Strategic Design, Syntheses of Novel Pyrazole-Based Cyclometalated Palladacycles and their Utilization as Pre-catalysts in Organic Syntheses

By

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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.

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List of Publications arising from the thesis

Published:

1. "Synthesis of a cyclometalated 1,3,5-triphenylpyrazole palladium dimer and its activity towards cross-coupling reactions", Ramesh Mamidala, Vanga Mukundam, Kunchala Dhanunjayarao and Krishnan Venkatasubbaiah*, *Dalton Trans.*, **2015**, *44*, 5805–5809.

2. "Cyclometalated palladium pre-catalyst for N-alkylation of amines using alcohols and regioselective alkylation of sulfanilamide using aryl alcohols", Ramesh Mamidala, Vanga Mukundam, Kunchala Dhanunjayarao and Krishnan Venkatasubbaiah*, *Tetrahedron*, **2017**, *73*, 2225–2233.

3. "Isolation and characterization of regioisomers of pyrazole-based palladacycles and their use in α-alkylation of ketones using alcohols", Ramesh Mamidala, Shaikh Samser, Nishant Sharma, Upakarasamy Lourderaj, and Krishnan Venkatasubbaiah*, *Organometallics*, **2017**, *36*, 3343–3351.

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4. "Chemoselective alkylation of aminoacetophenones with alcohols by using a palladacycle- phosphine catalyst", Ramesh Mamidala, M. Siva Subramani, Shaikh Samser, and Krishnan Venkatasubbaiah*.

Manuscripts in preparation:

5. "An efficient cyclometalated palladacycle for methylation of ketones and amines using methanol as a C-1 source", Ramesh Mamidala, Priyabrata Biswal and Krishnan Venkatasubbaiah*.

6. "Strategic design and synthesis of pyrazole-based palladacycles *via* C─H activation, an effect of trifluoromethyl group on regioselective cyclopalladation", Ramesh Mamidala and Krishnan Venkatasubbaiah*.

Other publications:

7. "Synthesis and optical properties of salicylaldimine-based diboron complexes", Kunchala Dhanunjayarao, Vanga Mukundam, Ramesh Mamidala and Krishnan Venkatasubbaiah*, *Eur. J. Inorg. Chem.*, **2014**, 539–545.

8. "Characterization and aggregation induced enhanced emission properties of tetraaryl pyrazole decorated cyclophosphazenes", Vanga Mukundam, Kunchala Dhanunjayarao, Ramesh Mamidala and Krishnan Venkatasubbaiah*, *J. Mater. Chem. C,* **2016**, *4*, 3523–3530.

Ramesh Mamidala

List of Conferences

1. "Synthesis of a cyclometalated 1,3,5-triphenylpyrazole palladium dimer and its activity towards cross-coupling reactions", R. Mamidala, V. Mukundam, K. Dhanunjayarao and K. Venkatasubbaiah* in Indo-French Symposium on Metal-Organic Frameworks held on (24-26)th February 2014 organized by School of Chemical Sciences, NISER Bhubaneswar, India. (**Poster Presentation**)

2. "Regio-isomers of Pyrazole Based Palladacycle: Synthesis, Isolation and Their Uses in α-Arylation of Ketones", R. Mamidala, S. Samser and K. Venkatasubbaiah* in Modern Trends in Inorganic Chemistry held on (11-14)th December 2017 organized by CSIR-NCL, Pune In association with IISER, Pune and S. P. Pune University, Pune, India. (**Poster Presentation**)

3. "Regio-isomers of Pyrazole Based Palladacycle: Synthesis, Isolation and Their Uses in α-Arylation of Ketones", R. Mamidala, S. Samser and K. Venkatasubbaiah* in Inter IISER & NISER Chemistry Meet held on (22-24)th December 2017 organized by NISER Bhubaneswar, India. (**Poster Presentation**)

4. "Tetraaryl Pyrazole Supported Polymers and Cyclophosphazenes: Synthesis and Photophysical Properties", V. Mukundam, K. Dhanunjayarao, R. Mamidala and K. Venkatasubbaiah* in 19th CRSI National Symposium in Chemistry held on (14-16)th July 2016 organized by Department of Chemistry, University of North Bengal, Darjeeling, India. (**Poster Presentation**)

5. Participated in XI-JNOST Conference for Research Scholars held on (14-17)th December 2015, NISER Bhubaneswar, India.

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And I dedicate this to my late brother-in-law, Ankam Venkatesham.

Ramesh Mamidala

CONTENTS

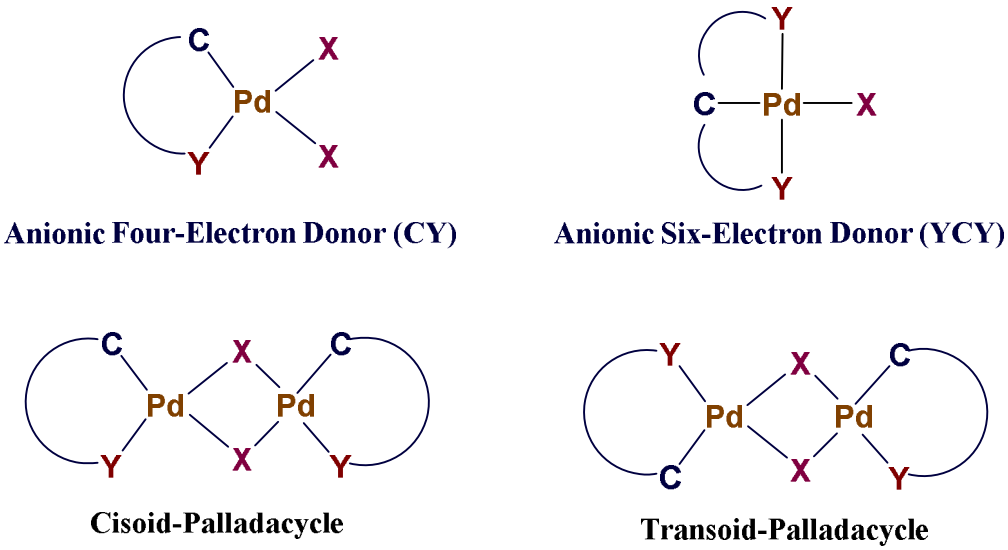
SYNOPSIS

The thesis entitled "*Strategic Design, Syntheses of Novel Pyrazole Based Cyclometalated Palladacycles and their Utilization as Pre-Catalysts in Organic Syntheses*" dissociated into seven chapters.

CHAPTER-I: Introduction to cyclometalated palladium compounds

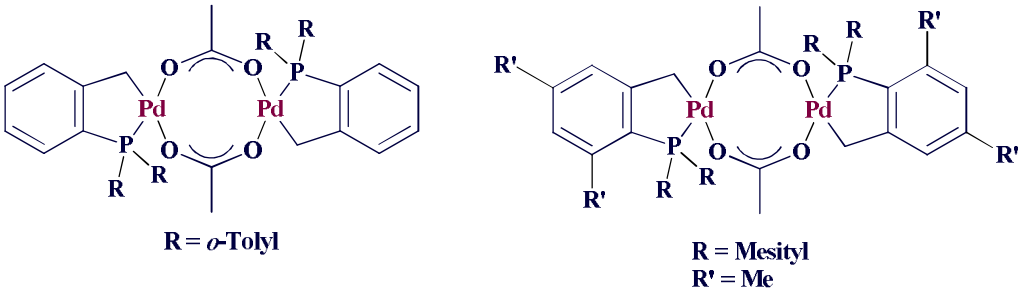
This part deals with the history, classification of palladacycles and their catalytic applications as pre-catalysts in C─C and C─N bond formations.

Palladium compounds containing at least one palladium-carbon bond intramolecularly stabilized by at least one donor atom termed cyclopalladated compounds or palladacycles are one of the most popular classes of organopalladium derivatives. Palladacycles are divided into two types (Scheme 1); anionic four-electron donor (CY) or six-electron donor (YCY). The former usually exist as halogen or acetate bridged dimers, as two geometric isomers (*cisoid* and *transoid* conformations).1 A short survey of palladacycles will be presented in this part.



Scheme 1: Classification of palladacycles

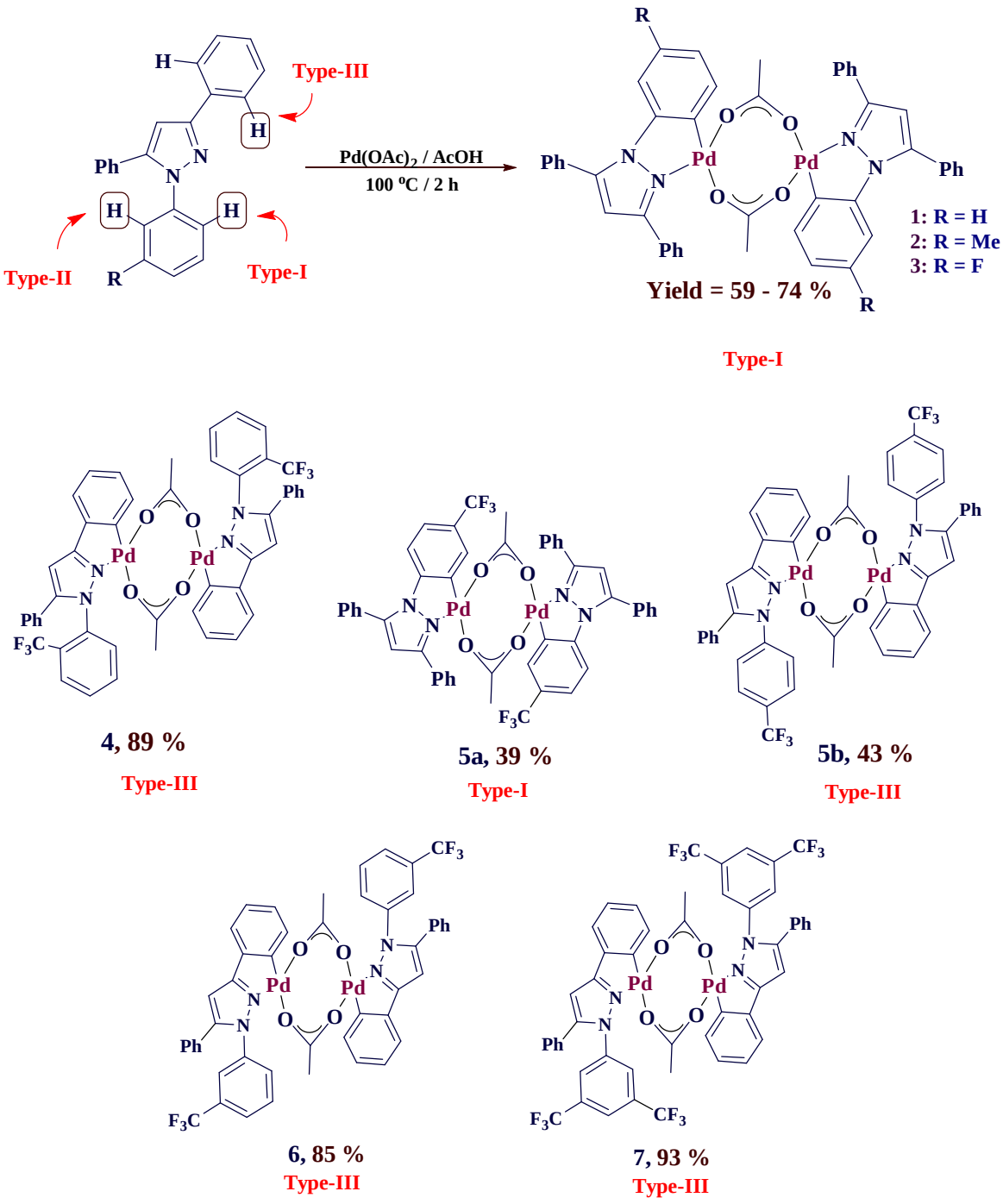
In 1995 Herrmann and co-workers successfully synthesized tri(*o*-tolyl)phosphine based palladacycle and utilized as pre-catalyst in Heck, Suzuki and Buchwald-Hartwig reactions (Scheme 2).[2] Since then numerous five-membered [3] and six membered [4] palladacycles were reported. The catalytic applications of palladacycles will be presented in this part.



Scheme 2: Herrmann and Beller's phosphapalladacycles

CHAPTER-II: Design and synthesis of pyrazole-based palladacycles *via* C─H activation

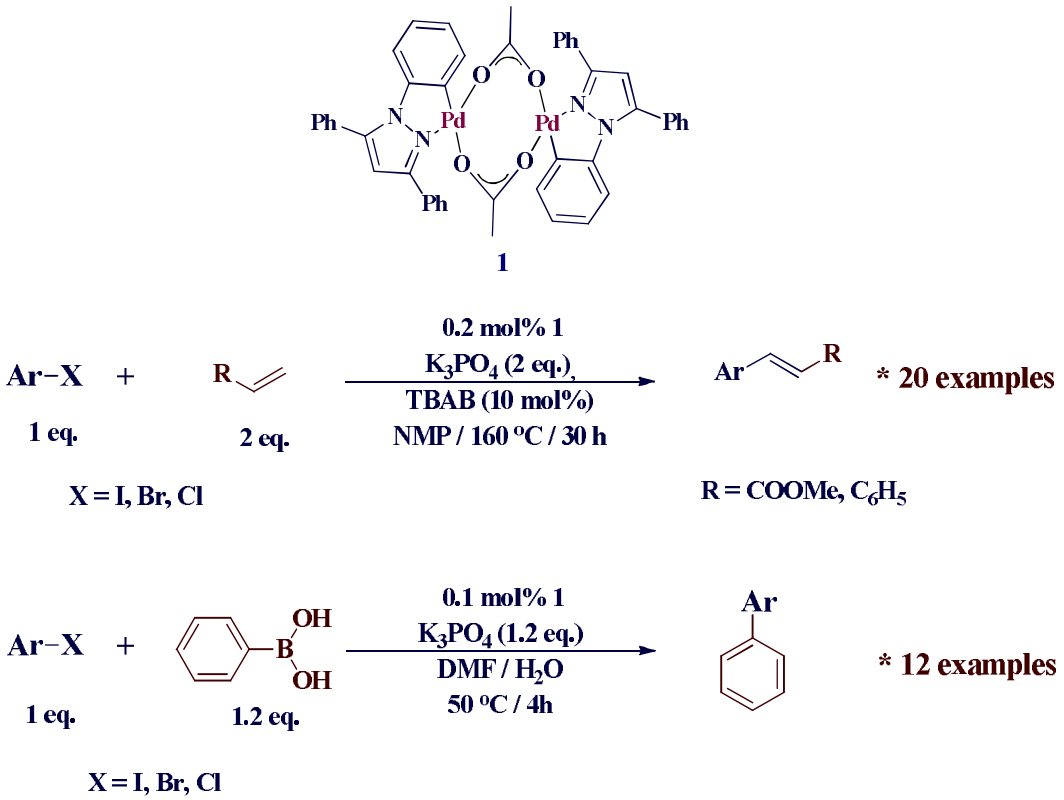
Pyrazoles are an important class of heterocyclic aromatic compounds having adjacent nitrogen atoms in a five-membered ring system. Nitrogen-directed cyclopalladation of an aromatic ring is the most direct route to synthesis C,N-palladacycles,[3, 4] therefore, we examined C─H activation of 1,3,5-triphenylpyrazoles as ligands with $Pd(OAc)_2$ (Scheme 3). The results are quite interesting when R = H, Me and F, the C─H activation proceeded on the N-phenyl of pyrazole (type-I, palladacycles **1-3**). However, when R = CF_3, we observed C─H activation on 3-phenyl as well as N-phenyl of pyrazole (type I and type III, Palladacycles **4-7**). The effect of -CF_3 group on *ortho, meta* and *para* position of N-phenyl ring was evaluated. These results are presented in this chapter.



Scheme 3: palladacycles

CHAPTER-III: 1,3,5-Triphenylpyrazole palladium dimer and its activity towards cross-coupling reactions

This chapter deals with the palladium catalyzed Suzuki–Miyaura and Mizoroki–Heck reactions, which are most important C─C bond forming reactions in organic synthesis. Normally, 1 to 5 mol% of palladium catalyst along with phosphine ligands is utilized to perform these cross-coupling reactions. As organophosphines are air-sensitive, expensive and poisonous, 1,3,5-triphenylpyrazole acetate-bridged palladacycle-**1** used as phosphine free catalyst to promote the cross-coupling reactions.[5] The activity of the palladacycle in the Mizoroki–Heck, and Suzuki–Miyaura cross-coupling reactions were evaluated (Scheme 4). The palladacycle pre-catalyst showed a wide substrate scope, both in Mizoroki–Heck in N-methyl-2-pyrrolidone (NMP) as well as in Suzuki–Miyaura cross-coupling reactions in N,N'-dimethylformamide and water using low catalyst loadings *viz.*, 0.2 mol% and 0.1 mol% respectively.

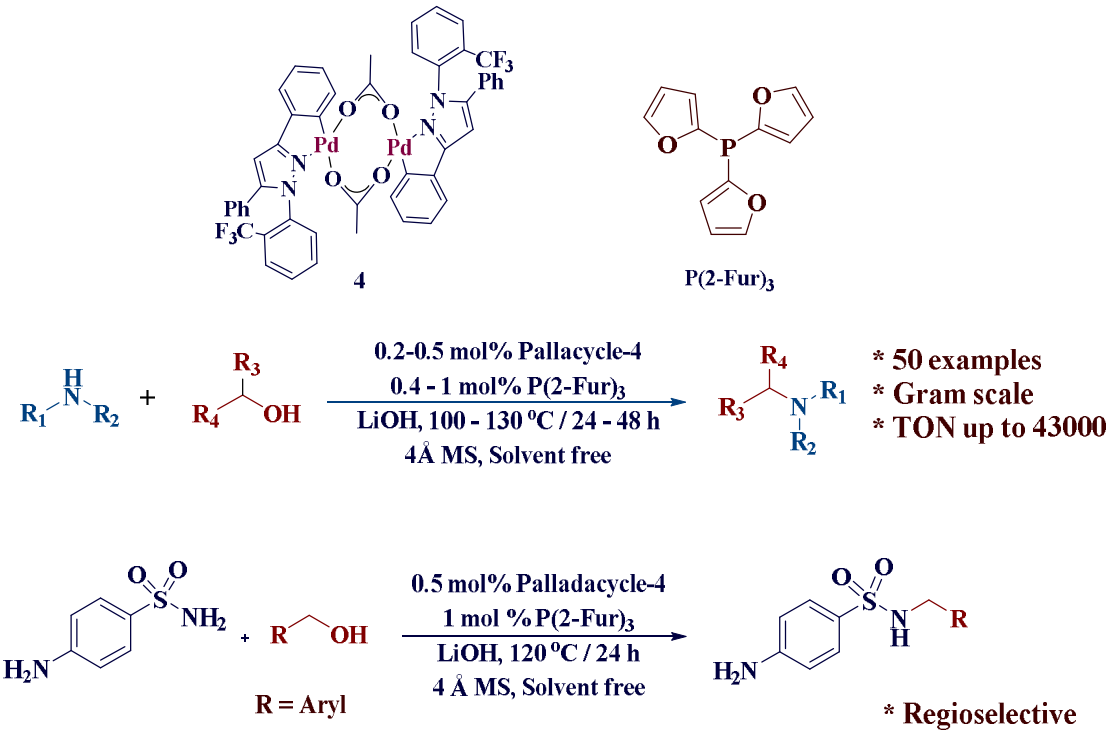


Scheme 4: Mizoroki–Heck and Suzuki–Miyaura cross-coupling reactions

CHAPTER-IV: Cyclometalated palladium pre-catalyst for N-alkylation of amines using alcohols and regioselective alkylation of sulfanilamide using aryl alcohols

Chapter-IV discusses N-alkylation of amines and sulfanilamide using alcohols as substrates using palladacycle-**4** and phosphine, involving hydrogen borrowing strategy.[6] N-alkylation of primary and secondary amines resulted in high isolated yields at 100-130 °C, under solvent-free conditions. More challenging secondary aliphatic, as well as aromatic alcohols, were also successfully utilized as alkylating agents under similar reaction conditions. The turn over number reached up to 43000 for N-benzylation of aniline using benzyl alcohol. Notably, regioselective N-alkylation of 2-aminobenzothiazole and 4-aminobenzenesulfonamide to the

corresponding 2-N-(alkylamino) azoles and 4-amino-(N-alkyl)benzenesulfonamides using alcohols as alkylating agents have been achieved. Furthermore, we established the synthetic utility of palladacycle-**4** in the synthesis of Piribedil, which is clinically used for the treatment of Parkinson's disease.



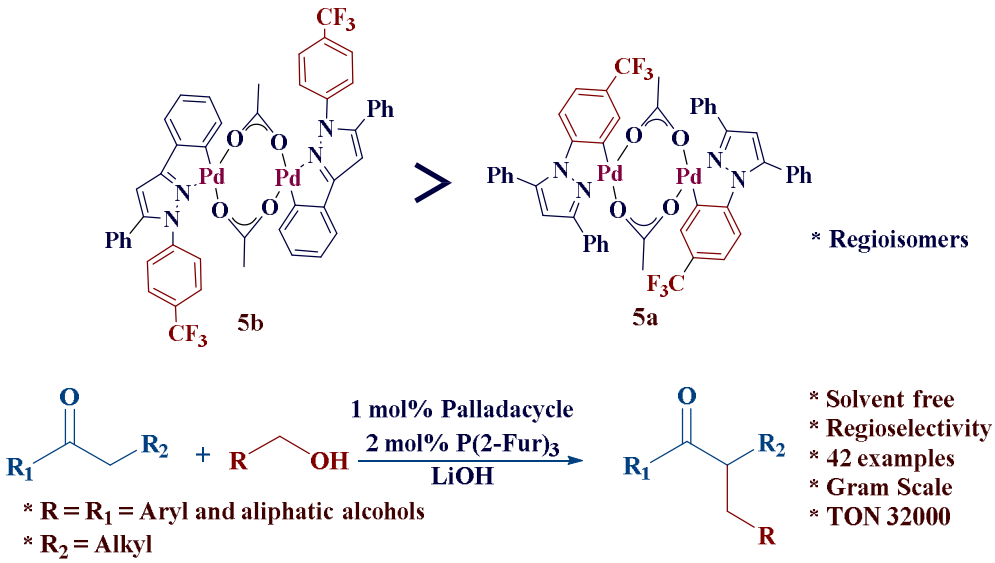
Scheme 5: N-Alkylation of amines

CHAPTER-V: Isolation, characterization of regioisomers of pyrazole-based palladacycles and their evaluation in C-alkylation of ketones using alcohols

Chapter-V describes C-alkylation of ketones,[7] using palladacycles-**5a** and **5b** which are regio-isomers. The substrate scope and limitations using the palladacycle-**5b** for the C-alkylation of various ketones under the optimized reaction conditions were presented (Scheme 6). In most of the cases, electron rich as well as electron

deficient substituted acetophenones or benzyl alcohols were successfully converted to the desired products in good to excellent isolated yields under mild reaction conditions. The turn over number reached up to 32000 for α-alkylation of acetophenone using benzyl alcohol. The present catalytic system was also successfully applied for α-alkylation of biologically important steroidal substrates such as β-pregnenolone, estrone, and *trans*-dehydroandrosterone under the reaction conditions. We also examined the synthetic utility of our palladacycle-**5b** in the synthesis of Donepezil, which is used in the treatment of Alzheimer disease.

As quinolines are an important class of heterocyclic compounds, we tested palladacycle-5b as a catalyst for the synthesis of quinoline derivatives starting from ketones and 2-amino benzyl alcohol. Under the optimized reaction conditions, good to excellent isolated yields were obtained when we used electron rich as well as electron deficient acetophenones. Non-activated methylene ketones were also successful to yield the corresponding quinoline derivatives.



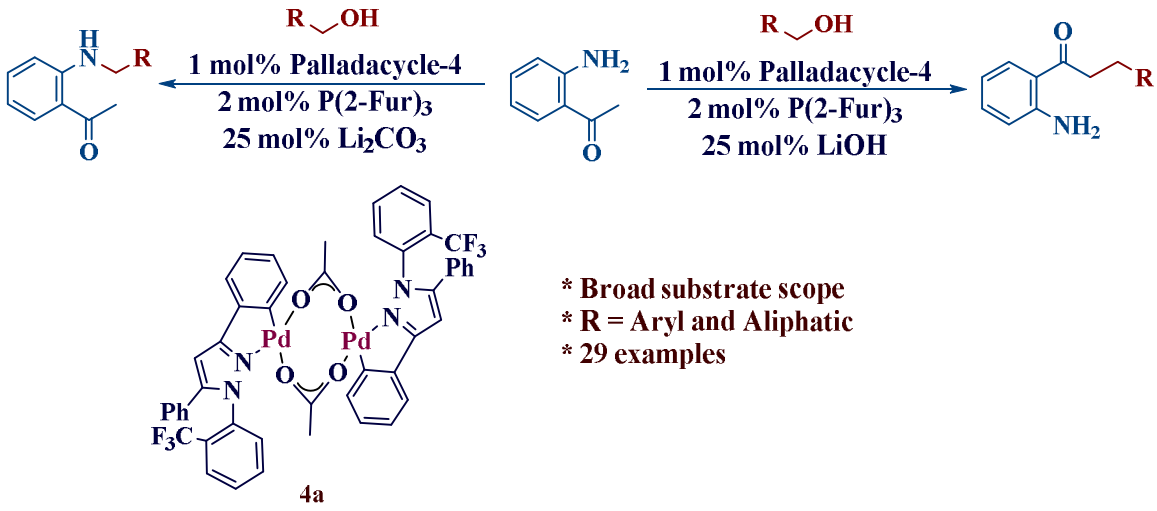
Scheme 6: C-alkylation of ketones

CHAPTER-VI: Highly chemoselective alkylation of aminoacetophenones using pyrazole-based palladacycle

Chapter-VI deals with the chemoselective alkylation of bifunctional aminoacetophenones[8] using palladacycle-**4** and $P(2\text{-Fur})_3$. C-alkylation of aminoacetophenones proceeds smoothly using LiOH as a base at 80 ^{o}C (Scheme 7). Benzyl alcohols bearing electron-donating or electron-withdrawing groups were readily alkylated to corresponding C-alkylated products under the optimized condition. Furthermore, the catalytic system was efficient to tolerate challenging aliphatic alcohols to yield the corresponding C-alkylated products.

N-alkylation of aminoacetophenones proceeds using Li_2CO_3 as a base at 140 ^{o}C (Scheme 7). The substitutions on benzyl alcohol and aminoacetophenone with electron-withdrawing groups or electron-donating groups were tolerated under the optimized reaction condition. The least reactive and challenging aliphatic alcohols such as 1-butanol and 1-hexanol were also successfully converted to the corresponding N-alkylated products.

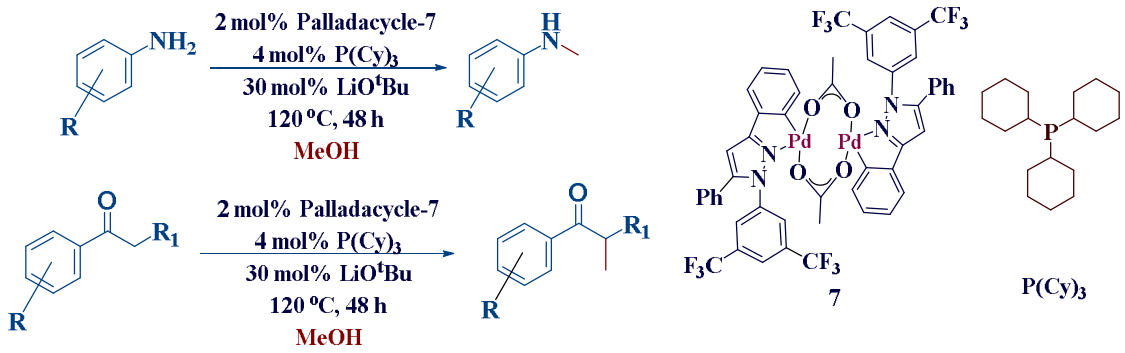
Notably, the methodology is not only limited to 2'-aminoacetophenone and its derivatives but also 4'-aminoacetophenone and 3'-aminoacetophenone were converted to N-alkylated or C-alkylated products in good yield. Furthermore, we broaden the scope of the *hydrogen borrowing* catalysis for the chemoselective synthesis of Donepezil.



Scheme 7: Chemoselective alkylation of aminoacetophenones

CHAPTER-VII: An efficient cyclometalated palladacycle for methylation of ketones and amines using methanol as a C-1 source

Chapter-VII describes the methylation of ketones and amines using palladacycle-**7** and $P(Cy)_3$. Methylation of ketones [9a] and amines [9b] is one of the most important organic reactions and widely utilized for the synthesis of numerous fine chemicals. Traditionally, the N-methylation or C-methylation is performed using highly toxic and hazardous methylating agents in the presence of bases. The use of hydrogen borrowing methodology using methanol as the environmentally benign methylating agent has emerged as a powerful method. The palladacycle-**7** in methylation of ketones and amines using LiO^tBu as a base at 120 ^oC has been studied. Arylketones and anilines bearing electron-donating or electron-withdrawing groups were readily methylated to the corresponding products under the reaction condition (Scheme 8).



Scheme 8: Methylation of ketones and amines

References:

1. J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.*, 2005, **105**, 2527.

2. (a) W. A. Herrmann, C. Brossmer, K. Ofele, C. Reisinger, T. Priermeier, M. Beller and H. Fischer, *Angew. Chem. Int. Ed.*, 1995, **34**, 1844. (b) M. Beller, H. Fischer, W. A. Herrmann, K. Ofele and C. Brossmer, *Angew. Chem. Int. Ed.*, 1995, **34**, 1848.

3. (a) M. Ohff, A. Ohff and D. Milstein, *Chem. Commun.*, 1999, 357 (b) X. Gai, R. Grigg, M. I. Ramzan, V. Sridharan, S. Collard and J. E. Muir, *Chem. Commun.*, 2000, 2053.

4. (a) J. M. Chitanda, D. E. Prokopchuk, J. W. Quail and S. R. Foley, *Dalton Trans.*, 2008, 6023 (b) S. E. Bajwa, T. E. Storr, L. E. Hatcher, T. J. Williams, C. G. Baumann, A. C. Whitwood, D. R. Allan, S. J. Teat, P. R. Raithby and I. J. S. Fairlamb, *Chem. Sci.*, 2012, **3**, 1656.

5. R. Mamidala, V. Mukundam, K. Dhanunjayarao and K. Venkatasubbaiah, *Dalton Trans.*, 2015, **44**, 5805.

6. R. Mamidala, V. Mukundam, K. Dhanunjayarao and K. Venkatasubbaiah, *Tetrahedron*, 2017, **73**, 2225.

7. (a) M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala and J. Park, *Angew. Chem. Int. Ed.,* 2005, **44**, 6913. (b) Y. M. A. Yamada, Y. Uozumi, *Org. Lett.,* 2006, **8**, 1375. (d) O. Kose and S. Saito, *Org. Biomol. Chem.,* 2010, **8**, 896. (d) Y. Obora, *ACS Catal.,* 2014, **4**, 3972.

8. S. Bhat and V. Sridharan, *Chem. Commun.,* 2012, **48**, 4701.

9. (a) L. K. M. Chan, D. L. Poole, D. Shen, M. P. Healy and T. J. Donohoe, *Angew. Chem. Int. Ed.,* 2014, **53**, 761. (b) T. T. Dang, B. Ramalingam and A. M. Seayad, *ACS Catal*., 2015, **5**, 4082.

List of figures

List of schemes

List of tables

List of Abbreviations

Ac	Acetyl
Ar	Aryl
Et	Ethyl
equiv	Equivalents
h	Hours
Me	Methyl
dba	Dibenzylideneacetone
Ph	Phenyl
OMe	Methoxy
NMP	N-Methyl-2-pyrrolidone
rt	Room temperature
tBu	Tertiary butyl
iPr	Isopropyl
TBAB	Tetrabutyl ammonium fluoride
DMSO	Dimethyl sulfoxide
DMF	N,N'-dimethyl formamide
DMAc	N,N'-dimethyl acetamide
PPh_3	Triphenylphosphine
AlPhos	Di-1-adamantyl(4″-butyl-2″,3″,5″,6″-tetrafluoro-2′,4′,6′-triisopropyl-2-methoxy-meta-terphenyl)phosphine
BrettPhos	2-(Dicyclohexylphosphino)3,6-dimethoxy-2′,4′,6′-triisopropyl-1,1′-biphenyl

tBuBrettPhos	2-(Di-*tert*-butylphosphino)-2′,4′,6′- triisopropyl-3,6-dimethoxy-1,1′-biphenyl
RockPhos	2-Di(*tert*-butyl)phosphino-2′,4′,6′-triisopropyl-3-methoxy-6-methylbiphenyl
Me_4tBuXPhos	2-Di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl
OMs	Mesylate
Pd	Palladium
Ru	Ruthenium
Ir	Iridium
Rh	Rhodium
Mn	Manganese
Pt	Platinum
cod	Cyclooctadiene
Cp*	Pentamethylcyclopentadiene
NHC	N-heterocyclic carbene
Ph*	1,2,3,4,5-pentamethylbenzene
TON	Turn over number
ESI	Electrospray ionization
HRMS	High-resolution mass spectra
NMR	Nuclear magnetic resonance
ppm	Parts per million
MHz	Megahertz
PTFE	Polytetrafluoroethylene
Mp	Melting point

Cyclometalated palladium compounds

1.1 Introduction

Organometallic and coordination chemistry are two domains of chemistry that are complementary. Coordination complexes consist of one or more metals centers surrounded by ligands, organic or inorganic, ions or molecules that can have an independent existence. The organometallic chemistry is defined as the chemistry of compounds containing metal-carbon bond, however, in a general manner, this term is attributed to the chemistry made of organic transformations assisted by metals. This chapter describes a general introduction of palladacycles and their utilization as pre-catalyst for organic transformations. Palladium compounds containing at least one palladium-carbon bond intramolecularly stabilized by at least one donor atom termed cyclopalladated compounds or palladacycles, are one of the most popular classes of organopalladium derivatives. Palladacycles are divided into two types (Figure 1.1): anionic four-electron donor (CY) or six-electron donor (YCY). The former usually exist as halogen or acetate bridged dimers, as two geometric isomers (*cisoid* and *transoid* conformations).[1]

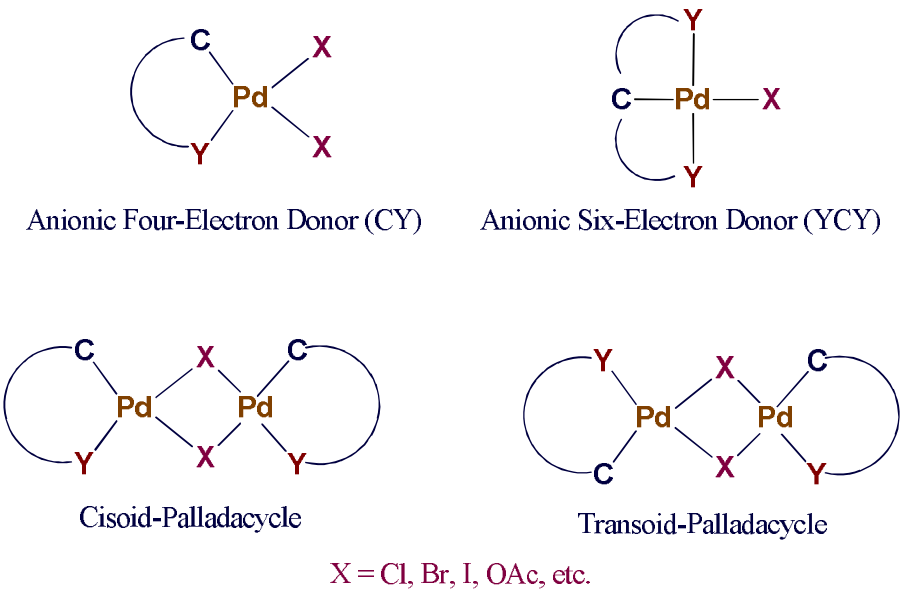


Figure 1.1: Classification of palladacycles

It is in the mid-sixties that the first cyclometallated complexes were prepared by Cope *et al*. by reacting aromatic azo compounds and potassium tetrachloroplatinate(II) or palladium(II)dichloride.[2] However, two years before a cyclopentadienyl nickel compound with similar azobenzene ligand was obtained by Dubeck *et al* (Figure 1.2).[3]

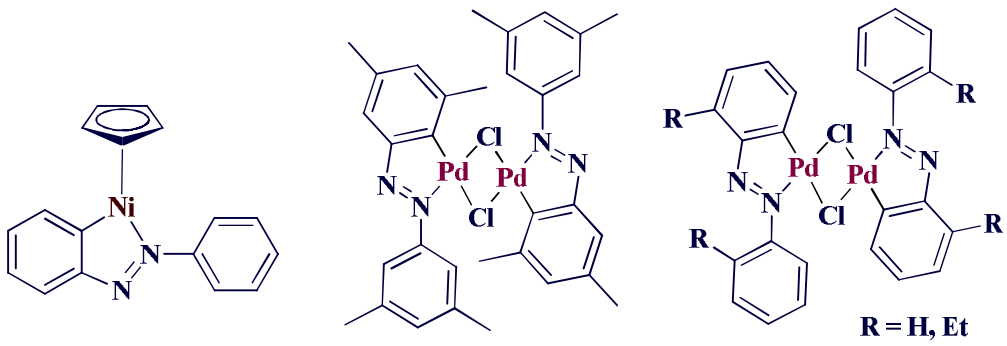


Figure 1.2: Origine of metallacycles

Since then, hundreds of palladacycles have been reported; the most common have five-membered 1,[4] and six-membered 4a,[5] rings. Seven-membered palladacycles

are relatively scarce.[6] S. R. Foley and co-workers reported isoindolilinime based six-membered palladacycle,[5c] and Ian.J. S. Fairlamb and co-workers reported papaverine based six-membered palladacycle (Figure 1.3).[5d] Anil J. Elias and co-workers reported cyclopalladation of cyclobutadiene-bound phenyl groups of Cobalt sandwich compounds[6a] and recently J. Vicente and co-workers synthesized 3-phenylpropylamine based seven-membered palladacycles.[6b] Later, several groups reported regioselective cyclopalladation of imines[7] and oxazolines.[8]

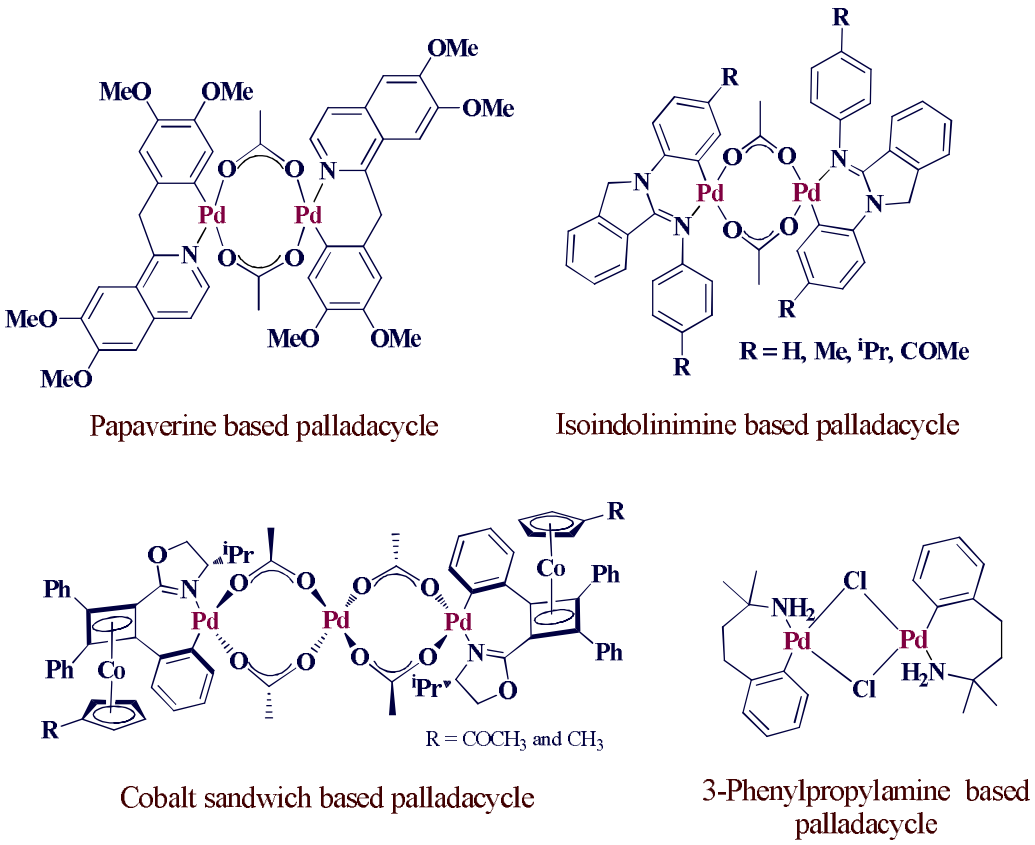
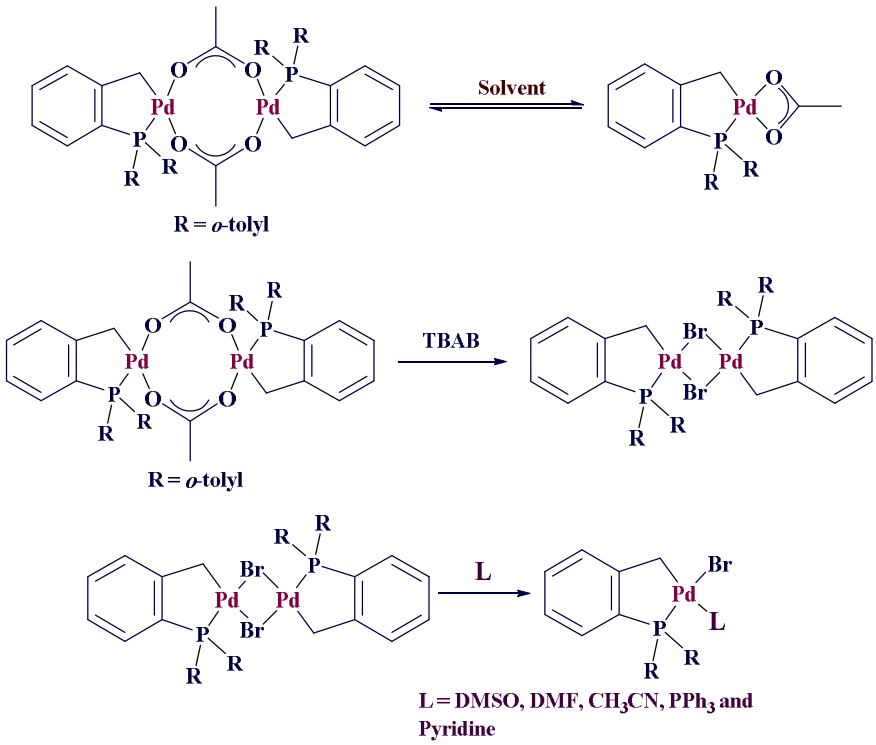


Figure 1.3: Six and seven-membered palladacycles

Although there are several methods available for the generation of palladacycles such as C─H activation, oxidative addition, and transmetalation, the direct chelation assisted palladation of C─H bonds is the most simple and direct method for the

construction of palladacycles. The acetate bridged palladacycles are fluxional molecules and the *trans*-form exclusively exists in solution. Monomer and dimer equilibrium in solution due to weakly bound acetate anions as well as the participation of coordinating solvents favour bridge-splitting of the dimers and are the reason for this observation.[9] The labile acetate anions are easily exchanged by salt metathesis with tetrabutylammonium halides. The resulting dimers are equally stable, but less soluble in non-coordinating solvents like dichloromethane or toluene. Upon addition of coordinating solvents like acetonitrile or upon addition of monodentate ligands PPh_3 or pyridine, the solubility is increased due to the formation of monomeric palladacycles (Scheme 1.1).



Scheme 1.1: The fluxional behaviour of acetate bridged palladacycles in solution

Early in palladacycle's history, palladacycles were classified as catalytically inactive complexes.[7] In 1995 Herman and co-workers tri(*o*-tolyl)phosphine based

palladacycle synthesized and used as pre-catalyst for Heck, Suzuki and Buchwald-Hartwig reactions successfully (Figure 1.4, A).[9] Since then over the past decade they have proven themselves to be convenient and efficient catalyst precursors for the construction of both C─C and C─N bonds. Palladacyclic catalysts have been successfully employed in Heck[10] and Suzuki couplings,[11] Buchwald-Hartwig aminations,[12] and other coupling reactions.[13] In addition to being important pre-catalysts, palladacycles are intermediates in many of these and other palladium-mediated reactions.

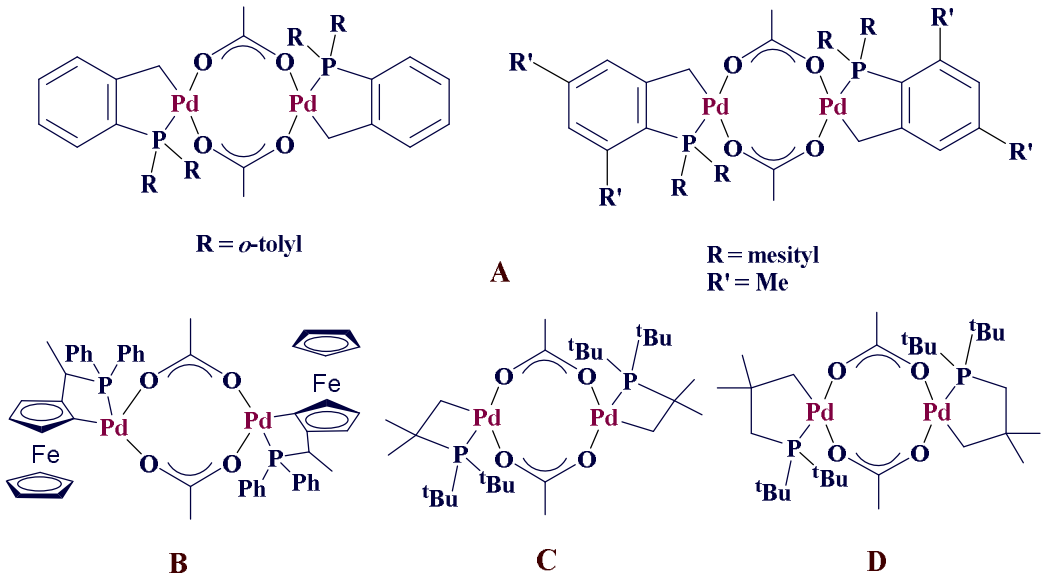
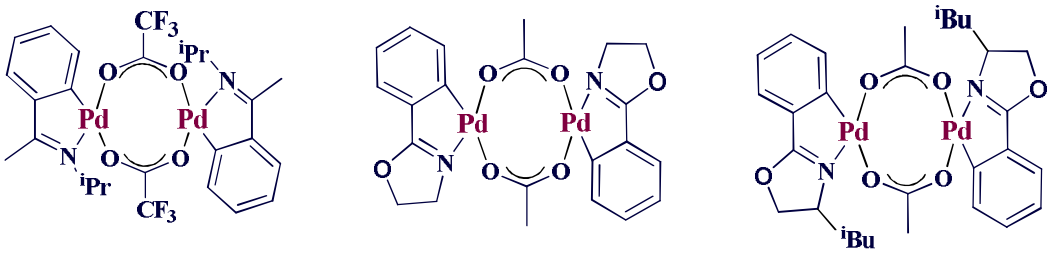


Figure 1.4: Representative examples for phosphapalladacycles

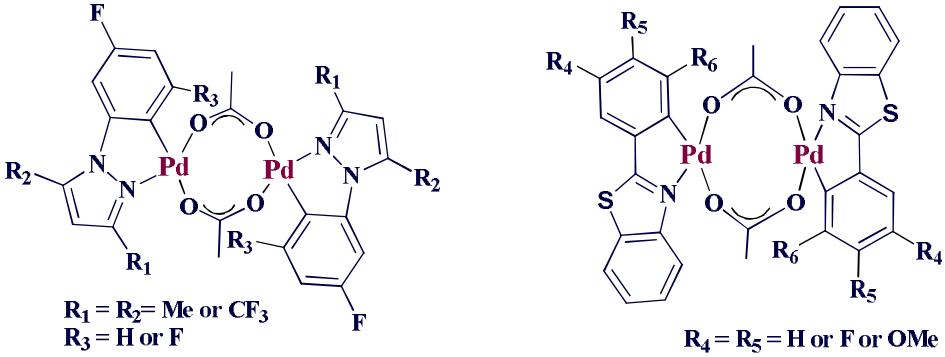
A catalyst system prepared in situ from palladium acetate and tri-*o*-tolylphosphine has significantly lower activity than that from the direct use of isolated one. Relative to the catalyst systems $Pd(OAc)_2$+ *n* phosphine (*n* = 2-6) in common practice, they offer a saving of several phosphine equivalents. The TON reached up to $2x10^5$ and $7x10^4$ for Heck and Suzuki reactions respectively.[9a, 9b] The first palladium catalyzed amination of aryl chlorides also reported using the phosphapalladcycle.[9c]

Qiao-Sheng Hu and co-workers reported ferrocene-based phosphapalladacycle for 1,4-additions of aryl boronic acids with *α,β*-unsaturated ketones and 1,2-additions of aryl boronic acids with aldehydes and *α*-ketoesters (Figure 1.4, B).[14] Then, J. P. Stambuli and co-workers reported cyclometalated tri-*tert*-butyl phosphine palladium acetate complex for amination of *ortho*-substituted aryl bromides using *o*-bromotoluene and dibutylamine (Figure 1.4, C).[15] Recently, K. H. Shaughnessy and co-workers reported di-*tert*-butylneopentylphosphine palladacycle selective cross-dimerization of terminal aryl acetylenes with terminal propargyl alcohols and amides (Figure 1.4, D).[16]

Phosphines are not only considered expensive, air sensitive but are also available in a fewer variety. The number of systematic studies of phosphapalladacycles is rather limited. This is likely due to a lack of variety of phosphines in which electronic properties can be varied in a systematic way. A formidable challenge lies in utilizing inexpensive phosphine equivalent N-based precursors for the palladacycles preparation because of their wide diversity and ready availability. In general, N-based palladacycles offer phosphine free coupling reactions and exhibit higher air and thermal stability over the conventional palladium sources. D. Milstein and co-workers reported imine based palladacycles and utilized these in Heck and Suzuki reactions (Figure 1.5).[17] Later R. Grigg and co-workers reported pyrazole and benzothiazole based palladacycles for Heck reactions (Figure 1.5).[18]



D. Milstein and co-workers imine based palladacycles



R. Grigg and co-workers palladacycles

Figure 1.5: Representative examples for N-based palladacycles

The use of biaryl phosphine as supporting ligands in palladium catalysis has played an important role in the development of synthetic methods that can be used to form C─C, C─N, C─O, and C─F bonds in a wide variety of settings. To facilitate the use of these ligands, Stephen L. Buchwald and co-workers have developed several generations of palladacyclic pre-catalysts (G1−G5, Figure 1.6).[19] These pre-catalysts can be used to promote cross-coupling reactions with high efficiency.

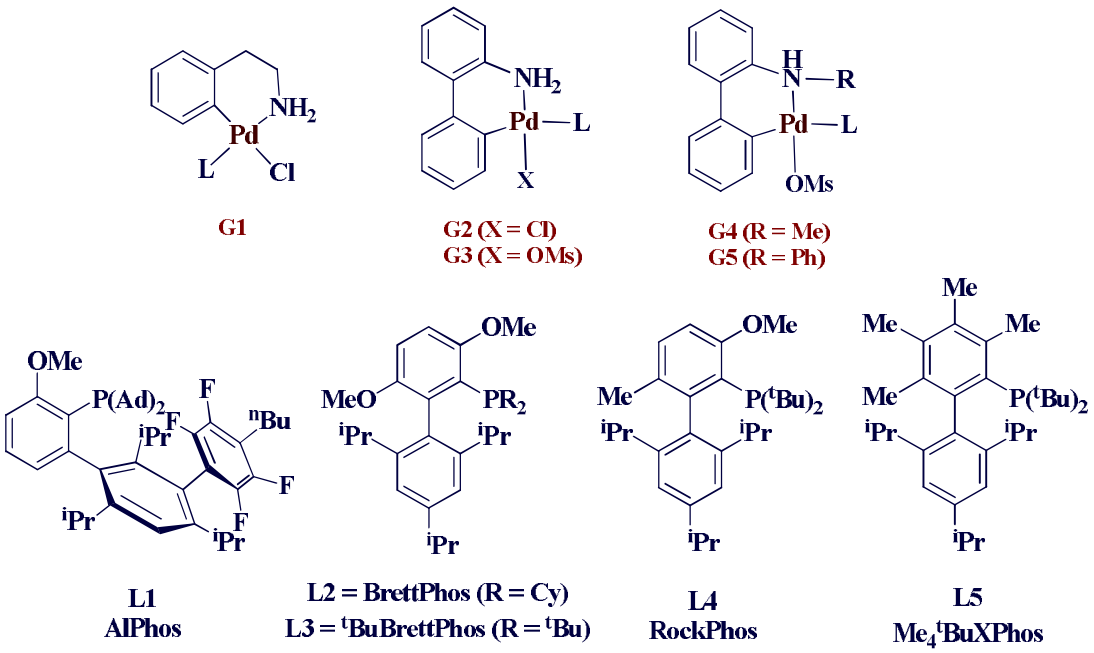


Figure 1.6: Evolution of pre-catalysts developed by the Buchwald group and selected bulky supporting ligands

As mentioned *vide supra*, the palladium or palladacycles catalysis is well studied towards cross-coupling reactions to enable C─C and C─N bond formation (Figure 1.7).[20]

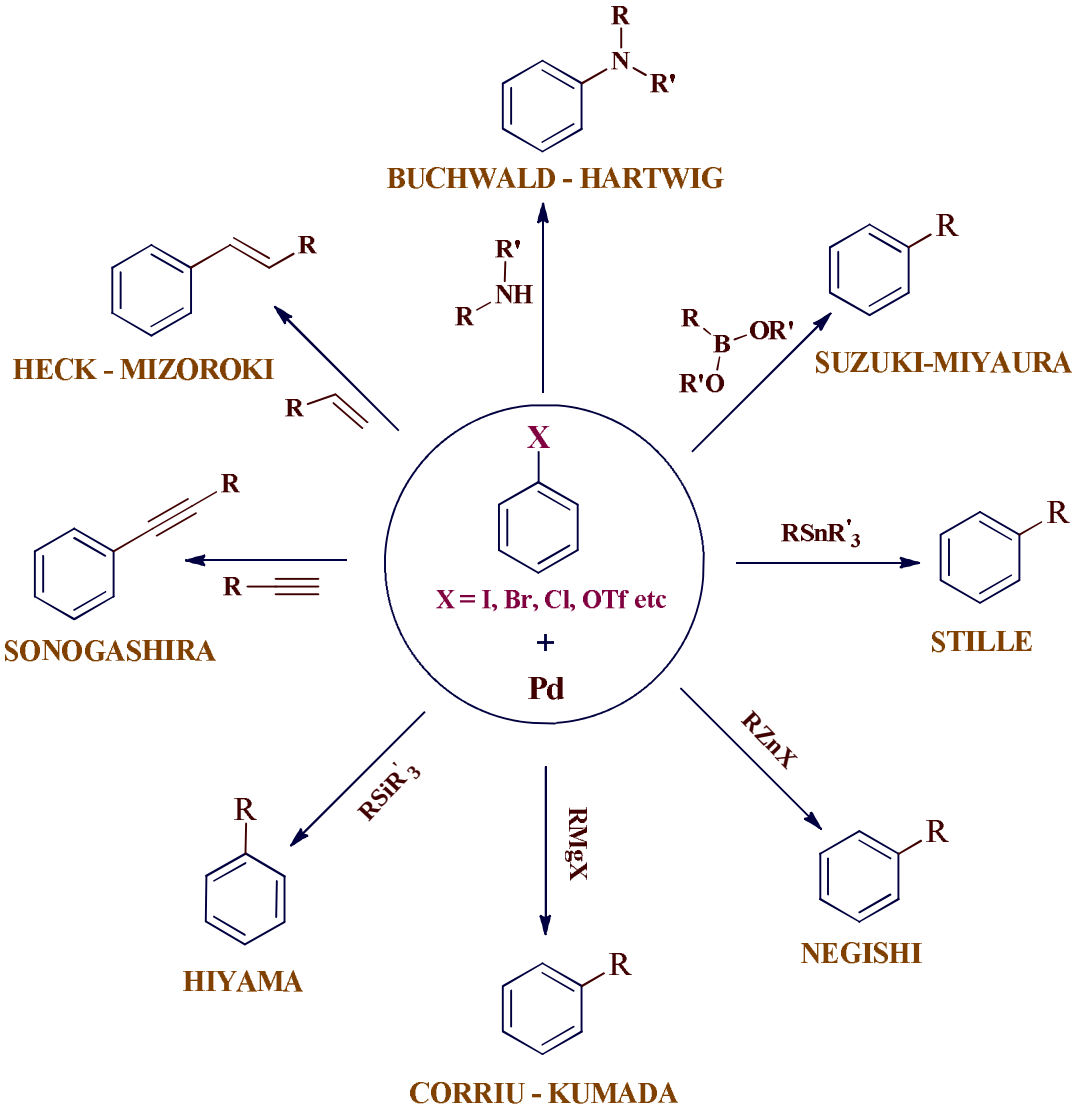
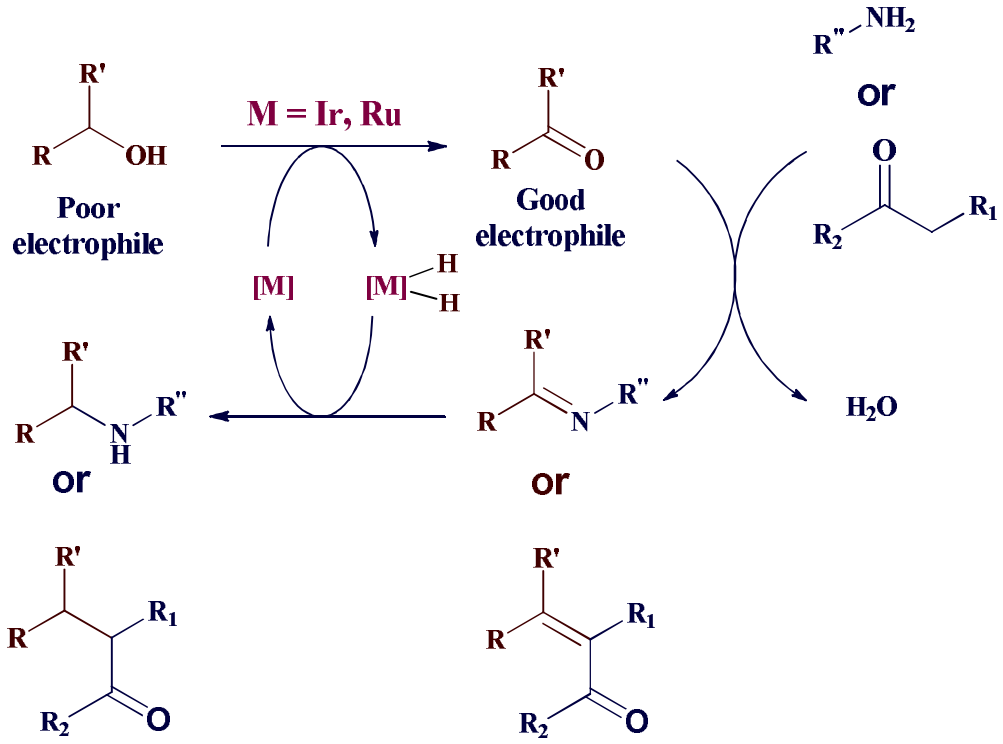


Figure 1.7: Representative examples for palladium catalyzed C─C and C─N bond formation

On the other hand, *borrowing hydrogen* methodology is of a great interest nowadays in C─C and C─N bond formation processes (Scheme 1.2).[21-40] The *borrowing hydrogen* methodology is also called *hydrogen auto-transfer* process. Due to the stability of metal hydride complexes, most metal catalysts are inactive in the *borrowing hydrogen* methodology. Ideally, the hydrogenation step is irreversible, resulting in the product. Most common catalysts used for the *borrowing hydrogen* are Ru and Ir.[30] This interest includes the use of amines and ketones with less toxic and

more readily available alcohols as the alkylating agents in a greener approach. In this method, as shown in Scheme 1.2, the inactive alcohols are converted in situ to a more reactive and highly electrophilic carbonyl intermediate by temporary removal of hydrogen toward nucleophilic addition reactions. This carbonyl compound undergoes condensation with the amine or ketone to form an imine or *α,β*-unsaturated carbonyl intermediate, which, upon catalytic hydrogenation by transferring the borrowed hydrogen, forms the final alkylated product. In this overall process, water is produced as the only by-product. Thus, the *borrowing hydrogen* methodology is probably one of the best possibilities not only from a chemical point of view but also from an economical and environmental point of view. Based on these aspects, the *borrowing hydrogen* methodology received high attention in the last years.



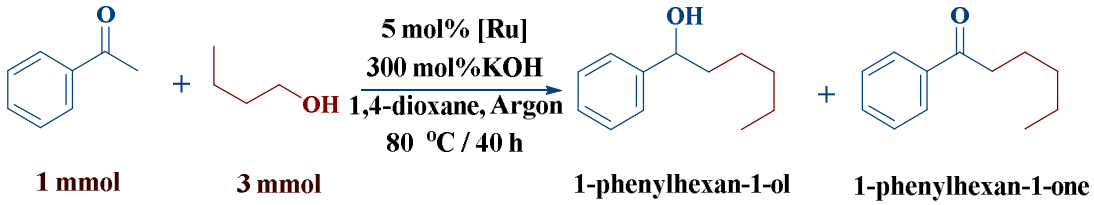
Scheme 1.2: C─C and C─N bond formation using borrowing hydrogen methodology

R. Grigg and co-workers reported the first N-alkylation of amines using alcohols catalyzed by rhodium, iridium and ruthenium based catalysts in 1981.[21] Primary and secondary alcohols effect alkylation of primary and secondary amines in the presence of rhodium, iridium, and ruthenium compounds at <100 ^{o}C, whereby selective monoalkylation of primary amines can be achieved, and heterocyclic rings can be constructed by both inter- and intra-molecular processes. The catalytic activity was found to decrease in the order $IrCl_3.H_2O$-PPh_3 > Na_2IrCl_6-PPh_3 > $RhC1_3.3H_2O$-PPh_3 > $RuC1_3.3H_2O$-PPh_3 > 5% Pd-C. 5% Rh-C did not show any catalytic activity.

Then in 1984 Yoshihisa Watanabe and co-workers reported ruthenium-catalyzed N-alkylation and N-benzylation of aminoarenes with alcohols.[22] Aminoarenes were readily converted into secondary and tertiary amines by the reaction at 150-180 ^{o}C with primary alcohols in the presence of a catalytic amount of a ruthenium complex. dichlorotris(tripheny1phosphine)ruthenium was the most effective catalyst precursor. Secondary amines were obtained in excellent yields when aminoarenes reacted with an equimolar amount of alcohols. With excess alcohols, tertiary amines were obtained predominantly. Kinetic measurements revealed that the rate had a zero-order dependence on aminoarene concentration and first-order dependence on alcohol concentration and initial concentration of the ruthenium catalyst. Again the same group, Yoshihisa Watanabe, and co-workers reported N-alkylation and N-allylation using primary alcohols catalyzed by the platinum complex.[23] Aniline reacted with ethanol in the presence of $PtCl_2(PhCN)_2$ and $SnCl_2.2H_2O$ as a catalyst to give N,N'-diethylaniline in high yield. Without $SnCl_2.2H_2O$ or with triphenylphosphine ligand, conversion of aniline was low and N-monoalkylanilines were obtained in only low yields. Aliphatic amines were also N-alkylated in high yields. The similar reaction using allylic alcohols gave N-allylated

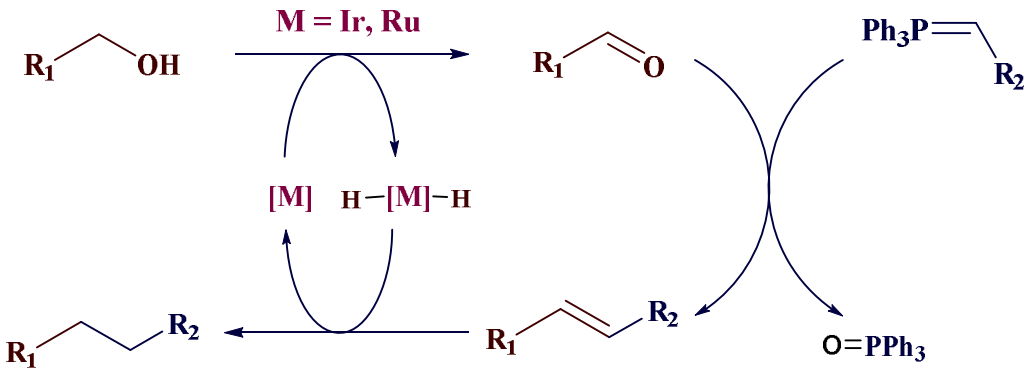
products. The catalysis based on Pt complexes is quite different from that of Ru. $RuCl_2(PPh_3)_3$ catalyzed the N-heterocyclization to give quinolines in high yields, while with Pt catalyst such an N-heterocyclization did not take place at all. In separate experiments, the present Pt catalyst system did not catalyze an isomerization of the allylic alcohols to the corresponding aldehydes, while $RuCl_2(PPh_3)_3$ did.

In 2001, C.S. Cho and co-workers reported an unusual type of ruthenium-catalyzed transfer hydrogenation of ketones with alcohols accompanied by C─C coupling.[24] The reaction of acetophenone with butanol gives rise to unconventional alkylated products, 1-phenylhexan-1-ol and 1-phenylhexan-1-one, rather than the expected direct transfer hydrogenation product, 1-phenylethanol (Scheme 1.3). The best result in terms of both overall yield and the relative amount of 1-phenylhexan-1-ol to 1-phenylhexan-1-one is best accomplished by $RuCl_2(PPh_3)_3$ under the standard set of reaction conditions.



Scheme 1.3: Ruthenium-catalyzed transfer hydrogenation of ketones with alcohols

In 2002, J.M.J. Williams and coworkers have developed a new methodology for the one-pot conversion of alcohols to alkanes by Iridium mediated catalytic electronic activation (Scheme 1.4).[25a] Then the same group showed ruthenium complexes to perform efficient transfer hydrogenation reactions between alcohols and alkenes; in combination with an in situ Wittig reaction, indirect formation of C–C bonds have been achieved from alcohols.[25b]



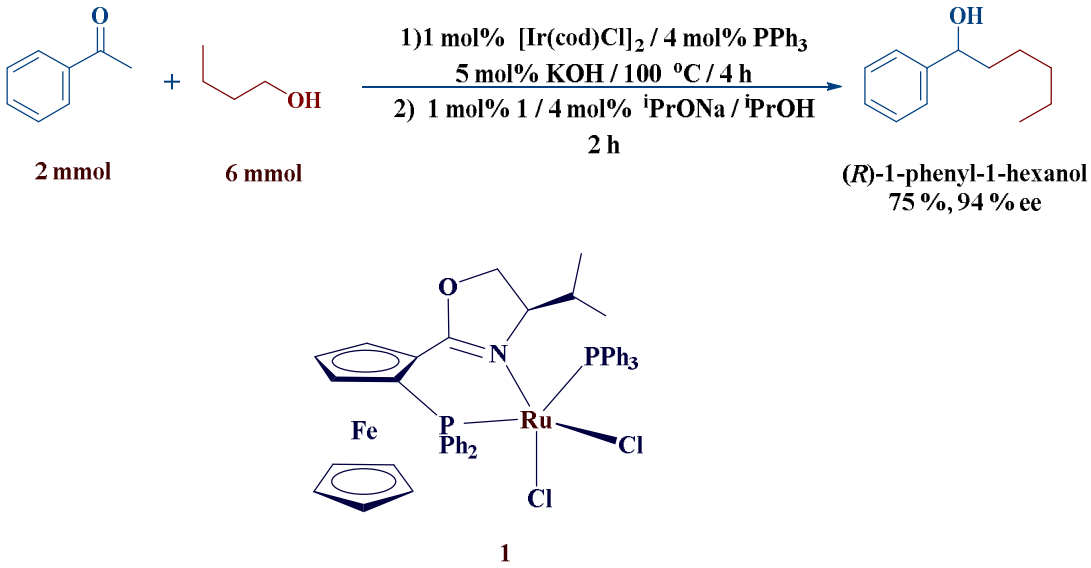
Scheme 1.4: Indirect Wittig reaction of alcohols

In 2004, Yasutaka Ishii and co-workers have developed the direct *α*-alkylation method of ketones with alcohols catalyzed by iridium complexes without any solvents.[26] This method provides a very convenient route to aliphatic ketones to which a carbonyl function can be introduced into the desired position by selecting the ketones and alcohols employed. They have found that the selective *α*-alkylation of ketones with alcohols is achieved under the influence of catalytic amounts of $[Ir(cod)Cl]_2$ and a base such as KOH without any solvent to give *α*-alkylated ketones in good yields. This method provides a novel route to *α*-alkylated ketones from ketones and alcohols without formation of any waste.

In 2005, Miguel Yus and co-workers have developed the electrophilic *α*-alkylation of ketones with alcohols was accomplished by a $[Ru(DMSO)_4]Cl_2$ catalyzed process.[27] The reaction can be successfully governed to produce either the expected ketones or their related alcohols only by changing the reaction conditions. When 2-aminobenzyl alcohol was used, a cyclization process took place to yield 2,3-disubstituted quinolines.

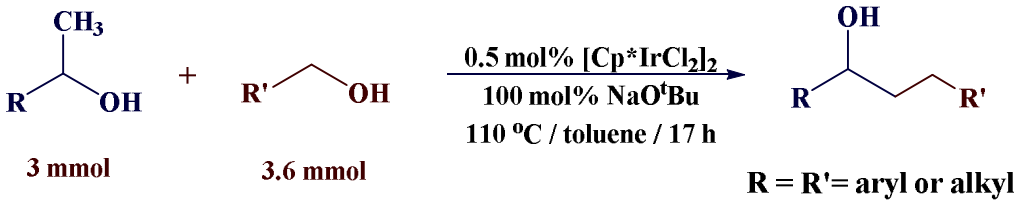
In 2006, Yoshiaki Nishibayashi and co-workers have disclosed that asymmetric *α*-alkylative reduction of prochiral ketones with primary alcohols catalyzed by both iridium and ruthenium complexes gave the corresponding optically

active alcohols with the elongation of the carbon skeleton and with a high enantio-selectivity (Scheme 1.5).[28] The compatibility between iridium and ruthenium complexes is an essential factor in directly obtaining optically active alcohols with elongation of the carbon skeleton.



Scheme 1.5: Asymmetric *α*-alkylative reduction of a ketone with an alcohol catalyzed by iridium and ruthenium

In 2005, Ryohei Yamaguchi and co-workers have shown a new efficient system for the *β*-alkylation of secondary alcohols with primary alcohols catalyzed by a Cp*Ir complex (Scheme 1.6).[29] Moreover, the present system requires an extra addition of neither hydrogen acceptor nor donor. In addition, almost equimolar amount of substrates are sufficient to obtain good yields of products. After that several groups reported C─C and C─N bond formations using *borrowing hydrogen* method.[30]



Scheme 1.6: *β*-alkylation of secondary alcohols with primary alcohols

Although number of progress has been made using Ru[31] and Ir[32] metal complexes, numerous other metal catalyzed N-alkylation of amines or C-alkylation of ketones using alcohols are also reported.[33–40]

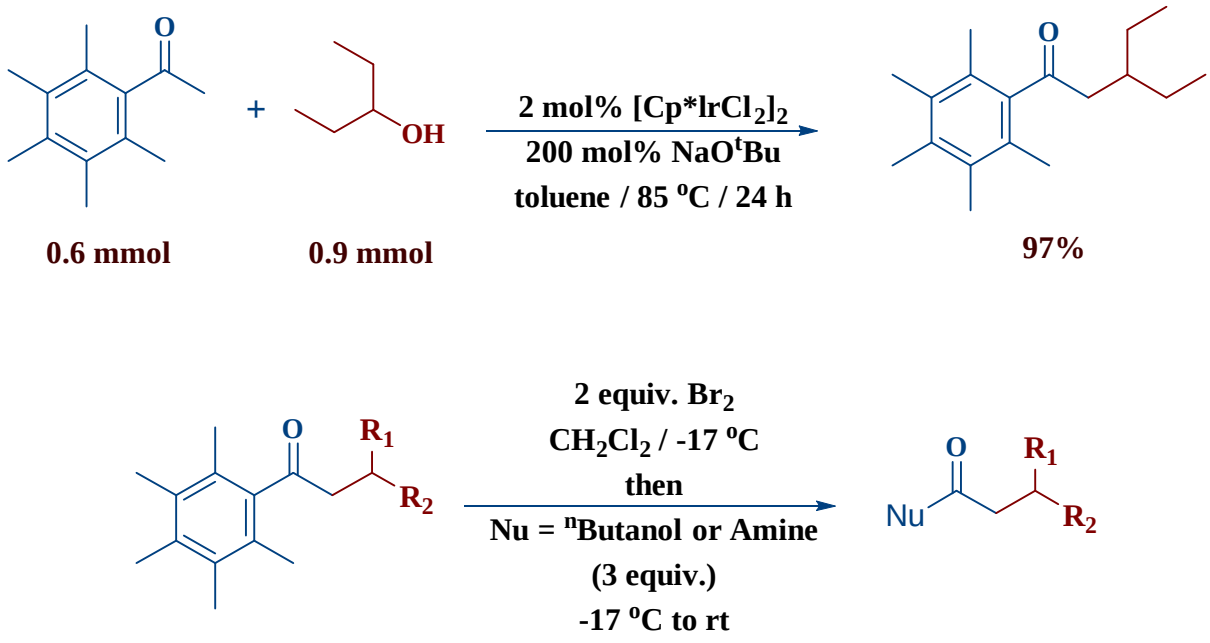
Recently Frank Glorius and co-workers have developed a Ru(II)-NHC catalyzed practical and scalable *α*-alkylation of methylene ketones with primary alcohols to give rise to a variety of branched ketones. In general, good to excellent yields of the *α*-branched products were obtained either without or with only a minimal excess of the alcohol substrate. This protocol significantly broadens the scope of borrowing hydrogen catalysis in alkylation reactions, enabling the access to the useful drug donepezil in a single synthetic step. Furthermore they exploited the inherent reactivity of methyl *vs* methylene ketones to accomplish the double alkylation of methyl ketones in a one-pot procedure with a single catalyst.[31c]

James M. Takacs and co-workers demonstrated that a new ruthenium complex catalyzes the amination of primary and secondary alcohols and the regioselective mono- and sequential diamination of diols via the *borrowing hydrogen* pathway. Several variations on new intra and intermolecular cyclizations of amino alcohols, diols, and diamines lead to heterocyclic ring systems.[31i]

Travis J. Williams and co-workers reported a (pyridyl)phosphine-ligated ruthenium(II) catalyst for the chemoselective benzylic N-alkylation of amines, *via* a hydrogen-borrowing mechanism. The catalyst operates under mild conditions, neat,

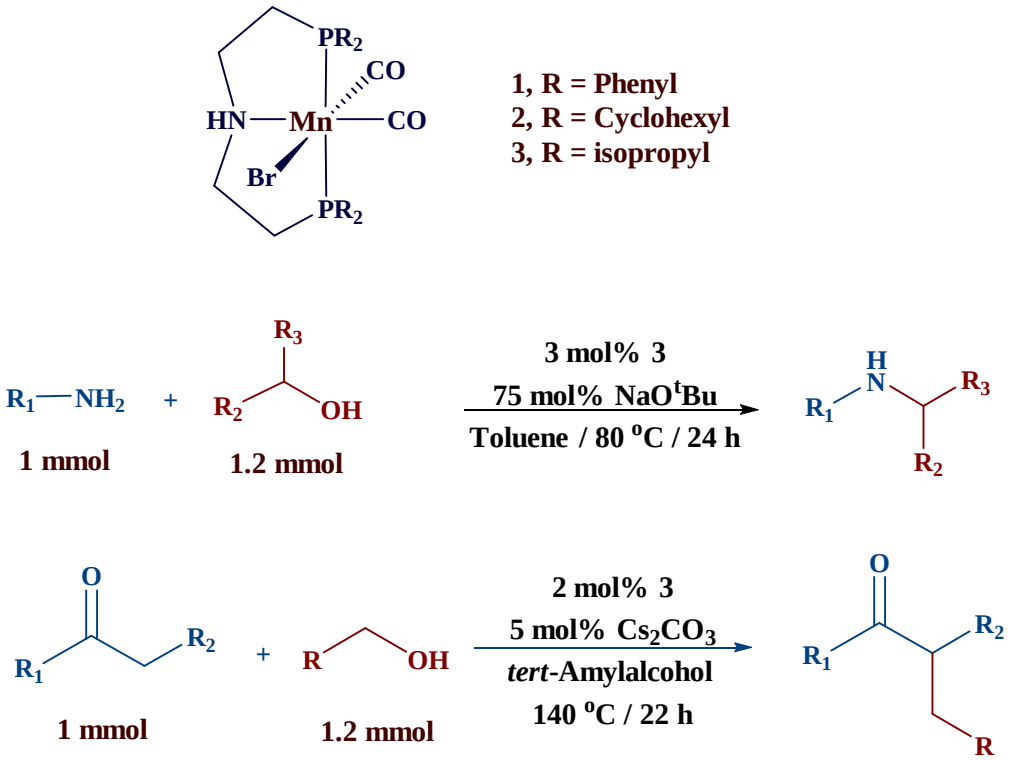
and without a base or other additive. These conditions offer remarkable functional group compatibility for applications in organic synthesis, including reactions involving phenols and anilines, which are very difficult to achieve.[31j]

Timothy J. Donohoe and co-workers recently reported *borrowing hydrogen* with secondary alcohols for the first time. They have shown that enolate alkylation using secondary alcohols can be achieved under *borrowing hydrogen* conditions to provide a number of *β*-branched products. The use of Ph* as a design element was crucial to the success of this methodology, preventing self-condensation of aryl ketone. Slow oxidation of the secondary alcohol coupling partner under the catalytic conditions then enabled the formation of the desired cross-coupled products. Finally, the Ph* group was readily cleaved to provide a series of *β*- branched esters and amides (Scheme 1.7).[32e]



Scheme 1.7: *Borrowing hydrogen* with secondary alcohols

Matthias Beller and co-workers developed the use of earth-abundant and cheap non-noble metal catalysts for this process. They showed that the selective N-alkylation of amines with alcohols can be catalyzed by defined PNP manganese pincer complexes. A variety of substituted anilines are monoalkylated with different (hetero)aromatic and aliphatic alcohols. The catalyst was also active for the chemoselective monomethylation of primary amines using methanol under mild conditions.[39b] The same group has developed the first manganese catalyzed alkylation of ketones and related compounds with primary alcohols. This straightforward transformation takes place with an air- and water-stable manganese(I) PNP pincer pre-catalyst. A low base concentration and broad applicability are notable features of this *borrowing hydrogen* methodology (Scheme 1.8).[39a]



Scheme 1.8: *Borrowing hydrogen* catalyzed by PNP manganese pincer complexes

1.2 References:

1. J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.,* 2005, **105**, 2527.
2. (a) A. C. Cope and Siekman, *J. Am. Chem. Soc*., 1965, **87**, 3272. (b) A. C. Cope and E. C. Friedrich, *J. Am. Chem. Soc*., 1968, **90**, 909.
3. J. P. Kleiman and M. Dubeck, *J. Am. Chem. Soc.,* 1963, **85**, 1544.
4. (a) V. Farina, *Adv. Synth. Catal*., 2004, **346**, 1553; (b) M. Micksch, M. Tenne and T. Strassner, *Organometallics*, 2014, **33**, 3966.
5. (a) M. Nonoyama, *Transition Met. Chem.*, 1982, **7**, 281; (b) B. J. Burke and L. E. Overman, *J. Am. Chem. Soc.,* 2004, **126**, 16820; (c) J. M. Chitanda, D. E. Prokopchuk, J. W. Quail and S. R. Foley, *Dalton Trans.,* 2008, 6023; (d) S. E. Bajwa, T. E. Storr, L. E. Hatcher, T. J. Williams, C. G. Baumann, A. C. Whitwood, D. R. Allan, S. J. Teat, P. R. Raithby and I. J. S. Fairlamb, *Chem. Sci.,* 2012, **3**, 1656.
6. (a) J. Singh, D. Kumar, N. Singh, and A. J. Elias, *Organometallics*, 2014, **33**, 1044; (b) R. F. Pedreño, E. G. Sánchez, M. J. O. Madrid, D. Bautista, E. M. Viviente, I. S. Llamas, and J. Vicente, *Inorg. Chem*., 2016, **55**, 5520.
7. (a) J. Albert, J. Granell, and J. Sales, *Organometallics*, 1986, **5**, 2568; (b) J. Albert, R. M. Ceder, M. Gomez, J. Granell, J. Sales, *Organometallics*, 1992, **11**, 1536; (c) M. Gomez, J. Granell, and M. Martinez, *Organometallics,* 1997, **16**, 2539; (d) H. Qian, Z. Yin, T. Zhang, S. Yan, Q. Wang and C. Zhang, *Organometallics*, 2014, **33**, 6241.
8. (a) O. N. Gorunova, K. J. Keuseman, B. M. Goebel, N. A. Kataeva, A. V. Churakov, L. G. Kuzmina, V. V. Dunina, and I. P. Smoliakova, *J. Organomet. Chem.*, 2004, **689**, 2382; (b) K. J. Keuseman and I. P. Smoliakova,

Organometallics, 2005, **24**, 4159; (c) A. Mercier, S. Wagschal, L. Guenee, C. Besnard and E. P. Kundig, *Organometallics*, 2013, **32**, 3932.

9. (a) W. A. Herrmann, C. Brossmer, K. O¨fele, C. P. Reisinger, T. Priermeier, M. Beller and H. Fischer, *Angew. Chem. Int. Ed.*, 1995, **34**, 1844; (b) M. Beller, H. Fischer, W. A. Herrmann, K. Öfele and C. Brossmer, *Angew. Chem. Int. Ed.,* 1995, **34**, 1848; (c) M. Beller, T. H. Riermeier, C. P. Reisinger and W. A. Herrmann, *Tetrahedron Lett*., 1997, **38**, 2073.

10. I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009.

11. N. Miyaura and A. Suzuki, *Chem. Rev*., 1995, **95**,2457.

12. P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.,* 2016, **116**, 12564.

13. C. Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 5062.

14. P. He, Y. Lu, C. G. Dong and Q. S. Hu, *Org. Lett.*, 2007, **9**, 343.

15. W. H. Henderson, J. M. Alvarez, C. C. Eichman and J. P. Stambuli, *Organometallics*, 2011, **30**, 5038.

16. M. G. Lauer, B. R. Headford, O. M. Gobble, M. B. Weyhaupt, D. L. Gerlach†., M. Zeller, and K. H. Shaughnessy, *ACS Catal.,* 2016, **6**, 5834.

17. (a) M. Ohff, A. Ohff and D. Milstein, *Chem. Commun.*, 1999, 357; (b) H. Weissman and D. Milstein, *Chem. Commun.*, 1999, 1901.

18. X. Gai, R. Grigg, M. I. Ramzan, V. Sridharan, S. Collard and J. E. Muir, *Chem. Commun.,* 2000, 2053.

19. (a) M. R. Biscoe, B. P. Fors and S. L. Buchwald, *J. Am. Chem. Soc.,* 2008, **130**, 6686; (b) R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461; (c) N. C. Bruno, M. T. Tudge and S. L. Buchwald, *Chem. Sci.*, 2013, **4**, 916; (d) B. T. Ingoglia and S. L. Buchwald, *Org. Lett.,* 2017, **19**, 2853.

20. (a) J. deVries, Palladium-Catalyzed Coupling Reactions. In *Top. Organomet. Chem.*, Springer Berlin Heidelberg: (2012); Vol. 42, pp 1-34; (b) C. C. C. Johansson Seechurn.; T. J. Colacot., Chapter 3. Pd-Phosphine Pre-catalysts for Modern Cross-Coupling Reactions. In *New Trends in Cross-Coupling: Theory and Applications*, The Royal Society of Chemistry: p 91; (c) C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 5062; (d) N. T. S. Phan, M. VanDerSluys and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 609; (e) W. J. Sommer, K. Yu, J. S. Sears, Y. Ji, X. Zheng, R. J. Davis, C. D. Sherrill, C. W. Jones and M. Weck, *Organometallics*, 2005, **24**, 4351.

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

22. Y. Watanabe, Y. Tsuji, H. Ige, Y. Ohsugi and T. Ohta, *J. Org. Chem.*, 1984, **49**, 3359.

23. Y. Tsuji, R. Takeuchi, H. Ogawa, and Y. Watanabe, *Chem. Lett.*, 1986, 293.

24. C. S. Cho, B. T. Kim, T. J. Kim and S. C. Shim, *J. Org. Chem.*, 2001, **66**, 9020.

25. (a) M. G. Edwards and J. M. J. Williams, *Angew. Chem. Int. Ed.*, 2002, **41**, 4740; (b) M. G. Edwards, R. F. R. Jazzar, B. M. Paine, D. J. Shermer, M. K. Whittlesey, J. M. J. Williams and D. D. Edney, *Chem. Commun.*, 2004, 90.

26. K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 72.

27. R. Martınez, G. J. Brand, D. J. Ramon and M. Yus, *Tetrahedron Lett.*, 2005, **46**, 3683.

28. G. Onodera, Y. Nishibayashi and S. Uemora, *Angew. Chem., Int. Ed.*, 2006, **45**, 3819.

29. K.-i. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka and R. Yamaguchi, *Org. Lett.*, 2005, **7**, 4017.

30. Selected reviews for hydrogen borrowing C─C and C─N bond formation; (a) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555; (b) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (c) Q.Yang, Q.Wang and Z. Yu, *Chem. Soc. Rev.*, 2015, **44**, 2305; (d) F. Huang, Z. Liu, and Z. Yu, *Angew. Chem. Int. Ed.*, 2016, **55**, 862.

31. Ruthenium: *(i)* Selected examples for *α*-Alkylation of ketones; (a) R. Martínez, G. J. Brand, D. J. Ramón, and M. Yus, *Tetrahedron Lett.*, 2005, **46**, 3683; (b) T. Kuwahara, T. Fukuyama, and I. Ryu, *Org. Lett.*, 2012, **14**, 4703; (c) C. Schlepphorst, B. Maji, and F. Glorius, *ACS Catal.*, 2016, **6**, 4184; (d) G. Chelucci, *Coord. Chem. Rev.*, 2017, **331**, 1; (ii) Selected examples for N-Alkylation of amines; (e) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131,** 1766; (f) D. Weickmann, W. Frey and B. Plietker, *Chem. Eur. J.*, 2013, **19**, 2741; (g) S. Pei Shan, T. T. Dang, A. M. Seayad and B. Ramalingam, *ChemCatChem*, 2014, **6**, 808; (h) L. M. Broomfield, Y. Wu, E. Martin and A. Shafir, *Adv. Synth. Catal.*, 2015, **357**, 3538; (i) K. O. Marichev and J. M. Takacs, *ACS Catal.*, 2016, **6**, 2205; (j) J. J. A. Celaje, X. Zhang, F. Zhang, L. Kam, J. R. Herron, and T. J. Williams, *ACS Catal.*, 2017, **7**, 1136.

32. Iridium: (i) Selected examples for *α*-Alkylation of ketones; (a) Y. Obora and Y. Ishii, *Synlett.*, 2011, 30; (b) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825; (c) F. Li, J. Ma, and N. Wang, *J. Org. Chem.*, 2014, **79**, 10447; (d) P. Liu, R. Liang,

L. Lu, Z. Yu, and F. Li, *J. Org. Chem.*, 2017, **82**, 1943; (e) W. M. Akhtar, C. B. Cheong, J. R. Frost, K. E. Christensen, N. G. Stevenson, and T. J. Donohoe, *J. Am. Chem. Soc.*, 2017, **139**, 2577; (ii) Selected examples for N-Alkylation of amines; (f) R. Kawahara, K.-i. Fujita and R. Yamaguchi, *Adv. Synth. Catal.*, 2011, *353*, 1161; (g) I. Cumpstey, S. Agrawal, K. E. Borbas and B. Martin-Matute, *Chem. Commun.*, 2011, **47**, 7827; (h) A. Bartoszewicz, R. Marcos, S. Sahoo, A. K. Inge, X. Zou and B. Martín-Matute, *Chem. Eur. J.*, 2012, **18**, 14510; (i) Y.-H. Chang, Y. Nakajima and F. Ozawa, *Organometallics*, 2013, **32**, 2210; (j) X. Jiang, W. Tang, D. Xue, J. Xiao and C. Wang, *ACS Catal.*, 2017, **7**, 1831; (k) C. Wanga and J. Xiao, *Chem. Commun.*, 2017, **53**, 3399.

33. **Rhodium:** P. Satyanarayana, G. M. Reddy, H. Maheswaran, and M. L. Kantam, *Adv. Synth. Catal.*, 2013, **355**, 1859.
34. **Rhenium:** P. Piehl, M. Pena-Lopez, A. Frey, H. Neumann and M. Beller, *Chem. Commun.*, 2017, **53**, 3265.
35. **Palladium:** (a) A. Martínez-Asencio, M. Yus and D. J. Ramón, *Synthesis*, 2011, **2011**, 3730; (b) T. T. Dang, B. Ramalingam, S. P. Shan and A. M. Seayad, *ACS Catal.*, 2013, **3,** 2536; (c) R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Tetrahedron*, 2017, **73**, 2225.
36. **Cobalt:** (a) G. Zhang, Z. Yin and S. Zheng, *Org. Lett.*, 2016, **18**, 300; (b) G. Zhang, J. Wu, H. Zeng, S. Zhang, Z. Yin, and S. Zheng, *Org. Lett.*, 2017, **19**, 1080.
37. **Iron:** (a) S. Elangovan, J.-B. Sortais, M. Beller, and C. Darcel, *Angew. Chem. Int. Ed.*, 2015, **54**, 14483; (b) M. Mastalir, B. Stoger, E. Pittenauer, M. Puchberger, G. Allmaier, and K. Kirchner, *Adv. Synth. Catal.*, 2016, **358**, 3824.

38. Osmium: M. L. Buil, M. A. Esteruelas, J. Herrero, S. Izquierdo, I. M. Pastor, and M. Yus, *ACS Catal.*, 2013, **3**, 2072.

39. Manganese: (a) M. Pena-Lopez, P. Piehl, S. Elangovan, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2016, **55**, 14967; (b) S. Elangovan, J. Neumann, J. B. Sortais, K. Junge, C. Darcel, M. Beller, *Nat. Commun*., 2016, **7**, 12641.

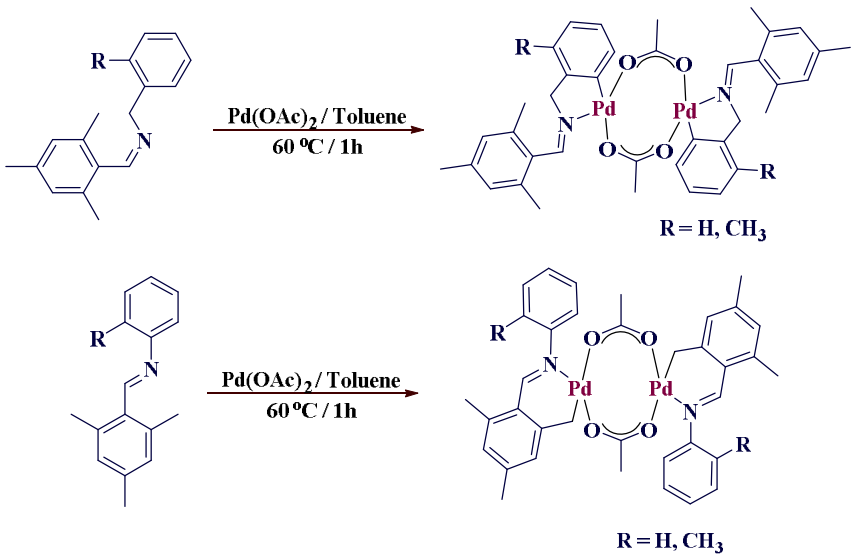
40. Copper: (a) X. Cui, F. Shi, M. K. Tse, D. Go¨rdes, K. Thurow, M. Beller, and Y. Deng, *Adv. Synth. Catal.*, 2009, **351**, 2949; (b) A. Martinez-Asencio, D. J. Ramon and M. Yus, *Tetrahedron*, 2011, **67**, 3140; (c) S. Liao, K. Yu, Q. Li, H. Tian, Z. Zhang, X. Yu and Q. Xu, *Org. Biomol. Chem.*, 2012, **10**, 2973; (d) F. Li, H. Shan, Q. Kang and L. Chen, *Chem. Commun.*, 2011, **47**, 5058; (b) Z. Xu, D. -S. Wang, X. Yu, Y. Yang, and D. Wang, *DOI*: 10.1002/adsc.201700179.

Design and synthesis of pyrazole based palladacyles *via* C─H activation

2.1 Introduction

Intramolecular activation of aromatic C─H bonds of coordinated ligands by transition metals and the resulting cyclometallates represent an active area of research in the context of regiospecific organic and organometallic synthesis. The rigid nature and the strong coordination ability of the ligands make their complexes robust and less sensitive to air and moisture. In recent years, N-based ligands have attracted lot of attention for the design and synthesis of new metallacycles especially palladacycles. As a consequence, a vast literature on cyclopalladated complexes with various ligands that undergo palladation is available.[1] Among the several available methods for the preparation of palladacycles, *ortho*-palladation or chelation assisted palladation of C─H bonds is an attractive methodology.[2] Although C─H bond activation has been thoroughly studied, the recognition of chemically similar C─H bonds has turned out to be an arduous task. Different approaches have been identified to achieve C─H bond activation of chemically similar environment. In many instances the regio-isomers have been isolated and structurally characterized.

In 1997, Manuel Martinez and co-workers reported cyclopalladation reactions of benzylidenebenzylamines, anilines, and propylamine with palladium acetate.[3] The cyclometalated compounds were formed *via* C─H electrophilic bond activation to produce different types of palladacycles, depending upon the polyfunctional nature of the ligand selected. In one case a five-membered *endo* metallacycle was formed via aromatic C─H bond activation (Scheme 2.1, top). In the other instance the activation of aliphatic C─H bond has been achieved to form *endo* six-membered metallacycle (Scheme 2.1, bottom).



Scheme 2.1: Regioselectivity in cyclopalladation of benzylideneamines

In 2004, Irina P. Smoliakova and co-workers reported oxazoline based palladacycles bearing an *endo*- or *exo*-C─N bond by direct *ortho*-palladation of *(R)*-2,4-diphenyl- or *(R)*-2-methyl-4-phenyl-2-oxazolines.[4a] Again in 2005, the same group reported cyclopalladation of *(S)*-4-*tert*-butyl-2-methyl-2-oxazoline at the nonactivated *tert*-butyl group using palladium(II) acetate in acetic acid to afford an oxazoline-derived *exo*-palladacycle with an (sp^3)C─Pd bond (Figure 2.0).[4b]

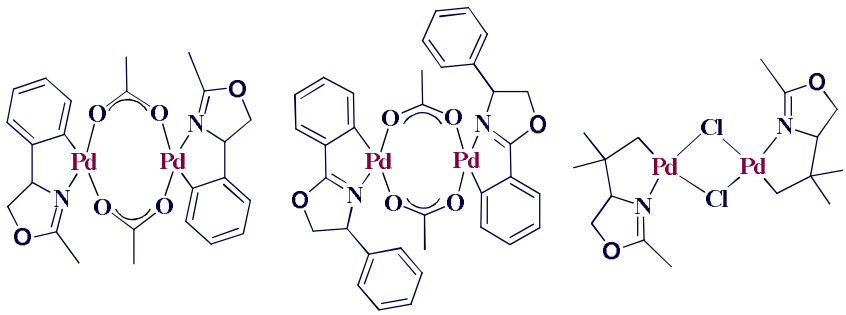
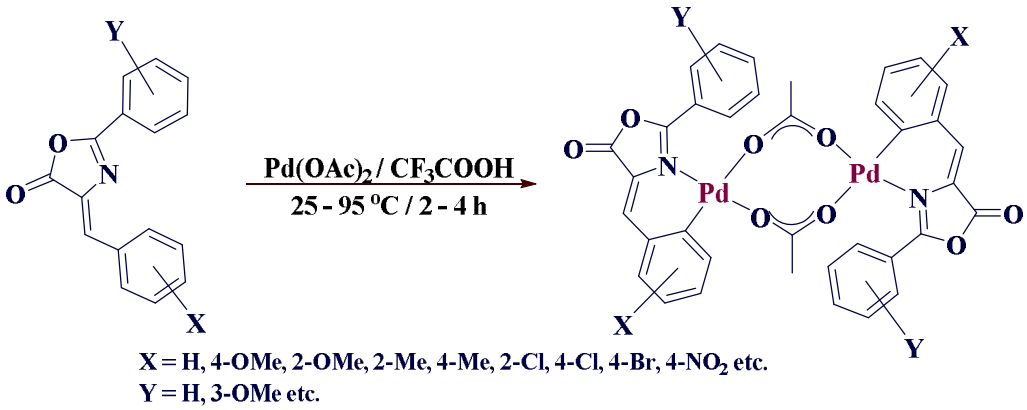


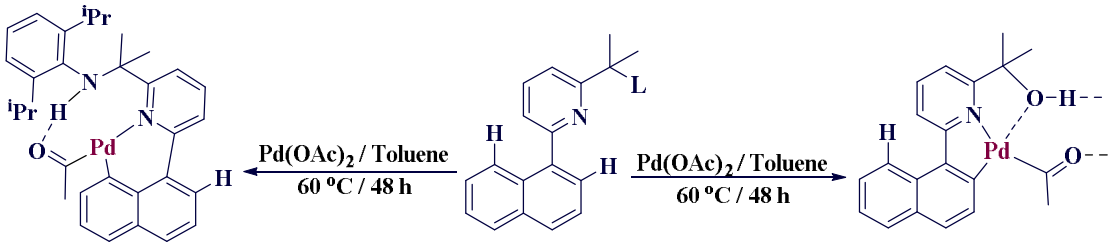
Figure 2.0: Regioselectivity in oxazoline based palladacycles

In 2011, Esteban P. Urriolabeitia and co-workers described orthopalladated complexes derived from (Z)-2-aryl-4-arylidene-5(4H)-oxazolones.[5] The reaction of the oxazolone with palladium acetate activated the *ortho* C─H bond of the arylidene ring to produce regioselectively a six-membered ring over five-membered ring (Scheme 2.2).



