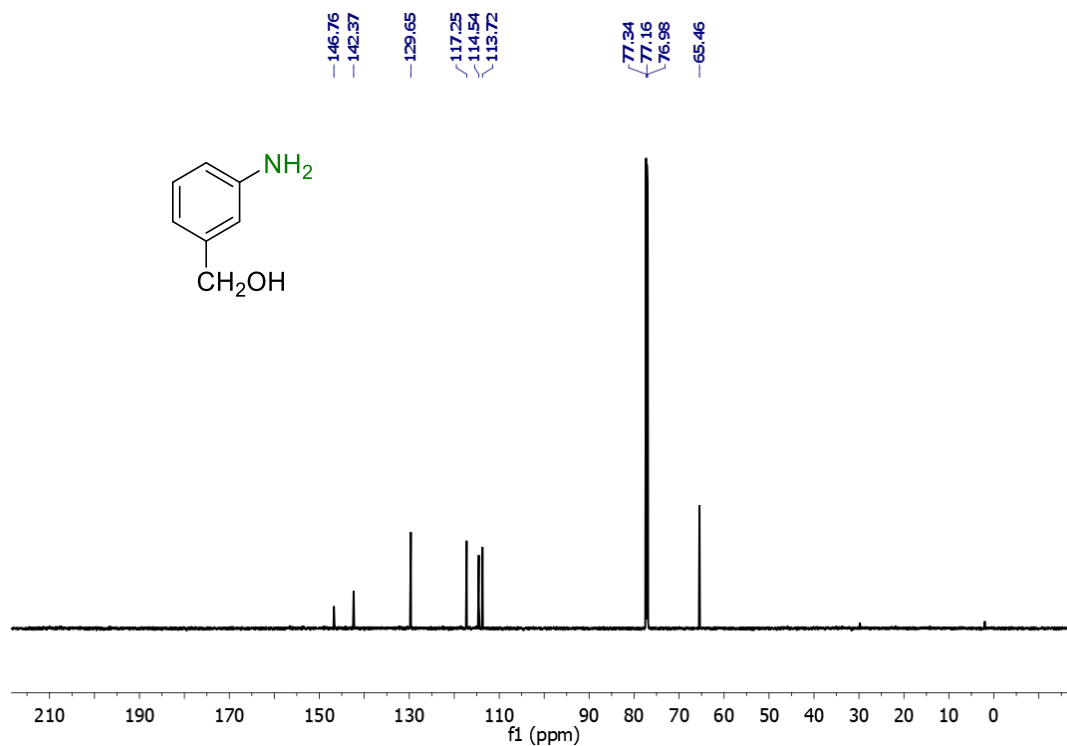
Figure 4.6 ^{13}C{^{1}H} NMR (400 MHz) spectrum of (3-aminophenyl)methanol (**A$_{3a}$**) in CDCl$_3$ at r.t.
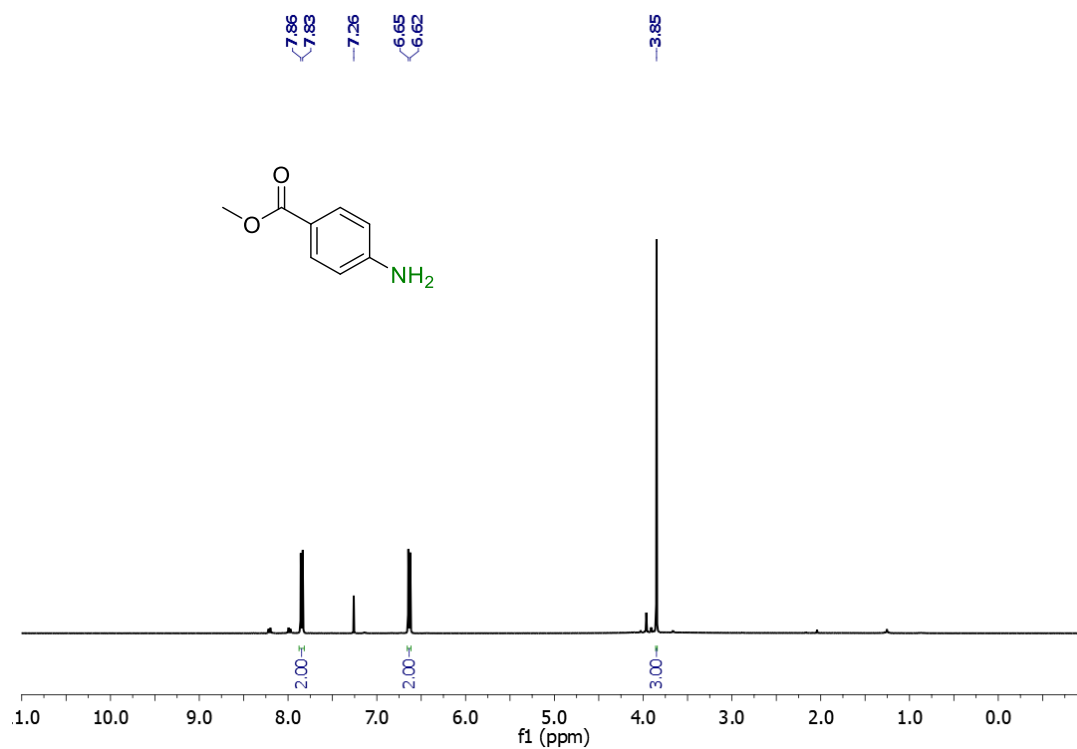
Figure 4.7 ^{1}H NMR (400 MHz) spectrum of 4-aminobenzoate (**P$_{4j}$**) in CDCl$_3$ at r.t.
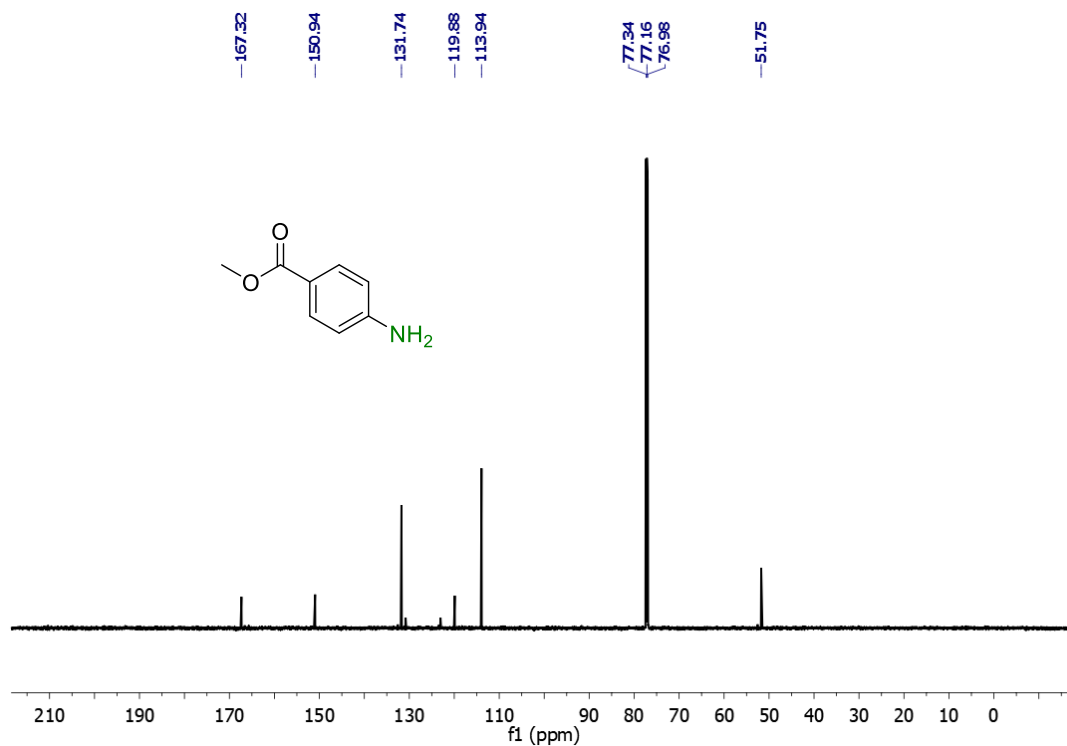
Figure 4.8 ^{13}C{^{1}H} NMR (400 MHz) spectrum of 4-aminobenzoate (**P$_{4j}$**) in CDCl$_3$ at r.t.
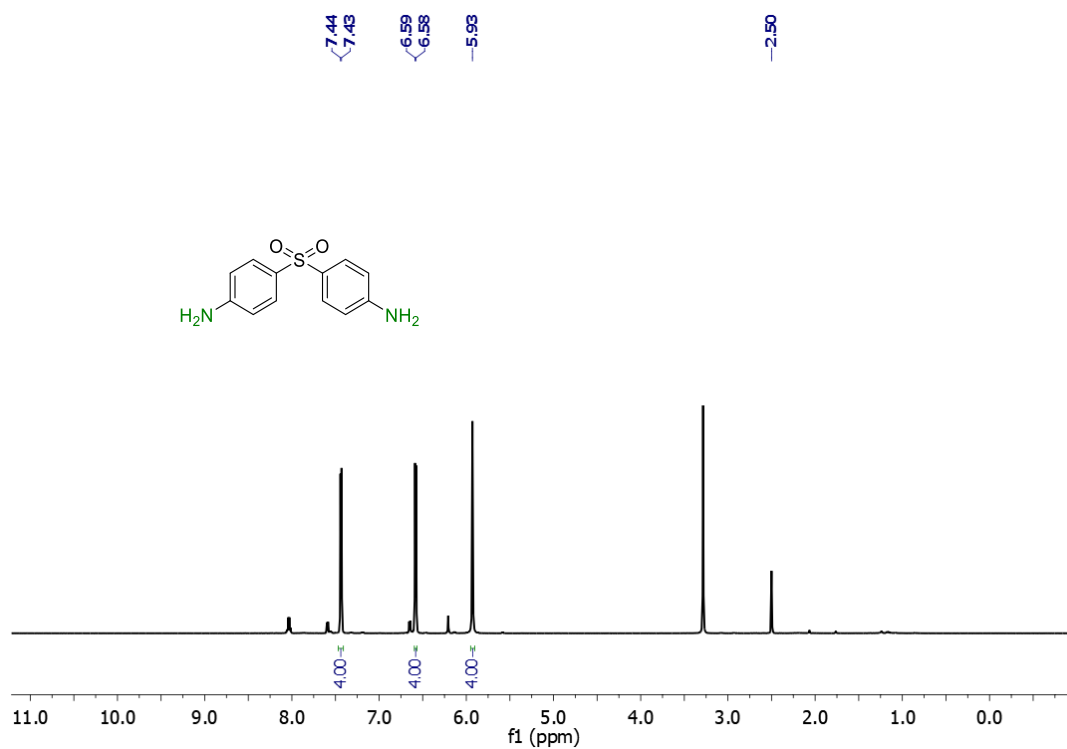
Figure 4.9 ^{1}H NMR (700 MHz) spectrum of Dapsone in DMSO-d_6 at r.t.
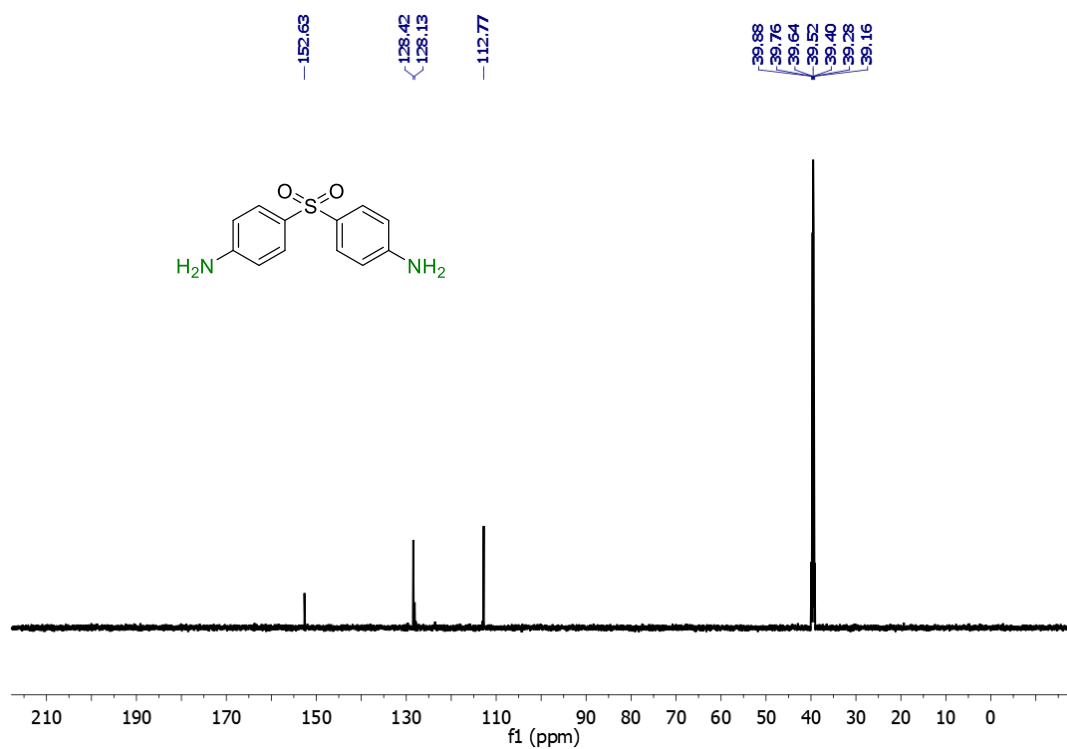
Figure 4.10 ^{13}C{^{1}H} NMR (700 MHz) spectrum of Dapsone in DMSO-d_6 at r.t.
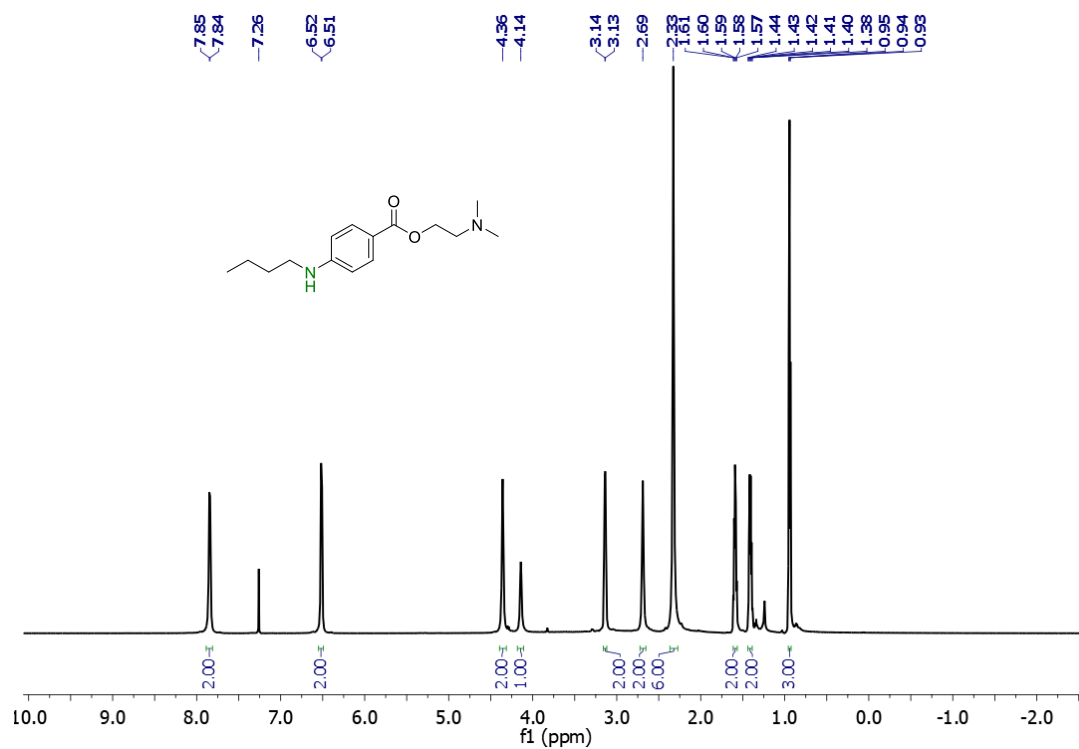
Figure 4.11 ^{1}H NMR (700 MHz) spectrum of tetracaine in CDCl$_3$ at r.t.
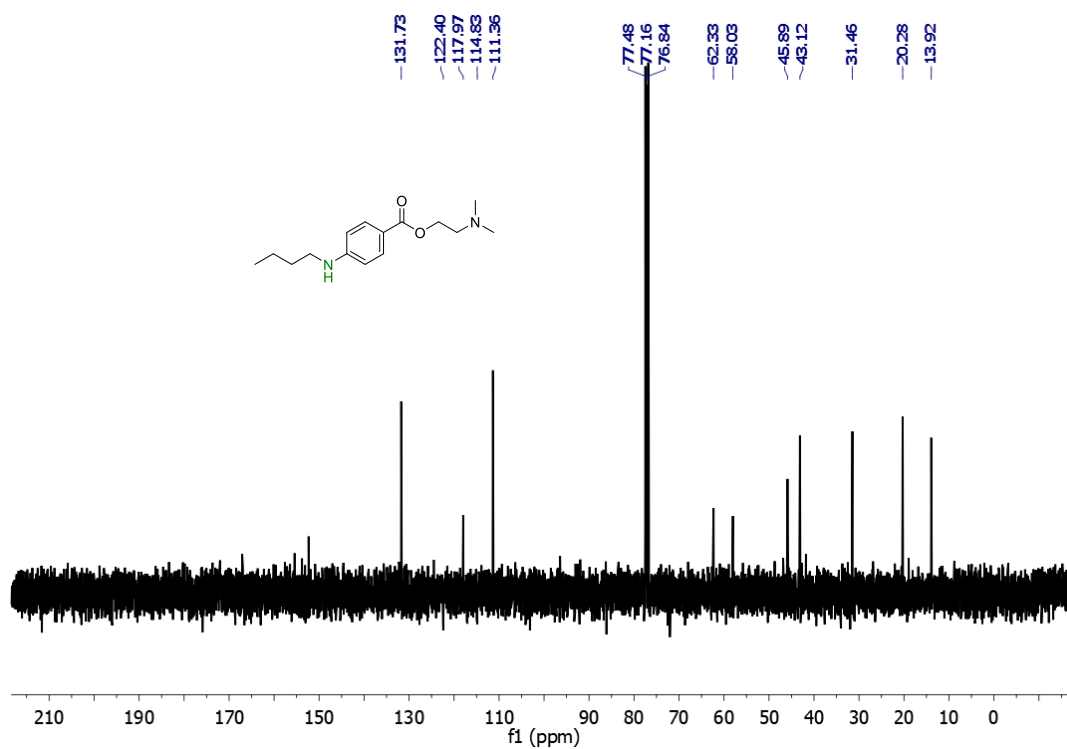
Figure 4.12 ^{13}C{^{1}H} NMR (101 MHz) spectrum of tetracaine in CDCl$_3$ at r.t.
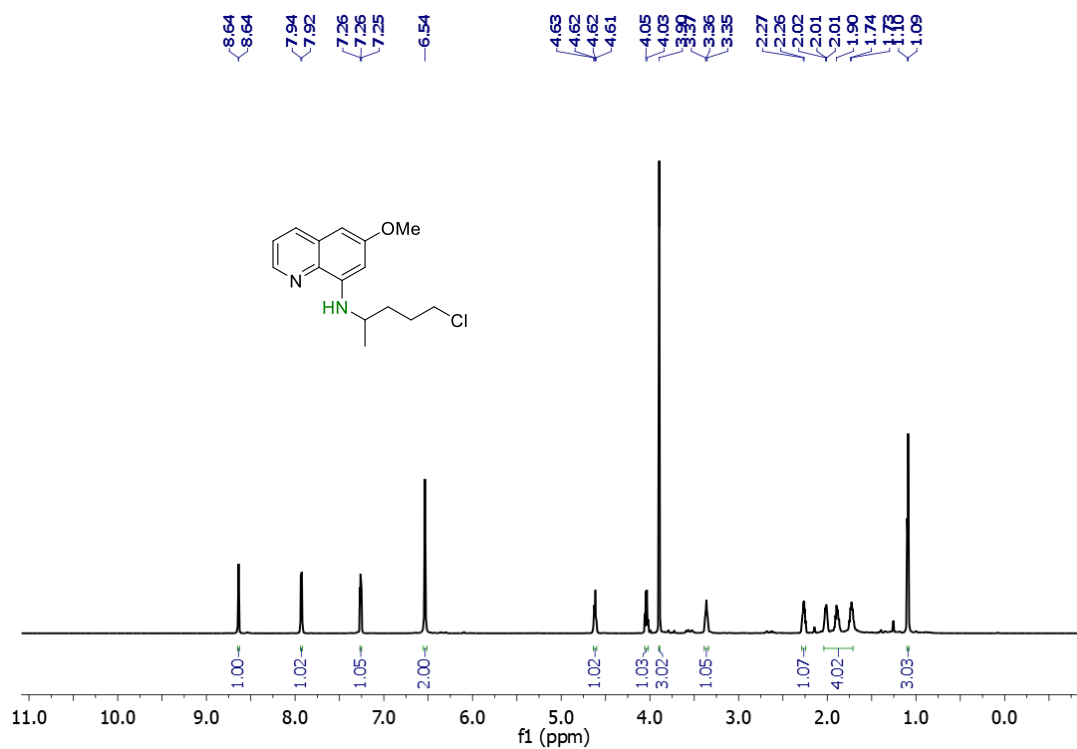
Figure 4.13 ^{1}H NMR (700 MHz) spectrum of compound **C** in CDCl$_3$ at r.t.
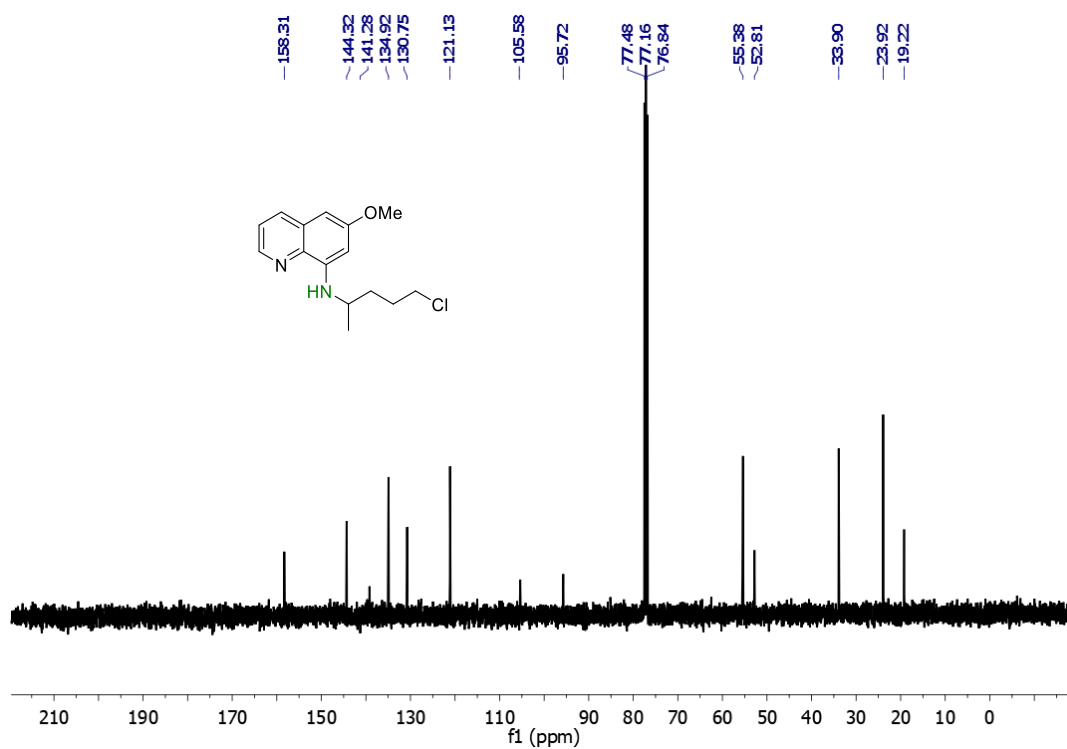
Figure 4.14 ^{13}C{^{1}H} NMR (101 MHz) spectrum of compound **C** in CDCl$_3$ at r.t.

