Activation of methanol as a C1 source using Pd, Ru and Co-compounds to make new C-C bonds

By

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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.

Priyabrata Biswal

LIST OF PUBLICATIONS

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1. ***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.
2. ***Biswal, P.**; Samser, S.; Meher, S. K.; Chandrasekhar, V.; Venkatasubbaiah, K., Palladium-catalyzed synthesis of α-methyl ketones from allylic alcohols and methanol. *Adv. Synth. Catal.* **2022**, *364*, 413–419.
3. ***Biswal, P.**; Subramani, M. S.; Samser, S.; Chandrasekhar, V.; Venkatasubbaiah, K., Ligand-controlled ruthenium-catalyzed borrowing hydrogen and interrupted borrowing hydrogen methodologies: functionalization of ketones using methanol as a C1 source. *J. Org. Chem.* **2022**, 10.1021/acs.joc.2c00653.
4. [#]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.
5. 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.
6. 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.
7. 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.
8. Sa, S.; Ponniah, S. J.; **Biswal, P.**; Sathesh, V.; Murali, A.C.; Venkatasubbaiah, K., Distannadithiophenes and their application towards hydroboration of carbonyl compounds. *Eur. J. Inorg. Chem.* **2022**, 10.1002/ejic.202200283

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1. *__Biswal, P.__; Pullarat, S. S; Samser, S.; Chandrasekhar, V.; Venkatasubbaiah, K., Ruthenium catalyzed one-pot sequential synthesis of substituted pyridine from allyl alcohol and methanol *via* isomerization-methylenation.

CONFERENCES

- Pyrazole Based Palladacycle for Methylation of Ketones and Amines using Methanol as a C-1 Source. **Biswal, P.**; Chandrasekhar, V.; Venkatasubbaiah, K., in the 1st international conference, 'Main Group Molecules to Materials' (MMM-I) held at IISc, Banglore during October 28 th to 31st 2018. (**Poster presentation**)
- Palladacycle-Phosphine Mediated α-Methylation of Ketones and N-Methylation of Amines Using Methanol. **Biswal, P.**; Chandrasekhar, V.; Venkatasubbaiah, K., in the international conference, 'The Present and Future of Excellence in Organic Synthesis' (PFEOS-2021) held at Tezpur University, Assam, India during January 7 to 8, 2021. (**Poster presentation**)
- Cobalt(II) porphyrin mediated selective synthesis of 1,5-diketones via an interrupted Borrowing hydrogen strategy using methanol as a C1 source. Biswal, P.; Chandrasekhar, V.; Venkatasubbaiah, K., in the 2nd international conference, 'Main Group Molecules to Materials' (MMM-II) held at NISER, Bhubaneswar during December 13 th to15 th 2021. (**Poster presentation**)

Priyabrata

Priyabrata Biswal

Dedicated to

my lovely wife

Ms. Suprava Mohanty

Priyabrata Biswal

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Priyabrata Biswal

CONTENTS

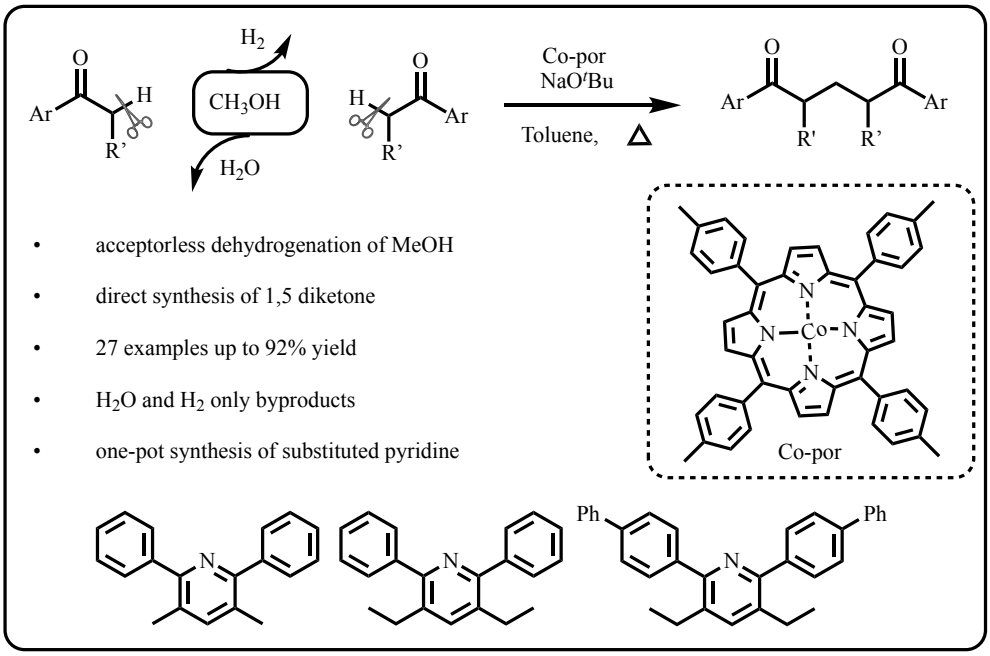
SYNOPSIS

This thesis has been organized in to five chapters. **Chapter 1** is divided into two parts. The first part of this chapter briefly discussed about the history of activation and functionalization of methanol through borrowing hydrogen method (**BH**) and interrupted borrowing hydrogen (**I-BH**) method utilizing Pd, Ru and Co catalysts. The second part of this chapter discussed about the redox-isomerization of allyl alcohol by different metal catalysts and the use of allyl alcohol as enolate precursor for the synthesis of different valuable molecules via a tandem process of isomerization and functionalization.

Chapter 2: Cobalt(II) porphyrin mediated selective synthesis of 1,5-diketones via an interrupted borrowing hydrogen strategy using methanol as a C1 source.

This chapter describes a unique approach for the activation of methanol to synthesis 1,5- diketones using a simple cobalt(II)porphyrin. The developed approach is based on the activation and utilisation of methanol as a C1 source using an I-BH method. The established methodology has been elegantly employed for the coupling of methanol with a wide range of ketones having various substituents as well as hetero aryl ketones to yield 1,5-diketones as well as H_2 and H_2O as environmentally benign byproducts. Control experiments and deuterium-labelling study reveals that the reaction proceeds via the condensation of ketones with in-situ generated formaldehyde from methanol to generate an α-methylenated intermediate. The resultant α-methylenated intermediate via 1,4-Michael addition condense with another molecule of ketone to give the desired 1,5 diketone products. This protocol was successfully utilised for the synthesis of substituted pyridines *via* sequential addition. Pyridines thus synthesized have shown

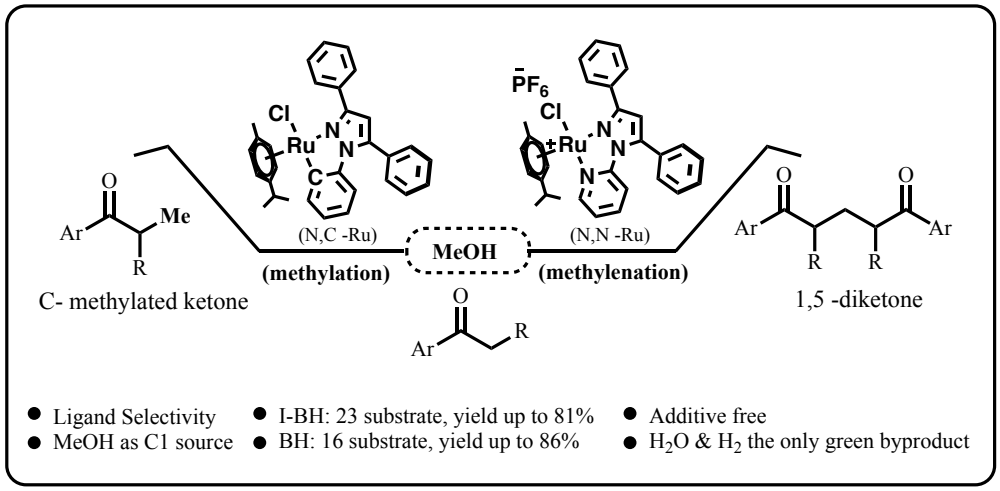
Aggregate Induced Emission Enhancement (AIEE) properties which may have potential application in making organic light emitting diodes.



Chapter 3: Ligand controlled ruthenium catalyzed BH and I-BH switchable selectivity; functionalization of ketones using methanol as a C1 source.

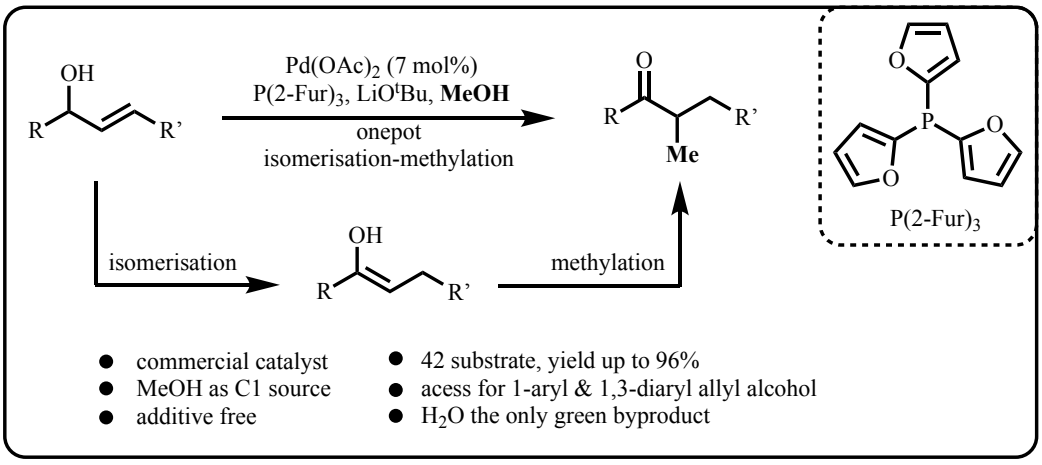
This chapter describes a unique ligand selective protocol for the synthesis of α-methylated ketones and 1,5-diketones utilising N,C−Ru and N,N−Ru catalysts respectively. It proceeds through a ligand selective BH and I-BH methods for the activation of methanol as a C1 source. This protocol tolerates a variety of ketones having different electron withdrawing and electron donating substituents as well as alicyclic ketones and heteroaryl ketones to give the desired α-methylated ketones and 1,5-diketones. Control experiments and isotopic labelling experiments reveal that an in situ formed formaldehyde is one of the crucial elements in this ligand-controlled selective protocol, which upon reaction with a ketone generates enone as an intermediate. This enone intermediate undergoes two competing transformations depending on the ligand attached to the ruthenium. A methylated product is obtained

using the N,C−Ru catalyst through the BH method, and a 1,5-diketone product is obtained through the I-BH method using the N,N−Ru catalyst.



Chapter 4: Palladium catalyzed synthesis of α-methyl ketones from allyl alcohol and methanol

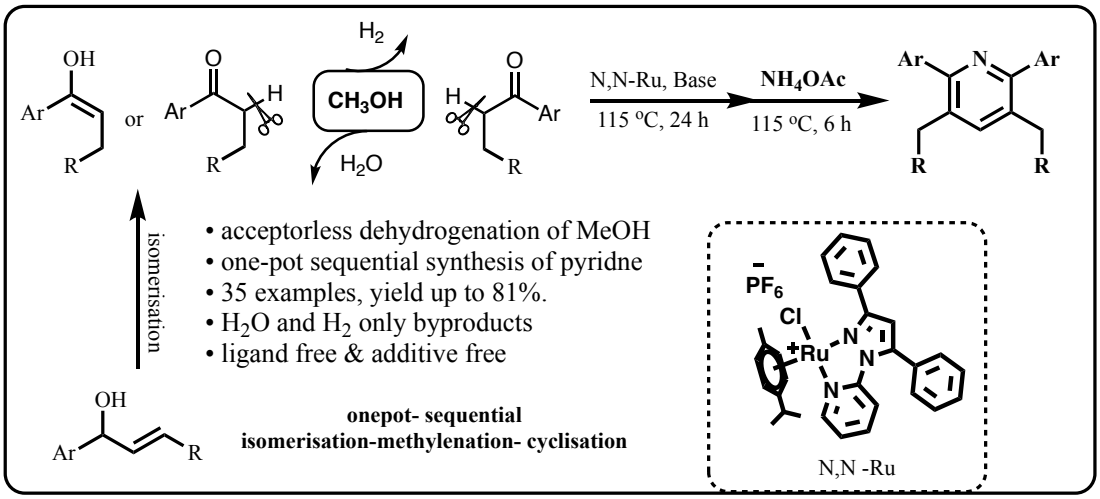
Chapter 4 provides a brief discussion about the one-pot isomerization and methylation of allyl alcohol to synthesize α-methylated ketones catalyzed by commercially available $Pd(OAc)_2$. This protocol is based on the tandem isomerization and methylation of allyl alcohol utilizing methanol as C1 source through borrowing hydrogen method. Using methanol as a C1 source, a broad variety of 1,3-diaryl



propenols and 1-aryl propenols with distinct electron withdrawing and electron donating substituents were screened. The isotopic labelling using CD_3OD reveal the involvement of a palladium hydride species and a palladium enolate species in the catalytic process. Control experiments and the isotopic labelling studies reveals the involvement of BH pathway in these isomerization-methylation reaction.

Chapter 5: Ruthenium catalyzed one-pot sequential synthesis of substituted pyridines from allyl alcohols and methanol *via* isomerization-methynelation.

This chapter describes a one-pot isomerization and methylenation of allyl alcohol, followed by a sequential addition protocol to synthesize symmetrical pyridines. This protocol was catalyzed by N,N-coordinated ruthenium catalyst for the isomerization-methylenation of allyl alcohol utilizing MeOH as a C1 source through I-BH strategy.



A wide variety of 1,3-diaryl propenols and 1-aryl propenols with distinct electron withdrawing and electron donating substituents provides the desired pyridine products in good yield. Mechanistic study confirms the formation of 1,5-diketone from allyl alcohol and MeOH via a methylenated intermediate, which upon reaction with NH_4OAc produced the desired pyridine.

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List of Abbreviations

^{1}H NMR	Proton nuclear magnetic resonance
^{13}C NMR	Carbon-13 nuclear magnetic resonance
^{19}F NMR	Fluorine-19 nuclear magnetic resonance
IR-spectroscopy	Infrared spectroscopy
UV-Vis	Ultraviolet–Visible
ESI	Electrospray ionization
DFT	Density functional theory
HRMS	High-resolution mass spectrometry
XRD	X-ray diffraction
AIEE	Aggregation induced emission enhancement
ppm	Parts per million
MeOH	Methanol
CD_3OD	Deuterated methanol
HCHO	Formaldehyde
TEMPO	2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
CH_2Cl_2	Dichloromethane
$CHCl_3$	Chloroform
DCE	1,2-Dichloroethane
CH_3CN	Acetonitrile
EtOH	Ethanol
THF	Tetrahydrofuran
H_2O	Water
DMSO	Dimethyl sulfoxide
DMF	Dimethylformamide
$CDCl_3$	Deuterated chloroform
NH_4OAc	Ammonium acetate
$NH_2OH.HCl$	Hydroxylamine hydrochloride
$NH_2NH_2.H_2O$	Hydrazine hydrate
AcOH	Acetic acid
LiO^tBu	Lithium tert-butoxide
NaO^tBu	Sodium tert-butoxide

KO^tBu	Potassium tert-butoxide
KOH	Potassium hydroxide
NaOH	Sodium hydroxide
LiOH	Lithium hydroxide
Na_2CO_3	Sodium carbonate
K_2CO_3	Potassium carbonate
Cs_2CO_3	Cesium carbonate
NH_4PF_6	Ammonium hexafluorophosphate
TON	Turn over number
NHC	N-heterocyclic carbene
PEG	Polyethylene glycol
IL	Ionic Liquid
PVP	Polyvinyl pyridine
PS	Polystyrene
TBAB	Tetrabutylammonium bromide
DESs	Deep eutectic solvents
BINOL	Binaphthol
BPA	BINOL phosphoric acid
Dppe	1,2-Bis(diphenylphosphino)ethane
TBHP	Tert-butyl hydroperoxide
Pd	Palladium
Co	Cobalt
Ru	Ruthenium
Ir	Iridium
Mn	Manganese
ND	Not detected

CHAPTER 1

Methanol activation through BH and I-BH methods using Pd, Ru, Co-catalysts or precatalysts and allyl alcohol isomerization and functionalization

1.1 Introduction

One of the major goals in chemical research is to increase the molecular complexity of a basic organic substrate with high atom economy, selectivity and high yielding by accompanying environmental benign methods using naturally abundant feedstocks.[1,2] In this context, the hydrogen borrowing (BH) method also known as hydrogen auto transfer process and the interrupted hydrogen borrowing (I-BH) method have received a lot of attention for their ability to synthesize new C-C and C-X (X=hetero atom) bonds using alcohol as a "greener" and "renewable" reagent and alternative to traditional alkylating agents (**Figure 1.1**).[2] In recent years utilisation of these alcohols as alkylating reagents employing sustainable and environmental benign process has gained key importance in organic synthesis as they are widespread in nature, inexpensive and nontoxic.[2] These approaches provide a greener alternative to regular C-C and C-N bond forming reactions, since they are generating only H_2O and/or H_2 as the byproduct. The replacement of traditional alkylating reagents or precursors,[3] which are mainly expensive, hazardous and waste-generating with these "greener" and "renewable" alternatives such as alcohol [2] *via* the BH and I-BH protocols is a key challenge for both academic research and industrial production.

1.2. Methanol activation: Introduction and history

Methanol amongst all alcohols is the simplest aliphatic alcohol, economically cheap, naturally abundant and a biodegradable liquid. Its yearly production surpasses 100 million metric tonnes due to its extensive use and continues to grow at a rate of 4–5 percent each year.[4] In terms of methanol synthesis, the first commercialized process that generated methanol as a by-product was the destructive distillation of wood.[5] Methanol is currently manufactured from syngas using catalysts for industrial need,[6] additionally it can be produced from natural gas, municipal waste, coal, and biomass.

Methanol, on the other hand is recognised as the most affordable energy storage (H_2) substance[7] as well as a viable alternative fuel for total internal combustion.[8] Nonetheless, methanol activation is a highly challenging process due its higher dehydrogenation energy ($\Delta H = +84$ kJ mol^{-1}) compared to benzyl and other long chain alcohols like ethanol ($\Delta H = +68$ kJ mol^{-1}) to produce the corresponding transient aldehydes as intermediate.[9] Transition metal catalysed activation of methanol to make different organic molecules is in great demand and will remain as a key research topic due to its immense demand both in academic and industry (**Figure 1.2**).

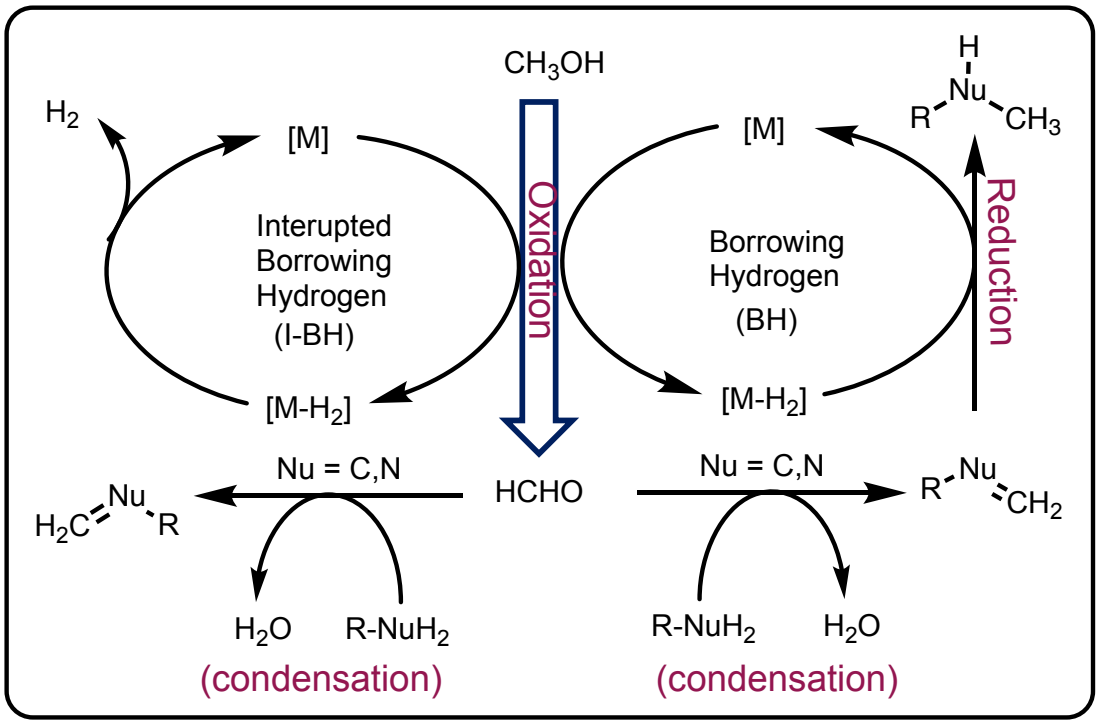


Figure 1.1. Schematic view of borrowing hydrogen and interrupted borrowing hydrogen

The "methyl" group is one of the most valuable substituents present in many drugs, biomolecules, and natural products (**Figure 1.3 & 1.4**).[10] In particular, the incorporation of the "methyl" group to make H_3C-C and H_3C-N bond has a special advantage, as it constitutes a major chemical motif for many compounds that are biologically and pharmaceutically active and also for the synthesis of fine chemicals.[10]

For instance, when the C- H bond adjacent to an oxygen atom of the Aprepitant drug is replaced with a C- CH_3 bond through methylation, it's *in vivo* efficiency and activity dramatically got enhanced.[11] As a result, C-methylation of diverse chemical compounds has been reported in recent years, which involves numerous important discoveries. N-methylation of amines also plays a crucial role in biological processes, gene regulation, protein function, RNA processing.[12] Nevertheless, many carbonyl compounds with β-methoxy substituents and β-hydroxy substituents in their chemical motif have shown wide range of applications either as building blocks or synthetic intermediates. They are also found as structural motif's in many drug molecules and biologically active compounds.

1.2.1 Borrowing hydrogen and Interrupted borrowing hydrogen

In recent years, organic chemist put key focus on methylation process due to the tremendous benefits of "methyl" substitution in bioactive molecules. Traditionally, the "methyl" group was introduced in organic molecules by employing the classical methylating reagents such as Grignard reagents, methyl halide, dimethyl sulphate, diazomethane, tetramethylammonium chloride, methyl triflate, and methyl fluorsulfonate in both laboratory and industry.[3, 13] However, the classical reagents mentioned above have major drawbacks such as toxicity and corrosiveness which makes these processes ecologically unfavourable. Furthermore, substrates having structurally diversified functional groups are often non-selective and less feasible in these classical methods. To avert these problems, it is highly desirable to find out more convenient and non-hazardous greener and sustainable C1 source reagents to reduce their production cost.[14] Amongst the different methylating reagents, methanol gains focus as

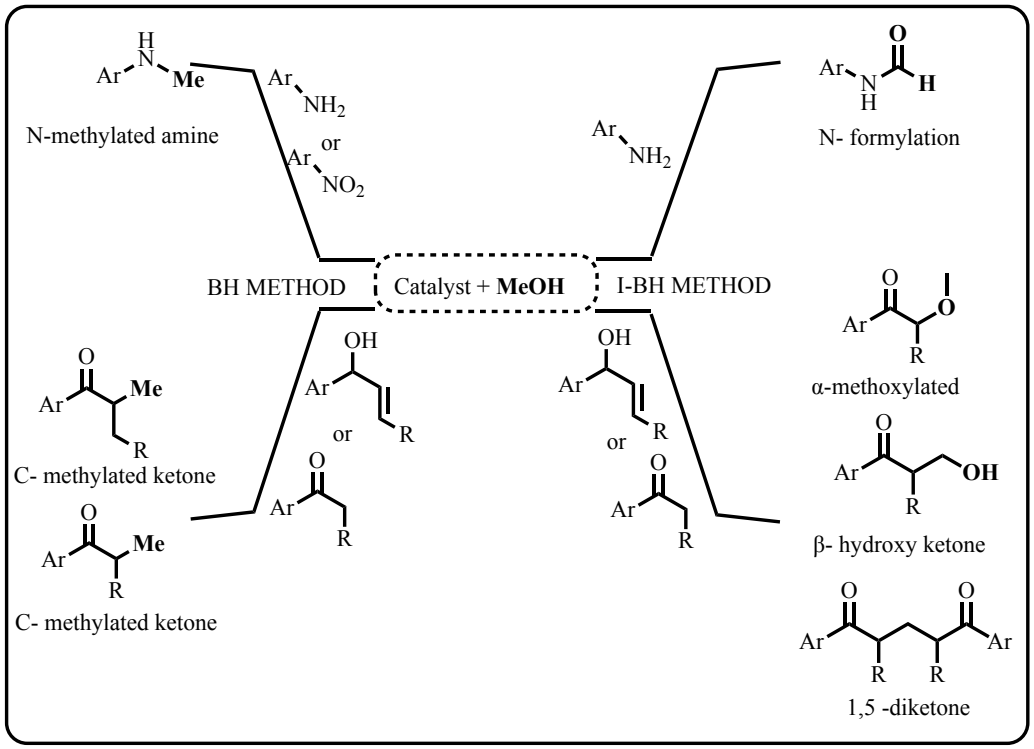


Figure 1.2. Borrowing hydrogen and Interrupted borrowing hydrogen products

a C1 source or an alternative green methylating agent, due to its importance in both organic synthesis and drug discovery. "Methanol" is a less-hazardous and biodegradable one-carbon (C1) source, and generates only H_2O and H_2 gas as the by-product through BH and I-BH processes.[15,16] Despite the fact that methylation with methanol is challenging, it has the benefit of not requiring any additional acidic or reducing agents for the selective catalytic methylation. In recent years, utilisation of methanol for the synthesis of methylated (α-methylated ketone, N-methylated amine) and methylenated (methyl ether, β-hydroxy ketone, 1,5-diketone, α,β-unsaturated ketone, N-formylated amine) compounds by BH[15] and I-BH[16] respectively have gained attention. Significant efforts have been undertaken over the past several years to develop highly efficient homogeneous and heterogeneous catalysts for catalytic methanol activation *via* the BH and I-BH processes.

