Pyrazole and BINOL phosphoric acid based palladium catalysts and their application in organic transformations

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

a. Published

*1. Samser, S.; Biswal, P.; Meher, S. K.; Venkatasubbaiah, K., Palladium mediated one-pot synthesis of 3-aryl-cyclohexenones and 1, 5-diketones from allyl alcohols and aryl ketones. *Org. Biomol. Chem*. **2021**, *19*, 1386-1394.

*2. Samser, S.; Mohapatra, O; Biswal, P.; Venkatasubbaiah, K., Palladium-mediated tandem isomerization–methylenation of allyl alcohols: One-Pot Synthesis of 1,5-Diketones. *J. Org. Chem*., **2021**, *86,* 13744-13753

3. Mamidala, R.; **Samser, S**.; Sharma, N.; Lourderaj, U.; Venkatasubbaiah, K., Isolation and characterization of regioisomers of pyrazole-based palladacycles and their use in α-alkylation of ketones using alcohols. *Organometallics* **2017,** *36*, 3343-3351.

4. Mamidala, R.; Subramani, M. S.; **Samser, S**.; Biswal, P.; Venkatasubbaiah, K., Chemoselective alkylation of aminoacetophenones with alcohols by using a palladacycle-phosphine catalyst. *Eur. J. Org. Chem.* **2018,** *2018*, 6286-6296.

5. Mamidala, R.; Biswal, P.; Subramani, M. S.; **Samser, S**.; Venkatasubbaiah, K., Palladacycle-phosphine catalyzed methylation of amines and ketones using methanol. *J. Org. Chem* **2019,** *84*, 10472-10480.

6. Biswal, P.; **Samser, S**.; Nayak, P.; Chandrasekhar, V.; Venkatasubbaiah, K., Cobalt (ii) porphyrin mediated selective synthesis of 1, 5-diketones via an interrupted-borrowing hydrogen strategy using methanol as a C1 source. *J. Org. Chem.* **2021,** *86*, 6744-6754.

7. Biswal, P., Samser, S., Meher, S.K., Chandrasekhar, V. and Venkatasubbaiah, K., Palladium-Catalyzed Synthesis of α-Methyl Ketones from Allylic Alcohols and Methanol. *Adv. Synth. Catal*. **2021,** https://doi.org/10.1002/adsc.202101101.

b. Manuscript under preparation

*1. Samser, S.; Venkatasubbaiah, K., Synthesis of β-amino ketones by redox coupling of allyl alcohols and aryl amines using pyrazole based palladacycle. (Manuscript under preparation)

*2. Samser, S.; Venkatasubbaiah, K., Synthesis and characterization of polystyrene supported pyrazole based palladium catalysts and their application in acceptorless dehydrogenative coupling of secondary alcohols. (Manuscript under preparation)

*3. Samser, S.; Mohapatra, O; Venkatasubbaiah, K., Synthesis of α-branched ketones from secondary alcohols using triple dehydrogenative method. (Manuscript under preparation)

Conferences

1. Regio-isomers of pyrazole based palladacycle: synthesis, isolation and their uses in α-alkylation of ketones. **Samser, S.** Mamidala, R and Venkatasubbaiah, K.in biennial symposium, 'Modern Trends in Inorganic Chemistry' (MTIC-XVII) held at CSIR-NCL, Pune and IISER, Pune during 11th to 14th December 2017. **(Poster presentation)**

2. Regio-isomers of pyrazole based palladacycle: synthesis, isolation and their uses in α-alkylation of ketones. **Samser, S.** Mamidala, R and Venkatasubbaiah, K. in 'Inter IISER and NISER Chemistry Meet (IINCM-2017)' held at NISER, Bhubaneswar during 22nd to 24th December, 2017. **(Poster presentation)**

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Shaikh Samser

Shaikh Samser

Dedicated to My

Mother

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Shaikh Samser.

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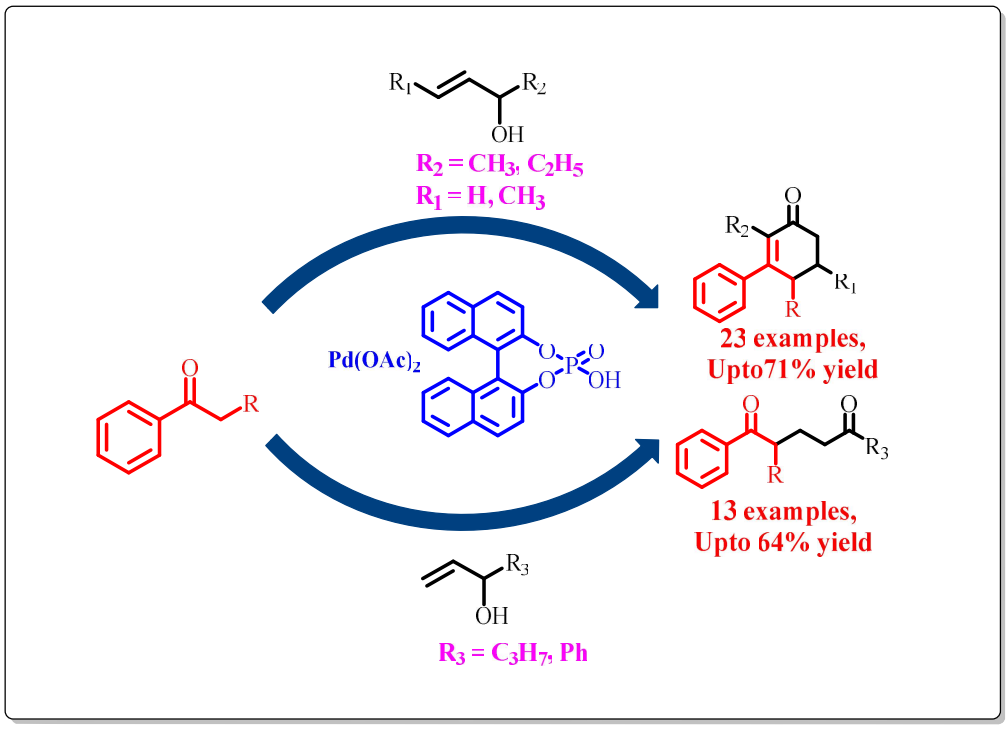
Contents

SYNOPSIS

This thesis has been organized into six chapters. Chapter 1 is divided into two parts. The first part briefly discusses about the history of palladacycles and their application as homogeneous and heterogeneous catalysts in cross-coupling reactions. The second part of this chapter discusses about isomerization of allyl alcohol by different metal catalysts. The use of allyl alcohol as an enolate precursor in tandem reactions for the synthesis of important molecules have been described.

Chapter 2: Palladium mediated one-pot synthesis of 3-arylcyclohexenone and 1,5-diketones from allyl alcohols and arylketones.

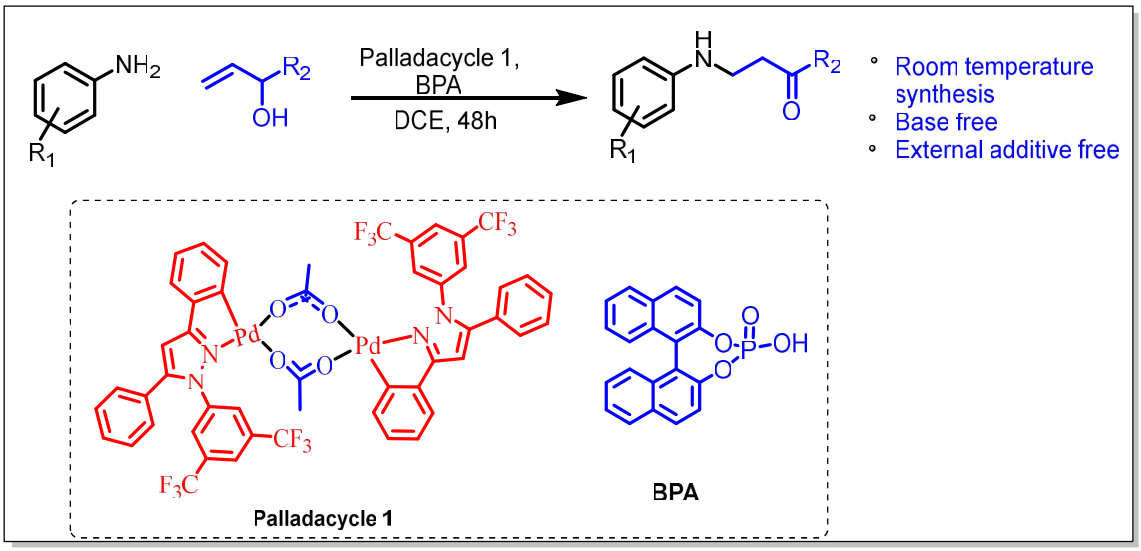
This chapter discusses about a new palladium and BINOL phosphoric acid system for the synthesis of 3-arylcyclohexenone and 1,5-diketones. The developed protocol is based on the tandem isomerization of allyl alcohol followed by functionalization by an arylketone. This protocol tolerated different functional groups present on the aryl ketone and substitution by long chain aliphatic or aryl group at C1 position of the allyl



alcohols resulted in the synthesis of 1,5- diketone exclusively. Mechanistic studies revealed the in situ conversion of allyl alcohol to the corresponding vinyl ketone which undergoes Michael addition in presence of the base followed by intramolecular aldol condensation to produce the annulated product. In case of higher aliphatic chain length or substitution by aryl group at C1 position the reaction does not undergo aldol condensation thereby, only the 1,5-diketone formation occurs.

Chapter 3: Synthesis of β-amino ketones by redox coupling of allyl alcohols and aryl amines using pyrazole based palladacycle

Using the tandem isomerization-functionalisation approach we reacted aryl amines with allyl alcohols for the synthesis of β-aminoketones. Pyrazole based palladacycle was used as catalyst along with BINOL phosphoric acid as the ligand. Unlike the previous reports, this reaction was carried out in room temperature and does not involve the use of any external additive or base. Using different types of arylamines various types of β-aminoketones were synthesized. Mechanistic investigations revealed the

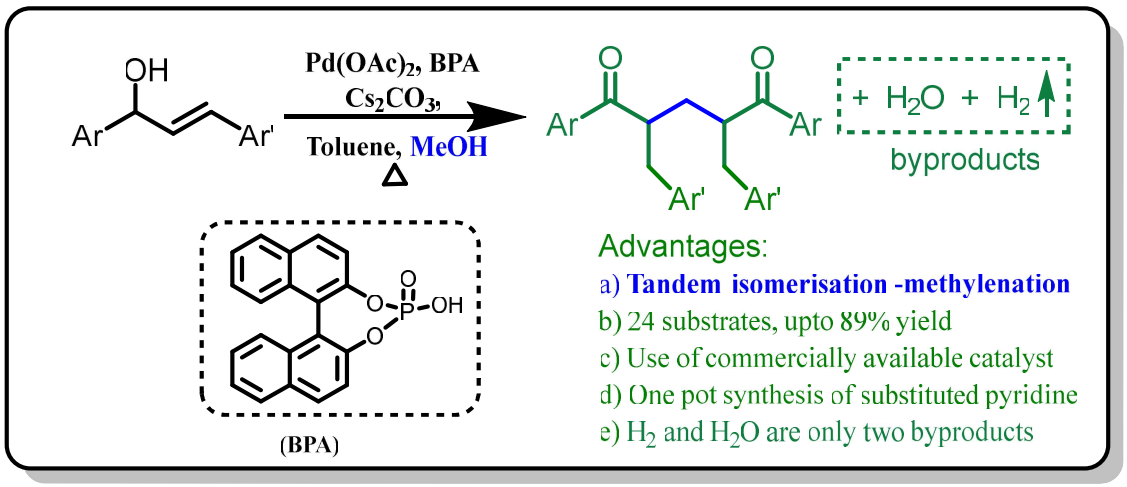


conversion of allyl alcohol to the vinyl ketone which undergoes aza-Michael addition with the amines to form the β-aminoketone. Active species for the reaction was also

isolated as the BPA co-ordinated metal complex and studied for the above mentioned reaction.

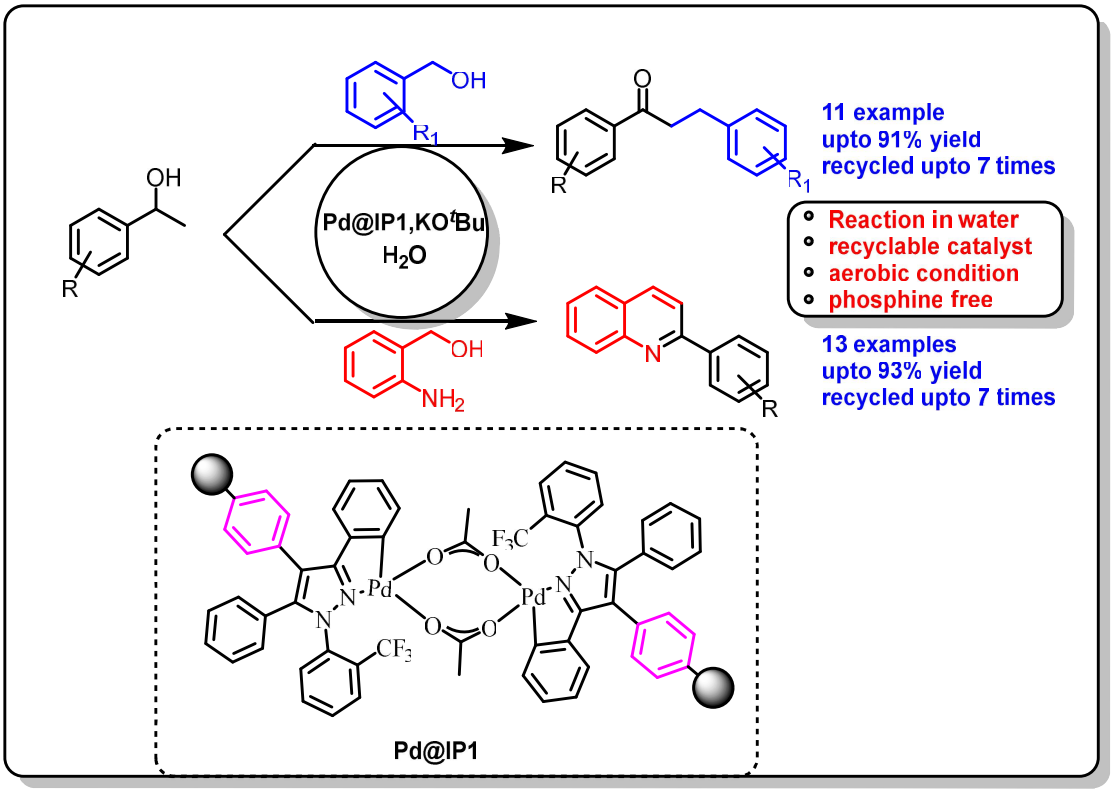
Chapter 4: Tandem isomerization and methylenation of allyl alcohol: one pot synthesis of 1,5-diketones

This chapter discusses about the tandem isomerisation and methylenation of allyl alcohol. Using the palladium and BINOL phosphoric acid system, we reacted allyl alcohols with methanol for the formation of 1,5-diketones. 1,3-Diaryl and 1-aryl substituted allyl alcohols were screened for this reaction. Different additive screening were also carried out to check the compatibility of different functional group under the current protocol. Mechanistic investigation confirms the formation of saturated ketone from allyl alcohols which upon reacting with formaldehyde, the product formed from methanol, gives α-methylene species. The α-methylene ketone reacts with another molecule of ketone *via* Michael addition to form the 1,5-diketone. Using this protocol, substituted pyridines were also synthesised using one pot sequential method.



Chapter 5: Synthesis and characterization of polystyrene supported pyrazole based palladium catalysts and their application in acceptorless dehydrogenative coupling of secondary alcohols

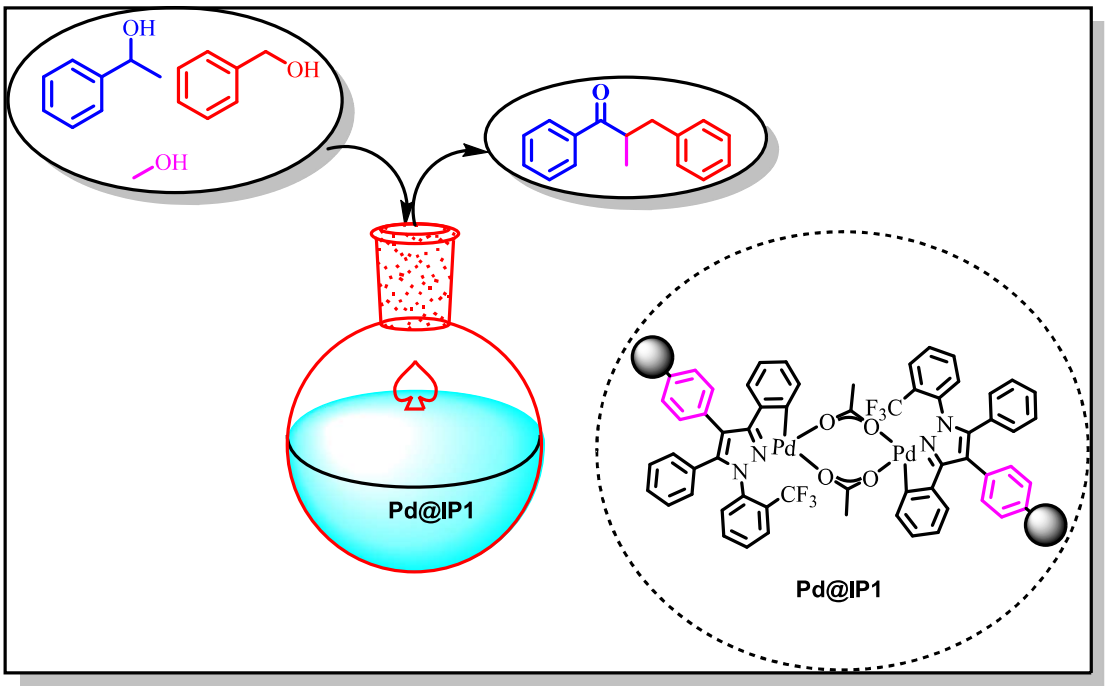
In this chapter, we discuss about the synthesis of three polystyrene supported pyrazole based palladacycle and their application in acceptorless dehydrogenative coupling of secondary alcohols. Two soluble polymers P1 and P2 were prepared from the free radical polymerization of monomer M1 and M2 respectively. Insoluble resin IP1 was prepared by the cross polymerization of monomer M2 and divinyl benzene in 1:2 ratio. Subsequently, three metal catalysts(Pd@P1, Pd@P2 and Pd@IP1) were prepared by the palladation of P1, P2 and IP1. These catalysts were screened for dehydrogenative cross coupling of secondary alcohol in the synthesis of α-alkylated ketones and quinolines. The catalyst anchored to the insoluble resin IP1 was more active. The



catalyst was reused seven times for both the alkylation and quinoline reactions and was further characterized by TEM, solid state NMR and XPS.

Chapter 6: Synthesis of α-branched ketones from secondary alcohols using triple dehydrogenative method

In this chapter, we report one-pot synthesis of α-methylated branched ketones. Although few reports for the synthesis of α-methylated branched ketones from ketones are available, use of secondary alcohols as a reagent have been scarcely studied. As secondary alcohols are prone to self-coupling which results in the formation of β-branched ketones. In this regard, we present here a novel method for the production α-methylated branched ketones from secondary alcohols and methanol catalyzed by a reusable polystyrene supported palladium catalyst. Various types of branched ketones were produced by varying primary and secondary alcohol. Deuterium labelling experiment shows the involvement of hydrogen from secondary as well as primary alcohols.



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^{1}H NMR	Proton nuclear magnetic resonance
^{13}C NMR	Carbon-13 nuclear magnetic resonance
^{31}P NMR	Phosphorous-31 nuclear magnetic resonance
^{19}F NMR	Fluorine-19 nuclear magnetic resonance
ESI	Electrospray ionization
DFT	Density functional theory
HRMS	High-resolution mass spectrometry
GPC	Gel permeation chromatography
XRD	X-ray diffraction
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
DCE	1,2-Dichloroethane
EtOH	Ethanol
THF	Tetrahydrofuran
DMF	Dimethylformamide
$CDCl_3$	Deuterated chloroform
AcOH	Acetic acid
Na_2CO_3	Sodium carbonate
K_2CO_3	Potassium carbonate
Cs_2CO_3	Cesium carbonate
TON	Turn over number
MAO	Methylaluminoxane
NHC	N-heterocycliccarbene
PEG	Polyethylene glycol

IL	Ionic liquid
PVP	Polyvinylpyridine
PS	Polystyrene
GO	Graphene oxide
XPS	X- ray photoelectron spectroscopy
TBAB	Tetrabutylammonium bromide
DESs	Deep eutectic solvents
BINOL	Binaphthol
BPA	BINOL phosphoric acid
Dppe	Diphenyl phosphine ethane
N.D	Notr detected
GC	Gas chromatography
GC-MS	Gas chromatography- mass spectrometry
TBHP	Tert-butyl hydroperoxide
M_n	Number average molecular weight
M_w	Weight average molecular weight
PDI	Poly dispersity index
ICP-AES	Inductively coupled plasma atomic emission spectroscopy
ICP-OES	Inductively coupled plasma optical emission spectroscopy
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)

Chapter 1

General Introduction

1.1. Introduction

With the emergence of transition metal catalysts, cross coupling reactions have gained enormous importance and are the most widely studied transformation among the synthetic chemist.[1] This has been recognized with the 2010 Nobel prize to Professors Suzuki, Negishi and Heck. Among the various metal explored for such transformation, palladium based catalysts have emerged as the most preferred catalysts despite their high cost compared to other metals.[2] Palladium catalysts, as compared to other metal complexes, are more stable under air and moisture, offer a diverse functional group tolerance and high turnover number (TON).[3] With the advents of palladacycles with tunable steric and electronic properties have further enhanced the application of palladium catalysts for important transformations. Furthermore, the drawbacks of homogeneous catalysis in case of palladacycles have also been averted by anchoring the catalysts to a solid support such as silica,[4] polymer[5] etc. This chapter presents a brief historical overview of palladacycles, reports of homogeneous and heterogeneous palladacycles, isomerization of allyl alcohols and tandem functionalization.

1.2. Palladacycles: Introduction and history

Palladium complexes containing a metal carbon bond and stabilised by a donor atom are termed as palladacycles. These complexes are categorized into four electron donor CY type palladacycle and six electron donor YCY type palladacycle, also called as pincer palladium complexes (figure 1.1). The CY type complexes generally exist as a chloro or acetate bridged dimer complexes and can take the cisoid or transoid geometry (figure 1.1). The CY type palladacycle can be further categorized into neutral dimer (**1**)[6], monomeric (**2**)[7], bis-cyclopalladated (**3**)[8], cationic (**4**)[9] and anionic (**5**)[10] depending upon the nature of the co-ordinated ligand to the metal complex (figure 1.2).

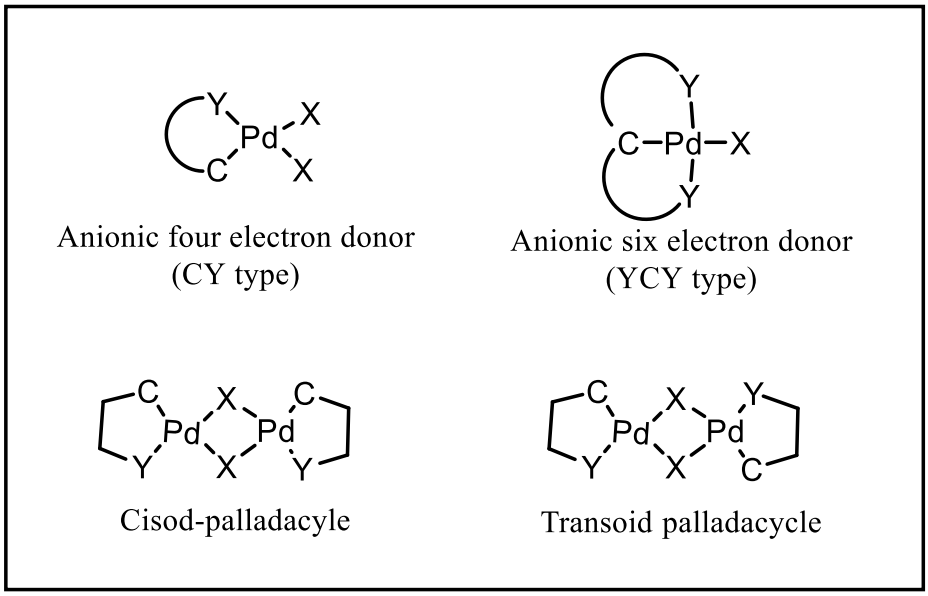


Figure 1.1. Types of palladacycles

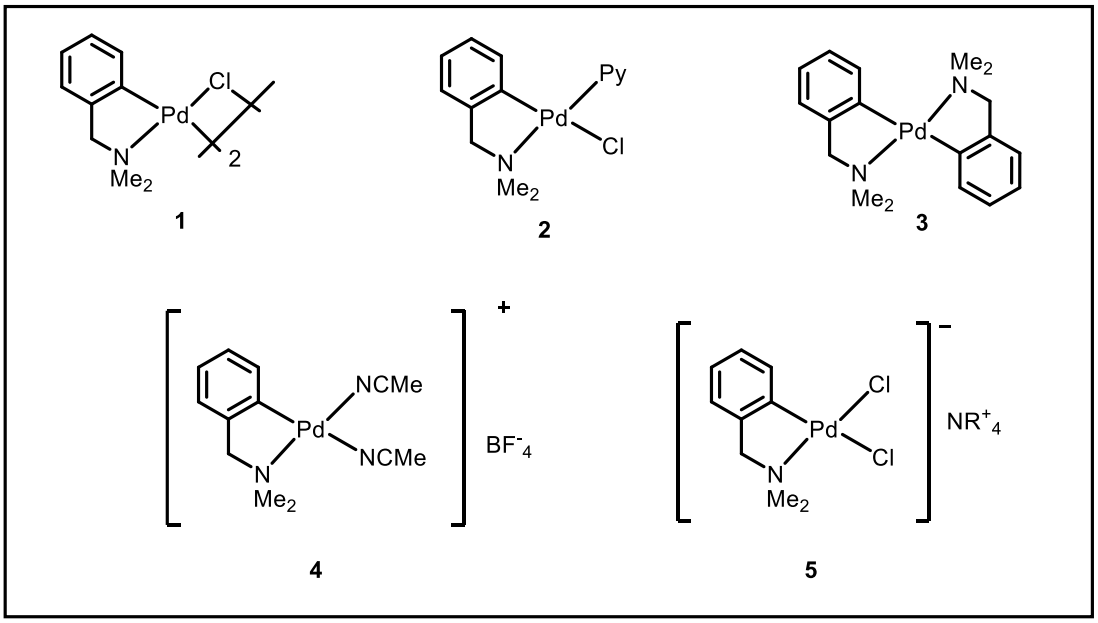
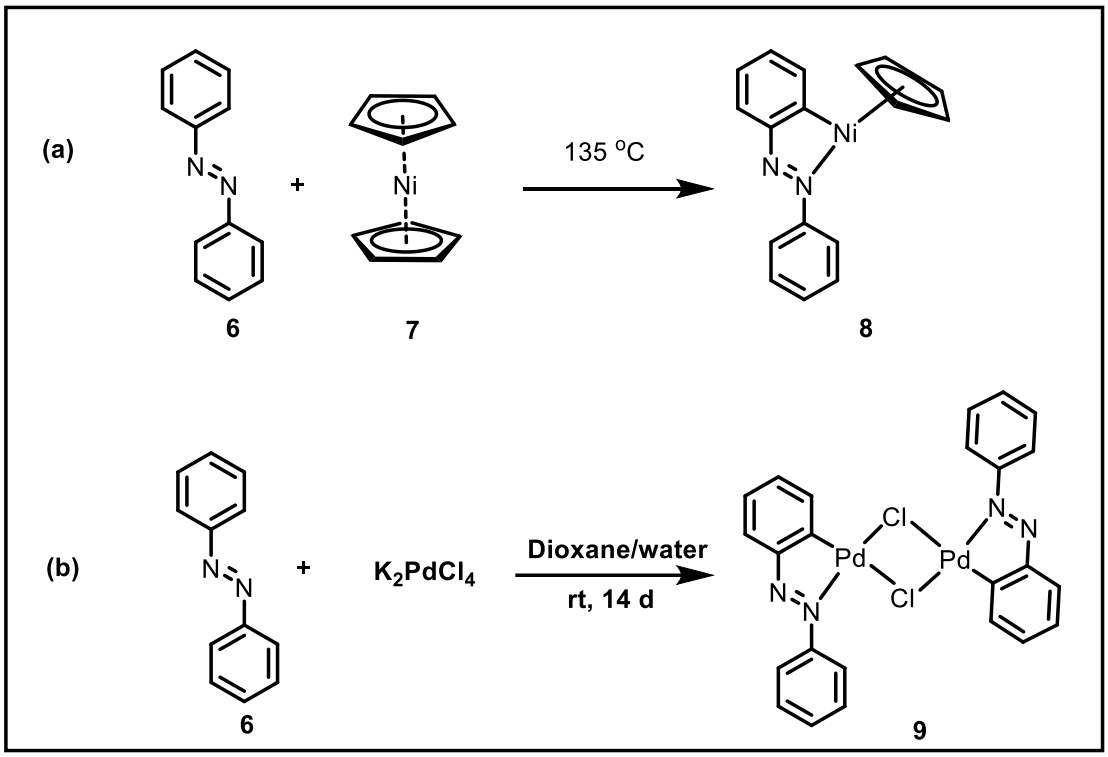


Figure 1.2. Types of CY-type palladacycles

In the early 1963, Dubeck[11] and group reported the synthesis of a cyclometallated nickel complex by reacting azobenzene with dicyclopentadienylnickel (scheme 1.1(a)). This discovery inspired the group of Arthur Cope[12], who reacted the azobenzene with different palladium and platinum salts (scheme 1.1(b)). The corresponding metal complexes obtained were thermally more stable as compared to the precursor metal

salts. Platinum complex did not melt before decomposition which occurred at 270 ^{o}C. The palladium analogue was stable upto 279-281 ^{o}C. After a series of experiments, they confirmed the cyclometallated structure as is depicted in Scheme 1.1.



Scheme1.1. Synthesis of (a) nickelacycle and (b) palladacycle

1.2.1. Palladacycles in homogeneous catalysis:Recent reports

Earlier in the history of palladacycles, they were considered as inactive for cross coupling reactions. Breakthrough report by Herman's group led to the foundation for their use as precatalyst for various transformations. Herman and co-worker reported the synthesis of phospha palladacycle[13] which was thermally more stable than their corresponding palladacycle and used it as precatalyst in Heck olefination reactions. This adduct, offered a higher TON, minimized the use of higher phosphine ligands. This report led to the synthesis of a series of palladacycles with different steric and electronic properties based on the requirement of reaction conditions. Gumusada *et al.*[14] synthesised a Pd-N-heterocycle carbene complex (**10,** figure 1.3) which was air and

moisture stable under both solid and solution state. The carbene based catalyst was further used in the Suzuki-Miyaura reaction. However, the presence of N-allyl substituent on the imidazol-2-ylidene entity caused it to be a less effective catalytic system. Buchwald's group have synthesised three generation of amine based palladacycle[15] for C-N cross coupling reactions with each generation of catalyst overcoming the drawback of its predecesor. The first generation of catalyst **G1** (**11**, figure 1.3) offered a low shortlife in solution and required higher temperature for its activation. Second generation catalyst **G2** (**12**, figure 1.3) offered a low solubility in solution and was not stable for an extended time in solution state. Moreover, bulkier phosphine ligands required for C-N bond formation could not be incorporated into the complex. Third generation catalyst **G3** (**13**, figure 1.3) circumvent these drawbacks and have been in use for many breakthrough reactions[16].

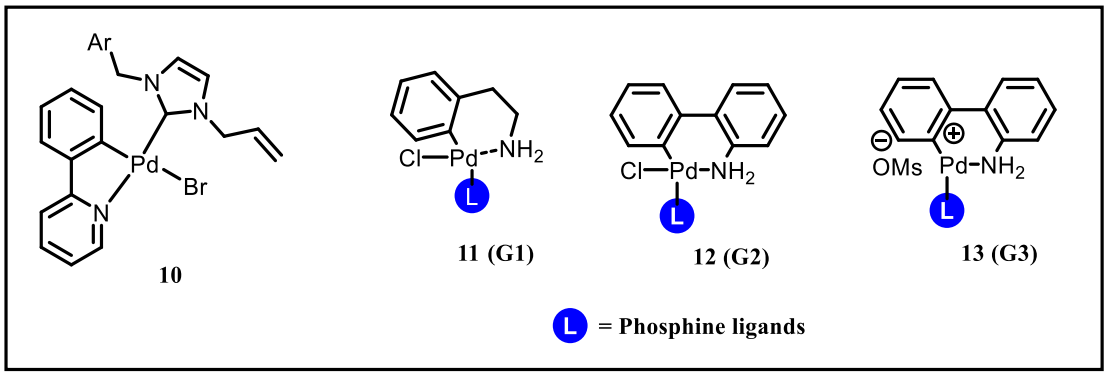
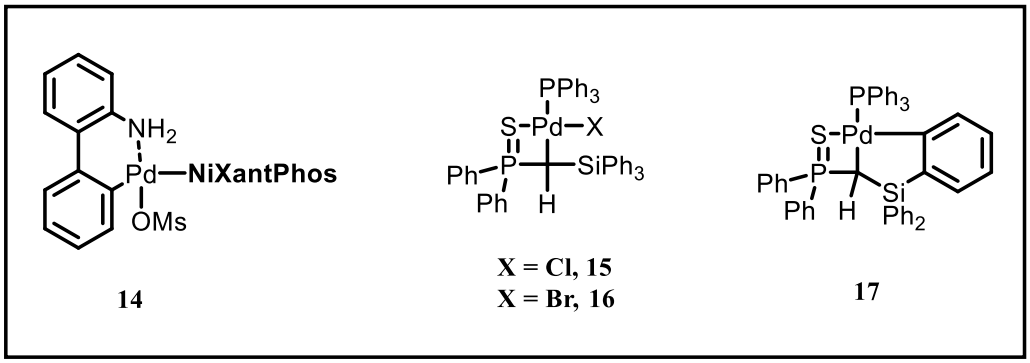


Figure 1.3. Gumusada's and Buchwald's groups' catalysts

Jia *et al.*[17] employed a NiXantPhos-based palladacyclic system (**14**, Figure 1.4) as a precatalyst for the synthesis of diaryl sulfoxides from aryl benzyl sulfoxides and electronically deactivated aryl chlorides. In this report a single catalytic system promoted three distinct transformations *viz* α-arylation of benzyl sulfoxides, generation of sulfenate anion and S-arylation of sulfenate anions to produce the desired diaryl sulfoxides. Gessner's group[18] prepared a series of mono and bis-cyclopalladated with

a silyl substituted thio-phosphinoyl ligand. The monomeric complexes, **15** and **16** (figure 1.4), were prepared by oxidative addition of the halogenated ligand and the bis-cylopalladated complex were preapred by oxidative addition of the halogen ligand followed by dehydrohalogenation by a metal base. Both the complexes were used as precatalyst in Suzuki-Miyaura cross coupling reaction. The monomeric complex was proven to be more active compared to its bis-cyclopalladated analogues.



14 **X = Cl, 15** **X = Br, 16** **17**

Figure 1.4. Jia's and Gessner's groups' palladacycles

Kapdi and co-worker[19] presented two imine based palladacycles **18** and **19** (figure 1.5), co-ordinated to acetate and maleimide anion respectively and additionally stabilised by a phosphine ligand. Employing these two catalyst, they developed a site-selective Suzuki−Miyaura cross-coupling of dibromoanthracene *via* a unique and unprecedented one-pot sequential triple arylation protocol. Maleimide co-ordinated complex showed better catalytic activity as compared to acetate co-ordinated counterpart because of the better π-accepting capability of maleimide than the acetate. Yan *et al.*[20] reported six ferrocenylpyridine palladacycle complexes (**20**-**25,** figure 1.5) with different 4-substituted pyridine as ancillary ligands. The different 4-substituted pyridine ligands alter the steric as well as electron density on the metal centre. The catalytic efficiency of all the six palladacycles were tested with Suzuki coupling reaction along with triphenylphosphine ligated complex **26** (figure 1.5) as a reference. All the catalyst were

highly efficient in comparison to the phosphine co-ordinated complexes under aerobic conditions.

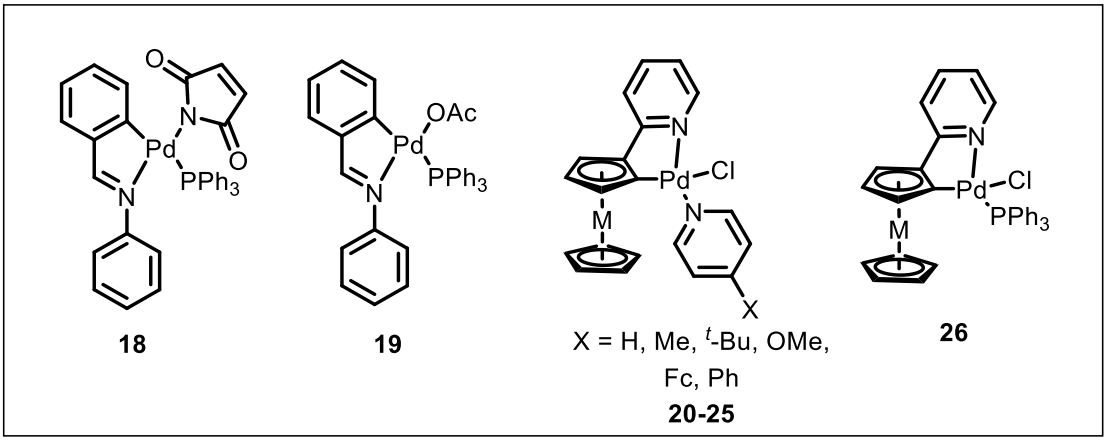


Figure 1.5. Kapdi's and Yan's groups' palladacycles

Muller[21] and co-worker presented a systematic preparation of partially halogenated benzylphosphanes and their corresponding palladacycles in order to find the reactivity difference between halogenated and non-halogenated benzylphosphane palladacycles. The acetate bridged (**27**-**29**, figure 1.6) and the bromide bridged (**30**-**32,** figure 1.6) dimer complexes were prepared and studied for Mizoroki-Heck reaction between bromobenzene and butylacrylate with 0.1% loading of Palladium. These experiments revealed that simple benzylphosphane palladacycles gave better activity over their halogenated counterparts. Dong[22] *et al.* studied the reactivity differences between C(sp^3), N-chelated (**34,** figure 1.6) and C(sp^2), N-chelated (**33,** figure 1.6) phosphane-sulfonate palladacycle complexes. With methylaluminoxane (MAO) as the co-catalyst,

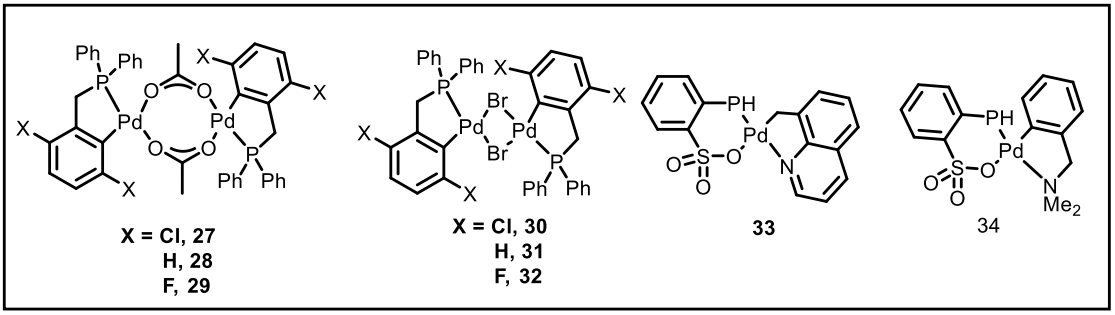


Figure 1.6. Muller and Dong groups' palladacycles

these catalysts were employed in the vinyl polymerisation of norbornene. The C(sp^3),N- chelated palladacycle exhibited a higher catalytic activity than the C(sp^2),N-chelated palladacycle.

Dharani[23] *et al.* presented tetraneuclear palladacycles (**40**-**42**, figure 1.7) based on 3-acetyl-7-methoxy-2H-chromen-2-one (**35**-**39**, figure 1.7) derived Schiff bases. The catalysts were prepared by reacting 3-acetyl-7-methoxy-2H-chromen-2-one derived Schiff bases with potassium salt of tetrachloropalladate. These catalysts were studied for their catalytic efficiency in Suzuki coupling reaction in aqueous medium. The catalytic efficiency of the tetranuclear palladium complexes were compared with that of the mononuclear complexes (**43**, figure 1.7). Tetranuclear complexes were more active and contrary to the general trend in palladium catalysis, these catalysts tolerated the halo substituted *viz*. –Cl, -Br and –I substrates in Suzuki coupling.

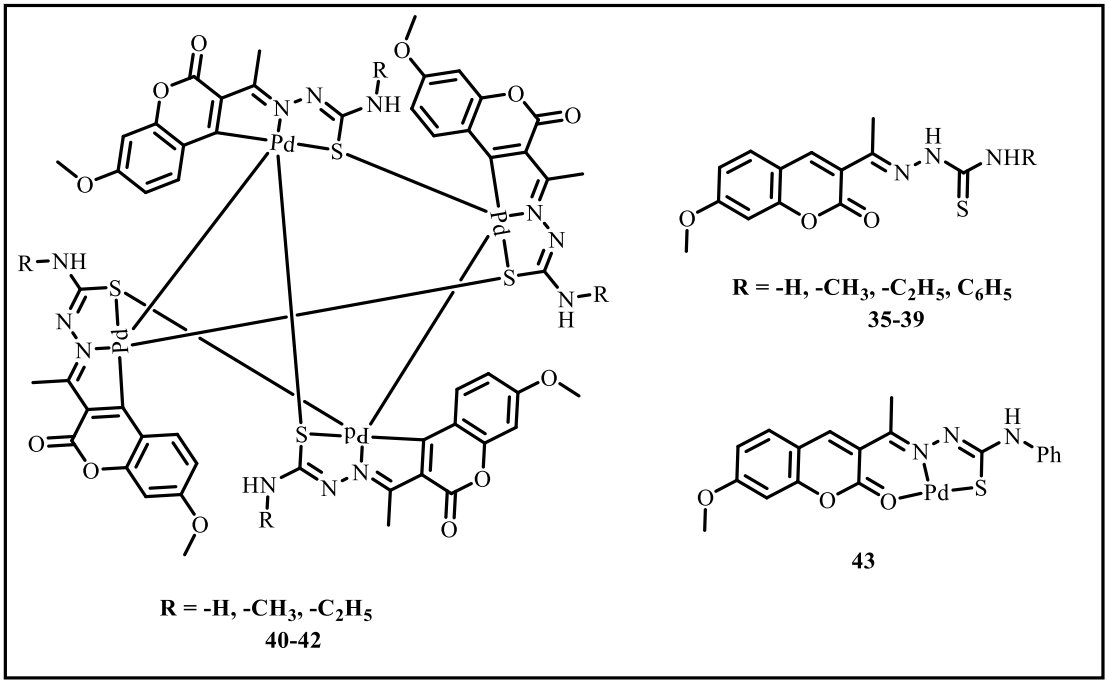


Figure 1.7. Dharani groups' tetranuclear and mononuclear palladacycles

Krishnan and co-workers reported a series of 1,3,5-triphenyl pyrazole based palladacycles with varying substitution of trifluoromethyl group on the phenyl rings at

1 and 3 positions of the pyrazole moiety. The unsubstituted triphenyl pyrazole based palladacycle[24] (**44**, Figure 1.8) was used as precatalyst in the phosphine free Mizoroki-Heck and Suzuki-Miyaura cross coupling reactions with palladium loading as low as 0.2 mol% and 0.1 mol% respctively. The palladacycle shown a wide variety of substrate scope in both the coupling reactions. *Ortho* substitution on the N-phneyl ring on the pyrazole by $-CF_3$ group resulted palladacycle **45** (Figure 1.8)**.**[25] This catalyst was used as a precatalyst in N-alkylation reaction employing alcohols as the coupling partner under hydrogen borrowing strategy and resulted in N-alkylated amines in good to excellent yield at 100-130 ^oC under solvent free condition. $-CF_3$ group at the *para* position of the N-phenyl ring led to two regio-isomeric form of the resulting palladacycle *via* C-H activation of either the N-phenyl (**46**, Figure 1.8) or C-phenyl ring (**47**, Figure 1.8).[26] The regio-isomers were isolated by crystallisation. Out of the two palladacycles,**47** was more reactive for the α-alkylation of the ketones. DFT studies

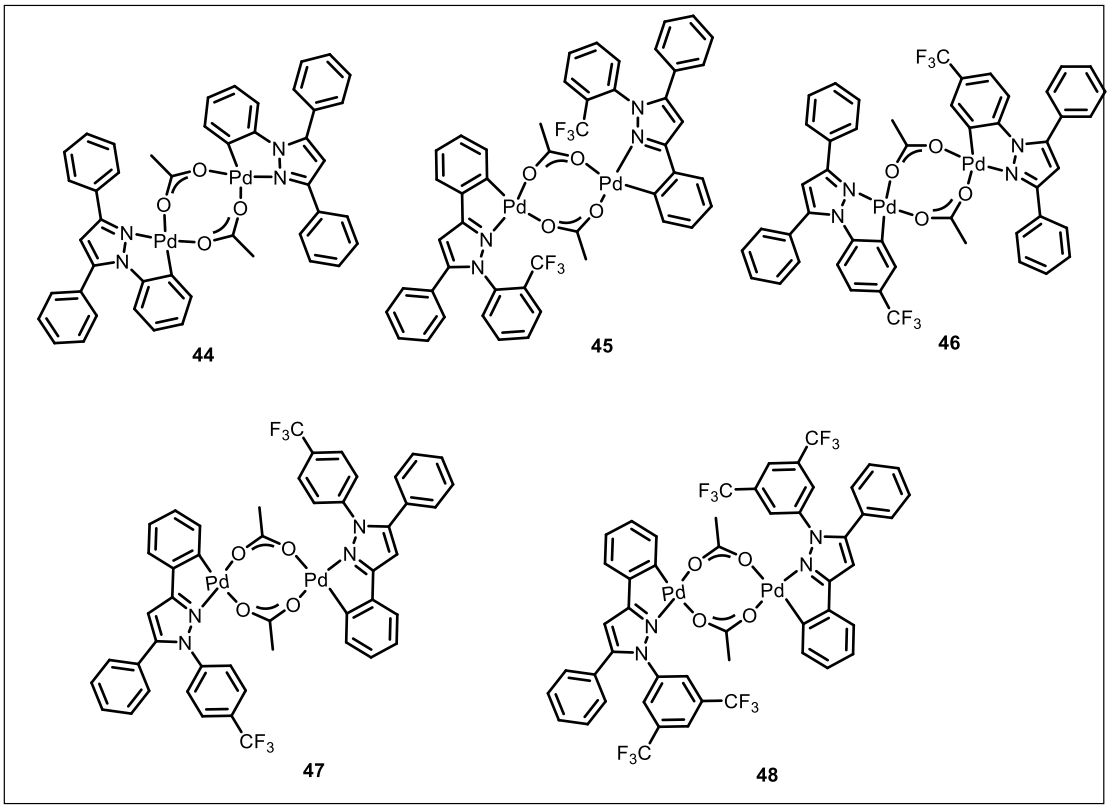


Figure 1.8. Krishnan groups' palladacycles

showed that palladacycle **47** offers a lower energy barrier as compared to **46** for the α-alkylation reaction. Substitution by two $-CF_3$ groups further enhanced the catalytic activity of the pyrazole based palladacycle and the resultant complex **48** (figure 1.8) was used in the activation of methanol for α-methylation of ketones and N-methylation of amines.[27]

Ying and co-workers[28] prepared a diverse library of N-heterocyclic carbene (NHC) ligated palladacycles (**49-58**, figure 1.9). The catalysts were prepred by heating the acetate bridged palladacycles with an imidazolium salt. The catalytic ability of these palladacycles were tested under Suzuki reaction condition for the coupling of deactivated aryl chlorides under aerobic condition. Among the various catalyst screened, the *o*-palladated acetanilide **58** outperformed all of them and the reaction was carried out at room temperature under very mild and weakly basic condition. sp^2-sp^2, sp^2-sp^3, sp^3-sp^2 and sp^3-sp^3 coupling of various challenging substrates were achieved

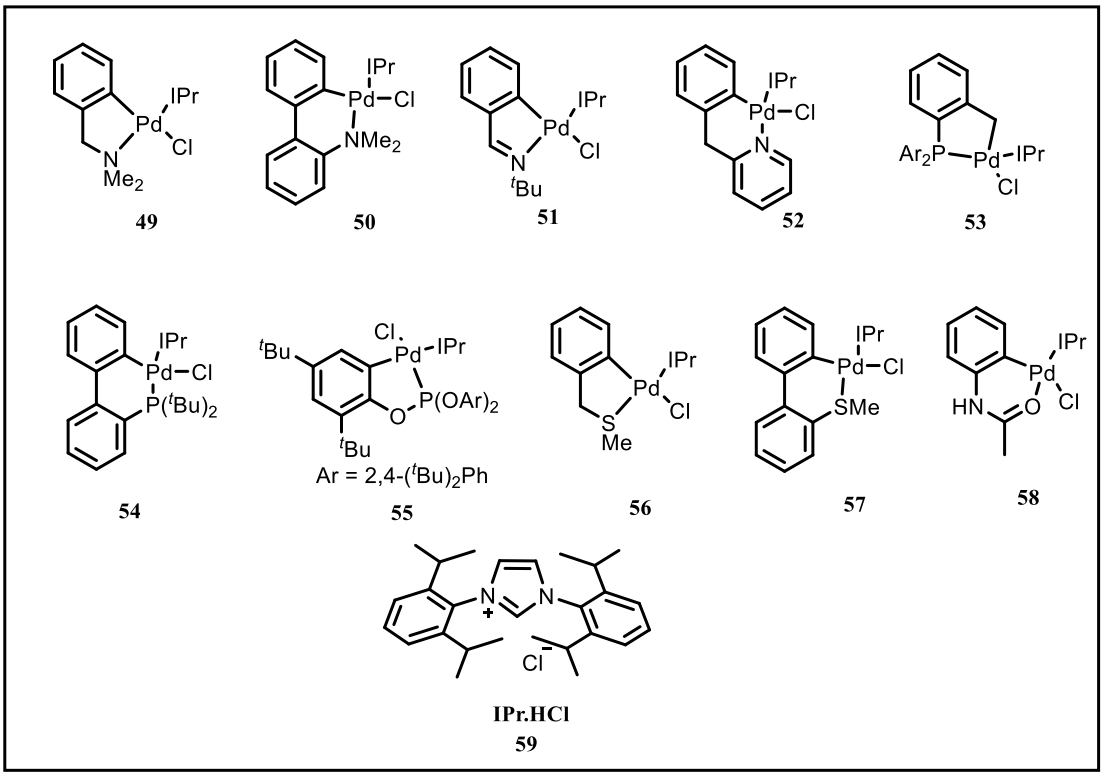


Figure 1.9. Ying groups' library of NHC-palladacycles

using the acetanilide ligated NHC-palladacycle. Using the same catalyst, for the first time, palladium mediated Suziki coupling at 0 ^{o}C was also achieved.

Nolan and co-workers[29] reported saturated NHC complexes of N,N-dimethyl biphenylamine palladacycles (**60**-**63**, figure 1.10). SMes and SIPr were used as the NHCs for the prepartion of the catalysts. The catalytic efficiency of these catalysts were evaluated in Buchwald-Hartwig amination reactions. SIPr ligated palldium complex showed superior activity and short reaction time. A wide range of deactivated aryl chlorides, primary and secondary aryl and alkyl amines were well tolerated by the catalyst. Upon comparing these saturated NHC catalysts with their unsaturated analogues did not show any difference in activity.

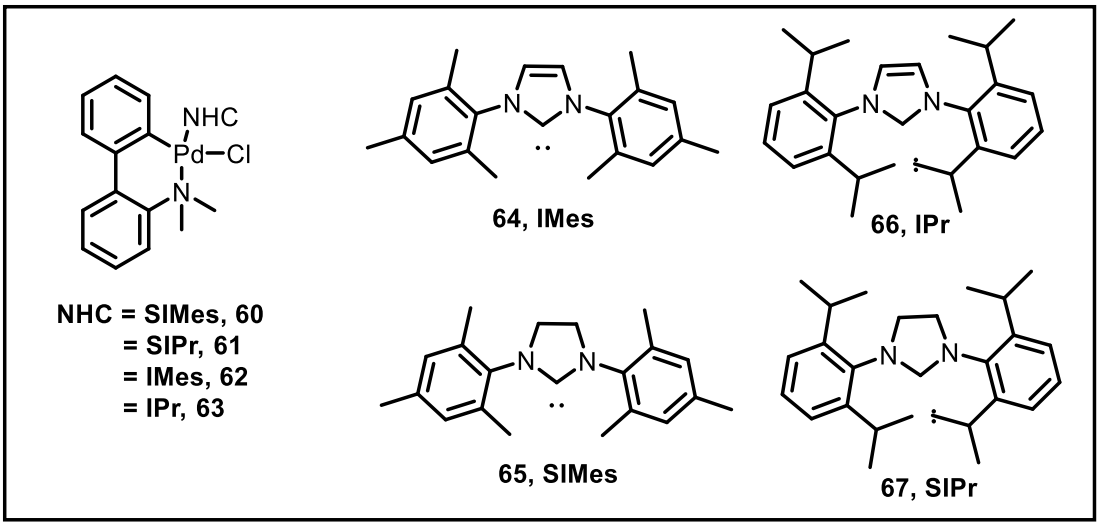


Figure 1.10. Nolan's NHC-palladacycles

In general,palladacycles will have N, O, P, S, Se or As as the donor atom, however, carbon as a donor atom was also realised in many instances. C-C type palladacycles are generally implicated as intermediates in the catalytic reactions.[30] However, use of preformed C-C type palladacycles for organic transformations are rare. Lenarda[31] *et al* synthesised the first ever C-C type palladacycle **68** (figure 1.11) *via* the addition of 1,1,2,2-tetracyclopropane to Pd[PPh_2R] (R = Ph, Me). Since then , the development pf C-C type palladacycles has grown considerably. However, their use as precatalyst in

cross-coupling reactions are extremely rare. Fizia[32] *et al.* reported the cyclopalladation at the periphery of a NHC ligand for the synthesis of highly active C-C type palladacycle for Suzuki-Miyaura coupling reaction. Cyclopalladation of 2,4-dichloropyrimidine, 4-(2-dialkylamino)pyrimidinyl functionalised mesitylimidazolium chlorides (**69-72**, figure 1.11) with $PdCl_2$ in presence of K_2CO_3 produced the C-C co-ordinated palladium complexes (**73-76**, figure 1.11). All the four catalysts were tested for the cross-coupling of deactivated chloroarenes. All the catalysts showed almost identical catalytic activity. The C-C type palladacycles releases anionic and strongly nucleophilic Pd(0) species, which allowed for the use of low catalyst loading and extremely short reaction time for the cross coupling reaction.

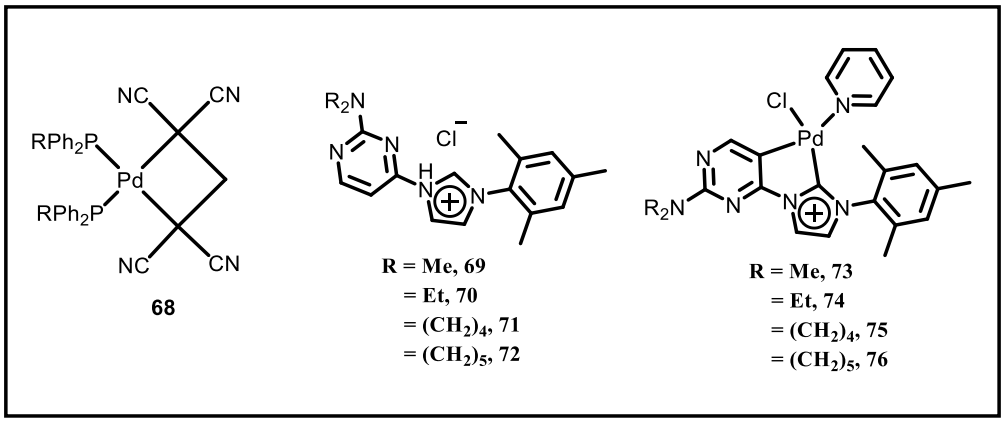


Figure 1.11. Lenarda's (68) and Fizia's C-C type palladacycles (73-76)

Lee[33] and co-worker prepared two series of ligands based on C-2 phenylimidazole and imidazo[1,2-a]pyridine moieties containing N-CH_2(C=O)Ar substituent on the imidazole ring (**77-84**, figure 1.12). Upon reaction with $Pd(OAc)_2$, both ligands underwent double C-H activation at the *o*-aryl carbon and methylene sites on the N-CH_2(C=O)Ar substituent producing five membered C-C type palladacycles (**80-86**, figure 1.12). These complexes were screened for Mizoroki-Heck reaction in ionic salt as solvent. The catalyst based on imidazo[1,2-a] pyridine containing 4-methoxy phenyl ring was the most efficient among the five complexes screened and was capable of

coupling electronically activated aryl chlorides and sterically hindered aryl bromides. This catalyst was further employed in one-pot Mizoroki-Heck coupling/ trans esterification with activated aryl chloride as substrates.

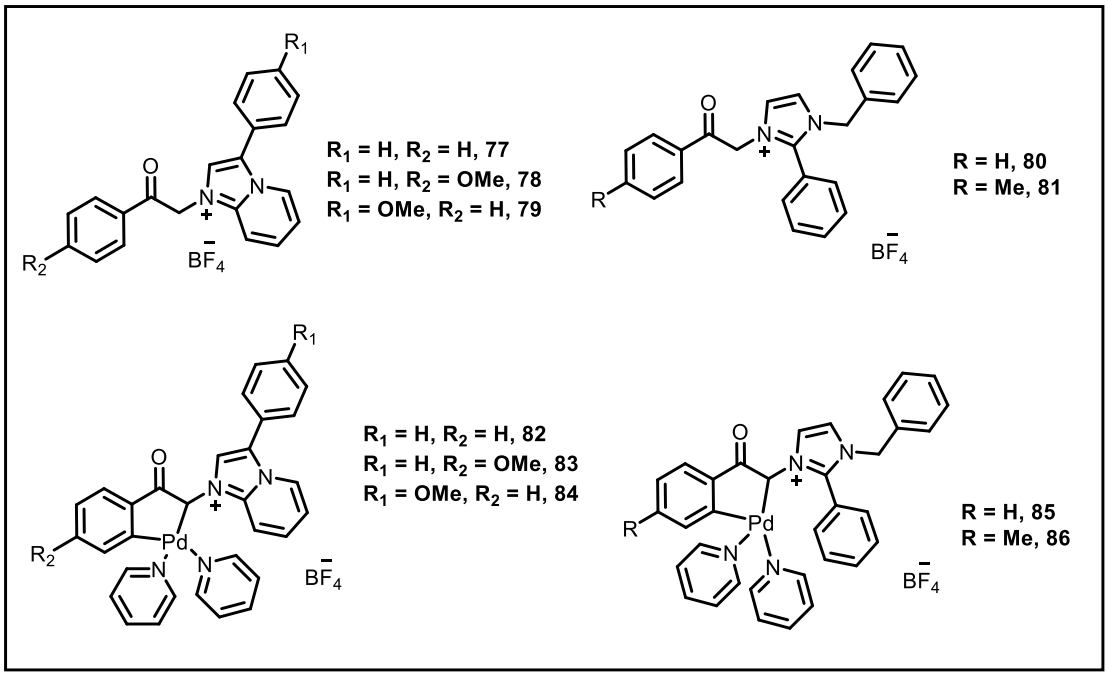


Figure 1.12. Lee's ligands and C-C type palladacycles

1.2.2. Palladacycles in heterogeneous catalysis: Recent reports

Palladacycles offer higher activity and regioselectivity over the conventional palladium complex. However, like other homogeneous catalyst, they suffers from few drawbacks *viz* reusability of the expensive metal catlyst, their separation from the final product, expensive reliance upon the use of additional ligands such as phosphines and carbenes which are expensive and sensitive to air and moisture. Furthermore, the use of such ligands forces the reaction to be carried out in anhydrous and anaerobic conditions. An alternative solution to avoid such problems is to anchor the catalyst on a solid support *viz* silica, polymer, clay etc. which makes their separation from the reaction mixture simpler and can be used for further transformations. Reactivity of such catalysts does not necessarily rely on the use of additional ligands.