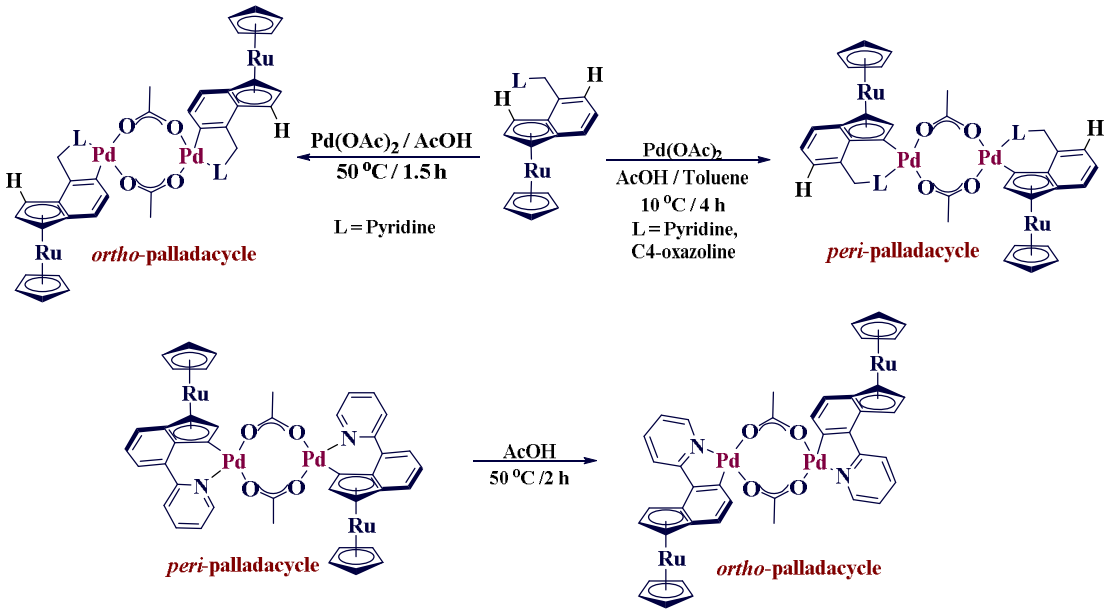
Scheme 2.2: Orthopalladated complexes derived from (Z)-2- aryl-4-arylidene-5(4H)-oxazolones

In 2013, Gregory A. Solan and co-workers demonstrated the preferential palladation of naphthalene ring using N-donors as directing ligands (Scheme 2.3).[6] Different chelates were used to control the regioselectivity of palladation at the *peri*- or *ortho*-position to naphthyl ring.



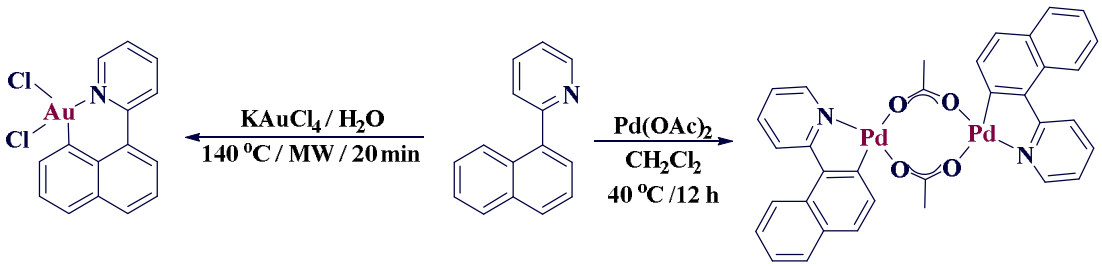
Scheme 2.3: Palladation of naphthalene ring using N-donors as directing ligands

In mid of 2013, E. Peter Kündig and co-workers investigated the cyclopalladation of planar chiral pyridine and oxazoline derivatives (Scheme 2.4).[7] The challenge associated with the presence of two nonequivalent metalation sites was successfully overcomed by an appropriate adjustment of the reaction conditions, enabling the access to both six (*peri*)- and five-membered (*ortho*) chelates. A *peri* → *ortho* isomerization was identified in the pyridine-based system.



Scheme 2.4: Cyclopalladation of planar chiral pyridine and oxazoline derivatives

Recently, Wendt and co-workers reported metal controlled regio-selectivity in the directed aromatic substitution of 2-(1-naphthyl)-pyridine.[8] They have found that cyclometalation of the 2-(1-naphthyl)-pyridine with gold and palladium precursors proceeds with completely different regioselectivities, cyclopalladation results in a five-membered metallacycle, cycloauration displays a completely orthogonal regioselectivity, resulting in the sixmembered ring analogue (Scheme 2.5).

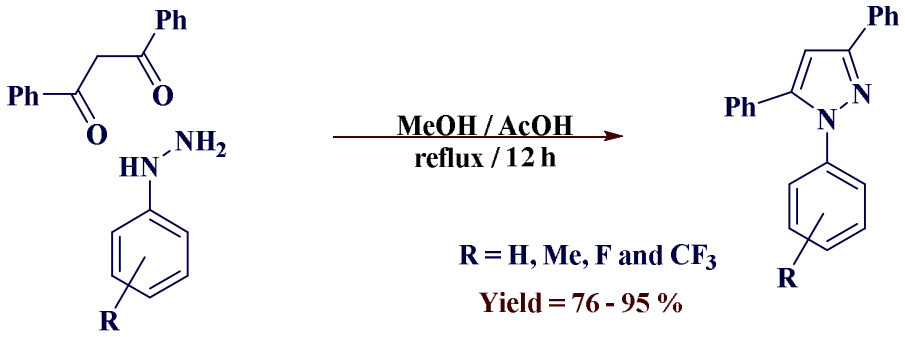


Scheme 2.5: Metal controlled regio-selectivity in 2-(1-naphthyl)-pyridine

To the best of our knowledge the regioselectivity in cyclopalladation have not been studied by changing the electronic effect. In order to examine this, we chose 1,3,5-triphenylpyrazoles as the potential ligand system which have two C─H bonds in closer proximity with directing basic nitrogen, and investigated the cyclopalladation by tuning electronic properties on the N-phenyl ring of the pyrazole.

2.2 Results and discussions

The pyrazole ligands were readily synthesized by the condensation of commercially available 1,3-diphenylpropane-1,3-dione and corresponding phenylhydrazines in mixture of acetic acid and methanol under reflux condition (Scheme 2.6). This method produced the products 1,3,5-triphenyl pyrazole, 3,5-diphenyl-1-(*m*-tolyl)-1H-pyrazole and 1-(3-fluorophenyl)-3,5-diphenyl-1H-pyrazole in 86%, 79% and 84% isolated yields, respectively. These ligands were fully characterized using standard analytical techniques like ^{1}H, ^{13}C, ^{19}F NMR, and HRMS. Next, typical cyclopalladation reaction in acetic acid was carried out to get the acetate bridged dimeric complexes (Scheme 2.7).



Scheme 2.6: Synthesis of 1,3,5-triphenylpyrazoles

The ligand, 1,3,5-triphenylpyrazole is a versatile heterocyclic compound which is having three phenyl rings on pyrazole core. Among the three phenyl rings, two phenyl rings are in close proximity of the free N-atom of the pyrazole. There are three possibilities for the C─H bond activation mentioned as type-I, type-II and type-III (Scheme 2.7). Under the typical reaction conditions the C─H bond activation preceded on the N-phenyl of the pyrazole (Type-I, palladacycle-**1** to palladacycle-**3**). We observed clean type-I C─H bond activated palladacycles with moderate yields 59% (palladacycle-**1**), 64% (palladacycle-**2**) and 74% (palladacycle-**3**)). The palladacycles are characterized by NMR, LCMS and elemental analysis.

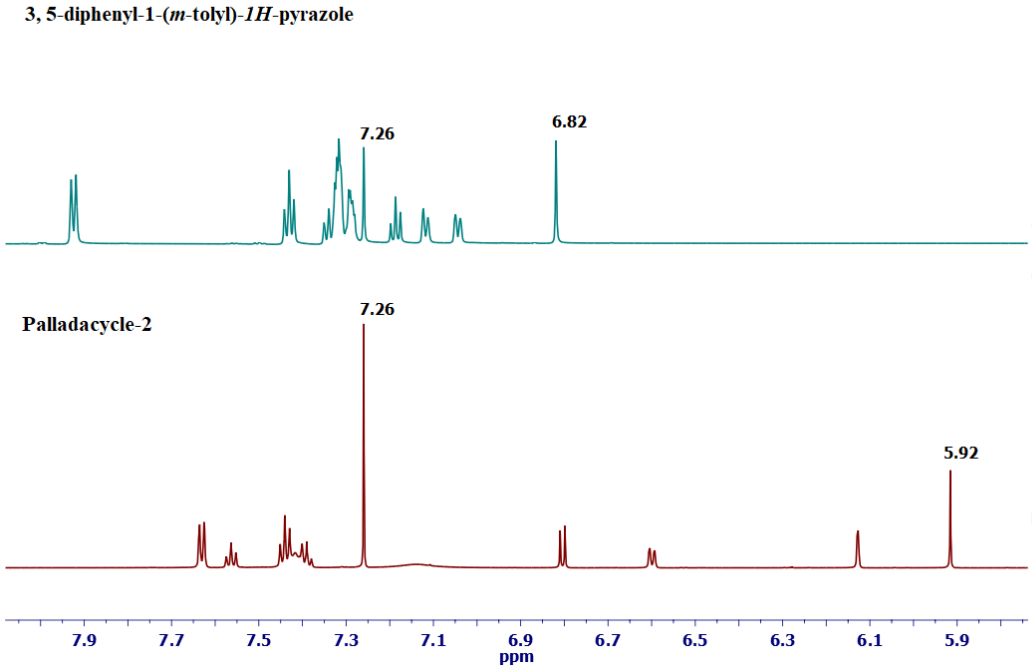
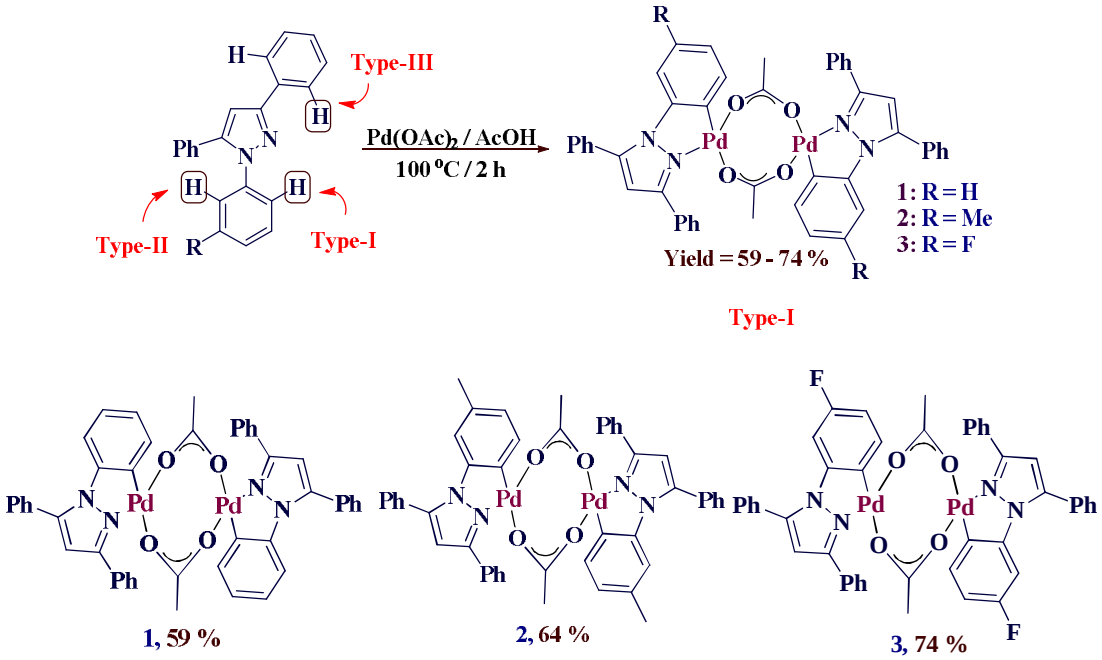


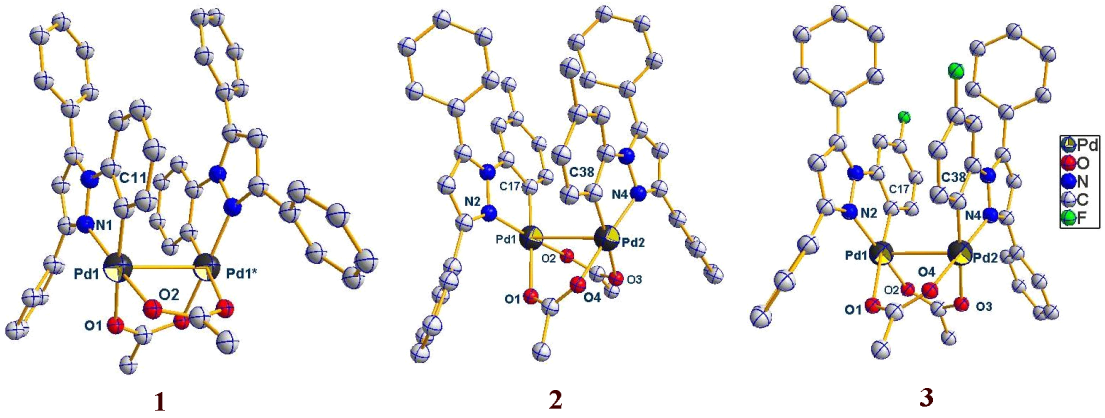
Figure 2.1: ^{1}H NMR spectra for 3, 5-diphenyl-1-(*m*-tolyl)-1H-pyrazole and palladacycle-**2**

The NMR showed distinct peaks for pyrazoles and their corresponding palladacycles. A representative ^{1}H NMR in $CDCl_3$ for 3,5-diphenyl-1-(*m*-tolyl)-1H-pyrazole and its corresponding palladacycle-**2** is shown in figure 2.1. The pyrazole hydrogen resonates at 6.82 ppm for the 3, 5-diphenyl-1-(*m*-tolyl)-1H-pyrazole whereas for the corresponding palladacycle-**2** it resonates at 5.92 ppm.



Scheme 2.7: Cyclopalladation of 1,3,5-triphenylpyrazoles

The molecular structures of the palladacycles were further confirmed by using single crystal X-ray analysis. Palladacycle-**1** crystallizes in the monoclinic space group C2/c, whereas palladacycle-**2** and palladacycle-**3** crystallizes in the triclinic, P-1 and orthorhombic, Pca2 respectively (Table 2.1). X-ray analysis reveals that all palladacycles-**1** to **3** are dimeric in nature, bridged together by acetates with the pyrazole ligands aligned in a staggered fashion (Figure 2.2). The geometry around the palladium atoms exhibits a distorted square planar geometry.



1 **2** **3**

Figure 2.2: Molecular structures of palladacycles **1**, **2** and **3**. Hydrogen atoms are omitted for clarity

The Pd─C (1.9518(27) Å for **1**; 1.961 (28) Å for **2**; 1.9419 (56) Å for **3**) and Pd─N (2.0175(17) Å for **1**; 2.0248(26) Å for **2**; 2.0151 (55) Å for **3**) distances are comparable with reported cyclometalated palladium compounds (Table 2.0).[9] The Pd─C distance in palladacycle-**3** is shorter than the corresponding distance in palladacycle-**1** and palladacycle-**2**. However, the Pd…Pd distance in palladacycle-**3** (2.8532(5) Å) is slightly shorter than the Pd…Pd distance observed in palladacycle-**1** (2.9365(3) Å) and palladacycle-**2** (2.8829(5) Å).

Table 2.0: Selected bond distances and bond angles for palladacycles 1, 2 and 3

	Palladacycle-**1**
Pd1─Pd1* (Å)	2.937(3)
Pd1─C11 (Å)	1.952(3)
Pd1─N1 (Å)	2.018(2)
Pd1─O1 (Å)	2.044(2)
Pd1─O2 (Å)	2.144(2)

C11─Pd1─N1 (°)	80.86(8)
O1─Pd1─O2 (°)	89.99(7)
C11─Pd1─O1 (°)	91.10(8)
O1─Pd1─N1 (°)	171.39(7)
C11─Pd1─O2 (°)	175.94(8)
N1─Pd1─O2 (°)	98.25(7)
C11─Pd1─Pd1* (°)	99.40(6)
N1─Pd1─Pd1* (°)	100.02(5)
O1─Pd1─Pd1* (°)	84.26(4)
O2─Pd1─Pd1* (°)	76.81(5)

	Palladacycle-**2**	Palladacycle-**3**
Pd1─Pd2 (Å)	2.883(5)	2.853(5)
Pd1─C17 (Å)	1.961(3)	1.942(6)
Pd1─N2 (Å)	2.025(3)	2.015(6)
Pd1─O1 (Å)	2.124(2)	2.128(4)
Pd1─O2 (Å)	2.049(2)	2.036(4)
C17─Pd1─N2 (°)	80.00(1)	80.39(2)
O1─Pd1─O2 (°)	89.19(8)	87.58(1)
C17─Pd1─O1 (°)	178.20(1)	177.70(2)
N2─Pd1─O1 (°)	97.37(9)	98.43(2)
C17─Pd1─O2 (°)	92.38(1)	93.25(2)
N2─Pd1─O2 (°)	172.04(9)	172.37(2)
C17─Pd1─Pd2 (°)	102.85(8)	100.61(2)

N2─Pd1─Pd2 (°)	106.37(7)	104.27(1)
O1─Pd1─Pd2 (°)	78.32(6)	77.74(9)
O2─Pd1─Pd2 (°)	79.30(6)	80.94(1)
Pd2─C38 (Å)	1.953(3)	1.960(6)
Pd2─N4 (Å)	2.015(3)	2.001(5)
Pd2─O3 (Å)	2.142(3)	2.031(4)
Pd2─O4 (Å)	2.041(4)	2.133(4)
C38─Pd2─N4 (°)	80.56(1)	81.07(1)
O3─Pd2─O4 (°)	89.45(9)	87.58(1)
C38─Pd2─O3 (°)	172.33(1)	93.89(2)
N4─Pd2─O3 (°)	96.52(1)	172.77(2)
C38─Pd2─O4 (°)	94.30(1)	175.33(2)
N4─Pd2─O4 (°)	171.15(1)	97.86(2)
C38─Pd1─Pd2 (°)	94.90(9)	95.76(2)
N4─Pd1─Pd2 (°)	107.46(8)	101.73(2)
O3─Pd1─Pd2 (°)	79.13(6)	83.86(1)
O4─Pd1─Pd2 (°)	80.03(6)	79.98(9)

Table 2.1: Crystal data and structure refinement parameters for the palladacycles-1 to 3

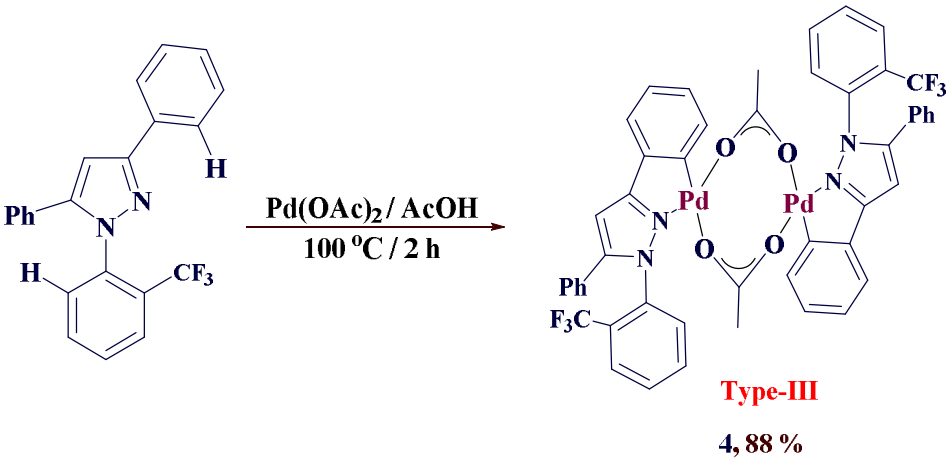
Identification code	Palladacycle-**1**	Palladacycle-**2**	Palladacycle-**3**
Empirical formula	$C_{46}H_{36}N_4O_4Pd_2.CH_2Cl_2$	$C_{52}H_{47}N_4O_5Pd_2$	$C_{46}H_{34}F_2N_4O_6Pd_2$
Formula weight	1006.51	1020.73	987.57
Temperature/K	296.15	296.15	100 (2)

Crystal system	Monoclinic	Triclinic	Orthorhombic
Space group	C2/c	P-1	Pca2
a/Å	18.0741(4)	9.2363(3)	19.2105(12)
b/Å	16.5018(4)	17.2681(5)	17.0639(11)
c/Å	15.3290(3)	17.3174(5)	13.7730(8)
α/°	90	116.768(2)	90
β/°	114.5910(10)	97.744(2)	90
γ/°	90	90.041(2)	90
Volume/Å^3	4157.28(16)	2437.64(13)	4514.9(5)
Z	4	2	4
ρ_{calc}g/cm^3	1.608	1.391	1.456
μ/mm^{-1}	1.044	0.787	0.855
F(000)	2024	1038.0	1984
Radiation/λ[MoKα]	0.71073	0.71073	0.71073
θrange/^{o}	1.92 to 30.57	2.648 to 58.476	2.12 to 28.84°
Index ranges	−25 ≤ h ≤ 25 −23 ≤ k ≤ 23 −21 ≤ l ≤ 20	−12 ≤ h ≤ 12 −23 ≤ k ≤ 23 −23 ≤ l ≤ 23	−24<=h<=25 −22<=k<=22 −18<=l<=17
Reflections collected	34962	42463	61435
Independent reflections	6333 [R_{int} = 0.0382]	13189 [R_{int} = 0.0396]	11214 [R_{int} = 0.1002]
Data/restraints/parameters	6333/0/269	13189/0/572	11214/1/545
Goodness-of-fit on F^2	1.109	1.069	0.978

Final R indexes	R_1 = 0.0307	R_1 = 0.0424	R_1 = 0.0533
[I>=2σ (I)]	wR_2 = 0.0788	wR_2 = 0.1074	wR_2 = 0.1194
Final R indexes	R_1 = 0.0428	R_1 = 0.0561	R_1 = 0.0740
[all data]	wR_2 = 0.0910	wR_2 = 0.1135	wR_2 = 0.1271
Largest diff. peak/ hole/eÅ^{-3}	0.647/ −0.569	1.91/-0.91	1.299 and -0.895

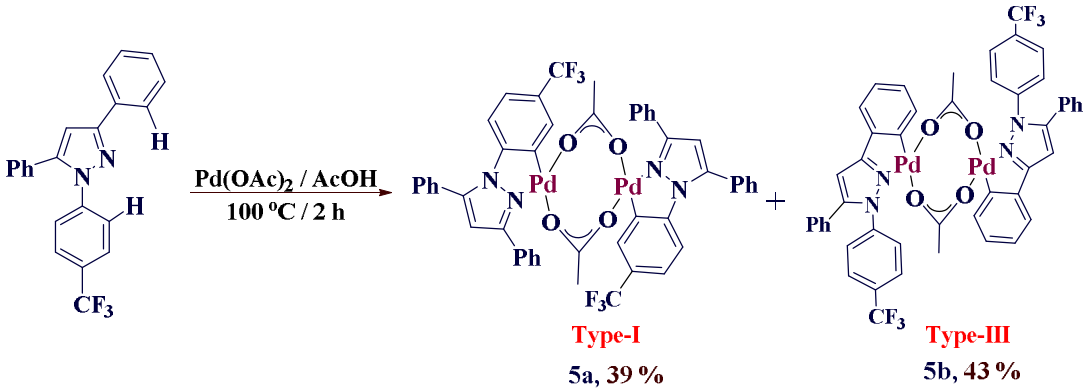
In order to know the positional effect of CF_3 on N-phenyl we prepared the corresponding *o*-CF_3, *m*-CF_3 and *p*-CF_3 substituted pyrazole derivatives from commercially available 1,3-diphenyl-1,3-propanedione and corresponding phenylhydrazines in 76%, 88% and 95% isolated yield respectively. Under the reaction condition mentioned above we examined cyclopalladation of the 3,5-diphenyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazole and noticed that the C─H activation proceeded on 3-phenyl of the pyrazole and not on the N-phenyl of the pyrazole (Scheme 2.8, type-III, palladacycle-**4**). We observed exclusively type-III C─H bond activation with 89% isolated yield. The formation of palladacycle-**4** was analysed using ^{1}H, ^{19}F, ^{13}C and HRMS. ^{1}H NMR in $CDCl_3$ showed the pyrazole hydrogen peak at 6.89 ppm for the 3,5-diphenyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazole where as the corresponding palladacycle-**4** resonated at 6.30 ppm. Similarly, ^{19}F NMR in $CDCl_3$ showed the peak at -60.8 ppm for the 3,5-diphenyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazole where as the corresponding palladacycle-**4** resonated at -60.2 ppm. The molecular structure of the palladacycle-**4** was further established by using single X-ray diffraction analysis (Figure 2.3). The geometry around palladium atoms exhibits a distorted square planar geometry. The Pd─C (1.9763 (99) Å) and Pd─N (2.0253 (84) Å) distances are comparable with reported

cyclometalated palladium compounds.[9] The Pd…Pd distance in palladacycle-**4** (3.0642(10) Å) is higher than the Pd…Pd distance observed in palladacycle-**1**, palladacycle-**2** and palladacycle-**3**.



Scheme 2.8: Cyclopalladation of 3,5-diphenyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazole

The pyrazole ligand, 3,5-diphenyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole, under the cyclopalladation reaction condition yielded the acetate bridged dimeric complex (Scheme 2.9). The resultant solid was crystallized from dichloromethane and *n*-hexane. When we analysed the crystals in a microscope, we noticed two different types of crystals. The two forms were then separated by fractional crystallization. The first crop was isolated as a light yellow crystal with 39% yield (palladacycle-**5a**, type-I), whereas the third crop was isolated as yellowish green crystals with 43% yield (palladacycle-**5b**, type-III).



Scheme 2.9: Cyclopalladation of 3,5-diphenyl-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole

The ^{1}H NMR in $CDCl_3$ showed distinct peaks for both the isomers, notably the pyrazole hydrogen resonate at 6.06 and 6.26 ppm for the palladacycles-**5a** and **5b** respectively (Figure 2.3). Similarly, the acetate protons are resonating at 1.22 and 1.33 ppm for the palladacycle-**5a** and palladacycle-**5b** respectively. The ^{19}F NMR spectrum of palladacycles-**5a** and **5b** show singlet at -62.4 and -63.6 ppm respectively.

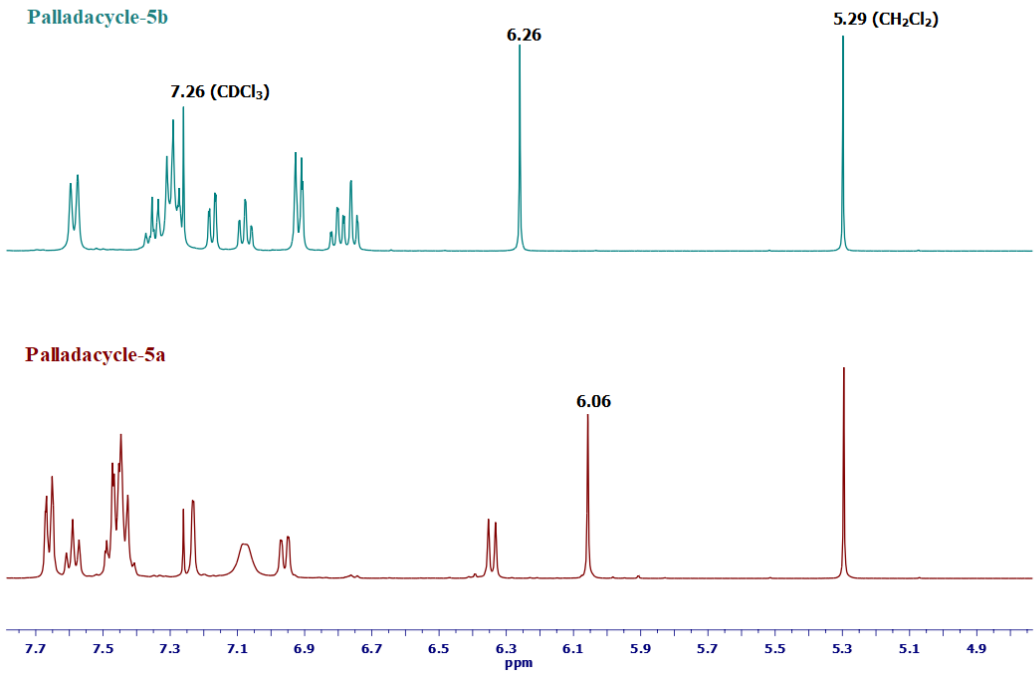


Figure 2.3: ^{1}H NMR spectra for palladacycle-**5a** and palladacycle-**5b** (only aromatic region shown in the figure for clarity)

The structures of palladacycles-**5a** and **5b** were further unambiguously established by X-ray diffraction analysis. Palladacycle-**5a** crystallizes in the triclinic space group P-1, whereas palladacycle-**5b** crystallizes in the orthorhombic space group Pccn (Table 2.3). X-ray analysis reveals that both palladacycles-**5a** and **5b** are dimeric in nature, bridged together by acetates with the pyrazole ligands aligned in a staggered fashion (Figure 2.4). The geometry around palladium atoms in both the structures exhibits a distorted square planar geometry. The Pd─C (1.978(3) Å for **5b**; 1.940 (3) Å for **5a**) and Pd─N (2.024(3) Å for **5b**; 2.015(3) Å for **5a**) distances are comparable with reported cyclometalated palladium compounds (Table 2.2).[9] The Pd─C distance in palladacycle-**5a** is shorter than the corresponding distance in palladacycle-**5b**. However, the Pd…Pd distance (2.848(5) Å) in palladacycle-**5b** is slightly shorter than the Pd…Pd distance (2.8884(5) Å) observed in palladacycle-**5a**.

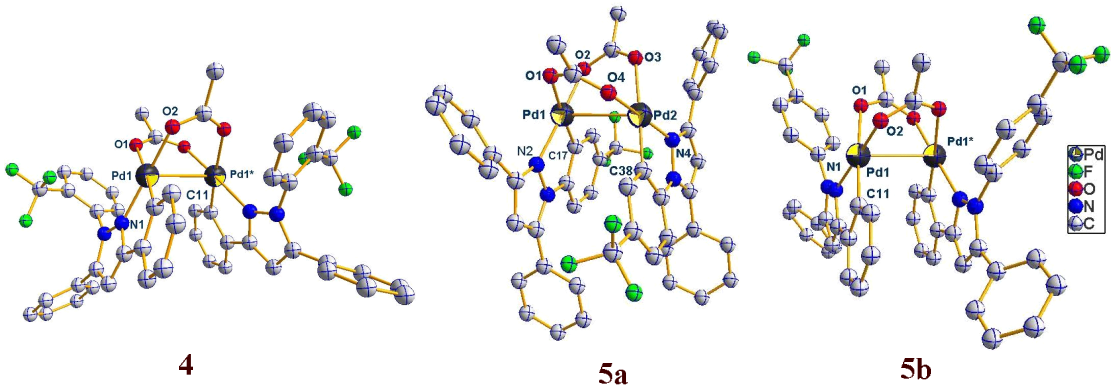


Figure 2.4: Molecular structures of palladacycles-**4**, **5a** and **5b**. Hydrogen atoms are omitted for clarity

Table 2.2: Selected bond distances and bond angles for palladacycles 4, 5a and 5b

	Palladacycle-**4**	Palladacycle-**5b**
Pd1─Pd1* (Å)	3.064(1)	2.848(3)
Pd1─C11 (Å)	1.977(1)	1.978(3)
Pd1─N1 (Å)	2.025(8)	2.024(3)
Pd1─O1 (Å)	2.132(8)	2.151(2)
Pd1─O2 (Å)	2.026(9)	2.052(3)
C11─Pd1─N1 (^{o})	80.12(4)	80.49(1)
O1─Pd1─O2 (^{o})	87.84(3)	86.29(9)
C11─Pd1─O1 (^{o})	174.86(4)	176.99(1)
O1─Pd1─N1 (^{o})	99.86(3)	99.69(9)
C11─Pd1─O2 (^{o})	91.80(4)	93.73(1)
N1─Pd1─O2 (^{o})	171.10(3)	173.02(1)
C11─Pd1─Pd1* (^{o})	109.81(3)	98.21(9)

N1─Pd1─Pd1* (°)	104.94(2)	101.92(9)
O1─Pd1─Pd1* (°)	75.20(2)	78.81(6)
O2─Pd1─Pd1* (°)	81.24(3)	82.68(7)

	Palladacycle-**5a**
Pd1─Pd2 (Å)	2.888(5)
Pd1─C17 (Å)	1.940(2)
Pd1─N2 (Å)	2.015(3)
Pd1─O1 (Å)	2.132(2)
Pd1─O2 (Å)	2.035(3)
C17─Pd1─N2 (°)	80.70(1)
O1─Pd1─O2 (°)	87.27(1)
C17─Pd1─O1 (°)	176.03(1)
N2─Pd1─O1 (°)	99.54(1)
C17─Pd1─O2 (°)	92.89(1)
N2─Pd1─O2 (°)	171.27(1)
C17─Pd1─Pd2 (°)	97.62(9)
N2─Pd1─Pd2 (°)	103.77(8)
O1─Pd1─Pd2 (°)	78.47(7)
O2─Pd1─Pd2 (°)	82.85(7)
Pd2─C38 (Å)	1.948(3)
Pd2─N4 (Å)	2.014(2)
Pd2─O3 (Å)	2.130(2)
Pd2─O4 (Å)	2.035(2)

C38─Pd2─N4 (°)	80.88(1)
O3─Pd2─O4 (°)	88.29(9)
C38─Pd2─O3 (°)	178.78(1)
N4─Pd2─O3 (°)	99.11(1)
C38─Pd2─O4 (°)	91.86(1)
N4─Pd2─O4 (°)	170.58(1)
C38─Pd1─Pd2 (°)	101.40(8)
N4─Pd1─Pd2 (°)	106.07(7)
O3─Pd1─Pd2 (°)	77.42(7)
O4─Pd1─Pd2 (°)	81.14(7)

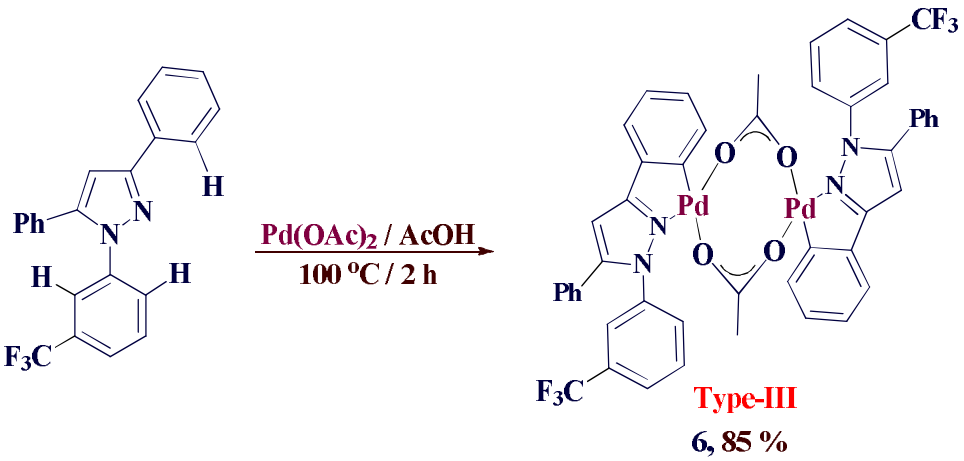
Table 2.3: Crystal data and structure refinement parameters for the palladacycles-4, 5a and 5b

Identification code	Palladacycle-**4**	Palladacycle-**5a**	Palladacycle-**5b**
Empirical formula	$C_{48}H_{34}N_4O_4F_6Pd_2$	$C_{48}H_{34}N_4O_4F_6Pd_2$	$C_{48}H_{34}N_4O_4F_6Pd_2$
Formula weight	1057.65	1057.65	1057.65
T [K]	296.15	296.15	296.15
wavelength [Å]	0.71073 Å	0.71073 Å	0.71073 Å
crystal system	Orthorhombic	Triclinic	Orthorhombic
space group	Fdd2	P-1	Pccn
a [Å]	29.518(5)	12.5806(4)	27.3687(6)
b [Å]	33.652(6)	13.4047(4)	7.6079(2)
c [Å]	9.1542(14)	16.5104(8)	22.5235(5)

α [°]	90	110.580(2)	90
β [°]	90	106.147(2)	90
γ [°]	90	99.622(2)	90
V [Å^3]	9093(3)	2392.68(16)	4689.81(19)
Z	8	2	4
ρcalc [g cm^{-3}]	1.545	1.586	1.618
μ (MoKα) [mm-1]	0.863	0.934	0.954
F (000)	4224.0	1140.0	2280.0
θ range [°]	1.83–25.36	2.74–28.32	2.78– 26.79
limiting indices	-35<=h<=34	-16<=h<=15	-34 ≤ h ≤ 34
	-40<=k<=40	-17<=k<=17	-9 ≤ k ≤ 9
	-5<=l<=11	-22<=l<=22	-28 ≤ l ≤ 28
reflections collected	20854	39212	58819
independent reflections	3059 [*R*(int) = 0.1063]	11845 [*R*(int) = 0.0416]	5005 [*R*(int) = 0.0522]
absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents	Semi-empirical from equivalents
refinement method	Full-matrix least square on *F2*	Full-matrix least square on *F2*	Full-matrix least square on *F2*
data / restraints / parameters	3059 / 1 / 290	11845 / 0 / 607	5005/0/304
Goodness-of-fit on *F2*	1.211	1.014	1.063

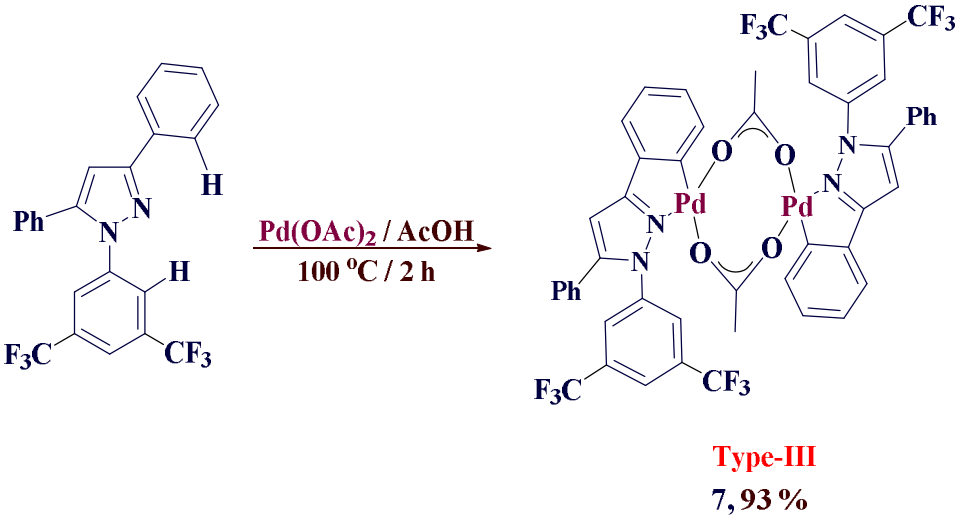
final R indices	*R1* = 0.0406	*R1* = 0.0369	*R1* = 0.0380
[I >2σ(I)] [a]	*wR2* = 0.1056	*wR2* = 0.0877	*wR2* = 0.0873
R indices (all data)	*R1* = 0.0568	*R1* = 0.0568	*R1* = 0.0536
[a]	*wR2* = 0.1335	*wR2* = 0.1003	*wR2* = 0.0962
$peak_{max}/hole_{min}$	1.10 and -0.61	0.83 and -0.57	0.77/-0.85
[e $Å^{-3}$]			

Next, we investigated the C─H activation of 3,5-diphenyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole, to our surprise type-III C─H activation was observed (Scheme 2.10) in 85% yield. The formation of palladacycle-**6** was analysed using ^{1}H, ^{19}F, ^{13}C and LCMS. ^{1}H NMR in $CDCl_3$ showed the pyrazole hydrogen peak at 6.85 ppm for the 3,5-diphenyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole where as the corresponding palladacycle-**6** resonated at 6.33 ppm. Similarly, ^{19}F NMR in $CDCl_3$ showed the pyrazole hydrogen peak at -63.8 ppm for the 3,5-diphenyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole where as the corresponding palladacycle-**6** resonated at -63.7 ppm

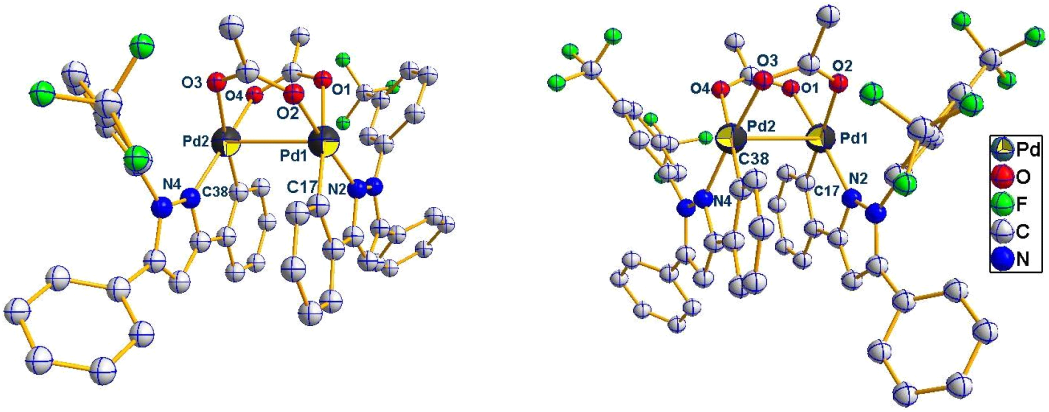


Scheme 2.10: Cyclopalladation of 3,5-diphenyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole

Then we investigated cyclopalladation of 1-(3,5-bis(trifluoromethyl)phenyl)-3,5-diphenyl-1H-pyrazole. As expected the C─H activation proceeded on 3-phenyl of the pyrazole (Scheme 2.11) with isolated yield of 93%. The palladacycles-**6** and **7** were fully characterized by NMR, LCMS and elemental analysis. The structures of palladacycle-**6** and palladacycle-**7** were further confirmed by single X-ray diffraction analysis (Figure 2.5 and table 2.5). Palladacycle-**6** crystallizes in the monoclinic space group $P2_1$ and palladacycle-**7** crystallizes in the triclinic space group P-1 (Table 2.5). The geometry around the palladium atoms in both palladacycle-**6** and palladacycle-**7** exhibits a distorted square planar geometry. The Pd─C (1.9755 (1) Å for **6**; 1.9706 (3) Å for **7**) and Pd─N (2.0278(1) Å for **6**; 2.034 (3) Å for **7**) distances are comparable with reported cyclometalated palladium compounds (Table 2.4).[9] The Pd…Pd distance in palladacycle-**7** (2.873(5) Å) is higher than the Pd…Pd distance observed in palladacycle-**6** (2.8629(13) Å) and palladacycle-**5b**, and slightly shorter than palladacycle-**4** and palladacycle-**5a**.



Scheme 2.11: Cyclopalladation of 1-(3,5-bis(trifluoromethyl)phenyl)-3,5-diphenyl-1H-pyrazole



6 7

Figure 2.5: Molecular structures of palladacycles-**6** and **7**. Hydrogen atoms are omitted for clarity

Table 2.4: Selected bond distances and bond angles for palladacycles-6 and 7

	Palladacycle-**6**	Palladacycle-**7**
Pd1─Pd2 (Å)	2.863(1)	2.873(5)
Pd1─C17 (Å)	1.976(2)	1.971(3)
Pd1─N2 (Å)	2.028(1)	2.034(3)
Pd1─O1 (Å)	2.163(9)	2.138(2)
Pd1─O2 (Å)	2.028(9)	2.034(2)
C17─Pd1─N2 (°)	80.61(5)	80.32(1)
O1─Pd1─O2 (°)	88.29(4)	88.04(9)
C17─Pd1─O1 (°)	174.63(4)	91.13(9)
N2─Pd1─O1 (°)	99.57(4)	171.31(9)
C17─Pd1─O2 (°)	92.15(5)	179.01(1)
N2─Pd1─O2 (°)	170.01(4)	100.53(9)

C17─Pd1─Pd2 (°)	96.53(4)	100.84(9)
N2─Pd1─Pd2 (°)	104.19(3)	97.30(8)
O1─Pd1─Pd2 (°)	78.20(2)	85.83(8)
O2─Pd1─Pd2 (°)	83.36(3)	78.56(7)
Pd2─C38 (Å)	1.973(1)	1.965(4)
Pd2─N4 (Å)	2.031(1)	2.035(3)
Pd2─O3 (Å)	2.035(1)	2.142(2)
Pd2─O4 (Å)	2.152(8)	2.021(3)
C38─Pd2─N4 (°)	80.15(5)	80.14(1)
O3─Pd2─O4 (°)	89.37(4)	89.69(9)
C38─Pd2─O3 (°)	92.25(5)	179.00(1)
N4─Pd2─O3 (°)	170.09(4)	99.38(9)
C38─Pd2─O4 (°)	174.58(4)	90.78(1)
N4─Pd2─O4 (°)	98.79(4)	170.92(1)
C38─Pd1─Pd2 (°)	96.11(4)	103.96(1)
N4─Pd1─Pd2 (°)	103.13(3)	98.08(9)
O3─Pd1─Pd2 (°)	83.89(2)	76.96(7)
O4─Pd1─Pd2 (°)	78.92(3)	84.33(8)

Table 2.5: Crystal data and structure refinement parameters for the palladacycle-7

Identification code	Palladacycle-**6**	Palladacycle-**7**
Empirical formula	$C_{48}H_{34}F_6N_4O_4Pd_2$	$C_{50}H_{32}F_{12}N_4O_4Pd_2.(CH_2Cl_2)_2.(CHCl_2)$

Formula weight	1057.59	1447.36
Temperature/K	296.15	296.15
Crystal system	monoclinic	triclinic
Space group	$P2_1$	P-1
a/Å	10.1713(11)	12.6732(14)
b/Å	17.3718(18)	15.4639(7)
c/Å	12.3107(12)	16.0509(8)
α/°	90	114.873(2)
β/°	103.357(5)	96.893(3)
γ/°	90	94.600(3)
Volume/$Å^3$	2116.4(4)	2803.2(4)
Z	2	2
$\rho_{calc}g/cm^3$	1.660	1.715
μ/mm^{-1}	0.927	1.016
F(000)	1056.0	1434.0
Radiation	MoKα (λ = 0.71073)	MoKα (λ = 0.71073)
θ range [°]	3.4 to 54.956	3.95 to 56.77
Index ranges	-13 ≤ h ≤ 13, -22 ≤ k ≤ 22, -15 ≤ l ≤ 15	-16 ≤ h ≤ 16, -20 ≤ k ≤ 20, -21 ≤ l ≤ 19
Reflections collected	30053	45908
Independent reflections	9621 [R_{int} = 0.0821, R_{sigma} = 0.0833]	13761 [R_{int} = 0.0369, R_{sigma} = 0.0373]

Data/restraints/parameters	9621/1/569	13761/0/759
Goodness-of-fit on F^2	1.030	1.033
Final R indexes [I>=2σ (I)]	R_1 = 0.0805, wR_2 = 0.1973	R_1 = 0.0416, wR_2 = 0.1044
Final R indexes [all data]	R_1 = 0.0918, wR_2 = 0.2089	R_1 = 0.0530, wR_2 = 0.1124
Largest diff. peak/hole / e $Å^{-3}$	7.26/-1.50	1.43/-1.73

2.3 Conclusion

In conclusion, we examined C−H bond activation of 3,5-diphenyl-1-(R-phenyl)-1H-pyrazoles (R = H, Me, F and CF_3) as ligands with $Pd(OAc)_2$ via nitrogen-directed cyclopalladation of the aromatic ring. When R = H, Me and F on the 3-position of N-phenyl of the pyrazole, the activation proceeded on the 3-position of N-phenyl of the pyrazole (Type-I). Then we studied effect of -CF_3 group on *ortho, meta* and *para* position of N-phenyl ring of the pyrazole. In case of *o*-CF_3 and *m*-CF_3 substituted on the N-phenyl ring, the C─H activation proceeded on the 5-phenyl ring (Type-III). However, CF_3 substituted on the para position of the N-phenyl ring yielded both type-I and type-III activated palladacycles. From all these observations it is noteworthy to mention that not only steric and (or) electronic nature and also the position of the R group playing a crucial role in the regio-selective C─H activation of pyrazoles to form palladacycles.

2.4 Experimental Section:

2.4.1 General information

All reagents and solvents were obtained from commercial sources. All 400 (or) 700 MHz ^{1}H, 100 (or) 176 MHz ^{13}C, 376 MHz ^{19}F spectra were recorded on a spectrometer operating at 400 (or) 700 MHz. All ^{1}H and ^{13}C NMR spectra were referenced internally to solvent signals. ^{19}F NMR spectra, to α,α,α-trifluorotoluene (0.05% in $CDCl_3$; δ = -63.73). High resolution mass spectra (HRMS) were recorded with using microTOF-QII mass spectrometer. Single-crystal X-ray diffraction data were collected at 100 K (or) 296 K using, Mo-K*α* radiation (0.71073 Å). Crystallographic data for all palladacycles and details of X-ray diffraction experiments and crystal structure refinements are given in Table 2.1, Table 2.2 and Table 2.4. SADABS absorption corrections were applied in both cases. The structures were solved and refined with SHELX suite of programs. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The H-atoms were placed at calculated positions and were refined as riding atoms.

2.4.2 General procedure for synthesis of 1,3,5-triphenyl pyrazole derivatives:

1,3-Diphenylpropane-1,3-dione (10 mmol) and corresponding phenyl hydrazine (10 mmol) were taken in a 100 mL round bottom flask. Then 10 mL of methanol and 10 mL of acetic acid were added to the flask and the reaction mixture was refluxed for 12 h. To the reaction mixture, saturated sodium carbonate solution was added and the compound was extracted using dichloromethane. The solvent was removed under vacuum and the residue was purified by column chromatography (*n*-hexane–ethyl acetate as an eluent).

1,3,5-triphenyl pyrazole [10]**:** Prepared from 1,3-diphenylpropane-1,3-dione (2.24 g, 10.0 mmol) and phenyl hydrazine (1.08 g, 10.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (2.56 g, 8.6 mmol, 86%). Mp = 131-132 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8 Hz, 2H, ArH), 7.29–7.47 (m, 13H, ArH), 6.83 (s, 1H, 4-pyrazole-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 144.7, 139.8, 132.7, 130.4, 129.1, 128.9, 128.8, 128.7, 128.6, 128.4, 127.8, 126.1, 125.6, 105.3 ppm. HRMS (ESI): calcd for $C_{21}H_{16}N_2$ ($[M+H]^+$): 297.1386, found: 297.1373. Elemental analysis calcd (%) for $C_{21}H_{16}N_2$: C 85.11, H 5.44, N 9.45; found: C 84.95, H 5.29, N 9.40. IR (cm^{-1}): 3061 (m), 3047 (m), 1595 (m), 1494 (s), 1362 (m), 1065 (m), 764 (s), 693 (s).

3, 5-diphenyl*-1-*(m-tolyl)*-1*H*-*pyrazole [11]**:** Prepared from 1,3-diphenylpropane-1,3-dione (2.24 g, 10.0 mmol) and *m*-tolylphenyl hydrazine hydrochloride (1.59 g, 10.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (2.45 g, 7.9 mmol, 79%). Mp = 75-76 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (s, ArH, 1H), 7.48-7.33 (m, ArH, 9H), 7.21 (t, *J* = 8 Hz, ArH, 1H), 7.15-7.08 (m, ArH, 2H), 6.86 (s, 4Pz-H, 1H), 2.37 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.9, 144.4, 140.1, 139.1, 133.2, 130.7, 128.8, 128.7, 128.6, 128.5, 128.3, 128.0, 126.0, 125.9, 122.5, 105.1, 21.4 ppm. HRMS (ESI): calcd for $C_{22}H_{19}N_2$ ($[M+H]^+$): 311.1543, found: 311.1561. IR (cm^{-1}): 3047 (s), 1489 (s), 1460 (s), 1363 (m), 799 (m), 766 (s), 695 (s), 501 (m).

1-(3-fluorophenyl)-3,5-diphenyl*-1*H*-*pyrazole [17]**:** Prepared from 1,3-diphenylpropane-1,3-dione (2.24 g, 10.0 mmol) and 3-fluorophenyl hydrazine hydrochloride (1.63 g, 10.0 mmol). After purification by column chromatography, the

compound was isolated as a white solid (2.64 g, 8.4 mmol, 84%). Mp = 118-119 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.94 (d, *J* = 8 Hz, ArH, 2H), 7.48-7.20 (m, ArH, 10H), 7.12 (d, *J* = 8 Hz, ArH, 1H), 7.02 (t, *J* = 8Hz, ArH, 1H), 6.84 (s, 4Pz-H, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.7 (d, *J* = 246 Hz), 152.4, 144.7, 141.6 (d, *J* = 10.2 Hz), 132.9, 130.4, 130.1 (d, *J* = 9.0 Hz), 128.9, 128.8, 128.7, 128.3, 126.0, 120.8 (d, *J* = 3.2 Hz), 114.3 (d, *J* = 21.1 Hz), 112.7 (d, *J* = 24.7 Hz), 105.9 ppm.^{19}F NMR (376 MHz, $CDCl_3$) δ -112.27 ppm. HRMS (ESI): calcd for $C_{21}H_{16}N_2F$ ($[M+H]^+$): 315.1292, found: 315.1286. IR (cm^{-1}): 3061 (m), 1599 (m), 1492 (s), 1459 (s), 1196 (m), 873 (m), 766 (s), 699 (s).

3,5-Diphenyl*-1-*(2-(trifluoromethyl) phenyl)*-1*Hpyrazole [12]**:** Prepared from 1,3-Diphenylpropane-1,3-dione (2.54 g, 11.30 mmol) and (2- (trifluoromethyl)phenyl) hydrazine (2.00 g, 11.30 mmol). After purification by column chromatography, the compound was isolated as a white solid (3.14 g, 8.6 mmol, 76%). Mp = 109 -110 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.92 (d, *J* = 8 Hz, ArH, 2H), 7.82 (t, *J* = 4 Hz, ArH, 1H), 7.55 (t, *J* = 4 Hz, ArH, 2H), 7.44 (t, *J* = 8 Hz, ArH, 2H), 7.35 (t, *J* = 8 Hz, ArH, 2H), 7.28-7.24 (m, ArH, 5H), 6.89 (s, 4Pz-H, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.2, 146.3, 138.3, 133.0, 132.6, 130.7, 129.9, 129.3, 128.8, 128.6, 128.4, 128.3, 128.2, 127.9 (q, *J* = 5.0 Hz), 126.1, 104.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = 60.81 ppm. HRMS (ESI): calcd. for $C_{22}H_{15}F_3N_2$ ($[M+H]^+$): 365.1260, found: 365.1273. Elemental analysis calcd (%) for $C_{22}H_{15}F_3N_2$: C 72.52, H 4.15, N 7.69; found: C 72.60, H 4.22, N 7.58.; IR (cm^{-1}): 3064 (m), 1501 (m), 1485 (m), 1465 (m),1315 (s), 1154 (m), 1137 (s), 1113 (m), 761 (s), 596 (s).

3,5-Diphenyl-1-(4-(trifluoromethyl) phenyl)-1H-pyrazole [10]**:** Prepared from 1,3-Diphenylpropane-1,3-dione (1.00 g, 4.5 mmol) and (4-(trifluoromethyl)phenyl) hydrazine (0.86g, 4.9 mmol). After purification by column chromatography, the compound was isolated as a white solid (1.55 g, 4.25 mmol, 95%). Mp = 114-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.3 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 3H), 7.40–7.36 (m, 4H), 7.32–7.29 (m, 2H), 6.86 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 144.9, 142.8, 132.6, 130.3, 129.0, 128.9, 128.9, 128.5, 126.2 (q, *J* = 3.7 Hz), 126.0, 125.0, 106.4 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.29 ppm. IR (KBr): ν (cm^{-1}) = 3067 (m), 1613 (m), 1485 (m), 1411 (m), 1364 (m), 1326 (s), 1168 (s), 1126 (s), 766 (s), 698 (s). HRMS (ESI): calcd. for $C_{22}H_{15}F_3N_2$ ([M+H]): 365.1260, found: 365.1245.

3,5-Diphenyl-1-(3-(trifluoromethyl) phenyl)-1H-pyrazole [13]**:** Prepared from 1,3-Diphenylpropane-1,3-dione (2.42 g, 10 mmol) and (3-(trifluoromethyl)phenyl) hydrazine (1.76g, 10 mmol). After purification by column chromatography, the compound was isolated as a white solid (3.21 g, 8.8 mmol, 88%). Mp = 40-41 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 7.2 Hz, 3H), 7.74 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.51–7.42 (m, 4H), 7 .39–7.35 (m, 4H), 7.30–7.29 (m, 3H), 6.85 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 144.8, 140.6, 132.8, 130.3, 129.5, 129.0, 128.9, 128.9 (d, *J* = 1.0 Hz), 128.4, 128.1, 126.0, 123.9 (d, *J* = 3.8 Hz), 122.0 (d, *J* = 3.9 Hz), 106.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.79 ppm. IR (KBr): ν (cm^{-1}) = 3069 (m), 2811 (m), 1596 (m), 1459 (m), 1365 (s), 1326 (s), 1169 (m), 1125 (s), 1066 (m), 809 (s), 694 (s). HRMS (ESI): calcd. for $C_{22}H_{15}F_3N_2$ ([M+H]): 365.1260, found: 365.1256.

1-(3,5-bis(trifluoromethyl)phenyl)-3,5-diphenyl-1H-pyrazole [17]**:** Prepared from 1,3-Diphenylpropane-1,3-dione (2.42 g, 10 mmol) and 3,5-bis((trifluoromethyl)phenyl) hydrazine (2.44 g, 10 mmol). After purification by column chromatography, the compound was isolated as a white solid (3.93 g, 9.1 mmol, 91%). Mp = 88-89 °C. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 7.1 Hz, 1H), 7.83 (s, 1H), 7.75 (s, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.44–7.38 (m, 2H), 7.30 (d, *J* = 6.5 Hz, 1H), 6.87 (s, 1H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 153.4, 145.0, 141.2, 132.5, 132.4, 132.3, 129.9, 129.5, 129.2, 129.0 (d, *J* = 6.8 Hz), 128.8, 126.1, 124.4 (d, *J* = 3.3 Hz), 123.7, 122.1, 120.3 (q, *J* = 3.7 Hz)., 107.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -64.13 ppm. IR (cm^{-1}): 3075 (m), 2936 (m), 1480 (m), 1384 (s), 1279 (s), 1187 (m), 1135 (s), 892 (m), 764 (m), 698 (m). HRMS (ESI): calcd. for $C_{23}H_{14}F_6N_2$ ([M+H]): 433.1134, found: 433.1142.

2.4.3 General procedure for synthesis of palladacycles:

Palladium acetate (5 mmol) and corresponding 1,3,5-triphenylpyrazole (5 mmol) were suspended in glacial acetic acid (15 mL) and the mixture was heated in an oil bath (100 °C, 2 h). The reaction mixture was filtered through celite to remove palladium black and the resultant solution was concentrated. The residue was re-dissolved in dichloromethane, layered with *n*-hexane and stored at 5 °C for 24 h and filtered through celite (1cm height) silicagel (100-200 mesh, 1cm height) to remove palladium black traces, and repeated the same three times. The solution was concentrated and recrystallized from a mixture of dichloromethane and *n*-hexane.

Palladacycle-1 [14]**:** Prepared from palladium acetate (1.00 g, 4.4 mmol) and 1,3,5-triphenylpyrazole (1.31 g, 4.4 mmol). Yield: 1.21 g (59%). Mp 219-220 ^{o}C

(decompose). ^{1}H NMR (400 MHz, C_6D_6) δ = 7.67 (d, *J* = 8 Hz, 4H, ArH), 7.42 (d, *J* = 8 Hz, 4H, ArH), 7.23–7.07 (m, 10H, ArH), 6.98–6.89 (m, 6H, ArH), 6.72 (t, *J* = 8 Hz, 2H, ArH), 6.50 (t, *J* = 8 Hz, 2H, ArH), 6.40 (d, *J* = 8 Hz, 2H, ArH), 5.57 (s, 2H, ArH), 1.49 (s, 6H, Me) ppm. ^{13}C NMR (100 MHz, C_6D_6) δ = 180.3, 153.7, 143.1, 141.1, 134.6, 133.2, 129.9, 129.6, 129.5, 129.2, 128.8, 128.2, 127.9, 123.4, 122.7, 111.9, 109.5, 22.7 ppm. HRMS (ESI): calcd for $C_{44}H_{34}N_4O_2Pd_2$ ($[M - OAc]^+$): 863.0690, found: 863.0614. Elemental analysis calcd (%) for $C_{46}H_{38}N_4O_4Pd_2$: C 59.82, H 4.15, N 6.07; found: C 59.65, H 3.99, N 6.27. IR (cm^{-1}): 3052 (m), 2928 (m), 1575 (s), 1412 (s), 1342 (m), 1002 (m), 758 (s), 696 (s).

Palladacycle-2 [17]**:** Prepared from palladium acetate (1.00 g, 4.4 mmol) and 3, 5-diphenyl-1-(*m*-tolyl)-1H-pyrazole (1.37 g, 4.4 mmol). Yield: 1.34 g (64%). Mp 188-189 ^{o}C (decompose). ^{1}H NMR (400 MHz, C_6D_6) δ = 7.72 (d, *J* = 7.2 Hz, 4H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.24–7.16 (m, 6H), 7.11 (t, *J* = 7.5 Hz, 6H), 6.98 (d, *J* = 7.1 Hz, 4H), 6.62 (d, *J* = 7.8 Hz, 2H), 6.25 (s, 2H), 5.64 (s, 2H), 1.83 (s, 6H), 1.48 (s, 6H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ = 181.3, 154.5, 143.8, 141.8, 133.8, 132.4, 131.7, 130.9, 130.5, 130.3, 129.9, 129.4, 129.0, 128.6, 128.3, 128.1, 127.8, 125.0, 113.8, 110.0, 23.4, 21.2 ppm. Elemental analysis calcd (%) for $C_{48}H_{40}N_4O_4Pd_2.(C_7H_8)_{0.3}$: C 61.57, H 4.37, N 5.73; found: C 61.71, H 4.13, N 5.93. IR (cm^{-1}): 3057 (m), 1572 (s), 1469 (m), 1412 (s), 1373 (m), 802 (m), 763 (s), 699 (s).

Palladacycle-3 [17]**:** Prepared from palladium acetate (1.00 g, 4.4 mmol) and 1-(3-fluorophenyl)-3,5-diphenyl-1H-pyrazole (1.38 g, 4.4 mmol). Yield: 1.56 g (74%). Mp 224-225 ^{o}C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62–7.57 (m, 6H), 7.45–7.41 (m, 10H), 7.16–7.15 (m, 4H), 6.85 (t, *J* = 8.7 Hz, 2H), 6.58 (t, *J* = 8.7 Hz, 2H),

6.08 (d, *J* = 10.7 Hz, 2H), 5.98 (s, 2H), 1.27 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.4, 160.0 (d, *J* = 237 Hz), 154.6, 142.9, 142.8, 142.6, 133.6 (d, *J* = 8 Hz), 130.3, 129.8, 129.3, 129.1, 129.0, 128.2, 127.0 (d, *J* = 3 Hz), 110.6, 110.5, 100.7 (d, *J* = 28 Hz), 23.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -119.13 ppm. Elemental analysis calcd (%) for $C_{46}H_{34}F_2N_4O_4Pd_2.(CH_2Cl_2)_{0.2}$: C 56.94, H 3.56, N 5.75; found: C 56.82, H 3.72, N 5.88. IR (cm^{-1}): 3061 (m), 1575 (s), 1467 (m), 1414 (s), 1370 (m), 1194 (m), 871 (m), 761 (s), 697 (s).

Palladacycle-4 [15]**:** Prepared from palladium acetate (1.23 g, 5.50 mmol) and 3, 5-diphenyl-1-(2-(trifluoromethyl) phenyl)-1H-pyrazole (2.00 g, 5.50 mmol). Yield : 2.57 g (4.8 mmol, 88%). Mp 218-219 ^{o}C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8 Hz, ArH, 2H), 7.50 (t, *J* = 8 Hz, ArH, 2H), 7.41 (t, *J* = 8 Hz, ArH, 2H), 7.28-7.21 (m, ArH, 6H), 7.17-7.15 (m, ArH, 2H), 7.04 ((t, *J* = 8 Hz, ArH, 2H), 6.95 (d, *J* = 8 Hz, ArH, 6H), 6.88-6.82 (m, ArH, 4H), 6.30 (s, 4Pz-H, 2H), 1.42 (s, OAc) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.6, 159.6, 146.6, 137.8, 134.6, 132.3, 131.7, 131.2, 130.1, 129.5, 129.1, 128.9, 128.8, 128.4, 127.9 (q, *J* = 5.0 Hz), 125.1, 124.1, 122.2, 101.4, 24.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -60.2 ppm. Elemental analysis calcd (%) for $C_{48}H_{36}F_6N_4O_4Pd_2$: C 54.41, H 3.42, N 5.29; found: C 54.30, H 3.29, N 5.22. IR (cm^{-1}): 3055 (m), 1593 (s), 1576 (s), 1505 (m), 1419 (m), 1316 (s), 1140 (s), 765 (s), 697 (m).

Palladacycles 5a and 5b [16]**:** Palladium acetate (0.31 g, 1.4 mmol) and 3,5-diphenyl-1-(4-(trifluoromethyl) phenyl)-1H-pyrazole (0.50 g, 1.4 mmol) were suspended in glacial acetic acid (5 mL) and the mixture was heated on oil bath (100 °C, 1 h). The reaction mixture was filtered through celite to remove palladium black and the

resultant solution was concentrated. The residue was re-dissolved in dichloromethane, layered with *n*-hexane and stored at 5 °C for 24 h and filtered through celite (1cm height) silicagel (100-200 mesh, 1cm height) to remove palladium black traces and repeated the same three times. The solvents were removed under vacuum and the yellow product (0.65 g, Yield: 90%) was recrystallized sequentially from a mixture of dichloromethane and *n*-hexane. First batch of recrystallization gave palladacycle-5a (0.28 g, 39.2%) as a pale yellow solid, second batch of recrystallization gave mixture of palladacycles (0.06 g, 8.1%) in which palladacycle-5b was major and third batch of recrystallization gave palladacycle-5b (0.31g, 43.0%) as a dark yellow solid.

***Palladacycle 5a*:** Mp = 216–219 °C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 6.7 Hz, 4H), 7.59 (t, *J* = 7.5 Hz, 2H), 7.50–7.41 (m, 10H), 7.24 (s, 2H), 7.08 (d, *J* = 4.4 Hz, 4H), 6.96 (d, *J* = 9.7 Hz, 2H), 6.35 (d, *J* = 8.4 Hz, 2H), 6.06 (s, 2H), 1.22 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 182.4, 155.3, 145.8, 143.0, 134.1, 130.3, 129.7 (2C), 129.5, 129.3 (q, *J* = 3.5 Hz), 129.0 (2C), 128.4, 121.3 (q, *J* = 3.7 Hz), 111.7 (d, *J* = 160.3 Hz), 22.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.41 ppm. Elemental analysis calcd (%) for $C_{48}H_{34}F_6N_4O_4Pd_2.(CH_2Cl_2)_{0.5}$: C 52.95, H 3.21, N 5.09; found: C 52.69, H 3.67, N 5.96. IR (cm^{-1}) = 3060 (m), 1570 (s), 1479 (m), 1417 (s), 1320 (s), 1167 (m), 1118 (s), 763 (s), 698 (s).

***Palladacycle 5b*:** Mp = 221–223 °C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 8.4 Hz, 4H), 7.37–7.27 (m, 10H), 7.18 (d, *J* = 7.2 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 2H), 6.92 (d, *J* = 7.1 Hz, 4H), 6.82–6.74 (m, 4H), 6.26 (s, 2H), 1.33 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.4, 160.1, 146.3, 145.3, 138.8, 137.2, 131.7, 129.3, 129.0 (2C), 128.6, 128.0, 125.7 (q, *J* = 2.9 Hz), 123.25 (d, *J* = 194.0 Hz),

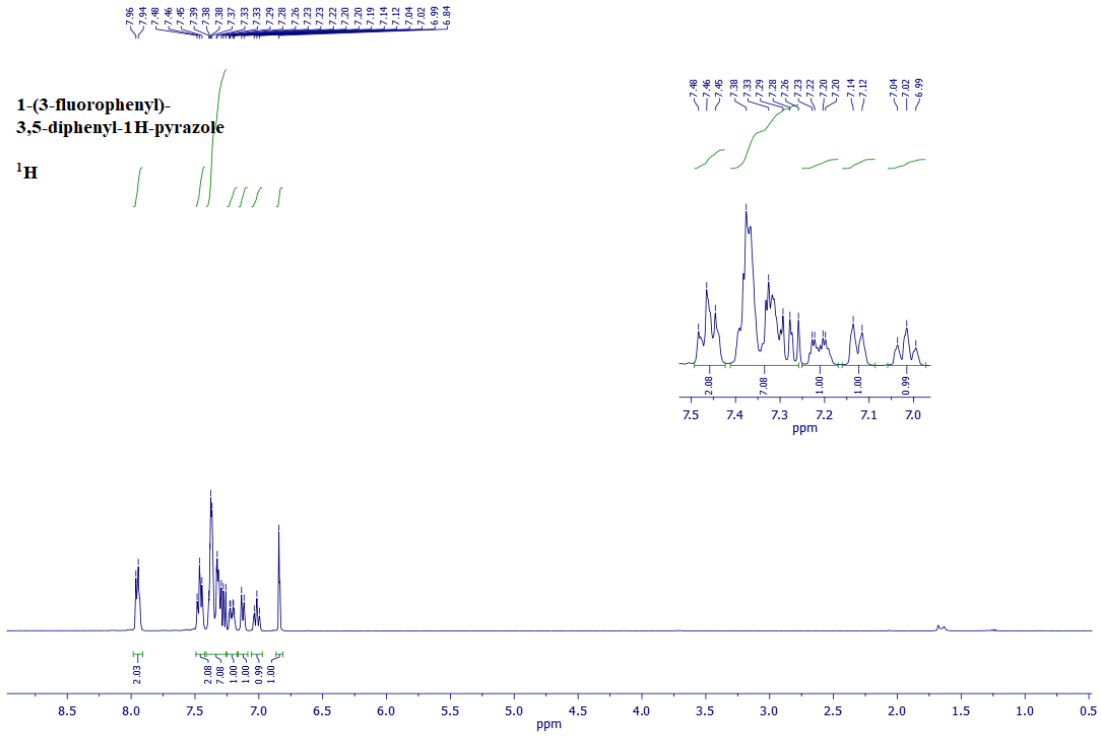
102.7, 23.3 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -63.64 ppm. Elemental analysis calcd (%) for $C_{48}H_{34}F_6N_4O_4Pd_2.(CH_2Cl_2)_{0.2}$: C 53.87, H 3.23, N 5.21; found: C 53.40, H 3.36, N 5.76. IR (cm^{-1}) = 3054 (m), 1570 (s), 1414 (s), 1325 (s), 1159 (m), 1128 (s), 758 (s), 700 (s).

Palladacycle-6 [17]***:*** Prepared from palladium acetate (1.00 g, 4.4 mmol) and 3,5-diphenyl-1-(3-(trifluoromethyl) phenyl)-1H-pyrazole (1.60 g, 4.4 mmol). Yield: 1.97 g (85%). Mp 220-221 ^{o}C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56–7.49 (m, 6H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.25 (t, *J* = 7.4 Hz, 4H), 7.20 (d, *J* = 7.3 Hz, 2H), 7.12 (s, 2H), 7.06 (t, *J* = 7.3 Hz, 2H), 6.89–6.78 (m, 6H), 6.75 (d, *J* = 6.9 Hz, 2H), 6.33 (s, 2H), 1.32 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.1, 160.0, 145.8 (d, *J* = 63.4 Hz), 136.9 (d, *J* = 95.0 Hz), 131.8, 129.3, 129.1, 128.8, 128.4, 125.8, 125.2 (q, *J* = 4.1 Hz), 124.3, 122.2, 102.4, 23.2 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -63.72 ppm. Elemental analysis calcd (%) for $C_{48}H_{34}F_6N_4O_4Pd_2$: C 54.41, H 3.24, N 5.30; found: C 54.69, H 3.02, N 5.52. IR (cm-1) = 3061 (m), 2914 (m), 1593 (m), 1576 (s), 1420 (s), 1380 (m), 1327 (s), 1176 (m), 1123 (s), 1070 (m), 804 (m), 758 (s), 697(s).

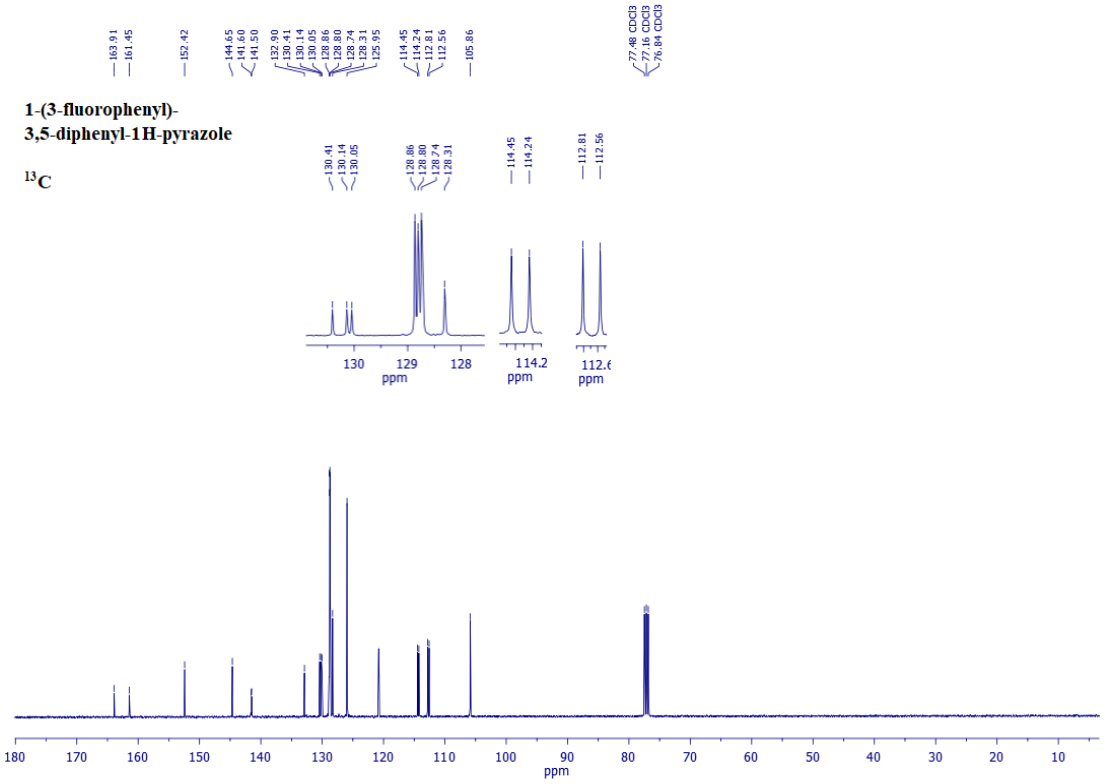
Palladacycle-7 [17]**:** Prepared from palladium acetate (1.00 g, 4.4 mmol) and 1-(3,5-bis(trifluoromethyl)phenyl)-3,5-diphenyl-1H-pyrazole (1.90 g, 4.4 mmol). Yield: 2.44 g (91%). Mp 227-229 ^{o}C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (s, 2H), 7.34 (m, 12H), 7.08 (t, *J* = 7.3 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 6H), 6.68 (d, *J* = 7.6 Hz, 2H), 6.47 (s, 2H), 1.35 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 180.1, 160.7, 146.2, 146.1, 137.1, 136.7, 131.8, 129.8, 129.2, 128.7, 127.9 (q, *J* = 3.6 Hz), 126.3, 124.5, 124.1, 122.6, 122.1 (q, *J* = 3.5 Hz), 121.4, 103.0, 23.1 ppm. ^{19}F NMR (376

MHz, $CDCl_3$) δ = -63.78 ppm. Elemental analysis calcd (%) for $C_{50}H_{32}F_{12}N_4O_4Pd_2$: C 50.31, H 2.70, N 4.69; found: C 50.69, H 2.40, N 5.02. IR (cm^{-1}) = 3060 (m), 1575 (s), 1418 (s), 1394 (s), 1280 (s), 1184 (s), 1139 (s), 1139 (s), 899 (m), 760 (m), 700 (m).

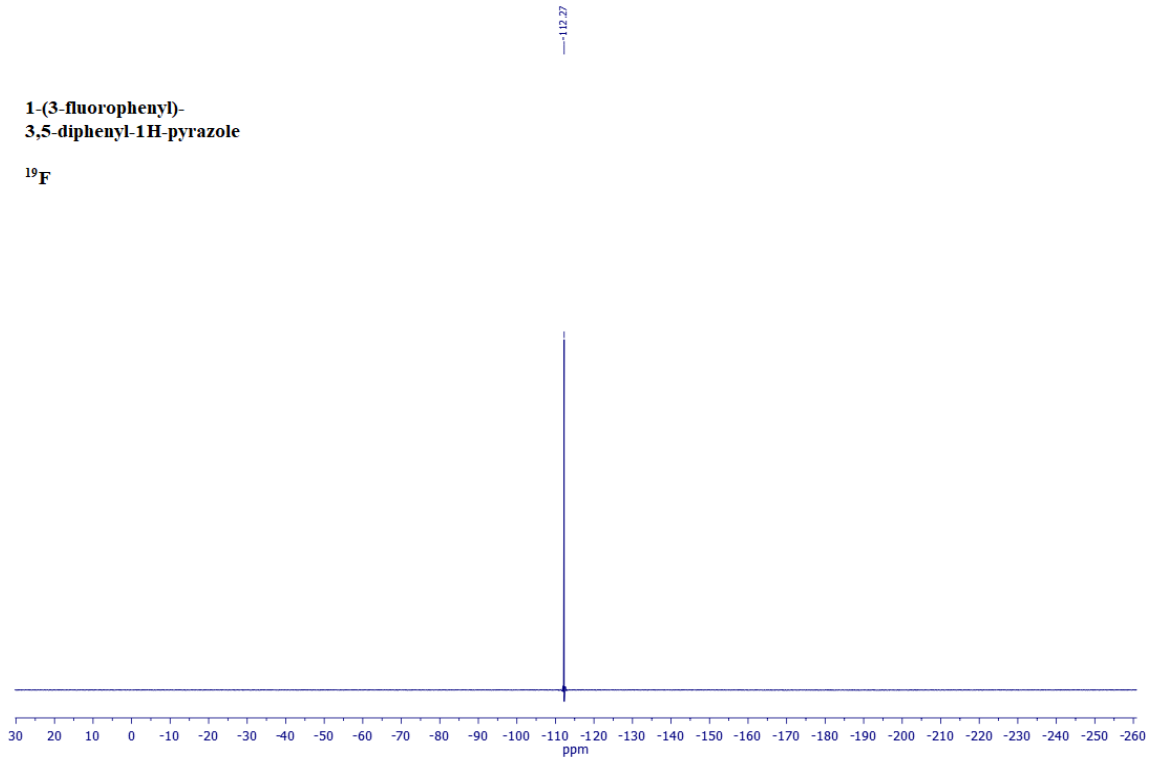
2.5 NMR spectra for new compounds



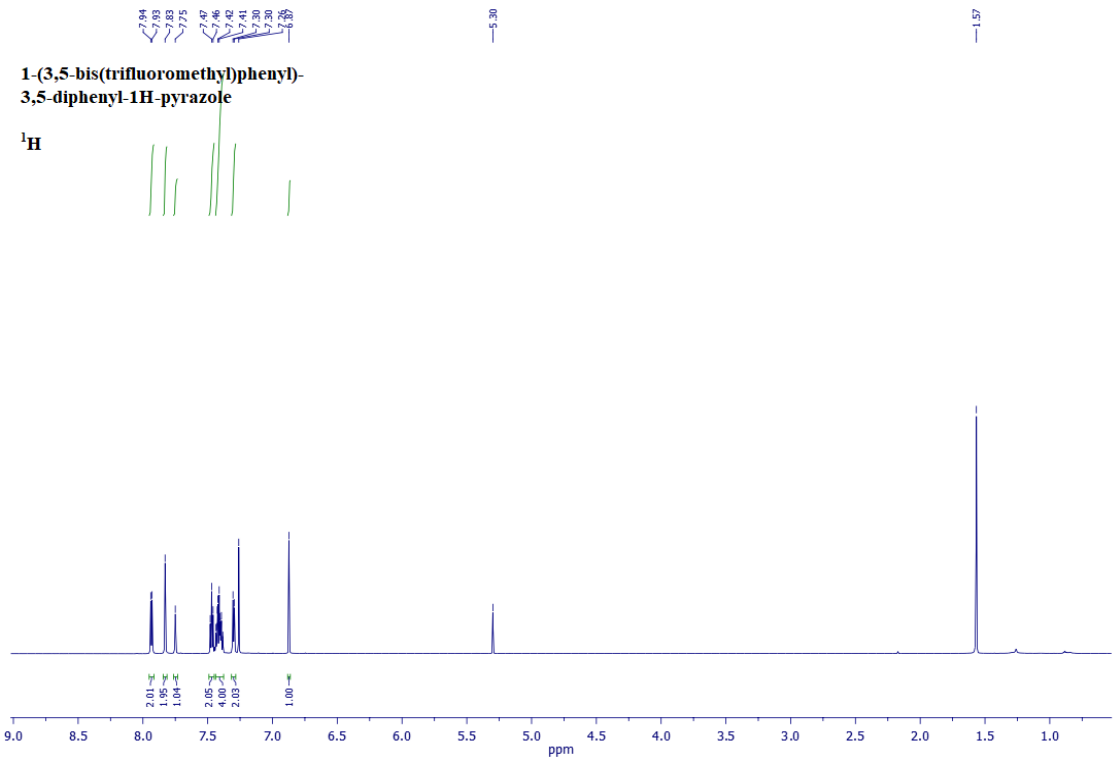
^1H NMR of 1-(3-fluorophenyl)-3,5-diphenyl-1H-pyrazole



^{13}C NMR of 1-(3-fluorophenyl)-3,5-diphenyl-1H-pyrazole



^{19}F NMR of 1-(3-fluorophenyl)-3,5-diphenyl-1H-pyrazole



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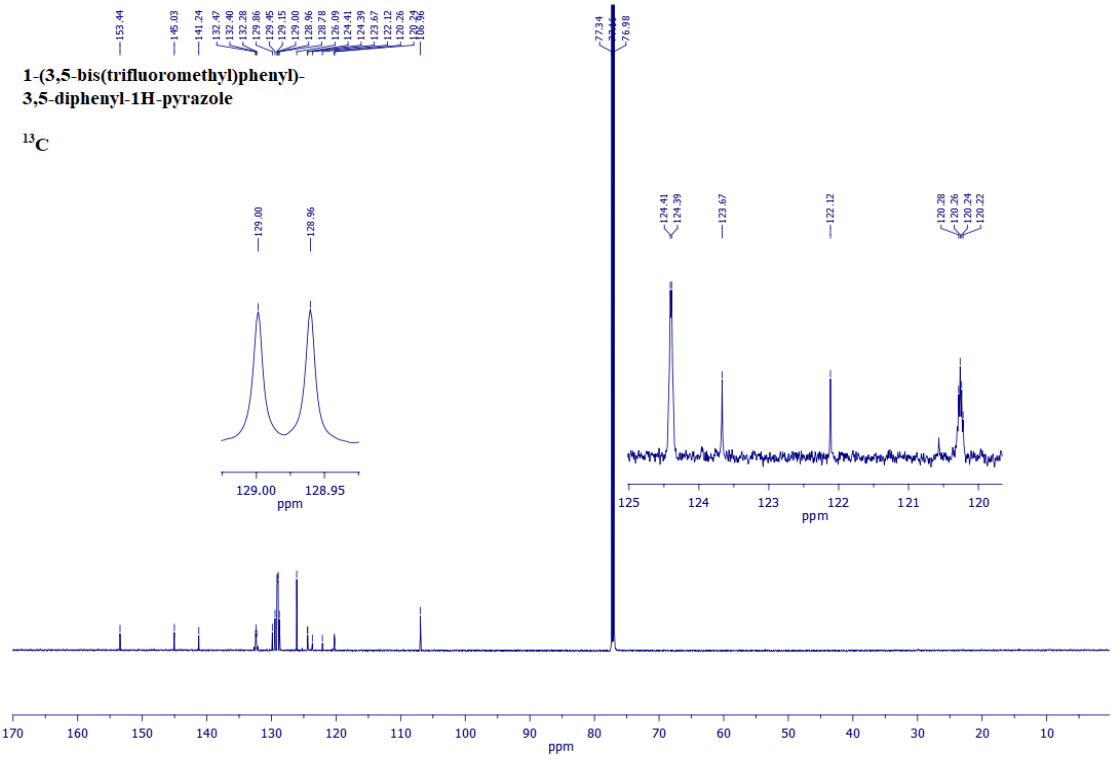

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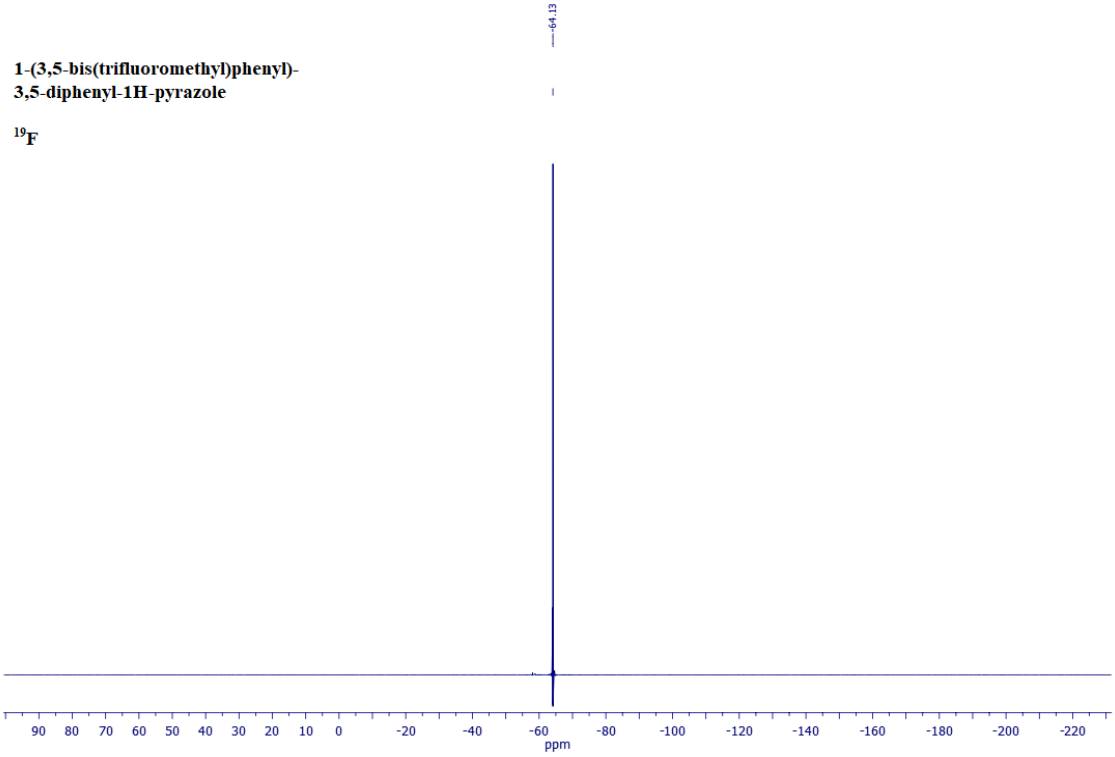
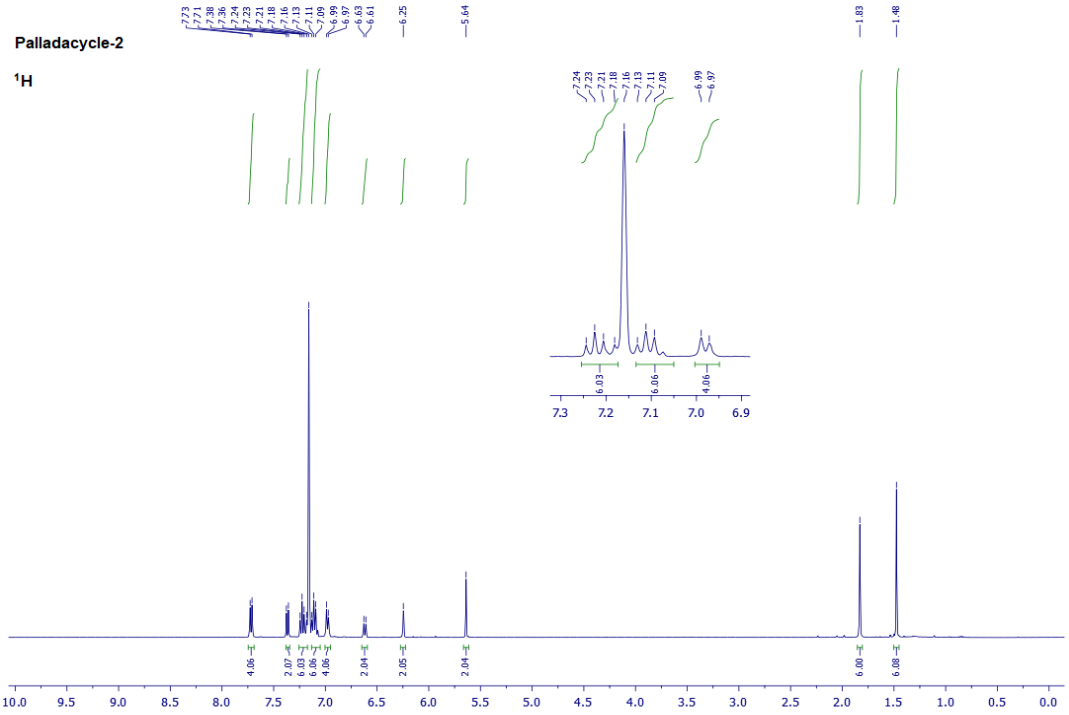


^{19}F NMR of 1-(3,5-bis(trifluoromethyl)phenyl)-3,5-diphenyl-1H-pyrazole



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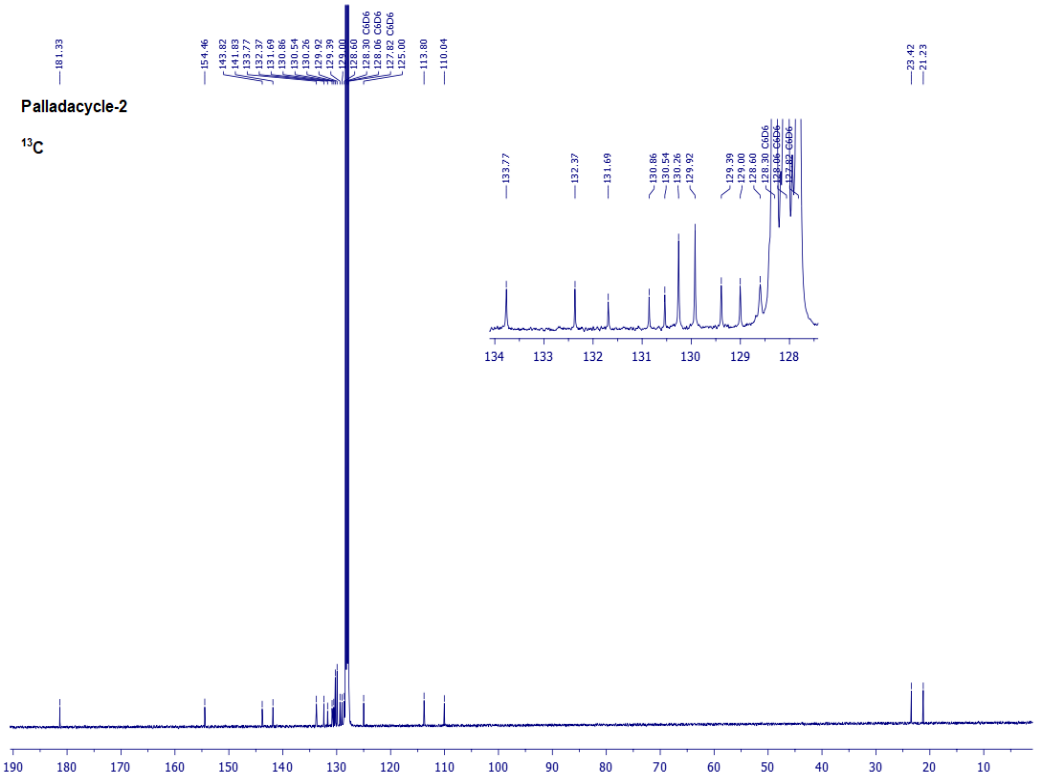

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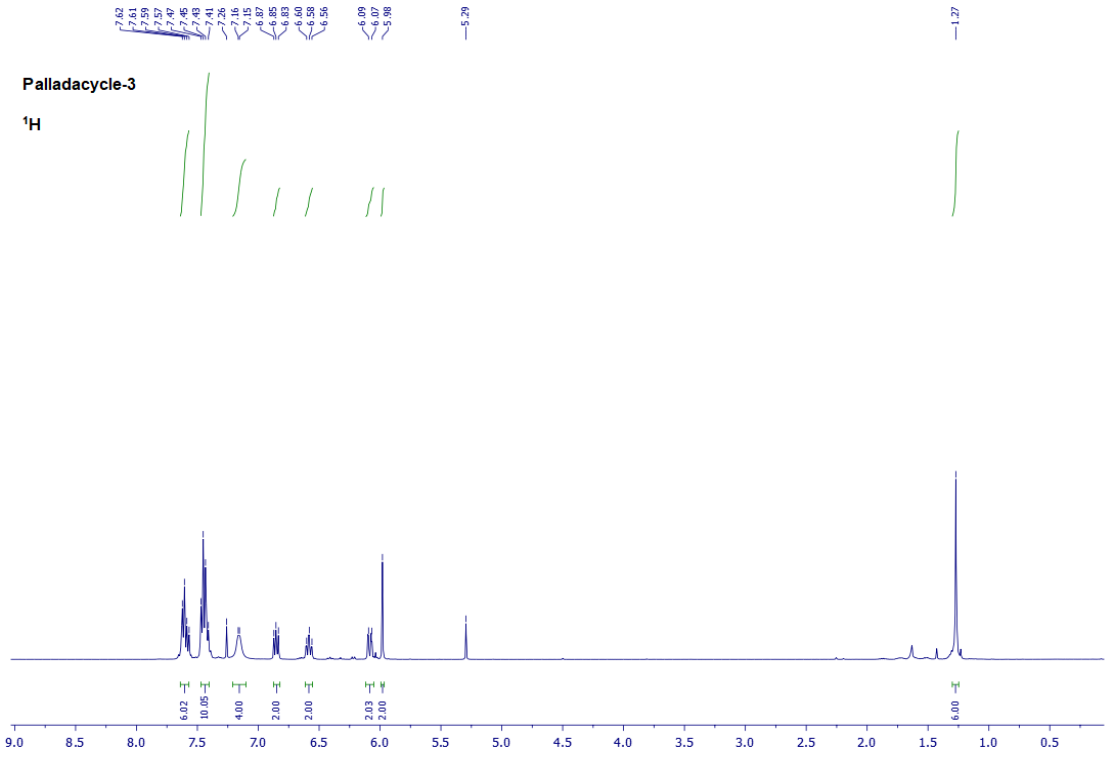