Chapter 5

Cobalt Catalyzed Chemodivergent Synthesis of Cyclic amines and Lactams from Ketoacids and Anilines using Hydrosilylation

5.1 ABSTRACT

Commercially available $Co_2(CO)_8$ was utilized as an efficient catalyst for chemodivergent synthesis of pyrrolidines and pyrrolidones from levulinic acid and aromatic amines under slightly different hydrosilylation conditions. 1.5 and 3 equiv. of phenylsilane selectively yielded pyrrolidone and pyrrodiline pyrrolidine, respectively. Various ketoacids and amines were successfully tested. Plausible mechanism involves the condensation of levulinic acid and amine to forms an imine which cyclizes to 3-pyrrolin-2-one followed by reduction to pyrrolidone. Final reduction of pyrrolidone gave pyrrolidine.

5.2 INTRODUCTION

N-substituted pyrrolidines and pyrrolidones are important organic moieties which find extensive applications in the production of pesticides, printing ink, fiber dyes and pharmaceuticals.[1] The development of efficient and selective synthesis of N-substituted pyrrolidines and pyrrolidones is crucial for fabricating diverse derivatives with tailored properties.[2] Current research is focused on developing new eco-friendly methods that can enhance the efficiency and selectivity. In this context, one of the most appealing strategies to synthesize these structural motifs involves the reductive amination of ketoacid followed by an intramolecular cyclization. The use of cheap and bio-abundant ketoacid feedstocks that are derived from lignocellulosic biomass opens up novel possibilities for developing more economical and sustainable processes.[3] Levulinic acid (LA) is readily accessible from biomass waste and US Department of Energy has identified it as one of the twelve priority chemicals for future research.[4] LA holds a key position as an important platform chemical to

synthesize a diverse range of value-added chemicals such as γ-valerolactone, 2-methyl-tetrahydrofuran, 1,4-pentanediol and N-substituted pyrrolidones and pyrrolidines.[5] Several noble metal-based heterogeneous catalysts were used to synthesize pyrrolidones through reductive amination of LA using H_2 as reductant.[6] However, the high cost associated with these catalysts and the need for intricate reaction setups have posed significant challenges. A few homogeneous catalysts were reported for the synthesis of the lactams using molecular hydrogen or formic acid.[7] These reports were predominantly focused on heavy metals which tend to be scarce, expensive and toxic. Moreover, catalyst-free systems have also been developed to synthesize lactams using Leuckart-Wallach mechanism, albeit under very harsh reaction conditions.[8] In contrast to the synthesis of pyrrolidones, direct synthesis of pyrrolidines from LA and primary amines has received limited attention due to the absence of effective catalytic methods for reducing amides to amines. The choice of reducing agents for the synthesis of pyrrolidones is limited to mostly H_2 or HCOOH. Hydrosilanes are efficient and mild reducing agents, extensively applied in the reduction of various functionalities.[9] Given its broad functional group tolerance, hydrosilanes can be served as potential reducing agents in present reductive amination for the synthesis of pyrrolidones and pyrrolidines (Scheme 5.2.1). In 2015, Fu and co-workers first reported boron catalyzed reductive amination of LA with aniline to produce 2-methyl-1-phenylpyrrolidine using polymethylhydroxysilane.[10] The same boron catalyst was employed by Zhang group for this purpose utilizing phenylsilane as a reducing agent.[11] Several metal catalysts were also utilized for this purpose. In 2016, Sakai and coworkers reported the synthesis of N-substituted pyrrolidone and pyrrolidine under hydrosilylation condition by switching the catalyst from $In(OAc)_3$ to InI_3.[12] On the other hand, the Liu group utilized $AlCl_3$ and $RuCl_3$ to carry out the synthesis of N-substituted pyrrolidone and pyrrolidine, respectively.[13] In the context of sustainability, there is an urgent need to use base metal catalysts that are earth-

abundant, cheap and less-toxic. Published reports on the synthesis of pyrrolidone and pyrrolidine using hydrosilylation is limited. Darcel and co-workers used

Scheme 5.2.1 Metal catalyzed pyrrolidone/pyrrolidine synthesis using hydrosilylation

a) Previous works: Pyrrolidone synthesis using hydrosilylation

b) Previous works: Pyrrolidine synthesis using hydrosilylation

c) This work: Selective synthesis of pyrrolidone and pyrrolidine
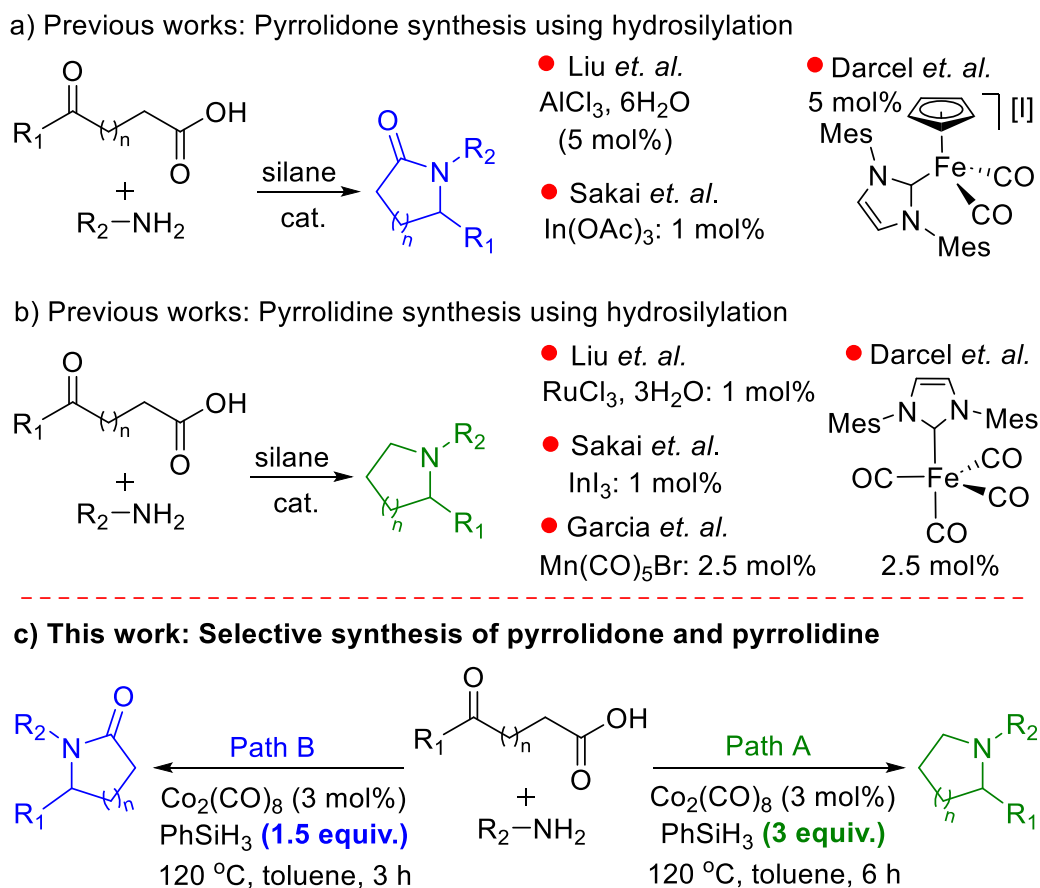
[CpFe(CO)$_2$(IMes)][I] as an effective catalyst for the synthesis of pyrrolidones.[14] If the catalyst was switched to [Fe(CO)$_4$(IMes)], pyrrolidines were achieved selectively. In 2020, Garcia group reported manganese catalyzed reductive amination of LA to synthesize pyrrolidines. In addition to the development of Fe- and Mn-catalyst, it is essential to investigate other base metal catalysts for this purpose. Cobalt has proven to be a highly effective metal in hydrosilylations and there are substantial reports on the reduction of different functionalities using silane.[16] Cobalt has already been used in LA valorization under hydrogenation.[17] However, the same has not been yet reported with cobalt using silane as a reducing agent. Herein, we report the utilization of a commercially available Co-catalyst for

the reductive amination/cyclization of ketoacids and amines to selectively synthesize pyrrolidines and pyrrolidones under slightly different hydrosilylation conditions (Scheme 5.2.1)

5.3 RESULTS AND DISCUSSIONS

$Co_2(CO)_8$ has emerged as an efficient catalyst for the hydrosilylation of acrylates, nitriles, amides, alkenes, alkynes, and esters.[18] Recently, we reported $Co_2(CO)_8$ catalyzed reduction of nitroarenes using phenylsilane under thermal and photochemical conditions.[19] So, inspired by the reports on Co-catalyzed LA valorization and the high efficiency of $Co_2(CO)_8$ as catalyst in hydrosilylation, we set out to explore the synthesis of pyrrolidines and pyrrolidones from LA and primary amine with silane as reductant and $Co_2(CO)_8$ as catalyst. Toluidine (**S₁**) and levulinic acid (**A₁**) were taken as model substrates and the results are summarised in Table 5.3.1. When a mixture of equimolar **S₁** and **A₁** with 4 equiv. phenylsilane and 5 mol% catalyst was heated at 120 °C for 24 h, a complete conversion of substrates was observed, solely forming the respective pyrrolidine product **P₁₁** (entry 1). Reducing the time gradually to 6 h also provided **P₁₁** in 91% isolated yield (entry 1). Further reduction of reaction time to 2 h, a small amount of unreacted starting materials was observed (entry 3); however, we achieved full conversion of substrates in 4 h (entry 2). By reducing the silane loading to 3 equiv., we obtained full conversion also in 4 h using a catalyst loading of 5 mol% (entry 4) and 4 mol% (entry 5). A further reduction in catalyst loading to 3 mol% failed to give full conversion in 4 h (entry 6). A slight increase in reaction time to 6 h led to the complete conversion of substrates with an isolated yield of 89% (entry 7). Then we varied catalyst loading and reaction temperature separately. If the temperature (100 °C) and catalyst loading (2 mol%) were reduced any further, complete conversion could not be achieved (entry 8 and 9). We also performed a blank test. The reaction failed to proceed in the absence of $Co_2(CO)_8$ (entry 10). Afterward, we tested a few different silanes such as triethylsilane, TMDS and

PMHS. No conversion to pyrrolidine product was observed with triethylsilane (entry 11). However, we noted 25 and 62% conversion to desired product with PMHS and TMDS, respectively (entry 12 and 13); increasing the reaction time did not improve the yield. Therefore, the following condition were regarded as the optimized reaction conditions: 3 mol% $Co_2(CO)_8$, 3 equiv. $PhSiH_3$, 120 °C, 6 h (entry 7).

Table 5.3.1 Catalytic performance of $Co_2(CO)_8$ for the synthesis of pyrrolidine P_{11}.[a]
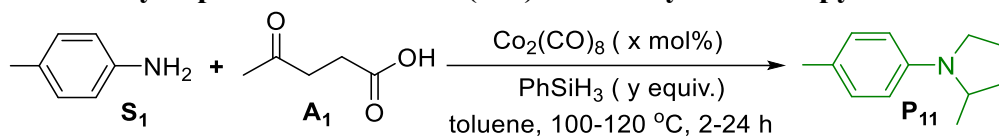
en	catalyst (mol%)	silane (equiv.)	temp (°C)	time (h)	yield[b] (%)
1	5	$PhSiH_3$ (4)	120	24/12/6	>99 (91[c])
2	5	$PhSiH_3$ (4)	120	4	>99 (90[c])
3	5	$PhSiH_3$ (4)	120	2	87
4	5	$PhSiH_3$ (3)	120	4	>99
5	4	$PhSiH_3$ (3)	120	4	>99
6	3	$PhSiH_3$ (3)	120	4	92
7	**3**	**$PhSiH_3$ (3)**	**120**	**6**	**>99 (89[c])**
8	3	$PhSiH_3$ (3)	100	6	90
9	2	$PhSiH_3$ (3)	120	6	83
10	no	$PhSiH_3$ (3)	120	6	0
11	3	Et_3SiH (3)	120	6	<5
12	3	PMHS (3)	120	6	25

| 13 | 3 | TMDS (3) | 120 | 6 | 62 |

In this type of reaction, pyrrolidone is formed as an intermediate which is further reduced to pyrrolidine in presence of additional silane. The formation of pyrrolidone showed a significant dependence on the amount of silane used. We set out to investigate if selective formation of pyrrolidone could be achieved with less silane (Table 5.3.2). We observed that

Table 5.3.2 Optimization for reductive amination/cyclization of LA under hydrosilylation.[a]
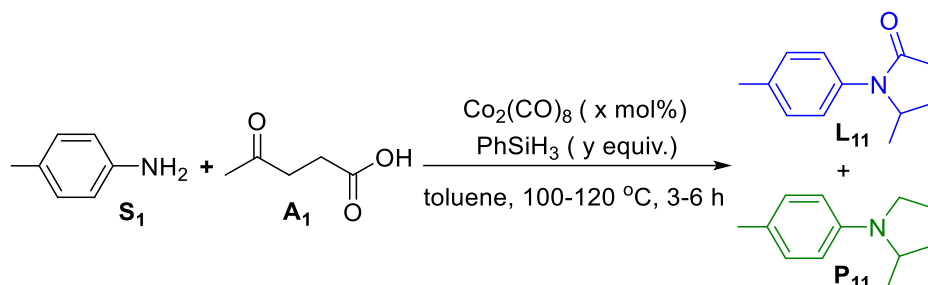
en	catalyst	PhSiH₃	temp	time	yield[b] (%)	
	(mol%)	(equiv.)	(°C)	(h)	**P₁₁**	**L₁₁**
1	3	2.5	120	6	92	8
2	3	2	120	6	33	67
3	3	1.5	120	6	0	>99
4	3	1	120	6	0	57
5	**3**	**1.5**	**120**	**3**	**0**	**>99 (86)[c]**
6	3	1.5	100	3	0	80
7	2	1.5	120	3	0	88

decrease in phenylsilane loading from the optimized condition of pyrrolidine synthesis caused the reaction to shift towards pyrrolidone (**L₁₁**). When 2.5 equiv. PhSiH₃ was used in presence of 3 mol% catalyst, a 9:1 mixture of **P₁₁** and **L₁₁** was observed in 6 h at 120 °C

(entry 1). In presence of 2 equiv. of $PhSiH_3$, the reaction was more favorable to L_{11} (67%, entry 2). Complete selectivity to L_{11} was achieved when silane loading was reduced to 1.5 equiv. (entry 3). A substantial amount of starting material remained unreacted when 1 equiv. phenylsilane was used (entry 4). The reaction time was further reduced to 3 h and we achieved complete conversion to L_{11} with excellent isolated yield (entry 5, optimized condition). Small amount of unreacted starting materials was noted with lowering the temperature (100 °C, entry 6) and catalyst loading (2 mol%, entry 7).

After optimizing the reaction conditions, we focused to expand the substrate scope. At first, the reactivity of various primary aromatic amines (S_x) was tested for the synthesis of pyrrolidines (Scheme 5.3.1). Various anilines with diverse substituents were reacted with levulinic acid (A_1) to form the corresponding pyrrolidines P_{x1} (After optimizing the reaction conditions, we focused to expand the substrate scope. At first, the reactivity of various primary amines (S_x) was tested for the synthesis of pyrrolidines (Scheme 5.3.1). Various anilines with diverse substituents were reacted with levulinic acid (A_1) to form the corresponding pyrrolidines P_{x1} (P_{21}: 85%, P_{31}: 87%, P_{41}: 74%, P_{51}: 63%, P_{61}: 78%, P_{71}: 68%, P_{81}: 80%, P_{91}: 78%, P_{101}: 58%, P_{111}: 75%, P_{121}: 67%, P_{131}: 55%) in decent to excellent yields. The reaction conditions effectively tolerate a wide range of electron-donating and electron-withdrawing functional groups such as methyl, methoxy, hydroxyl, chloro, bromo and trifluoromethyl and thereby offering convenient synthetic modification. Interestingly, the reaction of 4-iodoaniline with levulinic acid resulted in the formation of dehalogenated product (P_{21}: 58%). This suggests that present optimized catalytic condition could not tolerate the presence of iodo substituent. The electronic nature of the substituents on aryl amines appear to influence the outcome of the reaction. Anilines with strong electron-withdrawing group such as trifluoromethyl yielded relatively poor yields (P_{101}: 52%). We further broaden the substrate scope by including polycyclic amines. 1-Naphthylamine, 8-aminoquinoline and

2-aminofluorene were tested and desired pyrrolidine products (P_{111}, P_{121}, P_{131}) were obtained. Subsequently, we advanced to explore various ketoacids for the formation of different N-heterocycles. When 5-oxohexanoic acid (A_2) was reacted with 4-methylaniline, the corresponding piperidine derivative was isolated in good yield (P_{12}: 85%). Thereafter, various aromatic amines with varying substituents were reacted with 5-oxohexanoic acid. Substituted aryl amines with electron donating and electron withdrawing groups gave the corresponding piperidine products in 70-80% yield (P_{22}: 80%, P_{32}: 83%, P_{42}: 70%, P_{62}: 74%, P_{82}: 76%, P_{92}: 72%). We also witnessed the successful use of 6-oxoheptanoic acid (A_3) resulting in azepane derivatives P_{x3} in good yields (P_{13}: 74%, P_{23}: 77%, P_{83}: 73%, P_{113}: 80%). Additionally, we tested phenyl-substituted keto acids such as 4-oxo-4-phenylbutanoic acid (A_4) and 5-oxo-5-phenylpentanoic acid (A_5). Reaction of aromatic amines with 4-oxo-4-phenylbutanoic acid (A_4) and 5-oxo-5-phenylpentanoic acid (A_5) yielded the corresponding pyrrolidines (P_{14}: 72%, P_{24}: 68%, P_{34}: 64%, P_{84}: 55%) and piperidines (P_{15}: 80%, P_{25}: 77%, P_{65}: 70%, P_{85}: 73%, P_{95}: 75%), respectively, in satisfactory to good yields. Finally, the utilization of 2-formylbenzoic acid (A_6), instead of linear ketoacid, was examined under optimized reaction conditions and a variety of N-arylisoindoline derivatives P_{x6} were furnished in good isolated yields (P_{16}: 88%, P_{26}: 85%, P_{46}: 76%, , P_{86}: 78%, P_{96}: 74%, P_{126}: 60%, P_{146}: 69%, P_{156}: 52%). Similar to chloro and bromo substituents, fluoro group (P_{156}) was also tolerated. It should be noted that this catalytic protocol was not effective for several aromatic amines. We performed the reaction of levulinic acid with 4-vinylaniline, 3-ethynylaniline, 4-aminobenzoic acid, 4-aminobenzamide, 4-amino-N-methylbenzamide and 4-aminobenzonitrile under optimized reaction conditions; however, no desired product was observed. So, aromatic amines bearing alkenyl, alkynyl, carboxylic acids, cyano, primary and secondard amide groups were not tolerated. We also tested aliphatic amine. Reaction of *n*-octyl amine with levulinic acid and 5-oxohexanoic acid did not yield desired products.