Zhang[34] *et al* reported a phosphine free water soluble polyethylene glycol (PEG) click triazole palladacycle (**87**, figure 1.13). As a precatalyst, the palladacycle exhibited superior catalytic efficiency for Suzuki-coupling reaction in neat water with an exceptionally high TON of upto 9 x 10^{-5}. Moreover the palladacycle was also used in copper free Sonogashira raction in aqueous condition with no homocoupled by products. After the reactions, the catalyst was separated by simple extraction method and was further used for three additional runs without any significant decrease in its catalytic activity. Bahadorikhalili[35] *et al.* presented a highly water dispersible palladium nanocatalyst (**88**, figure 1.13) which was fabricated by immobilising palladium onto the surface of PEGylated imidazolium based phosphinite ionic liquid (IL) functionalised γ-Fe_2O_3@SiO_2 core. The nano catalyst showed an improved catalytic activity for Sonogashira and Mizoroki-Heck reactions. The catalyst shows exceptional catalytic activity in the reduction of 4-nitrophenol to 4-aminophenol. The catalytic acivity of the nano catalyst remained indefectible for several runs. The catalyst showed exceptional thermal stability, reusability and aqueous compatibility. The IL spacer improves the solubility of the catalyst making the active palladium site more exposed to the substrates like homogeneous catalysis. Furthermore, the magnetic nature of the support renders the separation of the catalyst simpler by applying an external magnetic device.

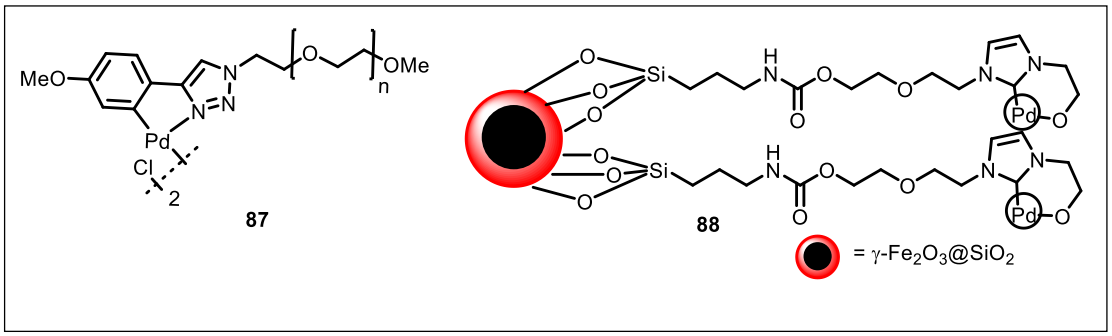


Figure 1.13. Zhang's (87) and Bahadorikhalili (88) palladacycles

Najera's[36] group synthesised a novel polymer anchored oxime palladacycle **89** (figure 1.14) derived from Kaiser oxime resin (1% divinylbenzene cross-linked) and compared its reactivity with the corresponding oxime based dimeric palladacycle **90**(figure 1.14). The polymer supported palladacycles proved to be an efficient precatalyst for the Heck coupling reaction with aryl halides in DMF or aqueous condition with high TON upto 10^5. High yields of >90% were achieved in recycling experiment for the arylation of acrylates using the catalyst for 8 cycles. However, the reaction time increased from 1.6 hour for the 1st cycle to 10 hours in the 8th cycle. The catalytic efficiency of the supported catalyst **89** is marginally lower than the corresponding dimeric complex **90**, however, it offered the advantage of reusability for 8 cycles with an excellent yield. Poisoning studies showed the polymer supported acted as the precursor for Pd(0) species. Using the same catalyst (**89**) as the source of Pd(0), Najera's group reported chemoselective Heck coupling of acrolein diethyl acetal and aryl halides.[37] In this reaction, the catalyst was reused five times with short reaction time without competitive dehalogenation. In another report[38] Najera's group anchored an oxime based palladacycle to a clay composite support (**91**, figure 1.14) and used it as an effective catalyst for Sonogashira reaction. The palladium composite **91** promoted the coupling of aryl chlorides, bromides and iodides with various terminal alkynes in a greener condition i.e absence of copper catalyst and phosphine ligands in PEG200 as the reaction medium. The catalyst was recovered using centrifugation and was reused for

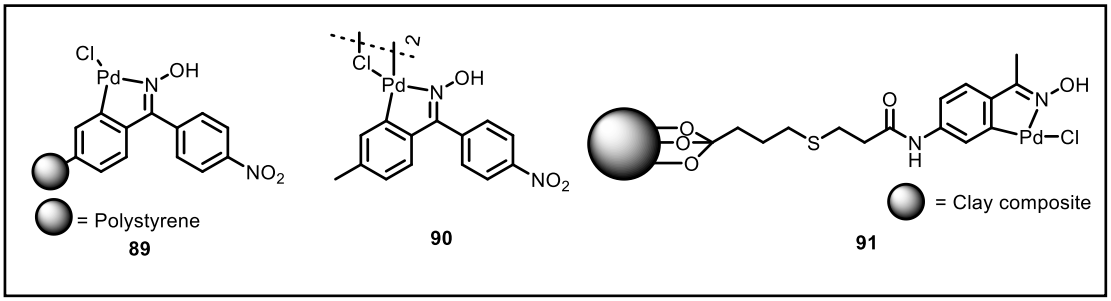


Figure 1.14. Najera's PS (89) and clay anchored (91) palladacycles.

at least nine cycle with marginal decrease in its catalytic activity. The catalytic efficiency of the palladium composite was similar to its corresponding dimeric complex (without the clay support). The true heterogeneous nature of the catalyst was further confirmed by poisoning test *viz*. addition of polyvinylpyridines (PVP), mercury and hot filtration test.

Group of Leyva,[39] anchored a preformed oxime based palladacycle onto a mercaptopropyl modified high surface silica support. High catalytic activity of the anchored complex **92** (figure 1.15) was observed in Suzuki copling of *p*-bromoacetophenone with phenyl boronic acid in water. High stability of the catalyst **92** was studied with recycling experiment where the catalyst remain reactive upto 8 cycles without any decrease in its cataytic activity and resulting in >99% yield of the reaction. To study the effect of various supports on the catalytic efficiency,[40] Leyva's group anchored the oxime derived palladacycle to high surface silica (**92**), MCM-41 (**93**, figure 1.15), styrene-divinylbenzene crosslinked (**94**, figure 1.15**)** and ethylenglycol-dimethyl acrylate polymer (**95**, figure 1.15) and used them as precatalysts in the Suzuki

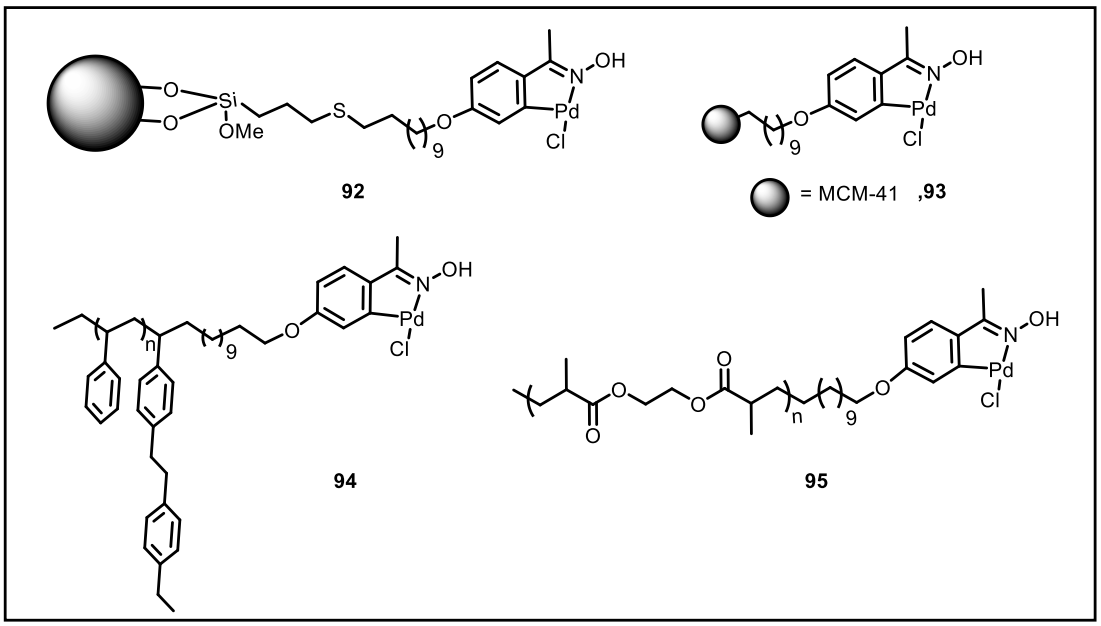


Figure 1.15. Leyva's supported oxime palladacycles

coupling reaction of *p*-chloroacetophenone with phenylboronic acid in water. Remarkable differences in the catalytic activity was observed. >99% conversion was recorded in case of catalyst anchored to silica (**92**) in two hours whereas MCM-41 supported catalyst (**93**) resulted in 94% conversion. Polymer supported catalysts (**94, 95**) were inefficient as compared to the silica and MCM-41 support as they resulted in 76% conversion in 13 hours. Reusability experiments further confirmed high activity of silica supported catalysts over other three supported complexes.

Lin[41] *et al* immobilised Herrmann's phosphane type palladacycle on a polystyrene support and employed it as a precatalyst in various C-C coupling reaction *viz* Heck–Mizoroki, Suzuki–Miyaura and Sonogashira reactions. The supported palladium complex **97 (**figure 1.16) shown higher reactivity in comparison to the unsupported palladacycle i.e Herrmann's palladacycle. The catalyst was recoverable by simple precipitation and filtration process. Lee and co-worker[42] studied the electronic effect on the reactivity of the palladacycle by immobilising electron rich oxime based palladacycle to a polystyrene support. In this regard, a series of electron rich alkoxy

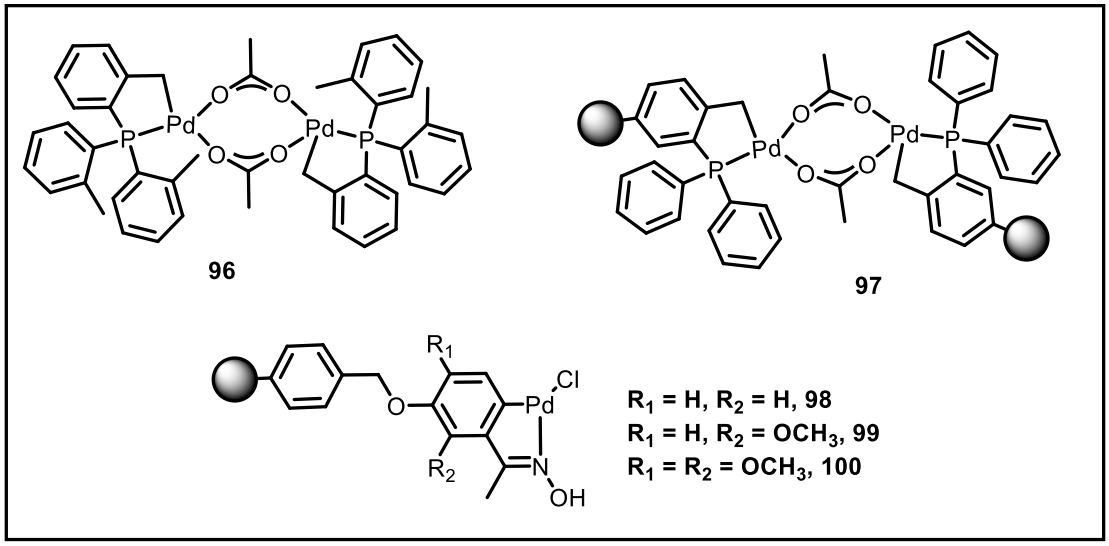


Figure 1.16. Herrmann's palladacycles (96), Lin's supported palladacycle and Lee's oxime based palladacycle

substituted polystyrene supported oxime based palladacycles (**98-100**, figure 1.16) were synthesized and were studied for their catalytic activity in Suzuki coupling reactions. Unlike Najera's Oxime based PS supported palladacycle **89**, the alkoxy substituted palladacycles shown higher catalytic activity in Suzuki reaction. The catalytic activity of the oxime based palladacycle increased with the increase in electron richness of the ligand which was controlled by the number of alkoxy substitution on the oxime ligands. Evidently,the most electron rich palladacycle **100** containing three alkoxy group afforded best catalytic activity.

Alonso and co-workers[43] studied the anchoring of palladacycles on carbonaceous materials *viz*. graphene oxide (GO) by synthesizing a GO supported oxime palladacycles. The synthetic protocol involved were strring and/or ultrasonication of THF solution of palladacycles suspended on GO. XPS analysis of the palladacycles (**101-103**) and their GO supported counterparts showed similar binding energies associated with cyclometallated oxime structures. The catalyst prepared *via* stirring of THF solution of palladium complex showed higher catalytic activity in the Suzuki coupling of aryl bromides and aryl boronic acids utilising as low as 0.002 mol% of palladium at room temperature in aqueous conditions. Recycling experiments showed that the catalyst was active upto 2 runs beyond which its activity drastically decreased. The reason for the loss of activity was attributed to the oxidation and metal agglomeration process.

Mohamed *et al*[44] immobilised ortho-palladated dimethylbenzylamine onto amorphous silica and macroporous polystyrene support and compared its efficiency in catalytic methanolysis of phosphorothionate pesticides *viz*. fenitrothion, diazinon, coumaphos, and dichlofenthion. Both the solid supported catalyst showed excellent catalytic activity in the methanolysis of phosphorothionate esters with the silica supported

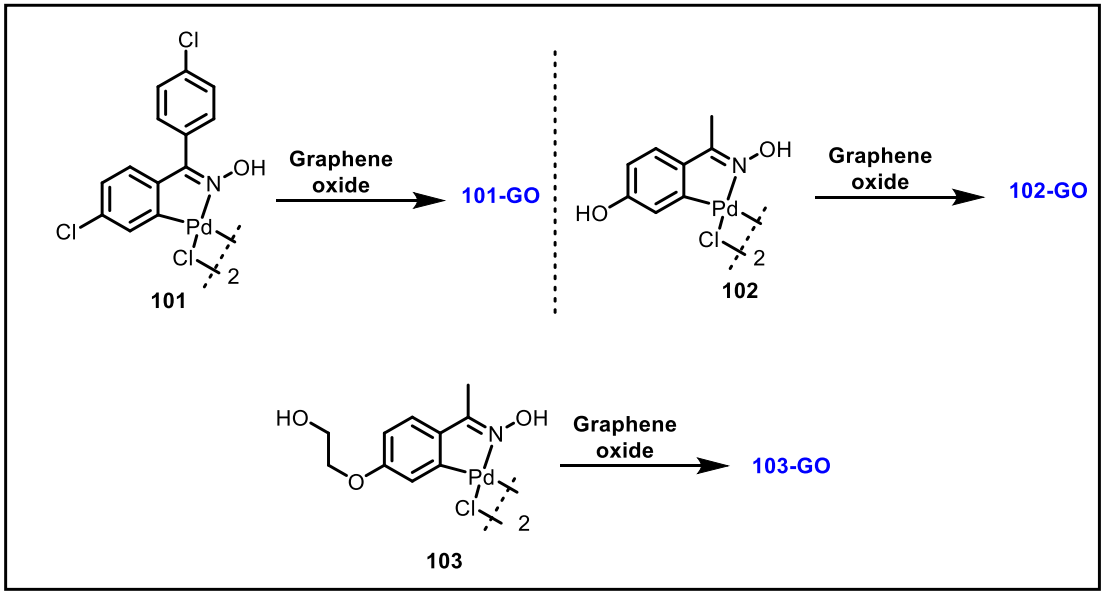


Figure 1.17. Alonso's graphene oxide supported palladacycles

catalyst showing slighltly higher activity. In case of the silica support, the higher concentration of active sites accessible to the reaction solvent and the hydrophillic surface which allows better interaction of the palladacycles with the methanol solvent, was believed to be the factors for higher catalytic activity. In case of polystyrene supported catalyst, it was found that it underwent 30-50% loss of palladium after the first cycle without any loss in catalytic activity. This showed the desorption of a catalytically inactive palladium species which was chemi- or physisorbed onto the polymeric support. Lu *et al.*[45] reported a modified oxime derived palladacycles supported on silica gel for the methanolysis of phosphorothionate pesticides. They synthesised both mononuclear (**105** and **106**, figure 1.18) and dinuclear palladacyles (**107 and 108**, figure 1.18) and immobilised on silica gel. Under the homogeneous catalysis, the palladacycles performed effectively for the methanolysis reaction however, they suffered from the formation of catalytically inactive dimeric form. Silica immobilised palladacycles (**109** and **110**, figure 1.18) were very active and reusable upto 10 runs for the degradation of a series of phosphorothionate pesticides up to 4.9×10^8 folds.

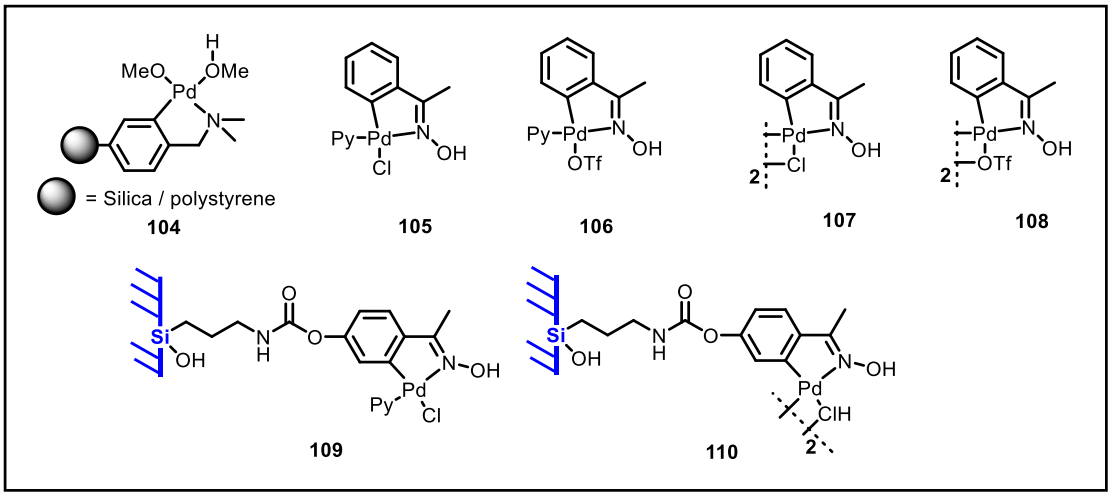


Figure 1.18. Mohamed's (104) and Lu's supported palladacycles

Parish and Buchwald[46] showed the use of polystyrene-supported dialkylphosphinobiphenyl as ligand in homogeneous catalysis affords higher catalytic activity. Inspired by this result, Scordia and co-workers[47] reproted the polystyrene-immobilised dicyclohexylphenylphosphine adducts of phosphite- and amine- based palladacycles (**111** aand **112**, figure 1.19). Homogeneous analogues of the PS-phosphine adducts were also synthesised for comparison (**113** and **114**, figure 1.19). These complexes were tested for their catalytic activity in Suzuki coupling of non-activated, activated and deactivated aryl chlorides. In case of phosphite based palladacycles, immobilisation on the polystyrene support enhanced its catalytic activity in comparison to the homogeneous analogue. The catalysts were not recyclable as they lose their activity right after the first run, however they are easily separated by filtration

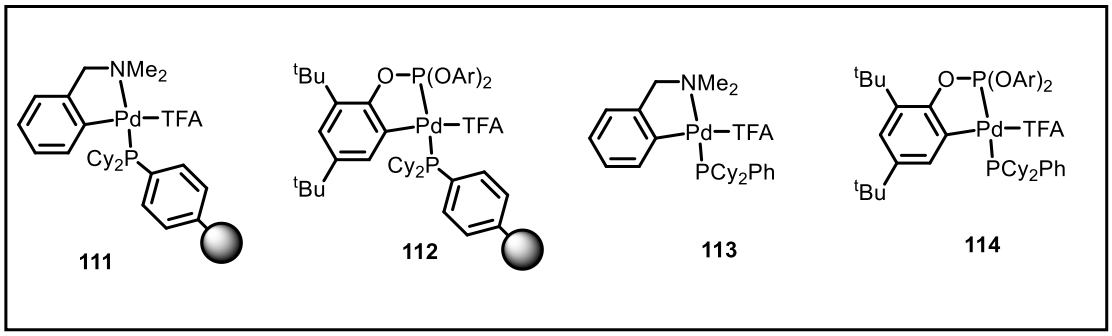


Figure 1.19. Scordia's supported and unsupported palladacycles

which causes low contamination of the product by palladium residues.

Liu *et al.*[48] synthesised a star shaped immobilised oxime based palladacycle. In this complex, multiple star shaped ligands and palladium precursors are combined through the chloro bridge forming a self supported system. These heterogeneous solid catalysts were higly stable and effective catalysts for Suzuki cross coupling of various aryl chlorides and bromides. Their activity were comparable to the homogeneous analogues. Metal leaching was observed in presence of tetrabutylammonium bromide (TBAB).

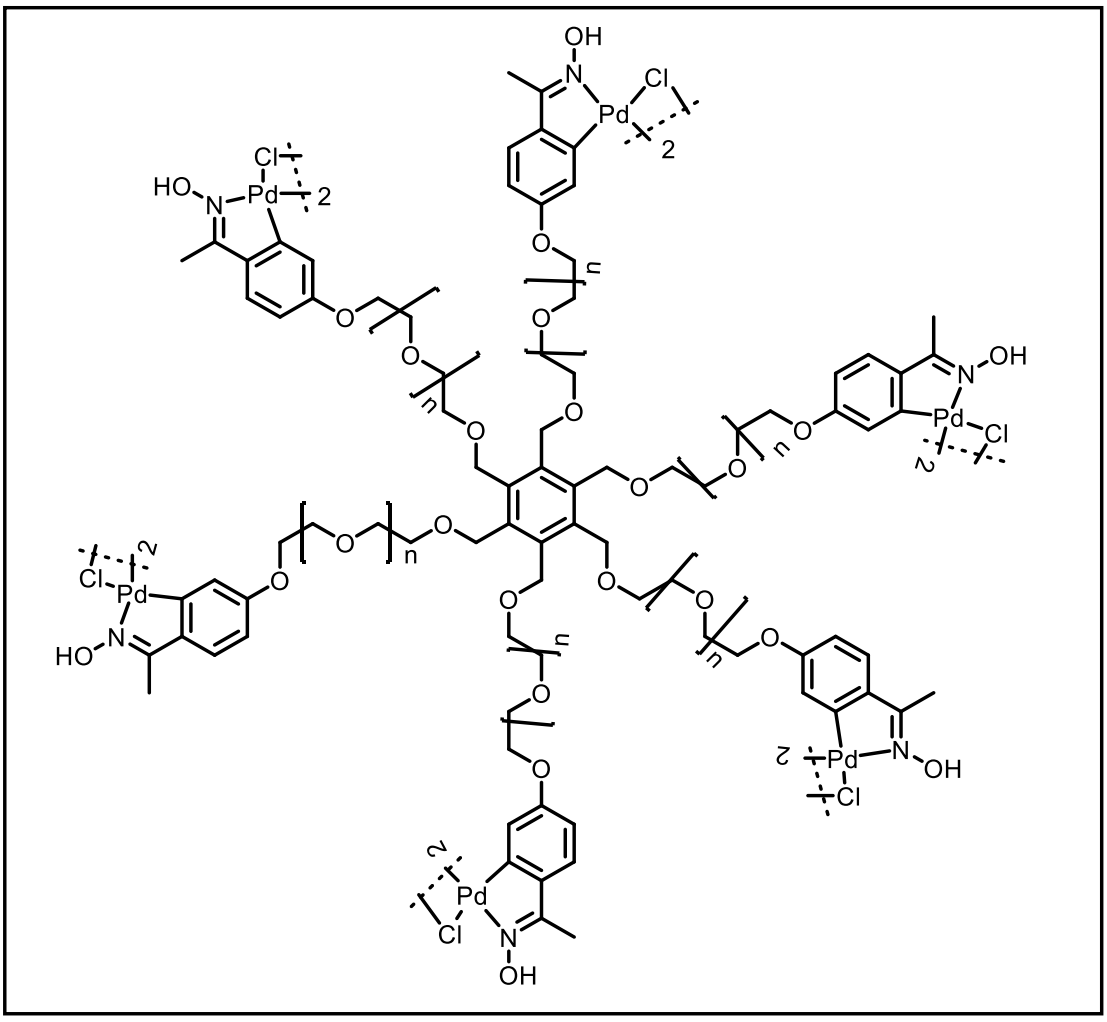
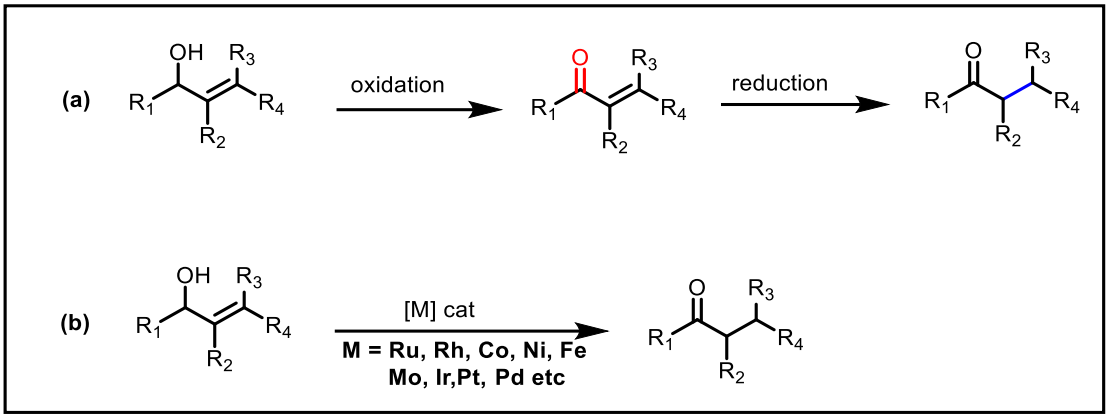


Figure 1.20. Liu's star shaped immobilised palladacycle.

1.3. Isomerisation of allyl alcohol: precursor for ketone and enolate

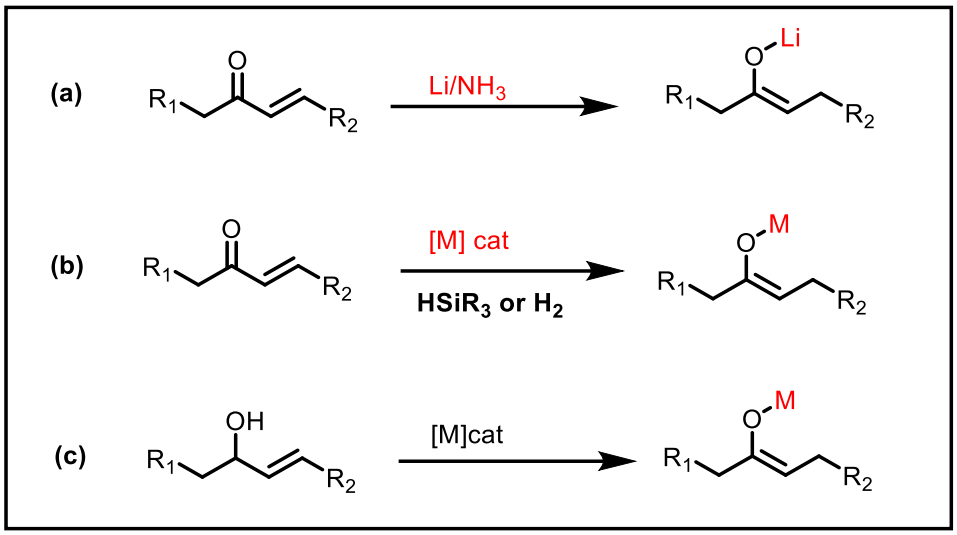
Isomerisation of allyl alcohol to carbonyl compound is an useful synthetic process which is conventionally carried out in a two step processes of sequential oxidation-

reduction method (scheme 1.2a). The one pot isomerisation proces is atom economic[49] and avoids the use of stochiometric amount of toxic and costly reagents. This one pot process is also highly chemoselctive and can be carried out in presence of additional functional groups such as alcohol, ketone and double bond. Additionally, allyl alcohols also act as an enolate precursors which are important intermediates for the construction



Scheme 1.2. (a) Conventioanl two step isomerisation and (b) one step redox isomerisation of allyl alcohols

of carbon-carbon and carbon-heteroatom bond formation reactions. Enolates can be formed from the deprotonation of ketones, however, it produces a mixture of regioisomers. Furthermore, in some instances formation of one regioisomer is favored

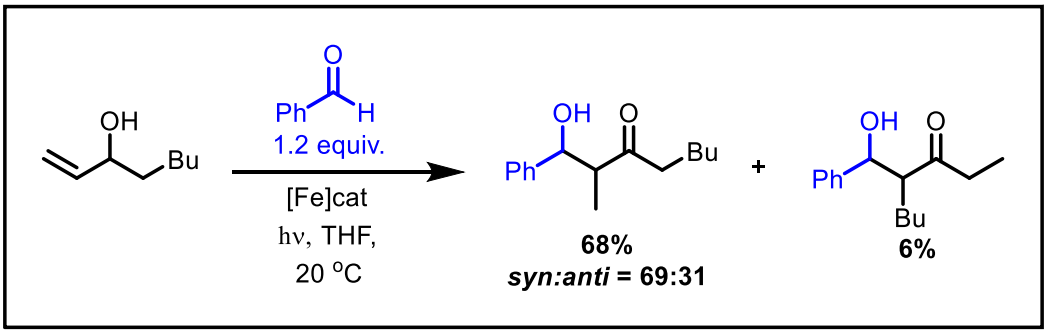


Scheme 1.3. Generation of enolates from enones and allyl alcohol

both kinetically and thermodynamically and thus the synthesis of non-favored regio isomer becomes difficult. Alternatively, different synthetic enolate equivalents can be used *viz.* reduction of enone by lithium in liquid ammonia or the transition metal mediated in situ formation of enolate formation from enones. The former method suffers form low functional group tolerance and the latter requires stochiometric amount of reductant such as silanes[50] or dihydrogen.[51] On the other hand transition metal mediated isomerisation of allyl alcohol to the enone or ketone circumvent such drawbacks. As an enolate and ketone precursors, allyl alcohols are used in tandem reaction for the formation of C-C and C-heteroatom bond formation reactions.[52]

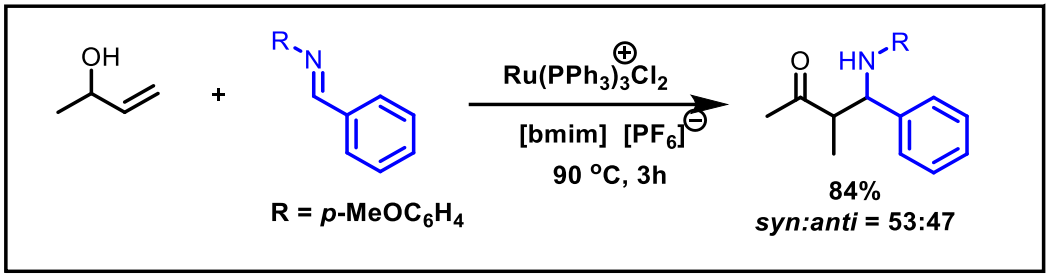
1.3.1. Tandem isomerisation and functionalisation of allyl alcohols

The tandem isomerisation-functionalisation process is a highly atom economic reaction with few limitations that needs to be overcome. Protonation of the enolate intermediate and/or the tautomerisation of the enolic compound produces saturated carbonyl compounds and thereby reduces the yield of the concomitant functionalisation reaction. Hence, an excess amount allyl alcohol is generally used for such tandem reactions. The first catalytic isomerisation-functionalisation of allyl alcohols was reported by Gree and co-workers[53] by using iron carbonyl complex. Using the iron catalyst the coupled allyl alcohols with various aldehyde to form aldol products in high yields. Small amount of undesired aldol products from the isomerised ketone were also observed.



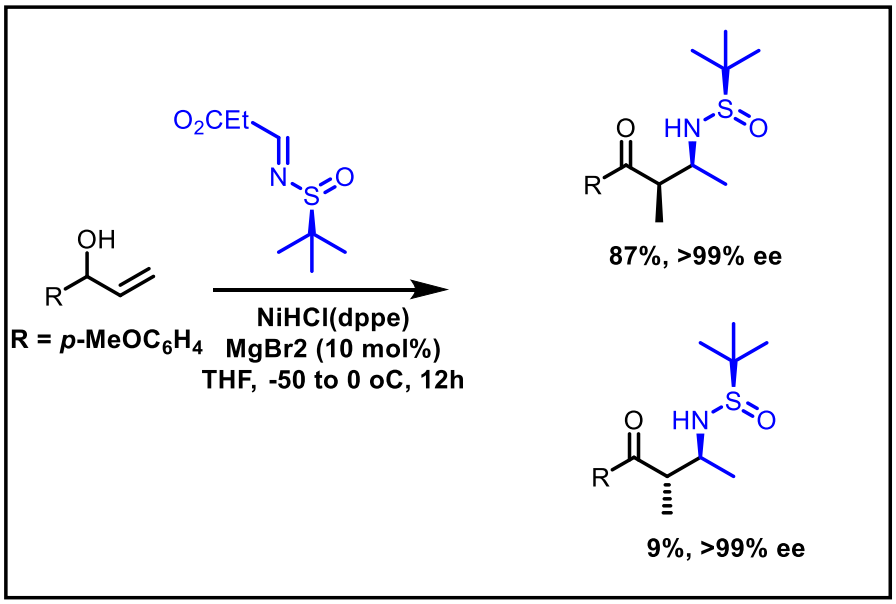
Scheme 1.4. Tandem isomerisation-aldol condensation catalysed by $Fe(CO)_5$

Li and co-worker[54] reported $Ru(PPh_3)_3Cl_2$ mediated coupling of allylic alcohols with various aldehydes for the synthesis of aldol type products in good yields. In another work,[55] they reported the use of $In(OAc)_3$ as additive which further enhanced the yield of the aldol type products. Further extension of this work included imine as electrophile for the coupling with allylic alcohols for the synthesis of β-aminoketones (Scheme 1.5).[55] Unlike the work of Gree and co-workers, Li's work involved the use of excess allyl alcohols.



Scheme 1.15. Tandem isomerisation-Mannich type reaction of allyl alcohols

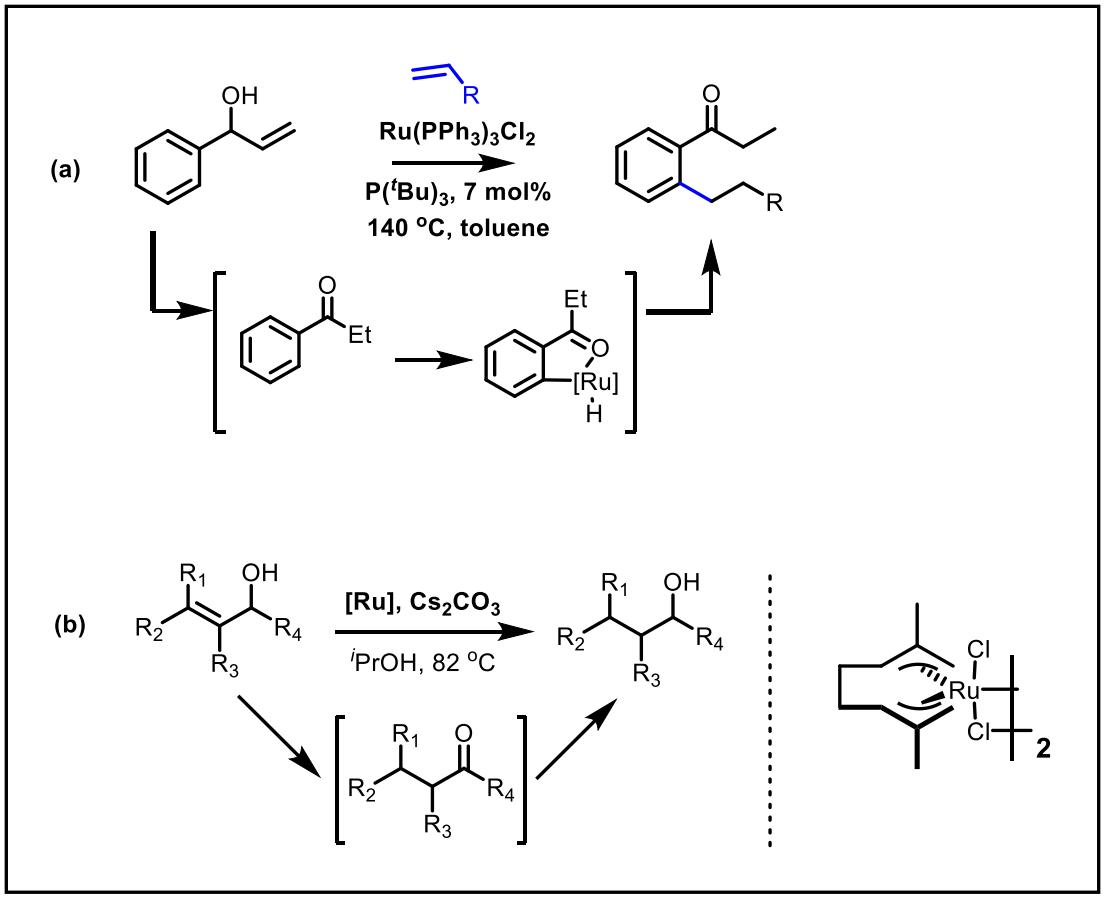
Gree and co-workers[56] also reported $Fe(CO)_5$ catalysed Mannich type reaction for the synthesis of β-aminoketones and β-aminoalcohols using N-phenylsulfonyl imines as



Scheme 1.6. Diastereo and enantioselective tandem isomerisation and Mannich type reaction of allyl alcohols.

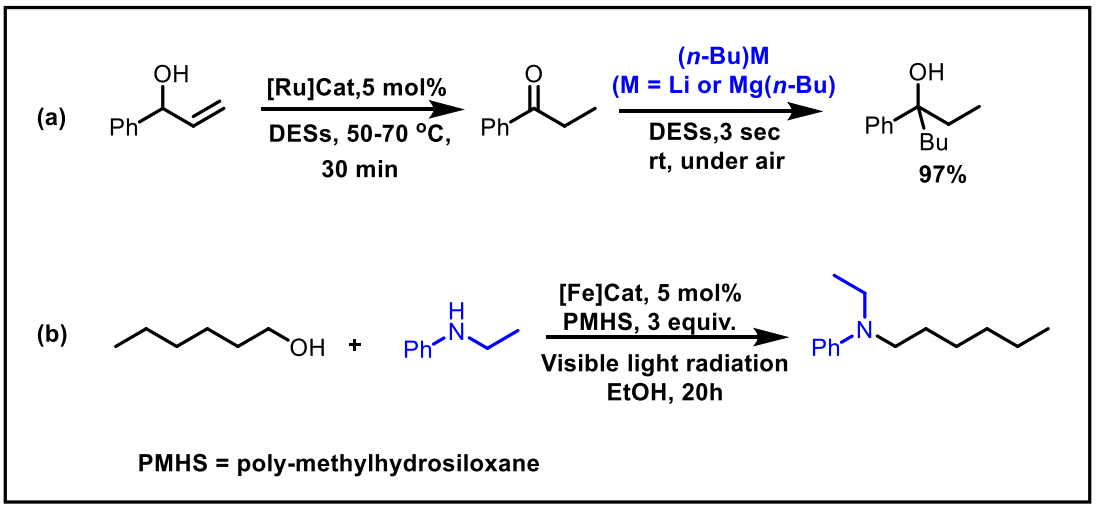
the electrophiles. They also used enantiopure N-*tert*-butylsulfinimines for the enantio and diastereoselective synthesis of β-aminoketones (scheme 1.6). This method was further utilised for the synthesis of *ent*-Funebrine and *ent*-Nikkomycins.[57]

Martin-Matute and co-worker[58] combined the isomerisation of allyl alcohols with Murai[59] type C-H activation using a $Ru(PPh_3)_3Cl_2$. The in-situ generated ketones from the isomerisation of allyl alcohols assisted the aromatic C-H bond cleavage by chelation (scheme 1.7.a). Both the isomerisation and chelation assisted C-H actvation were carried out by the single catalyst. Cardieno *et al.*[60] reported a ruthenium catalysed isomerisation of allyl alcohol and transfer hydrogenation using isopropanol as the hydrogen source (scheme 1.7.b). Kinetic experiments further confirmed the formation of the ketone form the isomerisation of allyl alcohol followed by the hydrogenation.



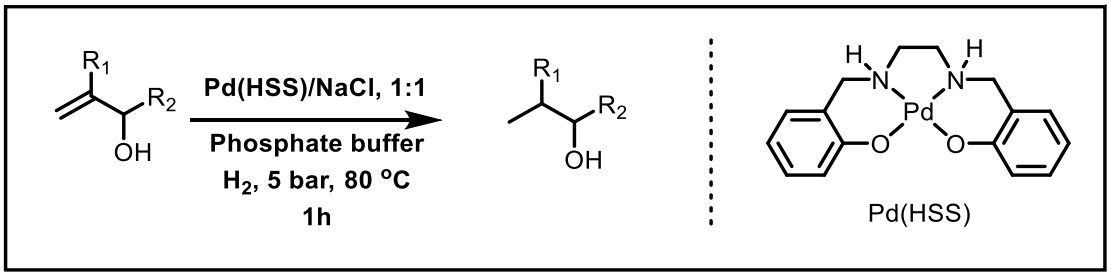
Scheme 1.7. (a) Tandem isomerisation-C-H functionalisation and (b) tandem isomerisation-hydrogenation of allyl alcohols.

Cicco *et al.*[61] combined the ruthenium catalysed isomerisation of allyl alcohols with the chemoselective addition of organolithium/magneium compounds for the synthesis of tertiary alcohols in a deep eutectic solvents (DESs). Tertiary alcohols were synthesised in high yield upto 97%. Darcel and co-worker[62] developed a three steps-one sequence process for the synthesis of N-alkylated amines form allyl alcohols and primary and secondary anilines. The process involves isomerisation of allyl alcohols, condensation with amines followed by reduction by the addition of hydrogen.



Scheme 1.8. (a) Tandem isomerisation and adition of organolithium/magnesium to allyl alcohols and (b) tandem isomerisation-condensation-reduction of allyl alcohols

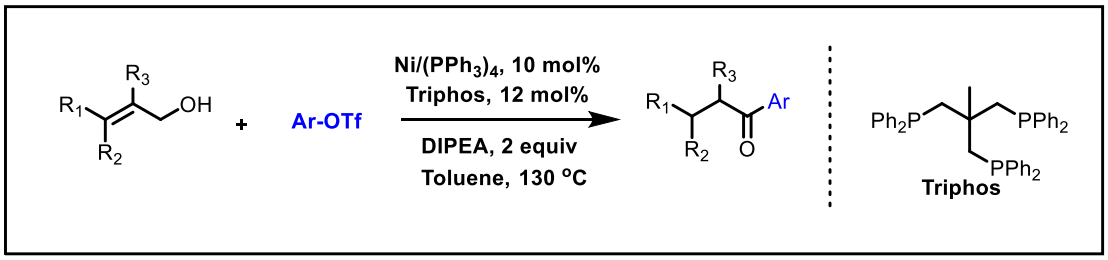
Voronova *et al.*[63] developed a water soluble Pd(II) complex of disulfonated tetrahydrosalen. The complex was used in the redox isomeriation and hydrogenation of allyl alcohol with dihydrogen used as the hydride source (scheme 1.9). DFT studies



Scheme 1.9. Tandem isomerisation-hydrogenation of allyl alcohols

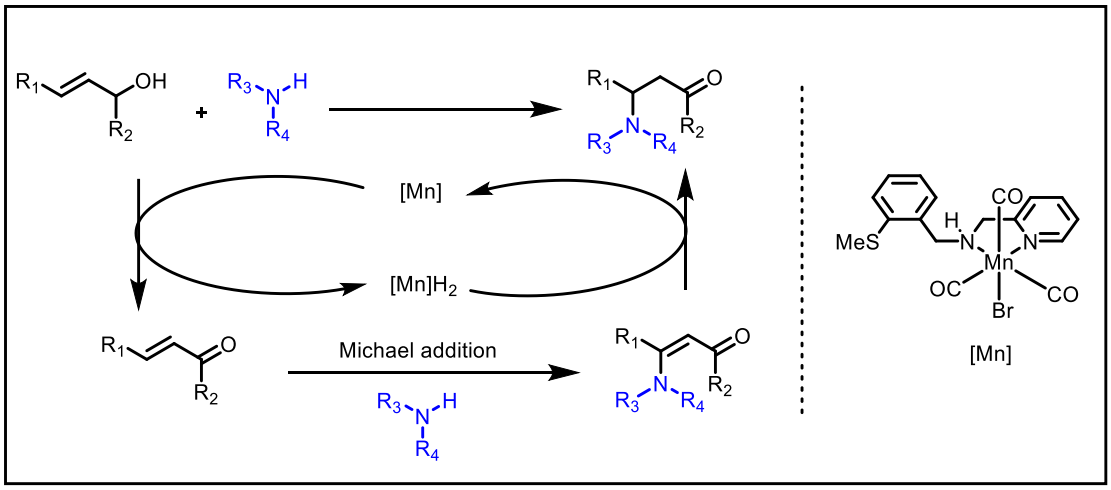
revealed that the hydrogen is heterolytically activated. Both the redox isomerisation and hydrogenation occurred through concerted transfer of hydrogen form alcohol and hydride from the metal hydride species.

Wang *et al.*[64] reported redox neutral cross coupling of allyl alcohols with aryltriflates producing ketones using commercially available nickel/Triphos system (scheme 1.10). A wide range of alkenyl primary alcohols and aryltriflates were converted to ketone with wide functional group tolerance. Using this protocol, a large set of complex molecule were converted into functionalised ketones.



Scheme 1.10. Tandem isomerisation of allyl alcohols followed by coupling with aryltriflates

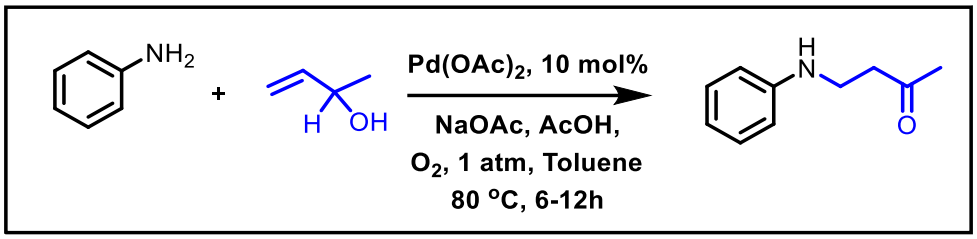
Maji and co-worker[65] presented manganese(I) catalysed hydroamination of allyl alcohols through hydrogen borrowing approach which enabled the synthesis of γ-aminoalcohols. A wide range of aromatic and aliphatic amines, natural product



Scheme 1.11. Hydroamination of allyl alcohols *via* hydrogen borrowing method

derivatives *viz*. lithocholic acid, linoleic acid and citronellal and drug molecuules *viz*. urapidil, trifluoperazine and fluoxetine were prepared using the hydroamination method.

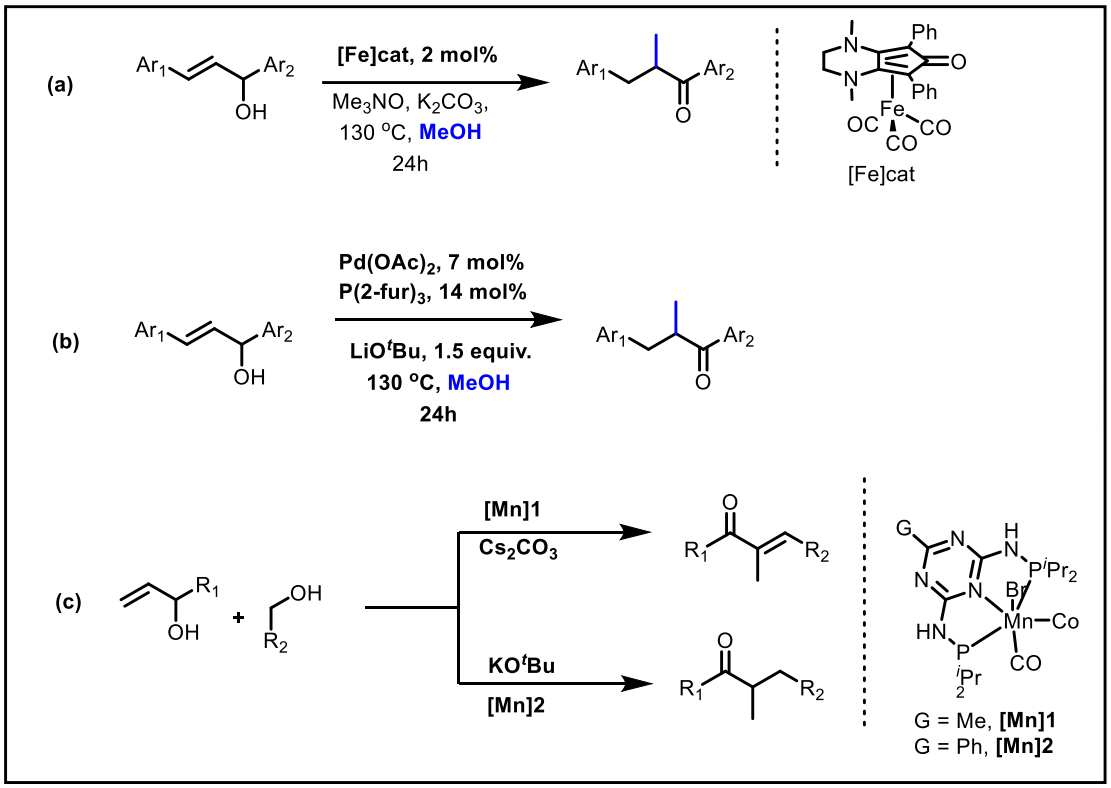
Kapur and co-worker[66] reported oxidative coupling of allyl alcohols with anilines for the synthesis of β-aminoketones which were further converted to substituted quinoline in one pot sequential method. Detailed investigation revealed the oxidation of allyl alcohol took place prior to the Michael addition with the aniline moiety. Further extension of this method were applied for the synthesis of indoline using intramolecular α-arylation and one pot domino annulation.



Scheme 1.12. Oxidative coupling of allyl alcohols with aniline

Morril and co-worker[67] reported tendem isomeriation and methylenation of allyl alcohols for the synthesis of α-methylated ketones using a (cyclopentadienone)iron(0) carbonyl complex as the precatalyst and methanol as a C1 source (scheme 1.13.a). A number of 1-phenyl substituted secondary allyl alcohols were converted to the corresponding methyl ketones in good yields. Similar report were presented by our group[68] using commercially available palladium acetate as the catalyst (scheme 1.13.b). Unlike Morrils's report, this work does not involve the use of external additive to carry out such tandem reaction. A range of monophenyl and diphenyl substituted secondary alcohols were screened using this method and produced the α-methylketones in excellent yields. Gunanathan and co-workers[69] reported the cross coupling of allyl alcohol with primary alcohol using manganese based pincer catalyst. The selective cross coupling of the two alcohols resulted in α-alkenyl ketones *via*. acceptorless

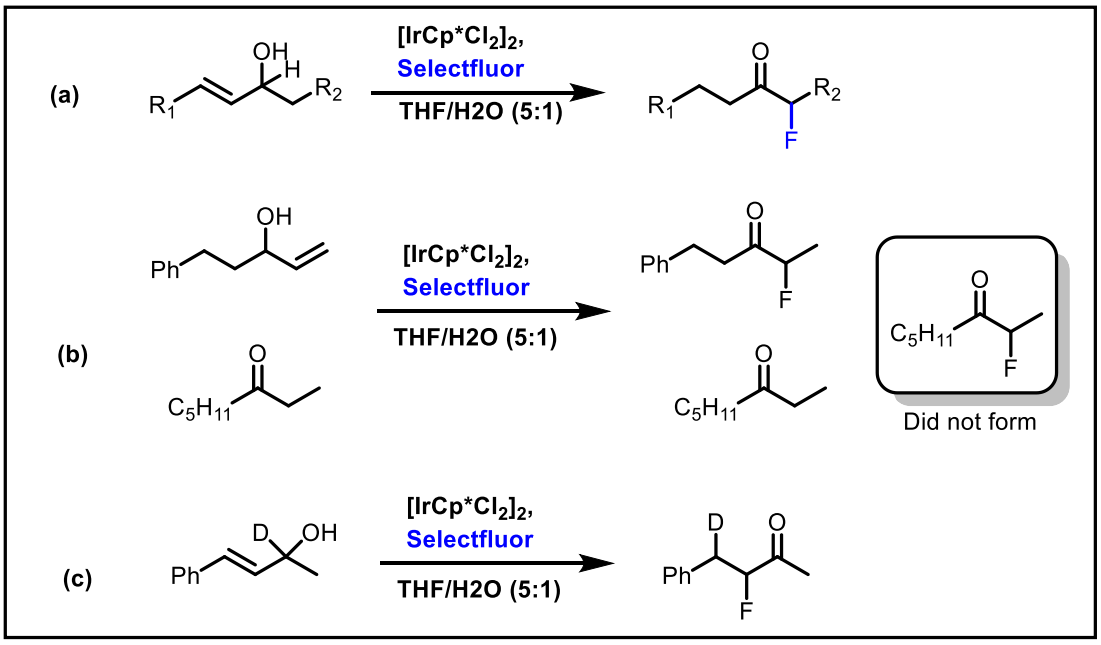
dehydrogenative coupling and α-alkylated ketones *via*. borrowing hydrogen methodology (scheme 1.13.c).



Scheme 1.13. (a) and (b) Tandem isomerisation and methylation of allyl alcohol and (c) tandem isomerisation and alkylation/alkenylation of allyl alcohols

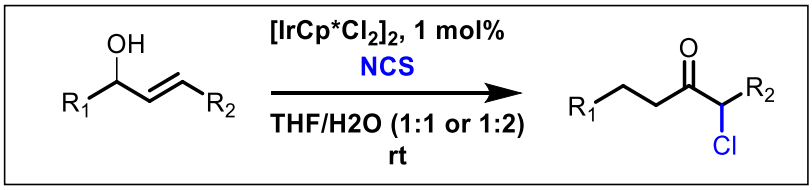
Group of Martin-Matute[70] combined the isomerisation of allyl alcohol and the electrophilic fluorination of allyl alcohol using an iridium catalyst (scheme1.14.a). After screening a library of fluorinating agents, Selectfluor in THF/water mixture was the most effective for the isomerisation-fluorination reaction. Using this protocol, regioselective synthesis of a single constitutional isomer of the α-fluoroketone was achieved. The preence of additional ketone group did not impact the outcome of the reaction as the protocol showed complete chemoselectivity for allyl alcohols. Using this to their advantage, the author reported the synthesis of fluorinated 1,3-diketones. Crosover experiment (scheme 1.14.b) confirmed that the reaction does not proceed through the formation of non-fluorinated ketone rather from the 1,3-hydride shift.

Fluorination of the deuterium labelled allyl alcohol further confirmed the claim of intramolecular 1,3-hydride shift (scheme 1.14.b).



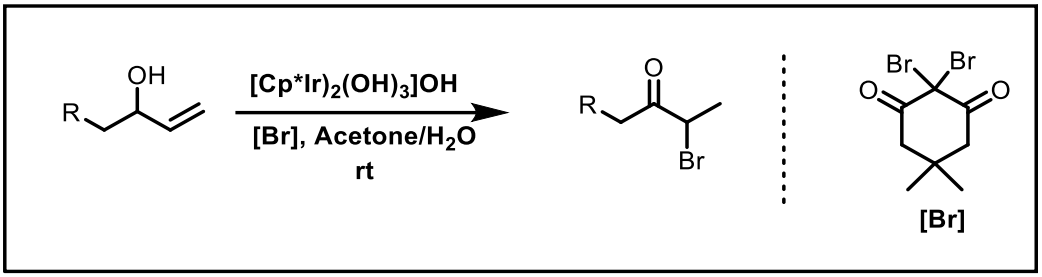
Scheme 1.14. Tandem isomerisation-fluorination of allyl alcohols

Using the similar 1,3-hydride approach, Martin-Matute and co-worker also reported the synthesis of α-chlorinated ketone from N-chlorosuccinimide in THF/water mixture (scheme 1.15).[71] A wide range of primary and secondary allyl alcohols were chlorinated in good yields and producing a single constitutional isomers. In another study,[72] the Martin-Matute's group used the iridium catalyst for the chlorination of allyl alcohol in acetone using BINOL phosphoric acid as an additive. DFT study indicated that the addition of phosphoric acid opens up a lower transition state for the isomerisation of allyl alcohol at ambient temperture and thereby enhancing the yield of the chlorination reaction when carried out in acetone instead of water.



Scheme 1.15. Isomerisation-chlorination of allyl alcohols

The same group also reported the synthesis of α-brominated ketone and aldehyde from the allyl alcohol isomerisation follwed by bromination by an iridium based catalyst.[73] 2,2-dibromodimedone was used as the brominating source as other brominating agent either failed or resulted in less yield or lesser regioselectivity of the brominated product. Single constitutional isomer of a variety of brominated aldehydes or ketones were produced from various primary and secondary allylic alcohols.



Scheme 1.16. Allyl alcohol isomerisation-bromination

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Chapter 2

Palladium mediated one pot synthesis of 3-arylcyclohexenone and 1,5-diketones from allyl alcohols and aryl ketones

2.1. Introduction

There is considerable interest in the use of allylic alcohols as building blocks in organic synthesis since they react as alkylating or allylating compounds to yield diverse products.[1] As the hydroxyl group in allylic alcohols is considered to be a weak leaving group, usually they need a prefunctional transformation of allylic alcohols into esters, halides, sulfonates, carboxylates, *etc*.[2] A stoichiometric amount of Lewis acid such as BEt_3 or $Ti(O\text{-}iPr)_4$ may optionally be triggered to activate them, but all these approaches lead to the production of substantial wastes and affect the atom economy of the reaction, which can be prevented by direct catalytic activation.[2] Allylic alcohols can be used as enolate precursors in tandem reactions leading to the formation of a new C–C bond.[3] The enol formed during the reaction tautomerizes to the corresponding carbonyl compounds, which can be achieved by simple metal-catalysed isomerisation.[3] This isomerization reaction is green, effective, safe and environment friendly, and occurs in one step without generating by-products and without the need for toxic reagents, unlike the classical oxidation.[4]

Grée and co-workers coupled allyl alcohols with various aldehydes using an iron carbonyl complex resulting in aldol products.[5] The same group reported the synthesis of β-aminoketones from allyl alcohols and *N*-*tert*-butanesulfinimines using a tandem isomerisation-Mannich reaction approach.[6] Martín-Matute group reported the *ortho*-alkylation of ketones using tandem isomerisation and C–H activation of allyl alcohols.[7] They also reported the synthesis of α-fluorinated ketones by combining the isomerisation of allyl alcohols to ketones followed by α-fluorination.[8] In addition, allylic alcohols also act as the enolate precursor as this moiety has a β-electrophilic centre that fosters nucleophilic addition (1,4-addition), which results in β-functionalised carbonyl compounds. In this regard, it is worth mentioning that Kapur

and co-workers reported the coupling of allyl alcohols with various anilines using a Pd-catalyst to afford β-amino ketones.[9]

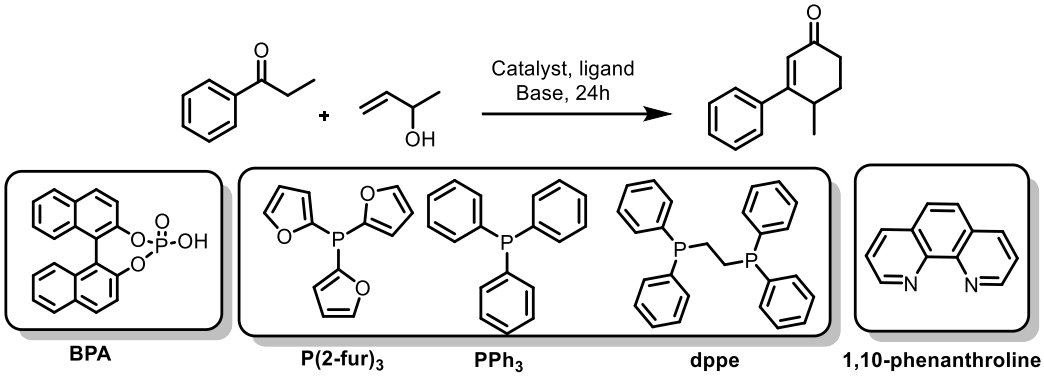
Herein, we report the synthesis of 3-aryl-2-cyclohexenones and 1,5-diketones by coupling allyl alcohols with a variety of ketones using a palladium−BINOL phosphoric acid system.