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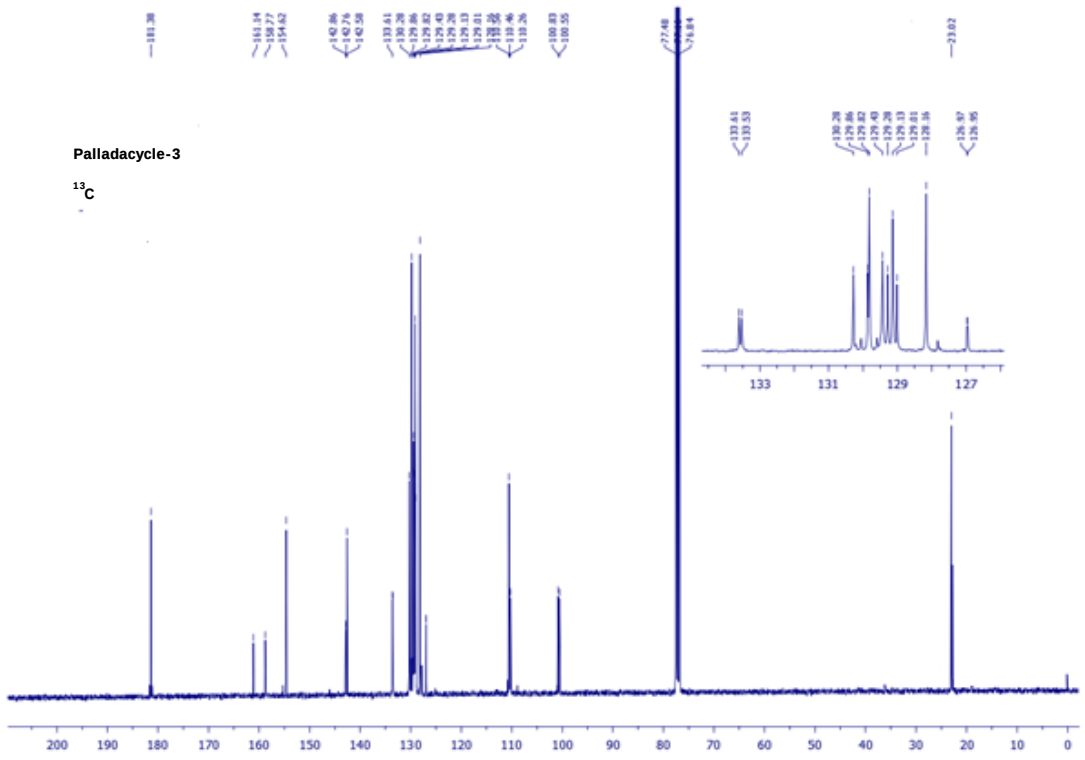

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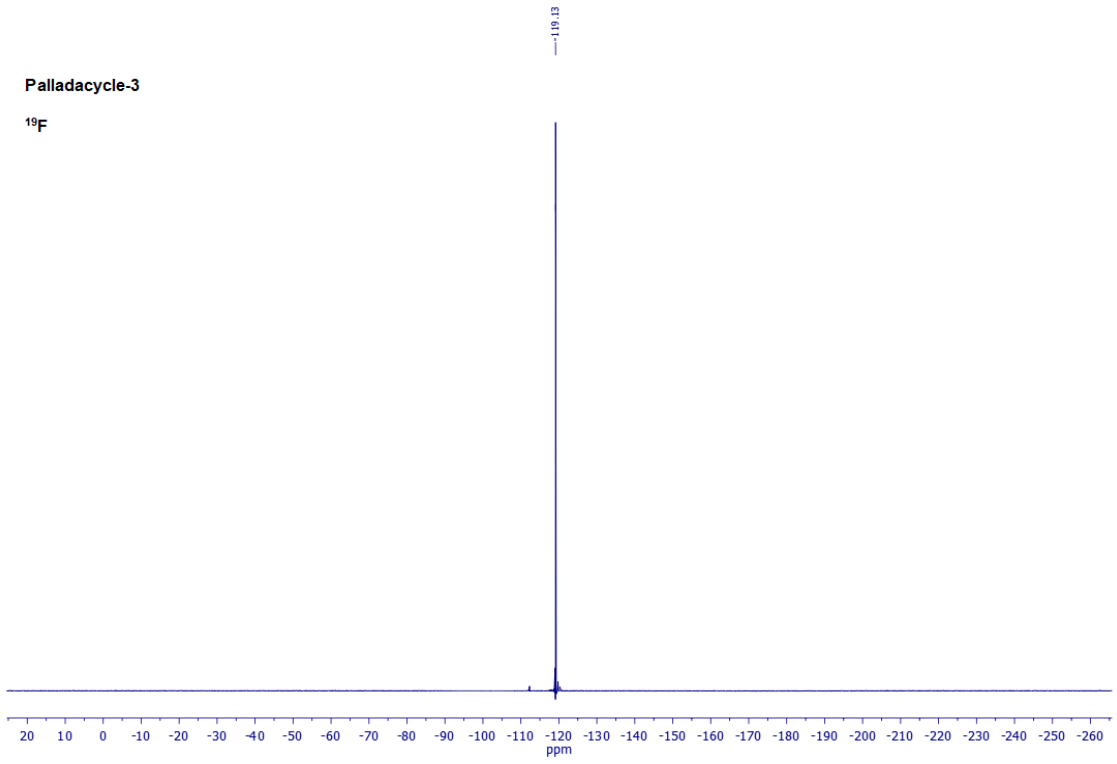
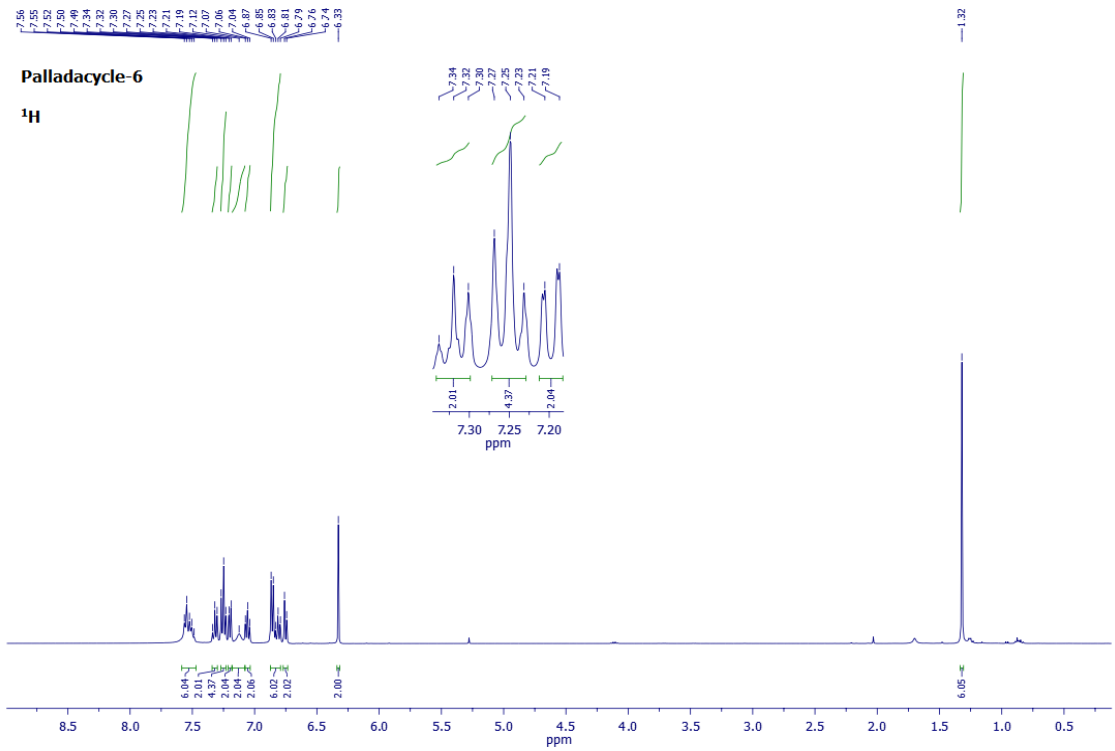
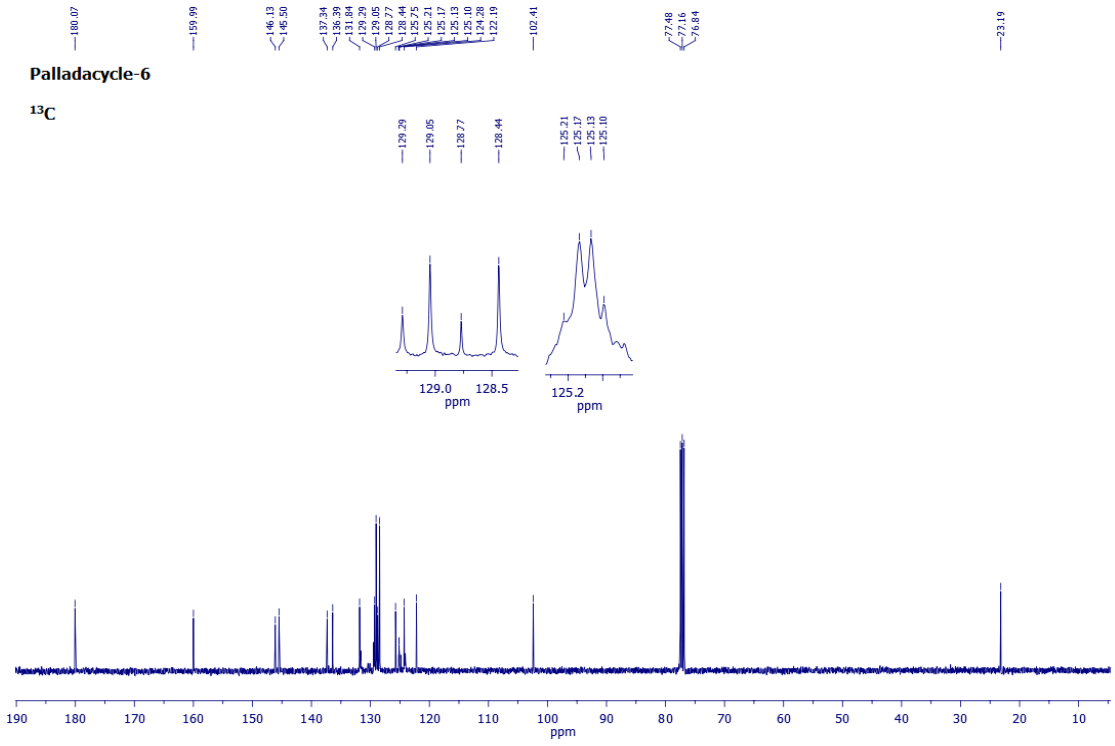


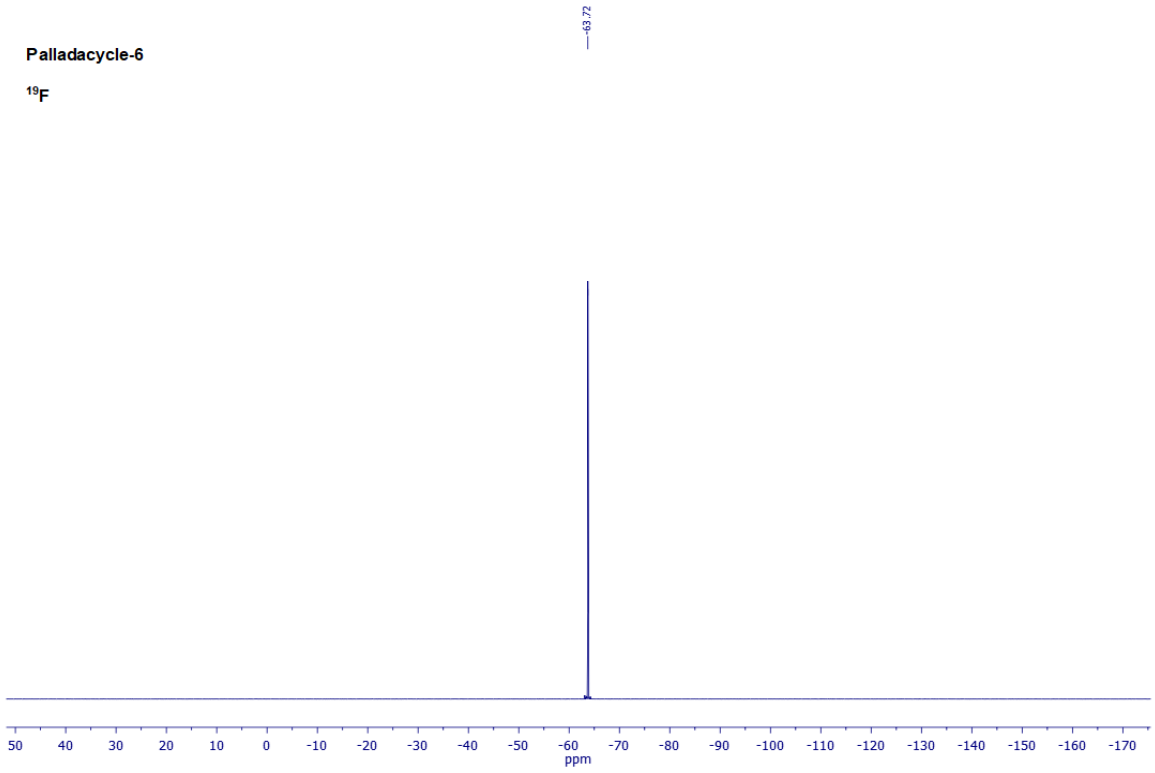
^{19}F NMR of palladacycle-**3**



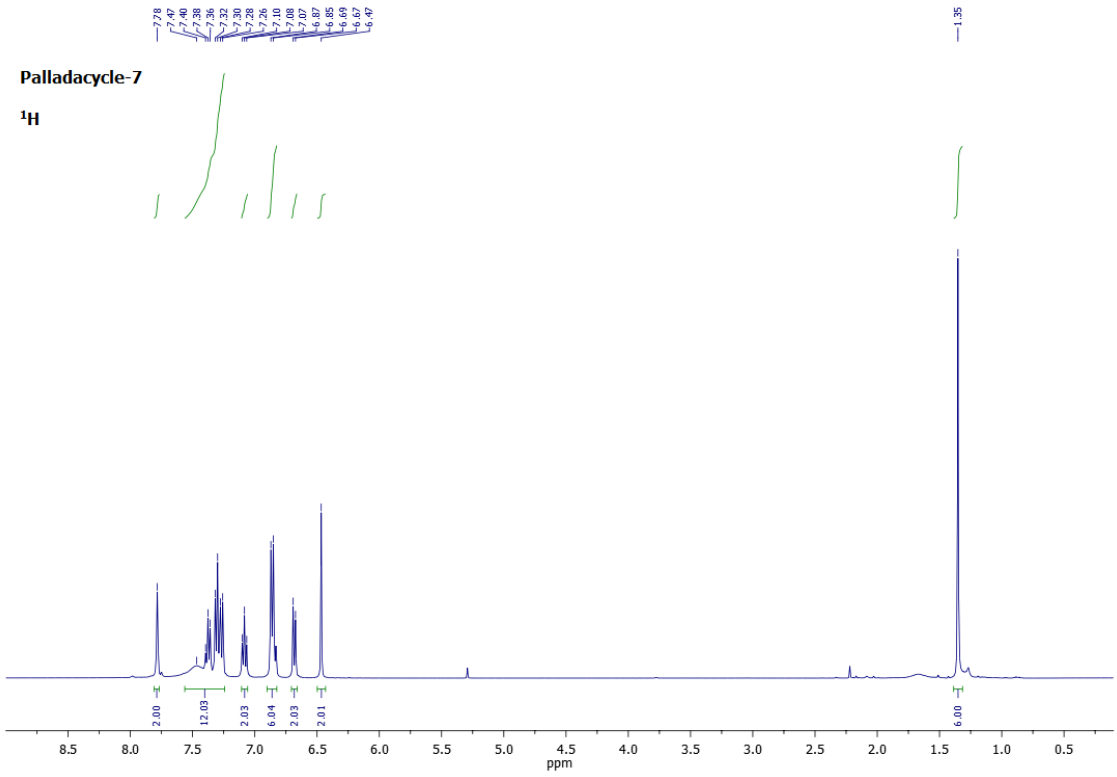
^{1}H NMR of palladacycle-**6**



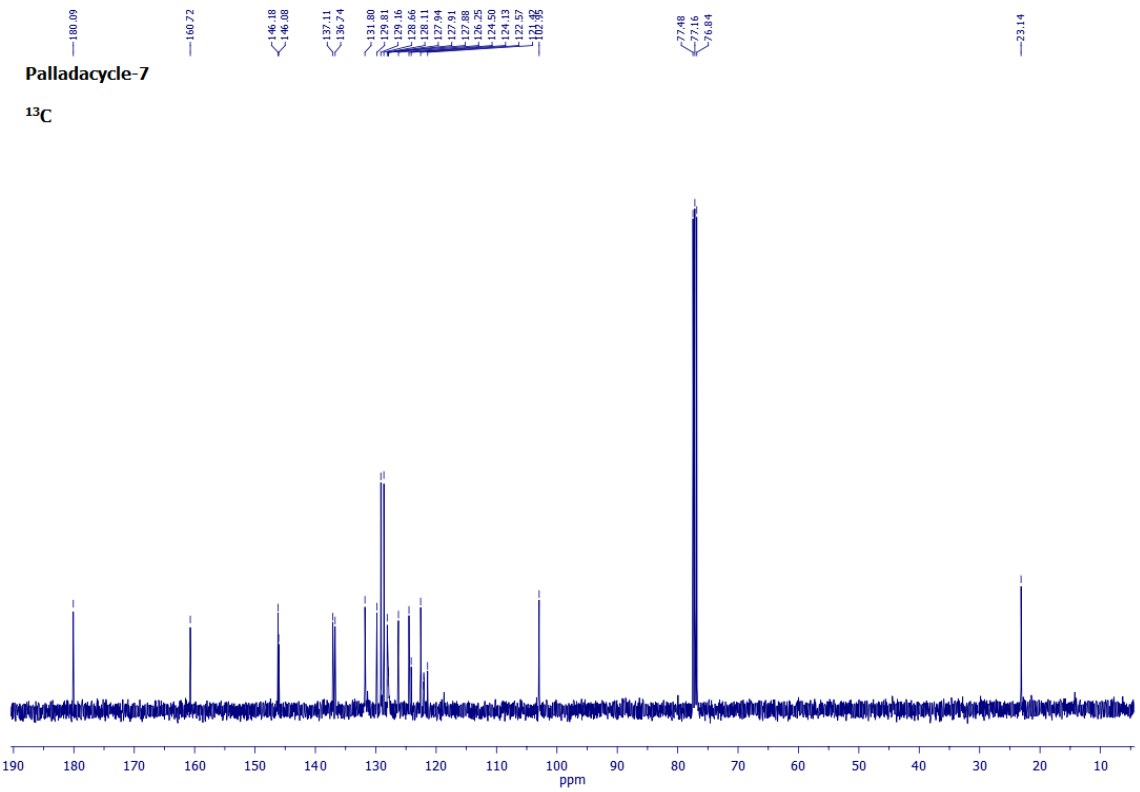
^{13}C NMR of palladacycle-**6**



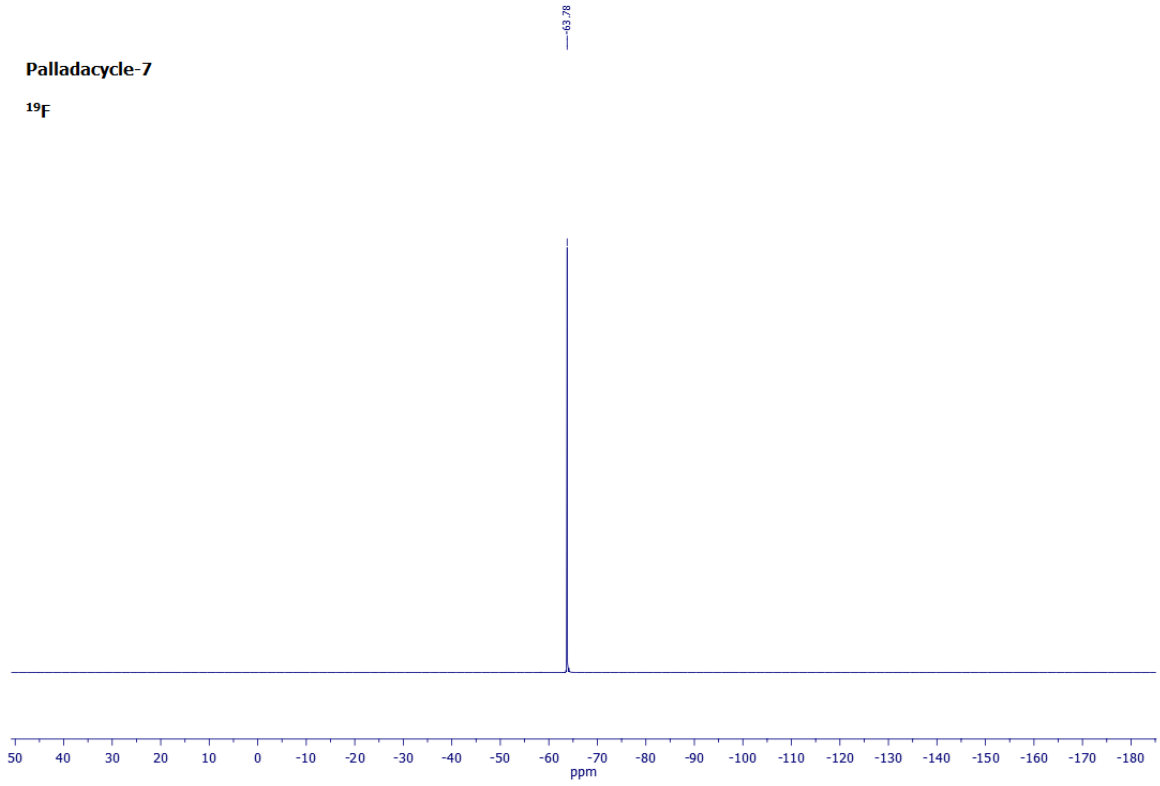
^{19}F NMR of palladacycle-**6**



^{1}H NMR of palladacycle-**7**



^{13}C NMR of palladacycle-**7**



^{19}F NMR of palladacycle-**7**

2.6 References:

1. (a) V. V. Dunina, O.A.Zalevskaya and V.M.Potapov, *Russ. Chem. Rev.,* 1988, **57**, 250; (b) W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, and H. Fischer, *Angew. Chem. Int. Ed.*, 1995, **34**, 1844; (c) I. P. Beletskaya and A. V. Cheprakov, *J. Organomet. Chem.,* 2004, **689**, 4055; (d) V. V. Dunina and O. N. Gorunova, *Russ. Chem. Rev.,* 2005, **74**, 871; (e) J. Dupont, C. S. Consorti, and J. Spencer, *Chem. Rev.,* 2005, **105**, 2527.

2. (a) M. Nonoyama, *Transition Met. Chem.,* 1982, **7**, 281; (b) R. Bosque and F. Maseras, *Eur. J. Inorg. Chem.,* 2005, **2005**, 4040; (c) T. W. Lyons and M. S. Sanford, *Chem. Rev.,* 2010, **110**, 1147; (d) K. M. Engle, T.-S. Mei, M. Wasa and J. Q. Yu, *Acc. Chem. Res.,* 2012, **45**, 788; (e) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, *Org. Chem. Front.,* 2014, **1**, 843; (f) S.-Y. Zhang, Q. Li, G. He, W. A. Nack and G. Chen, *J. Am. Chem. Soc.,* 2015, **137**, 531; (g) R. Frutos-Pedreño, E. García-Sánchez, M. J. Oliva-Madrid, D. Bautista, E. Martínez-Viviente, I. Saura-Llamas, and J. Vicente, *Inorg. Chem.,* 2016, **55**, 5520.

3. M. Gomez, J. Granell and M. Martinez, *Organometallics*, 1997, **16**, 2539.

4. (a) O. N. Gorunova, K. J. Keuseman, B. M. Goebel, N. A. Kataeva, A. V. Churakov, L. G. Kuz'mina, V. V. Dunina and I. P. Smoliakova, *J. Organomet. Chem.,* 2004, **689**, 2382; (b) K. J. Keuseman, I. P. Smoliakova and V. V. Dunina, *Organometallics,* 2005, **24**, 4159.

5. G. D. Roiban, E. Serrano, T. Soler, G. Aullón, I. Grosu, C. Cativiela, M. Martínez and E. P. Urriolabeitia, *Inorg. Chem.*, 2011, **50**, 8132.

6. W. B. Cross, E. G. Hope, Y.-H. Lin, S. A. Macgregor, K. Singh, G. A. Solan and N. Yahya, *Chem. Commun.,* 2013, **49**, 1918.

7. A. Mercier, S. Wagschal, L. Gue´ne´e, C. Besnard and E. P. Ku¨ndig, *Organometallics,* 2013, **32**, 3932.

8. M. Kondrashov, S. Raman and O. F. Wendt, *Chem. Commun.*, 2015, **51**, 911.

9. (a) J. L. Serrano, L. García, J. Pérez, E. Pérez, J. M. Galiana, J. García, M. Martínez, G. Sánchez and I. da Silva, *Dalton Trans.*, 2011, **40**, 156; (b) M. Micksch, M. Tenne and T. Strassner, *Organometallics*, 2014, **33**, 3966.

10. S. Mukherjee, P. S. Salini, A. Srinivasan and S. Peruncheralathan, *Chem. Commun.*, 2015, **51**, 17148.

11. X. Fan, T. Lei, C. Zhou, Q. Meng, B. Chen, C. Tung and L. Wu, *J. Org. Chem.*, 2016, **81**, 7127.

12. Z. Gondaand and Z.Novak, *Chem. Eur. J.,* 2015, **21**, 16801.

13. H. Cho, F. Török and B. Török, Green Chem., 2014, **16**, 3623.

14. R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Dalton Trans.*, 2015, **44**, 5805.

15. R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Tetrahedron*, 2017, **73**, 2225.

16. R. Mamidala, S. Samser, N. Sharma, U. Lourderaj and K. Venkatasubbaiah, Organometallics, 2017, 36, 3343.

17. New compound.

Cyclometalated 1,3,5-triphenyl pyrazole palladium dimer as a catalyst (or) pre-catalyst towards cross-coupling reactions

3.1 Introduction

The palladium catalyzed Suzuki-Miyaura and Mizoroki-Heck reactions are the most important C─C bond forming reactions and play vital roles in modern organic synthesis.[1-7] Usually, 1 to 5 mol% of palladium loading along with phosphine ligands are utilized to perform these cross-coupling reactions.[8-10] As organophosphines are air-sensitive, expensive and poisonous, several research groups have concentrated on developing phosphine free catalyst systems [11-22] for the C─C bond formation reactions. Palladacycles [23-31] are important organometallic compounds that contain one or two intramolecularly stabilized neutral donor atoms and one palladium-carbon bond. They have gained considerable interest owing to their stability towards air and moisture and also their potential applications in material science, catalysis, and organic synthesis, biological and medicinal chemistry.

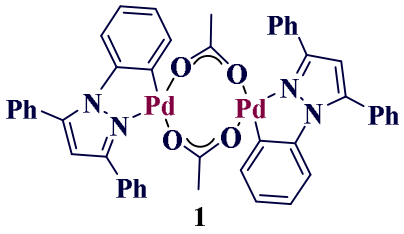
Herrmann and co-workers reported the first application of cyclopalladated tri-*o*-tolyl-phosphine complex for cross-coupling reactions,[32] raised high expectations for the palladacycles. Since, then several groups have reported numerous CN,[33-46] CS,[47,48] and CP [39, 49-53] palladacycle catalysts or pre-catalysts and pincer [54-57] palladium complexes. The CN palladacycles [35-53] gained interest since the pioneering work of Milstein and co-workers [35,36] on imine-based palladacycles for the cross-coupling reactions. The importance of the CN palladacycles expanded significantly by Buchwald,[46,47] Gladysz,[39,40] Najera,[42,43] Nowotny [37] and others. All these palladacycles are bench stable and showed high activity over conventional Pd(0) catalysts. Inspired by all these reports we concentrated in the synthesis of new and

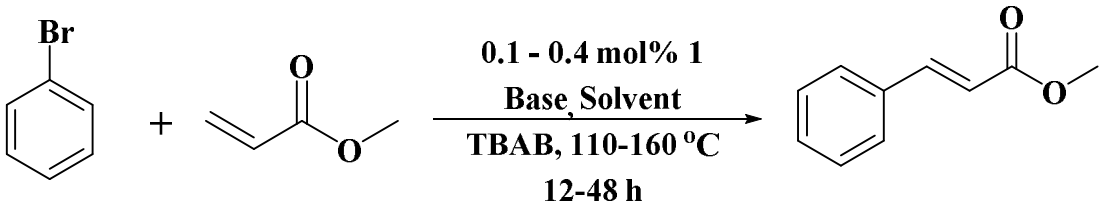
simple palladacycles. Although several reports exist on the synthesis and characterization of pyrazole (CN) palladacycles,[58-60] surprisingly so far there is only one report for the Heck reaction.[44] Inspired and motivated by the importance of C─C bond forming reactions using palladacycles the catalytic activity of palladacycle-**1** towards Suzuki-Miyaura and Mizoroki-Heck reactions are presented here.[72]

3.2 Results and Discussions

The synthesis and characterization of palladacycle-**1** are presented in chapter-II. First, we evaluated the activity of the palladacycle-**1** towards the Mizoroki-Heck reaction. The coupling between bromobenzene and methyl acrylate was chosen as the model reaction. No detectable conversion was observed in the absence of an additive, K_2CO_3 as a base and DMF as a solvent at 110 ^oC (Table 3.1, entry 1), however with the increase in temperature to 140 °C we observed ca., 22% of the desired product. To further improve the efficiency of the product formation, we varied catalyst loading, temperature, bases, and solvents. The use of NMP as a solvent at 0.2 mol% pre-catalyst loading gave 81% yield of the desired *trans*-methyl cinnamate (Table 3.1, entry 15). With these optimized conditions in hand, we also examined the reaction between bromobenzene and styrene. The reaction proceeds smoothly and gave an essentially quantitative yield of the desired product (99%), which is the best catalytic efficiency of our palladacycle-**1** under these reaction conditions.

Table 3.1: Optimization of Heck cross coupling reaction of bromobenzene and methyl acrylate using palladacycle-1[a]





Entry	Cat. (mol%)	Base	Solvent	TBAB (mol%)	T (°C)	Time (h)	Yield[b] (%)
1	0.1	K_2CO_3	DMF	-	110	12	trace
2	0.1	K_2CO_3	DMF	-	130	12	12
3	0.1	K_2CO_3	DMF	-	130	30	21
4	0.1	K_2CO_3	DMF	-	140	30	22
5	0.1	K_2CO_3	DMF	10	140	30	32
6	0.1	K_3PO_4	DMF	10	140	30	54
7	0.1	K_3PO_4	DMF	10	160	30	57
8	**0.2**	**K_3PO_4**	**DMF**	**10**	**160**	**30**	**62**
9	0.2	K_3PO_4	DMAc	10	160	30	45
10	0.2	$K_3PO_4.H_2O$	DMF	10	160	30	15
11	0.4	K_3PO_4	DMF	10	160	30	49[c]
12	0.4	K_3PO_4	DMAc	10	160	30	65
13	0.2	K_3PO_4	DMF	20	160	30	61
14	0.2	K_3PO_4	DMF	20	160	48	63

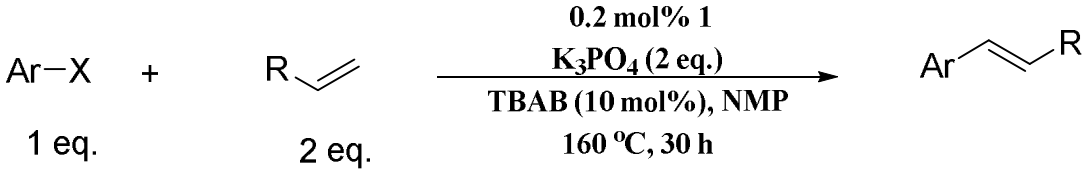
15	**0.2**	**K_3PO_4**	**NMP**	**10**	**160**	**30**	**81**

[a]Reaction conditions: 1 equiv of bromobenzene, 2 equiv of methyl acrylate, 2 equiv of base, TBAB: Tetrabutylammoniumbromide, DMAc: dimethylacetamide, NMP: N-methyl-2-pyrrolidone; [b]isolated yield after chromatography; [c]biphenyl product was also observed, [d]turn over number, based on a number of moles of the isolated product.

As our catalyst is analogous to the catalyst reported by Grigg and co-workers,44 we briefly studied the efficacy of our palladacycle-**1** in the Heck reaction (iodobenzene and methyl acrylate) using one of the lowest catalyst loading given in Grigg's work. It was found that the turnover number (TON) of our catalyst reached up to $1.88x10^6$ with 86% isolated yield, under identical conditions used in Grigg and co-workers.[44] As expected, a decrease in TONs was observed when the temperature of the reaction medium reduced from 110 °C to 90 °C. However at the same catalyst loading employing K_3PO_4 as a base (reaction conditions used in this work) resulted in TON of $1.92x10^6$ and 96% isolated yield. The observed high catalytic efficiency may be (a) due to the electronic effect of two phenyl rings present in our ligand and/or (b) due to NMP/K_3PO_4. It should be noted that NMP was reported as a good stabilizing agent for Pd-colloids in ligand free Heck reactions.[62] In some instance [63] the reactions were performed around 120 °C to get moderate yields. It was also evident from the literature, Pd-cycles act as a source of Pd(0) which can be released at a slower rate [64] than that of the catalytic reaction. To explore the scope of the reactions catalyzed by our palladacycle pre-catalyst under the above mentioned reaction condition, we examined the cross-coupling of a variety of aryl bromides with methyl acrylate and/or styrene. The results are presented in table 3.2. To our delight, the Heck arylation of aryl bromides proceeded smoothly under these conditions yielding the corresponding

products in moderate to good yields, however, activated 4-bromobenzonitrile converted to the desired product with low yields (Table 3.2, entry 9, 10). Apart from aryl bromides, aryl iodides could also be coupled under the same reaction conditions (Table 3.2, entry 13-16). Unfortunately, our pre-catalyst is not active enough to handle aryl chlorides, however, activated aryl chloride gave the desired product in low yields.

Table 3.2 : Palladacycle-1 catalyzed Heck reactions of aryl halides with terminal olefins



Entry	Ar-X	R	Yield[a] (%)	TON[c]
1	C_6H_5Br	─ COOMe	81 (82)[d]	404
2		─ C_6H_5	98	496
3	4-OMe-C_6H_4Br	─ COOMe	96	480
4		─ C_6H_5	98	486
5	2-OMe-C_6H_4Br	─ COOMe	64	317
6		─ C_6H_5	78	390
7	4-Ph-C_6H_4Br	─ COOMe	84	423
8		─ C_6H_5	72	360
9	4-CN-C_6H_4Br	─ COOMe	47	231
10		─ C_6H_5	37	184
11	1-CH_3-3-CH_3-	─ COOMe	93	467

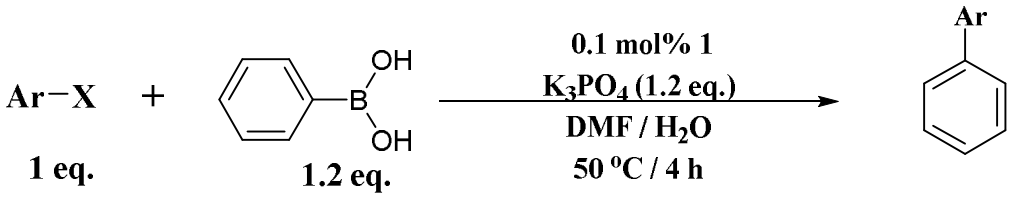
	C_6H_3Br			
12		$-C_6H_5$	95	473
13	C_6H_4I	-COOMe	99[b]	497
14		$-C_6H_5$	99b (99)[d]	496
15	4-Me-C_6H_4I	-COOMe	86[b]	421
16		$-C_6H_5$	84[b]	419
17	4-CF_3-C_6H_4Cl	-COOMe	31	154
18		$-C_6H_5$	69	346
19	4-COMe-C_6H_4Cl	-COOMe	trace	-
20		$-C_6H_5$	54 (53)[d]	269

[a]Isolated yield after chromatography; [b]TBAB was not used, [c]turn over number (TON), based on number of moles of the isolated product, [d]reactions were performed using 6 mmol of aryl halide.

We next investigated whether our palladacycle-**1** could also facilitate the Suzuki-Miyaura reactions. The reactions were carried out relatively milder condition in the presence of water and the results are presented in table 3.3. In a typical reaction, 1 equivalent of aryl bromide was reacted with 1.2 equivalents of phenyl boronic acid in the presence of 0.1 mol% of the palladacycle-**1**, 1.2 equivalent of K_3PO_4 at 50 °C for 4 h. Both electron-rich, as well as electron-poor aryl bromides and aryl iodides, could be converted to the desired products in moderate to high yields (Table 3.3, entries 1-7). Later we sub*J*ected our palladacycle-**1** pre-catalyst to cross-coupling between phenyl boronic acid and aryl chlorides. Not surprisingly, under the conditions mentioned above the aryl chlorides could not be converted effectively (Table 3.3, entry 8), however, 4 to 41% yields were achieved at elevated temperature

(100 °C). We have not made any attempts to determine whether unreacted palladacycle-**1** or other palladium containing species could be detected at the end of the catalytic reactions. However, a blank run was carried out after the catalytic run to test whether residual catalyst present in the system or not. As expected no product formation was observed.

Table 3.3: Palladacycle-1 catalyzed Suzuki reactions of aryl halides with phenylboronic acid



Entry	Ar-X	Yield[a] (%)
1	4-OMe-C_6H_4Br	99(99)[d]
2	2-OMe-C_6H_4Br	98
3	4-Ph-C_6H_4Br	81(82)[d]
4	4-CN-C_6H_4Br	94
5	1-CH_3-3-CH_3-C_6H_3Br	93
6	4-CHO-C_6H_4Br	99
7	4-CH_3-C_6H_4I	99(99)[d]
8	4-$COCH_3$-C_6H_4Cl	trace
9	4-$COCH_3$-C_6H_4Cl	38[b]

10	4-CF_3-C_6H_4Cl	41[b](40)[d]
11	4-CH_3-C_6H_4Cl	11[b]
12	4-OCH_3-C_6H_4Cl	4[b]

[a]Isolated yield after chromatography; [b]reactions were performed at 100 [o]C for 6 h, [c]turn over number (TON), based on number of moles of the isolated product, [d]reactions were performed using 6 mmol of aryl halide.

3.3 Conclusion

In summary, we have studied palladacycle-**1** in Suzuki-Miyaura and Mizoroki-Heck cross-coupling reactions. The palladacycle-**1** showed appreciable catalytic activity for the Mizoroki-Heck reaction, moreover, it showed good catalytic activity towards Suzuki-Miyaura under mild reaction conditions.

3.4 Experimental Section

3.4.1 General information

All reagents and solvents were obtained from commercial sources. Solvents were purified according to standard procedures. All 400 MHz ^1H, 100 MHz ^{13}C, 376 MHz ^{19}F spectra were recorded on a spectrometer operating at 400 MHz. All ^1H and ^{13}C NMR spectra were referenced internally to solvent signals. ^{19}F NMR spectra, to α,α,α-trifluorotoluene (0.05% in $CDCl_3$; δ = -63.73). High-resolution mass spectra (HRMS) were recorded with using the micro TOF-QII mass spectrometer.

3.4.2 General Procedure for Mizoroki–Heck Reactions

A Schlenk tube was charged with aryl halide (3.18 mmol), potassium phosphate (6.36 mmol), tetra-*n*-butyl ammonium bromide (0.31 mmol) and the palladacycle-**1** ($6.4x10^{-3}$ mmol). The tube was connected to a vacuum line under argon and purged three times. N-methyl-2-pyrrolidone (4 mL) and the olefin (6.36 mmol) were added. The reaction mixture was stirred at 160 °C for 30 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL) and filtered through celite (1cm height) silica gel (100-200 mesh, 1cm height) the filtration process was repeated with fresh ethyl acetate (2x10 mL). The combined organic solution was washed with water and brine solution. The organic phase was dried over anhydrous sodium sulphate. After removal of the solvent, the residue was subjected to column chromatography on silica gel using ethyl acetate and hexanes mixtures to afford the Mizoroki–Heck product in high purity.

3.4.3 General Procedure for Suzuki Reactions

A Schlenk tube was charged with aryl halide (3.21 mmol), potassium phosphate (3.85 mmol), phenylboronic acid (3.85 mmol) and the palladacycle-**1** ($3.2x10^{-3}$ mmol). The tube was connected to a vacuum line under argon and purged three times. A mixture of dimethylformamide and distilled water (1:1, 4 mL) was added. The reaction mixture was stirred at 50-100 °C for 4-6 h. A similar purification method (*vide supra)* was used to get the Suzuki coupled product.

3.4.4 Analytical data for the products

trans-Methyl cinnamate (Table 3.2, entry 1) [22]***:*** Prepared from bromobenzene (0.5 g, 3.18 mmol) and methylacrylate (0.55 g, 6.37 mmol). After purification by column

chromatography, the compound was isolated as a white solid (0.42 g, 2.57 mmol, 81%). Mp = 37-38 ^{o}C. HRMS (ESI): calcd. for $C_{10}H_{10}O_2$ ([M+H]$^+$): 163.0754 , found: 163.0762. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 16 Hz, 1H, CH=CH), 7.54-7.51 (m, 2H, ArH), 7.39 (t, *J* = 4 Hz, 3H, ArH), 6.45 (d, *J* = 16 Hz, 1H, CH=CH), 3.81 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 144.9, 134.4, 130.3, 128.9, 128.1, 117.8, 51.7 ppm.

(E)-1,2-diphenylethene (Table 3.2, entry 2) [22]**:** Prepared from bromobenzene (0.5 g, 3.18 mmol) and styrene (0.66 g, 6.37 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.56 g, 3.12 mmol, 98%). Mp = 124-125 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66-7.64 (m, 4H, ArH), 7.51-7.35 (m, 6H, ArH), 7.26-7.18 (.m, 2H, CH=CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.5, 128.8, 127.8, 126.7 ppm.

Methyl (E)-3-(4-methoxyphenyl)acrylate (Table 3.2, entry 3) [21]**:** Prepared from bromoanisole (0.3 g, 1.60 mmol) and methylacrylate (0.28 g, 3.21 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.30 g, 1.54 mmol, 96%). Mp = 92-93 ^{o}C. HRMS (ESI): calcd. for $C_{11}H_{12}O_3$ ([M + Na]$^+$): 215.0679 , found: 215.0689. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.66 (d, *J* = 16 Hz, 1H, CH=CH), 7.48 (d, *J* = 8 Hz, 2H, ArH), 6.91 (d, *J* = 8 Hz, 2H, ArH), 6.32 (d, *J* = 16 Hz, 1H, CH=CH), 3.83 (s, 3H, OMe), 3.77 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* = 167.8, 161.4, 144.5, 129.7, 127.1, 115.3, 114.3, 55.3, 51.6 ppm.

(E)-1-methoxy-4-styrylbenzene (Table 3.2, entry 4) [21]**:** Prepared from 4-bromoanisole (0.3 g, 1.60 mmol) and styrene (0.33 g, 3.21 mmol). After purification by column

chromatography, the compound was isolated as a white solid (0.33 g, 1.57 mmol, 98%). Mp = 134-135 ^{o}C. HRMS (ESI): calcd. for $C_{15}H_{14}O$ ($[M+H]^{+}$): 212.1151 , found: 212.1127. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.47 (m, 4H, ArH), 7.37 (t, *J* = 8 Hz, 2H, ArH), 7.26 (t, *J* = 8 Hz, 1H, ArH), 7.12 (d, *J* = 16 Hz, 1H,CH=CH), 6.98 (d, *J* = 16 Hz, 1H,CH=CH), 6.93 (d, *J* = 8 Hz, 2H, ArH), 3.85 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 137.7, 130.2, 128.7, 128.3, 127.8, 127.3, 126.7, 126.3, 114.2, 55.4 ppm.

Methyl (E)-3-(2-methoxyphenyl)acrylate (Table 3.2, entry 5) [37]**:** Prepared from 4-bromobiphenyl (0.3 g, 1.60 mmol) and methylacrylate (0.28 g, 3.21 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.20 g, 1.02 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 16 Hz, 1H, CH=CH), 7.50 (d, *J* = 8 Hz, 1H, ArH) , 7.35 (t, *J* = 8 Hz, 1H, ArH), 6.90-6.98 (m, 2H, ArH), 6.53 (d, *J* = 16 Hz, 1H, CH=CH), 3.88 (s, 3H, OMe), 3.80 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.0, 158.4, 140.3, 131.5, 128.9, 123.4, 120.7, 118.3, 111.2, 55.5, 51.6 ppm.

(E)-1-methoxy-2-styrylbenzene (Table 3.2, entry 6) [65]**:** Prepared from 2-bromoanisole (0.3 g, 1.60 mmol) and styrene (0.33 g, 3.21 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.26 g, 1.25 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63-7.48 (m, 4H, ArH), 7.36 (t, *J* = 8 Hz, 2H, ArH), 7.28-7.24 (m, 2H, ArH), 7.13 (d, *J* = 16 Hz, 1H, CH=CH), 6.99 (t, *J* = 8 Hz, 1H, ArH), 6.92 (d, *J* = 16 Hz, 1H, CH=CH), 3.90 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 138.0, 129.1, 128.7, 128.6, 127.4, 126.6, 126.5, 126.4, 123.5, 120.8, 111.0, 55.6 ppm.

Methyl (E)-3-([1,1'-biphenyl]-4-yl)acrylate (Table 3.2, entry 7) [37]**:** Prepared from 4-bromobiphenyl (0.3 g, 1.29 mmol) and methylacrylate (0.22 g, 2.57 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.26 g, 1.09 mmol, 84%). Mp = 148-149 ^{o}C. HRMS (ESI): calcd. for $C_{16}H_{14}O_2$ ([M+H]+): 239.1067 , found: 239.1064. 1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 16 Hz, 1H, CH=CH), 7.58-7.64 (m, 6H, ArH) , 7.48-7.44 (t, *J* = 8 Hz, 2H, ArH) , 7.36-7.40 (t, *J* = 8 Hz, 2H, ArH), 6.49 (d, *J* = 16 Hz, 1H, CH=CH), 3.83 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 144.4, 143.1, 140.2, 133.4, 128.9, 128.6, 127.9, 127.6, 127.1, 117.7, 51.8 ppm.

(E)-4-styryl-1,1'-biphenyl (Table 3.2, entry 8) [66]**:** Prepared from 4-bromobiphenyl (0.3 g, 1.29 mmol) and styrene (0.27 g, 2.57 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.24 g, 0.94 mmol, 72%). Mp = 219-220 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.59 (m, 6H, ArH), 7.55 (d, *J* = 8 Hz, 2H, ArH), 7.46 (t, *J* = 8 Hz, 2H, ArH), 7.41- 7.35 (m, 3H, ArH), 7.30-7.25 (m, 1H, ArH), 7.17 (s, 2H, CH=CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 139.7, 136.7, 135.7, 128.1, 128.1, 128.0, 127.5, 127.0, 126.7, 126.7, 126.3, 126.2, 125.9 ppm.

Methyl (E)-3-(4-cyanophenyl)acrylate (Table 3.2, entry 9) [67]**:** Prepared from 4-bromobenzonitrile (0.3 g, 1.65 mmol) and methylacrylate (0.28 g, 3.30 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.15 g, 0.80 mmol, 47%). Mp = 106-107 ^{o}C. HRMS (ESI): calcd. for $C_{11}H_9O_2N$ ($[M+H]^+$): 188.0706 , found: 188.0703. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58-7.67

(m, 5H), 6.50 (d, *J* = 16 Hz), 3.81 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 142.4, 138.7, 132.7, 128.4, 121.4, 118.3, 113.4, 52.0 ppm.

(E)-4-styrylbenzonitrile (Table 3.2, entry 10) [51]**:** Prepared from 4-bromobenzonitrile (0.3 g, 1.65 mmol) and styrene (0.34 g, 3.30 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.13 g, 0.61 mmol, 37%). Mp = 119-120 ^{o}C. HRMS (ESI): calcd. for $C_{15}H_{11}N$ ($[M+H]^+$): 206.0964 , found: 206.0963. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.53 (m, 6H, ArH), 7.40 (t, *J* = 8 Hz, 2H, ArH), 7.32 (t, *J* = 8 Hz, 1H, ArH), 7.20 (d, *J* = 16 Hz, 1H, CH=CH), 7.07 (d, *J* = 16 Hz, 1H, CH=CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 136.3, 132.5, 132.4, 128.9, 128.7, 126.9, 126.9, 126.7, 119.1, 110.6 ppm.

Methyl (E)-3-(3,5-dimethylphenyl)acrylate (Table 3.2, entry 11) [68]**:** Prepared from 5-bromo-*m*-xylene (0.3 g, 1.62 mmol) and methylacrylate (0.28 g, 3.24 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.29 g, 1.50 mmol, 93%). Mp = 49-50 ^{o}C. HRMS (ESI): calcd. for $C_{12}H_{14}O_2$ ($[M+H]^+$): 191.1067 , found: 191.1067. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 16 Hz, 1H, CH=CH), 7.13 (s, 2H, ArH), 7.01 (s, 1H, ArH), 6.36 (d, *J* = 16 Hz, 1H, CH=CH), 3.80 (s, 3H, OMe), 2.32 (s, 6H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 145.2, 138.4, 134.3, 132.1, 126.0, 117.3, 51.6, 21.2 ppm.

(E)-1,3-dimethyl-5-styrylbenzene (Table 3.2, entry 12) [68]**:** Prepared from 5-bromo-*m*-xylene (0.3 g, 1.62 mmol) and styrene (0.34 g, 3.24 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.32 g, 1.54 mmol, 95%). Mp = 134-135 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8 Hz,

2H, ArH), 7.37 (t, *J* = 8 Hz, 2H, ArH), 7.26 (t, *J* = 8 Hz, 1H, ArH), , 7.16 (s, 2H, ArH), 7.14-7.04 (m, 2H, CH=CH), 6.93 (s, 1H, ArH), 2.36 (s, 6H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 136.8, 136.6, 128.8, 128.2, 128.0, 127.6, 126.8, 125.8, 123.8, 20.6 ppm.

Methyl (E)-3-(p-tolyl)acrylate (Table 3.2, entry 15) [19]**:** Prepared from 4-iodotoluene (0.3 g, 1.38 mmol) and methylacrylate (0.24 g, 2.75 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21 g, 1.18 mmol, 86%). Mp = 59-60 ^{o}C. HRMS (ESI): calcd. for $C_{11}H_{12}O_2$ ($[M+H]^+$): 177.0910 , found: 177.0924. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 16 Hz, 1H, CH=CH), 7.44 (d, *J* = 8 Hz, 2H, ArH), 7.21 (d, *J* = 8 Hz, 2H, ArH), 6.42 (d, *J* = 16 Hz, 1H, CH=CH), 3.82 (s, 3H, OMe), 2.39 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 144.9, 140.7, 131.7, 129.6, 128.1, 116.7, 51.6, 21.5 ppm.

(E)-1-methyl-4-styrylbenzene (Table 3.2, entry 16) [19]**:** Prepared from 4-Iodotoluene (0.3 g, 1.38 mmol) and styrene (0.34 g, 2.75 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.22 g, 1.15 mmol, 84%). Mp = 122-123 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8 Hz, 2H, ArH), 7.46 (d, *J* = 8 Hz, 2H, ArH), 7.40 (t, *J* = 8 Hz, 2H, ArH),, 7.31-7.18 (m, 4H, ArH), 7.17-7.08 (m, 2H, CH=CH), 2.41 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.55, 134.6, 129.4, 128.7, 128.6, 127.7, 127.4, 126.5, 126.4, 21.3 ppm.

Methyl (E)-3-(4-(trifluoromethyl)phenyl)acrylate (Table 3.2, entry 17) [69]**:** Prepared from 4-chlorobenzotrifluoride (0.3 g, 1.66 mmol) and methylacrylate (0.29 g, 3.32 mmol). After purification by column chromatography, the compound was isolated as

light yellow solid (0.12 g, 0.52 mmol, 31%). Mp = 76-77 ^{o}C. HRMS (ESI): calcd. for $C_{11}H_9O_2F_3$ ($[M+H]^+$): 231.0627, found: 231.0649. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 16 Hz, 1H, CH=CH), 7.64-7.61 (m, 4H, ArH), 6.50 (d, *J* = 16 Hz, 1H, CH=CH), 3.81 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 143.0, 137.8, 128.2, 125.9, 125.2, 122.5, 120.4, 51.9 ppm.

(E)-1-styryl-4-(trifluoromethyl)benzene (Table 3.2, entry 18) [70]**:** Prepared from 4-chlorobenzotrifluoride (0.3 g, 1.66 mmol) and styrene (0.35 g, 3.32 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.29 g, 1.15 mmol, 69%). Mp = 136-137 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (s, 4H, ArH), 7.52 (d, *J* = 8 Hz, 2H, ArH), 7.37 (t, *J* = 8 Hz, 2H, ArH), 7.29(t, *J* = 8 Hz, 1H, ArH), 7.18 (d, *J* = 16 Hz, 1H, CH=CH), 7.12(d, *J* = 16 Hz, 1H, CH=CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 136.7, 131.2, 128.8, 128.3, 127.1, 126.8, 126.6, 125.7, 125.6, 125.6, 125.6 ppm.

(E)-1-(4-styrylphenyl)ethan-1-one (Table 3.2, entry 20) [37]**:** Prepared from 4-chloroacetophenone (0.3 g, 1.94 mmol) and styrene (0.40 g, 3.88 mmol). After purification by column chromatography, the compound was isolated as a light yellow solid (0.23 g, 1.04 mmol, 54%). Mp = 144-145 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8 Hz, 2H, ArH), 7.60-7.54 (m, 4H, ArH), 7.39 (t, *J* = 8 Hz, 2H, ArH), 7.31 (t, *J* = 8 Hz, 1H, ArH), 7.23 (d, *J* = 16 Hz, 1H, CH=CH), 7.13 (d, *J* = 16 Hz, 1H, CH=CH), 2.61 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 142.0, 136.7, 136.0, 131.5, 128.9, 128.8, 128.3, 127.5, 126.8, 126.5, 26.6 ppm.

4-Methoxy-1,1'-biphenyl (Table 3.3, entry 1) [15]**:** Prepared from 4-bromoanisole (0.3 g, 1.60 mmol) and benzeneboronic acid (0.23 g, 1.92 mmol). After purification by column chromatography, the compound was isolated as a light yellow solid (0.29 g, 1.58 mmol, 99%). Mp = 89-90 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.55 (m, 4H, ArH), 7.51-7.43 (m, 2H, ArH), 7.40-7.34 (m, 1H, ArH), 7.07-7.00 (m, 2H, ArH), 3.90 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 140.9, 140.9, 133.8, 133.8, 128.8, 128.2, 126.8, 114.3, 55.4 ppm.

2-Methoxy-1,1'-biphenyl (Table 3.3, entry 2) [46]**:** Prepared from 2-bromoanisole (0.3 g, 1.60 mmol) and benzeneboronic acid (0.23 g, 1.92 mmol). After purification by column chromatography, the compound was isolated as a light yellow liquid (0.29 g, 1.58 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8 Hz, 2H, ArH), 7.42 (t, *J* = 8Hz, 2H, ArH), 7.35-7.31 (m, 3H, ArH), 7.06-6.99 (m, 2H, ArH), 3.82 (s, 3H, OMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 155.1, 138.6, 130.9, 130.7, 129.6, 128.6, 128.0, 126.9, 120.8, 111.2, 55.6 ppm.

1,1':4',1''-Terphenyl (Table 3.3, entry 3) [41]**:** Prepared from 4-bromobiphenyl (0.3 g, 1.29 mmol) and benzeneboronic acid (0.19 g, 1.54 mmol). After purification by column chromatography, the compound was isolated as a light yellow solid (0.24 g, 1.04 mmol, 81%). Mp = 211-212 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71-7.67 (m, 8H, ArH), 7.49 (t, *J* = 8 Hz, 4H, ArH), 7.39 (t, *J* = 8 Hz, 3H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7, 140.2, 128.9, 127.5, 127.4, 127.1 ppm.

[1,1'-biphenyl]-4-carbonitrile (Table 3.3, entry 4) [18]**:** Prepared from 4-bromobenzonitrile (0.3 g, 1.65 mmol) and benzeneboronic acid (0.24 g, 1.98 mmol).

After purification by column chromatography, the compound was isolated as a light yellow solid (0.28 g, 1.56 mmol, 94%). Mp = 88-89 ^{o}C. HRMS (ESI): calcd. for $C_{13}H_9N$ ($[M+H]^+$): 180.0808 , found: 180.0807. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74-7.67 (m, 4H, ArH), 7.60 (d, *J* = 8 Hz, 2H, ArH), 7.51-7.41 (m, 3H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 139.2, 139.0, 132.6, 129.1, 128.7, 127.7, 127.2, 119.0, 110.9 ppm.

3,5-Dimethyl-1,1'-biphenyl (Table 3.3, entry 5) [71]**:** Prepared from 5-bromo-*m*-xylene (0.3 g, 1.62 mmol) and benzeneboronic acid (0.24 g, 1.95 mmol). After purification by column chromatography, the compound was isolated as a light yellow liquid (0.27 g, 1.50 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8 Hz, 2H, ArH), 7.46 (t, *J* = 8 Hz, 2H, ArH), 7.37 (m, 1H, ArH), 7.25 (s, 2H, ArH), 7.05 (s, 1H, ArH), 2.43 (s, 6H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5, 141.3, 138.3, 128.9, 128.7, 127.2, 127.1, 125.1, 21.4 ppm.

[1,1'-biphenyl]-4-carbaldehyde (Table 3.3, entry 6) [52]**:** Prepared from 4-bromobenzaldehyde (0.3 g, 1.62 mmol) and benzeneboronic acid (0.24 g, 1.95 mmol). After purification by column chromatography, the compound was isolated as a light yellow solid (0.29 g, 1.61 mmol, 99%). Mp = 60-61 ^{o}C. HRMS (ESI): calcd. for $C_{13}H_{10}O$ ($[M+H]^+$): 183.0804 , found: 183.0808. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.07 (s, 1H, CHO), 7.94 (d, *J* = 8 Hz, 2H, ArH), 7.76 (d, *J* = 8 Hz, 2H, ArH) , 7.65 (d, *J* = 8 Hz, 2H, ArH), 7.51-7.41 (m, 3H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.0, 147.2, 139.7, 135.2, 130.3, 129.0, 128.5, 127.7, 127.4 ppm.

4-Methyl-1,1'-biphenyl (Table 3.3, entry 7) [15]**:** Prepared from 4-iodotoluene (0.3 g, 1.38 mmol) and benzeneboronic acid (0.20 g, 1.65 mmol). After purification by column chromatography, the compound was isolated as a light yellow solid (0.23 g, 1.37 mmol, 99%). Mp = 49-50 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8 Hz, 2H, ArH), 7.54 (d, *J* = 8 Hz, 2H, ArH), 7.49 (t, *J* = 8 Hz, 2H, ArH), 7.39 (t, *J* = 8 Hz, 1H, ArH), 7.32 (d, *J* = 8 Hz, 2H, ArH),, 2.46 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2, 138.4, 137.1, 129.5, 128.8, 127.0, 127.0, 21.2 ppm.

1-([1,1'-biphenyl]-4-yl)ethan-1-one (Table 3.3, entry 9) [15]**:** Prepared from 4-chloroacetophenone (0.3 g, 1.94 mmol) and benzeneboronic acid (0.28 g, 2.33 mmol). After purification by column chromatography, the compound was isolated as a light yellow liquid (0.14 g, 0.73 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8 Hz, 2H, ArH), 7.73-7.65 (m, 4H, ArH), 7.50 (t, *J* = 8 Hz, 2H, ArH), 7.45-7.41 (m, 1H, ArH), 2.67 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 145.8, 139.9, 135.9, 129.0, 128.9, 128.3, 127.3, 127.2, 26.7 ppm.

4-(trifluoromethyl)-1,1'-biphenyl (Table 3.3, entry 10) [47]**:** Prepared from 4-chlorobenzotrifluoride (0.3 g, 1.66 mmol) and benzeneboronic acid (0.24 g, 1.99 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.15 g, 0.68 mmol, 41%). Mp = 69-70 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (s, 4H, ArH), 7.62 (d, *J* = 8 Hz, 2H, ArH), 7.51-7.40 (m, 3H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 139.8, 129.0, 128.2, 127.4, 127.3, 125.7, 125.7 ppm.

3.5 Notes and references

1. A. de MeiJere and F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH: Weinheim, 2004.

2. N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457.

3. N. Miyaura, *Cross-Coupling Reactions: A Practical Guide*, Springer Verlag: Berlin, 2002.

4. C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 5062.

5. R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461.

6. G. C. Fu, *Acc. Chem. Res.*, 2008, **41**, 1555.

7. C. Torborg and M. Beller, *Adv. Synth. Catal.*, 2009, **351**, 3027.

8. N. T. S. Phan, M. VanDerSluys and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 609.

9. V. Farina, *Adv. Synth. Catal.*, 2004, **346**, 1553.

10. V. Chandrasekhar and R. S. Narayanan, *Tetrahedron Lett.*, 2011, **52**, 3527.

11. C. W. K. Gstottmayr, V. P. W. Bohm, E. Herdtweck, M. Grosche and W. Herrmann, *Angew. Chem. Int. Ed.*, 2002, **41**, 1363.

12. O. Navarro, R. A. Kelly and S. P. Nolan, *J. Am. Chem. Soc.*, 2003, **125**, 16194.

13. P. A. Gossage, H. A. Jenkins and P. N. Yadav, *Tetrahedron Lett.*, 2004, **45**, 7689.

14. B. Tao and D. W. Boykin, *J. Org. Chem.*, 2004, **69**, 4330.

15. J. H. Li, W. J. Liu and Y. X. Xie, *J. Org. Chem.*, 2005, **70**, 5409.

16. K. M. Wu, C. A. Huang, K. F. Peng and C. T. Chen, *Tetrahedron*, 2005, **61**, 9679.

17. M. R. Buchmeiser and K. Wurst, *J. Am. Chem. Soc.*, 1999, **121**, 11101.

18. R. K. Das, B. Saha, S. M. W. Rahaman and J. K. Bera, *Chem. Eur. J.*, 2010, **16**, 14459.

19. T. Mino, Y. Shirae, Y. Sasai, M. Sakamoto and T. FuJita, *J. Org. Chem.*, 2006, **71**, 6834.

20. G. A. Grasa, A. C. Hillier and S. P. Nolan, *Org. Lett.*, 2001, **3**, 1077.

21. S. B. Park and H. Alper, *Org. Lett.*, 2003, **5**, 3209.

22. J. C. Xiao, B. Twamley and J. M. Shreeve, *Org. Lett.*, 2004, **6**, 3845.

23. W. A. Herrmann, K. Ofele, D. v. Preysing and S. K. Schneider, *J. Organomet. Chem.*, 2003, **687**, 229.

24. I. P. Beletskaya and A. V. Cheprakov, *J. Organomet. Chem.*, 2004, **689**, 4055.

25. E. Alacid, D. A. Alonso, L. Botella, C. NáJera and M. C. Pacheco, *The Chemical Record*, 2006, **6**, 117.

26. J. Dupont, M. Pfeffer and J. Spencer, *Eur. J. Inorg. Chem.*, 2001, 1917.

27. J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.*, 2005, **105**, 2527.

28. V. V. Dunina and O. N. Gorunova, *Russ. Chem. Rev.*, 2005, **74**, 871.

29. M. Ghedini, I. Aiello, A. Crispini, A. Golemme, M. La Deda and D. Pucci, *Coord. Chem. Rev.*, 2006, **250**, 1373.

30. A. C. F. Caires, *Anti-Cancer Agents Med. Chem.*, 2007, **7**, 484.

31. A. Garoufis, S. K. HadJikakou and N. HadJiliadis, *Coord. Chem. Rev.*, 2009, **253**, 1384.

32. W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller and H. Fischer, *Angew. Chem., Int. Ed.*, 1995, **34**, 1844.

33. M. Ohff, A. Ohff and D. Milstein, *Chem. Commun.*, 1999, 357.

34. M. Nowotny, U. Hanefeld, H. v. Koningsveld and T. Maschmeyer, *Chem. Commun.*, 2000, 1877.

35. T. Rosner, *J.* Le Bars, A. Pfaltz and D. G. Blackmond, *J. Am. Chem. Soc.*, 2001, **123**, 1848.

36. C. Rocaboy and *J.* A. Gladysz, *New J. Chem.*, 2003, **27**, 39.

37. D. A. Alonso, C. Ná*J*era and M. C. Pacheco, *Adv. Synth. Catal.*, 2002, **344**, 172.

38. C. Baleizao, A. Corma, H. Garcia and A. Leyva, *J. Org. Chem.*, 2003, **69**, 439.

39. C. S. Consorti, M. L. Zanini, S. Leal, G. Ebeling and *J.* Dupont, *Org. Lett.*, 2003, **5**, 983.

40. N. C. Bruno, M. T. Tudge and S. L. Buchwald, *Chem. Sci.*, 2013, **4**, 916.

41. M. Micksch, M. Tenne and T. Strassner, *Organometallics*, 2014, **33**, 3966.

42. P. R. Likhar, S. M. Salian, S. Roy, M. L. Kantam, B. Sridhar, K. V. Mohan and B. *J*agadeesh, *Organometallics*, 2009, **28**, 3966.

43. E. A. B. Kantchev, G. R. Peh, C. Zhang and *J.* Y. Ying, *Org. Lett.*, 2008, **10**, 3949.

44. X. Gai, R. Grigg, M. I. Ramzan, V. Sridharan, S. Collard and *J.* E. Muir, *Chem. Commun.*, 2000, 2053.

45. *J.* M. Chitanda, D. E. Prokopchuk, *J.* W. Quail and S. R. Foley, *Dalton Trans.*, 2008, 6023.

46. O. Navarro, N. Marion, Y. Oonishi, R. A. Kelly and S. P. Nolan, *J. Org. Chem.*, 2006, **71**, 685.

47. D. Zim, A. S. Gruber, G. Ebeling, *J.* Dupont and A. L. Monteiro, *Org. Lett.*, 2000, **2**, 2881.

48. A. S. Gruber, D. Zim, G. N. Ebeling, A. L. Monteiro and *J*. R. Dupont, *Org. Lett.*, 2000, **2**, 1287.

49. M. Beller, H. Fischer, W. A. Herrmann, K. Öfele and C. Brossmer, *Angew. Chem. Int. Ed.*, 1995, **34**, 1848.

50. L. F. Tietze, H. Schirok, M. Wöhrmann and K. Schrader, *Eur. J. Org. Chem.*, 2000, **2000**, 2433.

51. W. A. Herrmann, C. Brossmer, C.-P. Reisinger, T. H. Riermeier, K. Öfele and M. Beller, *Chem. Eur. J.*, 1997, **3**, 1357.

52. S. Gibson, D. F. Foster, G. R. Eastham, R. P. Tooze and D. *J*. Cole-Hamilton, *Chem. Commun.*, 2001, 779.

53. M. Catellani, E. Motti and M. Minari, *Chem. Commun.*, 2000, 157.

54. M. Albrecht and G. van Koten, *Angew. Chem. Int. Ed.*, 2001, **40**, 3750.

55. *J*. T. Singleton, *Tetrahedron*, 2003, **59**, 1837.

56. W. *J*. Sommer, K. Yu, *J*. S. Sears, Y. *J*i, X. Zheng, R. *J*. Davis, C. D. Sherrill, C. W. *J*ones and M. Weck, *Organometallics*, 2005, **24**, 4351.

57. N. Selander and K. *J*. Szabo, *Chem. Rev.*, 2011, **111**, 2048.

58. *J*. L. Serrano, L. Garcia, *J*. Perez, E. Perez, *J*. M. Galiana, *J*. Garcia, M. Martinez, G. Sanchez and I. d. Silva, *Dalton Trans.*, 2011, **40**, 156.

59. G. B. Caygill and P. *J*. Steel, *J. Organomet. Chem.*, 1987, **327**, 115.

60. A. Gonzalez, C. Lopez, X. Solans, M. Font-Bardia and E. Molins, *J. Organomet. Chem.*, 2008, **693**, 2119.

61. *J*. E. Bercaw, A. C. Durrell, H. B. Gray, *J*. C. Green, N. Hazari, *J*. A. Labinger and *J*. R. Winkler, *Inorg. Chem.*, 2010, **49**, 1801.

62. M. T. Reetz and *J*. G. de Vries, *Chem. Commun.*, 2004, 1559.

63. C. E. Willans, *J*. M. C. A. Mulders, *J*. G. de Vries and A. H. M. de Vries, *J. Organomet. Chem.*, 2003, **687**, 494.(the reagents used in this study are activated)

64. The release rate will depend on the reaction conditions, the reagents used and the structure of the catalyst.

65. *J*.-Y. Lee, *J*.-S. Shen, R.-*J*. Tzeng, I.-C. Lu, *J*.-H. Lii, C.-H. Hu and H. M. Lee, *Dalton Trans.*, 2016, **45**, 10375.

66. D. A. Alonso, C. N´a*J*era and M. C. Pacheco, *Adv. Synth. Catal*., 2002, **344**, 172.

67. A. Zhdanko, A. Schmauder, C. I. Ma, L. D. Sibley, D. Sept, F. Sasse and M. E. Maier, *Chem. Eur. J*., 2011, **17**, 13349.

68. B. Gole, U. Sanyal, R. Baner*J*ee and P. S. Mukher*J*ee, *Inorg. Chem*., 2016, **55**, 2345.

69. P. K. Hota, G. Vi*J*aykumar, A. Pariyar, S. C. Sau, T. K. Sen and S. K. Mandal, *Adv. Synth. Catal*., 2015, **357**, 3162.

70. C. Shen, H. Y. Shen, M. Yang, C. C. Xia and P. F. Zhang, *Green Chem.*, 2015, **17**, 225.

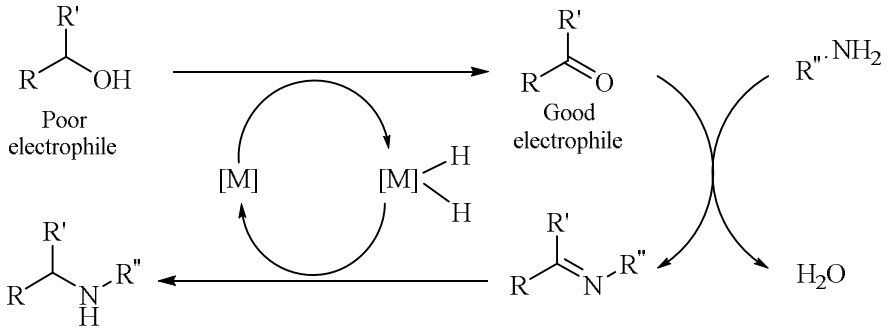
71. B. R. Barnett, L. A. Labios, *J*. M. Stauber, C. E. Moore, A. L. Rheingold, and *J*. S. Figueroa, *Organometallics*, 2017, **36**, 944.

72. R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Dalton Trans.*, 2015, **44**, 5805.

Cyclometalated palladium pre-catalyst for N-alkylation of amines using primary and secondary alcohols, and regioselective alkylation of sulfanilamide using aryl alcohols

4.1. Introduction

Metal catalyzed C─C and C─N bond formation reactions are powerful tools that are widely utilized by the synthetic chemist in a great number of syntheses.[1] Key to the success of such catalytic reactions are the development of new ligands and (or) pre-catalysts. N-alkylation of amines is one of the important C─N bond formation reactions [2] applied in the synthesis of pharmaceuticals, pesticides and functional materials. Traditionally, reactive alkyl halides have been used for the production of N-alkylated amines which often produces over-alkylated products. This method not only reduces the overall yield of the product but also produces stoichiometric amounts of inorganic waste. On the other hand use of alcohols as alkylating reagents has emerged as an interesting greener approach, owing to the fact that it produces only water as a byproduct by using "*borrowing hydrogen*" methodology.[2] As alluded in the literature,[2,5c] the poor electrophilic alcohols are activated to more active carbonyl intermediates by temporary removal of hydrogen from the alcohols. In the presence of amine the insitu formed carbonyl is converted into imine, which upon hydrogenation forms the final alkylated amine by transferring the borrowed hydrogen (Scheme 4.1).



Scheme 4.1: C─N bond formation by *borrowing hydrogen*

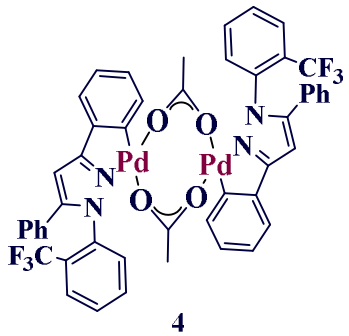
Various catalytic systems using different metals have been developed and used for the N-alkylation of amines using alcohols.[2-7] However in comparison with the Ru [3] and Ir [4] based catalysts, there are limited studies on the development of Pd-based [5] catalysts or pre-catalysts, especially homogeneous [5c,5e] pre-catalysts for N-alkylation of amines using alcohols. Recently Ramón and co-workers [5e] reported $Pd(OAc)_2$ (1 mol%) in the presence of 100 mol% of CsOH at temperatures of 130−150 °C in toluene as the solvent. Using benzylic alcohols as the alkylating agent, up to 99% yield of the alkylated amine was reported. However, this system was not active under the optimized conditions when aliphatic or secondary alcohols wereused as the alkylating agents. In 2013, Seayad and co-workers [5c] reported, $PdCl_2$ as a catalyst in the presence of dppe or Xantphos(*t*-Bu) as the ligand for the N-alkylation of primary and cyclic secondary amines, with TON up to 900 using neat reagents (no solvent) at temperatures of 90-150 °C. It is noteworthy to mention that an improved TON of about 46000 was reported using supported-palladium NiXantphos complex.[5b] Keeping these reported results in mind we focused our efforts in developing more active homogenous catalysts for the N-alkylation of amines using alcohols.

Palladacycles [8] are the most promising and versatile catalysts (or) pre-catalyst in carbon-carbon and carbon-heteroatom bond forming reactions. Owing to their facile synthesis, easy handling and possibility of tuning electronic and steric properties many research groups have devoted their efforts in synthesizing new palladacycles and studying their applications in catalysis, organic synthesis, materials and medicinal chemistry. Although ample reports exist for the dehydrogenation of alcohols,[8c] C─N and C─C bond formations using alkyl or aryl halides as reagents and palladacycles as catalyst or pre-catalyst.[9] Surprisingly, to the best of our knowledge none of the palladacycle based pre-catalysts have been tested for the N-alkylation of amines and sulfanilamide using alcohols as reagent. Herein, we report a new palladacycle which is stable in air- and moisture and highly active towards N-alkylation of amines and sulfanilamide.

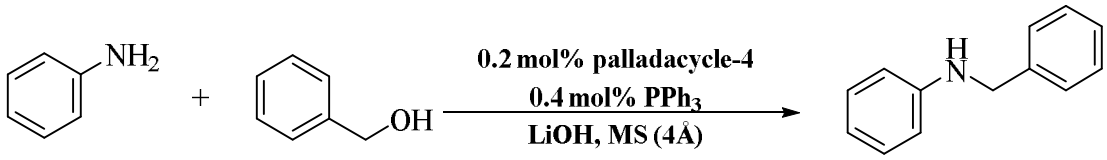
4.2. Results and discussions

The synthesis and characterization of palladacycle-**4** is described in chapter-II. Initially, we studied the reaction of benzyl alcohol with aniline as a model reaction using different bases/solvents, 4Å molecular sieves for 24 h by using 0.2 mol% of palladacycle-**4** and 0.4 mol% of PPh_3 (1:1 ratio metal to ligand) as a ligand at 120 °C. After screening various solvents and bases, we found that LiOH (50 mol%) was the best choice under solvent free conditions (Table 4.1). When carbene was used as a ligand, a low yield of only 19% was observed. When we lowered the temperature from 120 °C to 100 °C using PPh_3 as a ligand the yield got reduced from 91% to 26%.

Table 4.1: Optimization of N-alkylation of aniline with benzyl alcohol using palladacycle-4[a]



4

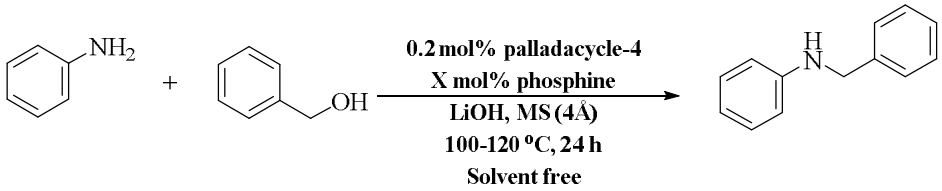


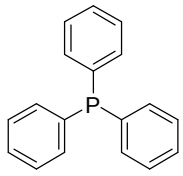
S.No.	Base	Solvent	Yield[b] (%)
1	LiOH	Benzene	Trace
2	LiOH	Toluene	19
3	LiOH	*o*-Xylene	27
4	LiOH	TBB	76
5	LiOH	-	91
6	$LiOH.H_2O$	-	82
7	KO^tBu	-	76
8	Cs_2CO_3	-	Trace
9	K_3PO_4	-	Trace
10	KOH	-	Trace
11	NaOH	-	Trace
12[c]	LiOH	-	90
13[d]	LiOH	-	73

[a]Reaction condition: aniline (3.0 mmol), benzyl alcohol (3.6 mmol), LiOH 1.5 mmol, palladacycle-**4** $6.0x10^{-3}$ mmol, PPh_3 $12.0x10^{-3}$ mmol, TBB = *tert*-butyl benzene, [b]isolated yield after column chromatography, [c]50 mol% LiOH was used, [d]25 mol% LiOH was used

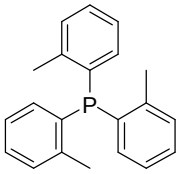
To determine which phosphine is best suited for a particular reaction, in many instances it is necessary to rely on a trial and error type screening process.[12] Keeping this in mind we examined the effect of different phosphines at 100 °C. The combination of the palladacycle-**4** with $P(2\text{-Fur})_3$ gave an almost quantitative yield (98%) of the N-alkylated product. Next, the amount of $P(2\text{-Fur})_3$ loading with respect to pre-catalyst or palladacycle-**4** was evaluated. It was found that 2:1 ratio of the $P(2\text{-Fur})_3$ to pre-catalyst is optimum to get maximum yield of the desired product (see table 4.2, entries 8, 9, 10 and 11). In the absence of $P(2\text{-Fur})_3$, the combination of the pre-catalyst with the base gave a low yield of 12% (Table 4.2, entry 14). Under similar conditions, in the absence of the pre-catalyst no product formation was observed (Table 4.2, entry 13), however palladium precursors such as $Pd(OAc)_2$, $PdCl_2$ or $Pd_2(dba)_3$ gave lower yields, 26%, 46% and 37% respectively (Table 4.2, entry 16, 17 & 18). It is noteworthy that N-phenyl ring of pyrazole ligand with electron withdrawing group ($-CF_3$) gave high yields of the N-alkylated product. However, palladacycle-1 [10a] did not yield any product under the reaction conditions mentioned *videsupra*.

Table 4.2: Phosphines Screening for palladacycle-4 catalyzed N-alkylation of aniline using benzyl alcohol[a]

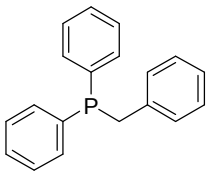




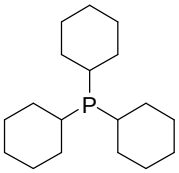
PPh_3



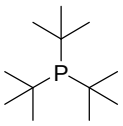
$P(o\text{-}Tol)_3$



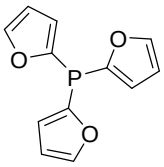
$P(Bn)(Ph)_2$



$P(Cy)_3$



$P(^tBu)_3$



$P(2\text{-}Fur)_3$

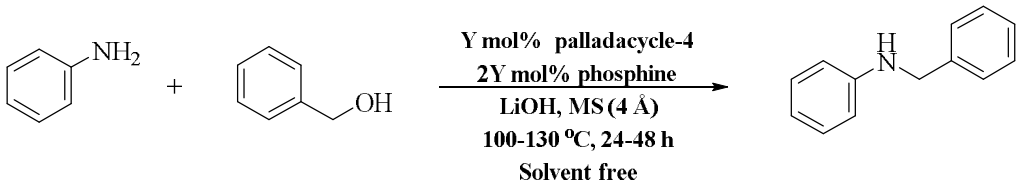
S.No.	Phosphine	X	Phosphine/ Palladacycle-4	T (^oC)	Yield[b] (%)
1	PPh_3	0.4	2	120	91
2	PPh_3	0.4	2	110	54
3	PPh_3	0.4	2	100	26
4	$P(2\text{-}Tol)_3$	0.4	2	100	19
5	$P(Bn)(Ph)_2$	0.4	2	100	24
6	$P(Cy)_3$	0.4	2	100	6
7	$P(^tBu)_3$	0.4	2	100	trace
8	$P(2\text{-}Fur)_3$	0.4	2	100	98
9	$P(2\text{-}Fur)_3$	0.2	1	100	91
10	$P(2\text{-}Fur)_3$	0.6	3	100	64

11	$P(2\text{-Fur})_3$	0.1	0.5	100	81
12	$P(2\text{-Fur})_3$	0.4	2	100	28[c]
13	$P(2\text{-Fur})_3$	0.4	-	100	0[d]
14	-	-	-	100	12[e]
15	$P(2\text{-Fur})_3$	0.4	2	100	56[f]
16	$P(2\text{-Fur})_3$	0.4	-	100	26[g]
17	$P(2\text{-Fur})_3$	0.4	-	100	46[h]
18	$P(2\text{-Fur})_3$	0.4	-	100	37[i]

[a]Reaction condition: aniline 3 mmol, benzyl alcohol 3.2 mmol, LiOH 1.5 mmol, [b]isolated yield after column chromatography, [c]LiOH was not used, [d]palladacycle-**4** was not used, [e]$P(2\text{-Fur})_3$ was not used, [f]molecular sieves were not used, [g]instead of palladacycle-**4**, 0.4 mol% $Pd(OAc)_2$ was used, [h]instead of palladacycle-**4**, 0.4 mol% $PdCl_2$ was used, [i]instead of paladacycle-**4**, 0.2 mol% $Pd_2(dba)_3$ was used

The efficiency of the catalyst for the N-alkylation of aniline using benzyl alcohol as an alkylating agent was studied by gradually decreasing the pre-catalyst loading from 0.2 mol% to 0.001 mol% and by increasing the temperature from 100 °C to 130 °C (Table 4.3). With 0.01 mol% of pre-catalyst at 100 °C, 93% (TON = 4600) of the N-alkylated product was observed. When the catalyst loading was lowered to 0.001 mol%, the pre-catalyst exhibited higher turnover number (43000) at 130 °C, which is among the highest TON's (Table 4.3, entry 11) reported for any homogeneous Pd-based catalytic system till date for N-alkylation of amines using aniline and benzyl alcohol.

Table 4.3: Palladacycle-4 efficiency for N-alkylation of aniline using benzyl alcohol[a]



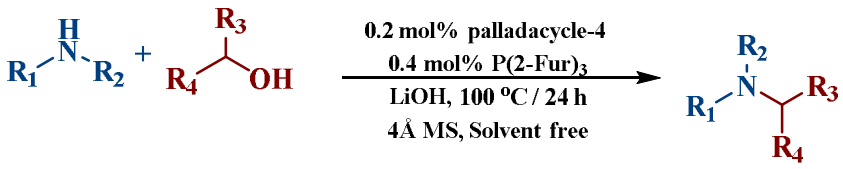
S.No.	Y	T (°C)	Time (h)	Yield[b] (%)	TON[c]
1	0.2	100	24	98	245
2	0.1	100	24	91	453
3	0.05	100	24	85	845
4	0.025	100	24	81	1621
5	0.1	110	24	96	482
6	0.05	110	24	92	917
7	0.025	110	24	87	1734
8	0.01	110	24	83	4142
9	0.01	110	48	93	4643
10[d]	0.001	120	48	61	30013
11[d]	0.001	130	48	89	43358

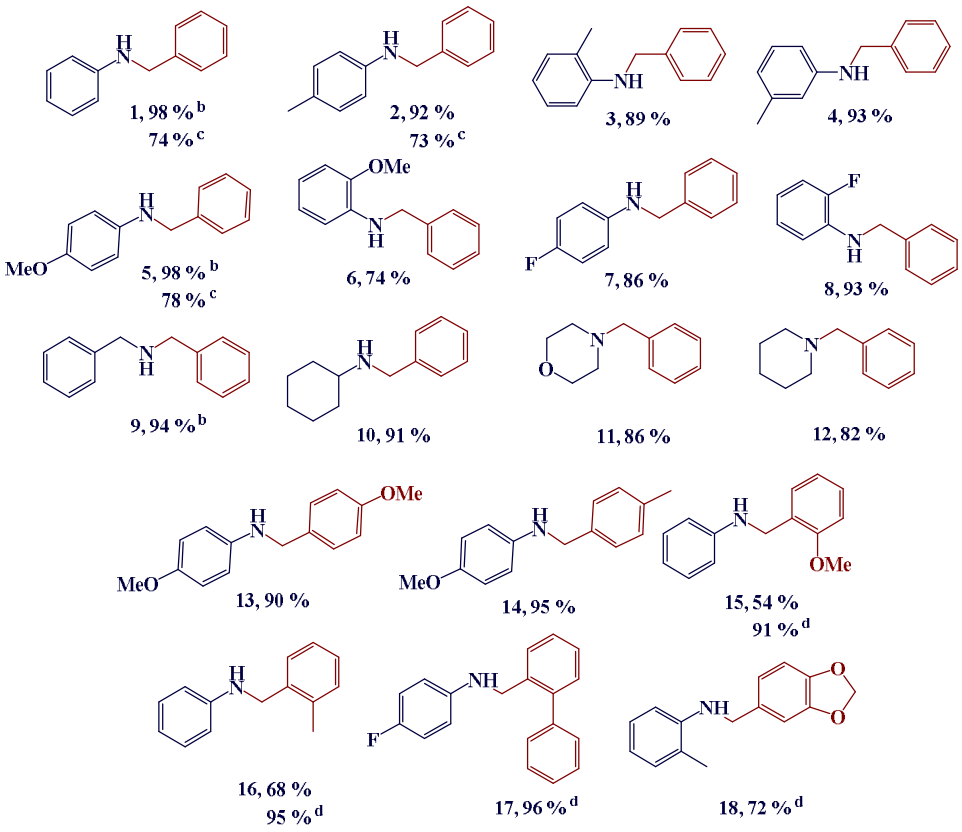
[a]Reaction condition: aniline 5.3 mmol, benzyl alcohol 6.4 mmol, LiOH 2.65 mmol, [b]isolated yield after column chromatography, [c]turn over number (TON) based on the isolated product, [d]gram scale: aniline (10.7 mmol), benzyl alcohol 12.8 mmol, LiOH 5.3 mmol; average isolated yield of two runs.

With these optimized conditions, we examined the substrate scope of the reaction using various substituted anilines, secondary amines and heterocyclic

amines with benzylalcohol at 100 °C using 0.2 mol% of pre-catalyst (Table 4.4). As presented in table 4.4, most of the amines underwent the coupling reactions with benzyl alcohol to yield the desired product in good to excellent yields. Aromatic amines such as aniline, *o,p*-methoxy aniline, *o,m,p*-methyl aniline, *o,p*-fluoroaniline and benzylamine were alkylated to give the corresponding N-benzyl amines in isolated yields of 74 to 98% (Table 4.4, entries 1-9). Cyclic secondary amines were also readily alkylated to the corresponding tertiary amines in good yields (Table 4.4, entries 11 and 12). Aromatic primary alcohols such as *p*-methyl benzyl alcohol, *p*-methoxy benzyl alcohol were also used as alkylating agents (Table 4.4, entries 14, 15). Sterically hindered *o*-methyl benzyl alcohol, *o*-methoxy benzyl alcohol and 2-biphenyl methanol were also efficiently utilized as alkylating agents at 120 °C (Table 4.4, entries 15, 16 and 17). *o*-Toluidine was also successfully alkylated with 3,4-methylenedioxy benzyl alcohol (Table 4.4, entry 18).

Table 4.4: N-Alkylation of various amines using benzyl alcohol[a]



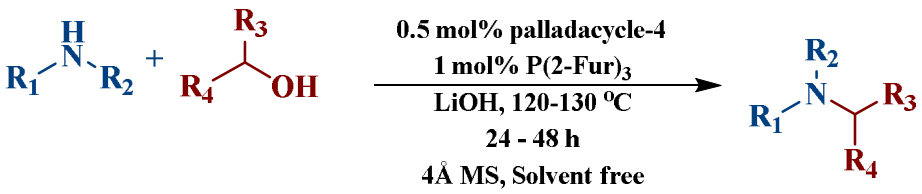


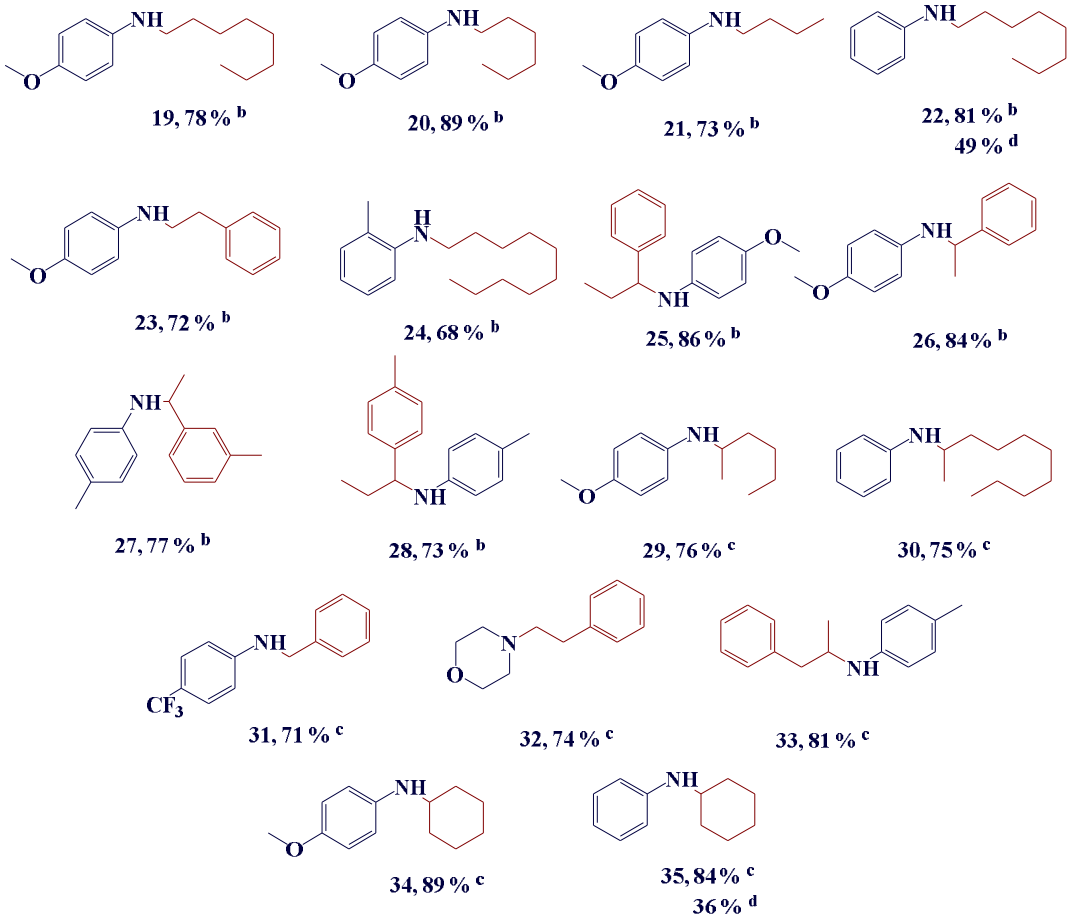
[a]Reaction condition: amine 3 mmol, benzyl alcohol 3.6 mmol, LiOH 1.5 mmol, palladacycle-**4** $6.0x10^{-3}$ mmol, $P(2\text{-Fur})_3$ $12.0x10^{-3}$ mmol, [b]average isolated yields of two runs, [c]in *tert*-butylbenzene (concentration = 1M), [d]reactions were performed at 120 °C.

The least reactive and more challenging alcohols such as aliphatic alcohols and secondary alcohols were also tested for N-alkylation using our pre-catalyst (Table 4.5). The reaction between aliphatic alcohols such as 1-octanol, 1-hexanol, *n*-butanol with *p*-methoxy aniline or aniline provided the corresponding N-alkylated product in good isolated yield of more than 72% (Table 4.5, entries 19, 20, 21 and 22). The reactions of benzyl alcohol with *p*-trifluoromethylaniline and 2-phenylethanol with *p*-methoxyaniline progressed well to give the corresponding secondary amines in 71% and 72% isolated yields respectively (Table 4.5, entries 31 & 23). To our delight, a good yield of N-alkylated morpholine was achieved with 2-phenylethanol as an alkylating

reagent (Table 4.5, entry 32). When we applied this approach to the more challenging secondary alcohols such as 1-phenylpropanol, 1-phenylethanol,1-(3-methylphenyl)ethanol, 1-(4-methylphenyl)-1-propanol, 2-hexanol, 2-decanol, 1-phenyl 2-propanol and cylohexanol at 120 °C (or) 130 °C, they were successfully alkylated to the corresponding amines (Table 4.5, entries 25-30, 33-35).

Table 4.5: N-Alkylation of various amines using primary and secondary alcohols[a]

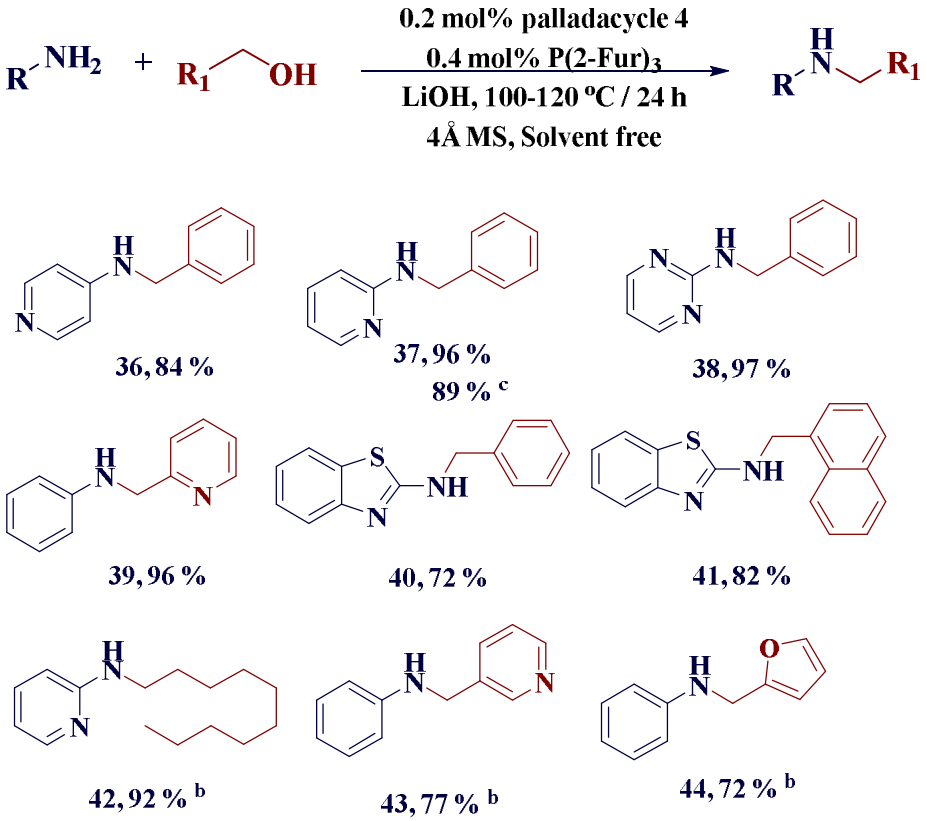




[a]Reaction condition: amine 3.0 mmol, alcohol 6.0 mmol, LiOH 1.5 mmol, palladacycle-**4** $1.5x10^{-2}$ mmol, $P(2\text{-Fur})_3$ $3.0x10^{-2}$ mmol, [b]reactions were performed at 120 ^oC for 24 h, [c]reactions were performed at 130 ^oC for 48 h, [d]in *tert*-butylbenzene (concentration = 1M)

Heteroaromatic amines, such as 4-aminopyridine, 2-aminopyridine and 2-aminopyramidine, were also efficiently alkylated under these conditions to give the products 36, 37, and 38 in 84%, 96% and 97% yields respectively (Table 4.6). 2-Aminopyridine was successfully alkylated with 1-decanol and gave quantitative yield of the corresponding product (Table 4.6, entry 42). Heteroaromatic aryl alcohols such as 2-pyridinemethanol, 3-pyridinemethanol and furfuryl alcohol were also efficiently utilized as alkylating reagents at moderate temperatures (Table 4.6, entries 39, 43 and 44). Interestingly, 2-amino benzothiazole (Table 4.6, entries 40 and 41) selectively alkylated at primary amine with benzyl alcohol and 1-naphthyl methanol.[13] As reported in the literature the regioselective N-alkylation of 2-amino benzothiozole is a challenging task, here we show that our pre-catalyst has the potential to prepare 2-(N-alkyamine)benzothiazoles *via* regioselective N-alkylation of 2-amino benzothioazoles with benzylic alcohols. Compared to the solvent free condition, the use of representative reactions using non-polar solvent (*tert*-butylbenzene) gave relatively lowyields for the N-alkylation of amines (Table 4.4, entries 1, 2 and 5; table 4.5, entries 22 and 35; table 4.6, entry 37).