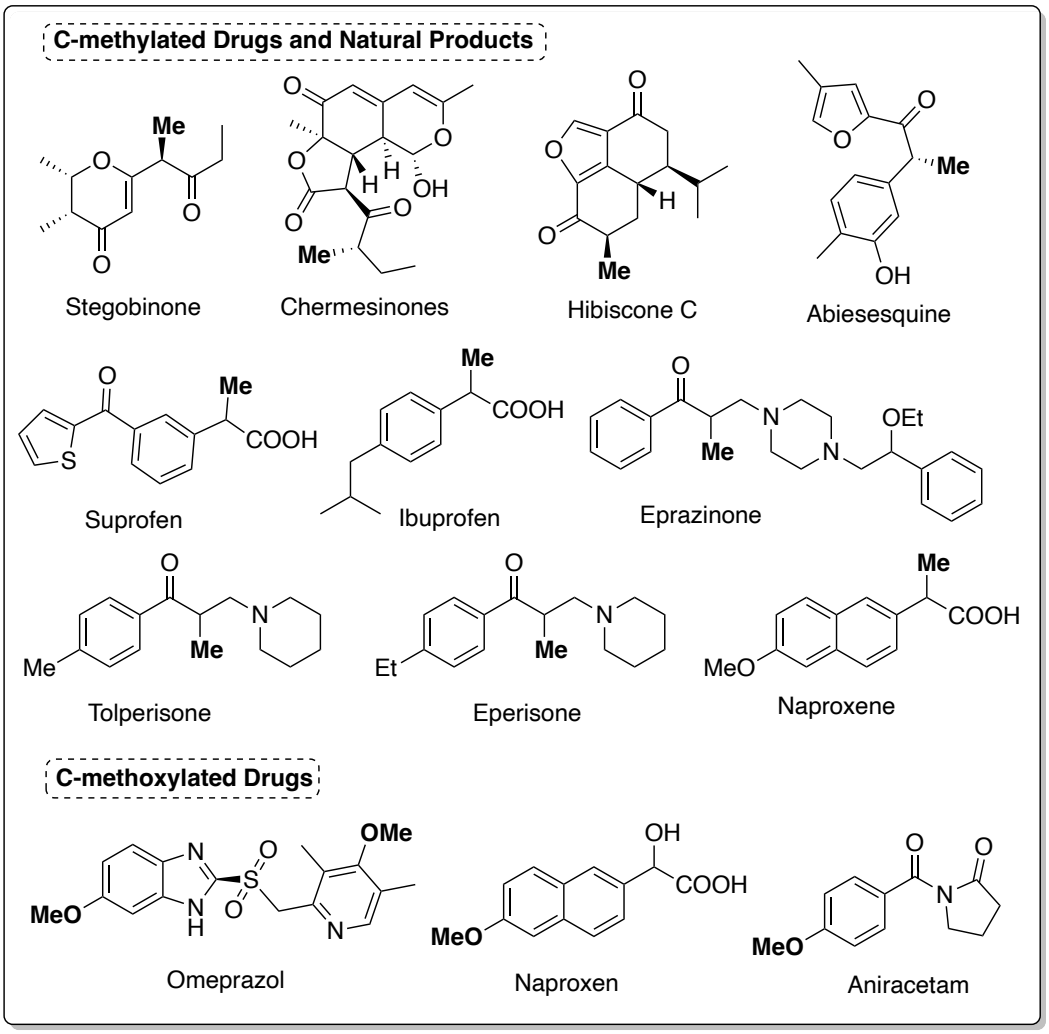


Figure 1.3. Natural products and drug molecules containing α-methyl groups

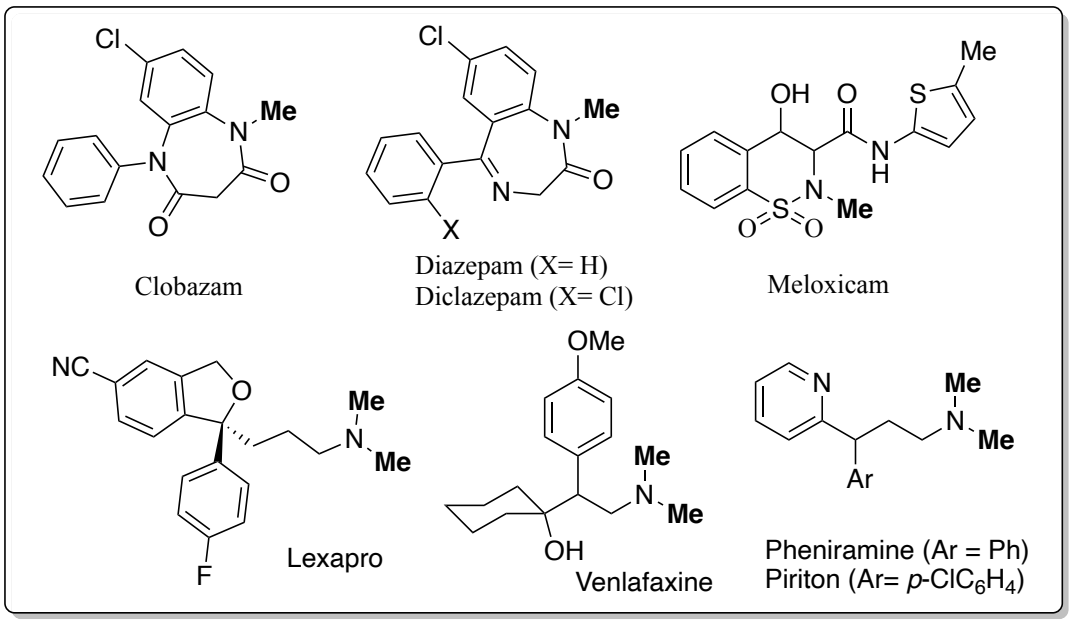


Figure 1.4. Natural products and drugs molecules containing N-methyl groups

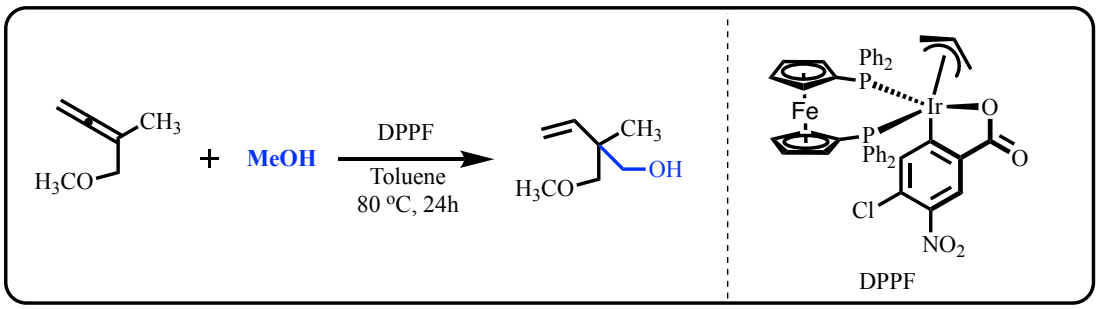
1.2.2 C-Methylation (C-CH_3 bond formation) using BH methodology: Recent reports

The chemistry of borrowing hydrogen (BH) method also termed as hydrogen auto-transfer method is a highly effective system for activation of alcohols such as methanol to produce a "methyl" branched molecule *via* C-C cross coupling reaction with corresponding precursors through reverse hydrogenation without direct hydrogen gas exposure. This methodology follows three basic steps such as: (i) dehydrogenation, (ii) intermediate reactions, and (iii) reverse hydrogenation. This technique generally involves a transition metal catalyst to start the activation of less reactive methanol through dehydrogenation. Subsequently, the metal catalyst is converted into the metal hydride temporarily by converting the methanol into a more reactive substrate *i.e.*, formaldehyde. The more reactive formaldehyde after reacting with the precursor is transformed into the corresponding unsaturated molecule *via* aldol condensation. The metal hydride produced at first in the dehydrogenation process transfer the hydride to the unsaturated molecule to give the desired "methyl" branched product by regenerating the active metal catalyst, which will be used for the catalytic cycle. The major advantages of the borrowing hydrogen methodology are (i) It's a simple one-pot reaction, thus it does not require tedious work-up. (ii) The hydrogenation step is thermodynamically favoured, and this shifts all three equilibriums towards the formation of final product resulting in high yields. (iii) The sole by-product is water making it ecologically favourable which again simplifies the purification process. (iv) The reverse reduction step proceeds without direct hydrogen gas exposure. Overall, the BH strategy can be considered as a unique example of green chemistry and a powerful approach in view of synthetic, economic, and environmental aspects. This strategy has

a lot of promise in terms of natural products or pharmaceutical drug molecule production.

1.2.2.1 α-Methylation of ketones

In 2011, Krische and co-worker reported a homogeneous iridium catalyst coordinated with a diphenylphosphino ferrocene moiety and utilised it for the synthesis of homoallylic alcohols from 1,1-disubstituted allenes using methanol as a C1 source.[17] This is the first example studied to use methanol as a reagent to create a hydroxy-methylation products through a C-C coupling process. (**Scheme 1.1**).



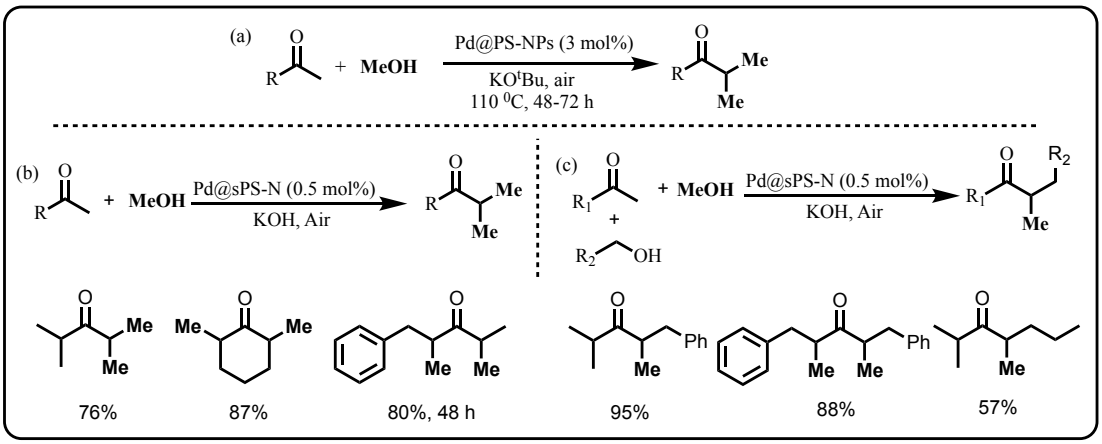
Scheme 1.1 Hydroxy-methylation of allenes

<u>Palladium catalysed α-methylation of ketones</u>

In the year of 2017, Das and co-workers[18] reported polymer stabilized palladium (Pd@PS) nanoparticles for the α-alkylation, α-ethylation and α-methylation of acyclic, cyclic, and aliphatic ketones utilizing long chain alkyl and benzyl alcohols, ethanol and methanol as reagents (**Scheme 1.2.a**). This protocol focuses more on the alkylation and ethylation of ketones, whereas methylation is limited to eight substrates. Lack of Pd leaching from the catalyst makes the catalytic cycle and the catalyst more efficient in terms of reusability and catalytic efficiency.

In the same year, Hou and co-workers[19] reported an amine-functionalized syndiotactic polystyrene (sPS–N) system having Pd nanoparticles immobilised on it as

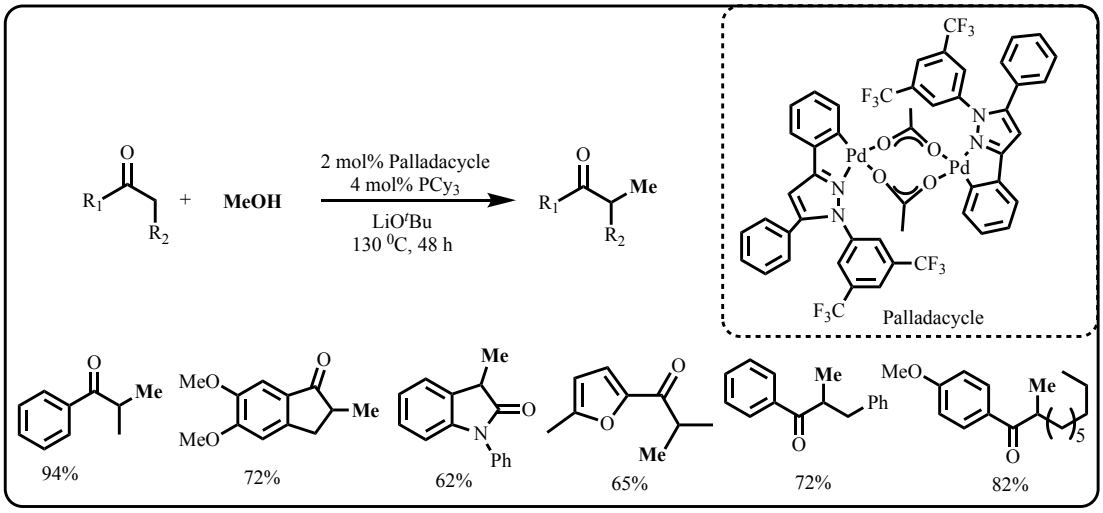
a heterogeneous catalyst (**Scheme 1.2.b**). They effectively utilised the catalyst for the di-methylation of ketones having different functional groups including highly challenging alkyl ketones at a low catalyst loading (0.5 mol%). The reaction proceeded in an aerobic environment, resulting in the desired methylated product in up to 97% yield. With the objective of extending the synthetic utility of the catalytic protocol, they also demonstrated three-component alkylation-methylation reactions using this Pd heterogeneous catalyst and extended to various methyl ketones by utilizing methanol along with higher alcohols (**Scheme 1.2.c**). The heterogeneous catalyst, Pd@sPS–N was successfully recycled up to five times and found no substantial decrease in the catalytic activity.



Scheme 1.2. Heterogeneous palladium catalysed methylation of ketones

In 2019, our group[15e] for the first time developed a homogeneous palladacycle combined with a phosphine ligand as a precatalyst for the methylation of ketones utilizing methanol as a C1 source. Ketones with various functional groups were screened using the palladacycle-phosphine precatalyst to produce the methylated products in good to excellent yield (**Scheme 1.3**). The catalytic cycle is triggered by the formation of a palladium methoxide complex which upon β-hydride elimination produce the reactive formaldehyde and palladium hydride species. This reactive

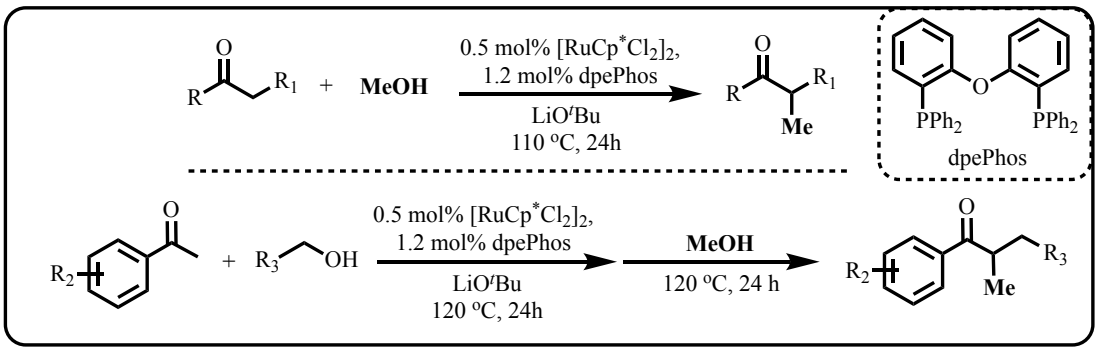
formaldehyde *via* condensation reaction with different ketones generate the corresponding methylenated ketone intermediate which further undergoes reduction by the palladium hydride species, that resulted in α-methylated ketone product.



Scheme 1.3. Homogeneous palladium catalysed methylation of ketones

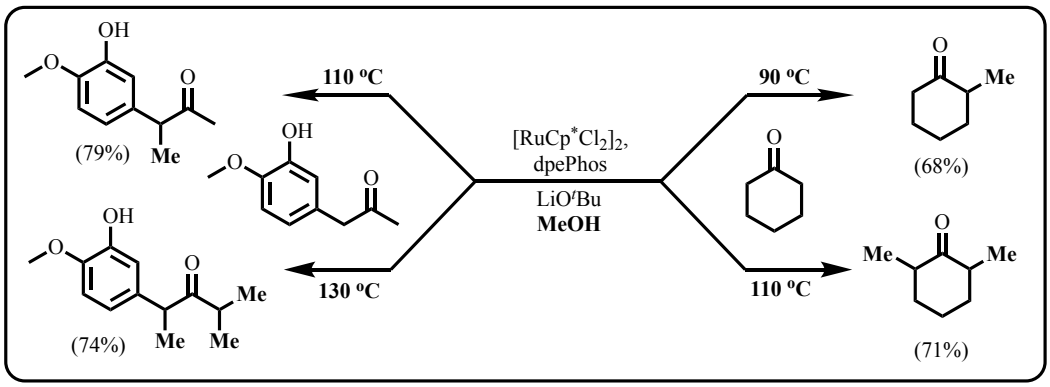
Ruthenium catalysed α-methylation of ketones.

Seayad and co-workers[15b] in 2016 created a successful and cost-effective approach for the α-methylation of ketones using a ruthenium catalyst by utilising methanol as a C1 source (**Scheme 1.4.a**). The catalytic system was effective for the methylation of ketones as well as for sequential alkylation-methylation of ketones using methanol. Moreover, the catalytic system works smoothly in the presence of sub-stoichiometric quantity of LiO^{t}Bu and the in-situ generated Ru-Cp*(dpePhos)Cl catalyst.

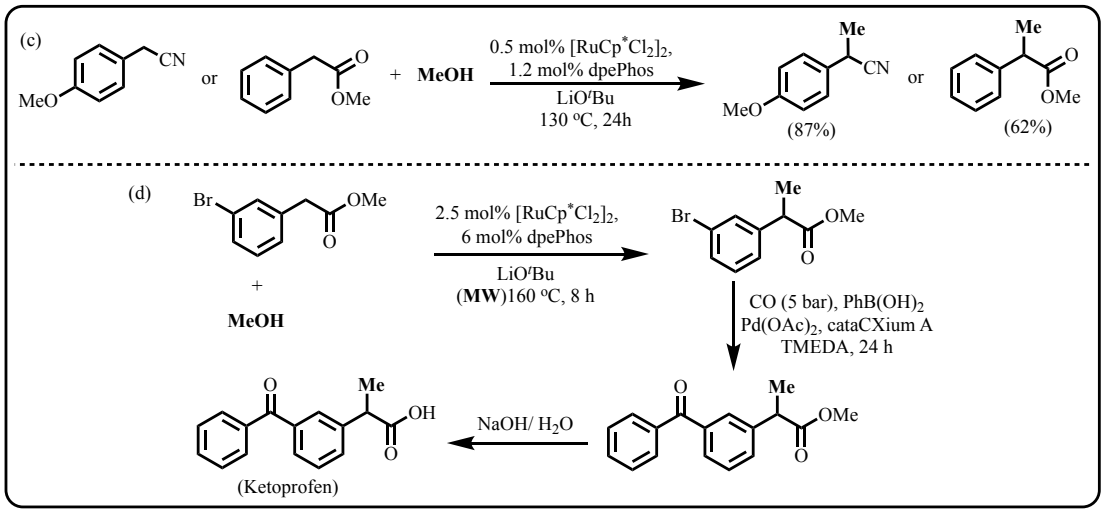


Scheme 1.4. (a)Ruthenium catalysed methylation and alkylation-methylation of ketones

Further experiments reveal that, temperature play a crucial role to regulate the regioselectivity *viz.* mono- or di-methylation of ketones (**Scheme 1.4.b**). Mono methylated products were observed at low temperature and dimethylated products were observed at high temperature.



Scheme 1.4. (b)Ruthenium catalysed temperature control methylation of ketones

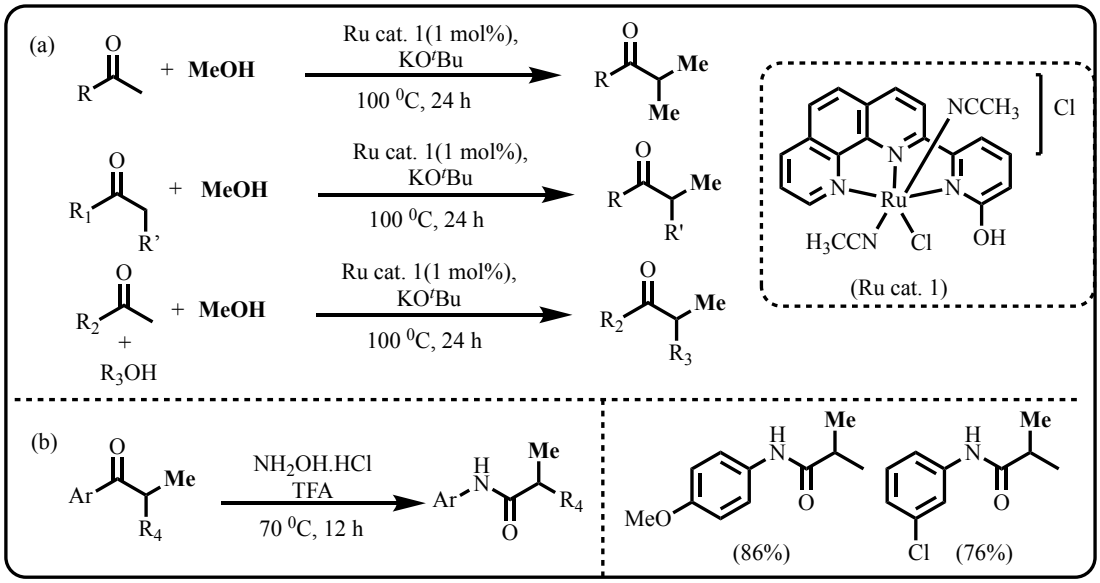


Scheme 1.4. (c) Ruthenium catalysed methylation of esters and nitriles (d) Synthesis of ketoprofen.

An added advantage of this protocol is that, it can be extended to methylation of esters and methylation of nitriles as well (**Scheme 1.4.c**). To highlight the potential benefits of this process, ketoprofen a nonsteroidal anti-inflammatory drug was catalytically

synthesised using this methodology from easily accessible starting ingredients (**Scheme 1.4.d**).

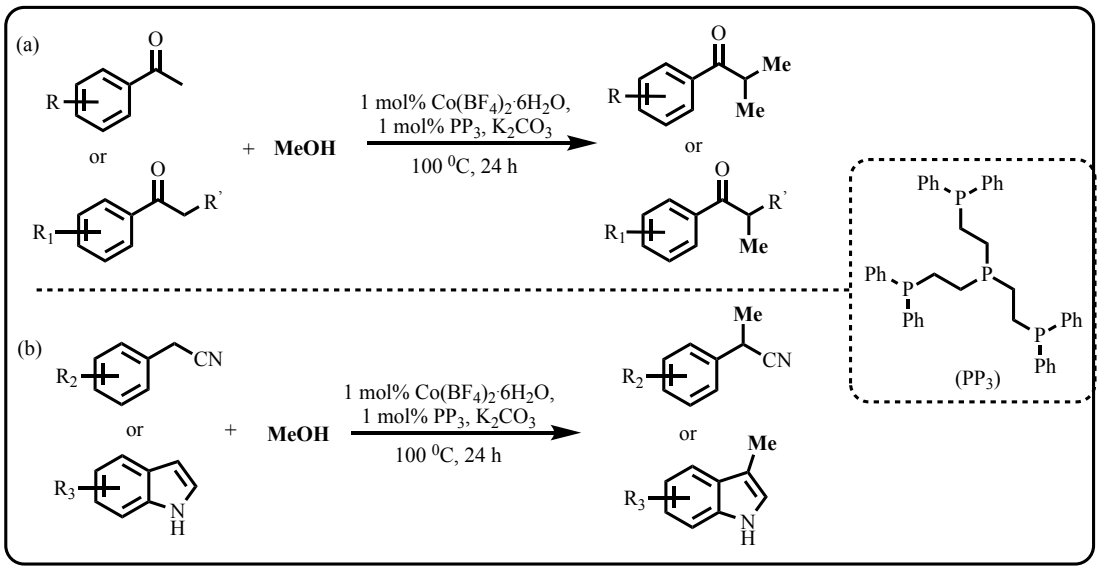
Multicomponent reactions are one of the most efficient and highly cost-effective tools in synthetic chemistry to create new bonds in a single step for the preparation of highly functionalized complex molecular systems. In 2017, Kundu and co-workers[20] reported a Ru(II) catalysed multicomponent reaction for the synthesis of α-branched methylated ketones (**Scheme 1.5.**). This non-phosphine-based catalyst efficiently produced various methylated ketones as well as various α-branched methylated ketones utilizing methanol along with higher alcohols. Furthermore, they were able to convert these methylated ketone products into the corresponding acetanilide derivatives to demonstrate the protocol's synthetic utility. The catalyst loading was lowered to 0.5 mol % at 85 °C for α-methylation of ketones utilising methanol as a methylating agent, which was further reduced to 0.1 mol % at 120 °C.