2.2. Results and discussion

We recently reported α-alkylation of ketones and *N*-alkylation of amines using alcohols as an alkylating agent.[10] We were curious to investigate the reactivity of allyl alcohols as an alkylating agent. The reaction of 3-buten-2-ol with propiophenone was studied using palladium acetate, BINOL phosphoric acid (BPA) and NaOH as the catalyst, ligand and base, respectively, with the expectation to obtain a *C*-alkylated product. To our surprise, we isolated 33% of 3-aryl-2-cyclohexenone (a Robinson annulated product[11]) from the reaction mixture (Table 2.1, entry 1). As 3-aryl-2-cyclohexenones[12] act as feedstock for the synthesis of substituted phenols apart from acting as structural motifs in bioactive molecules, we decided to explore this reaction. Changing the palladium source to $Pd_2(dba)_3$ did not yield any product (Table 2.1, entry 2); however, $PdCl_2$ resulted in 29% of the product (Table 2.1, entry 3). Upon the addition of 4 Å molecular sieves to the reaction mixture, the product was isolated in 71% yield (Table 2.1, entry 4). Little or no conversion was observed when phosphine or pyridine ligands were used instead of BPA (Table 2.1, entries 10, 11, 14 and 15). A further decrease of catalyst loading resulted in lower yields (Table 2.1, entries 16 and 17).

With the optimised conditions in hand, we checked the substrate scope of Robinson annulation with different aryl ketones and allylic alcohols. Acetophenone reacted with

Table 2.1 Optimisation of Robinson's annulation using allyl alcohols[a]

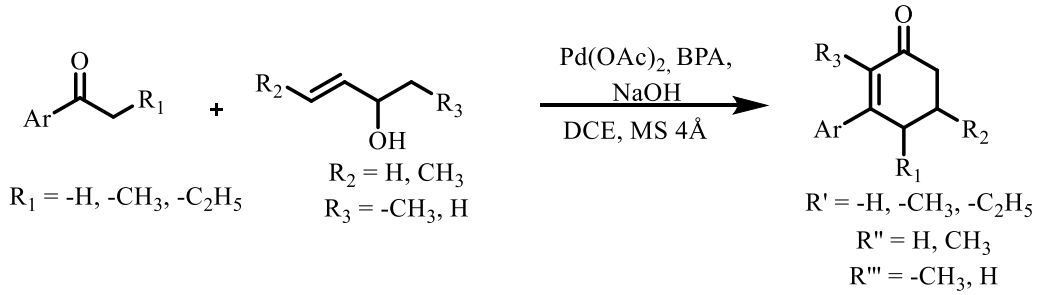


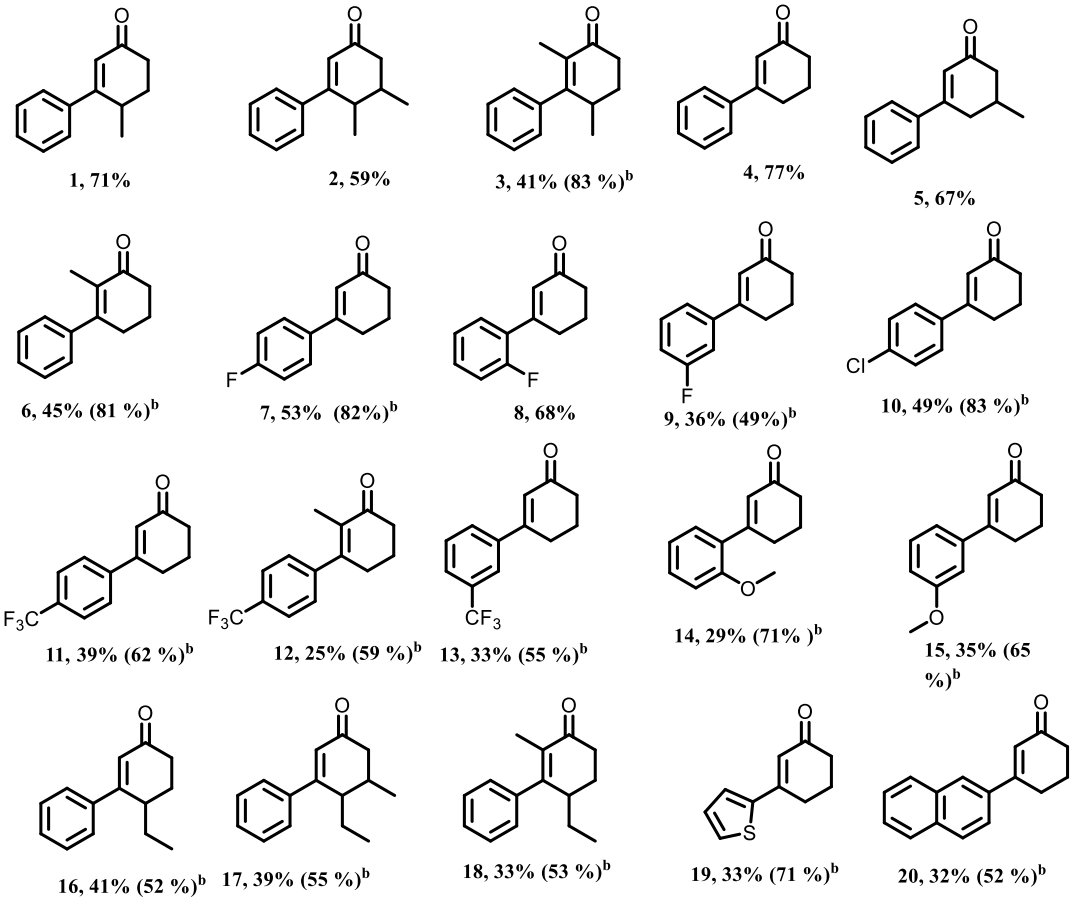
S. no	Catalyst (mol%)	Ligand (mol%)	Base (equiv.)	Yield (%)[c]
1	$Pd(OAc)_2$(10)	BPA(10)	NaOH(1)	33
2	Pd_2dba_3 (10)	BPA(10)	NaOH(1)	ND
3	$PdCl_2$(10)	BPA(10)	NaOH(1)	29
4[b]	$Pd(OAc)_2$(10)	BPA(10)	NaOH(1)	71
5[b]	$Pd(OAc)_2$(10)	BPA(20)	NaOH(1)	70
6[b]	$Pd(OAc)_2$(10)	BPA(10)	LiOH(1)	trace
7[b]	$Pd(OAc)_2$(10)	BPA(10)	Cs_2CO_3(1)	70
8[b]	$Pd(OAc)_2$(10)	BPA(10)	LiO^tBu(1)	25
9[b]	$Pd(OAc)_2$(10)	BPA(10)	KOH(1)	45
10[b]	$Pd(OAc)_2$(10)	PPh_3(10)	NaOH(1)	trace
11[b]	$Pd(OAc)_2$(10)	P(2-fur)$_3$(10)	NaOH(1)	ND
12[b]	-	BPA(10)	NaOH(1)	trace
13[b]	$Pd(OAc)_2$(10)	-	NaOH(1)	37
14[b]	$Pd(OAc)_2$(10)	dppe	NaOH(1)	trace
15[b]	$Pd(OAc)_2$(10)	1,10-phenanthroline	NaOH(1)	ND
16[b]	$Pd(OAc)_2$(5)	BPA(5)	NaOH(1)	53
17[b]	$Pd(OAc)_2$(7)	BPA(7)	NaOH(1)	61

[a]Reaction conditions: acetophenone (1 mmol), allyl alcohol (2 mmol), 0.8 mL of DCE (solvent) was stirred at room temperature for 24 h. [b]4Å molecular sieves was used. [c]Isolated yield after column chromatography. dppe = 1,2-Bis(diphenylphosphino)ethane, ND=not detected.

3-buten-2-ol, 3-penten-2- ol and 1-penten-3-ol to give the corresponding annulated products in 77%, 67% and 45% yield, respectively (Table 2.2, compounds **4**, **5** and **6**). Acetophenone bearing fluorine at the *para* and *ortho* positions yielded the corresponding products **7** and **8** in good yields. However, *meta* substituted acetophenone (3-fluoroacetophenone) resulted in a decrease in the product yield (Table 2.2, compound **9**). Our methodology has good tolerance towards $–CF_3$ and –Cl substitution on acetophenone (Table 2.2, compounds **10–13**). Electron donating –OMe at the *ortho* and *meta* positions gave lower yields (Table 2.2, compounds **14** and **15**). Butyrophenone with 3-buten-2-ol resulted in 41% yield (Table 2.2, compound **16**). Moreover, propiophenone and butyrophenone underwent annulation with 3-penten-2-ol to yield the corresponding products in 59% and 39% yields, respectively (Table 2.2, compounds **2** and **17**). On careful examination of the products **2** and **17**, we noticed the presence of two isomers, as is evident by GC, GC-MS, and NMR. The peaks at RT 13.14 and RT 12.63 (figure 2.1 and 2.2) correspond to the molecular weight of 214 which is the molecular weight of the corresponding annulated product of butyrophenone with 3-penten-2- ol. From GC, the ratio of the two isomers was found to be 4 : 1 (figure 2.3). Similarly, the ratio of isomers in the case of the annulated product of propiophenone and 3-penten-2-ol was found to be 6.1 : 1 (compound **2**, Fig. 2.4 and 2.5). Heteroaromatic substrate, 2-acetylthiophene, produced the annulated compound in 33% yield (Table 2.2, compound **19**). A trace amount of conversion was observed in the case of 2-acetylpyridine possibly owing to the coordination of the palladium metal to the N-atom of the pyridine moiety. 2,6-Dimethoxyacetophenone

Table 2.2. Substrate scope of Robinson's annulation for aryl ketones[a]





[a] Reaction conditions: 1 mmol ketone, 2 mmol allylic alcohol, 1 × 10−1 mmol $Pd(OAc)_2$, 1 × 10^{-1} mmol of BINOL phosphoric acid, 1 mmol NaOH, 4 Å molecular sieves and 0.8 mL of DCE were stirred at room temperature for 24 h. [b] 6 mmol allylic alcohol − GC conversion.

failed to give the product, whereas 4-bromoacetophenone underwent electrophilic substitution. 2-Acetylnaphthalene gave a moderate yield of 32% (Table 2.2, compound **20**). 1-Tetralone and 1-indanone with 3-penten- 2-ol resulted in 31% and 25% of the

isolated product, respectively (Table 2.3, compounds **22** and **23**). To our delight, compound **22** crystallized in a monoclinic system with a space group *P21/n* which

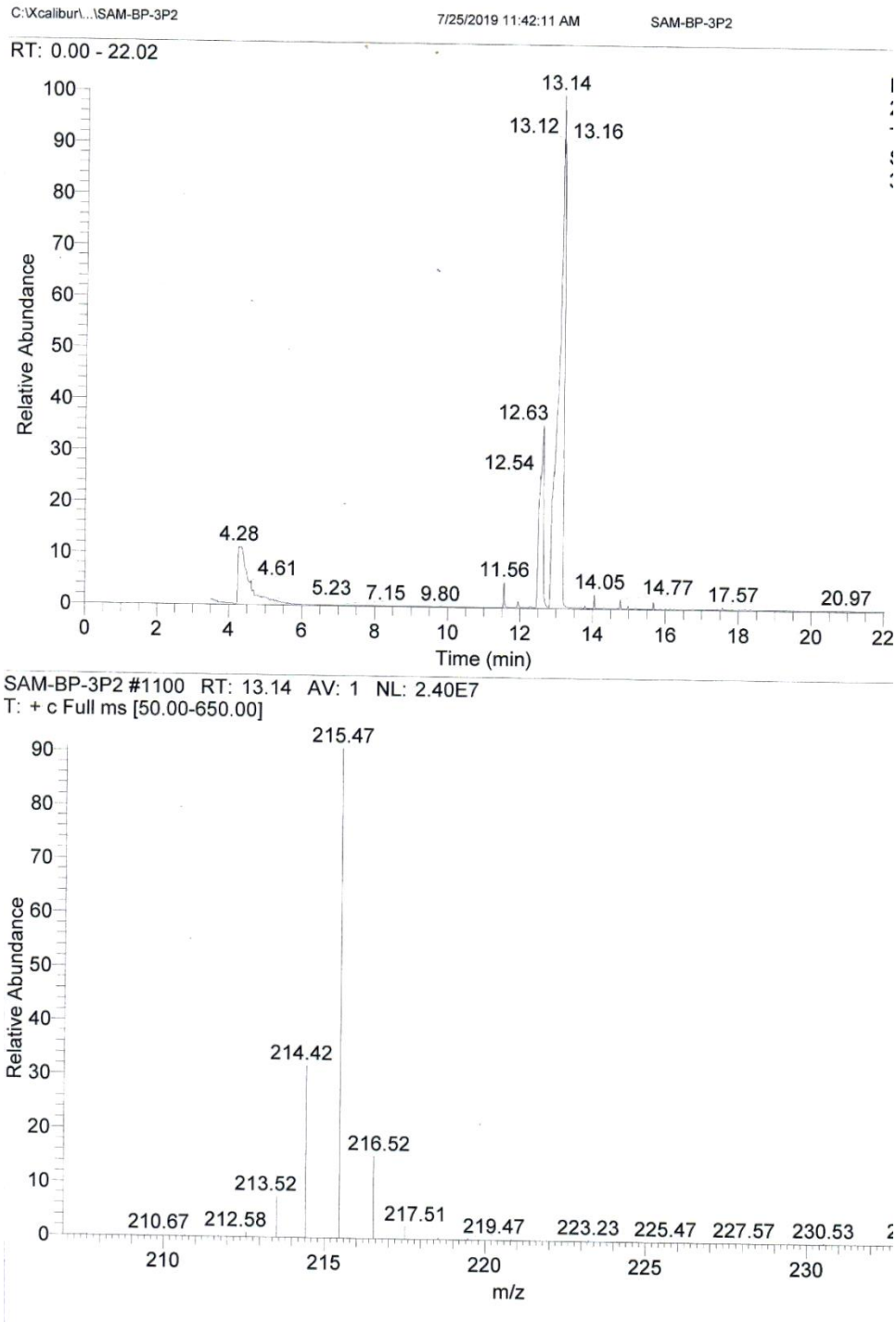


Figure 2.1 GC-MS of compound 17 at RT 13.14

was analysed using single crystal X-ray crystallography. The molecular structure of compound 22 is presented in figure 2.7 and the crystallographic datails presented in the

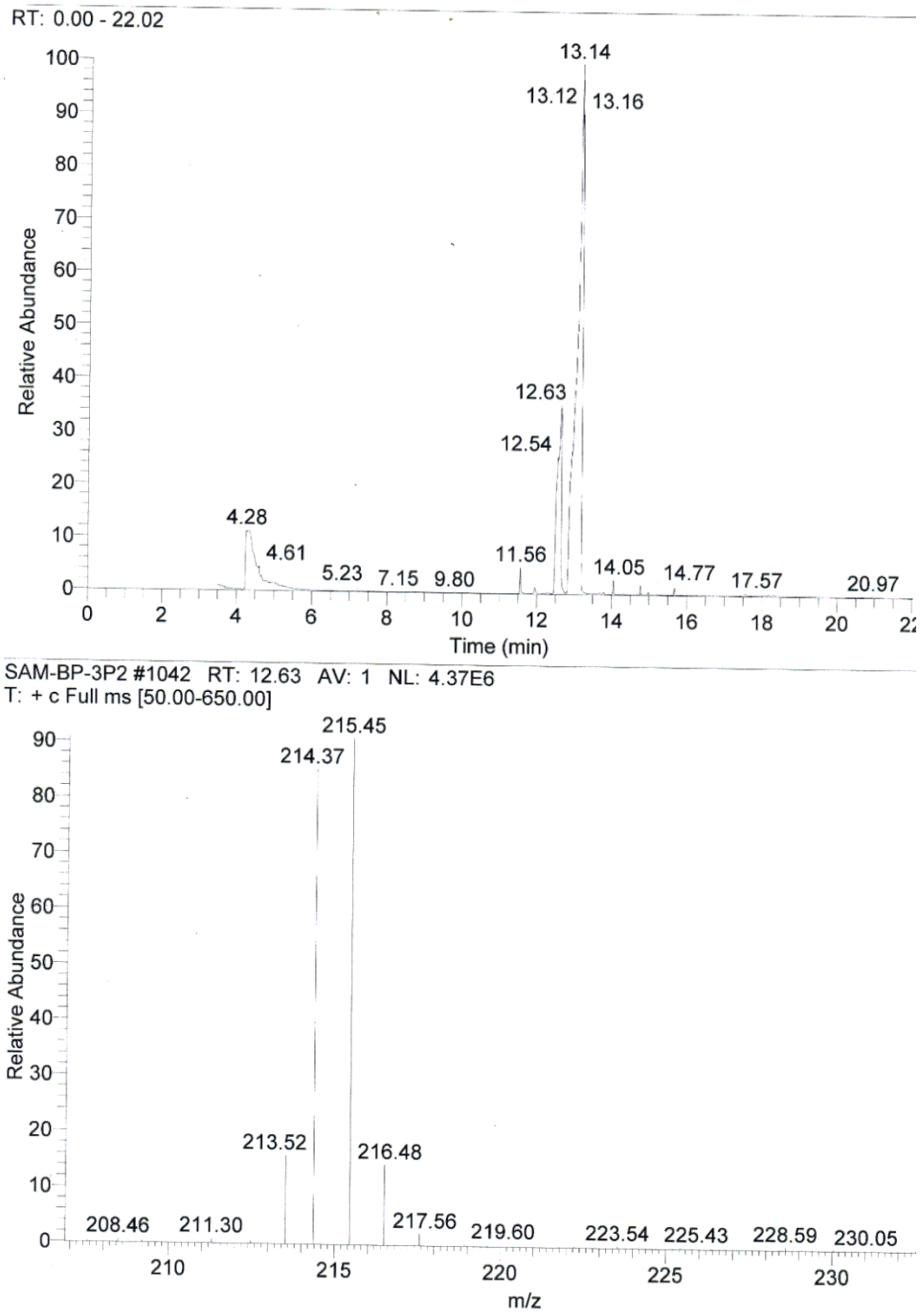
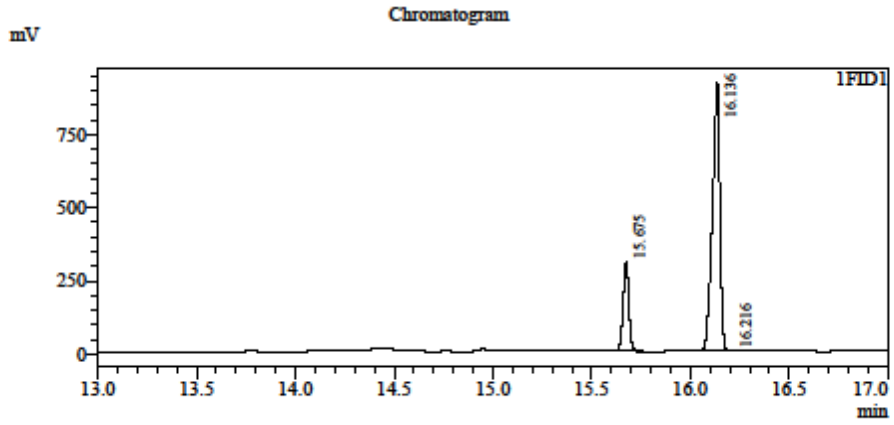


Figure 2.2. GC-MS of compound 17 at RT 13.14

table 2.4. Furthermore, 1-tetralone on reaction with 3- buten-2-ol gave the corresponding annulated product in moderate yield (Table 2.3, compound 21). The reaction did not proceed with aliphatic and alicyclic systems such as 3-methylbutanone, acetone, cyclopropylmethyl ketone and cyclohexyl methyl ketone. Under the experimental conditions mentioned, a gram-scale experiment of the desired

propiophenone (10 mmol) was performed. The reaction proceeded smoothly and gave product 1 in 58% yield (1.078 g).



Peak Table

FID1

Peak#	Ret. Time	Area	Area%	Height	Name
1	15.675	619394	20.293	301607	
2	16.136	2429079	79.584	907586	
3	16.216	3731	0.122	2010	
Total		3052204	100.000	1211203	

Figure 2.3. GC trace of compound 17

To our surprise, increasing the alkyl chain from 1-penten-3- ol to 1-hexen-3-ol resulted in 1,5-diketone as the only product. Our attempts to make the annulated product from 1-hexen-3-ol failed. As 1,5 diketones play a significant role in organic chemistry for the synthesis of many heterocycles,[13] we screened the potential of this methodology. Propiophenone and butyrophenone afforded the diketone in 58% and 33% yield respectively (Table 2.5, compounds **24** and **25**). Interestingly, acetophenone gave a low yield of 26% (Table 2.5, compound **27**). Substitution with electron-withdrawing and electron-donating groups did not have much impact on the yield of the reaction (Table 2.5, compound 28–30). 1-Tetralone resulted in 26% of the product with 1-hexen-3-ol(Table 2.5, compound **26**). Since cyclohexenones acted as precursors for phenols as mentioned *vide supra*, we attempted to prepare substituted phenols in one pot using our methodology. However, our methodology failed to yield aromatized phenols. A similar result was also observed by Liu and co-workers[14] when they used palladium acetate

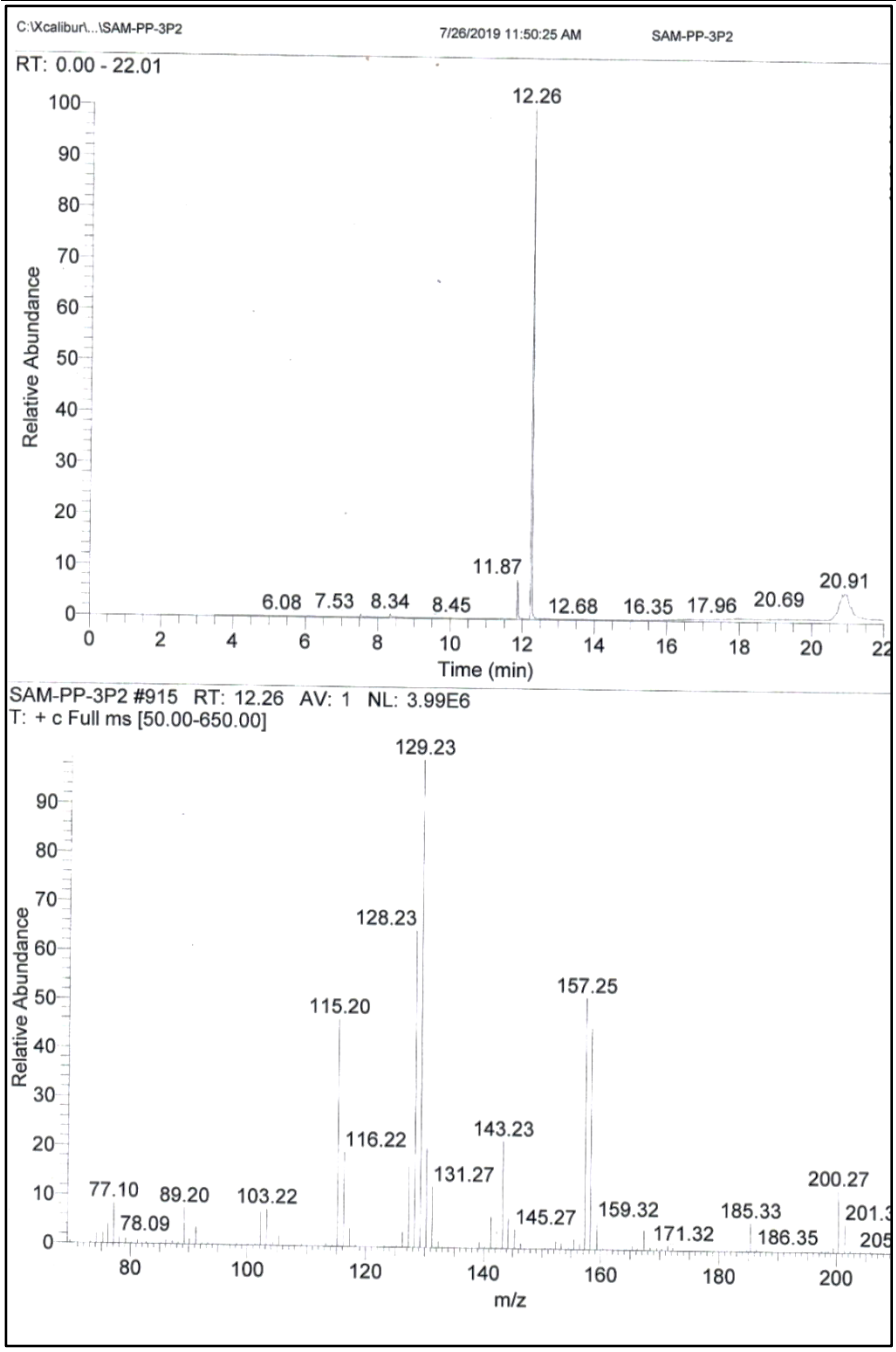


Figure 2.4. GC-MS of compound 2 at RT 12.26

as a catalyst.

To gain insight into the mechanism of the reaction, control experiments were carried out. Under the optimized conditions, without a base, the reaction of 1-penten-3-ol (without acetophenone, using NMR) revealed the formation of 3-pentanone along with 3-pentenone.[15] (Scheme 2.1 and Figure 2.9). Yet another control reaction carried out

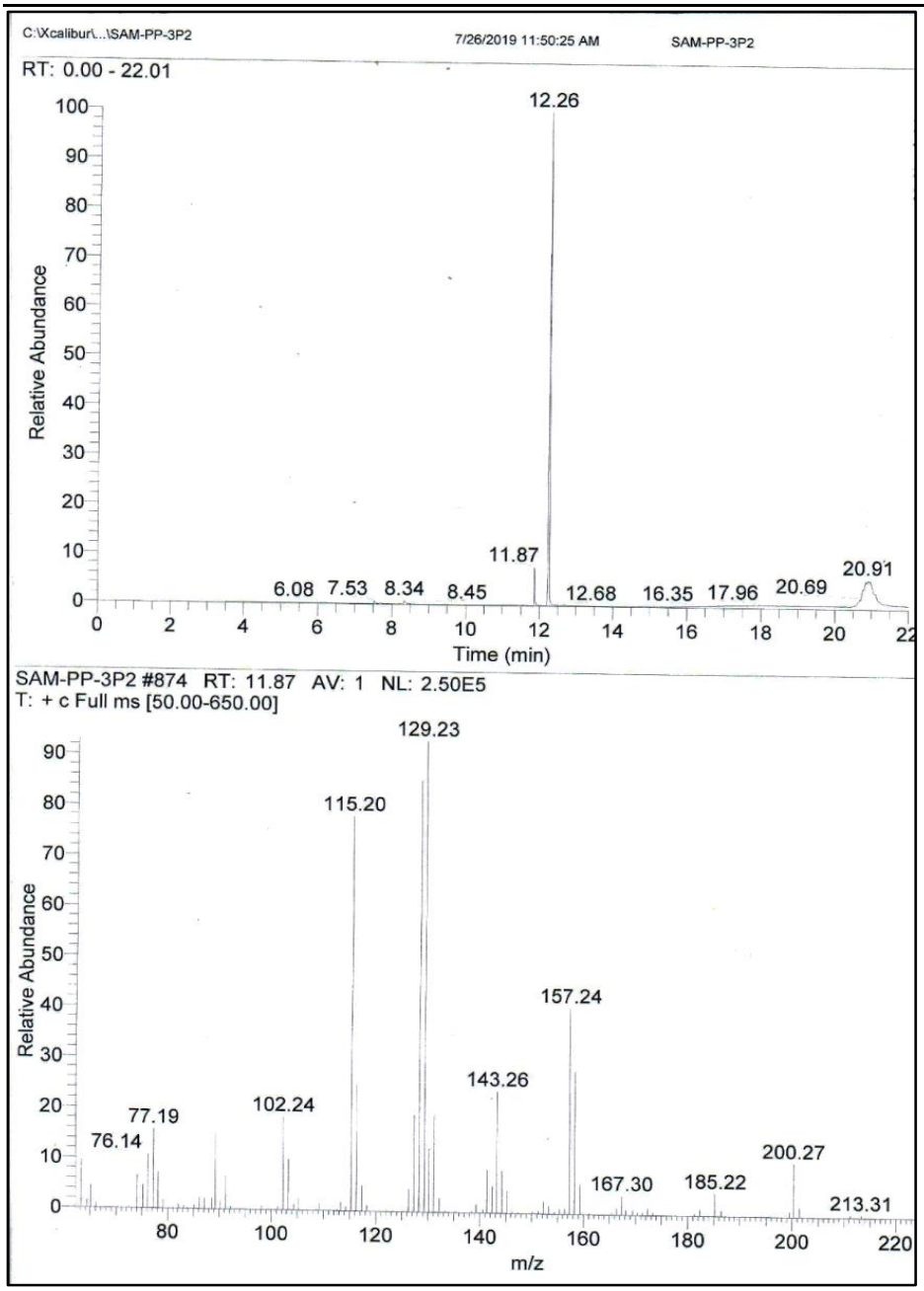
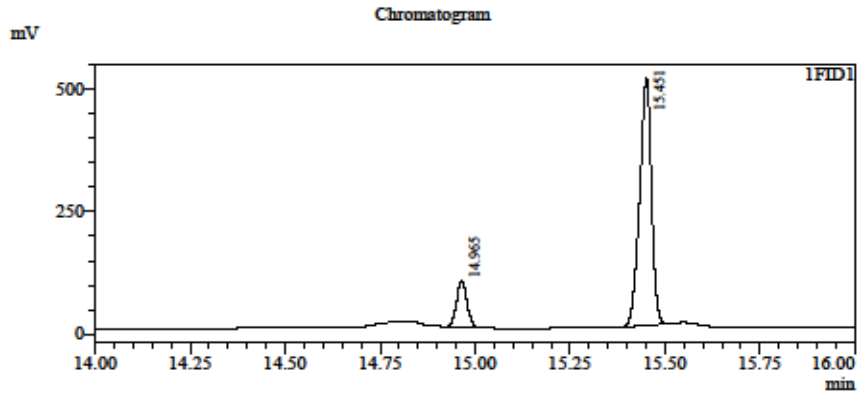


Figure 2.5. GC-MS of compound 2 at RT 11.87

in the presence of a base resulted in, exclusively, a saturated ketone. These results suggest that under the reaction conditions, the allyl alcohol is converted to the corresponding saturated ketone. The evolution of hydrogen gas was studied as reported in the literature.[16] We have taken 1-penten-3-ol under standard conditions without the base and in another chamber, phenylacetylene and palladium charcoal were taken in methanol. The crude NMR of the reaction mixture of the second chamber showed the



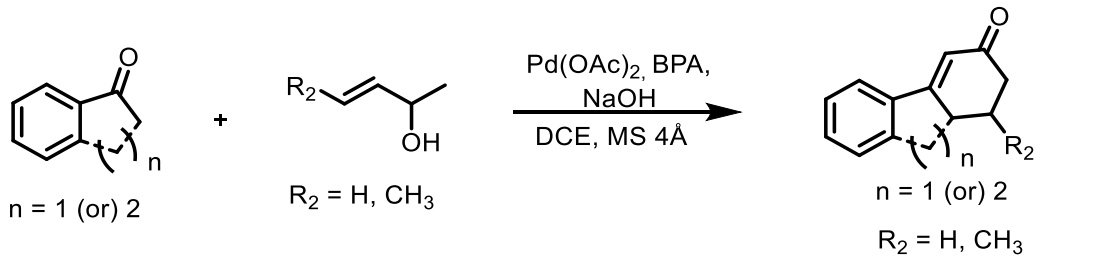
Peak Table

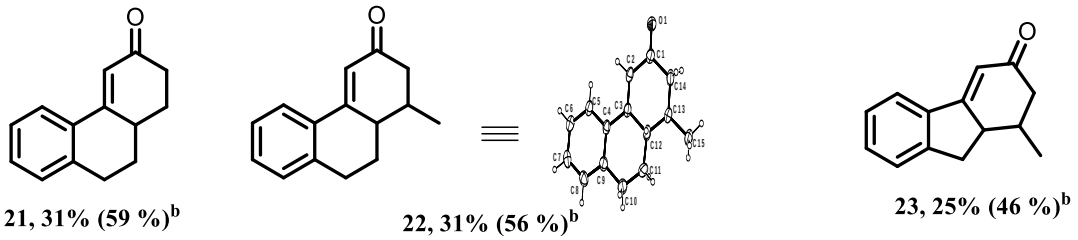
FID1

Peak#	Ret. Time	Area	Area%	Height	Name
1	14.965	179470	14.096	93137	
2	15.451	1093715	85.904	498102	
Total		1273185	100.000	591239	

Figure 2.6. GC trace of compound 2

Table 2.3. Substrate scope of Robinson's annulation for cyclic aryl ketones[a]





[a]Reaction conditions: 1 mmol ketone, 2 mmol allylic alcohol, 1 x 10^{-1} mmol $Pd(OAc)_2$, 1 x 10^{-1} mmol of BINOL phosphoric acid, 1 mmol NaOH, 4Å molecular sieves, 0.8 mL of DCE was stirred at room temperature for 24 h. [b]6 mmol allylic alcohol was used-GC conversion.

presence of styrene along with ethyl benzene which supports that dehydrogenation takes place during the course of the reaction. The base plays a major role in the conversion of diketone to the corresponding annulated product. In order to prove the role of the base, we stirred diketone (33) in the presence of NaOH which resulted in the

annulated product 3 in quantitative yield[17]. We repeated a few reactions using 6 equivalents of allylic alcohols under the optimized conditions. In most cases, we observed higher conversions (Tables 2.2–2.4), suggesting that the formation of species **32** limits the yield in these reactions.

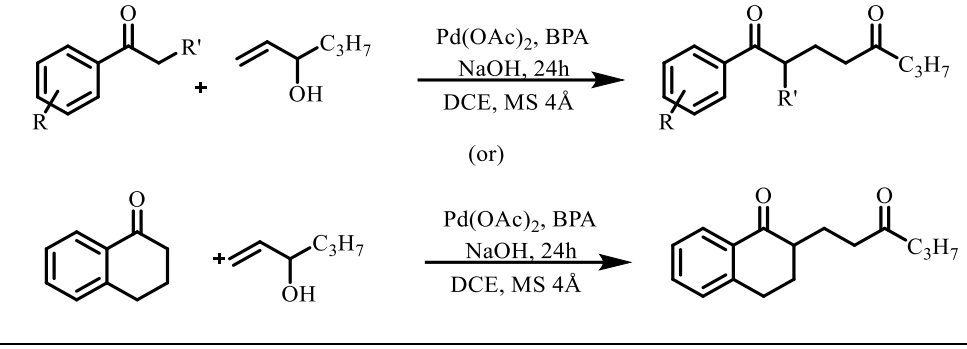
Table 2.4. Crystal data and structure refinement parameters for compound 22.

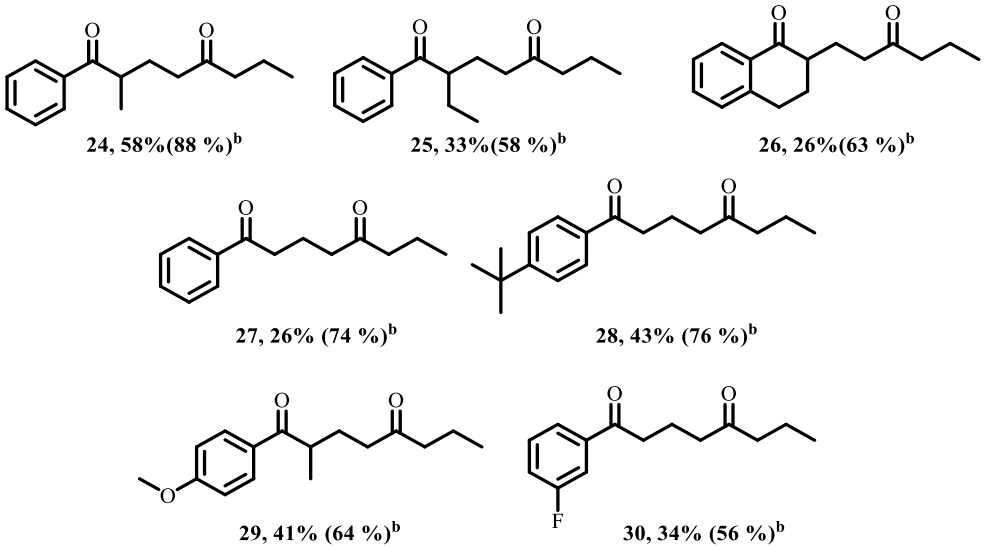
Empirical formula	$C_{15}H_{16}O$
Formula weight	212.28
Temperature/K	114.5(1)
Crystal system	monoclinic
Space group	*P2₁/n*
a/Å	8.9714(15)
b/Å	6.6608(7)
c/Å	19.405(3)
α/°	90
β/°	98.551(15)
γ/°	90
Volume/Å^3	1146.7(3)
Z	4
ρcalcg/cm^3	1.230
μ/mm^{-1}	0.580
F(000)	456.0
Radiation	CuKα (λ = 1.54184)
2 θ range for data collection/°	9.218 to 133.184
Index ranges	$-10 \leq h \leq 10$, $-7 \leq k \leq 6$, $-23 \leq l \leq 23$
Reflections collected	13865
Independent reflections	1899 [R_{int} = 0.1362, R_{sigma} = 0.0616]
Data/restraints/parameters	1899/0/146
Goodness-of-fit on F^2	1.280
Final R indexes [I>=2σ (I)]	R_1 = 0.1022, wR_2 = 0.2919
Final R indexes [all data]	R_1 = 0.1201, wR_2 = 0.3190
Largest diff. peak/hole / e Å^{-3}	0.44 and -0.34

Based on the findings from the control experiments and a recent study,[18] we propose the following mechanism (Scheme 2.2). The palladium complex reacts with an allyl alcohol to give the corresponding metal alkoxide B, which can undergo β-hydride elimination to form the intermediate C. The intermediate C can result in the formation of the corresponding enol[18a] which can either undergo keto–enol tautomerisation to

form the observed species 32 or react with the ketone in the presence of a base to form the enolic species E which results in the diketone product F. The diketone in the presence of a base undergo aldol condensation to form the annulated product. However,

Table 2.5. Substrate scope for the synthesis of 1,5-diketone[a]





[a] Reaction conditions: 1 mmol ketone, 2 mmol allylic alcohol, 1 x 10^{-1} mmol $Pd(OAc)_2$, 1 x 10^{-1} mmol of BINOL phosphoric acid, 1 mmol NaOH, 4Å molecular sieves, 0.8 mL of DCE was stirred at room temperature for 24 h. [b]6 mmol allylic alcohol-GC conversion.

when we used 1-hexen-3-ol, the annulation did not proceed. The presence of α-hydrogen is essential for the formation of an annulated product. To further support this hypothesis, we reacted propiophenone, acetophenone and butyrophenone with phenylallyl alcohol under the optimized reaction conditions, which resulted in 1,5-diketones (34–36) as the only product (Scheme 2.1.c).

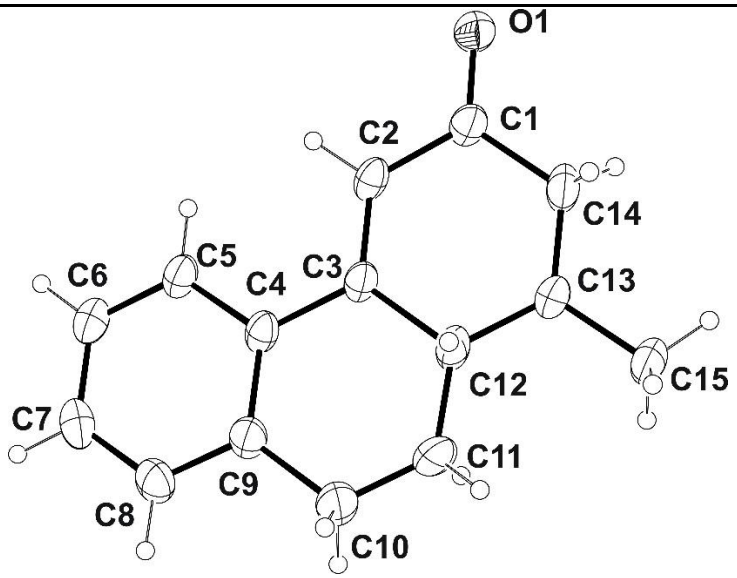


Figure 2.7. Molecular structure for compound 22. (50% probability thermal ellipsoids). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (degree): C1-C2 1.459, C1-C4 1.502, C1-O1 1.227, C2-C3 1.350, C13-C14 1.419, C13-C15 1.510, O1-C1-C14 120.85, O1-C1-C2 122.04, C14-C13-C15 116.35, C11-C12-C13 125.90, C4-C3-C2 121.68

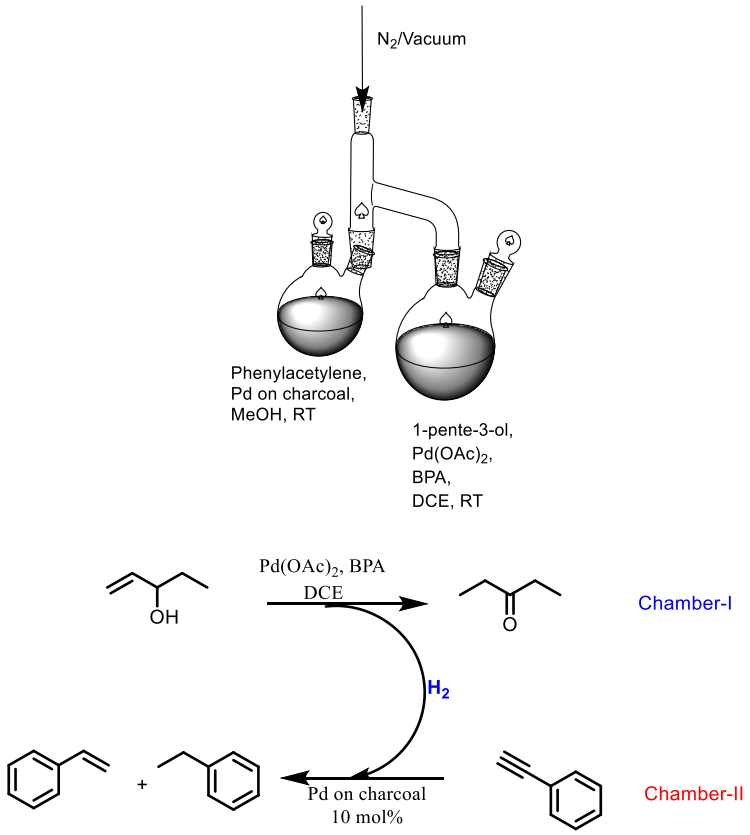


Figure 2.8. Two chamber reaction set up for hydrogen evolution reaction

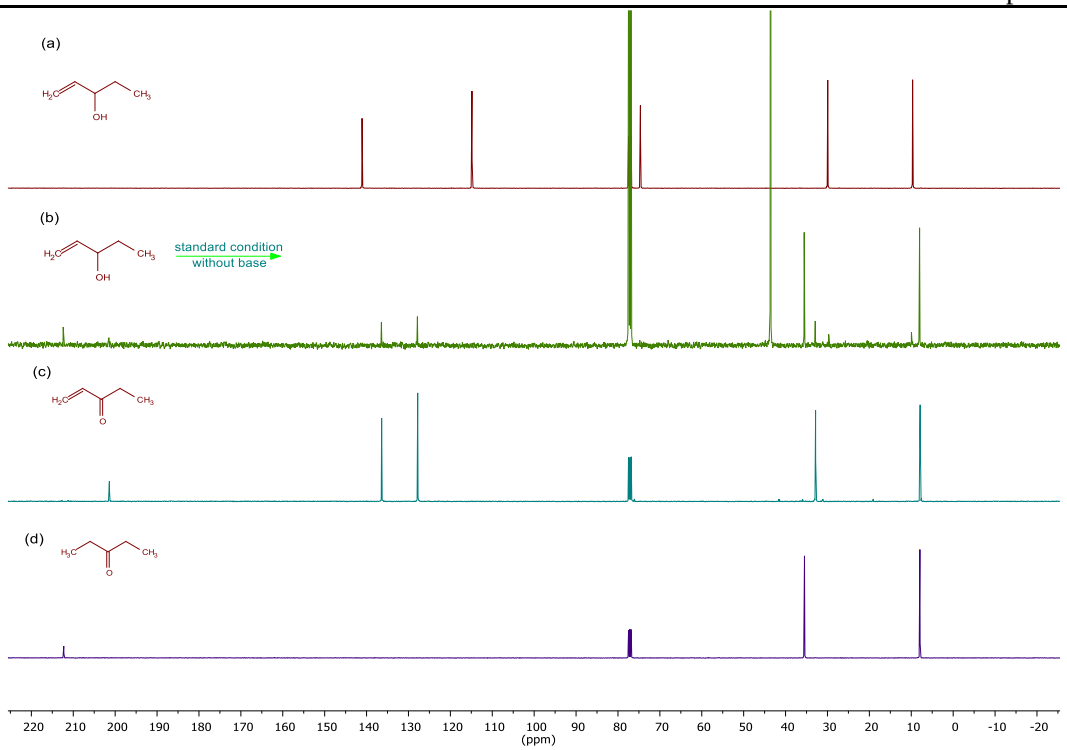


Figure 2.9: Stacking of crude ^{13}C NMR of control experiment (Scheme 2.1.a). ^{13}C NMR spectrum of (a) pure 1-penten-3-ol (b) reaction mixture of Scheme 1a (without base). (c) pure 1-penten-3-one and (d) pure 3-pentanone.

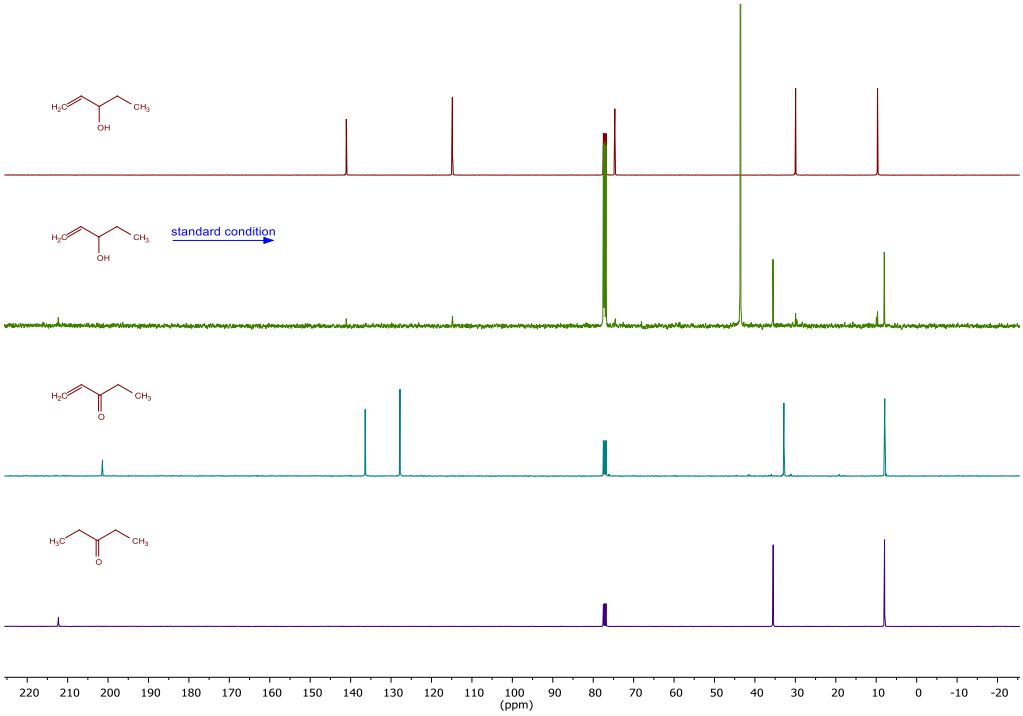
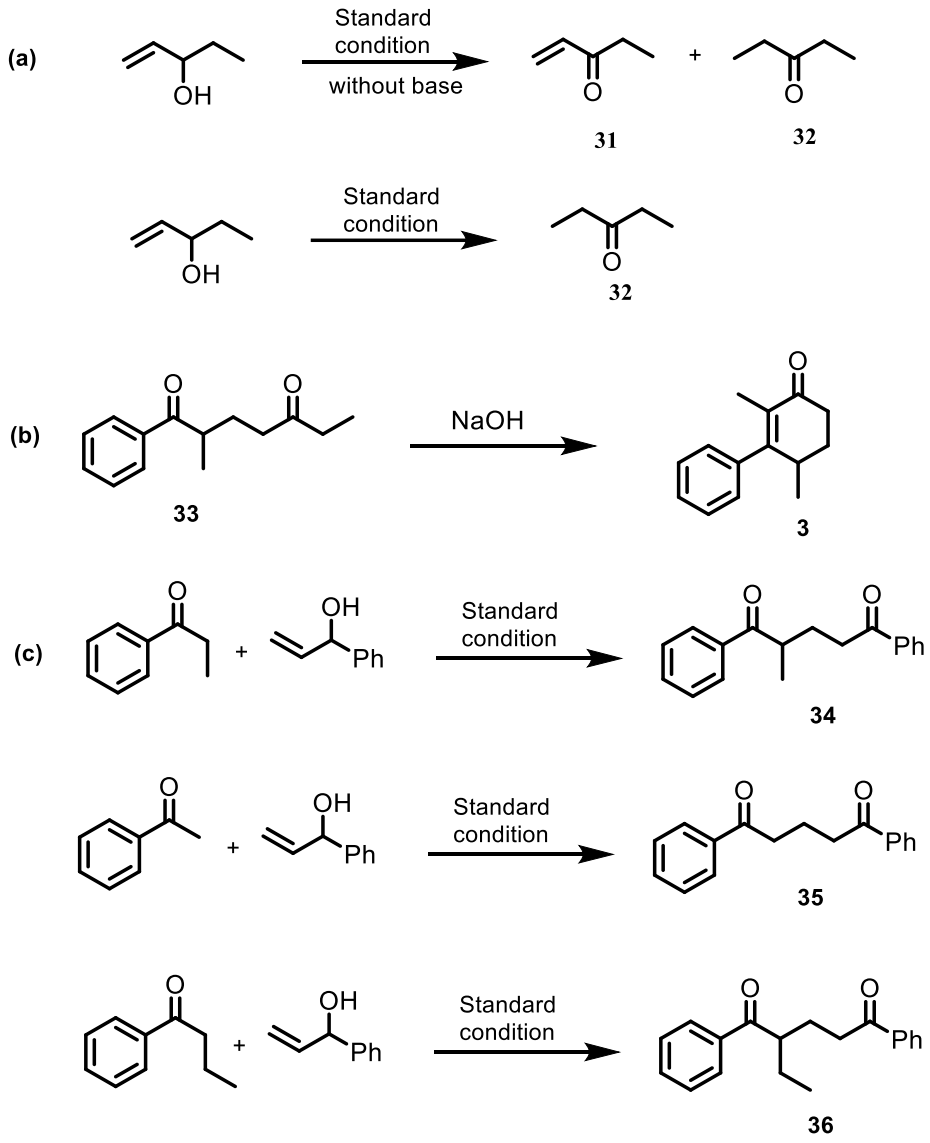


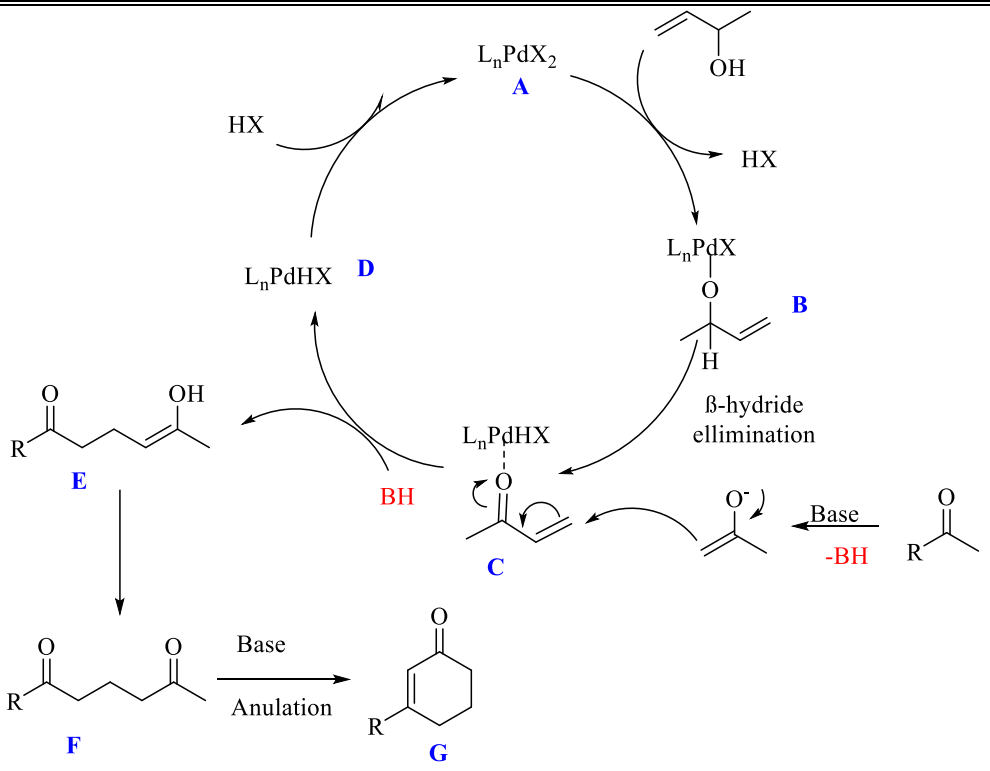
Figure 2.10: Stacking of crude ^{13}C NMR of control experiment (Scheme 2.1.a). ^{13}C NMR spectrum of (a) pure 1-penten-3-ol (b) reaction mixture of Scheme 1a (with base).(c) pure 1-penten-3-one and (d) pure 3-pentanone.



Scheme 2.1. Control experiments

2.3. Conclusion

In summary, we have developed a new palladium-BINOL phosphoric acid system for the synthesis of 3-aryl substituted cyclohexenones or 1,5-diketones. The developed method has shown good tolerance to different functional groups. The reaction of aryl ketones with 3-buten-2-ol, 3-penten-2-ol or 1-penten-3-ol resulted in Robinson's annulated products; however, 1-hexen- 3-ol yielded 1,5-diketones as the only product.



Scheme 2.2. Proposed mechanism

2.4. Experimental Section

2.4.1. General Information:

All reagents and solvents were obtained from commercial sources. Solvents were purified according to standard procedures. BINOL phosphoric acid (BPA)[19] and 2-methyl-1-phenylheptane-1,5-dione (compound **33**)[20] were synthesized following the literature reported 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. ^{19}F NMR spectra were externally referenced to α,α,α- trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). ^{31}P spectrum was referenced externally to H_3PO_4 in D_2O(δ = 0). High-resolution mass spectra (HRMS) were recorded using Bruker microTOF-QII mass spectrometer. Single-crystal X-ray diffraction data were collected at 114 K using Cu-Kα radiation (1.54184 Å). Sodium hydroxide was grounded to powder form using mortar and pestle and was kept under

vacuum when not in use.

2.4.2. General procedure for annulations and diketone reaction:

Palladium acetate (0.022 g, 0.1 mmol), BINOL phosphoric acid (0.035 g, 0.1 mmol) and sodium hydroxide (0.039g, 1.00 mmol) were taken in a scintillation vial. Aryl ketone(1.00 mmol), allyl alcohol (2.00 mmol) and 0.8 mL of dichloroethane (DCE) were added to it. Finally, 4Å molecular sieves was added to the reaction mixture and stirred at room temperature for 24 hours. Then the reaction mixture was evaporated under vacuum and purified by flash column chromatography in ethyl acetate and *n*-hexane (1:4) as an eluent.

2.4.3. Analytical data for annulated compounds

6-Methyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[21] (Table 2.2, **1**): Prepared from propiophenone (0.134g, 1.00 mmol) and 3-buten-2-ol (0.144g, 2.00 mmol). After purification by column chromatography the compound was isolated as a yellow liquid (0.132g, 71%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.49 – 7.48 (m, 2H), 7.41 – 7.37 (m, 3H), 6.25 (s, 1H), 3.18 – 3.13 (m, 1H), 2.60 (ddd, *J*=17.7, 12.9, 5.0, 1H), 2.44 (ddd, *J*=17.2, 4.6, 4.6, 1H), 2.34 – 2.29 (m, 1H), 2.04 – 1.90 (m, 1H), 1.18 (d, *J*=7.2, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 199.84, 165.40, 138.41, 129.89, 128.91, 126.76, 125.22, 33.29, 31.27, 29.67, 18.44. HRMS (ESI): calculated for $C_{13}H_{14}O$ ($[M+H]^+$): 187.1117, found: 187.1126.

5,6-Dimethyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (Table 2.2, **2**): Prepared from propiophenone (0.134g, 1.00 mmol) and 3-penten-2-ol (0.172g, 2.0 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.118g, 59%). Data for major isomer is given. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.54 – 7.52 (m, 2H), 7.43 – 7.39 (m, 3H), 6.28 (s, 1H), 2.98 (dq, *J*=8, 4, 1H), 2.54 – 2.41 (m, 2H), 2.37 – 2.29 (m, 2H), 1.13 (d, *J*=6.8, 3H), 1.04 (d, *J*=7.1, 3H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ = 200.35, 166.64, 138.17, 130.08, 128.96, 126.78, 124.50, 40.11, 36.87, 32.90, 18.78, 12.13. HRMS (ESI): calculated for $C_{14}H_{16}O$ ($[M+H]^+$): 201.1274, found: 201.1268.

2,6-Dimethyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (Table 2.2, **3**)**:** Prepared from propiophenone (0.134g, 1.00 mmol) and 1-penten-3-ol (0.172g, 2.0 mmol). After purification by column chromatography the compound was isolated as colorless oil (0.082 g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (t, *J*=7.4, 2H), 7.32 (t, *J*=7.1, 1H), 7.12 (d, *J*=7.2, 2H), 2.84 – 2.76 (m, 1H), 2.65 (ddd, *J*=16.6, 11.4, 4.8, 1H), 2.46 (ddd, *J*=16.9, 6.3, 4.8, 1H), 2.34 – 2.28 (m, 1H), 1.91 – 1.84 (m, 1H), 1.62 (s, 3H), 1.02 (d, *J*=7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.06, 161.53, 140.65, 131.23, 128.45, 127.74, 127.39, 35.73, 34.34, 29.95, 18.20, 13.14. HRMS (ESI): calculated for $C_{14}H_{16}O$ ($[M+Na]^+$): 223.1093, found: 223.1093.

5,6-Dihydro-[1,1'-biphenyl]-3(4H)-one[21] (Table 2.2, **4**): Prepared from acetophenone (0.120g, 1.00 mmol) and 3-buten-2-ol (0.142g, 2.0 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.118g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.56 – 7.52 (m, 2H), 7.43 – 7.39 (m, 3H), 6.42 (s, 1H), 2.81 – 2.74 (m, 2H), 2.49(t, *J*=8.0, 2H), 2.19 – 2.13 (m, 6.2, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.08, 159.96, 130.12, 128.90, 126.22, 125.59, 37.41, 28.26, 22.96. HRMS (ESI): calculated for $C_{12}H_{12}O$ ($[M+H]^+$): 173.0961, found: 173.0962.

5-Methyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[22] (Table 2.2, **5**): Prepared from acetophenone (0.120g, 1.00 mmol) and 3-penten-2-ol (0.172g, 2.0 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.098g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 – 7.52(m, 2H), 7.43 – 7.39 (m, 3H), 6.41 (s,1H), 2.84 (dd, *J*=17.3, 3.8, 1H), 2.56 (dd, *J*=16.1, 3.6, 1H), 2.49– 2.42 (m, 1H), 2.38 – 2.26 (m, 1H), 2.17 (dd, *J*=16.1, 12.1, 1H), 1.17 (d, *J*=6.5, 3H). ^{13}C NMR

(101 MHz, $CDCl_3$) δ = 200.33, 159.24, 138.93, 130.10, 128.89, 126.26, 125.26, 45.59, 36.68, 30.47, 21.44. HRMS (ESI): calculated for $C_{13}H_{14}O$ ($[M+H]^+$): 187.1117, found: 187.1121.