Table 4.6: N-Alkylation of amines using heteroaryl amines and (or) heteroaryl alcohols[a]

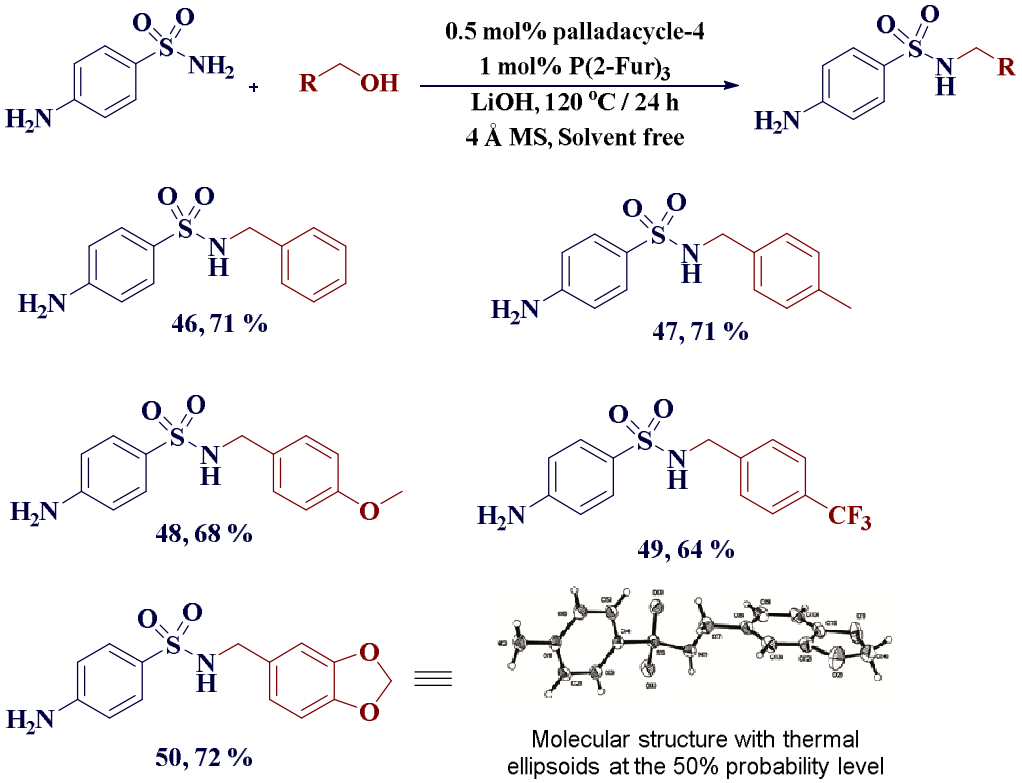


[a]Reaction condition: amine 3.0 mmol, benzyl alcohol 6.0 mmol, LiOH 1.5 mmol, palladacycle-**4** 6.0×10^{-3} mmol), $P(2\text{-Fur})_3$ 12.0×10^{-3} mmol, [b]reactions were performed using 0.5 mol% palladacycle-**4**, 1 mol% $P(2\text{-Fur})_3$ and at 120 °C, [c]in *tert*-butylbenzene (concentration = 1M)

Inspired by the results discussed *vide supra* and the regioselective N-alkylation of sulfanilamides using alcohols reported by Feng Li and co-workers [14a, 14b] we attempted N-alkylation of sulfanilamide using alcohols. To our delight our pre-catalyst successfully alkylated sulfanilamide, regioselectively, at moderate temperatures (Table 4.7, entries 45–49). As representative examples, single crystals of product 49, were grown and analysed using X-ray crystallography to confirm the regioselectivity (Table 4.7, entry 49). Benzyl alcohol having electron withdrawing group $-CF_3$ gave the N-alkylated product in 64% yield.

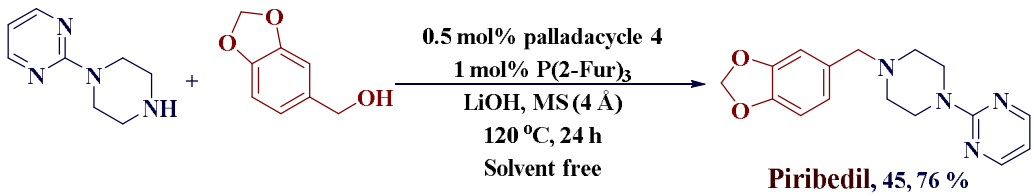
Furthermore, benzyl alcohol bearing electron donating group such as methyl and methoxy gave the desired products 46 and 47 in 71% and 68% yield respectively.

Table 4.7: Regioselective N-Alkylation of sulfanilamide using aryl alcohols[a]



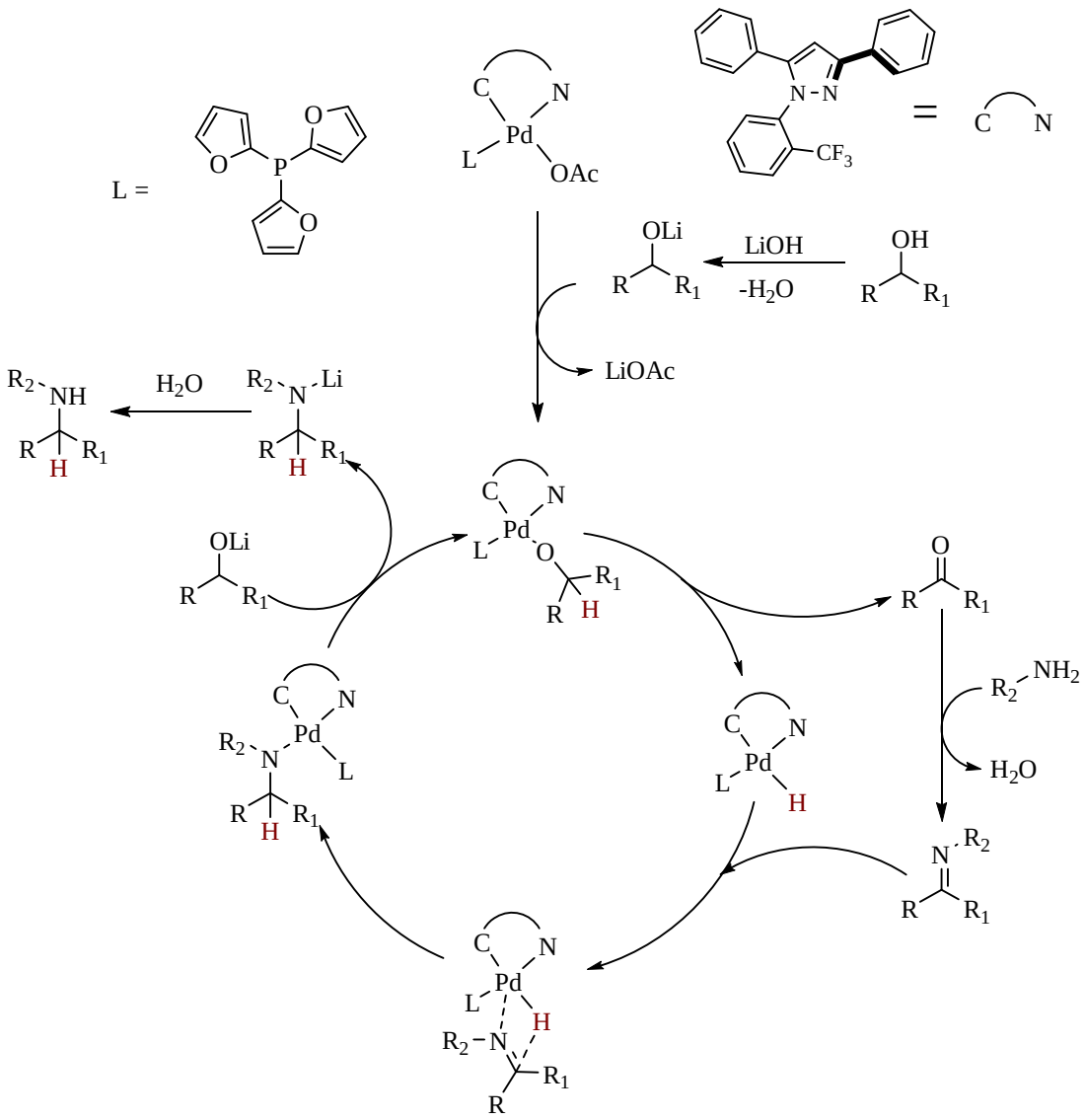
[a]Reaction condition: sulfanilamide 3.0 mmol, aryl alcohol 6.0 mmol, LiOH 1.5 mmol, palladacycle-**4** $1.5x10^{-2}$ mmol, $P(2\text{-Fur})_3$ $3.0x10^{-2}$ mmol

Furthermore, we established the synthetic utility of our palladacyle in the synthesis of piribedil,[3d] which is clinically used for the treatment of Parkinson's disease. To our delight the reaction of 1-(pyrimidin-2yl)piperazine with piperonyl alcohol in the presence of 0.5 mol% of palladacycle-**4** afforded 76% isolated yield (Scheme 4.2).



Scheme 4.2: Synthesis of piribedil using palladacycle-**4**

To acquire insight into the reaction mechanism, an NMR experiment was carried out using benzyl alcohol and aniline as substrates. The formation of aldehyde and imine was observed in its ^{1}H NMR, suggesting that abstraction of hydrogen atom takes place to generate benzaldehyde followed by condensation of amine to form imine. Plausible mechanism is proposed based on the results we obtained. Finally, the desired product is obtained by hydrogenation of the imine as shown in Scheme 4.3.[5c, 15]



Scheme 4.3: Proposed catalytic pathway for N-alkylation of amines using alcohols

4.3. Conclusion

In summary, we have demonstrated that a pyrazole based palladacycle-**4** utilized as a versatile catalyst or pre-catalyst for the N-alkylation of amines using alcohols as reagents under solvent free condition. Our palladacycle-**4** provided very high turnover numbers for N-alkylation of amines compared to the palladium based homogeneous catalysts or pre-catalysts reported in the

literature. Notably, our palladacycle-**4** has been shown to be an active regioselective catalyst for the mono alkylation of sulfanilamide.

4.4. Experimental Section

4.4.1 General information

All reagents and solvents were obtained from commercial sources. Solvents were purified according to standard procedures. All 400 MHz ^{1}H, 100 MHz ^{13}C, 376 MHz ^{19}F spectra were recorded on a spectrometer operating at 400 MHz. All ^{1}H and ^{13}C NMR spectra were referenced internally to solvent signals. ^{19}F NMR spectra, to α,α,α-trifluorotoluene (0.05% in $CDCl_3$; δ = -63.73). High resolution mass spectra (HRMS) were recorded with using microTOF-QII mass spectrometer. Single-crystal X-ray diffraction data were collected at 296 K using, Mo-K*α* radiation (0.71073 Å). SADABS absorption corrections were applied in both cases. The structure was solved and refined with SHELX suite of programs. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The H atoms were placed at calculated positions and were refined as riding atoms.

4.4.2 General procedure for N-alkylation of amines using benzyl alcohol

An oven dried Schlenk tube was charged with amine (3.0 mmol), alcohol (3.6 mmol), LiOH (1.5 mmol), palladacycle-**4** (6.0 $x10^{-3}$ mmol, 0.2 mol%), P(2-Fur)$_3$ (12.0 $x10^{-3}$ mmol, 0.4 mol%) and activated *4Å* MS (100 mg) in argon atmosphere. The reaction mixture was stirred at 100 ^{o}C for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (10 mL), and washed with water followed by brine solution. The organic phase was dried

over anhydrous sodium sulphate. After removal of the solvent, the crude was subjected to column chromatography on silica gel using ethyl acetate and hexanes mixtures to afford the N-alkylated product.

4.4.3 General procedure for N-alkylation of amines using primary and secondary alcohols

A similar protocol as mentioned for N-alkylation of amines using benzyl alcohol was used. The quantities involved are as follows: Amine (3.0 mmol), alcohol (6.0 mmol), LiOH (1.5 mmol), palladacycle-**4** ($1.5x10^{-2}$ mmol 0.5 mol%), $P(2\text{-Fur})_3$ ($1.5x10^{-2}$ mmol, 1.0 mol%) and activated *4Å* MS (100 mg). The reaction mixture was stirred at 120–130 ^{o}C for 24-48 h.

4.4.4 Procedure for N-alkylation of 2-aminobenzothiazole using aryl alcohols

An oven dried Schlenk tube was charged with LiOH (1.5 mmol), palladacycle-**4** ($6x10^{-3}$ mmol, 0.2 mol%), $P(2\text{-Fur})_3$ ($12x10^{-3}$ mmol, 0.4 mol%) and activated *4Å* MS (100 mg). The tube was connected to a vacuum line under argon and purged three times. To the reaction mixture 2-aminobenzothiazole (3.0 mmol) and alcohol (6.0 mmol) were added. The Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 100 ^{o}C for 24 h. At the end of the reaction time, the reaction mixture was cooled to room temperature, diluted with methanol (5 mL), and the tube was washed with methanol three more times (3x2 mL). The methanol solution was concentrated under vacuum and the crude was subjected to column chromatography on silica gel using ethyl acetate and hexane mixtures to afford the N-alkylated product.

4.4.5 Procedure for N-alkylation of sulfanilamide using aryl alcohols

An oven dried Schlenk tube was charged with LiOH (1.5 mmol), palladacycle-**4** ($1.5x10^{-2}$ mmol), $P(2\text{-Fur})_3$ ($3x10^{-2}$ mmol) and activated 4Å MS (100 mg). The tube was connected to a vacuum line under argon and purged three times. To the reaction mixture sulfanilamide (3.0 mmol) and aryl alcohol (6.0 mmol) were added. The Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 120 °C for 24 h. At the end of the reaction time, the reaction mixture was cooled to room temperature, diluted with methanol (5 mL), and the tube was washed with methanol three more times (3x2 mL). The methanol solution was concentrated under vacuum and the crude was subjected to flash column chromatography on silica gel using ethyl acetate and hexane mixtures to afford the N-alkylated product.

4.4.6 Procedure for gram scale reaction for N-benzylation of aniline using benzyl alcohol

A similar protocol as mentioned for N-alkylation of amines using benzyl alcohol was used. The quantities involved are as follows: Amine (1.0 g, 10.7 mmol), alcohol (12.8 mmol), LiOH (5.3 mmol), palladacycle-**4** ($1.1x10^{-7}$mmol, 0.001 mol%), $P(2\text{-Fur})_3$ ($2.2x10^{-7}$mmol, 0.002 mol%) and activated *4Å* MS (300 mg). The reaction mixture was stirred at 130 ^{o}C for 48 h. Yield =1.75 g (89%).

4.4.7 Analytical data for N-alkylated products

N-benzylaniline (Table 4.4, entry 1) [5e]***:*** Prepared from aniline (0.30 g, 3.2 mmol) and benzyl alcohol (0.42 g, 3.8 mmol). After purification by column

chromatography, the compound was isolated as a yellow liquid (0.58 g, 3.1 mmol, 98%). ^{1}H NMR (400MHz, $CDCl_3$): δ = 7.28-7.39 (m, ArH, 5H), 7.18 (t, *J* = 8 Hz, ArH, 2H), 6.72 (t, *J* = 8 Hz, ArH, 1H), 6.64 (d, *J* = 8 Hz, ArH, 2H), 4.34 (s, 2H), 4.03 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 139.6, 129.4, 128.8, 127.6, 127.4, 117.7, 112.9, 48.5 ppm. HRMS (ESI): calcd. for $C_{13}H_{13}N$ ($[M+H]^+$): 184.1121, found: 184.1147.

N-benzyl-4-methylaniline (Table 4.4, entry 2) [5c]***:*** Prepared from *p*-toludine (0.30 g, 2.8 mmol) and benzyl alcohol (0.36 g, 3.3 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.50 g, 2.5 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.30 (m, ArH, 5H), 7.01 (d, ArH, *J* = 8 Hz, 2H), 6.59 (d, ArH, *J* = 8 Hz, 2H), 4.34 (s, 2H), 2.27 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 139.7, 129.9, 128.7, 127.7, 127.3, 127.0, 113.2, 48.8, 20.5 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}N$ ($[M+H]^+$): 198.1277, found: 198.1302.

N-benzyl-2-methylaniline (Table 4.4, entry 3) [15]***:*** Prepared from *o*-toludine (0.30 g, 2.8 mmol) and benzyl alcohol (0.36 g, 3.3 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.49 g, 2.5 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47-7.34(m, ArH, 5H), 7.20- 7.15 (m, ArH, 2H), 6.76 (t, ArH, *J* = 8 Hz, 1H), 6.69 (t, ArH, *J* = 8 Hz, 1H), 4.44(s, ,2H), 2.24 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 139.9, 139.6, 130.2, 128.8, 127.7, 127.4, 127.3, 122.1, 117.4, 110.2, 48.4, 17.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}N$ ($[M+H]^+$): 198.1277, found: 198.1307.

N-benzyl-3-methylaniline (Table 4.4, entry 4) [15]**:** Prepared from *m*-toludine (0.30 g, 2.8 mmol) and benzyl alcohol (0.36 g, 3.3 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.51 g, 2.6 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.29 (m, ArH, 5H), 7.09 (t, ArH, *J* = 8 Hz, 1H), 6.57, (d, ArH, *J* = 8 Hz, 1H), 6.51-6.47 (m,ArH, 2H), 4.34 (s, 2H), 2.29 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.2, 139.5, 139.2, 129.3, 128.7, 127.7, 127.4, 118.8, 113.9, 110.3, 48.6, 21.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}N$ ($[M+H]^+$): 198.1277, found: 198.1301.

N-benzyl-2-methoxyaniline (Table 4.4, entry 5) [5e]**:** Prepared from *p*-anisidine (0.30 g, 2.4 mmol) and benzyl alcohol (0.32 g, 2.9 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.51 g, 2.4 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.29 (m, ArH, 5H), 6.79 (d, ArH, *J* = 8 Hz, 2H), 6.62 (d, ArH, *J* = 8 Hz, 2H), 4.30 (s, 2H), 3.76(s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 142.5, 139.7, 128.7, 127.7, 127.3, 115.0, 114.3, 55.9, 49.4 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NO$ ($[M+H]^+$): 214.1226, found: 214.1252.

N-benzyl-2-methoxyaniline (Table 4.4, entry 6) [5e]**:** Prepared from *o*-anisidine (0.30 g, 2.4 mmol) and benzyl alcohol (0.32 g, 2.9 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.38 g, 1.8 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.34 (m, ArH, 4H), 7.28 (t, ArH, *J* = 8 Hz, 1H), 6.87-6.80 ((m, ArH, 2H), 6.70 (t, ArH, *J* = 8 Hz, 1H), 6.62 (d, ArH, *J* = 8 Hz, 1H), 4.37 (s, 2H), 3.86 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0, 139.6, 128.7, 127.7, 127.3, 121.4, 116.9, 110.4,

109.6, 55.6, 48.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NO$ ($[M+H]^+$): 214.1226, found: 214.1260.

N-benzyl-4-fluoroaniline (Table 4.4, entry 7) [5b]**:** Prepared from 4-fluoroaniline (0.30 g, 2.7 mmol) and benzyl alcohol (0.35 g, 3.2 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.46 g, 2.3 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.27 (m, ArH, 5H), 6.89 (t, ArH, *J* = 8 Hz, 2H), 6.60 -6.57 (m, ArH, 2H), 4.30 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 154.9, 144.4, 139.2, 128.8, 127.7, 127.5, 115.8 (d, *J* = 22.3 Hz), 113.9 (d, *J* = 7.4 Hz), 49.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{12}FN$ ($[M+H]^+$): 202.1027, found: 202.1053.

N-benzyl-2-fluoroaniline (Table 4.4, entry 8) [16]**:** Prepared from 2-fluoroaniline (0.30 g, 2.7 mmol) and benzyl alcohol (0.35 g, 3.2 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.50 g, 2.5 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41-7.30 (m, ArH, 5H), 7.03-6.96 (m, ArH, 2H), 6.72-6.63 (m, ArH, 2H), 4.39 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 150.5, 139.1, 136.7 (d, *J* = 11.7 Hz), 128.8, 127.5, 127.5, 124.7, 124.7, 117.0 (d, *J* = 7.0 Hz), 114.5 (d, *J* = 18.4 Hz), 112.5, 112.5, 48.0 ppm. HRMS (ESI): calcd. for $C_{13}H_{12}FN$ ($[M+H]^+$): 202.1027, found: 202.1058.

Dibenzylamine (Table 4.4, entry 9) [5c]**:** Prepared from benzyl amine (0.30 g, 2.8 mmol) and benzyl alcohol (0.36 g, 3.3 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.51 g, 2.6

mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.14 (m, ArH, 10H), 3.72 (s, 4H), 1.75 (br, NH, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.3, 128.5, 128.3, 127.1, 53.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}N$ ($[M+H]^+$): 198.1277, found: 198.1306.

N-benzylcyclohexanamine (Table 4.4, entry 10) [5b]***:*** Prepared from cyclohexyl amine (0.30 g, 3 mmol) and benzyl alcohol (0.39 g, 3.6 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.52 g, 2.7 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.24 (m, ArH, 5H), 3.81 (s, 2H), 2.52-2.46 (m, 1H), 1.90 (d, *J* = 12 Hz, 1H), 1.76-1.72 (m, 2H),1.63-1.59 (m, 1H), 1.48 (br, NH, 1H), 1.31-1.08 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 128.5, 128.2, 126.9, 56.3, 51.2, 33.7, 26.3, 25.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}N$ ($[M+H]^+$): 190.1590, found: 190.1619.

4-benzylmorpholine (Table 4.4, entry 11) [5b]***:*** Prepared from morpholine (0.30 g, 3.4 mmol) and benzyl alcohol (0.45 g, 4.1 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.52 g, 2.9 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.32 (m, ArH, 5H), 3.71 (t, *J* = 4 Hz, 4H), 3.50 (s,2H) 2.45 (t, *J* = 4 Hz, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 129.3, 128.7, 128.4, 127.3, 127.1 , 67.1, 63.59, 53.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}NO$ ($[M+H]^+$): 178.1226, found: 178.1258.

1-benzylpiperidine (Table 4.4, entry 12) [5c]***:*** Prepared from piperidine (0.30 g, 3.5 mmol) and benzyl alcohol (0.46 g, 4.2 mmol). After purification by column

chromatography, the compound was isolated as a yellow liquid (0.50 g, 2.9 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33-7.25 (m, ArH, 5H), 3.49 (s,2H), 2.39 (s, 4H), 1.60-1.57 (m, 4H), 1.45-1.43 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.7, 129.4, 128.2, 126.9, 64.0, 54.6, 26.1, 24.5 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}N$ ($[M+H]^+$): 176.1434, found: 176.1458.

4-methoxy-N-(4-methoxybenzyl)aniline (Table 4.4, entry 13) [17]**:** Prepared from *p*-anisidine (0.37 g, 3.0 mmol) and 4-methoxy benzyl alcohol (0.49 g, 3.6 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.65 g, 2.7 mmol, 90%). Mp = 94–96 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, *J* = 8 Hz, ArH, 2H), 6.87 (d, *J* = 12 Hz, ArH, 2H), 6.78 (d, *J* = 8 Hz, ArH, 2H), 6.60 (d, *J* = 8 Hz, ArH, 2H), 4.21 (s, 2H), 3.81 (s, 3H), 3.75 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 152.3, 142.6, 131.8, 128.9, 115.0, 114.3, 114.1, 55.9, 55.4, 48.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NO_2$ ($[M+H]^+$): 244.1332, found: 244.1326.

4-methoxy-N-(4-methylbenzyl)aniline (Table 4.4, entry 14) [17]**:** Prepared from *p*-anisidine (0.37 g, 3 mmol) and 4-methyl benzyl alcohol (0.44 g, 3.6 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.65 g, 2.8 mmol, 95%). Mp = 68–69 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8 Hz, ArH, 2H), 7.17 (d, *J* = 8 Hz, ArH, 2H), 6.79 (d, *J* = 8 Hz, ArH, 2H), 6.62 (d, *J* = 8 Hz, ArH, 2H), 4.26 (s, 2H), 3.77 (s, 3H), 2.37 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 142.7, 136.9, 136.7, 129.4, 127.7, 115.0, 114.2, 55.9, 49.1, 21.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NO$ ($[M+H]^+$): 228.1383, found: 228.1391.

N-(2-methoxybenzyl)aniline (Table 4.4, entry 15) [5c]**:** Prepared from aniline (0.28 g, 3 mmol) and 2-methyl benzyl alcohol (0.82 g, 6 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.58 g, 2.7 mmol, 91%). Mp = 86–87 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.28 (m, ArH, 2H), 7.20 (t, *J* = 8 Hz, ArH, 2H), 6.96-6.91 (m, ArH, 2H), 6.75-6.68 (m, ArH, 3H), 4.37 (s, 2H), 4.15 (br, -NH-, 1H), 3.89 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 148.5, 129.3, 129.0, 128.4, 127.5, 120.6, 117.4, 113.2, 110.4, 55.4, 43.6 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NO$ ($[M+H]^+$): 214.1226, found: 214.1202.

N-(2-methylbenzyl)aniline (Table 4.4, entry 16) [18]**:** Prepared from aniline (0.28 g, 3 mmol) and 2-methyl benzyl alcohol (0.73 g, 6 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.56 g, 2.8 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 4 Hz, ArH, 1H), 7.24-7.20 (m, ArH, 5H), 6.76 (t, *J* = 8 Hz, ArH, 1H), 6.66 (d, *J* = 8 Hz, ArH, 2H), 4.30 (s, 2H), 3.87 (br, -NH-, 1H), 2.41 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 137.1, 136.4, 130.5, 129.4, 128.4, 127.5, 126.3, 117.6, 112.8, 46.5, 19.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}N$ ($[M+H]^+$): 198.1277, found: 198.1271.

N-([1,1'-biphenyl]-2-ylmethyl)-4-fluoroaniline (Table 4.4, entry 17) [33]**:** Prepared from 4-fluoro aniline (0.33 g, 3 mmol) and 2-biphenyl methanol (1.10 g, 6 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.80 g, 2.9 mmol, 96%). Mp = 89–90 ^{o}C. ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 7.52-7.30 (m, ArH, 9H), 6.85 (t, *J* = 8 Hz, ArH, 2H), 6.45–6.42 (m, ArH, 2H), 4.22 (s, 2H), 3.77 (br, -NH-, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1, 154.8, 144.4 (d, *J* = 1.6 Hz), 141.8, 141.0, 136.4, 130.4, 129.1, 128.7, 128.5, 127.8, 127.4 (d, *J* = 6.8 Hz), , 115.7 (d, *J* = 22.3 Hz), 113.8 (d, *J* = 7.4 Hz), 47.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{16}FN$ ($[M+H]^+$): 278.1340, found: 278.1373.

N-(benzo[d][1,3]dioxol-5-ylmethyl)-2-methylaniline (Table 4.4, entry 18) [33]**:** Prepared from *o*-toluidine (0.32 g, 3 mmol) and 3,4-methylenedioxy benzyl alcohol (0.91 g, 6 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.52 g, 2.1 mmol, 71%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.12-7.07 (m, ArH, 2H), 6.86 (t, *J* = 8 Hz, 2H), 6.78 (d, *J* = 8 Hz, ArH, 1H), 6.68 (t, *J* = 8 Hz, ArH, 1H), 6.59 (t, *J* = 8 Hz, ArH, 1H), 5.95 (s, 2H), 4.28 (s, 2H), 3.80 (br, -NH-, 1H), 2.16 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.1, 146.9, 146.1, 133.5, 130.2, 127.3, 122.1, 120.8, 117.4, 110.1, 108.5, 108.2, 101.1, 48.3, 17.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO_2$ ($[M+H]^+$): 242.1176, found: 242.1158.

4-methoxy-N-octylaniline (Table 4.5, entry 19) [19]**:** Prepared from *p*-anisidine (0.30 g, 2.4 mmol) and 1-octanol (0.63 g, 4.8 mmol). After purification by column chromatography, the compoundwas isolated as a yellow liquid (0.44 mg, 1.9 mmol, 78%). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 8 Hz, ArH, 2H), 6.58 (d, *J* = 8 Hz, ArH, 2H), 3.75 (s, 3H), 3.06 (t, *J* = 8 Hz, 2H), 1.62-1.58 (m, 2H), 1.31-1.28 (m, 10H), 0.89 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 142.9, 134.7, 115.0, 114.2, 55.9, 45.2, 31.9, 29.8, 29.6, 29.4,

27.3, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{25}NO$ ($[M+H]^+$): 236.2009, found: 236.2035.

N-hexyl-4-methoxyaniline (Table 4.5, entry 20) [20]**:** Prepared from *p*-anisidine (0.30 g, 2.4 mmol) and 1-hexanol (0.49 g, 4.8 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.44 g, 2.1 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 8 Hz, ArH, 2H), 6.57 (d, *J* = 8 Hz, ArH, 2H), 3.75 (s, 3H), 3.06 (t, *J* = 8 Hz, 2H), 1.64-1.57 (m, 2H), 1.42-1.31 (m, 6H), 0.91 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 143.0, 115.0, 114.1, 55.9, 45.2, 31.8, 29.8, 27.0, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{21}NO$ ($[M+H]^+$): 208.1696, found: 208.1721.

N-butyl-4-methoxyaniline (Table 4.5, entry 21) [21]**:** Prepared from *p*-anisidine (0.30 g, 2.4 mmol) and 1-butanol (0.36 g, 4.8 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.31 g, 1.8 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 8 Hz, ArH, 2H), 6.58 (d, *J* = 8 Hz, ArH, 2H), 3.75 (s, 3H), 3.07(t, *J* = 8 Hz, 2H), 1.64-1.56 (m, 2H), 1.48-1.39 (m, 2H), 0.96 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 143.0, 115.0, 114.2, 55.9, 44.9, 31.9, 20.5, 14.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{17}NO$ ($[M+H]^+$): 180.1383, found: 180.1410.

N-octylaniline (Table 4.5, entry 22) [5b]**:** Prepared from aniline (0.30 g, 3.2 mmol) and 1-octanol (0.84 g, 6.4 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.53 g, 2.6 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (t, *J* = 8 Hz, ArH, 2H),

6.73(t, *J* = 8 Hz, ArH, 1H), 6.63 (d, *J* = 8 Hz, ArH, 2H), 3.39 (br, NH, 1H), 3.12 (t, *J* = 8 Hz, 2H), 1.67-1.61 (m,2H), 1.45-1.34 (m, 10H), 0.94 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 129.3, 117.2, 112.8, 44.1, 31.9, 29.7, 29.5, 29.4, 27.3, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{23}N$ ($[M+H]^+$): 206.1903, found: 206.1928.

4-methoxy-N-phenethylaniline (Table 4.5, entry 23) [22]**:** Prepared from *p*-anisidine (0.30 g, 2.4 mmol) and 2-phenyl ethanol (0.59 g, 4.8 mmol). After purification by column chromatography, the compoundwas isolated as a yellow liquid (0.39 g, 1.7 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 8 Hz, ArH, 2H), 7.24 (t, *J* = 8 Hz, ArH, 3H), 6.79 (d, *J* = 8 Hz, ArH, 2H), 6.59 (d, *J* = 8 Hz, ArH, 2H), 3.76 (s, 3H), 3.37 (t, *J* = 8 Hz, 2H), 2.91 (t, *J* = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 142.4, 139.5, 129.2, 128.9, 128.7, 126.5, 115.1, 114.5, 55.9, 46.2, 35.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NO$ ($[M+H]^+$): 228.1383, found: 228.1404.

N-decyl-2-methylaniline (Table 4.5, entry 24) [33]**:** Prepared from *o*-toluidine (0.32 g, 3.0 mmol) and 1-decanol (0.95 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.50 g, 2.0 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (t, *J* = 8 Hz, ArH, 1H), 7.05 (d, *J* = Hz, ArH, 1H), 6.64 (dd, *J* = 15.4, 7.8 Hz, ArH, 2H), 3.45 (br, NH, 1H), 3.16 (t, *J* = 8 Hz, 2H), 2.14 (s, 3H), 1.71-1.64 (m, 2H), 1.45-1.29 (m, 14H), 0.90 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6, 130.1, 127.3, 121.8, 116.7, 109.7, 44.1, 32.0, 29.8, 29.7, 29.6, 29.5, 27.4, 22.8,

17.6, 14.3 ppm. HRMS (ESI): calcd. for $C_{17}H_{29}N$ ($[M+H]^+$): 248.2373, found: 248.2378.

4-methoxy-N-(1-phenylpropyl)aniline (Table 4.5, entry 25) [23]**:** Prepared from *p*-anisidine (0.30 g, 2.4 mmol) and 1-phenyl-1-propanol (0.66 g, 4.8 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.50 g, 2.1 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.24 (m, ArH, 5H), 6.69 (d, *J* = 8 Hz, ArH, 2H), 6.49 (d, *J* = 8 Hz, ArH, 2H), 4.18 (t, *J* = 8 Hz, 1H), 3.71 (s, 3H), 1.90-1.77 (m, 2H), 0.96 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 144.3, 141.9, 128.6, 126.9, 126.7, 114.9, 114.6, 60.7, 55.9, 31.8, 10.9 ppm. HRMS (ESI): calcd. for $C_{16}H_{19}NO$ ($[M+H]^+$): 242.1539, found: 242.1567.

4-methoxy-N-(1-phenylethyl)aniline (Table 4.5, entry 26) [23]**:** Prepared from *p*-anisidine (0.30 g, 2.4 mmol) and 1-phenyl ethanol (0.59 g, 4.8 mmol). After purification by column chromatography, the compoundwas isolated as a yellow liquid (0.46 g, 2 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39- 7.31 (m, ArH, 4H), 7.23 (t, *J* = 8 Hz, ArH, 1H), 6.70 (d, *J* = 8 Hz, ArH, 2H), 6.48 (d, *J* = 8 Hz, ArH, 2H), 4.45-**4**.40 (m, *J* = 8 Hz, 1H), 3.71 (s, 3H), 1.50 (d, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0, 145.6, 141.7, 128.7, 126.9, 126.0, 114.9, 114.7, 55.9, 54.4, 25.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NO$ ($[M+H]^+$): 228.1383, found: 228.1413.

4-methyl-N-(1-(m-tolyl)ethyl)aniline (Table 4.5, entry 27) [33]**:** Prepared from *p*-toluidine (0.32 g, 3 mmol) and 1-(3-methylphenyl)ethanol (0.82 g, 6 mmol).

After purification by column chromatography, the compound was isolated as a yellow liquid (0.52 g, 2.3mmol, 77%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.16 (m, ArH, 3H), 7.04 (d, *J* = 8 Hz, ArH, 1H), 6.91 (d, *J* = 8 Hz, ArH, 2H), 6.45 (d, *J* = 8 Hz, ArH, 2H), 4.45-4.40 (m, 2H), 3.88 (br, NH, 1H), 2.35 (s, 3H), 2.21 (s, 3H), 1.49 (d, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 145.3, 138.3, 129.7, 128.6, 127.7, 126.7, 123.0, 113.5, 53.8, 25.2, 21.7, 20.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{19}N$ ($[M+H]^+$): 226.1590, found: 226.1602.

4-methyl-N-(1-(p-tolyl)propyl)aniline (Table 4.5, entry 28) [33]***:*** Prepared from *p*-toluidine (0.32 g, 3.0 mmol) and 1-(4-methylphenyl)-1-propanol (0.90 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.52g, 2.2mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 8 Hz, ArH, 2H), 7.11 (d, *J* = 8 Hz, ArH, 2H), 6.89 (d, *J* = 8 Hz, ArH, 2H), 6.44 (d, *J* = 8 Hz, ArH, 2H), 4.18 (t, *J* = 8 Hz, 1H), 3.93 (br, NH, 1H), 2.33 (s, 3H), 2.19 (s, 3H), 1.84-1.76 (m, 2H), 0.95 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5, 141.2, 136.4, 129.7, 129.3, 126.5, 126.3, 113.5, 59.8, 31.8, 21.2, 20.5, 10.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{21}N$ ($[M+H]^+$): 240.1747, found: 240.1730.

N-(hexan-2-yl)-4-methoxyaniline (Table 4.5, entry 29) [24]***:*** Prepared from *p*-anisidine (0.30 g, 2.4 mmol) and 2-hexanol (0.49 g, 4.8 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.38 g, 1.8 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 12 Hz, ArH, 2H), 6.55 (d, *J* = 12 Hz, ArH, 2H), 3.76 (s, 3H), 3.40-3.35

(m, 1H), 1.39-1.34 (m, 6H), 1.15 (d, *J* = 8 Hz, 3H), 0.92 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 142.1, 115.1, 114.8, 55.9, 49.6, 37.1, 28.5, 22.9, 20.9, 14.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{21}NO$ ($[M+H]^+$): 208.1696, found: 208.1713.

N-decylaniline (Table 4.5, entry 30) [25]**:** Prepared from aniline (0.28 g, 3.0 mmol) and 2-decanol (0.95 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.52 g, 2.2 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (t, *J* = 8 Hz, ArH, 2H), 6.66 (t, *J* = 8 Hz, ArH, 1H), 6.56 (d, *J* = 8 Hz, ArH, 2H), 3.49-3.41 (m, 1H), 1.61–1.54 (m, 2H), 1.45-1.27 (m, 12H), 1.16 (d, *J* = 8 Hz, 3H), 0.88 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 129.4, 113.2, 48.6, 43.9, 37.4, 32.0, 29.8, 29.7, 29.5, 29.4, 26.3, 24.0, 22.8, 20.9, 14.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{27}N$ ($[M+H]^+$): 234.2216, found: 234.2218.

N-benzyl-4-(trifluoromethyl) aniline (Table 4.5, entry 31) [5b]**:** Prepared from 4-(trifluoromethyl)aniline (0.30 g, 1.8 mmol) and benzyl alcohol (0.40 g, 3.7 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.45 g, 1.7 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43-7.37 (m, ArH, 7H), 6.63 (d, *J* = 8 Hz, ArH, 2H), 4.38 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 138.6, 128.9, 127.7, 127.5, 126.8 (q, *J* = 3.8 Hz), 119.3, 119.0, 112.1, 47.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{12}F_3N$ ($[M+H]^+$): 252.0995, found: 252.1000.

4-phenethylmorpholine (Table 4.5, entry 32) [26]**:** Prepared from morpholine (0.30 g, 3.4 mmol) and 2-phenyl ethanol (0.84 g, 6.8 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.48 g, 2.5 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 8 Hz, ArH, 2H), 7.20(d, *J* = 8 Hz, ArH, 3H), 3.75 (t, *J* = 4 Hz, 4H), 2.81 (t, *J* = 8 Hz, 2H), 2.62-2.52 (m, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.3, 128.8, 128.5, 126.2, 67.1, 61.0, 53.8, 33.4 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}NO$ ($[M+H]^+$): 192.1383, found: 192.1407.

4-methyl-N-(1-phenylpropan-2-yl)aniline (Table 4.5, entry 33) [27]**:** Prepared from *p*-toluidine (0.32 g, 3.0 mmol) and 1-phenyl 2-propanol (0.82 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.55 g, 2.4 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, *J* = 8 Hz, ArH, 2H), 7.29-7.22 (m, ArH, 3H), 7.04 (d, *J* = 8 Hz, ArH, 2H), 6.60 (d, *J* = 8 Hz, ArH, 2H), 3.80-3.76 (m, 1H), 3.01-2.96 (m, 1H), 2.75-2.70 (d, 1H), 2.29 (s, 3H), 1.18 (d, *J* = 4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 138.8, 130.0, 129.6, 128.4, 126.6, 126.4, 113.8, 49.9, 42.4, 20.5, 20.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{19}N$ ($[M+H]^+$): 226.1590, found: 226.1588.

N-cyclohexyl-4-methoxyaniline (Table 4.5, entry 34) [26]**:** Prepared from *p*-anisidine (0.30 g, 2.4 mmol) and cyclohexanol (0.49 g, 4.8 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.44 g, 2.2 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (d, *J* = 8Hz, ArH, 2H), 6.57 (d, *J* = 8Hz, ArH, 2H), 3.75 (s, 3H), 3.21-3.14 (m,

1H), 3.00 (br, NH, 1H), 2.07-2.04 (m, 2H), 1.78-1.64 (m, 3H), 1.41-1.08 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 141.7, 115.0, 114.9, 55.9, 52.9, 33.7, 26.1, 25.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}NO$ ($[M+H]^+$): 206.1539, found: 206.1569.

N-cyclohexylaniline (Table 4.5, entry 35) [5c]***:*** Prepared from aniline (0.30 g, 3.2 mmol) and cyclohexanol (0.64 g, 6.4 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.47 g, 2.7 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, *J* = 8 Hz, ArH, 2H), 6.68 (t, *J* = 8 Hz, ArH, 1H), 6.60 (d, *J* = 8 Hz, ArH, 2H), 3.31- 3.24 (m, 1H), 2.10-2.06 (m,2H), 1.81-1.76 (m, 2H), 1.70-1.65 (m, 1H), 1.45-1.13 (m, 5H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.4, 116.9, 113.3, 33.6, 26.1, 25.1 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}N$ ($[M+H]^+$): 176.1434, found: 176.1451.

N-benzylpyridin-4-amine (Table 4.6, entry 36) [5e]***:*** Prepared from 4-aminopyridine (0.30 g, 3.2 mmol) and benzyl alcohol (0.41 g, 3.8 mmol). After purification by column chromatography, the compound was obtained as a white solid (0.49 g, 2.6 mmol, 84%). Mp = 108-109 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8 Hz, ArH, 2H), 7.35-7.31 (m, ArH, 5H), 6.45-6.46 (m, ArH, 2H), 4.87 (br, NH, 1H), 4.35 (d, *J* = 4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 150.0, 149.9, 138.0, 128.9, 127.7, 127.4, 107.8, 46.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{12}N_2$ ($[M+H]^+$): 185.1073, found: 185.1088.

N-benzylpyridin-2-amine (Table 4.6, entry 37) [5e]***:*** Prepared from 2-aminopyridine (0.30 g, 3.2 mmol) and benzyl alcohol (0.41 g, 3.8 mmol). After

purification by column chromatography, the compound was obtained as a white solid (0.56 g, 3 mmol, 96%). Mp = 95-96 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10-8.09 (m, ArH, 1H), 7.39-7.26 (m, ArH, 6H), 6.59 (t, *J* = 8 Hz, ArH, 1H), 6.36 (d, *J* = 8 Hz, ArH, 1H), 5.14 (br, NH, 1H), 4.50 (d, *J* = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 148.3, 139.3, 137.6, 128.7, 127.5, 127.3, 113.2, 106.9, 46.4 ppm. HRMS (ESI): calcd. for $C_{12}H_{12}N_2$ ($[M+H]^+$): 185.1073, found: 185.1098.

N-benzylpyrimidin-2-amine (Table 4.6, entry 38) [5e]***:*** Prepared from 2-aminopyramidine (0.30 g, 3.1 mmol) and benzyl alcohol (0.41 g, 3.7 mmol). After purification by column chromatography, the was obtained as a half-white solid (0.57 g, 3.1 mmol, 98%). Mp = 81-82 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, ArH, 2H), 7.35-7.24 (m, ArH, 5H), 6.46 (t, *J* = 4 Hz, ArH, 1H), 6.28 (br, NH, 1H), 4.62 (d, *J* = 4Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 158.1, 139.2, 128.7, 127.7, 127.3, 110.7, 45.6 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}N_3$ ($[M+H]^+$): 186.1026, found: 186.1055.

N-(pyridin-2-ylmethyl)aniline (Table 4.6, entry 39) [28]***:*** Prepared from aniline (0.28 g, 3.0 mmol) and 2-pyridine methanol (0.65 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.53 g, 2.9 mmol, 96%). Mp = 50–51 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 4 Hz, ArH, 1H), 7.64 (t, *J* = 8 Hz, ArH, 1H), 7.33 (d, *J* = 8 Hz, ArH, 1H), 7.18 (t, *J* = 8 Hz, ArH, 3H), 6.72 (t, *J* = 8 Hz, ArH, 1H), 6.67 (d, *J* = 8 Hz, ArH, 2H), 4.47 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7,

149.4, 148.0, 136.8, 129.4, 122.2, 121.7, 117.7, 113.2, 49.5 ppm. HRMS (ESI): calcd. for $C_{12}H_{12}N_2$ ($[M+H]^+$): 185.1073, found: 185.1083.

N-benzylbenzo[d]thiazol-2-amine (Table 4.6, entry 40) [5e]**:** Prepared from 2-Amino benzothiazole (0.45 g, 3.0 mmol) and benzyl alcohol (0.65 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.52 g, 2.1 mmol, 72%). Mp = 165–166 ^oC. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.51 (t, *J* = 4 Hz, NH, 1H), 7.66 (d, *J* = 8 Hz, ArH, 1H), 7.40-7.33 (m, ArH, 5H), 7.26 (t, *J* = 8 Hz, ArH, 1H), 7.22 (t, *J* = 8 Hz, ArH, 1H), 7.02 (t, *J* = 8 Hz, ArH, 1H), 4.60 (d, *J* = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.2, 152.4, 138.9, 130.4, 128.4, 127.4, 127.0, 125.5, 120.9, 120.9, 118.1, 47.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{12}N_2S$ ($[M+H]^+$): 241.0794, found: 241.0804.

N-(naphthalen-1-ylmethyl)benzo[d]thiazol-2-amine (Table 4.6, entry 41) [29]**:** Prepared from 2-Amino benzothiazole (0.45 g, 3.0 mmol) and benzyl alcohol (0.95 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.72 g, 2.5 mmol, 83%). Mp = 147–148 ^oC. ^1H NMR (400 MHz, DMSO-d_6): δ = 8.55 (s, NH, 1H), 8.13 (d, *J* = 8 Hz, ArH, 1H), 7.96 (d, *J* = 8 Hz, ArH, 1H), 7.87 (d, *J* = 8 Hz, ArH, 1H), 7.67 (d, *J* = 8 Hz, ArH, 1H), 7.60-7.41 (m, ArH, 5H), 7.23 (t, *J* = 8 Hz, ArH, 1H), 7.03 (t, *J* = 8 Hz, ArH, 1H), 5.08 (s, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.9, 152.5, 134.0, 133.4, 131.0, 128.6, 127.8, 126.4, 125.8, 125.6, 125.6, 125.5, 123.5, 121.0, 120.9, 118.1, 45.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{14}N_2S$ ($[M+H]^+$): 291.0950, found: 291.0954.

N-decylpyridin-2-amine (Table 4.6, entry 42) [30]**:** Prepared from 2-amino pyridine (0.28 g, 3.0 mmol) and 1-decanol (0.95 g, 6.0 mmol). After purification by column chromatography, the compoundwas isolated as a yellow liquid (0.65 g, 2.8mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8 Hz, ArH, 1H), 7.40 (d, *J* = 8 Hz, ArH, 1H), 6.53 (t, *J* = 8 Hz, ArH, 1H), 6.35 (d, *J* = 8 Hz, ArH, 1H), 4.50 (br, NH, 1H), 3.63 (t, *J* = 8 Hz, 2H), 3.25-3.20 (m, 2H), 1.64-1.52 (m, 2H), 1.33-1.26 (m, 12H), 0.86 (t, *J* = 8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 148.3, 137.6, 112.7, 106.4, 63.2, 42.5, 32.9, 32.0, 29.7, 29.6, 27.2, 25.9, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{26}N_2$ ($[M+H]^+$): 235.2169, found: 235.2180.

N-(pyridin-3-ylmethyl)aniline (Table 4.6, entry 43) [28]**:** Prepared from aniline (0.28 g, 3.0 mmol) and 3-pyridine methanol (0.65 g, 6.0 mmol). After purification by column chromatography, the compoundwas isolated as a white solid (0.42 g, 2.3mmol, 96%). Mp = 92–93 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (s, ArH, 1H), 8.54 (d, *J* = 4 Hz, ArH, 1H), 7.70 (d, *J* = 8 Hz, ArH, 1H), 7.28 (t, *J* = 8 Hz, ArH, 1H), 7.20 (t, *J* = 8 Hz, ArH, 2H), 6.76 (t, *J* = 8 Hz, ArH, 1H), 6.64 (d, *J* = 8 Hz, ArH, 2H), 4.38 (s, 2H), 4.13 (br, NH, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3, 148.8, 147.7, 135.2, 129.4, 123.6, 118.2, 113.1, 45.9 ppm. HRMS (ESI): calcd. for $C_{12}H_{12}N_2$ ($[M+H]^+$): 185.1073, found: 185.1083.

N-(furan-2-ylmethyl)aniline (Table 4.6, entry 44) [5e]**:** Prepared from aniline (0.28 g, 3.0 mmol) and furfuryl alcohol (0.59 g, 6.0 mmol). After purification

by column chromatography, the compoundwas isolated as a yellow liquid (0.37 g, 2.1mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 d, *J* = 4 Hz, ArH, 1H), 7.21 (t, *J* = 8 Hz, ArH, 2H), 6.77 (t, *J* = 8 Hz, ArH, 1H), 6.69 (d, *J* = 8 Hz, ArH, 2H), 6.35-6.34 (m, ArH, 1H), 6.25 (d, *J* = 4 Hz, ArH, 1H), 4.34 (s, 2H), 4.03 (br, -NH-, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.9, 147.8, 142.0, 129.3, 118.2, 113.3, 110.5, 107.1, 41.5 ppm. HRMS (ESI): calcd. for $C_{11}H_{11}NO$ ($[M+H]^+$): 174.0913, found: 174.0939.

4-amino-N-benzylbenzenesulfonamide (Table 4.7, entry 45) [31]**:** Prepared from sulfanilamide (0.52 g, 3.0 mmol) and benzyl alcohol (0.65 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.56 g, 2.2 mmol, 71%). Mp = 138–139 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.49 (d, *J* = 8.8 Hz, 2H), 7.34–7.30 (m, 4H), 7.25–7.21 (m, 1H), 7.00 (s, 1H, -NH), 6.90 (s, 2H, $-NH_2$), 6.64 (d, *J* = 8.8 Hz, 2H), 4.34 (s, 2H). ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 151.2, 139.4, 130.3, 128.4, 127.3, 127.1, 111.1, 45.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{14}N_2O_2S$ ($[M+H]^+$): 263.0849, found: 263.0888.

4-amino-N-(4-methylbenzyl)benzenesulfonamide (Table 4.7, entry 46) [31]**:** Prepared from sulfanilamide (0.52 g, 3.0 mmol) and 4-methylbenzyl alcohol (0.73 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.59 g, 2.1mmol, 71%). Mp = 148–149 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.56 (t, *J* = 8 Hz, NH, 1H), 7.44 (d, *J* = 8 Hz, ArH, 2H), 7.14-7.09 (m, ArH, 4H), 6.61 (d, *J* = 8 Hz, ArH, 2H), 5.93 (s, NH_2, 2H), 3.82 (d, *J* = 8 Hz, 2H), 2.27 (s, 3H) ppm. ^{13}C NMR (100

MHz, DMSO-d_6) δ = 153.1, 136.7, 135.6, 129.3, 129.1, 128.1, 126.2, 113.3, 46.5, 21.3 ppm. HRMS (ESI): calcd. for $C_{14}H_{16}N_2O_2S$ ($[M+H]^+$): 277.1005, found: 277.1031.

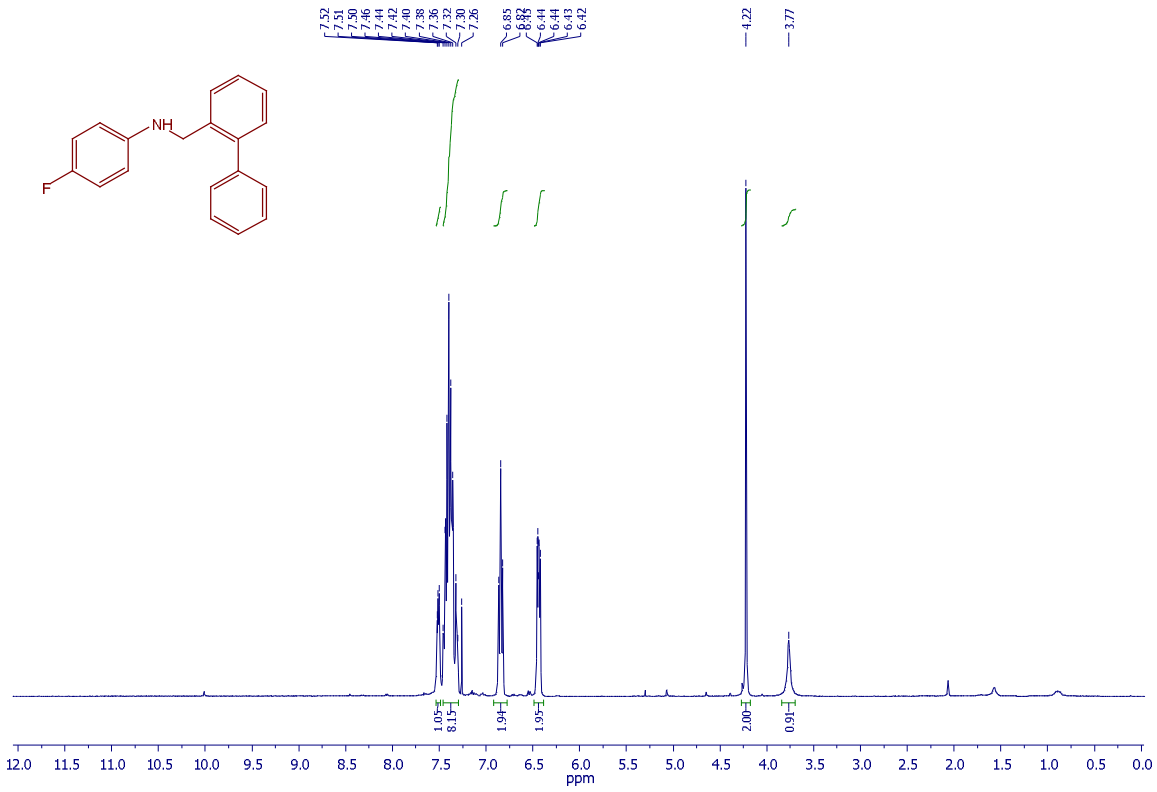
4-amino-N-(4-methoxybenzyl)benzenesulfonamide (Table 4.7, entry 47) [31]***:*** Prepared from sulfanilamide (0.52 g, 3.0 mmol) and 4-methoxybenzyl alcohol (0.83 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.59 g, 2.0mmol, 68%). Mp = 129–130 ^oC. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.47 (d, *J* = 8 Hz, ArH, 2H), 7.25 (d, *J* = 8 Hz, ArH, 2H), 6.90-6.88 (m, ArH, 2H and NH_2, 2H), 6.61 (d, *J* = 8 Hz, ArH, 2H), 4.25 (d, *J* = 4 Hz, 2H), 3.72 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.8, 150.9, 130.7, 129.8, 128.0, 126.9, 113.4, 110.7, 54.7, 44.9 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}N_2O_3S$ ($[M-H]^+$): 291.0798, found: 291.0762.

4-amino-N-(4-(trifluoromethyl)benzyl)benzenesulfonamide (Table 4.7, entry 48) [31]***:*** Prepared from sulfanilamide (0.52 g, 3.0 mmol) and 4-(trifluoro)methyl benzyl alcohol (1.05 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.63g, 1.9 mmol, 64%). Mp = 174–175 ^oC. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.77 (t, *J* = 8 Hz, NH, 1H), 7.64 (d, *J* = 8 Hz, ArH, 2H), 7.49-7.42 (m, ArH, 4H), 6.59 (d, *J* = 8 Hz, ArH, 2H), 5.94 (s, NH_2, 2H), 3.97 (d, *J* = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.6, 143.2, 128.5, 128.2, 125.4, 125.0 (q, *J* = 3.7 Hz), 112.7, 45.5 ppm. ^{19}F NMR (376 MHz, DMSO-d_6): δ = -61.80. HRMS (ESI): calcd. for $C_{14}H_{13}F_3N_2O_2S$ ($[M+H]^+$): 331.0723, found: 331.0760.

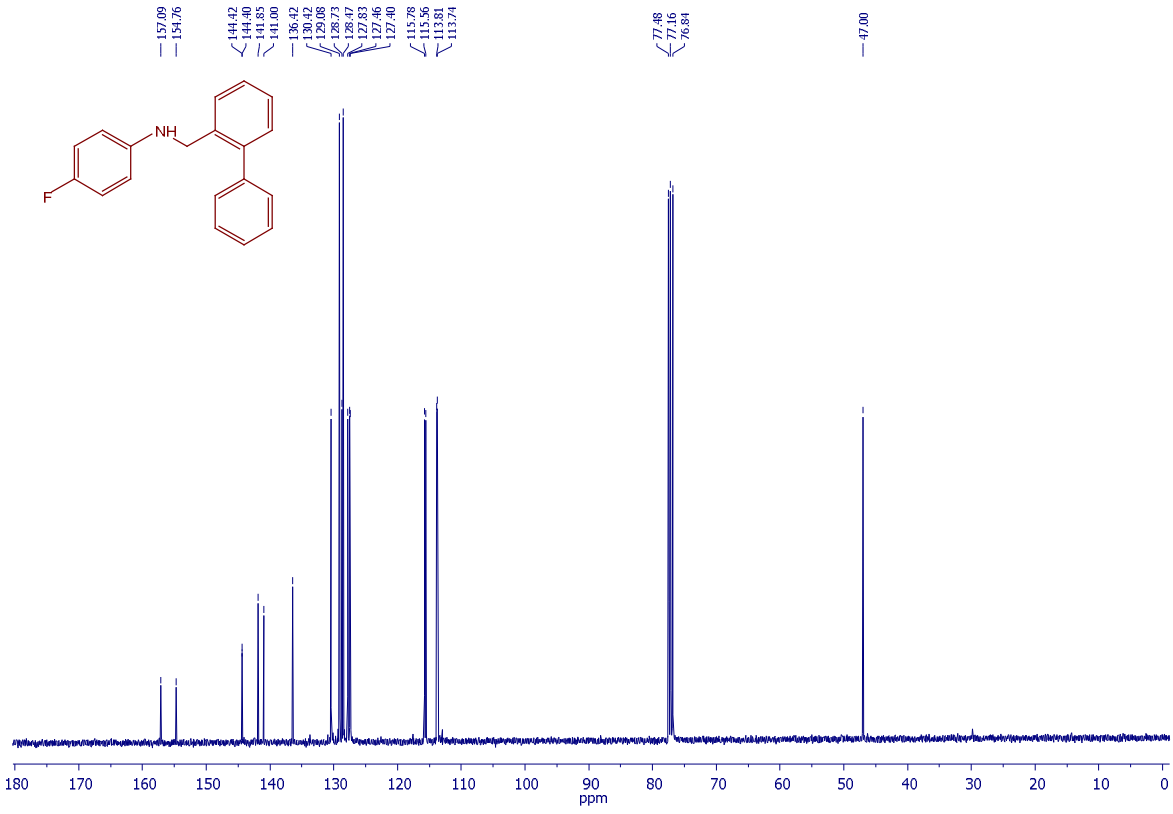
4-amino-N-(benzo[d][1,3]dioxol-5-ylmethyl)benzenesulfonamide (Table 4.7, entry 49) [33]**:** Prepared from sulfanilamide (0.52 g, 3.0 mmol) and 3,4-methylenedioxy benzyl alcohol (0.91 g, 6.0 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.66 g, 2.1 mmol, 72%). Mp = 146–147 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.56 (t, *J* = 8 Hz, NH, 1H), 7.41 (d, *J* = 8 Hz, ArH, 2H), 6.79 (d, *J* = 8 Hz, ArH, 1H), 6.75 (s, ArH, 1H), 6.68 (d, *J* = 8 Hz, ArH, 1H), 6.59 (d, *J* = 8 Hz, ArH, 2H), 5.96 (s, 2H), 5.91 (s, NH_2, 2H), 3.78 (d, *J* = 8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.0, 147.7, 146.8, 132.4, 129.0, 126.3, 121.4, 113.2, 108.7, 108.4, 101.4, 46.5 ppm. HRMS (ESI): calcd. for $C_{14}H_{14}N_2O_4S$ ($[M+H]^+$): 307.0747, found: 305.0731.

2-[4-(benzo[1,3]dioxol-5-ylmethyl)piperazin-1-yl]pyrimidine (scheme 4.2, 50) [32]**:** Prepared from 2-(piperazin-1-yl)pyrimidine (0.30 g, 1.8 mmol) and 1,3-Benzodioxole-5-methanol (0.55 g, 3.6 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.41 g, 1.4 mmol, 76%). Mp = 96-97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ =8.28 (d, *J* = 4 Hz, ArH, 2H), 6.85 (s, ArH, 1H), 6.74 (s, ArH, 2H), 6.47 (t, *J* = 8 Hz, ArH, 1H), 5.93 (s, 2H), 3.89 (t, *J* = 8 Hz, 4H), 3.65 (s, 2H), 2.67 (t, *J* = 8 Hz, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.8, 157.8, 147.8, 146.8, 131.8, 122.4, 109.9, 109.7, 108.0, 101.0, 62.9, 52.9, 43.7 ppm. HRMS (ESI): calcd. for $C_{16}H_{18}N_4O_2$ ($[M+H]^+$): 299.1516, found: 299.1503.

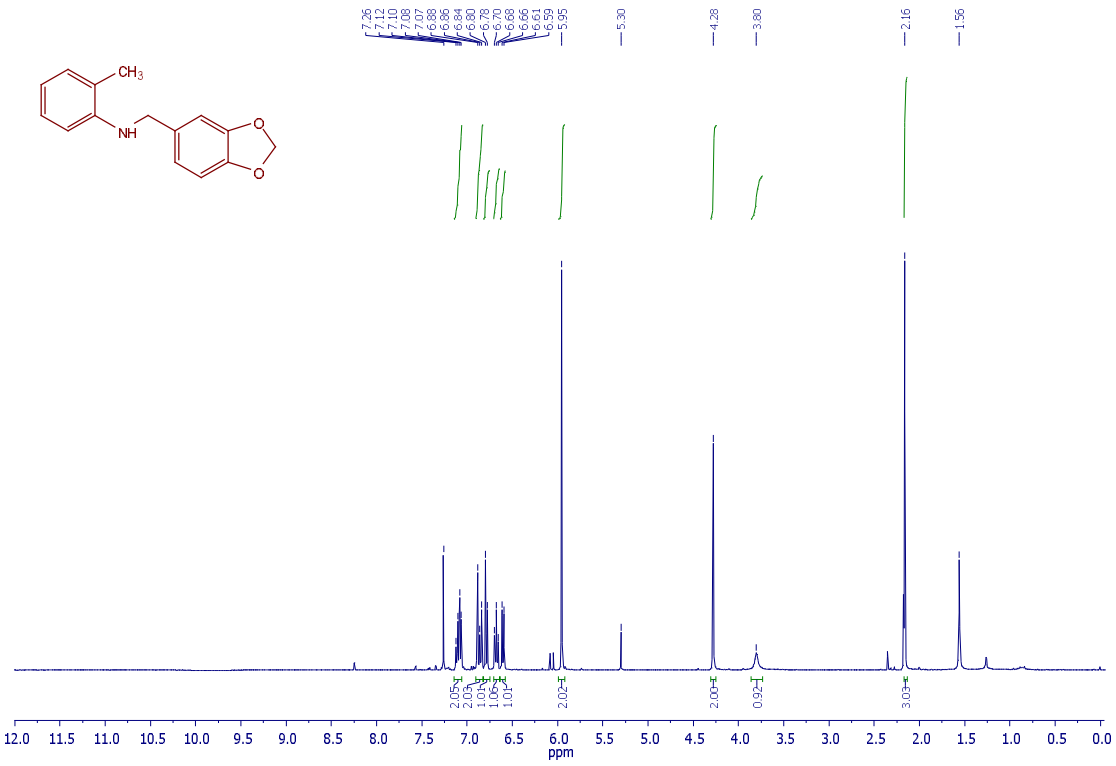
4.5 NMR spectra for new compounds



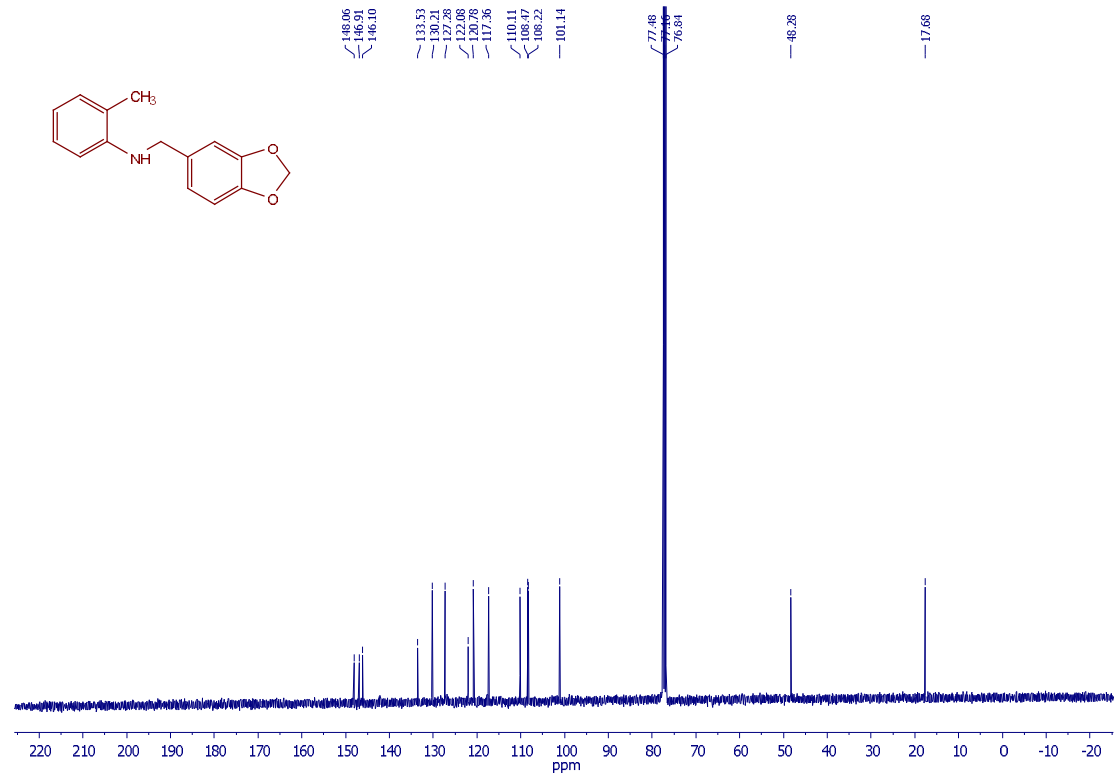
^{1}H NMR Spectrum of Compound 17



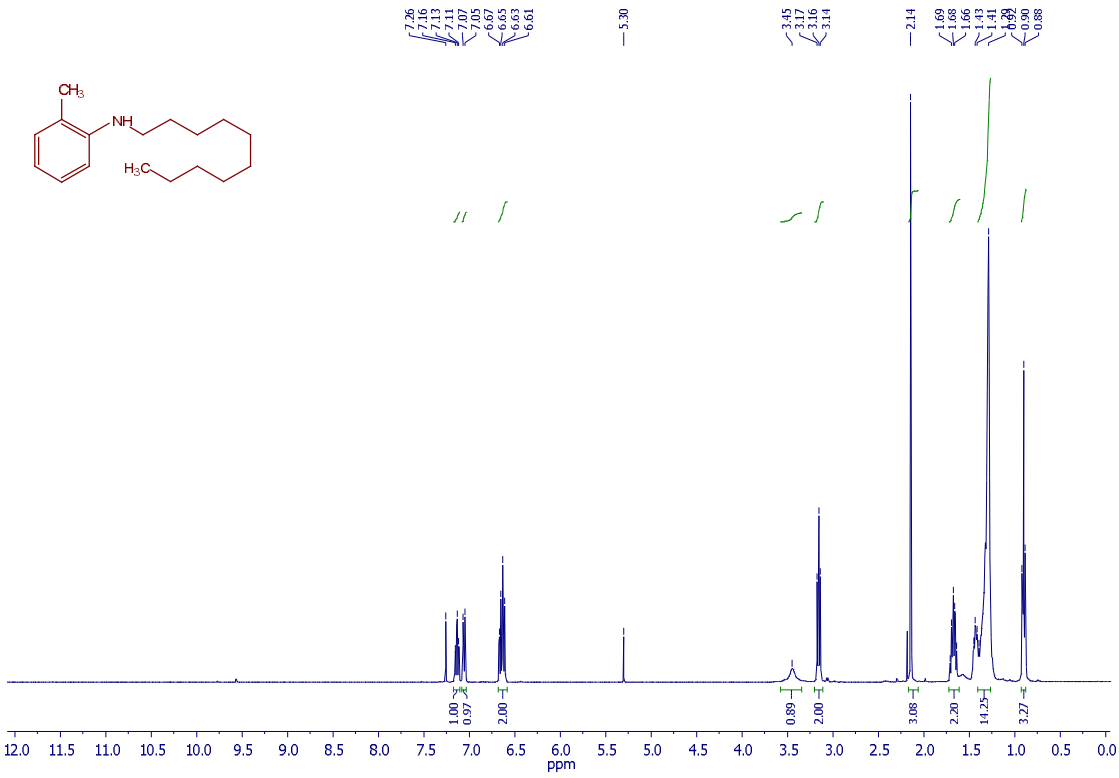
^{13}C NMR Spectrum of Compound 17



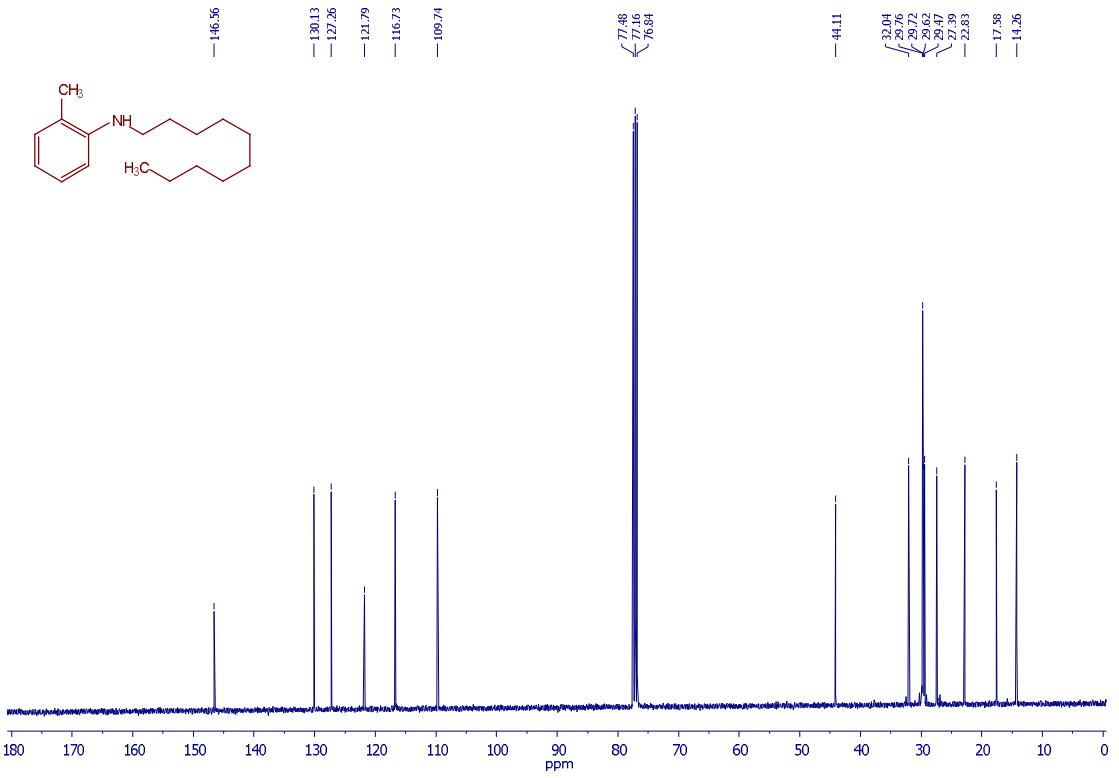
^{1}H NMR Spectrum of Compound 18



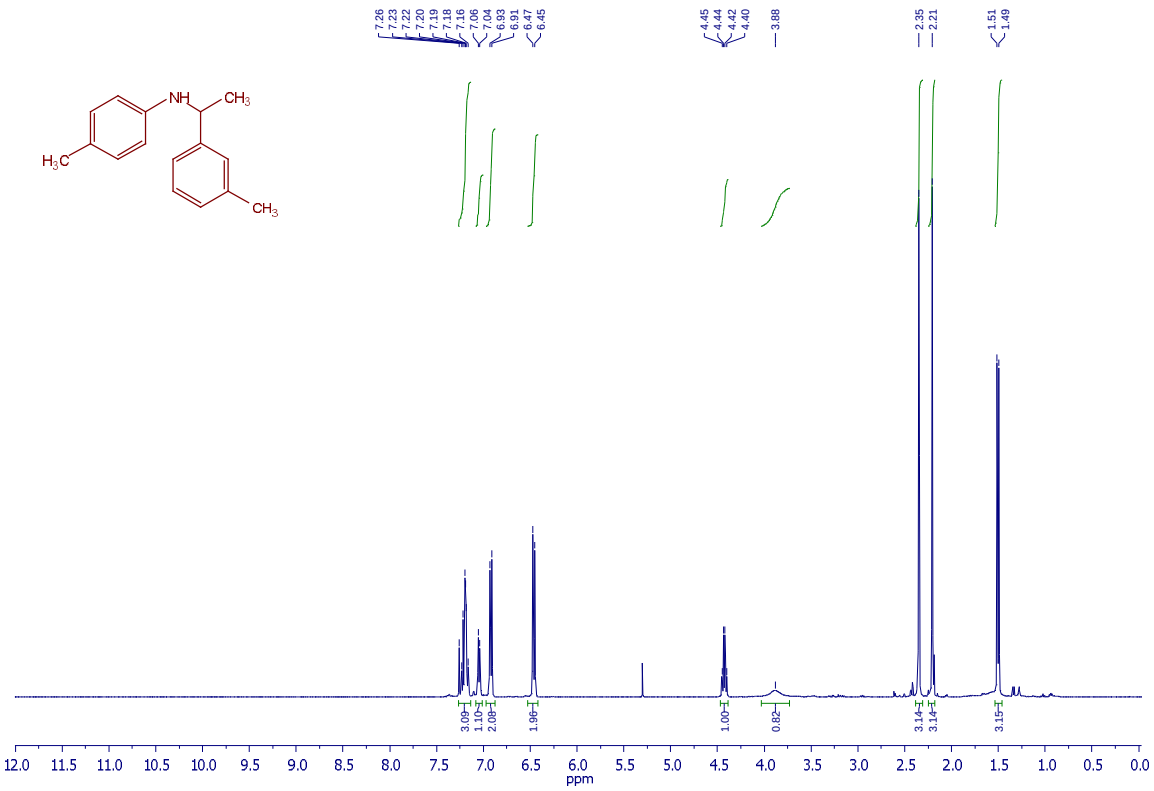
^{13}C NMR Spectrum of Compound 18



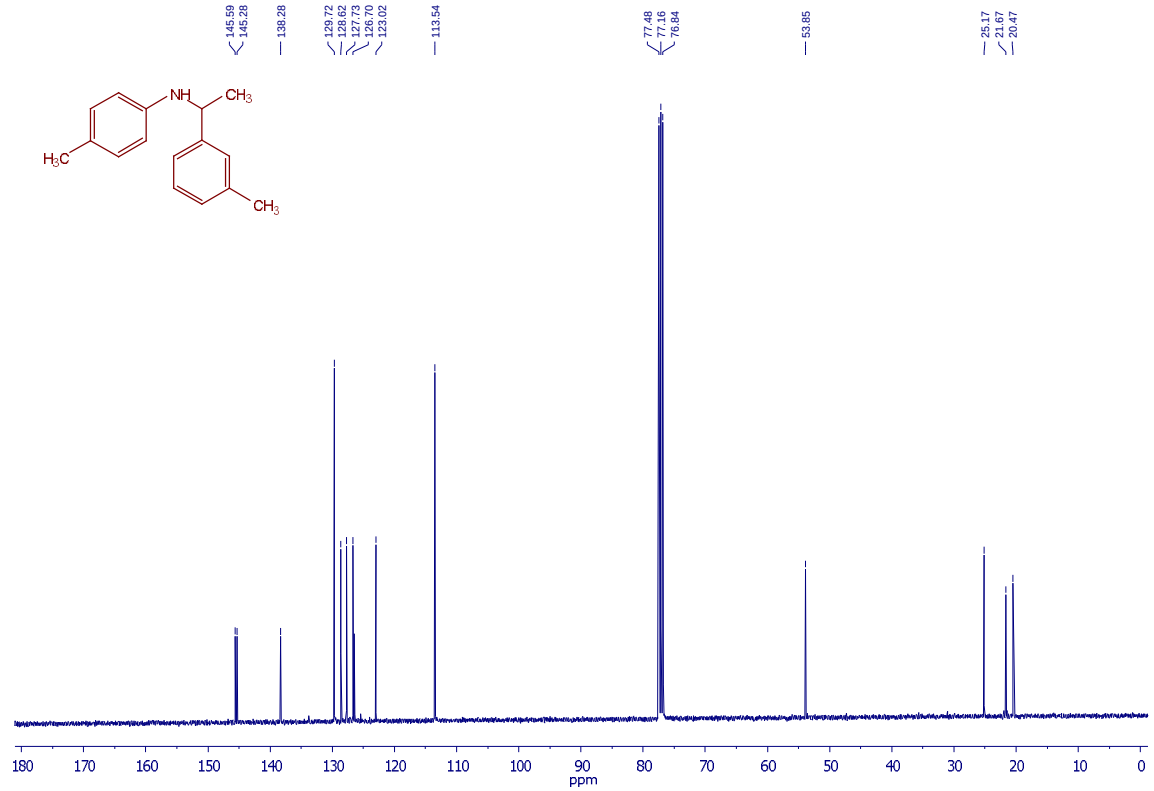
^{1}H NMR Spectrum of Compound 24



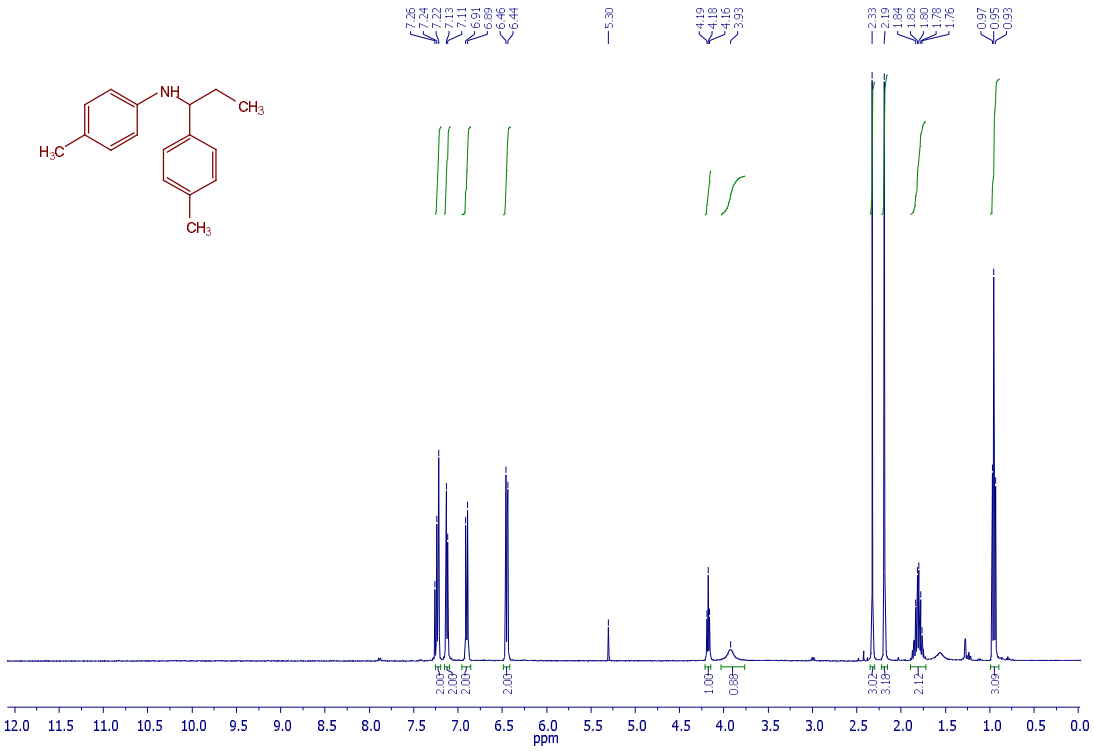
^{13}C NMR Spectrum of Compound 24



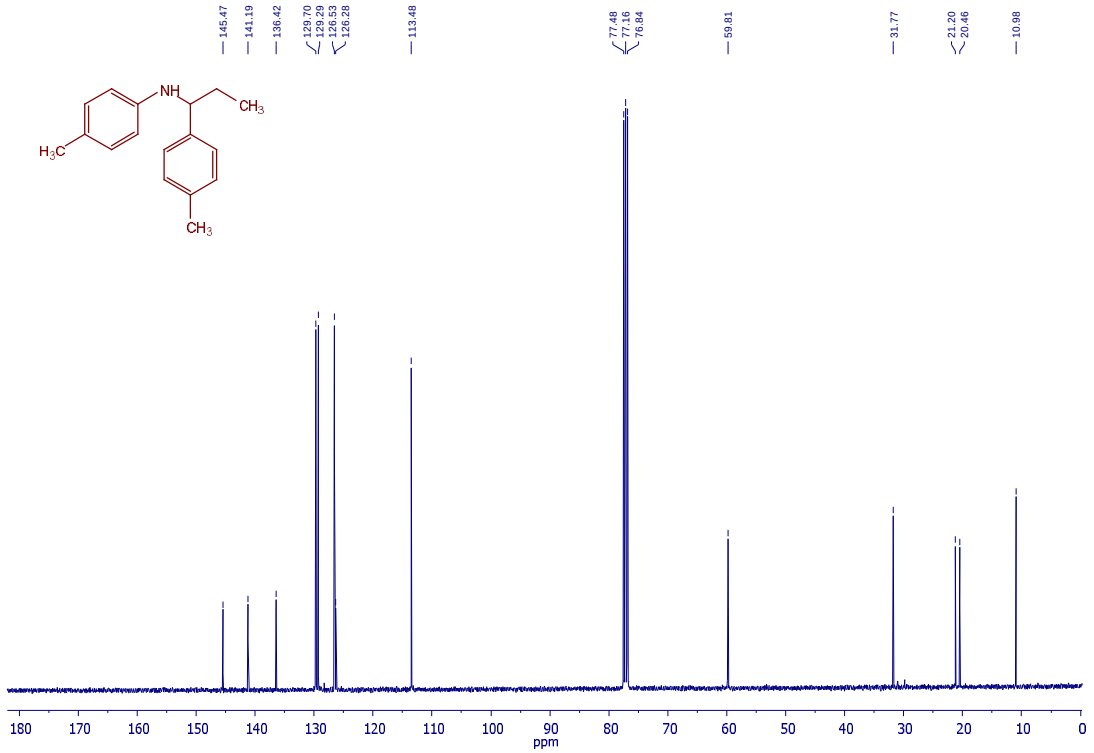
^{1}H NMR Spectrum of Compound 27



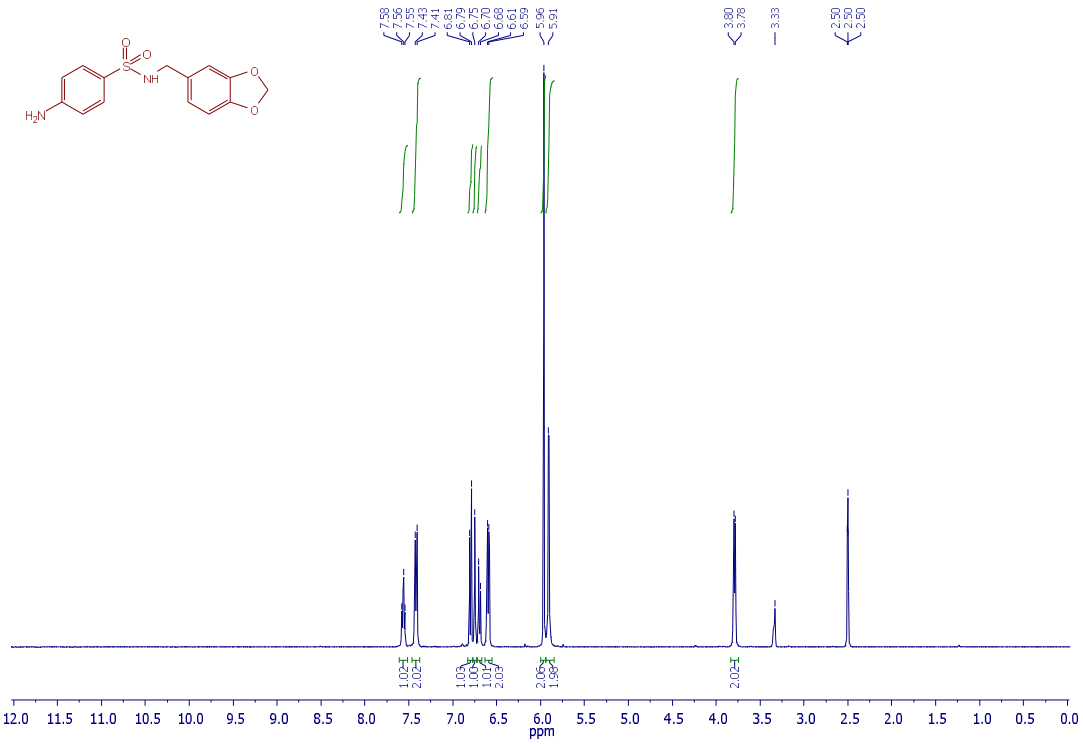
^{13}C NMR Spectrum of Compound 27



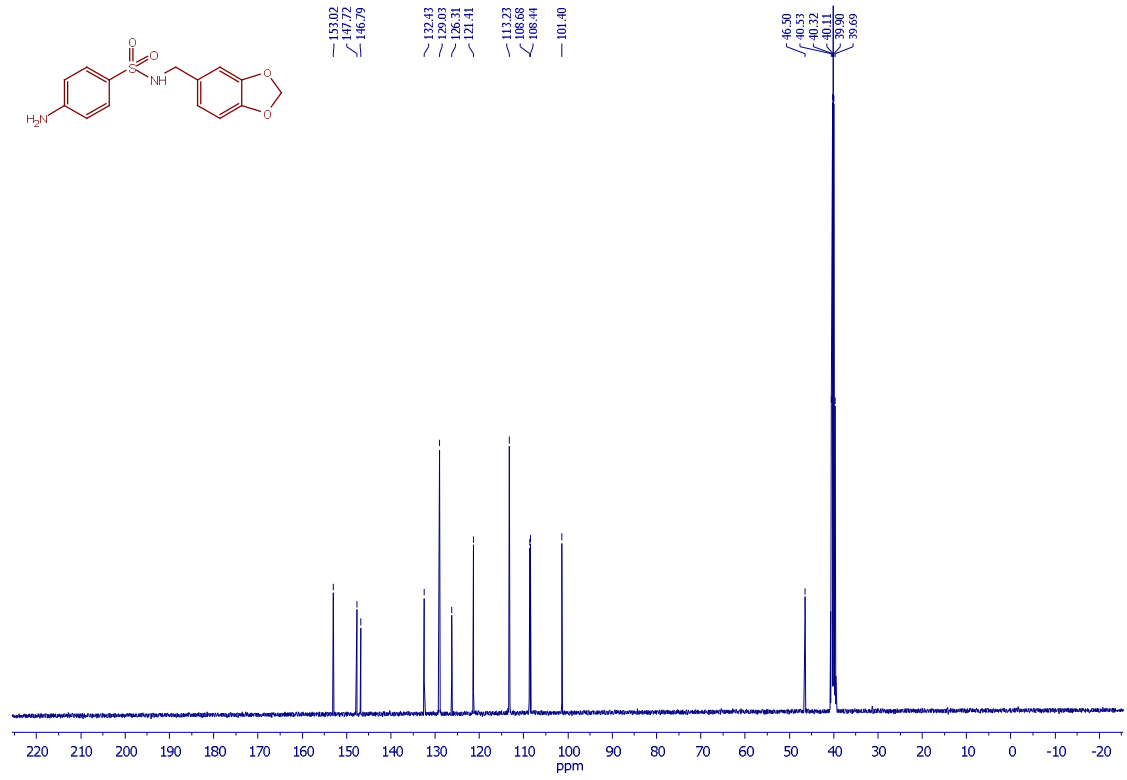
^{1}H NMR Spectrum of Compound 28



^{13}C NMR Spectrum of Compound 28



^{1}H NMR Spectrum of Compound 49



^{13}C NMR Spectrum of Compound 49

4.6 Notes and references

1. a) J. deVries, Palladium-Catalyzed Coupling Reactions. In *Top. Organomet. Chem.*, Springer Berlin Heidelberg: (2012); Vol. 42, pp 1-34; (b) C. C. C. Johansson Seechurn.; T. J. Colacot., Chapter 3. Pd-Phosphine Pre-catalysts for Modern Cross-Coupling Reactions. In *New Trends in Cross-Coupling: Theory and Applications*, The Royal Society of Chemistry: p 91; (c) C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 5062; (d) N. T. S. Phan, M. VanDerSluys and C. W. Jones, *Adv. Synth. Catal.*, 2006, **348**, 609; (e) W. J. Sommer, K. Yu, J. S. Sears, Y. Ji, X. Zheng, R. J. Davis, C. D. Sherrill, C. W. Jones and M. Weck, *Organometallics*, 2005, **24**, 4351.

2. Selected reviews for hydrogen borrowing with N-alkylation (a) Q. Yang, Q. Wangand and Z. Yu, *Chem. Soc. Rev.*, 2015, **44**, 2305; (b) J. Muzart, *Eur. J. Org. Chem.*, 2015, **2015**, 5693; (c) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853; (d) G. Guillena, D. J. Ramón and M. Yus, *Chem. Rev.*, 2010, **110,** 1611; (e) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, J. M. J., *Dalton Trans.*, 2009, 753; (f) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams *Adv. Synth. Catal.*, 2007, **349**, 1555.

3. (a) S. Pei Shan, T. T. Dang, A. M. Seayad and B. Ramalingam, *ChemCatChem*, 2014, **6**, 808; (b) D. Weickmann, W. Frey and B. Plietker, *Chem. Eur. J.*, 2013, **19**, 2741; (c) S. Agrawal, M. Lenormand and B. Martín-Matute, *Org. Lett.*, 2012, **14,** 1456; (d) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams,

J. Am. Chem. Soc., 2009, **131,** 1766; (e) S. Ganguly, F. L. Joslin and D. M. Roundhill, *Inorg. Chem.*, 1989, **28**, 4562.

4. (a) A. Wetzel, S. Wöckel, M. Schelwies, M. K. Brinks, F. Rominger, P. Hofmann and M. Limbach, *Org. Lett.*, 2013, **15**, 266; (b) Y.-H. Chang, Y. Nakajima and F. Ozawa, *Organometallics*, 2013, **32**, 2210; (c) A. Bartoszewicz, R. Marcos, S. Sahoo, A. K. Inge, X. Zou and B. Martín-Matute, *Chem. Eur. J.*, 2012, **18**, 14510; (d) R. Kawahara, K.-i. Fujita and R. Yamaguchi, *Adv. Synth. Catal.*, 2011, **353**, 1161; (e) I. Cumpstey, S. Agrawal, K. E. Borbas and B. Martin-Matute, *Chem. Commun.*, 2011, **47**, 7827; (f) S. Michlik and R. Kempe, *Chem. Eur. J.*, 2010, **16**, 13193.

5. (a) X. Liu, P. Hermange, J. Ruiz and D. Astruc, *ChemCatChem*, 2016, **8**, 1043; (b) T. T. Dang, S. P. Shan, B. Ramalingam and A. M. Seayad, *RSC Advances*, 2015, **5**, 42399; (c) T. T. Dang, B. Ramalingam, S. P. Shan and A. M. Seayad, *ACS Catal.*, 2013, **3,** 2536; (d) Y. Shiraishi, K. Fujiwara, Y. Sugano, S. Ichikawa and T. Hirai, *ACS Catal.*, 2013, **3**, 312; (e) A. Martínez-Asencio, M. Yus and D. J. Ramón, *Synthesis*, 2011, 3730.

6. (a) L. He, Y. Qian, R.-S. Ding, Y.-M. Liu, H.-Y. He, K.-N. Fan and Y. Cao, *ChemSusChem*, 2011, **5**, 621; (b) C.-H. Tang, L. He, Y.-M. Liu, Y. Cao, H.-Y. He and K.-N. Fan, *Chem. Eur. J.*, 2011, **17,** 7172; (c) L. He, X.-B. Lou, J. Ni, Y.-M. Liu, Y. Cao, H.-Y. He and K.-N. Fan, *Chem. Eur. J.*, 2010, **16**, 13965.

7. (a) K. Shimizu, K. Shimura, M. Nishimura and A. Satsuma, *RSC Advances*, 2011, **1**, 1310; (b) X. Cui, Y. Zhang, F. Shi and Y. Deng, *Chem. Eur. J.*, 2010, **17**, 1021.

8. (a) M. Ghedini, I. Aiello, A. Crispini, A. Golemme, M. La Deda and D. Pucci, *Coord. Chem. Rev.*, 2006, **250**, 1373; (b) J. Singh, D. Kumar, N. Singh and A.

J. Elias, *Organometallics*, 2014, **33**, 1044; (c) T.-K. Zhang, D.-L. Mo, L.-X. Dai and X.-L. Hou, *Org. Lett.*, 2008, **10**, 5337; (d) J. Dupont, C. S. Consorti and J. Spencer, *Chem. Rev.*, 2005, **105**, 2527.

9. (a) P. Gautam and B. M. Bhanage, *J. Org. Chem.*, 2015, **80,** 7810; (b) S. Ge, W. Chaładaj and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136,** 4149; (c) E. Alacid and C. Nájera, *Adv. Synth. Catal.*, 2007, **349**, 2572; (d) M. S. Viciu, R. A. Kelly, E. D. Stevens, F. Naud, M. Studer and S. P. Nolan, *Org. Lett.*, 2003, **5**, 1479; (e) M. Fox, X. Huang, A. Chieffi and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 1360.

10. (a) R. Mamidala, V. Mukundam, K. Dhanunjayarao and K. Venkatasubbaiah, *Dalton Trans.*, 2015, **44**, 5805; (b) X. Gai, R.Grigg, M. I. Ramzan, V. Sridharan, S. Collard and J. E. Muir, *Chem. Commun.*, 2000, 2053; (c) Z. Gondaand, Z. Novak, *Chem. Eur. J.*, 2015, **21**, 16801.

11. (a) Both electronic and steric factors play a crucial role for the observed catalytic activity.

12. N. G. Andersen and B. A.Keay *Chem. Rev.*, 2001, **101**, 997.

13. (a) F.Li, H.Shan, Q. Kang and L. Chen, *Chem. Commun*., 2011, **47**, 5058; (b) F. Li, H. Shan, Q. Kang, L. Chen and P. Zou, *Chem. Commun*., 2012, **48**, 603.

14. (a) B. Ding, Z. Zhang, Y. Liu, M. Sugiya, T. Imamoto and W. Zhang, *Org. Lett.*, 2013, **15**, 3690; (b) S. Gowrisankar, H. NeumannandM.Beller, *Angew. Chem. Int. Ed.*, 2011, **50,** 5139; (c) S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 11592; (d) J. A. Müller, C. P.GollerandM. S. Sigman, *J. Am. Chem. Soc*., 2004, **126**, 9724.

15. K. Shimizu, N. Imaiida, K. Kon, S. M. A. H. Siddiki and A. Satsuma, *ACS Catal.*, 2013, **3**, 998.

16. Y. Zhao, S. W. Foo and S. Saito, *Angew. Chem. Int. Ed*., 2011, **50**, 3006.

17. J. W. Park, and Y. K. Chung , *ACS Catal.*, 2015, **5**, 4846.

18. J. Li and P. G. Andersson, *Chem. Commun.*, 2013, **49**, 6131.

19. Q. Peng, Y. Zhang, F. Shi and Y. Deng, *Chem. Commun*., 2011, **47**, 6476.

20. A. Wetzel, S. Wöckel, M. Schelwies, M. K. Brinks, F. Rominger, P. Hofmann and M. Limbach, *Org. Lett.*, 2013**, 15**, 266.

21. E. Byun, B. Hong, K. A. De Castro, M. Lim and H. Rhee, *J. Org. Chem.*, 2007, **72**, 9815.

22. E. K. J. Lui and L. L. Schafer, *Adv. Synth. Catal*., 2016, **358**, 713.

23. Q. P. B. Nguyen and T. H. Kim, *Synthesis*, 2012, **44**, 1977.

24. H. Pan, T. W. Ng and Y. Zhao, *Org. Biomol. Chem*., 2016, **14**, 5490.

25. M. B. Gasc, J. Perie and A. Lattes, *Tetrahedron*, 1978, **34**, 1943.

26. X. Cui, X. Dai, Y. Deng and F. Shi, *Chem. Eur. J*., 2013, **3**, 998.

27. A. Heutling, F. Pohlki, I. Bytschkov and S. Doye, *Angew. Chem. Int. Ed*., 2005, **44**, 2951.

28. H. Yang, X. Cui, X. Dai, Y. Deng and F. Shi1, *Nat. Commun*., 2015, **6**, 7478.

29. F. Li, H. Shan, Q. Kang and L. Chen, *Chem. Commun*., 2011, **47**, 5058.

30. S. Usui, H. Fujieda, T. Suzuki, N. Yoshida, H. Nakagawa and N. Miyata, *Bioorg. Med. Chem. Lett*., 2006, **16**, 3249.