Scheme 1.5. (a) Ruthenium catalysed methylation and alkylation-methylation of ketones (b) Synthesis of acetanilide derivatives

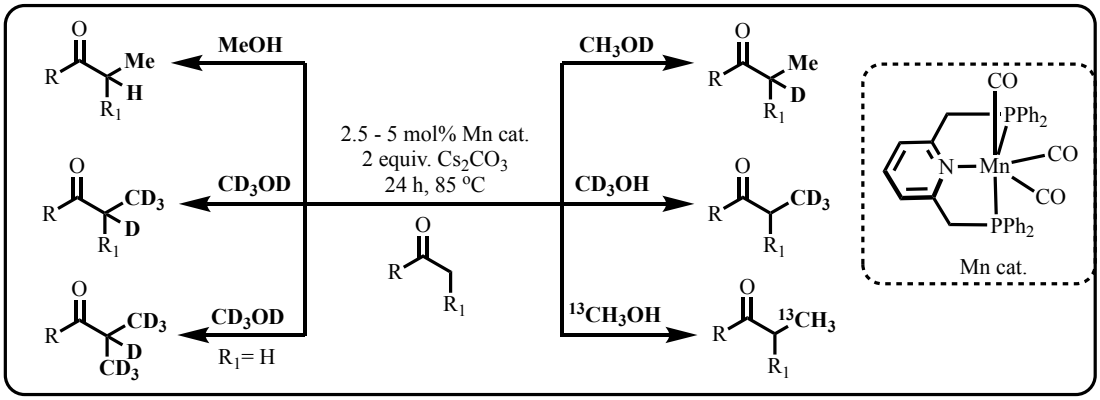
Cobalt catalyzed α-methylation of ketones

All of the preceding findings represent Ru and Pd metal catalysed highly efficient methylation of ketone, ester and nitrile utilising methanol as a C1 source. Despite these advances, the utilisation of earth abundant first row transition metal catalysts for more sustainable processes continues to be a significant challenge in methylation chemistry. In 2017, Liu and co-workers[15d] created a highly efficient Co-based catalytic system that is highly effective for the methylation of C(sp^3)-H and C(sp^2)-H bonds using methanol as a C1 source. The catalytic system showed high functional group tolerance for the methylation of aryl and alkyl ketones, aryl acetonitriles and aryl indoles with wide substrate scope.



Scheme 1.6. (a) Cobalt catalysed methylation of ketones (b) Cobalt catalysed methylation of nitriles and indoles

Rueping and co-workers[15g] reported the synthesis of deuterium methylated ketones using Mn-pincer complex as a catalyst and deuterated methanol as a C1 source reagent. Deuterated methanol, such as, CD_3OD, CD_3OH and $^{13}CH_3OD$ rendered the corresponding methylated ketone products from ketones with various functional groups, as well as cyclic and hetero-aromatic derivatives (**Scheme 1.7.**).



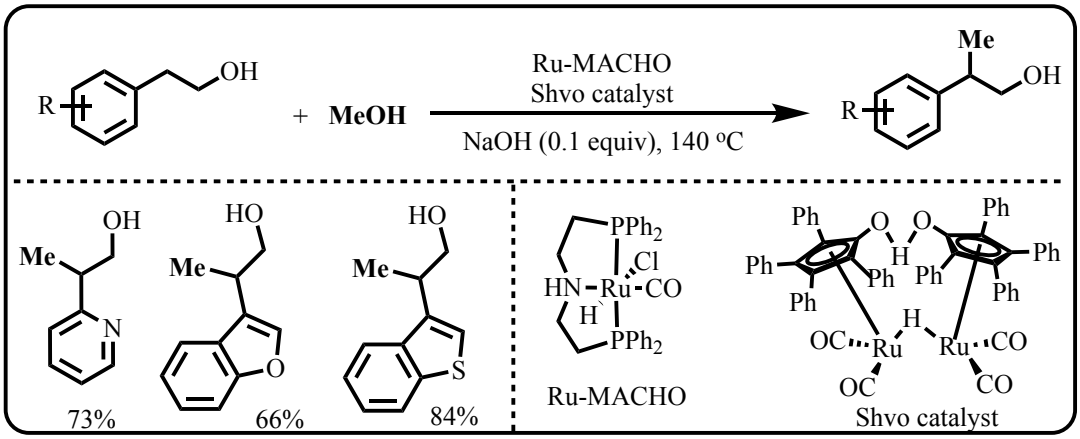
Scheme 1.7. Manganese catalysed deutero-methylation of ketones

1.2.2.2 β-Methylation of alcohols

Alcohols derived from biomass are appealing, green and sustainable starting materials for the production of enhanced biofuels, fine chemicals, and biologically active compounds. Functionalisation of alcohols to produce β-branched alcohol molecules *via* C-C coupling is immensely useful on the aspect of its industrial and other application, especially the β-methylation of alcohol. The methylation of alcohols at its β-position is accomplished with multi-step processes, such as, (i) oxidation of alcohols to the corresponding carbonyl groups, (ii) C–C coupling between those in-situ formed carbonyl groups, and lastly (iii) stoichiometric reduction of these coupled products. Traditionally, β-methylation of alcohols are carried out by using toxic and hazardous, classical methylating reagents in excess quantities. As alluded in the previous sections, these reagents generate a stoichiometric amount of waste. To address these challenges, the utilisation of methanol as a green C1 source employing hydrogen-borrowing technique with water as the sole by-product has received considerable interest. On that account, a number of precious and non-precious metal-based catalysts have been identified for the β-methylation of alcohols using methanol as a C1 source.

<u>Ruthenium catalysed β-methylation of alcohols</u>

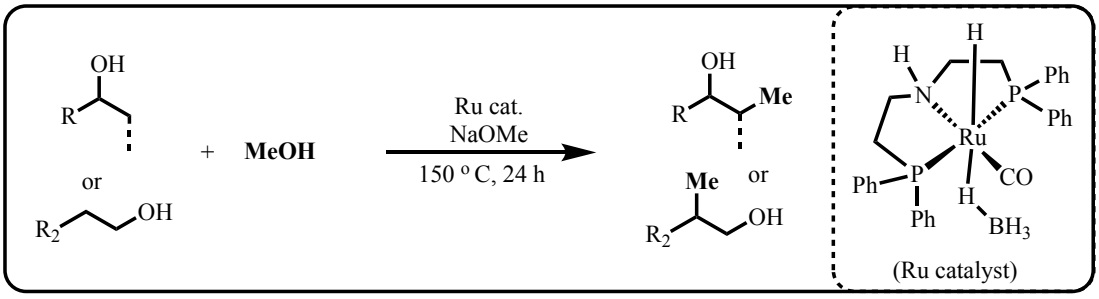
In 2014, Beller and co-workers[21] reported a PNP-ligand based Ru-MACHO along with Shvo's diruthenium complex as catalysts to investigate the β-methylation of aryl alcohols using methanol as a C1 feedstock (**Scheme 1.8**). Various aryl alcohols with different substituent like pyridine, protection-free indole, benzofuran and benzothiophene scaffolds underwent β-methylation. Furthermore, kinetic experiments revealed that the product yields get improved by employing the bimetallic catalytic system. Notably, this catalytic protocol provided new root to synthesize β-methylated alcohol products, that would otherwise be prepared *via* hydroformylation-reduction sequences combining with a poisonous CO in an additional hydrogen gas by employing a high pressure infrastructure.



Scheme 1.8. Ruthenium-MACHO catalysed β-methylation of alcohols

Leitner and co-workers[22] in 2019 demonstrated a Ru catalyst having a PNP-ligand skeleton for the β-methylation of alcohols (**Scheme 1.9**). The Ru pre-catalyst (Ru–MACHO–BH) was employed for methylation reaction utilising methanol as the greener methylating reagent and achieved up to 18000 turnover numbers. Furthermore, this catalytic protocol was accomplished using only 0.1 mol% Ru catalyst for the methylation process. The base plays an important role in establishing the product

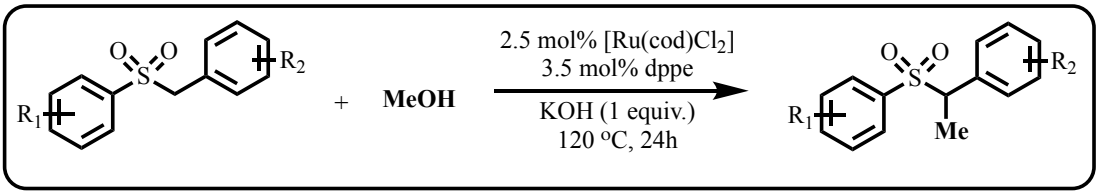
selectivity; for example, NaOMe exclusively produced the di-methylated product, whereas NaO^{t}Bu resulted in mono-methylated product.



Scheme 1.9. PNP-ruthenium pincer catalysed β-methylation of alcohols

1.2.2.3 α-methylation of sulfones

Sulfones with a methyl substituent at the α-position represnts numerous biologically active chemicals, medicines, and natural compounds such as certinib (a tyrosine kinase inhibitor which is used for the treatment of lung cancer), dorzolamide (for the treatment of increased intraocular pressure) etc. Zhong and co-workers[23] have demonstrated a simple and efficient Ru(II) catalyzed redox neutral process for methylating sulfones using methanol as a C1 source (**Scheme 1.10**). Using a stoichiometric amount of base, this catalytic approach produced a variety of value-added methylated sulfones with diverse functional groups in high yield.



Scheme 1.10 Ruthenium catalysed α-methylation of sulfones

1.2.3 N-Methylation (N-CH_3 bond formation) using BH methodology: Recent reports

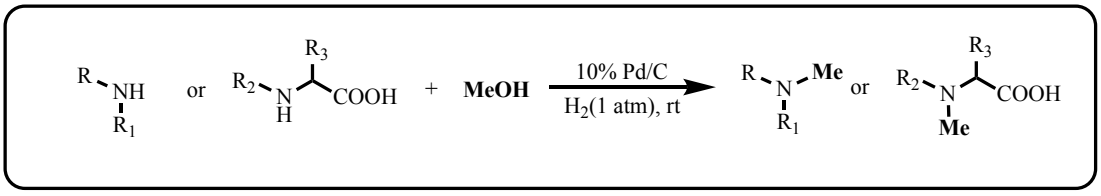
One of the most important transformations in the production of dyes, medicines, agrochemicals, and other biologically active natural compounds is N-methylation of amines and its derivatives. Traditionally, this transformation was achieved by employing toxic and carcinogenic methyl halides or other strong methylating reagents. The major drawbacks of the traditional methods consist of over-alkylated product formation and stoichiometric amount of waste generation. As a result, the development of sustainable process that used green methylating agents was highly sought after, methanol was a more feasible and alternative green methylating reagent in this aspect. Specifically, N-methylation of amines is highly important as it plays a crucial role in biological processes, gene regulation, protein function, RNA processing.[12]

1.2.3.1 N–Methylation of amines

To overcome the drawbacks of traditional approaches discussed *vide supra* for N-methylation of amines, the utilisation of methanol *via* the hydrogen borrowing methodology as a green C1 source act as a valuable replacement over the conventional methods. In the early 1980s, the first report of metal catalysed amine methylation using methanol was published.[24] Recently, N-methylation using methanol has gained attention. The following section will discuss N-methylation using Pd, Ru and Co-complexes.

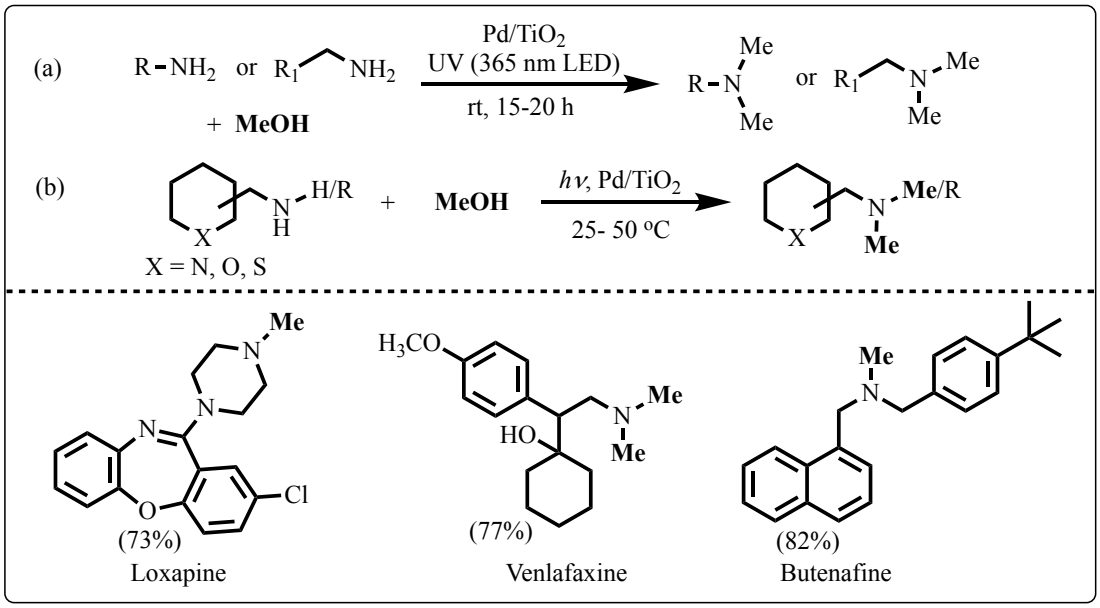
Palladium-catalysed N–methylation of amines

In 2010, Huang and co-workers[25] presented a Pd/C heterogeneous catalyst for the direct N-methylation of amines and amino acids employing methanol under 1 bar hydrogen pressure **(Scheme 1.11**). Not only secondary amines such as piperazines but also amino acids and amino alcohols undergo N-methylation using this protocol.



Scheme 1.11. Heterogeneous palladium catalysed N-methylation of amines

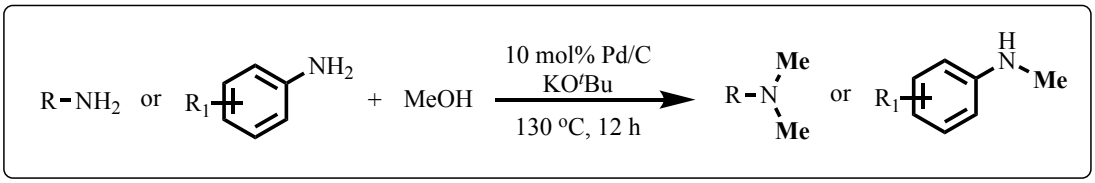
Shi and co-workers,[26] described TiO_2 supported palladium nanoparticles (Pd/TiO_2) for the synthesis of N-methylated amines with methanol under UV irradiation at room temperature. A wide range of secondary, aliphatic, aromatic, and heterocyclic amines were N-methylated in high yields (**Scheme 1.12.a**).



Scheme 1.12. Pd/TiO_2-based photocatalytic N-methylation of amines

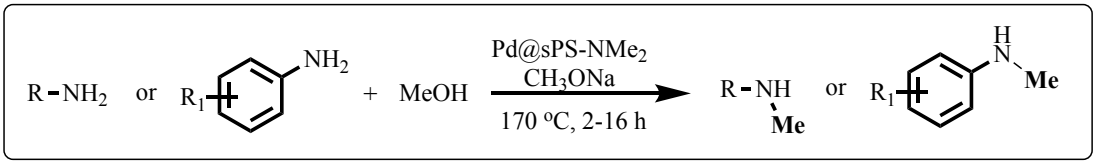
Naka and co-workers[27] developed a similar Pd/TiO_2-based photocatalytic system for the N-methylation of heterocyclic amines (**Scheme 1.12.b**). The catalyst Pd/TiO_2 was also recycled up to five times without any significant loss of catalytic activity. The catalytic system was extended for the synthesis of several important pharmaceutical drugs, such as Loxapine, Venlafaxine and Butenafine.

In 2019, Hou and co-workers[28] described an activated-carbon-based palladium catalyst (Pd/C) for the selective N-mono methylation of anilines (**Scheme 1.13**). Four N-methylated compounds were synthesized in gram scale to demonstrate the efficiency of the catalytic protocol. In the same year, Natte and co-workers[29] used commercially available Pd/C as an efficient catalyst for the N-methylation of amines (**Scheme 1.13**). The synthesis of hordenine an alkaloid was achieved with 57% yield. Competitive experiments between an aromatic and an aliphatic amine revealed that the catalytic protocol has excellent selectivity and reactivity for the aromatic amine towards mono-methylation.



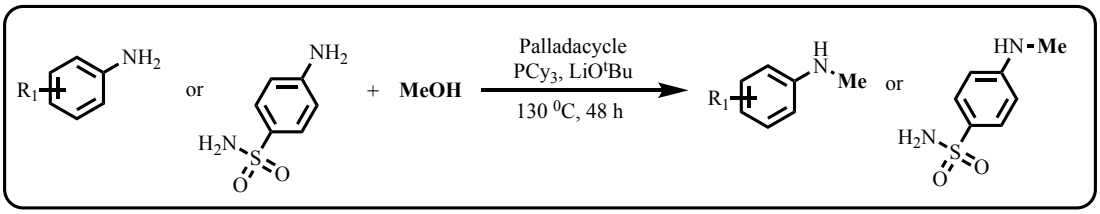
Scheme 1.13. Heterogeneous (Pd/C) catalysed N-methylation of anilines

Recently, Hou and co-workers[30] described the selective N-mono methylation of various primary amines utilizing methanol, and a Palladium supported on dimethyl amino-functionalized syndiotactic polystyrene (Pd@sPS-NMe_2) under air (**Scheme 1.14**). The excellent catalytic activity observed might be attributed to its ultra-fine palladium nanoparticles and strong amine-adsorption capacity. Furthermore, they reported that the catalyst was extremely robust, and it could be recovered and reused for up to ten times without losing activity or selectivity for methylation.



Scheme 1.14 Polystyrene supported Palladium catalysed N-methylation of amines

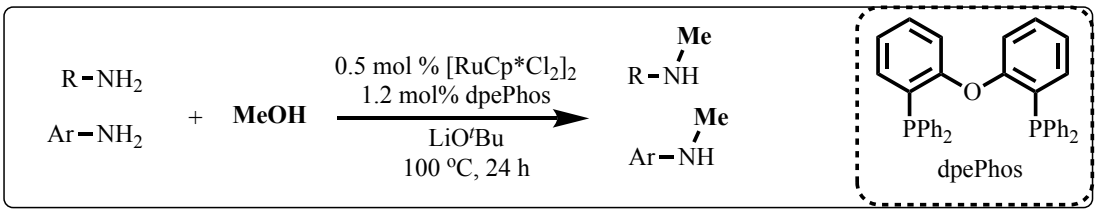
In 2019, our group[15e] reported the methylation of amines catalysed by a homogeneous palladium catalyst using methanol as a methylating reagent. We also demonstrated the chemo-selective methylation of sulfonamide using methanol as C1 source.



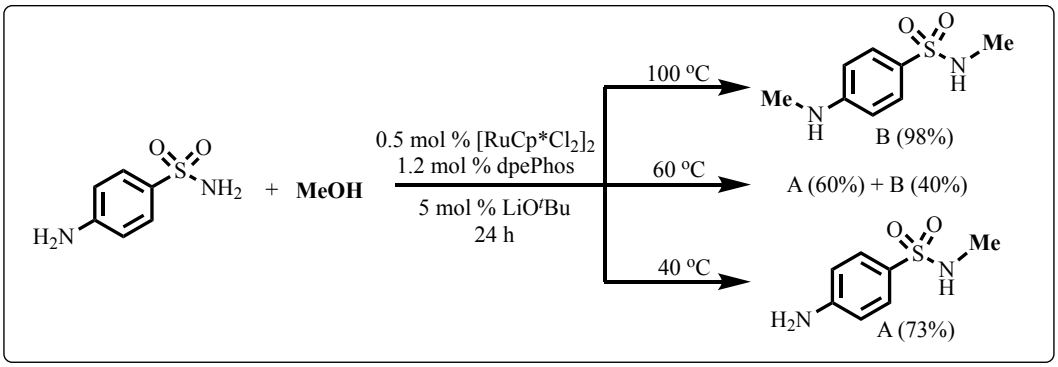
Scheme 1.15 Homogeneous palladium catalysed N-methylation of amines

Ruthenium catalysed N–methylation of amines

In 2015, Seayad and co-workers[31] reported an in situ generated complex from simple $[RuCp^*Cl_2]_2$ and dpePhos ligand as an active catalyst for the selective N-mono methylation of aromatic primary amines and sulfanilamides as well as N,N-dimethylation of primary aliphatic amines (**Scheme 1.16**).



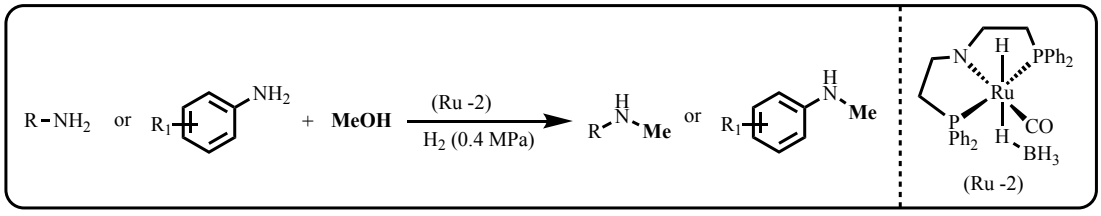
Scheme 1.16. Ruthenium (II) dimer catalysed N-methylation of amines



Scheme 1.17. Temperature dependent N-methylation selectivity of sulfanilamide

They also demonstrated the temperature dependent N-methylation of sulfanilamide (**Scheme 1.17**); at low temperature chemoselective N-methylation of sulfonamide was observed instead of primary amine. However, at high temperature the dimethylated product was observed, where both sulfonamide and primary amine group got methylated. In sulfanilamide, the nucleophilicity of sulfonamide group is more due to the presence of electron-donating amino group, whereas the nucleophilicity of primary amine group is less due to the presence of electron-withdrawing sulfonamide group.

In 2018, Hong and co-workers[32] employed a PNP-Ru catalyst for the N-mono methylation of amines (**Scheme 1.18**) utilizing methanol as a C1 source along with H_2. The catalytic system was successfully applied for mono methylation of structurally and functionally varied amines including primary aliphatic amines.

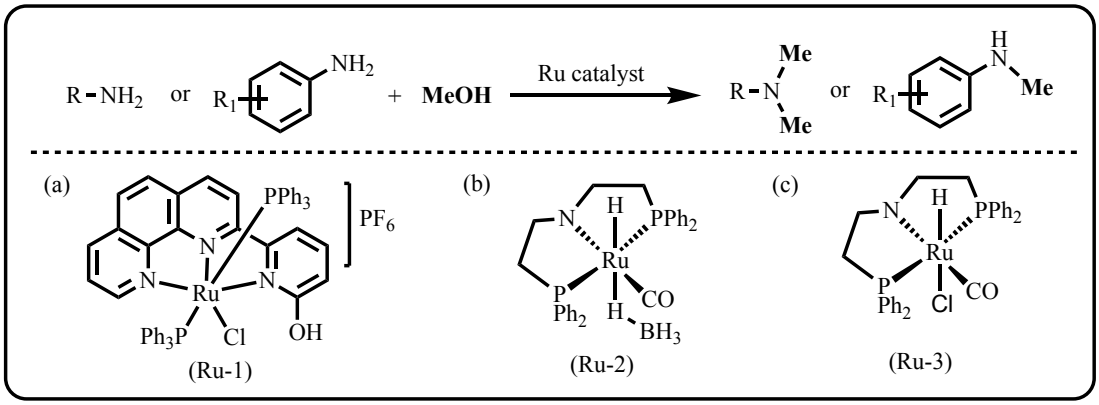


Scheme 1.18 PNP-ruthenium complex catalyzed N-methylation of amines

In 2018, Kayaki and co-workers[33] reported the N-mono methylation of aromatic amines using a Ru–PNP pincer (Ru-3) catalyst using a very low catalyst loading (0.02−0.1 mol %) at 150 °C (**Scheme 1.19.a**). The catalytic system was successfully applied for N-CD_3 formation using CD_3OD.