2-Methyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[23] (Table 2.2, **6**): Prepared from acetophenone (0.120g, 1.00 mmol) and 1-penten-3-ol (0.172g, 2.0 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.083g, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (t, *J*=7.5, 2H), 7.35 – 7.29(m, 1H), 7.20 (d, *J*=8.1, 2H), 2.63 (t, *J*=4.0, 2H), 2.53 (t, *J*=4.0, 2H), 2.10(p, *J*=4.0, 2H), 1.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.08, 156.61, 141.37, 131.88, 128.35, 127.85, 127.10, 37.80, 32.98, 22.83, 12.89. HRMS (ESI): calculated for $C_{13}H_{14}O$ ($[M+H]^+$): 187.1117, found: 187.1104.

4'-Fluoro-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[24] (Table 2.2, **7**): Prepared from 4-fluoroacetophenone (0.138g, 1.00 mmol) and 3-buten-2-ol (0.144g, 2.0 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.10 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 – 7.49 (m, 2H), 7.12 – 7.08 (m, 2H), 6.37 (s, 1H), 2.75 (t,*J* = 6.6, 2H), 2.48 (t,*J*=6.7, 2H), 2.15 (p, *J*=6.2, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.84, 163.91(d, *J* = 251), 158.59, 134.99, 128.14(d, *J* = 9), 125.41, 115.95(d, *J* = 21), 37.28, 28.28, 22.89. HRMS (ESI): calculated for $C_{12}H_{11}FO$ ($[M+H]^+$): 191.0867, found: 191.0871.

2'-Fluoro-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[4a] (Table 2.2, **8**): Prepared from 2-fluoroacetophenone (0.138g, 1.00 mmol) and 3-buten-2-ol (0.144g, 2.0 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.135g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38 – 7.32 (m, 2H), 7.19– 7.16 (m, 1H), 7.10 (dd, *J*=11.1, 8.5, 1H), 6.28 (s, 1H), 2.76 (t, *J*=5.8, 2H), 2.50 (t, *J*=8.0, 2H), 2.14 (p, *J*=6.2, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.71, 159.96(d, *J* = 251), 157.36

(d, *J* = 3), 134.60, 131.07(d, *J* = 8) , 128.98, 124.56(d, *J* = 4), 116.650(d, *J* = 23), 37.54, 29.81, 23.28. HRMS (ESI): calculated for $C_{12}H_{11}FO$ ([M+H]): 191.0867, found: 191.0879.

3'-Fluoro-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[4a] (Table 2.2, **9**): Prepared from 3-fluoroacetophenone (0.138g, 1.00 mmol) and 3-buten-2-ol (0.144g, 2.00 mmol).After purification by column chromatography the compound was isolated as colorless liquid (0.068g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.36 (m, 1H), 7.33 – 7.30 (m, 1H), 7.23 – 7.20 (m, 1H), 7.10 (tdd, *J*=8.2, 2.5, 1.1, 1H), 6.39 (s, 1H), 2.74 (td, *J*=6.2, 2H), 2.52 – 2.44 (m, 2H), 2.21 – 2.10 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.81, 163.07(d, *J* = 247), 158.36(d, *J*=2.6), 141.26 (d, *J*=7.5), 130.44 (d, *J*=8.4), 126.27, 121.89 (d, *J*=2.9), 116.87 (d, *J*=21.4), 113.23 (d, *J*=22.3), 22.84, 28.21, 37.36. ^{19}F NMR (376 MHz, $CDCl_3$) δ= -112.15. HRMS (ESI): calculated for $C_{12}H_{11}FO$ ($[M+H]^+$): 191.0867, found: 191.0871.

4'-Chloro-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[4a] (Table 2.2, **10**): Prepared from 4-chloroacetophenone (0.155g, 1.00 mmol) and 3-buten-2-ol (0.144g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.10 g, 49%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.46 (d, *J*=8.6, 2H), 7.38 (d, *J*=8.6, 2H), 6.38 (s, 1H), 2.73 (t, *J*=6, 2H), 2.48 (t, *J*=6.8, 2H), 2.15 (p, *J*=6.2, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 199.79, 158.43, 137.31, 136.16, 129.13, 127.49, 125.76, 37.30, 28.13, 22.85.HRMS (ESI): calculated for $C_{12}H_{11}ClO$ ($[M+Na]^+$): 229.0391, found: 229.0402.

4'-(Trifluoromethyl)-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[4a] (Table 2.2, **11**): Prepared from 4'-(trifluoromethyl)acetophenone (0.188g, 1.00 mmol) and 3-buten-2-ol (0.144g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow gel (0.094g, 39%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.66 (d, *J*=8.3, 2H), 7.62 (d, *J*=8.2, 2H), 6.42 (s, 1H), 2.77 (t, *J*=5.9, 2H), 2.50 (t, *J*=6.8, 2H),

2.18 (p, *J*=6.3, 2H). ^{13}C NMR (176 MHz, $CDCl_3$) δ = 199.63, 158.20, 142.57, 131.71(q, *J*=32), 128.51, 127.03, 126.54, 125.85(q, *J*=3.5), 123.95(q, *J*=271), 37.32, 28.27, 22.85. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.58. HRMS (ESI): calculated for $C_{13}H_{11}F_3O$ ($[M+H]^+$): 241.0835, found: 241.0849.

2-Methyl-4'-(trifluoromethyl)-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (Table 2.2, **12**): Prepared from 4'-(trifluoromethyl)acetophenone (0.188g, 1.00 mmol) and 1-penten-3-ol (0.172g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.063g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$)δ = 7.65 (d, *J*=8.3, 2H), 7.31 (d, *J*=7.9, 2H), 2.63 – 2.58 (m, 2H), 2.54 (t, *J*=8.0, 2H), 2.11 (p, *J*=8.0, 2H), 1.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.66, 154.83, 145.08, 132.74, 130.08(q, *J*=33), 125.60(q, *J*=4), 124.04(q, *J*=273) 37.83, 32.84, 22.91, 12.94. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.57. HRMS (ESI): calculated for $C_{14}H_{13}F_3O$ ($[M+H]^+$): 255.0991, found: 255.0987

3'-(Trifluoromethyl)-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[14b] **(**Table 2.2, **13**): Prepared from 3'-(trifluoromethyl)acetophenone (0.188g, 1.00 mmol) and 3-buten-2-ol (0.144g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow gel(0.079g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.76 (s, 1H), 7.71 (d, *J*=7.8, 1H), 7.66 (d, *J*=7.8, 1H), 7.54 (t, *J*=7.8, 1H), 6.43 (s, 1H), 2.79 (td, *J*=6.1, 1.4, 2H), 2.51 (t, *J*=8.0, 2H), 2.19 (p, *J*=6.3, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.61, 158.10, 139.87, 129.49, 129.39, 126.71, 126.58(q, *J*=4), 123.029 (q, *J*=4), 37.31, 28.23, 22.85. ^{19}F NMR (376 MHz, $CDCl_3$) δ = -62.69. HRMS (ESI): calculated for $C_{13}H_{11}F_3O$ ($[M+Na]^+$): 263.0654, found: 263.0651.

2'-Methoxy-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[4a] **(**Table 2.2, **14**): Prepared from 2'-methoxyacetophenone(0.15g, 1.00 mmol) and 3-buten-2-ol(0.144g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow gel

(0.0586g, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.30 (m, 1H), 7.20 (dd, *J*=7.2, 1.7, 1H), 7.00 –6.90 (m, 2H), 6.20 (s, 1H), 3.84 (s, 3H), 2.74 (td, *J*=6.2, 1.2, 2H), 2.48 (t, *J*=8.0, 2H), 2.10 (p, *J*=8.0, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.35, 161.89, 156.74, 130.46, 129.79, 128.89, 128.34, 120.88, 111.29, 55.59, 37.69, 30.21, 23.45. HRMS (ESI): calculated for $C_{13}H_{14}O_2$ ($[M+H]^+$): 203.1067, found: 203.1087.

3'-Methoxy-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[4a] **(**Table 2.2, **15**): Prepared from 3'-methoxyacetophenone(0.15g, 1.00 mmol) and 3-buten-2-ol(0.144g, 2.00 mmol). After purification by column chromatography the compound was isolated as white solid (0.0586g, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (t, *J*=8.0, 1H), 7.14 – 7.11 (m, 1H), 7.05 – 7.04 (m, 1H),6.41 (s, 1H), 3.83 (s, 3H), 2.76 (td, *J*=6.1, 1.5, 2H), 2.49 (t, *J*=8.0, 2H), 2.15 (p, *J*=4.0, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.19, 159.90, 140.41, 129.89, 125.73, 118.69, 115.56, 111.83, 100.05, 55.48, 37.42, 28.33, 22.93. HRMS (ESI): calculated for $C_{13}H_{14}O_2$ ($[M+H]^+$): 203.1067, found: 203.1075.

6-Ethyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one[25] (Table 2.2, **16**): Prepared from butyrophenone (0.148 g, 1.00 mmol) and 3-buten-2-ol (0.144g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.082g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 –7.49 (m, 2H), 7.41 – 7.38 (m, 3H), 6.24 (s, 1H), 2.94 –2.88 (m, 1H), 2.54 (ddd, *J*=17.9, 12.2, 6.1, 1H), 2.47 – 2.40 (m, 1H), 2.26 – 2.05 (m, 2H), 1.61 – 1.43 (m, 2H), 0.95 (t, *J*=7.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.92, 165.07, 138.78, 129.88, 128.91, 126.74, 125.50, 38.11, 33.07, 29.84, 25.26, 24.71, 12.81. HRMS (ESI): calculated for $C_{14}H_{16}O$ ($[M+Na]^+$): 223.1093, found: 223.1076.

6-Ethyl-5-methyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (Table 2.2, **17**): Prepared from butyrophenone (0.148g, 1.00 mmol) and 3-penten-2-ol (0.172g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow liquid

(0.0792g, 37%). Only the major isomer data is presented. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.51 – 7.46 (m, 2H), 7.42 – 7.39 (m, 3H), 6.24 (s, 1H), 2.91 – 2.79 (m, 1H), 2.58 – 2.46 (m, 1H), 2.36 (d, *J*=9.9, 2H), 1.78 – 1.65 (m, 2H), 1.50 – 1.39 (m, 1H), 1.17 (d, *J*=6.9, 3H), 0.75 (t, *J*=7.5, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.60, 166.72, 139.87, 129.85, 128.89, 126.72, 125.49, 43.51, 41.30, 33.62, 21.42, 18.85, 13.64. HRMS (ESI): calculated for $C_{15}H_{18}O$ ($[M+Na]^+$): 237.1250, found: 237.1240.

6-Ethyl-2-methyl-5,6-dihydro-[1,1'-biphenyl]-3(4H)-one (Table 2.2, **18**): Prepared from butyrophenone (0.148g, 1.00 mmol) and 1-penten-3-ol (0.172g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.071g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (t, *J*=7.3, 2H), 7.32 (t, *J*=7.3, 1H), 7.13 (d, *J*=6.9, 2H), 2.64 – 2.52 (m, 2H), 2.46 – 2.39 (m, 1H), 2.28 – 2.19 (m, 1H), 2.07 – 2.00 (m, 1H), 1.63 (s, 3H), 1.45 – 1.35 (m, 2H), 0.85 (t, *J*=7.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.17, 161.08, 140.80, 131.36, 128.39, 127.78, 127.62, 42.50, 33.87, 25.25, 23.94, 13.19, 12.64. HRMS (ESI): calculated for $C_{15}H_{18}O$ ($[M+Na]^+$): 237.1250, found: 237.1265.

3-(Thiophen-2-yl)cyclohex-2-en-1-one[23] (Table 2.2, **19**): Prepared from 2-acetylthiophene (0.126 g, 1.00 mmol) and 3-buten-2-ol (0.144 g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.0587 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (d, *J*=5.0, 1H), 7.38 (d, *J*=3.7, 1H), 7.09 (dd, *J*=5.1, 3.8, 1H), 6.43 (s, 1H), 2.79 (t, *J*=6.0, 2H), 2.46 (t, *J*=6.6, 2H), 2.14 (p, *J*=6.3, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.59, 152.58, 131.42, 128.89, 128.40, 127.45, 122.87, 37.37, 28.17, 22.58. HRMS (ESI): calculated for $C_{10}H_{10}OS$ ($[M+H]^+$): 179.0525, found: 179.0537.

3-(Naphthalen-2-yl)cyclohex-2-en-1-one[23] (Table 2.2 **20**): Prepared from 2-acetylnaphthalene (0.17 g, 1.00 mmol) and 3-buten-2-ol (0.144 g, 2.00 mmol). After

purification by column chromatography the compound was isolated as yellow liquid (0.071 g, 32%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.01 (s, 1H), 7.89 – 7.82 (m, 3H), 7.65 (dd, *J*=8.7, 1.9, 1H), 7.55 – 7.49 (m, 2H), 6.57 (s, 1H), 2.94 – 2.87 (m, 2H), 2.56 – 2.49 (m, 2H), 2.24 – 2.18 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.05, 159.60, 136.09, 134.11, 133.22, 128.82, 128.63, 127.80, 127.33, 126.84, 126.27, 125.89, 123.44, 37.47, 28.23, 22.99. HRMS (ESI): calculated for $C_{16}H_{14}O$ ($[M+H]^+$): 223.1117, found: 223.1119.

1,9,10,10-Tetrahydrophenanthren-3(2H)-one[26] **(**Table 2.3, **21**): Prepared from 1-tetralone (0.146g, 1.00 mmol) and 3-buten-2-ol (0.144g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow gel(0.061g, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, *J*=8.3, 1H), 7.33 (t, *J*=7.4, 1H), 7.29 – 7.23 (m, 1H), 7.20 (t, *J*=7.0, 1H), 6.66 (s, 1H), 3.05 – 2.87 (m, 2H), 2.71 – 2.42 (m, 3H), 2.24 – 2.18 (m, 1H), 2.10 – 2.04 (m, 1H), 1.88 – 1.77 (m, 1H), 1.62 (dq, *J*=12.7, 5.3, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.37, 158.41, 139.93, 131.40, 130.68, 129.76, 126.72, 125.31, 120.52, 37.52, 37.27, 30.68, 30.44, 30.13. HRMS (ESI): calculated for $C_{14}H_{14}O$ ($[M+Na]^+$): 221.0937, found: 221.0944.

1-Methyl-1,9,10,10a-tetrahydrophenanthren-3(2H)-one (Table 2.3, **22**): Prepared from 1-tetralone (0.146g, 1.00 mmol) and 3-penten-2-ol (0.172g, 2.00 mmol). After purification by column chromatography the compound was isolated as white solid (0.066g, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (d, *J*=8.0, 1H), 7.32 (t, *J*=8.0, 1H), 7.26 – 7.18 (m, 2H), 6.66 (s, 1H), 2.96 – 2.92 (m, 2H), 2.52 (dd, *J*=12.0, 4.0, 1H), 2.38 – 2.33 (m, 3H), 2.05 – 1.93 (m, 1H), 1.51 – 1.40 (m, 1H), 1.19 (d, *J*=4.0, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.20, 158.23, 140.06, 131.68, 130.60, 129.61, 126.76, 125.67, 120.79, 46.08, 44.25, 35.35, 30.16, 27.38, 19.68. HRMS (ESI): calculated for $C_{15}H_{16}O$ ($[M+H]^+$): 213.1274, found: 213.1277.

1-Methyl-1,2,9,9a-tetrahydro-3H-fluoren-3-one (Table 2.3, **23**): Prepared from 1-indanone (0.132g, 1.00 mmol) and 3-penten-2-ol (0.172g, 2mmol). After purification by column chromatography the compound was isolated as yellow gel (0.0495g, 25%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.59 (d, *J*=7.7, 1H), 7.43 – 7.35 (m, 2H), 7.31 (t, *J*=7.5, 1H), 6.33 (s, 1H), 3.30 (dd, *J*=15.8, 7.7, 1H), 2.87 – 2.78 (m, 1H), 2.73 (dd, *J*=15.8, 6.8, 1H), 2.24 – 2.04 (m, 2H), 1.18 (d, *J*=6.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 200.37, 148.06, 138.37, 131.91, 127.54, 125.76, 123.13, 117.49, 100.07, 49.22, 46.90, 36.96, 35.95, 29.85, 20.11. HRMS (ESI): calculated for $C_{14}H_{14}O$ ($[M+Na]^+$): 221.0937, found: 221.0939.

2.4.4. Analytical data for diketone compounds

2-Methyl-1-phenyloctane-1,5-dione (Table 2.5, **24**): Prepared from propiophenone (0.134g, 1.00 mmol) and 1-hexen-3-ol (0.20 g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.135g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 – 7.91 (m, 2H), 7.53 – 7.49 (m, 1H), 7.44 – 7.41 (m, 2H), 3.52 (sext, *J*=8.0, 1H), 2.49 – 2.41 (m, 1H), 2.38 – 2.23 (m, 3H), 2.08 – 1.99 (m, 1H), 1.78 – 1.66 (m, 1H), 1.52 (sext, *J*=8.0, 2H), 1.15 (d, *J*=8.0, 3H), 0.85 (t, *J*=8.0, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.70, 203.87, 136.42, 133.03, 128.68, 128.31, 77.40, 77.08, 76.77, 44.74, 39.82, 39.49, 27.17, 17.43, 17.26, 13.70. HRMS (ESI): calculated for $C_{15}H_{20}O_2$ ($[M+Na]^+$): 255.1356, found: 255.1365.

2-Ethyl-1-phenyloctane-1,5-dione (Table 2.5, **25**): Prepared from butyrophenone (0.148g, 1.00 mmol) and 1-hexen-3-ol (0.20 g, 2.00 mmol). After purification by column chromatography the compound was isolated as yellow liquid (0.081g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 – 7.97 (m, 2H), 7.15 – 7.10 (m, 3H), 2.97 (t, *J*=8.0, 2H), 2.54 – 2.50 (m, 2H), 2.38 (t, *J*=8.0, 2H), 2.00 (p, *J*=8.0, 2H), 1.64 – 1.55 (m, 3H), 0.93 – 0.88 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.93, 204.13, 137.45,

133.17, 128.80, 128.32, 46.44, 44.84, 40.01, 25.59, 25.27, 17.35, 13.82, 11.82. HRMS (ESI): calculated for $C_{16}H_{22}O_2$ ($[M+H]^+$): 247.1693, found: 247.1688.

2-(3-Oxohexyl)-3,4-dihydronaphthalen-1(2H)-one (Table 2.5, **26**): Prepared from 1-tetralone (0.146g, 1.00 mmol) and 1-hexen-3-o l (0.20 g, 2.00 mmol). After purification by column chromatography the compound was isolated as white solid (0.0635g, 26 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.00 (d, *J*=7.8, 1H), 7.48 – 7.40 (m, 1H), 7.32 – 7.26 (m, 1H), 7.22 (d, *J*=7.7, 1H), 3.03 – 2.96 (m, 2H), 2.59 (t, *J*=7.5, 2H), 2.55 – 2.46 (m, 1H), 2.40 (t, *J*=7.3, 2H), 2.25 – 2.04 (m, 2H), 1.97 – 1.75 (m, 2H), 1.60 (sext, *J*=7.4, 2H), 0.91 (t, *J*=7.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.20, 200.25, 144.00, 133.39, 132.54, 128.84, 127.48, 126.73, 46.85, 44.88, 40.37, 29.20, 28.59, 24.17, 17.45, 13.90. HRMS (ESI): calculated for $C_{16}H_{20}O_2$ ($[M+Na]^+$): 267.1356, found: 267.1369.

1-Phenyloctane-1,5-dione[17] (Table 2.5, **27**): Prepared from acetophenone (0.120g, 1.00 mmol) and 1-hexen-3-ol (0.20 g, 2.00 mmol). After purification by column chromatography, the compound was isolated as white solid (0.062g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 – 7.95 (m, 2H), 7.58 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 3.01 (t, *J*=8.0, 2H), 2.53 (t, *J*=8.0, 2H), 2.39 (t, *J*=7.4, 2H), 2.02(p, *J*=4.0, 2H), 1.66 – 1.54 (m, 2H), 0.91 (t, *J*=7.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.99, 200.00, 136.97, 133.21, 128.75, 128.20, 77.48, 77.16, 76.84, 44.91, 41.78, 37.66, 18.44, 17.45, 13.90. HRMS (ESI): calculated for $C_{14}H_{18}O_2$ ($[M+Na]^+$): 241.1199, found: 241.1205.

1-(4-(Tert-butyl)phenyl)octane-1,5-dione (Table 2.5, **28**): Prepared from 4'-tert-butylacetophenone (0.176 g, 1.00 mmol) and 1-hexen-3-ol (0.20 g, 2.00 mmol). After purification by column chromatography, the compound was isolated as colorless oil (0.118g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 (d, *J*=8.8, 2H), 7.47 (d, *J*=8.8, 2H), 2.98 (t, *J*=8.0, 2H), 2.52 (t, *J*=8.0, 2H), 2.38 (t, *J*=8.0, 2H), 2.02 (p, *J*=8.0, 2H), 1.65 – 1.22 (m, 2H), 1.34 (s, 9H), 0.91 (t, *J*=8.0, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ

= 211.02, 199.70, 156.94, 139.26, 134.41, 128.18, 125.68, 44.90, 41.84, 37.57, 35.25, 31.23, 18.56, 17.45, 13.90. HRMS (ESI): calculated for $C_{18}H_{26}O_2$ ($[M+Na]^+$): 297.1825, found: 297.1818.

1-(4-Methoxyphenyl)-2-methyloctane-1,5-dione (Table 2.5, **29**): Prepared from 4'-methoxypropiophenone (0.164 g, 1.00 mmol) and 1-hexen-3-ol (0.20 g, 2.00 mmol). After purification by column chromatography, the compound was isolated as a colorless oil (0.107g, 41%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.95 (d, *J*=8.8, 2H), 6.93 (d, *J*=8.0, 2H), 3.86 (s, 3H), 3.50 (sext, *J*=8.0, 1H), 2.51– 2.43 (m, 1H), 2.38 – 2.30 (m, 2H), 2.09 – 2.00 (m, 2H), 1.76 – 1.68 (m, 1H), 1.55 (sext, *J*=8.0, 2H), 1.15 (d, *J*=8.0, 3H), 0.87 (t, *J*=8.0, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.82, 202.40, 163.50, 130.62, 129.40, 113.83, 55.45, 44.73, 39.90, 39.08, 27.39, 17.59, 17.28, 13.72. HRMS (ESI): calculated for $C_{16}H_{22}O_3$ ($[M+H]^+$): 263.1642, found: 263.1611.

1-(3-Fluorophenyl)octane-1,5-dione (Table 2.5, **30**): Prepared from 3'-fluoroacetophenone (0.138g, 1.00 mmol) and 1-hexen-3-ol (0.20 g, 2.00 mmol). After purification by column chromatography, the compound was isolated as a colorless oil (0.08g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 – 7.73 (m, 1H), 7.65 – 7.62 (m, 1H), 7.46 – 7.41 (m, 1H), 7.28 – 7.23 (m, 1H), 2.99 (t, *J*=7.0, 2H), 2.53 (t, *J*=7.0, 2H), 2.39 (t, *J*=7.0, 2H), 2.01 (p, *J*=7.0, 2H), 1.60 (sext, *J*=7.0, 2H), 0.91 (t, *J*=7.0, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.51, 202.30, 163.14 (d, *J*=247), 139.03 (d, *J*=7), 139.06 (d, *J*=7), 124.27, 120.45 (d, *J*=21), 115.22 (d, *J*=23), 44.96, 44.21, 39.64, 25.44, 17.40, 13.84.^{19}F NMR (376 MHz, $CDCl_3$) δ -111.42. HRMS (ESI): calculated for $C_{14}H_{17}FO_2$ ($[M+Na]^+$): 259.1105, found: 259.1110.

2-Methyl-1,5-diphenylpentane-1,5-dione[27] (Scheme 2.1, **34**): Prepared from propiophenone (0.134g, 1.00 mmol) and 1-phenylprop-2-en-1-ol (0.268 g, 2.00 mmol). Compound was isolated as white solid (0.162g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ =

8.00 – 7.98 (m, 2H), 7.94 – 7.92 (m, 2H), 7.58 – 7.52 (m, 2H), 7.48-7.42 (m, 3H), 3.66 (sext, *J*=7.0, 1H), 3.14– 3.06 (m, 1H), 2.95 – 2.87 (m, 1H), 2.32 – 2.24 (m, 1H), 1.97 – 1.89 (m, 1H), 1.25 (d, *J*=7.0, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.05,200.05, 136.94, 136.55, 133.20, 128.84, 128.73, 128.52, 128.19, 39.89, 35.99, 27.87, 17.78. HRMS (ESI): calculated for $C_{18}H_{18}O_2$ ($[M+Na]^+$): 289.1199, found: 289.1200.

1,5-Diphenylpentane-1,5-dione (Scheme 2.1, **35**)**:** Prepared from acetophenone (0.12 g, 1.00 mmol) and α-vinylbenzyl alcohol (0.537 g, 4.00 mmol). After column chromatography, the compound was isolated as white solid (0.108 g, 43%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.98 (d, *J*=7.3, 4H), 7.56 (t, *J*=7.4, 02H), 7.46 (t, *J*=7.7, 4H), 3.13 (t, *J*=7.0, 4H), 2.21 (p, *J* = 8.0, 2H). ^{13}C NMR (101 MHz,$CDCl_3$) δ 18.89, 37.76, 128.22, 128.76, 133.22, 137.01, 200.03. HRMS (ESI): calculated for $C_{17}H_{16}O_2$ ($[M+Na]^+$) : 275.1043, found : 275.1024.

2-Ethyl-1,5-diphenylpentane-1,5-dione (Scheme 2.1, **36**)**:** Prepared from butyrophenone (0.148 g, 1.00 mmol) and α-vinylbenzyl alcohol (0.537 g, 4.00 mmol). After column chromatography, the compound was isolated as colorless oil (0.132 g, 47%). ^{1}H NMR (400 MHz, $CDCl_3$). δ = 8.00 – 7.94 (m, 2H), 7.93 – 7.86 (m, 2H), 7.57-7.52 (m, 2H), 7.48-7.40 (m, 4H), 3.62 – 3.49 (m, 1H), 3.10-3.02 (m, 1H), 2.89-2.81 (m, 1H), 2.27-2.17 (m, 1H), 2.07 – 1.95 (m, 1H), 1.90-1.79 (m, 1H), 1.67 – 1.50 (m, 1H), 0.92 (t, *J*=7.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 11.84, 25.80, 36.08, 46.76, 128.18, 128.41, 128.71, 128.85, 133.18, 136.95, 137.48, 200.11, 204.10. HRMS (ESI): calculated for $C_{19}H_{20}O_2$ ($[M+Na]^+$) : 303.1356, found : 303.1352.

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Chapter 3

Palladacycle assisted synthesis of β-amino ketones from allyl alcohols and aryl amines

3.1. Introduction

Ever since the pioneer work by Hermann and Beller[1], different types of palladacycles have been prepared[2] and classified according to the co-ordinationg atom, ligand or functional groups. Palladacycle offers the advantage such as fair thermal stability, facile synthesis and the ability to modulate its steric and electronic properties as per the required reaction condition. Palladacycle act as a reservoir for active Pd(0) species[3]. Combined with phosphine[4] and carbenes[5] as ligands, palladacycle has emerged as the powerful pre-catalyst which is thermally stable as compared to the traditional palladium catalysts. In recent years, we have synthesised pyrazole based palladacycles and have been effectively using in C-C and C-N bond forming reactions[6].

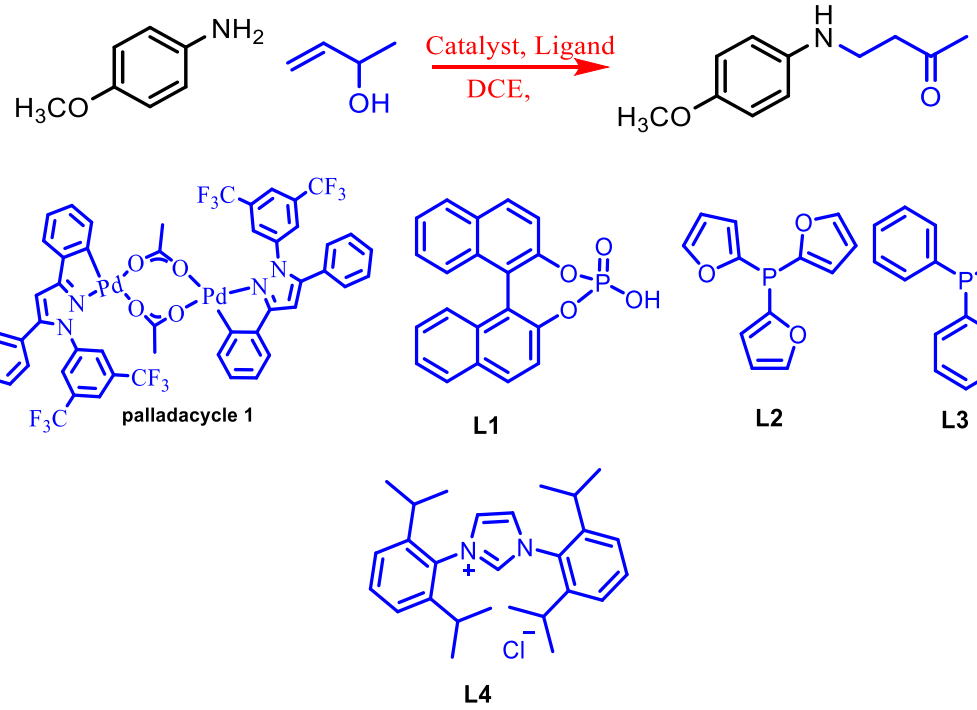
Allyl alcohols are important alkylating and allylating agents. In presence of transition metal, allyl alcohol undergoes isomerisation to its corresponding ketone. This isomerisation is 100% atom economic and is carried out in one pot, ultimately avoiding the conventional two-step process of oxidation and reduction. It avoids the use of stoichiometric amount of reagents and generation of waste materials. As enolate precursors, allyl alcohols can be used in tandem reaction for the formation of new C-C and C-hetero bonds[7]. Numerous such reports are available which utilise transition metal catalysed tandem isomerisation-functionalistion approach[7]. However, in most cases the requirement of high catalyst loading and the harsh reaction conditions limits the practicability of this method. In this regard, use of BINOL phosphoric acid(BPA) stands apart, which is easy to synthesise and handle. Apart from being an excellent ligand and Bronsted base in asymmetric reactions, BPA has also been used for the isomerisation-chlorination reaction in a recent report by Martin-Matute and co-workers[8]. They found that the use of BPA in the isomerisation of allyl alcohol opens up a lower energy transition state which affords the isomerisation reaction at room temperature. Using

similar approach, we recently reported palladium-BPA catalysed Robinson annulation of ketones with allyl alcohols at room temperature affording 3-arylcyclohexenones and 1,5-diketones[9]. We were curious to apply this approach in the synthesis of β-aminoketone by oxidative coupling of allyl alcohol with amines.

β-Amino carbonyl compounds are important intermediates in the synthesis of β-lactams, β-amino alcohols and other nitrogen heterocycles[10]. Traditionally, β-amino carbonyl compounds have been synthesised by Aza-Michael addition[11] and Mannich reaction[12]. Aza-Michael addition involves the addition of amines to highly electrophilic and labile vinyl ketones. It uses harsh reaction conditions such as high temperature, high acidic or basic conditions. Mannich reaction offers a three component one pot synthesis of β-amino ketones but suffers from the use of high temperature. In this regard, alcohol, which undergoes oxidation in the presence of transition metals offers an alternate approach. Laserna *et al.* reported Gold catalysed hydroamination of propargylic alcohol to produce β-amino ketones[13]. Llopis reported the hydrogenation of β-keto-γ-acetal enamides to the corresponding α-acetal-β-amino ketones[14]. Jiang and co-workers reported the oxidative amination of homoallylic alcohols to afford β-aminoketones with the use of stoichiometric amount of external oxidant TBHP[15]. Kapur and co-workers reported the oxidative coupling of allyl alcohols in presence of atmospheric oxygen as the oxidant which also involves the use of acid and stoichiometric amount of base[16]. Both the reports of Jiang and Kapur involve the use of external oxidant, base and high temperature. In this chapter, we will discuss about the room temperature oxidative coupling of allyl alcohols with amines by palladacycle and BPA system without using any base and external oxidant at room temperature.

3.2.Results and Discussion

Table 3.1. Optimization table for the synthesis of β-aminoketone



Entry	Catalyst (X mol%)	Ligand (2X mol%)	Solvent	Time (h)	Allyl alcohol (equiv)	Yield (%)[a]
1	**1**(2.5)	**L1**	DCE	24	2	25
2	**1**(2.5)	**L1**	THF	48	4	26
3	**1**(2.5)	**L1**	DCE	24	4	65
4[b]	**1**(2.5)	**L1**	DCE	48	4	46
5[c]	**1**(2.5)	**L1**	DCE	48	4	Trace
6	**1**(2.5)	**L1**	DCE	48	4	(82)
7[d]	**1**(2.5)	**L4**	DCE	48	4	15
8	**1**(2.5)	**L3**	DCE	48	4	7
9	**1**(2.5)	**L2**	DCE	48	4	40
10[e]	**1**(2.5)	**L1**	DCE	48	4	ND
11	$Pd(OAc)_2$(2.5)	**L1**	DCE	48	4	45
12	$PdCl_2$(2.5)	**L1**	DCE	48	4	ND
13	$Pd(dba)_2$(2.5)	**L1**	DCE	48	4	34

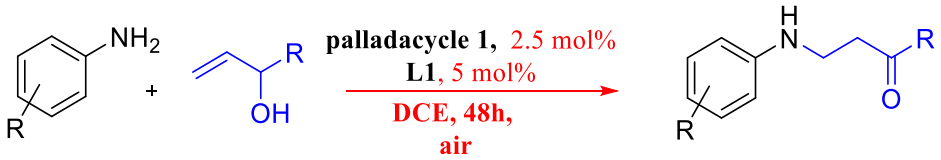
14[f]	**1**(5)	**L1**	DCE	48	4	(87)
15[f]	**1**(2.5)	**L1**	DCE	48	4	(85)
16[f]	**1**(1)	**L1**	DCE	48	4	42
17[f]	**1**(2.5)	-	DCE	48	4	60
18[f]	--	**L1**	DCE	48	4	ND

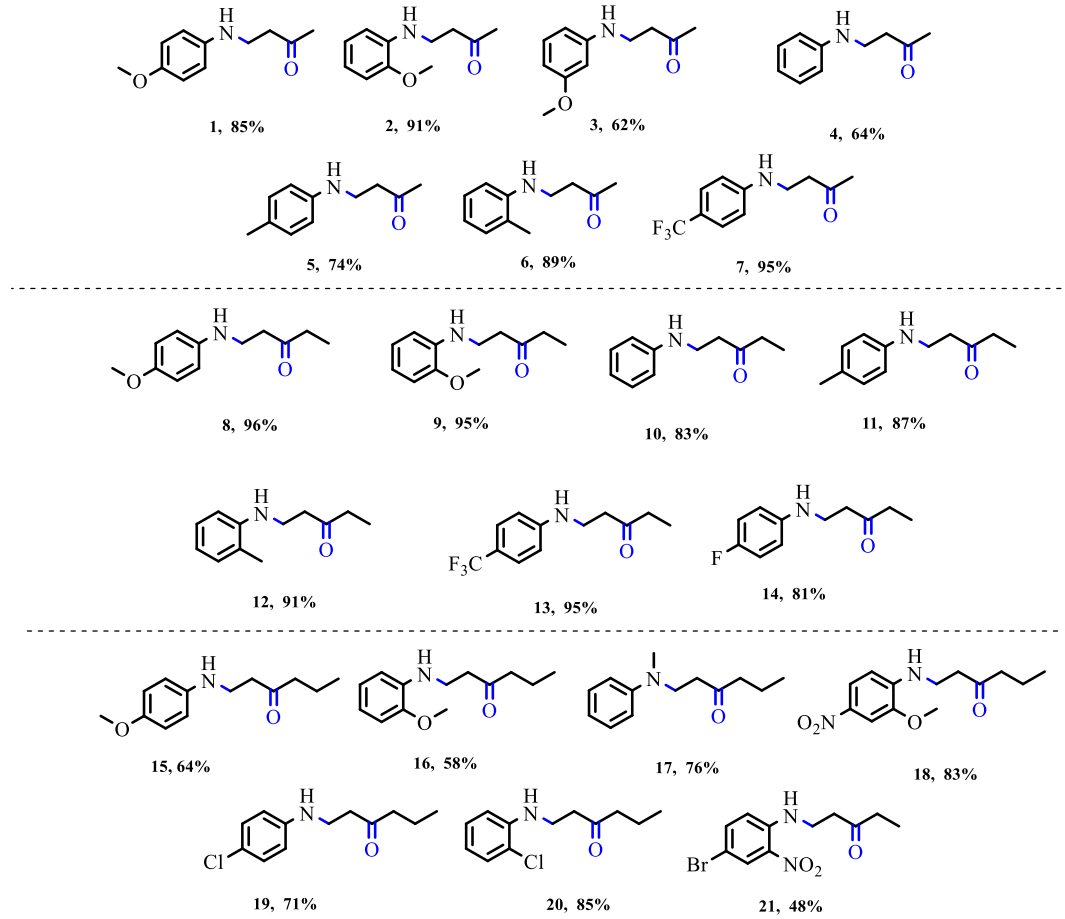
Reaction conditions = 0.5 mmol of *p*-anisidine, 2 mmol of 3-buten-2-ol, 1 mL of solvent was used. [a] NMR yield using toluene as an internal standard. [b] reaction was carried out at 40 ^{o}C. [c] reaction was carried out at 60 ^{o}C. [d] 2 x 10^{-2} mmol of KO^{t}Bu was added. [e] 1 mmol of LiOH was added. [f] Reactions were carried out in aerobic condition . Yields in paranthesis are isolated yields, ND = not detected

p-Anisidine and 3-buten-2-ol were chosen as the model substrates in presence of pyrazole based palladacycle **1** and BINOL phosphoric acid **L1** as the catalyst and ligand in DCE at room temperature. 25% of the desired β-amino ketone was observed (table 3.1, entry **1**). Upon changing the solvent to THF, did not increase the yield of the reaction even after 48 hours (table 3.1**,** entry **2**). Increasing the amount of allyl alcohol to 4 equivalent, increased the reaction yield to 65% (table 3.1**,** entry **3**). Increasing the temperature to 40 ^{o}C and 60 ^{o}C did not improve the yield. On the contrary, the yield got reduced (table 3.1**,** entries **4** and **5**). The yield of the product got improved to 82% when the reaction was carried out for 48h with 4 equivalent of allyl alcohol. Use of carbene and phosphine ligands such as IPr.HCl, triphenyl phosphine and tris(2-furyl)phosphine did not improve the yield (table 3.1, entries 7-9). Addition of LiOH (table 3.1, entry 10) as a base to the reaction did not produce the desired product. Use of different palladium sources such as $Pd(OAc)_2$ and $Pd(dba)_2$ as catalysts resulted in 45% and 34% yield respectively (table 3.1, entries 11 and 13). The reaction did not proceed with $PdCl_2$ (table 3.1, entry 12). Use of 2.5 mol% of Pd in aerobic condition was found out to be the lowest catalyst loading for the reaction to proceed with good yield (table 3.1, entry 15). In the absence of BINOL phosphoric acid the reaction proceeds with 60% yield

(table 3.1, entry 17) whereas the reaction in the absence of catalyst but with BINOL phosphoric acid did not give any noticeable change (table 3.1, entry 18).

Table 3.2. Scope of redox coupling of allyl alcohols with aryl amines.





Reaction condition: 0.5 mmol of amines, 2 mmol of allyl alcohols, 2.5 x 10^{-2} mmol of palladacycle **1**, 5.0 x 10^{-2} mmol of **L1**, 1 mL of DCE, 48h, rt. All yields are isolated yields.

Having optimized the reaction, we proceeded to check the substrate scope of the oxidative coupling reaction. With 3-buten-2-ol, electron donating methoxy groups at *ortho* and *para* position of the aniline afforded the β-aminoketone product in excellent yield (table 3.2, compounds 1 and 2). Substantial decrease in the yield was observed in

case of *m*-anisidine(table 3.2, compound 3). Methyl substituted aniline *viz* –*p*-toluidine (table 3.2, compound 5) and *o*-toluidine (table 3.2, compound 6) resulted in 74% and 89% yield of the product. Oxidative coupling of aniline with 3-buten-2-ol proceeded smoothly resulting in 64% yield (table 3.2, compound 4). Electron withdrawing trifluoromethyl substituted aniline afforded an excellent yield of 95% (table 3.2, compound 7). Increasing the alkyl chain in the allyl alcohol had no impact in the reaction yield. With 1-penten-3-ol, (*o* and *p*) anisidine (table 3.2, compounds 8 and 9) and (*o* and *p*) toluidine(table 3.2, compounds 11 and 12) resulted in excellent yield. The increase in the alkyl chain resulted in a better yield in case of aniline as compared to 3-buten-3-ol (table 3.2, compound 10). Electron withdrawing $-CF_3$ and fluoro group also resulted in excellent reaction yield (table 3.2, compounds 13 and 14). Further increase of alkyl chain in allyl alcohol resulted in the decrease of reaction yield in case of aniline with electron donating substitutions (table 3.2, compounds 15-16). Electron withdrawing group had little impact with increase in alkyl chain from 1-penten-3-ol to 1-hexne-3-ol as the anilines with chloro (*o* and *p*), nitro proceeded with good yields ranging from 71-85% yield (table 3.2, compounds 18-21). Lesser yield in case of 4-bromo-2-nitro aniline can be attributed to the tendency of the bromo group to undergo substitution reaction instead of the desired oxidative coupling. N-Substituted aniline *viz* N-methylaniline also resulted in good yields (Table 3.2, compound 17). *Ortho* and *para* anisidine suffered a decrease in reaction yield with 1-hexen-3-ol. Primary allyl alcohol such as 2-buten-1-ol and trans-2-hexen-1-ol failed to give the desired product as the corresponding aldehyde formed is very reactive and undergoes condensation with the allyl alcohol. The reaction did not proceed with heteroarenes such as 2-aminopyridine, 4-aminopyridine and 8-aminoquinoline even at elevated temperature and at inert condition which can be attributed to the possible co-ordination of palladium

to the nitrogen atom. Substituted allyl alcohols such as α-vinylbenzyl alcohol, 1,3-diphenyl-2-propen-1-ol and 4-phenylbut-3-en-2-ol were incompatible for this protocol.

Next, we focused on studying the mechanism of the reaction and in this regard, we tried few control reactions. Reacting 1-penten-3-ol under the optimized condition without the amine, we observed carbonyl peak in ^{13}C NMR (crude) which matched with that of 1-penten-3-one. This result suggested the possible conversion of the allyl alcohol to the corresponding vinyl ketone during the reaction. To prove this hypothesis, 1-penten-3-one was reacted with p-anisidine under the optimized condition which afforded the desired product in 93% yield thus, suggesting that the reaction proceeds through aza-Michael pathway. Further, to isolate the active species and to investigate the role of BPA in the reaction, we reacted the palladacycle **2** (scheme **3.1),** with silver R-

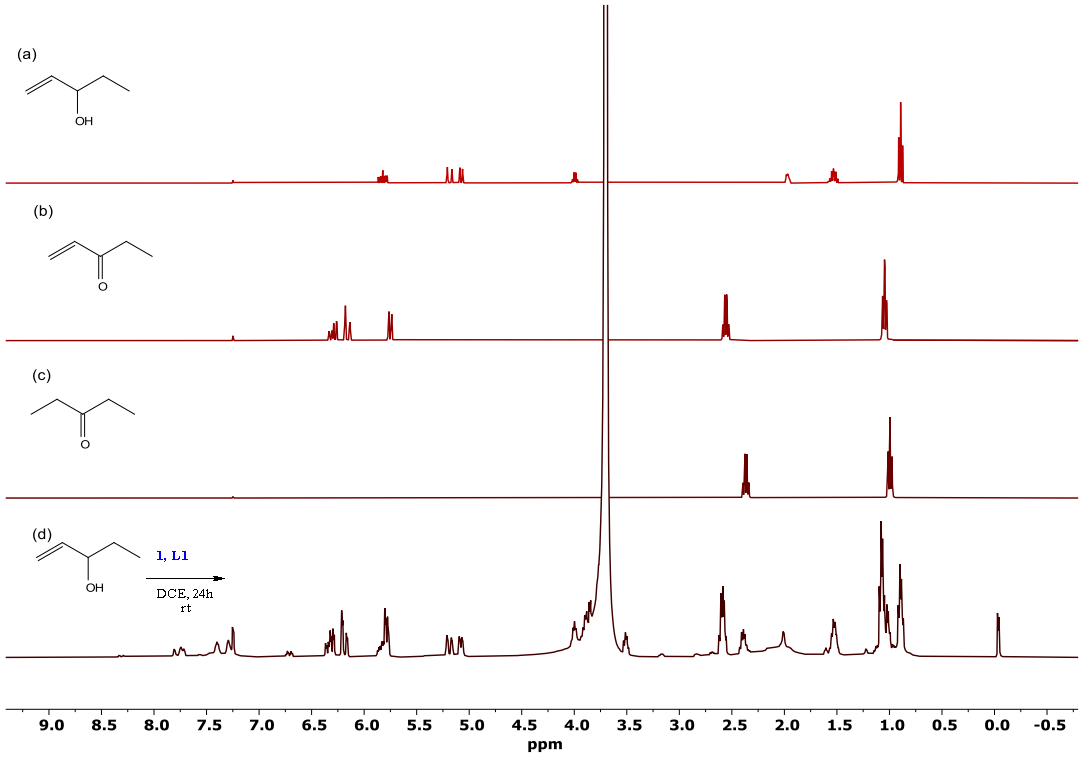


Figure 3.1: Stacking of ^{1}H NMR of (a) 1-penten-3-ol, (b) 1-penten-3-one, (c) 3-pentanone and (d) crude reaction mixture of 1-penten-3-ol at optimised condition after 24h

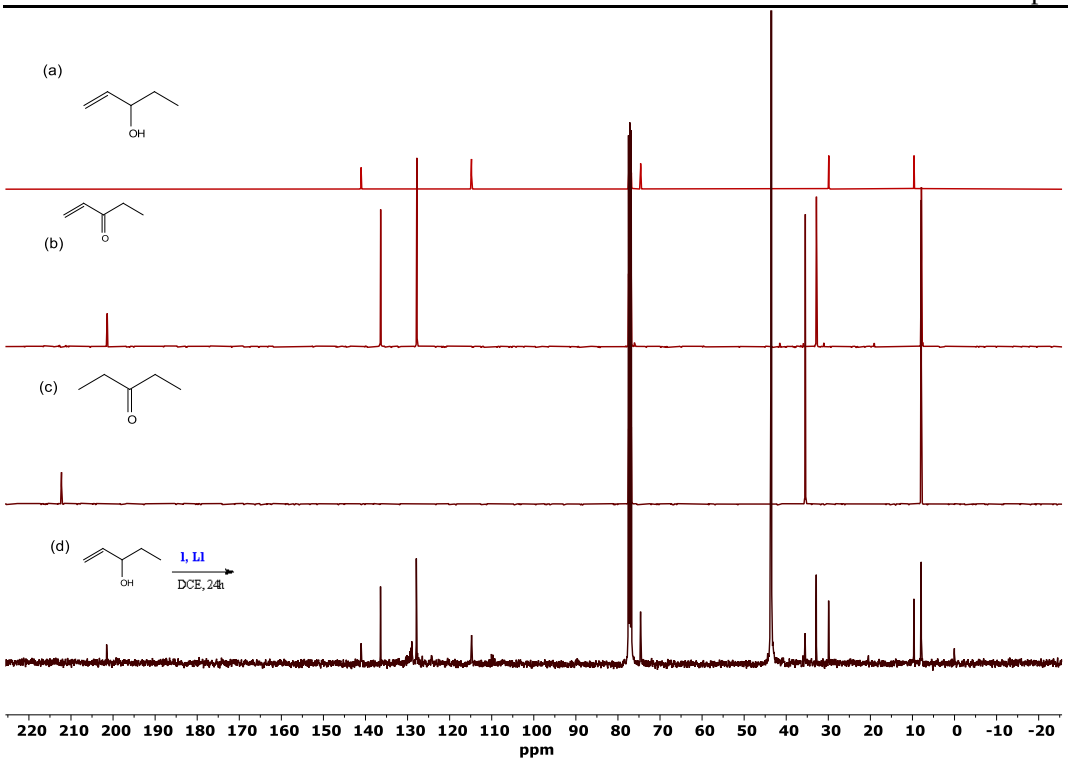
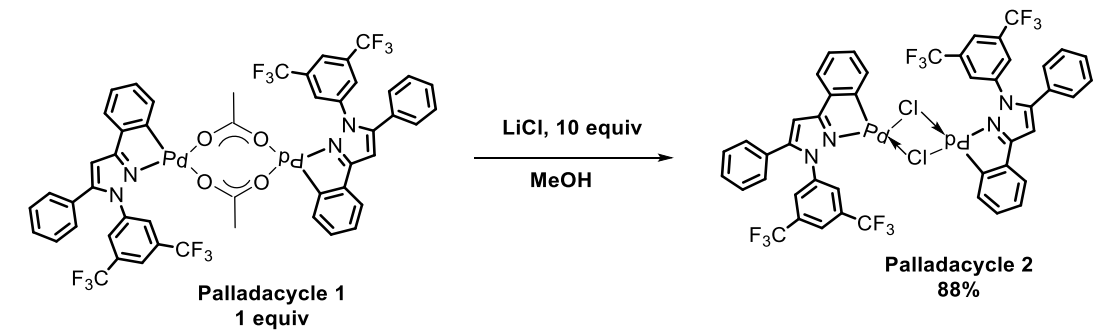
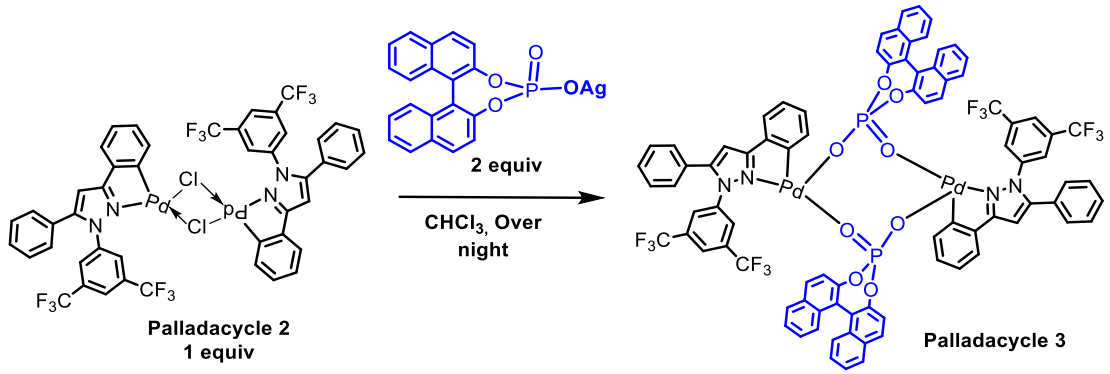


Figure 3.2: Stacking of ^{13}C NMR of (a) 1-penten-3-ol, (b) 1-penten-3-one, (c) 3-pentanone and (d) crude reaction mixture of 1-penten-3-ol at optimized condition after 24 h.

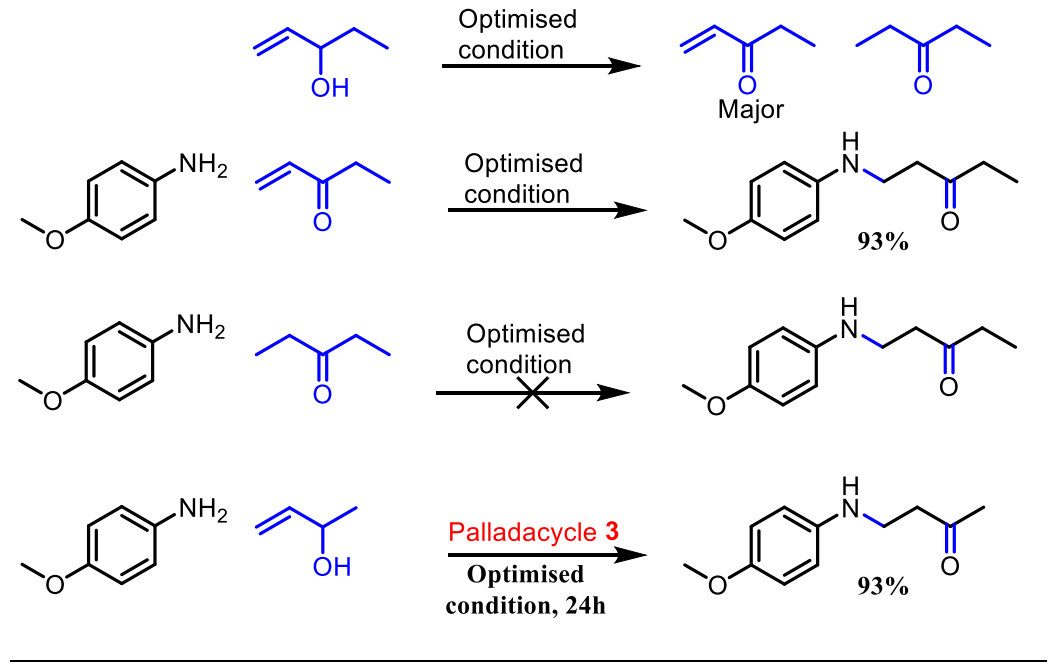
BINOL[17] phosphate in chloroform at room temperature with vigorous stirring. After celite filtration followed by crystallization in DME and hexane at low temperature resulted in yellow crystals of R-BPA[17] co-ordinated palladacycle **3** (scheme **3.2**). The molecular structures of Palladacycle **2** and **3** are presented in Figure **3.3** and **3.4** and the data is presented in table **3.3** . The isolated complex was used in the catalytic reaction and produced similar yield in 24h.



Scheme 3.1: Synthesis of palladacycle 2



Scheme 3.2: Synthesis of palladacycle 3



Scheme 3.3. Control reactions

Based on the above information and our recent report[9], we propose the following mechanism. In the presence of the metal catalyst, hydroxyl group of the allyl alcohol is dehydrogenated and palladium gets added to to form species **B.** The species **B** undergoes β-hydride elimination resulting in the formation of the vinylic ketone species **C.** This species undergoes Michael addition with the aniline resulting in the enolic species **E** which tautomerises to produce the β-aminoketone (Scheme **3.4.a)**.

Alternatively, the species **C** can produce the methyl vinyl ketone which then undergoes 1,4-addition to yield the β-aminoketone(Scheme **3.4.b**).

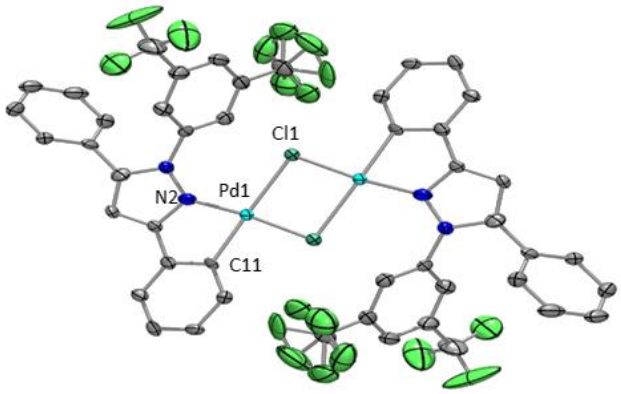


Figure 3.3. Molecular structure of palladacycle **2** (50% probability thermal ellipsoids). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (degree): Pd1-Cl1 2.459, Pd1-N2 2.040, Pd1-C11 1.985, Pd1-Pd1* 3.531, N2-Pd1-C11 80.88, N2-Pd1-Cl1 101.18, C11-Pd1-Cl1 93.15, Cl1-PD1-Cl1* 84.83

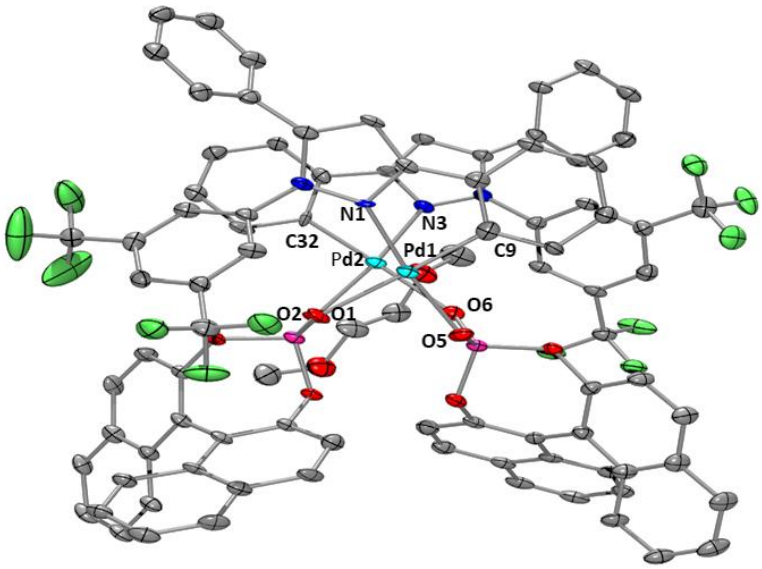
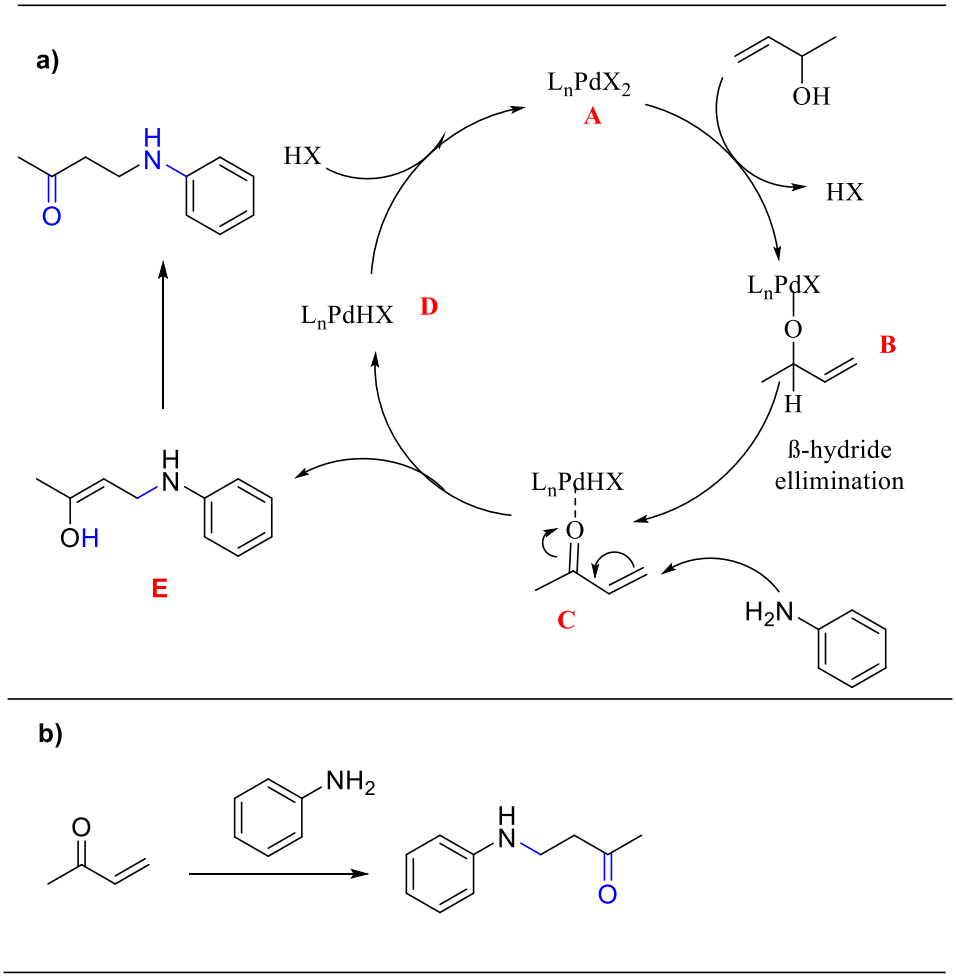


Figure 3.4. Molecular structure of palladacycle **3** (30% probability thermal ellipsoids). Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (degree): Pd2-C32 1.968, Pd2-N3 2.033, Pd2-O2 2.051, Pd2-O6 2.171, Pd1-N1 2.045, Pd1-C9 1.954, Pd1-O1 2.152, Pd1-O5 2.059, Pd1-Pd2 2.226, C32-Pd2-N3 80.44, O2-Pd2-C32 91.52, O2-Pd2-O6 87.70, N3-Pd2-O6 100.04, N1-Pd1-C9 80.11, C9-Pd1-O5 92.63, O1-Pd1-O5 88.51, N1-Pd1-O1 98.74

Table 3.3. Crystal data and structure refinement parameters for the palladacycle 2 & 3

Compound	**Palladacycle 2**	**Palladacycle 3**
Empirical formula	$C_{46}H_{26}Cl_2F_{12}N_4Pd_2$	$C_{90}H_{60}F_{12}N_4O_{10}P_2Pd_2$
Formula weight	1146.41	1860.16
Temperature/K	107(10)	112.2(4)
Crystal system	trigonal	monoclinic
Space group	*R-3*	$P2_1$
a/Å	27.7832(6)	14.2159(5)
b/Å	27.7832(6)	19.6780(4)
c/Å	15.2098(4)	15.4208(5)
α/°	90	90
β/°	90	115.902(4)
γ/°	120	90
Volume/Å^3	10167.6(5)	3880.5(2)
Z	9	2
ρ_{calc}g/cm^3	1.685	1.592
μ/mm^{-1}	8.294	4.948
F(000)	5076.0	1876.0
Radiation	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.876 to 133.162	6.912 to 155.518
Index ranges	-31 ≤ h ≤ 30, -33 ≤ k ≤ 34, -10 ≤ l ≤ 18	-18 ≤ h ≤ 17, -24 ≤ k ≤ 24, -19 ≤ l ≤ 19
Reflections collected	14690	52529
Independent reflections	3906 [R_{int} = 0.1140, R_{sigma} = 0.0687]	15378 [R_{int} = 0.0986, R_{sigma} = 0.0708]
Data/restraints/parameters	3906/69/325	15378/1/1084
Goodness-of-fit on F^2	1.338	1.025
Final R indexes [I>=2σ (I)]	R_1 = 0.1006, wR_2 = 0.2893	R1 = 0.0922, wR2 = 0.2250
Final R indexes [all data]	R_1 = 0.1038, wR_2 = 0.2945	R_1 = 0.1108, wR_2 = 0.2359
Largest diff. peak/hole / e Å^{-3}	2.96/-2.71	5.31/-1.68

Flack parameter	-0.025(15)



Scheme 3.4. Proposed mechanism

3.3. Conclusion

In conclusion, we have developed a method for the synthesis of β-aminoketone with excellent yields at room temperature using palladacycle **1** and BPA. This protocol tolerated different functional group to produce variety of β-aminoketone. Primary and substituted allyl alcohol did not undergo this reaction. Mechanistic investigations were carried out, which suggest the involvement of a metal enolate species leading to the formation of desired vinyl ketone. During the reaction, allyl alcohol is converted to the

corresponding vinyl ketone which undergoes Michael addition with the amine to afford the β-aminoketone product having H_2 as the only environment friendly by product. Active species of the BPA co-ordinated metal complex was isolated and the species showed excellent result and reduces the reaction time to 24 hour.