31. L. Lu, J. Ma, P. Qu and F. Li, *Org. Lett.*, 2015, **17**, 2350.

32. A. J. A. Watson, A. C. Maxwell and J. M. J. Williams, *J. Org. Chem.*, 2011, **76**, 2328.

33. R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Tetrahedron*, 2017, **73**, 2225.

Isolation and characterization of regio-isomers of pyrazole based palladacycle, and their use in α-alkylation of ketones using alcohols

5.1 Introduction

Palladacycles are an important class of organometallic compounds. The interest in the use of palladacycles has been due to their various applications such as in catalysis, medicinal science, and organic synthesis.[1] Since the discovery of the application of palladacycle in catalysis by Herrmann and co-workers in 1995, intense research has been focused on the palladacycles synthesis, structural analysis, and application towards catalysis.[1a] Among the several available methods for the preparation of palladacycles, *ortho*-metallation of C─H bonds is an attractive methodology.[2] Although C─H bond activation has been thoroughly studied, the recognition of chemically similar C─H bonds have turned out to be a challenging task. Different approaches have been identified to achieve C─H bond activation of chemically similar environments.[3] In many instances, the regio-isomers have been isolated and structurally characterized. For example, Solan and co-workers demonstrated the preferential palladation of naphthalene ring using N-donors as directing ligands.[3h] Recently, Wendt and co-workers[3i] reported metal controlled regio-selectivity in the directed aromatic substitution of 2-(1-naphthyl)-pyridine. Although, the regio-isomers of palldacycles have been reported, in many instances their applications for catalysis have not been examined.

α-Alkylation of carbonyl compounds is one of the most fundamental reactions used to form a C─C bond. Traditionally, the α–alkylation of ketones was achieved by the reaction of ketones with electrophiles such as alkyl halides. However, this method involves the use of toxic organo halides and formation of large amount of inorganic

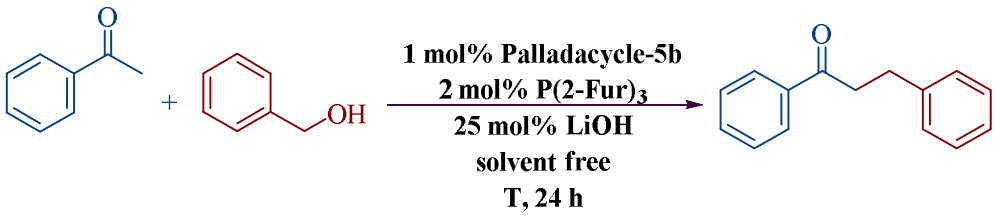
salts as waste. An alternative, greener approach for the *α*-alkylation of ketones is to use alcohols as an alkylating agent.[4] Over the last decade, several groups have reported various metal catalyzed methods for the *α*–alkylation of ketones using alcohols as an alkylating agent.[5-12] For instance, Chao and co-workers reported the *α*-alkylation of ketones by trialkylamines under heterogeneous Pd/C catalysis.[13] A homogeneous pincer type Pd–NHC catalyst was reported for the *α*-alkylation of acetophenone using benzyl alcohol at 125 °C, giving a mixture of alcohol and ketone as products.[14] More recently, Beller and co-workers elegantly reported the manganese based catalytic system for the *α*-alkylation of ketones.[12] However, many of these catalytic systems suffer from low product selectivity, low yield, and high reaction temperature. As discussed in the previous chapters, we have also been pursuing the synthesis of 1,3,5-triphenyl based palladacycles and their application towards catalysis.[15] In this chapter-V, we describe here the regio-isomers of palladacycles **5a** and **5b** activity towards *α*-alkylation of ketones. As alluded *vide supra*, the reactivity difference in regio-isomers especially the palladacycles have not been examined. We also discuss the activity of regio-isomers of the palladacycles **5a** and **5b** as catalysts, which have been studied by experiments and DFT calculations.

5.2 Results and Discussions

The synthesis and characterization of 3,5-diphenyl-1-(4-(trifluoromethyl) phenyl)-1H-pyrazole ligand, palladacycle-**5a** and **5b** were presented in chapter-II. To explore the optimum reaction conditions for the alkylation of acetophenone with benzyl alcohol, we have screened various bases and temperatures using palladacycle-**5b** and the ancillary ligand $P(2\text{-}Fur)_3{=}P(C_4H_3O)_3$ under solvent-free conditions. Of the different conditions screened, LiOH at 80 °C, resulted quantitative yield of the

desired product using palladacycle-**5b** (Table 5.1, entry 4). However, use of the palladacycle-**5a** gave relatively low yield (Table 5.1, entries 1 and 16). When the reaction was performed using commercially available palladium sources such as $Pd(OAc)_2$, $PdCl_2$, and $Pd_2(dba)_3$, no product formation was observed under similar reaction conditions (Table 5.1, entries 13, 14, and 15 respectively).

Table 5.1: Optimization of *α*-alkylation of acetophenone with benzyl alcohol using palladacycles-5a and 5b[a]



S.No.	Base	T (^oC)	Yield[b] (%)
1[c]	LiOH	50	56
2	LiOH	50	78
3	LiOH	60	82
4	LiOH	80	98
5	$LiOH.H_2O$	80	89
6	$CsOH.H_2O$	80	92
7	KO^tBu	80	ND
8	Cs_2CO_3	80	ND
9	K_3PO_4	80	ND

10	KOH	80	Trace
11	NaOH	80	Trace
12	Li_2CO_3	80	21
13[d]	LiOH	80	ND
14[e]	LiOH	80	Trace
15[f]	LiOH	80	ND
16[c]	LiOH	80	91

[a]Reaction conditions: Acetophenone 1.0 mmol, benzyl alcohol 1.2 mmol, LiOH 0.25 mmol, palladacycle-**5b** $1x10^{-2}$ mmol, P(2-Fur)$_3$ $2x10^{-2}$ mmol. [b]Isolated yield after column chromatography, [c]palladacycle-**5a** was used, [d]instead of palladacycle-**5b**, 2 mol% $Pd(OAc)_2$ was used. [e]instead of palladacycle-**5b**, 2 mol% $PdCl_2$ was used, [f]instead of palladacycle-**5b**, 1 mol% $Pd_2(dba)_3$ was used. ND: Not Detected.

The catalytic performance of the palladacycles-**5a** and **5b** were evaluated using the model substrates acetophenone and benzyl alcohol. The reactions were performed under solvent-freeconditions at 60 °C using 1 mol% of catalyst. The catalytic performance of the palladacycles-**5a** and **5b** are compared in figure 5.1. At 60 °C using 1 mol% of catalyst loading, palladacycle-**5b** displayed superior activity over palladacycle-**5a**. Although both the palldacycles were active for the α-alkylation of acetophenone with benzyl alcohol, we chose palladacyle-**5b** for further studies because of its superior activity over palladacycle-**5a**. In order to know the catalytic efficiency of palladacycle-**5b**, we examined a 2.0 g (16.7 mmol) scale reaction by loading 0.001 mol% catalyst at 130 °C for 48 h. Palladacycle-**5b** exhibited high turnover number (TON) up to 32000 (66%).

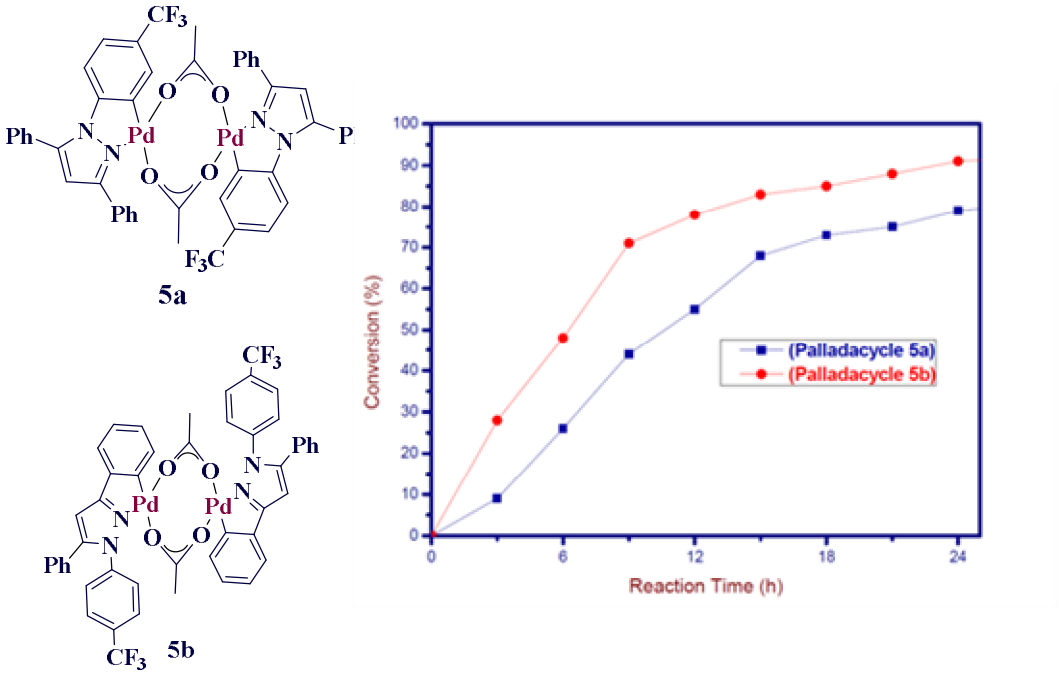
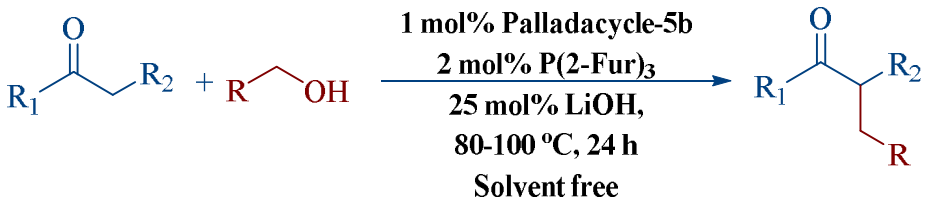


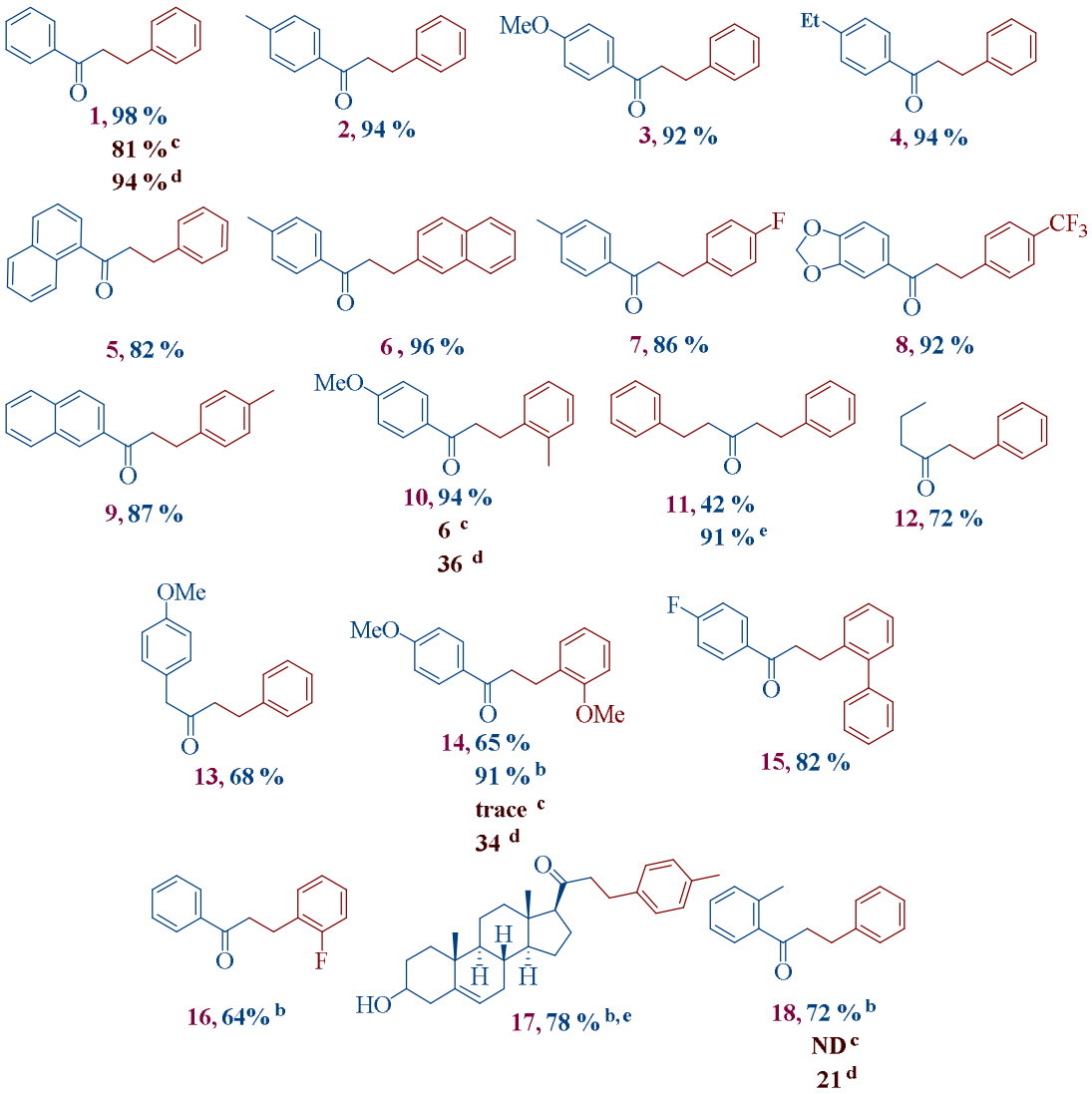
Figure 5.1: Reactivity study of palladacycles **5a** and **5b** using acetophenone and benzyl alcohol at 60 °C. Reaction conditions: 0.5 mmol acetophenone, 0.6 mmol benzyl alcohol, 25 mol% LiOH, 1 mol% palladacycle-**5b**, and 2 mol% $P(2\text{-Fur})_3$. Conversions were analysed using ^1H NMR by taking *p*-xylene as the internal standard.

Encouraged by these results, we have evaluated the substrate scope and limitations using palladacycle-**5b** for the alkylation of various ketones using different aryl and aliphatic primary alcohols. In most cases, electron rich as well as electron deficient substituted acetophenones or benzyl alcohols were successfully alkylated to the desired products in good to excellent isolated yields under mild reaction conditions (Table 5.2, entries 1-9). *Ortho*-substituted benzylic alcohols (or) aryl ketones (Table 5.2, entries 10, 14, 15, 16 and 18) as well as aliphatic ketones (Table 5.2, entry 11) were selectively alkylated to the corresponding α-alkylated ketones. Substrates having two α-carbons that are prone to potential alkylation generally show selectivity issues. Interestingly, we found that the present catalytic system offers a

regio-selective alkylation in the case of 2-pentanone and 1-(4-methoxyphenyl)propan-2-one with benzyl alcohol (Table 5.2, entries 12 and 13). The present catalytic system was also successfully applied to the *α*-alkylation of biologically important steroid *β*-pregnenolone. In general, *β*-pregnenolone under metal reaction condition is susceptible to isomerization of C=C bond to produce progesterone, which has an *α,β*-unsaturated ketone moiety.[16] Under the optimized conditions, the reaction of *β*-pregnenolone with 4-methyl benzyl alcohol proceeded smoothly to give the corresponding *α*-alkylated product (Table 5.2, entry 17) in 78% yield, without affecting the other functional groups such as C=C and –OH.

Table 5.2: Scope of the *α*-alkylation of aryl ketones using aryl and aliphatic alcohols [a]



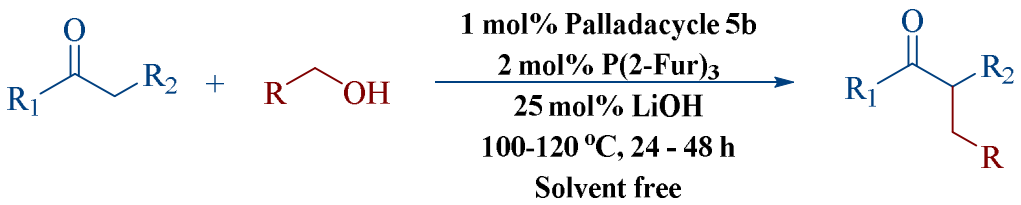


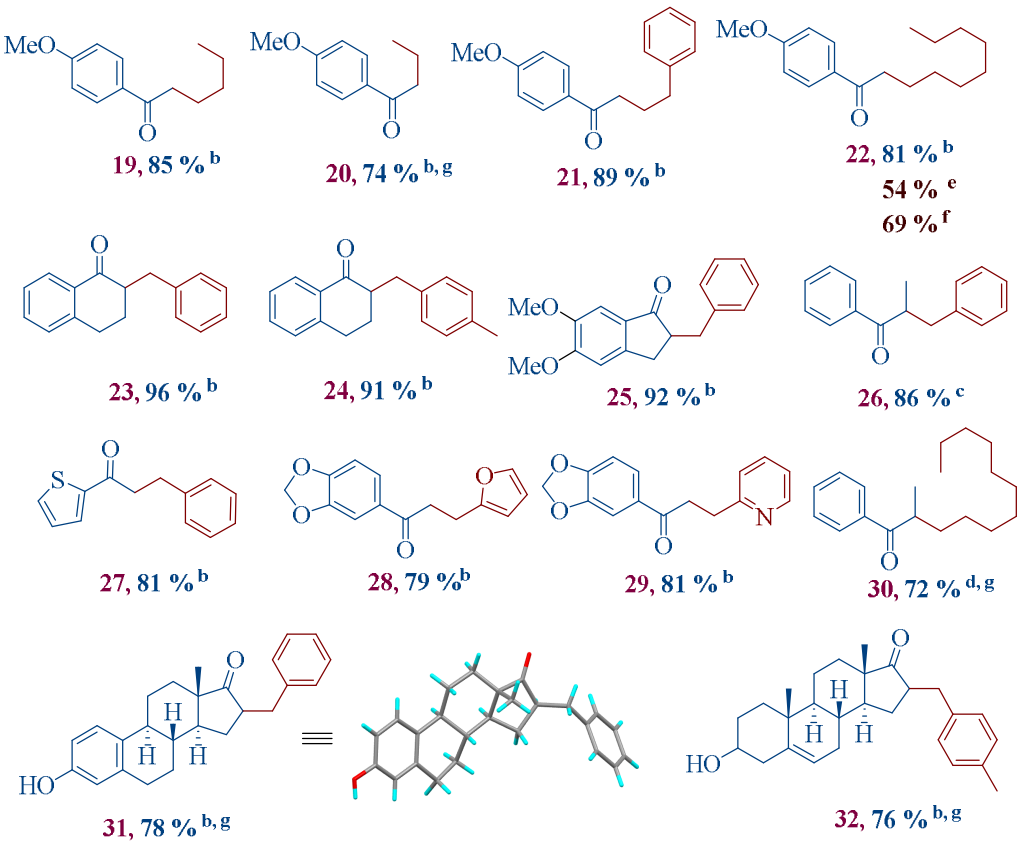
[a]Reaction conditions: Aryl ketone 1 mmol, alcohol 1.2 mmol, LiOH 0.25 mmol, palladacycle-**5b** $1x10^{-2}$ mmol, $P(2\text{-Fur})_3$ $2x10^{-2}$ mmol, [b]reactions were performed at 100 °C for 24 h and 2 mmol alcohol was used, [c]reactions were performed using palladacycle-**5a** for 12 h, [d]reactions were performed using palladacycle-**5b** for 12 h, [e]3 mmol alcohol was used.

In addition, we also explored this methodology to substrates like aliphatic alcohols or methylene ketones at slightly higher temperature. Aliphatic alcohols such as 1-butanol, ethanol, 2-phenyl ethanol, and 1-octanol could be used as electrophilic partner for obtaining the corresponding ketones (Table 5.3, entries 19-22). The alkylation of cyclic or methylene ketones such as 1-tetralone, 5,6-dimethoxy-1-

indanone or propiophenone, resulted in the corresponding alkylated products in good to excellent isolated yields (Table 5.3, entries 23-26). Good to excellent yields were also achieved in the case of heteroaryl ketones or heteroaryl alcohols as coupling partners at relatively mild conditions (Table 5.3, entries 27, 28 and 29). While, it has been a challenge to alkylate non-activated methylene ketones with less reactive aliphatic alcohols, in our case, the alkylation of methylene ketones with aliphatic alcohols were carried at moderate temperatures (Table 5.3, entry 30). To increase the adaptability of our catalytic system, we applied our strategy toestrone and *trans*-dehydroandrosterone.The reaction of estrone with benzyl alcohol and *trans*-dehydroandrosterone with *p*-methylbenzyl alcohol proceeded smoothly to the corresponding alkylated products in 78% and 76% yields, respectively (Table 5.3, entries 31 and 32). It should be noted that selective mono benzylation of *trans*-dehydroandrosterone was achieved without isomerisation under the optimized reaction conditions. It is worth mentioning that our protocol offers the *α*-alkylation of *β*-pregnenolone, estrone and *trans*-dehydroandrosterone without the use of any protection and de-protection of other functional groups.[12]

Table 5.3: Scope of the *α*-alkylation of aryl (or) heteroaryl ketones using aryl (or) hetero aryl alcohols[a]

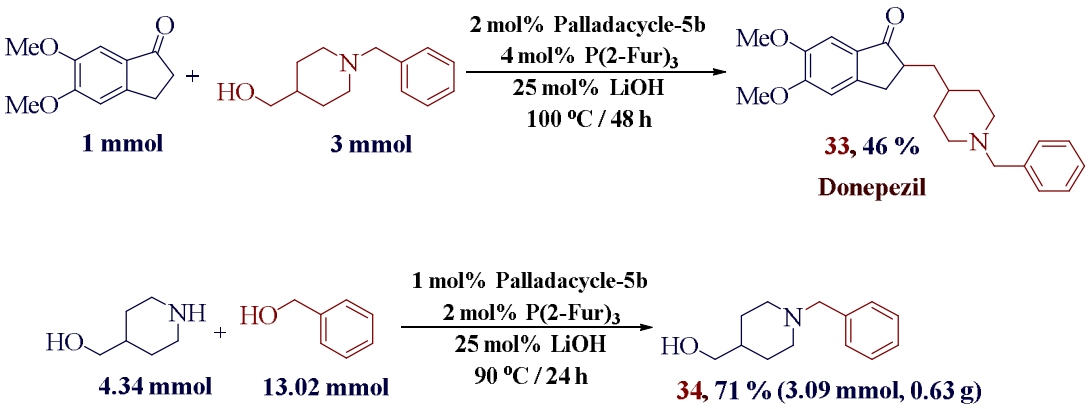




[a]Reaction conditions: Aryl ketone 1 mmol, alcohol 2 mmol, LiOH 0.25 mmol, palladacycle-**5b** $1x10^{-2}$ mmol, $P(2\text{-Fur})_3$ $2x10^{-2}$ mmol, [b]reactions were performed at 100 °C for 24 h, [c]reactions were performed at 120 °C for 24, [d]reactions were performed at 120 °C for 48 h and 2 mol% palladacycle-**5b**, 25 mol% LiO^tBu were used, [e]reactions were performed using palladacycle-**5a** for 12 h, [f]reactions were performed using palladacycle-**5b** for 12 h, [g]alcohol 3 mmol was used.

Another important biologically active molecule is donepezil which is used in the treatment of Alzheimer's disease.[17] Using palladacycle-**5b**, we were able to synthesize donepezil starting from N-benzyl-4-piperidinemethanol and 5,6–dimethoxy indanone in moderate yield (46%, Scheme 5.1), which is marginally higher than the yields reported by Glorius and co-workers [6d] using Ru-based catalytic system. We further tested the synthetic utility of the catalyst for the alkylation of 4-piperidine methanol with benzyl alcohol to get N-benzyl-4-piperidinemethanol

(Scheme 5.1). The yields were comparable or better than the yields reported by Yamada and co-workers using Ir-based catalytic system.[18]

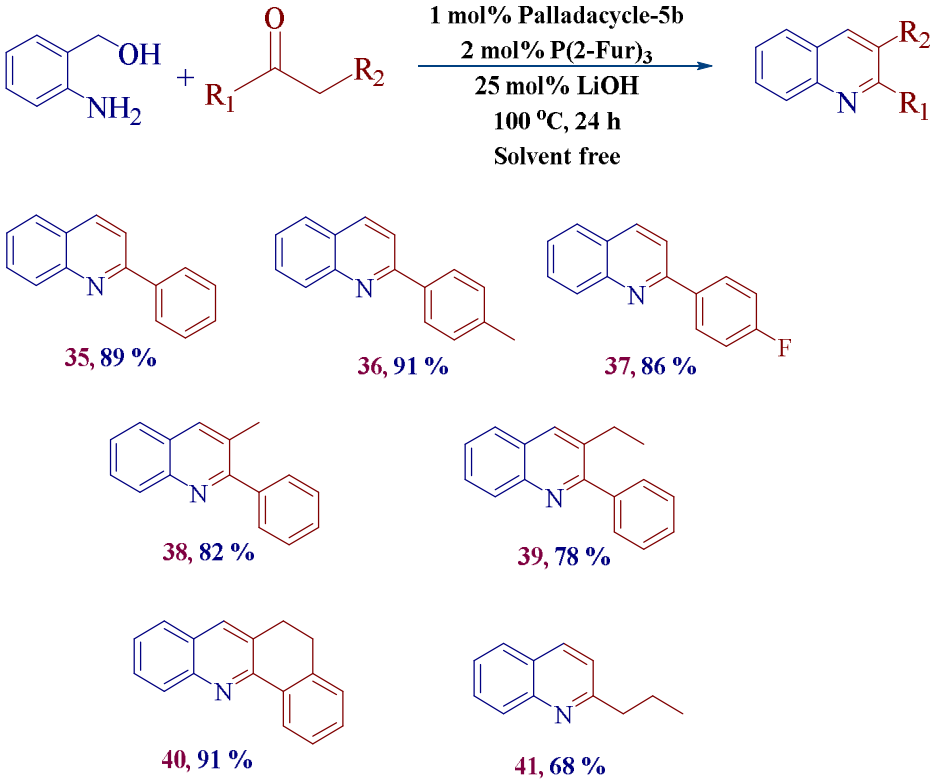


Scheme 5.1: Synthesis of donepezil and N-benzyl 4-piperidinemethanol

Quinolines are an important class of heterocyclic compounds used in the design of pharmacologically active compounds that are used as anti-inflamatory, anti-malarial, and anti-asthmatic drugs.[19] They can be prepared by using conventional Friedländer annulation reaction from 2-aminobenzaldehyde and ketones.[20] However, the low stability of 2-aminobenzaldehyde and self-condensation by-product limits the use of this method. Modified Friedländerquinoline synthesis using more stable 2-aminobenzylacohol under hydrogen-borrowing conditions have been reported as a versatile method.[21] Using palladacycle-**5b**, with the optimized conditions for the α-alkylation of ketones mentioned above, 2-aminobenzylalcohol were reacted with acetophenoneto provide the corresponding qunoline in 89% yield (Table 5.4, entry 35). Good isolated yields were obtained when we used 4-methyl acetophenone and 4-fluoro acetophenone (Table 5.4, entries 36 and 37). Propiophenone, butyrophenone, and 1-tetralone were also reacted with 2-aminobenzylacohol to yield the corresponding quinoline derivatives in 82%, 78%, and 91%, respectively (Table 5.4,

entries 38, 39 and 40). Palladacycle-**5b** showed regio-selectivity towards the formation of 2-propyl quinoline, when used 2-pentanone as a substrate (Table 5.4, entry 41).

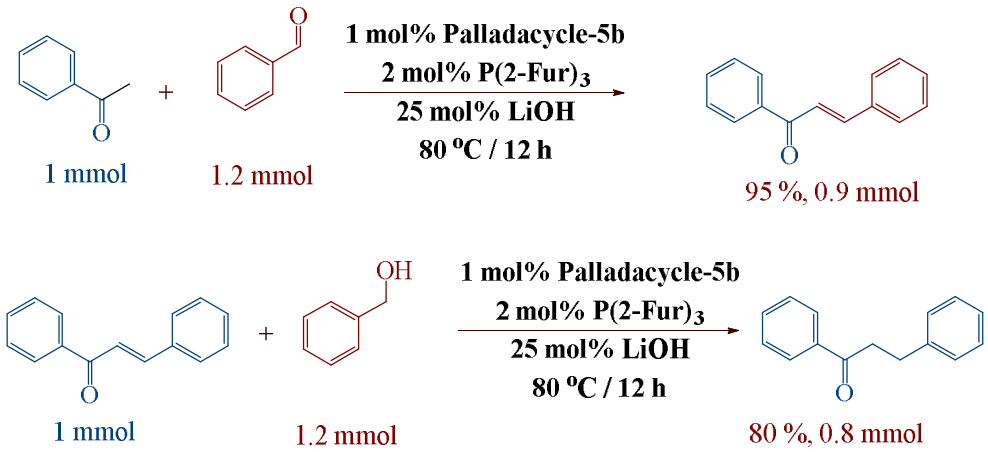
Table 5.4: Synthesis of quinolines using 2-aminobenzyl alcohol and ketones[a]



[a]Reaction conditions: 2-Amino benzylalcohol 1 mmol, ketone 1.2 mmol, LiOH 0.25 mmol, palldacycle-**5b** $1x10^{-2}$ mmol, and $P(2\text{-Fur})_3$ $2x10^{-2}$ mmol.

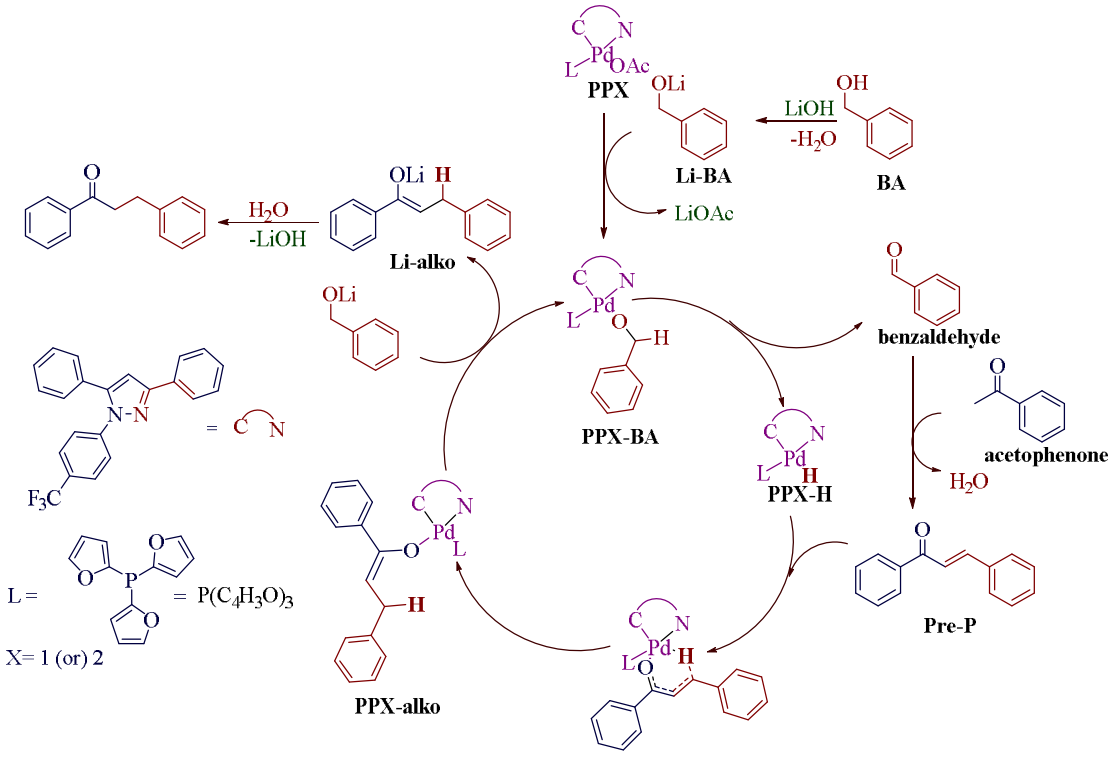
Further, we investigated the catalytic activity of the palladacycles-**5a** and **5b** by choosing 12 h reaction time at respective temperatures that are listed in Tables 5.2 (entries 1, 10, 14 and 18) and 5.3 (entry 22). Palladacycle-**5b** exhibited better yields over palladacyle-**5a**. Notably, a remarkable difference was observed when *ortho*-substituted acetophenone or *ortho*-benzyl alcohols were used as substrates and in such

cases palladacycle-**5a** was almost unreactive or not efficient to produce the desired products (Table 5.2, entries 10, 14, and 18).



Scheme 5.2: Control experiments

It is of interest to understand the mechanism for the catalytic reaction. As shown in scheme 5.3, we have proposed a plausible mechanism for the reaction based on our experimental results and literature reports [22] for *α*-alkylation of ketones with alcohols. Reaction of lithium alkoxide with *in situ* formed phosphine coordinated palladium species (**PPX**) generated the palladium alkoxide species (**PPX-BA**) which undergone β-hydride elimination to generate the Pd─H (**PPX-H**) intermediate and the aldehyde. The *in situ* generated base catalyzed *α*,β-unsaturated carbonyl compound access the Pd─H which upon reaction with alcohol releases the product. Control experiments were performed to validate the proposed mechanism (Scheme 5.2). Reaction of acetophenone with benzaldehyde under the optimized reaction conditions resulted only *α*,β-unsaturated compound in 95% yield. Reaction of *α*, β-unsaturated compound with benzyl alcohol in the presence of palladacycle-**5b** (1 mol%), P(2-Fur)$_3$ (2 mol%), and LiOH (25 mol%) at 80 °C for 12 h resulted in 80% of the desired product. These results support our proposed mechanism.



Scheme 5.3: Proposed catalytic pathway for α-alkylation of ketones using alcohols

To probe the high activity of palladacycle-**5b** over **5a** for the α-alkylation of ketones using alcohols, the mechanism of the catalytic reactions were investigated using DFT methods (ESI). The free energy profiles for the reaction between acetophenone and benzyl alcohol using both the palladacycles (**5a** and **5b**)-phosphine **PP1** and **PP2** were mapped. Optimized geometries of both these catalysts (Figure 5.2) suggest that they have a planar geometry around Pd. In **PP1**, the distances Pd-P, Pd-O, and Pd-N are 2.3, 2.11, and 2.15 Å respectively. On the other hand, in **PP2**, Pd-P, Pd-O, and Pd-N distances are 2.54, 2.06, and 2.18 Å respectively. Palladacycles **PP1** and **PP2** have a free energy difference of 12.03 kcal/mol with **PP1** being more stable than **PP2**. The initial step in the catalytic reactivity is the reaction of LiOH with benzyl alcohol (**BA**) giving lithium benzyloxide (**Li-BA**). The free energy change

during the reactions was computed with respect to the reactants **PP1 +Li-BA** and **PP2 +Li-BA** respectively.

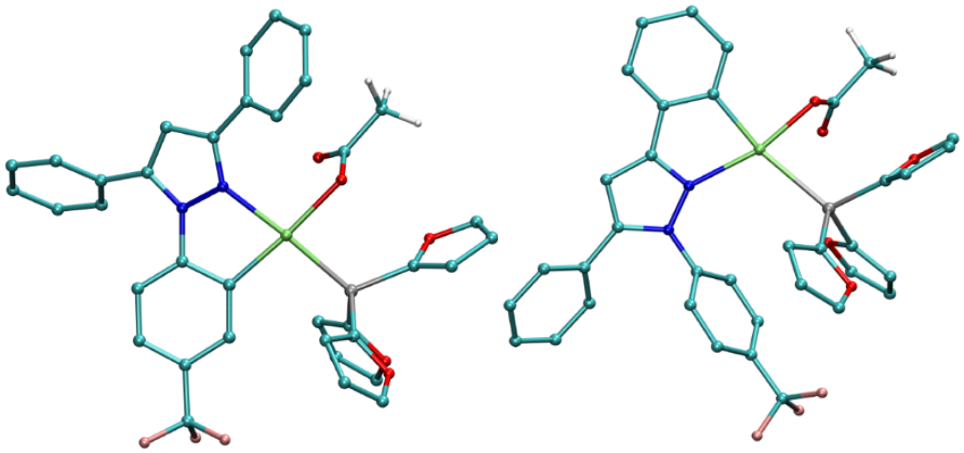


Figure 5.2: Optimized geometries of palladacycle-phosphine catalysts **5a (PP1 : left)** and **5b (PP2 : right)**. Phenyl & furyl H atoms not shown for clarity

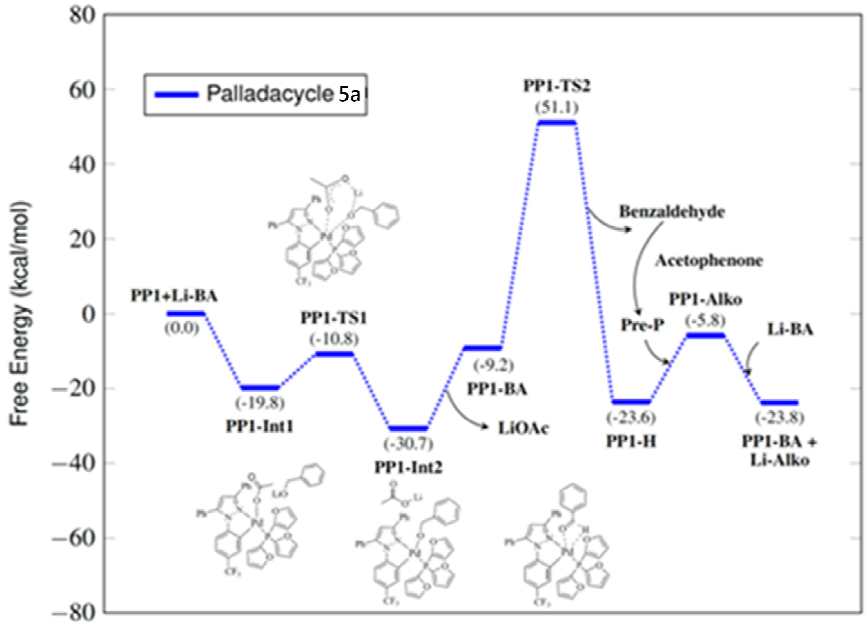


Figure 5.3: Free energy profile for reaction between Li-BA with PP1

The free energy profile for the catalytic cycle of **PP1** is given in Figure 5.3. In the presence of base (LiOH), **BA** is converted to lithiated benzyl alcohol (**Li-BA)** with

H_2O as the side product. **Li-BA** then reacts with the catalyst **PP1** to form an intermediate **PP1-Int1** which has a free energy of -19.8 kcal/mol with respect to the reactants. In complex **PP1-Int1**, the Pd-O(**Li-BA**) and Li(**Li-BA**)-O(**OAc**) distances are 4.14 and 1.84 Å respectively. **PP1-Int1** is converted to another complex **PP1-Int2** that involves thetransfer of Li atom from **Li-BA** to the **OAc** groupalong with the formation of a new bond between Pd and O atom of **Li-BA** through a transition state **PP1-TS1**. Pd-O(**Li-BA**) and Li-O(**OAc**) distances in **PP1-TS1** are 2.54 and 1.78 Å respectively. In **PP1-Int2**,the distances Pd-O(**Li-BA**) and Li-O(**OAc**) are 2.11 and 1.92 Å respectively. Then lithium acetate (**LiOAc**)dissociates from catalyst **PP1** resulting in the benzylated complex with **PP1, PP1-BA**. Pd-O(**BA**) distance in **PP1-BA** is 2.06 Å. **PP1-BA** has a free energy of -9.2 kcal/mol. **PP1-BA** is then converted to complex **PP1-H** (with benzaldehydeas the intermediate)that involves the transfer of H atom from benzyl CH_2 to Pd atom through a transition state **PP1-TS2**. **PP1-TS2** has a free energy of 51.1 kcal/mol. Pd─H(-CH_2 benzyl) distances in **PP1-BA**, **PP1-TS2,** and **PP1-H** are 3.1, 2.93, and 1.59 Å respectively. The intermediate benzaldehydethen reacts with the reactant acetophenone to give the pre-product (**Pre-P**) with the removal of H_2O. **Pre-P** then reacts with **PP1-H** to form an alkoxide complex **PP1-Alko** which has a free energy of -5.8 kcal/mol. **PP1-Alko** complex is formed by H atom transfer from Pd atom to the double bond of **Pre-P** accompanied with the bond formation between O atom of **Prep-P** and Pd atom. This is apparent from the Pd─H bond distances that are 1.59 Å in **PP1-H** and 5.1 Å in **PP1-Alko**. Also, Pd-O(**Pre-P**) distance in **PP1-Alko** is 2.1 Å. In the final step, **PP1-Alko** reacts with **Li-BA** to form lithiatedalkoxide, **Li-Alko**and regenerates the active species **PP1-BA** for the next cycle. The free energy change for the formation of **Li-Alko** and **PP1-BA** is -23.8kcal/mol. **Li-Alko**then reacts with H_2O to give the final product of this reaction.

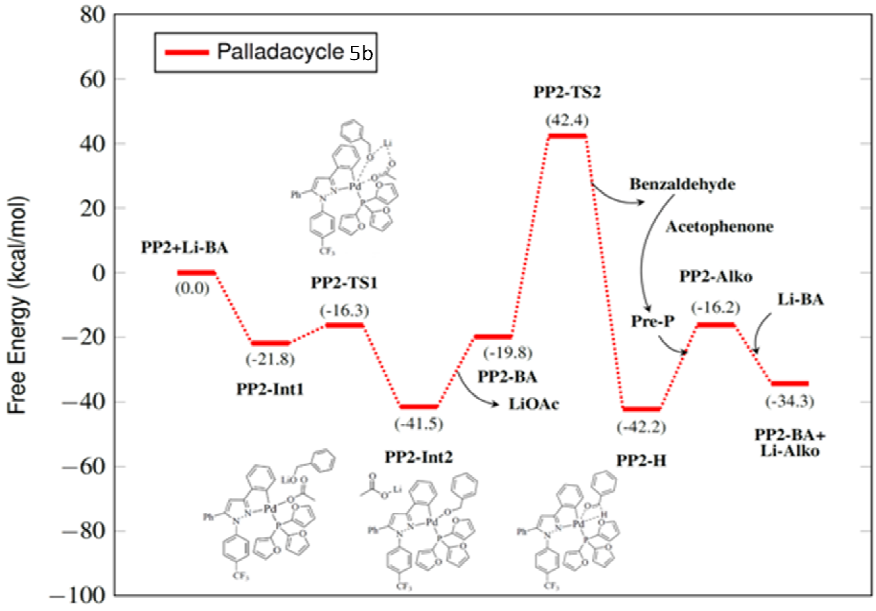


Figure 5.4: Free energy profile for reaction between **Li-BA** with **PP2**

The free energy profile (Figure 5.4) was mapped for the same reaction using palladacycle **PP2** as catalyst. The first step is the formation of a complex **PP2-Int1** where **Li-BA** comes close to Pd metal, with Pd-O(**Li-BA**) and Li- O(OAc) distances being 3.5 and 1.9 Å respectively. It has a free energy of -21.8 kcal/mol and is more stable than the similar intermediate **PP1-Int1** by 2 kcal/mol. **PP2-Int1** is converted to another complex **PP2-Int2** through a transition state **PP2-TS1** which has a barrier of 4.9 kcal/mol. The similar step was encountered in the case of the reaction catalyzed by **PP1** (**PP1-TS1**) with a barrier of 9 kcal/mol indicating that the reaction catalyzed by catalyst **PP2** would be more favorable than by catalyst **PP1**. Like **PP1-TS1,** this transition state also corresponds to the transfer of Li atom from **Li-BA** to the leaving group **LiOAc** and the formation of a new bond between Pd metal and O atom of **Li-BA**. **PP2-TS1** connects to **PP2-Int2** on the other side with a free energy change of -41.5 kcal/mol. **PP2-Int2** is more stable than **PP1-Int2** by 10.8 kcal/mol. The leaving

group **LiOAc** then dissociates to give **PP2-BA** having a free energy change of -19.8 kcal/mol. **PP2-BA** is more stabilized than **PP1-BA** by 10.6 kcal/mol making the reaction more favorable when catalyst **PP2** is used. In the next step, **PP2-BA** is converted to **PP2-H** via transition state **PP2-TS2** which is 42.4 kcal/mol higher than reactants. The products (**PP2-H**) for this step using **PP2** are stabilized by 18.6 kcal/mol more than the products using **PP1** (**PP1-H**). In the next step, **PP2-H** reacts with **Pre-P** to form **PP2-Alko** as the product with free energy change of -16.2 kcal/mol. It is more stable than that of **PP1-Alko** by 10.4 kcal/mol. In the final step, **PP2-Alko** reacts with **Li-BA** to regenerate **PP2-BA** (active species) and **Li-Alko**with a free energy change of -34.3 kcal/mol. Product obtained in this step is also more stable than that obtained using catalyst **PP1** by 10.5 kcal/mol. **Li-Alko**can then react with water to give the final product. In addition, another reaction path involving an isomer of palladacycle**2** with the phosphine ligand trans to pyrazole nitrogen (**PP3**) was also studied. The free energy profile for this path was found to be similar to that for **PP1**. Hence, this path was ruled out to account for the observed experimental results.

The free energies of the important intermediates and transition states for the reaction paths using palladcycles-**5a** and **5b** are compared. Of interest is the difference in free energies ($\Delta\Delta G$) of the concerned stationary points (k) along the path for the two reactions i.e. $\Delta\Delta G = \Delta G_k$(**PP2**)$-\Delta G_k$(**PP1**). We can see that overall energies for reaction using **PP2** are lower than that when using **PP1** with the largest stabilization of 18.6 kcal/mol for **PP2-H** compared to that of **PP1-H**. In addition, the overall barrier for the reaction using **PP2** (**2TS2** vs **1TS2**) is lowered by ~ 9 kcal/mol compared that when using **PP1**. These findings indicate that reaction using **PP2** is expected to be favorable than **PP1** consistent with the experiments.

5.3 Conclusion

In summary, we successfully studied applications of palladacycles **5a** and **5b** as catalysts for the *α*-alkylation of ketones using alcohols under solvent free conditions. Experimental studies reveal that palladacycle-**5b** is more active than palladacycle-**5a**. Comparison of the energy profiles for reactions involving palladacycles-**5a** and **5b** using DFT methodsreveal that the reactions proceed through similar pathways. However, the intermediates and transition states are more stabilized for the reaction involving **5b**. In addition, the overall free energy barrier for the reaction using palladacycle-**5b** is stabilized by ~ 9 kcal/mol compared to palladacycle-**5b**. Hence, palldacycle-**5b** is expected to be more favorable than palldacycle-**5a** which is consistent with experimental results. Our catalytic system broadens the scope of the hydrogen borrowing catalysis in alkylation reaction. Furthermore, we were able to exploit this catalytic system for the synthesis of biologically active and important molecule donepezil.

5.4 Experimental section:

5.4.1 General information

All chemicals were used as received from commercially available sources. NMR spectra were recorded on Bruker ARX 400 spectrometer at room temperature. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR chemical shifts in ppm were referenced internally to its proton resonance of incomplete deuterated solvent signals. ^{19}F NMR spectra were externally reference to *α,α,α*-trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). Electron spray ionization mass spectra were recorded on a Bruker microTOF-QII spectrometry. IR spectra were recorded with Perkin Elmer instrument. Single-crystal X-ray

diffraction data were collected at 296 K using, Mo-Kα radiation (0.71073 Å). Crystallographic data for the palladacycle1&2 and compound 30 and details of X-ray diffraction experiments and crystal structure refinements are given in Table S1. SADABS absorption corrections were applied in both cases. The structures were solved and refined with SHELX suite of programs. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The H atoms were placed at calculated positions and were refined as riding atoms.

5.4.2 General procedure for α-alkylation of ketones using alcohols

An oven dried Schlenk tube was charged with palladacycle **5b** or **5a** ($1x10^{-2}$ mmol to $2x10^{-2}$ mmol), P(2-Fur)$_3$ ($2x10^{-2}$ mmol to $4x10^{-2}$ mmol). Under inert atmosphere LiOH (0.25 mmol), ketone (1.0 mmol), alcohol (1.2 mmol to 2.0 mmol) were added to the reaction mixture and the system was purged with nitrogen gas for 10 minutes. Then the Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 80-130 ^{o}C for 24-48 h. The reaction mixture was cooled to room temperature, diluted and washed with dichloromethane (3x5 mL), and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using ethyl acetate and *n*-hexanes mixtures to afford the α-alkylated product in high purity.

5.4.3 General procedure for the synthesis of quinolines

An oven dried Schlenk tube was charged with palladacycle-**5b** ($1x10^{-2}$ mmol), P(2-Fur)$_3$ ($2x10^{-2}$ mmol). Under inert atmosphere, LiOH (0.25 mmol), ketone (1.2 mmol), 2-aminobenzyl alcohol (1.0 mmol) were added to the reaction mixture and the system was purged with nitrogen gas for 10 minutes. Then the Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 100 ^{o}C for 24 h. The reaction

mixture was cooled to room temperature, diluted and washed with dichloromethane (3x5 mL), and concentrated under vacuum. The crude product was subjected to column chromatography on silica gel using ethyl acetate and *n*-hexanes mixtures to afford the corresponding quinoline derivative products in high purity.

5.4.4 Analytical data for *α*-alkylated products

1,3-diphenylpropan-1-one (Table 5.2, entry 1) [23]**:** Prepared from acetophenone (0.12 g, 1.0mmol) and benzyl alcohol (0.13 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21 g, 0.9 mmol, 98%). Mp = 72-73 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.1 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.35–7.22 (m, 5H), 3.33 (t, *J* = 7.7 Hz, 2H), 3.10 (t, *J* = 7.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3, 141.4, 136.9, 133.1, 128.7, 128.6, 128.5, 128.1, 126.2, 40.5, 30.2 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}ONa$ ($[M+Na]^+$): 233.0937, found: 233.0942.

3-phenyl-1-(p-tolyl)propan-1-one (Table 5.2, entry 2) [23]**:** Prepared from 4'-methyl acetophenone (0.13 g, 1.0 mmol) and benzyl alcohol (0.13 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21 g, 0.9 mmol, 94%). Mp = 68-69 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.2 Hz, 2H), 7.34–7.21 (m, 7H), 3.29 (t, *J* = 7.5 Hz, 2H), 3.08 (t, *J* = 7.5 Hz, 2H), 2.42 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.9, 143.9, 141.5, 134.5, 129.4, 128.6, 128.5, 128.3, 126.2, 40.4, 30.3, 21.7 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}O$ ($[M+H]^+$): 225.1274, found: 225.1281.

1-(4-methoxyphenyl)-3-phenylpropan-1-one (Table 5.2, entry 3) [24]**:** Prepared from 4'-methoxy acetophenone (0.15 g, 1.0 mmol) and benzyl alcohol (0.13 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.22 g, 0.9 mmol, 92%), Mp = 96-97 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.9 Hz, 2H), 7.33–7.20 (m, 5H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 3.26 (t, *J* = 7.8 Hz, 2H), 3.07 (t, *J* = 7.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9, 163.5, 141.5, 130.4, 130.0, 128.6, 128.5, 126.1, 113.8, 55.5, 40.2, 30.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}O_2$ ($[M+H]^+$): 241.1223, found: 241.1233.

1-(4-ethylphenyl)-3-phenylpropan-1-one (Table 5.2, entry 4) [24]**:** Prepared from 4'-ethyl acetophenone (0.15 g, 1.0mmol) and benzyl alcohol (0.13 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.22 g, 0.9 mmol, 94%), Mp = 65-66 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8 Hz, 2H), 7.31–7.22 (m, 7H), 3.31 (t, *J* = 8 Hz, 2H), 3.10 (t, *J* = 8 Hz, 2H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.9, 150.0, 141.5, 134.7, 128.6, 128.5, 128.3, 128.2, 126.2, 40.4, 30.3, 28.9, 15.3ppm.HRMS (ESI): calcd. for $C_{17}H_{18}O$ ($[M+H]^+$): 239.1430, found: 239.1442.

1-(naphthalen-1-yl)-3-phenylpropan-1-one (Table 5.2, entry 5) [25]**:** Prepared from 1-acetonaphthone (0.17 g. 1.0 mmol) and benzyl alcohol (0.13 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21 g, 0.8 mmol, 82%), Mp = 54-55 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.95–7.87 (m, 3H), 7.62–7.53 (m, 2H), 7.33 (dd, *J* = 11.3, 4.8 Hz, 4H), 7.25–7.20 (m, 1H), 3.45 (t, *J* = 7.6 Hz, 2H), 3.15 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.3, 141.5, 135.7, 134.3, 132.7, 129.8,

129.7, 128.7, 128.6, 127.9, 126.9, 126.3, 123.9, 40.7, 30.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{16}O$ ($[M+H]^+$): 261.1274, found: 261.1277.

3-(naphthalen-2-yl)-1-(p-tolyl)propan-1-one (Table 5.2, entry 6) [25]**:** Prepared from 4'-methyl acetophenone (0.13 g. 1.0 mmol) and 2-naphthalenemethanol (0.19 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.26 g, 0.9 mmol, 96%), Mp = 90-91 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.74 (t, *J* = 4 Hz, 1H), 7.55–7.47 (m, 2H), 7.41 (d, *J* = 4.1 Hz, 2H), 7.25–7.23 (m, 3H), 3.53(t, *J* = 8 Hz, 2H), 3.40 (d, *J* = 8 Hz, 2H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1, 144.0, 137.6, 134.5, 134.1, 131.8, 129.4, 129.1, 128.3, 127.1, 126.3, 126.2, 125.8, 125.7, 123.7, 39.8, 27.4, 21.8 ppm. HRMS (ESI): calcd. for $C_{20}H_{18}O$ ($[M+H]^+$): 275.1430, found: 275.1426.

3-(4-fluorophenyl)-1-(p-tolyl)propan-1-one (Table 5.2, entry 7) [26]**:** Prepared from 4'-methyl acetophenone (0.13 g. 1.0mmol) and 4-fluoro benzylalcohol (0.15 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21 g, 0.8 mmol, 86%), Mp = 67-68 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.2 Hz, 2H), 7.26–7.18 (m, 4H), 6.97 (t, *J* = 8.7 Hz, 2H), 3.25 (d, *J* = 7.6 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.84, 161.53 (d, *J* = 243.7 Hz), 144.07, 137.13 (d, *J* = 3.2 Hz), 134.49, 129.96 (d, *J* = 7.8 Hz), 129.44, 128.29, 115.36 (d, *J* = 21.1 Hz), 40.45, 29.50, 21.77 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -118.33 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}FO$ ($[M+H]^+$): 243.1180, found: 243.1171.

1-(benzo[d][1,3]dioxol-5-yl)-3-(4-(trifluoromethyl)phenyl)propan-1-one (Table 5.2, entry 8) [41]**:** Prepared from 3',4'-methylenedioxy acetophenone (0.16 g. 1.0mmol) and 4-trifluoro benzylalcohol (0.21 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.29 g, 0.9 mmol, 92%), Mp = 62-63 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (d, *J* = 8.2 Hz, 3H), 7.43 (d, *J* = 1.7 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 2H), 3.24 (t, *J* = 7.7 Hz, 2H), 3.11 (t, *J* = 7.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.7, 152.0, 148.4, 145.6, 131.7, 129.5, 128.9, 128.6 (d, *J* = 32.3 Hz), 125.5 (q, *J* = 3.8 Hz), 124.4, 123.1, 108.0 (d, *J* = 8.0 Hz), 102.0, 39.7, 30.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.34 ppm. HRMS (ESI): calcd. for $C_{17}H_{13}F_3O_3$ ($[M+H]^+$): 323.0890, found: 323.0897.

1-(naphthalen-2-yl)-3-(p-tolyl)propan-1-one (Table 5.2, entry 9) [41]**:** Prepared from 2-acetylnaphthalene (0.17 g. 1.0 mmol) and 4-methyl benzylalcohol (0.15 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.24 g, 0.8 mmol, 87%), Mp = 108-109 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1H), 8.05 (d, *J* = 8.6 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H),7.88 (t, *J* = 7.6 Hz, 2H), 7.62 -7.53 (m, 2H), 7.17 (dd, *J* = 23.5, 7.8 Hz, 4H), 3.43(t, *J* = 7.6 Hz, 2H), 3.10 (t, *J* = 7.7 Hz, 2H), 2.34 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 138.4, 135.8, 135.7, 134.4, 132.7, 129.8, 129.7, 129.4, 128.6, 128.6, 128.5, 127.9, 126.9, 124.0, 40.9, 30.0, 21.2 ppm. HRMS (ESI): calcd. for $C_{20}H_{18}ONa$ ($[M+Na]^+$): 297.1250, found: 297.1255.

1-(4-methoxyphenyl)-3-(o-tolyl)propan-1-one (Table 5.2, entry 10) [27]**:** Prepared from 4'-methoxy acetophenone (0.15 g, 1.0 mmol) and 2-methyl benzylalcohol (0.15 g, 1.2

mmol). After purification by column chromatography, the compound was isolated as a white solid (0.24 g, 0.9 mmol, 94%), Mp = 82-83 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.8 Hz, 2H), 7.21–7.12 (m, 4H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H), 3.21 (t, *J* = 7.6 Hz, 2H), 3.05 (t, *J* = 7.6 Hz, 2H), 2.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 163.6, 139.7, 136.1, 130.4, 130.4, 130.1, 128.8, 126.4, 126.3, 113.9, 55.6, 38.9, 27.8, 19.5 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}O_2$ ($[M+H]^+$): 255.1380, found: 255.1393.

1, 5-diphenylpentan-3-one (Table 5.2, entry 11) [26]**:** Prepared from acetone (58 mg, 1.0 mmol) and benzylalcohol (0.32 g, 3.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.22 g, 0.9 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 4H), 7.24–7.14 (m, 6H), 2.91 (t, *J* = 7.6 Hz, 4H), 2.73 (t, *J* = 7.6 Hz, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 141.1, 128.6, 128.4, 126.2, 44.6, 29.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}O$ ($[M+H]^+$): 239.1430, found: 239.1431.

1-phenylhexan-3-one (Table 5.2, entry 12) [28]**:** Prepared from 2-pentanone (86 mg, 1.0 mmol) and benzylalcohol (0.13 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as colourless liquid (0.13 g, 0.7 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 6.4 Hz, 3H), 2.91 (t, *J* = 7.6 Hz, 2H), 2.73 (t, *J* = 7.7 Hz, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 1.60 (dd, *J* = 14.8, 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.4, 141.3, 128.6, 128.4, 126.2, 45.1, 44.4, 29.9, 17.4, 13.8 ppm. HRMS (ESI): calcd. for $C_{12}H_{16}ONa$ ($[M+Na]^+$): 199.1093, found: 199.1092.

1-(4-methoxyphenyl)-4-phenylbutan-2-one (Table 5.2, entry 13) [29]**:** Prepared from 4-methoxyphenylacetone (0.16 g, 1.0 mmol) and benzylalcohol (0.13 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as white solid (0.17 g, 0.7 mmol, 68%), Mp = 66-67 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 6.9 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.80 (s, 3H), 3.60 (s, 2H), 2.87 (t, *J* = 7.4 Hz, 2H), 2.76 (t, *J* = 7.3 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 158.8, 141.1, 130.5, 128.6, 128.5, 126.2, 114.3, 55.4, 49.6, 43.4, 29.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}O_2$ ($[M+H]^+$): 255.1380, found: 255.1391.

3-(2-methoxyphenyl)-1-(4-methoxyphenyl)propan-1-one (Table 5.2, entry 14) [30]**:** Prepared from 4'-methoxy acetophenone (0.15 g, 1.0 mmol) and 2-methoxy benzylalcohol (0.27 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.25 g, 0.9 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.8 Hz, 2H), 7.21 (t, *J* = 6.4 Hz, 2H), 6.96–6.83 (m, 4H), 3.86 (s, 3H), 3.84 (s, 3H), 3.21 (d, *J* = 7.6 Hz, 2H), 3.04 (d, *J* = 7.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 163.4, 157.6, 130.5, 130.3, 130.2, 129.8, 127.6, 120.7, 113.8, 110.4, 55.6, 55.3, 38.8, 26.1 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}O_3$ ($[M+H]^+$): 271.1329, found: 271.1339.

3-([1,1'-biphenyl]-2-yl)-1-(4-fluorophenyl)propan-1-one (Table 5.2, entry 15) [41]**:** Prepared from 4'-fluoro acetophenone (0.14 g, 1.0mmol) and 2-biphenylmethanol (0.22 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a pale yellow liquid (0.25 g, 0.8 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.46–7.25 (m, 9H), 7.03 (t, *J* = 8.6 Hz,

2H), 3.07–3.04 (m, 2H), 3.00–2.96 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.9, 165.8 (d, *J* = 254.6 Hz), 141.9 (d, *J* = 34.1 Hz), 138.7, 138.5, 133.1, 130.8 (d, *J* = 9.3 Hz), 130.4, 129.6, 129.3, 128.7, 128.5, 128.2, 127.9, 127.2, 126.4, 115.7 (d, *J* = 21.8 Hz), 40.3, 28.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -106.40 ppm. HRMS (ESI): calcd. for $C_{21}H_{17}FO$ ($[M+H]^+$): 305.1336, found: 305.1352.

3-(2-fluorophenyl)-1-phenylpropan-1-one (Table 5.2, entry 16) [31]**:** Prepared from acetophenone (0.12 g, 1.0mmol) and 2-fluoro benzyl alcohol (0.25 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.15 g, 0.6 mmol, 64%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.4 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 6.7 Hz, 1H), 7.23–7.00 (m, 3H), 3.32 (t, *J* = 7.6 Hz, 2H), 3.10 (t, *J* = 7.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.1, 161.4 (d, *J* = 244.9 Hz), 141.4, 136.9, 133.2, 131.0 (d, *J* = 5.0 Hz), 128.7, 128.2,126.3, 124.2 (d, *J* = 3.5 Hz), 115.4 (d, *J* = 21.9 Hz), 38.9, 24.1ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -119.40. HRMS (ESI): calcd. for $C_{15}H_{13}FO$ ($[M+H]^+$): 229.1023, found: 229.1018.

1-((8S,9S,10R,13S,14S,17S)-3-hydroxy-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl)-3-(p-tolyl)propan-1-one (Table 5.2, entry 17) [41]**:** Prepared from β-pregnenolone (0.32 g, 1.0 mmol) and 4-methyl benzyl alcohol (0.37 g, 3.0mmol). After purification by column chromatography, the compound was isolated as a white solid (0.33 g, 0.8 mmol, 78%), Mp = 116-117 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.05 (m, 4H), 5.34 (d, *J* = 5.1 Hz, 1H), 3.58–3.46 (m, 1H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.70–2.64 (m, 2H), 2.49 (t, *J* = 8.9 Hz, 1H), 2.31 (s, 3H), 2.24–2.15 (m, 2H),

2.04–1.93 (m, 2H), 1.84 (d, *J* = 9.8 Hz, 2H), 1.69–1.36 (m, 11H), 1.27–1.07 (m, 3H), 1.00 (s, 3H), 0.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.8, 140.9, 138.5, 135.6, 129.2, 128.4, 121.5, 71.8, 63.2, 57.1, 50.1, 46.3, 44.4, 42.4, 39.1, 37.4, 36.6, 32.0, 31.9, 31.7, 29.5, 24.7, 23.1, 21.2, 21.1, 19.5, 13.5 ppm. HRMS (ESI): calcd. for $C_{29}H_{40}O_2Na$ ($[M+Na]^+$): 443.2921, found: 443.2926.

3-phenyl-1-(o-tolyl)propan-1-one (Table 5.2, entry 18) [24]**:** Prepared from 2'-methyl acetophenone (0.13 g, 1.0 mmol) and benzylalcohol (0.22 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.16 g, 0.7 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.8 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.33–7.21 (m, 7H), 3.25 (t, *J* = 7.6 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.50 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5, 141.3, 138.2, 138.0, 132.1, 131.3, 128.6, 128.5, 128.5, 126.2, 125.8, 43.3, 30.4, 21.4 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}O$ ($[M+H]^+$): 225.1274, found: 225.1267.

1-(4-methoxyphenyl)hexan-1-one (Table 5.3, entry 19) [32]**:** Prepared from 4'-methoxy acetophenone (0.15 g, 1.0mmol) and 1-butanol (0.15 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a white solid (0.17 g, 0.8 mmol, 85%). Mp = 39-40 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 2.93–2.85 (m, 2H), 1.74–1.68 (m, 2H), 1.41–1.31 (m, 4H), 0.90 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 163.4, 130.4, 130.3, 113.8, 55.6, 38.4, 31.7, 24.5, 22.7, 14.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}O_2$ ($[M+H]^+$): 207.1380, found: 207.1386.

1-(4-methoxyphenyl)butan-1-one (Table 5.3, entry 20) [32]**:** Prepared from 4'-methoxy acetophenone (0.15 g, 1.0mmol) and ethanol (0.14 g, 3.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.13 g, 0.7 mmol, 74%). ^{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), 2.89 (t, *J* = 7.3 Hz, 2H), 1.80–1.71 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.2, 163.4, 130.4, 130.4, 113.8, 55.6, 40.3, 18.1, 14.1ppm. HRMS (ESI): calcd. for $C_{11}H_{14}O_2$ ($[M+H]^+$): 179.1067, found: 179.1075.

1-(4-methoxyphenyl)-4-phenylbutan-1-one (Table 5.3, entry 21) [33]**:** Prepared from 4'-methoxy acetophenone (0.15 g, 1.0mmol) and 2-phenyl ethanol (0.24 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a white solid (0.23 g, 0.9 mmol, 89%), Mp = 57-58 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.9 Hz, 2H), 7.32–7.29 (m, 2H), 7.23–7.19 (m, 3H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 2.94 (t, *J* = 7.3 Hz, 2H), 2.73 (t, *J* = 7.6 Hz, 2H), 2.13–2.05 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.7, 163.4, 141.8, 130.3, 130.2, 128.6, 128.4, 125.9, 113.7, 55.5, 37.4, 35.3, 26.0 ppm. HRMS (ESI): calcd. for $C_{17}H_{18}O_2$ ($[M+H]^+$): 255.1380, found: 255.1387.

1-(4-methoxyphenyl)decan-1-one (Table 5.3, entry 22) [32]**:** Prepared from 4'-methoxy acetophenone (0.15 g, 1.0mmol) and 1-octanol (0.26 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21 g, 0.8 mmol, 81%), Mp = 46-47 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.91 (m, 2H), 6.93–6.89 (m, 2H), 3.85 (s, 3H), 2.88 (dd, *J* = 12.2, 7.7 Hz, 2H), 1.69 (dd, *J* = 12.9, 6.0 Hz, 2H), 1.33–1.25 (m, 12H), 0.87 (t, *J* = 5.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 199.3, 163.4, 130.4, 130.3, 113.7, 55.5, 38.4, 32.0, 29.6, 29.6, 29.5, 29.4, 24.7, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{26}O_2$ ($[M+H]^+$): 263.2006, found: 263.2008.

2-benzyl-3,4-dihydronaphthalen-1(2H)-one (Table 5.3, entry 23) [23]**:** Prepared from 1-tetralone (0.15 g, 1.0 mmol) and benzyl alcohol (0.22 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.23 g, 0.9 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.7 Hz, 1H), 7.47 (t, *J* = 8.1 Hz, 1H), 7.34–7.30 (m, 3H), 7.25–7.22 (m, 4H), 3.50 (dd, *J* = 13.6, 3.9 Hz, 1H), 2.96–2.92 (m, 2H), 2.78–2.72 (m, 1H), 2.66 (dd, *J* = 13.6, 9.6 Hz, 1H), 2.14–2.10 (m, 1H), 1.85–1.75 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 144.2, 140.2, 133.4, 129.4, 128.8, 128.5, 127.7, 126.8, 126.3, 49.6, 35.8, 28.8, 27.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{16}O$ ($[M+H]^+$): 237.1274, found: 237.1276.

2-(4-methylbenzyl)-3,4-dihydronaphthalen-1(2H)-one (Table 5.3, entry 24) [34]**:** Prepared from 1-tetralone (0.15 g, 1.0 mmol) and 4-methylbenzyl alcohol (0.24 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.23 g, 0.9 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 7.1 Hz, 1H), 7.46 (t, *J* = 6.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.12 (s, 4H), 3.45 (dd, *J* = 13.7, 4.0 Hz, 1H), 2.93 (m, 2H), 2.75–2.70 (m, 1H), 2.61 (dd, *J* = 13.7, 9.6 Hz, 1H), 2.33 (s, 3H), 2.15–2.08 (m, 1H), 1.81–1.78 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.5, 144.2, 140.2, 133.4, 129.4, 128.8, 128.5, 127.7, 126.8, 126.3, 49.6, 35.8, 28.8, 27.8 ppm. HRMS (ESI): calcd. for $C_{18}H_{18}O$ ($[M+H]^+$): 251.1430, found: 251.1420.

2-benzyl-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (Table 5.3, entry 25) [35]**:** Prepared from 5,6-dimethoxy indanone (0.19 g, 1.0mmol) and benzyl alcohol (0.22 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a white solid (0.26 g, 0.9 mmol, 92%), Mp = 128-129 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.19 (m, 6H), 6.80 (s, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.36 (dd, *J* = 13.9, 3.6 Hz, 1H), 3.08–2.97 (m, 2H), 2.75 (d, *J* = 16.6 Hz, 1H), 2.63 (dd, *J* = 13.8, 10.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.6, 155.7, 149.5, 149.0, 139.9, 129.3, 129.0, 128.6, 126.4, 107.5, 104.5, 56.3, 56.2, 49.2, 37.4, 32.0 ppm. HRMS (ESI): calcd. for $C_{18}H_{18}O_3Na$ ($[M+Na]^+$): 305.1148, found: 305.1158.

2-methyl-1,3-diphenylpropan-1-one (Table 5.3, entry 26) [24]**:** Prepared from propiophenone (0.13 g, 1.0 mmol) and benzyl alcohol (0.22 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.19 g, 0.8 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.6 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.30–7.18 (m, 5H), 3.81–3.73 (m, 1H), 3.19 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.71 (dd, *J* = 13.7, 7.8 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.8, 140.0, 136.5, 133.0, 129.2, 128.7, 128.5, 128.4, 126.3, 42.8, 39.5, 17.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}O$ ($[M+H]^+$): 225.1274, found: 225.1277.

3-phenyl-1-(thiophen-2-yl)propan-1-one (Table 5.3, entry 27) [24]**:** Prepared from 2-acetylthiophene (0.13 g, 1.0 mmol) and benzyl alcohol (0.22 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.17 g, 0.8 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 4.5 Hz, 1H), 7.62 (d, *J* = 4.9 Hz, 1H), 7.33–7.20 (m, 5H), 7.13–7.10 (m, 1H), 3.24 (t, *J* = 7.6

Hz, 2H), 3.08 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.3, 144.3, 141.1, 133.7, 131.9, 128.7, 128.5, 128.2, 126.3, 41.2, 30.5 ppm. HRMS (ESI): calcd. for $C_{13}H_{12}OS$ ($[M+H]^+$): 217.0682, found: 217.0684.

1-(benzo[d][1,3]dioxol-5-yl)-3-(furan-2-yl)propan-1-one (Table 5.3, entry 28) [41]**:** Prepared from 3,4-methylenedioxy acetophenone (0.16 g, 1.0 mmol) and 2-furylmethanol (0.19 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.19 g, 0.8 mmol, 79%). Mp = 95-96 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.45 (d, *J* = 1.5 Hz, 1H), 7.30 (d, *J* = 1.3 Hz, 1H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.28–6.27 (m, 1H), 6.04 (s, 3H), 3.25 (t, *J* = 7.6 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 155.0, 151.9, 148.4, 141.2, 131.8, 124.4, 110.4, 108.0, 108.0, 105.4, 102.0, 36.8, 22.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{12}O_4Na$($[M+Na]^+$): 267.0628, found: 267.0632.

1-(benzo[d][1,3]dioxol-5-yl)-3-(pyridin-2-yl)propan-1-one (Table 5.3, entry 29) [36]**:** Prepared from 3,4-methylenedioxy acetophenone (0.16 g, 1.0mmol) and 2-pyridinemethanol (0.22 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.21 g, 0.8 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 4.5 Hz, 1H), 7.74 (m, 1H), 7.61 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.43 (m, 2H), 7.26–7.20 (m, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.03 (s, 2H), 3.52 (t, *J* = 7.1 Hz, 2H), 3.30 (t, *J* = 7.1 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 160.2, 152.0, 148.3, 147.4, 138.4, 131.7, 124.7, 124.6, 122.0, 108.0, 102.9, 37.8, 31.4 ppm. HRMS (ESI): calcd. for $C_{15}H_{13}NO_3$ ($[M+H]^+$): 256.0968, found: 256.0971.

2-methyl-1-phenyldodecan-1-one (Table 5.3, entry 30) [41]**:** Prepared from propiophenone (0.13 g, 1.0mmol) and 1-decanol (0.32 g, 2.0mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.20 g, 0.7 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.6 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.47 (m, 1H), 1.84–1.75 (m, 1H), 1.47–1.39 (m, 1H), 1.29 –1.24 (m, 16H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.7, 136.9, 132.9, 128.7, 128.4, 40.7, 33.9, 32.0, 29.9, 29.7, 29.6, 29.4, 27.5, 22.8, 17.3, 14.2 ppm. HRMS (ESI): calcd. for $C_{19}H_{30}O$ ($[M+H]^+$): 275.2369, found: 275.2381.

(8R,9S,13S,14S)-16-benzyl-3-hydroxy-13-methyl-7,8,9,11,12,13,15,16-octahydro-6H-cyclopenta[a]phenanthren-17(14H)-one (Table 5.3, entry 31) [37]**:** Prepared from estrone (0.27 g, 1.0 mmol) and benzylalcohol (0.32 g, 3.0mmol). After purification by column chromatography, the compound was isolated as a white solid (0.28 g, 0.7 mmol, 78%),Mp = 231-232 ^{o}C. ^{1}H NMR (400 MHz, DMSO) δ = 8.99 (s, 1H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.20 (d, *J* = 7.4 Hz, 3H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.5 Hz, 1H), 6.43 (s, 1H), 3.03 (dd, *J* = 13.4, 3.9 Hz, 1H), 2.70 (dd, *J* = 17.5, 10.9 Hz, 3H), 2.28 (d, *J* = 12.6 Hz, 1H), 2.11 (d, *J* = 9.2 Hz, 1H), 1.92–1.75 (m, 3H), 1.50–1.21 (m, 7H), 0.62 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO): δ = 155.4, 140.2, 137.5, 130.4, 129.4, 128.7, 126.5, 126.4, 115.4, 113.2, 50.8, 48.3, 48.3, 44.0, 37.8, 37.1, 32.1, 29.4, 27.7, 26.7, 25.9, 13.8 ppm. HRMS (ESI): calcd. for $C_{25}H_{28}O_2$ ($[M+H]^+$): 361.2162, found: 361.2151.

(8R,9S,10R,13S,14S)-3-hydroxy-10,13-dimethyl-16-(4-methylbenzyl)-3,4,7,8,9,10,11,12,13,14,15,16-dodecahydro-1H-cyclopenta[a]phenanthren-17(2H)-one (Table 5.3, entry 32) [41]**:** Prepared from *trans*-dehydroandrosterone (0.29 g, 1.0mmol) and 4-methyl benzylalcohol (0.37 g, 3.0mmol). After purification by column chromatography, the compound was isolated as a white solid (0.30 g, 0.7 mmol, 76%), Mp = 168-169 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10–7.05 (m, 4H), 5.34–5.30 (m, 1H), 3.55–3.47 (m, 1H), 3.16 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.61 (dd, *J* = 13.7, 9.8 Hz, 1H), 2.37 (d, *J* = 9.4 Hz, 1H), 2.32 (s, 3H), 2.21 (d, *J* = 11.2 Hz, 1H), 1.95 (dd, *J* = 11.6, 4.3 Hz, 1H), 1.88–1.80 (m, 4H), 1.69–1.62 (m, 2H), 1.52–1.43 (m, 3H), 1.31 (t, *J* = 6.4 Hz, 3H), 1.08 (s, 1H), 1.01 (s, 3H), 0.92–0.86 (m, 3H), 0.70 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 136.9, 135.9, 129.2, 129.0, 121.1, 71.8, 51.5, 50.5, 50.4, 48.2, 42.4, 37.4, 37.3, 36.8, 32.0, 31.7, 31.1, 31.1, 28.4, 22.8, 21.2, 20.5, 19.5, 14.5, 14.3, 13.5 ppm. HRMS (ESI): calcd. for $C_{27}H_{36}O_2Na$ ($[M+Na]^+$): 415.2608, found: 415.2615.

2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (scheme 5.1, compound 33) [35]***:*** Prepared from 5,6-dimethoxy indanone (0.19 g, 1.0mmol) and (1-benzylpiperidin-4-yl)methanol (0.62 g, 3.0mmol). After purification by column chromatography, the compound was isolated as a yellow semi-liquid (0.18 g, 0.46 mmol, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.31 (m, 4H), 7.27–7.23 (m, 1H), 7.15 (s, 1H), 6.84 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.56 (s, 2H), 3.22 (dd, *J* = 17.6, 8.1 Hz, 1H), 2.96–2.92 (m, 2H), 2.71–2.65 (m, 2H), 2.06–1.99 (m, 2H), 1.93–1.86 (m, 1H), 1.71–1.67 (m, 2H), 1.45–1.25 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.8, 155.6, 149.5, 148.8, 137.6, 129.5, 129.4, 128.3, 127.3, 107.4,

104.5, 63.2, 56.3, 56.2, 45.5, 38.7, 34.3, 33.5, 32.7, 31.6 ppm. HRMS (ESI): calcd. for $C_{24}H_{29}NO_3$ ($[M+H]^+$): 380.2220, found: 380.2226.

(1-benzylpiperidin-4-yl)methanol (scheme 5.1, compound 34) [40]**:** Prepared from 4-piperidinemethanol (0.50 g, 4.34 mmol) and benzyl alcohol (1.41 g, 13.02 mmol). After purification by column chromatography, the compound was isolated as a light yellow semi-liquid (0.63 g, 3.09 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.29 (m, 5H), 3.52 (d, *J* = 4.0 Hz, 2H), 3.50–3.47 (m, 2H), 2.92 (d, *J* = 11.2 Hz, 2H), 1.98 (t, *J* = 11.6 Hz, 3H), 1.71 (d, *J* = 12.7 Hz, 2H), 1.50 (br, 1H), 1.31 (d, *J* = 11.9 Hz, 2H) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 129.4, 128.3, 127.2, 68.0, 63.5, 53.5, 38.6, 28.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}NO$ ($[M+H]^+$): 206.1539, found: 206.1543.

2-phenylquinoline (Table 5.4, entry 35) [38]**:** Prepared from 2-aminobenzyl alcohol (0.12 g, 1.0 mmol) and acetophenone (0.14 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.18 g, 0.9 mmol, 89%), Mp = 81-82 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25–8.18 (m, 4H), 7.85 (dd, *J* = 19.0, 8.3 Hz, 2H), 7.74 (t, *J* = 8.4 Hz, 1H), 7.56–7.46 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 148.2, 139.6, 137.1, 129.9, 129.7, 129.5, 129.0, 127.7, 127.6, 127.3, 126.4, 119.1ppm. HRMS (ESI): calcd. for $C_{15}H_{11}N$ ($[M+H]^+$): 206.0964, found: 206.0975.

2-(p-tolyl) quinoline (Table 5.4, entry 36) [38]**:** Prepared from 2-aminobenzyl alcohol (0.12 g, 1.0mmol) and 4'-methyl acetophenone (0.16 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.20 g, 0.9

mmol, 91%), Mp = 82-83 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.6 Hz, 2H), 8.08 (d, *J* = 8.1 Hz, 2H), 7.84 (dd, *J* = 18.6, 8.3 Hz, 2H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 2.44 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 139.7, 137.0, 137.0, 136.7, 129.9, 129.7, 129.6, 127.7, 127.6, 127.2, 126.3, 119.1, 21.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{13}N$ ($[M+H]^+$): 220.1121, found: 220.1117.

2-(4-fluorophenyl) quinoline (Table 5.4, entry 37) [38]**:** Prepared from 2-aminobenzyl alcohol (0.12 g, 1.0 mmol) and 4'-fluoro acetophenone (0.16 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.19 g, 0.8 mmol, 86%), Mp = 93-94 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.15 (m, 4H), 7.83 (d, *J* = 8.5 Hz, 2H), 7.74 (t, *J* = 7.0 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 8.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9 (d, *J* = 249.3 Hz), 156.3, 137.2, 135.8 (d, *J* = 2.4 Hz), 130.0, 129.6 (d, *J* = 8.5 Hz), 129.0,127.8, 127.6, 127.2, 126.5, 118.8, 115.9 (d, *J* = 21.6 Hz) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -113.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{10}NF$ ($[M+H]^+$): 224.0870, found: 224.0869.

3-methyl-2-phenylquinoline (Table 5.4, entry 38) [38]**:** Prepared from 2-aminobenzyl alcohol (0.12 g, 1.0mmol) and propiophenone (0.16 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.18 g, 0.8 mmol, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.3 Hz, 1H), 8.04 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.55–7.43 (m, 4H), 2.47 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 146.6, 140.9, 137.0, 129.4, 129.3, 129.0, 128.9, 128.4, 128.3, 127.7, 126.8, 126.6, 20.7 ppm. HRMS (ESI): calcd. for $C_{16}H_{13}N$ ($[M+H]^+$): 220.1121, found: 220.1115.

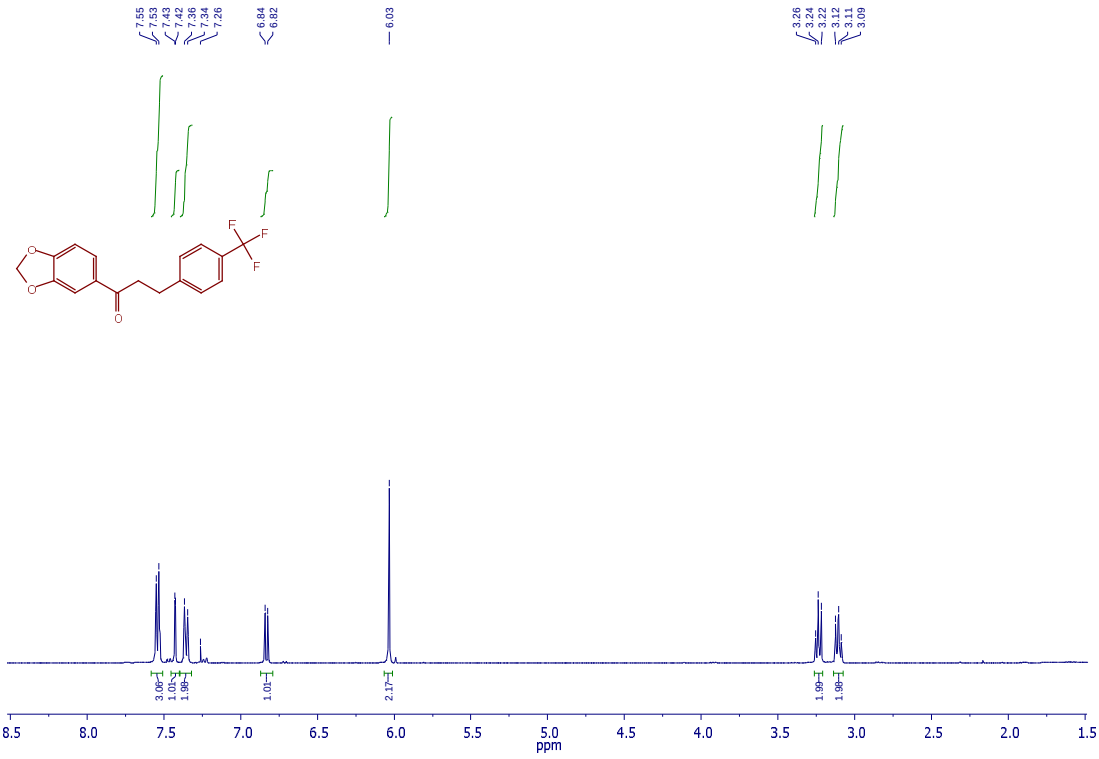
3-ethyl-2-phenylquinoline (Table 5.4, entry 39) [38]**:** Prepared from 2-aminobenzyl alcohol (0.12 g, 1.0mmol) and butyrophenone (0.18 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.18 g, 0.8 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25–8.11 (m, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.57–7.44 (m, 6H), 2.81 (q, *J* = 7.5 Hz, 2H), 1.21 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.4, 145.1, 135.7, 135.5, 129.3, 128.9, 128.5, 128.5, 127.9,127.6, 127.1, 126.8, 126.0 26.1, 14.8 ppm. HRMS (ESI): calcd. for $C_{17}H_{15}N$ ($[M+H]^+$): 234.1277, found:234.1283.

5,6-dihydrobenzo[c]acridine (Table 5.4, entry 40) [38]**:** Prepared from 2-aminobenzyl alcohol (0.12 g, 1.0 mmol) and 1-tetralone (0.17 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21 g, 0.9 mmol, 91%), Mp = 65-66 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 7.6 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.91 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.50–7.43 (m, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 3.12 (t, *J* = 7.7 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 147.6, 139.5, 134.7, 133.9, 130.7, 129.8, 129.4, 128.8, 128.1, 128.0, 127.4, 127.0, 126.2, 126.2, 28.9, 28.5 ppm. HRMS (ESI): calcd. for $C_{17}H_{13}N$ ($[M+H]^+$): 232.1121, found: 232.1122.

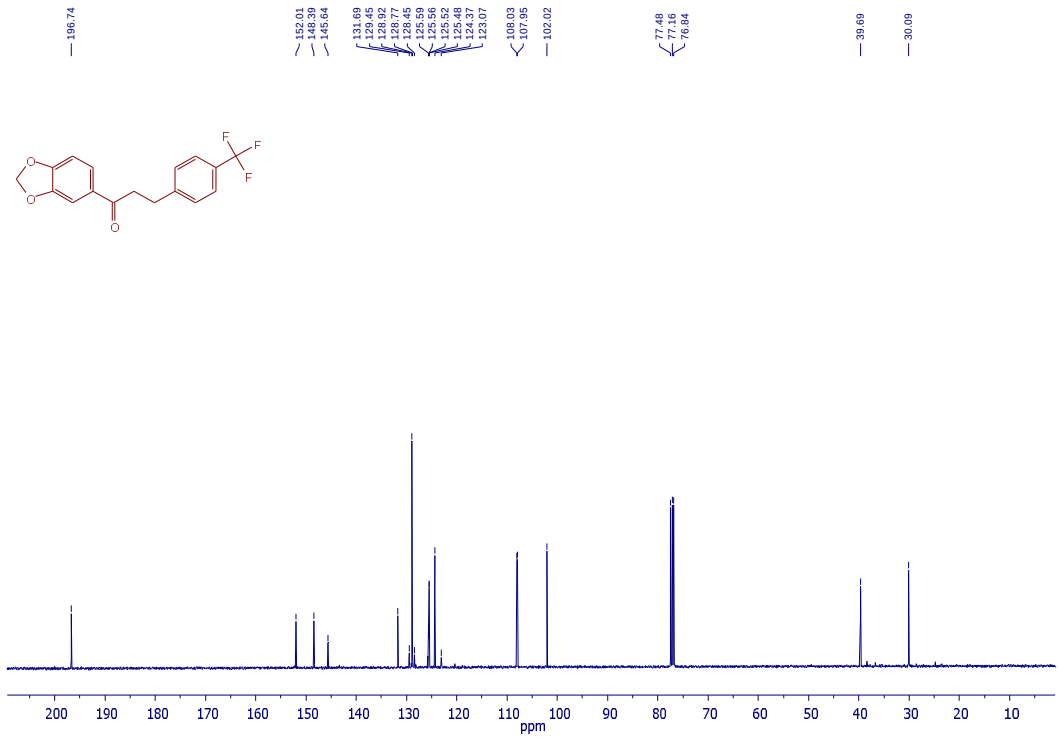
2-propylquinoline (Table 5.4, entry 41) [39]**:** Prepared from 2-aminobenzyl alcohol (0.12 g, 1.0mmol) and 2-pentanone (0.10 g, 1.2 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.12 g, 0.7 mmol,

68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.70 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 2.99 (d, *J* = 7.7 Hz, 2H), 1.90–1.81 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 147.7, 136.6, 129.6, 128.7, 127.6, 126.9, 125.9, 121.5, 41.1, 23.4, 14.1 ppm. HRMS (ESI): calcd. for $C_{12}H_{13}N$ ($[M+H]^+$): 172.1121, found: 172.1126.