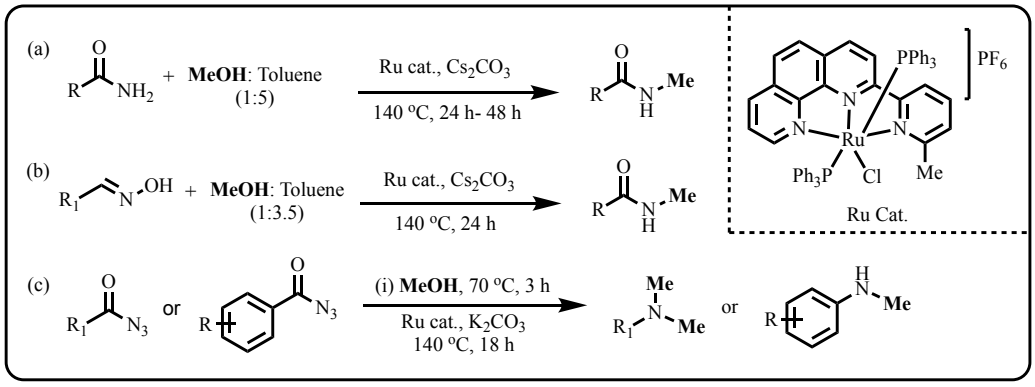
In the same year, Kundu and co-workers[34] demonstrated the N-alkylation and N-methylation of amines using **Ru-1** catalyst, six examples of N-methylation products were reported in up to 84% isolated yield (**Scheme 1.19.b**). In 2019, Hong and co-

workers[35] employed PNP-Ru catalyst (Ru-2) for the N,N-dimethylation of aliphatic amines (**Scheme 1.19.c**) utilizing methanol and NaOMe as a base at 160 °C.



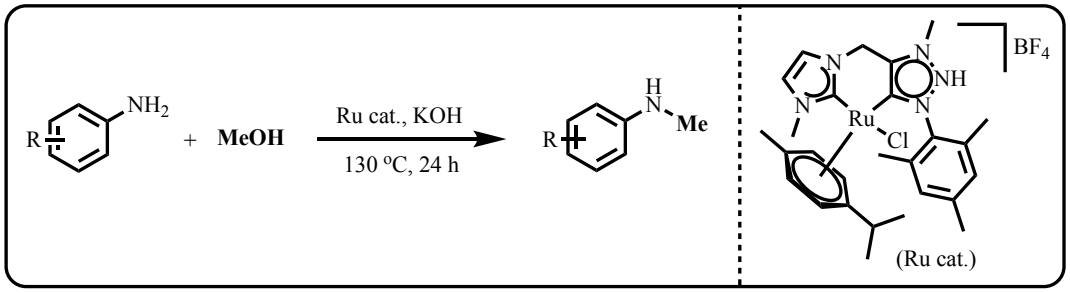
Scheme 1.19 Ruthenium complex catalyzed N-methylation of amines

Recently, Kundu and co-workers[36] reported the N-methylation of amides employing a Ru-NNN pincer catalyst in a 1:5 ratio of methanol and toluene mixture at 140 °C (**Scheme 1.20a**). Kinetic investigations showed that N-methylation of amide is slower than C-methylation of ketone and N-methylation of amine. In the same year, they also reported the transformation of aldoxime into N-methylated amides[37] using the same Ru-NNN pincer catalyst (**Scheme 1.20b**). Kinetic analysis and control tests reveal that, ruthenium metal transformed aldoxime to nitrile, which later resulted into amide *via*



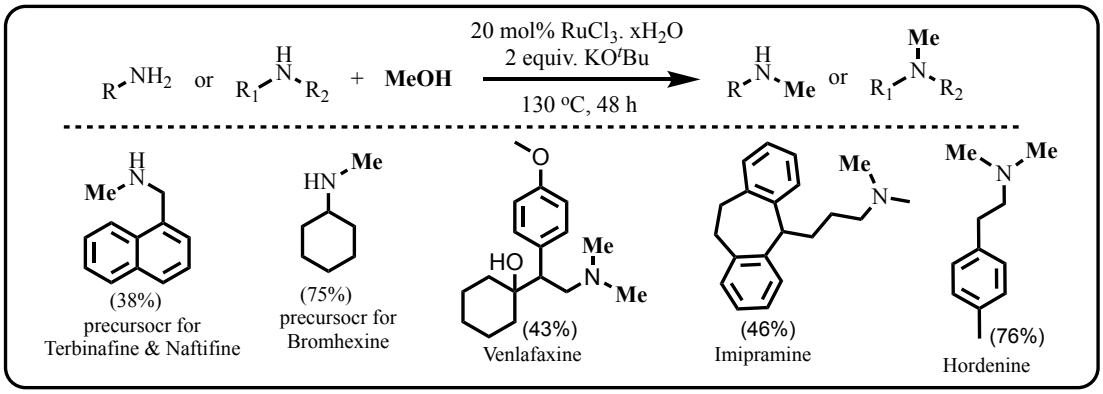
Scheme 1.20. NNN-ruthenium complex catalysed (a) N-methylation of amides (b) N-methylation of aldoximes in to methylated amides (c) N-methylation of azides

the five-membered intermediate cycle. More recently, the same group also explored the catalytic efficiency of the Ru-NNN pincer catalyst for the methylation of acyl azides.[38] The methylation process completed in two phases; it undergoes a hydrogen borrowing reaction followed by a Curtius rearrangement (**Scheme 1.20c**). Similarly, in 2020, Rit and co-workers[39] developed a N-heterocyclic-carbene-based Ru catalyst and successfully utilized it for the N-methylation of amines using methanol (**Scheme 1.21**).



Scheme 1.21. N-heterocyclic-carbene based ruthenium catalysed N-methylation of amines

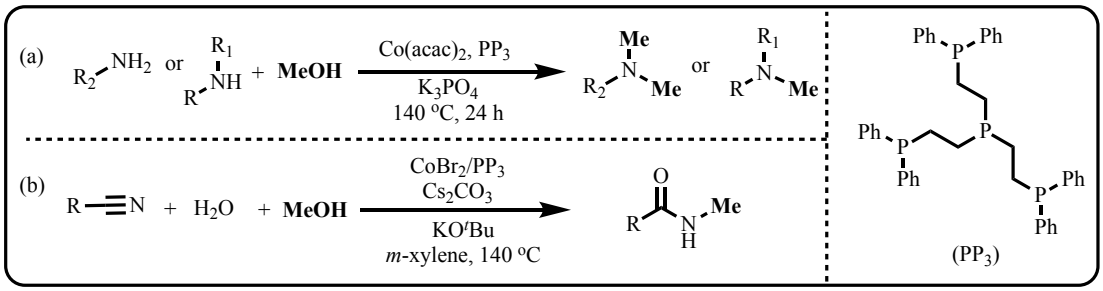
Natte and co-workers[40] recently developed a simple method for N-methylation of amines utilizing $RuCl_3 \cdot xH_2O$ as a catalyst and KO^{t}Bu as a base at 130 °C. They utilized this protocol to make precursors of a variety of drug molecules, such as Terbinafine and Naftifine (treat fungal infections), Bromhexine (cure respiratory tract disorders), Venlafaxine, Imipramine (drug molecule) and Hordenine (**Scheme 1.22**).



Scheme 1.22. Ruthenium (III)chloride catalysed N-methylation of amines

Cobalt-catalysed N–methylation of amines

Cobalt based compounds also utilised as catalyst for N-methylation of amines. Liu and co-workers[41] reported a $Co(acac)_2$/phosphine-based system for the mono and di methylation of amines using methanol (**Scheme 1.23.a**). In 2019, Kundu and co-workers[42] developed a similar Co/phosphine-based system to synthesize N-methylated amides from nitriles utilizing methanol (**Scheme 1.23.b**). Further studies utilizing H_2O[18] and CD_3OD under the optimal conditions reveal that N-methylation of amides proceed slower compared to the hydration of nitriles. Hammett's study revealed that electron withdrawing groups facilitate the reaction.



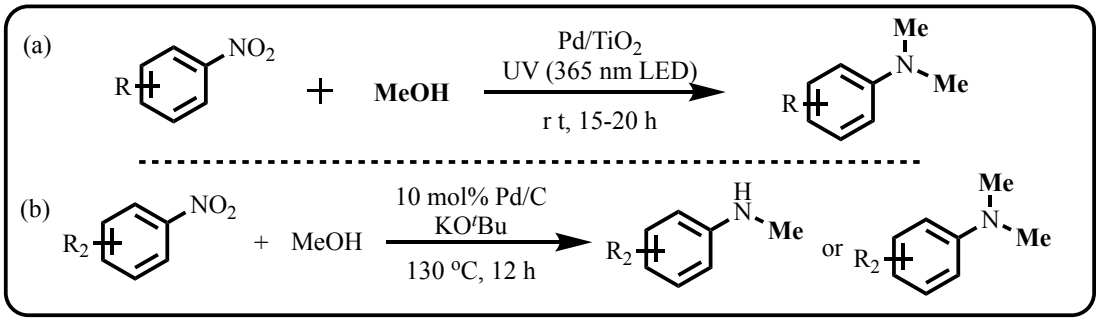
Scheme 1.23. Cobalt catalysed (a) N-methylation of amines (b) N-methylation of nitriles

1.2.3.2 N-Methylation of nitroarenes

To overcome the drawbacks experienced by the traditional methods discussed *vide supra* for the N-methylation of amines, BH process was developed employing methanol as a C1 source. Recently, simpler and straightforward technique utilising affordable and abundant nitroarenes is proposed to make N-methylated anilines *via* BH process. Moreover, this process is an atom-economical process, which also avoids the hydrogenation of the nitroarenes.

Palladium catalysed N-Methylation of nitroarenes

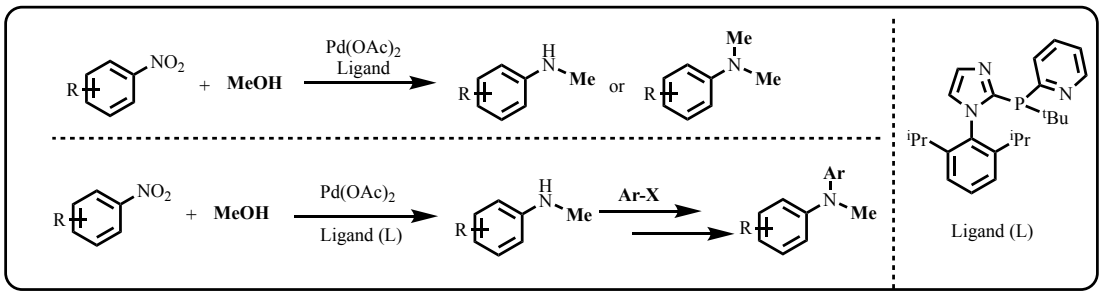
In 2015, Shi and co-workers[26] described TiO_2 supported palladium nanoparticles (Pd/TiO_2) as catalyst for the synthesis of N-methylated amines from nitroarenes utilizing methanol under UV irradiation at room temperature. The methodology tolerated a wide range of nitro arenes (**Scheme 1.24.a**). Further, in 2019, Natte and co-workers[29] described an activated-carbon-based palladium catalyst (Pd/C) for the selective N-mono methylation of nitroarenes at low temperature, however at higher temperature di-methylation predominates (**Scheme 1.24.b**). Under this catalytic protocol, they successfully methylated the anti-inflammatory drug "nimesulide" using CH_3OH and CD_3OH as a C1 source. However, they observed decrease in catalytic activity for this activated-carbon-based palladium catalyst (Pd/C) during the recycling experiments.



Scheme 1.24 Heterogeneous palladium catalysed N-methylation of nitroarenes

Beller and co-workers[43] developed a catalytic system in combination with $Pd(OAc)_2$ and imidazole-based phosphine ligands for the N-methylation of nitroarenes utilizing methanol (**Scheme 1.25**). This protocol gave good yields of methyl amines starting from nitroarenes and heterocyclic arenes with different functional groups. However, nitro derivatives with electron-withdrawing and halogenated substituents were not compatible. The catalytic protocol was also extended for the synthesis of CD_3-labelled

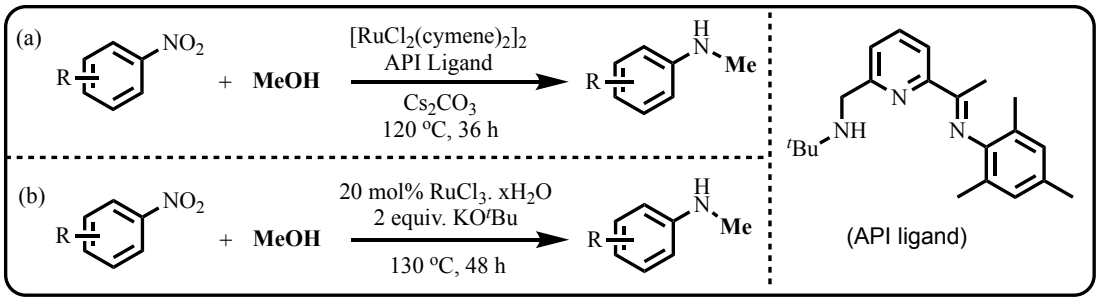
amines and a calcium channel blocker, which is used as an antihypertensive drug. It was hypothesised that the phosphine–pyridine part may be triggering the oxidation of methanol, and the bulky part of the ligand driving the C-N bond formation.



Scheme 1.25. Homogeneous palladium catalysed N-methylation of nitroarenes

Ruthenium catalysed N-methylation of nitroarenes

Yang and co-workers[44] in 2019 introduced a combination of $[RuCl_2(cymene)_2]_2$ along with N,N,N-pincer ligand for the selective mono methylation of nitroarenes to N-methylamines with good tolerance to various functional groups (**Scheme 1.26.a**). Recently, Natte and co-workers[40] reported another Ru-based catalytic system ($RuCl_3 \cdot xH_2O$) for the N-methylation of a variety of nitro arenes (**Scheme 1.26.b**).



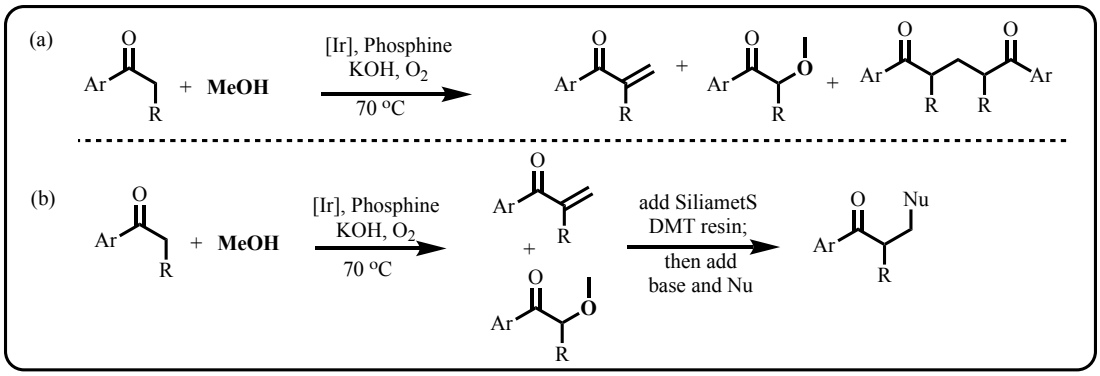
Scheme 1.26. Ruthenium catalysed N-methylation of nitroarenes

1.2.4 C-Methylenation (-CH_2- bond formation) *via* I-BH methodology: Recent reports

Alcohols which are rich source of energy can be transformed to functional groups, such as amides, amines, carboxylic acids, esters, and imines.[45] Dehydrogenation of alcohols is one of the important transformations, however the dehydrogenative transformation

of alcohols to carbonyl compounds occurs in the absence of an oxidizing agent, *via* I-BH methodology, hence, it is considered as a more environmentally friendly reaction which liberates H_2 and H_2O as the byproducts.[16,45] Among all alcohols, methanol gains more focus as a green renewable C1 feedstock that has been used to make C−CH_2− and N−CH_2− bonds. During the past decade, α-methylation of ketones by BH method has been elegantly applied utilising methanol as a reagent.[15] However, studies to generate α-methylenated architectures using I-BH protocol are limited.[16] The α-methylenated intermediates without further reduction undergoes different I-BH transformations and form products such as α-methoxy ketone, β-hydroxy ketone, 1,5-diketones depending on the reaction conditions. Among the different I-BH products, 1,5-diketones, have gained attraction due to their potential biological and pharmacological activity.[46] Furthermore, 1,5-diketones have also proven to be invaluable building blocks for the synthesis of many heterocyclic[47] and polyfunctional[48] compounds.

Iridium catalysed α-methylenation of ketones

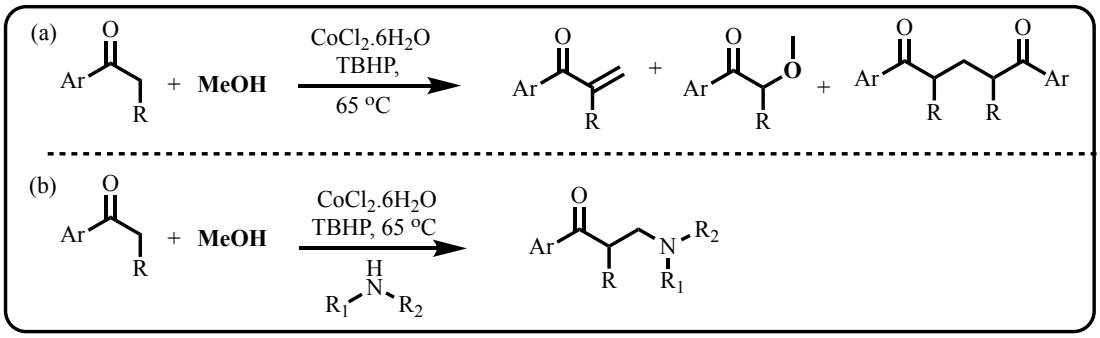


Scheme 1.27. Iridium catalysed α-methylenation of ketones

In 2015, for the first time Donohoe and co-workers[16c] developed a ligand selective BH and I-BH protocol using an Iridium catalyst. Among the two different phosphine ligands studied, the bulkier phosphine ligand selectively resulted I-BH product (**Scheme 1.27.a**). They scrutinised different ketones utilising methanol to yield the α-

methylenated ketones and methoxymethyl ketones. They also examined the one-pot methylenation and conjugate addition of different nucleophiles (**Scheme 1.27.b**).

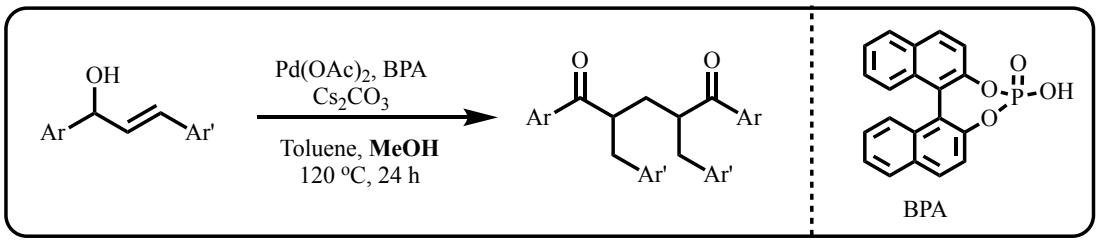
Cobalt catalysed α-methoxymethylation of ketones



Scheme 1.28. Cobalt catalysed α-methylenation of ketones

Later in 2018, Xiao and co-workers[16d] demonstrated α-methoxymethylation of ketones using $CoCl_2 \cdot 6H_2O$ as a catalyst and *tert*-butyl hydroperoxide (TBHP) as an external oxidant and screened variety of ketones using this protocol (**Scheme 1.28.a**). They further extend the catalytic protocol for α-aminomethylation of ketones utilizing amine as a nucleophile by a one pot methylenation/aza-Michael addition sequence (**Scheme 1.28.b**).

Palladium catalysed isomerization-methylenation of allyl alcohols



Scheme 1.29 Palladium catalysed synthesis of 1,5-diketone from allyl alcohols

In 2021, our group[16b] demonstrated palladium acetate and binol phosphoric acid catalysed synthesis of 1,5-diketones from allyl alcohols through isomerization-methylenation protocol utilizing methanol as a C1 source (**Scheme 1.29**). The practical utility of this methodology was explained by synthesizing pyridines *via sequential*

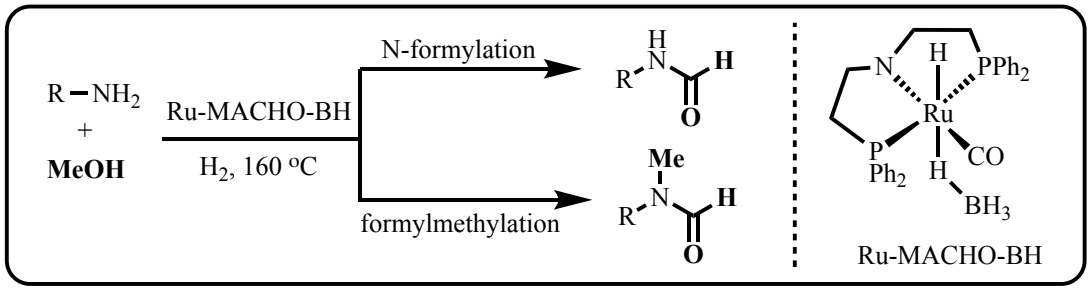
addition.

1.2.5 N-formylation using I-BH methodology: Recent reports

Formamides are key intermediates for the synthesis of heterocycles, bioactive molecules and pharmaceuticals.[49] Classical approaches for the formylation processes involve the use of toxic formylating reagents in excess, for instance, formic acid, formate salts, formaldehyde, chloral, etc., which are harmful for the environment are used in superstoichiometric amount. Therefore, the use of more sustainable technology for the synthesis of formamides has attracted significant attention. In this context, the utilization of methanol as a formylating reagent through I-BH method has several benefits and represents an atom-economical route.

Ruthenium catalysed N- formylation of amines

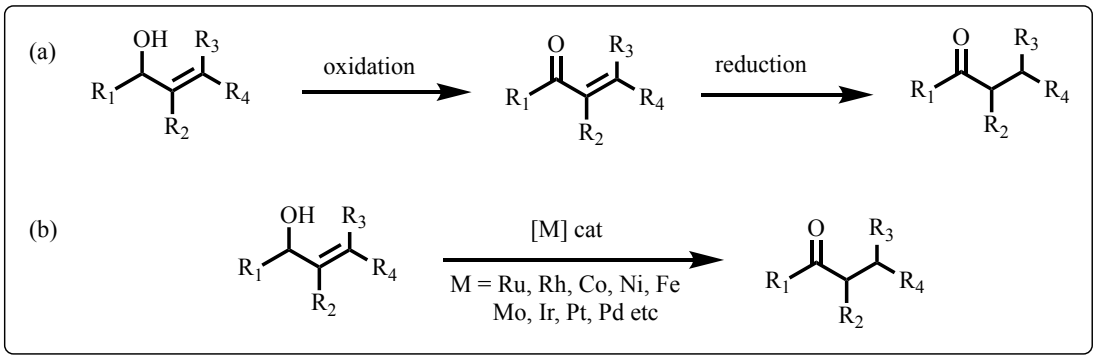
In 2019, Hong and co-workers[35] employed Ru catalyst for the N-formylation and N,N-formylation methylation of aliphatic amines (**Scheme 1.30**) utilizing methanol at 160 °C. The reaction temperature and hydrogen gas pressure are the key factors in determining the product class. Initially, dehydrogenation of methanol to formaldehyde took place, followed by reaction with amine results N-formylated product. The, N-formylated amine formed acts as an intermediate species; depending on the pressure of hydrogen gas, it was transformed into imine (high H_2 pressure) followed by hydrogenation to give formyl methylated amine.



Scheme 1.30. Ruthenium catalysed N- formylation of amines

1.3 Isomerisation and functionalisation of allyl alcohol

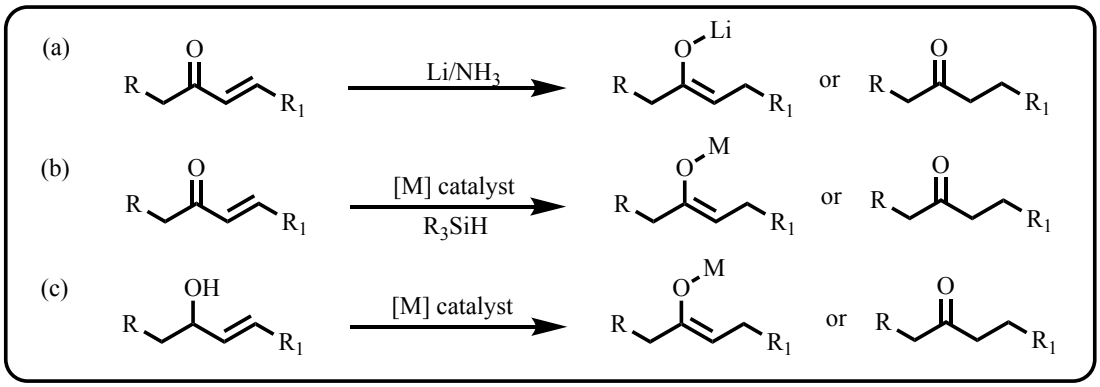
Traditionally, isomerisation of allyl alcohols to carbonyl compounds were carried out *via* two phase successive oxidation-reduction method (**Scheme 1.31.a**). The metal catalysed one pot isomerisation of allyl alcohol to carbonyl compound is a useful synthetic process, as it is an atom economical process and eliminates the employment of any stochiometric quantity of hazardous and expensive reagents[50] (**Scheme 1.31.b**). This one pot process is extremely chemoselective and can be carried out in the presence of additional functional groups such as alcohol, ketone and any double bond. Furthermore, allyl alcohols also behaved as enolate precursors, which is a crucial intermediate in the formation of carbon-carbon and carbon-heteroatom bonds.