3.4. Experimental section

3.4.1 General Information: All chemicals were used as received from commercially available sources such as Sigma-Aldrich, Alfa-aesar, TCI, and Spectrochem. 1,2-Dichloroethane was distilled from CaH_2. THF was distilled from Na/Benzophenone prior to use. All reactions were carried out in open air unless notified. NMR spectra were recorded on Bruker ARX 400 and Bruker Advance 700 spectrometer at room temperature. ^{1}H (400 MHz or 700 MHz) and ^{13}C (100 MHz or 176 MHz) NMR chemical shifts in ppm were referenced internally to solvent signals. ^{19}F NMR spectra were externally referenced to α,α,α- trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). ^{31}P NMR (161 MHz) spectra were externally referenced to H_3PO_4 in D_2O (δ = 0). High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF-QII mass spectrometer. Single-crystal X-ray diffraction data for palladacycle **2** and **3** were collected on a Rigaku SuperNova fine-focused dual diffractometer, with Cu Kα radiation (λ = 1.54178 Å) equipped with a PILATUS200K detector. Using Olex2, the structures were solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization. All non-hydrogen atoms were refined with anisotropic displacement coefficients. The H atoms were placed at calculated positions and were refined as riding atoms

3.4.2. General procedure for the synthesis of β-aminoketones: To a screw cap scintillation vial, aryl amine (0.5 mmol), allyl alcohol (2.0 mmol), catalyst (0.0125

mmol) and BINOL phosphoric acid (0.025 mmol) were charged under air. The reaction mixture was allowed to stir at room temperature for 48 hour. The reaction mixture was diluted with CH_2Cl_2 (3 x 5 mL), and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using ethyl acetate and *n*-hexane mixtures to afford the β-aminoketones as pure product.

3.4.3. Synthesis of BINOL phosphoric acid: (S)-BINOL (1.0 g, 3.5 mmol) was dissolved in pyridine (10 mL). Phosphorous oxychloride (0.65 mL, 7 mmol) was added dropwise at room temperature with rapid stirring and the resulting solution was stirred at 60 °C for 12 hours. Water (10 mL) was added and the resulting biphasic suspension was stirred at 50 °C for a further 2 hours. The reaction mixture was diluted with CH_2Cl_2 and pyridine was extracted by washing with 1N HCl aq. The combined organic phase was dried over Na_2SO_4 and concentrated. The crude solid was purified by flash silica gel chromatography (5% MeOH in CH_2Cl_2) to yield the product as ivory-white solid(1.08 g, 90%).

3.4.4. Synthesis of palladacycle 2 (Scheme 3.1): Palladacycle **1** (1.0 g, 0.83 mmol) was taken in a 100 mL round bottomed flask and was dissolved in methanol. LiCl (0.35g, 8.3 mmol) was added to it and was stirred overnight at RT. Then, excess amount of water was added to it which resulted in precipitation. The reaction mixture was filtered and the residue was washed with excess water to remove any lithium salt. The residue was dried and dissolved in chloroform and was layered with hexane for crystallisation at low temperature. Yellow crystals were obtained in 88% (0.83g) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 2H), 7.77 (s, 4H), 7.40 – 7.35 (m, 2H), 7.34 – 7.30 (m, 4H), 7.24 (dd, *J* = 7.4, 1.6 Hz, 2H), 7.11 (d, *J* = 6.9 Hz, 4H), 7.05 (t, *J* = 7.4 Hz, 2H), 6.83 (t, *J* = 7.7 Hz, 2H), 6.69 (d, *J* = 8.2 Hz, 2H), 6.67 (s, 2H). ^{13}C{^{1}H, ^{19}F} NMR (101 MHz, $CDCl_3$) δ 160.97, 147.94, 144.58, 137.80, 136.08, 133.19, 132.95,

130.05, 129.22, 129.09, 129.05, 128.03, 127.26, 125.29, 123.65, 123.30, 102.38. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.72. Elemental analysis calcd (%) for $C_{46}H_{26}Cl_2F_{12}N_4Pd_2$: C 48.19, H 2.29, N 4.89. Found: C 49.12, H 2.68, N 4.66. HRMS (ESI): calculated for $C_{46}H_{26}Cl_2F_{12}N_4Pd_2$ ($[M + H]^+$) : 1144.9656, found : 1144.9118.

3.4.5. Synthesis of palladacycle 3 (Scheme 3.2): Palladacycle **2** (0.5g, 0.437 mmol) was dissolved in chloroform. Silver BINOL phosphate (0.39g, 0.874 mmol) was added to it. The reaction was ran for overnight with vigorous stirring. After a fast celite filtration, the solvent was evaporated under vacuum, yellow solid was obtained. The compound was dissolved in DME and layered with hexane for crystallisation at low temperature. Yellow crystals were obtained in 76% (0.58g) yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 16.2, 8.5 Hz, 4H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 2H), 7.50 – 7.41 (m, 8H), 7.40 – 7.35 (m, 7H), 7.35 – 7.33 (m, 3H), 7.32 (d, *J* = 2.7 Hz, 3H), 7.28 (d, *J* = 7.2 Hz, 4H), 7.25 – 7.22 (m, 5H), 7.18 (t, *J* = 7.2 Hz, 2H), 7.03 (t, *J* = 7.4 Hz, 2H), 6.92 (s, 2H), 6.90 – 6.86 (m, 4H), 6.40 (s, 2H). $^{13}C\{^1H, ^{19}F\}$ NMR (101 MHz, $CDCl_3$) δ 160.25, 148.40, 147.80, 145.86, 143.83, 136.92, 136.04, 132.67, 132.19, 131.70, 131.48, 130.83, 130.41, 129.73, 129.13, 128.77, 128.50, 128.39, 127.52, 126.60, 126.16, 125.82, 125.67, 125.04, 124.64, 122.62, 122.16, 121.52, 121.11, 120.88, 103.08. ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.58. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.69, -62.70. Elemental analysis calcd (%) for $C_{86}H_{50}F_{12}N_4O_8P_2Pd_2$: C 58.35, H 2.85, N 3.17. Found: C 57.86, H 3.00, N 3.26. HRMS (ESI): calculated for $C_{86}H_{50}F_{12}N_4O_8P_2Pd_2$ ($[M + H]^+$) : 1791.0878, found : 1791.0872.

3.4.6. Analytical data for β-aminoketones:

4-((4-Methoxyphenyl)amino)butan-2-one (table 3.2, compound 1)[18] : Prepared from *p*-anisidine (0.061g, 0.5 mmol) and 3-buten-2-ol (0.144 g , 2.0 mmol). After purification by column chromatography, the compound was isolated as brown liquid

(0.084g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.77 (d, *J* = 8.9, 2H), 6.59 (d, *J* = 8.9, 2H), 3.74 (s, 3H), 3.35 (t, *J*=6.1, 2H), 2.72 (t, *J*=6.1, 2H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.32, 152.57, 141.81, 115.03, 114.84, 55.88, 42.72, 39.76, 30.38. HRMS (ESI): calculated for $C_{11}H_{15}NO_2$ ($[M + H]^+$) : 194.1176, found : 194.1182

4-((2-Methoxyphenyl)amino)butan-2-one (table 3.2, compound 2)[19] : Prepared from *o*-anisidine (0.061g, 0.5 mmol) and 3-buten-2-ol (0.144g, 2.0 mmol). After purification by column chromatography, the compound was isolated as brown liquid (0.0878g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (t, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.75 – 6.64 (m, 2H), 3.83 (s, 3H), 3.44 (t, *J* = 6.3 Hz, 2H), 2.80 (t, *J* = 6.3, 2H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$)) δ 207.87, 147.39, 137.32, 117.36, 110.43, 109.78, 55.55, 42.91, 38.56, 30.39. HRMS (ESI): calculated for $C_{11}H_{15}NO_2$ ($[M + H]^+$) : 194.1176, found : 194.1202.

4-((3-Methoxyphenyl)amino)butan-2-one (table 3.2, compound 3)[18] : Prepared from *m*-anisidine (0.061g, 0.5 mmol) and 3-buten-2-ol (0.144g, 2.0 mmol). After purification by column chromatography, the compound was isolated as brown liquid (0.06g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, *J* = 8.1 Hz, 1H), 6.27 (d, *J* = 8.1Hz, 1H), 6.21 (d, *J* = 8.0 Hz, 1H), 6.15 (m, 1H), 3.76 (s, 3H), 3.39 (t, *J* = 6.1 Hz, 2H), 2.73 (t, *J* = 6.1 Hz, 2H), 2.15 (s, 3H)·. ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.23, 160.90, 149.15, 130.11, 106.16, 102.73, 98.99, 55.14, 42.59, 38.36, 30.35. HRMS (ESI): calculated for $C_{11}H_{15}NO_2$ ($[M + H]^+$) : 194.1176, found : 194.1201

4-(Phenylamino)butan-2-one (table 3.2, compound 4)[18] : Prepared from aniline (0.046g, 0.5 mmol) and 3-buten-2-ol (0.144g, 2.0 mmol). After purification by column chromatography, the compound was isolated as brown liquid (0.052g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (t, *J* = 6.9 Hz, 2H), 6.73 (t, *J* = 8.0 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 2H), 3.41 (d, *J* = 8.2 Hz, 2H), 2.75 (t, *J* = 8.1 Hz, 2H), 2.16 (s, 3H).^{13}C NMR (101

MHz, $CDCl_3$) δ 208.19, 147.39, 129.47, 118.15, 113.46, 42.60, 38.77, 30.44. HRMS (ESI): calculated for $C_{10}H_{13}NO$ ($[M + H]^+$) : 164.1070, found : 164.1100

4-(*p*-Tolylamino)butan-2-one (table 3.2, compound 5)[18] : Prepared from *p*-toluidine (0.053g, 0.5 mmol) and 3-buten-2-ol (0.144g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow liquid (0.065g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.99 (d, *J*=8.2, 2H), 6.55 (d, *J*=8.3, 2H), 3.39 (t, *J*=6.1, 2H), 2.74 (t, *J*=6.1, 2H), 2.23 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 208.35, 145.60, 129.95, 127.02, 113.45, 42.79, 38.93, 30.47, 20.54. HRMS (ESI): calculated for $C_{11}H_{15}NO$ ($[M+H]^+$): 178.1226, found: 178.1221

4-(*o*-tolylamino)butan-2-one (table 3.2, compound 6) : Prepared from *o*- toluidine (0.053g, 0.5 mmol) and 3-buten-2-ol (0.144g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow liquid **(**0.0788g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (t, *J* = 7.7 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.67 (t, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 3.47 (t, *J* = 6.1 Hz, 2H), 2.79 (t, *J* = 6.1 Hz, 2H), 2.17 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.30, 145.68, 130.35, 127.16, 122.66, 117.30, 109.75, 77.48, 77.16, 76.84, 42.65, 38.44, 30.38, 17.51. HRMS (ESI): calculated for $C_{11}H_{15}NO$ ($[M + H]^+$): 178.1226, found: 178.1254.

4-((4-(Trifluoromethyl)phenyl)amino)butan-2-one (table 3.2, compound 7) : Prepared from 4-(trifluoromethyl)aniline (0.080g, 0.5 mmol) and 3-buten-2-ol (0.144g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellowish white solid (0.1098g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (d, *J*=8.5, 2H), 6.62 (d, *J*=8.5, 2H), 3.45 (t, *J*=6.0, 2H), 2.77 (t, *J*=6.0, 2H), 2.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.84, 150.20, 126.85, 126.82, 126.78, 126.74, 123.71, 119.03, 112.14, 42.35, 37.99, 30.42. HRMS (ESI): calculated for $C_{11}H_{12}F_3NO$ ($[M + H]^+$) : 232.0944, found : 232.0958

1-((4-Methoxyphenyl)amino)pentan-3-one (table 3.2, compound 8)[19] : Prepared from *p*-anisidine (0.061g, 0.5mmol) and 1-penten-3-ol (0.172g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow solid (0.099g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.78 (d, *J*=8.8, 2H), 6.59 (d, *J*=8.8, 2H), 3.74 (s, 3H), 3.37 (t, *J*=6.1, 2H), 2.71 (t, *J*=6.1, 2H), 2.44 (q, *J* = 7.3, 2H), 1.05 (t, *J*=7.3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.04, 152.50, 141.93, 115.02, 114.77, 55.87, 41.40, 39.85, 36.41, 7.77. HRMS (ESI): calculated for $C_{12}H_{17}NO_2$ ($[M + H]^+$) : 208.1332, found : 208.1349.

1-((2-Methoxyphenyl)amino)pentan-3-one (table 3.2, compound 9) : Prepared from *o*-anisidine (0.061g, 0.5 mmol) and 1-penten-3-ol (0.172g, 2.0 mmol). After purification by column chromatography, the compound was isolated as brown liquid (0.098g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.87 (t, *J*=8.1, 1H), 6.77 (d, *J*=7.9, 1H), 6.71 – 6.60 (m, 2H), 3.83 (s, 3H), 3.45 (t, *J*=6.4, 2H), 2.75 (t, *J*=6.4, 2H), 2.45 (q, *J*=7.3, 2H), 1.06 (t, *J*=7.3, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.55, 147.13, 137.71, 121.26, 116.76, 109.88, 109.59, 55.42, 41.61, 38.32, 36.35, 7.70. HRMS (ESI): calculated for $C_{12}H_{17}NO_2$ ($[M+Na]^+$): 230.1151, found: 230.1166

1-(Phenylamino)pentan-3-one (table 3.2, compound 10)[20] : Prepared from aniline (0.046g, 0.5 mmol) and 1-penten-3-ol (0.1722g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow liquid (0.073g, 83%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 2H), 6.71 (t, *J* = 7.2 Hz, 1H), 6.62 (d, *J* = 7.7 Hz, 2H), 3.43 (t, *J* = 6.1 Hz, 2H), 2.73 (t, *J* = 5.9 Hz, 2H), 2.44 (q, *J* = 7.3 Hz, 2H), 1.06 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 210.97, 129.45, 117.80, 113.22, 41.40, 38.81, 36.47, 7.80. HRMS (ESI): calculated for $C_{11}H_{15}NO$ ($[M + H]^+$) : 178.1226, found : 178.1253

1-(*p*-Tolylamino)pentan-3-one (table 3.2, compound 11)[20] : Prepared from *p*-toluidine (0.053g, 0.5 mmol) and 1-penten-3-ol(0.1722g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow solid (0.083g, 87%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 6.99 (d, *J*=8.1, 2H), 6.57 (d, *J*=8.4, 2H), 3.40 (t, *J*=6.2, 2H), 2.72 (t, *J*=6.2, 2H), 2.43 (q, *J*=7.3, 2H), 2.24 (s, 3H), 1.05 (t, *J*=7.3, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 211.02, 145.18, 129.94, 127.42, 113.72, 41.33, 39.33, 36.44, 20.52, 7.78. HRMS (ESI): calculated for $C_{12}H_{17}NO$ ($[M + H]^+$) : 192.1383, found : 192.1382

1-(*o*-Tolylamino)pentan-3-one (table 3.2, compound 12)[21] : Prepared from *o*-toluidine (0.053g, 0.5 mmol) and 1-penten-3-ol (0.1722g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow liquid (0.087g, 91%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.13 (t, *J*=7.7, 1H), 7.06 (d, *J*=7.3, 1H), 6.67 (t, *J*=7.3, 1H), 6.63 (d, *J*=8.0, 1H), 3.48 (t, *J*=6.2, 2H), 2.76 (t, *J*=6.2, 2H), 2.45 (q, *J*=7.3, 2H), 2.12 (s, 3H), 1.07 (t, *J*=7.3, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 211.14, 145.75, 130.35, 127.18, 122.68, 117.28, 109.79, 41.33, 38.63, 36.46, 17.55, 7.76. HRMS (ESI): $C_{12}H_{17}NO$ ($[M+Na]^+$): 214.1202, found: 214.1205.

1-((4-(Trifluoromethyl)phenyl)amino)pentan-3-one (table 3.2, compound 13) : Prepared from 4-(trifluoromethyl)aniline (0.080g, 0.5 mmol) and 1-penten-3-ol (0.1722g, 2.0 mmol). After purification by column chromatography, the compound was isolated as brown solid (0.116g, 95%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 7.40 (d, *J*=8.5, 2H), 6.62 (d, *J*=8.5, 2H), 3.46 (t, *J*=6.1, 2H), 2.74 (t, *J*=6.0, 2H), 2.50 – 2.38 (m, 2H), 1.06 (t, *J*=7.3, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 210.62, 149.99, 126.85, 126.83, 126.81, 126.79, 125.78, 124.25, 119.73, 119.55, 119.36, 119.17, 112.40, 40.94, 38.35, 36.49, 7.76. HRMS (ESI): calculated for $C_{12}H_{14}F_3NO$ ($[M + H]^+$) : 246.1100, found : 246.1100.

1-((4-Fluorophenyl)amino)pentan-3-one (table 3.2, compound 14)[22] : Prepared from 4-fluoroaniline (0.055g, 0.5 mmol) and 1-penten-3-ol (0.172 g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow solid (0.079g, 81%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 6.88 (m, 2H), 6.57 – 6.51 (m, 2H), 3.89 (s, 1H), 3.37 (t, *J*=6.1, 2H), 2.71 (t, *J*=6.1, 2H), 2.44 (q, *J*=7.3, 2H), 1.06 (t, *J*=7.3, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 210.97, 156.78, 155.44, 144.24, 115.91, 115.79, 114.17, 114.13, 41.27, 39.42, 36.50, 7.81. HRMS (ESI): calculated for $C_{11}H_{14}FNO$ ([M + H]$^+$) : 196.1132, found : 196.1159

1-((4-methoxyphenyl)amino)hexan-3-one (table 3.2, compound 15) : Prepared from *p*-anisidine (0.061 g, 0.5mmol) and 1-hexen-3-ol (0.200 g, 2.0 mmol). After purification by column chromatography, the compound was isolated as brown liquid (0.07g, 64%). ^{1}H NMR (700 MHz, $CDCl_3$) δ = 6.78 (d, *J*=8.8, 2H), 6.63 (d, *J*=8.4, 2H), 3.75 (s, 3H), 3.37 (t, *J*=6.2, 2H), 2.71 (t, *J*=5.9, 2H), 2.39 (t, *J*=7.3, 2H), 1.60 (h, *J*=7.4, 2H), 0.90 (t, *J*=7.4, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 210.64, 152.83, 141.47, 115.18, 115.07, 55.92, 45.24, 41.67, 40.15, 17.31, 13.84. HRMS (ESI): calculated for $C_{13}H_{19}NO_2$ ([M + H]$^+$) : 222.1489, found : 222.1494

1-((2-Methoxyphenyl)amino)hexan-3-one (table 3.2, compound 16) : Prepared from *o*-anisidine (0.061 g, 0.5mmol) and 1-hexen-3-ol (0.200 g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow liquid (0.064g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.0 Hz, 1H), 6.68 (t, *J* = 7.7 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 3.83 (s, 3H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 6.3 Hz, 2H), 2.40 (t, *J* = 7.3 Hz, 2H), 1.61 (sextet, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.21, 147.19, 137.72, 121.30, 116.83, 109.97, 109.63, 55.46, 45.20, 42.00, 38.33, 17.23, 13.77. HRMS (ESI): calculated for $C_{13}H_{19}NO_2$ ([M + H]$^+$) : 222.1489, found : 222.1499

1-(Methyl(phenyl)amino)hexan-3-one (table 3.2, compound 17)[23] : Prepared from N-methylaniline (0.053 g, 0.5mmol) and 1-hexen-3-ol (0.200 g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow liquid (0.078g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.19 (m, 2H), 6.76 – 6.68 (m, 3H), 3.64 (t, *J* = 7.0 Hz, 2H), 2.92 (s, 3H), 2.67 (t, *J* = 7.0 Hz, 2H), 2.38 (t, *J* = 7.3 Hz, 2H), 1.59 (sextet, *J* = 7.3 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.42, 148.67, 129.40, 116.94, 112.61, 47.66, 45.60, 39.43, 38.72, 17.25, 13.82. HRMS (ESI): Calculated for $C_{13}H_{19}NO$ ($[M+H]^+$): 206.1539, found: 206.1553

1-((2-Methoxy-4-nitrophenyl)amino)hexan-3-one (table 3.2, compound 18) : Prepared from 2-methoxy-4-nitroaniline (0.084 g, 0.5mmol) and 1-hexen-3-ol (0.200g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow solid (0.11g, 83%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.9 Hz, 1H), 7.61 (s, 1H), 6.54 (d, *J* = 8.9 Hz, 1H), 3.91 (s, 3H), 3.54 (t, *J* = 6.2 Hz, 2H), 2.77 (t, *J* = 6.2 Hz, 2H), 2.42 (t, *J* = 7.3 Hz, 2H), 1.62 (sextet, *J* = 7.4 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 209.56, 145.65, 143.54, 137.64, 119.91, 106.87, 105.01, 77.34, 77.16, 76.98, 56.06, 45.26, 41.33, 37.76, 17.29, 13.80. HRMS (ESI): calculated for $C_{13}H_{18}N_2O_4$ ($[M + Na]^+$) : 289.1159, found : 289.1187

1-((4-Chlorophenyl)amino)hexan-3-one (table 3.2, compound 19) : Prepared from 4-chloroaniline (0.063 g, 0.5 mmol) and 1-hexen-3-ol (0.200g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow solid (0.08g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 3.39 (t, *J* = 6.1 Hz, 2H), 2.72 (t, *J* = 6.1 Hz, 2H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.60 (sextet, *J* = 7.4 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.28, 145.51, 129.35, 115.06, 45.25, 41.26, 39.45, 17.30, 13.82. HRMS (ESI): calculated for $C_{12}H_{16}ClNO$ ($[M + Na]^+$) : 248.0813, found : 248.0818

1-((2-Chlorophenyl)amino)hexan-3-one (table 3.2, compound 20) : Prepared from 2-chloroaniline (0.063g, 0.5mmol) and 1-hexen-3-ol (0.2g, 2.0 mmol). After purification by column chromatography, the compound was isolated as yellow liquid (0.095g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.74 (t, *J* = 6.4 Hz, 2H), 2.40 (t, *J* = 7.3 Hz, 2H), 1.61 (sextet, *J* = 7.5 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.96, 143.66, 129.40, 127.90, 119.68, 117.60, 111.33, 45.33, 41.74, 38.37, 17.29, 13.81. HRMS (ESI): calculated for $C_{12}H_{16}ClNO$ ($[M + Na]^+$) : 248.0813, found : 248.0814

1-((4-Bromo-2-nitrophenyl)amino)hexan-3-one (table 3.2, compound 21) : Prepared from 4-bromo-2-nitroaniline (0.108g, 0.5mmol) and 1-hexen-3-ol (0.2g, 2.0 mmol). After purification by column chromatography, the compound was isolated as orange solid (0.075g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.50 (d, *J* = 9.1 Hz, 1H), 6.79 (d, *J* = 9.2 Hz, 1H), 3.59 (m, 2H), 2.81 (t, *J* = 6.6 Hz, 2H), 2.44 (t, *J* = 7.3 Hz, 2H), 1.63 (dq, *J* = 14.7, 7.1 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.65, 144.16, 139.14, 132.52, 129.15, 115.39, 106.75, 45.31, 41.51, 37.65, 17.29, 13.81. HRMS (ESI): calculated for $C_{12}H_{15}BrN_2O_3$ ($[M+H]^+$): 315.0339, found: 315.0353.

3.5. References

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Chapter 4

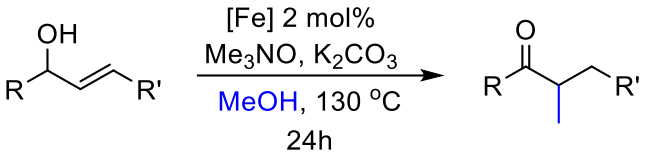
Palladium-Mediated Tandem Isomerization–Methylenation of Allyl Alcohols: One-Pot Synthesis of 1,5-Diketones

4.1. Introduction

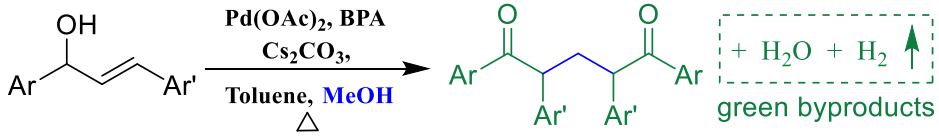
1,5-Diketones are important structural moieties observed in natural products[1] and in medicinal compounds. They also serve as versatile building blocks for the synthesis of biologically important five and six membered rings such as cyclopentane,[2] cyclohexenone,[3] pyridine[4] and piperidine.[5] Furthermore, they offer ozone free approach for the synthesis of ozonides.[6] The classical approaches for the synthesis of 1,5-diketones involves condensation between α,β-unsaturated ketones with silylenol ethers (or) ketones.[7] Additionally, 1,5-diketones are also synthesised using radical addition to alkenes[8] and aldehydes,[9] rhodium catalysed hydroacylation,[10] ruthenium catalysed three component reaction.[11] In spite of this progress, the development of alternative general methods for the synthesis of substituted 1,5-diketones is much sought after.

Redox isomerisation of allylic alcohols[12] to the synthetically important enolisable carbonyl compounds have made them important structural motifs in synthetic chemistry. The isomerisation process is atom economic and avoids the use of toxic and costly reagents. Since allylic alcohols act as readily available carbonyl precursor, they can be further functionalised to form new C-C or C-heteroatom bond. There are numerous reports for the conversion of allylic alcohols to important compounds by combining C-C bond formation. However, there is only one report which involves isomerisation followed by functionalisation using methanol as the C1 source for the synthesis of α-methylated ketones utilising (cyclopentadienone)iron(0) carbonyl complex.[13] In this chapter, we present the synthesis of 1,5-diketones starting from allylic alcohols and methanol *via* tandem isomerisation followed by methylenation using commercially available $Pd(OAc)_2$ as a catalyst. To the best of our knowledge, this is the first report of tandem isomerisation-functionalisation of allylic alcohols to 1,5-diketones using methanol.

Morril and co-worker, *Org. Lett*. **2019**, *21,* 7914-7918



Scheme 4.1. Synthesis of α-methyl ketones using isomerisation-methylation.



Advantages:

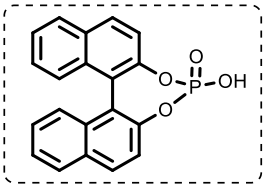
a) **Tandem isomerisation -methylenation**

b) 24 substrates, upto 89% yield

c) Use of commercially available catalyst

d) One pot synthesis of substituted pyridine

e) H_2 and H_2O are only two byproducts



(BPA)

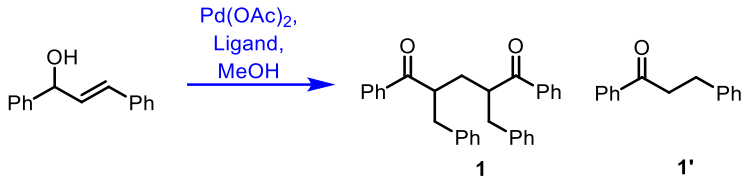
Scheme 4.2. This report: Synthesis of 1,5-diketones using one pot isomerisation-methylenation

4.2. Result and Discussion

To scrutinize the isomerisation-methylenation reaction, 1,3-diphenyl-1,3-propen-1-ol was chosen as the model substrate. As $Pd(OAc)_2$ and BINOL phosphoric acid (BPA) have been established by us and others for the isomerisation of allylic alcohols,[3] we started the reaction with 10 mol% of $Pd(OAc)_2$ and BPA each, with 1 equivalent of LiO^tBu as a base at 60 °C for 24h. This results in less than 20 % of 1,5-diketone along with <20 % of the isomerised product (Table 4.1, entry 1). Bases such as NaO^tBu and KO^tBu did not bring any noticeable difference to the reaction conversion as most of the starting material remained unreacted (Table 4.1, entry 2 and 3). Na_2CO_3 and K_2CO_3 produced the isomerised ketone exclusively (Table 4.1, entry 4 and 5). To our delight, use of Cs_2CO_3 gave the desired product (diketone) in 45% isolated yield (Table 4.1, entry 6). The yield of the product increased to 56%, when the temperature was raised to 120 °C (Table 4.1, entry 7). A mixture of toluene and methanol in 3:1 ratio as the

reaction medium gave 68% yield of the diketone (Table 4.1, entry 8). Further increase of the base to 2.5, 3.0 and 5.0 equivalent yielded 79, 89 and 91% of the product

Table 4.1. Optimisation Table for the synthesis of 1,5-diketone using tandem isomerisation-methylenation reaction[a]



1 1'

Sl no	Ligand	Base	solvent	T (ºC)	Yield	
					1	1'
1[b]	BPA (10)	LiO^tBu (1)	MeOH	60	<20	<20
2[b]	BPA (10)	KO^tBu (1)	MeOH	60	<20	Trace
3[b]	BPA (10)	NaO^tBu (1)	MeOH	60	<20	
4	BPA (10)	Na_2CO_3 (1)	MeOH	60	-	58
5	BPA (10)	K_2CO_3 (1)	MeOH	60	-	45
6	BPA (10)	Cs_2CO_3 (1)	MeOH	60	45	23
7	BPA (10)	Cs_2CO_3 (1)	MeOH	120	56	Trace
8	BPA (10)	Cs_2CO_3 (1)	Toluene/ MeOH (3:1)	120	68	Trace
9	BPA (10)	Cs_2CO_3 (2.5)	Toluene/ MeOH (3:1)	120	79	Trace
10	BPA (10)	Cs_2CO_3 (3)	Toluene/ MeOH (3:1)	120	89	-
11	BPA (10)	Cs_2CO_3 (5)	Toluene/ MeOH (3:1)	120	91	-
12	BPA (10)	Cs_2CO_3 (5)	Toluene/ MeOH (3:1)	100	77	Trace
13[c]	**BPA (5)**	**Cs_2CO_3 (3)**	**Toluene/ MeOH (3:1)**	**120**	**86**	-

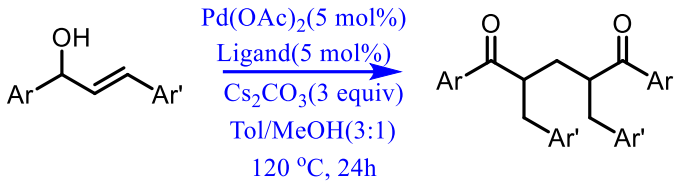
[a]Reaction conditions: 1,3-Diphenyl-1,3-propen-1-ol (0.5 mmol), methanol (1 mL), reaction carried out under aerobic condition, [b] starting material remained unreacted, [c] $Pd(OAc)_2$ (5.0 mol%)

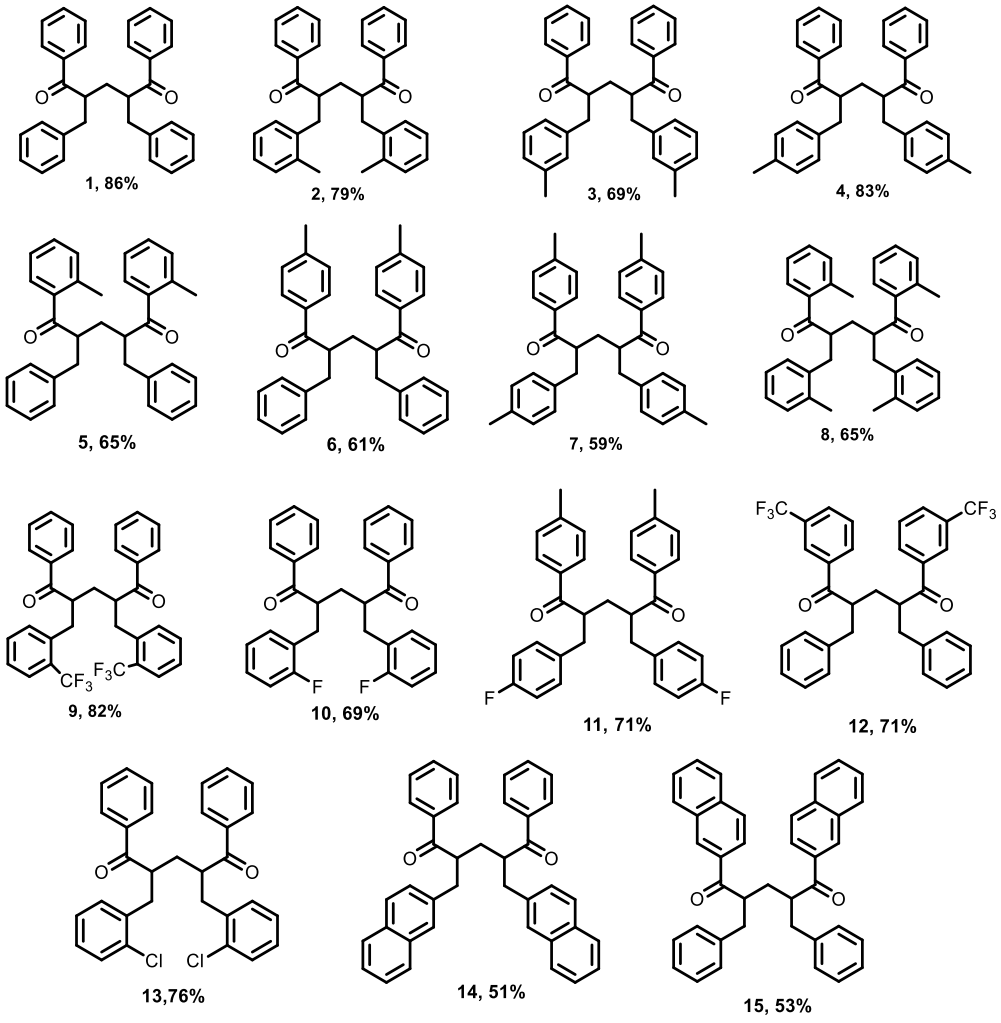
respectively (Table 4.1, entries 9-11). Decrease of temperature to 100 ^{o}C drastically decreased the product yield (Table 4.1, entry 12). Based on the optimisation studies, the metal and ligand loading were found out to be 5 mol% each (Table 4.1, entry 13).

Having optimized the reaction condition, the scope and limitation of this transformation was investigated. We approached the substrate scope by dividing the allylic alcohols into 1,3-diaryl propenols and 1-aryl propenols. Aryl groups with electron-donating substitution (*o,m,p*-CH_3) at the 1 & 3-positions of allylic alcohols were well tolerated and resulted in good yields (Table 4.2, **2-8**). Furthermore, aryl groups with CF_3 at the 1 & 3-positions of allylic alcohols also produced the 1,5-diketones in good yields (Table 4.2, **9** & **12**). The protocol tolerated aryl groups with electron-withdrawing halogens (-F & -Cl) at the 3-position of allylic alcohols (Table 4.2, **10**-**11**, **13**). However, aryl groups with halogens at the 1-position of allylic alcohols either resulted in complex mixture or underwent substitution reaction (not shown). Allylic alcohols having fused ring systems such as naphthyl at the 1 & 3-positions are well tolerated in this transformation and produced the desired 1,5-diketones **14** & **15** in 51% & 53% respectively (Table 4.2). Substrates bearing nitrile and nitro groups produced a complex reaction mixture owing to the competitive reduction of the functional groups. We extended the isomerisation-methylenation reaction scope to 1-aryl propenols. Under the optimized conditions α-vinyl benzyl alcohol gave excellent yield of 89% of the desired product (Table 4.3, **16**). Aryl groups with -CH_3, -OCH_3, -OBn (Table 4.3, **17**, **18** & **22**), sterically bulky dimethoxy (Table 4.3, **20**) and isobutyl (Table 4.3, **21**) substituents did not have much impact on the yield of the reaction and produced moderate to good yields. 4-Fluoro-α-vinylbenzyl alcohol underwent substitution reaction to produce the methoxy substituted diketone (Table 4.3, **18**). Naphthyl (Table 4.3, **19**) and biphenyl (Table 4.3, **23**) substitutions were also screened for the isomerisation-methylenation

reaction which resulted in 62% and 69% yield respectively. Aliphatic allylic alcohols such as 3-buten-2-ol and 1-penten-3-ol did not undergo this conversion even at elevated temperature.

Table 4.2. Substrate scope for the synthesis of 1,5-diketones using 1,3-diaryl propenols and methanol

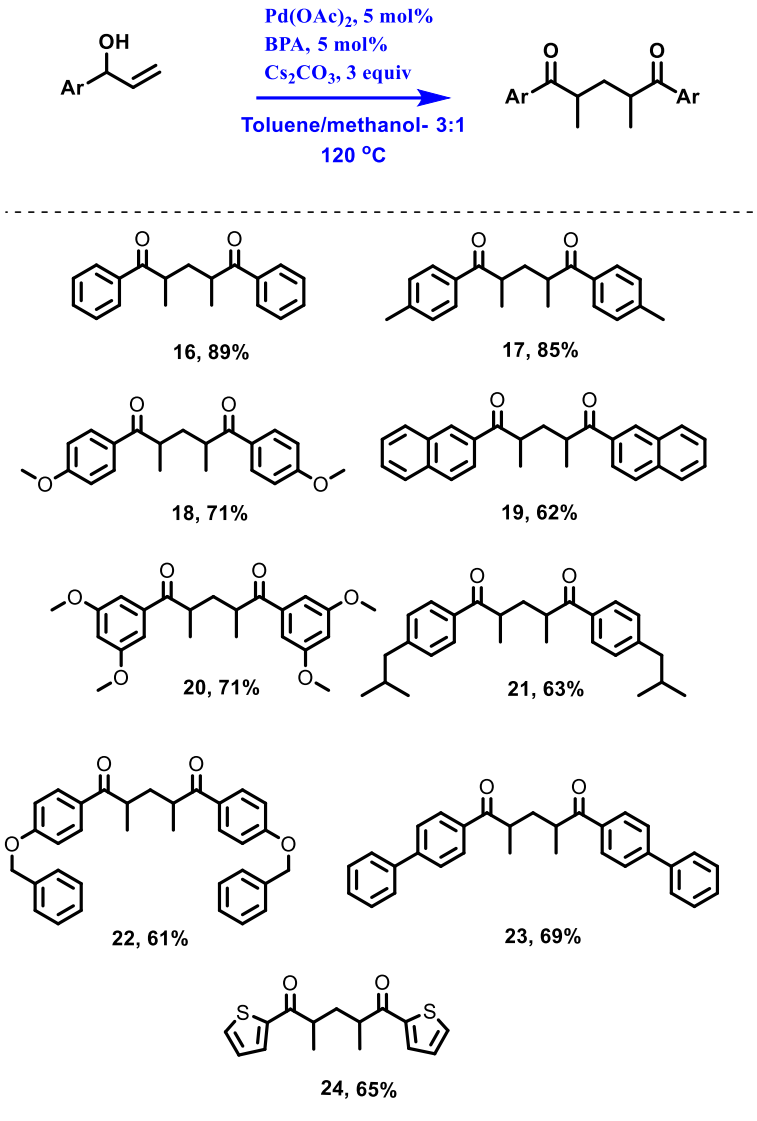




Reaction details: Allylic alcohol (0.5 mmol), toluene (3 mL), MeOH (1 mL), $Pd(OAc)_2$ (2.5×10^{-2} mmol), BPA (2.5×10^{-2} mmol), Cs_2CO_3 (1.5 mmol).

The robustness of this methodology was studied in the presence of additives with different functional groups which may otherwise interfere in the reactivity as mentioned by Glorious co-workers.[15] Under the optimized conditions, equimolar amount of additive was added along with α-vinylbenzyl alcohol (**16a**) as the model system. With bromobenzene, 39% of the diketone product was observed whereas the bromobenzene

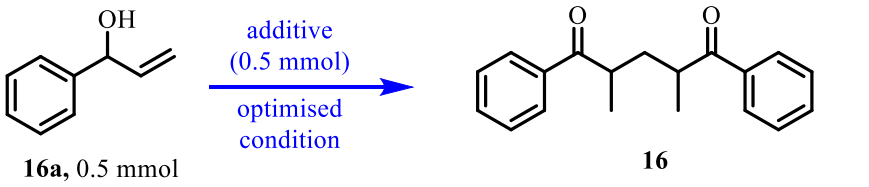
Table 4.3. Substrate scope for the synthesis of 1,5-diketones using 1-aryl propenols and methanol



Reaction details: Allylic alcohol (0.5 mmol), toluene (3 mL), MeOH (1 mL), $Pd(OAc)_2$ (2.5×10^{-2} mmol), BPA (2.5×10^{-2} mmol), Cs_2CO_3 (1.5 mmol).

was completely consumed as halogen group easily cleaves under the reaction conditions. In the presence of aniline and acetanilide as additives, 51% and 71% of the product was observed respectively and 57% of the aniline and 89% of the acetanilide were recovered. With benzaldehyde, 47% of the product was isolated and the recovery of the additive was 69%. Sulfur containing, benzothiazole had a moderate impact on the reactivity as 82% of thiazole was recovered with 64% of diketone. Surprisingly, 2,6-lutidine, which is expected to co-ordinate with the palladium centre and thus affect the reactivity, had little impact on the reaction. The additive pyridine was recovered

Table 4.4. additive screening for isomerisation-methylenation

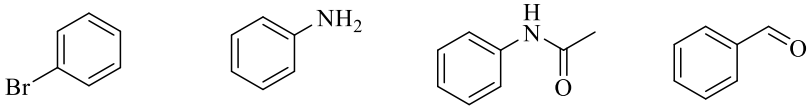


16a, 0.5 mmol

16

P = PRODUCT YIELD

A = ADDITIVE RECOVERED

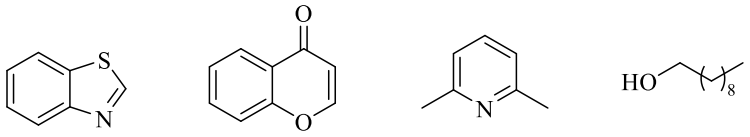


P = 39%
A = nil

P = 51
A = 57

P = 71
A = 89

P = 47
A = 69

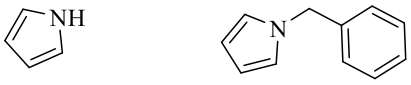


P = 64
A = 82

P = 67
A = 91

P = 71
A = 74

P = 73
A = 67



P = 39
A = --

P = 65
A = 76

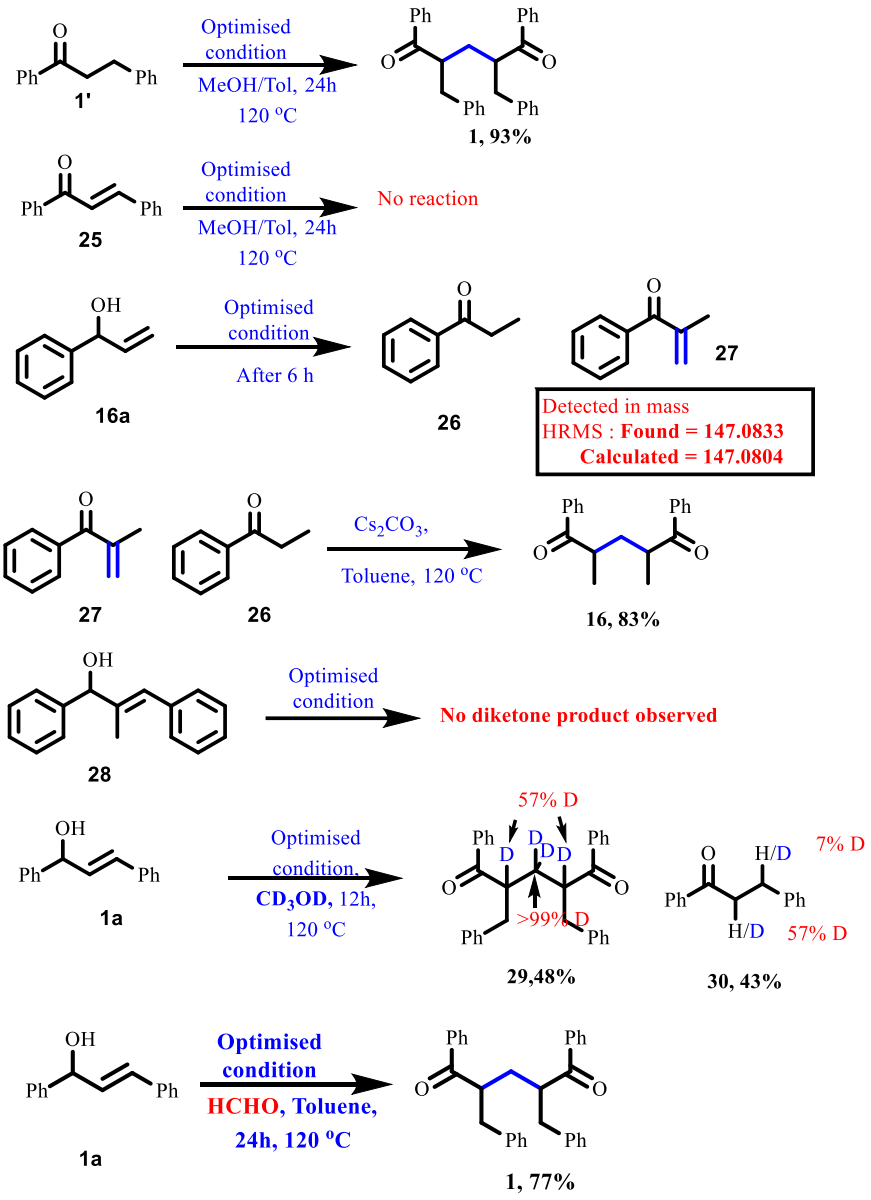
Reaction details: Allyl alcohol 0.5 mmol, additive 0.5 mmol ,Toluene 3 mL, MeOH 1 mL, $Pd(OAc)_2$ 2.5 x 10^{-2} mmol, BPA 2.5 x 10^{-2} mmol, Cs_2CO_3 1.5 mmol**.**

in 74% with 71% of the diketone. 67% of 1-decanol and 91% 4H-chromen-4-one were recovered from the reaction. Low recovery of 1-decanol can be attributed to the tendency of alcohol to undergo dehydrogenation to the corresponding aldehydes in the presence of metal complexes. With pyrrole as an additive, 39% of the product was isolated where as the starting material decomposed completely. Pyrrole protected with benzyl group resulted in 67% of the starting material with 73% product.

To realise the mechanism of the protocol, control experiments were performed. From the literature,[3] it was known that allylic alcohols isomerise to the corresponding vinyl ketones as well as saturated ketones. When we subjected vinyl ketone and saturated ketone to the methylenation reaction under the optimised reaction conditions, only the saturated ketone resulted in the desired diketone product (Scheme 4.3). Mass analysis of the reaction mixture of α-vinylbenzyl alcohol (**16a**) which was subjected to the isomerisation-methylenation reaction reveals the presence of propiophenone and α-methylenated propiophenone (**27**). We believe that this intermediate upon reacting with propiophenone in the presence of a base in toluene produce the desired diketone product. This reveal that the saturated ketone and its α-methylene substituted analogue are the two possible intermediates in the reaction. It is worth noting that β-position of the allyl alcohol should be unoccupied so as to produce the α-methylenated saturated ketone which ultimately yields the desired diketone. To confirm this, we reacted β-methyl substituted allylic alcohol (**28**) under the optimised reaction conditions and as expected, no diketone product was observed.

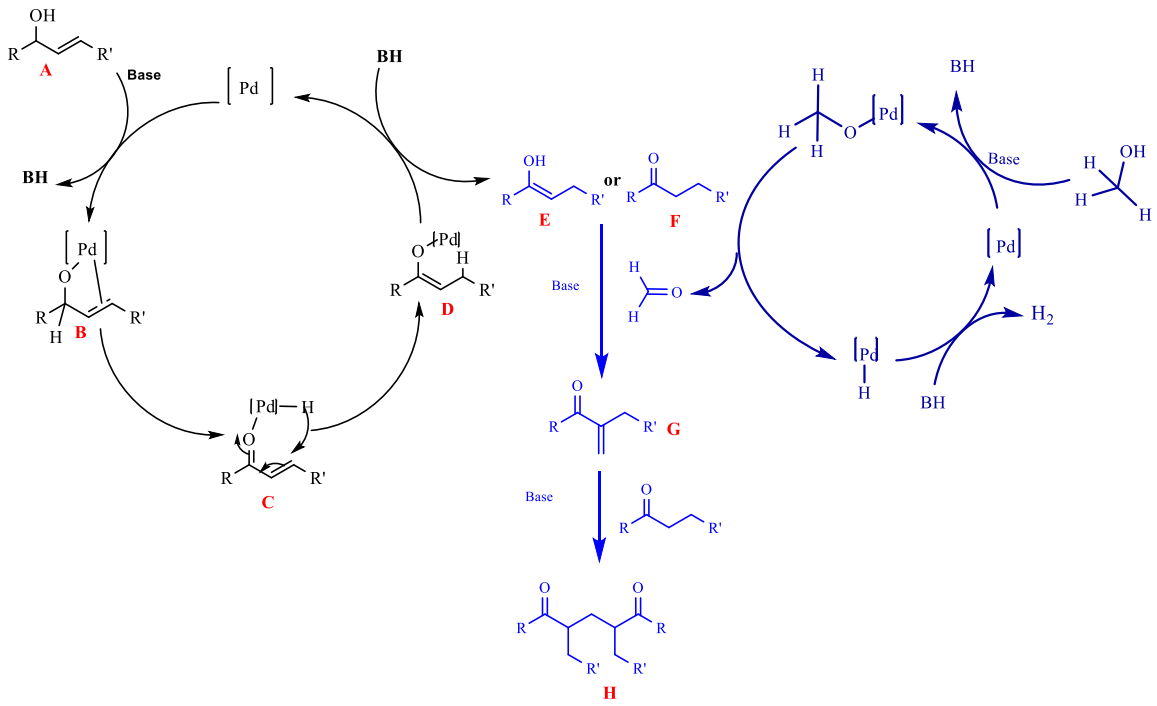
When we performed the isomerisation-methylenation reaction of 1,3-diphenyl-2-propen-1-ol (**1a**) using deuterated methanol for 12h, we observed compound 29 (99%

deuteration at the 3-position, 69% deuteration at the 2-position) and **30** (57% deuteration at the 2-position and 7% deuteration at the benzyl position). This experiment reveals that during the isomerisation of allylic alcohol, majority of the hydrogen added to the double bond comes from the dehydrogenation of the allylic alcohol. Hydrogen released from the methanol dehydrogenation also gets added to the allylic double bond by proton-deuterium exchange.



Scheme 4.3. Control reactions

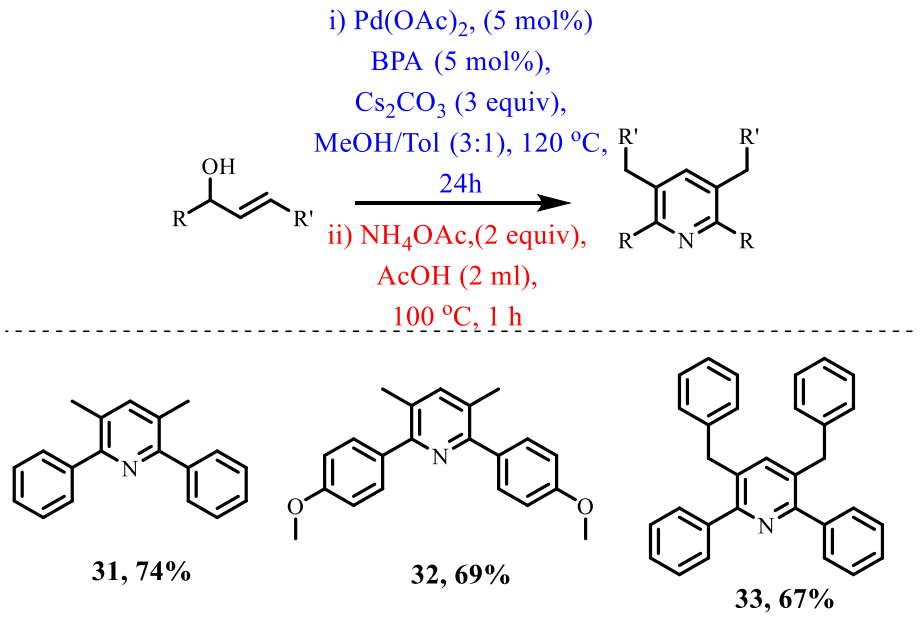
Based on the above findings and recent reports,[14] we propose the following mechanism(scheme 4.3). Allylic alcohol **A** is deprotonated in the presence of a base to produce the species **B** which undergoes β hydride elimination leading to species **C**. Species **C** undergoes 1,4-hydride addition resulting in the formation of enolic species **D** which either results in the enol **E** and/or can further tautomerise to yield ketone **F.** Formaldehyde produced from methanol in the presence of palladium adds to the ketone product **F** resulting in α-methylenated species **G** through aldol condensation. The aldol product thus produced undergoes Michael addition with **F** to yield the 1,5-diketone product. Use of formaldehyde instead of methanol afforded the desired product in a 77% yield (scheme 4.3), which further supports the proposed mechanism.



Scheme 4.4. Proposed mechanism

Pyridines are important heterocycles present in biologically relevant molecules and also act as ligands to make coordination compounds. Since, 1,5-diketones acts as good precursors for the synthesis of pyridines, we extended our methodology for the

sequential one pot synthesis of pyridines. After the first step, ammonium acetate in acetic acid was added to the reaction mixture and heating was continued for another hour which resulted in substituted pyridines in good yields. Using this sequential methodology, 1-phenylprop-2-en-1-ol, 1-(4-methoxyphenyl)prop-2-en-1-ol and 1,3-diphenylprop-2-en-1-ol were successfully converted to the corresponding pyridines in 74%, 69% and 67% yield respectively. To further check the synthetic utility of this protocol, gram scale reactions were carried out using 1-phenylprop-2-en-1-ol which resulted in 76% isolated yield.



Scheme 4.5. One pot synthesis of substituted pyridines

4.3. Conclusion

In conclusion, we have developed a new methodology for the synthesis of 1,5-diketones by tandem isomerisation-methylenation of allylic alcohols. Various allylic alcohols and different additives were screened to check the scope and limitation of the methodology. Mechanistic studies reveal that the reaction proceeds through Michael

addition between the isomerised ketone and α-methylene species. This protocol was further extended for the synthesis of substituted pyridines *via* sequential addition.

4.4. Experimental section

4.4.1. General information:

All reagents and solvents were obtained from commercial sources; allyl alcohols were synthesized following literature reported methods[1,2]. Solvents were purified according to standard procedures. BINOL phosphoric acid (BPA) was synthesized following the literature reported procedures[3]. All 400 MHz ^{1}H, 101 MHz ^{13}C, 377 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 were externally referenced to α,α,α- trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). IR spectra were recorded with the Perkin Elmer instrument. High-resolution mass spectra (HRMS) were recorded using Bruker microTOF-QII mass spectrometer. Unless mentioned, all reactions were carried out under aerobic condition and at 0.5 mmol scale. Diastereomeric ratio were determined from ^{1}H NMR. Diastereomers were identified as per the recent report[14].

4.4.2. General procedure for isomerisation-methylenation reaction :

Palladium acetate (0.0056g, 0.025 mmol), BPA (0.0087g, 0.025 mmol) and Cs_2CO_3 (0.48g, 1.5 mmol) were added to a oven dried pressure tube. Allyl alcohol (0.5 mmol) was added to it. Toluene and methanol in the ratio 3:1 were added to it. Then the pressure tube was closed with PTFE stopper and the reaction mixture was stirred at 120 ˚C (oil bath temperature) for 24 h. Then the solvent was evaporated under vacuum and the reaction mixture was dissolved in CH_2Cl_2. Aqueous and organic layers were separated, Organic layers were collected by washing with CH_2Cl_2 (3 x 25mL). The

crude mixture was purified by column chromatography using *n*-hexane:EtOAc (19:1 to 9:1).

4.4.3. General procedure for additive screening in isomerisation-methylenation reaction:

Palladium acetate (0.0056g, 0.025 mmol), BPA (0.0087g, 0.025 mmol) and Cs_2CO_3 (0.48g, 1.5 mmol) were added to a oven dried pressure tube. Allyl alcohol (0.5 mmol) was added to it. Equimolar amount (0.5 mmol) of the additive was added. Toluene and methanol in the ratio 3:1 were added to it. Then the pressure tube was closed with PTFE stopper and the reaction mixture was stirred at 120 ˚C (oil bath temperature) for 24 h. Then the reaction mixture were either subjected to direct column chromatography or gas chromatography analysis in case of a volatile additive.

4.4.4. General procedure for the one-pot synthesis of substituted pyridine :

Palladium acetate (0.0056g, 0.025 mmol), BPA (0.0087g, 0.025 mmol) and Cs_2CO_3 (0.48g, 1.5 mmol) were added to a oven dried pressure tube. Allyl alcohol (0.5 mmol) was added to it. Toluene and methanol in the ratio 3:1 were added to it. Then the pressure tube was closed with PTFE stopper and the reaction mixture was stirred at 120 ˚C (oil bath temperature) for 24 h. Then the reaction was cooled down to room temperature. Ammonium acetate (1 mmol) and acetic acid (2 mL) were added to it and the tube was sealed. The reaction was heated at 100 ºC for 1 hour. Then the solvent was evaporated under vacuum and the reaction mixture was dissolved in CH_2Cl_2. Aqueous and organic layers were separated, Organic layers were collected by washing with CH_2Cl_2 (3 x 25mL). The crude mixture was purified by column chromatography using *n*-hexane:EtOAc (9:1).