Scheme 5.3.1 Cobalt-catalyzed synthesis of pyrrolidines and related cyclic amines
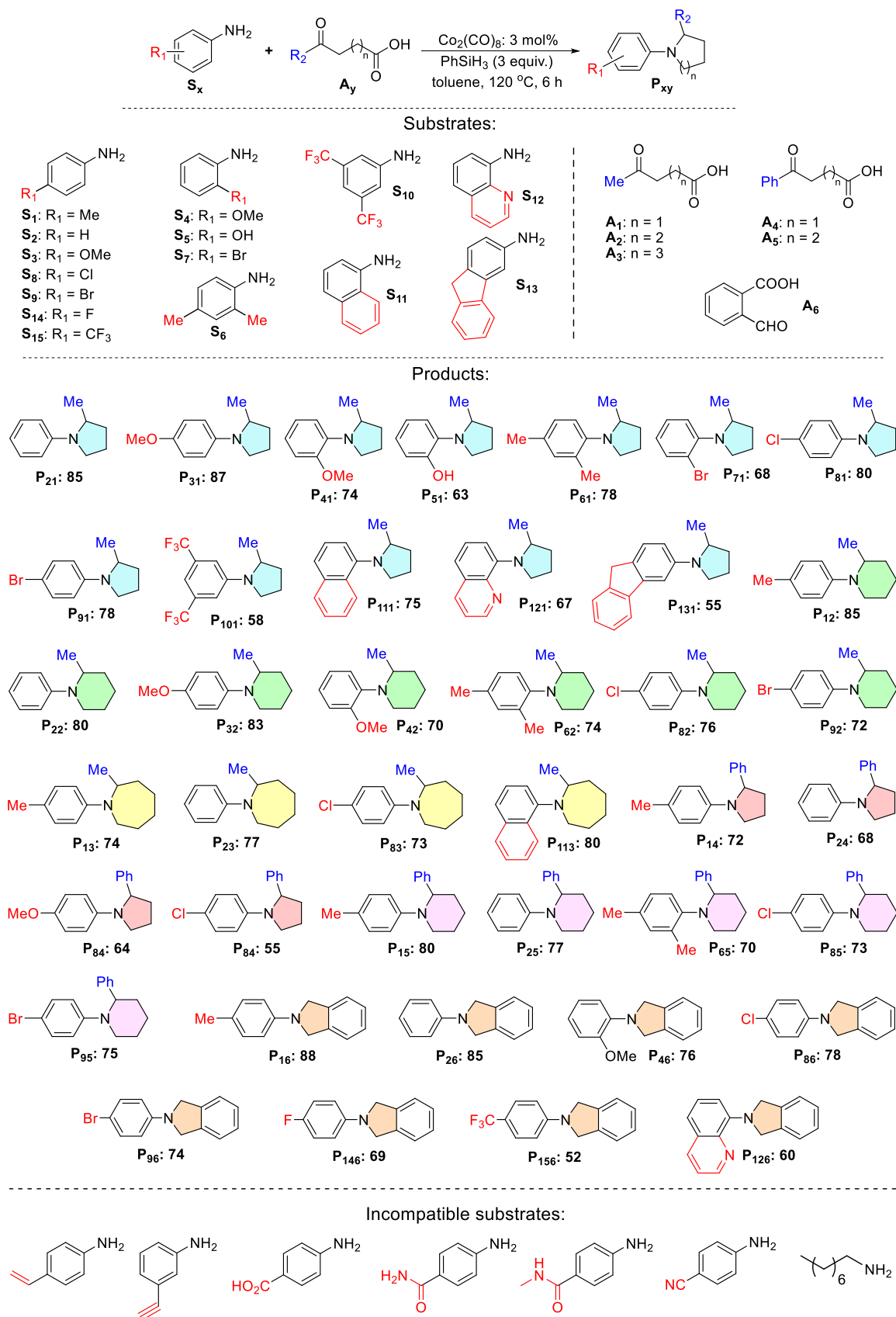
Next, we set out to expand the substrate scope of pyrrolidones and related lactams (Scheme 5.3.2). First, various aromatic amines (S_x) with electron donating and withdrawing groups were tested with LA (A_1) and corresponding pyrrolidones were isolated in good to excellent yields Cobalt-catalyzed synthesis of pyrrolidones (L_{21}: 80%, L_{31}: 83%, L_{41}: 62%, L_{61}: 74%, L_{81}: 72%, L_{91}: 75%). Other ketoacids such 5-oxohexanoic acid (A_2), 6-oxoheptanoic acid (A_3) and 2-formylbenzoic acid (A_6) were also successfully examined and corresponding lactams (L_{xy}) were obtained in good yields (L_{12}: 83%, L_{22}: 78%, L_{92}: 73%, L_{23}: 83%, L_{83}: 77%, L_{16}: 86%, L_{86}: 71%). To check the robustness of this method, we successfully performed gram scale synthesis of P_{11} (93%) and L_{12} (91%).

Scheme 5.3.2 Cobalt-catalyzed synthesis of pyrrolidones
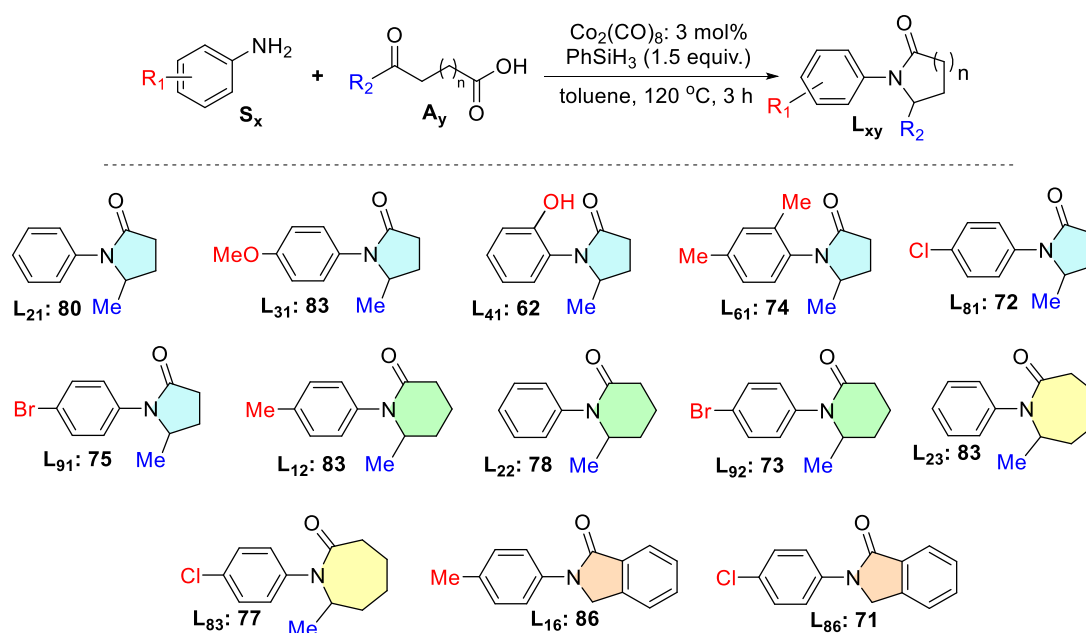
To understand the reaction pathway, we performed a couple of control experiments (Scheme 5.3.3). At first, we performed a standard reaction for synthesis of pyrrolidine **P_{11}** by using the optimized reaction condition in presence of a drop of mercury (Scheme 5.3.3a). We did not observe any negative effect on the yield of **P_{11}**. A reaction under optimized condition was also performed in presence of 1 equiv. of 1,10-phenanthroline with respect to the catalyst loading (Scheme 5.3.3a) and we isolated the desired product in good yield (84%).[20] Thus, the

Scheme 5.3.3 Control experiments and plausible reaction pathway

a) Catalyst poisoning test:
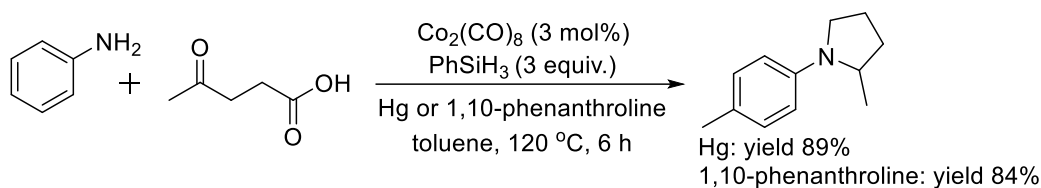
b) Identification of 5-methyl-1-phenyl-1,5-dihydro-pyrrol-2-one followed by the hydrosilylation to 5-methyl-1-phenylpyrrolidin-2-one:
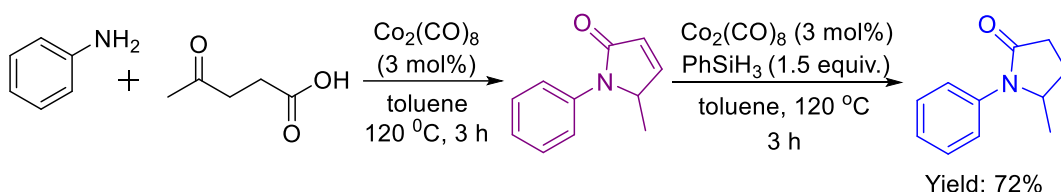
c) Hydrosilylation of 5-methyl-1-phenylpyrrolidin-2-one to 2-methyl-1-(p-tolyl)pyrrolidine:
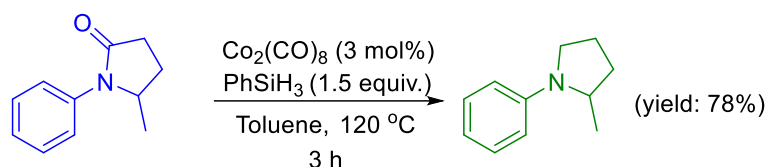
d) Proposed reaction pathway:
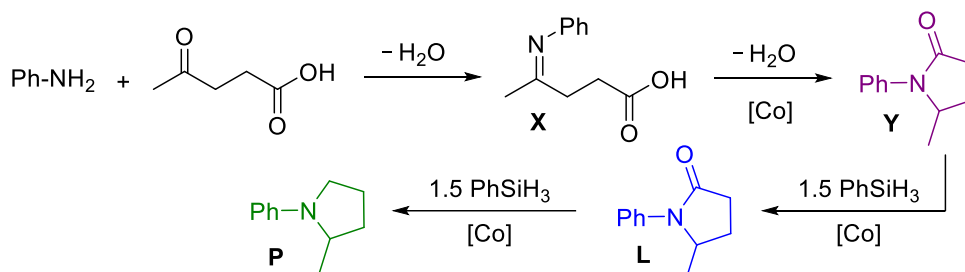
possibility of a heterogeneous reaction was ruled out. We also performed a reaction of aniline, levulinic acid and silane in absence of cobalt complex. We did not observe formation of any desired product which established the active role of $Co_2(CO)_8$ in this catalytic reaction. Then, an equimolar mixture of LA and aniline with catalytic amount of $Co_2(CO)_8$ were reacted in absence of silane (Scheme 5.3.3b). The resultant mixture was analyzed by mass spectrometry which clearly showed the formation of 5- methyl-1-phenyl-1,5-dihydro-pyrrol-2-one. Instead of our best attempts, we failed to isolate 5- methyl-1-phenyl-1,5-dihydro-pyrrol-2-one from the above reaction mixture. If 1.5 equiv. of $PhSiH_3$ was added to the above

reaction mixture, we noted the formation of pyrrolidone L_{21}. Thereafter, pyrrolidone L_{21} was further reacted with another 1.5 equiv. of $PhSiH_3$ and pyrrolidone L_{21} was reduced to pyrrolidine P_{21} (Scheme 5.3.3c). So, based on the experimental evidences and past reports,[13] a plausible mechanism is proposed (Scheme 5.3.3d). The condensation of LA and aromatic amine forms an imine (X) which cyclizes (catalyzed by cobalt) to 3-pyrrolin-2-one intermediate Y. Then Y was reduced to pyrrolidone (L) which was further reduced to pyrrolidine (P). Based on the past reports,[18b, 18d, 18f] we propose that oxidative addition of Si-H bond on $Co_2(CO)_8$ resulted in the formation of $HCo^I(CO)_4$ and $Co^I(CO)_4(SiR_3)$ and the cobalt(I) species acted as active catalyst in hydrosilylation. The coordination of imine (X) with cobalt catalyst followed by cyclization yielded intermediate Y. The alkene moiety in Y and finally the keto group in pyrrolidone L were reduced via hydrosilylation by cobalt(I) active catalyst to give final pyrrolidine product P. Although we could not see the formation of silylester by any experimental technique, the possible formation of silylesters[14a] and the reduction of imine cannot be ruled out.

5.4 CONCLUSION

In conclusion, a switchable protocol for the synthesis of N-substituted pyrrolidines to pyrrolidones under hydrosilylation condition was described using commercial $Co_2(CO)_8$ catalyst. No additional ligand or additive was needed. Prior to this study, only Fe and Mn as base metal catalysts were reported; cobalt has not been employed for this purpose before. To the best of our knowledge, this is the first example of metal catalyst which can be used to selectively synthesize pyrrolidone and pyrrolidine under slightly different hydrosilylation conditions. Biomass-derived levulinic acid and other ketoacids were used in combination with various aryl amines and diverse functionalities were well tolerated.

5.5 EXPERIMENTAL SECTION

General experimental. All air and moisture-sensitive experiments such as catalytic reductive amination of ketoacids using hydrosilanes were performed under dry nitrogen atmosphere using standard Schlenk or glovebox (MBraun) techniques. The typical synthetic procedure was performed in Ace pressure tubes purchased from Sigma-Aldrich. For the air-sensitive experiments, solvents (toluene and THF) were distilled, degassed, and stored over 3 Å molecular sieves. Solvents (hexanes, petroleum ether, ethyl acetate, MeOH and THF) were purchased from Merck, Finar, and Rankem. For recording NMR spectra of air- and moisture-sensitive samples, $CDCl_3$ was degassed and stored over 3 Å molecular sieves. $CDCl_3$ was purchased from Sigma Aldrich. Co_2CO_8, $PhSiH_3$, Et_3SiH, PMHS, TMDS and all the ketoacids and amines as substrates for hydrosilylation were purchased from Sigma Aldrich, Alfa Aesar and TCI Chemicals and used without further purification.

^1H and $^{13}C\{^1H\}$ NMR spectra were recorded using Bruker AV-400 , AV-700 and JEOL-400 (^1H at 400 MHz and $^{13}C\{^1H\}$ at 101 MHz). ^1H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethylsilane (δ 0.00 ppm) and $^{13}C\{^1H\}$ NMR chemical shifts are referenced in ppm with respect to $CDCl_3$ (δ 77.16 ppm). The coupling constants (J) are reported in hertz (Hz). The following abbreviations are used to describe multiplicity: s = singlet, bs = broad signal, d = doublet, t = triplet, q = quartet, m = multiplet. High-resolution mass spectra were recorded on a Bruker micrOTOF-Q II Spectrometer.

General procedure for reaction optimization of pyrrolidine synthesis. In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (2/3/4/5 mol%), *p*-toluidine (0.027 g, 0.25 mmol), phenylsilane (0.81 g, 0.75 mmol), levulinic acid (0.029 g, 0.25 mmol) and toluene (1 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at appropriate temperature (100-120 °C) in a preheated oil bath for 2 to 24 h. After cooling to r.t., MeOH (1 mL) and *p*-xylene (0.027 g, 0.25 mmol) were added to the resultant mixture.

The mixture was then analyzed by GC to determine the yield of the corresponding pyrrolidine product. Thereafter, water (3 mL) was added to the previous mixture and the mixture was extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. All volatiles were removed under a high vacuum to give crude product. Occasionally, the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

General procedure for reaction optimization of pyrrolidone synthesis: In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (2/3 mol%), *p*-toluidine (0.027 g, 0.25 mmol), phenylsilane (0.041 g, 0.375 mmol), levulinic acid (0.029 g, 0.25 mmol) and toluene (1 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at appropriate temperature (100-120 °C) in a preheated oil bath for 3 to 6 h. After cooling to r.t., MeOH (1 mL) and *p*-xylene (0.027 g, 0.25 mmol) were added to the resultant mixture. The mixture was then analyzed by GC to determine the yield of the corresponding pyrrolidone product. Thereafter, water (3 mL) was added to the previous mixture and the mixture was extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. All volatiles were removed under a high vacuum to give crude product. Occasionally, the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

General procedure for the synthesis of cyclic amines (substrate scope). In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (0.005 g, 3 mol%), aromatic amine (0.5 mmol, 1 equiv.), phenylsilane (0.162 g, 1.5 mmol, 3 equiv.), ketoacid (0.5 mmol, 1 equiv.) and toluene (2 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 120 °C in a preheated oil bath for 6 h. After cooling to r.t., MeOH (1 mL) and water (3 mL) (occasionally 10 wt% of NaOH solution (3 mL)) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was

collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

General procedure for the synthesis of lactams (substrate scope). In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (0.005 g, 3 mol%), aromatic amine (0.5 mmol, 1 equiv.), phenylsilane (0.081 g, 0.75 mmol, 1.5 equiv.), ketoacid (0.5 mmol, 1 equiv.) and toluene (2 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 120 °C in a preheated oil bath for 6 h. After cooling to r.t., MeOH (1 mL) and water (3 mL) (occasionally 10 wt% of NaOH solution (3 mL)) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

General procedure for gram scale synthesis of 2-methyl-1-(p-tolyl)pyrrolidine (P$_{11}$). In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (0.102 g, 3 mol%), *p*-toluidine (1.070 g, 10 mmol), phenylsilane (3.240 g, 30 mmol), levulinic acid (1.160 g, 10 mmol) and toluene (10 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 120 °C in a preheated oil bath for 6 h. After cooling to r.t., MeOH (10 mL) and water (30 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 15 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (98:2) as eluent. P$_{11}$: (1.63 g, 93%).

General procedure for gram scale synthesis of 6-methyl-1-(p-tolyl)piperidin-2-one (L$_{12}$). In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (0.102 g, 3 mol%), *p*-

toluidine (1.080 g, 10 mmol), phenylsilane (1.620 g, 15 mmol), 5-oxohexanoic acid (1.301 g, 10 mmol) and toluene (10 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 120 °C in a preheated oil bath for 6 h. After cooling to r.t., MeOH (10 mL) and water (30 mL) were added to the resultant mixture. The mixture was then extracted with Et$_2$O (3 x 15 mL). The organic layer was collected and dried over anhydrous Na$_2$SO$_4$. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate (3:2) as eluent. L$_{12}$: (1.84 g, 91%).

Catalyst poisoning test: In a dried pressure tube fitted with a magnetic stir bar, Co$_2$(CO)$_8$ (0.003 g, 3 mol%), *p*-toluidine (0.027 g, 0.25 mmol), levulinic acid (0.029 g, 0.25 mmol), phenylsilane (0.81 g, 0.75 mmol), toluene (1 mL) and a drop of Hg or 1,10-phenanthroline (from a stock solution; 0.001 g, 3 mol%) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 120 °C in a preheated oil bath for 6 h. After cooling to r.t., MeOH (1 mL) and *p*-xylene (0.027 g, 0.25 mmol) were added to the resultant mixture. The mixture was then analyzed by GC to determine the yield of the corresponding pyrrolidone product.