Scheme 1.31. (a) Conventional two step isomerisation and (b) One-step redox isomerisation of allyl alcohols

Enolates can be obtained by the deprotonation of ketones, however, a mixture of regioisomers is produced in this process, whereas in some cases, only one regioisomer formation is kinetically and thermodynamically favourable making the synthesis of the non-favoured regioisomer challenging. Different synthetic enolates can also be generated by reducing enone with lithium in liquid ammonia or by transition metal-mediated reduction using hydrogen source. The former method suffers from low functional group tolerance and the latter requires stochiometric amount of reductant such as silanes[51] or dihydrogen[52] **(Scheme 1.32.)**. However, transition metal catalysed

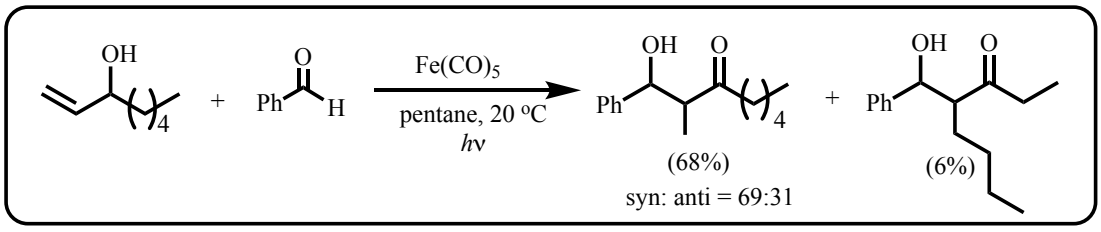
isomerisation of allyl alcohol to enolate or ketone overcome these drawbacks. Utilising this process, allyl alcohols were employed in tandem reaction for the production of C-C and C-heteroatom bonds.[53]



Scheme 1.32 Generation of enolates or ketones from enone and allyl alcohol

1.3.1 Tandem isomerisation and functionalisation of allyl alcohols

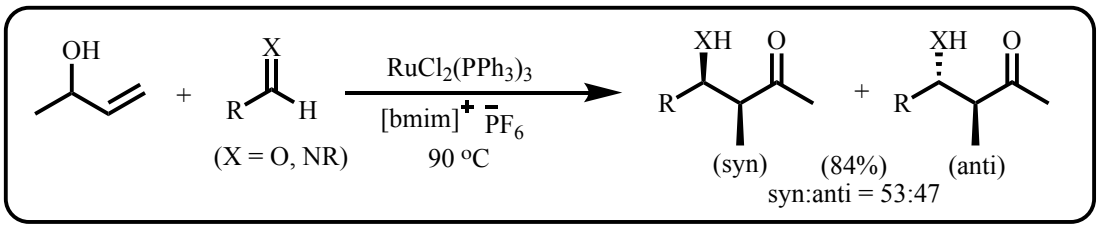
The tandem isomerisation-functionalisation process of allyl alcohol is a highly valuable and atom economical reaction. In the presence of any electrophile like aldehyde or imine results in aldol or Mannich type products respectively, however, absence of any electrophile forms the corresponding carbonyl compounds. The first catalytic isomerisation-functionalisation of allyl alcohols was reported by Gree and co-workers[54] by using an iron carbonyl complex . They used it to couple allyl alcohols with various aldehydes to form aldol products in high yields **(Scheme 1.33)**. A small amount of unwanted aldol compound was also found from the isomerised ketone.



Scheme 1.33 Tandem isomerisation aldol condensation catalysed by $Fe(CO)_5$

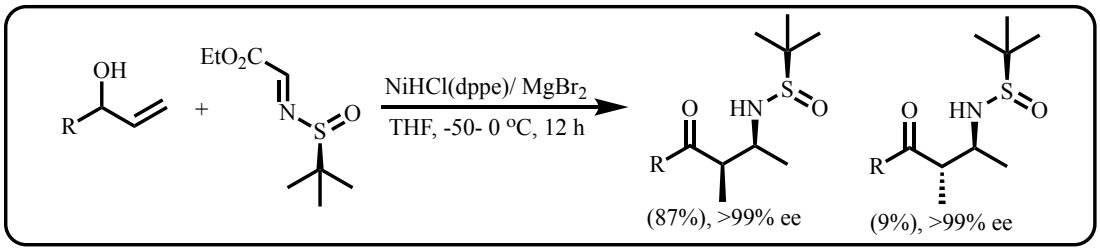
Li and co-workers[55] reported the isomerisation-functionalization of allylic alcohols with different aldehydes in H_2O or protic solvent using a $Ru(PPh_3)_3Cl_2$ catalyst

for the synthesis of aldol type products in good yield. The yield of the products was further enhanced by the use of $In(OAc)_3$ as an additive[56]. Further extension of this work included imine as an electrophile to couple with allylic alcohols through a Mannich-type reaction for the synthesis of β-aminoketones in methanol[55] and later they explored the same reaction using by $Ru(PPh_3)_3Cl_2$ as a catalyst in ionic liquid[56] (**Scheme 1.34**).



Scheme 1.34 Tandem isomerisation-Mannich type reaction of allyl alcohols

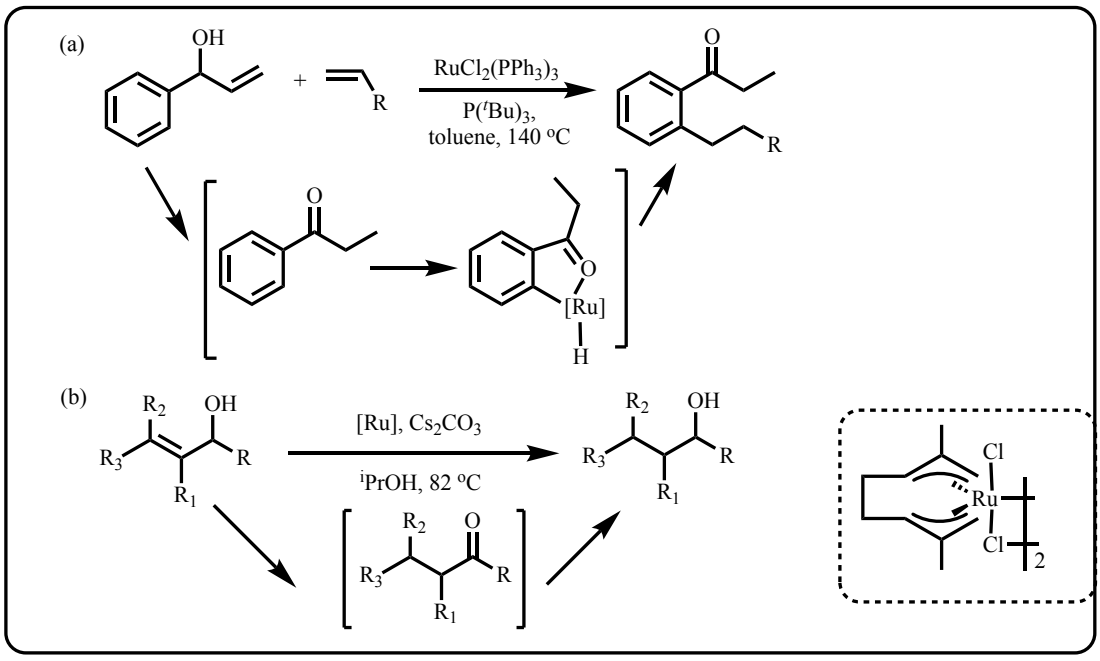
Gree and co-workers[57] reported $Fe(CO)_5$ catalysed Mannich type reaction for the synthesis of β-aminoketones and β-aminoalcohols using N-phenylsulfonyl imines as the electrophiles. Later, they also reported a catalytic system consisting of Ni complex along with $MgBr_2$ and scrutinized it for enantio- and diastereo-selective synthesis of β-aminoketones by employing enantiopure N-*tert*-butylsulfinimines (**Scheme 1.35**). This method was further utilised for the synthesis of *ent*-Funebrine and *ent*-Nikkomycins.[58]



Scheme 1.35 Diastereoselective and enantioselective isomerization-Mannich type reaction

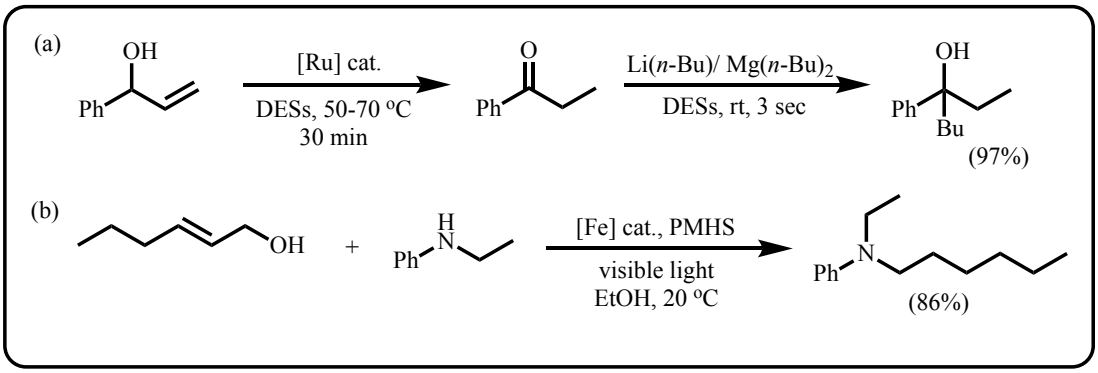
Martin-Matute and co-workers[59] combined the isomerisation of allyl alcohols with Murai[60] type C-H activation using a $Ru(PPh_3)_3Cl_2$. Allyl alcohols were isomerised to generate ketones by the ruthenium catalyst; the *in situ* generated ketones further assisted the aromatic C-H bond cleavage by chelation (**scheme 1.36.a**). The ruthenium catalyst

was used for both isomerisation and chelation assisted C-H activation. Nebra and co-workers[61] demonstrated a ruthenium catalysed isomerisation hydrogenation of allyl alcohol to a secondary alcohol using isopropanol as the hydrogen source (**scheme 1.36. b**). Kinetic investigations verified the formation of the ketone from allyl alcohol *via* isomerisation followed by hydrogenation by isopropanol.



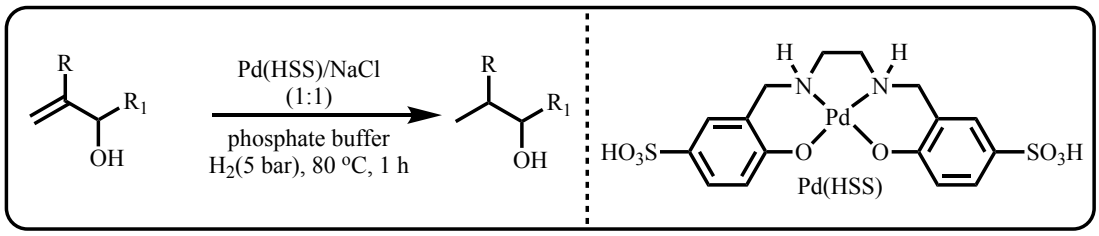
Scheme 1.36. (a) Tandem isomerisation-C-H functionalisation (b) Tandem isomerisation-hydrogenation of allyl alcohols

Capriati and co-workers[62] synthesised tertiary alcohols in deep eutectic solvents (DESs) by a two-step process of ruthenium catalysed isomerisation of allyl alcohols to corresponding ketones followed by the chemoselective addition of organolithium/ magnesium compounds in high yield up to 97% (**Scheme 1.37.a**). Darcel and co-workers[63] developed a sequential three step process for the synthesis of N-alkylated amines from allyl alcohols and primary and secondary anilines. This process involves isomerisation of allyl alcohols, condensation with amines followed by reduction by the addition of hydrogen (**Scheme 1.37.b**).



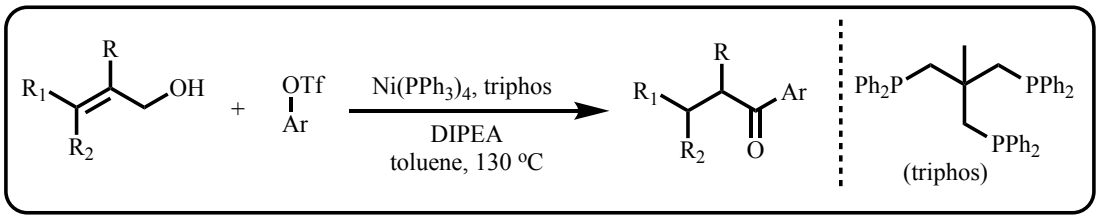
Scheme 1.37. (a) Tandem isomerisation and addition of organolithium/magnesium to allyl alcohols and (b) Tandem isomerisation-condensation-reduction of allyl alcohols

Joo and co-workers[64] developed a water soluble disulfonated tetrahydrosalen ligated Pd(II) complex and utilized it for the redox isomerisation and hydrogenation of allyl alcohol to a secondary alcohol using dihydrogen as the hydride source (**scheme 1.38**). DFT calculations showed that H_2 is heterolytically activated resulting in a Pd(II)−hydride complex. Both hydrogenation and redox isomerization of allyl alcohol take place *via* a concerted transfer of a proton and a hydride from the catalyst to the allylic alcohol resulting in a secondary alcohol.



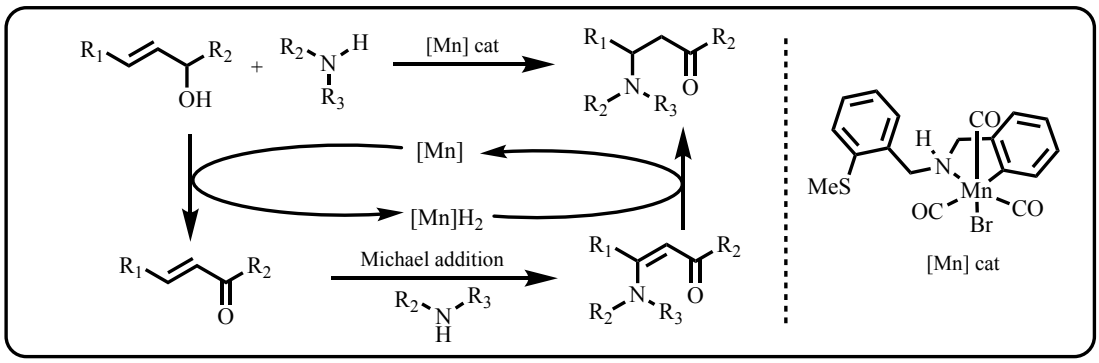
Scheme 1.38. Tandem isomerisation-hydrogenation of allyl alcohols

Rong and co-workers[65] reported a commercially available nickel catalyst along with a triphos ligand to demonstrate the synthesis of various ketones by redox neutral cross coupling of allyl alcohols with aryl triflates (**scheme 1.39**). A wide variety of complex allyl alcohols with aryl triflates were transformed into functionalised ketones using this protocol with extensive functional group tolerance.



Scheme 1.39. Tandem isomerisation of allyl alcohols followed by coupling with aryltriflates

Maji and co-workers[66] demonstrated the synthesis of γ-aminoalcohols *via* hydroamination of allyl alcohols through hydrogen borrowing approach utilizing a manganese(I)

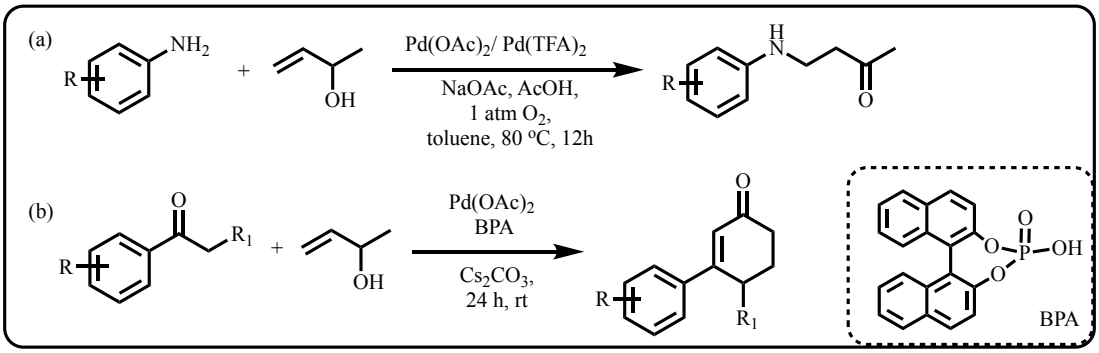


Scheme 1.40. Hydroamination of allyl alcohols *via* hydrogen borrowing method

catalyst. Utilising this method, a wide range of aromatic and aliphatic amines, natural product derivatives *viz*. lithocholic acid, linoleic acid and citronellal and drug molecules *viz*. urapidil, trifluoperazine and fluoxetine were prepared (**Scheme 1.40**).

Kapur and co-workers[67] described the synthesis of β-aminoketones under oxygen atmosphere using a simple commercial palladium catalyst *via* oxidative coupling of allyl alcohols with anilines, which were further converted to substituted quinolines in one pot sequential method as a synthetic utility of these compounds (**Scheme 1.41.a**). Control experiments and further investigation reveals that the formation of enone took place by oxidation of allyl alcohol prior to the reaction with aniline moiety *via* Michael addition. Further extension of this method was applied for the synthesis of indoline using intramolecular α-arylation and one pot domino

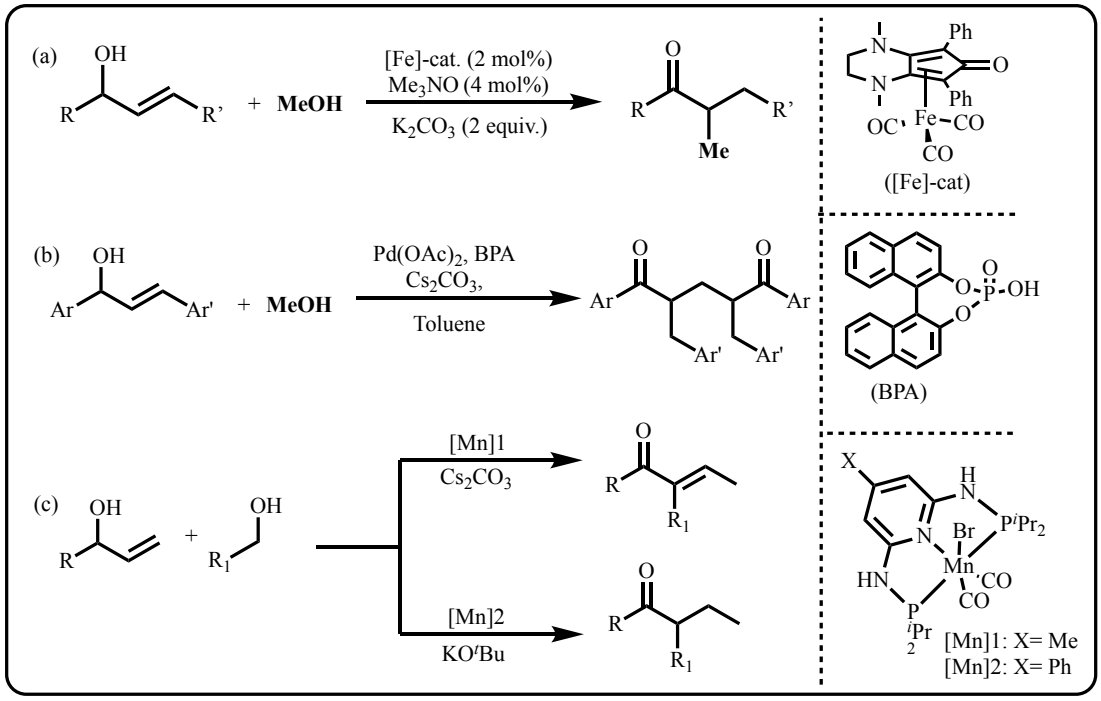
annulation. Recently, our group[68] demonstrated the synthesis of aryl cyclohexenones and 1,5-diketones *via* oxidative coupling of allyl alcohols with aryl ketones using a simple commercially available palladium acetate along with binol phosphoric acid (BPA) as catalyst without using any additional oxidant (**Scheme 1.41.b**).



Scheme 1.41. Oxidative coupling of allyl alcohols with anilines and ketones

More recently, Morrill and co-workers[69] reported tandem isomerisation and methylation of allyl alcohols for the synthesis of α-methylated ketones utilising a (cyclopentadienone)iron(0) carbonyl complex as the precatalyst and methanol as a C1 source (**Scheme 1.42.a**). A number of 1-phenyl substituted secondary allyl alcohols were converted to the corresponding methyl ketones in good yields. From our group,[16b] we demonstrated commercially available palladium acetate along with binol phosphoric acid (BPA) as a catalytic system for the synthesis of 1,5-diketones *via* isomerisation-methylenation of allyl alcohols employing methanol as a C1 source without using any additional oxidant (**Scheme 1.42.b**). A wide variety of monoaryl and diaryl allyl alcohols were converted to the corresponding 1,5-diketones utilising this catalytic protocol. Gunanathan and co-workers[70] recently reported the cross coupling of allyl alcohols with primary alcohols using a PNN-manganese pincer catalyst. The base selective cross coupling of allyl alcohols with primary alcohols resulted in α-alkenyl ketones in presence of Cs_2CO_3 as a base *via* acceptorless dehydrogenative

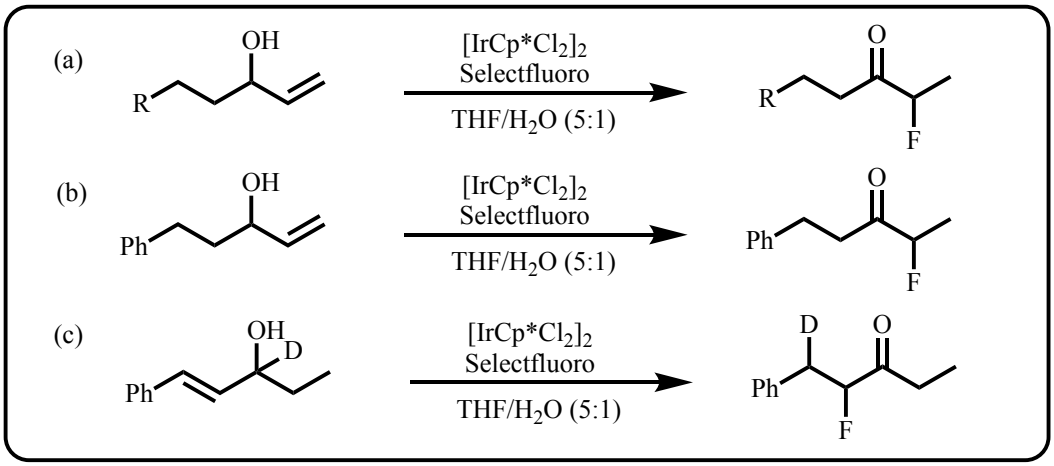
coupling, whereas the presence of KO^{t}Bu as a base it resulted in α-alkylated ketones *via* borrowing hydrogen methodology (**Scheme 1.42.c**).



Scheme 1.42. (a) Tandem isomerisation and methylation of allyl alcohol (b) Tandem isomerisation and methylenation of allyl alcohol and (c) Tandem isomerisation and alkylation/alkenylation of allyl alcohols.

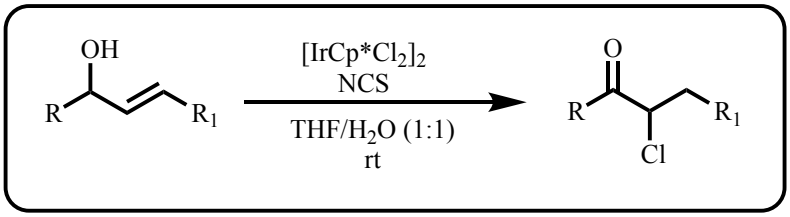
Martin-matute and co-worker[71] reported the isomerisation fluorination of allyl alcohols using an iridium catalyst (**Scheme1.43.a**). After screening a variety of fluorinating agents for this electrophilic fluorination, Selectfluor in THF/water mixture was found to be the most effective for the isomerisation-fluorination reaction. The presence of additional ketone group had no effect on the desired product formation. As the protocol demonstrated a perfect chemoselectivity for allyl alcohols, regioselective synthesis of a single constitutional isomer of the α-fluoro ketone was achieved. Crossover experiment (**Scheme 1.43.b**) confirmed that the reaction does not proceed through the formation of non-fluorinated ketone rather the 1,4-hydride shift. Further, the

fluorination of the deuterium labelled allyl alcohol supported the claim of intramolecular 1,4-hydride shift (**Scheme 1.43.c**).