4.4.5. Analytical data of all compounds:

2,4-Dibenzyl-1,5-diphenylpentane-1,5-dione[14]: (Table 4.2, **1**)

Prepared from (E)-1,3-diphenylprop-2-en-1-ol (0.105g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 86% (0.092g) Diastereomeric ratio : 1.18:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.0 Hz, 4H), 7.60 – 7.48 (m, 6H), 7.43 (t, *J* = 7.6 Hz, 4H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.26 – 6.99 (m, 20H), 6.97 (d, *J* = 6.5 Hz, 4H), 3.77 (p, *J* = 7.0 Hz, 2H), 3.69 (p, *J* = 7.1 Hz, 2H), 3.01 (td, *J* = 13.5, 7.4 Hz, 4H), 2.70 (dd, *J* = 13.7, 6.7 Hz, 2H), 2.63 (dd, *J* = 13.7, 6.7 Hz, 2H), 2.39 (dt, *J* = 14.0, 7.1 Hz, 1H), 2.12 (t, *J* = 6.3 Hz, 2H), 1.73 (dt, *J* = 13.7, 6.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.98, 203.24, 139.37, 138.96, 137.34, 136.97, 133.27,132.95, 129.05, 129.03, 128.83, 128.58, 128.54, 128.50, 128.12, 126.50, 126.44, 46.08, 45.80,39.90, 38.48, 34.69, 34.41. FT-IR (ATR, neat): 2922, 1675, 1595, 1494, 1446, 1375, 1283,1222, 1180, 1028, 1000, 966, 784, 749, 695 cm^{-1}.

2,4-Bis(2-methylbenzyl)-1,5-diphenylpentane-1,5-dione: (Table 4.2, **2**)

Prepared from (E)-1-phenyl-3-(*o*-tolyl)prop-2-en-1-ol (0.112g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 79 % (0.090g). Diastereomeric ratio : 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 4H), 7.53 (t, *J* = 7.4 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 4H), 7.41 (t, *J* = 7.7 Hz, 4H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.14 (t, *J* = 7.7 Hz, 4H), 7.09 – 6.92 (m, 16H), 3.78 (p, *J* = 7.3 Hz, 2H), 3.71 (p, *J* = 7.1 Hz, 2H), 3.04 – 2.91 (m, 4H), 2.72 (td, *J* = 13.7, 6.8 Hz, 4H), 2.50 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.28 (s, 6H), 2.19 (t, *J* = 7.9 Hz, 2H), 2.13 (s, 6H), 1.87 – 1.75 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.55, 203.59, 137.46, 137.40, 137.14, 136.91, 136.07, 133.19, 132.86, 130.48, 130.44, 129.83, 129.59, 128.69, 128.39, 127.92, 126.58, 126.54, 126.11, 126.04, 77.48, 77.16, 76.84, 44.47, 37.45, 36.04, 35.19, 34.70, 19.70, 19.67. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd

for $[C_{33}H_{32}O_2+Na]^+$:483.2295, Found : 483.2281. FT-IR (ATR, neat): 2967, 1675, 1595, 1579, 1492, 1446, 1236, 1181, 966, 743, 696, 685 cm^{-1}.

2,4-Bis(3-methylbenzyl)-1,5-diphenylpentane-1,5-dione: (Table 4.2, **3**)

Prepared from (E)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-ol (0.112g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 69 % (0.079g). Diastereomeric ratio : 1.18:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.0 Hz, 4H), 7.60 – 7.48 (m, 5H), 7.44 (t, *J* = 7.6 Hz, 5H), 7.39 – 7.33 (m, 2H), 7.20 (t, *J* = 7.8 Hz, 4H), 7.11 – 7.01 (m, 4H), 6.92 (t, *J* = 8.1 Hz, 4H), 6.87 (s, 4H), 6.82 – 6.74 (m, 4H), 3.76 (p, *J* = 8.0 Hz, 2H), 3.70 (p, *J* = 8.0 Hz, 2H),2.98 (td, *J* = 13.4, 7.2 Hz, 4H), 2.67 (dd, *J* = 13.7, 6.8 Hz, 2H), 2.58 (dd, *J* = 13.7, 6.9 Hz, 2H), 2.38 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.25 (s, 6H), 2.20 (s, 6H), 2.11 (t, *J* = 8.0 Hz, 2H), 1.72 (dt, *J* = 13.7, 6.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.01, 203.32, 139.36, 138.87, 138.11, 138.01, 137.39, 136.93, 133.21, 132.89, 129.87, 129.74, 128.77, 128.51, 128.47, 128.40, 128.12, 127.20, 127.16, 126.01, 46.00, 45.77, 39.76, 38.42, 34.66, 34.46, 21.46, 21.42. HRMS (ESI-TOF) *m/z* $[M+nNa]^+$ Calcd for $[C_{33}H_{32}O_2+Na]^+$:483.2295, Found : 483.2326. FT-IR (ATR, neat): 2923, 1677, 1595, 1579, 1485, 1446, 1377, 1288, 1222, 1001, 971, 781, 695 cm^{-1}.

2,4-Bis(4-methylbenzyl)-1,5-diphenylpentane-1,5-dione: (Table 4.2, **4**)

Prepared from (E)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-ol (0.112g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 83% (0.095g). Diastereomeric ratio : 1.34:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.3 Hz, 4H), 7.55 (t, *J* = 7.2 Hz, 6H), 7.44 (t, *J* = 7.7 Hz, 4H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 4H), 7.07 – 6.92 (m, 12H), 6.87 (d, *J* = 7.8 Hz, 4H), 3.77 (p, *J* = 7.0 Hz, 2H), 3.69 (p, *J* = 7.1 Hz, 2H), 2.99 (td, *J* = 13.2, 7.0 Hz, 4H), 2.65 (dd, *J* = 13.7, 6.9 Hz, 2H), 2.58 (dd, *J* = 13.7, 6.9 Hz, 2H), 2.37 (dt, *J* = 13.9,

7.1 Hz, 1H), 2.27 (s,6H), 2.25 (s, 6H), 2.09 (t, *J* = 7.0 Hz, 2H), 1.71 (dt, *J* = 13.7, 6.7 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 203.98, 203.25, 137.29, 136.85, 136.26, 135.88, 135.82, 133.16, 132.87, 129.22, 129.19, 128.88, 128.85, 128.76, 128.58, 128.49, 128.15, 128.11, 46.03, 45.79, 39.30, 37.94, 34.39, 34.20, 21.12, 21.09. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{33}H_{32}O_2+Na]^+$:483.2295, Found : 483.2283. FT-IR (ATR, neat): 2920, 1677, 1596, 1514, 1446, 1377, 1283, 1222, 1181, 1001, 967, 793, 692 cm^{-1}.

2,4-Dibenzyl-1,5-di-*o*-tolylpentane-1,5-dione: (Table 4.2, **5**)

Prepared from (E)-3-phenyl-1-(*o*-tolyl)prop-2-en-1-ol (0.112g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 65% (0.074g). Diastereomeric ratio**:** 1.25:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 4H), 7.42 (d, *J* = 8.3 Hz, 4H), 7.27 – 7.20 (m, 5H), 7.18 (d, *J* = 7.6 Hz, 3H), 7.16 – 7.11 (m, 7H), 7.08 (d, *J* = 8.0 Hz, 5H), 6.98 – 6.94 (m, 8H), 3.74 (p, *J* = 6.9 Hz, 2H), 3.66 (p, *J* = 7.0 Hz, 2H), 3.00 (td, *J* = 13.3, 7.4 Hz, 4H), 2.68 (dd, *J* = 13.7, 6.7 Hz, 2H), 2.62 (dd, *J* = 13.6, 6.6 Hz, 2H), 2.40 (s, 6H), 2.39 – 2.30 (m, 1H), 2.27 (s, 6H), 2.08 (t, *J* = 8.0 Hz, 2H), 1.70 (dt, *J* = 13.7, 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.56, 202.79, 144.08, 143.61, 139.50, 139.09, 134.83, 134.41, 129.49, 129.10, 129.02, 128.61, 128.51, 128.48, 128.24, 126.40, 126.32, 45.89, 45.54, 39.89, 38.37, 34.90, 34.53, 21.77, 21.62. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{33}H_{32}O_2+H]^+$:461.2475, Found : 461.2456. FT-IR (ATR, neat): 2920, 1672, 1605, 1494, 1453, 1407, 1290, 1239, 1180, 965, 824, 750, 699 cm^{-1}.

2,4-Dibenzyl-1,5-di-*p*-tolylpentane-1,5-dione [14] **:** (Table 4.2, **6**)

Prepared from (E)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-ol (0.112g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 61% (0.070g). Diastereomeric ratio**:** 1.36:1. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 4H), 7.54 (d, *J* = 7.7 Hz, 5H), 7.45 (q, *J* = 7.6, 6.6 Hz, 6H), 7.36 (t, *J* = 7.4 Hz, 3H), 7.19 (t, *J* = 7.7 Hz, 4H), 7.08 – 7.00 (m, 4H), 6.98 – 6.88 (m, 6H), 6.81 – 6.72 (m, 4H), 3.74 (p, *J* = 6.9 Hz, 2H), 3.66 (p, *J* = 7.0 Hz, 2H), 2.97 (td, *J* = 13.7, 7.2 Hz, 4H), 2.66 (dd, *J* = 13.7, 6.9 Hz, 2H), 2.57 (dd, *J* = 13.7, 6.9 Hz, 2H), 2.37 (dt, *J* = 13.9, 7.1 Hz, 1H), 2.24 (s, 6H), 2.19 (s, 6H), 2.10 (t, *J* = 7.0 Hz, 2H), 1.71 (dt, *J* = 13.6, 6.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.03, 203.33, 139.36, 138.87, 138.12, 138.02, 136.91, 133.23, 132.91, 129.87, 129.75, 128.78, 128.60, 128.57, 128.51, 128.48, 128.41, 128.13, 127.21, 127.17, 126.01, 45.99, 45.76, 39.76, 38.40, 34.45, 21.48, 21.44. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{33}H_{32}O_2+Na]^+$:483.2295, Found : 483.2277.

2,4-Bis(4-methylbenzyl)-1,5-di-*p*-tolylpentane-1,5-dione : (Table 4.2, **7**) Prepared from (E)-1,3-di-(*p*-tolyl)prop-2-en-1-ol (0.119g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 59% (0.072g). Diastereomeric ratio**:** 1.51:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 4H), 7.45 (d, *J* = 7.9 Hz, 3H), 7.24 (d, *J* = 7.8 Hz, 5H), 7.07 – 6.91 (m, 15H), 6.88 – 6.83 (m, 5H), 3.73 (p, *J* = 6.8 Hz, 2H), 3.64 (p, *J* = 7.1 Hz, 2H), 2.97 (td, *J* = 13.0, 7.0 Hz, 4H), 2.62 (dd, *J* = 13.8, 6.9 Hz, 2H), 2.56 (dd, *J* = 13.8, 6.8 Hz, 2H), 2.41 (s, 6H), 2.36 – 2.20 (m, 19H), 2.05 (t, *J* = 7.1 Hz, 2H), 1.73 – 1.64 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.52, 207.16, 138.87, 138.25, 137.53, 137.41, 136.17, 131.85, 131.71, 131.27, 131.13, 130.60, 130.11, 129.94, 128.12, 127.82, 126.71, 126.66, 126.15, 125.76, 125.70, 48.44, 47.95, 36.77, 35.90, 34.93, 34.12, 20.92, 20.86, 19.62, 19.55. HRMS (ESI-TOF) *m/z* $[M+nNa]^+$ Calcd for $[C_{35}H_{36}O_2+Na]^+$:511.2608, Found : 511.2599. FT-IR (ATR, neat): 2919, 1675, 1606, 1514, 1444, 1407, 1377, 1240, 1180, 1118, 965, 806 cm^{-1}.

2,4-Bis(2-methylbenzyl)-1,5-di-*o*-tolylpentane-1,5-dione : (Table 4.2, **8**)

Prepared from (E)-1,3-di-*o*-tolylprop-2-en-1-ol (0.119g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 65% (0.079g). Diastereomeric ratio**:** 1.42:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 4H), 7.43 (d, *J* = 8.2 Hz, 3H), 7.26 – 7.18 (m, 5H), 7.09 – 6.89 (m, 16H), 6.87 – 6.81 (m, 4H), 3.71 (p, *J* = 6.9 Hz, 2H), 3.62 (p, *J* = 6.9 Hz, 2H), 3.01 – 2.89 (m, 4H), 2.61 (dd, *J* = 13.8, 6.9 Hz, 2H), 2.54 (dd, *J* = 13.7, 6.8 Hz, 2H), 2.39 (s, 6H), 2.37 – 2.26 (m, 1H), 2.27 (s, 6H), 2.24 (s, 6H), 2.23 (s, 6H), 2.03 (t, *J* = 7.7 Hz, 2H), 1.65 (dt, *J* = 14.2, 7.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.57, 202.85, 143.94, 143.52, 136.45, 136.02, 135.79, 135.73, 134.91, 134.46, 129.45, 129.17, 129.12, 128.99, 128.90, 128.87, 128.65, 128.29, 45.92, 45.63, 39.33, 37.92, 34.65, 34.40, 21.75, 21.60, 21.11, 21.07. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{35}H_{36}O_2+H]^+$:489.2788, Found : 489.2765. FT-IR (ATR, neat): 2919, 1673, 1606, 1514, 1444, 1407, 1377, 1291, 1239, 1180, 1118, 964, 806, 775cm^{-1}.

1,5-Diphenyl-2,4-bis(2-(trifluoromethyl)benzyl)pentane-1,5-dione : (Table 4.2, **9**): Prepared from (E)-1-phenyl-3-(2-(trifluoromethyl)phenyl)prop-2-en-1-ol.(0.139g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 82% (0.116 g). Diastereomeric ratio**:** 1:1**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.1 Hz, 4H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.44 – 7.37 (m, 4H), 7.35 – 7.25 (m, 8H), 7.20 (q, *J* = 7.3 Hz, 4H), 7.16 – 7.10 (m, 4H), 7.08 (d, *J* = 7.4 Hz, 3H), 7.01 (t, *J* = 7.9 Hz, 7H), 3.82 (p, *J* = 7.2 Hz, 2H), 3.65 (p, *J* = 7.2 Hz, 2H), 3.11 – 2.96 (m, 4H), 2.88 – 2.77 (m, 4H), 2.38 (dt, *J* = 14.1, 7.0 Hz, 1H), 2.02 (t, *J* = 7.9 Hz, 2H), 1.59 – 1.49 (m, 1H(merged with water peak)). ^{19}F decoupled ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.87, 203.00, 137.53, 137.38, 137.33, 136.77, 133.34, 133.04, 132.09, 131.93, 131.80, 128.76, 128.71, 128.62, 128.50, 128.47, 128.00, 126.77, 126.70, 126.35, 126.31, 44.81, 44.76, 36.67, 35.57, 35.30, 34.64. ^{19}F NMR (376 MHz, $CDCl_3$)

δ -59.13, -59.11. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{33}H_{26}F_6O_2+H]^+$:569.1910, Found : 569.1882. FT-IR (ATR, neat): 2976, 1677,1596, 1448, 1311, 1178, 1156, 1114, 1060, 1038, 768 cm^{-1}.

2,4-Bis(2-fluorobenzyl)-1,5-diphenylpentane-1,5-dione: (Table 4.2, **10**) Prepared from (E)-3-(2-fluorophenyl)-1-phenylprop-2-en-1-ol (0.114g, 0.5 mmol). After purifi--cation by column chromatography an inseparable mixture of two diastereomers was isolated in 69% (0.080 g). Diastereomeric ratio**:** 1.23:1**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.0 Hz, 4H), 7.63 (d, *J* = 8.0 Hz, 3H), 7.59 – 7.52 (m, 2H), 7.46 (d, *J* = 8.4 Hz, 5H), 7.40 – 7.37 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 4H), 7.18 – 7.06 (m, 6H), 7.06 – 6.88 (m, 10H), 3.97 – 3.78 (m, 4H), 3.03 (td, *J* = 14.5, 7.1 Hz, 4H), 2.80 (dd, *J* = 13.6, 7.2 Hz, 2H), 2.73 (dd, *J* = 13.7, 6.9 Hz, 2H), 2.48 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.13 (t, *J* = 8.1 Hz, 2H), 1.74 – 1.63 (m, 1H). ^{19}F decoupled ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.46, 202.84, 137.07, 136.61, 133.32, 133.04, 131.76, 131.68, 128.76, 128.54, 128.43, 128.35, 128.12, 126.12, 125.83, 124.14, 124.10, 115.37, 44.31, 44.00, 34.11, 33.85, 33.32, 32.21. ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.33, -117.44. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{31}H_{26}F_2O_2+H]^+$:469.1974, Found : 469.1962. FT-IR (ATR, neat): 2976, 1677, 1595, 1490, 1446, 1276, 1227, 1182, 1102, 1001, 966, 754, 695 cm^{-1}.

2,4-Bis(4-fluorobenzyl)-1,5-di-*p*-tolylpentane-1,5-dione[14] : (Table 4.2, **11**)

Prepared from (E)-3-(4-fluorophenyl)-1-(*p*-tolyl)prop-2-en-1-ol (0.121g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 71% (0.088 g). Diastereomeric ratio**:** 1.27:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.9 Hz, 4H), 7.39 (d, *J* = 8.0 Hz, 4H), 7.24 (d, *J* = 7.9 Hz, 4H), 7.04 – 6.76 (m, 20H), 3.70 (p, *J* = 6.9 Hz, 2H), 3.60 (p, *J* = 7.1 Hz, 2H), 2.95-2.80 (m, 4H), 2.66 (dd, *J* = 13.8, 6.5 Hz, 2H), 2.60 (dd, *J* = 13.7, 6.1 Hz, 2H), 2.41 (s, 6H), 2.40 – 2.29 (m, 1H), 2.27 (s, 6H), 2.05 (t, *J* = 7.1 Hz, 2H), 1.64 – 1.56 (m, 1H).

^{19}F decoupled ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.43, 202.53, 144.31, 143.84, 135.05, 134.73, 134.60, 134.31, 130.41, 130.38, 129.55, 129.15, 128.52, 128.18, 115.25, 45.91, 45.55, 39.18, 37.45, 34.86, 34.46, 21.73, 21.58. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.68, -116.70.

2,4-Dibenzyl-1,5-bis(3-(trifluoromethyl)phenyl)pentane-1,5-dione : (Table 4.2, **12**): Prepared from (E)-3-phenyl-1-(3-(trifluoromethyl)phenyl)prop-2-en-1-ol (0.139g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 71% (0.101 g). Diastereomeric ratio**:** 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.87 (m, 4H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.57 (s, 2H), 7.48 (dt, *J* = 14.7, 8.1 Hz, 6H), 7.16 (t, *J* = 7.9 Hz, 2H), 7.06 (td, *J* = 13.5, 11.4, 7.2 Hz, 12H), 6.96 (d, *J* = 7.4 Hz, 4H), 6.89 (d, *J* = 7.3 Hz, 4H), 3.59 (dp, *J* = 14.6, 7.1 Hz, 4H), 2.98 – 2.80 (m, 4H), 2.69 (dd, *J* = 13.5, 6.3 Hz, 2H), 2.54 (dd, *J* = 13.7, 7.2 Hz, 2H), 2.36 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.12 (t, *J* = 7.1 Hz, 2H), 1.70 (dt, *J* = 13.4, 6.4 Hz, 1H). ^{19}F decoupled ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.87, 201.80, 138.80, 138.34, 137.63, 137.13, 131.56, 131.38, 131.01, 129.70, 129.46, 129.41, 129.13, 128.95, 128.90, 128.76, 128.71, 126.79, 126.76, 125.33, 124.74, 46.38, 46.03, 40.33, 38.86, 35.19, 34.15. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.63, -62.90. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{33}H_{26}F_6O_2+H]^+$:569.1910, Found : 569.1879. FT-IR (ATR, neat): 1685, 1596, 1328, 1166, 1124, 1098, 1072, 693 cm^{-1}.

2,4-Bis(2-chlorobenzyl)-1,5-diphenylpentane-1,5-dione : (Table 4.2, **13**)

Prepared from (E)-3-(2-chlorophenyl)-1-phenylprop-2-en-1-ol (0.122g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 76% (0.095g). Diastereomeric ratio**:** 1.61:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.8 Hz, 5H), 7.52 (t, *J* = 7.6 Hz, 6H), 7.40 (t, *J* = 7.6 Hz, 5H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.23 – 7.12 (m, 6H), 7.11 – 6.94

(m, 10H), 4.02 (p, *J* = 6.9 Hz, 2H), 3.90 (p, *J* = 7.2 Hz, 2H), 3.04 (td, *J* = 14.0, 6.7 Hz, 4H), 2.86 (td, *J* = 14.0, 6.7 Hz, 4H), 2.46 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.12 (t, *J* = 7.0 Hz, 2H), 1.65 (dt, *J* = 13.8, 6.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.86, 203.10, 137.34, 136.79, 136.71, 136.54, 134.10, 133.96, 133.29, 132.97, 132.09, 131.79, 129.65, 129.57, 128.69, 128.59, 128.45, 128.09, 126.89, 126.85, 43.43, 43.33, 37.85, 36.70, 34.86, 34.35. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{31}H_{26}Cl_2O_2+H]^+$:501.1383, Found : 501.1353. FT-IR (ATR, neat): 2972, 1677, 1595, 1474, 1446, 1222, 1051, 969, 753, 701, 685 cm^{-1}.

2,4-Bis(naphthalen-2-ylmethyl)-1,5-diphenylpentane-1,5-dione: (Table 4.2, **14**): Prepared from (E)-3-(naphthalen-2-yl)-1-phenylprop-2-en-1-ol (0.130g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 51% (0.068g). Diastereomeric ratio**:** 1:1.51. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 6.6 Hz, 5H), 7.78 – 7.72 (m, 4H), 7.72 – 7.57 (m, 11H), 7.53 – 7.47 (m, 4H), 7.44 – 7.39 (m, 10H), 7.40 – 7.31 (m, 7H), 7.22 (dd, *J* = 8.4, 1.8 Hz, 2H), 7.17 (t, *J* = 7.7 Hz, 3H), 7.10 (d, *J* = 8.3 Hz, 2H), 3.88 (h, *J* = 7.1 Hz, 4H), 3.19 (dd, *J* = 13.8, 6.8 Hz, 4H), 2.87 (dd, *J* = 13.7, 6.9 Hz, 2H), 2.78 (dd, *J* = 13.7, 7.1 Hz, 2H), 2.51 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.22 (t, *J* = 7.1 Hz, 2H), 1.84 (dt, *J* = 13.5, 6.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.77, 203.11, 137.19, 136.93, 136.72, 136.46, 133.55, 133.25, 132.99, 132.27, 132.22, 128.77, 128.54, 128.43, 128.27, 128.21, 128.11, 127.67, 127.63, 127.58, 127.54, 127.31, 126.11, 126.06, 125.53, 125.49, 46.02, 45.62, 39.83, 38.63, 34.44. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{39}H_{32}O_2+Na]^+$: 555.2295, Found : 555.2283. FT-IR (ATR, neat): 3056, 2925, 1676, 1596, 1446, 1363, 1236. 1001, 956, 855, 817, 754, 686, 645 cm^{-1}.

2,4-Dibenzyl-1,5-di(naphthalen-2-yl)pentane-1,5-dione: (Table 4.2, **15**)

Prepared from (E)-1-(naphthalen-2-yl)-3-phenylprop-2-en-1-ol (0.130g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 53% (0.070g). Diastereomeric ratio**:** 1:1.58. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.6 Hz, 5H), 7.78 – 7.72 (m, 4H), 7.70 – 7.63 (m, 6H), 7.63 – 7.57 (m, 5H), 7.53 – 7.47 (m, 4H), 7.44 – 7.40 (m, 10H), 7.39 – 7.36 (m, 5H), 7.35 – 7.31 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 3H), 7.17 (t, *J* = 7.6 Hz, 3H), 7.11 (d, *J* = 8.4 Hz, 3H), 3.89 (p, *J* = 7.0 Hz, 4H), 3.20 (dd, *J* = 13.8, 6.8 Hz, 4H), 2.87 (dd, *J* = 13.8, 6.9 Hz, 2H), 2.78 (dd, *J* = 13.7, 7.1 Hz, 2H), 2.51 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.84 (dt, *J* = 13.6, 6.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.77, 203.12, 137.21, 136.93, 136.74, 136.47, 133.56, 133.25, 132.98, 132.28, 132.23, 128.77, 128.54, 128.44, 128.27, 128.22, 128.12, 127.68, 127.63, 127.58, 127.54, 127.32, 126.11, 126.06, 125.53, 125.50, 46.02, 45.63, 39.83, 38.64, 34.59, 34.44. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{39}H_{32}O_2+Na]^+$: 555.2295, Found : 555.2279. FT-IR (ATR, neat): 2922, 1670, 1626, 1597, 1494, 1453, 1276, 1178, 1123, 929, 859, 819, 157, 697 cm^{-1}.

2,4-Dimethyl-1,5-diphenylpentane-1,5-dione: (Table 4.3, **16**)

Prepared from 1-phenylprop-2-en-1-ol (0.067g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 89% (0.062g). Diastereomeric ratio: 1.19:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.3 Hz, 4H), 7.77 (d, *J* = 7.4 Hz, 4H), 7.57 (t, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 4H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 6.9 Hz, 4H), 3.61 (sextet, *J* = 7.0 Hz, 2H), 3.51 (sextet, *J* = 7.0 Hz, 2H), 2.44 (dt, *J* = 14.0, 7.2 Hz, 1H), 2.01 (t, *J* = 7.1 Hz, 2H), 1.49 (dt, *J* = 13.6, 7.1 Hz, 1H), 1.21 (d, *J* = 7.0 Hz, 6H), 1.17 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.39, 203.87, 136.55, 136.33, 133.19, 133.02, 128.83, 128.65, 128.53, 128.23, 38.62, 38.18, 37.37, 37.05, 18.76, 17.67. HRMS (ESI-TOF) *m/z*

$[M+Na]^+$ Calcd for $[C_{19}H_{20}O_2+Na]^+$:303.1356, Found : 303.1356. FT-IR (ATR, neat): 2969, 1675, 1595, 1446, 1376, 1241, 1219, 1142, 1001, 970, 792, 697, 685 cm^{-1}.

2,4-Dimethyl-1,5-di-*p*-tolylpentane-1,5-dione[14] : (Table 4.3, **17**)

Prepared from 1-(*p*-tolyl)prop-2-en-1-ol (0.074g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 71% (0.054g). Diastereomeric ratio: 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.9 Hz, 4H), 7.58 (d, *J* = 7.9 Hz, 4H), 7.19 (d, *J* = 8.0 Hz, 4H), 7.01 (d, *J* = 7.9 Hz, 4H), 3.49 (sextet, *J* = 6.9 Hz, 2H), 3.38 (sextet, *J* = 6.9 Hz, 2H), 2.36 – 2.28 (m, 7H), 2.23 (s, 6H), 1.89 (t, *J* = 7.1 Hz, 2H), 1.37 (dt, *J* = 13.9, 7.1 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 6H), 1.06 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.02, 203.48, 143.89, 143.67, 133.97, 133.73, 129.45, 129.23, 128.61, 128.31, 38.40, 37.96, 37.48, 37.17, 21.66, 21.55, 18.80, 17.66. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{21}H_{24}O_2+H]^+$: 309.1849, Found : 309.1844. FT-IR (ATR, neat): 2981, 1673, 1605, 1226, 1208, 1180, 970, 827, 746, cm^{-1}.

1,5-Bis(4-methoxyphenyl)-2,4-dimethylpentane-1,5-dione[14] : (Table 4.3, **18**)

Prepared from 1-(4-methoxyphenyl)prop-2-en-1-ol (0.082g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 85% (0.072g). Diastereomeric ratio**:** 1.1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.0 Hz, 4H), 7.71 (d, *J* = 6.8 Hz, 4H), 6.94 (d, *J* = 9.0 Hz, 4H), 6.73 (d, *J* = 6.6 Hz, 4H), 3.83 (s, 6H), 3.75 (s, 6H), 3.53 (sextet, *J* = 6.9 Hz, 2H), 3.40 (sextet, *J* = 7.0 Hz, 2H), 2.37 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.94 (t, *J* = 7.2 Hz, 2H), 1.41 (dt, *J* = 13.9, 7.1 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 6H), 1.12 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.00, 202.43, 163.52, 163.34, 130.76, 130.45, 129.49, 129.23, 113.89, 113.65, 55.47, 55.36, 38.05, 37.88, 37.76, 37.45, 18.91, 17.69. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{21}H_{24}O_4+Na]^+$:363.1567, Found : 363.1567. FT-IR

(ATR, neat): 1667, 1595, 1573, 1508, 1459, 1419, 1376, 1308, 1244, 1224, 1170, 1142, 1117, 1028, 972, 839, 761, 605 cm^{-1}.

2,4-Dimethyl-1,5-di(naphthalen-2-yl)pentane-1,5-dione : (Table 4.3, **19**)

Prepared from 1-(naphthalen-2-yl)prop-2-en-1-ol (0.092g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 69% (0.065g). Diastereomeric ratio: 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 2H), 8.14 (d, *J* = 8.6 Hz, 2H), 8.09 (s, 2H), 8.04 (d, *J* = 7.9 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H), 7.91 – 7.85 (m, 4H), 7.71 – 7.50 (m, 10H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 3.83 (sextet, *J* = 6.9 Hz, 2H), 3.68 (sextet, *J* = 7.0 Hz, 2H), 2.59 (dt, *J* = 14.1, 7.2 Hz, 1H), 2.13 (t, *J* = 7.2 Hz, 2H), 1.61 (dt, *J* = 14.1, 7.2 Hz, 1H), 1.31 – 1.25 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.70, 203.89, 135.75, 135.44, 133.85, 133.64, 132.79, 132.33, 130.28, 129.90, 129.45, 128.71, 128.62, 128.57, 128.36, 127.85, 127.50, 126.87, 126.55, 124.40, 123.90, 38.66, 38.45, 38.39, 37.49, 19.27, 17.95. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{27}H_{24}O_2+H]^+$:381.1849, Found : 381.1841. FT-IR (ATR, neat): 2966, 1672, 1626, 1547, 1529, 1369, 1277, 1178, 1121, 981, 939, 863, 823, 774, 759 cm^{-1}.

1,5-Bis(3,5-dimethoxyphenyl)-2,4-dimethylpentane-1,5-dione: (Table 4.3, **20**)

Prepared from 1-(3,5-dimethoxyphenyl)prop-2-en-1-ol (0.097g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 71% (0.071g). Diastereomeric ratio: 1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 4H), 6.87 (s, 4H), 6.66 (s, 2H), 6.52 (s, 2H), 3.87 (s, 12H), 3.73 (s, 12H), 3.52 (sextet, *J* = 6.9 Hz, 2H), 3.39 (sextet, *J* = 6.9 Hz, 2H), 2.42 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.96 (t, *J* = 7.2 Hz, 2H), 1.44 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.22 – 1.12 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.29, 203.47, 161.08, 160.89, 138.58, 138.29, 106.29, 105.92, 105.56, 105.39, 55.75, 55.51, 38.72, 38.51, 38.07, 37.47, 18.94, 17.77. HRMS (ESI-

TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{33}H_{32}O_2+Na]^+$: 423.1778, Found : 423.1763. FT-IR (ATR, neat): 1677, 1589, 1454, 1424, 1344, 1310, 1293, 1204, 1152, 1066, 1005, 925, 854, 820 cm^{-1}.

1,5-Bis(4-isobutylphenyl)-2,4-dimethylpentane-1,5-dione: (Table 4.3, **21**)

Prepared from 1-(4-isobutylphenyl)prop-2-en-1-ol (0.095g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 63% (0.062g). Diastereomeric ratio: 1:1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.8 Hz, 4H), 7.70 (d, *J* = 8.1 Hz, 4H), 7.27 (d, *J* = 7.5 Hz, 4H), 7.09 (d, *J* = 7.8 Hz, 4H), 3.60 (sextet, *J* = 7.0 Hz, 2H), 3.47 (sextet, *J* = 6.8 Hz, 2H), 2.54 (d, *J* = 7.3 Hz, 4H), 2.45 (d, *J* = 7.1 Hz, 4H), 2.43 – 2.38 (m, 1H), 1.99 (t, *J* = 7.2 Hz, 2H), 1.91 (dt, *J* = 13.4, 6.7 Hz, 2H), 1.83 (dt, *J* = 13.5, 6.7 Hz, 2H), 1.47 (dt, *J* = 13.9, 7.1 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 6H), 1.16 (d, *J* = 6.9 Hz, 6H), 0.92 (d, *J* = 6.6 Hz, 12H), 0.87 (d, *J* = 6.6 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.28, 203.74, 147.74, 147.57, 134.31, 134.10, 129.60, 129.54, 129.39, 128.58, 128.32, 45.53, 45.41, 38.54, 38.09, 37.61, 37.27, 30.25, 30.17, 22.52, 22.49, 22.45, 18.93, 17.79. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{27}H_{36}O_2+H]^+$: 393.2788, Found : 393.2773. FT-IR (ATR, neat): 2956, 1676, 1605, 1462, 1414, 1367, 1264, 1226, 1182, 974, 908, 855, 733 cm^{-1}.

1,5-Bis(4-(benzyloxy)phenyl)-2,4-dimethylpentane-1,5-dione: (Table 4.3, **22**)

Prepared from 1-(4-(benzyloxy)phenyl)prop-2-en-1-ol (0.120g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 61% (0.075g). Diastereomeric ratio: 1.1:1. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.3 Hz, 4H), 7.76 (d, *J* = 8.4 Hz, 4H), 7.45 – 7.40 (m, 8H), 7.38 (d, *J* = 5.4 Hz, 9H), 7.36 – 7.33 (m, 3H), 7.05 (d, *J* = 8.5 Hz, 4H), 6.86 (d, *J* = 8.5 Hz, 4H), 5.15 (s, 4H), 5.04 (s, 4H), 3.55 (sextet, *J* = 7.2 Hz, 2H), 3.44 (sextet, *J* = 6.8 Hz, 2H), 2.40 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.98 (t, *J* = 7.2 Hz, 2H), 1.45 (dt, *J* = 14.0, 7.2 Hz, 1H),

1.19 (d, *J* = 6.7 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.19, 202.62, 162.78, 162.65, 136.33, 136.20, 130.91, 130.63, 129.81, 129.53, 128.85, 128.82, 128.73, 128.38, 127.63, 127.60, 127.37, 114.84, 114.60, 70.26, 70.21, 38.22, 37.88, 37.49, 19.06, 17.80. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{33}H_{32}O_4+Na]^+$: 515.2193, Found : 515.2164. FT-IR (ATR, neat): 2930, 1670, 1597, 1453, 1420, 1378, 1305, 1244, 1224, 1222, 1172, 1124, 1024, 972, 839 cm^{-1}.

1,5-Di([1,1'-biphenyl]-4-yl)-2,4-dimethylpentane-1,5-dione[14]: (Table 4.3, **23**)

Prepared from 1-([1,1'-biphenyl]-4-yl)prop-2-en-1-ol (0.105g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 69% (0.074g). Diastereomeric ratio: 1.1:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.0 Hz, 4H), 7.84 (d, *J* = 8.0 Hz, 4H), 7.75 (d, *J* = 8.0 Hz, 4H), 7.66 (d, *J* = 7.7 Hz, 4H), 7.56 – 7.45 (m, 12H), 7.45 – 7.32 (m, 8H), 3.69 (sextet, *J* = 7.0 Hz, 2H), 3.56 (sextet, *J* = 7.0 Hz, 2H), 2.52 (dt, *J* = 14.0, 7.1 Hz, 1H), 2.07 (t, *J* = 7.2 Hz, 2H), 1.55 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.33 – 1.10 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.20, 203.49, 145.86, 145.69, 139.96, 139.72, 135.25, 134.95, 129.19, 129.10, 129.06, 129.02, 128.97, 128.93, 128.84, 128.32, 128.24, 127.49, 127.37, 127.26, 77.48, 77.16, 76.84, 38.52, 38.30, 38.07, 37.22, 19.00, 17.79. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{31}H_{28}O_2+H]^+$: 433.2162, Found : 433.2134. FT-IR (ATR, neat): 3205, 1672, 1603, 1494, 1080, 1029, 724, 692 cm^{-1}.

2,4-Dimethyl-1,5-di(thiophen-2-yl)pentane-1,5-dione[14] : (Table 4.3, **24**)

Prepared from 1-(thiophen-2-yl)prop-2-en-1-ol (0.07g, 0.5 mmol). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 65% (0.047g). Diastereomeric ratio: 1.13:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.8 Hz, 2H), 7.65 (d, *J* = 4.9 Hz, 2H), 7.53 (d, *J* = 4.9 Hz, 2H), 7.43 (d, *J* = 3.8 Hz, 2H), 7.16 (dd, *J* = 4.9, 3.8 Hz, 2H), 6.91 (dd, *J* = 5.0, 3.8 Hz, 2H), 3.42 (sextet, *J* = 7.0

Hz, 2H), 3.30 (sextet, *J* = 7.0 Hz, 2H), 2.43 (dt, *J* = 13.6, 7.2 Hz, 1H), 1.99 (t, *J* = 8.0 Hz, 2H), 1.51 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.22 (d, *J* = 3.9 Hz, 6H), 1.21 (d, *J* = 3.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.32, 196.77, 144.11, 143.89, 134.13, 132.43, 132.06, 128.51, 128.16, 40.54, 40.07, 37.86, 37.81, 19.31, 17.84. FT-IR (ATR, neat): 2992, 1650, 1593, 1412, 1237, 1220, 1056, 845, 720 cm^{-1}.

2,4-Dibenzyl-1,5-diphenylpentane-1,5-dione-2,3,3,4-d4 : (Scheme 4.3, **29**)

Prepared from (E)-1,3-diphenylprop-2-en-1-ol (0.105g, 05 mmol) and CD_3OD (1 mL). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 48% (0.051g,(based on the molecular weight of the corresponding protonated compound). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.7 Hz, 4H), 7.53 (d, *J* = 8.1 Hz, 5H), 7.44 (t, *J* = 7.7 Hz, 5H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.23 – 7.03 (m, 20H), 6.97 (d, *J* = 7.3 Hz, 4H), 3.73 (dt, *J* = 29.1, 7.0 Hz, 1H), 3.01 (t, *J* = 13.3 Hz, 3H), 2.66 (dd, *J* = 29.1, 13.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.97, 203.24, 139.35, 138.94, 137.31, 136.93, 133.26, 132.94, 129.11, 129.02, 129.00, 128.81, 128.68, 128.57, 128.53, 128.50, 128.46, 128.40, 128.10, 126.48, 126.42, 45.91, 45.63, 39.84, 39.76, 38.41, 38.33.FT-IR (ATR, neat): 2921, 1675, 1596, 1487, 1446, 1267, 1219, 697.HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{31}H_{24}D_4O_2+H]^+$: 437.2413, Found : 437.2428.

1,3-Diphenylpropan-1-one-2-d: (Scheme 4.3, **30**)

Prepared from (E)-1,3-diphenylprop-2-en-1-ol(0.105g, 05 mmol) and CD_3OD (1 mL). After purification by column chromatography an inseparable mixture of two diastereomers was isolated in 43% (0.045g) (based on the molecular weight of the corresponding protonated compound). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.8 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.17 (m, 4H), 7.15 (t, *J* = 7.3 Hz, 1H), 3.23 (p, *J* = 7.1, 6.4 Hz, 1H), 3.01 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (101

MHz, $CDCl_3$) δ 199.41, 141.40, 136.98, 133.19, 129.20, 128.73, 128.65, 128.55, 128.50, 128.17, 126.26, 40.57, 40.41, 40.22, 40.03, 30.21. FT-IR (ATR, neat): 2997, 1681, 1447, 1268, 743, 690. HRMS (ESI-TOF) *m/z* $[M]^+$ Calcd for $[C_{15}H_{12}D_2O]^+$: 212.1165, Found : 212.1181.

3,5-Dimethyl-2,6-diphenylpyridine[14]: (Scheme 4.5, **31**)**:** Prepared from 1-phenylprop-2-en-1-ol (0.067g, 0.5 mmol). After purification by column chromatography the compound was isolated in 74% yield (0.047g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 4H), 7.50 – 7.47 (m, 1H), 7.47 – 7.40 (m, 4H), 7.39 – 7.34 (m, 2H), 2.39 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.89, 141.26, 140.80, 129.34, 129.24, 128.18, 127.78, 19.75. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{19}H_{17}N+H]^+$:260.1434, Found : 260.1450.

2,6-Bis(4-methoxyphenyl)-3,5-dimethylpyridine[18]: (Scheme 4.5, **32**)

Prepared from 1-(4-methoxyphenyl)prop-2-en-1-ol (0.082g, 0.5 mmol). After purification by column chromatography the compound was isolated in 69% (0.055g,) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.6 Hz, 4H), 7.44 (s, 1H), 6.97 (d, *J* = 8.8 Hz, 4H), 3.85 (s, 6H), 2.41 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.28, 155.37, 141.32, 133.43, 130.59, 128.63, 113.52, 55.41, 19.86. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{21}H_{21}NO_2+H]^+$:320.1645, Found : 320.1667.

3,5-Dibenzyl-2,6-diphenylpyridine: (Scheme 4.5, **33**)

Prepared from (E)-1,3-diphenylprop-2-en-1-ol (0.105g, 05 mmol). After purification by column chromatography the compound was isolated in 67% (0.068g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 4H), 7.39 – 7.31 (m, 7H), 7.25 – 7.12 (m, 6H), 6.97 (d, *J* = 7.6 Hz, 4H), 4.01 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.77, 141.10, 140.57, 140.35, 132.43, 129.35, 128.84, 128.57, 128.22, 128.17, 127.98, 126.24, 38.26. HRMS (ESI-TOF) *m/z* $[M+nH]^+$ Calcd for $[C_{31}H_{25}N+H]^+$: 412.2060, Found : 412.2081.

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Chapter 5

Synthesis and characterization of polystyrene supported pyrazole based palladium catalysts and their application in acceptorless dehydrogenative coupling of secondary alcohols

5.1. Introduction

Ever since the advent of the cross-coupling reactions such as Heck, Suzuki, Sonagashira and Buchwald-Hartwig reactions and their potential application in the synthesis of important natutal and medicinal compounds,[1] homogeneous palladium catalysts have gained enormous importance. As the catalyst's efficiency can be improved by tuning ligands such as phosphenes and carbenes etc, palladim catalysts are even more relevant in current times. However, homogeneous catalysts suffer from 1) lack of reusability of the catalyst, 2) separation of the metal from products and 3) use of organic solvents in most cases as the medium which are expensive, toxic, flammable and (or) volatile. Furthermore, the ligands used in the homogeneous catalysis are often expensive, toxic and are highly sensitive to air and moisture. These drawbacks make homogeneous catalysis undesirable from an industrial and economic perspective despite of its high selectivity and activity.

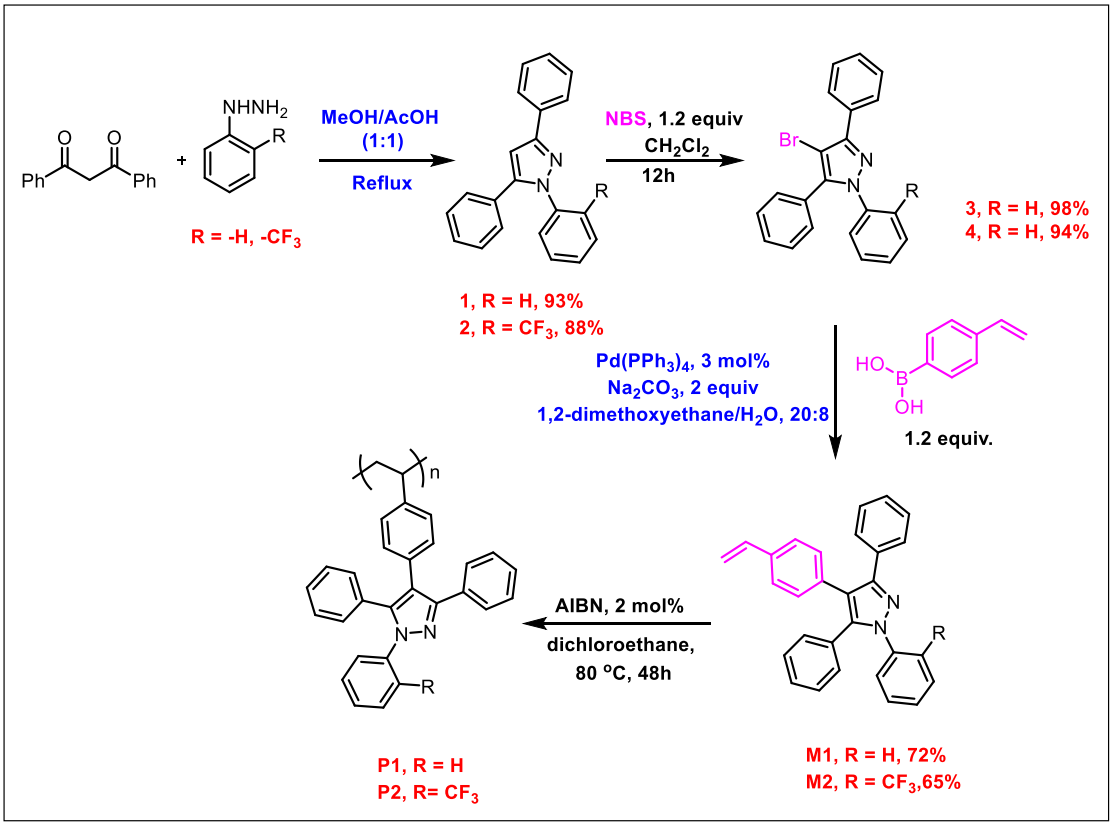
The drawbacks mentioned above can be averted by immobilizing an already active homogeneous catalyst to a solid support such as polymer[3] and other supports. The method of anchoring catalyst makes the separation simpler and offers reusability of the expensive metal catalyst. Among the several supports, polymer anchored palladium catalyst, specially polystyrene[3b] based palladium catalyst are studied to a greater extent. Polystyrene (PS) anchored palladium catalysts are borderline catalyst which offers the advantages of reusability and simpler purification of the heterogeneous system while retaining selectivity of the homogeneous system. However, in many instances upon longer stirring with organic solvents, polystyrene supported palladium have shown leaching of metal. This problem can be avoided with the use of environment friendly, low cost, non-flammable and non-toxic solvent such as water.

PS-supported palladium catalysts have been used in various cross-coupling reactions. Wang[4] and co-workers reported PS-supported palladium catalysed cross-coupling of sodium tetraphenylborane with aryl bromides in water under microwave irradiation condition. The catalyst was reused 10 times without any loss of activity and metal content. Lee's[5] group reported carbene functionalised macroporous PS-supported catalyst for the Suzuki coupling of deactivated arylhalides with the catalyst recyclability of 5 cycles without any decrease in its activity. Bakherad[6] *et al.* used thio-semi carbazole functionalised PS-resin supported palladium for Heck and Suzuki reaction. Excellent catalytic activity was shown upto 4-cycles. Using PS-supported palladium, Das and co-workers[7] have reported multicomponent synthesis of various heterocycles. Although palladacycle based homogeneous catalysis were studied to a greater extent, immobilization of palladacycle on polystyrene was less explored and also studied specially for cross-coupling ractions *viz* Suzuki, Sonagashira and Heck reactions. However, Malinakova's group[9] utilized PS-supported palladacycle for the synthesis of benzopyrans with excellent activity and palladium recovery. We have developed pyrazole based palladacycles and used them effectively in Suzuki and Heck cross-coupling[10], C-C[11] and C-N[12] bond forming reactions *via* borrowing hydrogen methodology. Herein, we report the synthesis and catalytic activity of three new polystyrene supported pyrazole based palladacycles. These catalysts were used in the synthesis of quinoline and α-alkylated ketones from secondary alcohols using double dehydrogenative approach in water. The catalytic recyclability was also studied.

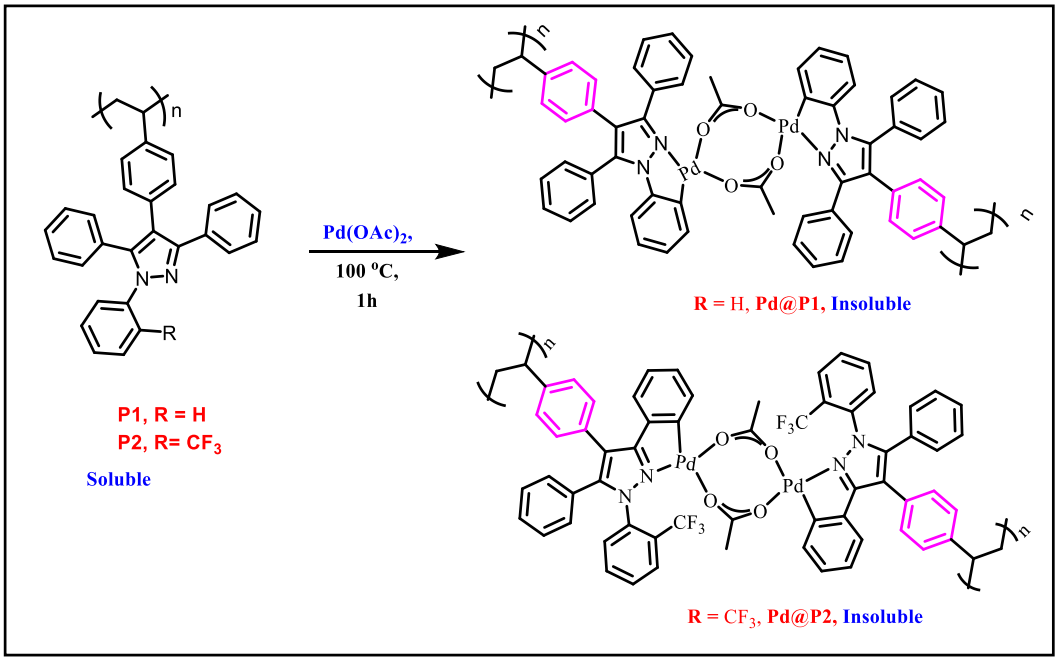
5.2. Results and Discussion

The monomer **M1** and **M2** were prepared following the literature reported procedure[15]. 1,3-Diketone was reacted with phenyl hydrazine in methanol and acetic acid to produce the triaryl pyrazole. The triaryl pyrazole product was brominated using N-

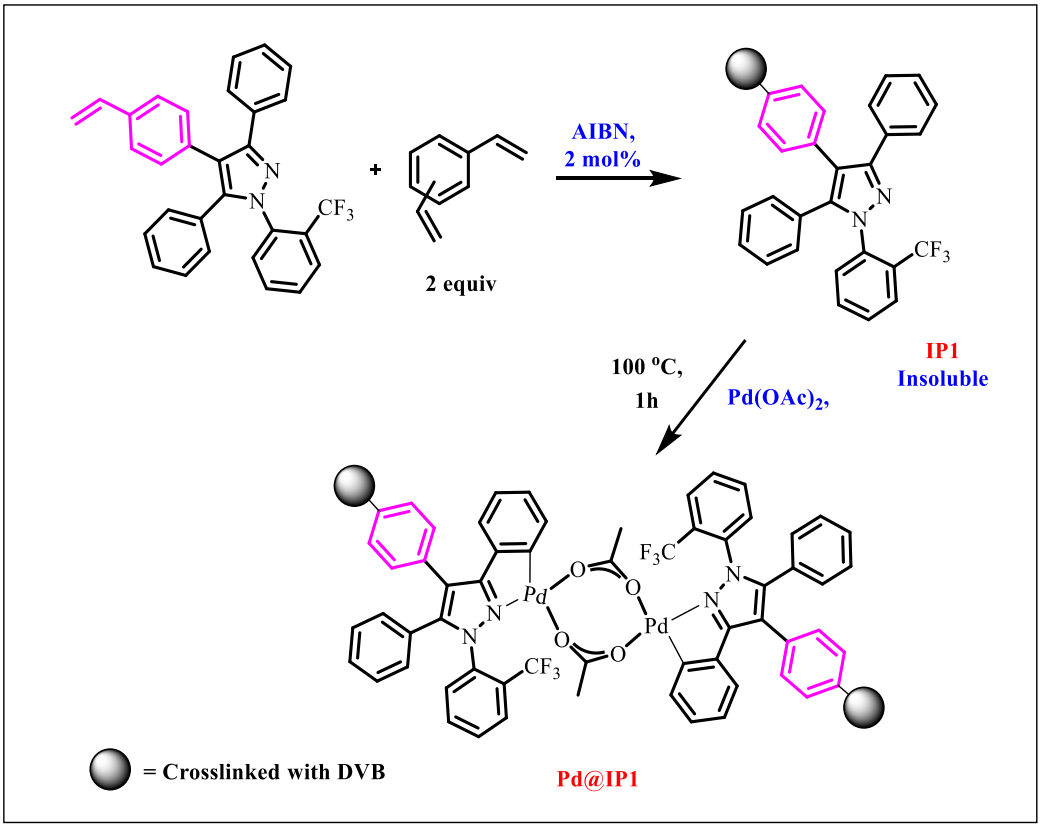
bromosuccinimide. The bromopyrazole product thus formed was made to react with 4-vinylphenyl boronic acid under Suzuki reaction condition to afford the styryl pyrazole monomers **M1** and **M2**. The monomers were then subjected to free radical polymerisation using AIBN in DCE at 80 ^{o}C to produce polymer **P1** and **P2** (Scheme 1). From gel permeation chromatography (GPC) analysis (with respect to polystyrene standards), the number average (M_n) and weight average (M_w) molecular weight of the polymer **P1** was found out to be 23500 Dalton and 55600 Dalton respectively, with poly dispersity index (PDI = M_w/M_n) of 2.3. Similarly, for the polymer **P2** the M_n and M_w are 62300 Dalton and 116369 Dalton and the PDI is 1.8. Insoluble resin **IP1** was prepared by reacting monomer **M2** with divinylbenzene in 1:2 ratio under free radical polymerisation condition using AIBN in DCE at 80 ^{o}C. The polymer **P1**, **P2** and **IP1** were subjected to palladation in acetic acid at 100 ^{o}C for 1 hour using palladium acetate