Stoichiometric reaction of LA and aniline with Co$_2$(CO)$_8$ catalyst to detect intermediate: In a dried pressure tube fitted with a magnetic stir bar, Co$_2$(CO)$_8$ (0.003 g, 3 mol%), aniline (0.023 g, 0.25 mmol), levulinic acid (0.029 g, 0.25 mmol) and toluene (1 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 120 °C in a preheated oil bath for 3 h. After cooling to r.t., mass sample was taken and 5-methyl-1-phenylpyrrolidin-2-one was clearly identified. Then, phenylsilane (0.041 g, 0.375 mmol) was added into the same solution under nitrogen atmosphere and stirred for another 3 h at 120 ^{0}C. After that MeOH (1 mL) and water (3 mL) were added to the resultant mixture. The mixture was then extracted with Et$_2$O (3 x 5 mL). The organic layer was collected and dried over

anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

Hydrosilylation of 5-methyl-1-phenylpyrrolidin-2-one to 2-methyl-1-(p-tolyl)pyrrolidine: In a dried pressure tube fitted with a magnetic stir bar, $Co_2(CO)_8$ (0.003 g, 3 mol%), 5-methyl-1-phenylpyrrolidin-2-one (0.044 g, 0.25 mmol), phenylsilane (0.041 g, 0.375 mmol), toluene (1 mL) were added successively under a nitrogen atmosphere. The reaction mixture was heated at 120 °C in a preheated oil bath for 3 h. After cooling to r.t. MeOH (1 mL) and water (3 mL) were added to the resultant mixture. The mixture was then extracted with Et_2O (3 x 5 mL). The organic layer was collected and dried over anhydrous Na_2SO_4. Thereafter, all volatiles were removed and the crude product was purified by column chromatography using silica as the stationary phase and a mixture of petroleum ether and ethyl acetate as eluent.

Following known compounds are characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopies and new compounds are characterized by ^1H and $^{13}C\{^1H\}$ NMR spectroscopies and HRMS

2-methyl-1-(p-tolyl)pyrrolidine (P_{11}):[17] Obtained as a result of the equimolar reaction between *p*-toluidine and levulinic Acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (P_{11}: 0.078 g, 89%). ^1H NMR (400 MHz, CDCl$_3$) δ 7.09 (d, J = 7.8 Hz, 2H), 6.58 (d, J = 7.8 Hz, 2H), 3.92 – 3.86 (m, 1H), 3.49 – 3.44 (m, 1H), 3.22 – 3.17 (m, 1H), 2.31 (s, 3H), 2.12 – 2.00 (m, 3H), 1.78 – 1.71 (m, 1H), 1.22 (d, J = 6.2, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 145.4, 129.8, 124.3, 112.0, 53.9, 48.6, 33.3, 23.4, 20.4, 19.6.

2-methyl-1-phenylpyrrolidine (P_{21}):[13] Obtained as a result of the equimolar reaction between aniline and levulinic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (P_{21}: 0.068 g,

85%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.26 (t, J = 7 Hz, 2H), 6.69 – 6.62 (m, 3H), 3.92 – 3.87 (m, 1H), 3.49 – 3.45 (m, 1H), 3.22 – 3.16 (m, 1H), 2.10 – 2.00 (m, 3H), 1.76 – 1.72 (m, 1H), 1.21 (d, J = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 147.4, 129.3, 115.3, 111.9, 53.7, 48.3, 33.2, 23.4, 19.5.

1-(4-Methoxyphenyl)-2-methylpyrrolidine (P$_{31}$):[17] Obtained as a result of the equimolar reaction between *p*-anisidine and levulinic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{31}$**: 0.083 g, 87%). 1H NMR (400 MHz, CDCl$_3$) δ 6.85 (d, J = 9.0 Hz, 2H), 6.55 (d, J = 9.0 Hz, 2H), 3.85 – 3.76 (m, 4H), 3.43 – 3.38 (m, 1H), 3.14 – 3.08 (m, 1H), 2.09 – 1.93 (m, 3H), 1.72 – 1.64 (m, 1H), 1.18 (d, J = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 150.7, 135.9, 115.2, 112.9, 56.1, 54.3, 49.1, 33.3, 23.5, 19.7.

1-(2-methoxyphenyl)-2-methylpyrrolidine (P$_{41}$): Obtained as a result of the equimolar reaction between *o*-anisidine and levulinic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{41}$**: 0.071 g, 74%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.91 – 6.81 (m, 4H), 3.98 – 3.89 (m, 1H), 3.85 (s, 3H), 3.74 – 3.68 (m, 1H), 2.99 – 2.93 (m, 1H), 2.22 – 2.14 (m, 1H), 1.97 – 1.89 (m, 1H), 1.87 – 1.78 (m, 1H), 1.66 – 1.57 (m, 1H), 1.03 (d, J = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 151.6, 138.9, 121.0, 120.2, 117.3, 111.6, 55.5, 54.4, 51.6, 33.7, 23.5, 19.0. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{12}$H$_{18}$NO: 192.1388, found 192.1381.

2-(2-methylpyrrolidin-1-yl)phenol (P$_{51}$):[21] Obtained as a result of the equimolar reaction between 2-aminophenol and levulinic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{51}$**: 0.056 g, 63%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.18 (d, J = 7.8 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 6.67 – 5.88 (brs, 1H), 3.30 – 3.16 (m, 2H), 2.86 – 2.80 (m, 1H), 2.19 – 2.11 (m, 1H), 1.99 – 1.89 (m, 2H), 1.62 – 1.53 (m, 1H), 0.98

(d, J = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 153.9, 135.9, 126.4, 122.5, 120.1, 113.6, 60.17, 55.5, 33.1, 23.0, 19.2.

1-(2,4-dimethylphenyl)-2-methylpyrrolidine (P$_{61}$): Obtained as a result of the equimolar reaction between 2,4-dimethylaniline and levulinic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{61}$**: 0.074 g, 78%). ^1H NMR (400 MHz, CDCl$_3$) δ 7.05 – 6.94 (m, 3H), 3.67 – 3.54 (m, 2H), 2.80 – 2.74 (m, 1H), 2.34 (s, 3H), 2.32 (s, 3H), 2.22 – 2.14 (m, 1H), 2.01 – 1.79 (m, 2H), 1.66 – 1.57 (m, 1H), 1.06 (d, J = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 146.1, 135.9, 132.6, 132.0, 126.8, 118.8, 55.4, 53.5, 33.8, 23.5, 20.7, 19.2, 19.2. HRMS (ESI) m/z: [(M + H)$^+$] calcd for C$_{13}$H$_{20}$N: 190.1614, found 190.1620.

1-(2-bromophenyl)-2-methylpyrrolidine (P$_{71}$):[17] Obtained as a result of the equimolar reaction between 2-bromoaniline and levulinic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{71}$**: 0.081 g, 68%). ^1H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, J = 8.0 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.80 (t, J = 7.7 Hz, 1H), 3.94 – 3.86 (m, 2H), 2.90 – 2.84 (m, 1H), 2.22 – 2.14 (m, 1H), 1.99 – 1.91 (m, 1H), 1.86 – 1.74 (m, 1H), 1.65 – 1.55 (m, 1H), 1.03 (d, J = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 148.2, 134.3, 127.7, 122.4, 120.4, 117.6, 55.0, 53.0, 33.8, 23.9, 19.0.

1-(4-chlorophenyl)-2-methylpyrrolidine (P$_{81}$):[17] Obtained as a result of the equimolar reaction between 4-chloroaniline and levulinic Acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{81}$**: 0.078 g, 80%). ^1H NMR (400 MHz, CDCl$_3$) δ 7.16 (d, J = 8.7 Hz, 2H), 6.49 (d, J = 8.7 Hz, 2H), 3.89 – 3.78 (m, 1H), 3.41- 3.36 (m, 1H), 3.17 – 3.11 (m, 1H), 2.15 – 1.95 (m, 3H), 1.76 – 1.68 (m, 1H), 1.17 (d, J = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, CDCl$_3$) δ 145.9, 129.0, 119.9, 112.9, 53.9, 48.4, 33.2, 23.4, 19.2.

1-(4-bromophenyl)-2-methylpyrrolidine (P$_{91}$):[17] Obtained as a result of the equimolar reaction between 4-bromoaniline and levulinic Acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{91}$**: 0.094 g, 78%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.25 (d, J = 8.0 Hz, 2H), 6.42 (d, J = 8.0 Hz, 2H), 3.83 – 3.77 (m, 1H), 3.38 – 3.33 (m, 1H), 3.13 – 3.07 (m, 1H), 2.09 – 1.93 (m, 3H), 1.73 – 1.65 (m, 1H), 1.12 (d, J = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 146.2, 131.9, 113.5, 107.0, 53.9, 48.3, 33.2, 23.4, 19.2.

1-(3,5-bis(trifluoromethyl)phenyl)-2-methylpyrrolidine (P$_{101}$):[17] Obtained as a result of the equimolar reaction between 3,5-bis(trifluoromethyl)aniline and levulinic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{101}$**: 0.086 g, 58%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.08 (s, 1H), 6.88 (s, 2H), 3.98 – 3.92 (m, 1H), 3.49 – 3.44 (m, 1H), 3.26 – 3.20 (m, 1H), 2.18 – 2.03 (m, 3H), 1.80 – 1.76 (m, 1H), 1.20 (d, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 147.34, 132.4 (q, J = 33.4 Hz), 124.8 (q, J = 272.8 Hz), 111.0 (q, J = 3.5 Hz), 107.9 (m), 54.1, 48.3, 33.1, 23.2, 18.7.

2-methyl-1-(naphthalen-1-yl)pyrrolidine (P$_{111}$):[17] Obtained as a result of the equimolar reaction between 1-napthylamine and levulinic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{111}$**: 0.079 g, 75%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.29 – 8.23 (m, 1H), 7.85 – 7.78 (m, 1H), 7.51 – 7.38 (m, 4H), 7.05 (d, J = 7.4 Hz, 1H), 3.89 – 3.75 (m, 2H), 2.96 – 2.90 (m, 1H), 2.28 – 2.21 (m, 1H), 2.07 – 1.98 (m, 1H), 1.92 – 1.81 (m, 1H), 1.76 – 1.67 (m, 1H), 1.09 (d, J = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 147.1, 135.0, 130.2, 128.2, 126.0, 125.7, 124.9, 124.7, 122.1, 114.2, 55.8, 55.5, 33.8, 23.6, 18.8.

8-(2-methylpyrrolidin-1-yl)quinoline (P$_{121}$): Obtained as a result of the equimolar reaction between 8-aminoquinoline and levulinic acid. A mixture of petroleum ether and ethyl acetate

(9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{121}$**: 0.071 g, 67%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.81 (dd, *J* = 8.0, 1.1 Hz, 1H), 8.05 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.41 – 7.21 (m, 4H), 6.92 (d, *J* = 8.0 Hz, 1H), 4.62 – 4.54 (m, 1H), 4.15 – 4.09 (m, 1H), 3.41 – 3.29 (m, 1H), 2.32 – 2.25 (m, 1H), 2.07 – 2.00 (m, 1H), 1.94 – 1.86 (m, 1H), 1.80 – 1.69 (m, 1H), 1.10 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 146.6, 142.3, 136.1, 129.9, 128.2, 126.9, 120.7, 117.7, 113.3, 55.4, 53.1, 33.9, 24.0, 19.2. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{14}$H$_{16}$N$_2$: 212.1313, found 212.1317.

1-(9H-fluoren-2-yl)-2-methylpyrrolidine (P$_{131}$): Obtained as a result of the equimolar reaction between 2-aminofluorene and levulinic Acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a white solid (**P$_{131}$**: 0.068 g, 55%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.79 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 4.05 – 3.92 (m, 1H), 3.85 (s, 2H), 3.56 – 3.45 (m, 1H), 3.31 – 3.20 (m, 1H), 2.10 – 2.01 (m, 3H), 1.78 – 1.70 (m, 1H), 1.23 (d, *J* = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 147.0, 145.3, 142.8, 142.2, 129.9, 126.7, 124.7, 124.5, 120.7, 118.3, 111.0, 108.4, 54.0, 48.6, 37.2, 33.2, 23.4, 19.5. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{18}$H$_{20}$N: 250.1596, found 250.1600.

2-methyl-1-(p-tolyl)piperidine (P$_{12}$):[14] Obtained as a result of the equimolar reaction between *p*-toluidine and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{12}$**: 0.080 g, 85%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.08 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.74 – 3.62 (m, 1H), 3.12 – 2.90 (m, 2H), 2.29 (s, 3H), 1.88 – 1.54 (m, 6H), 0.97 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 149.5, 129.6, 129.5, 119.1, 52.5, 47.3, 32.4, 26.4, 20.7, 20.6, 14.9.

2-methyl-1-phenylpiperidine (P₂₂):[17] Obtained as a result of the equimolar reaction between aniline and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P₂₂**: 0.070 g, 80%). ¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.24 (m, 2H), 6.96 (d, J = 8.0 Hz, 2H), 6.84 (t, J = 7.2 Hz, 1H), 3.96 – 3.85 (m, 1H), 3.25 – 3.21 (m, 1H), 3.02 – 2.94 (m, 1H), 1.92 – 1.58 (m, 6H), 1.00 (d, J = 6.2 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 151.6, 129.1, 119.4, 117.9, 51.6, 45.2, 32.0, 26.2, 20.0, 14.1.

1-(4-methoxyphenyl)-2-methylpiperidine (P₃₂):[14] Obtained as a result of the equimolar reaction between *p*-anisidine and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P₃₂**: 0.085 g, 83%). ¹H NMR (400 MHz, CDCl₃) δ 6.99 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H), 3.40 – 3.33 (m, 1H), 3.03 – 2.95 (m, 1H), 2.92 – 2.86 (m, 1H), 1.88 – 1.80 (m, 1H), 1.75 – 1.62 (m, 3H), 1.55 – 1.45 (m, 2H), 0.90 (d, J = 6.2 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 154.8, 146.0, 122.4, 114.3, 55.6, 54.4, 50.7, 33.3, 26.6, 21.9, 16.6.

1-(2-methoxyphenyl)-2-methylpiperidine (P₄₂):[14] Obtained as a result of the equimolar reaction between *o*-anisidine and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P₄₂**: 0.071 g, 70%). ¹H NMR (400 MHz, CDCl₃) δ 7.01 – 6.85 (m, 4H), 3.85 (s, 3H), 3.49 – 3.41 (m, 1H), 3.23 – 3.14 (m, 1H), 2.71 – 2.61 (m, 1H), 1.89 – 1.77 (m, 1H), 1.70 – 1.60 (m, 3H), 1.54 – 1.43 (m, 2H), 0.91 (d, J = 6.2 Hz, 3H). ¹³C{¹H} NMR (101 MHz, CDCl₃) δ 154.3, 141.5, 123.6, 122.9, 120.7, 111.7, 55.6, 52.6, 50.8, 33.5, 26.7, 22.4, 17.1.

1-(2,4-dimethylphenyl)-2-methylpiperidine (P₆₂): Obtained as a result of the equimolar reaction between 2,4-dimethylaniline and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale

yellow oil (**P$_{62}$**: 0.075 g, 74%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.02 – 6.96 (m, 3H), 2.97 – 2.86 (m, 2H), 2.53 – 2.47 (m, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 1.79 – 1.75 (m, 2H), 1.67 – 1.62 (m, 2H), 1.48 – 1.33 (m, 2H), 0.82 (d, *J* = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 149.1, 135.7, 133.2, 131.4, 126.8, 122.7, 54.9, 35.1, 27.2, 24.5, 21.0, 19.8, 17.7. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{14}$H$_{22}$N: 204.1752, found 204.1744.

1-(4-chlorophenyl)-2-methylpiperidine (P$_{82}$):[14] Obtained as a result of the equimolar reaction between 4-chloroaniline and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{82}$**: 0.080 g, 76%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.18 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 3.91 – 3.82 (m, 1H), 3.22 – 3.12 (m, 1H), 3.0 – 2.88 (m, 1H), 1.86 – 1.56 (m, 6H), 0.98 (d, *J* = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 150.1, 129.0, 124.0, 118.8, 51.7, 45.1, 31.8, 26.1, 19.7, 13.9.

1-(4-bromophenyl)-2-methylpiperidine (P$_{92}$):[14] Obtained as a result of the equimolar reaction between 4-bromoaniline and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{92}$**: 0.091 g, 72%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 8.0 Hz, 2H), 3.95 – 3.84 (m, 1H), 3.23 – 3.17 (m, 1H), 2.95 – 2.87 (m, 1H), 1.92 – 1.51 (m, 6H), 0.99 (d, *J* = 6.2, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 150.5, 131.9, 119.0, 111.1, 51.4, 44.6, 31.6, 26.1, 19.5, 13.7.

2-methyl-1-(p-tolyl)azepane (P$_{13}$): Obtained as a result of the equimolar reaction between *p*-toluidine and 6-oxoheptanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{13}$**: 0.075 g, 74%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.03 (d, *J* = 8.2 Hz, 2H), 6.61 (d, *J* = 8.2 Hz, 2H), 3.75 – 3.69 (m, 1H), 3.45 – 3.35 (m, 1H), 3.23 – 3.13 (m, 1H), 2.24 (s, 3H), 2.13 – 2.06 (m, 1H), 1.80 – 1.67 (m, 4H), 1.47 – 1.20 (m, 3H), 1.12 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz,

CDCl$_3$) δ 146.6, 130.0, 123.4, 110.3, 52.6, 42.7, 37.8, 30.2, 27.8, 25.8, 20.2, 18.1. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{14}$H$_{22}$N: 204.1752, found 204.1757.

2-methyl-1-phenylazepane (P$_{23}$):[14] Obtained as a result of the equimolar reaction between aniline and 6-oxoheptanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{23}$**: 0.073 g, 77%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.24 – 7.19 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 2H), 6.61 (t, *J* = 7.2 Hz, 1H), 3.80 – 3.71 (m, 1H), 3.48 – 3.38 (m, 1H), 3.23 – 3.17 (m, 1H), 2.15 – 2.07 (m, 1H), 1.85 – 1.63 (m, 4H), 1.49 – 1.40 (m, 1H), 1.33 – 1.26 (m, 2H), 1.14 (d, *J* = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 148.7, 129.5, 114.5, 110.4, 52.6, 42.6, 37.8, 30.2, 27.7, 25.7, 18.0.

1-(4-chlorophenyl)-2-methylazepane (P$_{83}$): Obtained as a result of the equimolar reaction between 4-chloroaniline and 6-oxoheptanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{83}$**: 0.082 g, 73%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.14 (d, *J* = 8.0 Hz, 2H), 6.59 (d, *J* = 8.0 Hz, 2H), 3.71 – 3.66 (m, 1H), 3.43 – 3.31 (m, 1H), 3.26 – 3.13 (m, 1H), 2.14 – 2.07 (m, 1H), 1.84 – 1.69 (m, 3H), 1.63 – 1.55 (m, 1H), 1.48 – 1.22 (m, 3H), 1.12 (d, *J* = 6.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 147.2, 129.1, 117.0, 111.5, 53.0, 42.8, 37.6, 30.0, 27.5, 25.7, 18.0. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{13}$H$_{19}$NCl: 224.1206, found 224.1208.

2-methyl-1-(naphthalen-1-yl)azepane (P$_{113}$): Obtained as a result of the equimolar reaction between 1-napthylamine and 6-oxoheptanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{113}$**: 0.096 g, 80%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.37 – 8.30 (m, 1H), 7.85 – 7.78 (m, 1H), 7.61 – 7.39 (m, 4H), 7.26 – 7.21 (m, 1H), 3.73 – 3.65 (m, 1H), 3.39 – 3.30 (m, 2H), 2.13 – 2.07 (m, 1H), 1.92 – 1.82 (m, 3H), 1.69 – 1.55 (m, 4H), 0.91 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 150.9, 136.0, 131.6, 128.3, 125.9, 125.7, 125.1, 124.8, 123.3,

121.6, 57.6, 51.3, 37.1, 30.8, 29.7, 25.6, 19.3. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for $C_{17}H_{22}N$: 240.1752, found 240.1755.

2-phenyl-1-(p-tolyl)pyrrolidine (P$_{14}$): Obtained as a result of the equimolar reaction between *p*-toluidine and 4-oxo-4-phenylbutanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{14}$**: 0.085 g, 72%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33 – 7.21 (m, 5H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.44 (d, *J* = 8.0 Hz, 2H), 4.70 (d, *J* = 8.0 Hz, 1H), 3.77 – 3.68 (m, 1H), 3.44 – 3.38 (m, 1H), 2.45 – 2.36 (m, 1H), 2.23 (s, 3H), 2.04 – 1.97 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 145.4, 145.1, 136.0, 129.6, 128.6, 126.7, 126.1, 112.5, 63.2, 49.5, 36.3, 23.3, 20.4. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for $C_{17}H_{20}N$: 238.1604, found 238.1610.