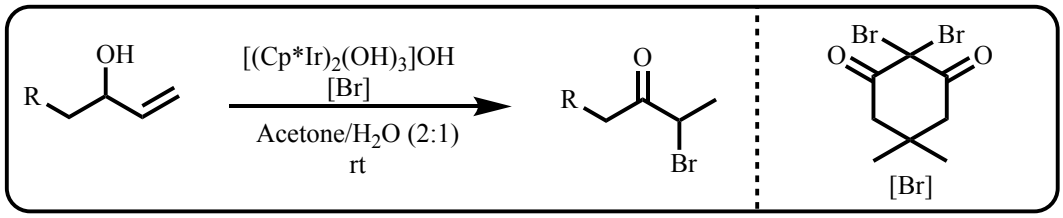
Scheme 1.43. Tandem isomerisation-fluorination of allyl alcohols

Further, Martin-Matute and co-workers[72] reported iridium catalysed synthesis of α-chlorinated ketone compounds from allyl alcohols using N-chlorosuccinimide as a chlorinating reagent in THF/water mixture (**scheme 1.44**). Utilising this protocol, a wide range of primary and secondary allyl alcohols were chlorinated in good yields with single constitutional isomer. In another study Martin-Matute and co-workers[73] reveal the usage of extra additive such as BINOL phosphoric acid in the reaction conditions for the synthesis of α-chlorinated ketones using an iridium catalyst. The DFT study reveal that, the addition of phosphoric acid lowers the transition state for the isomerisation of allyl alcohol at room temperature, and increases the yield of the chlorination process when carried out in acetone rather than water.



Scheme 1.44. Tandem isomerisation-chlorination of allyl alcohols

The same group also reported the isomerisation and bromination of allyl alcohols utilizing an iridium-based catalyst,[74] which resulted α-brominated ketones (**Scheme 1.45**). Among the different brominating reagents screened, 2,2-dibromodimedone was found to be suitable candidate for this transformation. Alternative brominating agents screened, either failed or resulted in lower yield or less regioselectivity of the brominated products. Employing diverse primary or secondary allylic alcohols under this catalytic cycle, a single constitutional isomer of a variety of brominated aldehydes or ketones were obtained.



Scheme1.45 Tandem isomerisation-bromination of allyl alcohols

1.4. Reference

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CHAPTER 2

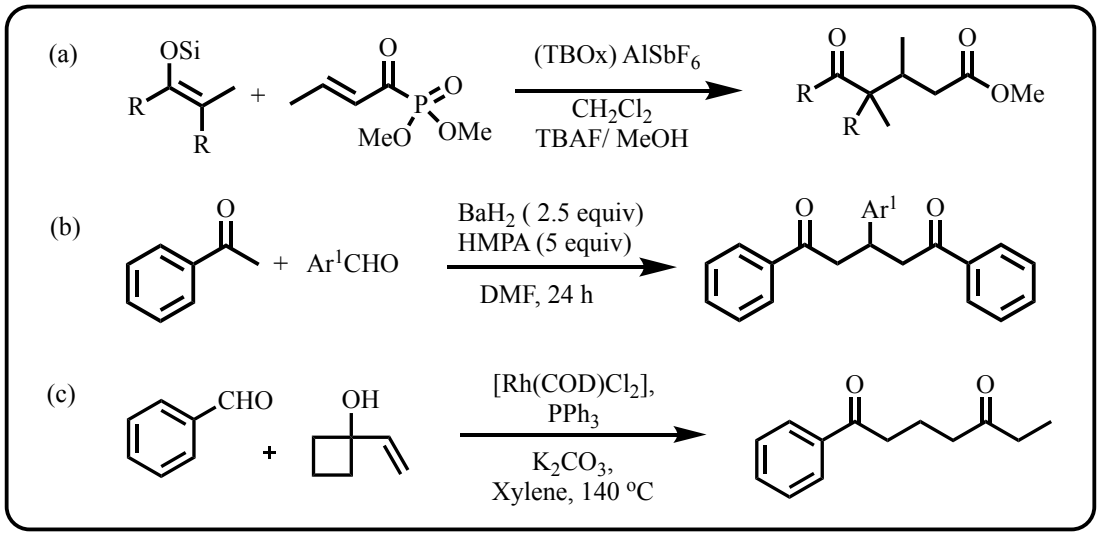
Cobalt(II)porphyrin mediated selective synthesis of 1,5-diketones *via* an interrupted-borrowing-hydrogen strategy using methanol as a C1 source

2.1 Introduction

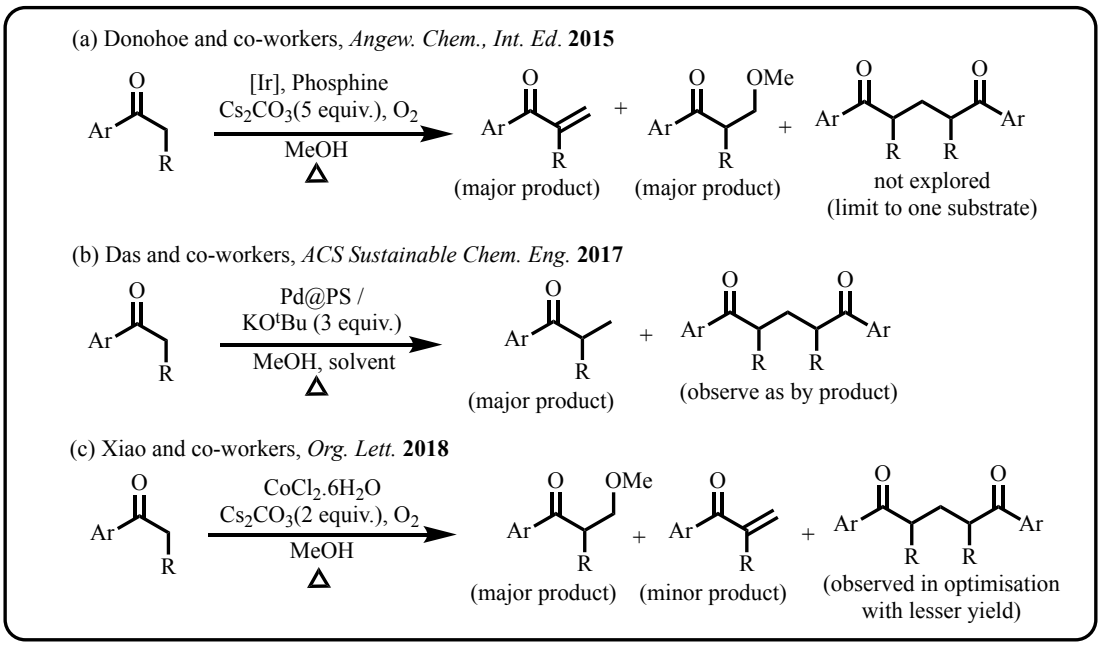
Formation of carbon-carbon bonds using commercially available feedstocks is a highly desirable goal in organic synthesis.[1] Over the last few decades, significant efforts have been made to develop environmentally benign acceptorless dehydrogenation of inexpensive substrates such as alcohols without having to use stoichiometric quantities of the oxidant.[2] Alcohols can be transformed into the corresponding carbonyl compounds using different metal complexes; the *in situ* formed carbonyl compounds can lead to successive reaction in the same pot to generate compounds with new functionalities.[2,3] Methanol is a cheap, abundant, and renewable C-1 feedstock that has been used to make C−C and C−N bonds.[2,3] During the past decade, selective α-methylation of ketones by borrowing hydrogen catalysis (BH) has been elegantly applied using methanol.[4] However, studies to generate α-methylenated architectures using interrupted-borrowing hydrogen strategy (I-BH) are limited.[4a, 5]

Diketones are versatile and important building blocks in the synthesis of a wide variety of organic molecules. Among the different diketones, 1,5-diketones have gained attraction due to their potential biological and pharmacological activities.[6] Furthermore, 1,5-diketones have also proven to be invaluable building blocks for the synthesis of many heterocyclic[7a-d] and polyfunctional[7e-f] (cyclopentenes, piperidines, pyridines and many other heterocyclic molecules) compounds. Traditionally, 1,5-diketones are synthesized through the condensation reaction between α, β-unsaturated ketones with ketones[8a] (Michael addition) or silyl enolethers (**Scheme 2.1.a**)[8b] also *via* condensation between aldehydes and aryl methyl ketones (**Scheme 2.1.b**).[8c,d] Metal complex catalysts are also used for the synthesis of 1,5-diketones.[8e-h] For example, Trost and co-workers used a Ru(II)-catalyst,[8e] and Zhang and Guo (**Scheme 2.1.c**) utilized a Rh(I)-catalyst for the synthesis of 1,5-diketones.[8i] However, selective synthesis of 1,5-

diketones from ketones and methanol using interrupted borrowing hydrogen strategy is scarcely reported. Donohoe[5a] group reported, synthesis of one symmetrical and two unsymmetrical 1,5-diketones using expensive Ir-complex (2 mol%) with excess of base and oxygen as an external oxidant (**Scheme 2.2.a**). Later, Das[5b] group reported a polymer supported palladium nano particle for synthesis of α-methylated ketones.

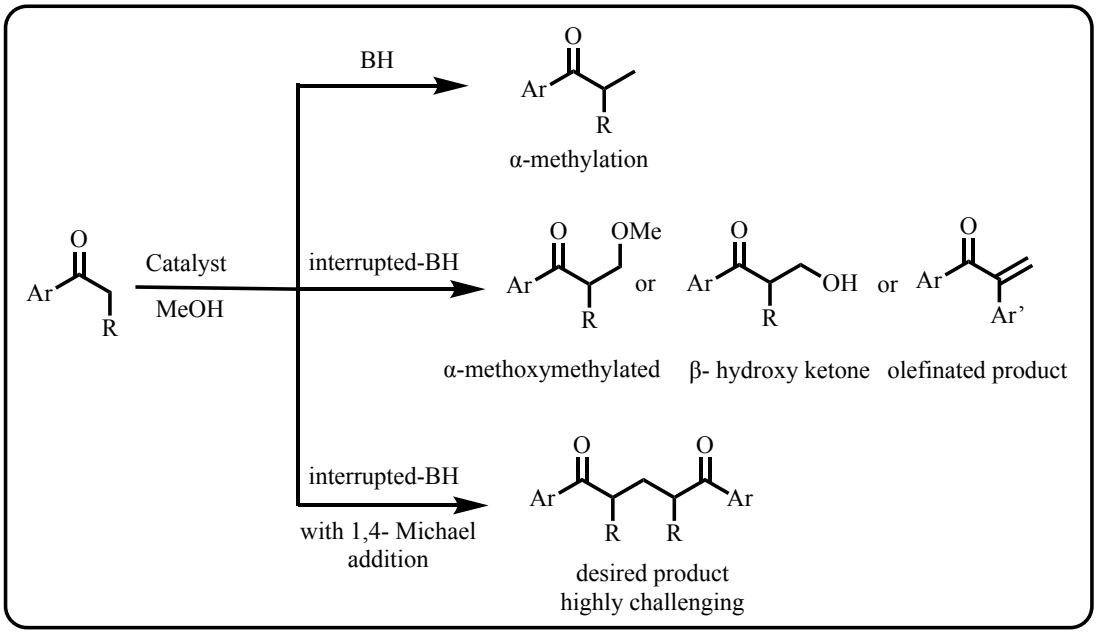


Scheme 2.1: Synthesis of 1,5-diketones using traditional methods

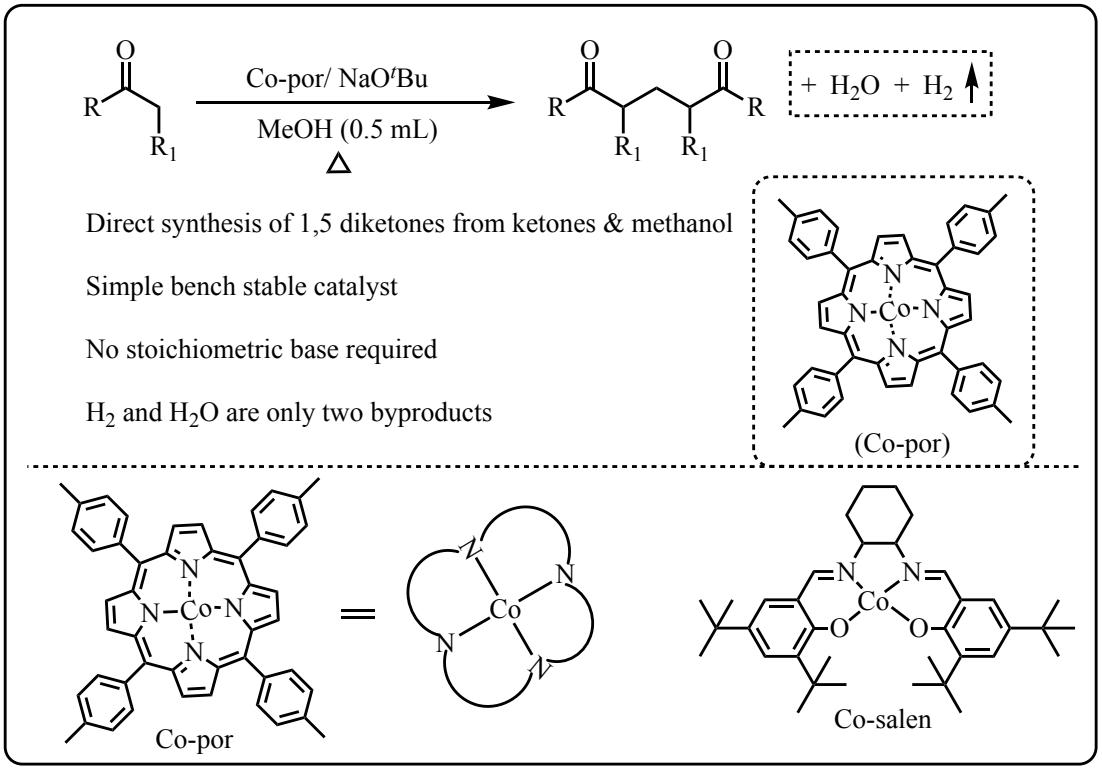


Scheme 2.2: Synthesis of 1,5-diketones using I-BH and BH methods

In this reaction they also observed symmetrical 1,5-diketone as a side product with less yield (20-40%) (**Scheme 2.2.b**). Recently, Xiao[5c] group demonstrated α-methoxymethylation and α-methylenation of ketones using a $CoCl_2 \cdot 6H_2O$ (10 mol%), Cs_2CO_3 (2 equiv.) and oxygen as an external oxidant; in course of the optimisation, they observed 1,5-diketone as a side product with 29% yield (**Scheme 2.2.c**). Lack of selectivity (**Scheme 2.3**) and inadequate substrate scope attracted our attention to find a method for the selective synthesis of 1,5-diketones. The major challenge in the selective synthesis of 1,5-diketones from ketones and methanol is to develop a sustainable I-BH methodology which can diminish the chances of formation of other side products as discussed *vide supra* (**Scheme 2.2**). Herein, we report a unique, simple Co(II)porphyrin mediated selective synthesis of symmetrical 1,5-diketones from ketones and methanol (**Scheme 2.4**) without using stochiometric base and external oxidant.



Scheme 2.3. Formation of 1,5-diketone over other competing I-BH products



Scheme 2.4. Our approach for the selective synthesis of 1,5-diketones

2.2 Results and discussion

The formation of minor quantities of 1,5-diketone during the synthesis of α-methoxy methylation of ketones using methanol[5c] as described above attracted our attention. We were intrigued by the possibility of using cobalt-based catalysts for the synthesis of 1,5-diketones. We believed interrupted-borrowing hydrogen strategy plays a major role in this reaction. Keeping this in mind, our initial investigation started with cobalt(II)porphyrin[10] (Co-por) as a catalyst, propiophenone and methanol as the model system to scrutinize the reaction conditions. Treatment of propiophenone (0.5 mmol) with methanol (0.5 mL), Co-por (2 mol %), and base (20 mol %) in dry toluene (0.5 mL) produced the desired product in 62 % isolated yield in the form of an inseparable diastereomers (**Table 2.1, entry 1**). The formation of diastereomers (**Figure 2.1**) were analysed and identified using NMR such as ^{1}H and COSY 2D experiments (**Figure 2.2-2.4**). ^{1}H NMR show two separate hydrogen resonance for each isomer in the aliphatic

region. Resonance at 2.01 (triplet), 3.51 (sextet), 1.22 (doublet) ppm belong to the anti-isomer and the resonance at 2.44 (doublet of triplet), 1.49 (doublet of triplet), 3.62 (sextet), 1.22 (doublet) ppm belong to the syn-isomer. All the correlations are assigned based on the COSY spectra given in **Figure 2.4**.

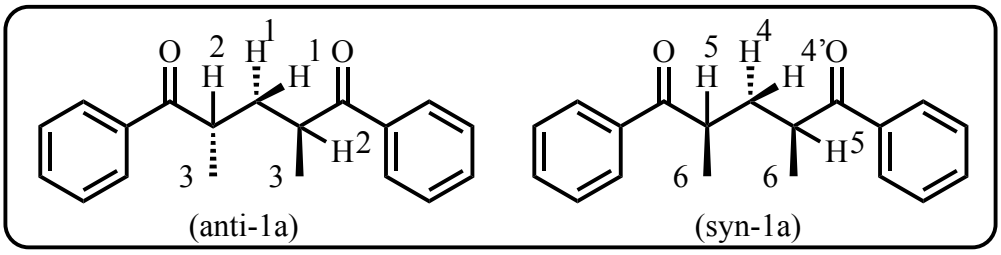
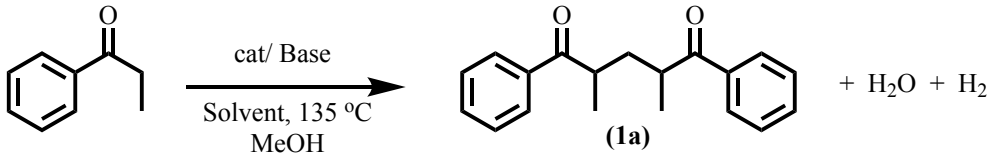


Figure 2.1. Representation of two diastereomers of compound 1a

Bases like KO^{t}Bu, LiO^{t}Bu, Na_2CO_3, KOH and NaOH gave a low yield (**Table 2.1, entries 2-6**). Further studies confirm that 3 mol% of Co-por and 30 mol% of base gave the desired product in higher yield (78 %) (**Table 2.1, entry 7**). Changing the cobalt source to Co-salen, $Co(acac)_2$, $CoCl_2$, and $CoBr_2$ resulted in lower yields (**Table 2.1, entries 9-12**). Use of polar solvents such as THF and dioxane resulted significant reduction in yield (**Table 2.1, entry 13-14**). Notably, on increasing the base load to 50 mol %, an impressive change in the isolated yield (92%) was observed (**Table 2.1, entry 15**). Further increase of catalyst load did not affect the product yield (**Table 2.1, entry 16**). Reaction without toluene gave comparatively low yield (**Table 2.1, entry 17**).

Table 2.1: Optimisation for 1,5-diketone synthesis using ketone and MeOH *via* I-BH method [a]



Entry	Catalyst (mol%)	Base (mol%)	T(°C) [d]	Solvent[c]	Yield (%)[b]
1	Co-por (2)	NaO^{t}Bu (20)	135	Toluene	62
2	Co-por (2)	KO^{t}Bu (20)	135	Toluene	45
3	Co-por (2)	LiO^{t}Bu (20)	135	Toluene	40
4	Co-por (2)	NaOH (20)	135	Toluene	ND
5	Co-por (2)	KOH (20)	135	Toluene	ND
6	Co-por (2)	Na_2CO_3 (20)	135	Toluene	ND
7	Co-por (3)	NaO^{t}Bu (30)	135	Toluene	78
8	Co-por (3)	NaO^{t}Bu (30)	100	Toluene	Trace
9	Co-salen (3)	NaO^{t}Bu (30)	135	Toluene	62
10	$Co(acac)_2$ (3)	NaO^{t}Bu (30)	135	Toluene	32
11	$CoCl_2$ (3)	NaO^{t}Bu (30)	135	Toluene	28
12	$CoBr_2$ (3)	NaO^{t}Bu (30)	135	Toluene	31
13	Co-por (3)	NaO^{t}Bu (30)	135	THF	35
14	Co-por (3)	NaO^{t}Bu (30)	135	1,4-dioxane	30
15	Co-por (3)	NaO^{t}Bu (50)	135	Toluene	92
16	Co-por (5)	NaO^{t}Bu (50)	135	Toluene	93
17	Co-por (3)	NaO^{t}Bu (50)	135	-----	76

[a]Reaction conditions: propiophenone $5x10^{-1}$ mmol, 0.5 mL CH_3OH, 24h. [b]All yields are isolated yields. [c]0.5 mL solvent. [d]Oil bath temperature.