Scheme 5.1. Synthesis of soluble polymer P1 and P2



Scheme 5.2. Synthesis of catalyst Pd@P1 and Pd@P2



Scheme 5.3. Synthesis of insoluble resin IP1 and catalyst Pd@IP1

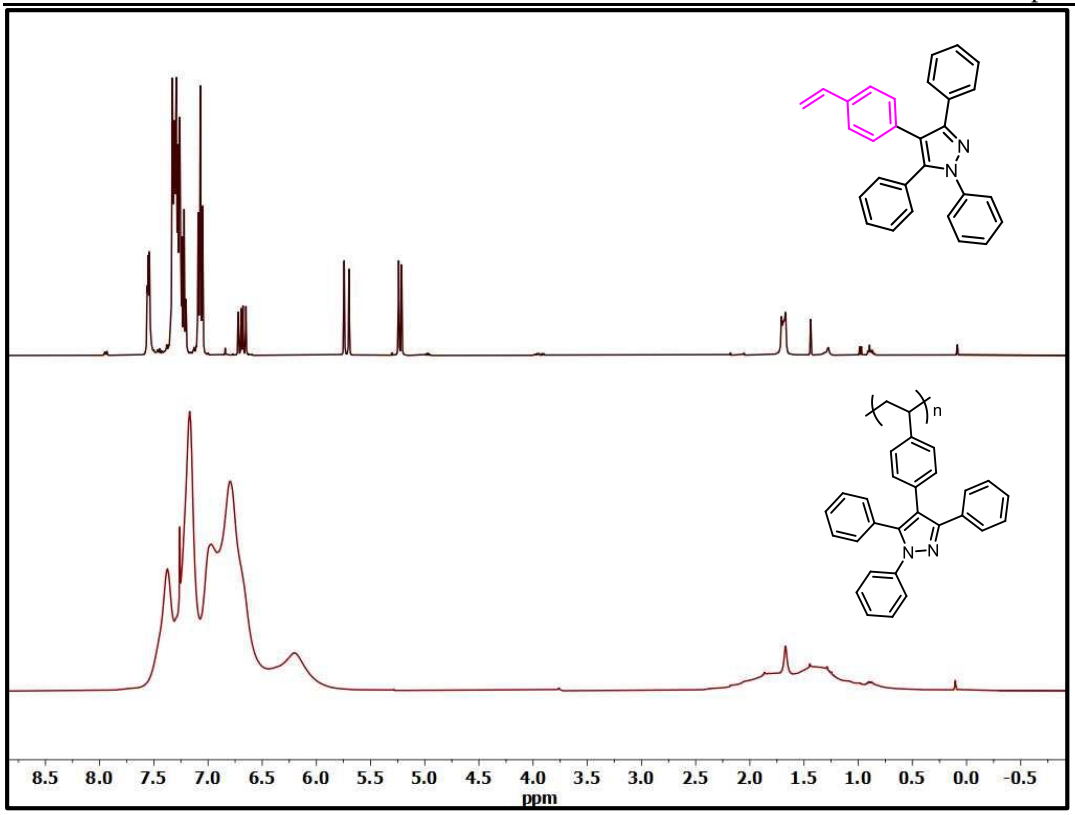


Figure 5.1. Stacking of ^{1}H NMR of M1 and P1

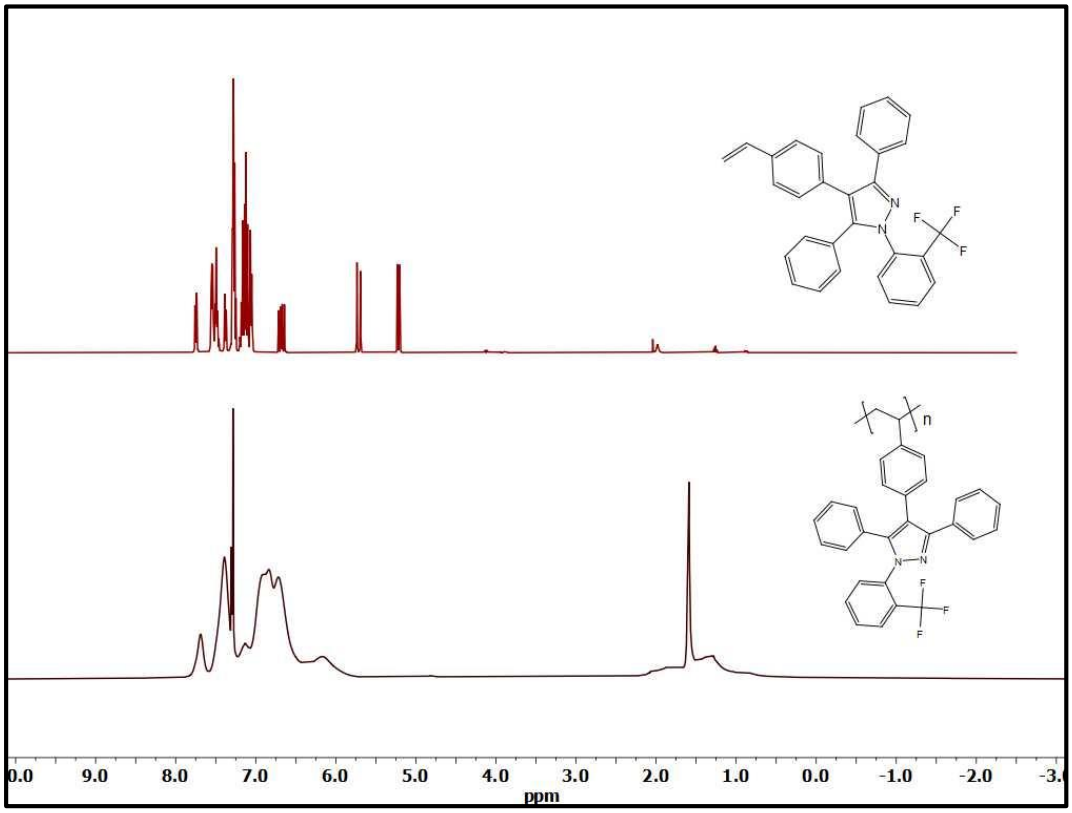


Figure 5.2. Stacking of ^{1}H NMR of M2 and P2

Table 5.1. Elemental analysis of catalysts by ICP-AES

Catalyst	Pd loading(mmolg^{-1})
Pd@P1	1.12
Pd@P2	1.6
Pd@IP1	0.972

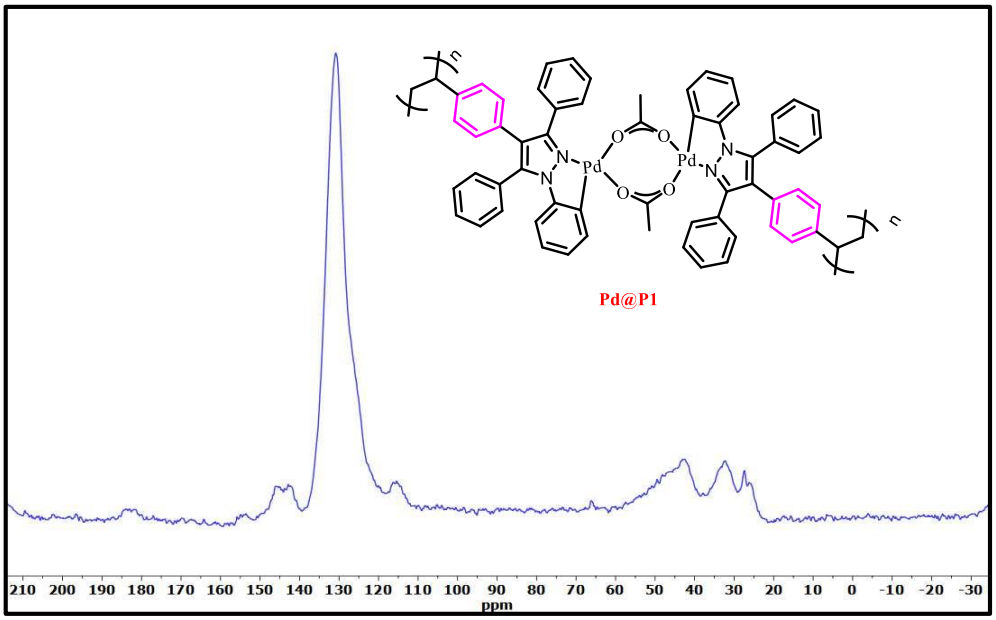


Figure 5.3. ^{13}C CP/TOSS NMR of Pd@P1

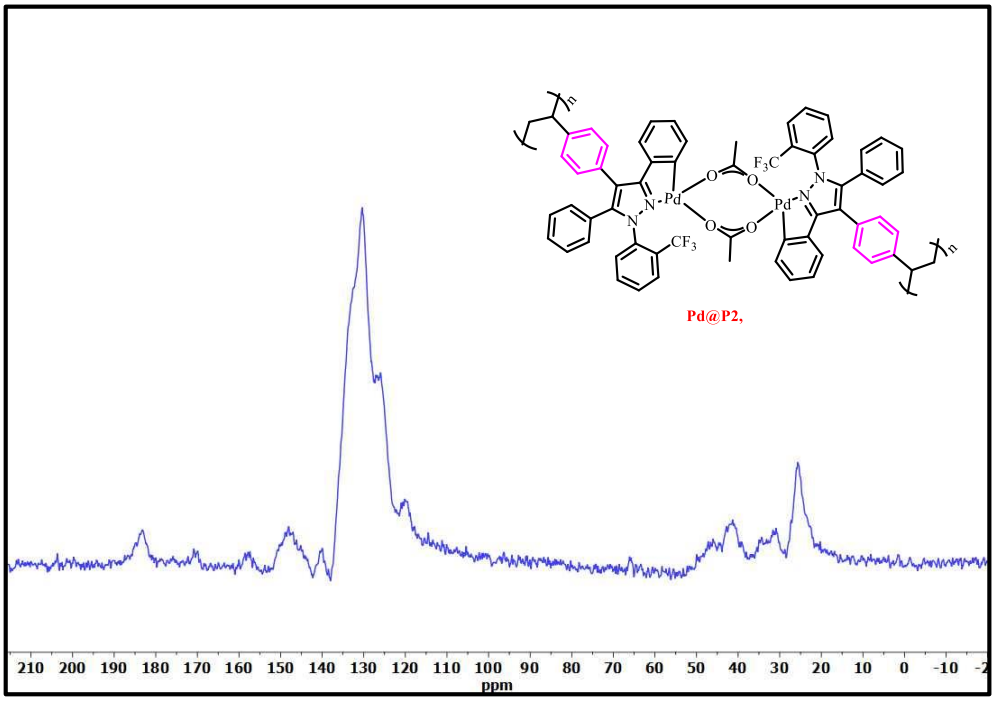


Figure 5.4. ^{13}C CP/TOSS NMR of Pd@P2

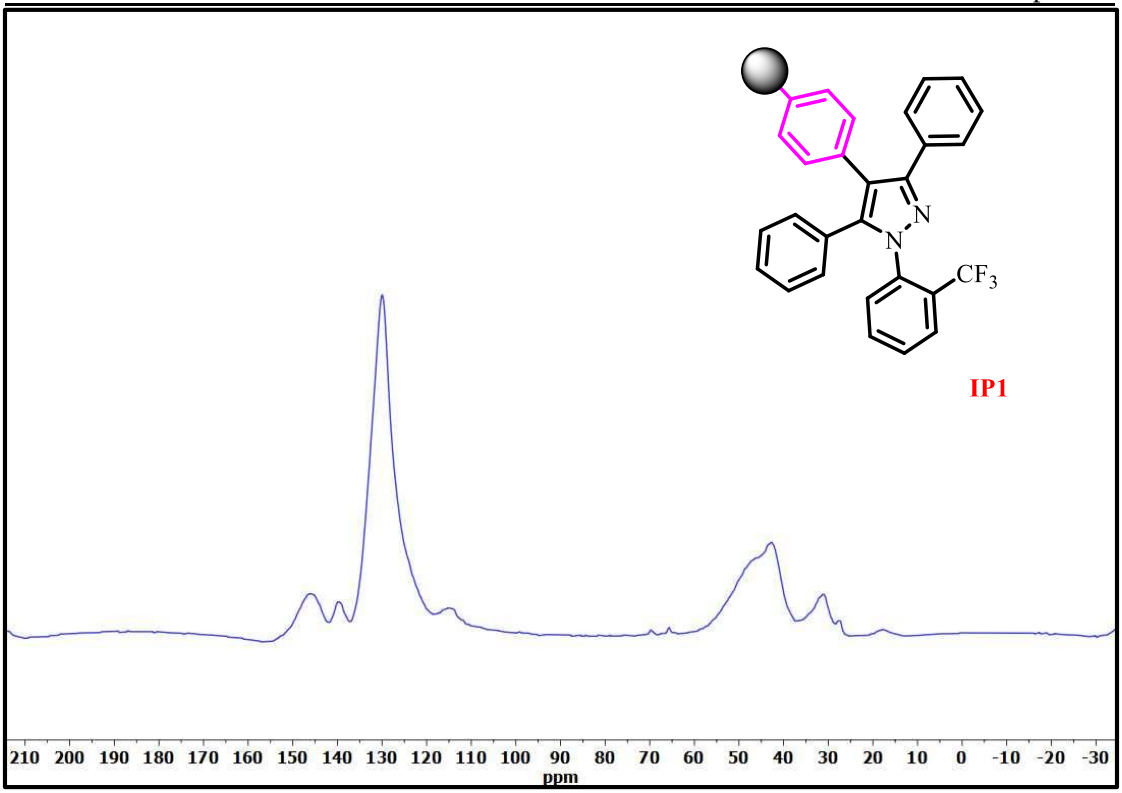


Figure 5.5. ^{13}C CP/TOSS NMR of IP1

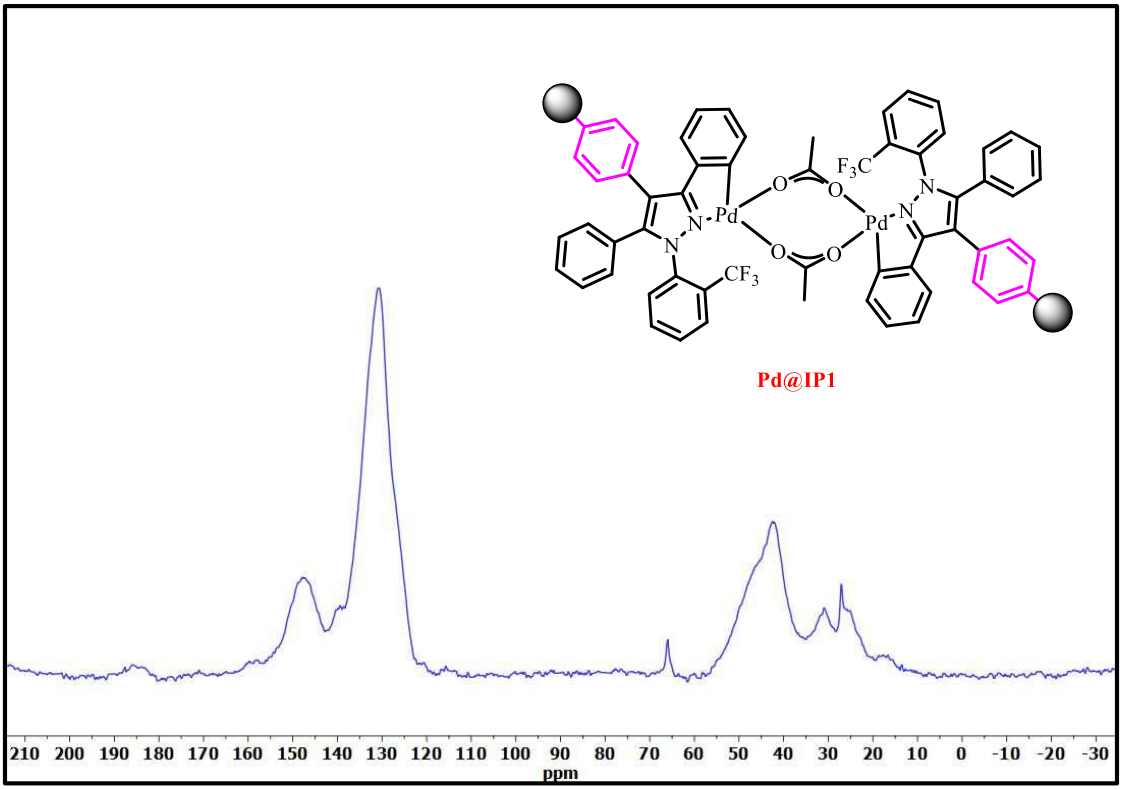


Figure 5.6. ^{13}C CP/TOSS NMR of Pd@IP1

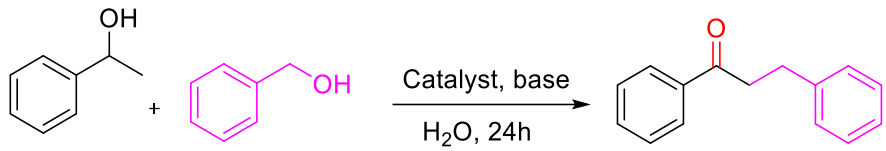
resulting in catalyst **Pd@P1**, **Pd@P2** and **Pd@IP1**. Summary of the elemenatal analysis of the catalysts prepared are presented in table **5.1**. These catalysts were further

characterised using solid state NMR CPTOSS.

Having synthesised and characterised the catalysts, their catalytic efficiency for C-C and C-N bond formation were studied. There have been numerous reports[13] for the synthesis of α-alkylated ketone starting from ketones and primary alcohols. Recently, more abundant secondary alcohols are being used for the β-alkylation of secondary alcohol leading to α-alkylated ketones[14]. However, most of the reports are based on ruthenium and iridium based catalyst and are heavily relied on the use of phosphine based ligands and thereby making the reaction to be carried out under anaerobic condition. Moreover, the application of noble metal catalyst in solvent free or in aqueous condition is very limited and there have been fewer reports for the same. We recently reported the solvent free synthesis of α-alkylation of ketone using pyrazole based palladacycle[11]. Herein, we report the β-alkylation of secondary alcohol with primary alcohol in water using a recyclable catalytic system. 1-Phenylethanol and benzyl alcohol were chosen as the model secondary and primary alcohol. Initial screening of the three PS-supported catalysts (table 5.2, entry 1-3) revealed that the activity follows Pd@IP1 > Pd@P2 > Pd@P2, which can be attributed to the available spaces between two pyrazole unit created by cross polymerization with divinylbenzene. Among the different bases screened, KO^{t}Bu resulted in 59% yield at 100 ^{o}C (table 5.2, entry 4-7). Further elevation in temperature to 120 ^{o}C caused an increase in reaction yield to 76% (Table 5.2, entry 8). Finally, by using 2 mL of water as the solvent resulted 92% of α-alkylated ketone (Table 5.2, entry 9). Decrease of metal loading or base loading resulted in substantial decrease in the product yield (Table 5.2, entry 10 and 11). The reaction does not proceed without the catalyst (Table 5.2, entry 12).

With the optimised conditions in hand, the scope and limitation of this protocol was screened. Electron donating as well as electron withdrawing groups were well tolerated

Table 5.2. Optimisation for the β-alkylation of 2º-alcohol



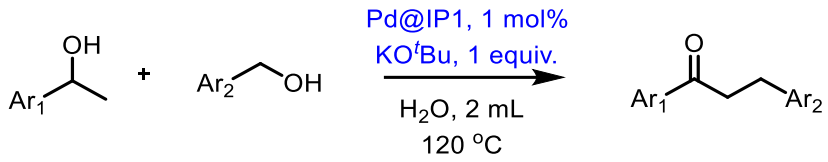
Sl no	Catalyst (mol%)	Base (equiv.)	Temp.(ºC)	Yield
1	**Pd@P1(1)**	NaOH(1)	100	28
2	**Pd@P2(1)**	NaOH(1)	100	32
3	**Pd@IP1(1)**	NaOH(1)	100	43
4	**Pd@IP1(1)**	KOH(1)	100	41
5	**Pd@IP1(1)**	LiO^{t}Bu(1)	100	38
6	**Pd@IP1(1)**	NaO^{t}Bu(1)	100	48
7	**Pd@IP1(1)**	KO^{t}Bu(1)	100	59
8	**Pd@IP1(1)**	KO^{t}Bu(1)	120	76
9[a]	**Pd@IP1(1)**	**KO^{t}Bu(1)**	**120**	**92**
10[a]	**Pd@IP1(0.5)**	KO^{t}Bu(1)	120	82
11[a]	**Pd@IP1(1)**	KO^{t}Bu(0.5)	120	77
12	--	KO^{t}Bu(1)	120	ND

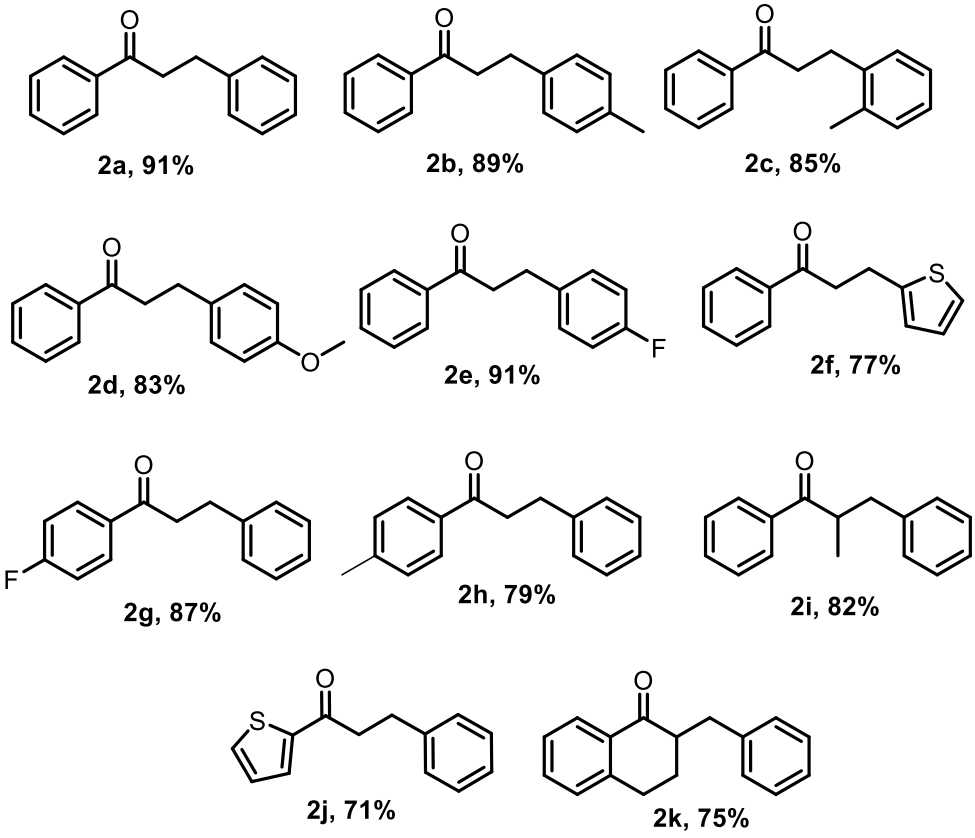
Reaction details: Benzyl alcohol 0.5 mmol, 1-phenyl ethanol 0.75 mmol, Catalyst 1 mol% of Pd,1 mL of H_2O [a] 2 mL H_2O used as solvent

and resulted in good yields. Substitution in primary alcohol by methyl (*o*, *p*), methoxy and fluoro group afforded the α-alkylated product in good to excellent yield (Table 5.3, 2b-2e). Heteroaryl primary alcohol such as 2-thiophenemethanol afforded the product in 77% yield (Table 5.3, 2f). Varying the secondary alcohol also had little impact on the reactivity of this protocol. 4-Fluoro-α-methylbenzyl alcohol produced the ketone

product in 87% yield (Table 5.3, 2g). Increase of aliphatic chain in the secondary alcohol did not impact the reactivity as 1-phenyl-1-propanol afforded the coupled ketone product in good yield (Table 5.3, 2i). Cyclic system such as 1,2,3,4-tetrahydronaphthalen-1-ol afforded the corresponding α-alkylated product in 75% yield (Table 5.3, 2k). This protocol has good tolerance towards heteroaryl substituted

Table 5.3. Substrate screening for the synthesis of α-alkylated ketone from alcohols

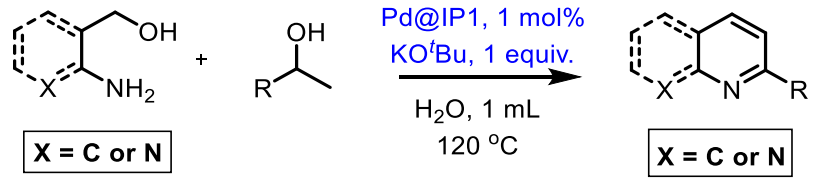


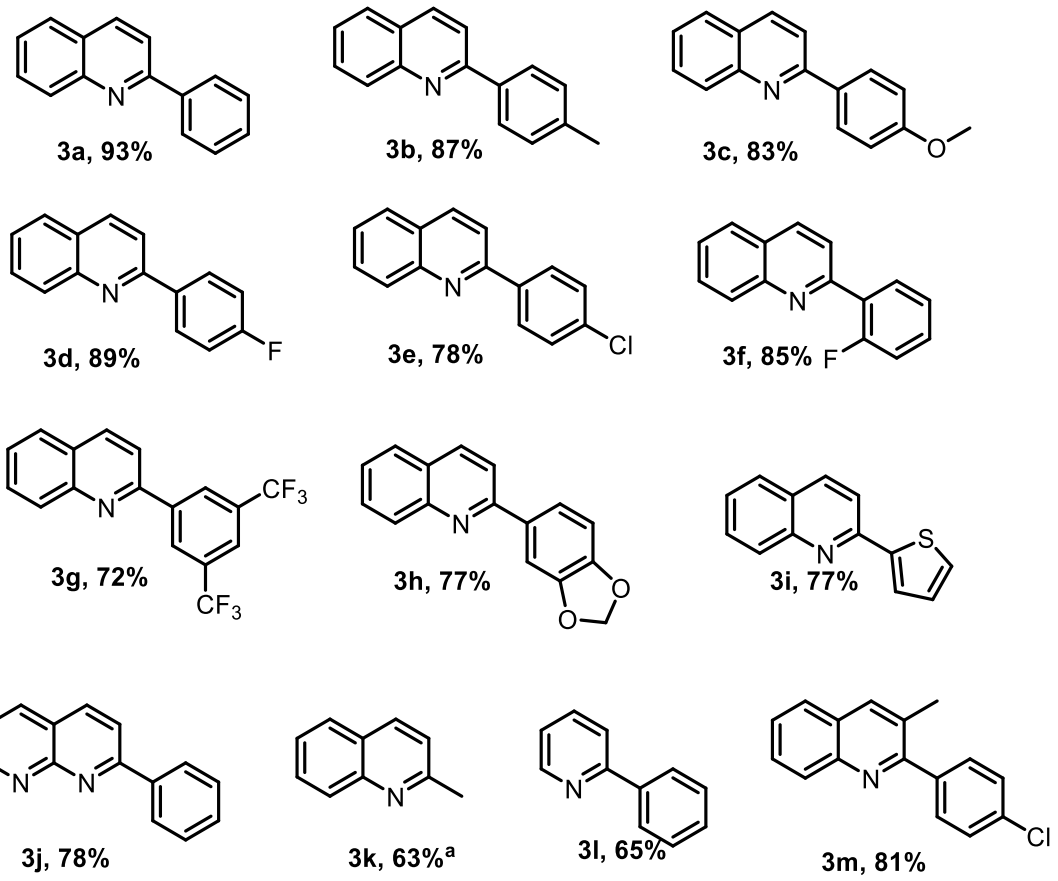


Reaction details: benzyl alcohol - 0.5 mmol, 1-phenylethanol - 0.75 mmol, KO^{t}Bu - 0.5mmol, Pd@IP1 - 1 mol%, water - 2 mL

secondary alcohol such as 1-(thiophen-2-yl)ethan-1-ol which resulted in 71% yield of the product (Table 5.3, 2j).

Table 5.4. Substrate screening for the synthesis of quinoline

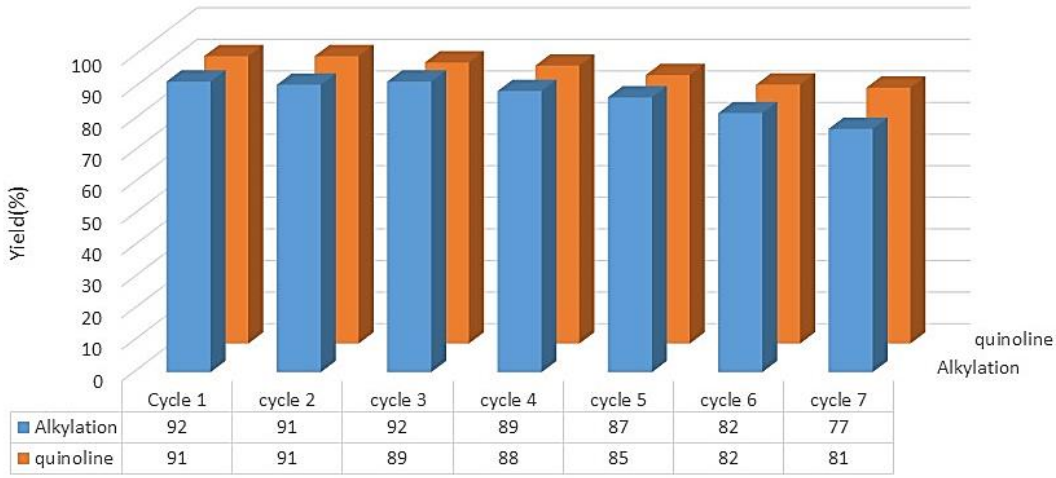




Reaction details: 2-aminobenzyl alcohol - 0.5 mmol, 1-phenylethanol - 0.75 mmol, KO^{t}Bu - 0.5mmol, Pd@IP1 - 1 mol%, water - 1 mL. [a] 0.5 mL of 2-propanol used

With this success, next we focused our attention for the synthesis of quinoline using the optimized conditions and catalyst mentioned above. 2-Aminobenzyl alcohol is made to react with 1.5 equivalent of 1-phenylethanol in aqueous condition (1 mL H_2O) and afforded the quinoline product in 93% yield. Substitutions such as $–CH_3$ and $–OCH_3$ on the aryl group of secondary alcohol afforded an excellent yield of the quinoline product (Table 5.4, 3b and 3c). In general, halo substituted compounds elevated temperature undergoes dehalogenation and thereby makes the compounds intolerable in any

protocol involving palladium catalyst. It is worth mentioning that due to the use of aqueous medium in this reaction, fluoro and chloro substituted secondary alcohols were well tolerated and afforded the product in 72-89% isolated yields (Table 5.4, 3d-3g and 3m). 1-Thiophenylethanol afforded the quinoline product in 77% isolated yield (Table 5.4, 3i). 1,8-Naphthyridine was also prepared using this protocol in 78% yield (Table 5.4, 3j). Using an excess amount of isopropanol (0.5 mL), we were able to synthesize 2-methylquinoline in 63% yield (Table 5.4, 3k). 3-Amino-1-propanol was converted to 2-phenyl pyridine in 65% yield (Table 5.4, 3l).



	Cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6	cycle 7
Alkylation	92	91	92	89	87	82	77
quinoline	91	91	89	88	85	82	81

Figure 5.7. Recycling experiment.

To check the reusability of the catalyst, we performed recycling experiments for both alkylation and quinoline synthesis. After the first run, the catalyst was filtered using frit apparatus and was washed with water, methanol and acetone three times each prior to the second run. This process was reiterated till 7 cycles. The catalyst shown excellent activity in both the reaction till the fourth run where the yield ranges from 93-89% in case of α-alkylation and 91-88% in case of quinoline synthesis (figure 5.7). After the fourth run, decrease in the reaction yields were observed in both the cases which eventually dropped down to 77% and 81% in case of alkylation reaction and quinoline

Synthesis respectively. ICP-OES analysis were carried out after the seventh cycle for each reaction. As can be seen in table 5.5 , palladium leaching was higher in case of catalyst recovered after the alkylation reaction as compared to that of quinoline synthesis.

Table 5.5. Palladium loading before and after reactions

Pd loading(mmolg-^{1}) (Fresh catalyst)	**Pd loading(mmolg-^{1}) After alkylation (7^{th} cycle)**	**Pd loading(mmolg-^{1}) After quinoline (7^{th} cycle)**
0.972	0.834	0.85

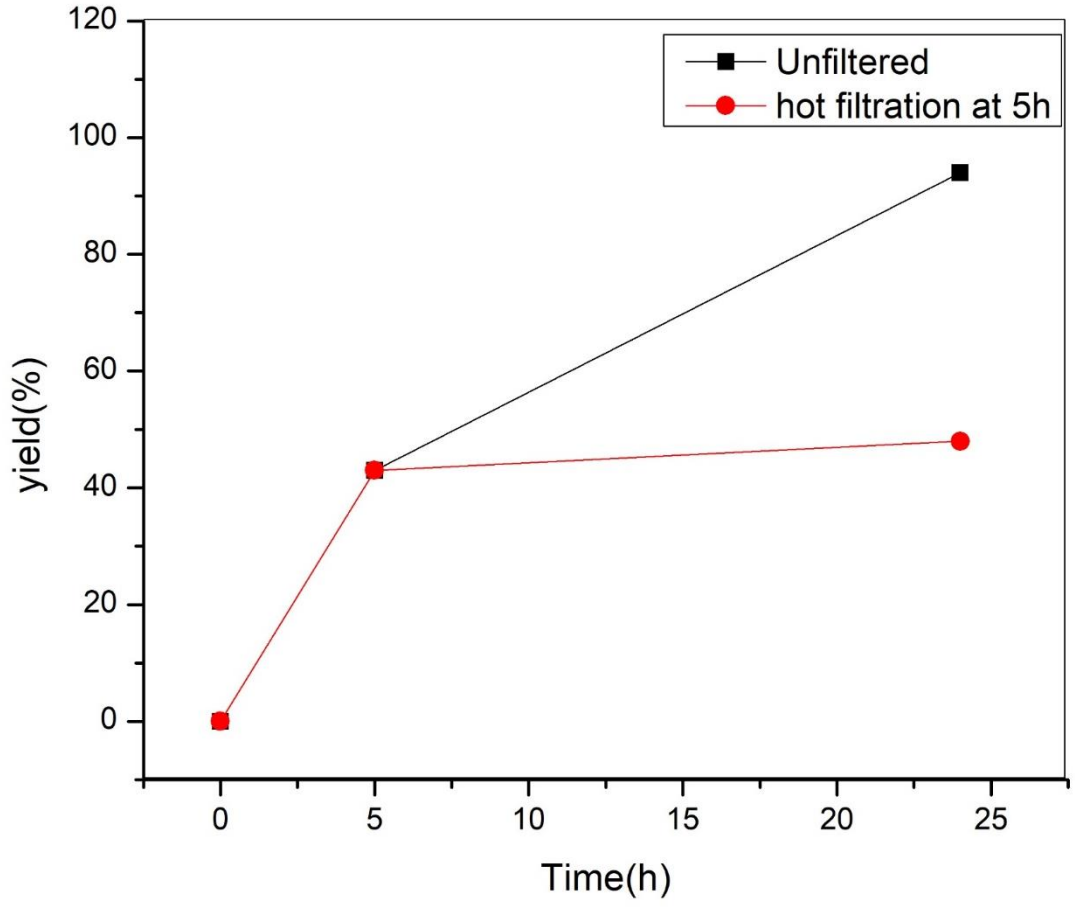


Figure 5.8. Hot filtration test

The heterogeneous nature of the catalyst was tested by hot filtration test. Two reactions

were run. In the first reaction, alkylation of alcohol was tested under the optimized condition. In the second reaction, after 5 hour of the reaction at hot condition, the reaction mixture was filtered and the filtrate was heated continuously for 19 hour after adding the required base. The first reaction gave a 93% of the product yield where as in the second reaction, after 5 hour 43% of product was observed which remained same after 24h (figure 5.8). After filtration there was no noticeable change to the reaction confirming the fact that the reaction does not occur through dissolved palladium and thus implies the heterogeneous nature of the catalyst.

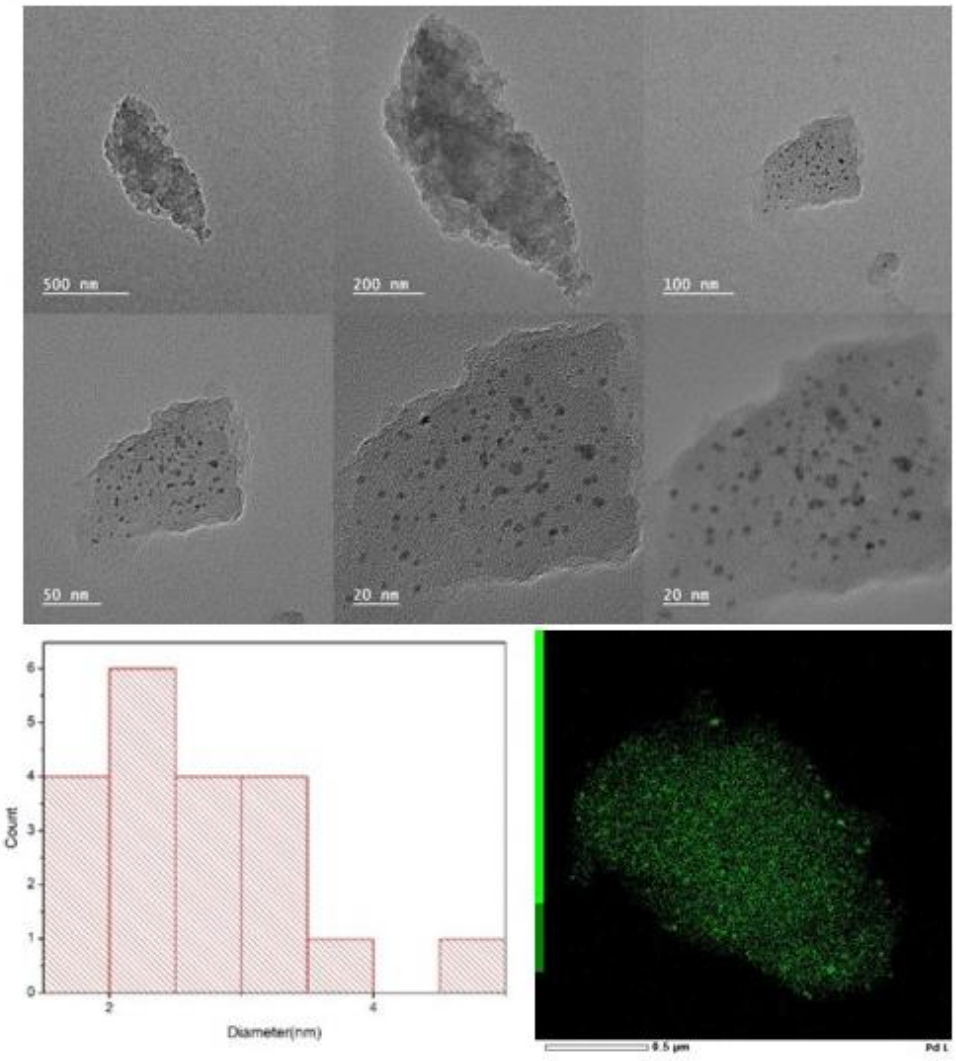


Figure 5.9. TEM images of fresh Pd@IP1 (top), particle size distribution (bottom left) and EDS mapping for palladium (bottom right)

The fresh and used catalysts were further characterised by TEM technique. As can be seen in figure 5.9- 5.11, average particle size of the fresh catalyst was in the range of 2-3 nm. After the seventh run of the alkylation reaction and quinoline synthesis, the average size of the particle was in the range of 4.5-5 nm and 3-4 nm respectively. These results suggested that the morphology of the palladium particles do not change during the course of the reaction. EDS spectrum further confirms the presence of palladium before and after use.

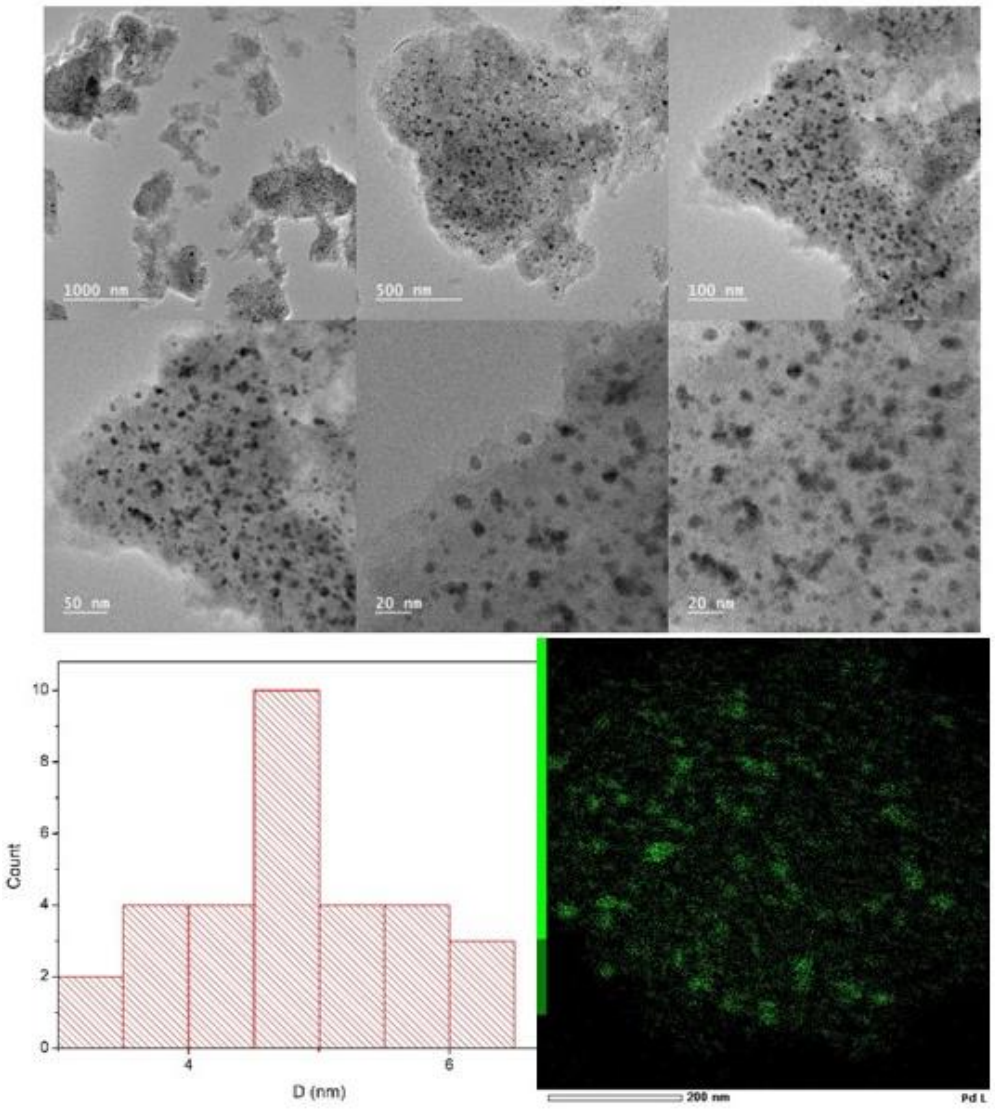


Figure 5.10. TEM images of Pd@IP1 after 7th cycle of alkylation (top), particle size distribution (bottom left) and EDS mapping for palladium (bottom right)

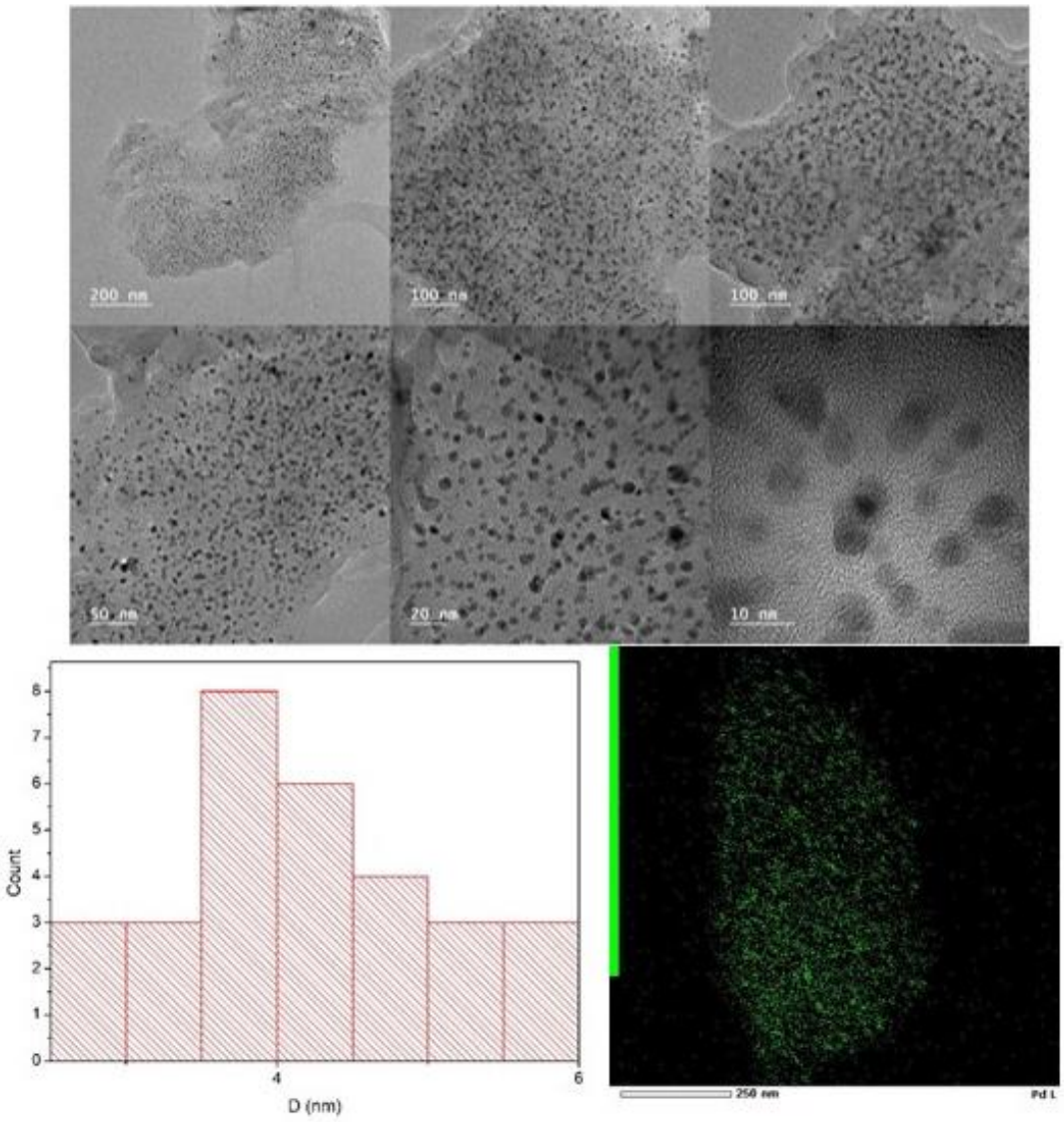


Figure 5.11. TEM images of Pd@IP1 after 7th cycle of quinoline synthesis (top), particle size distribution (bottom left) and EDS mapping for palladium (bottom right)

5.3. Conclusion

In conclusion, we have designed and synthesised three polystyrene supported palladium catalysts. Among the three studied, the catalyst **Pd@IP1** showed better activity. The catalysts were characterised using ^{13}C CPTOSS NMR, TEM and ICP techniques. Effective use of the catalyst in dehydrogenative cross coupling of secondary

alcohols were shown using different substrates. The recycling experiment reveal that the catalyst is stable under the experimental conditions with slight decrease in yield which is due to the metal leaching.

5.4. Experimental section

5.4.1. General information

Reagents and starting materials were purchased from Alfa-Aesar, Sigma-Aldrich and Spectrochem chemical companies and used as received unless otherwise noted. Chlorinated solvents were distilled from CaH_2. THF was distilled from Na/benzophenone prior to use. 1,3,5-Triphenyl-1H-pyrazole and 3,5-diphenyl-1-(2-(trifluoromethyl)phenyl)-1H-pyrazole were prepared according to literature procedure[15]. All 400 MHz ^{1}H and 100 MHz ^{13}C NMR, 377 MHz ^{19}F spectra and 81 MHz ^{31}P spectra were recorded on a Bruker ARX 400 spectrometer operating at 400 MHz and referenced internally to solvent signals. ^{19}F NMR spectra were externally referenced to α,α,α- trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). ^{31}P NMR spectra were externally referenced to H_3PO_4 in D_2O (δ = 0). High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF-QII mass spectrometer. Gelpermeation chromatography (GPC) analyses were performed on a Shimadzu- LC20AD system referenced to poly(styrene) standards. THF was used as the mobile

phase with a flow rate of 1.0 mL min^{-1}. Morphological study and elemental mapping analysis of the samples were performed using a transmission electron microscope (equipped with HRTEM, JEOL 2100F, operated at 200 kV). Particle size was measured using ImageJ software. The elemental composition of the synthesized catalysts were verified by using an inductively coupled plasma-optical emission spectrophotometer (iCAP 7000 ICP-OES).

5.4.2. Synthetic procedure for tetra aryl pyrazole M1: Monomer **M1** was prepared by following the literature reported method.[15] The quantities involved are as follows. Bromopyrazole **3** (1.00 g, 2.67 mmol), $Pd(PPh_3)_4$ (0.09 g,0.08 mmol) Na_2CO_3 (0.56 g, 5.34 mmol) and 4-vinylbenzeneboronic acid (0.47 g, 3.20 mmol) were taken in a 100 mL two neck round bottom flask. The whole set up was evacuated and nitrogen was purged into it. A degassed dimethoxyethane and water in 20:8 was added to it and was refluxed for 24 hour. Aqueous layer was separated and the organic layer was collected using dichloromethane (3 x 20 mL). The organic phase was dried with Na_2SO_4 and concentrated under vacuum. After purification by column chromatography, the compound was isolated as white solid (0.76 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.32 – 7.26 (m, 7H), 7.25 – 7.21 (m, 4H), 7.21 – 7.16 (m, 2H), 7.04 (t, *J* = 8.0 Hz, 4H), 6.65 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.69 (d, *J* = 17.6 Hz, 1H), 5.19 (d, *J* = 10.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.37, 141.54, 140.01, 136.75, 135.86, 133.19, 132.76, 130.90, 130.59, 130.17, 128.91, 128.62, 128.47, 128.37, 127.84, 127.41, 126.24, 125.49, 120.45, 113.67.

5.4.2.1. Synthetic procedure for tetra aryl pyrazole M2: Monomer **M2** was prepared using the procedure used for the preparation of . The quantities involved are as follows: Bromopyrazole **4** (1.5 g, 3.38 mmol), $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol), Na_2CO_3 (0.72 g, 6.76 mmol) and 4-vinylbenzeneboronic acid (0.60 g, 4.05 mmol). After purification by column chromatography, the compound as isolated as white solid (1.02 g, 65%). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 1H), 7.59 – 7.53 (m, 2H), 7.51 (t, *J* = 6.9 Hz, 2H), 7.42 – 7.37 (m, 1H), 7.32 – 7.26 (m, 5H), 7.20 – 7.04 (m, 7H), 6.69 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.73 (d, *J* = 17.6 Hz, 1H), 5.23 (d, *J* = 10.9 Hz, 1H). ^{19}F decoupled ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.30, 143.53, 137.82, 136.71, 135.94, 133.10, 132.65,

132.29, 131.04, 130.91, 130.41, 129.46, 129.31, 128.59, 128.32, 128.27, 127.85, 126.26, 124.47, 121.74, 119.81, 113.70. ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.61.

5.4.3. Synthetic procedure for soluble polymeric tetra aryl pyrazole P1[15]: A schlenk tube was charged with the monomer **M1** (0.500 g, 1.25 mmol) and free radical initiator azobisisobutyronitrile (0.004 g, 0.02 mmol). The entire system was purged with nitrogen followed by the addition of 1 mL of DCE. The entire system was degassed using the freeze-pump-thaw cycle for three times. Then the reaction was stirred for 24h at 80 ^{o}C. Then the reaction mixture slowly added to the distilled hexane in order to precipitate the polymeric material. The precipitate was then dissolved in dichloromethane and reprecipitated from the hexane. This process was reiterated three times. The resulting solid was dried under high vacuum to obtain the white solid. Yield = 0.400 g, (80%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.6-5.9 (aromatic H) and 2.39-0.51 (polymeric backbone). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.16, 141.18, 139.90, 133.37, 130.32, 128.81, 128.24, 127.70, 127.24, 125.25, 120.37, 39-41 (polymeric backbone).

5.4.3.1. Synthetic procedure for soluble polymeric tetra aryl pyrazole P2 : Polymer **P2** was prepared following the procedure used for the preparation of **P1**. The quantities involved are as follows: Monomer **M2** (0.5 g, 1.07 mmol) and azobisisobutyronitrile (0.004 g, 0.02 mmol). Yield = 0.38g (76%). ^{1}H NMR (400 MHz, $CDCl_3$) 7.8-5.9 (Aromatic H) and 2.12-0.57 (b, polymeric backbone). ^{13}C NMR (176 MHz, $CDCl_3$) δ 150.04, 143.22, 137.63, 133.12, 132.17, 130.80, 130.14, 129.36, 129.05, 128.02, 127.57, 125.36, 123.80, 122.25, 120.70, 119.79 and 39-41 (polymeric backbone). ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.48.

5.4.4. Synthetic procedure for insoluble resin IP1: A 100 mL two neck round bottom flask was charged with the monomer **M2** (0.5 g, 1.07 mmol) and azobisisobutyronitrile

(0.004 g, 0.02 mmol). Divinyl benzene (0.28 g, 2.14 mmol) was added to it. The set up was purged with nitrogen and then 1 mL DCE was added to it. The whole set up was degassed using freeze-pump-thaw cycle for three times. The reaction was stirred at 80 ^{o}C for 48h which resulted in the formation insoluble yellow compound. The insoluble compound was transferred to a frit connected to a conical flask and was washed three times with DCM, MeOH and acetone. The yellowish white compound obtained was grounded to a fine powder using mortar and pestle and was dried under high vacuum. Yield = 0.47 g, (94%). ^{13}C CPTOSS NMR (101 MHz) δ 153.47-109.49 and 62.77-23.49 (polymeric backbone).

5.4.5. Synthetic procedure for catalyst Pd@P1: 0.5 g of polymer P1 was suspended in 10 mL acetic acid at 100 ^{o}C. Palladium acetate (0.28 g) was added to it and was stirred for 1 hour. Then insoluble precipitates were filtered from the reaction mixture at hot condition. The residue was again washed with dichloromethane, methanol and acetone three times each. Then the brownish black solid obtained was grounded using mortar and pestle and was dried under high vacuum. Palladium content of the catalyst was estimated from ICP-AES analysis using HCl:HNO_3:H_2O_2(37%) in 3:1:1 ratio as the digesting solution under microwave digestion. Palladium loading = 1.12 mmolg^{-1}. ^{13}C CPTOSS NMR (101 MHz) δ 152.35-108.76 and 60.43-20.35(polymeric backbone).

Catalyst Pd@P2 and Pd@IP1 was prepared following the similar procedure as used for Pd@P1. Palladium loading = 1.6 mmolg^{-1}. ^{13}C CPTOSS NMR (101 MHz) δ 152.60-106.33 and 51.88-20.13 (polymeric backbone).

Catalyst Pd@IP1 was prepared following the similar procedure as used for Pd@P1. Palladium loading = 0.972 mmolg^{-1}. ^{13}C CPTOSS NMR (101 MHz) δ 161.11-106.33 and 57.58-10.42 (polymeric backbone).

5.4.6. General procedure for alkylation reaction: Catalyst (1 mol% of Pd), KO^{t}Bu (0.5 mmol), primary alcohol (0.5 mmol) and secondary alcohol (0.75 mmol) were added to a seal tube. Deionised water (2 mL) was added to it and the tube was sealed. The reaction was stirred at 120 ^{o}C. After 24 hour, the reaction mixture was filtered using a filter paper. Aqueous layer was separated from the reaction mixture and the organic layer was collected using dichloromethane (3 x 10 mL). The organic layer was dried on Na_2SO_4 and concentrated under vacuum. Product was purified by column chromatography.

5.4.7. General procedure for quinoline synthesis: Catalyst (1 mol% of Pd), KO^{t}Bu (0.5 mmol), 2-aminobenzyl alcohol (0.5 mmol) and secondary alcohol (0.75 mmol) were added to a seal tube. Deionised water (1 mL) was added to it and the tube was sealed. The reaction was stirred at 120 ^{o}C. After 24 hour, the reaction mixture was filtered using a filter paper. Aqueous layer was separated from the reaction mixture and the organic layer was collected using dichloromethane (3 x 10 mL). The organic layer was dried on Na_2SO_4 and concentrated under vacuum. Product was purified by column chromatography.

5.4.8. General Procedure for recycling experiment: Catalyst (1 mol% Pd), KO^{t}Bu (10 mmol), primary alcohol/aminobenzyl alcohol (10 mmol) and secondary alcohol (15 mmol) were added to a seal tube. Deionised water (15 mL) was added to it. Then the tube was sealed and the reaction was stirred at 120 ^{o}C. After 24 hour, the reaction mixture was filtered using frit apparatus. Then the catalyst was washed with water to remove excess base followed by washing with dichloromethane, methanol and acetone three times each. The catalyst was the dried under high vacuum for 3 hour and reused for the next cycle. This process was reiterated 7 times.

5.4.9. Analytical data for α-alkylated ketones:

1,3-Diphenylpropan-1-one[11] (Table 5.3, 2a): Prepared from 1-phenyl ethanol (0.091 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography(silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 91% (0.95 g).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.49 (t, *J* = 7.0 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.25 – 7.17 (m, 4H), 7.15 (t, *J* = 7.2 Hz, 1H), 3.24 (t, *J* = 7.7 Hz, 2H), 3.01 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.35, 141.41, 136.98, 133.18, 128.73, 128.66, 128.55, 128.16, 126.26, 40.57, 30.25.

1-Phenyl-3-(p-tolyl)propan-1-one[16] (Table 5.3, 2b): Prepared from 1-phenyl ethanol (0.091 g, 0.75 mmol) and 4-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography(silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 89% (0.099 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.0 Hz, 2H), 7.61 – 7.52 (m, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.20 – 7.09 (m, 4H), 3.29 (t, *J* = 7.6 Hz, 2H), 3.05 (t, *J* = 7.7 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.47, 138.30, 137.00, 135.74, 133.15, 129.32, 128.71, 128.41, 128.16, 40.73, 29.83, 21.12.

1-Phenyl-3-(o-tolyl)propan-1-one[16] (Table 5.3, 2c): Prepared from 1-phenyl ethanol (0.091 g, 0.75 mmol) and 2-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography(silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 85% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.60 – 7.54 (m, 1H), 7.50 – 7.44 (m, 2H), 7.22 – 7.13 (m, 4H), 3.27 (t, *J* = 8.1 Hz, 2H), 3.07 (t, *J* = 8.1 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.50, 139.51, 136.98, 136.12, 133.21, 130.47, 128.86, 128.75, 128.17, 126.45, 126.30, 39.23, 27.63, 19.47.

3-(4-Methoxyphenyl)-1-phenylpropan-1-one[16] (Table 5.3, 2d): Prepared from 1-phenyl ethanol (0.091 g, 0.75 mmol) and 4-methoxybenzyl alcohol (0.069 g, 0.5 mmol). After purification by column chromatography(silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 83% (0.099 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 3.79 (s, 3H), 3.27 (t, *J* = 7.6 Hz, 2H), 3.02 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.50, 158.10, 137.00, 133.42, 133.14, 129.46, 128.70, 128.15, 114.05, 55.37, 40.81, 29.39.

3-(4-Fluorophenyl)-1-phenylpropan-1-one[17] (Table 5.3, 2e): Prepared from 1-phenyl ethanol (0.091 g, 0.75 mmol) and 4-fluorobenzyl alcohol (0.063 g, 0.5 mmol). After purification by column chromatography(silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 91% (0.103). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 8.1 Hz, 2H), 6.98 (t, *J* = 8.8 Hz, 2H), 3.28 (t, *J* = 7.6 Hz, 2H), 3.05 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.14, 161.50(d, J_{C-F} =245.43Hz), 136.90, 133.24, 129.94(d, J_{C-F} = 8Hz), 128.74, 128.12, 115.34(d, J_{C-F} = 21Hz), 40.51, 29.36.

1-(4-Fluorophenyl)-3-phenylpropan-1-one[17](Table 5.3, 2g): Prepared from 1-(4-fluorophenyl) ethanol (0.105 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography(silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 87% (0.099 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.95 (m, 2H), 7.34 – 7.28 (m, 2H), 7.28 – 7.19 (m, 3H), 7.12 (t, *J* = 8.6 Hz, 2H), 3.28 (t, *J* = 7.9 Hz, 2H), 3.07 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.75, 165,83(d, J_{C-F} =254 Hz), 141.25, 133.38, 130.78(d, J_{C-F} =7Hz),

128.68, 128.54, 126.32, 115.81(d, J_{C-F} =22Hz), 40.49, 30.19. 19F (376 MHz, CDCl3) δ -105.13.

3-Phenyl-1-(p-tolyl)propan-1-one[11] (Table 5.3, 2h): Prepared from 1-(p-tolyl)ethanol (0.102 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography(silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 79% (0.088 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.17 (m, 7H), 3.28 (d, *J* = 8.0 Hz, 2H), 3.07 (t, *J* = 7.7 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.08, 143.99, 141.53, 134.48, 129.42, 128.65, 128.56, 128.30, 126.23, 40.49, 30.33, 21.77.

2-Methyl-1,3-diphenylpropan-1-one[11] (Table 5.3, 2i): Prepared from 1-phenyl-1-propanol (0.102 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography(silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 82% (0.091 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 6.8 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 2H), 7.21 – 7.11 (m, 3H), 3.73 (h, *J* = 6.8 Hz, 1H), 3.16 (dd, *J* = 13.6, 6.4 Hz, 1H), 2.73 – 2.59 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.80, 140.00, 136.49, 132.99, 129.16, 128.70, 128.44, 128.35, 126.27, 77.48, 77.16, 76.84, 42.81, 39.43, 17.48.

3-Phenyl-1-(thiophen-2-yl)propan-1-one[11] (Table 5.3, 2j): Prepared from 1-thiophen-2-ylethanol (0.096 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 77% (0.076 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 3.8, 1.1 Hz, 2H), 7.58 (dd, *J* = 4.9, 1.1 Hz, 2H), 7.26 – 7.24 (m, 2H), 7.08 (dd, *J* = 5.0, 3.8 Hz, 2H), 3.41 (dd, *J* = 16.0, 7.0 Hz, 2H), 3.25 (dd, *J* = 16.0,

7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.53, 144.33, 143.27, 133.90, 132.32, 128.78, 128.28, 127.54, 126.97, 45.44, 38.00.

2-Benzyl-3,4-dihydronaphthalen-1(2H)-one[11] (Table 5.3, 2k): Prepared from 1,2,3,4-tetrahydronaphthalen-1-ol (0.111 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 75% (0.088 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.26 – 7.20 (m, 4H), 3.51 (dd, *J* = 13.7, 3.9 Hz, 1H), 2.98 – 2.91 (m, 2H), 2.80 – 2.71 (m, 1H), 2.66 (dd, *J* = 13.7, 9.6 Hz, 1H), 2.16 – 2.07 (m, 1H), 1.86 – 1.73 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.56, 144.16, 140.16, 133.41, 132.57, 129.39, 128.84, 128.53, 127.66, 126.74, 126.26, 49.56, 35.77, 28.73, 27.76.

5.4.10. Analytical data for quinolines:

2-Phenylquinoline[11] (Table 5.4, 3a): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-aminobenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 93% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.5 Hz, 1H), 8.25 – 8.20 (m, 2H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.80 – 7.72 (m, 2H), 7.59 – 7.47 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.20, 148.22, 139.59, 136.69, 129.67, 129.60, 129.29, 128.80, 127.54, 127.44, 127.11, 126.21, 118.88.

2-(p-Tolyl)quinoline[11] (Table 5.4, 3b): Prepared from 1-(p-tolyl)ethanol (0.102 g, 0.75 mmol) and 2-aminobenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 87% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.1 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.1 Hz,

1H), 7.72 (t, *J* = 8.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.34 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.47, 148.41, 139.53, 137.00, 136.80, 129.78, 129.71, 127.57, 127.22, 126.21, 119.00, 21.48.

2-(4-Methoxyphenyl)quinoline[18] (Table 5.4, 3c): Prepared from 1-(4-methoxyphenyl)ethan-1-ol (0.114 g, 0.75 mmol) and 2-aminobenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 83% (0.097 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 12.5, 8.8 Hz, 4H), 7.83 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.95, 157.06, 148.43, 136.76, 132.40, 129.70, 129.65, 129.02, 127.56, 127.04, 126.05, 118.70, 114.36, 55.53.

2-(4-Fluorophenyl)quinoline[11] (Table 5.4, 3d): Prepared from 1-(4-fluorophenyl)ethan-1-ol (0.105 g, 0.75 mmol) and 2-aminobenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 89% (0.099 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.13 (m, 4H), 7.81 (d, *J* = 8.4 Hz, 2H), 7.77 – 7.70 (m, 1H), 7.56 – 7.50 (m, 1H), 7.21 (t, *J* = 8.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9 (d, *J* = 249.3 Hz), 156.3, 137.2, 135.8 (d, J_{C-F} = 2.4 Hz), 130.0, 129.6 (d, J_{C-F} = 8.5 Hz), 129.0,127.8, 127.6, 127.2, 126.5, 118.8, 115.9 (d, J_{C-F} = 21.6 Hz) ^{19}F NMR (376 MHz, CDCl3) δ -112.33.

2-(4-Chlorophenyl)quinoline[19] (Table 5.4, 3e): Prepared from 1-(4-chlorophenyl)ethan-1-ol (0.117 g, 0.75 mmol) and 2-aminobenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 78% (0.093 g). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 8.20 – 8.14 (m, 2H), 8.11 (d, *J* = 8.6 Hz, 2H), 7.83 – 7.77 (m, 2H), 7.73 (t, *J* = 8.4 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.49 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.04, 148.31, 138.11, 137.02, 135.62, 129.92, 129.78, 129.09, 128.89, 127.58, 127.30, 126.58, 118.61.

2-(2-Fluorophenyl)quinoline[21] (Table 5.4, 3f): Prepared from 1-(2-fluorophenyl)ethan-1-ol (0.105 g, 0.75 mmol) and 2-aminobenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 85% (0.094g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dd, *J* = 8.3, 2.5 Hz, 2H), 8.12 (t, *J* = 7.8 Hz, 1H), 7.89 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.58 – 7.52 (m, 1H), 7.47 – 7.39 (m, 1H), 7.36 – 7.29 (m, 1H), 7.24 – 7.17 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.86 (d, J_{C-F} = 250.4), 154.11, 148.41, 136.24, 131.61 (d, J_{C-F} =3.0), 130.9 (d, J_{C-F} = 9.0), 129.75 (d, J_{C-F} = 8.0), 128.10, 127.98, 127.57, 127.30, 126.70, 124.77 (d, J_{C-F} = 8.0), 122.53 (d, J_{C-F} = 8.0), 116.32 (d, J_{C-F} = 23.2).