1,2-diphenylpyrrolidine (P$_{24}$):[17] Obtained as a result of the equimolar reaction between aniline and 4-oxo-4-phenylbutanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{24}$**: 0.076 g, 68%). ^{1}H NMR (400 MHz, CDCl$_3$) 7.38 – 7.18 (m, 7H), 6.70 (t, *J* = 7.2 Hz, 1H), 6.56 (d, *J* = 8.2 Hz, 2H), 4.79 (d, *J* = 8.0 Hz, 1H), 3.80 – 3.75 (m, 1H), 3.51 – 3.45 (m, 1H), 2.50 – 2.40 (m, 1H), 2.13 – 1.98 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 147.4, 144.8, 129.1, 128.6, 126.8, 126.1, 115.9, 112.5, 63.1, 49.3, 36.2, 23.2.

1-(4-methoxyphenyl)-2-phenylpyrrolidine (P$_{34}$): Obtained as a result of the equimolar reaction between *p*-anisidine and 4-oxo-4-phenylbutanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{34}$**: 0.081 g, 64%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 – 7.24 (m, 5H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.50 (d, *J* = 8.0 Hz, 2H), 4.68 (d, *J* = 8.0 Hz, 1H), 3.76 – 3.70 (m, 4H), 3.44 – 3.38 (m, 1H), 2.49 – 2.39 (m, 1H), 2.10 – 2.00 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 145.2, 136.0, 130.0, 128.6, 126.7, 126.1, 115.0, 113.1, 63.5, 56.0, 49.8, 36.4, 23.4. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for $C_{17}H_{20}NO$: 254.1497, found 254.1493.

1-(4-chlorophenyl)-2-phenylpyrrolidine (P₈₄): Obtained as a result of the equimolar reaction between 4-chloroaniline and 4-oxo-4-phenylbutanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P₈₄**: 0.071 g, 55%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.32 – 7.18 (m, 5H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.40 (d, *J* = 8.0 Hz, 2H), 4.69 (d, *J* = 8.0 Hz, 1H), 3.70 – 3.64 (m, 1H), 3.42 – 3.36 (m, 1H), 2.46 – 2.36 (m, 1H), 2.06 – 1.95 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 145.7, 144.1, 128.9, 128.7, 128.2, 126.9, 126.0, 113.5, 63.2, 49.4, 36.2, 23.2. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{16}$H$_{17}$NCl: 258.1003, found 258.1007.

2-phenyl-1-(p-tolyl)piperidine (P₁₅): Obtained as a result of the equimolar reaction between *p*-toluidine and 5-oxo-5-phenylpentanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P₁₅**: 0.100 g, 80%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.23 (t, *J* = 7.2 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 6.85 (d, *J* = 8.0 Hz, 2H), 4.32 (dd, *J* = 8.0, 3.3 Hz, 1H), 3.47 – 3.42 (m, 1H), 3.14 – 3.06 (m, 1H), 2.22 (s, 3H), 2.02 – 1.61 (m, 6H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 150.0, 144.4, 129.9, 129.4, 128.3, 127.4, 126.3, 120.5, 62.4, 53.3, 34.8, 26.1, 23.1, 20.6. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{18}$H$_{22}$N: 252.1752, found 252.1762.

1,2-diphenylpiperidine (P₂₅):[14] Obtained as a result of the equimolar reaction between aniline and 5-oxo-5-phenylpentanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P₂₅**: 0.091 g, 77%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.30 – 7.22 (m, 4H), 7.19 – 7.13 (m, 3H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.77 (t, *J* = 7.2 Hz, 1H), 4.52 (d, *J* = 8.0 Hz, 1H), 3.46 – 3.40 (m, 1H), 3.31 – 3.25 (m, 1H), 2.06 – 1.93 (m, 2H), 1.80 – 1.74 (m, 2H), 1.63 – 1.52 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 152.0, 143.7, 128.9, 128.4, 127.4, 126.3, 119.7, 118.9, 61.2, 50.7, 33.6, 25.8, 22.2.

1-(2,4-dimethylphenyl)-2-phenylpiperidine (P$_{65}$): Obtained as a result of the equimolar reaction between 2,4-dimethylaniline and 5-oxo-5-phenyl-pentanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{65}$**: 0.093 g, 70%). ^{1}H NMR (700 MHz, CDCl$_3$) δ 7.20 – 7.02 (m, 5H), 6.87 – 6.82 (m, 2H), 6.71 (d, J = 7.8 Hz, 1H), 4.02 (d, J = 8.0 Hz, 1H), 3.14 – 3.06 (m, 1H), 2.56 – 2.48 (m 1H), 2.35 (s, 3H), 2.13 (s, 3H), 1.91- 1.63 (m, 6H). ^{13}C{^{1}H} NMR (176 MHz, CDCl$_3$) δ 148.7, 145.5, 134.2, 132.7, 131.4, 128.0, 127.3, 126.6, 126.3, 122.4, 65.5, 57.0, 37.9, 26.9, 25.5, 20.9, 17.6. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{19}$H$_{24}$N: 266.1909, found 266.1911.

1-(4-chlorophenyl)-2-phenylpiperidine (P$_{85}$): Obtained as a result of the equimolar reaction between 4-chloroaniline and 5-oxo-5-phenylpentanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{85}$**: 0.099 g, 73%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.26 – 7.06 (m, 7H), 6.81 (d, J = 8.0 Hz, 2H), 4.40 (dd, J = 8.0, 3.3 Hz, 1H), 3.41 – 3.37 (m, 1H), 3.21 – 3.15 (m, 1H), 2.02 – 1.91 (m, 2H), 1.78 – 1.53 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 150.7, 143.4, 130.0, 128.8, 128.5, 127.3, 126.5, 120.5, 61.5, 51.3, 33.9, 25.8, 22.2. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{17}$H$_{19}$NCl: 272.1175, found 272.1170.

1-(4-bromophenyl)-2-phenylpiperidine (P$_{95}$): Obtained as a result of the equimolar reaction between 4-bromoaniline and 5-oxo-5-phenylpentanoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**P$_{95}$**: 0.119 g, 75%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27 – 7.16 (m, 7H), 6.78 (d, J = 8.0 Hz, 2H), 4.52 – 4.43 (m, 1H), 3.44 – 3.39 (m, 1H), 3.28 – 3.22 (m, 1H), 2.05 – 1.93 (m, 2H), 1.82 – 1.56 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 150.9, 143.2, 131.7, 128.5, 127.2, 126.5, 120.4, 111.9, 61.1, 50.6, 33.6, 25.6, 21.9. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{17}$H$_{19}$NBr: 316.0623, found 316.0628.

2-(p-tolyl)isoindoline (P$_{16}$): Obtained as a result of the equimolar reaction between *p*-toluidine and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a white solid (**P$_{16}$**: 0.092 g, 88%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 – 7.33 (m, 4H), 7.17 (d, *J* = 8.2 Hz, 2H), 6.66 (d, *J* = 8.2 Hz, 2H), 4.66 (s, 4H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 145.3, 138.3, 130.0, 127.2, 125.3, 122.7, 111.7, 54.0, 20.4. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{15}$H$_{16}$N: 210.1283, found 210.1286.

2-phenylisoindoline (P$_{26}$):[17] Obtained as a result of the equimolar reaction between aniline and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale white solid (**P$_{26}$**: 0.083 g, 85%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 – 7.30 (m, 6H), 6.81 – 6.71 (m, 3H), 4.68 (s, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 147.3, 138.1, 129.5, 127.3, 122.7, 116.3, 111.7, 53.9.

2-(2-methoxyphenyl)isoindoline (P$_{46}$): Obtained as a result of the equimolar reaction between *o*-anisidine and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a pale yellow solid (**P$_{46}$**: 0.086 g, 76%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37 – 7.26 (m, 4H), 7.04 – 6.90 (m, 4H), 4.82 (s, 4H), 3.93 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 150.2, 138.8, 126.9, 122.3, 121.7, 119.5, 115.67, 112.7, 56.2, 56.1. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{15}$H$_{16}$NO: 226.1232, found 226.1230.

2-(4-chlorophenyl)isoindoline (P$_{86}$):[14] Obtained as a result of the equimolar reaction between 4-chloroaniline and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a white solid (**P$_{86}$**: 0.089 g, 78%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.24 (m, 6H), 6.64 – 6.58 (m, 2H), 4.61 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 144.4, 137.7, 129.2, 127.4, 122.7, 121.1, 112.6, 53.9.

2-(4-bromophenyl)isoindoline (P$_{96}$):[14] Obtained as a result of the equimolar reaction between 4-bromoaniline and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a white solid (**P$_{96}$**: 0.101 g, 74%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41 – 7.31 (m, 6H), 6.54 (d, J = 8.0 Hz, 2H), 4.59 (s, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 146.09, 137.63, 132.07, 127.39, 122.70, 113.20, 108.17, 53.87.

2-(4-fluorophenyl)isoindoline (P$_{146}$):[14] Obtained as a result of the equimolar reaction between 4-fluoroaniline and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a white solid (**P$_{146}$**: 0.073 g, 69%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.38 – 7.27 (m, 4H), 7.09 – 6.97 (m, 2H), 6.63 – 6.57 (m, 2H), 4.62 (s, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 155.5 (d, J = 234.0 Hz), 144.0 (d, J = 1.1 Hz), 138.0, 127.4, 122.7, 115.9 (d, J = 22.3 Hz), 112.2 (d, J = 7.3 Hz), 54.4.

2-(4-(trifluoromethyl)phenyl)isoindoline (P$_{156}$):[22] Obtained as a result of the equimolar reaction between 4-(trifluoromethyl)aniline and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a white solid (**P$_{156}$**: 0.068 g, 52%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (d, J = 8.7 Hz, 2H), 7.38 – 7.31 (m, 4H), 6.68 (d, J = 8.7 Hz, 2H), 4.69 (s, 4H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 149.2, 137.3, 127.6, 126.8 (q, J = 4.0 Hz), 124.0 (q, J = 271.7 Hz) 122.8, 118.01 (q, J = 33.3 Hz), 111.0, 53.8.

8-(isoindolin-2-yl)quinoline (P$_{126}$): Obtained as a result of the equimolar reaction between 8-aminoquinoline and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (9.8:0.2) was used as eluent for column chromatography. Isolated as a white solid (**P$_{126}$**: 0.074 g, 60%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.70 (dd, J = 8.2, 1.8 Hz, 1H), 7.96 (dd, J = 8.2, 1.8 Hz, 1H), 7.35 – 7.11 (m, 7H), 6.76 (d, J = 8.0 Hz, 1H), 5.14 (s, 4H). ^{13}C{^{1}H} NMR

(101 MHz, CDCl$_3$) δ 146.02, 145.73, 141.13, 138.56, 135.98, 130.20, 128.37, 127.36, 126.98, 122.35, 120.87, 116.52, 110.78, 57.64. HRMS (ESI) *m/z*: [(M + H)$^+$] calcd for C$_{17}$H$_{15}$N$_2$: 247.1235, found 247.1244.

5-methyl-1-(p-tolyl)pyrrolidin-2-one (L$_{11}$):[17] Obtained as a result of the equimolar reaction between *p*-toluidine and levulinic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{11}$**: 0.081 g, 86%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.23 – 7.16 (m, 4H), 4.27 – 4.19 (m, 1H), 2.61 – 2.51 (m, 2H), 2.39 – 2.30 (m, 4H), 1.77 – 1.70 (m, 1H), 1.17 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 174.4, 135.7, 135.0, 129.7, 124.3, 55.9, 31.3, 26.9, 21.1, 20.3.

5-methyl-1-phenylpyrrolidin-2-one (L$_{21}$):[17] Obtained as a result of the equimolar reaction between aniline and levulinic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{21}$**: 0.070 g, 80%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 – 7.31 (m, 4H), 7.23 – 7.16 (m, 1H), 4.34 – 4.23 (m, 1H), 2.67 – 2.48 (m, 2H), 2.40 – 2.30 (m, 1H), 1.78 – 1.69 (m, 1H), 1.19 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 174.3, 137.6, 129.0, 125.8, 124.1, 55.7, 31.4, 26.8, 20.2.

1-(4-methoxyphenyl)-5-methylpyrrolidin-2-one (L$_{31}$):[17] Obtained as a result of the equimolar reaction between *p*-anisidine and levulinic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{31}$**: 0.085 g, 83%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22 (d, *J* = 9.0, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 4.20 – 4.12 (m, 1H), 3.78 (s, 3H), 2.60 – 2.48 (m, 2H), 2.37 – 2.31 (m, 1H), 1.74 – 1.69 (m, 1H), 1.15 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 174.5, 157.8, 130.4, 126.2, 114.4, 56.2, 55.5, 31.2, 26.9, 20.4.

1-(2-hydroxyphenyl)-5-methylpyrrolidin-2-one (L$_{41}$):[21] Obtained as a result of the equimolar reaction between 2-aminophenol and levulinic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale

yellow oil (**L₄₁**: 0.059 g, 62%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.21 – 7.14 (m, 1H), 7.09 – 7.00 (m, 2H), 6.97 – 6.90 (m, 1H), 4.48 – 4.42 (m, 1H), 2.75 – 2.57 (m, 2H), 2.49 – 2.43 (m, 1H), 1.92 – 1.80 (m, 1H), 1.17 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 176.2, 151.8, 128.2, 126.0, 123.4, 120.8, 120.7, 57.0, 31.3, 27.5, 20.2.

1-(2,4-dimethylphenyl)-5-methylpyrrolidin-2-one (**L₆₁**):[23] Obtained as a result of the equimolar reaction between 2,4-dimethylaniline and levulinic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L₆₁**: 0.075 g, 74%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.07 (s, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 4.02 (m, 1H), 2.59 – 2.36 (m, 3H), 2.30 (s, 3H), 2.17 (s, 3H), 1.81 – 1.72 (m, 1H), 1.10 (d, *J* = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 174.5, 137.7, 136.0, 133.4, 131.9, 127.4, 56.8, 30.9, 27.8, 21.1, 20.3, 18.0.

1-(4-chlorophenyl)-5-methylpyrrolidin-2-one (**L₈₁**):[17] Obtained as a result of the equimolar reaction between 4-chloroaniline and levulinic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L₈₁**: 0.075 g, 72%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.33 – 7.26 (m, 4H), 4.31 – 4.22 (m, 1H), 2.65 – 2.49 (m, 2H), 2.41 – 2.32 (m, 1H), 1.79 – 1.71 (m, 1H), 1.19 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 174.4, 136.2, 131.0, 129.2, 125.1, 55.6, 31.4, 26.7, 20.1.

1-(4-bromophenyl)-5-methylpyrrolidin-2-one (**L₉₁**):[17] Obtained as a result of the equimolar reaction between 4-bromoaniline and levulinic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L₉₁**: 0.095 g, 75%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.30 – 4.23 (m 1H), 2.66 – 2.48 (m, 2H), 2.41 – 2.32 (m, 1H), 1.79 – 1.71 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 174.4, 136.7, 132.1, 125.3, 118.8, 55.5, 31.4, 26.7, 20.1.

6-methyl-1-(p-tolyl)piperidin-2-one (**L$_{12}$**):[13] Obtained as a result of the equimolar reaction between *p*-toluidine and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{12}$**: 0.084 g, 83%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.19 (d, J = 8.1 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 3.91 – 3.83 (m, 1H), 2.57 – 2.48 (m, 2H), 2.34 (s, 3H), 2.12 – 2.05 (m, 1H), 2.02 – 1.93 (m, 1H), 1.87 – 1.78 (m, 1H), 1.75 – 1.67 (m, 1H), 1.07 (d, J = 6.4 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 170.6, 138.9, 136.9, 129.8, 127.8, 55.8, 32.8, 30.8, 21.1, 20.9, 18.3.

6-methyl-1-phenylpiperidin-2-one (**L$_{22}$**):[13] Obtained as a result of the equimolar reaction between aniline and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{22}$**: 0.074 g, 78%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.44 – 7.37 (m, 2H), 7.30 – 7.24 (m, 1H), 7.15 (d, J = 8.0 Hz, 2H), 3.97 – 3.84 (m, 1H), 2.58 – 2.46 (m, 2H), 2.17 – 2.08 (m, 1H), 2.03 – 1.95 (m, 1H), 1.91 – 1.81 (m, 1H), 1.78 – 1.66 (m, 1H), 1.07 (d, J = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 170.6, 141.6, 129.3, 128.2, 127.3, 55.9, 32.8, 30.9, 20.9, 18.4.

1-(4-bromophenyl)-6-methylpiperidin-2-one (L$_{92}$):[12] Obtained as a result of the equimolar reaction between 4-bromoaniline and 5-oxohexanoic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{92}$**: 0.098 g, 73%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 3.92 – 3.84 (m, 1H), 2.57 – 2.47 (m, 2H), 2.13 – 2.05 (m, 1H), 2.03 – 1.94 (m, 1H), 1.88 – 1.78 (m, 1H), 1.75 – 1.68 (m, 1H), 1.06 (d, J = 6.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 170.6, 140.6, 132.4, 129.9, 120.9, 55.8, 32.8, 30.9, 21.0, 18.4.

7-methyl-1-phenylazepan-2-one (**L$_{23}$**):[17] Obtained as a result of the equimolar reaction between aniline and 6-oxoheptanoic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{23}$**: 0.084 g, 83%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.17 (t, J = 7.2 Hz, 2H), 6.72 – 6.60 (m, 3H), 3.49 –

3.43 (m, 1H), 2.40 – 2.33 (m, 2H), 1.68 – 1.59 (m, 3H), 1.48 – 1.43 (m, 3H), 1.18 (d, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 179.8, 147.2, 129.4, 117.5, 113.7, 48.8, 36.7, 34.1, 25.7, 24.8, 20.7.

1-(4-chlorophenyl)-7-methylazepan-2-one (**L$_{83}$**): Obtained as a result of the equimolar reaction between 4-chloroaniline and 6-oxoheptanoic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{83}$**: 0.091 g, 77%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.10 (d, J = 8.7 Hz, 2H), 6.52 (d, J = 8.7 Hz, 2H), 3.45 – 3.36 (m, 1H), 2.40 – 2.32 (m, 2H), 1.69 –1.38 (m, 6H), 1.16 (d, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 179.7, 145.8, 129.2, 114.7, 49.0, 36.6, 34.0, 25.6, 24.7, 20.6. HRMS (ESI) *m/z*: [(M + H)$^{+}$] calcd for C$_{13}$H$_{17}$ClNO: 238.1023, found 238.1017.

2-(p-tolyl)isoindolin-1-one (L$_{16}$):[24] Obtained as a result of the equimolar reaction between *p*-toluidine and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{16}$**: 0.096 g, 86%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.58 – 7.46 (m, 3H), 7.20 (d, J = 8.4 Hz, 2H), 4.77 (s, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 167.4, 140.2, 137.0, 134.2, 133.4, 132.0, 129.7, 128.4, 124.1, 122.7, 119.6, 50.9, 20.9.

2-(4-chlorophenyl)isoindolin-1-one (**L$_{86}$**):[24] Obtained as a result of the equimolar reaction between 4-chloroaniline and 2-formylbenzoic acid. A mixture of petroleum ether and ethyl acetate (3:2) was used as eluent for column chromatography. Isolated as a pale yellow oil (**L$_{86}$**: 0.086 g, 71%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, J = 7.7 Hz, 1H), 7.81 (d, J = 8.9 Hz, 2H), 7.61 – 7.47 (m, 3H), 7.35 (d, J = 8.9 Hz, 2H), 4.79 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, CDCl$_3$) δ 167.6, 140.0, 138.2, 133.0, 132.4, 129.6, 129.2, 128.6, 124.3, 122.8, 120.5, 50.7.