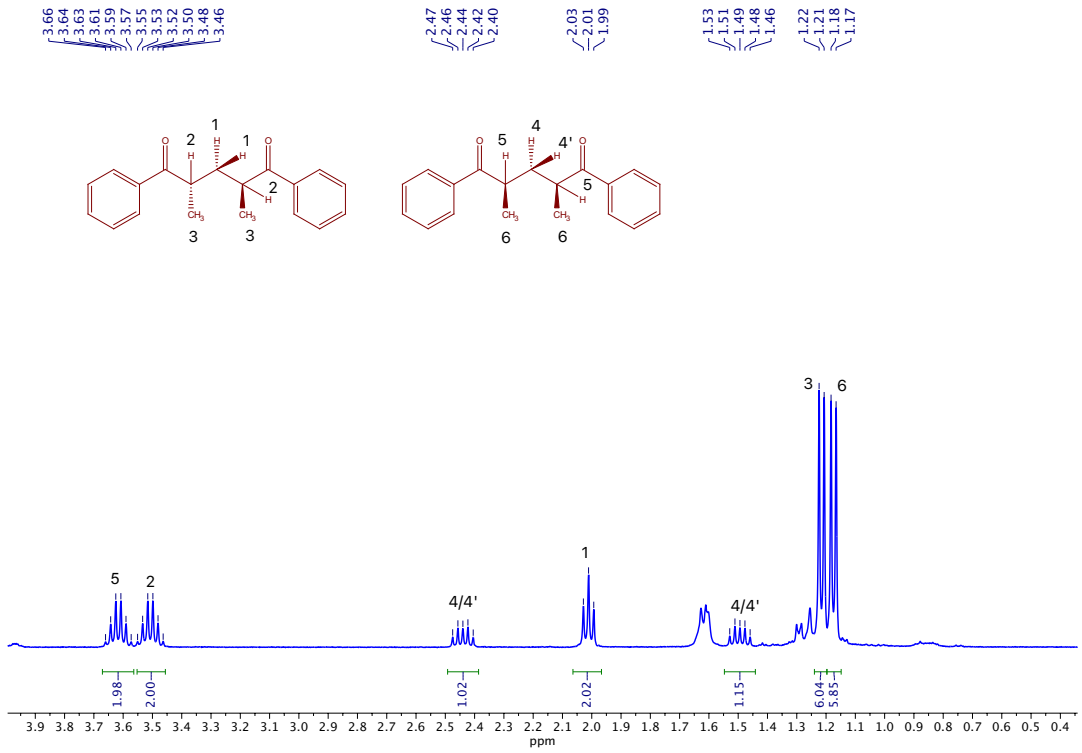


Figure 2.2: [1]H NMR spectrum (400 MHz) of compound **1a**

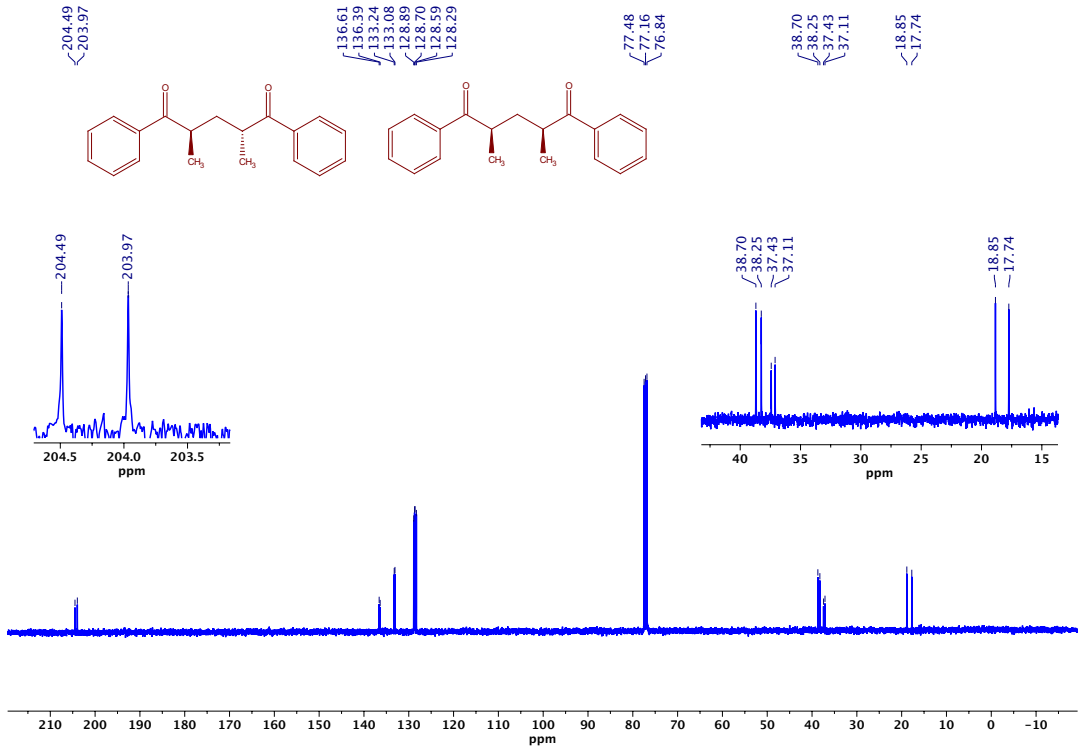


Figure 2.3: [13]C NMR spectrum (101 MHz) of compound **1a**

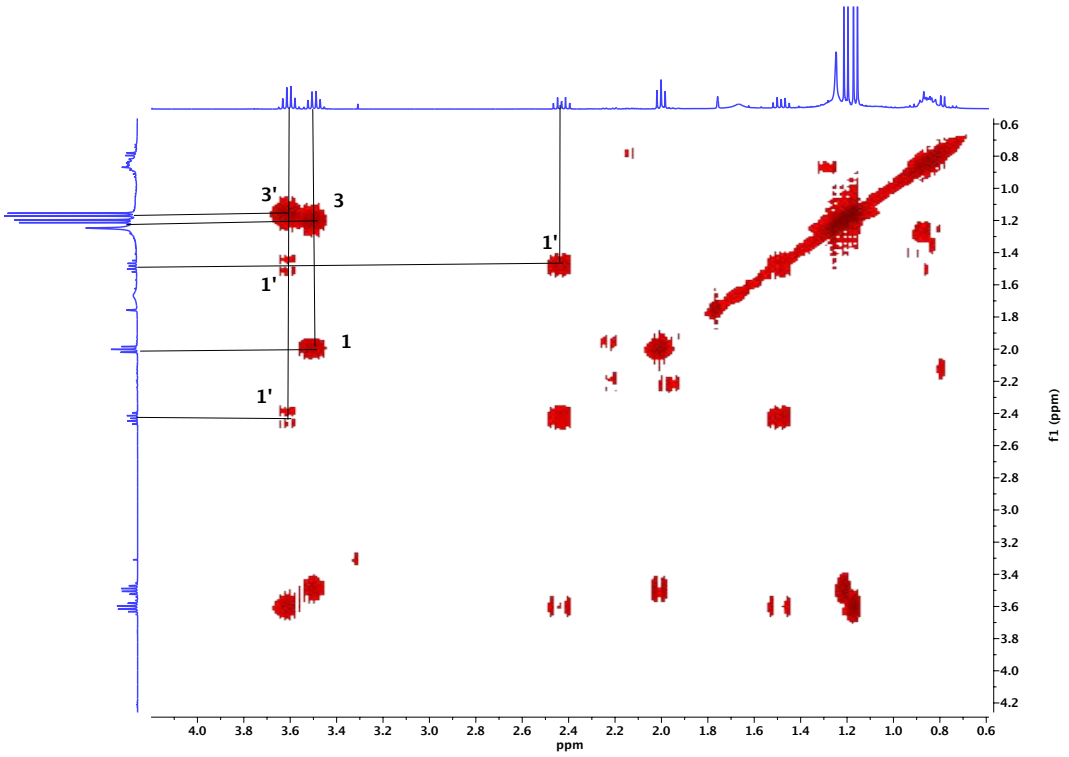
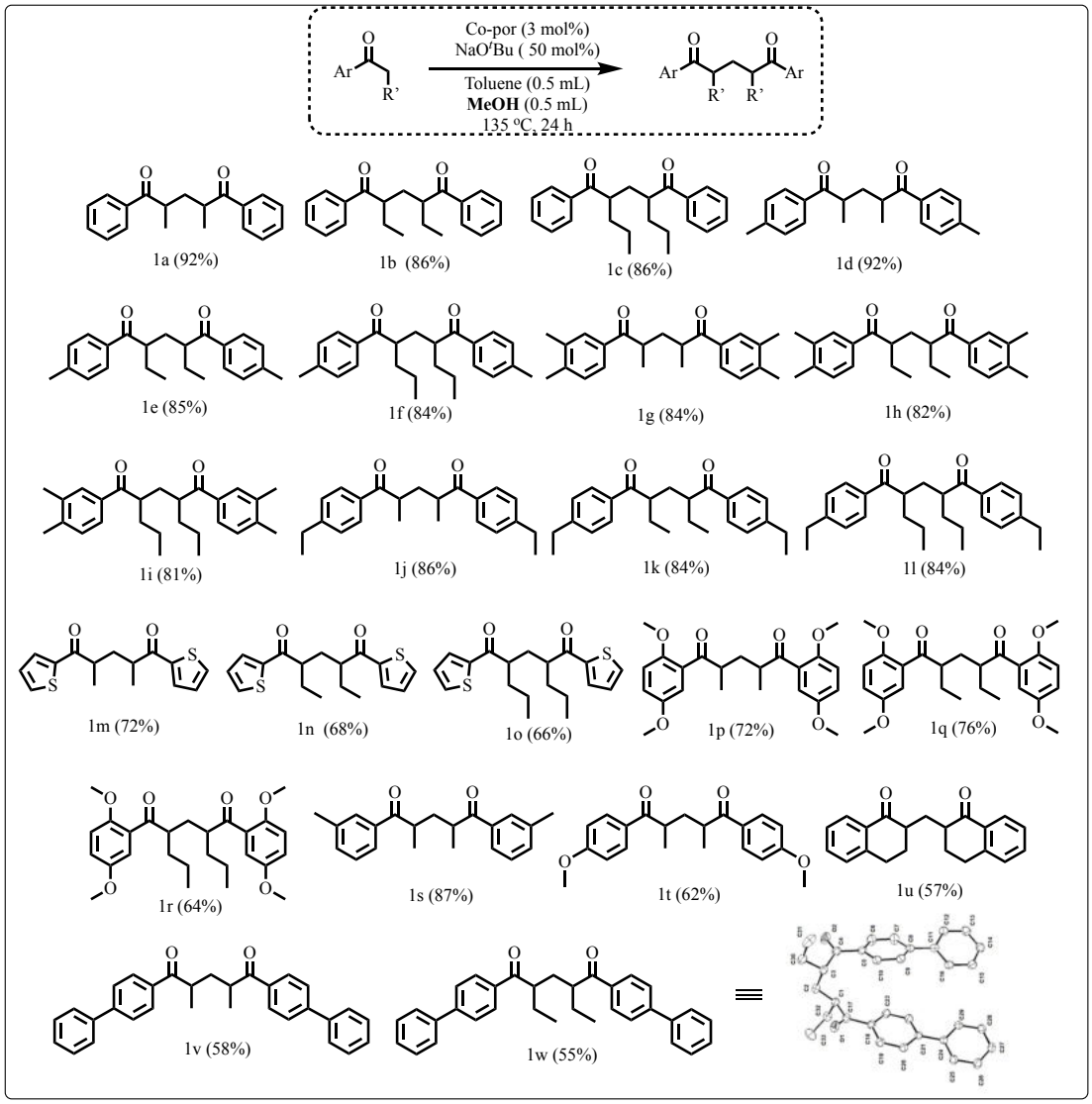


Figure 2.4: COSY 2D NMR spectrum of compound **1a**

The scope of the Co-por mediated synthesis of 1,5-diketones using the optimized reaction conditions was explored. Reaction of butyrophenone and 1-phenylpentan-1-one with methanol, exclusively yielded the corresponding 1,5-diketones in 86 % (**Table 2.2, 1b & 1c**). Substrates bearing electron-donating substituents (CH_3-, C_2H_5-) on the para position of aryl ketones under similar reaction conditions yielded 1,5-diketones in good yields (**Table 2.2, 1d-1f & 1j-1l**). 3,5-Dimethyl aryl ketones yielded the respective 1,5-diketones in 84 %, 82 % and 81 % respectively (**Table 2.2, 1g-1i**). Notably, thio ketones were found to be active enough to yield the desired products (**1m-1o)** in 72 %, 68 % and 66 % respectively. The catalytic system also tolerated 'methoxy' substitution on the phenyl and yielded the desired product in 62 %, 72 %, 76 % and 64 % respectively (**Table 2.2, 1t, 1p-1r**). *Meta* substituted propiophenone also gave the 1,5-diketone product in 87% yield

(**Table 2.2, 1s**). Surprisingly, alicyclic ketone gave the desired diastereomer product in 57 % yield (**Table 2.2, 1u**). To demonstrate the catalytic activity, we further explored

Table 2.2: Substrate scope for 1,5-diketones from mono aryl ketones[a,b]

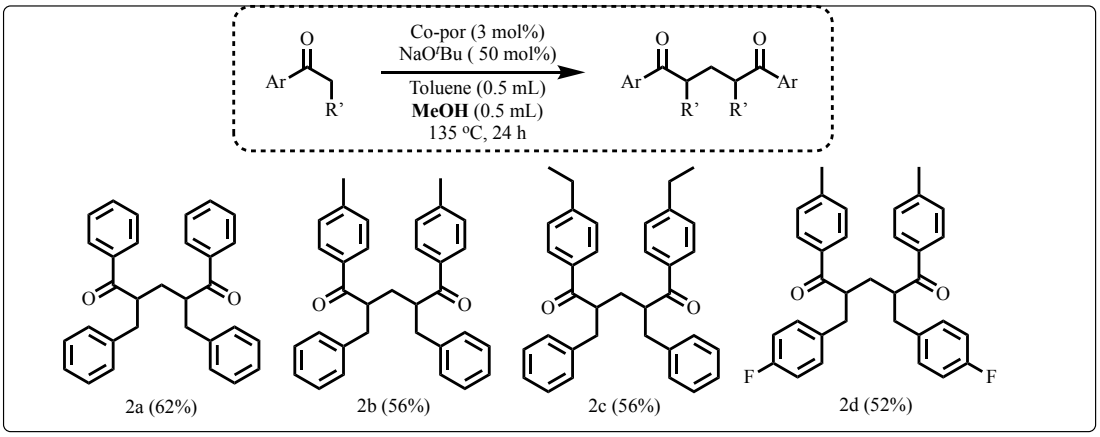


[a]Reaction conditions: ketone 0.5 mmol, catalyst $1.5x10^{-2}$ mmol and base $2.5x10^{-1}$ mmol. [b]All yields are isolated yields.

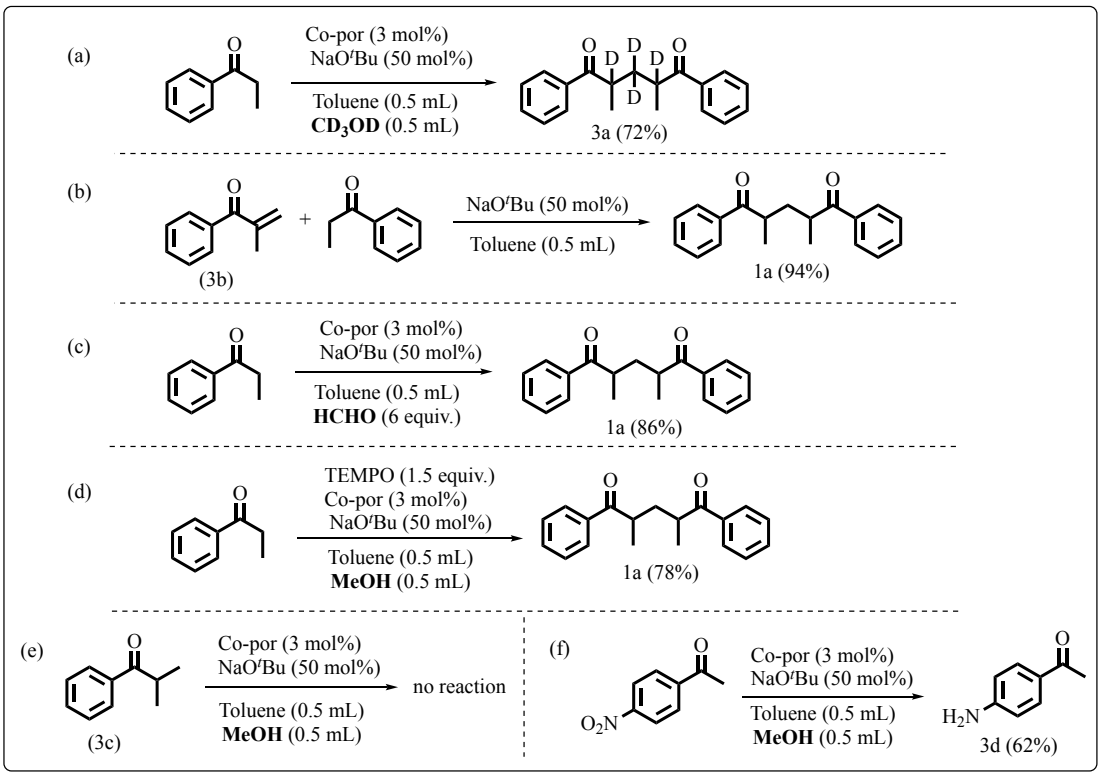
using biphenyl system. The reaction proceeded smoothly to yield the corresponding 1,5-diketones in 58 % and 55 % respectively (**Table 2.2, 1v & 1w**). However, halo aryl ketones under the optimized conditions did not yield the desired product. To our delight, compound **1w** crystallized in a monoclinic system ($P2_1/c$) which was analysed

using single crystal X-ray crystallography (**Table 2.4**). To check the practicability of our developed approach, gram scale reaction was carried out with propiophenone under the optimized condition, that resulted in 78% of the desired 1,5-diketone product (**1a**).

Table 2.3: Substrate scope for 1,5-diketones from di aryl ketones[a,b]



[a]Reaction conditions: ketone 0.5 mmol, catalyst $1.5x10^{-2}$ mmol and base $2.5x10^{-1}$ mmol. [b]All yields are isolated yields.

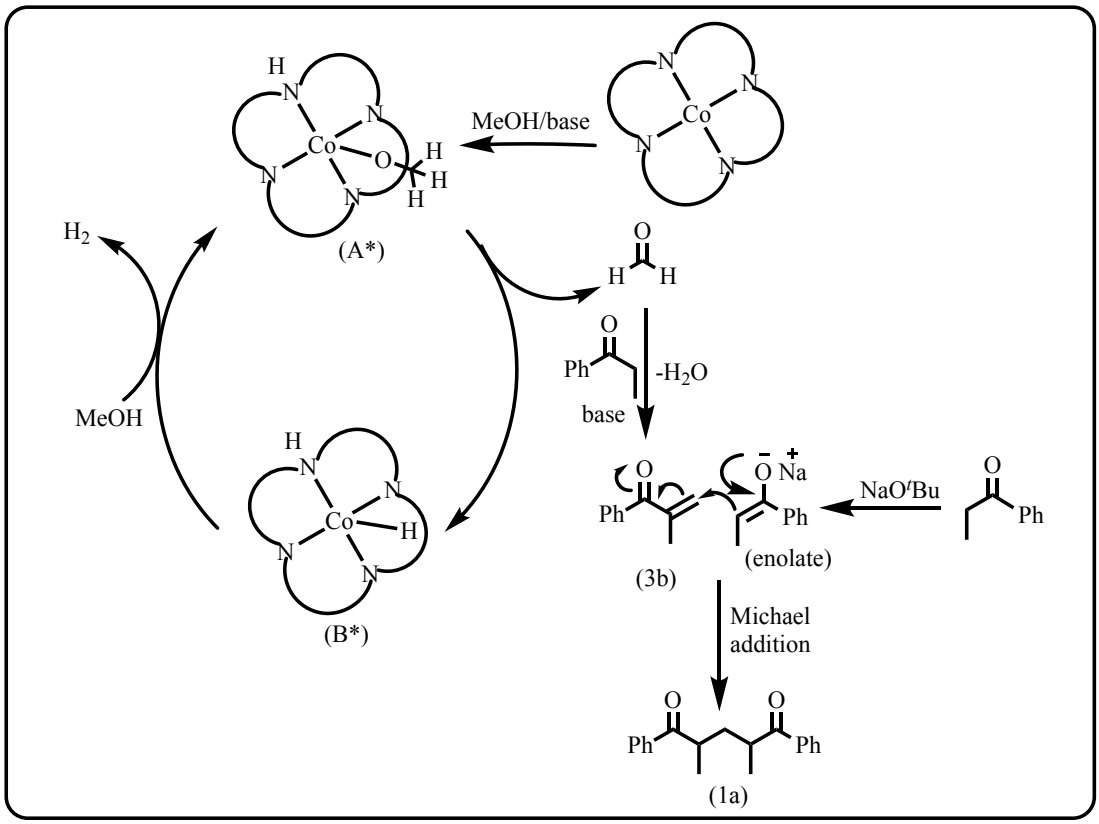


Scheme 2.5: Mechanistic studies for formation of 1,5-diketones

Motivated by these results, we next examined the reactivity of 3-phenylpropiophenones; the C-alkylated products that were synthesized using hydrogen borrowing methodology.[1d] Under the optimized conditions the reaction of 3-phenylpropiophenones gave the conjugate addition products in moderate yields (**Table 2.3, 2a-2d**). To check the reactivity of our approach, ethanol was used instead of methanol which resulted in a complex mixture. Further, we extended our method to acetophenone under the optimised reaction condition, less conversion of acetophenone was observed with a complex mixture.

Controlled experiments were performed to gain insights into the reaction mechanism. When propiophenone was reacted with deuterated methanol (CD_3OD), selectively deuterated 1,5-diketone product (**3a**) was obtained in 72 %. This observation indicates that the proton at the α-carbon has its origin from methanol during the course of the reaction (**Scheme 2.5.a**). The *in situ* generated formaldehyde after condensing with propiophenone yields the interrupted borrowed hydrogen product or the enone (**3b**). This transient α-methylenated ketone (**3b**) subsequently reacts with propiophenone *via* Michael addition to yield the 1,5-diketone product (**1a**) exclusively.[5] We believe that this step proceeds in the presence of a base. The reaction of propiophenone with paraformaldehyde instead of methanol gave the desired 1,5-diketone product in 86% isolated yield, which further supports that formaldehyde is formed during the course of the reaction. (**Scheme 2.5.c**). To confirm our hypothesis, we reacted the intermediate (**3b**) and propiophenone in presence of NaO^tBu (50 mol%) which resulted in the 1,5-diketone (**1a**) as the major product in 94% yield (**Scheme 2.5.b**). As expected, no conversion was observed, when we reacted **3c** in our standard experimental conditions, which indicates that (**3b**) is the intermediate formed during the course of the reaction (**Scheme 2.5.e**). In the latter reaction the α-position of the carbonyl moiety

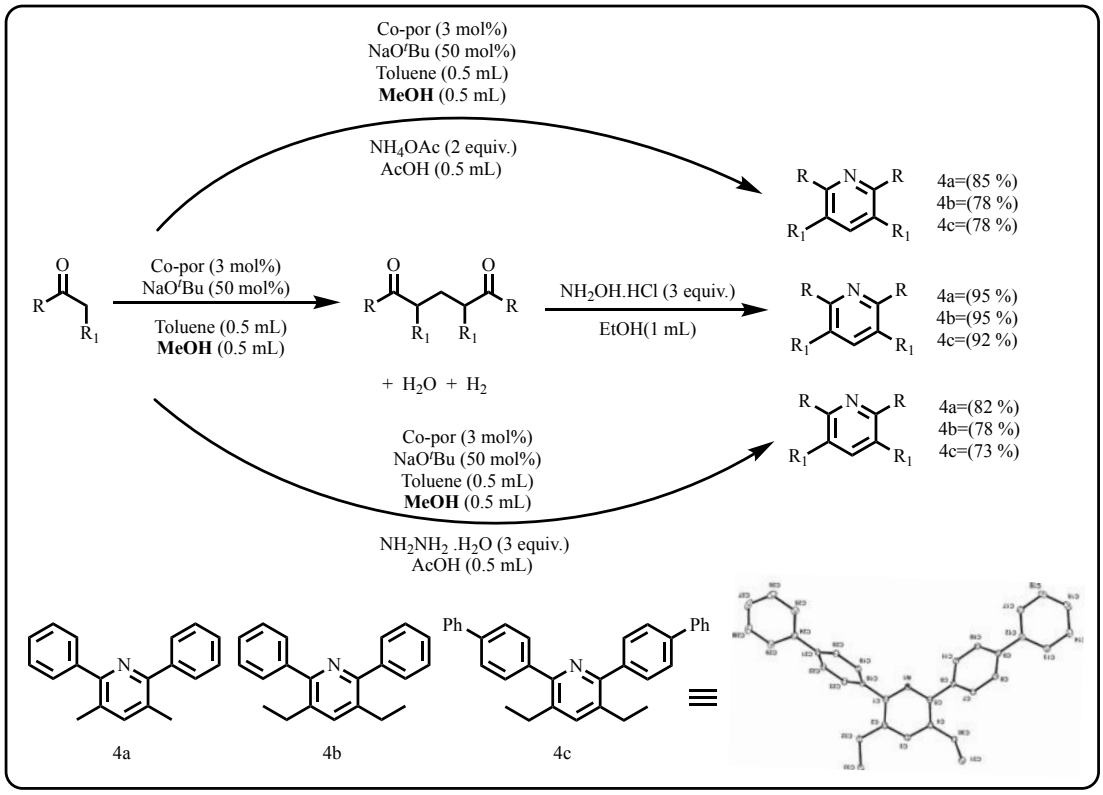
is occupied, hence, it hinders the formation of α-methylenated ketone (**3b**) intermediate. In addition, presence of TEMPO (1.5 equiv.) under the standard conditions used for the synthesis 1,5-diketones yielded 78% (**1a**) of the product; clarifying that the reaction did not adopt any free radical pathway (**Scheme 2.5.d**). The reaction of 4-nitroacetophenone under similar reaction conditions, produced 4-aminoacetophenone (**3d**) in 62% yield (**Scheme 2.4.f**). This justifies that, methanol is converting to formaldehyde with evolution of H_2 gas. Based on the controlled experiments and from the literature reports,[2a,11] a plausible mechanism for the reaction of propiophenone and methanol in presence of Co-por is proposed. (**Scheme 2.6**). We believe that the catalytic cycle is initiated by the formation of complex (A*) generated by MeOH in the presence of Co-por and base.



Scheme 2.6: Proposed mechanism

We speculate that complex (**A***) is liberating formaldehyde and metal hydride (**B***) species during the reaction. Then, the metal hydride (**B***) species regenerates the complex (**A***) with the liberation of H_2 gas on reaction with methanol. The ephemeral formaldehyde generates the α-methylenated intermediate (**3b**) on reaction with propiophenone. The resultant α-methylenated intermediate (**3b**) and propiophenone condense *via* Michael addition to give the desired 1,5-diketone (**1a**).

As alluded in the introduction, 1,5-diketones act as intermediates for the synthesis of heterocycles. We investigated transformation of diketones to pyridines (**Scheme 2.7**). For example, treatment of 1,5-diketones **1a**, **1b**, and **1w** with $NH_2OH.HCl$ resulted in the substituted pyridines **4a**, **4b** and **4c** respectively in good yields. Compounds **4a**, **4b** and **4c** were also synthesized in one-pot using sequential addition of reagents as shown in the **Scheme 2.7**. The formation of pyridines was



Scheme 2.7: Synthetic application of 1,5-diketones

confirmed using ^{1}H, ^{13}C NMR and HRMS. The molecular structure of **4c** was further confirmed by X-ray crystal structure analysis (**Table 2.4**). All the three pyridines showed interesting photophysical properties which exhibit absorption maxima (λ_{max}) at around 300 nm (**Figure 2.5**). We analyzed the photoluminescence (PL) behavior of the pyridines in solution and aggregate states. The emission of pyridines is weak in tetrahydrofuran (THF) solution and increases slowly (or) remains unchanged up to 60:40 (H_2O: THF) composition. Afterwards the intensity of the emission increased rapidly (**Figure 2.6-2.8**).

This phenomenon is called aggregation induced enhanced emission (AIEE) or aggregation induced emission (AIE). Molecules with AIEE properties are of interest due to their diverse applications as bioprobes, chemosensors stimuli-responsive nanomaterials, and active layers in the construction of efficient organic light-emitting diodes.[12] We believe that our protocol will help to make a wide variety of substituted pyridines that will show AIEE properties and also may have other potential applications as mentioned *vide supra.*

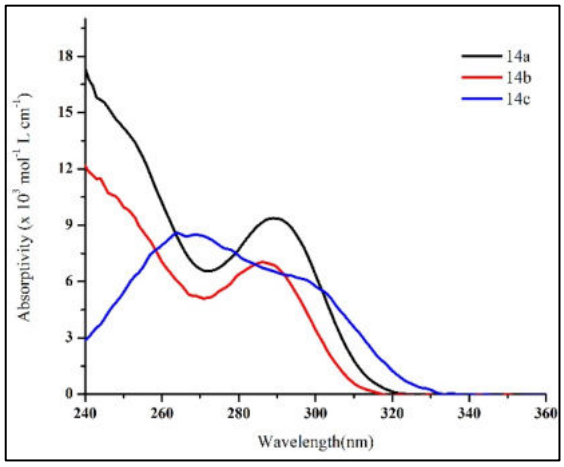


Figure 2.5: Absorption spectra of compounds **4a**-**4c**.