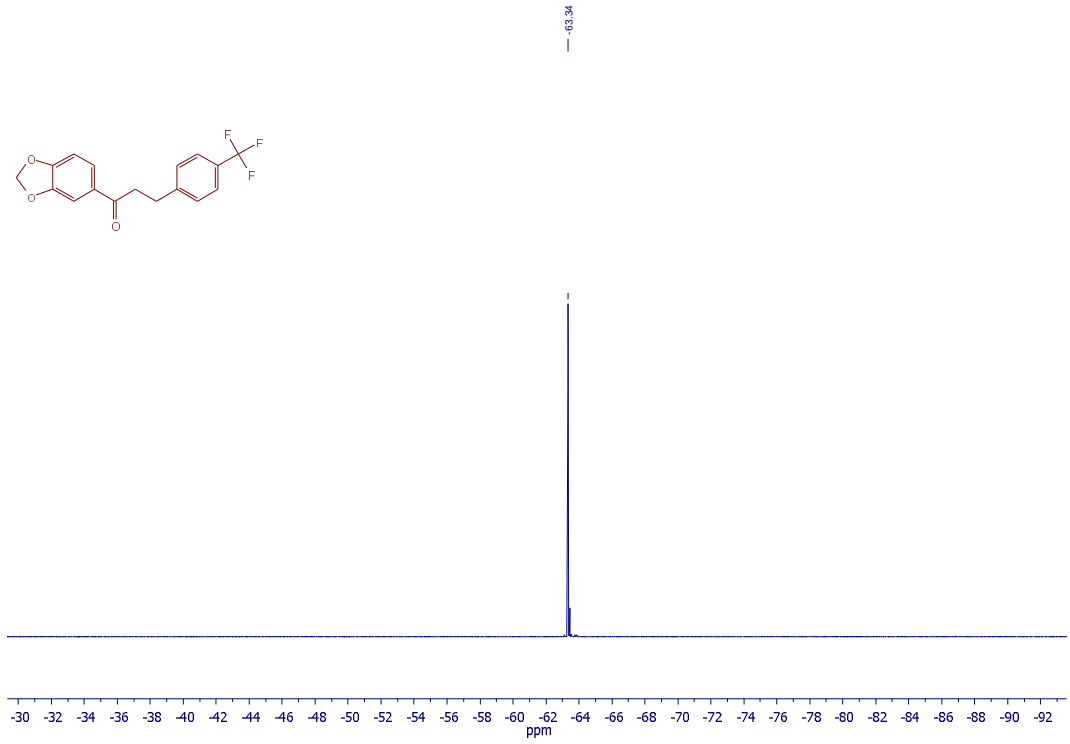
5.5 NMR spectra for new *α*-alkylated products



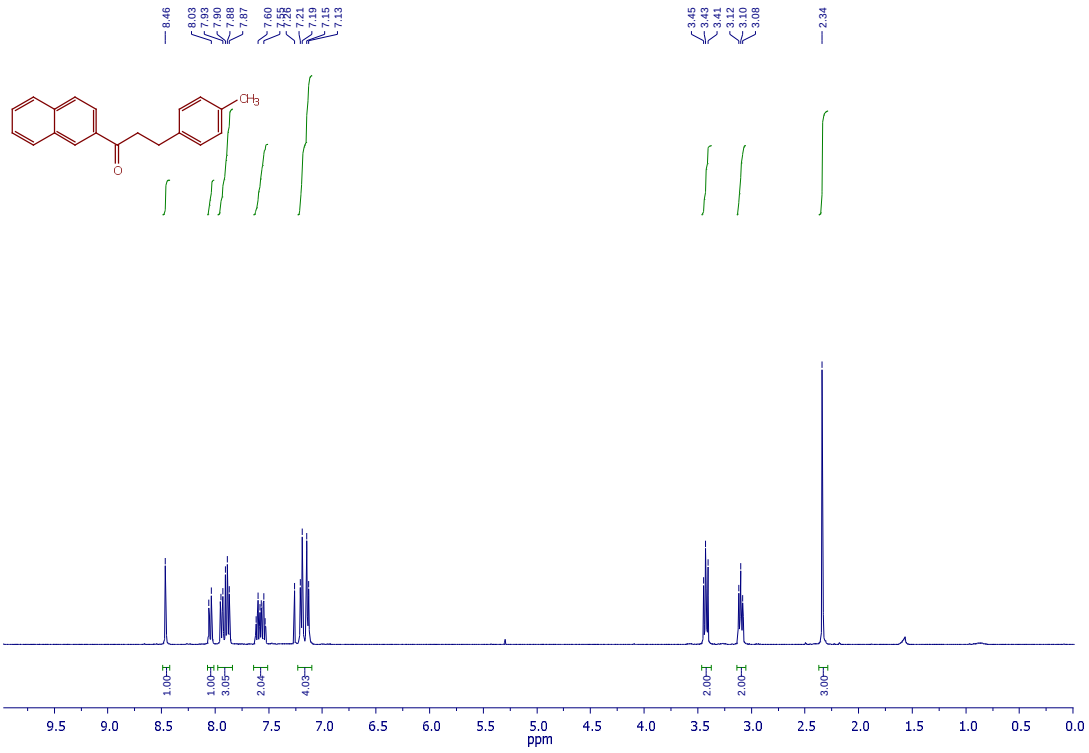
^{1}H NMR spectrum of compound 8



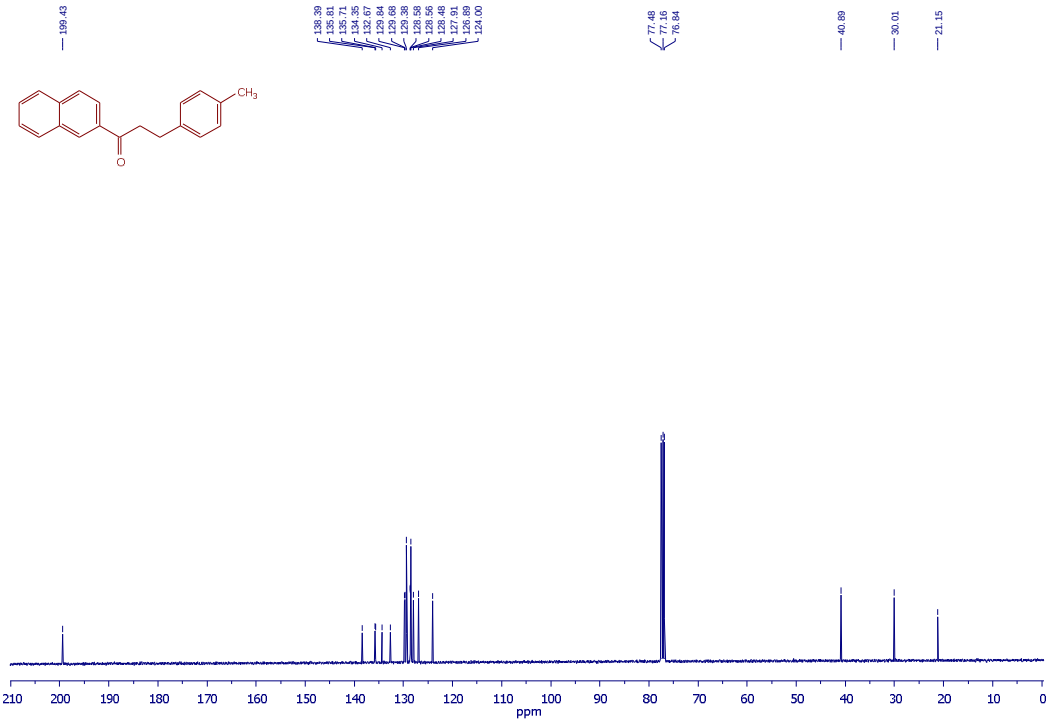
^{13}C NMR spectrum of compound 8



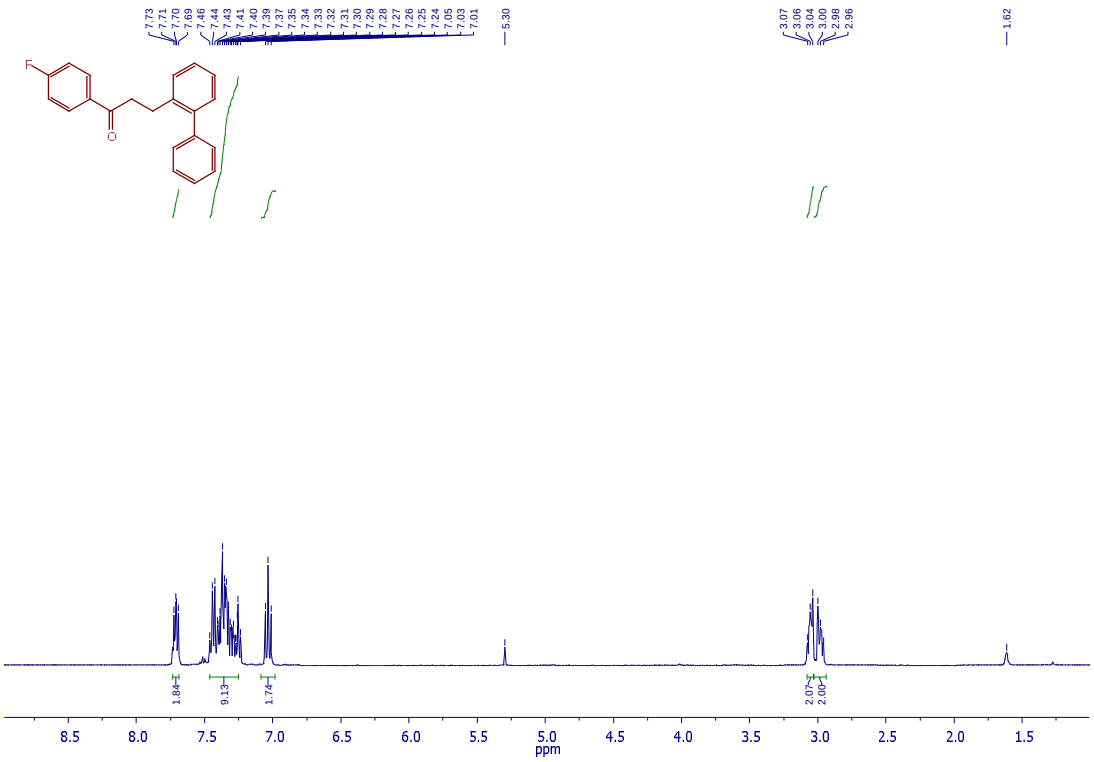
^{19}F NMR specrum of compound 8



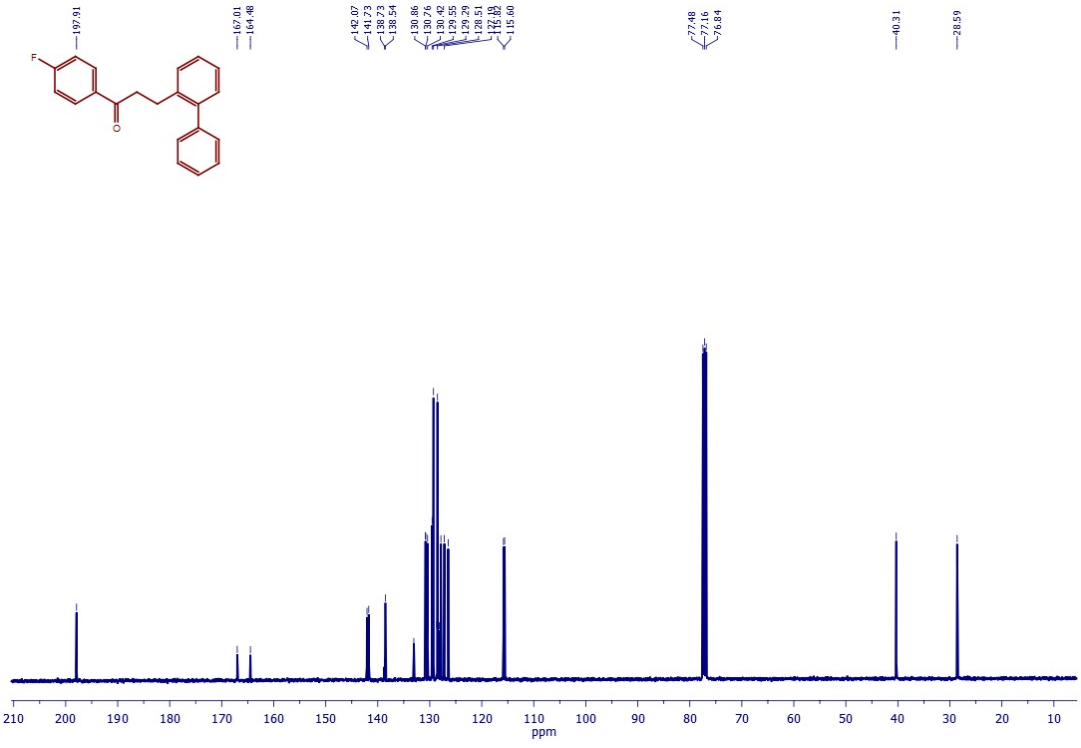
^{1}H NMR spectrum of compound 9



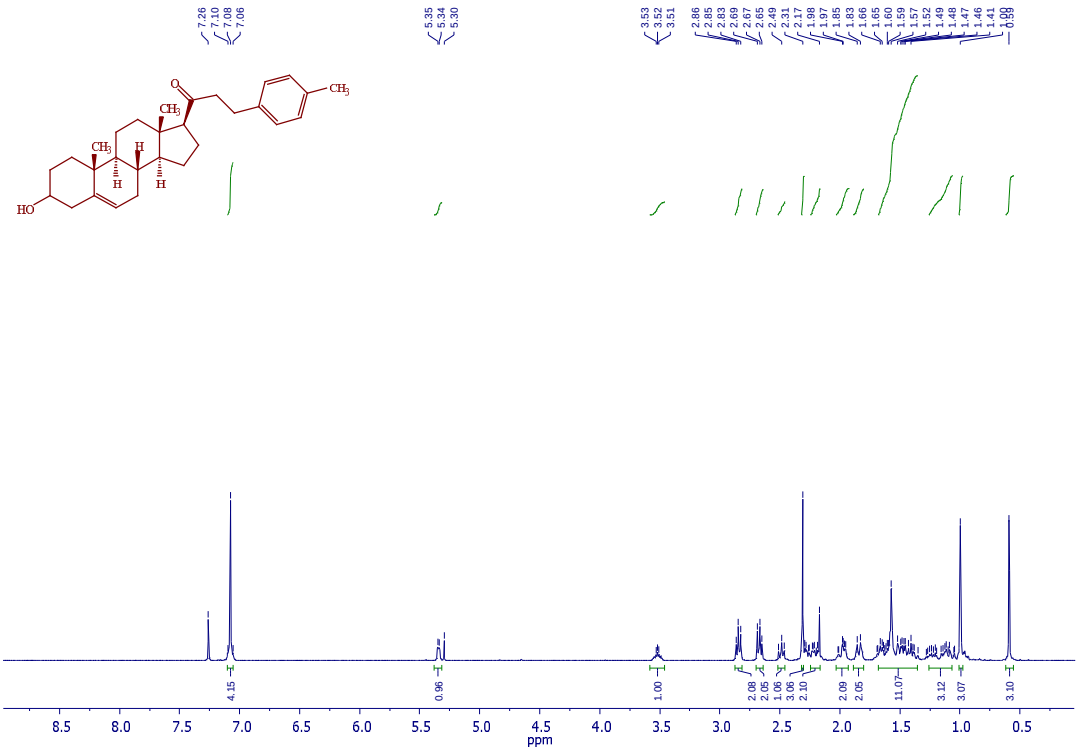
^{13}C NMR spectrum of compound 9



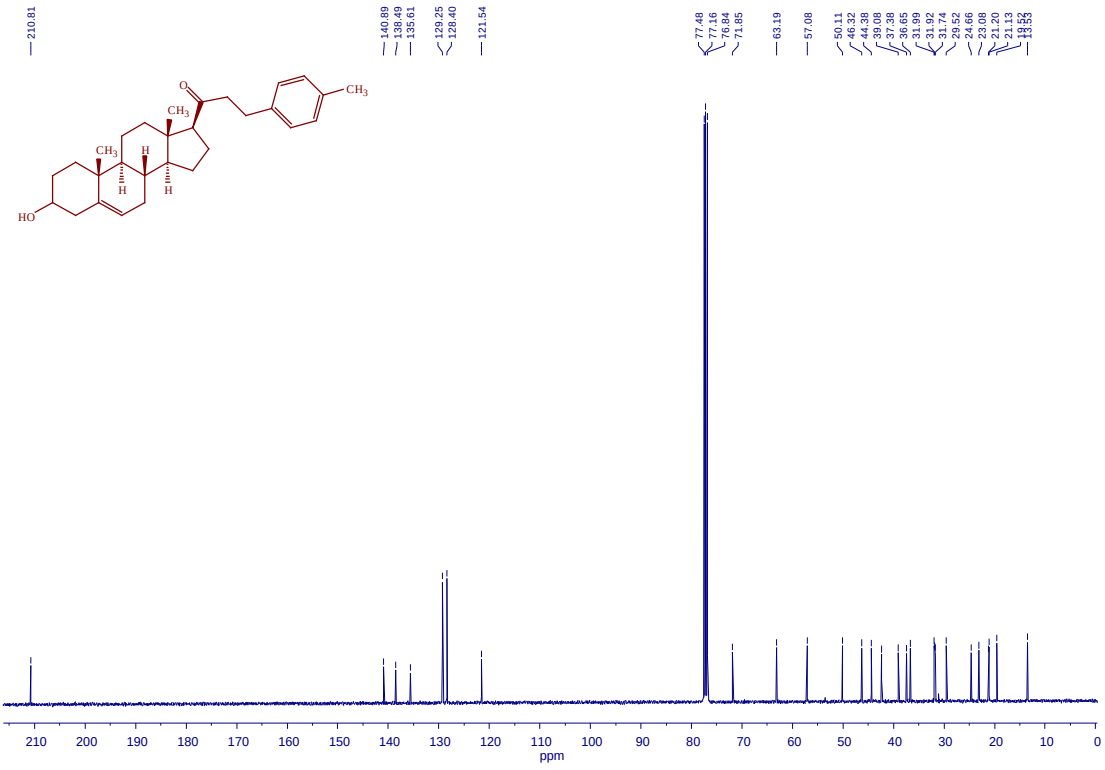
^{1}H NMR spectrum of compound 15



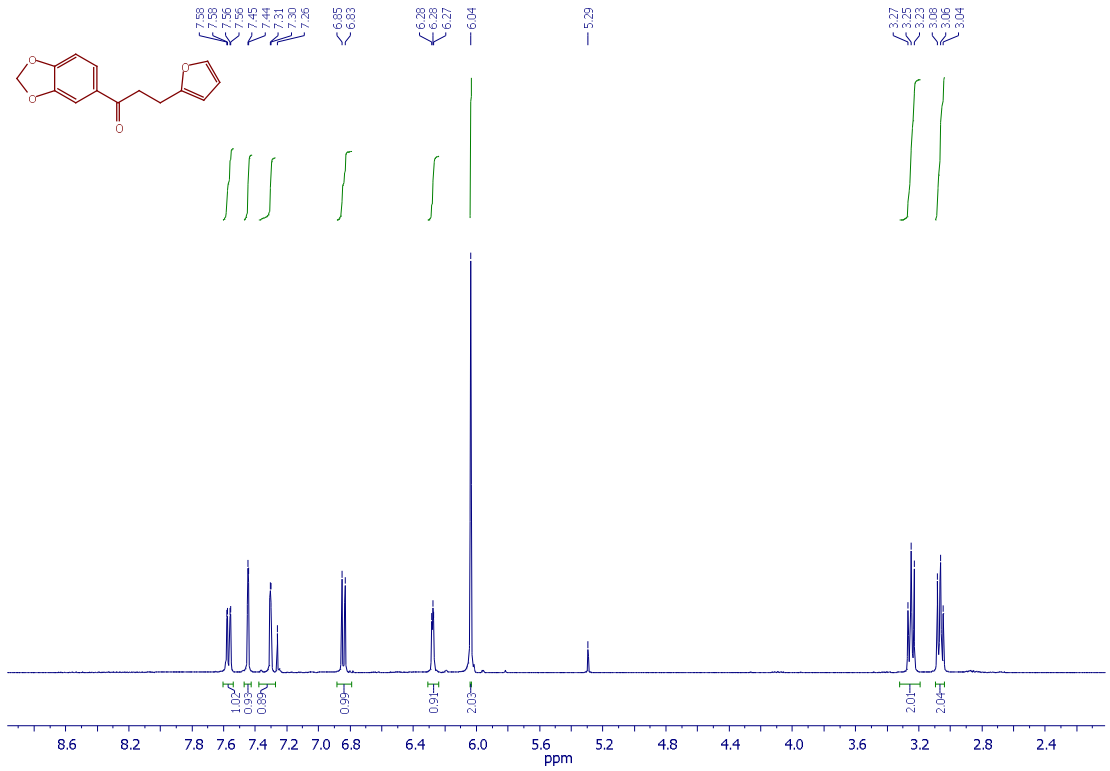
^{13}C NMR spectrum of compound 15



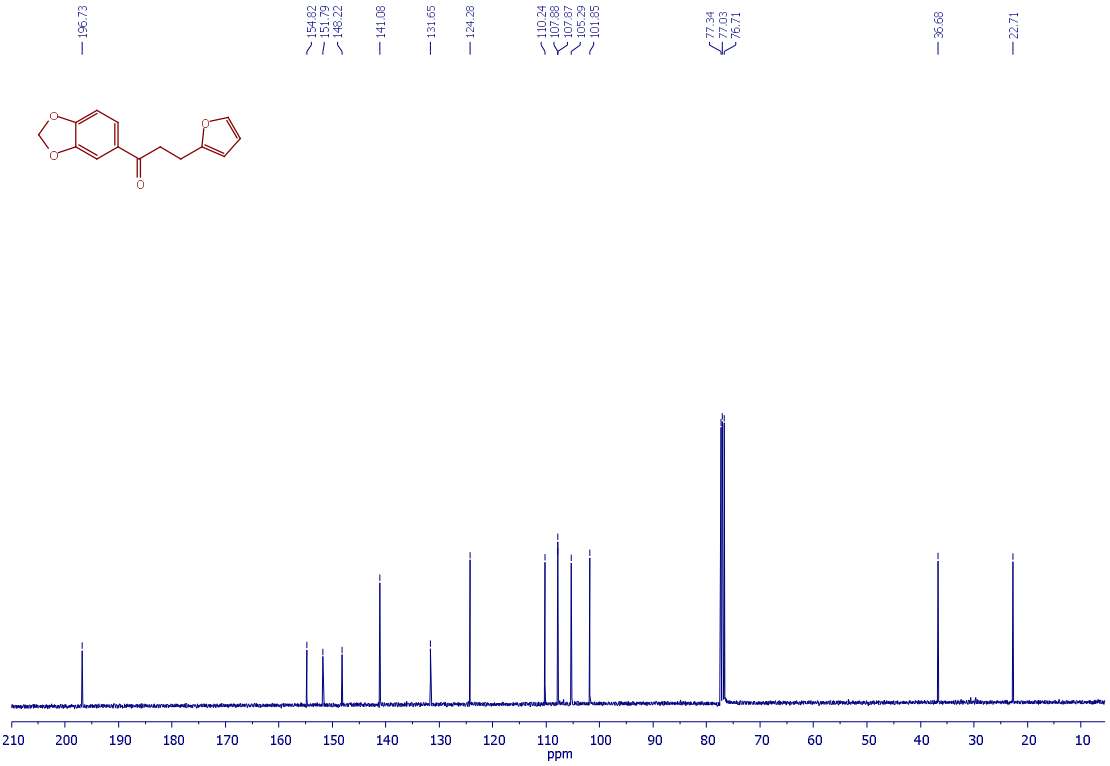
^{1}H NMR spectrum of compound 17



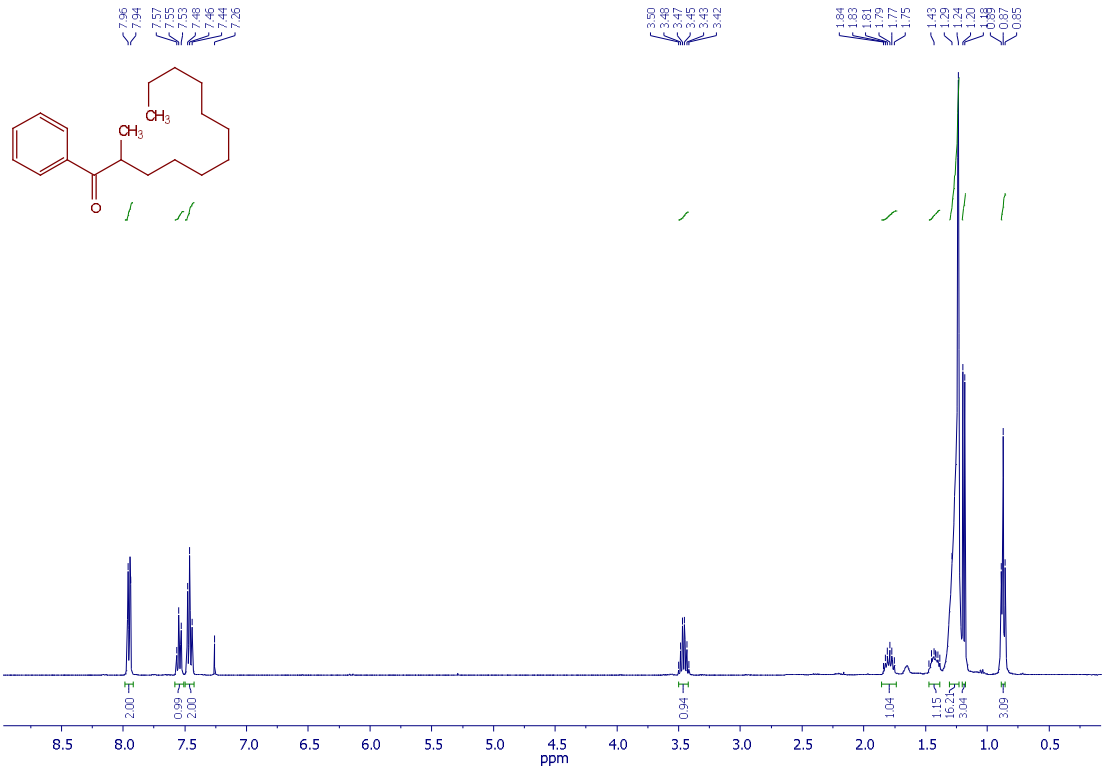
^{13}C NMR spectrum of compound 17



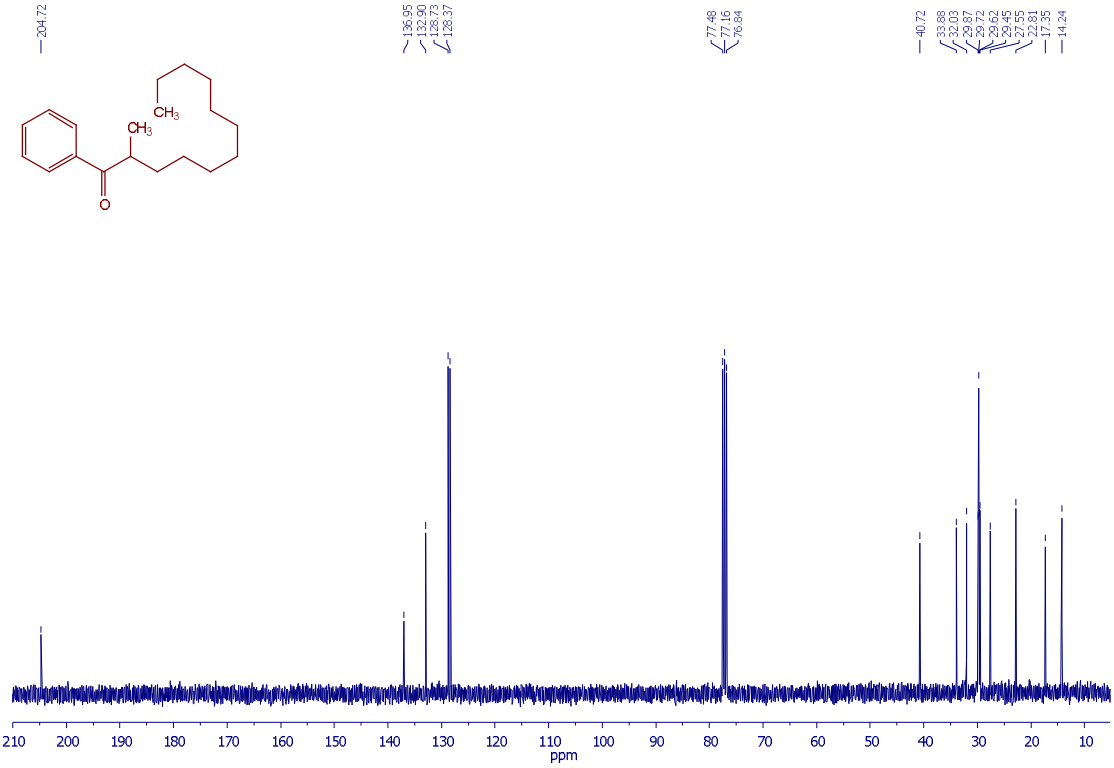
^{1}H NMR spectrum of compound 28



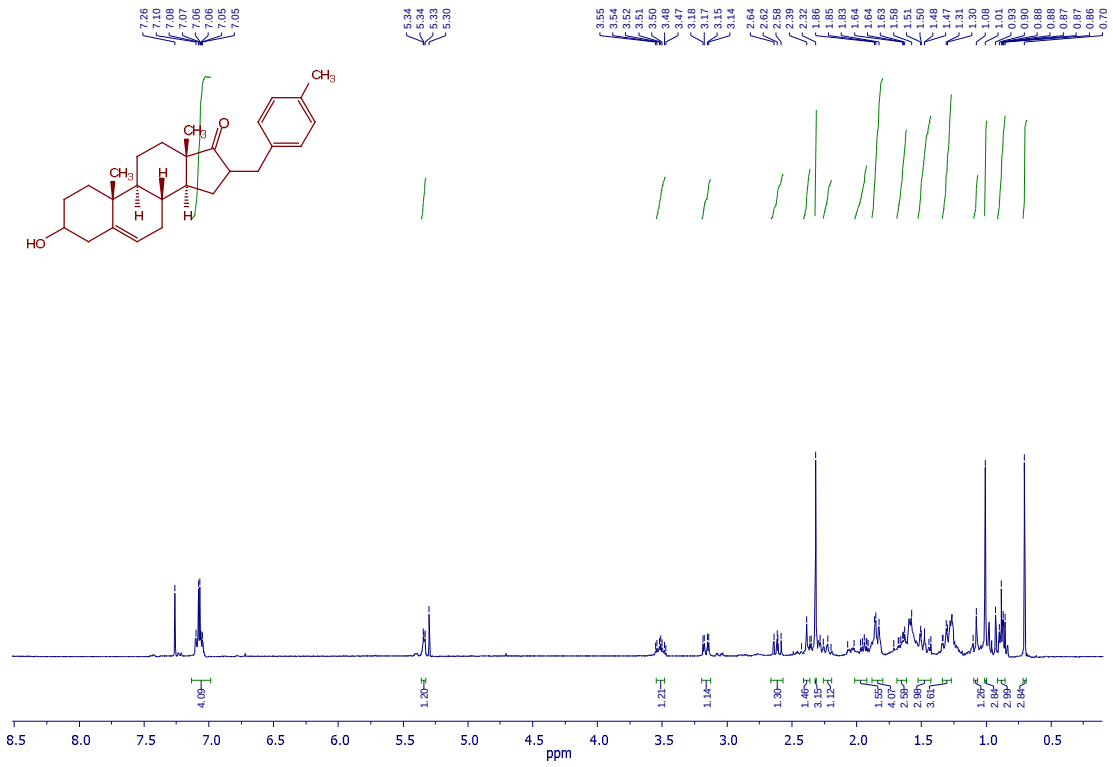
^{13}C NMR spectrum of compound 28



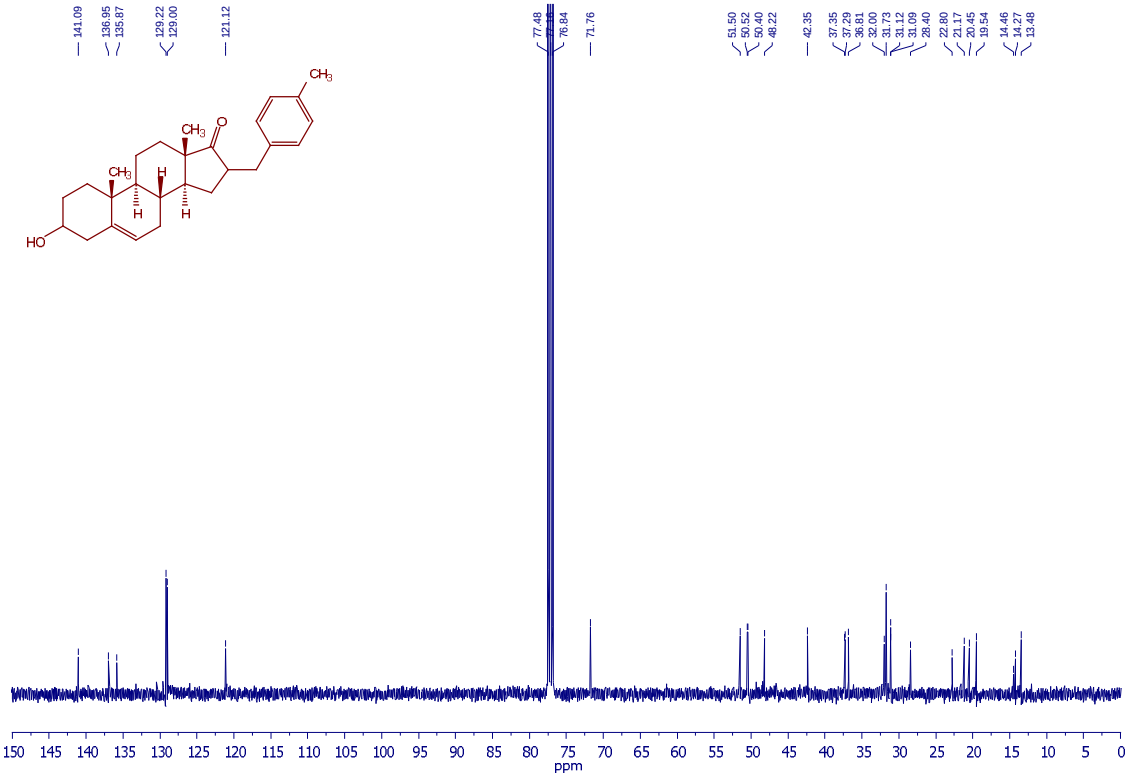
^{1}H NMR spectrum of compound 30



^{13}C NMR spectrum of compound 30



^{1}H NMR spectrum of compound 32



^{13}C NMR spectrum of compound 32

5.6 References

1. W. A. Herrmann, C. Brossmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, and H. Fischer, *Angew. Chem. Int. Ed.*, 1995, **34**, 1844; (b) W. A. Herrmann, K. Ofele, D. V. Preysing, and S. K. Schneider, *J. Organomet. Chem.*, 2003, **687**, 229; (c) I. P. Beletskaya and A. V. Cheprakov, *J. Organomet. Chem.*, 2004, **689**, 4055; (d) V. Farina, *Adv. Synth. Catal.*, 2004, **346**, 1553; (e) V. V. Dunina and O. N. Gorunova, *Russ. Chem. Rev.*, 2005, **74**, 871; (f) J. Dupont, C. S. Consorti, and J. Spencer, *Chem. Rev.*, 2005, **105**, 2527; (g) A. R. Kapdi and I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2014, **43**, 4751; (h) D.-L. Mo, T.-K. Zhang, G.-C. Ge, X.-J. Huang, C.-H. Ding, L.-X. Dai, and X.-L. Hou, *Synlett.*, 2014, **25**, 2686.

2. (a) M. Nonoyama, *Transition Met. Chem.*, 1982, **7**, 281; (b) R. Bosque and F. Maseras, *Eur. J. Inorg. Chem.*, 2005, **2005**, 4040; (c) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (d) K. M. Engle, T.-S. Mei, M. Wasa, and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (e) S.-Y. Zhang, Q. Li, G. He, W. A. Nack, and G. Chen, *J. Am. Chem. Soc.*, 2015, **137**, 531; (f) R. Frutos-Pedreño, E. García-Sánchez, M. J. Oliva-Madrid, D. Bautista, E. Martínez-Viviente, I. Saura-Llamas, and J. Vicente, *Inorg. Chem.*, 2016, **55**, 5520.

3. (a) A. J. Deeming and I. P. Rothwell, *J. Chem. Soc., Chem. Commun.*, 1978, 344; (b) J. Albert, J. Granell, J. Sales, X. Solans, and M. Font-Altaba, *Organometallics*, 1986, **5**, 2567; (c) J. Albert, M. Gomez, J. Granell, J. Sales, and X. Solans, *Organometallics*, 1990, **9**, 1405; (d) O. N. Gorunova, K. J. Keuseman, B. M. Goebel, N. A. Kataeva, A. V. Churakov, L. G. Kuz'mina, V. V. Dunina, and I. P. Smoliakova, *J. Organomet. Chem.*, 2004, **689**, 2382; (e) G.-D. Roiban, E. Serrano, T. Soler, G. Aullón, I. Grosu, C. Cativiela, M. Martíne, and E. P. Urriolabeitia, *Inorg. Chem.*, 2011, **50**, 8132; (f) A. Mercier, S. Wagschal, L. Guénée, C. l.

Besnard, and E. P. Kündig, *Organometallics*, 2013, **32**, 3932; (g) J. Wu, J. H. Barnard, Y. Zhang, D. Talwar, C. M. Robertson, and J. Xiao, *Chem. Commun.*, 2013, **49**, 7052; (h) W. B. Cross, E. G. Hope, Y.-H. Lin, S. A. Macgregor, K. Singh, G. A. Solan, and N. Yahya, *Chem. Commun.*, 2013, **49**, 1918; (i) M. Kondrashov, S. Raman, and O. F. Wendt, *Chem. Commun.*, 2015, **51**, 911.

4. (a) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (b) F. Huang, Z. Liu, and Z. Yu, *Angew. Chem. Int. Ed.*, 2016, **55**, 862.

5. Iridium: (a) K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, and Y. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 72; (b) G. Onodera, Y. Nishibayashi, and S. Uemura, *Angew. Chem., Int. Ed.*, 2006, **45**, 3819; (c) M. Morita, Y. Obora, and Y. Ishii, *Chem. Commun.*, 2007, 2850; (d) F. Li, J. Ma, and N. Wang, *J. Org. Chem.*, 2014, **79**, 10447; (e) J. R. Frost, C. B. Cheong, W. M. Akhtar, D. F. J. Caputo, N. G. Stevenson, and T. J. Donohoe, *J. Am. Chem. Soc.*, 2015, **137**, 15664; (f) P. Liu, R. Liang, L. Lu, Z. Yu, and F. Li, *J. Org. Chem.*, 2017, **82**, 1943; (g) W. M. Akhtar, C. B. Cheong, J. R. Frost, K. E. Christensen, N. G. Stevenson, and T. J. Donohoe, *J. Am. Chem. Soc.*, 2017, **139**, 2577.

6. Ruthenium: (a) R. Martínez, G. J. Brand, D. J. Ramón, and M. Yus, *Tetrahedron Lett.*, 2005, **46**, 3683; (b) R. Martínez, D. J. Ramón, and M. Yus, *Tetrahedron*, 2006, **62**, 8988; (c) T. Kuwahara, T. Fukuyama, and I. Ryu, *Org. Lett.*, 2012, **14**, 4703; (d) C. Schlepphorst, B. Maji, and F. Glorius, *ACS Catal.*, 2016, **6**, 4184.

7. Rhodium: P. Satyanarayana, G. M. Reddy, H. Maheswaran, and M. L. Kantam, *Adv. Synth. Catal.*, 2013, **355**, 1859.

8. Heterogeneous palladium: (a) M. S. Kwon, N. Kim, S. H. Seo, I. S. Park, R. K. Cheedrala, and J. Park, *Angew. Chem. Int. Ed.*, 2005, **44**, 6913; (b) Y. M. A. Yamada and Y. Uozumi, *Org. Lett.*, 2006, **8**, 1375; (c) G. Xu, Q. Li, J. Feng, Q.

Liu, Z. Zhang, X. Wang, X. Zhang, and X. Mu, *ChemSusChem*, 2014, **7**, 105; (d) T. T. Dang, S. P. Shan, B. Ramalingam, and A. M. Seayad, *RSC Advances*, 2015, **5**, 42399; (e) C. S. Cho, *J. of Mol. Catal. A: Chem.*, 2005, **240**, 55; (f) M. Bai, H. Xin, Z. Guo, D. Guo, Y. Wang, P. Zhao, and J. Li, *Appl. Surf. Sci.*, 2017, **391,** Part B, 617.

9. **Cobalt:** G. Zhang, J. Wu, H. Zeng, S. Zhang, Z. Yin, and S. Zheng, *Org. Lett.*, 2017, **19**, 1080.
10. **Iron:** S. Elangovan, J.-B. Sortais, M. Beller, and C. Darcel, *Angew. Chem. Int. Ed.*, 2015, **54**, 14483.
11. **Osmium:** M. L. Buil, M. A. Esteruelas, J. Herrero, S. Izquierdo, I. M. Pastor, and M. Yus, *ACS Catal.*, 2013, **3**, 2072.
12. **Manganese:** M. Pen˜a-Lo´pez, P. Piehl, S. Elangovan, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2016, **55**, 14967.
13. I. C. Yoon, T. G. Kim, and C. S. Cho, *Organometallics*, 2014, **33**, 1890.
14. O. Kose and S. Saito, *Org. Biomol. Chem.*, 2010, **8**, 896.
15. (a) R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Dalton Trans.*, 2015, **44**, 5805; (b) R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Tetrahedron*, 2017, **73**, 2225.
16. (a) M. L. S. Almeida, P. Kocovsky and J.-E. Backvall, *J. Org. Chem.*, 1996, **61**, 6587; (b) .Tsutsui, H. Sakamoto and K. Ukena, *J. Steroid Biochem. Mol. Biol.*, 2003, **85**, 311; (c) R. Kawahara, K. Fujita and R. Yamaguchi, *Angew. Chem. Int. Ed*., 2012, **51**, 12790.
17. (a) H. Sugimoto, Y. Iimura, Y. Yamanishi, and K. Yamatsu, *J. Med. Chem.*, 1995, **38**, 4821; (b) N. Niphade, A. Mali, K. Jagtap, R. C. Ojha, P. J. Vankawala, and V. T. Mathad, *Org. Process Res. Dev.*, 2008, **12**, 731.

18. H. Ohta, Y. Yuyama, Y. Uozumi, and Y. M. A. Yamada, *Org. Lett.*, 2011, **13**, 3892.

19. (a) M. T. H. Khan, *Top. Heterocycl. Chem.*, 2007, **11**, 213; (b) P. Narender, U. Srinivas, M. Ravinder, B. A. Rao, C. Ramesh, K. Harikishore, B. Gangadasu, U. S. N. Murthy, and V. J. Rao, *Bioorg. Med. Chem.*, 2006, **14**, 4600; (c) A. Busetti, D. E. Crawford, M. J. Earle, M. A. Gilea, B. F. Gilmore, S. P. Gorman, G. Laverty, A. F. Lowry, M. McLaughlin, and K. R. Seddon, *Green Chem.*, 2010, **12**, 420; (d) T. H. Thatcher, I. Luzina, R. Fishelevich, M. A. Tomai, R. L. Miller, and A. A. Gaspari, *J. Invest. Dermatol.*, 2006, **126**, 821; (e) R. Klingenstein, P. Melnyk, S. R. Leliveld, A. Ryckebusch, and C. Korth, *J. Med. Chem.*, 2006, **49**, 5300.

20. C.-C. Cheng and S.-J. Yan, in 'The Friedländer Synthesis of Quinolines', 2004.

21. (a) C. S. Cho and W. X. Ren, *J. Organomet. Chem.*, 2007, **692**, 4182; (b) H. Vander Mierde, P. Van Der Voort, D. De Vos, and F. Verpoort, *Eur. J. Org. Chem.*, 2008, 1625; (c) C. S. Cho, W. X. Ren, and N. S. Yoon, *J. Mol. Catal. A: chem.*, 2009, **299**, 117.

22. (a) B. Ding, Z. Zhang, Y. Liu, M. Sugiya, T.Imamoto and W.Zhang, *Org. Lett.*, 2013, **15**, 3690; (b) S. Gowrisankar, H.NeumannandM.Beller, *Angew. Chem. Int. Ed.*, 2011, **50,** 5139; (c) S.Gowrisankar, A. G. Sergeev, P.Anbarasan, A.Spannenberg, H. Neumann and M.Beller, *J. Am. Chem. Soc.*, 2010, **132**, 11592; (d) J. A.Müller, C. P.GollerandM. S.Sigman, *J. Am. Chem. Soc.*, 2004, **126**, 9724.

23. S. Elangovan, Jean-Baptiste Sortais, M. Beller, and C. Darcel, *Angew. Chem. Int. Ed*., 2015, **54,** 14483.

24. F. Li, J. Ma, and N. Wang, *J. Org. Chem.*, 2014, **79**, 10447.

25. M. Vellakkaran, M. M. S. Andappanb and N. Kommu, *Green Chem.*, 2014, **16**, 2788.

26. W. Dinga and Q. Song, *Org. Chem. Front*., 2016, **3**, 14.

27. P. Colbon, J. Ruan, M. Purdie, K. Mulholland and J. Xiao, *Org. Lett.*, 2011, **13**, 5456.

28. F. Alonso, P. Riente and M. Yus, *Eur. J. Org. Chem.*, 2008, 4908.

29. S. Fukuda, K. Tsuji, J. Musashi, R. Nonaka, T. Kimura and T. Satoh, *Synthesis*, 2011, 3615.

30. D. Shen, D. L. Poole, C. C. Shotton, A. F. Kornahrens, M. P. Healy and T. J. Donohoe, *Angew. Chem. Int. Ed*., 2015, **54**, 1642.

31. J. Yang, Y. W. Seto, and N. Yoshikai, *ACS Catal*., 2015, **5**, 3054.

32. H. G. Yayla, H. Wang, K. T. Tarantino, H. S. Orbe and R. R. Knowles, *J. Am. Chem. Soc*., 2016, **138**, 10794.

33. P. Colbon, J. Ruan, M. Purdie and J. Xiao, *Org. Lett*., 2010, **12**, 3670.

34. T. Kuwahara, T. Fukuyama and I. Ryu, *Org. Lett.*, 2012, **14**, 4703.

35. C. Schlepphorst, B. Maji and F. Glorius, *ACS Catal.*, 2016, **6**, 4184.

36. J. J. Li, J. J. Li, J. Li, A. K. Trehan, H. S. Wong, S. Krishnananthan, L. J. Kennedy, Q. Gao, A. Ng, J. A. Robl, B. Balasubramanian and B. Chen, *Org. Lett.*, 2008, **10**, 2897.

37. R. P. Boivin, V. Luu-The, R. Lachance, F. Labrie and D. Poirier, *J. Med. Chem.*, 2000**, 43**, 4465.

38. R. Wang, H. Fan, W. Zhao and F. Li, *Org. Lett*., 2016, **18**, 3558.

39. Q. Wang, M. Wang, H.Li, S. Zhu, Y. Liu and Y. Wu, *Synthesis*, 2016**, 48**, 3985.

40. H. Ohta, Y. Yuyama, Y. Uozumi and Y. M. A. Yamada, *Org. Lett.*, 2011, **13**, 3892.

41. R. Mamidala, S. Samser, N. Sharma, U. Lourderaj, and K. Venkatasubbaiah, *Organometallics,* 2017, **36**, 3343.

Chemoselective alkylation of aminoacetophenones with alcohols by using a palladacycle-phosphine catalyst

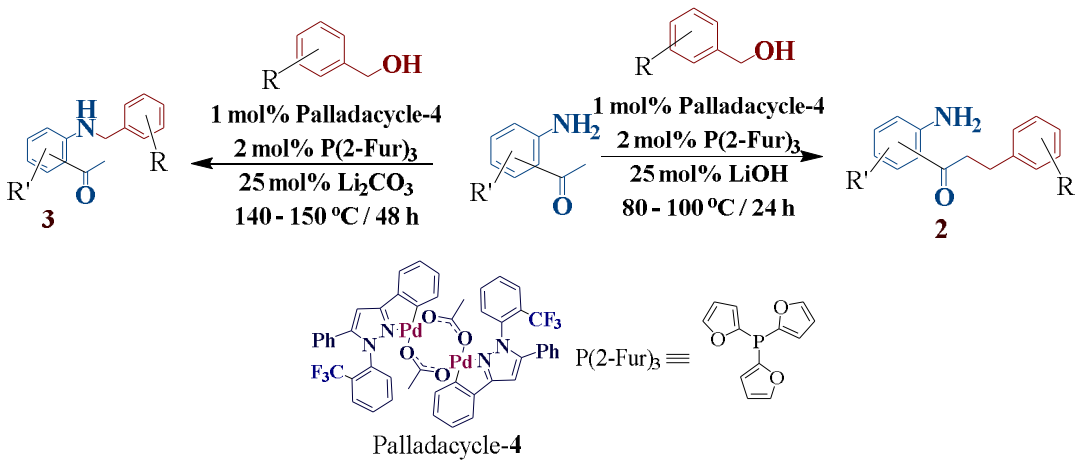
6.1 Introduction

Alkylation of ketones and amines are the important class of reactions in organic chemistry.[1] Classical methodologies for the alkylation of ketones and amines involves alkyl halides or alkyl sulfonates as alkylating agents.[2] Although most of these methods proved to be efficient in many instances they also produce wastes such as alky halides and (or) side-products. The use of borrowing hydrogen or hydrogen auto transfer strategy has been emerged as an environmentally friendly greener approach for the construction of C─C and C─N bonds as this method involves water as the only side product.[3] Over the past decade, several groups have been involved to develop methodologies for the alkylation of ketones[4] and amines[5] using alcohols as benign alkylating agents. Among the metal complexes,[6-15] a greater number of progress has been made using Ru [6] and Ir [7] metal complexes. It is interesting to note that Cho *et al* described Ru-based catalyst for the α-alkylation of ketones.[16] Meanwhile Ishi *et al* reported Ir-based catalyst for the same reaction.[17] Feringa and Barta demonstrated the alkylation of amines using alcohols.[18] More recently, Beller and co-workers elegantly utilized the hydrogen borrowing methodology for the synthesis of N-alkylated and C-alkylated products using manganese pincer complex.[14]

Development of efficient and selective transformation of molecules with more than one functional group is an important problem in organic synthesis. A chemo selective reaction offers minimization of the use of protecting or activating groups. Although there are numerous metal catalyzed [6-15] N-alkylation of amines or C-alkylation of ketones using alcohols are reported, chemoselective N-alkylation of

amines or C-alkylation of ketones using alcohols is a neglected area. Recently, Li and co-workers reported copper [15d] and Iridium [7h] catalyzed regioselective N-alkylation of 2-aminobenzothiazoles or amino-azoles with benzyl alcohols respectively. More recently, the same group reported regioselective N-alkylation of sulfanilamides using alcohols.[7k] 2'-Aminoacetophenones are important class of compounds in the preparation of isatin [19] and indole [20] derivatives. A survey on the literature revealed that there is only one report for the chemoselective alkylation of 2'-aminoacetophenones.[21b]

In 2000, Grigg and co-workers reported synthesis and application of pyrazole based palladacyclesas catalysis.[21a] Grigg and co-workers report on pyrazole based palldacycles and easy accessibility of pyrazoles, motivated us to develop variety of pyrazole based palldacycles. Recently, we demonstrated pyrazole based palladacycles as catalysts for the C—C and C—N bond forming reactions.[10c,22] As part of our efforts in the development of pyrazole based palladacycles for the activation of alcohols as electrophile, herein we report chemoselective alkylation of aminoacetophenones using palldacycle-phosphine complex (Scheme 6.1).



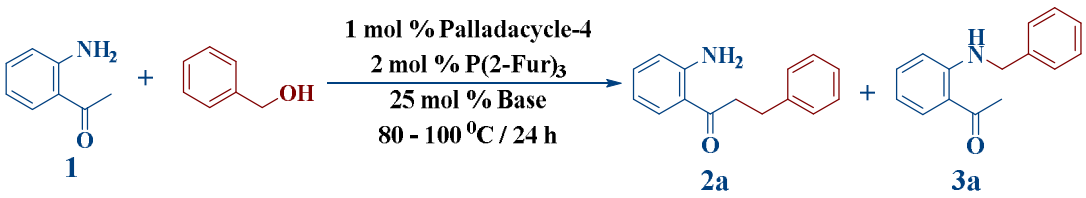
Scheme 6.1: Palladacycle-**4** catalyzed chemoselective alkylation of aminoacetophenones

6.2 Results and discussion

6.2.1 C-Alkylation of aminoacetophenones

Initially, to explore the alkylation reaction, 2'-aminoacetophenone and benzyl alcohol were chosen as the model substrates using 1 mol% of palldacycle-4, 2 mol% of P(2-Fur)$_3$, 25 mol% LiOH under solvent-free condition (Table 6.1). At 100 °C, use of 1.2 equivalents of benzyl alcohol resulted 18% of the N-alkylated product and 66% of the C-alkylated product (Table 6.1, entry 1). Surprisingly, when the reaction was carried out using 2 equivalents of benzyl alcohol, the reaction yielded exclusively the C-alkylated product in 95% isolated yield (Table 6.1, entry 2). Then, we evaluated different bases and temperature. Of the different bases screened, LiOH was found to be promising under solvent-free condition at 80 °C (Table 6.1, entry 3).

Table 6.1: Optimization of chemo selective C-alkylation of 2'-aminoacetophenone using benzyl alcohol[a]



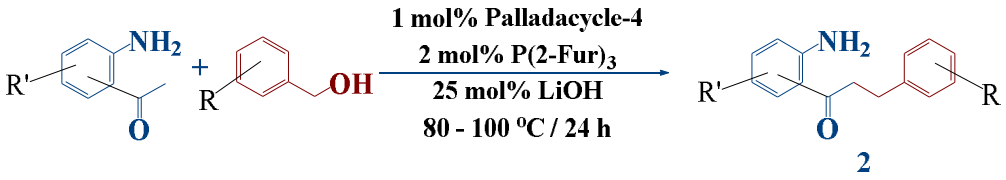
Entry	Base	T (^{o}C)	Yield [b] (%)	
			3a	2a
1[c]	LiOH	100	18	66
2	LiOH	100	<5	95
3	LiOH	80	trace	96
4	$CsOH.H_2O$	80	ND	88
5	Li_2CO_3	80	ND	ND

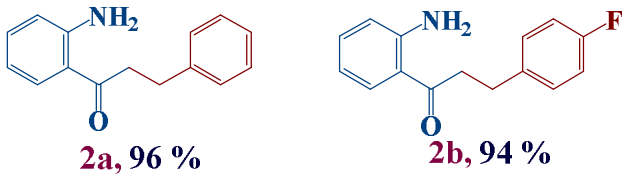
6	Cs_2CO_3	80	ND	ND
7	K_3PO_4	80	ND	ND
8	KOH	80	ND	trace
9	NaOH	80	ND	trace
10	KO^tBu	80	ND	76

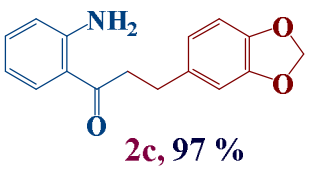
[a]Reaction condition: 2'-Aminoacetophenone 1 mmol, benzyl alcohol 2 mmol, LiOH 0.25 mmol, [b]isolated yield after column chromatography, [c]benzyl alcohol 1.2 mmol was used, ND: Not Detected

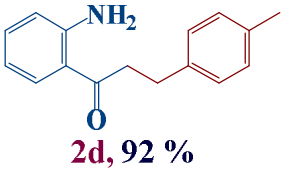
Having established the optimal reaction condition using the palladacycle-phosphine catalyst, the reaction scope was explored with a range of alcohols and aminoacetophenones. We found that benzyl alcohols bearing electron-donating or electron-withdrawing groups were readily alkylated to the corresponding C-alkylated products (Table 6.2, compounds **2a-2e**) in 88–97% isolated yields. Furthermore, heteroaromaticfurfuryl alcohol was also tolerated under the reaction conditions. (Table 6.2, compound **2h**). Challenging aliphatic alcohols such as 1-propanol, 1-hexanol and 1-decanol could be successfully converted to the corresponding C-alkylated products in 73%, 89% and 84% respectively (Table 6.2, compounds**2l**, **2m**, **2n**).

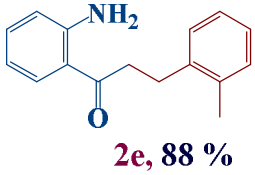
Table 6.2: Scope of chemoselective C-alkylation of aminoacetophenones using alcohols[a]

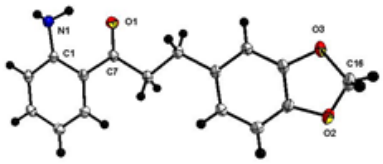


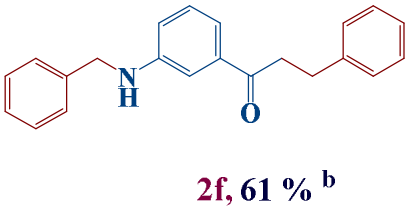


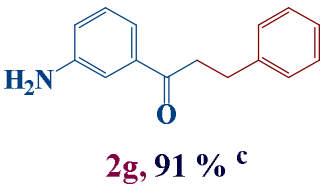


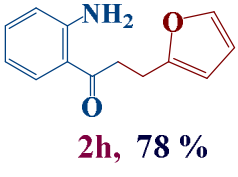


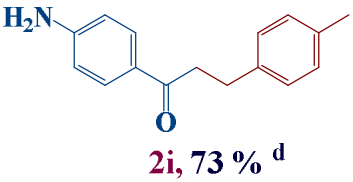


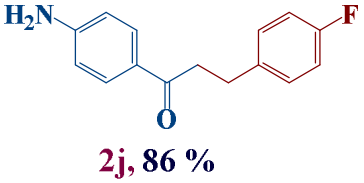


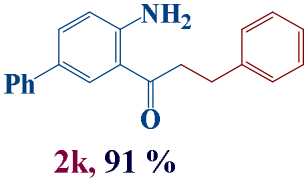


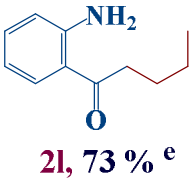


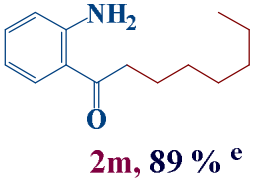


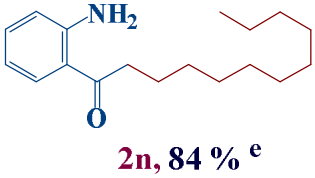












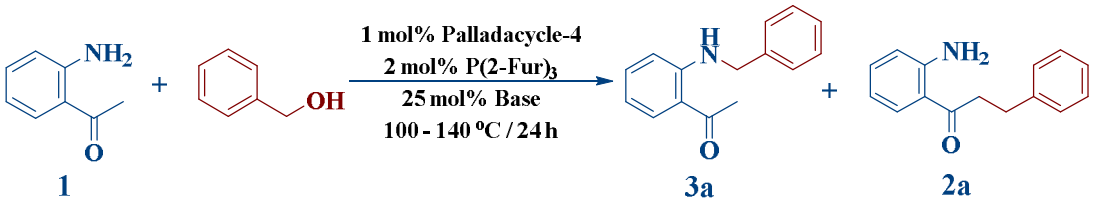
[a]Reaction condition: 2'-Aminoacetophenone 1 mmol, benzyl alcohol 2 mmol, LiOH 0.25 mmol, palladacycle-**4** $1x10^{-2}$ mmol, $P(2\text{-Fur})_3$ $2x10^{-2}$ mmol, isolated yield after column chromatography, [b]32% of compound **2g** was also isolated, [c]reaction was performed at 60 °C, [d]26% dialkylated compound was also isolated, [e]reactions were performed at 100 °C.

Encouraged by these results, next we explored the scope and limitation of different aminoacetophenones. 3'-Aminoacetophenone which is electronically different from 2'-aminoacetophenone was subjected to the reaction conditions, which resulted 32% of the desired mono C-alkylated product along with 61% of the undesired di-alkylated product (Table 6.2, compound **2f**). However, decreasing the temperature to 60 °C, resulted exclusively the C-alkylated product in 91% yield (Table 6.2, compound **2g**). Reaction of 4'-aminoacetophenone with 4-methyl benzyl alcohol or 4-fluoro benzyl alcohol yielded the desired C-alkylated products in 73% and 86% respectively (Table 6.2, entry **2i** and **2j**). We also observed 26% of the dialkylated product in case of 4'-aminoacetophenone and 4-methyl benzyl alcohol under the reaction conditions mentioned above. 1-(3-Amino-[1,1'-biphenyl]-4-yl)ethanone underwent the α-alkylation comfortably to yield **2k** in 91% yield.

6.2.2 N-Alkylation of aminoacetophenones

Next, we turned our attention to investigate the applicability of this method for the chemoselective N-alkylation of aminoacetophenones. Different bases at various temperatures were examined and the results are summarized in table 6.3. LiOH and $CsOH.H_2O$ failed to give the desired N-alkylated product even at 130 °C (Table 6.3, entries 1-5). Among the different bases tested Li_2CO_3 was found to be the only base produced the N-alkylated product at 130 °C with the use of 2 equivalents of benzyl alcohol (Table 6.3, entry 6). Increasing the amount of benzyl alcohol to 3 equivalents improved the yield of the N-alkylated product to 76% (Table 6.3, entry 7). As expected, running the reaction at 140 °C increased the yield to 95%. Hence, we selected the reaction of aminoacetophenones (1 mmol), benzyl alcohol (3 mmol), catalyst (1mol%), Li_2CO_3 (25 mol%) at 140 °C for 24 h as the best reaction condition.

Table 6.3: Optimization of Chemo selective N-alkylation of 2'-Aminoacetophenone using benzyl alcohol[a]



Entry	Base	T (^{o}C)	Yield [b] (%)	
			3a	2a
1[c]	LiOH	100	<5	95
2[c]	$CsOH.H_2O$	100	ND	73
3[c]	LiOH	120	ND	98
4[c]	LiOH	130	ND	97
5[c]	$CsOH.H_2O$	130	ND	89
6[c]	Li_2CO_3	130	54	ND
7[d]	Li_2CO_3	130	76	ND
8[d]	Cs_2CO_3	130	ND	ND
9[d]	K_3PO_4	130	ND	ND
10[d]	K_2CO_3	130	ND	ND
11[d]	Li_2CO_3	140	95	ND

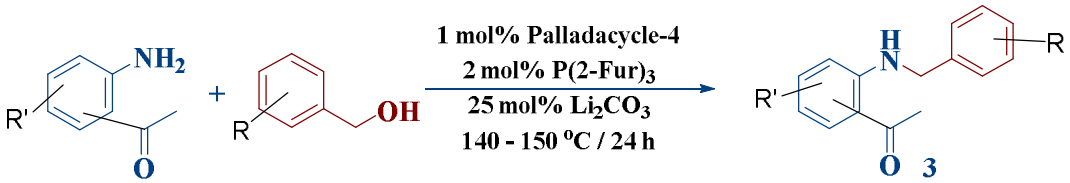
[a]Reaction condition: 2'-Aminoacetophenone 1 mmol, benzyl alcohol 2 mmol, base 0.25 mmol, [b]isolated yield after column chromatography, [c]benzyl alcohol 2 mmol was used, [d]benzyl alcohol 3 mmol was used, ND: Not Detected.

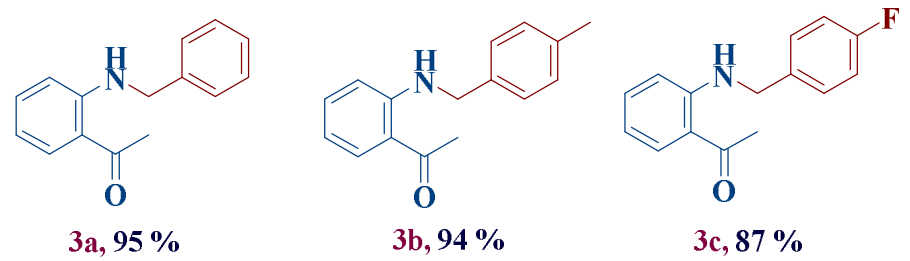
With the optimum reaction conditions, the scope of the palladacycle-phosphine promoted N-alkylation was studied with a range of benzyl alcohols and

aminoacetophenones and the results are presented in table 6.4. The substitutions on benzyl alcohol and aminoacetophenone with electron-withdrawing groups or electron-donating groups are tolerated. Benzyl alcohols such as 4-methyl benzyl alcohol, 4-fluoro benzyl alcohol, 3,4-methylenedioxy benzyl alcohol, 1-naphthyl methanol and 2-biphenyl methanol were converted to the desired products in excellent yields (Table 6.4, compounds **3a-3f**). The reaction with electron withdrawing substituted (F) 2'-aminoacetophenone was slow and gave the respective N-alkylated product in 49% (Table 6.4, compound **3k**). However, electron-donating group substituted (OMe) 2'-aminoacetophenone produced the respective N-alkylated product in 62% yield (Table 6.4, compound **3i**). Moreover, 2'-aminoacetophenone with phenyl at 5-position underwent N-alkylation comfortably to yield **3j** in 78%. Furthermore, when N-alkylation was applied to 4-aminoacetophenone it resulted the desired product in 68%. To our delight, the least reactive and challenging aliphatic alcohols such as 1-butanol and 1-hexanol were successfully alkylated to the corresponding products (Table 6.4, compounds **3l** and **3m**).

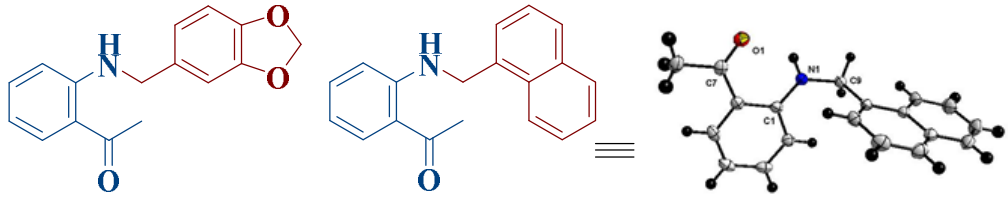
Donepezil is an important biologically active molecule which is used for the treatment of Alzheimer disease. We applied our catalytic protocol for the synthesis of donepenzil that involves chemoselective alkylation followed by N-alkylation. Although, 4-piperidinemethanol is prone to undergo self-coupling or N-alkylation, the reaction of 5,6-dimethoxy indanone with 4-piperidine methanol produced selectively the C-alkylated product (Scheme 6.2, compound **4**). The subsequentreaction of compound **4** with benzyl alcohol yielded donepezil under the conditions mentioned above. It is worth mentioning that our protocol does not need conventional mutagenic or toxic alkylating agents and represents one of the shortest route to make this biologically important molecule.

Table 6.4: Scope of chemoselective N-alkylation of aminoacetophenones using alcohols [a]

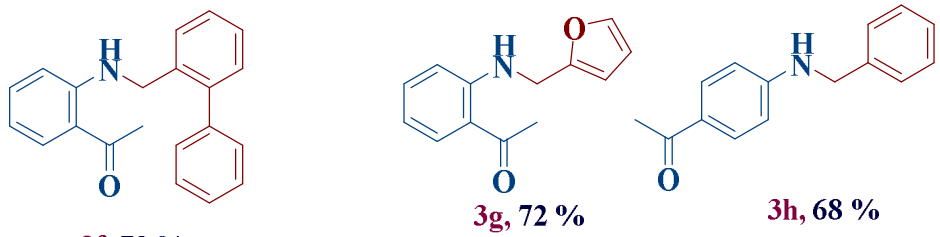




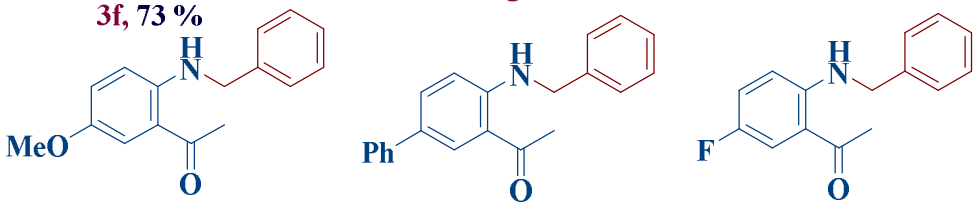
3a, 95 % 3b, 94 % 3c, 87 %



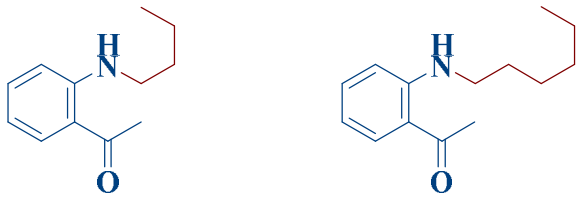
3d, 92 % 3e, 88 %



3f, 73 % 3g, 72 % 3h, 68 %

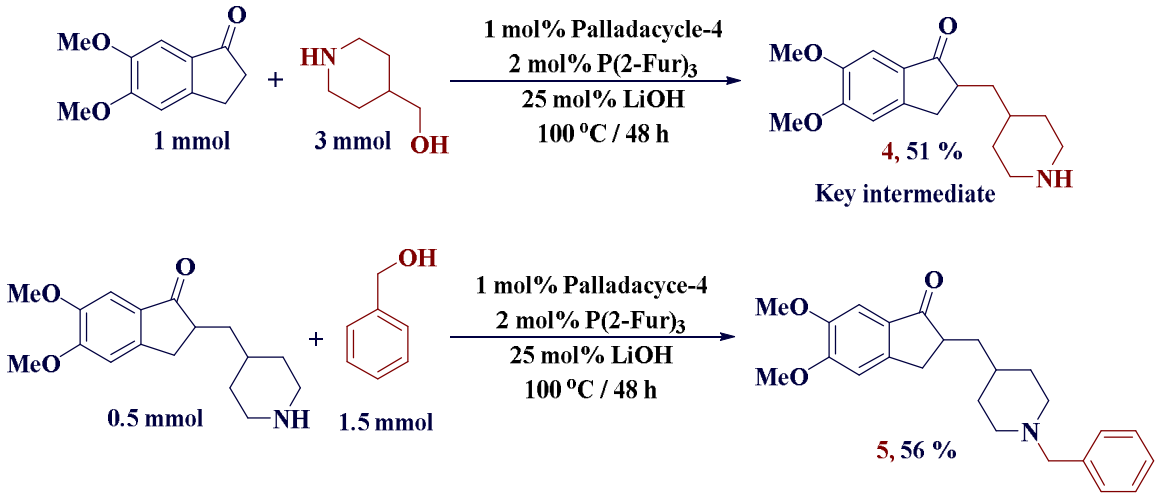


3i, 62 % 3j, 78 % 3k, 49 %



3l, 43 % [b] 3m, 22 % [b]

[a]Reaction condition: 2'-Aminoacetophenone 1 mmol, benzyl alcohol 2 mmol, Li_2CO_3 0.25 mmol, palladacycle-**4** $1x10^{-2}$ mmol, $P(2\text{-Fur})_3$ $2x10^{-2}$ mmol, isolated yield after column chromatography, [b]reactions were performed at 150 °C for 48 h.



Scheme 6.2: Chemoselective synthesis of donepezil

To know the bonding mode of the palladacycle-4 and the ancillary ligand phosphine, we attempted to grow single crystals of palladacycle-4 & tri(2-furl)phosphine. Although our attempts to crystallize palladacycle-tri(2-furl)phosphine had been unsuccessful, we were lucky to get crystals of palladacycle-triphenylphosphine and analysed using the single crystal X-ray diffraction technique (Table 6.5). The molecular structure of compound **P-PPh$_3$** is shown in Figure 6.1, along with selected bond lengths and bond angles. The Pd─C, Pd─N, Pd─P, and Pd─O bond lengths are comparable to the reported palladacycle complex of similar type.[23]

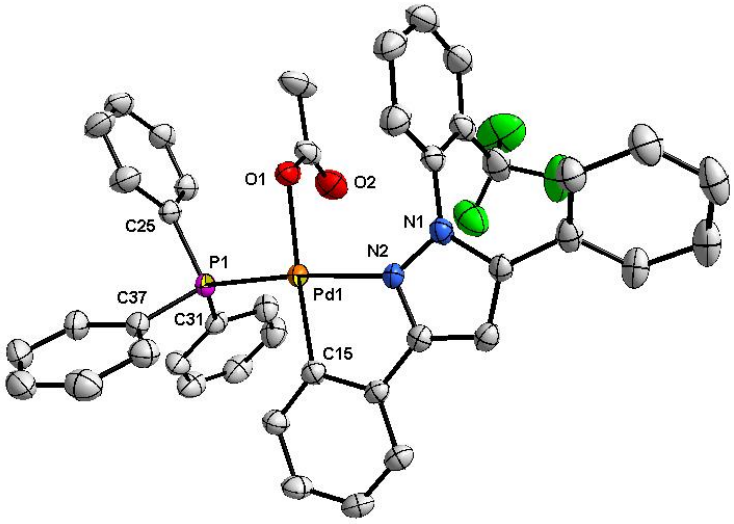


Figure 6.1. Molecular structure of P-PPh_3 (Thermal ellipsoids at 30% probability), Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (degree): Pd1-P1 2.2397(8), Pd1-O12.099(2), Pd1-N2 2.112(2),Pd1-C15 2.019(3), P1-C25 1.840(3), P1-C37 1.821(4), P1-C31 1.817(4), O1-Pd1-P1 90.59(6), O1-Pd1-N2 95.00(9), N2-Pd1-P1 174.41(7), C15-Pd1-P1 93.33(9), C15-Pd1-O1 176.05(11), C15-Pd1-N2 81.08(11).

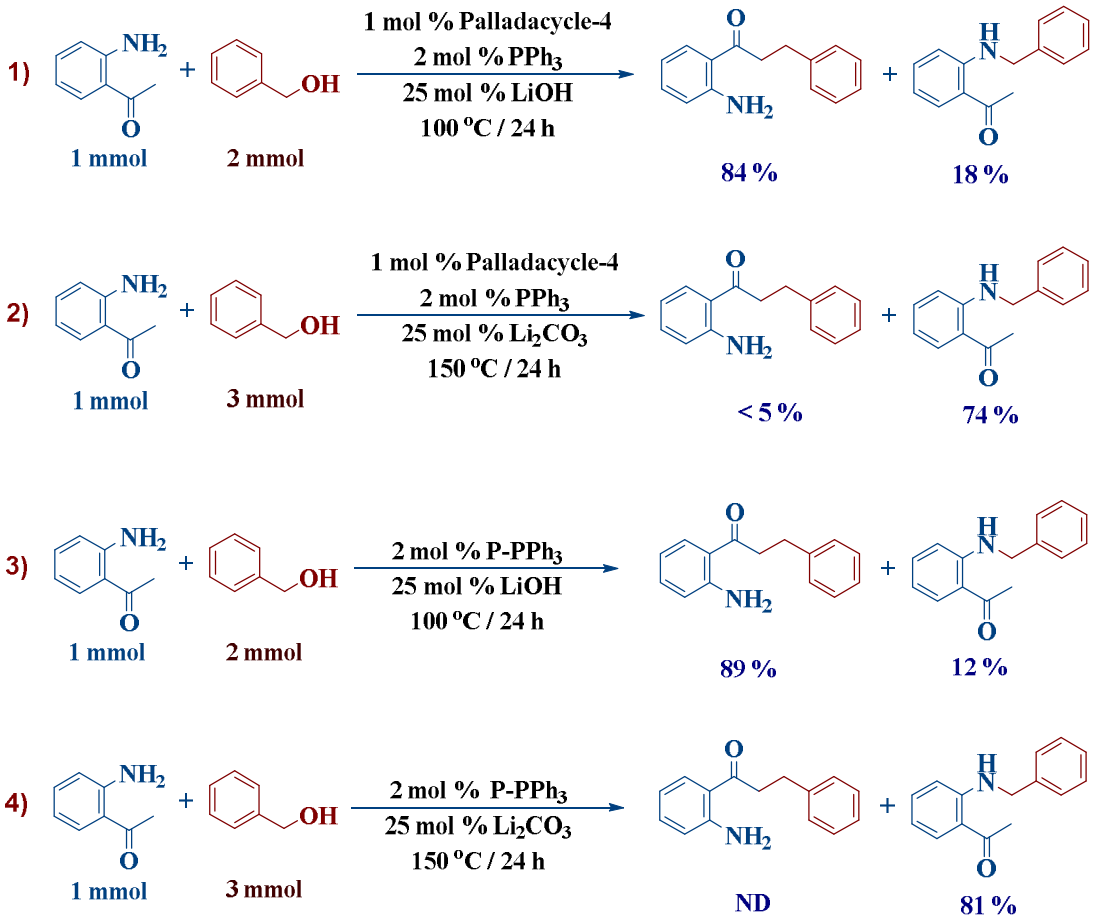
Table 6.5: Crystal data and structure refinement parameters for P-PPh_3

Identification code	**P-PPh_3**
Empirical formula	$C_{42}H_{32}F_3N_2O_2PPd$
Formula weight	791.06
Temperature/K	296.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	14.7824(5)
b/Å	14.1452(5)
c/Å	21.3761(7)
α/°	90
β/°	107.739(2)

γ/°	90
Volume/Å3	4257.2(3)
Z	4
ρ_{calc}g/cm3	1.234
μ/mm-1	0.520
F(000)	1608.0
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.506 to 56.692
Index ranges	-14 ≤ h ≤ 19 -18 ≤ k ≤ 18 -28 ≤ l ≤ 28
Reflections collected	71771
Independent reflections	10568 [R_{int} = 0.0801, R_{sigma} = 0.0545]
Data/restraints/parameters	10568/0/461
Goodness-of-fit on F2	0.800
Final R indexes [I>=2σ(I)]	R_1 = 0.0472, wR_2 = 0.1142
Final R indexes [all data]	R_1 = 0.0766, wR_2 = 0.1244
Largest diff. peak/hole / e Å-3	0.70/-1.29

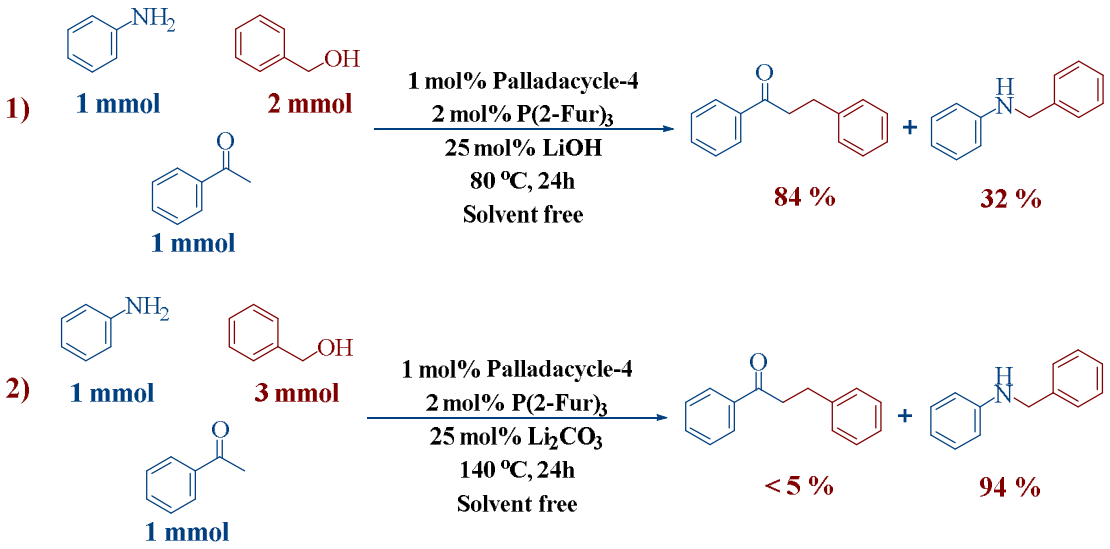
We repeated the reaction of 2'-aminoacetophenone with benzyl alcoholusing *in situ* generated palladacycle-**4**-triphenylphosphine and isolated palladacycle-**4**-triphenylphosphine (**P-PPh$_3$**). The results are summarized in scheme 6.3. The results showed that the product yields were slightly higher for the isolated **P-PPh$_3$** over the *in situ* generated complex leading us to conclude that the palladacycle-**4**-phosphine

complex is the active catalyst (or) pre-catalyst for the N-alkylation and C-alkylation reactions.



Scheme 6.3: Control experiments with and without isolated palladacycle-**4**-PPh_3

Controlled experiments were run with the combination of acetophenone, aniline and benzyl alcohol under the optimized conditions for N-alkylation and C-alkylation (Scheme 6.4). It is important to note that either N-alkylated (94%) or C-alkylated (84%) compound was observed as the major product,demonstrates that the reaction conditions play a very important role in achieving the chemoselectivity.



Scheme 6.4: Control experiments

6.3 Conclusion

In conclusion, we have established an efficient palladacycle-4-phosphine catalyzed chemoselective alkylation of aminoacetophenones. Our methodology has the advantage that, just by switching the base and temperature, the reaction changes from C-alkylated product to N-alkylated product. Using this protocol, a wide range of substituted alcohols was successfully alkylated to either the C-alkylated or N-alkylated products in good yields.

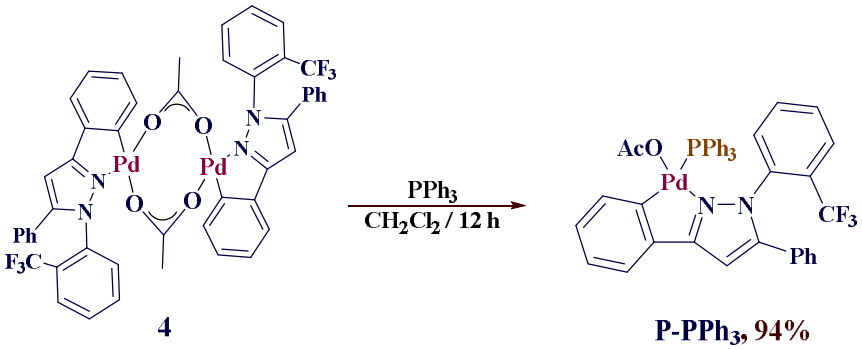
6.4 Experimental section

6.4.1 General information

All chemicals were used as received from commercially available sources. Acetonitrile was distilled over CaH_2 and toluene was dried using standard protocol. 1-(2-Amino-5-methoxyphenyl)ethanone, 1-(2-amino-5-fluorophenyl)ethanone and 1-(4-amino- [1,1'-biphenyl]-3-yl)ethanone were synthesized by following literature reported methods.[24] NMR spectra were recorded on Bruker ARX 400 spectrometer at

room temperature. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR chemical shifts in ppm were referenced internally to its proton resonance of incomplete deuterated solvent signals. ^{19}F NMR spectra were externally reference to *α,α,α*- trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). Electron spray ionization mass spectra were recorded on a Bruker microTOF-QII spectrometry. IR spectra were recorded with Perkin Elmer instrument. Single-crystal X-ray diffraction data were collected at 296 K using, Mo-K*α* radiation (0.71073 Å). SADABS absorption corrections were applied in both cases. The structures were solved and refined with SHELX suite of programs. All nonhydrogen atoms were refined with anisotropic displacement coefficients. The H atoms were placed at calculated positions and were refined as riding atoms.

6.4.2 Synthesis of P-PPh_3 [32]



Under argon, palladacycle-**4** (0.5 g, 0.47 mmol) and triphenyl phosphine (0.248 g, 0.94 mmol) were dissolved in dry dichloromethane and stirred overnight at room temperature. The solvents were removed under vacuum and the residue was washed with diethyl ether. The yellow product was recrystallized from a mixture of dichloromethane and hexanes. Yield: 0.70 g (0.9 mmol, 94%). Mp = 174-175 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79-7.69 (m, ArH, 7H), 7.50-7.21 (m, ArH, 17H), 7.12 (d, J = 4 Hz, ArH, 2H), 6.90 (t, J = 8 Hz, ArH, 1H), 6.76 (s, 4Pz-H, 1H), 6.46-6.38 (m, ArH, 2H), 1.80 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 148.3,

148.1, 147.1, 146.6, 139.4 (d, *J* = 13.0 Hz), 135.8 (d, *J* = 12.2 Hz), 135.2, 132.3, 131.7, 131.2, 130.7, 130.5 (d, *J* = 2.4 Hz), 130.2, 129.1 (d, *J* = 5.3 Hz), 128.9, 128.6, 128.1 (d, *J* = 10.9 Hz), 127.4 (q, *J* = 5.3 Hz), 126.9 (d, *J* = 5.8 Hz), 123.7 (d, *J* = 72.5 Hz), 101.7, 23.1 ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 46.19 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -60.69 ppm. HRMS (ESI): calcd. for $C_{40}H_{29}F_3N_2PPd$ ([M-$OCOCH_3$]$^+$): 731.1064, found: 731.1071. IR (KBr): υ (cm^{-1}) = 3055 (m), 2926 (m), 1577 (s), 1412 (s), 1317 (s), 1175 (s), 1115 (s), 761 (m), 722 (m), 695 (s), 542 (s).

6.4.3 General Procedure for C-Alkylation of aminoacetophenones

An Oven dried schlenk tube was charged with palladacycle-**4** ($1x10^{-2}$ mmol), P(2-Fur)$_3$ ($2x10^{-2}$ mmol). Inside Glove box LiOH (0.25 mmol) was added, and outside the Glove box under argon aminoacetophenone (1 mmol), alcohol (2 mmol) were added to the reaction mixture. The tube was connected to a vacuum line under argon and purged three times. Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 80-100 ^oC for 24 h. At the end of the reaction, the reaction mixture was cooled to room temperature, diluted with dichloromethane (5 mL), and concentrated under vacuum. The crude was subjected to column chromatography on silica gel using ethyl acetate and hexanes mixtures to afford the *α*-alkylated product in high purity.

6.4.4 General Procedure for N-Alkylation of aminoacetophenones:

An Oven dried schlenk tube was charged with palladacycle-**4** ($1x10^{-2}$ mmol to $2x10^{-2}$ mmol), P(2-Fur)$_3$ ($2x10^{-2}$ mmol to $4x10^{-2}$ mmol). Inside Glove box Li_2CO_3 (0.25 mmol) was added, and outside the Glove box under argon aminoacetophenone (1 mmol), alcohol (3 mmol) were added to the reaction mixture. The tube was connected

to a vacuum line under argon and purged three times. Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 140-150 ^{o}C for 24-48 h. At the end of the desired reaction time, the reaction mixture was cooled to room temperature, diluted with dichloromethane (5 mL), and concentrated under vacuum. The crude was subjected to column chromatography on silica gel using ethyl acetate and hexanes mixtures to afford the N-alkylated product in high purity.

6.4.5 Analytical data for alkylated products

1-(2-aminophenyl)-3-phenylpropan-1-one (Table 6.2, Compound 2a) [21b]**:** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and benzyl alcohol (0.22 g, 2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.22 g, 0.9 mmol, 96%). Mp = 78-79 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3 Hz, 1H), 7.35–7.22 (m, 6H), 6.65 (t, *J* = 8.4 Hz, 2H), 6.31 (s, 2H), 3.30 (t, *J* = 7.2 Hz, 2H), 3.08 (t, *J* = 7.2 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 150.5, 141.6, 134.3, 131.1, 128.6, 128.5, 126.1, 117.9, 117.5, 115.9, 41.0, 30.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ ($[M+H]^+$): 226.1226, found: 226.1235.

1-(2-aminophenyl)-3-(4-fluorophenyl)propan-1-one (Table 6.2, Compound 2b) [32]**:** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 4-fluorobenzyl alcohol (0.25 g, 2 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.23 g, 0.9 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.1 Hz, 1H), 7.29–7.16 (m, 3H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.62 (m, 2H), 3.23 (t, *J* = 7.6 Hz, 2H), 3.00 (t, *J* = 7.7 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.4, 161.5 (d, *J* = 243.7 Hz), 150.4, 137.2 (d, *J* = 3.2 Hz), 134.5, 131.1, 129.9 (d, *J* = 7.8 Hz), 118.0, 117.6, 116.0, 115.3 (d, *J* = 21.1 Hz), 41.1, 29.8 ppm. ^{19}F NMR

(376 MHz, $CDCl_3$): δ = -118.37 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}FNO$ ($[M+H]^+$): 244.1132, found: 244.1119.

1-(2-aminophenyl)-3-(benzo[d][1,3]dioxol-5-yl)propan-1-one (Table 6.2, Compound 2c) [25]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 3,4-methylenedioxybenzyl alcohol (0.30 g, 2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.26 g, 0.9 mmol, 97%). Mp = 94-95 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 6.75–6.61 (m, 5H), 5.92 (s, 2H), 3.23 (t, *J* = 7.9 Hz, 2H), 2.96 (t, *J* = 7.8 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 150.5, 147.8, 145.9, 135.4, 134.4, 131.1, 121.3, 118.0, 117.5, 116.0, 109.1, 108.4, 100.9, 41.3, 30.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}NO_3$ ($[M+H]^+$): 270.1125, found: 270.1111.

1-(2-aminophenyl)-3-(p-tolyl)propan-1-one (Table 6.2, Compound 2d) [32]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 4-methylbenzyl alcohol (0.24 g, 2 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.22 g, 0.9 mmol, 92%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.16–7.09 (m, 4H), 6.77–6.66 (m, 2H), 3.26 (t, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 138.5, 135.7, 134.4, 131.2, 129.3, 128.4, 118.3, 118.1, 117.0, 116.7, 41.3, 30.3, 21.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO$ ($[M+H]^+$): 240.1383, found: 240.1403.

1-(2-aminophenyl)-3-(o-tolyl)propan-1-one (Table 6.2, Compound 2e) [32]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 2-methylbenzyl alcohol (0.24 g, 2

mmol). After purification by column chromatography, the compound was isolated as a white solid (0.21 g, 0.8 mmol, 88%). Mp = 57-58 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.1 Hz, 1H), 7.31–7.26 (m, 1H), 7.20–7.14 (m, 4H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.68 (t, *J* = 7.6 Hz, 1H)., 3.23 (t, *J* = 7.6 Hz, 2H), 3.04 (t, *J* = 7.6 Hz, 2H), 2.36 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 149.6, 139.7, 136.2, 134.5, 131.1, 130.5, 128.8, 126.4, 126.3, 118.4, 118.0, 116.6, 39.8, 28.1, 19.5 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO$ ($[M+H]^+$): 240.1383, found: 240.1377.

1-(3-(benzylamino)phenyl)-3-phenylpropan-1-one (Table 6.2, Compound 2f) [32]***:*** Prepared from 3'-aminoacetophenone (0.14 g, 1 mmol) and benzyl alcohol (0.22 g, 2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.19 g, 0.6 mmol, 61%). Mp = 83-84 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.20 (m, 13H), 6.82 (dd, *J* = 8.4, 2.9 Hz, 1H), 4.37 (s, 2H), 3.25 (t, *J* = 7.7 Hz, 2H), 3.06 (t, *J* = 7.5 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8, 148.3, 141.5, 138.9, 138.0, 129.5, 128.9, 128.6, 128.5, 127.6, 127.5, 126.2, 117.7, 111.9, 48.4, 40.6, 30.4 ppm. HRMS (ESI): calcd. for $C_{22}H_{21}NO$ ($[M+H]^+$): 316.1696, found: 316.1714.

1-(3-aminophenyl)-3-phenylpropan-1-one (Table 6.2, Compound 2g) [32]***:*** Prepared from 3'-aminoacetophenone (0.14 g, 1 mmol) and benzyl alcohol (0.22 g, 2 mmol). After purification by column chromatography, the compound was isolated as a light yellow solid (0.21 g, 0.9 mmol, 91%). Mp = 91-92 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 8H), 6.90 (dd, *J* = 7.9, 3.1 Hz, 2H), 4.14 (s, 2H), 3.26 (t, *J* = 7.6 Hz, 2H), 3.06 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.6, 146.3,

141.4, 138.0, 129.6, 128.6, 128.5, 126.2, 120.0, 118.9, 114.4, 40.6, 30.3 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ ($[M+H]^+$): 226.1226, found: 226.1228.

1-(2-aminophenyl)-3-(furan-2-yl)propan-1-one (Table 6.2, Compound 2h) [21b]**:** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 2-furylmethanol (0.20 g, 2 mmol). After purification by column chromatography, the compound was isolated as a pale yellow solid (0.17 g, 0.7 mmol, 78%). Mp = 77-78 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 1.8 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 6.68 (t, *J* = 7.5 Hz, 2H), 6.32–6.31 (m, 1H), 6.07 (d, *J* = 3.1 Hz, 1H), 3.34 (t, *J* = 7.6 Hz, 2H), 3.09 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 155.2, 150.4, 141.2, 134.5, 131.1, 118.0, 117.5, 116.0, 110.4, 105.3, 37.5, 23.0 ppm. HRMS (ESI): calcd. for $C_{13}H_{13}NO_2$ ($[M+H]^+$): 216.1019, found: 216.1015.

1-(4-aminophenyl)-3-(p-tolyl)propan-1-one (Table 6.2, Compound 2i) [32]**:** Prepared from 4'-aminoacetophenone (0.14 g, 1 mmol) and 4-methylbenzyl alcohol (0.24 g, 2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.17 g, 0.7 mmol, 73%). Mp = 96-97 ^oC. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.7 Hz, 2H), 7.16–7.10 (m, 4H), 6.64 (d, *J* = 8.7 Hz, 2H), 3.19 (t, *J* = 7.5 Hz, 2H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 151.2, 138.7, 135.6, 130.6, 129.3, 128.4, 127.6, 113.9, 40.1, 30.2, 21.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO$ ($[M+H]^+$): 240.1383, found: 240.1401.

1-(4-aminophenyl)-3-(4-fluorophenyl)propan-1-one (Table 6.2, Compound 2j) [32]**:** Prepared from 4'-aminoacetophenone (0.14 g, 1 mmol) and 4-fluorobenzyl alcohol (0.25 g, 2 mmol). After purification by column chromatography, the compound was

isolated as a white solid (0.21 g, 0.8 mmol, 86%). Mp = 94-95 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.6 Hz, 2H), 7.21–7.17 (m, 2H), 6.96 (t, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 2H), 3.17 (t, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.5, 161.5 (d, *J* = 243.5 Hz), 151.2, 137.4 (d, *J* = 3.1 Hz), 130.7, 129.9 (d, *J* = 7.8 Hz), 128.6 (d, *J* = 5.5 Hz), 127.6, 115.3 (d, *J* = 21.1 Hz), 114.0, 39.9, 29.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -118.5 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}FNO$ ($[M+H]^+$): 244.1132, found: 244.1121.

1-(4-amino-[1,1'-biphenyl]-3-yl)-3-phenylpropan-1-one (Table 6.2, Compound 2k) [32]***:*** Prepared from 1-(4-amino-[1,1'-biphenyl]-3-yl)ethanone (0.21 g, 1 mmol) and benzyl alcohol (0.22 g, 2 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.27 g, 0.9 mmol, 91%). Mp = 122-123 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 2.1 Hz, 1H), 7.56–7.51 (m, 3H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.36–7.22 (m, 6H), 6.77 (d, *J* = 8.6 Hz, 1H), 3.37 (t, *J* = 7.7 Hz, 2H), 3.10 (t, *J* = 7.6 Hz, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.7, 149.6, 141.6, 140.6, 133.3, 129.5, 129.3, 128.9, 128.7, 128.6, 126.7, 126.4, 126.2, 118.2, 118.1, 41.2, 30.7 ppm. HRMS (ESI): calcd. for $C_{21}H_{19}NO$ ($[M+H]^+$): 302.1539, found: 302.1536.

1-(2-aminophenyl)pentan-1-one (Table 6.2, Compound 2l) [26]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 1-propanol (0.12 g, 2 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.13 g, 0.7 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.4 Hz, 1H), 7.27–7.23 (m, 1H), 6.67–6.63 (m, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 1.74–1.67 (m, 2H), 1.46–1.37 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ

= 203.3, 150.3, 134.2, 131.4, 118.2, 117.5, 115.9, 39.2, 27.2, 22.7, 14.1 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}NO$ ($[M+H]^+$): 178.1226, found: 178.1245.

1-(2-aminophenyl)octan-1-one (Table 6.2, Compound 2m) [27]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 1-hexanol (0.20 g, 2 mmol). After purification by column chromatography, the compound was isolated as colourless liquid (0.20 g, 0.8 mmol, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.1 Hz, 1H), 7.27–7.23 (m, 1H), 6.71–6.65 (m, 2H), 2.91(t, *J* = 7.6 Hz, 2H), 1.73–1.66 (m, 2H), 1.33–1.27 (m, 8H), 0.86 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4, 149.4, 134.3, 131.4, 118.7, 118.0, 116.6, 39.5, 31.9, 29.6, 29.3, 25.1, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}NO$ ($[M+H]^+$): 220.1696, found: 220.1705.

1-(2-aminophenyl)dodecan-1-one (Table 6.2, Compound 2n) [28]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 1-decanol (0.32 g, 2 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.23 g, 0.8 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 6.67–6.62 (m, 2H), 2.90 (t, *J* = 7.6 Hz, 2H), 1.73–1.65 (m, 2H), 1.32–1.24 (m, 16H), 0.86 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.4, 150.0, 134.2, 131.3, 118.4, 117.8, 116.2, 39.5, 32.0, 29.8, 29.8, 29.7, 29.6, 29.5, 25.1, 22.8, 14.2 ppm. HRMS (ESI): calcd. for $C_{18}H_{29}NO$ ($[M+Na]^+$): 298.2141, found: 298.2159.

1-(2-(benzylamino)phenyl)ethanone (Table 6.4, Compound 3a) [21b]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and benzyl alcohol (0.32 g, 3 mmol). After purification by column chromatography, the compound was isolated as a white solid

(0.21 g, 0.9 mmol, 95%). Mp = 78-79 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 1H), 7.34–7.26 (m, 6H), 6.78–6.66 (m, 2H), 4.47 (s, 2H), 2.60 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 149.9, 135.2, 132.8, 128.8, 127.5, 127.4, 118.8, 115.7, 113.4, 47.7, 28.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ ($[M+H]^+$): 226.1226, found: 226.1232.

1-(2-((4-methylbenzyl)amino)phenyl)ethanone (Table 6.4, Compound 3b) [32]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 4-methylbenzyl alcohol (0.37 g, 3 mmol). After purification by column chromatography, the compound was isolated as a bright yellow liquid (0.22 g, 0.9 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.19 (dd, *J* = 37.6, 7.7 Hz, 4H), 6.72–6.60 (m, 2H), 4.43 (s, 2H), 2.60 (s, 3H), 2.34 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 150.6, 137.0, 135.5, 135.2, 132.8, 129.5, 127.2, 127.1, 118.2, 114.9, 112.7, 46.9, 28.1, 21.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO$ ($[M+H]^+$): 240.1383, found: 240.1378.

1-(2-((4-fluorobenzyl)amino)phenyl)ethanone (Table 6.4, Compound 3c) [29]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 4-fluorobenzyl alcohol (0.38 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.21 g, 0.8 mmol, 87%). Mp = 85-86 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 1H), 7.33–7.29 (m, 3H), 7.02 (t, *J* = 8.7 Hz, 2H), 6.64–6.61 (m, 2H), 4.43 (s, 2H), 2.61 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 162.1 (d, *J* = 245.0 Hz), 150.8, 135.1, 134.5, 132.9, 128.7 (d, *J* = 8.0 Hz), 118.0, 115.6 (d, *J* = 21.4 Hz), 114.7, 112.2, 46.1, 28.1 ppm. ^{19}F NMR (376 MHz,

$CDCl_3$): δ = -116.7 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}FNO$ ($[M+H]^+$): 244.1132, found: 244.1121.

1-(2-((benzo[d][1,3]dioxol-5-ylmethyl)amino)phenyl)ethanone (Table 6.4, Compound 3d) [32]**:** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 3,4-methylenedioxybenzyl alcohol (0.46 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.25 g, 0.9 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.1 Hz, 1H), 7.34–7.28 (m, 1H), 6.82–6.74 (m, 3H), 6.67–6.59 (m, 2H), 5.92 (s, 2H), 4.35 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 150.8, 148.1, 146.8, 135.1, 132.8, 128.8, 120.3, 118.0, 114.6, 112.3, 108.4, 107.8, 101.1, 46.7, 28.1 ppm. HRMS (ESI): calcd. for $C_{16}H_{15}NO_3$ ($[M+H]^+$): 270.1125, found: 270.1113.

1-(2-((naphthalen-1-ylmethyl)amino)phenyl)ethanone (Table 6.4, Compound 3e) [29]**:** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 1-naphthylmethanol (0.48 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.24 g, 0.8 mmol, 88%). Mp = 109-110 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.9 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.57–7.47 (m, 3H), 7.43–7.39 (m, 1H), 7.33 (t, *J* = 8.6 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.66 (t, *J* = 7.6 Hz, 1H), 4.91 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 150.6, 135.2, 134.0, 132.8, 131.4, 129.0, 128.2, 126.5, 125.9, 125.7, 125.2, 123.1, 118.4, 115.1, 112.7, 45.1, 28.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{17}NO$ ($[M+H]^+$): 276.1383, found: 276.1380.

1-(2-(([1,1'-biphenyl]-2-ylmethyl)amino)phenyl)ethanone (Table 6.4, Compound 3f) [32]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 2-biphenylmethanol (0.55 g, 3 mmol). After purification by column chromatography, the compound was isolated as a white solid (0.22 g, 0.7 mmol, 73%). Mp = 107-108 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 1H), 7.49–7.23 (m, 10H), 6.59 (t, *J* = 8.0 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 4.35 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.0, 150.6, 141.7, 141.0, 135.8, 135.1, 132.8, 130.3, 129.2, 128.4, 128.0, 128.0, 127.3, 118.1, 118.0, 114.7, 114.5, 112.5, 112.3, 45.0, 28.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{19}NO$ ($[M+H]^+$): 302.1539, found: 302.1545.

1-(2-((furan-2-ylmethyl)amino)phenyl)ethanone (Table 6.4, Compound 3g) [21b]***:*** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 2-furyl methanol (0.29 g, 3 mmol). After purification by column chromatography, the compound was isolated as a red solid (0.16 g, 0.7 mmol, 72%). Mp = 71-72 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.1 Hz, 1H), 7.38–7.34 (m, 2H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.64 (t, *J* = 7.6 Hz, 1H), 6.32 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.24 (d, *J* = 3.9 Hz, 1H), 4.43 (s, 2H), 2.59 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.1, 152.2, 150.6, 142.1, 135.1, 132.8, 118.2, 114.9, 112.1, 110.5, 107.0, 40.3, 28.1 ppm. HRMS (ESI): calcd. for $C_{13}H_{13}NO_2$ ($[M+H]^+$): 216.1019, found: 216.1012.

1-(4-(benzylamino)phenyl)ethanone (Table 6.4, Compound 3h) [30]***:*** Prepared from 4'-aminoacetophenone (0.14 g, 1 mmol) and benzyl alcohol (0.32 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.15 g, 0.6 mmol, 68%). Mp = 84–85 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.6 Hz, 2H), 7.36–7.27 (m, 5H), 6.63 (d, *J* = 8.6 Hz, 2H), 4.68 (s, 2H), 2.49 (s, 3H)

ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.9, 151.4, 141.0, 130.9, 128.6, 127.6, 127.1, 113.8, 65.3, 26.1 ppm. HRMS (ESI): calcd. for $C_{15}H_{15}NO$ ($[M+H]^+$): 226.1226, found: 226.1237.

1-(2-(benzylamino)-5-methoxyphenyl)ethanone (Table 6.4, Compound 3i) [32]***:*** Prepared from 1-(2-amino-5-methoxyphenyl)ethanone (0.17 g, 1 mmol) and benzyl alcohol (0.32 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.16 g, 0.6 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.23 (m, 6H), 7.00 (dd, *J* = 9.2, 3.0 Hz, 1H), 6.64 (d, *J* = 9.2 Hz, 1H), 4.44 (s, 2H), 3.77 (s, 3H), 2.60 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.6, 149.1, 146.1, 139.1, 134.6, 129.9, 128.8, 127.1, 123.4, 116.3, 113.7, 56.3, 47.3, 28.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{17}NO_2$ ($[M+H]^+$): 256.1332, found: 256.1338.

1-(4-(benzylamino)-[1,1'-biphenyl]-3-yl)ethanone (Table 6.4, Compound 3j) [32]***:*** Prepared from 1-(4-amino-[1,1'-biphenyl]-3-yl)ethanone (0.21 g, 1 mmol) and benzyl alcohol (0.32 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.24 g, 0.7 mmol, 78%). Mp = 104-105 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 2.2 Hz, 1H), 7.60–7.53 (m, 3H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.38–7.30 (m, 6H), 6.77 (d, *J* = 8.8 Hz, 1H), 4.53 (d, *J* = 5.6 Hz, 2H), 2.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.2, 150.3, 140.7, 138.7, 133.9, 131.2, 129.0, 128.8, 127.6, 127.3, 127.1, 126.6, 126.3, 118.2, 112.9, 46.9, 28.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{19}NO$ ($[M+H]^+$): 302.1539, found: 302.1504.

1-(2-(benzylamino)-5-fluorophenyl)ethanone (Table 6.4, Compound 3k) [32]**:** Prepared from 1-(2-amino-5-fluorophenyl)ethanone (0.15 g, 1 mmol) and benzyl alcohol (0.32 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.12 g, 0.5 mmol, 49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (dd, *J* = 9.8, 3.0 Hz, 1H), 7.32–7.19 (m, 5H), 6.94–6.89 (m, 1H), 6.40 (dd, *J* = 9.3, 4.5 Hz, 1H), 4.66 (s, 1H), 3.15 (d, *J* = 6.8 Hz, 2H), 2.58 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1, 153.9, 146.8, 140.3 (d, *J* = 504.9 Hz), 129.6, 128.6 (d, *J* = 31.3 Hz), 127.1 (d, *J* = 61.5 Hz), 126.6, 122.7 (d, *J* = 22.9 Hz), 117.3 (d, *J* = 22.1 Hz), 114.6 (d, *J* = 6.9 Hz), 45.4, 28.1 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = -131.11 ppm. HRMS (ESI): calcd. for $C_{15}H_{14}FNO$ ($[M+H]^+$): 244.1132, found: 244.1111.