5.6 REFERENCES

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NMR SPECTRA OF SOME SUBSTRATE
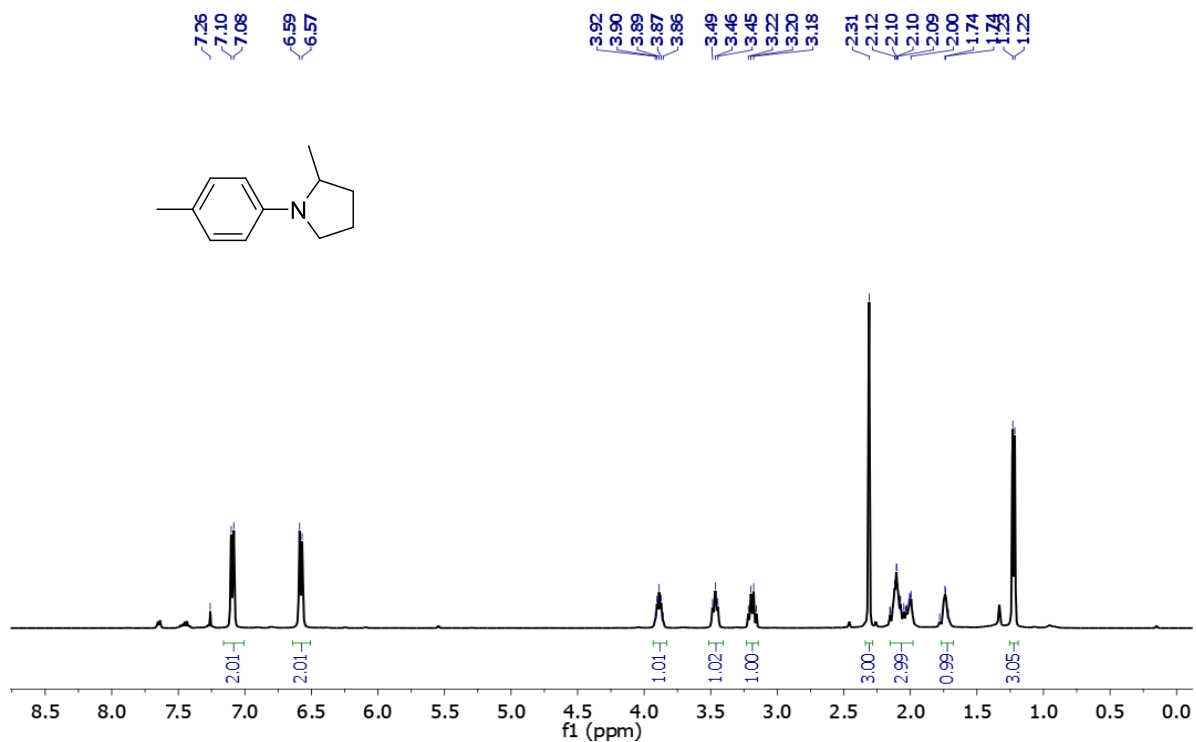
Figure 5.1 ^{1}H NMR (400 MHz) spectrum of 2-methyl-1-(p-tolyl)pyrrolidine (P$_{11}$) in CDCl$_3$ at r.t.
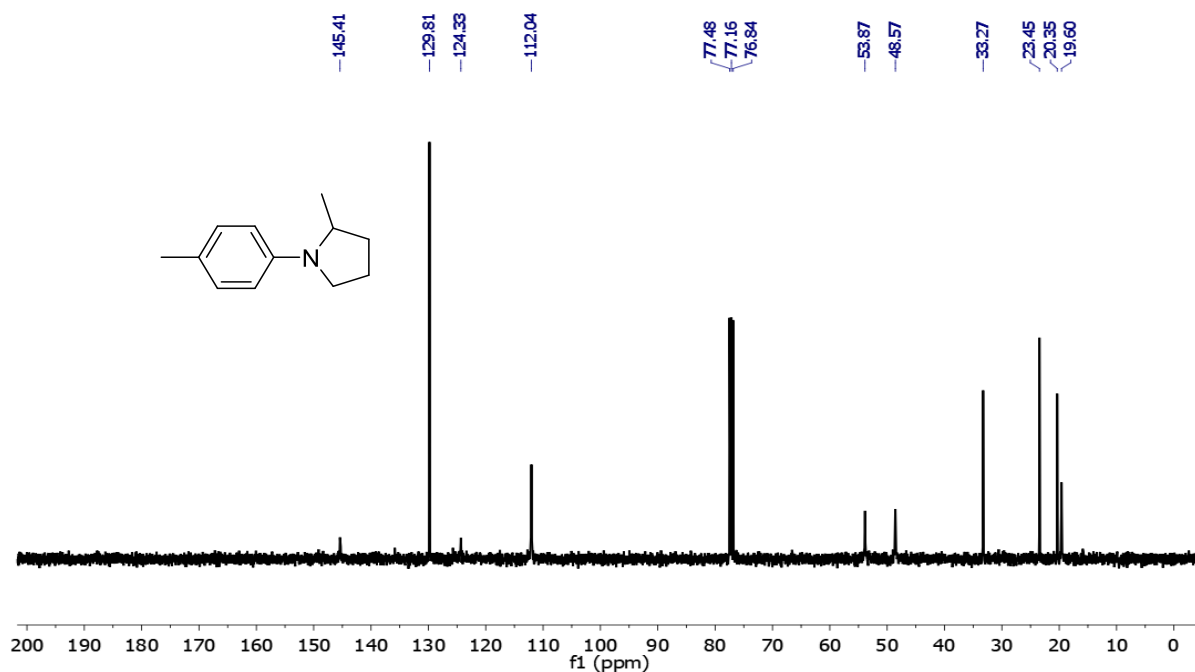
Figure 5.2 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 2-methyl-1-(p-tolyl)pyrrolidine (**P$_{11}$**) in CDCl$_3$ at r.t.
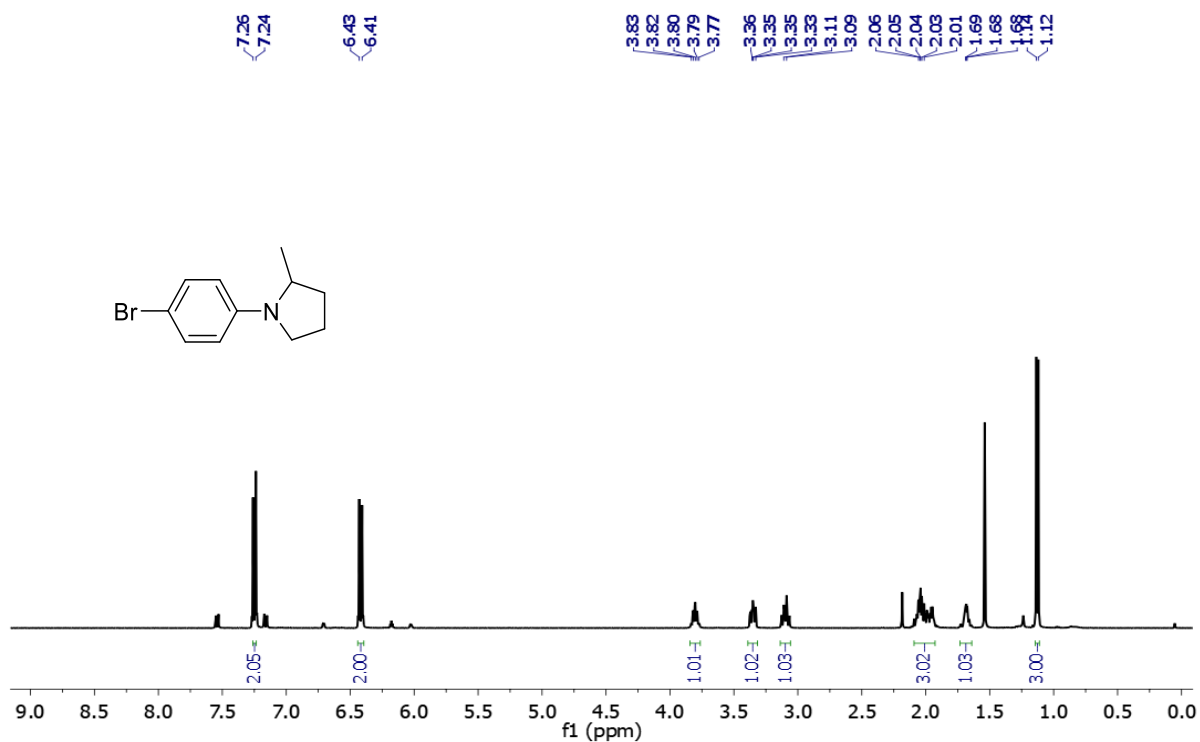
Figure 5.3 ^{1}H NMR (400 MHz) spectrum of 1-(4-bromophenyl)-2-methylpyrrolidine (**P$_{91}$**) in CDCl$_3$ at r.t.
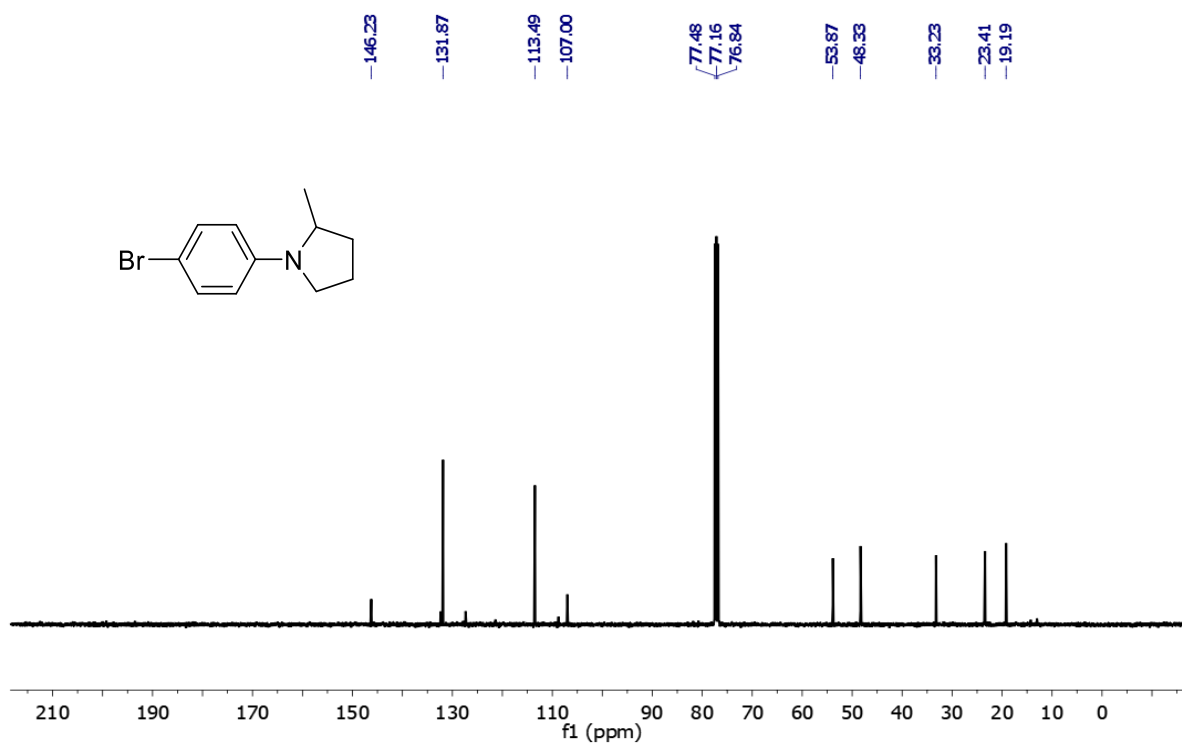
Figure 5.4 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 1-(4-bromophenyl)-2-methylpyrrolidine (**P$_{91}$**) in CDCl$_3$ at r.t.
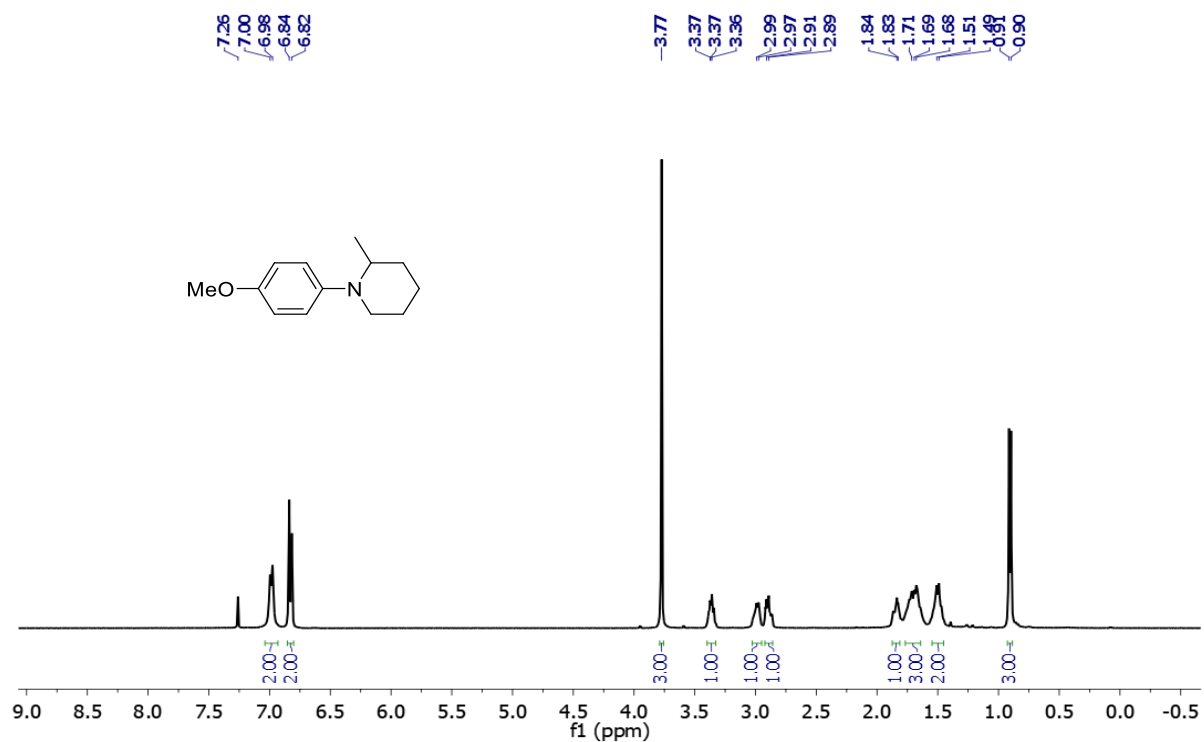
Figure 5.5 ^{1}H NMR (400 MHz) spectrum of 1-(4-methoxyphenyl)-2-methylpiperidine (**P$_{32}$**) in CDCl$_3$ at r.t
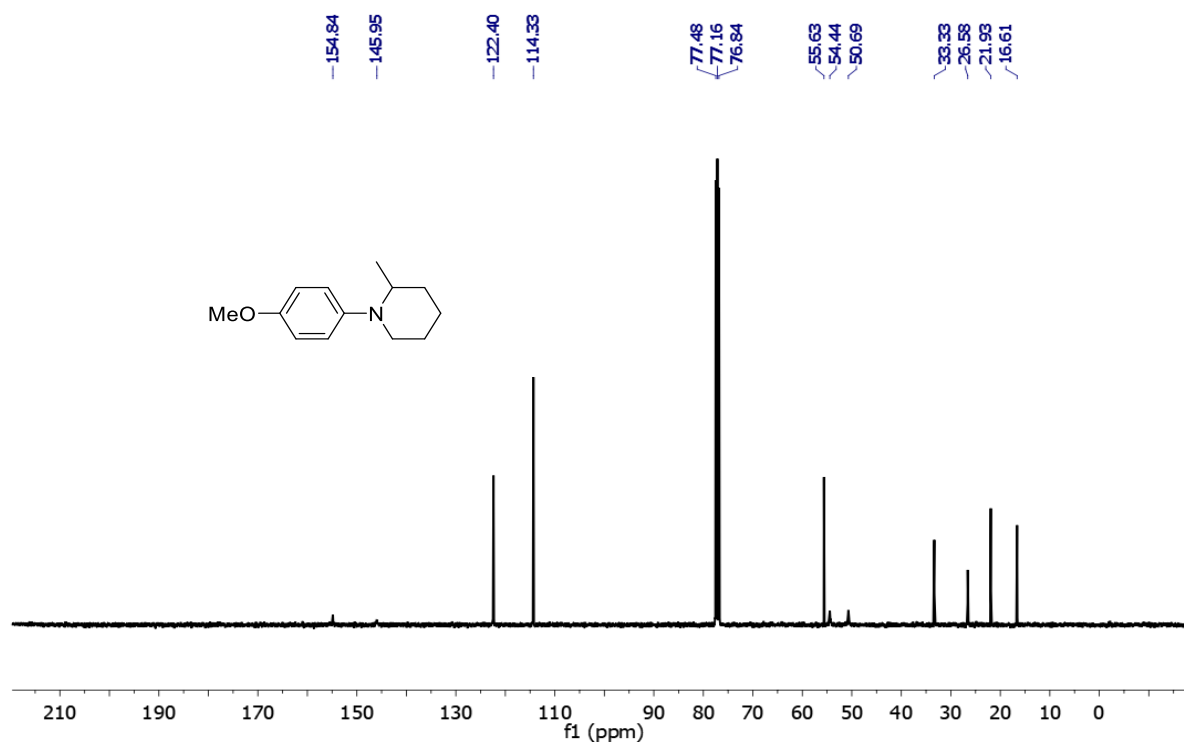
Figure 5.6 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 1-(4-methoxyphenyl)-2-methylpiperidine (**P$_{32}$**) in CDCl$_3$ at r.t
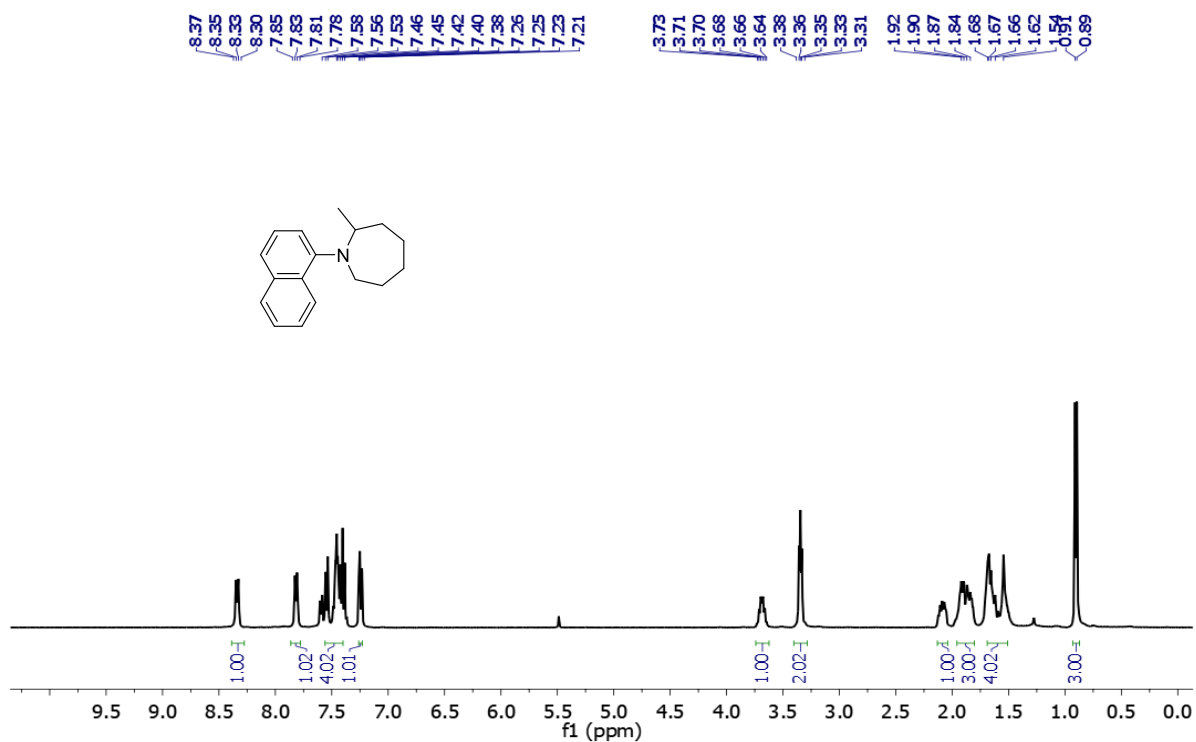
Figure 5.7 ^{1}H NMR (400 MHz) spectrum of 2-methyl-1-(naphthalen-1-yl)azepane (**P₁₁₃**) in CDCl₃ at r.t
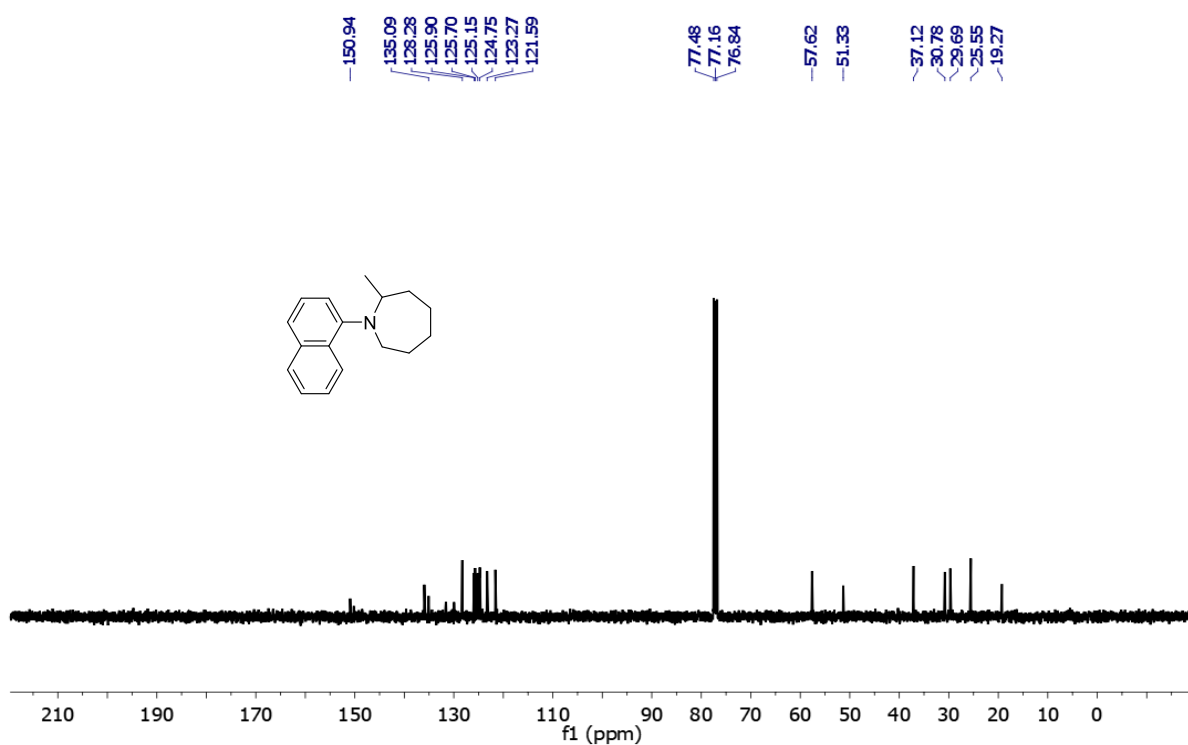