2-(3,5-Bis(trifluoromethyl)phenyl)quinoline[19] (Table 5.4, 3g): Prepared from 1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol (0.193 g, 0.75 mmol) and 2-aminobenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 72% (0.122 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 1H), 8.16 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.06 (d, *J* = 8.6 Hz, 2H), 7.85 – 7.81 (m, 1H), 7.77 – 7.71 (m, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.57 – 7.51 (m, 1H). ^{19}F decoupled ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.22, 138.67, 137.14, 132.13, 130.01, 129.86, 129.25, 127.64, 127.40, 126.68, 124.08, 118.67.

2-(Benzo[d][1,3]dioxol-5-yl)quinoline[20] (Table 5.4, 3h): Prepared from 1-(benzo[d][1,3]dioxol-5-yl)ethan-1-ol (0.124 g, 0.75 mmol) and 2-aminobenzyl alcohol

(0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 77% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 2H), 7.80 – 7.75 (m, 2H), 7.75 (d, *J* = 1.8 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.65 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.52 – 7.46 (m, 1H), 6.95 (d, *J* = 8.1 Hz, 1H), 6.03 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.75, 148.92, 148.48, 148.25, 136.79, 134.19, 129.75, 129.61, 127.52, 127.08, 126.16, 121.85, 118.71, 108.57, 108.00, 101.47.

2-(Thiophen-2-yl)quinoline[18] (Table 5.4, 3i): Prepared from 1-thiophen-2-ylethanol (0.096 g, 0.75 mmol) and 2-aminobenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 77% (0.080 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 11.8, 8.6 Hz, 2H), 7.80 – 7.63 (m, 4H), 7.48 (t, *J* = 5.8 Hz, 2H), 7.15 (t, *J* = 4.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.36, 148.14, 145.42, 136.66, 129.87, 129.27, 128.65, 128.15, 127.55, 127.22, 126.14, 125.94, 117.68.

2-Phenyl-1,8-naphthyridine[19] (Table 5.4, 3j): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and (2-aminopyridin-3-yl)methanol (0.062 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, DCM: methanol (98:2 to 9:1)), the compound was isolated in 78% (0.080 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (dd, *J* = 4.2, 2.0 Hz, 1H), 8.31 (dd, *J* = 8.2, 1.6 Hz, 2H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.18 (dd, *J* = 8.1, 2.0 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.55 – 7.42 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.41, 156.25, 153.95, 138.60, 137.86, 136.85, 130.22, 128.92, 128.03, 121.88, 121.81, 119.81.

2-Methylquinoline[18] (Table 5.4, 3k): Prepared from 2-propanol (0.5 mL) and 2-aminobenzyl alcohol (0.061 g, 0.5 mmol). After purification by column

chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 63% (0.045g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.92 (m, 2H), 7.70 (t, *J* = 8.1 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.47 – 7.37 (m, 1H), 7.25 – 7.16 (m, 1H), 2.70 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.98, 147.87, 136.17, 129.43, 128.62, 127.50, 126.48, 125.67, 122.00, 25.40.

2-Phenylpyridine[19] (Table 5.4, 3l): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 3-aminopropan-1-ol (0.037 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate (19:1)), the compound was isolated in 65% (0.051 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.8 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 2H), 7.73 (d, *J* = 2.9 Hz, 2H), 7.48 (t, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.53, 149.75, 139.48, 136.83, 129.04, 128.83, 126.99, 122.18, 120.65.

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Chapter 6

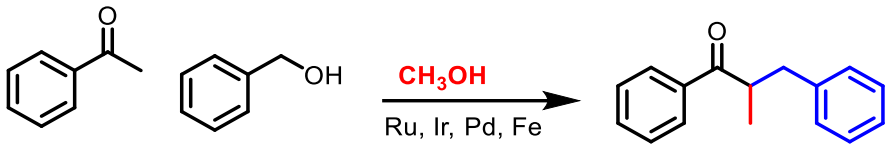
One-pot synthesis of α-branched ketones from secondary alcohols using triple dehydrogenative method

6.1. Introduction

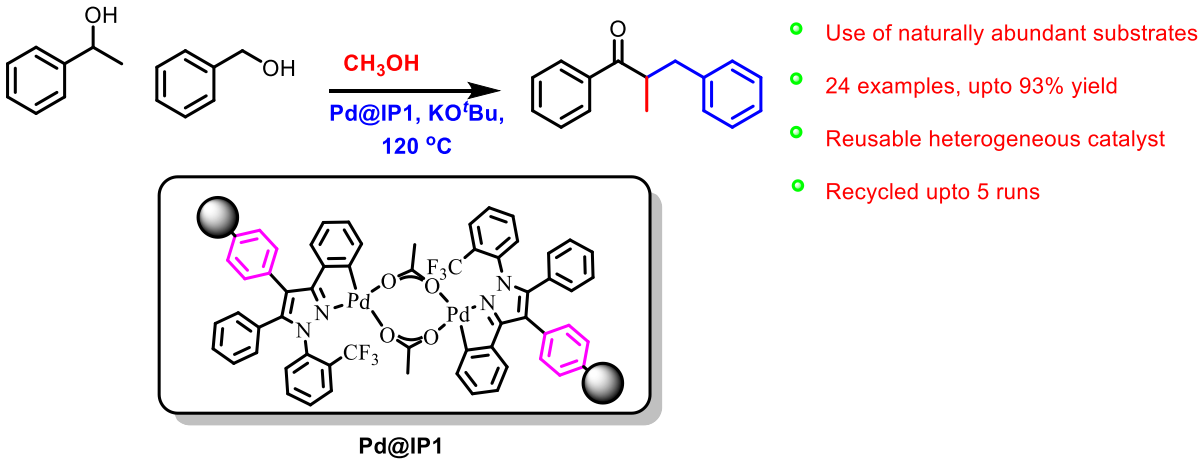
Minimising waste formation and energy consumption[1], use of greener and sustainable feedstock[2] and recyclable catalyst is an important aspect of sustainable and greener process.To attain sustainability in the synthesis of bulk and fine chemicals, chemists are continuously searching for alternative cleaner and environmentally friendly technologies[3]. In this regard, Multicomponent reactions[4] are an extremely economic and greener approach towards the synthesis of structurally complex and diverse molecule in a single step and thereby decrease energy consumption and waste formation. More significantly, use of heterogeneous catalysts for such multicomponent processes offer additional advantages of reusing the catalyst[5].

α-Branched methyl ketone is the class of substituted ketone which is found in various pharmaceutical compounds[6]. Methyl substitution in a molecule hugely alters its biological and physical properties[7]. In recent years, α-branched methylated ketones are prepared by α-methylation of substituted ketone or by sequential alkylation and methylation of ketones[8]. Lately, groups of Obora[9], Kundu[10], Renaud[11] and Hou[12] have reported one pot three component synthesis of α-branched ketones by catalytic cross coupling of ketones with a primary alcohol and methanol. However, there is no report for the use of secondary alcohol in the one pot synthesis of α-branched methylated ketones. Alcohols, despite being cheaper and easily available from abundant and indigestible bio-mass[13], have not been used in one pot synthesis of α-branched ketones. The major reason for such a scenario is the higher energy required for the activation of alcohols over ketones. Moreover, alcohols present an additional challenge of selectivity in alkylation-methylation reaction[14]. In case of one pot synthesis of α-branched ketones, the product has to be selectively formed among the three possible products as depicted in scheme 6.3(a). Whereas, in case of alcohol as the starting material, extra hydrogen

liberated through the dehydrogenation of secondary alcohols can further reduce the possible products (scheme 6.3 (b)) and thereby presenting a selectivity and purification issue. Furthermore, secondary alcohols are also prone to self-coupling resulting in β-branched ketones. Therefore, a protocol for the selective formation of α-branched ketones from cross coupling between secondary alcohols and primary alcohol and methanol is highly sought after. Herein, we report selective formation of α-branched methyl ketones from secondary alcohols catalysed by a cross-linked polystyrene supported pyrazole based palladium catalyst.



Scheme 6.1. Previous reports: One pot synthesis of α-branched methyl ketones using ketones

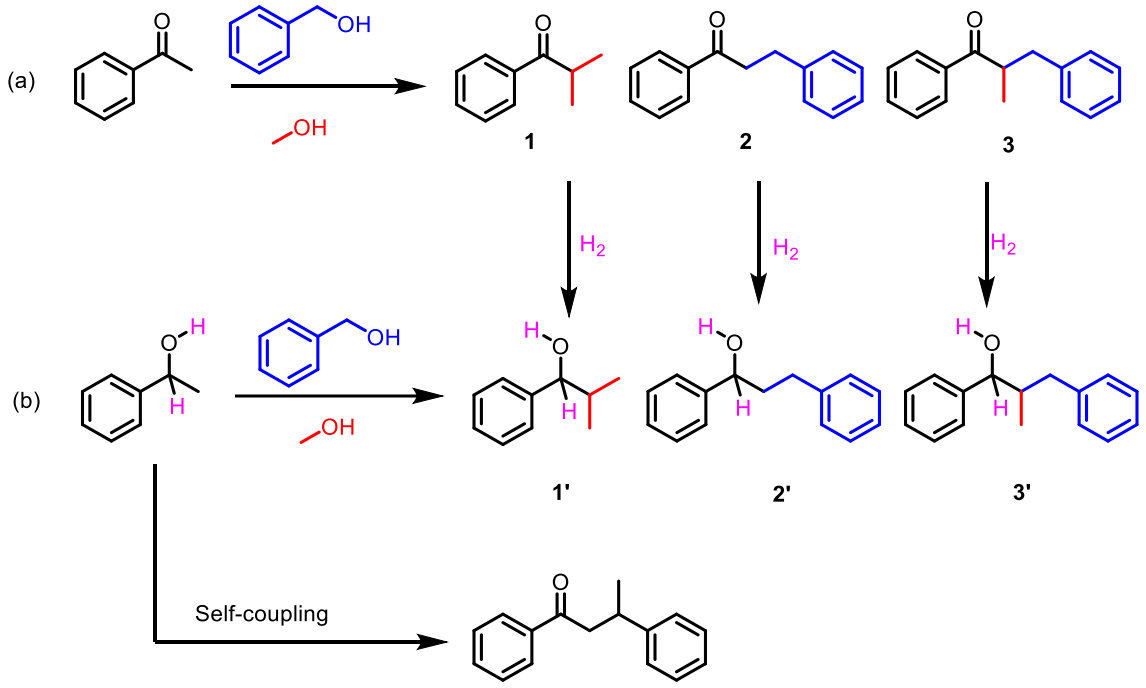


Scheme 6.2. This work: One pot synthesis of α-branched methyl ketones using secondary alcohols

6.2. Results and discussion

In the previous chapter, we have discussed about the synthesis and characterisation of polystyrene supported pyrazole based catalyst and its application in dehydrogenative

cross coupling of secondary alcohols. Cross-linked polymer supported catalyst showed better activity in comparison with other catalysts. In continuation of our effort to activate methanol and other alcohols, we reacted secondary alcohol with primary alcohol in the presence of methanol to obtain the α-branched methyl ketones. 1-(*p*-Tolyl)ethanol and benzyl alcohol were chosen as the secondary and primary alcohol. KO^{t}Bu was chosen as the base

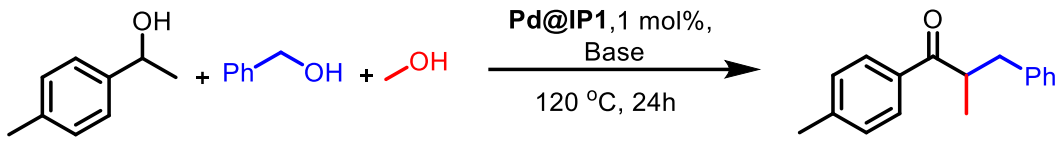


Scheme 6.3. Selectivity issues in one pot synthesis of α-branched methyl ketones from (a) ketones and (b) secondary alcohols.

as it has been used in the α-alkylation reported in the previous chapter. Initial screening of alcohols (primary and secondary) loading showed higher equivalent of secondary alcohol (1.5 equivalent) is suitable for the synthesis which resulted in 93% of the α-branched methyl ketones (table 6.1, entry 1-4). Further screening for different bases *viz*. LiO^{t}Bu, K_2CO_3, KOH and LiOH, resulted in lesser conversion as compared to that of KO^{t}Bu (table 6.1, entry 5-8). Further reduction in the base loading from 2 equivalent to 1 and 0.5 equivalent drastically decreases the reaction yield to 83% and 67%

respectively. Use of catalyst is essential for this conversion as no conversion was observed in the absence of the catalyst (table 6.2, entry 11).

Table 6.1. Optimisation table for one pot synthesis of α-branched methyl ketones.[a]



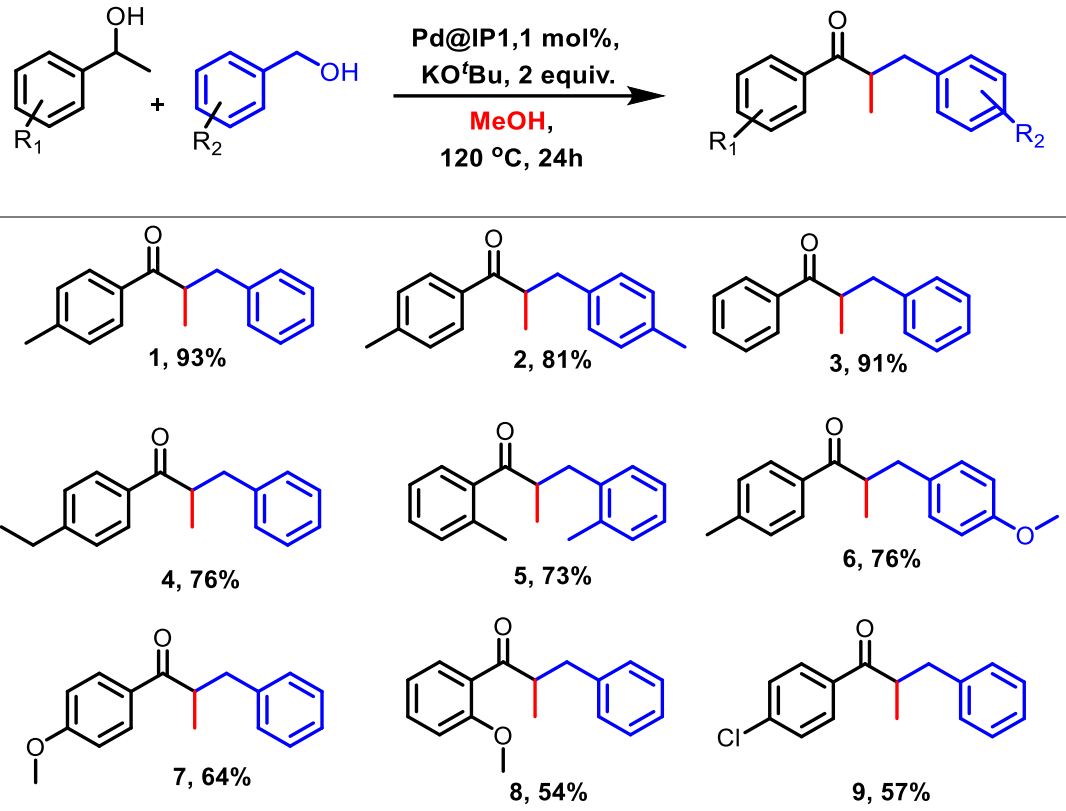
S.no	1°-alcohol (equiv.)	2°-alcohol (equiv.)	Base (equiv.)	Yield(%)[b]
1	1	1.2	KO^{t}Bu(2)	81
2	**1**	**1.5**	**KO^{t}Bu(2)**	**93**
3	1.2	1	KO^{t}Bu(2)	51
4	1.5	1	KO^{t}Bu(2)	46
5	1	1.5	LiO^{t}Bu(2)	54
6	1	1.5	K_2CO_3(2)	33
7	1	1.5	KOH(2)	67
8	1	1.5	LiOH(2)	Trace
9	1	1.5	KO^{t}Bu(1)	83
10	1	1.5	KO^{t}Bu(0.5)	67
11[c]	1	1.5	KO^{t}Bu(2)	N.D

[a]Reaction details: Catalyst(Pd@IP1 = 1 mol%, Temperature = 120 °C, time = 24h, [b] All yields are isolated yields, [c] No catalyst was used.

Having optimised the reaction conditions, scope and limitation of the one pot protocol was investigated. Methyl group at the *para* position of the aryl group on the secondary alcohol resulted in an excellent isolated yield of 93% for the corresponding methylated

ketone. (table 6.2, **1**). Trace amount of dimethylated ketone was observed in case of cross coupling between *p*-methyl substituted secondary and primary alcohol which lowers the overall yield of the reaction (table 6.2, **2**). *o*-Methyl substituted secondary and primary alcohols resulted in low yield of 73% (table 6.2, **5**).

Table 6.2. Scope of secondary alcohols in one pot synthesis of α-methyl branched ketones

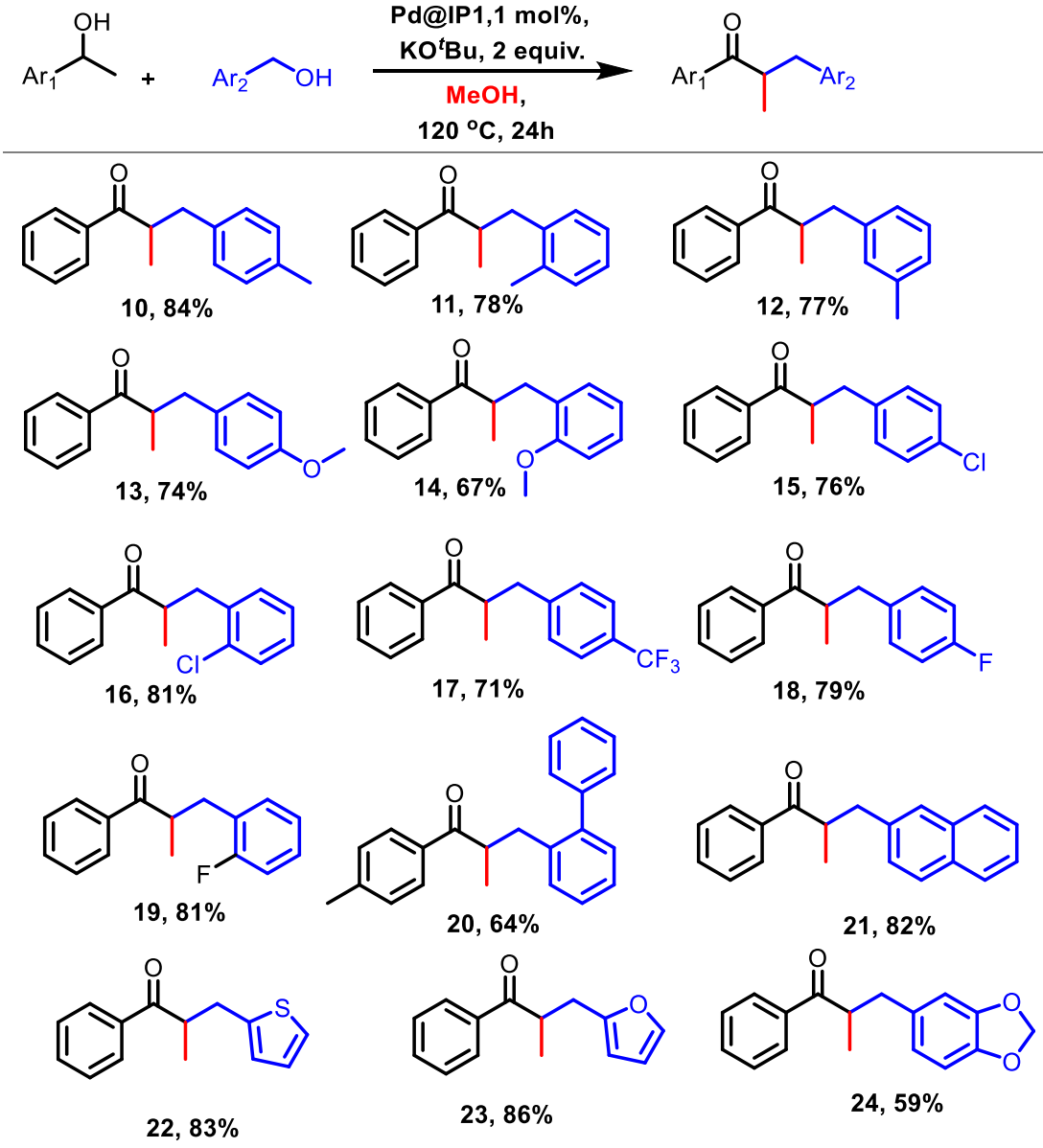


Reaction details: primary alcohol = 0.5 mmol, secondary alcohol = 0.75mmol, KO^{t}Bu = 1mmol, MeOH = 1.5 mL, Time = 24h, temperature = 120 °C All reactions were carried out under aerobic condition, all yields are isolated yields

as compared to *p*-methyl substituted alcohols. Sterically demanding ethyl (*p*) and methoxy (*o* and *p*) produced the methylated branched ketones in 76%, 64% and 54% yield respectively (table 6.2, **4, 7** and **8**). 57% of the methylated ketone was obtained in case of electron withdrawing substitution such as 4-Cl in the aryl ring of secondary alcohol (table 6.2, **9**). Substitution by fluoro group (*p* and *o*) resulted in the substitution reaction producing the corresponding methoxy substituted products **7** and **8**

respectively. 91% of the methylated product was isolated from the cross coupling of 1-phenylethanol and benzyl alcohol with methanol (table 6.2, **3**).

Table 6.3. Scope of primary alcohols in one pot synthesis of α-methyl branched ketones



Reaction details: primary alcohol = 0.5 mmol, secondary alcohol = 0.75mmol, KO^{t}Bu = 1mmol, MeOH = 1.5 mL, Time = 24h, temperature = 120 °C. All reactions were carried out under aerobic condition, all yields are isolated yields.

With 1-phenylethanol as the secondary alcohol, we varied different primary alcohols under the optimized condition. Methyl substitution at different position on the aryl ring of the benzyl alcohol resulted in good yields of the α- methyl product which varied from

77-84% (table 6.3, **10-12**). Methoxy substitution at 2 and 4 position of the aryl ring of primary alcohol resulted in 67% and 74% of the methylated ketone respectively (table 6.3, **14** and **13**). Electron withdrawing substitution, *viz* –Cl, -F, -CF_3, in the primary alcohol resulted in a good conversion ranging from 76-81% isolated yield (table 6.3, **15-19**). Biphenyl and fused ring system such as 2-naphthyl in the primary alcohol produced 64% and 82% isolated yield of the α-branched ketone (Table 6.3, **20** and 2**1**). 83% and 86% of methylated ketones were obtained in case of heteroaryl system such as thiophenyl alcohol and furfuryl alcohol respectively (table 6.3, **22** and **23**). Use of aliphatic system as primary alcohol *viz.* ethanol, 1-hexanol and *n*-butanol resulted in the dimethylated ketone as the sole product from this protocol (not shown).

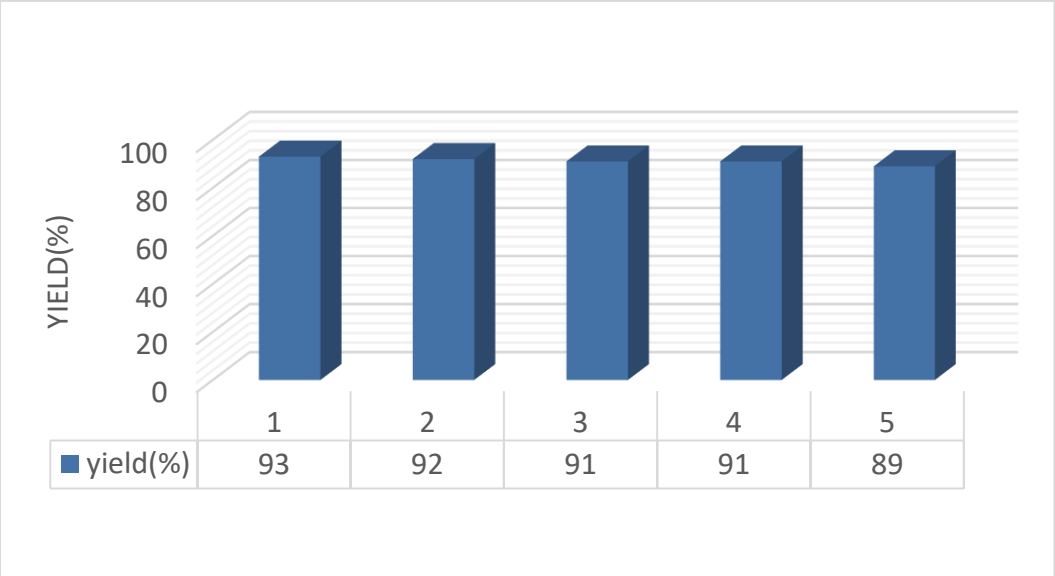
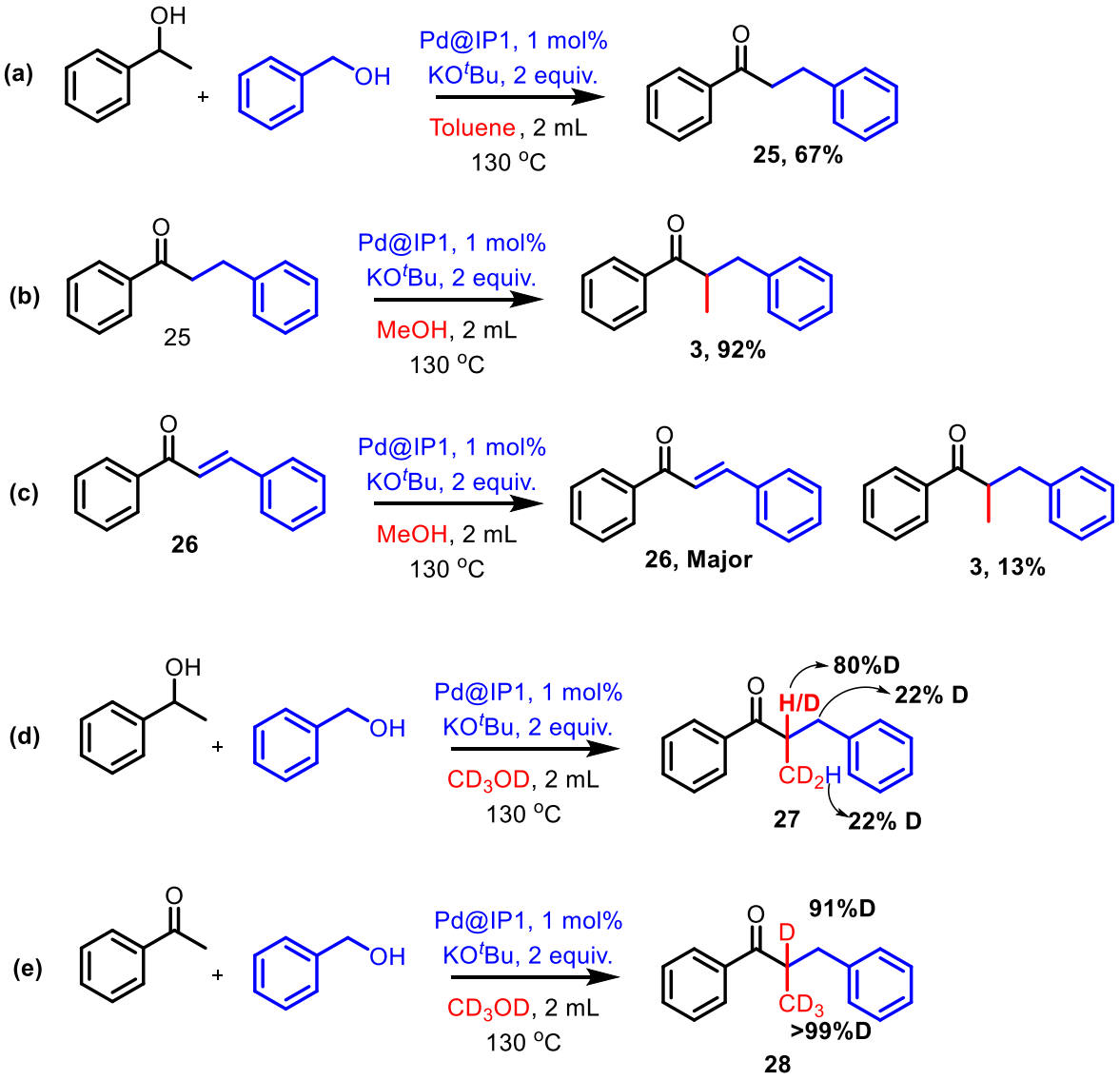


Figure 6.1. Recycling experiment.

Reaction details: benzyl alcohol - 3 mmol, 1-(*p*-tolyl)ethanol - 4.5 mmol, Pd@IP1 - 1 mol%, KO^{t}Bu-6 mmol, methanol - 10 mL, temperature - 120 ^{o}C, time - 24h

To further check the catalyst's stability under the current protocol, recycling experiments were carried out in 3 mmol scale. The catalyst showed an excellent activity

for five runs without any significant decrease in the reaction yield where the yield varied from 93% to 89%.



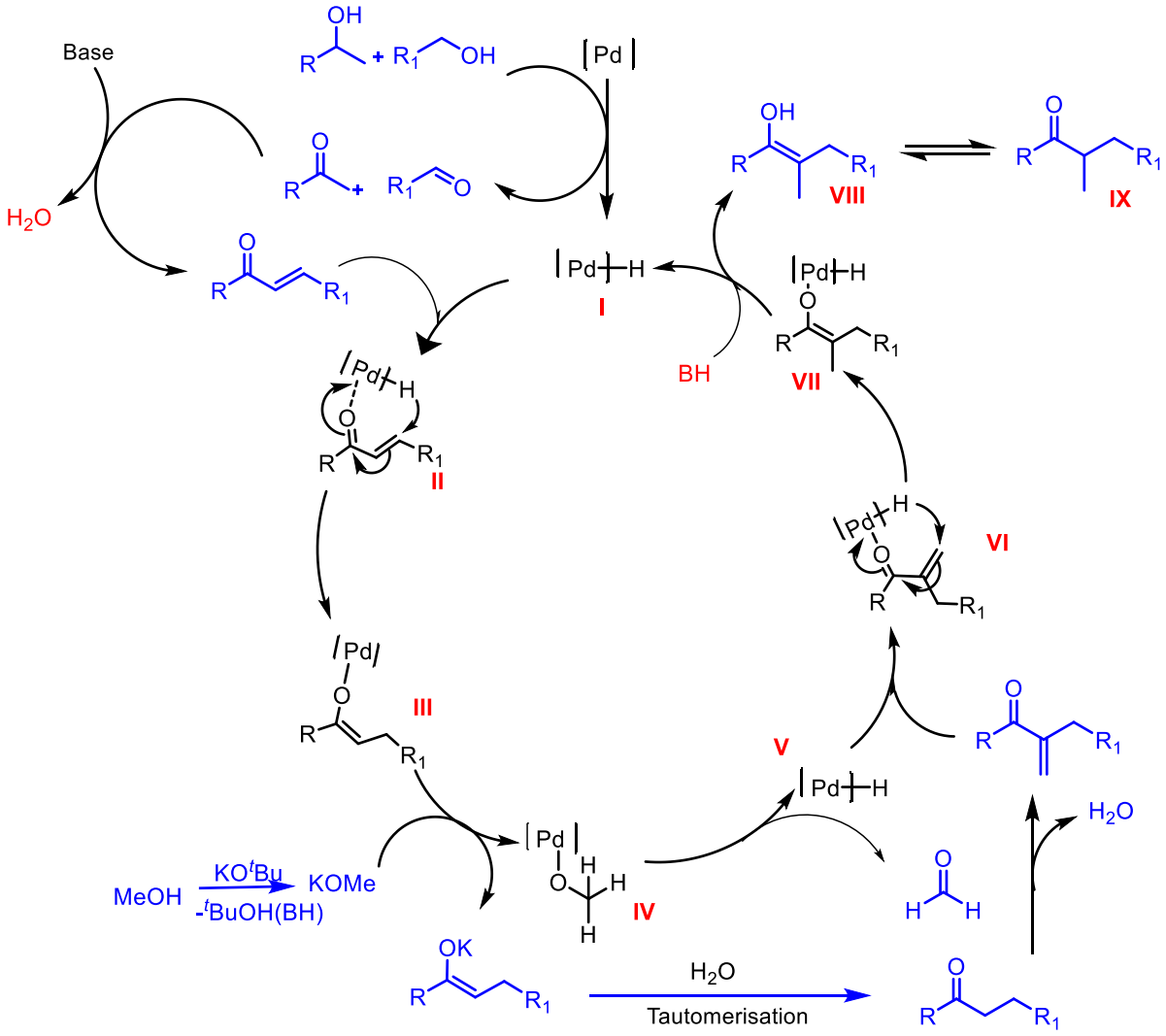
Scheme 6.4. Control reactions

Control reactions were carried out to probe the mechanism of this protocol (scheme 6.4). Secondary and primary alcohol when subjected to the optimised reaction conditions in toluene instead of methanol, resulted in the α-alkylated ketone (scheme 6.4(a)) which upon subjected to reaction with methanol produced the desired α-methylated branched ketones. This shows the reaction is proceeding *via* α-alkylation followed by methylation. As the α-alkylation proceeds through the formation of the

chalcone species, which under the one pot methylation protocol only resulted in trace amount of the desired product (scheme 6.4(c)). This shows the necessity of additional hydrogen required for the hydrogenation of the chalcone which is liberated from the alcohols under the optimised condition. Reaction carried out under the optimised condition in presence of fully CD_3OD produced 89% of the CD_2H labelled ketone (scheme 6.4(d)). 80% deuterium incorporation occurred at the α-position of the ketone along with 20% deuterium incorporation at the benzylic position. Similar reaction when carried out using acetophenone instead of the secondary alcohol, resulted in CD_3 labelled ketone with greater than 91% deuterium incorporation at the α-position and no deuterium incorporation occurred at the benzylic position (scheme 6.4(e)). This implies that both the primary and secondary alcohols are the source of hydride in this one pot process and the hydrogen deuterium exchange/scrambling occurs with methanol resulting in the deuterium incorporation at the benzylic position of the ketone.

Based on these findings, we propose the following mechanism (scheme 6.5). From the literature reports[16] of acceptorless borrowing hydrogen methodology, dehydrogenation of the alcohols to the corresponding carbonyl compound is well known. Accordingly, primary alcohol and secondary alcohol undergo dehydrogenation in presence of the metal catalyst to form the aldehyde and ketone respectively. The aldehyde and the ketone undergo aldol condensation to form the chalcone species. The chalcone species undergoes hydride addition from the metal hydride species to form the metal enolate species. This metal enolate species in presence of potassium methoxide produces the potassium enolate which upon tautomerisation produces the hydrogenated chalcone. Hydrogenated chalcone adds to the formaldehyde produced from the dehydrogenation of methanol to form the α-olefin species. Formation of CD_2H labelled ketone from the deuterated methanol justifies the formation of this species. The α-methylene species

undergo hydride addition and enolate formation *via* species **VI** and **VII** to form the enolic compound **VIII** which upon tautomerisation forms the desired α-methylated branched ketones **IX**.



Scheme 6.5. Proposed mechanism

6.3. Conclusion

We have reported a simple and novel method for the one pot synthesis of α-methylated branched ketones starting from secondary alcohols using a polystyrene anchored palladium catalyst under aerobic condition. Various primary and secondary alcohols were screened for the synthesis of different α-branched ketones. The catalyst was reused for five runs without any decrease in its activity.

6.4. Experimental section

6.4.1. General information

Reagents and starting materials were purchased from Alfa-Aesar, Sigma-Aldrich and Spectrochem chemical companies and used as received unless otherwise noted. All 400 MHz ^{1}H and 100 MHz ^{13}C NMR, 377 MHz ^{19}F spectra and 161 MHz ^{31}P spectra were recorded on a Bruker ARX 400 spectrometer operating at 400 MHz and referenced internally to solvent signals. ^{19}F NMR spectra were externally referenced to α,α,α-trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). ^{31}P NMR (161 MHz) spectra were externally referenced to H_3PO_4 in D_2O (δ = 0). High-resolution mass spectra (HRMS) were recorded on a Bruker microTOF-QII mass spectrometer. The elemental composition of the synthesized catalysts were verified by using an inductively coupled plasma-optical emission spectrophotometer (iCAP 7000 ICP-OES). Unless mentioned, all reactions were carried out under aerobic condition and at 0.5 mmol scale.

6.4.2. General procedure for one-pot methylation reaction: Catalyst (1 mol% of Pd), KO^{t}Bu (2 mmol), primary alcohol (0.5 mmol) and secondary alcohol (0.75 mmol) were added to a pressure tube. Methanol (1 mL) was added to it and the tube was sealed. The reaction was stirred at 120 ^{o}C. After 24 hour, the reaction mixture was filtered using a filter paper. Aqueous layer was separated from the reaction mixture and the organic layer was collected using dichloromethane (3 x 10 mL). The organic layer was dried on Na_2SO_4 and concentrated under vacuum. Product was purified by column chromatography.

6.4.3. Procedure for recycling experiment: Catalyst (1 mol% Pd), KO^{t}Bu (6 mmol), primary alcohol (3 mmol) and secondary alcohol (4.5 mmol) were added to a pressure tube. Methanol (10 mL) was added to it. Then the tube was sealed and the reaction was

stirred at 120 ºC. After 24 hour, the reaction mixture was filtered using frit apparatus. Then the catalyst was washed with water to remove excess base followed by washing with dichloromethane, methanol and acetone three times each. The catalyst was then dried under high vacuum for 3 hour. The catalyst obtained was reused for the next cycle. This process was reiterated 5 times.

6.4.4. Analytical data for the α-methylated ketones:

2-Methyl-3-phenyl-1-(*p*-tolyl)propan-1-one[9] (table 6.2, 1): Prepared from 1-(*p*-tolyl)ethanol (0. 102 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 93% (0.110 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.23 (dd, *J* = 7.7, 5.3 Hz, 4H), 7.20 – 7.14 (m, 3H), 3.71 (sextet, *J* = 7.0 Hz, 1H), 3.15 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.66 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.38 (s, 3H), 1.17 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.47, 143.80, 140.18, 134.04, 129.43, 129.20, 128.54, 128.46, 126.26, 42.69, 39.52, 21.69, 17.56.

2-Methyl-1,3-di-*p*-tolylpropan-1-one[12] (table 6.2, 2): Prepared from 1-(*p*-tolyl)ethanol (0. 102 g, 0.75 mmol) and 4-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 81% (0.102 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.11 – 7.03 (m, 4H), 3.70 (sextet, *J* = 8.0 Hz, 1H), 3.12 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.64 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.39 (s, 3H), 2.29 (s, 3H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.50, 143.73, 136.99, 135.64, 133.95, 129.36, 129.03, 128.50, 42.70, 38.99, 21.65, 21.07, 17.43.

2-Methyl-1,3-diphenylpropan-1-one[9] (table 6.2, 3): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and benzyl alcohol (0.054g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 91% (0.101 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.1 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.15 – 6.98 (m, 5H), 3.61 (sextet, *J* = 6.9 Hz, 1H), 3.04 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.56 (dd, *J* = 13.7, 7.8 Hz, 1H), 1.06 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.66, 139.93, 136.41, 132.93, 129.09, 128.64, 128.38, 128.28, 126.21, 77.48, 77.16, 76.84, 42.73, 39.36, 17.43.

1-(4-Ethylphenyl)-2-methyl-3-phenylpropan-1-one (table 6.2, 4): Prepared from 1-(4-ethylphenyl)ethanol (0.112 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 76% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.2 Hz, 2H), 7.25 – 7.19 (m, 4H), 7.19 – 7.11 (m, 3H), 3.70 (sextet, *J* = 6.9 Hz, 1H), 3.14 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.72 – 2.59 (m, 3H), 1.22 (t, *J* = 7.6 Hz, 3H), 1.16 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.46, 149.97, 140.17, 134.16, 129.19, 128.63, 128.45, 128.24, 128.20, 126.24, 42.70, 39.45, 28.99, 17.56, 15.29.

2-Methyl-1,3-di-*o*-tolylpropan-1-one (table 6.2, 5): Prepared from 1-(*o*-tolyl)ethanol (0.102 g, 0.75 mmol) and 2-methylbenzyl alcohol (0.061g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 73% (0.092 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 6.0 Hz, 1H), 7.17 – 6.97 (m, 6H), 3.48 (sextet, *J* = 6.9 Hz, 1H), 3.07 (dd, *J* = 13.9, 6.4 Hz, 1H), 2.58 (dd, *J* = 13.9, 7.9 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.49,

138.80, 138.22, 137.70, 136.23, 131.73, 130.88, 130.47, 129.97, 127.52, 126.45, 125.99, 125.65, 45.01, 36.25, 20.79, 19.68, 17.08.

3-(4-Methoxyphenyl)-2-methyl-1-(*p*-tolyl)propan-1-one (table 6.2, 6): Prepared from 1-(*p*-tolyl)ethanol (0. 102 g, 0.75 mmol) and 4-methoxybenzyl alcohol (0.069 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 76% (0.101 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.7 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.77 (s, 3H), 3.69 (sextet, *J* = 6.9 Hz, 1H), 3.11 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.63 (dd, *J* = 13.8, 7.8 Hz, 1H), 2.40 (s, 3H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.64, 158.05, 143.78, 134.02, 132.16, 130.10, 129.41, 128.51, 113.82, 55.28, 42.87, 38.61, 21.69, 17.48.

1-(4-Methoxyphenyl)-2-methyl-3-phenylpropan-1-one[9] (table 6.2, 7): Prepared from 1-(4-methoxyphenyl)ethanol (0.114 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 64% (0.081 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.28 – 7.22 (m, 2H), 7.21 – 7.16 (m, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 3.74 – 3.65 (sextet, 1H), 3.15 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.68 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.40, 163.47, 140.23, 130.67, 129.45, 129.19, 128.45, 126.24, 113.87, 55.55, 42.42, 39.59, 17.67.

1-(2-Methoxyphenyl)-2-methyl-3-phenylpropan-1-one[12] (table 6.2, 8): Prepared from 1-(2-methoxyphenyl)ethanol (0.114 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 54% (0.068 g). ^{1}H NMR

(400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.40 (ddd, *J* = 8.8, 7.4, 1.8 Hz, 1H), 7.25 – 7.20 (m, 2H), 7.19 – 7.14 (m, 3H), 6.98 – 6.88 (m, 2H), 3.84 (s, 3H), 3.71 (sextet, *J* = 6.9 Hz, 1H), 3.15 (dd, *J* = 13.5, 5.7 Hz, 1H), 2.55 (dd, *J* = 13.5, 8.7 Hz, 1H), 1.09 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.33, 157.91, 140.44, 132.97, 130.26, 129.26, 129.05, 128.31, 126.05, 120.80, 111.44, 55.57, 47.34, 39.27, 16.40.

1-(4-Chlorophenyl)-2-methyl-3-phenylpropan-1-one (table 6.2, 9): Prepared from 1-(4-chlorophenyl)ethanol (0.117 g, 0.75 mmol) and benzyl alcohol (0.054 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 57% (0.073 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 3.73 (sextet, *J* = 6.9 Hz, 1H), 3.15 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.67 (dd, *J* = 13.6, 7.8 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.84, 140.04, 136.52, 133.03, 129.19, 128.73, 128.47, 128.38, 126.29, 42.84, 39.45, 17.51.

2-Methyl-1-phenyl-3-(*p*-tolyl)propan-1-one[9] (table 6.3, 10): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 84% (0.100 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 2H), 7.57 – 7.51 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.08 (d, *J* = 1.8 Hz, 4H), 3.72 (sextet, *J* = 7.3 Hz, 1H), 3.13 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.64 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.29 (s, 3H), 1.19 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.97, 136.95, 136.55, 135.79, 133.03, 129.18, 129.09, 128.76, 128.43, 42.94, 39.01, 21.14, 17.43.

2-Methyl-1-phenyl-3-(*o*-tolyl)propan-1-one[19] (table 6.3, 11): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 78% (0.092 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 7.2 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.18 – 7.05 (m, 4H), 3.77 (sext, J = 7.0 Hz, 1H), 3.15 (dd, J = 14.0, 6.3 Hz, 1H), 2.74 (dd, J = 14.0, 7.9 Hz, 1H), 2.36 (s, 3H), 1.22 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.23, 138.22, 136.63, 136.31, 133.07, 130.45, 129.86, 128.75, 128.36, 126.43, 126.00, 41.40, 36.49, 19.81, 17.77.

2-Methyl-1-phenyl-3-(m-tolyl)propan-1-one[17] (table 6.3, 12): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 3-methylbenzyl alcohol (0.061 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 77% (0.091 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.61 – 7.51 (m, 1H), 7.51 – 7.41 (m, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.07 – 6.98 (m, 3H), 3.76 (sextet, *J* = 8.0 Hz, 1H), 3.16 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.67 (dd, *J* = 13.5, 7.9 Hz, 1H), 2.33 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.93, 139.96, 138.01, 136.53, 133.01, 130.01, 128.73, 128.40, 128.36, 127.04, 126.19, 42.83, 39.35, 21.50, 17.46.

3-(4-Methoxyphenyl)-2-methyl-1-phenylpropan-1-one[9] (table 6.3, 13): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-methoxybenzyl alcohol (0.069 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 74% (0.094 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.5 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.12 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.77 (s, 3H), 3.71 (sextet, *J* = 6.9 Hz, 1H), 3.11 (dd, *J* = 13.8, 6.4 Hz, 1H), 2.64 (dd, *J* = 13.7, 7.7 Hz, 1H), 1.19 (d, *J*

= 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.06, 158.11, 136.60, 133.02, 132.08, 130.13, 128.74, 128.39, 113.87, 55.33, 43.08, 38.61, 17.45.

3-(2-Methoxyphenyl)-2-methyl-1-phenylpropan-1-one[17] (table 6.3, 14): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-methoxybenzyl alcohol (0.069 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 67% (0.085 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.85 (t, *J* = 8.7 Hz, 2H), 3.91 – 3.81 (m, 4H), 3.19 (dd, *J* = 13.3, 5.4 Hz, 1H), 2.61 (dd, *J* = 13.3, 8.6 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.39, 157.61, 136.73, 132.89, 131.49, 128.60, 128.54, 128.18, 127.74, 120.44, 110.29, 55.27, 40.50, 35.25, 16.82.

3-(4-Chlorophenyl)-2-methyl-1-phenylpropan-1-one[18] (table 6.3, 15): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-chlorobenzyl alcohol (0.071 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 76% (0.098 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.1 Hz, 1H), 7.23 – 7.15 (m, 3H), 3.76 (sextet, *J* = 7.0 Hz, 1H), 3.18 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.70 (dd, *J* = 13.7, 7.8 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.87, 140.08, 136.61, 133.04, 129.22, 128.76, 128.50, 128.41, 126.32, 42.88, 39.50, 17.52.

3-(2-Chlorophenyl)-2-methyl-1-phenylpropan-1-one[20] (table 6.3, 16): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-chlorobenzyl alcohol (0.071 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 81% (0.104 g). ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.95 – 7.91 (m, 2H), 7.57 – 7.52 (m, 1H), 7.48 – 7.44 (m, 2H), 7.28 (dt, *J* = 6.8, 1.1 Hz, 1H), 7.25 (d, *J* = 1.0 Hz, 1H), 7.23 – 7.15 (m, 2H), 3.76 (sextet, *J* = 6.9 Hz, 1H), 3.18 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.70 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.92, 140.07, 136.54, 133.07, 129.22, 128.76, 128.50, 128.41, 126.32, 42.87, 39.47, 17.52.

2-Methyl-1-phenyl-3-(4-(trifluoromethyl)phenyl)propan-1-one[17] (table 6.3, 17): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-(Trifluoromethyl)benzyl alcohol (0.088 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 71% (0.103 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.59 – 7.53 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.45 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 3.77 (sextet, *J* = 7.0 Hz, 1H), 3.24 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.78 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (19F- decoupled) (101 MHz, $CDCl_3$) δ 203.18, 144.29, 136.37, 133.26, 129.54, 128.86, 128.72, 128.39, 125.43, 124.40, 42.63, 39.11, 17.90. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.25.

3-(4-Fluorophenyl)-2-methyl-1-phenylpropan-1-one[18] (table 6.3, 18): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 4-Fluorobenzyl alcohol (0.063 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 79% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.57 – 7.51 (m, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.15 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 3.72 (sextet, *J* = 7.0 Hz, 1H), 3.14 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.68 (dd, *J* = 13.8, 7.4 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.72, 161.5 (d, $J_{C\text{-}F}$ = 245.4 Hz), 136.50, 135.70 (d, $J_{C\text{-}F}$ = 3 Hz), 133.15, 130.58 (d, $J_{C\text{-}F}$ = 8.08 Hz), 128.79, 128.36, 115.25, (d, $J_{C\text{-}F}$ = 21 Hz), 42.96, 38.62, 17.66.^{19}F NMR (376 MHz, $CDCl_3$) δ -117.00, -117.03.

3-(2-Fluorophenyl)-2-methyl-1-phenylpropan-1-one[21] (table 6.3, 19): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-Fluorobenzyl alcohol (0.063 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 81% (0.098 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.23 – 7.13 (m, 2H), 7.05 – 6.96 (m, 2H), 3.83 (sextet, *J* = 6.9 Hz, 1H), 3.17 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.76 (dd, *J* = 13.7, 8.1 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.59, 161.44 (J_{C-F} = 245.4 Hz), 136.41, 133.10, 131.95 (J_{C-F} = 5.0 Hz), 128.76, 128.44, 128.20 (J_{C-F} = 8.0 Hz), 126.82 (J_{C-F} = 15.1 Hz), 124.04 (J_{C-F} = 3.0 Hz), 115.46, 115.35 (J_{C-F} = 22 Hz), 41.14, 33.23, 17.34. ^{19}F NMR (377 MHz, $CDCl_3$) δ -117.76.

3-([1,1'-Biphenyl]-4-yl)-2-methyl-1-phenylpropan-1-one (table 6.3, 20): Prepared from 1-(*p*-tolyl)ethanol (0. 102 g, 0.75 mmol) and 2-biphenylmethanol (0.092 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 64% (0.096 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 3H), 7.32 – 7.25 (m, 4H), 7.19 – 7.16 (m, 3H), 7.14 – 7.09 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 3.34 – 3.24 (m, 1H), 3.19 (dd, *J* = 13.6, 5.4 Hz, 1H), 2.50 (dd, *J* = 13.6, 9.2 Hz, 1H), 2.29 (s, 3H), 0.85 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.65, 143.60, 142.21, 142.11, 137.19, 133.79, 130.94, 130.39, 129.36, 129.30, 128.58, 128.43, 127.43, 127.14, 126.44, 40.81, 37.36, 21.71, 16.39.

2-Methyl-3-(naphthalen-2-yl)-1-phenylpropan-1-one[17] (table 6.3, 21): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-naphthalenemethanol (0.079 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 82% (0.112 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.5 Hz, 2H), 7.84 – 7.75 (m, 3H), 7.68 (s, 1H), 7.54 (t, *J* =

7.4 Hz, 1H), 7.45 (t, *J* = 7.1 Hz, 4H), 7.39 (d, *J* = 8.5 Hz, 1H), 3.88 (sextet, *J* = 6.9 Hz, 1H), 3.38 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.89 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.76, 137.54, 136.42, 133.56, 133.05, 132.17, 128.73, 128.37, 128.07, 127.66, 127.64, 127.58, 126.05, 125.41, 77.46, 77.16, 76.84, 42.76, 39.48, 17.59.

2-Methyl-1-phenyl-3-(thiophen-2-yl)propan-1-one[17] (table 6.3, 22): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 2-thiophenemethanol (0. 057 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 83% (0.095 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H), 7.60 – 7.53 (m, 1H), 7.50 – 7.42 (m, 2H), 7.10 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.88 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.80 (dd, *J* = 3.4, 1.1 Hz, 1H), 3.77 (sextet, *J* = 7.0 Hz, 1H), 3.38 (dd, *J* = 14.8, 6.7 Hz, 1H), 2.95 (dd, *J* = 14.8, 7.3 Hz, 1H), 1.26 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.25, 142.45, 136.26, 133.08, 128.71, 128.35, 126.82, 125.63, 123.62, 43.27, 33.26, 17.82.

3-(Furan-2-yl)-2-methyl-1-phenylpropan-1-one[20] (table 6.3, 23): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and furfuryl alcohol (0.049 g, 0.5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 86% (0.092 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.92 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.23 (m, 1H), 6.23 (t, *J* = 2.4 Hz, 1H), 6.00 (d, *J* = 3.1 Hz, 1H), 3.85 (sextet, *J* = 7.0 Hz, 1H), 3.13 (dd, *J* = 15.1, 6.4 Hz, 1H), 2.75 (dd, *J* = 15.1, 7.6 Hz, 1H), 1.21 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.43, 153.75, 141.35, 136.25, 133.16, 128.79, 128.46, 110.32, 106.63, 40.10, 31.72, 17.65.

3-(Benzo[d][1,3]dioxol-5-yl)-2-methyl-1-phenylpropan-1-one[11] (table 6.3, 24): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol) and 3,4-(methylenedioxy)benzyl

alcohol (0. 076 g, 0,5 mmol). After purification by column chromatography (silica gel 100-200 mesh, hexane: ethyl acetate in 99:1), the compound was isolated in 59% (0.079 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.8 Hz, 2H), 7.59 – 7.51 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 6.70 (d, *J* = 7.6 Hz, 2H), 6.64 (d, *J* = 7.9 Hz, 1H), 5.90 (s, 2H), 3.70 (sextet, *J* = 7.0 Hz, 1H), 3.08 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.62 (dd, *J* = 13.8, 7.6 Hz, 1H), 1.19 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.83, 147.64, 146.00, 136.55, 133.80, 133.06, 128.77, 128.39, 122.12, 109.55, 108.26, 100.91, 43.06, 39.18, 17.51.

2-benzyl-1-phenylpropan-1-one-2,3,3-d3 (scheme 6.4, 27): Prepared from 1-phenylethanol (0.091 g, 0.75 mmol), benzyl alcohol (0.054 g, 0.5 mmol) and methanol-d4 (1 mL). After purification by column chromatography the compound was isolated in 89% (0.099 g, based on the molecular weight of the protonated compound^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 2H), 7.54 – 7.48 (m, 1H), 7.45 – 7.41 (m, 2H), 7.23 (d, *J* = 7.5 Hz, 2H), 7.20 – 7.13 (m, 3H), 3.14 (d, *J* = 13.7 Hz, 1H), 2.66 (d, *J* = 13.7 Hz, 1H), 1.14 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.94, 140.06, 136.54, 133.05, 129.19, 129.11, 128.75, 128.72, 128.64, 128.54, 128.49, 128.42, 128.38, 128.16, 126.30, 126.25, 42.73, 42.67, 39.33, 16.86.

2-benzyl-1-phenylpropan-1-one-2,3,3,3-d4 (scheme 6.4, 28): Prepared from acetophenone (0.090 g, 0.75 mmol), benzyl alcohol (0.054 g, 0.5 mmol) and methanol-d4 (1 mL). After purification by column chromatography the compound was isolated in 93% (0.105 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.9 Hz, 2H), 7.25 – 7.20 (m, 4H), 7.20 – 7.08 (m, 4H), 3.13 (d, *J* = 13.9 Hz, 1H), 2.65 (d, *J* = 13.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.59, 143.75, 140.21, 134.05, 129.47, 129.21, 129.13, 128.54, 128.49, 126.28, 39.39.

6.5. References

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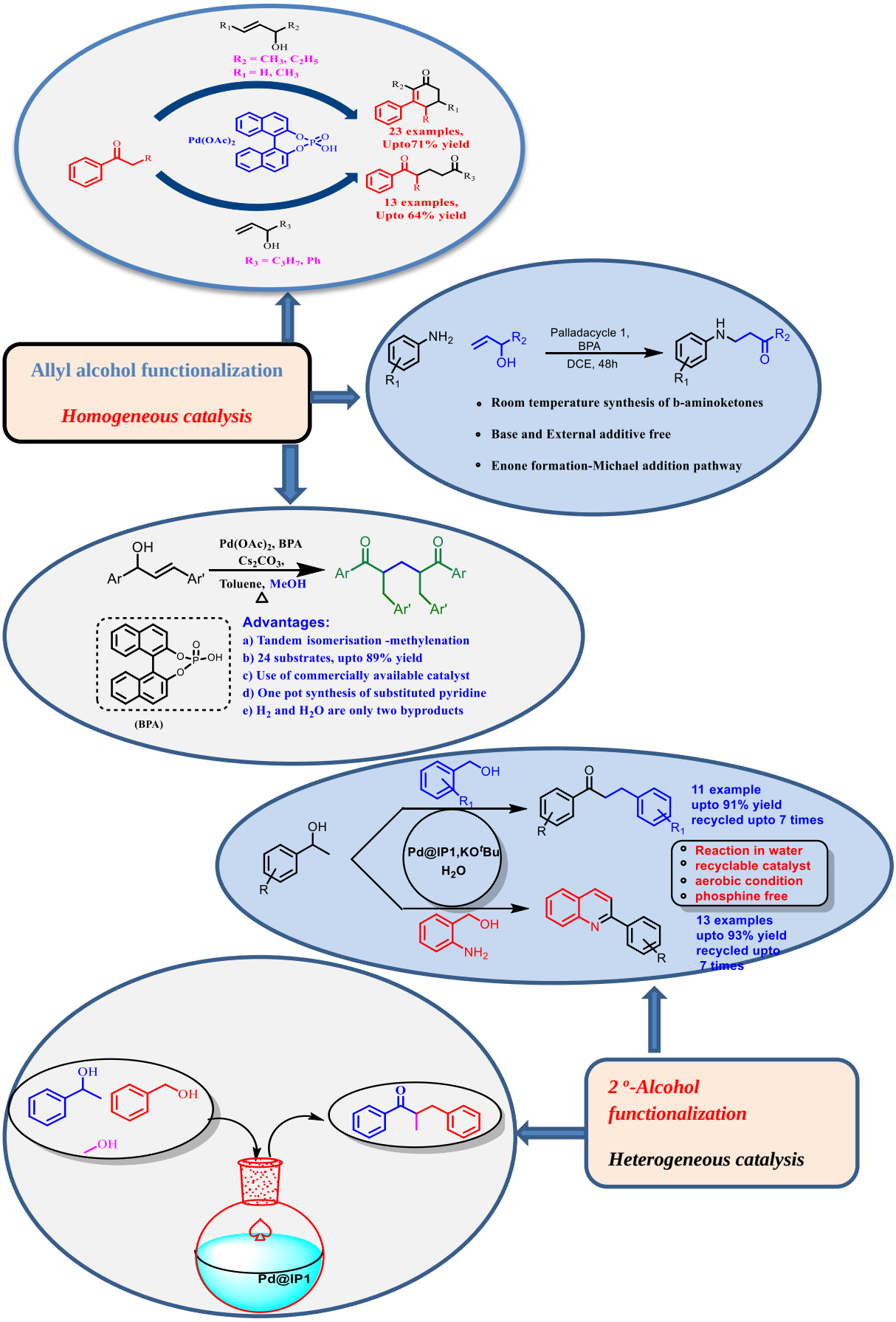
R2 = CH3, C2H5
R1 = H, CH3
Pd(OAc)2
23 examples,
Upto71% yield
13 examples,
Upto 64% yield
R3 = C3H7, Ph
Allyl alcohol functionalization
Homogeneous catalysis
Palladacycle 1,
BPA
DCE, 48h
Room temperature synthesis of b-aminoketones
Base and External additive free
Enone formation-Michael addition pathway
Pd(OAc)2, BPA
Cs2CO3,
Toluene, MeOH
(BPA)
Advantages:
a) Tandem isomerisation -methylenation
b) 24 substrates, upto 89% yield
c) Use of commercially available catalyst
d) One pot synthesis of substituted pyridine
e) H2 and H2O are only two byproducts
Pd@IP1,KO'Bu
H2O
11 example
upto 91% yield
recycled upto 7 times
Reaction in water
recyclable catalyst
aerobic condition
phosphine free
13 examples
upto 93% yield
recycled upto
7 times
2 º-Alcohol
functionalization
Heterogeneous catalysis
Pd@IP1