1-(2-(butylamino)phenyl)ethanone (Table 6.4, Compound 3l) [32]**:** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 1-butanol (0.22 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow liquid (0.08 g, 0.4 mmol, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.57 (t, *J* = 7.5 Hz, 1H), 3.20 (t, *J* = 7.0 Hz, 2H), 2.57 (s, 3H), 1.71–1.64 (m, 2H), 1.51–1.42 (m, 2H), 0.98 (d, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.9, 151.3, 135.1, 133.0, 117.5, 113.9, 111.9, 42.5, 31.3, 28.0, 20.5, 14.0 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}NO$ ($[M+H]^+$): 192.1383, found: 192.1378.

1-(2-(hexylamino)phenyl)ethanone (Table 6.4, Compound 3m) [32]**:** Prepared from 2'-aminoacetophenone (0.14 g, 1 mmol) and 1-hexanol (0.31 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow

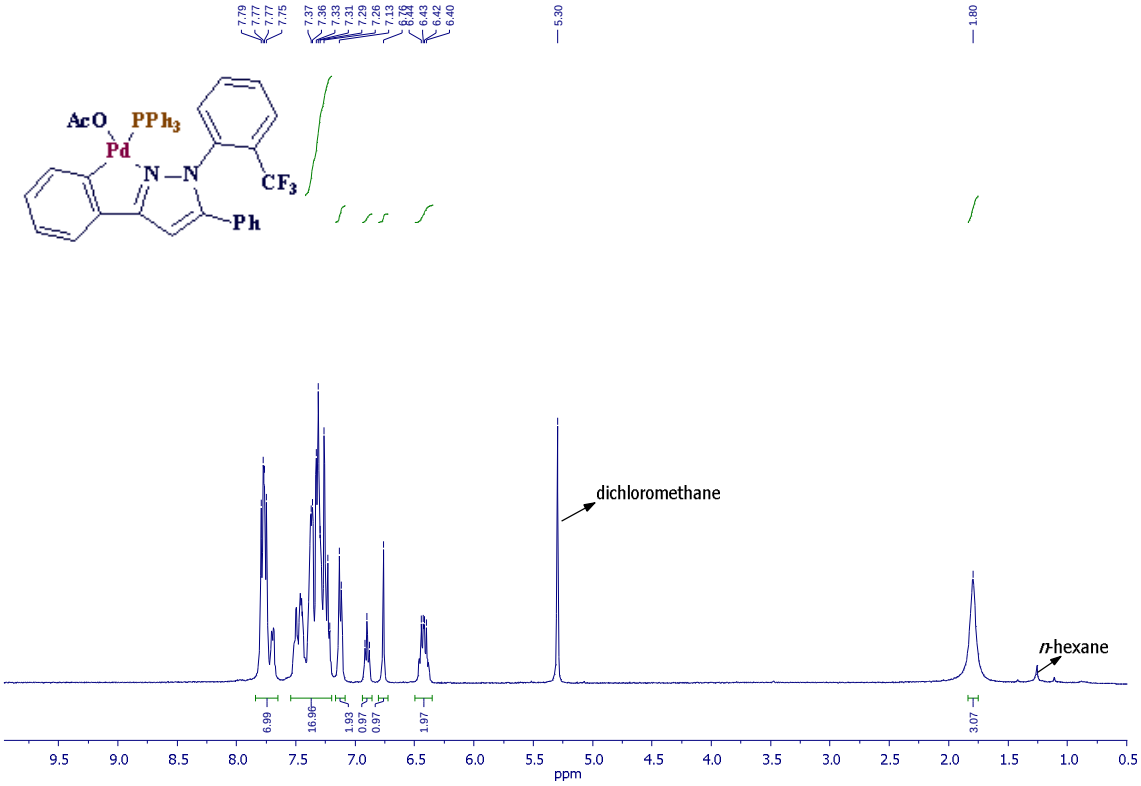
liquid (0.05 g, 0.2 mmol, 22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.35 (t, *J* = 7.0 Hz, 1H), 6.70 (d, *J* = 8.6 Hz, 1H), 6.57 (t, *J* = 7.0 Hz, 1H), 3.22–3.16 (m, 2H), 2.58 (s, 3H), 1.73–1.65 (m, 2H), 1.48–1.27 (m, 6H), 0.91 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$); δ = 200.8, 151.3, 135.1, 132.9, 117.4, 113.7, 111.8, 42.8, 31.7, 29.2, 28.0, 27.0, 22.7, 14.2 ppm. HRMS (ESI): calcd. for $C_{14}H_{21}NO$ ($[M+H]^+$): 220.1696, found: 220.1704.

5,6-dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydro-1H-inden-1-one (scheme 6.2, Compound 4) [31]**:** Prepared from 5,6-dimethoxy indanone (0.19 g, 1 mmol) and 4-piperidinemethanol (0.35 g, 3 mmol). After purification by column chromatography, the compound was isolated as a yellow solid (0.15 g, 0.5 mmol, 51%). Mp = 97-98 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (s, 1H), 6.85 (s, 1H), 3.95 (s, 1H), 3.90 (s, 1H), 3.23 (dd, *J* = 17.5, 8.1 Hz, 1H), 3.11–3.06 (m, 2H), 2.74–2.57 (m, 4H), 1.93–1.86 (m, 1H), 1.77–1.61 (m, 2H), 1.34–1.11 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 155.6, 149.6, 148.9, 129.5, 107.5, 104.5, 56.3, 56.2, 46.9, 46.8, 45.3, 39.5, 35.0, 34.5, 33.4, 33.1 ppm. HRMS (ESI): calcd. for $C_{17}H_{23}NO_3$ ($[M+H]^+$): 290.1751, found: 290.1763.

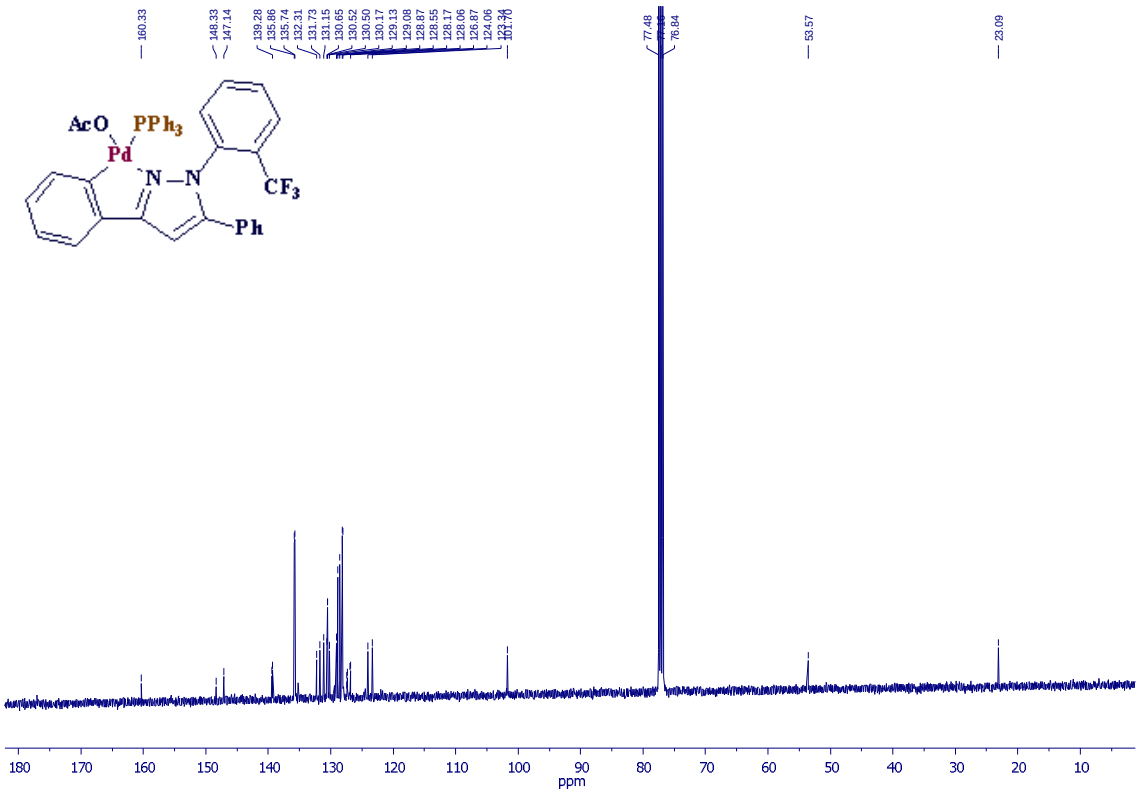
2-((1-benzylpiperidin-4-yl)methyl)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (scheme 6.2, Compound 5) [32]**:** Prepared from 5,6-dimethoxy-2-(piperidin-4-ylmethyl)-2,3-dihydro-1H-inden-1-one (0.14 g, 0.5 mmol) and benzylalcohol (0.16 g, 1.5 mmol). After purification by column chromatography, the compound was isolated as a yellow semi-liquid (0.11 g, 0.5 mmol, 56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.31 (m, 4H), 7.27–7.23 (m, 1H), 7.15 (s, 1H), 6.84 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 3.56 (s, 2H), 3.22 (dd, *J* = 17.6, 8.1 Hz, 1H), 2.96–2.92 (m, 2H), 2.71–2.65

(m, 2H), 2.06–1.99 (m, 2H), 1.93–1.86 (m, 1H), 1.71–1.67 (m, 2H), 1.45–1.25 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.8, 155.6, 149.5, 148.8, 137.6, 129.5, 129.4, 128.3, 127.3, 107.4, 104.5, 63.2, 56.3, 56.2, 45.5, 38.7, 34.3, 33.5, 32.7, 31.6. HRMS (ESI): calcd. for $C_{24}H_{29}NO_3$ ([M+H]$^+$): 380.2220, found: 380.2245.

6.5 NMR spectra for new compounds



^{1}H NMR of P-PPh_3



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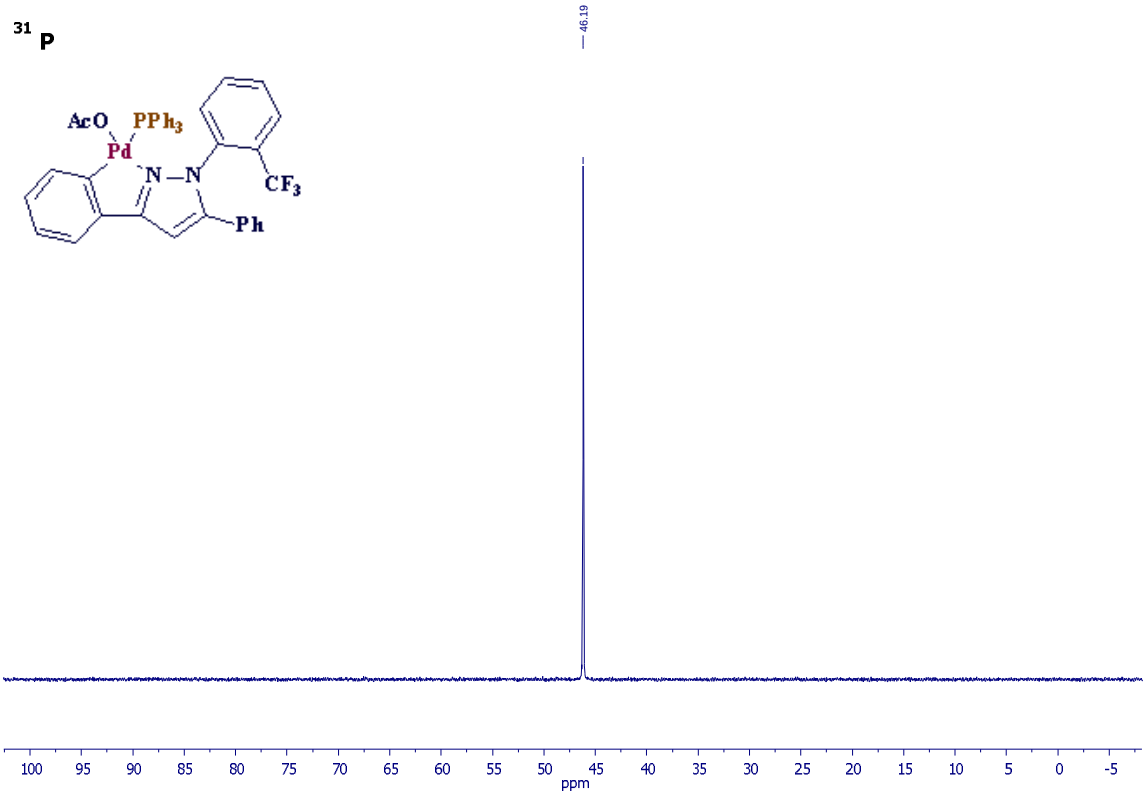

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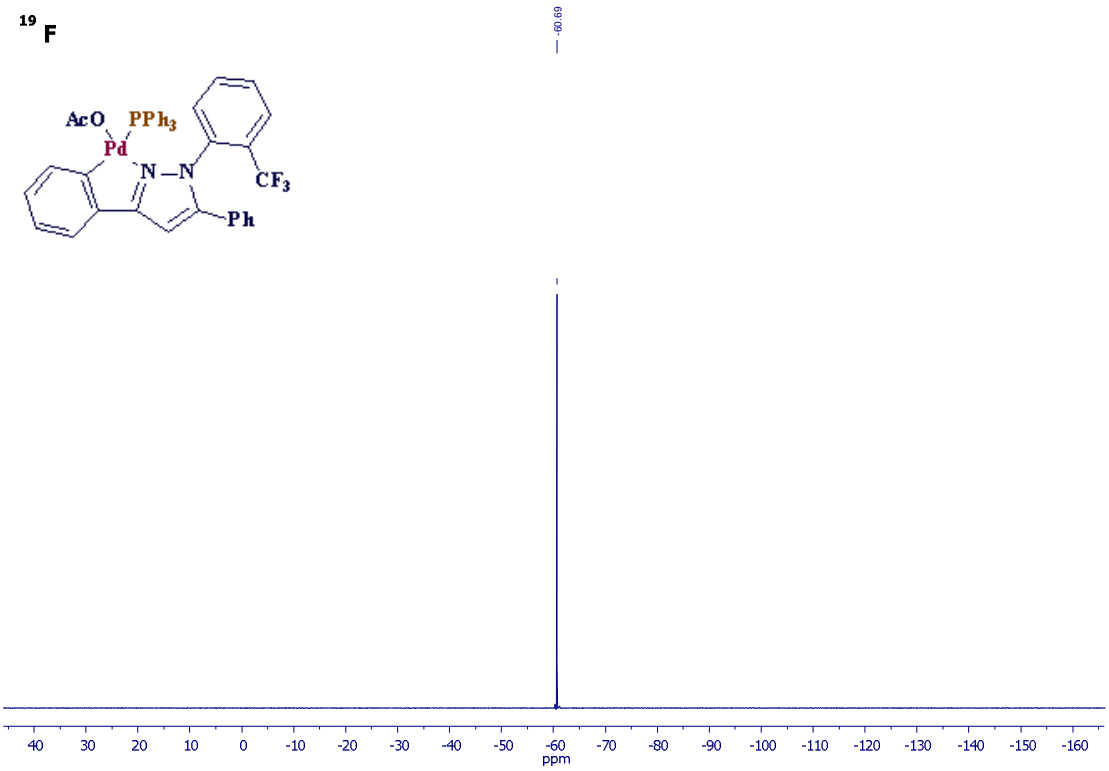

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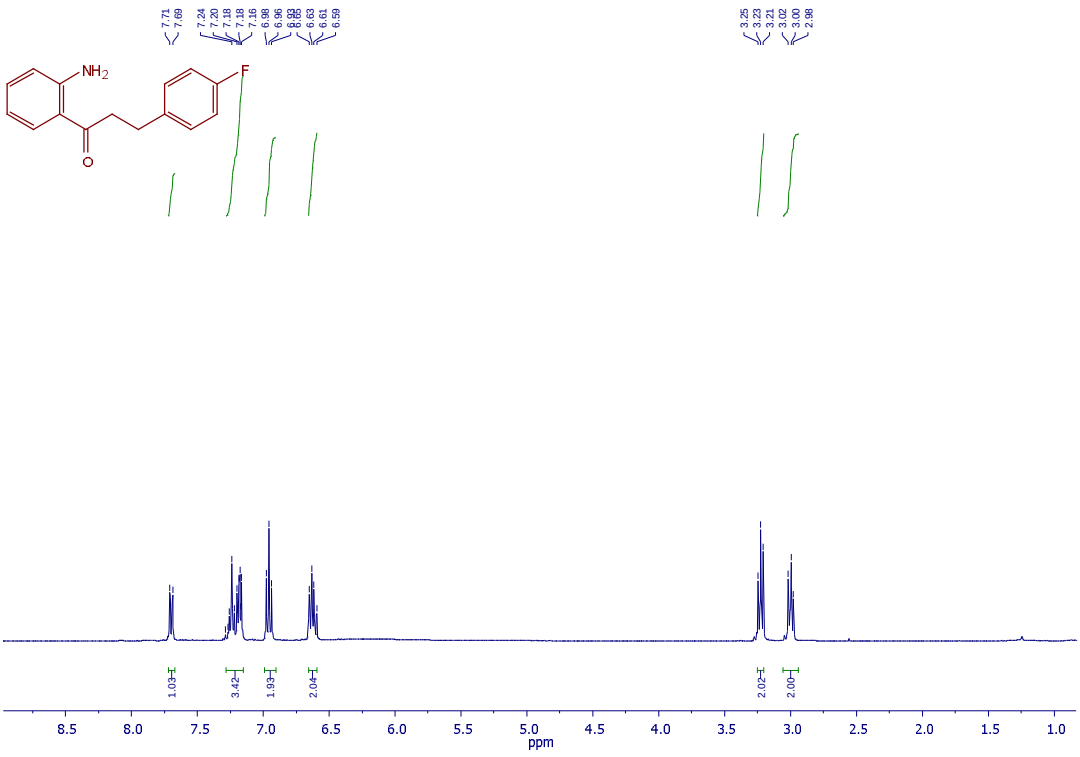
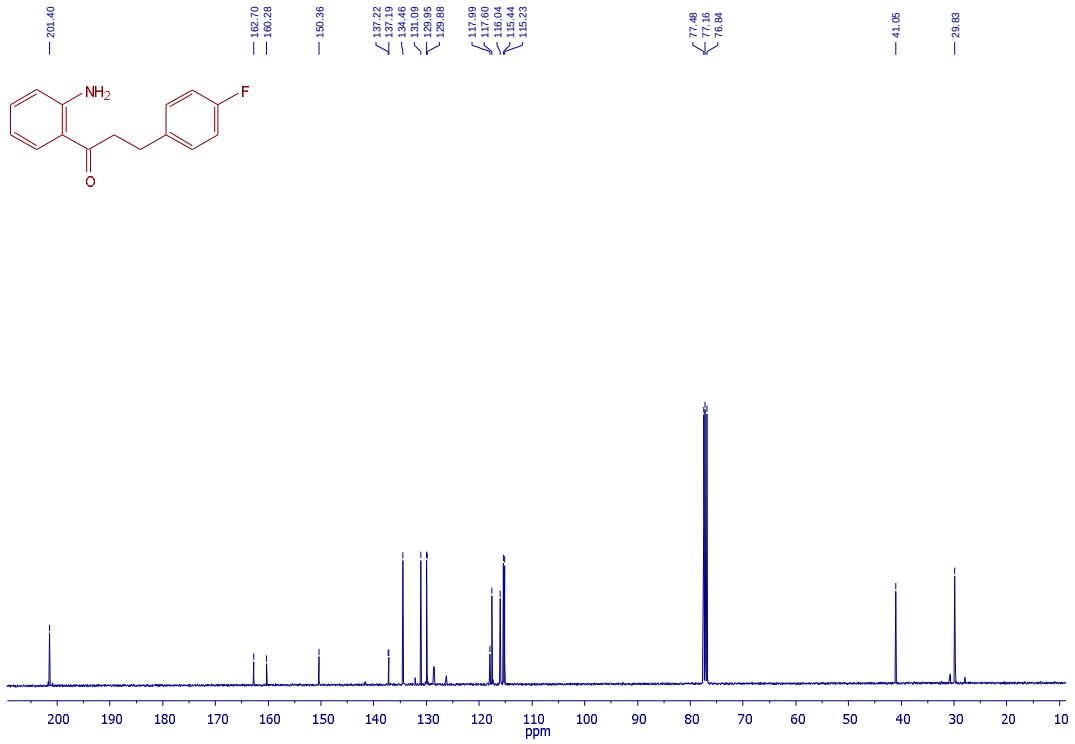


^{1}H NMR of Compound 2b



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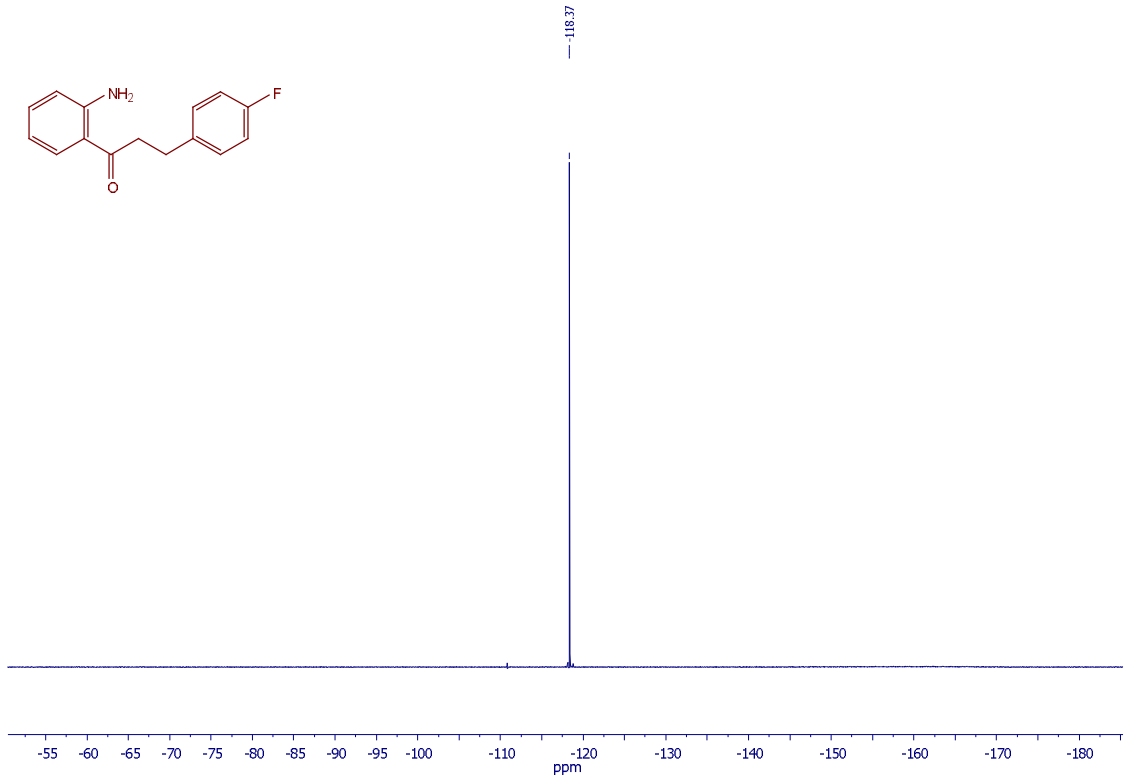

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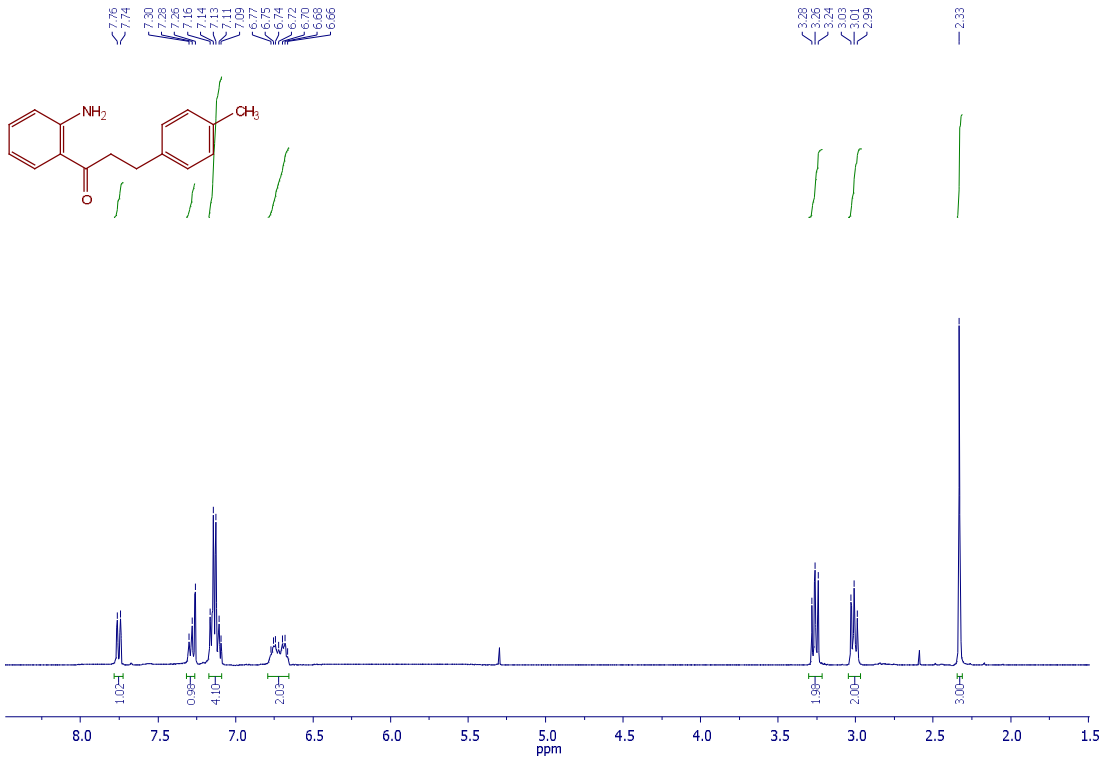

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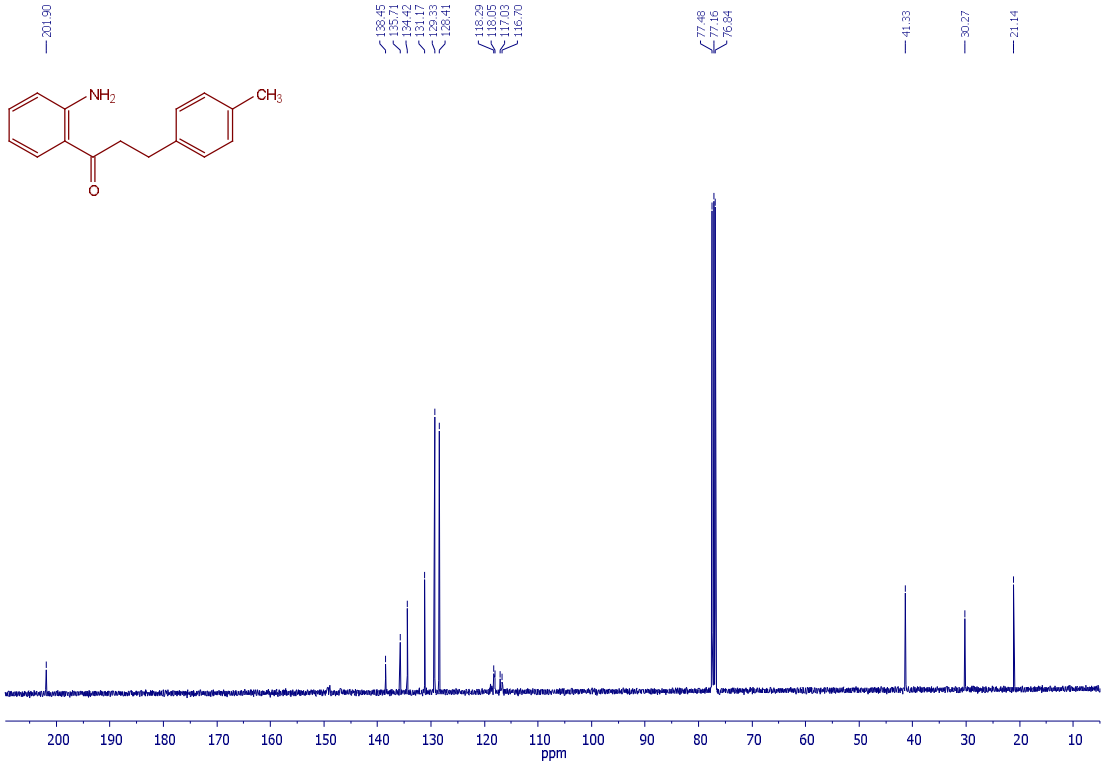

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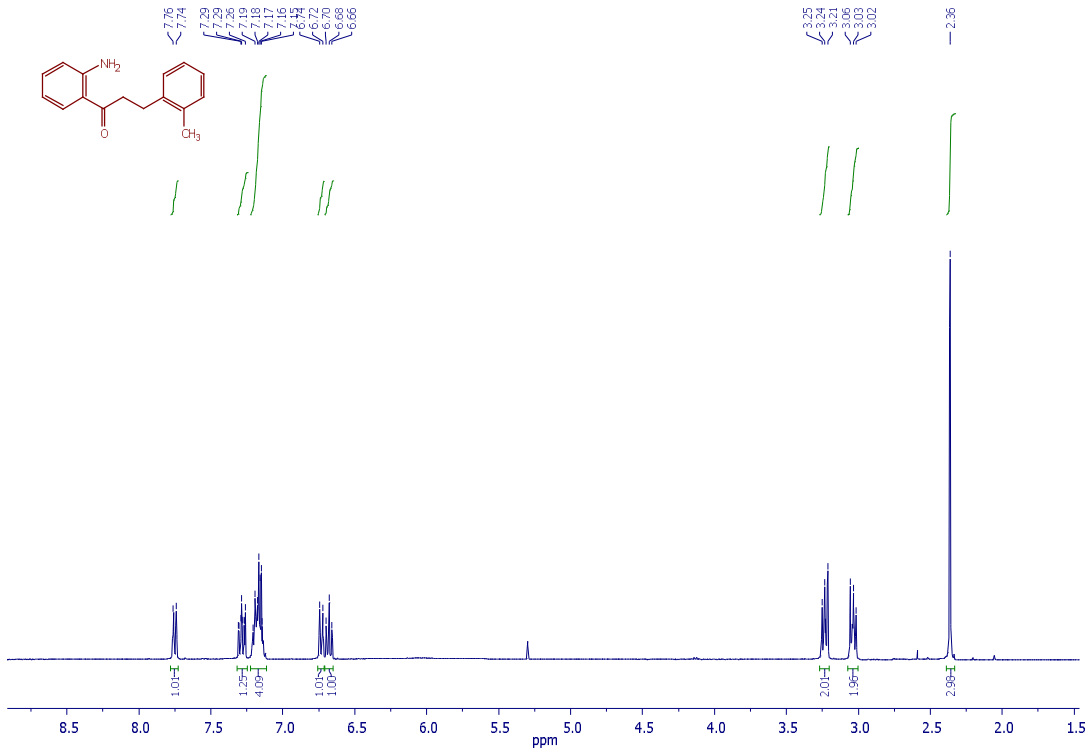

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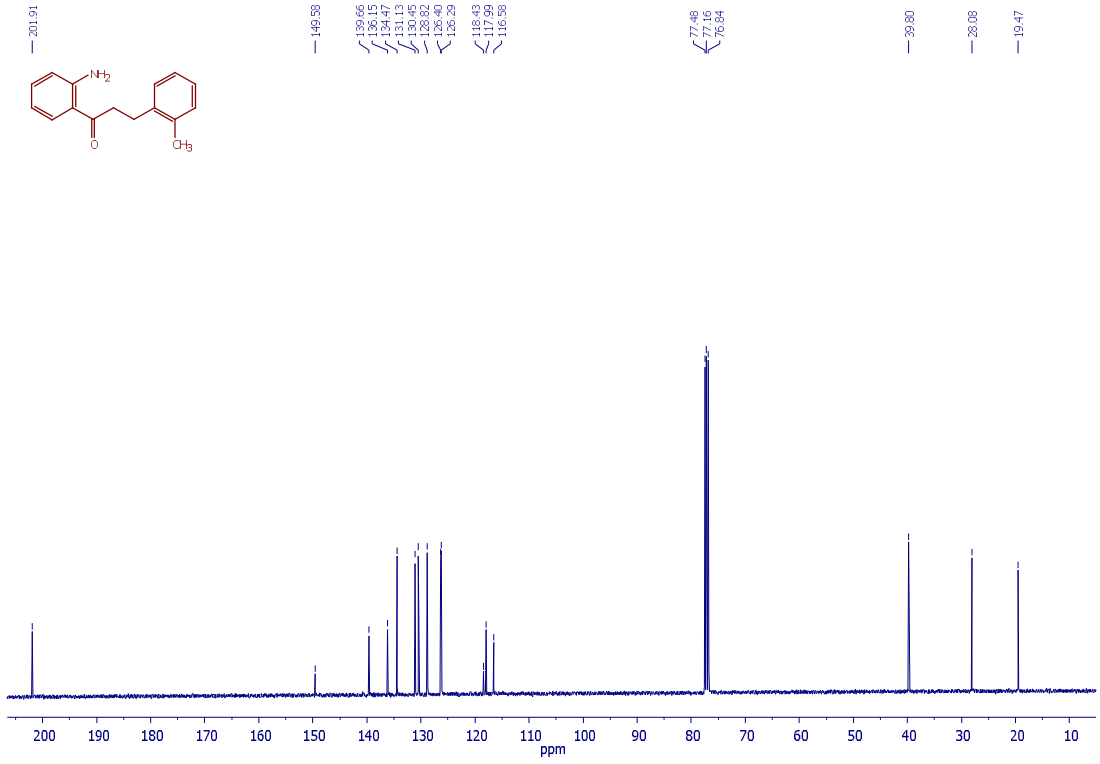

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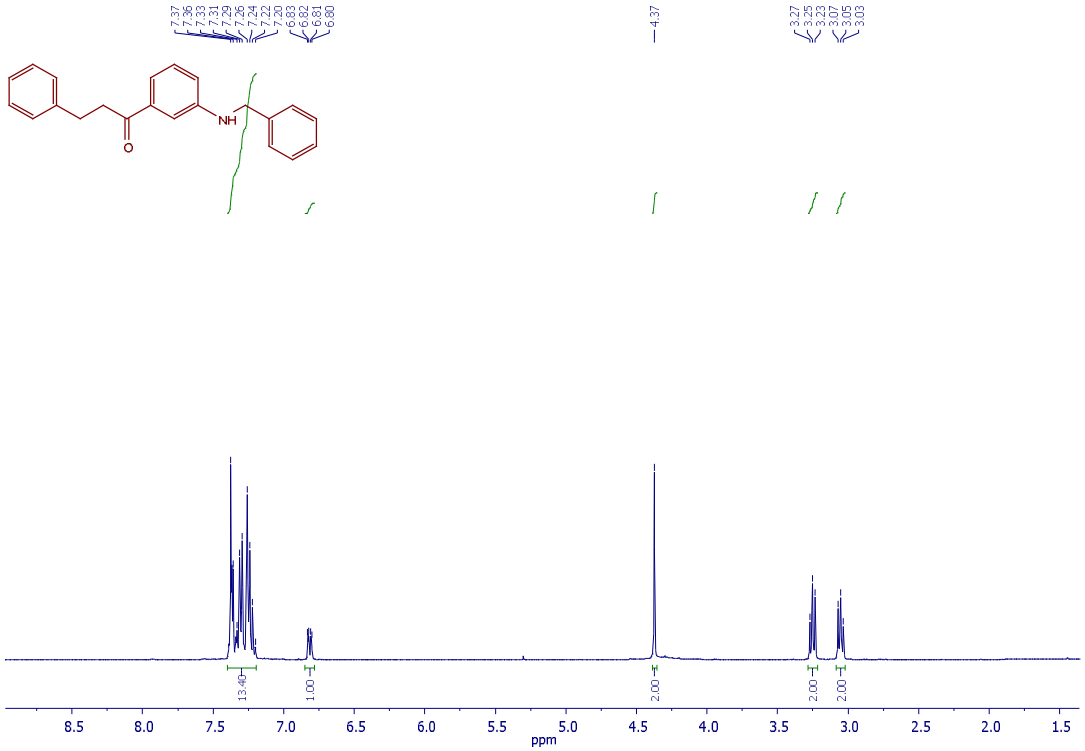
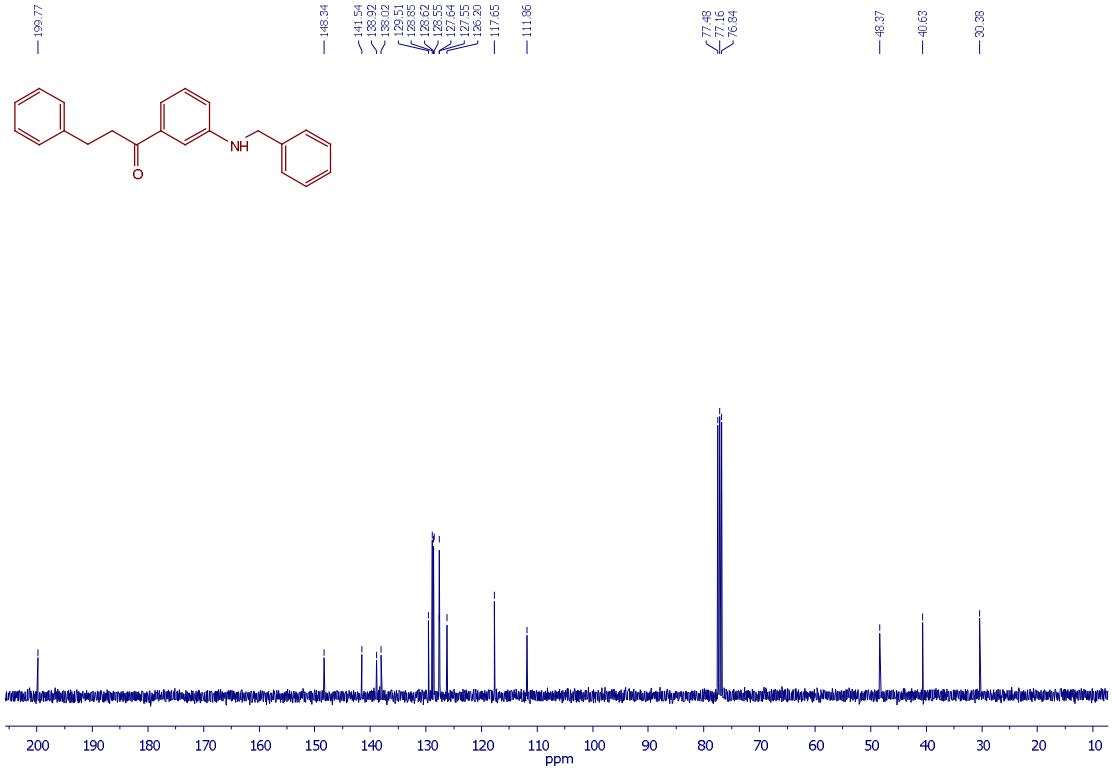


^{1}H NMR of Compound 2f



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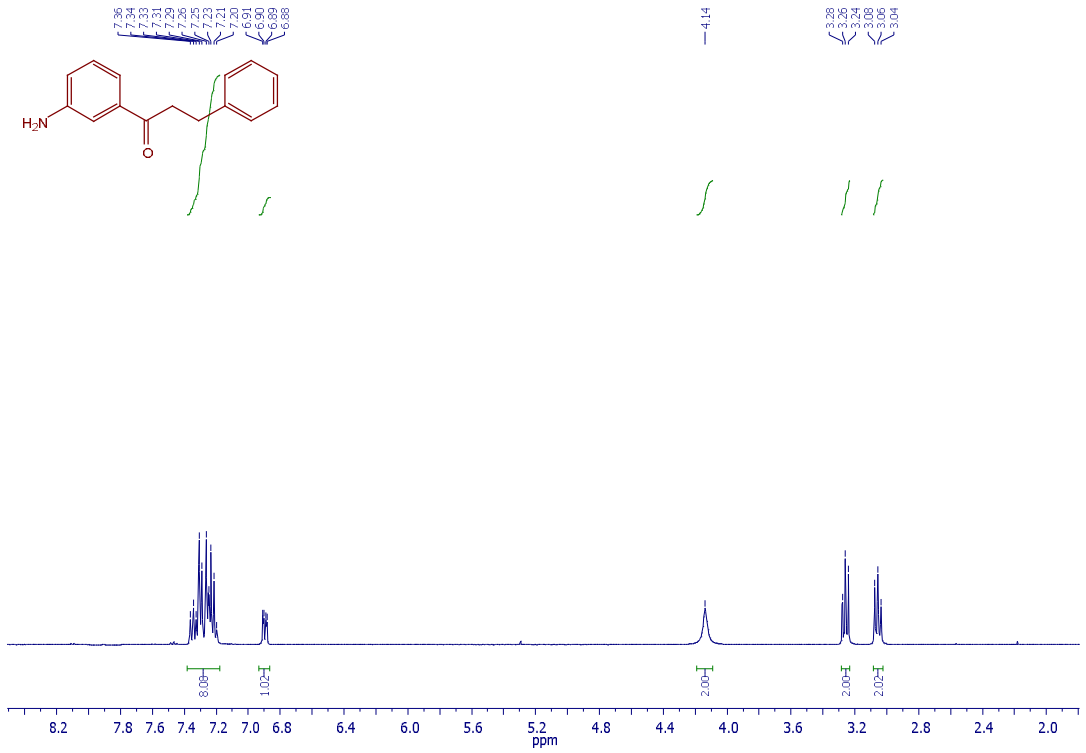
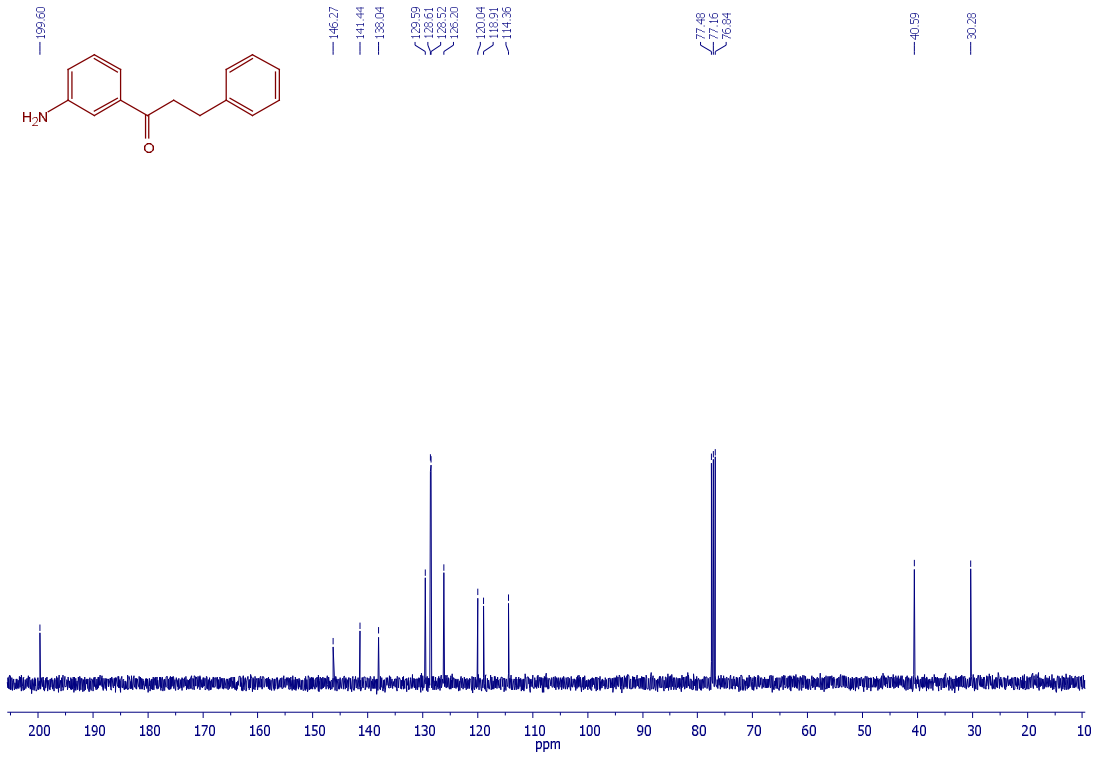
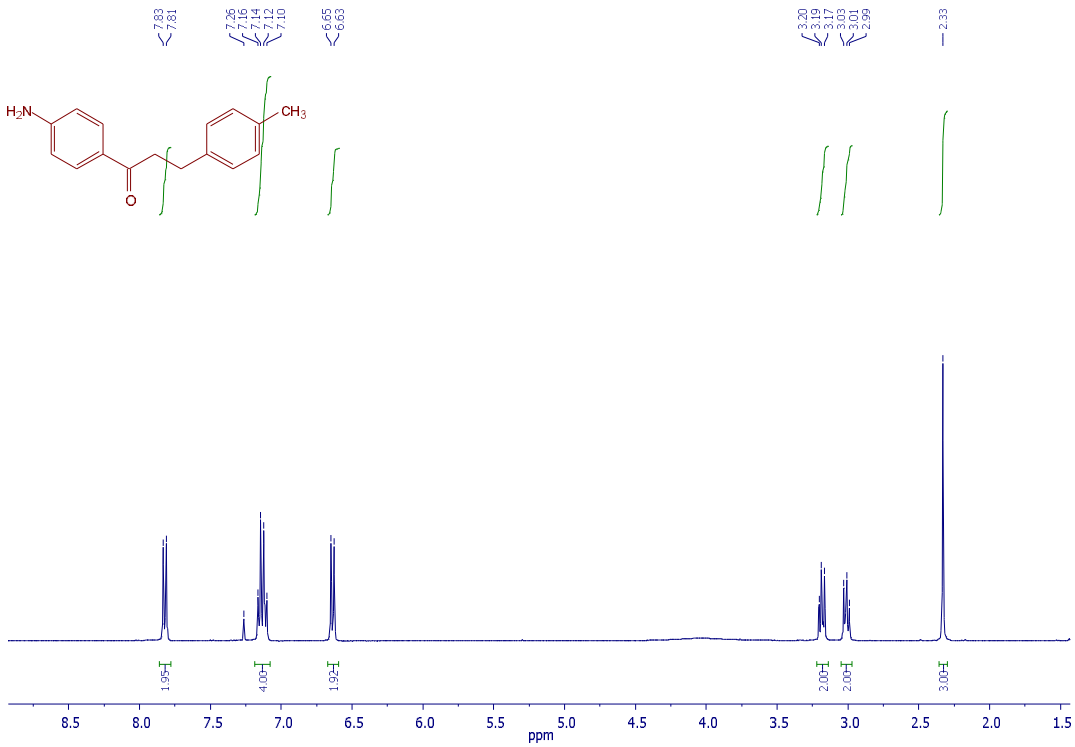


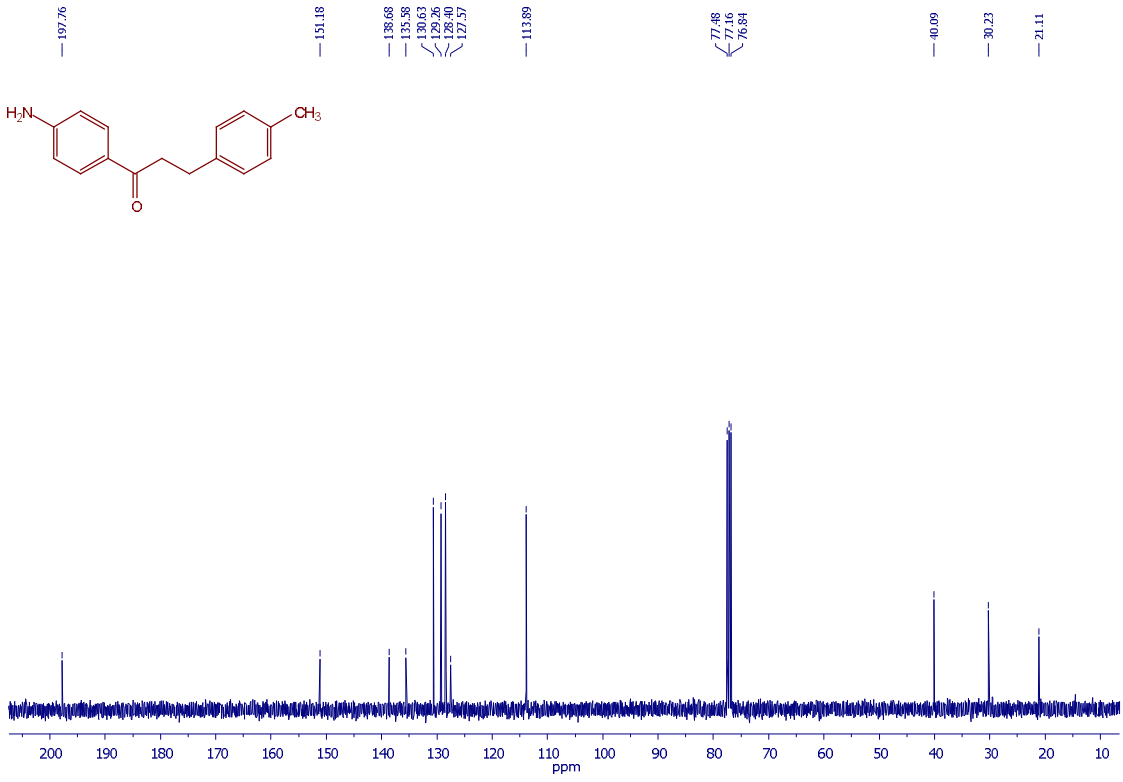
^{1}H NMR of Compound 2g



^{13}C NMR of Compound 2g



^{1}H NMR of Compound 2i



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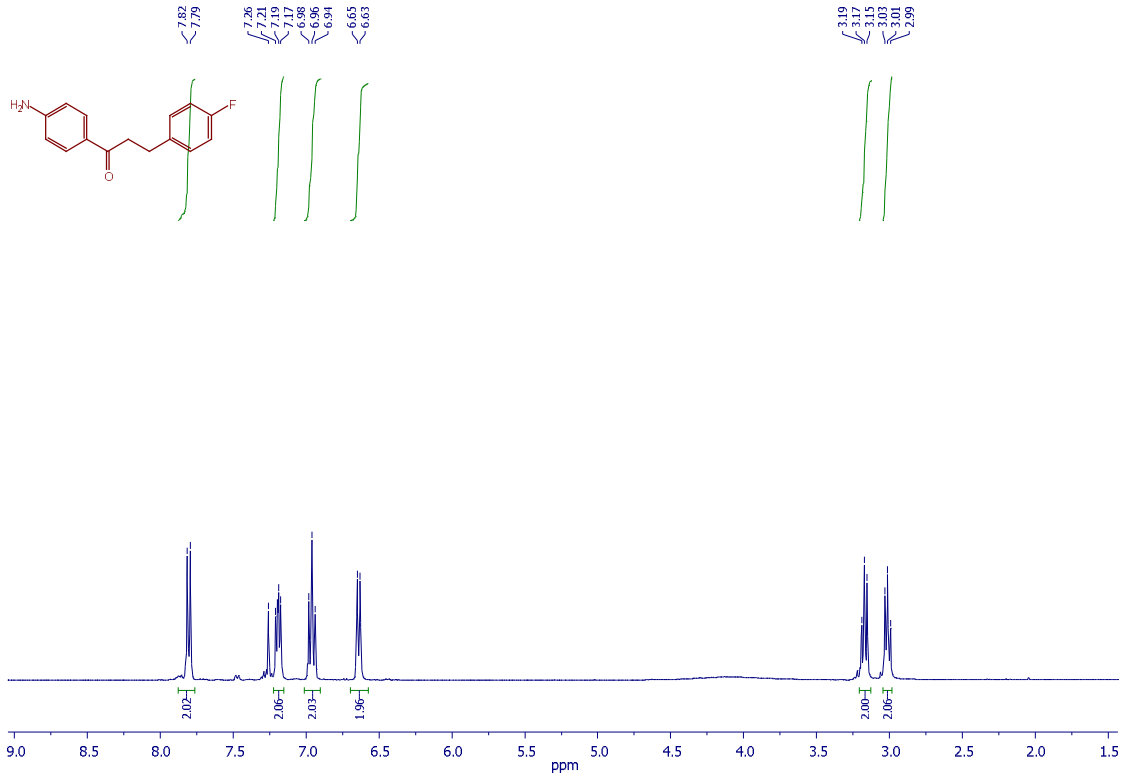

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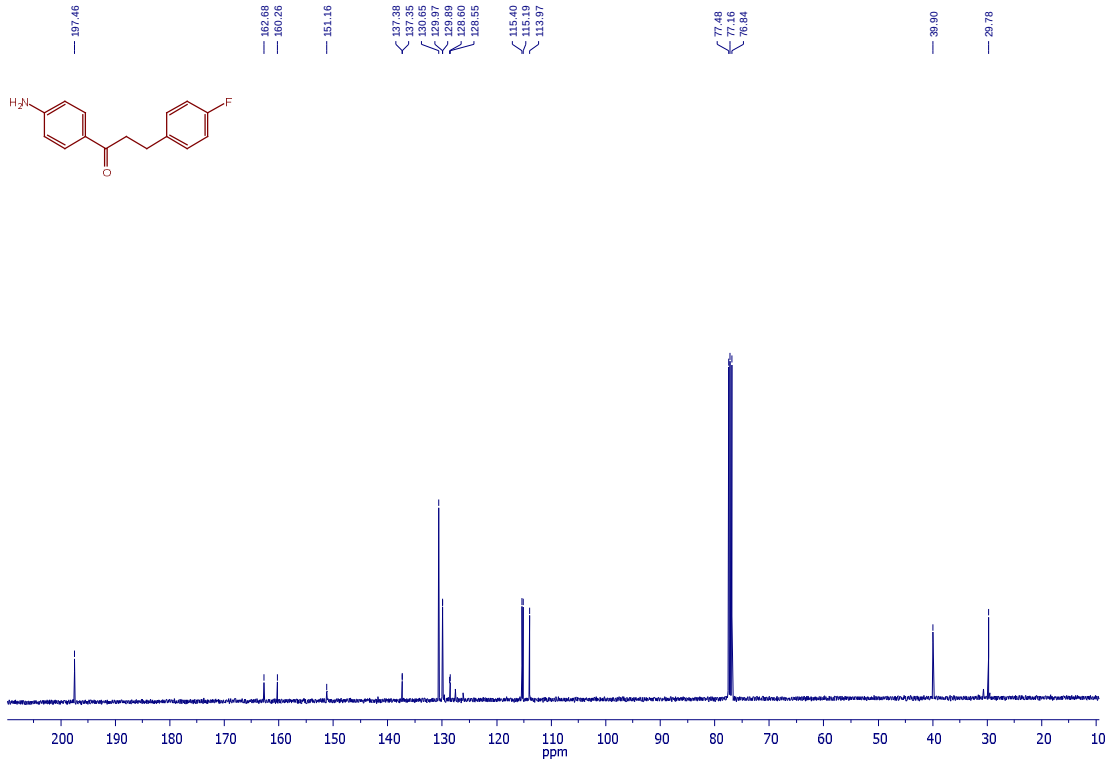

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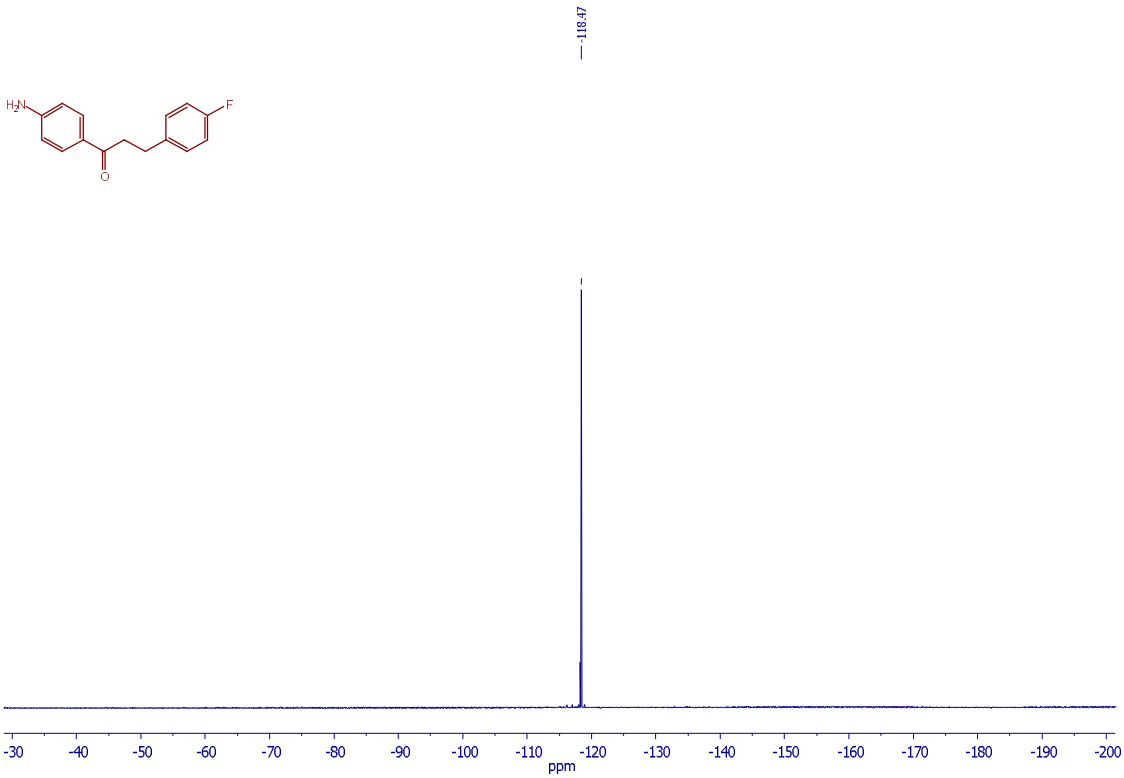
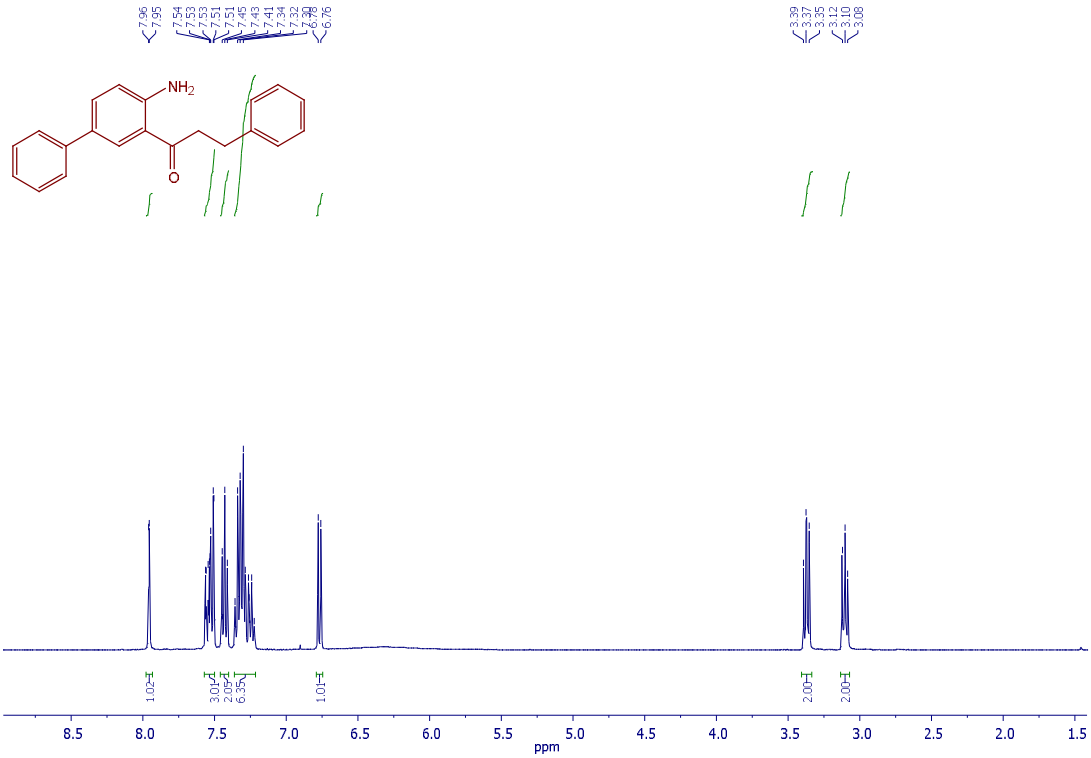
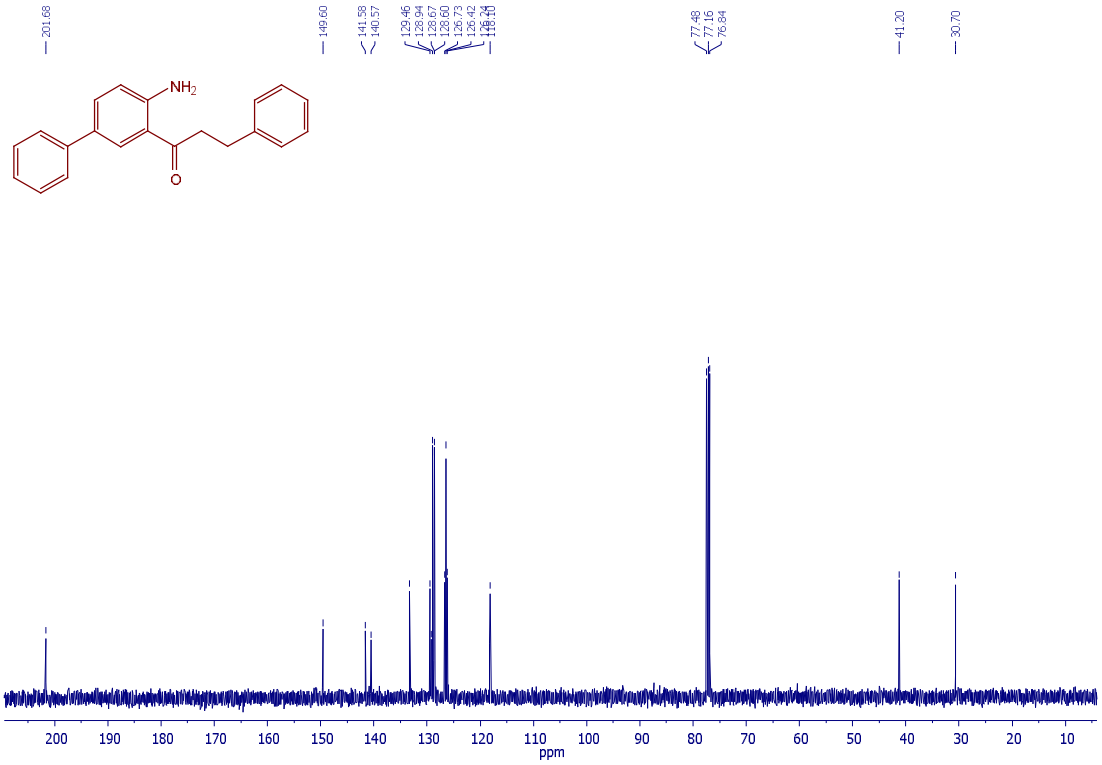


^{19}F NMR of Compound 2j



^{1}H NMR of Compound 2k



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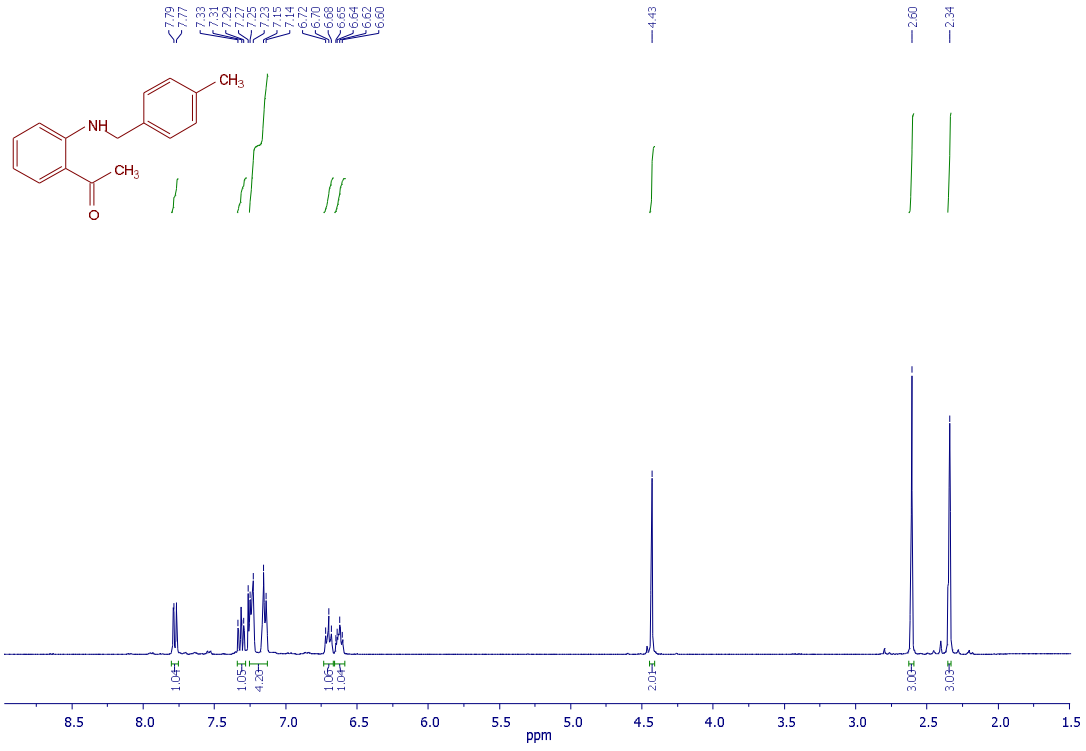
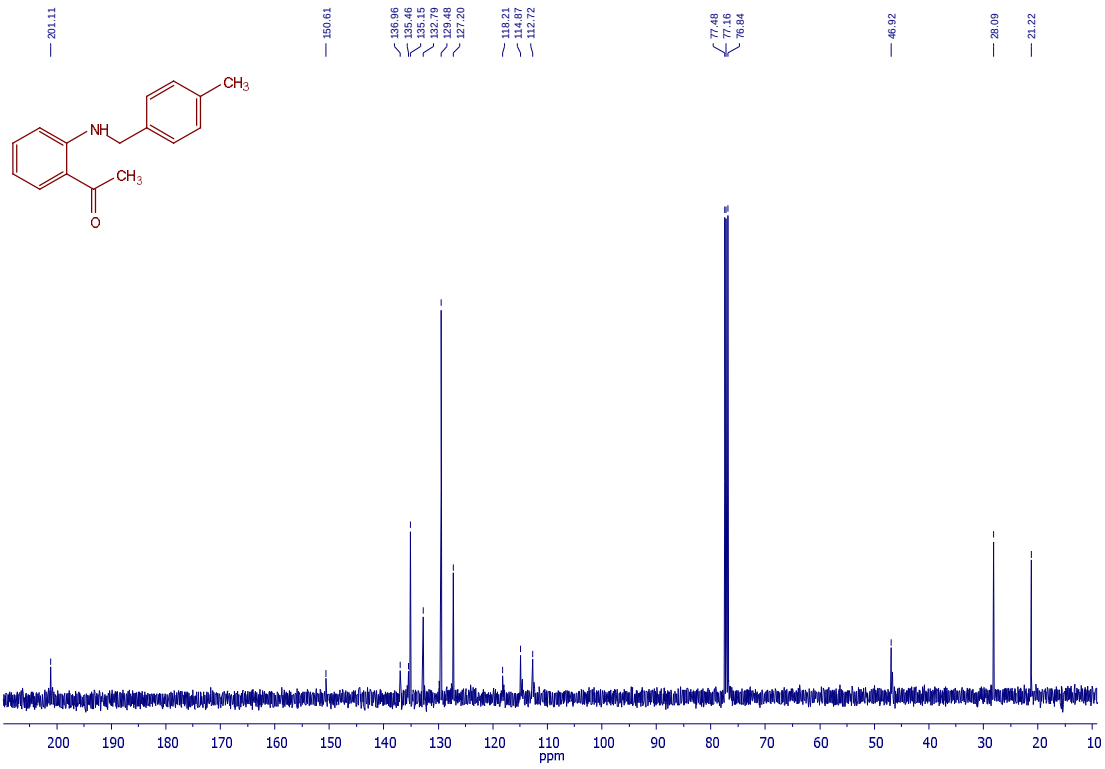


^{1}H NMR of Compound 3b



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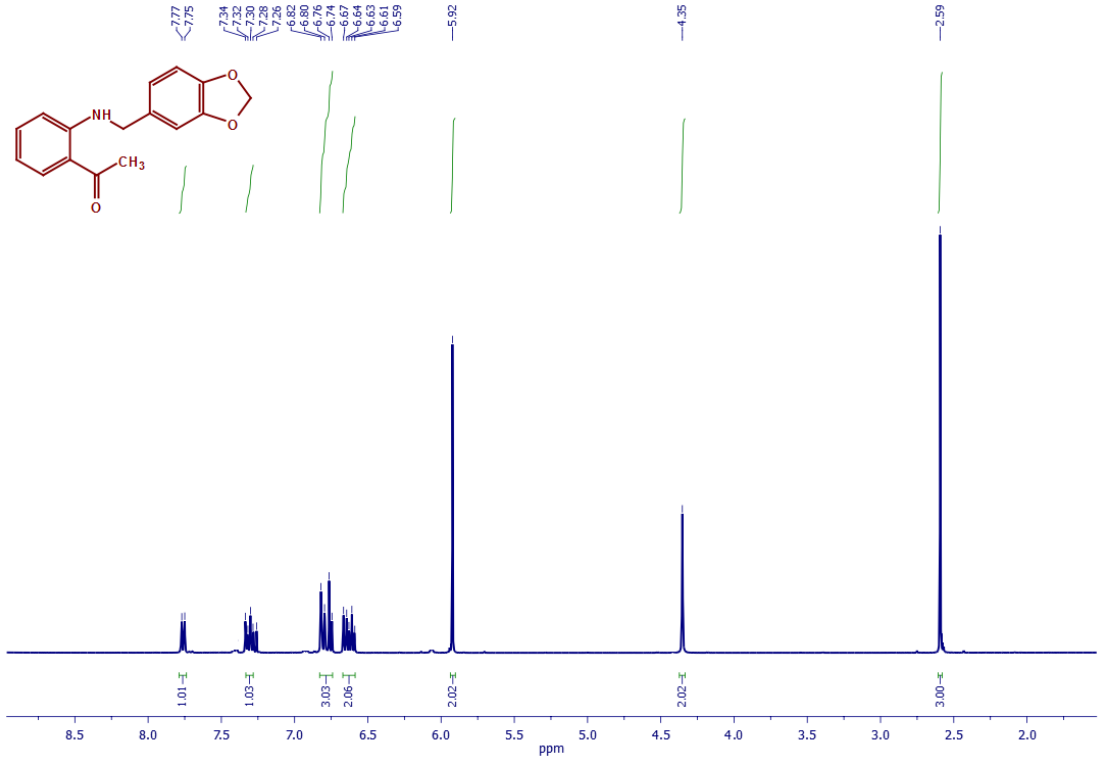

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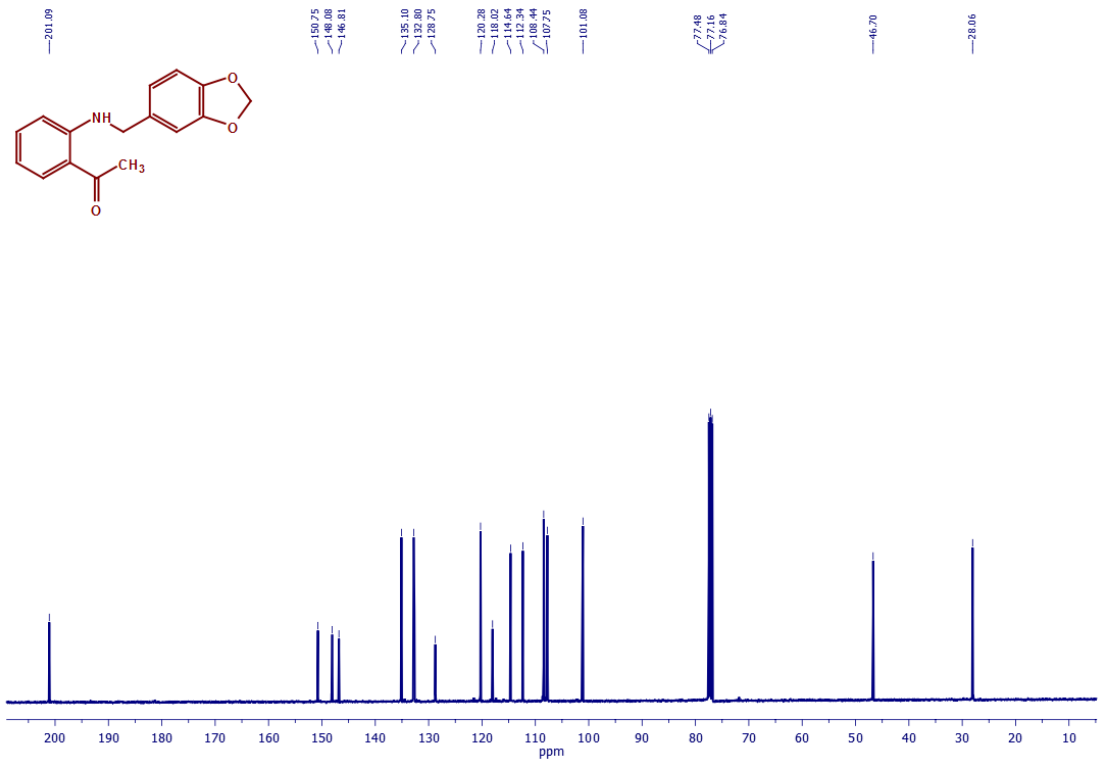

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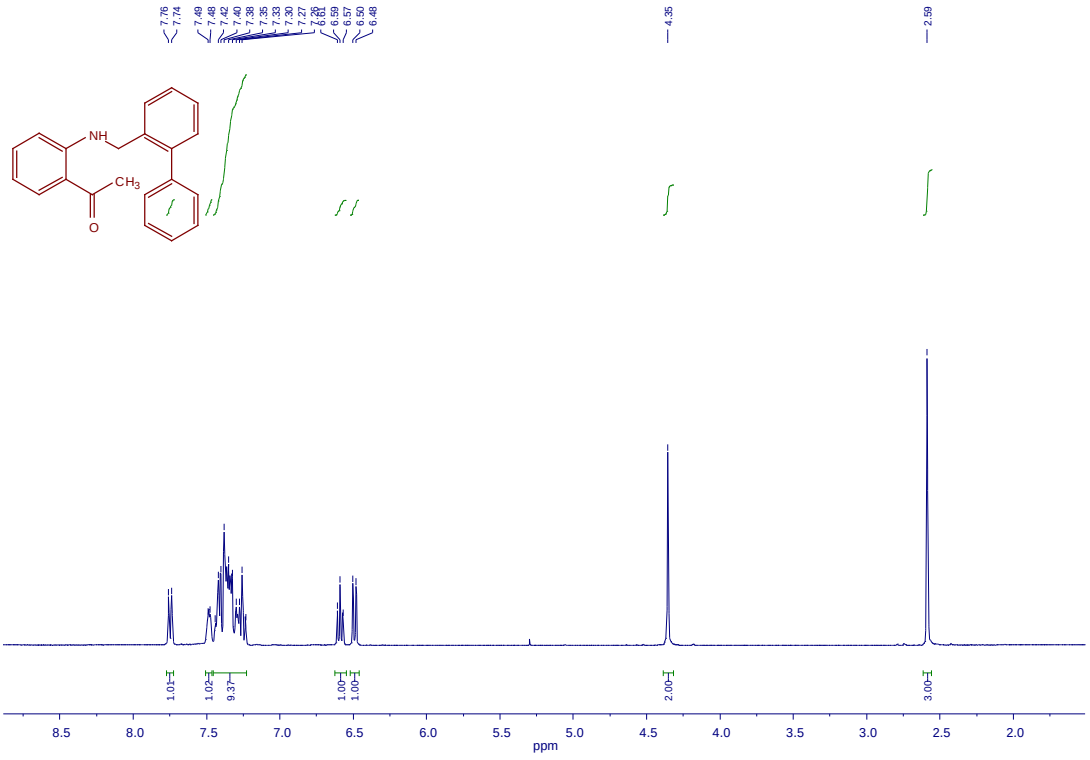

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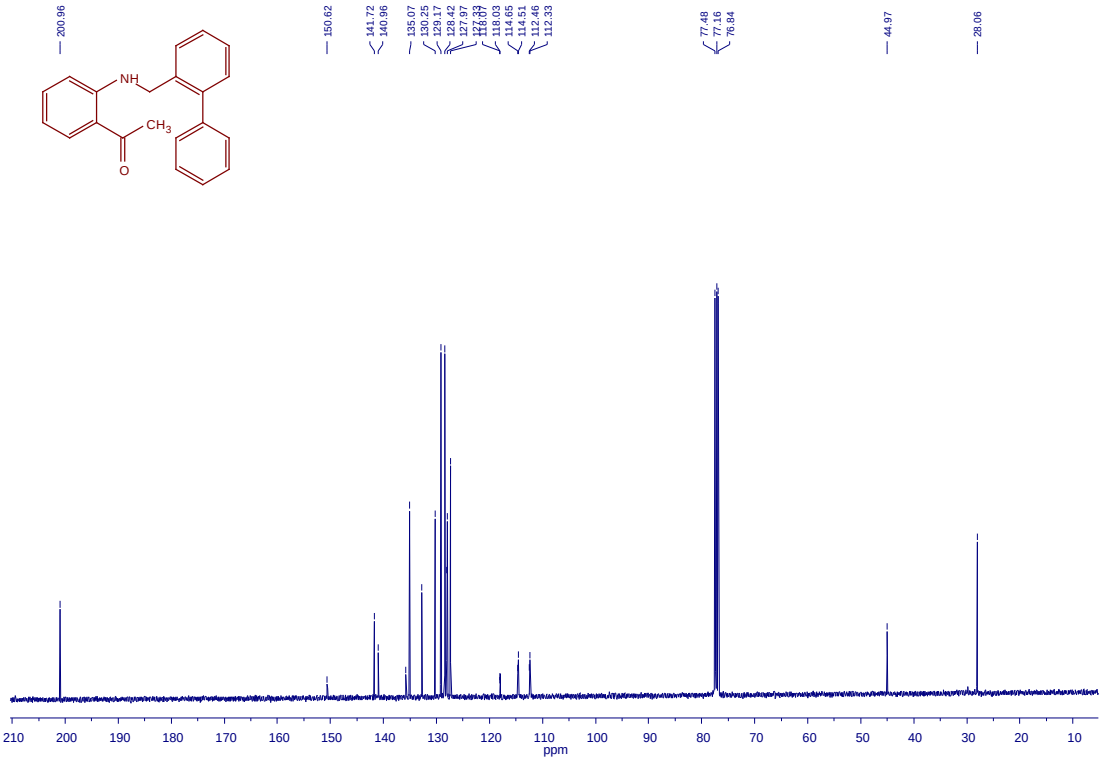

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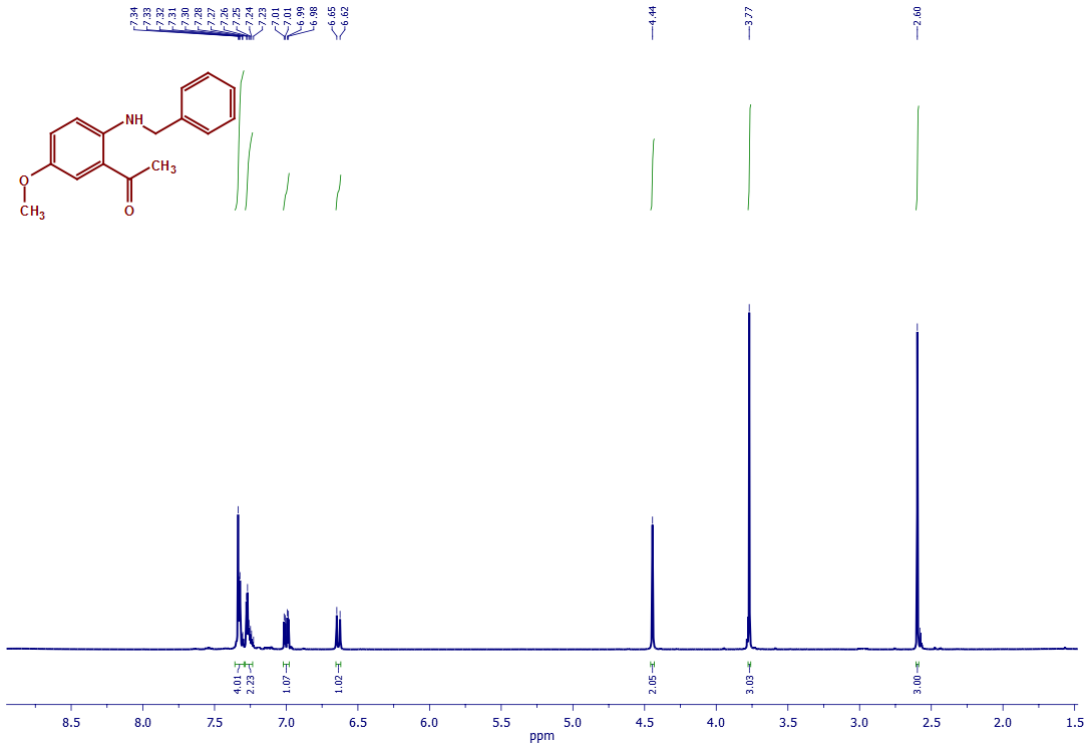

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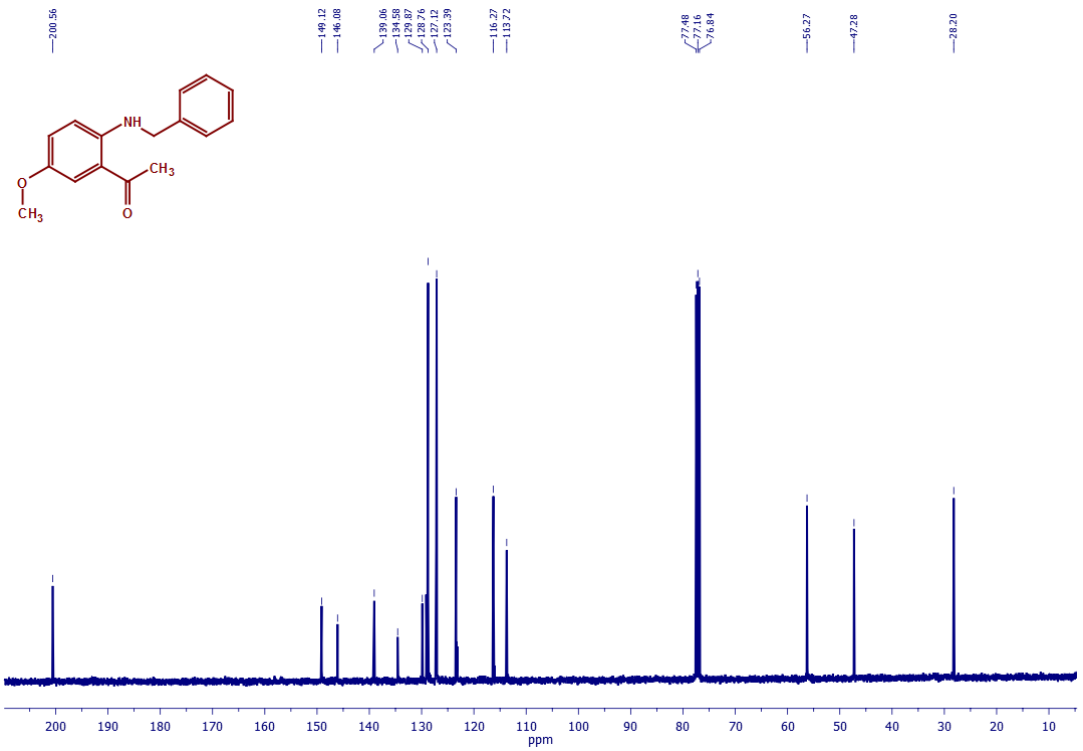

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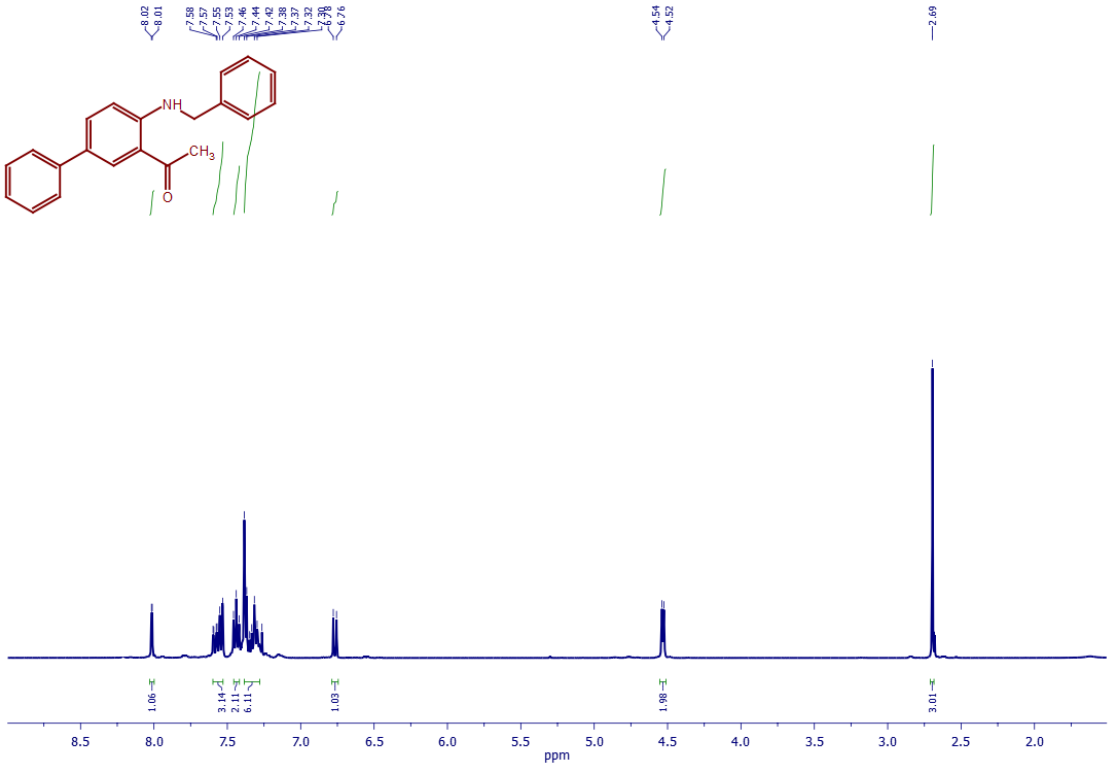

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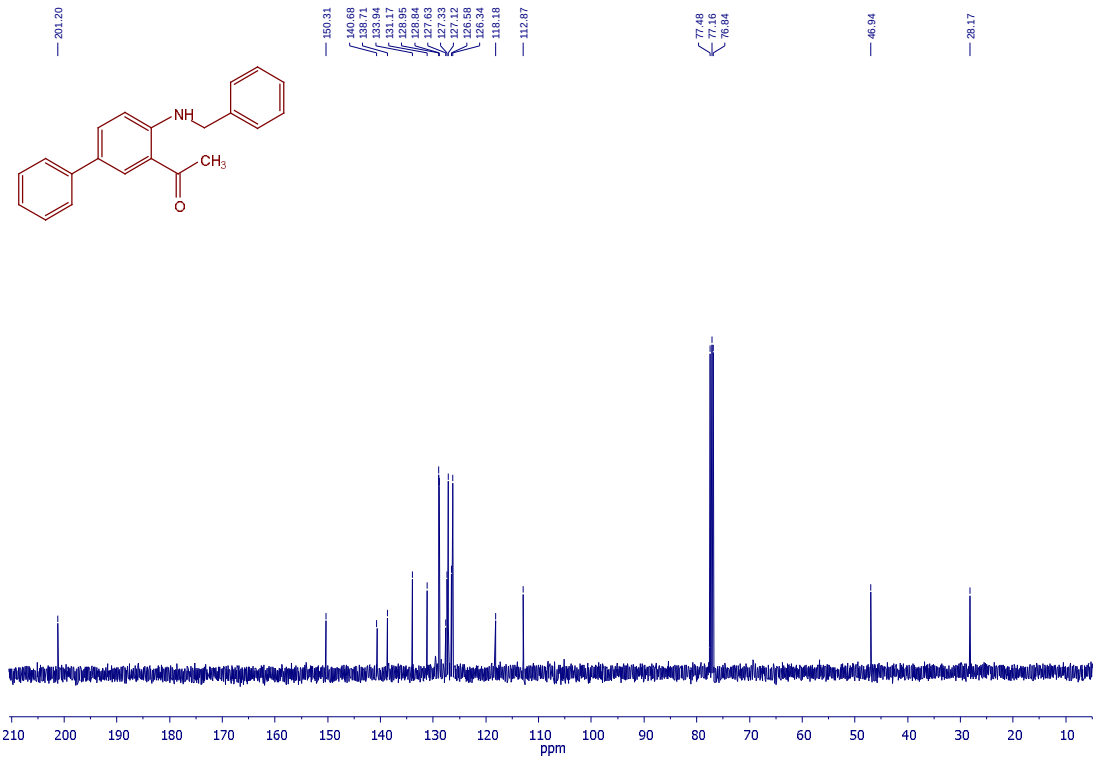

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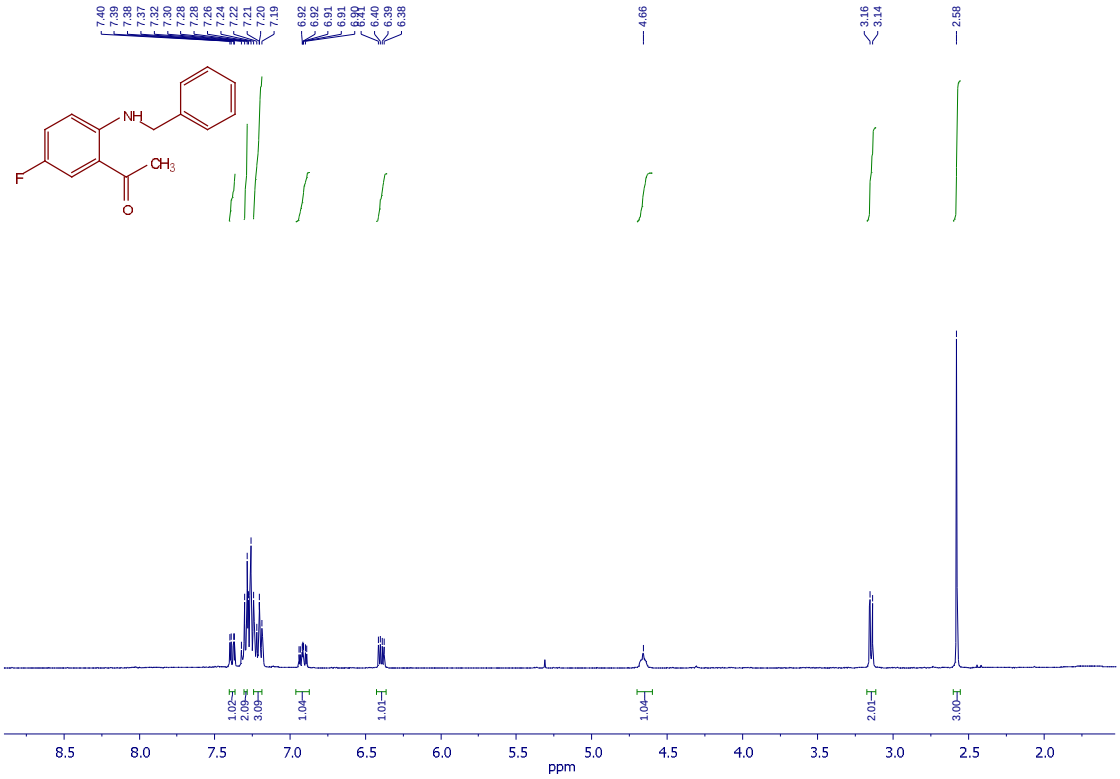

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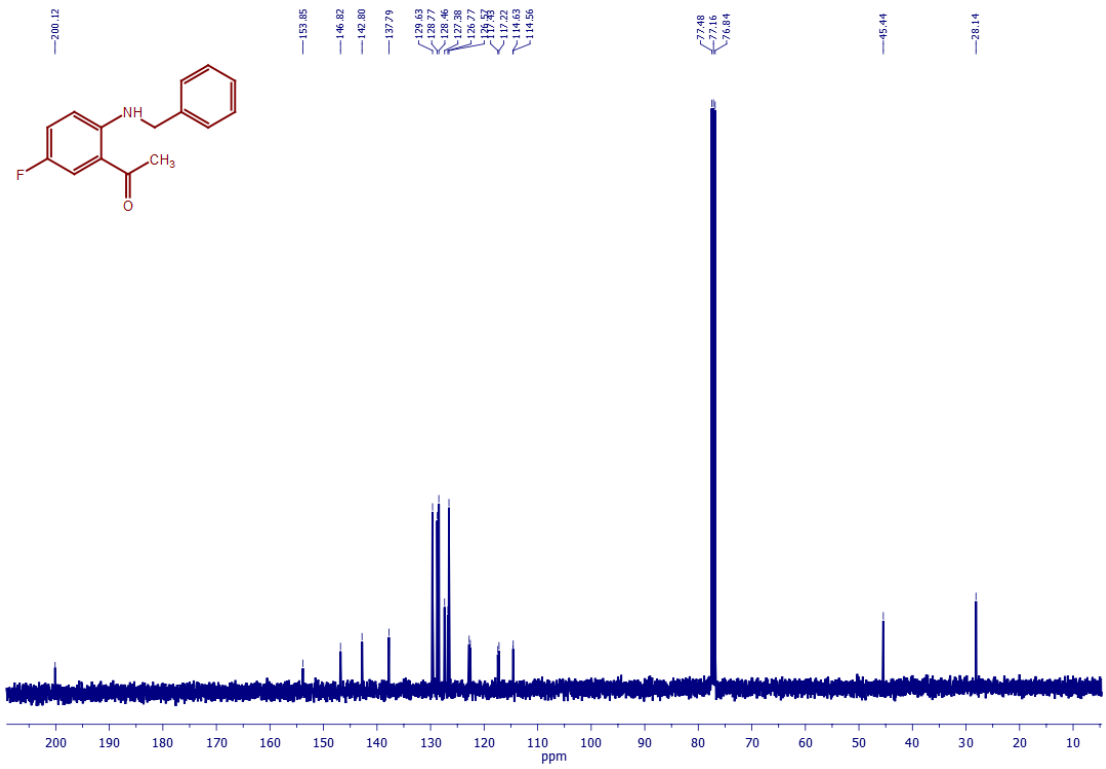
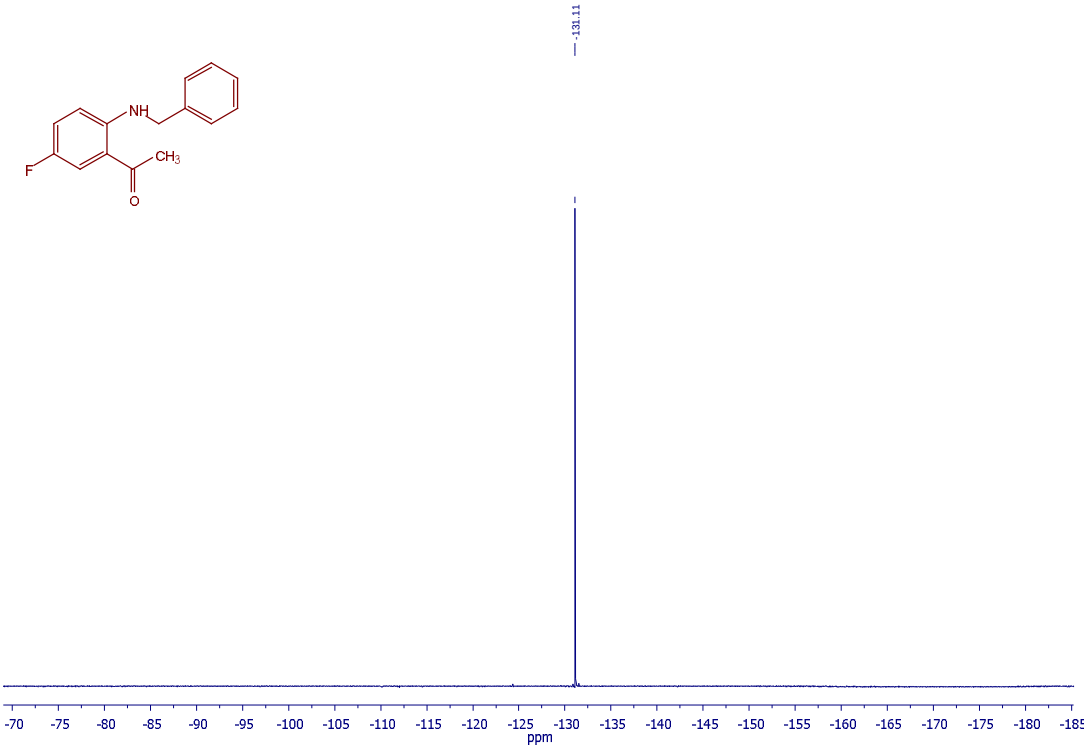


^{13}C NMR of Compound 3k



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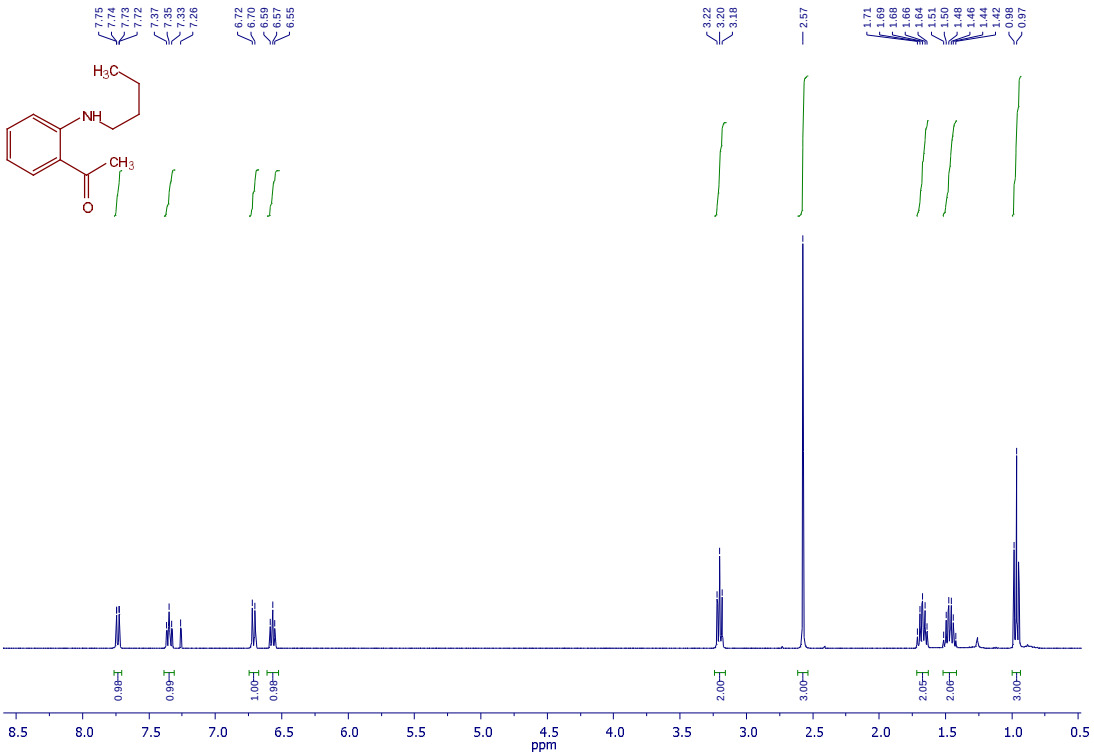
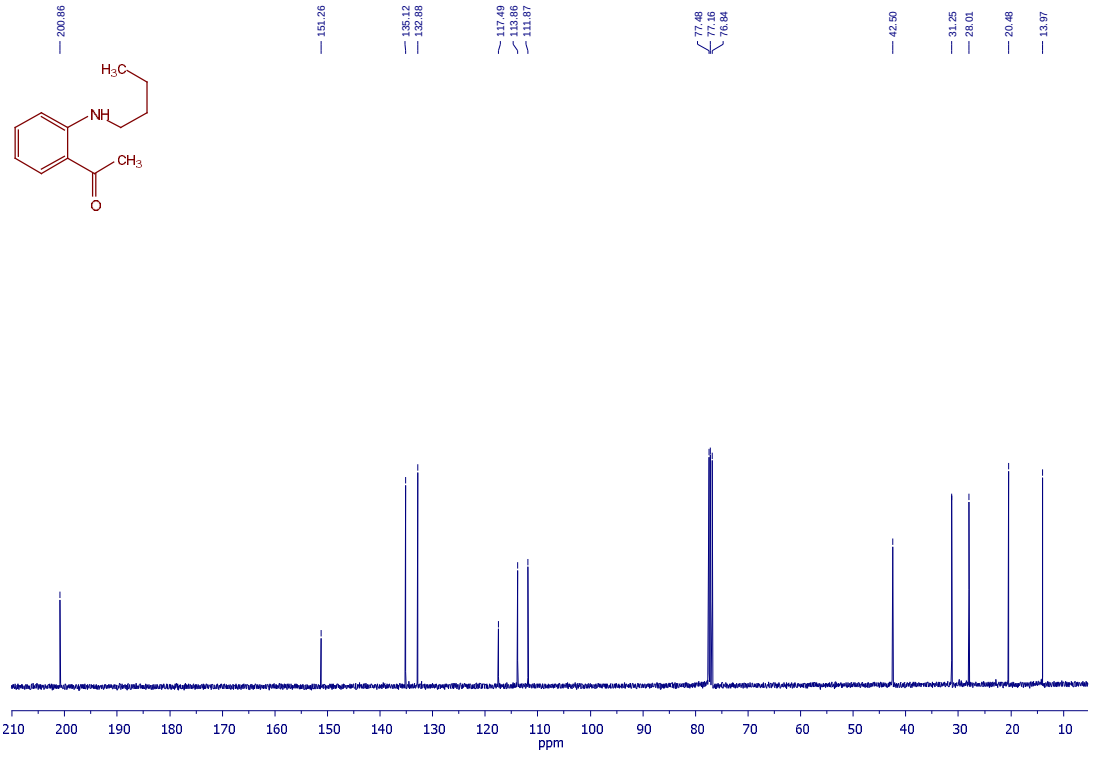


^{1}H NMR of Compound 3l



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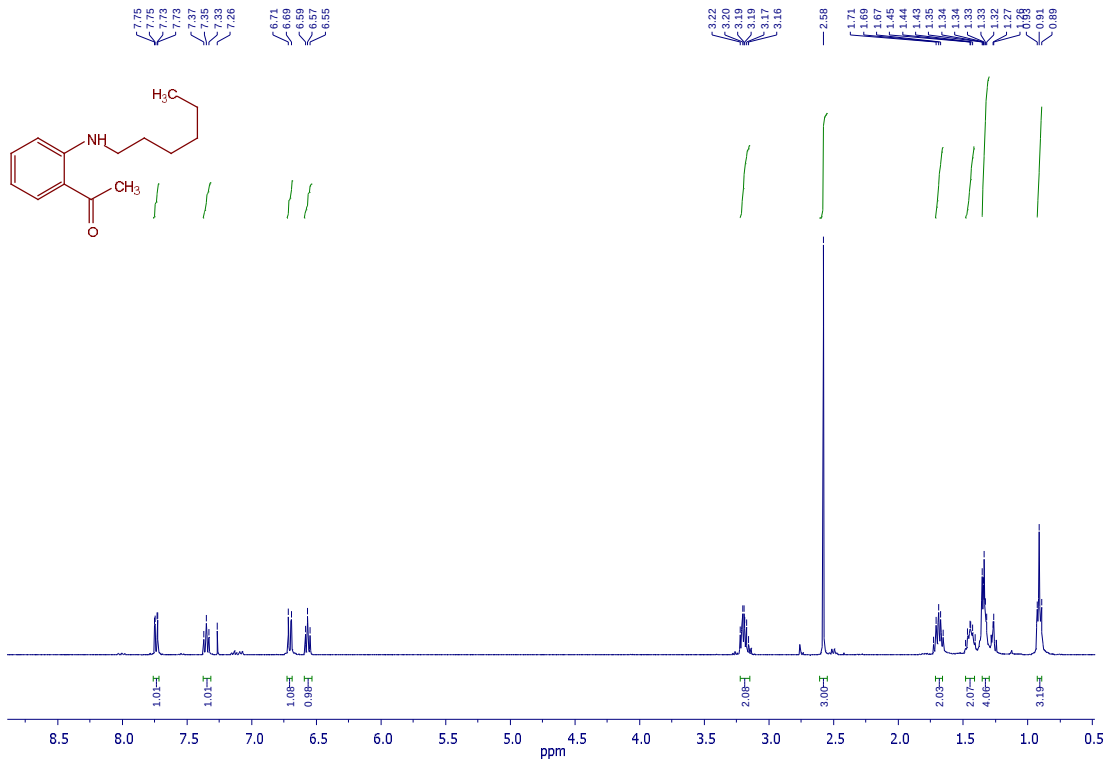

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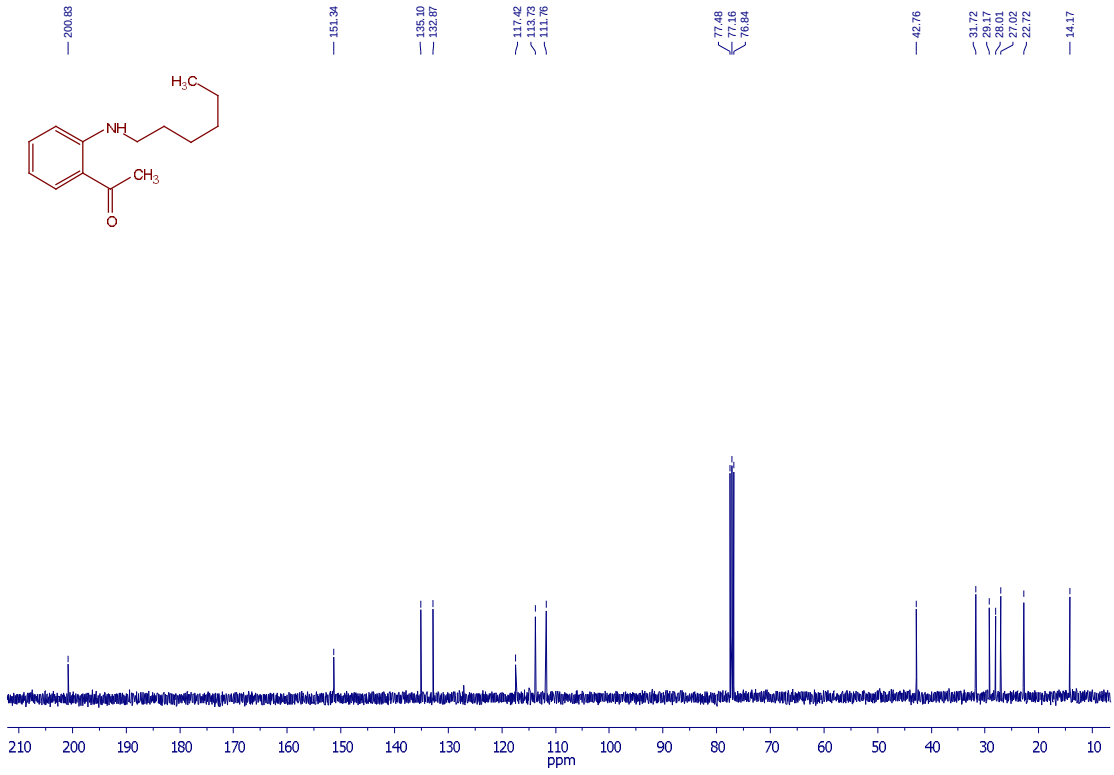


^{13}C NMR of Compound 3m

6.6 References

1. a) Modern amination methods, ed. A. Ricci, Wiley-VCH, Weinheim, 2000. (b) M. B. Smith and J. March, March's Advanced Organic Chemistry; Wiley-Interscience: New York, 2001; pp 499−501; (c) A. de Meijere and F. Diederich, in Metal-Catalyzed Cross Coupling Reactions, Wiley-VCH, Weinheim, 2004; (d) A. R. Cartolano and G. A. Vedage, in Kirk-OthmerEncyclopedia of Chemical Technology, John Wiley & Sons, Inc, New York, 2004, vol. 2, pp. 476–498; (e) Amines: Synthesis, Properties, and Applications, ed. S. A. Lawrence, Cambridge University, Cambridge, 2006; (f) Amino Group Chemistry: From Synthesis to the Life Sciences, ed. A. Ricci, Wiley-VCH, Weinheim, 2008; (g) F. Alonso, F. Foubelo, J. C. Gonzalez-Gomez, R. Martinez, D. J. Ramon, P. Riente and M. Yus, *Mol. Diversity*, 2010, **14**, 411–424; (h) Y. Obora, *ACS Catal*., 2014, **4**, 3972.