Figure 5.8 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 2-methyl-1-(naphthalen-1-yl)azepane (**P₁₁₃**) in CDCl₃ at r.t
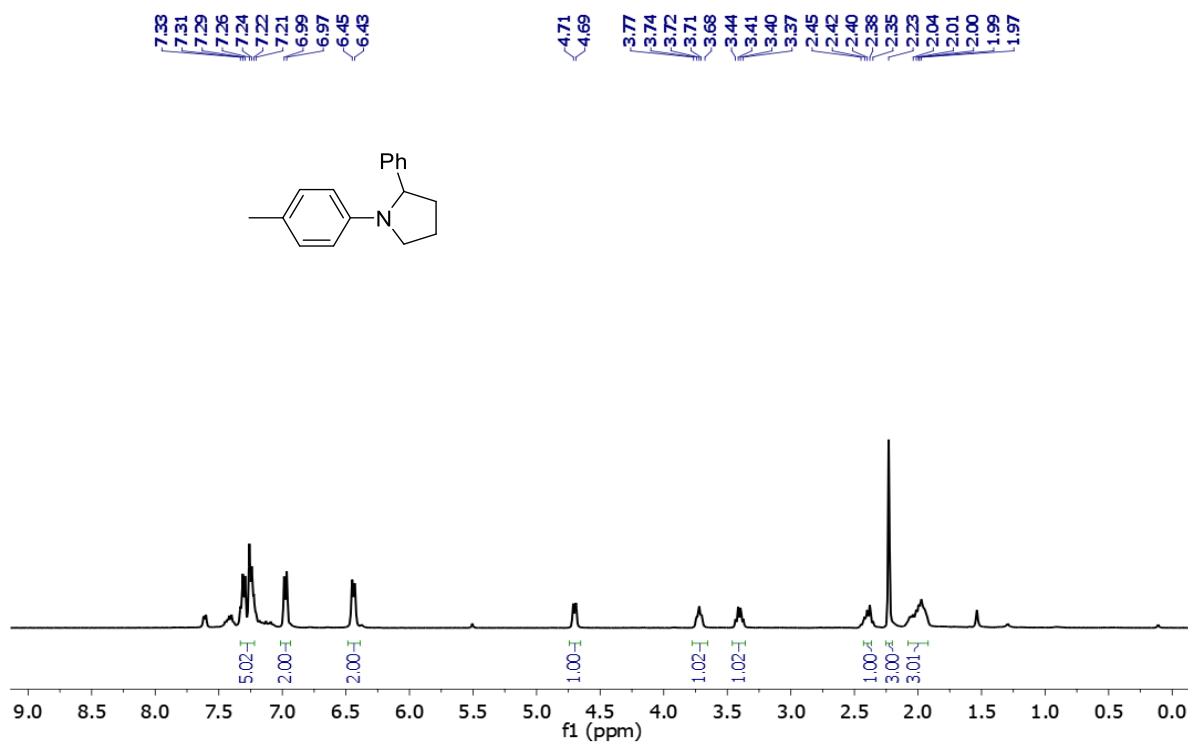
Figure 5.9 ^{1}H NMR (400 MHz) spectrum of 2-phenyl-1-(p-tolyl)pyrrolidine (**P$_{14}$**) in CDCl$_3$ at r.t.
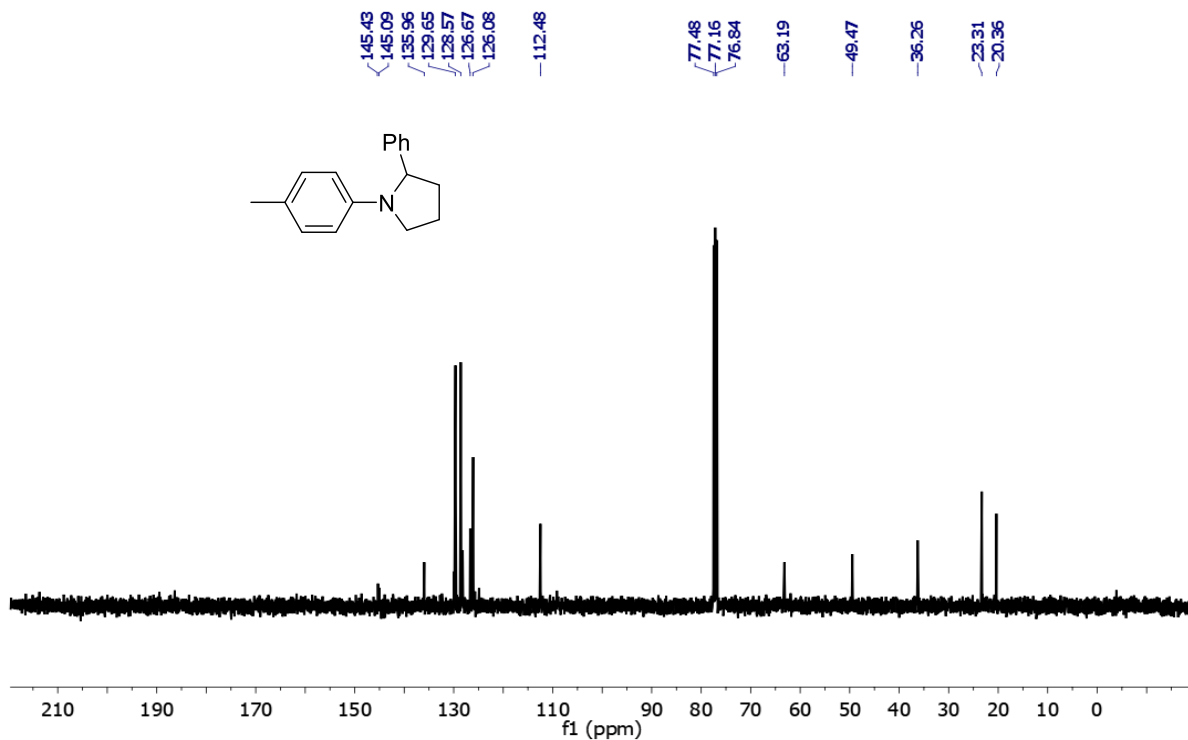
Figure 5.10 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 2-phenyl-1-(p-tolyl)pyrrolidine (**P$_{14}$**) in CDCl$_3$ at r.t.
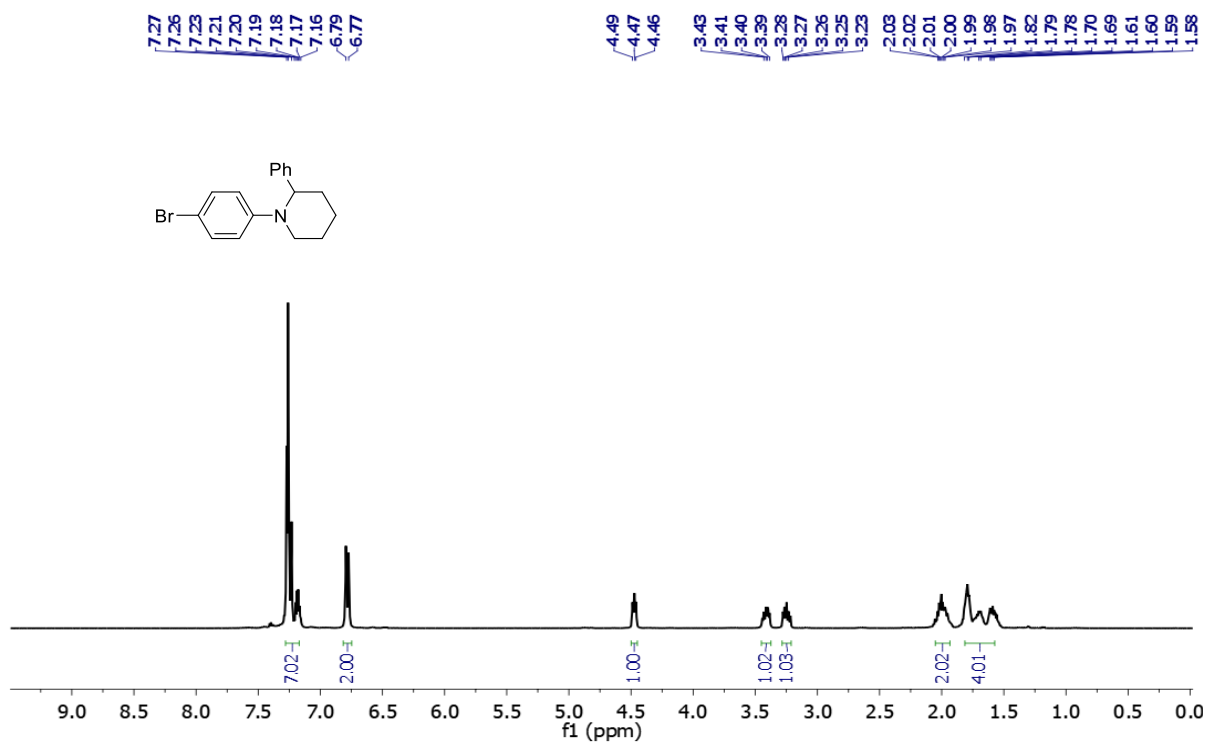
Figure 5.11 ¹H NMR (400 MHz) spectrum of 1-(4-bromophenyl)-2-phenylpiperidine (**P₉₅**) in CDCl₃ at r.t.
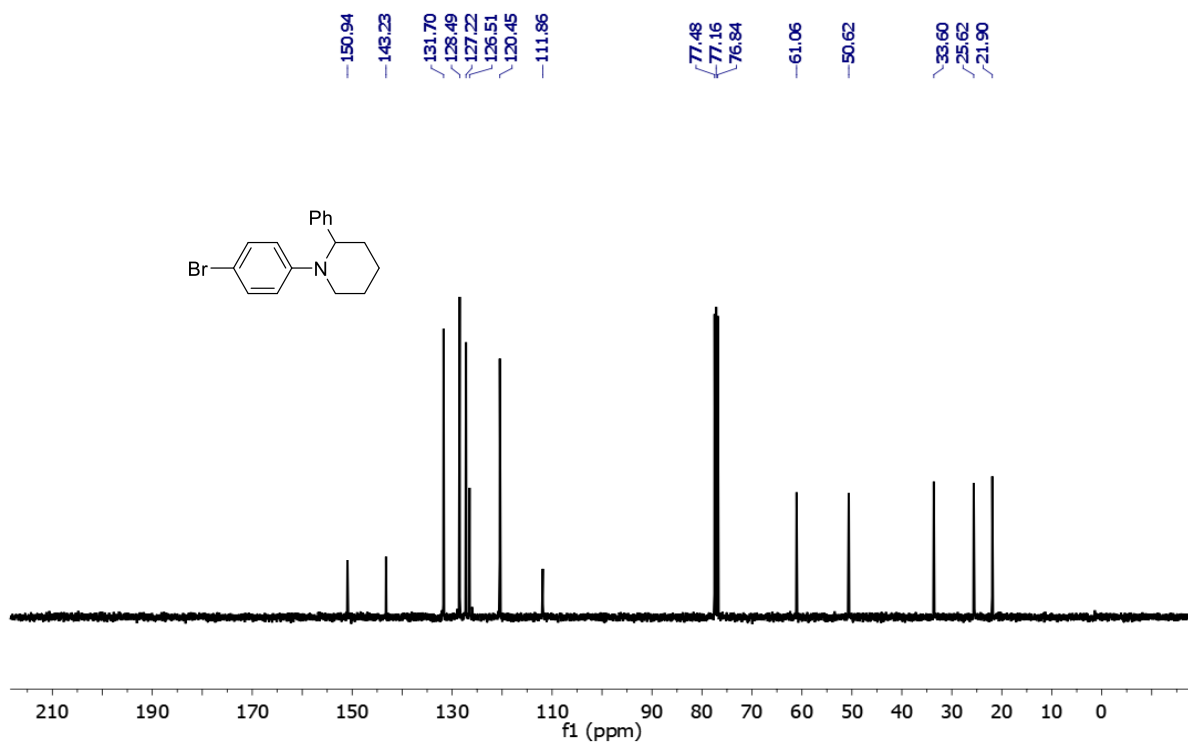
Figure 5.12 ¹³C{¹H} NMR (101 MHz) spectrum of 1-(4-bromophenyl)-2-phenylpiperidine (**P₉₅**) in CDCl₃ at r.t.
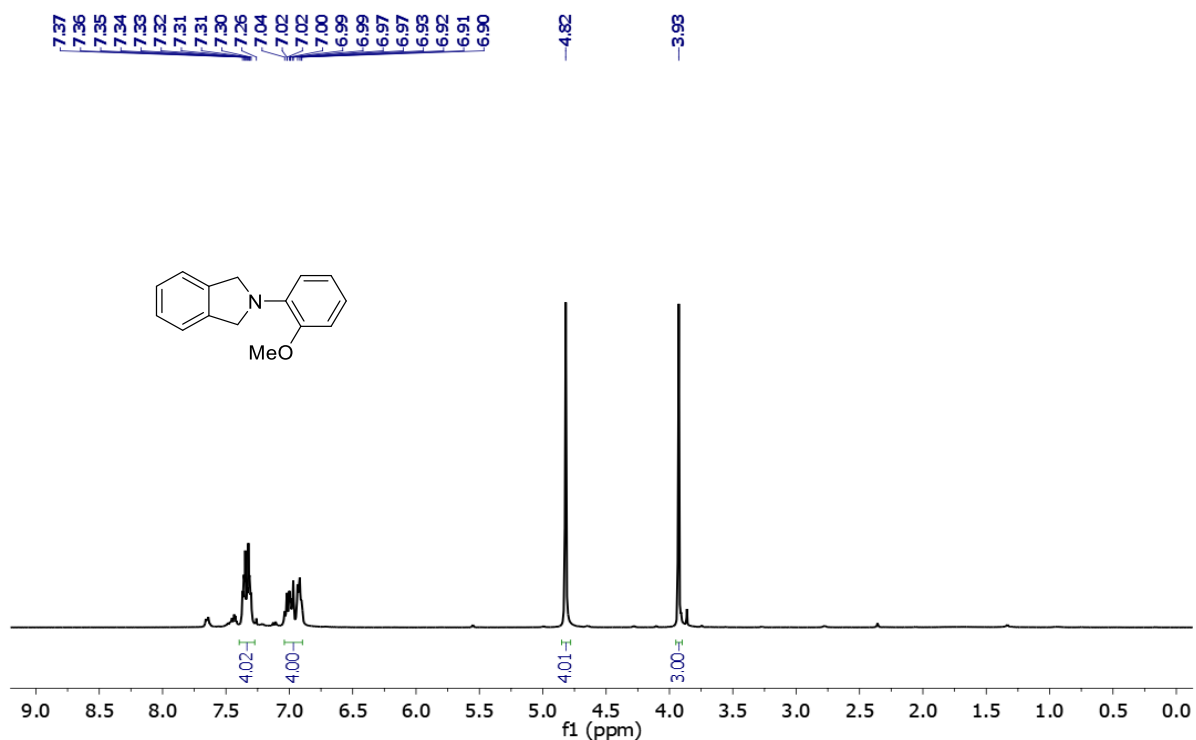
Figure 5.13 ^{1}H NMR (400 MHz) spectrum of 2-(2-methoxyphenyl)isoindoline (**P$_{46}$**) in CDCl$_3$ at r.t
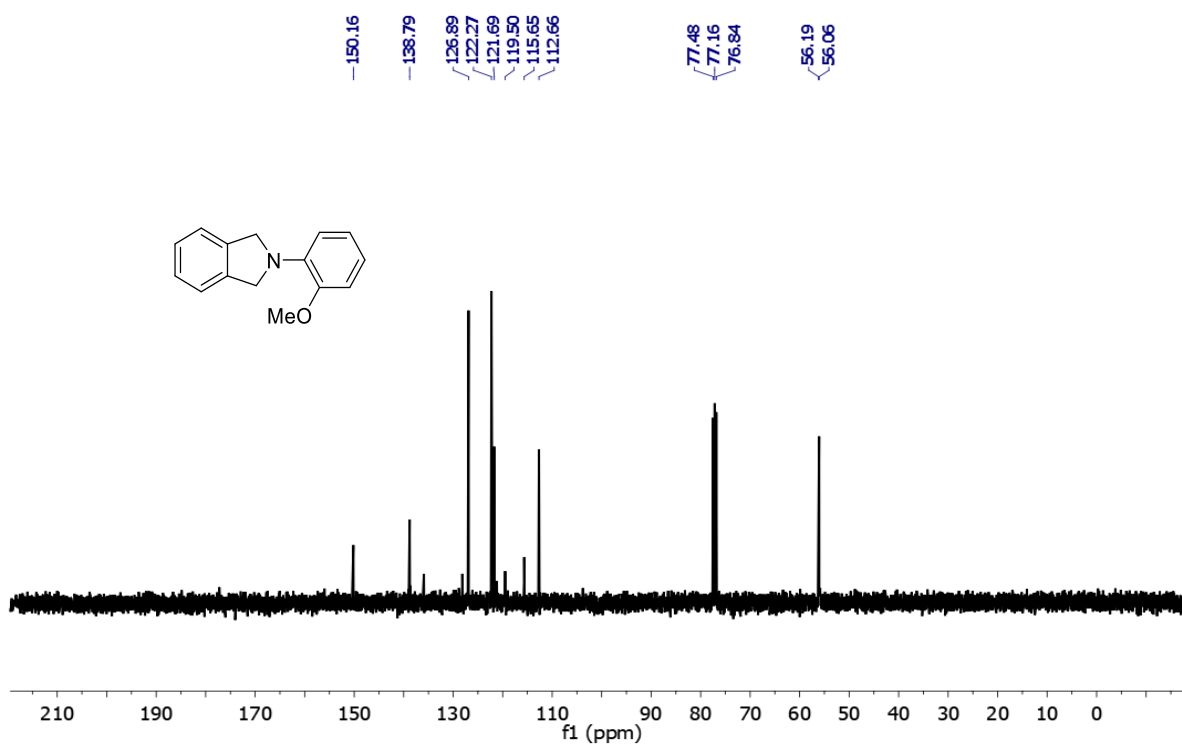
Figure 5.14 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 2-(2-methoxyphenyl)isoindoline (**P$_{46}$**) in CDCl$_3$ at r.t.
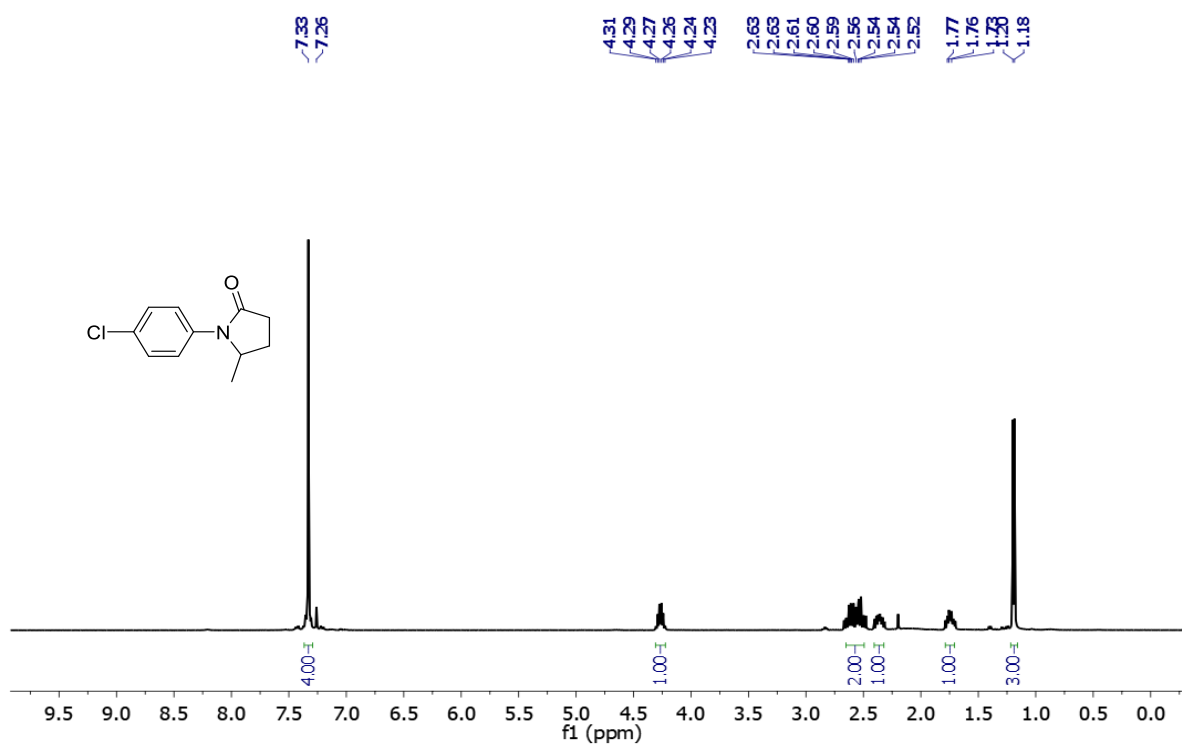
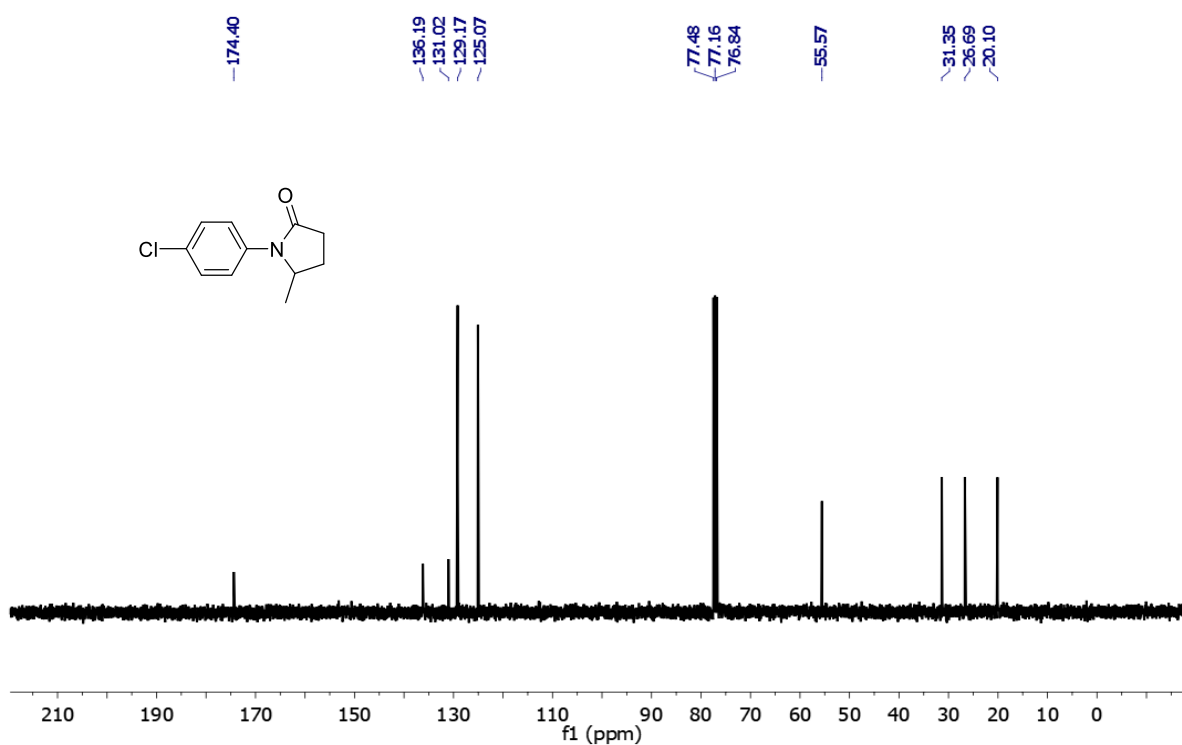**Figure 5.15** ¹H NMR (400 MHz) spectrum of 1-(4-chlorophenyl)-5-methylpyrrolidin-2-one (**L81**) in CDCl₃ at r.t.