2. (a) R. N. Salvatore, C. H. Yoon and K. W. Jung, *Tetrahedron*, 2001, **57**, 7785; (b) F. A. Carey and R. J. Sundberg, in Advanced Organic Chemistry, Part B: Reaction and Synthesis, Springer, 5th edn, 2007; (c) M. B. Smith and J. March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Wiley, 6th edn, 2007; (d) D. M. Hodgson and A. Charlton, *Tetrahedron*, 2014, **70**, 2207.

3. (a) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal*., 2007, **349**, 1555; (b) T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Dalton Trans*., 2009, 753; (c) A. J. A. Watson and J. M. J. Williams, *Science,* 2010, **329**, 635; (d) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev*., 2010, **110**, 681; (e) C. Gunanathan and D. Milstein, *Science,* 2013, **341**, 1229712; (f) K. Shimizu, *Catal. Sci. Technol*., 2015, **5**, 1412; (g) R. H. Crabtree, *Chem. Rev*., 2017, **117**, 9228.

4. (a) G. Guillena, D. J. Ramon and M. Yus, *Angew. Chem. Int. Ed*., 2007, **46**, 2358; (b) F. Huang, Z. Liu, and Z. Yu, *Angew. Chem. Int. Ed*., 2016, **55**, 862.

5. (a) G. Guillena, D. J. Ramon and M. Yus, *Chem. Rev.*, 2010, **110**, 1611; (b) S. Bahn, S. Imm, L. Neubert, M. Zhang, H. Neumann and M. Beller, *ChemCatChem*, 2011, **3**, 1853; (c) Q. Yang, Q. Wang and Z. Yu, *Chem. Soc. Rev.*, 2015, **44**, 2305.

6. **Ruthenium:***(i)* Selected examples for C-Alkylation of ketones; (a) R. Martínez, G. J. Brand, D. J. Ramón and M. Yus, *Tetrahedron Lett.*, 2005, **46**, 3683; (b) T. Kuwahara, T. Fukuyama and I. Ryu, *Org. Lett.*, 2012, **14**, 4703; (c) C. Schlepphorst, B. Maji and F. Glorius, *ACS Catal.*, 2016, **6**, 4184; (d) G. Chelucci, *Coord. Chem. Rev.*, 2017, **331**, 1. Selected examples for N-Alkylation of amines; (e) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson and J. M. J. Williams, *J. Am. Chem. Soc.*, 2009, **131,** 1766; (f) D. Weickmann, W. Frey and B. Plietker, *Chem. Eur. J.*, 2013, **19**, 2741; (g) S. Pei Shan, T. T. Dang, A. M. Seayad and B. Ramalingam, *ChemCatChem*, 2014, **6**, 808; (h) L. M. Broomfield, Y. Wu, E. Martin and A. Shafir, *Adv. Synth. Catal*., 2015, **357**, 3538; (i) K. O. Marichev and J. M. Takacs, *ACS Catal*., 2016, **6**, 2205; (j) J. J. A. Celaje, X. Zhang, F. Zhang, L. Kam, J. R. Herron and T. J. Williams, *ACS Catal.*, 2017, **7**, 1136.

7. **Iridium:** Selected examples for C-Alkylation of ketones; (a) Y. Obora and Y. Ishii, *Synlett*., 2011, 30; (b) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825; (c) F. Li, J. Ma, and N. Wang, *J. Org. Chem.*, 2014, **79**, 10447; (d) P. Liu, R. Liang, L. Lu, Z. Yu, and F. Li, *J. Org. Chem.*, 2017, **82**, 1943; (e) W. M. Akhtar, C. B. Cheong, J. R. Frost, K. E. Christensen, N. G. Stevenson, and T. J. Donohoe, *J. Am. Chem. Soc.*, 2017, **139**, 2577. Selected examples for N-Alkylation of amines; (f) R. Kawahara, K.-i. Fujita and R. Yamaguchi, *Adv. Synth. Catal.*, 2011, **353**, 1161; (g) I. Cumpstey, S. Agrawal, K. E. Borbas and B. Martin-Matute, *Chem. Commun.*, 2011, **47**, 7827; (h) F. Li, H. Shan, L. Chen, Q. Kang and P. Zou,

Chem. Commun., 2012, **48**, 603; (i) A. Bartoszewicz, R. Marcos, S. Sahoo, A. K. Inge, X. Zou and B. Martín-Matute, *Chem. Eur. J.*, 2012, **18**, 14510; (j) Y.-H. Chang, Y. Nakajima and F. Ozawa, *Organometallics*, 2013, **32**, 2210; (k) L. Lu, J. Ma, P. Qu and F. Li, *Org. Lett.*, 2015, **17**, 2350; (l) X. Jiang, W. Tang, D. Xue, J. Xiao and C. Wang, *ACS Catal.*, 2017, **7**, 1831; (m) C. Wanga and J. Xiao, *Chem. Commun.*, 2017, **53**, 3399.

8. **Rhodium:** P. Satyanarayana, G. M. Reddy, H. Maheswaran, and M. L. Kantam, *Adv. Synth. Catal.*, 2013, **355**, 1859.
9. **Rhenium:** P. Piehl, M. Pena-Lopez, A. Frey, H. Neumann and M. Beller, *Chem. Commun.*, 2017, **53**, 3265.
10. **Palladium:** (a) A. Martínez-Asencio, M. Yus and D. J. Ramón, *Synthesis*, 2011, 3730; (b) T. T. Dang, B. Ramalingam, S. P. Shan and A. M. Seayad, *ACS Catal.*, 2013, **3,** 2536; (c) R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Tetrahedron*, 2017, **73**, 2225.
11. **Cobalt:** (a) G. Zhang, Z. Yin and S. Zheng, *Org. Lett*., 2016, **18**, 300; (b) G. Zhang, J. Wu, H. Zeng, S. Zhang, Z. Yin and S. Zheng, *Org. Lett.*, 2017, **19**, 1080.
12. **Iron:** (a) S. Elangovan, J.-B. Sortais, M. Beller and C. Darcel, *Angew. Chem. Int. Ed.*, 2015, **54**, 14483; (b) M. Mastalir, B. Stoger, E. Pittenauer, M. Puchberger, G. Allmaier and K. Kirchner, *Adv. Synth. Catal.*, 2016, **358**, 3824.
13. **Osmium:** M. L. Buil, M. A. Esteruelas, J. Herrero, S. Izquierdo, I. M. Pastor and M. Yus, *ACS Catal.*, 2013, **3**, 2072.
14. **Manganese:**(a) M. Pena-Lopez, P. Piehl, S. Elangovan, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.*, 2016, **55**, 14967; (b) S. Elangovan, J. Neumann, J.-B. Sortais, K. Junge, C. Darcel and M. Beller, *Nat. Commun.*, 2016, **7**, 12641.

15. Copper: (a) X. Cui, F. Shi, M. K. Tse, D. Go¨rdes, K. Thurow, M. Beller and Y. Deng, *Adv. Synth. Catal.*, 2009, **351**, 2949; (b) A. Martinez-Asencio, D. J. Ramon and M. Yus, *Tetrahedron*, 2011, **67**, 3140; (c) S. Liao, K. Yu, Q. Li, H. Tian, Z. Zhang, X. Yu and Q. Xu, *Org. Biomol. Chem.*, 2012, **10**, 2973; (d) F. Li, H. Shan, Q. Kang and L. Chen, *Chem. Commun.*, 2011, **47**, 5058; (b) Z. Xu, D. -S. Wang, X. Yu, Y. Yang and D. Wang, *Adv. Synth. Catal.*, DOI: 10.1002/adsc.201700179.

16. C. S. Cho, B. T. Kim, T. J. Kim and S. C. Shim, *J. Org. Chem.*, 2001, **66**, 9020.

17. K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi and Y. Ishii, *J. Am. Chem. Soc.*, 2004, **126**, 72.

18. T. Yan, B. L. Feringa and K. Barta, *ACS Catal*., 2016, **6**, 381.

19. A. Ilangovan and G. Satish, *J. Org. Chem.*, 2014, **79**, 4984.

20. (a) A. F. Bella, A. M. Z. Slawin and J. C. Walton, *J. Org. Chem.*, 2004, **69**, 5926; (b) W.-T. Wei, X.-J. Dong, S.-Z. Nie, Y.-Y. Chen, X.-J. Zhang and M. Yan, *Org. Lett.*, 2013, **15**, 6018.

21. (a) X. Gai, R. Grigg, M. I. Ramzan, V. Sridharan, S. Collard and J. E. Muir, *Chem. Commun.*, 2000, 2053; (b) S. Bhat, V. Sridharan, *Chem. Commun.*, 2012, **48**, 4701.

22. R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Dalton Trans.*, 2015, **44**, 5805.

23. G. Sanchez, J. Garcia, D. Meseguer, J. L. Serrano, L. Garcia, J. Perez and G. Lopez, *Dalton Trans.*, **2003**, 4709.

24. P. Bichovski, T. M. Haas, D. Kratzert and J. Streuff, *Chem. Eur. J.*, 2015, **21**, 2339.

25. A. B. Richard and N. Baskar, *J. Heterocycl. Chem.*, 2011, **48**, 613.

26. X. Li, H. Li, W. Song, P.-S. Tseng, L. Liu, I. A. Guzei and W. Tang, *Angew. Chem. Int. Ed.,* 2015, **54**, 12905.

27. A. Carpita and A. Ribecai, *Tetrahedron Lett.,* 2009, **50**, 6877.

28. S. Ferrini, F. Ponticelli and M. Taddei, *J. Org. Chem.,* 2006, **71**, 9217.

29. W. Hu, J. P. Lin, L. R. Song and Y. Q. Long, *Org. Lett.,* 2015, **17**, 1268.

30. W. Zhou, M. Fan, J. Yin, Y. Jiang and D. Ma, *J. Am. Chem. Soc.,* 2015, **137**, 11942.

31. C. R. Elati, N. Kolla, S. R. Chalamala, P. J. Vankawala, V. Sundaram, H. Vurimidi and V. T. Mathad, *Synth. Commun*., 2006, **36**, 169.

32. New compound

An efficient cyclometalated palladium pre-catalyst for methylation of ketones and amines using methanol as a C-1 source

7.1 Introduction

An environmentally benign method with inexpensive substrates such as alcohols involving *borrowing hydrogen* has emerged as a powerful tool over the last few decades.[1] In particular, methylation has become an essential protocol for the synthesis of biologically active molecules.[2] Conventional methylation uses iodomethane, diazomethane, dimethyl sulfate and dimethyl carbonate as the common methylating reagent.[3] Use of these methods required highly toxic and hazardous methylating reagents or excess base. An additional drawback of these procedures is selectivity and the formation of a stoichiometric amount of waste. When dimethyl carbonate is used, CO_2 and methanol are produced as by-products that need to be potentially recycled. Hence, much attention has been focused on methanol as it serves as a cheaper, abundant and renewable C-1 source to enable atom economic C─C and C─N bond formations under *borrowing hydrogen* condition. This approach would provide an expedient route to this important class of compounds. Although, methanol is the simplest alcohol, relatively high energy is required to activate or dehydrogenate it compared with other alcohols such as ethanol and higher alcohols.[4]

There is numerous transition metal-based catalysts were reported for C-alkylation of ketones [5] using higher alcohols, however, few metals such as Rhodium,[6] Iridium [7] and Ruthenium [8] were successful for C-methylation of ketones using methanol. Palladium-based catalysts were examined for dehydrogenation of alcohols,[9] N-alkylation of amines[10] and C-alkylation of ketones.[11] Most recently, Zhaomin Hou and co-workers demonstrated poly(aminostyrene)-supported palladium catalyst for ketone methylation with methanol.[12] To the best of our knowledge this is the only report so far using palladium as a catalyst (or) pre-catalyst for C-methylation of ketones and there are no reports based on homogeneous palladium catalyst for C-methylation of ketones as well as N-methylation of amines using methanol.

The first C-methylation of ketones using methanol reported by Feng Li and co-workers using an iridium-Cp* complex.[7a] Later, Yasushi Obora and co-workers reported an Ir-phosphine catalyst.[7b] Recently, Donohoe and co-workers demonstrated

an Ir-phosphine and Rh-phosphine complexes catalyzed C-methylation under mild reaction conditions.[7c,6] An N-heterocyclic carbene based Ir complex was also reported by Andersson and co-workers.[7d] An efficient Ruthenium catalyst was reported, for the first time, to catalyze the C-methylation of ketones and esters using methanol as a green methylating agent by Seayad and co-workers.[8] In all these cases, expensive metals or higher catalyst loadings, excess bases and (or) higher temperature was used to get the products. In this chapter, we disclose the palladium-based catalytic system which is efficient for the methylation of ketones and amines using methanol as a methylating agent.

So far, only expensive metal catalysts such as rhodium, iridium and ruthenium complexes were successful for the C-methylation of ketones using methanol. So, developing a less expensive transition metal catalyst such as palladium using a suitable ligand that could be synthesized from cheaper, readily available and easily accessible starting materials could be advantageous for developing future sustainable catalytic methods.

7.2 Results and discussions

We developed and described in previous chapters a portfolio of methods for homogeneous pyrazole-based palladacycles that catalyze the N-alkylation of amines,[10c] C-alkylation of ketones[11b] using *borrowing hydrogen* as well as Suzuki and Heck coupling reactions.[13] Motivated by these results we continued our efforts in order to develop an efficient palladacycle-catalyst system by the strategic design of pyrazole ligand to methylate amines and ketones using methanol as a C-1 source. During the development of catalyst system we observed regioselective cyclopalladation as well as improvement of efficiency in activity towards methylation of ketones using methanol under reaction condition regulated by incorporation of CF_3-group on N-phenyl of the pyrazole ligand. Key to success is the incorporation of the CF_3-group on 1,3,5-triphenylpyrazole ligand with combination of suitable phosphine.

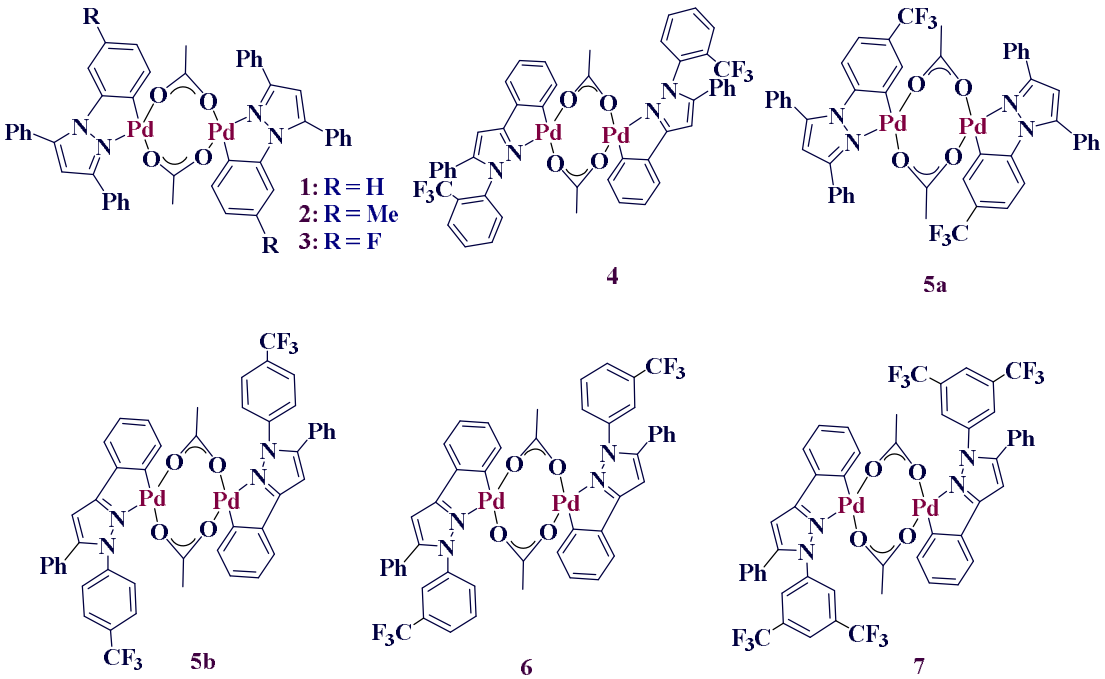
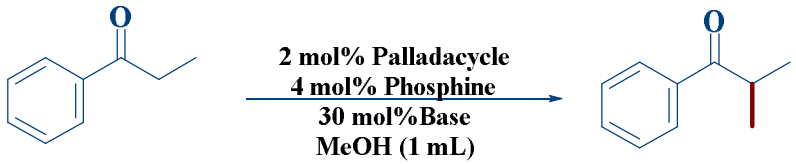


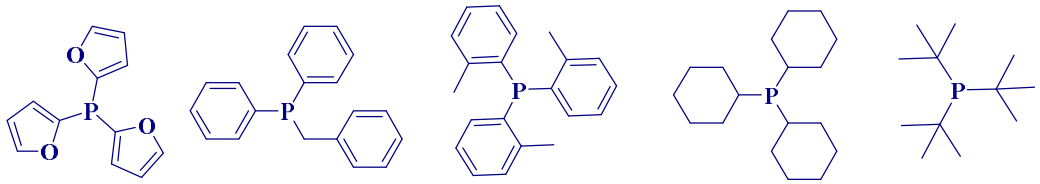
Figure 7.1: Palladacycles examined in methylation of ketones and amines using methanol

7.2.1 C-Methylation of ketones

We studied the reaction of propiophenone using 2 mol% palladacycle, 4 mol% of tri(2-furyl)phosphine and 30 mol% LiOH in methanol (1 mL) at 100 °C for 48 h (Table 7.1). Using palladacycles **1** (or) **2** (or) **3** under the reaction condition the formation of the desired product was not observed. Palladacycles-**4** and **5a** were also not successful. However, when we attempted palladacycle-**5b** and **6** the desired C-methylated product was obtained in a meager 12% and 11% isolated yield, showing that palladacycles-**1**, **2**, **3**, **4** and **5a** are not active, and palladacycle-**5b** and **6** are less active under the reaction conditions (Table 7.1, entries 1-7). With the aim of improving the efficiency of the catalytic system we designed palladacycle-**7** and examined the reaction. Interestingly, as we expected palladacycle-**7** showed superior activity with 76% isolated yield (Table 7.1, entry 8).

Table 7.1: C-methylation of ketones using propiophenone and methanol under various reaction condition[a]





S.No.	Palladacycle	Phosphine	Base	T (^{o}C)	Yield (%)[b]
1	1	$P(2\text{-Fur})_3$	LiOH	100	ND
2	2	$P(2\text{-Fur})_3$	LiOH	100	ND
3	3	$P(2\text{-Fur})_3$	LiOH	100	ND
4	4	$P(2\text{-Fur})_3$	LiOH	100	trace
5	5a	$P(2\text{-Fur})_3$	LiOH	100	ND
6	5b	$P(2\text{-Fur})_3$	LiOH	100	12
7	6	$P(2\text{-Fur})_3$	LiOH	100	11
8	**7**	**$P(2\text{-Fur})_3$**	**LiOH**	**100**	**76**
9	**7**	**$P(2\text{-Fur})_3$**	**LiOtBu**	**100**	**82**
10	7	$P(2\text{-Fur})_3$	$CsOH.H_2O$	100	ND
11	7	$P(2\text{-Fur})_3$	Cs_2CO_3	100	ND
12	7	$P(2\text{-Fur})_3$	KOtBu	100	41
13	7	$P(o\text{-Tol})_3$	LiOtBu	100	trace
14	7	$P(Bn)(Ph)_2$	LiOtBu	100	trace

15	**7**	**$P(Cy)_3$**	**LiOtBu**	**100**	**86**
16	7	$P(tBu)_3$	LiOtBu	100	72
17	7	$P(Cy)_3$	LiOtBu	110	91
18	**7**	**$P(Cy)_3$**	**LiOtBu**	**120**	**94**
19	-	$P(Cy)_3$	LiOtBu	120	ND[c]
20	7	$P(Cy)_3$	-	120	ND[d]
21	7	$P(Cy)_3$	LiOtBu	120	86[e]

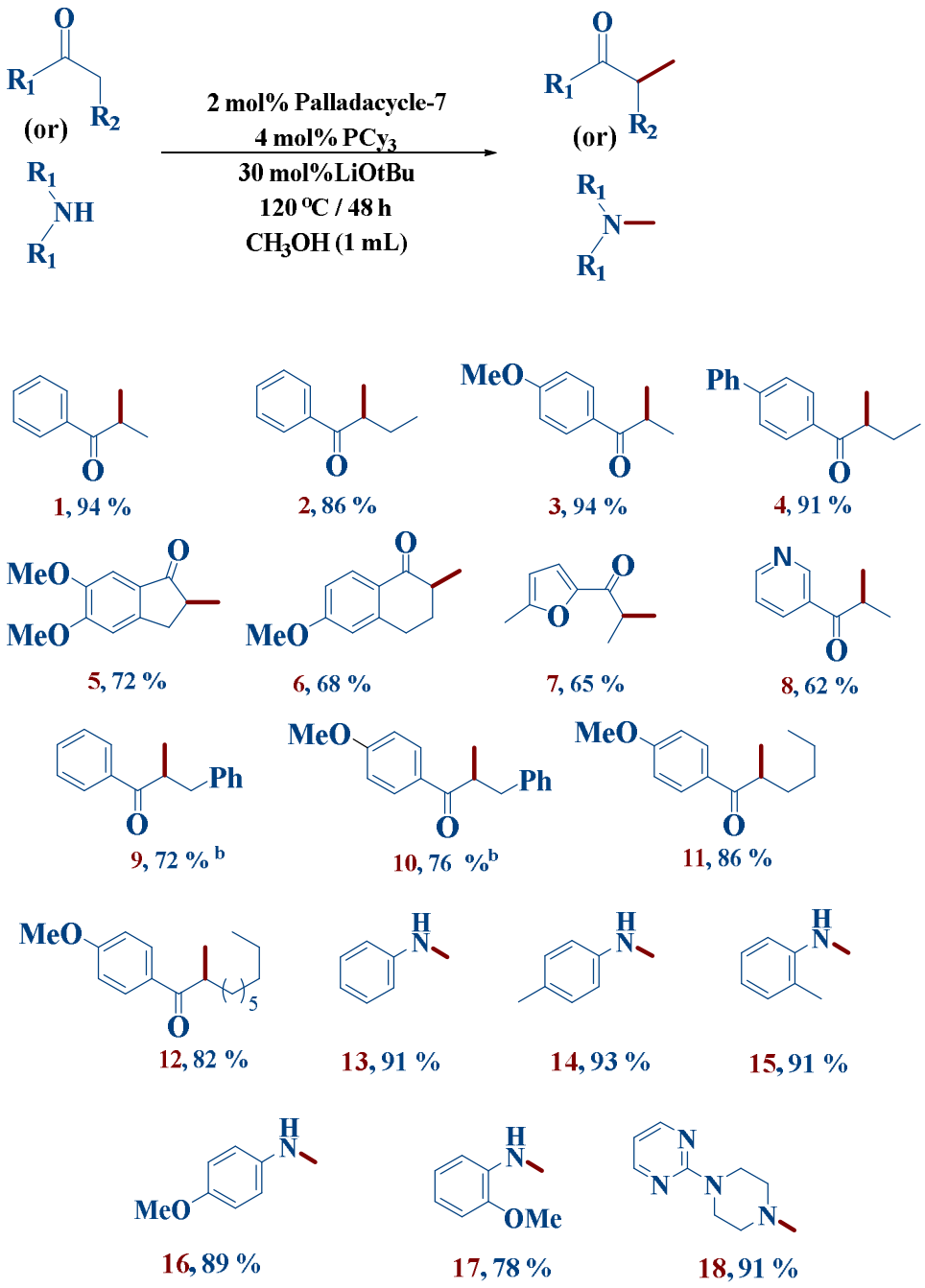
[a]Reaction condition: propiophenone 1 mmol, base 0.30 mmol, palladacycle $2x10^{-2}$ mmol, phosphine $4x10^{-2}$ mmol, [b]isolated yield, [c]reactions were performed without palladacycle-**7**, [d]reactions were performed without LiOtBu, [e]0.20 mmol LiOtBu was used.

We were delighted to observe an increased yield of up to 82% using LiOtBu instead of LiOH (Table 7.1, entry 9). Other bases such as $CsOH.H_2O$ and Cs_2CO_3 did not provide the desired product. However, KtOBu yielded the desired product in 41% yield (Table 7.1, entry 12). LiOH and LiOtBu were found to be suitable bases compared to others (Table 7.1, entries 10–12), may be due to the effective stabilization of various intermediates by the smaller Li^+ cation towards the in situ formed active Pd(II)─OMe species.

Next, we focused our attention on identifying an appropriate monodentate phosphine with the aim of improving the yield of the C-methylated product. P(*o*-Tol)$_3$ and P(Bn)(Ph)$_2$ were failed to give the product (Table 7.1, entries 13 and 14). Surprisingly, the yield of the C-methylated product improved to 86% when PCy_3 used, however, $P(tBu)_3$ yielded 72% under the equal reaction conditions (Table 7.1, entries 15 and 16). The donor strength, as well as steric effect of the phosphines, could be a factor for the enhancement in catalytic performance under the reaction conditions. Increasing the temperature to 110 ^oC and 120 ^oC resulted in 91% and 94% yield of the C-methylated product respectively (Table 7.1, entries 17 and 18). Furthermore, the reaction did not proceed in the absence of palladacycle-**7** and (or) LiOtBu (Table 7.1, entries 19 and 20), indicating the requirement of both the palladacycle-**7** and LiOtBu for C-methylation of propiophenone. The optimal reaction condition for C-

methylation using methanol is therefore 120 °C for 48 h with use of 2 mol% palladacycle-**7**, 4 mol% PCy_3, 30 mol% LiOtBu in methanol (1mL) for 1 mmol of propiophenone.

Table 7.2: Substrate scope for C-methylation of ketones using methanol a



[a]Reaction condition: aryl ketone (or) amine 1 mmol, base 0.30 mmol, palladacycle-**7** $2x10^{-2}$ mmol, phosphine $4x10^{-2}$ mmol , isolated yield, [b]reactions were performed using palladacycle-**7** $3x10^{-2}$ mmol, phosphine $6x10^{-2}$ mmol and 2 mL methanol at 130 °C for 48 h.

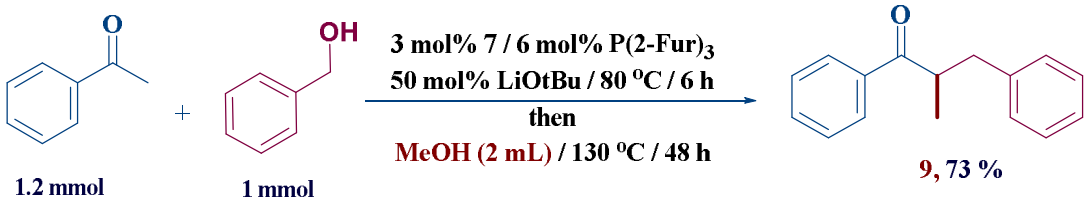
In order to explore the substrate scope and limitations of the method under these optimized reaction conditions, we examined different aryl ketones. Good to excellent isolated yields were achieved for the C-methylated ketone products 1, 2, 3 and 4 from the corresponding ketones, propiophenone, butyrophenone, 4'-methoxy propiophenone and 4-butyrobiphenyl, as shown in table 7.2. Cyclic ketones such as 5,6-dimethoxy indanone and 6-methoxy tetralone were smoothly methylated to the corresponding products in good yields (Table 7.2, compounds 5 and 6). Notably, our catalytic system tolerated heteroaryl ketones such as 2-methyl-5-propionyl furan and 3-propionyl pyridine to yield the corresponding C-methylated products in 65% and 62% respectively (Table 7.2, compounds 7 and 8). To demonstrate the usefulness of our catalytic system 1,3-diphenylpropan-1-one, 1-(4-methoxyphenyl)-3-phenylpropan-1-one, 1-(4-methoxyphenyl)hexan-1-one, and 1-(4-methoxyphenyl)decan-1-one were examined under the reaction conditions, to get the corresponding C-methylated compounds 9, 10, 11 and 12 in 72%, 76%, 86% and 82% isolated yields respectively.

7.2.2 N-Methylation of amines

Motivated by the results obtained for C-methylation of aryl ketones, next we concentrated on N-methylation of amines. N-Methylated amines have found applications as important drug molecules and natural products. However, these molecules are still synthesized using toxic and/or hazardous methyl halides or sulfates as alkylating agents. Till to date only limited studies based on transition metal-catalyzed N-methylation of amines using methanol have been described, especially metals such as Ru and Ir have been used for the N-methylation.[2c,2d] To the best of our knowledge, there exist no reports on palladium-catalyzed N-methylation of amines by methanol. In order to examine the efficiency of the palladacycle-**7** and phosphine system we performed N-methylation of aniline under reaction conditions mentioned before. To our delight, selective mono N-methylation of aniline proceeded smoothly and furnished the desired products in 91% isolated yield (Table 7.2, compound 13). Encouraged by these results, we explored the possibility to apply different amines under the reaction conditions. As shown in table 7.2, different anilines gave the N-methylated products in good to excellent isolated yields (Table 7.2, entries 14-17: 78%–93%). In most cases, the catalyst showed very good selectivity. 4-Methyl aniline and 4-methoxy aniline gave isolated yields of 93% and 89% respectively (Table 7.2, compounds 14 and 16), whereas sterically hindered 2-methyl aniline and 2-methoxy

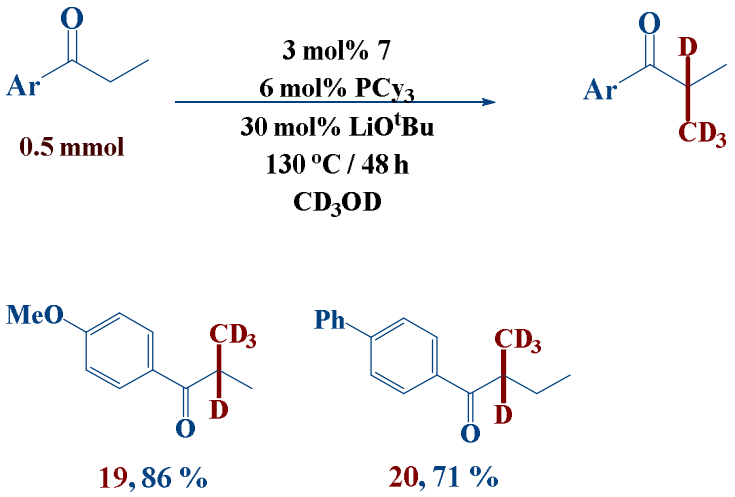
aniline gave a yield of 91% and 78% respectively (Table 7.2, compounds 15 and 17). Notably, only mono methylated products were observed in all the cases of aromatic primary amines. Aliphatic amines are generally more nucleophilic than aromatic amines. Interestingly, a heterocyclic aliphatic amine such as 1-(2-pyrimidyl)piperazine was also tolerated under the reaction conditions to give the corresponding methylated product in 91% isolated yield (Table 7.2, compound 18).

Encouraged by the results obtained for the methylation of ketones and amines, we then concentrated on sequential one-pot synthesis of 2-methyl-1,3-diphenylpropan-1-one that involves C-alkylation followed by C-methylation.[6,7b,7c,8] In order to examine this, 1.2 mmol acetophenone was treated with 1 mmol benzyl alcohol at 80 ^{o}C using 3 mol% palladacycle-**7**, 6 mol% tri(2-furyl)phosphine and 50 mol% LitOBu for 6 h under solvent-free condition. The subsequent methylation was accomplished by raising the temperature to 130 ^{o}C and adding methanol (Scheme 7.1). We were delighted to see that the present catalytic system is effective for this sequential reaction to give the 2-methyl-1,3-diphenylpropan-1-one in 73% isolated yield (Scheme 7.1) under the reaction conditions, and thus demonstrating a useful double-alkylation reaction to perform both carbon–carbon bond-forming steps in one pot synthesis.

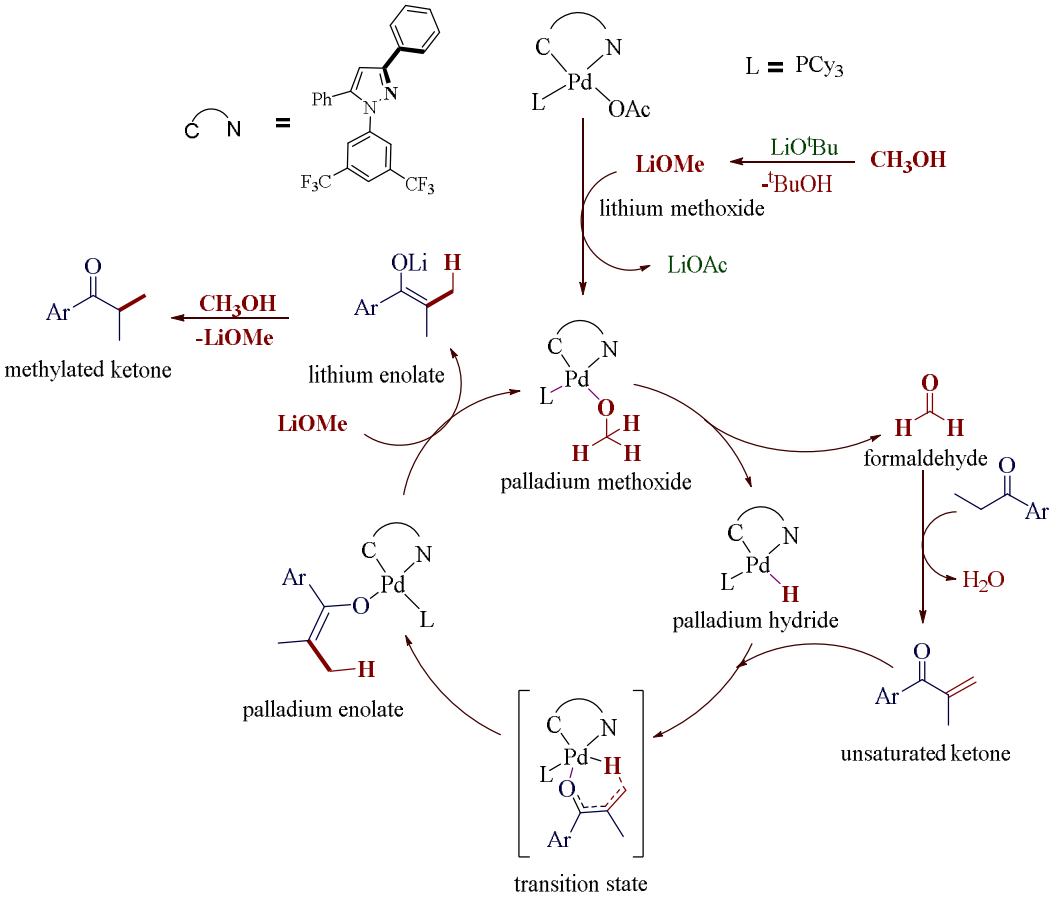


Scheme 7.1: One-pot synthesis of 2-methyl-1,3-diphenylpropan-1-one

Motivated by the results obtained, we envisaged that the present catalyst system could be used for the preparation of C-deuteromethylated ketones using CD_3OD as deuteromethyl source under the reaction conditions. To our delight, the present method successfully produced corresponding C-deuteromethylated compounds in good isolated yields using methanol-d_4 (Scheme 7.2). C-deuteromethylation of 4-methoxy propiophenone and 4-butyro biphenyl were converted to corresponding C-deuteromethylated compounds under the reaction condition in 86% and 71% isolated yield respectively (Scheme 7.2, entries 19 and 20).



Scheme 7.2: C-Deuteromethylation of aryl ketones using methanol-d_4



Scheme 7.3: The proposed catalytic cycle

We have proposed a plausible mechanism for the reaction based on our experimental results using methanol-*d4* (Scheme 7.2) and literature reports [7-10,11b] for C-methylation of ketones using methanol as shown in scheme 7.3. The reaction of

lithium methoxide with *in situ* formed phosphine coordinated palladium species generated the palladium methoxide species which undergone *β*-hydride elimination to generate the palladium hydride intermediate and formaldehyde. The *in situ* generated base catalyzed *α,β*-unsaturated carbonyl compound access the palladium hydride which upon reaction with lithiummethoxide releases the corresponding C-methylated product. And we believe that methylation of amines also could be followed a similar type of mechanism.

7.3 Conclusion

In conclusion, we have developed palladacycle-7 and phosphine catalyst system for the use of methanol as a C-1 source to methylate ketones and amines. The scope of this reaction includes ketones and amines, and consecutive one-pot double alkylation reaction provides a convenient route to 2-methyl-1,3-diphenylpropan-1-one from simple acetophenone. Furthermore, the catalytic system was successfully extended to C-deuteromethylation of methylene ketones using methanol-d_4 for the first time.

7.4 Experimental section

7.4.1 General information

All reagents and solvents were obtained from commercial sources. Solvents were purified according to standard procedures. All 400 (or) 700 MHz ^{1}H, 100 (or) 176 MHz ^{13}C spectra were recorded on a spectrometer operating at 400 (or) 700 MHz. All ^{1}H and ^{13}C NMR spectra were referenced internally to solvent signals. High-resolution mass spectra (HRMS) were recorded with using the microTOF-QII mass spectrometer.

7.4.2 General procedure for methylation of ketones and amines using methanol

An oven dried Schlenk tube was charged with palladacycle-7 ($2x10^{-2}$ mmol to $3x10^{-2}$ mmol), PCy_3 ($4x10^{-2}$ mmol to $6x10^{-2}$ mmol). Under inert atmosphere Li^{t}OBu (0.30

mmol), ketone or amine (1.0mmol) and methanol (1mL) were added to the reaction mixture. Then the Schlenk tube was closed with PTFE stopper and the reaction mixture was stirred at 120-130 ^{o}C for 48 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane, and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using ethyl acetate and *n*-hexanes mixtures to afford the corresponding methylated products in high purity.

7.4.3 Analytical data for methylated compounds

2-methyl-1-phenylpropan-1-one (Table 7.2, entry 1) [5e]**:** Prepared from propiophenone (0.13 g, 1 mmol). After purification by column chromatography, the compound was isolated as colourless liquid (0.15 g, 0.94 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.61–3.51 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.6, 136.3, 132.9, 128.7, 128.4, 35.5, 19.3 ppm.

2-methyl-1-phenylbutan-1-one (Table 7.2, entry 2) [5e]**:** Prepared from butyrophenone (0.15 g, 1 mmol). After purification by column chromatography, the compound was isolated as colourless liquid (0.14 g, 0.86 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.45–3.36 (m, 1H), 1.92–1.77 (m, 1H), 1.57–1.42 (m, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.6, 137.1, 132.9, 128.7, 128.3, 42.2, 26.8, 16.9, 12.1 ppm.

1-(4-methoxyphenyl)-2-methylpropan-1-one (Table 7.2, entry 3) [5e]**:** Prepared from 4-methoxypropiophenone (0.16 g, 1 mmol). After purification by column chromatography, the compound was isolated as colourless liquid (0.17 g, 0.94 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.84 (m, 2H), 6.93–6.81 (m, 2H), 3.79 (s, 3H), 3.45 (sept, *J* = 6.8 Hz, 1H), 1.13 (d, *J* = 6.8 Hz, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.1, 163.3, 130.6, 129.1, 113.7, 55.5, 35.0, 19.3 ppm.

1-([1,1'-biphenyl]-4-yl)-2-methylbutan-1-one (Table 7.2, entry 4) [14]**:** Prepared from 4-butyrobiphenyl (0.22 g, 1 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.22 g, 0.91 mmol, 91%). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 7.1 Hz, 2H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 1H), 3.45 (h, *J* = 6.8 Hz, 1H), 1.91–1.85 (m, 1H), 1.57–1.51 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 3H), 0.96 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ 204.1, 145.6, 140.0, 135.6, 129.0, 129.0, 128.3, 127.4, 127.3, 42.3, 26.8, 16.9, 11.9 ppm.

5,6-dimethoxy-2-methyl-2,3-dihydro-1H-inden-1-one (Table 7.2, entry 5) [15]**:** Prepared from 5,6-dimethoxyindanone (0.19 g, 1 mmol). After purification by column chromatography, the compound was isolated as a yellow colour solid (0.15 g, 0.72 mmol, 72%). Mp = 131–132 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (s, 1H), 6.86 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.30 (dd, *J* = 16.7, 7.3 Hz, 1H), 2.78–2.53 (m, 2H), 1.29 (d, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4, 155.6, 149.6, 148.8, 129.2, 107.5, 104.6, 56.34, 56.2, 42.3, 34.9, 16.8 ppm.

6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2H)-one (Table 7.2, entry 6) [15]**:** Prepared from 6-methoxy-1-tetralone (0.18 g, 1 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.13 g, 0.68 mmol, 68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.7 Hz, 1H), 6.78 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 3.82 (s, 3H), 3.01–2.86 (m, 2H), 2.55–2.66 (m, 1H), 2.18–2.11 (m, 1H), 1.87–1.77 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8, 163.5, 146.8, 130.0, 126.2, 113.2, 112.6, 55.5, 42.4, 31.6, 29.3, 15.7 ppm.

2-methyl-1-(5-methylfuran-2-yl)propan-1-one (Table 7.2, entry 7) [6]**:** Prepared from 1-(5-methylfuran-2-yl)propan-1-one (0.14 g, 1 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.099 g, 0.65 mmol, 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 3.4 Hz, 1H), 6.14 (dd, *J* = 3.4, 0.9 Hz, 1H), 3.30–3.23 (m, 1H), 2.38 (s, 3H), 1.18 (d, *J* = 6.9 Hz, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.3, 157.8, 150.9, 119.4, 108.9, 36.0, 19.2, 14.2 ppm.

2-methyl-1-(pyridin-3-yl)propan-1-one (Table 7.2, entry 8) [16]**:** Prepared from 3-propionylpyridine(0.14 g, 1 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (92 mg, 0.62 mmol, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 6.3 Hz, 2H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.29 (dd, *J* = 8.4, 4.1 Hz, 1H), 2.01–1.93 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H) ppm. ^{13}C (100 MHz, $CDCl_3$): δ = ppm: 203.1, 153.2, 149.7, 135.7, 131.4, 123.7, 35.9, 18.8 ppm.

2-methyl-1,3-diphenylpropan-1-one (Table 7.2, entry 9) [5e]**:** Prepared from 1,3-diphenylpropan-1-one (0.21 g, 1 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.16 g, 0.72 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99–7.93 (m, 2H), 7.61–7.54 (m, 1H), 7.51–7.45 (m, 2H), 7.34–7.17 (m, 5H), 3.85–3.75 (m, 1H), 3.21 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.73 (1H, dd, *J* = 13.7, 7.9 Hz), 1.24 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7, 139.9, 136.4, 132.9, 129.1, 128.6, 128.3, 128.3, 126.2, 42.7, 39.3, 17.4 ppm.

1-(4-methoxyphenyl)-2-methyl-3-phenylpropan-1-one (Table 7.2, entry 10) [5e]**:** Prepared from 1-(4-methoxyphenyl)-3-phenylpropan-1-one (0.24 g, 1 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.19 g, 0.76 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.9 Hz, 2H), 7.13 –7.28 (m, 5H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 3.65–3.74 (m, 1H), 3.15 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.68 (dd, *J* = 13.6, 7.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.2, 163.3, 140.0, 130.5, 129.3, 129.0, 128.3, 126.1, 113.7, 55.4, 42.3, 39.5, 17.5 ppm.

1-(4-methoxyphenyl)-2-methylhexan-1-one (Table 7.2, entry 11) [5d]**:** Prepared from 1-(4-methoxyphenyl)hexan-1-one (0.21 g, 1 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.19 g, 0.86 mmol, 86%). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.41 (h, *J* = 6.8 Hz, 1H), 1.82–1.73 (m, 1H), 1.46–1.38 (m, 1H), 1.34–1.22 (m, 4H), 1.17 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 203.3, 163.4, 130.6, 129.9, 113.9, 55.6, 40.2, 33.8, 29.8, 23.0, 17.5, 14.1 ppm.

1-(4-methoxyphenyl)-2-methyldecan-1-one (Table 7.2, entry 12) [21]**:** Prepared from 1-(4-methoxyphenyl)decan-1-one (0.26 g, 1 mmol). After purification by column chromatography, the compound was isolated as a colourless liquid (0.23 g, 0.82 mmol, 82%). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 3.40–3.36 (m, 1H), 1.77–1.73 (m, 1H), 1.40–1.21 (m, 13H), 1.14 (d, *J* = 6.9 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 203.1, 163.3, 130.5, 129.8, 113.8, 55.4, 40.2, 34.0, 31.9, 29.8, 29.5, 29.3, 27.5, 22.7, 17.5, 14.1 ppm.

N-methylaniline (Table 7.2, entry 13) [17]**:** Prepared from aniline (93 mg, 1 mmol). After purification by column chromatography, the compound was isolated as colourless liquid (97 mg, 0.91 mmol, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.20–7.32 (m, 2H), 6.61–6.83 (m, 3H), 3.72 (s, br, 1H), 2.89 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 149.5, 129.3, 117.4, 112.5, 30.8 ppm.

N,4-dimethylaniline (Table 7.2, entry 14) [17]**:** Prepared from *p*-toluidine (0.11 g, 1 mmol). After purification by column chromatography, the compound was isolated as pale yellow liquid (0.11 g, 0.93 mmol, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.2 Hz, 1H), 6.66 (d, *J* = 8.2 Hz, 1H), 2.84 (s, 1H), 2.26 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 146.5, 129.9, 127.5, 113.4, 31.7, 20.5 ppm.

N,2-dimethylaniline (Table 7.2, entry 15) [17]**:** Prepared from *o*-toluidine (0.11 g, 1 mmol). After purification by column chromatography, the compound was isolated as pale yellow liquid (0.11 g, 0.91 mmol, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.18 (m, 1H), 7.07 (m, 1H), 6.64–6.72 (m, 2H), 2.92 (s, 3H), 2.16 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 147.2, 130.1, 127.3, 122.1, 117.1, 109.4, 30.9, 17.5 ppm.

4-Methoxy-N-methylaniline (Table 7.2, entry 16) [18]**:** Prepared from *p*-anisidine (0.12 g, 1 mmol). After purification by column chromatography, the compound was isolated as pale yellow liquid (0.12 g, 0.89 mmol, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.80 (d, *J* = 9.2 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 2H), 3.75 (s, 3H), 2.81 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.1, 143.7, 114.9, 113.6, 55.8, 31.6 ppm.

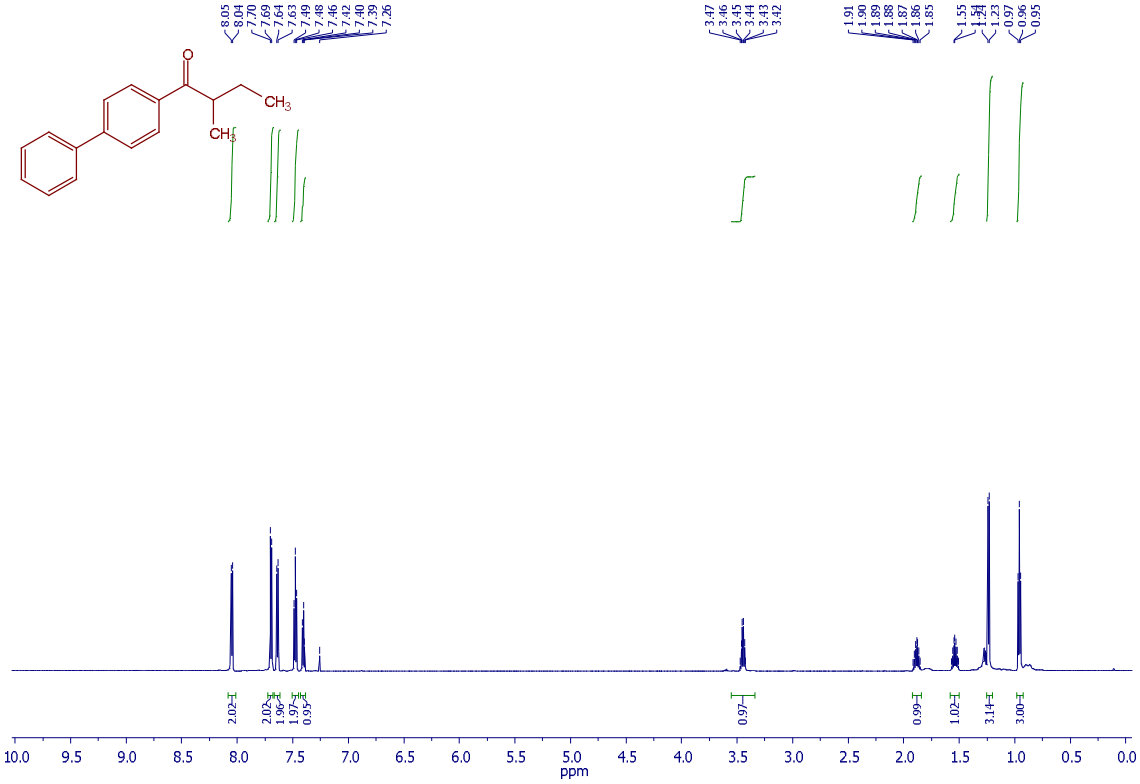
2-Methoxy-N-methylaniline (Table 7.2, entry 17) [19]**:** Prepared from *o*-anisidine (0.12 g, 1 mmol). After purification by column chromatography, the compound was isolated as pale yellow liquid (0.11 g, 0.78 mmol, 78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.00 − 6.96 (m, 1H), 6.84 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 6.77 − 6.73 (m, 1H), 6.68 (dd, *J* = 8.0 Hz, *J* = 1.6 Hz, 1H), 3.91 (s, 3H), 2.93 (s, 3H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 146.9, 139.4, 121.4, 116.4, 109.4, 109.3, 55.4, 30.4 ppm.

2-(4-methylpiperazin-1-yl)pyrimidine (Table 7.2, entry 18) [20]**:** Prepared from 2-(piperazin-1-yl)pyrimidine (0.16 g, 1 mmol). After purification by column chromatography, the compound was isolated as pale yellow liquid (0.16 g, 0.91 mmol, 91%). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 4.7 Hz, 2H), 6.46 (t, *J* = 4.7 Hz, 1H), 3.83 (s, 4H), 2.46 (d, *J* = 5.1 Hz, 4H), 2.32 (s, 3H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 161.8, 157.8, 110.0, 55.0, 46.2, 43.6 ppm.

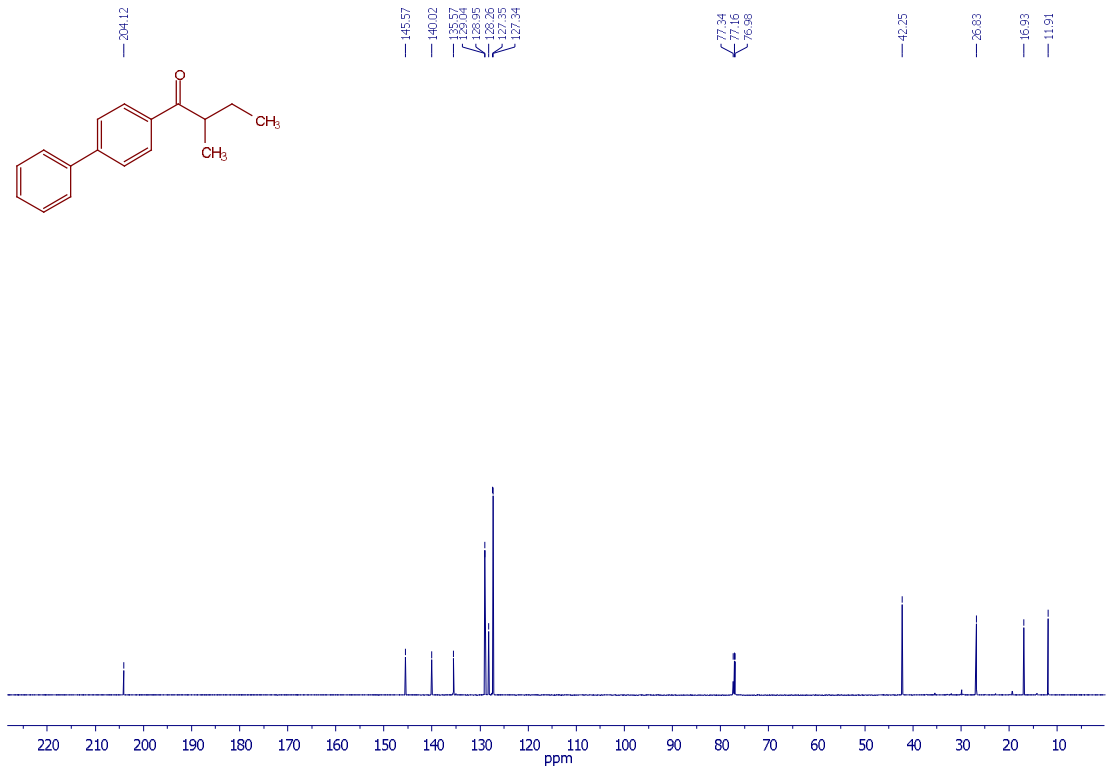
1-(4-methoxyphenyl)-2-methylpropan-1-one-2,3,3,3-d4 (scheme 7.2, entry 19) [21]**:** Prepared from 4-methoxypropiophenone (82 mg, 0.5 mmol). After purification by column chromatography, the compound was isolated as pale yellow liquid (79 mg, 0.43 mmol, 86%). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 1.15 (s, 3H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 199.6, 163.3, 130.2, 113.7, 55.4, 31.3–30.4 (m), 8.3 ppm.

1-([1,1'-biphenyl]-4-yl)-2-(methyl-d3)butan-1-one-2-d (scheme 7.2, entry 20) [21]**:** Prepared from 4-butyrobiphenyl (0.11 g, 0.5 mmol). After purification by column chromatography, the compound was isolated as white solid (0.12 g, 0.36 mmol, 71%). Mp = 86–87 ^{o}C. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.1 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 1.80–1.77 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = 200.4, 145.7, 140.1, 136.0, 129.1, 128.8, 128.3, 127.4, 127.4, 40.8–39.1 (m), 29.9, 18.0, 14.0 ppm.

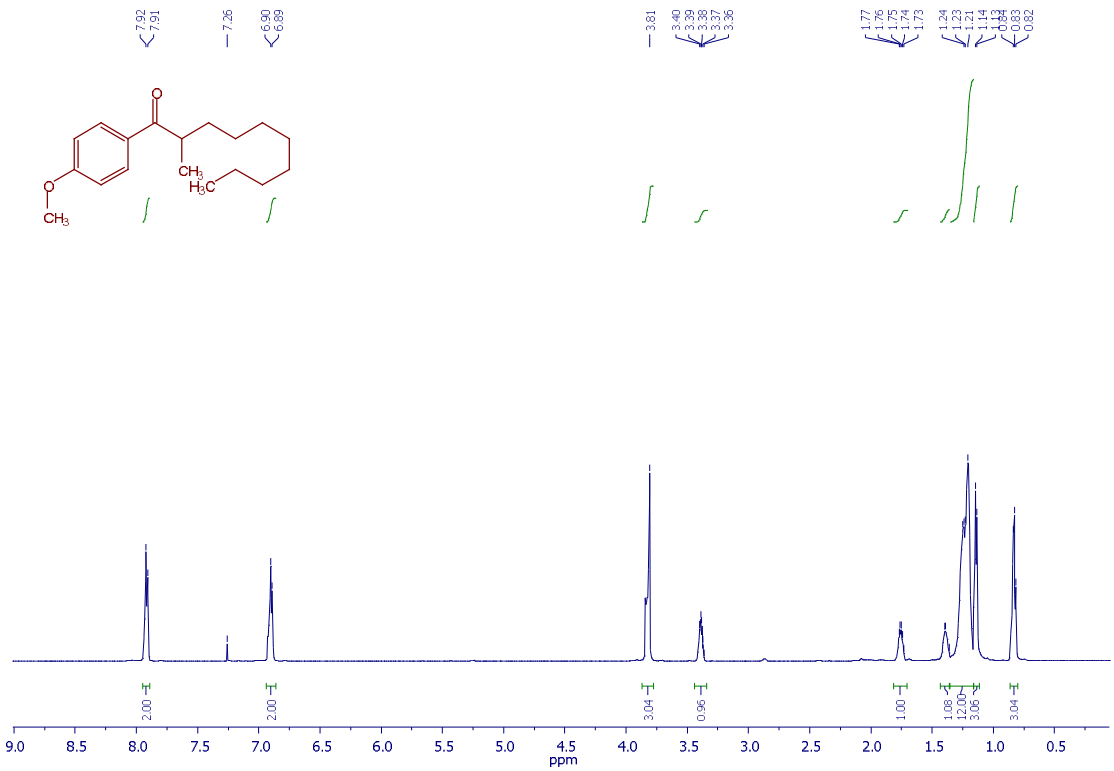
7.5 NMR spectra for new methylated compounds



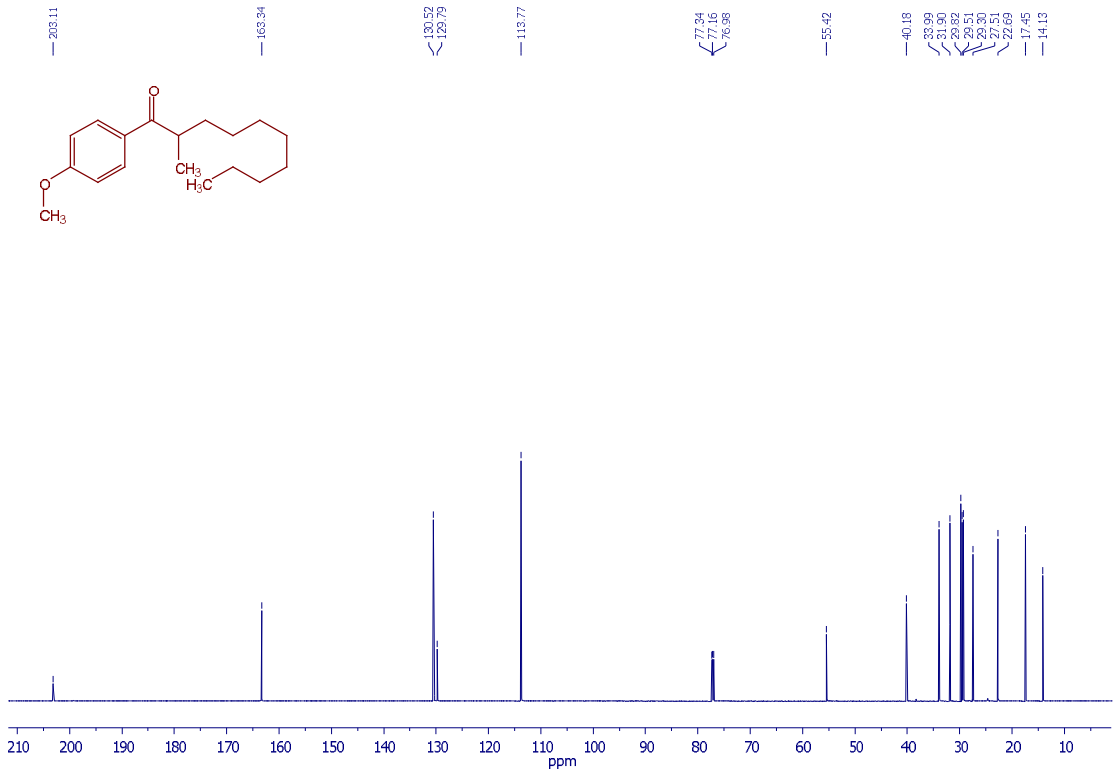
^{1}H NMR of compound 4



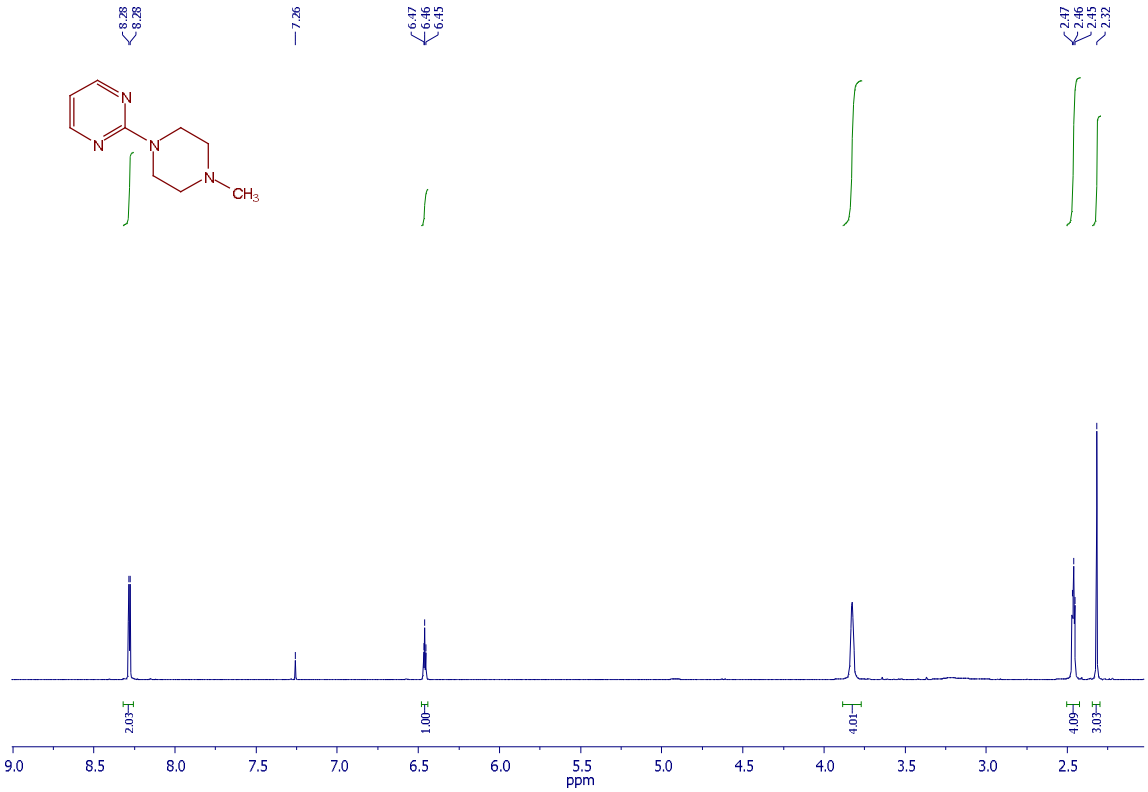
^{13}C NMR of compound 4



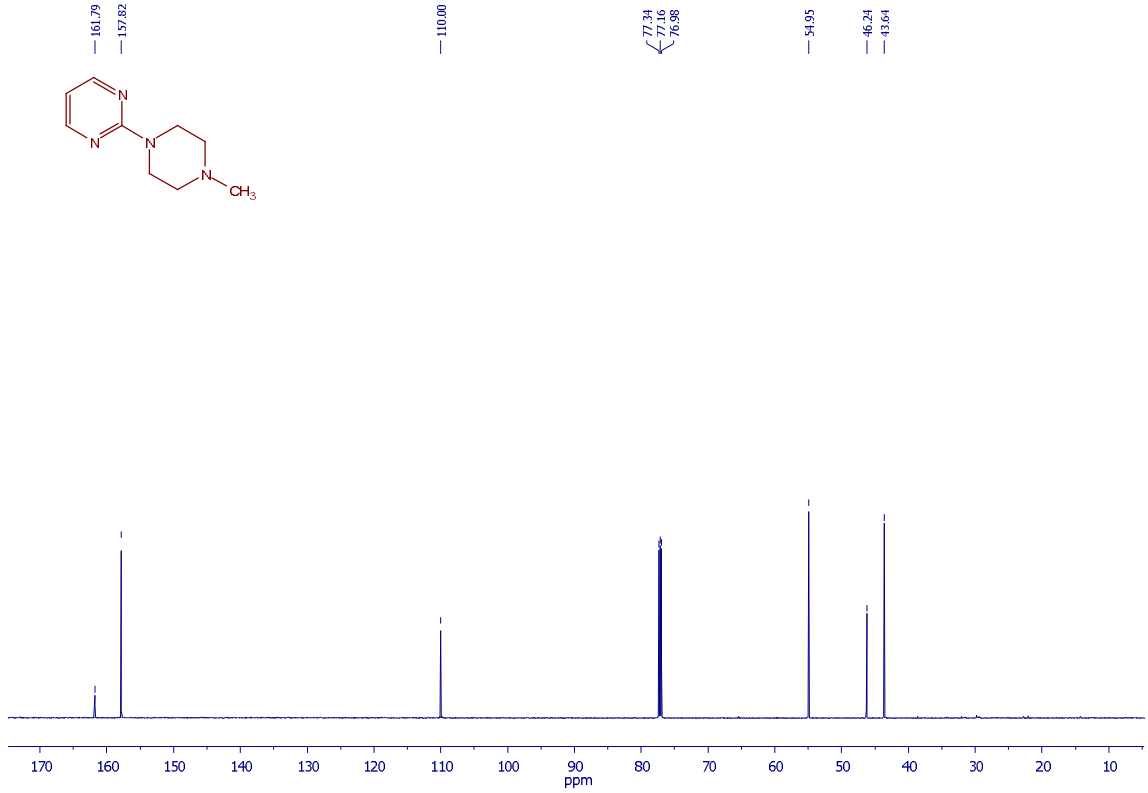
^{1}H NMR of compound 12



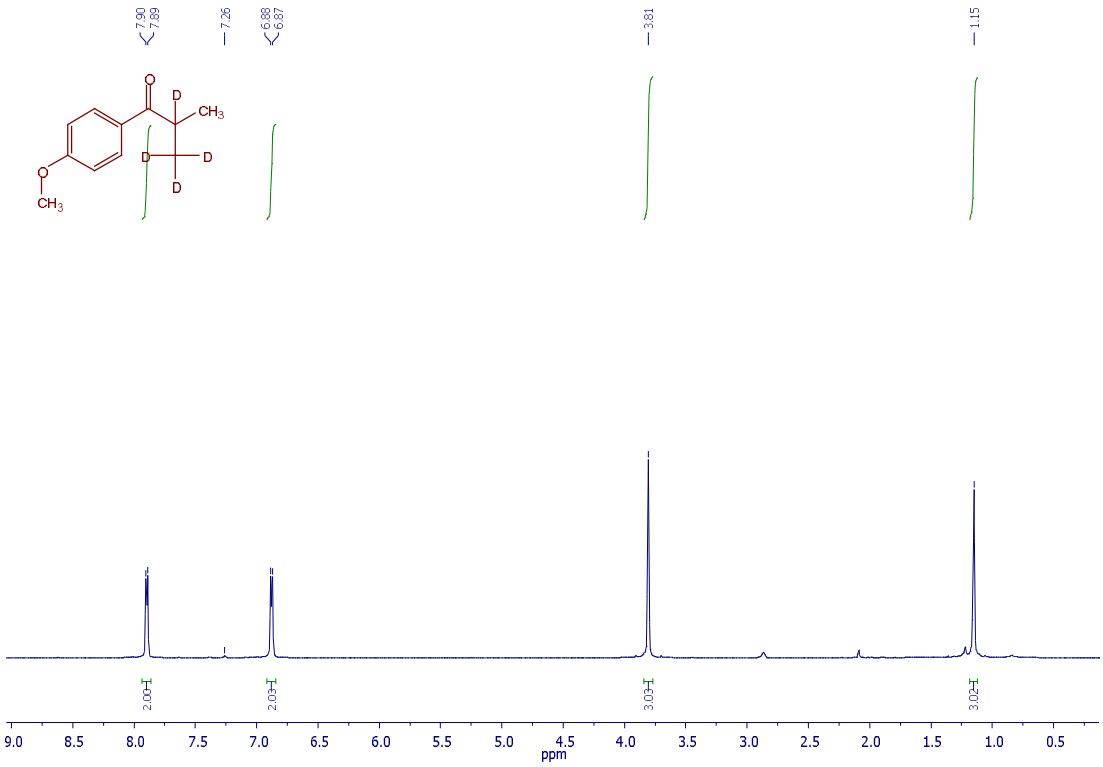
^{13}C NMR of compound 12



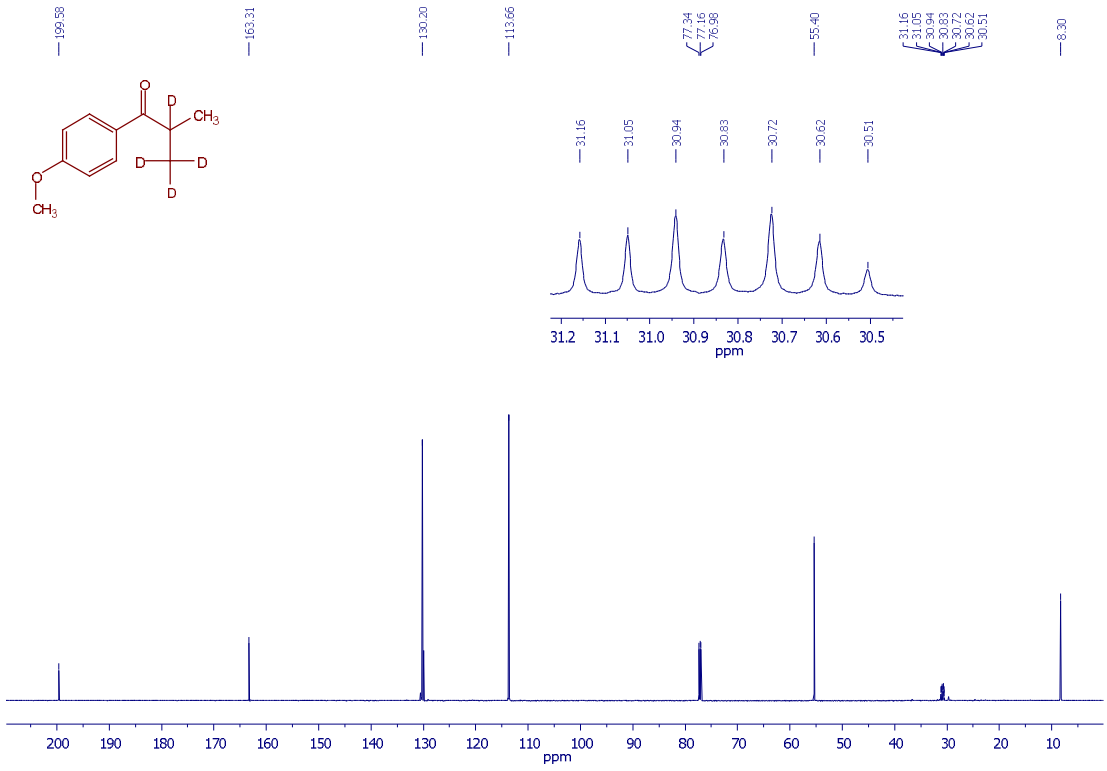
^{1}H NMR of compound 18



^{13}C NMR of compound 18



^{1}H NMR of compound 19



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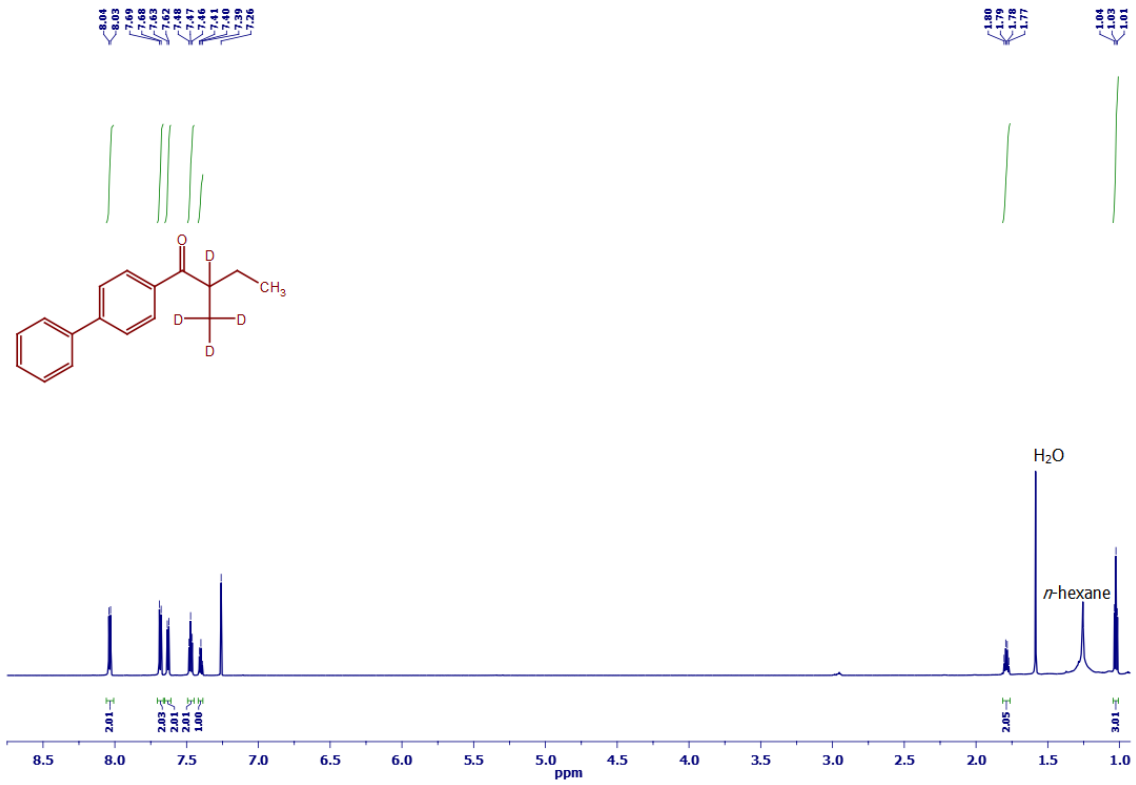
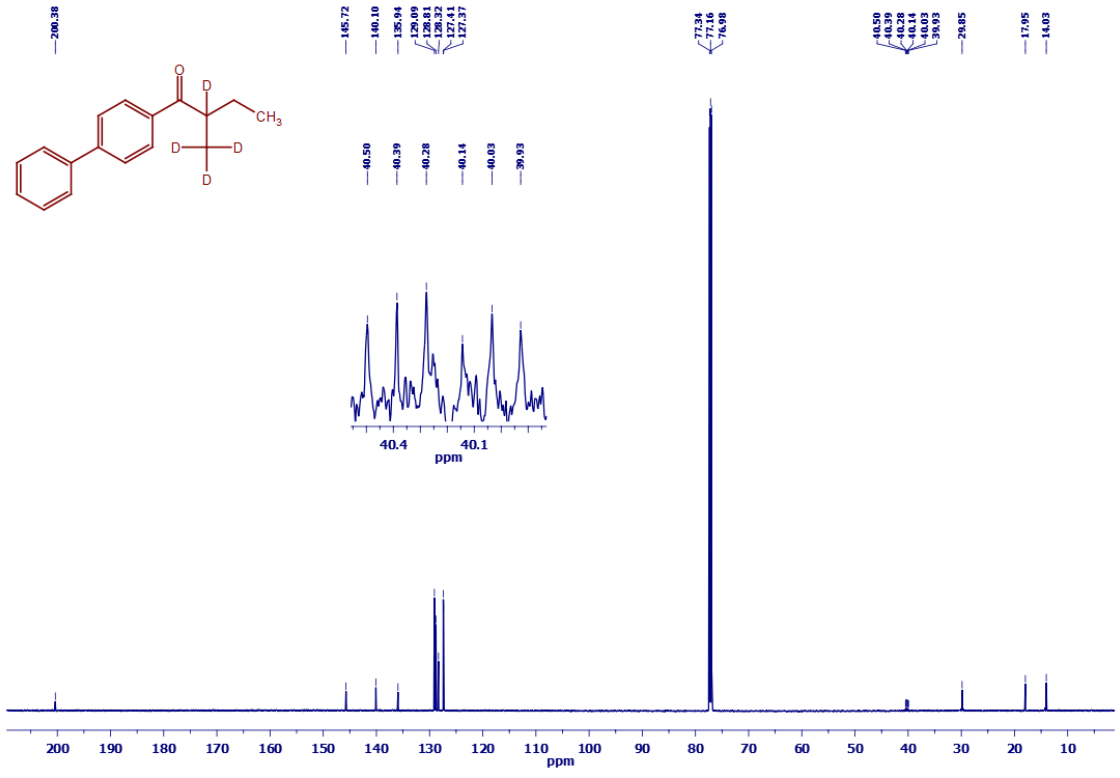


^{1}H NMR of compound 20



^{13}C NMR of compound 20

7.6 References

1. (a) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.*, 2010, **110**, 681; (b) F. Huang, Z. Liu, and Z. Yu, *Angew. Chem. Int. Ed.*, 2016, **55**, 862.

2. (a) E. J. Barreiro, A. E. Kummerle and C. A. M. Fraga, *Chem. Rev.*, 2011, **111**, 5215; (b) H. Schonherr and T. Cernak, *Angew. Chem. Int. Ed.*, 2013, **52**, 12256; (c) G. Yan, A. J. Borah, L. Wang and M. Yang, *Adv. Synth. Catal*., 2015, **357**, 1333; (d) K. Natte, H. Neumann, M. Beller and R. V. Jagadeesh, *Angew. Chem. Int. Ed*., 2017, **56**, 6384.

3. (a) Y. Yokoyama and K. Mochida, *J. Organomet. Chem*., 1995, **499**, C4–C6; (b) K. Maruoka, A. B. Concepcion and H. Yamamoto, *Synthesis*, 1994, 1283.

4. (a) J. M. Mayer, D. A. Hrovat, J. L. Thomas and W. T. Borden, *J. Am. Chem. Soc.*, 2002, **124**, 11142; (b) K W. H. Lin and H. F. Chang, *Catal. Today*, 2004, **97**, 181; (c) M. Qian, M. A. Liauw and G. Emig, *Appl. Catal. A: Gen*. 2003, **238**, 211; (d) N. Yamamoto, Y. Obora and Y. Ishii, *J. Org. Chem*., 2011, **76**, 2937.

5. (a) G. E. Dobereiner and R. H. Crabtree, *Chem. Rev.* 2010, **110**, 681; (b) F. Huang, Z. Liu, and Z. Yu, *Angew. Chem. Int. Ed.*, 2016, **55**, 862.

6. L. K. M. Chan, D. L. Poole, D. Shen, M. P. Healy and T. J. Donohoe, *Angew. Chem. Int. Ed.* 2014, **53**, 761.

7. (a) F. Li, J. Ma and N. Wang, *J. Org. Chem*. 2014, **79**, 10447; (b) S. Ogawa and Y. Obora, *Chem. Commun*. 2014, **50**, 2491; (c) D. Shen, D. L. Poole, C. C. Shotton, A. F. Kornahrens, M. P. Healy and T. J. Donohoe, *Angew. Chem. Int. Ed*. 2015, **54**, 1642; (d) X. Quan, S. Kerdphon and P. G. Andersson, *Chem. Eur. J.* 2015, **21**, 3576; (e) K. Oikawa, S. Itoh, H. Yano, H. Kawasaki and Y. Obora, *Chem. Commun.* 2017, **53**, 1080.

8. T. T. Dang and A. M. Seayad, *Adv. Synth. Catal*., 2016, **358**, 3373. K. Chakrabarti, M. Maji, D. Panja, B. Paul, S. Shee, G. K. Das and S. Kundu, *Org. Lett*., 2017, **19**, 4750.

9. (a) B. Ding, Z. Zhang, Y. Liu, M. Sugiya, T. Imamoto and W. Zhang, *Org. Lett.*, 2013, **15**, 3690; (b) S. Gowrisankar, H. Neumann and M. Beller, *Angew. Chem. Int. Ed.,* 2011, **50,** 5139; (c) S. Gowrisankar, A. G. Sergeev, P. Anbarasan, A. Spannenberg, H. Neumann and M. Beller, *J. Am. Chem. Soc.*, 2010, **132**, 11592; (d) J. A. Müller, C. P. Gollerand and M. S. Sigman, *J. Am. Chem. Soc*., 2004, **126**, 9724.

10. (a) A. Martínez-Asencio, M. Yus and D. J. Ramón, *Synthesis*, 2011, 3730; (b) T. T. Dang, B. Ramalingam, S. P. Shan and A. M. Seayad, *ACS Catal.*, 2013, **3,** 2536; (c) R. Mamidala, V. Mukundam, K. Dhanunjayarao and K. Venkatasubbaiah, *Tetrahedron* 2017, **73**, 2225.

11. (a) O. Kose and S. Saito, *Org. Biomol. Chem*. 2010, **8**, 896; (b) R. Mamidala, S. Samser, N. Sharma, U. Lourderaj and K. Venkatasubbaiah, *Organometallics*, 2017, **36**, 3343.

12. Z. Hou, L. Jiang, F. Guo, Y. Li and Z. Shi, *ChemCatChem*, 2017, **9**,3827.

13. R. Mamidala, V. Mukundam, K. Dhanunjayarao, and K. Venkatasubbaiah, *Dalton Trans.*, 2015, **44**, 5805.

14. D. Tilly, S. S. Samanta, A.-S. Castanet, A. De and J. Mortier, *Eur. J. Org. Chem.*, 2006, 174.

15. A. S.-K. Tsang, A. Kapat and F. Schoenebeck, *J. Am. Chem. Soc.*, 2016, **138**, 518.

16. Z. Li and V. Gevorgyan, *Angew. Chem. Int. Ed.*, 2011, **50**, 2808.

17. T. T. Dang, B. Ramalingam and A. M. Seayad, *ACS Catal.*, 2015, **5**, 4082.

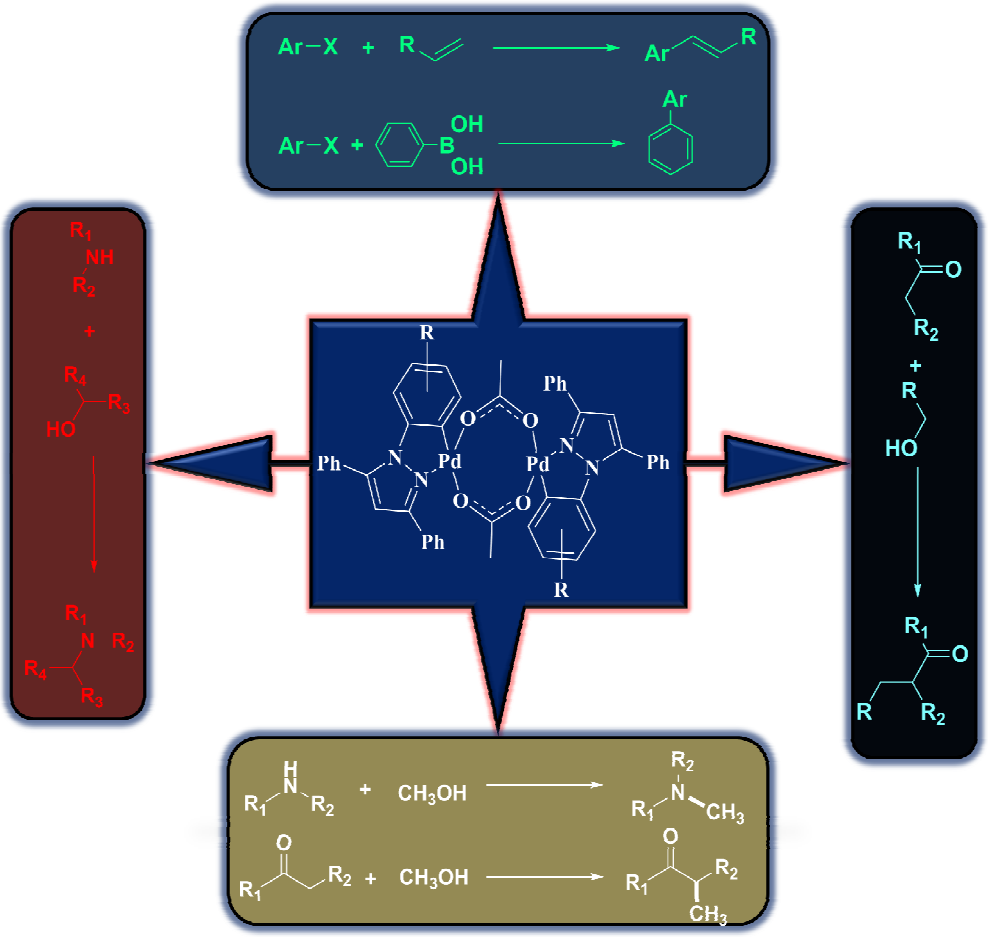
18. B. Paul, S. Shee, K. Chakrabarti, and S. Kundu, ChemSusChem, 2017, **10**, 2370.

19. T. Gao and P. Sun, *J. Org. Chem.*, 2014, **79**, 9888.

20. D. Zoua, H. Cuia, L. Qina, J. Li, Y. Wu and Y. Wu, *Synlett.*, 2011, 349.

21. New compound

Summary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R
Ar–X +
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OH
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NH
R2
+
R4
R3
HO
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R4
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R
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Pd
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R2
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HO
R1
O
R
R2
+ CH3OH
R2
N
R1
CH3
O
R1
R2 + CH3OH
O
R2
R1
CH3