Figure 5.16 ¹³C{¹H} NMR (101 MHz) spectrum of 1-(4-chlorophenyl)-5-methylpyrrolidin-2-one (**L81**) in CDCl₃ at r.t.
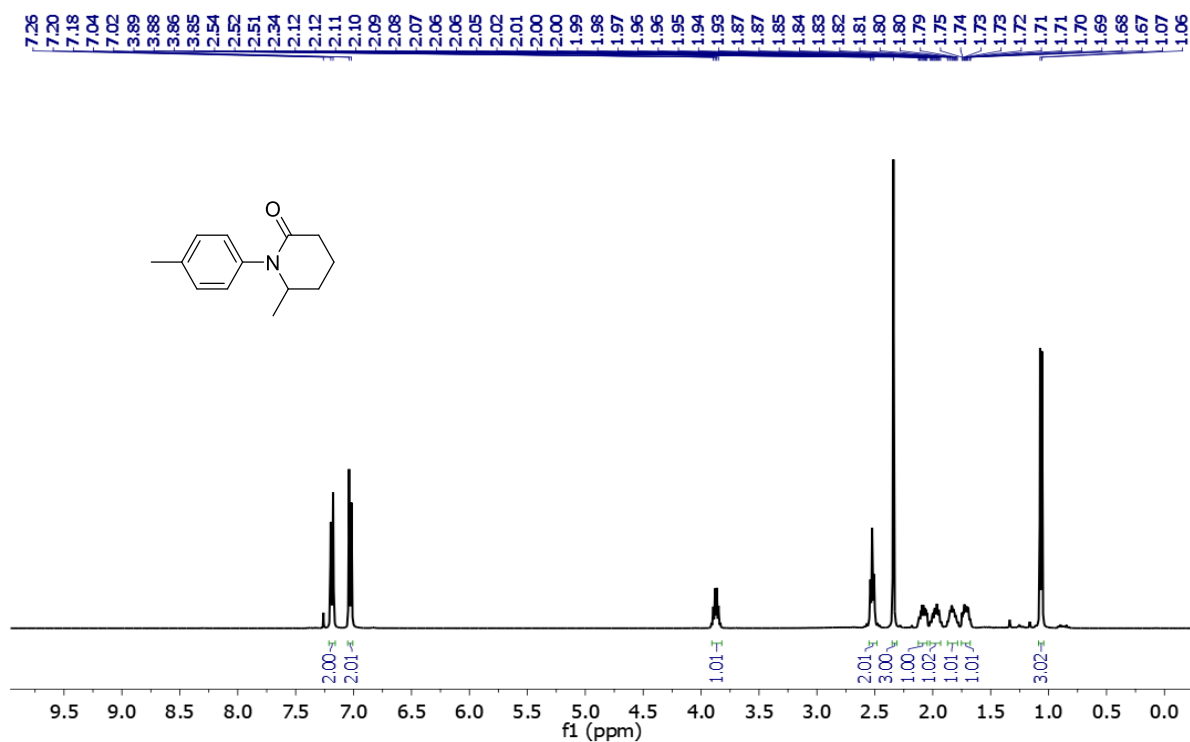
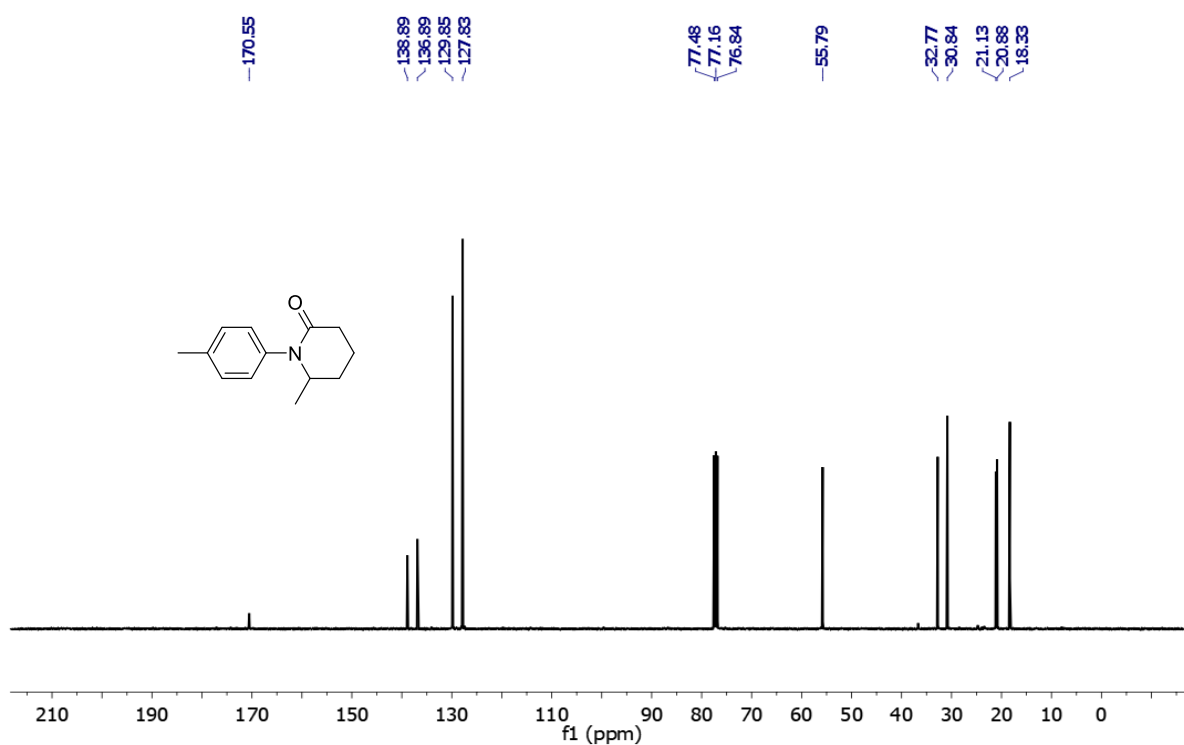**Figure 5.17** ^{1}H NMR (400 MHz) spectrum of 6-methyl-1-(p-tolyl)piperidin-2-one (**L$_{12}$**) in CDCl$_3$ at r.t

Figure 5.18 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 6-methyl-1-(p-tolyl)piperidin-2-one (**L$_{12}$**) in CDCl$_3$ at r.t
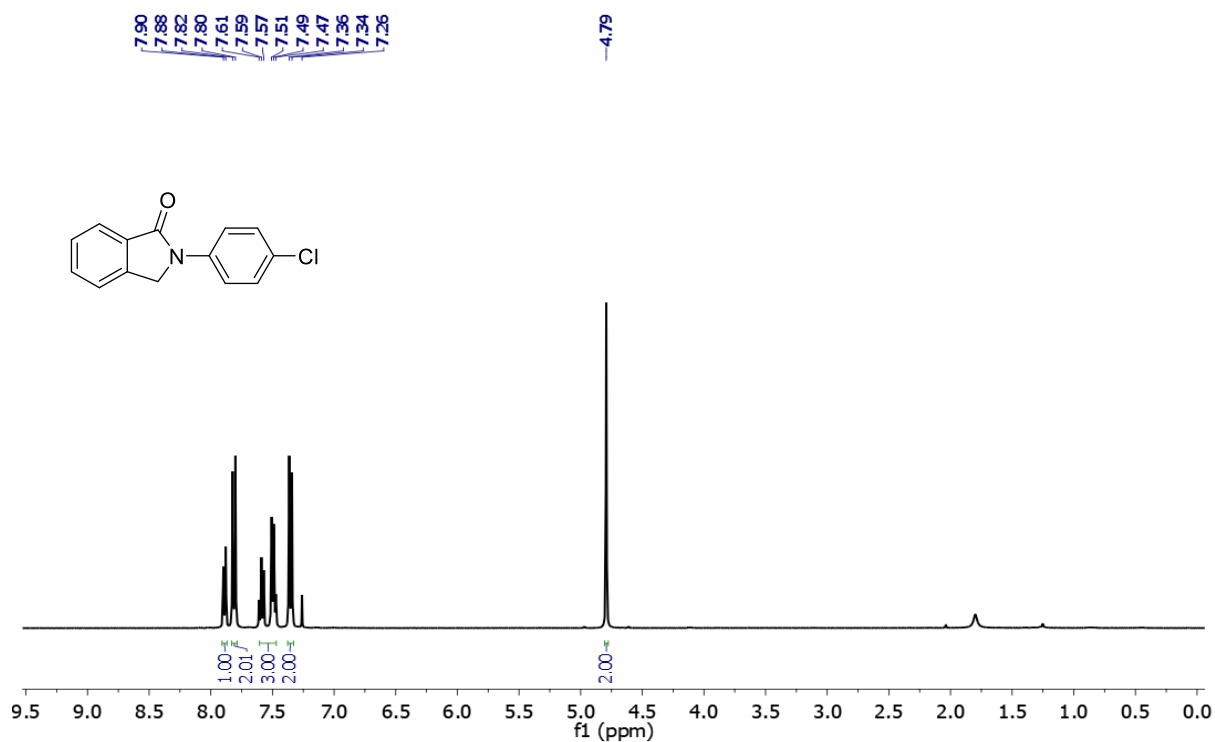
Figure 5.19 ^{1}H NMR (400 MHz) spectrum of 2-(4-chlorophenyl)isoindolin-1-one (**L$_{86}$**) in CDCl$_3$ at r.t
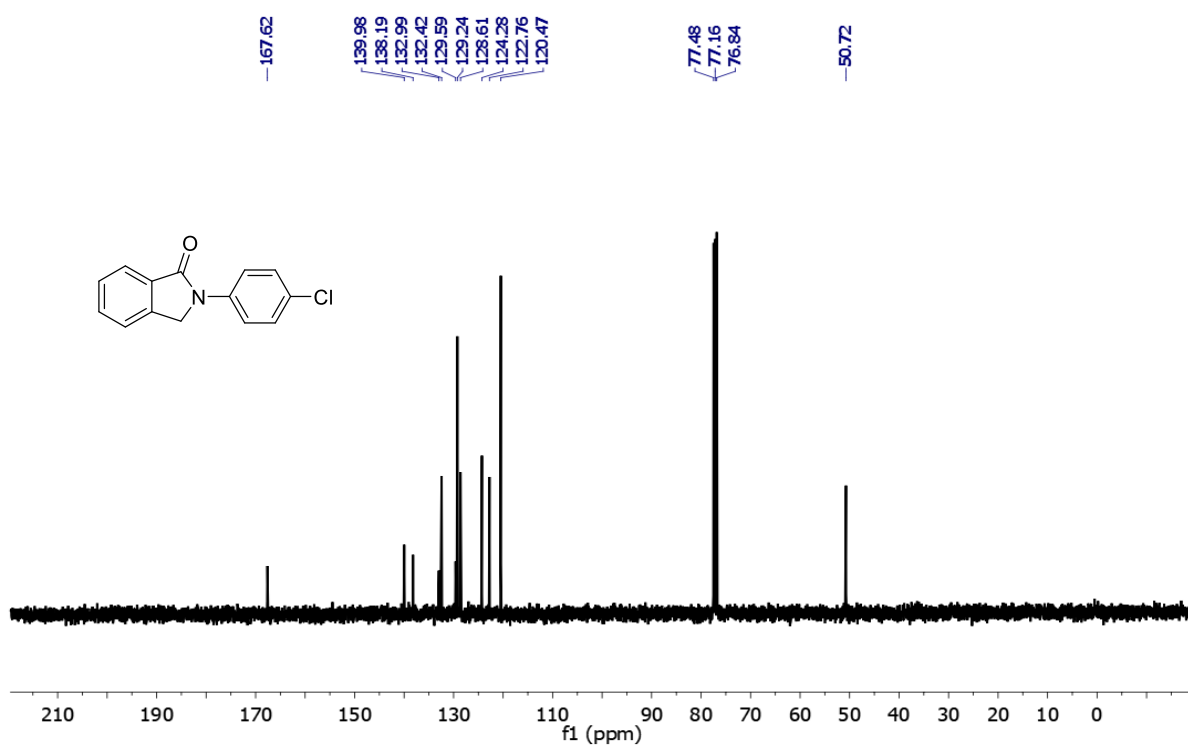

Figure 5.20 ^{13}C{^{1}H} NMR (101 MHz) spectrum of 2-(4-chlorophenyl)isoindolin-1-one (**L$_{86}$**) in CDCl$_3$ at r.t

Summary

In Chapter 1.1, the significance of alkylation reactions utilizing primary and secondary alcohols as alkylating agents is elucidated. A concise depiction of protic-pyrazole ligands and their dual characteristics in metal-ligand cooperation is provided. Additionally, the chapter delves into the discussion of acceptorless dehydrogenative coupling (ADC) and borrowing hydrogen (BH) strategies, contributing to the construction of new C−C and C−N bonds. The subsequent exploration of these pathways includes a comprehensive review of relevant literature reports centered on iridium complexes and their involvement in alkylation reactions.

Moving on to Chapter 1.2, the focus shifts to the importance of cobalt in hydrosilylation reactions. Hydrosilylation emerges as a preferable alternative for reduction processes, and the chapter details various literature reports highlighting cobalt-catalyzed hydrosilylation for the reduction of diverse functionalities.

In Chapter 2, We've developed an easily accessible and air-stable iridium(III) catalyst for α-alkylation of arylacetonitriles with challenging secondary alcohols, liberating water as a green byproduct. It demonstrates broad substrate compatibility and operates with remarkably low catalyst loading (down to 0.01 mol% [Ir]), surpassing previous cobalt and iridium catalysts. Our protocol also requires minimal base (30 mol%) and achieves faster reaction kinetics (24 vs 1 h; maximum TOF of 1−2 vs 10,000 h^{-1}), featuring solvent-free α-alkylation. The catalyst has proven effective in achieving high conversion quickly, following the borrowing hydrogen principle.

Chapter 3 demonstrates utilization the iridium-pyrazolato complex as a potent catalyst for the alkylation of ketones and nitriles using primary alcohols. Moreover, this catalyst shows promise in generating heterocycles through acceptorless dehydrogenative reactions. The

iridium catalyst has proven its excellence in facilitating α-alkylation reactions, achieving impressive conversion rates quickly and featuring a remarkably low catalyst loading (0.1/1 mol%). The substrate scope covers a wide range of arylacetonitriles, ketones, and various primary alcohols. Experimental evidence supports the adoption of the Borrowing Hydrogen pathway for alkylation and the dehydrogenative coupling approach for synthesizing quinolines. Thus, this catalyst operates proficiently in both dimensions within the same framework.

In chapter 4, we have developed a highly efficient $Co_2(CO)_8$ catalyzed hydrosilylation protocol for the reduction of nitroarenes to aromatic amines under both thermal and photochemical conditions. This marks the inaugural report on cobalt-catalyzed hydrosilylation of nitroarenes. Our protocol accommodates various nitroarenes with diverse electron-donating and -withdrawing functionalities, showcasing chemoselectivity towards nitro groups. The catalytic hydrosilylation found application in synthesizing key drug molecules and pharmaceutical intermediates. Our approach serves as an eco-friendly alternative to conventional methods, eliminating the need for stoichiometric amounts of toxic reducing agents. Based on experimental evidence, we propose a radical mechanism for the catalytic path.

In summary of chapter 5, we presented a versatile protocol for the synthesis of N-substituted pyrrolidines to pyrrolidones under hydrosilylation conditions, employing the commercial $Co_2(CO)_8$ catalyst. Notably, no additional ligand or additive was required. Prior to this investigation, only Fe and Mn were documented as base metal catalysts, with cobalt not having been utilized for this purpose. To our knowledge, this marks the first instance of a metal catalyst capable of selectively synthesizing pyrrolidone and pyrrolidine under slightly different hydrosilylation conditions. The study involved the use of biomass-derived levulinic

acid and other ketoacids in conjunction with various aryl amines, demonstrating excellent tolerance to diverse functionalities.

In summary, this work establishes effective catalytic methods for alkylations that prioritize atom efficiency and environmental friendliness. Notably, all reactions detailed in the thesis yield only water as a byproduct, aligning with principles of sustainable and eco-friendly chemistry. The phosphine-free iridium complex demonstrates superior efficacy in alcohol activation compared to previously reported methods. Further exploration of the reactivity of these complexes holds promise for studying the activation of small molecules and addressing various synthetic challenges. Cobalt carbonyl serves as a highly efficient catalyst for hydrosilylation, an aspect that remains relatively unexplored. This catalyst facilitates the reduction of a wide range of groups, providing versatility in its applications. The reduction of nitro groups was achieved under milder conditions, eliminating the need for complex ligand systems. Additionally, this catalyst was employed in seamlessly switching the synthesis between pyrrolidone and pyrrolidine, a process previously conducted with two different catalysts.