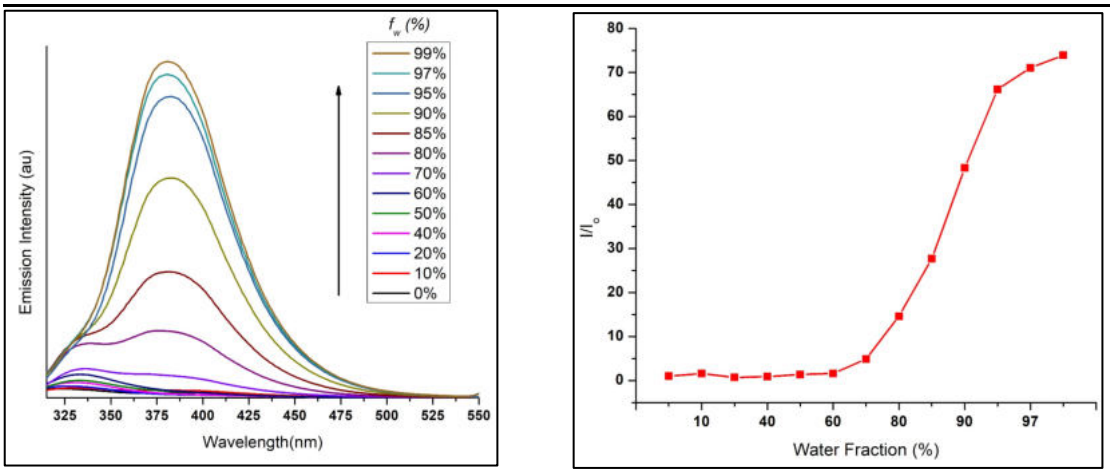


Figure 2.6: (Left) Emission spectra of **4a** in THF/water mixtures with different fractions of water (f_w) (concentration = 20 μM). (Right) Relative intensity *vs* water fraction (vol %) in THF/Water mixtures; [**4a**] = 20 μM.

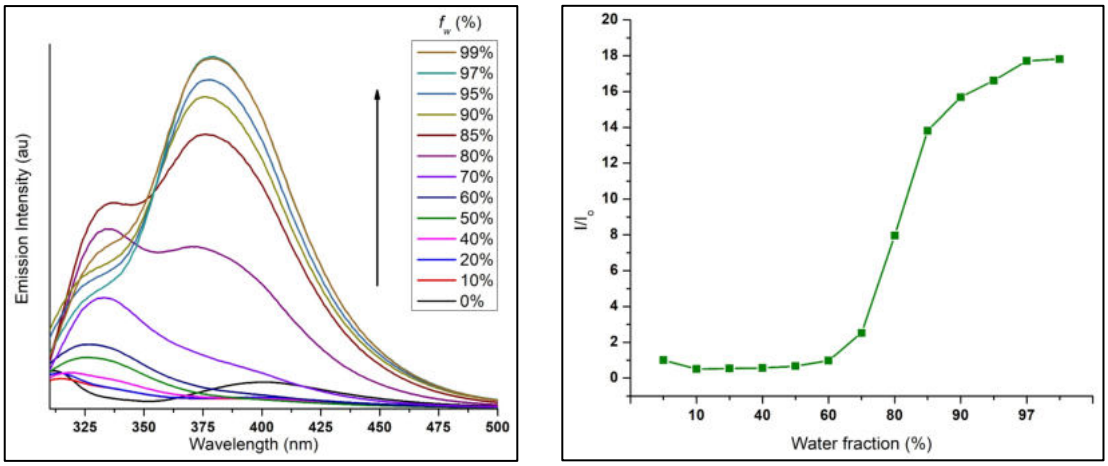


Figure 2.7: (Left) Emission spectra of **4b** in THF/water mixtures with different fractions of water (f_w) (concentration = 20 μM). (Right) Relative intensity *vs* water fraction (vol %) in THF/Water mixtures; [**4b**] = 20 μM.

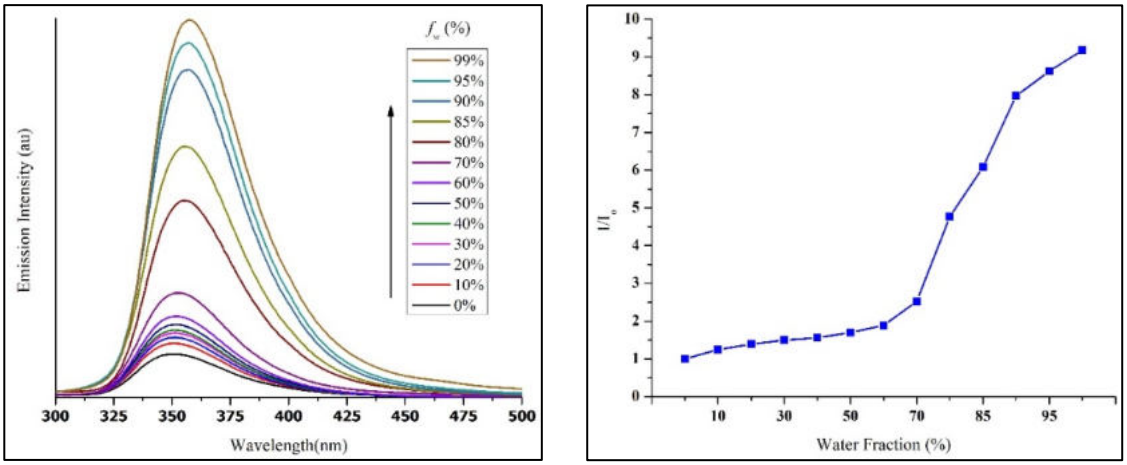


Figure 2.8: (Left) Emission spectra of **4c** in THF/water mixtures with different fractions of water (f_w) (concentration = 20 μM). (Right) Relative intensity *vs* water fraction (vol %) in THF/Water mixtures; [**4c**] = 20 μM.

Table 2.4: Crystal data and structure refinement parameters for compound **1w** & compound **4c.**

Identification code	Compound **1w**	Compound **4c**
Empirical formula	$C_{33}H_{32}O_2$	$C_{33}H_{29}N$
Formula weight	460.58	439.57
Temperature/K	100.00 (10)	100.00 (10)
Crystal system	monoclinic	triclinic
Space group	$P2_1/c$	P-1
a/Å	27.6970(3)	9.7589(2)
b/Å	9.8585(8)	11.4102(3)
c/Å	18.4737(1)	11.9765(4)
α/°	90	67.792(3)
β/°	95.6973(8)	77.710(3)

γ/°	90	77.985(2)
Volume/Å^3	5019.40(7)	1194.29(7)
Z	8	2
ρ_{calc}g/cm^3	1.219	1.222
μ/mm^{-1}	0.573	0.529
F(000)	1968.0	469.0
Radiation	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	6.414 to 160.198	8.062 to 155.698
Index ranges	-35 ≤ h ≤ 33, -9 ≤ k ≤ 12, -23 ≤ l ≤ 23	-12 ≤ h ≤ 12, -14 ≤ k ≤ 14, -9 ≤ l ≤ 14
Reflections collected	43563	18993
Independent reflections	10775 [R_{int} = 0.0260, R_{sigma} = 0.0197]	4976 [R_{int} = 0.0227, R_{sigma} = 0.0202]
Data/restraints/parameters	10775/0/636	4976/0/309
Goodness-of-fit on F^2	1.069	1.069
Final R indexes [I>=2σ (I)]	R_1 = 0.0485, wR_2 = 0.1292	R_1 = 0.0391, wR_2 = 0.1036
Final R indexes [all data]	R_1 = 0.0504, wR_2 = 0.1308	R_1 = 0.0414, wR_2 = 0.1049
Largest diff. peak/hole / e Å^{-3}	0.39/-0.24	0.21/-0.22

2.3. Conclusion

In summary, a novel interrupted-borrowing hydrogen strategy for coupling of methanol and ketones using bench stable Co(II)porphyrin complex is disclosed. Our environmentally benign method was employed on variety of ketones for the direct and selective synthesis of 1,5-diketones having H_2O and H_2 as the eco-friendly by-products. Control experiments and deuterium-labelling study showed that the reaction proceeds through an α-methylenated intermediate. The synthetic utility of this protocol was extended for the preparation of AIEE active pyridines which may have potential application in making organic light emitting diodes.

2.4 Experimental Section

2.4.1 General Information

All reagents and solvents were obtained from commercial sources; some of the starting material was synthesized by well-known Friedel-Craft acylation. Solvents were purified according to standard procedures. 3,5 di-*tert*-butyl salen, 5,10,15,20-tetra-*p*-tolylporphyrin, Co-por, Co-salen were synthesized following literature reported methods.[9] 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. IR spectra were recorded with the Perkin Elmer instrument. High-resolution mass spectra (HRMS) were recorded using Bruker microTOF-QII mass spectrometer. Single-crystal X-ray diffraction data were collected at 100 K using Cu-Kα radiation (1.54184 Å). Crystallographic data for compound **23** and **34** and details of X-ray diffraction experiments and crystal structure refinements are given in **Table 2.4**. The structures were solved and refined with SHELX suite of programs or Olex. All non- hydrogen atoms were refined with anisotropic displacement

coefficients. The H atoms were placed at calculated positions and were refined as riding atoms. (CCDC deposition no. 2046746-2046747).

Synthesis of Co-por[9a]

$Co(OAc)_2.4H_2O$ (7.43 g, 29.8 mmol, 10 equiv.) was added to a hot solution of 5,10,15,20-tetra-*p*-tolylporphyrin (2.0 g, 2.98 mmol, 1 equiv.) in DMF (100 mL). The resulting solution was refluxed for 6 h. The reaction mixture then was poured in to water. The solid was filtrated and dried over the vacuum. After purification by column chromatography the desired Co(II)porphyrin catalyst was isolated (yield: 1.65 g, 76%). UV−Vis (CH_2Cl_2): λ_{max} = 412 nm, 530 nm. HRMS (ESI-TOF) *m/z* $[M]^+$ Calcd for $[C_{48}H_{36}CoN_4]^+$: 727.2266, found: 727.2237.

Synthesis of Co-salen[9b]

$Co(OAc)_2.4H_2O$, (0.83 g, 3.32 mmol, 1.3 equiv.) in methanol (10 mL) was added dropwise to a solution of 3,5 di-*tert*-butyl salen (1.40 g, 2.56 mmol, 1 equiv.) in DCM (5 mL) at RT. The yellow solution turned red and a copious amount of precipitate was formed. The solid was collected, washed with ethanol and dried (yield: 1.20 g, 78%). HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{36}H_{51}CoN_2O_2+H]^+$: 603.3361, found: 603.3367.

2.4.2. General procedure for synthesis of 1,5-diketones

An oven-dried sealed tube was charged with Co-por (1.5×10^{-2} mmol, 0.03 equiv.), NaO^tBu (2.5×10^{-1} mmol, 0.5 equiv.). Under an inert atmosphere, ketone (0.5 mmol, 1 equiv.), methanol (0.5 mL) and toluene (0.5 mL) were added to the reaction mixture and the system was purged with nitrogen gas. Then, the sealed tube was closed with PTFE stopper and the reaction mixture was stirred at 135 ºC (oil bath temperature) for

24 h. The reaction mixture was transferred to a round bottom flask after cooling it to room temperature, the sealed tube was rinsed with methanol (2 x 5 mL), the combined organic mixture was concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the desired 1,5-diketone product in high purity. All the crude mixtures were purified by column chromatography using *n*-hexane: EtOAc (20:1-10:1). (Note: All reactions were carried out in a 50 mL sealed tube made up of a material that can withstand the internal pressure).

Procedure for gram scale 1,5-diketone synthesis:

An oven-dried sealed tube was charged with Co-por (3 x 10^{-1} mmol, 0.03 equiv.), NaO^{t}Bu (5 mmol, 0.5 equiv.). Under an inert atmosphere, ketone (10 mmol, 1 equiv.), methanol (5 mL) and toluene (5 mL) were added to the reaction mixture and the system was purged with nitrogen gas. Then, the sealed tube was closed with PTFE stopper and the reaction mixture was stirred at 135 ^{o}C (oil bath temperature) for 24 h. The reaction mixture was transferred to a round bottom flask after cooling it to room temperature. After purification by column chromatography an inseparable mixture of two diastereomers anti-1a and syn-1a in (1:1) ratio was isolated as a yellow liquid (1.092 g, 78%).

2.4.3. Analytical data for 1,5-diketone compounds

2,4-dimethyl-1,5-diphenylpentane-1,5-dione: (**Table 2.2, 1a**). [5b] Prepared from propiophenone (0.067 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1a and syn-1a in (1:1) ratio was isolated as a yellow liquid (0.063 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.5 Hz, 4H), 7.78 (d, J = 7.5 Hz, 4H), 7.58 (t, J = 7.3

Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 4H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 4H), 3.62 (sextet, *J* = 7.6 Hz, 2H), 3.51 (sextet, *J* = 7.6 Hz, 2H), 2.44 (dt, *J*=14.0, 7.1 Hz, 1H), 2.01 (t, *J* = 7.6 Hz, 2H), 1.49 (dt, *J* = *J*=14.0, 7.1 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.17 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.5, 203.9, 136.6, 136.4, 133.2, 133.0, 128.9, 128.7, 128.6, 128.3, 38.7, 38.2, 37.4, 37.1, 18.8, 17.7. HRMS (ESI-TOF) m/z $[M+Na]^+$ Calcd for $[C_{19}H_{20}O_2+Na]^+$: 303.1356, found: 303.1369.

2,4-diethyl-1,5-diphenylpentane-1,5-dione: (**Table 2.2, 1b**). [5b] Prepared from butyrophenone (0.074 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1b and syn-1b in (1:1.1) ratio was isolated as a yellow liquid (0.066 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.9 Hz, 4H), 7.70 (d, *J* = 7.9 Hz, 4H), 7.57 (t, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 4H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 4H), 3.45 (p, *J* = 7.9 Hz, 2H), 3.31 (p, *J* = 7.9 Hz, 2H), 2.31 (dt, *J*=14.0, 7.1 Hz, 1H), 2.06 (t, *J* = 7.9 Hz, 2H), 1.81 – 1.66 (m, 5H), 1.57 – 1.46 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 6H), 0.80 (t, *J* = 7.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.8, 203.9, 137.6, 137.3, 133.2, 133.0, 128.8, 128.6, 128.44, 128.1, 45.5, 45.1, 33.5, 33.2, 27.2, 25.4, 11.85, 11.7. HRMS (ESI-TOF) m/z $[M+Na]^+$ Calcd for $[C_{21}H_{24}O_2+Na]^+$: 331.1669, found: 331.1679.

1,5-diphenyl-2,4-dipropylpentane-1,5-dione: (**Table 2.2, 1c**). Prepared from 1-phenylpentan-1-one (0.081 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1c and syn-1c in (1.1:1) ratio was isolated as a yellow liquid (0.072 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.1 Hz, 4H), 7.68 (d, *J* = 7.1 Hz, 4H), 7.58 (t, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 4H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.29 –

7.23 (m, 4H), 3.52 (p, *J* = 8.0 Hz, 2H), 3.36 (p, *J* = 8.0 Hz, 2H), 2.29 (dt, *J* = 14.0, 7.2 Hz, 1H), 2.08 – 2.04 (m, 2H), 1.79 – 1.72 (m, 1H), 1.70 – 1.60 (m, 4H), 1.48– 1.39 (m, 4H), 1.34– 1.27 (m, 4H), 1.23 – 1.09 (m, 4H), 0.84 (t, *J* = 7.3 Hz, 6H), 0.78 (t, *J* = 7.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.9, 204.0, 137.5, 137.3, 133.2, 133.0, 128.8, 128.6, 128.4, 128.1, 43.9, 43.5, 36.3, 34.5, 34.2, 20.7, 20.6, 14.3, 14.2. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{23}H_{28}O_2+Na]^+$: 359.1982, found: 359.1999. FT-IR (ATR, neat): 2957, 2871, 1677, 1595, 1001, 701 cm^{-1}.

2,4-dimethyl-1,5-di-*p*-tolylpentane-1,5-dione: (**Table 2.2, 1d**). Prepared from 1-(*p*-tolyl)propan-1-one (0.074 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1d and syn-1d in (1.16:1) ratio was isolated as a yellow liquid (0.071 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 4H), 7.67 (d, *J* = 8.3 Hz, 4H), 7.30 (d, *J* = 7.9 Hz, 4H), 7.11 (d, *J* = 7.9 Hz, 4H), 3.58 (sextet, *J* = 8.0 Hz, 2H), 3.46 (sextet, *J* = 8.0 Hz, 2H), 2.42 (s, 6H), 2.42 – 2.37 (m, 1H), 2.33 (s, 6H), 1.98 (t, *J* = 8.0 Hz, 2H), 1.46 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.2, 203.7, 144.0, 143.8, 134.1, 133.8, 129.5, 129.3, 128.7, 128.4, 38.5, 38.1, 37.5, 37.3, 21.8, 21.7, 18.9, 17.7. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{21}H_{24}O_2+Na]^+$: 331.1669, found: 331.1654. FT-IR (ATR, neat): 2979, 1676, 1606, 1377, 1181, 742 cm^{-1}.

2,4-diethyl-1,5-di-*p*-tolylpentane-1,5-dione: (**Table 2.2, 1e**). Prepared from 1-(*p*-tolyl)butan-1-one (0.081 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1e and syn-1e in (1:1.4) ratio was isolated as a yellow liquid (0.071 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 4H), 7.59 (d, *J* = 8.2 Hz, 4H), 7.28 (d, *J* = 8.0

Hz, 4H), 7.05 (d, *J* = 8.0 Hz, 4H), 3.48 – 3.35 (m, 2H), 3.30 – 3.23 (m, 2H), 2.41 (s, 6H), 2.31 (s, 6H), 2.30 – 2.19 (m, 1H), 2.03 – 2.01 (m, 2H), 1.80 – 1.67(m, 4H), 1.65 – 1.57(m, 1H), 1.55 – 1.44 (m, 4H), 0.84 (t, *J* = 7.5 Hz, 6H), 0.78 (t, *J* = 7.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.4, 143.9, 143.6, 135.1, 134.8, 129.5, 129.2, 128.6, 128.3, 45.3, 45.0, 33.8, 33.5, 27.2, 25.4, 21.7, 21.6, 11.8, 11.7. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{23}H_{28}O_2+Na]^+$: 359.1982, found: 359.1990. FT-IR (ATR, neat): 2969, 2871, 1673, 1602, 1264, 1118, 732 cm^{-1}.

2,4-dipropyl-1,5-di-*p*-tolylpentane-1,5-dione: (**Table 2.2, 1f**). Prepared from 1-(*p*-tolyl)pentan-1-one (0.088 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1f and syn-1f in (1:1.4) ratio was isolated as a yellow liquid (0.076 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 4H), 7.57 (d, *J* = 8.2 Hz, 4H), 7.36 – 7.16 (d, *J* = 8.2 Hz, 4H), 7.04 (d, *J* = 8.1 Hz, 4H), 3.55 – 3.43 (m, 2H), 3.35 – 3.28 (m, 2H), 2.41 (s, 6H), 2.31 (s, 6H), 2.28 – 2.21 (m, 1H), 2.08 – 1.96 (m, 2H), 1.78 – 1.54 (m, 5H), 1.44 – 1.37 (m, 4H), 1.35 – 1.26 (m, 4H), 1.23 – 1.07 (m, 4H), 0.82 (t, *J* = 7.3 Hz, 6H), 0.77 (t, *J* = 7.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.60, 203.69, 143.94, 143.64, 135.05, 134.78, 129.51, 129.20, 128.56, 128.29, 43.69, 43.33, 36.42, 34.57, 34.46, 21.76, 21.63, 20.70, 20.60, 14.28, 14.26. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{25}H_{32}O_2+Na]^+$: 387.2295, found: 387.2276. FT-IR (ATR, neat): 2957, 2872, 1672, 1606, 1180, 736 cm^{-1}.

1,5-bis(3,4-dimethylphenyl)-2,4-dimethylpentane-1,5-dione: (**Table 2.2, 1g**). Prepared from 1-(3,4-dimethylphenyl) propan-1-one (0.081 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1g and syn-1g in (1:1.05) ratio was

isolated as a yellow liquid (0.071 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.78 (m, 4H), 7.51 – 7.49 (m, 4H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 3.57 (sextet, *J* = 8.0 Hz, 2H), 3.45 (sextet, *J* = 8.0 Hz, 2H), 2.55 – 2.50 (m, 1H) 2.34 (s, 6H), 2.33 (s, 6H), 2.23 (s, 6H), 2.16 (s, 6H), 1.97 (t, *J* = 8.0 Hz, 2H), 1.50 – 1.43 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.6, 203.9, 142.7, 142.4, 137.2, 136.9, 134.6, 134.3, 130.1, 129.8, 129.7, 129.5, 126.3, 126.0, 38.5, 38.1, 37.9, 37.3, 20.1, 20.0, 19.9, 19.7, 19.0, 17.8. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{23}H_{28}O_2+Na]^+$: 359.1982, found: 359.1963. FT-IR (ATR, neat): 2979, 2872, 1673, 1605, 1250, 1117, 735 cm^{-1}.

1,5-bis(3,4-dimethylphenyl)-2,4-diethylpentane-1,5-dione: (**Table 2.2, 1h**). Prepared from 1-(3,4-dimethylphenyl) butan-1-one (0.088 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1h and syn-1h in (1:1.4) ratio was isolated as a yellow liquid (0.074g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.73 (m, 4H), 7.44 – 7.42 (m, 4H), 7.23 (d, *J* = 7.7 Hz, 2H), 7.00 (d, *J* = 7.7 Hz, 2H), 3.41 (p, *J* = 8.0 Hz, 2H), 3.26 (p, *J* = 8.0 Hz, 2H), 2.33 (s, 6H), 2.32 (s, 6H), 2.30 – 2.33 (m, 1H), 2.21 (s, 6H), 2.10 (s, 6H), 2.03 – 2.00 (m, 2H), 1.80 – 1.66 (m, 4H), 1.64 – 1.61 (m, 1H), 1.56 – 1.43 (m, 4H), 0.84 (t, *J* = 7.5 Hz, 6H), 0.79 (t, *J* = 7.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.8, 203.7, 142.6, 142.3, 137.1, 136.7, 135.6, 135.3, 130.0, 129.7, 129.5, 129.4, 126.2, 125.9, 45.16, 44.9, 34.2, 33.6, 27.3, 25.4, 20.1, 19.9, 19.9, 19.7, 11.9, 11.7. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{25}H_{32}O_2+H]^+$: 365.2475, found: 365.2461. FT-IR (ATR, neat): 2969, 2871, 1672, 1605, 1264, 1118, 737 cm^{-1}.

1,5-bis(3,4-dimethylphenyl)-2,4-dipropylpentane-1,5-dione: (**Table 2.2, 1i**). Prepared from 1-(3,4-dimethylphenyl) pentan-1-one (0.095 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1i and syn-1i in (1:1.6) ratio was isolated as a yellow liquid (0.079 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.72 (m, 4H), 7.43 – 7.41 (m, 4H), 7.23 (d, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 7.6 Hz, 2H), 3.51 – 3.44 (m, 2H), 3.35 – 3.28 (m, 2H), 2.33 (s, 6H), 2.29 – 2.23 (m. 1H), 2.31 (s, 6H),2.21 (s, 6H), 2.10 (s, 6H), 2.04 – 2.00 (m, 2H), 1.74 – 1.57 (m, 5H), 1.47 – 1.36 (m, 4H), 1.35 – 1.26 (m, 4H), 1.24 – 1.12 (m, 4H), 0.82 (t, *J* = 7.3 Hz, 6H), 0.78 (t, *J* = 7.3 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.9, 204.0, 142.7, 142.3, 137.1, 136.7, 135.5, 135.2, 130.0, 129.7, 129.6, 129.4, 126.2, 125.9, 43.6, 43.4, 36.5, 34.8, 34.6, 20.7, 20.6, 20.1, 19.9, 19.9, 19.7, 14.3, 14.3. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{27}H_{36}O_2+H]^+$: 393.2788, found: 393.2776. FT-IR (ATR, neat): 2926, 1670, 1605, 1264, 1122, 736 cm^{-1}.

1,5-bis(4-ethylphenyl)-2,4-dimethylpentane-1,5-dione: (**Table 2.2, 1j**). Prepared from 1-(4-ethylphenyl) propan-1-one (0.081 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1j and syn-1j in (1.3:1) ratio was isolated as a yellow liquid (0.072 g, 86%). were isolated. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 4H), 7.70 (d, *J* = 8.3 Hz, 4H), 7.32 (d, *J* = 8.3 Hz, 4H), 7.14 (d, *J* = 8.3 Hz, 4H), 3.59 (sextet, *J* = 8.0 Hz, 2H), 3.48 (sextet, *J* = 8.0 Hz, 2H), 2.72 (q, *J* = 7.6 Hz, 4H), 2.63 (q, *J* = 7.6 Hz, 4H), 2.46 – 2.39 (m, 1H), 1.99 (t, *J* = 8.0 Hz, 2H), 1.50 – 1.43 (m, 1H), 1.27 (t, *J* = 7.6 Hz, 6H), 1.22 – 1.18 (m,12H), 1.16 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.2, 203.6, 150.1, 149.9, 134.3, 134.1, 128.82, 128.5, 128.4, 128.1, 38.5, 38.1, 37.6, 37.3, 29.1, 28.9, 18.9, 17.7, 15.3, 15.2. HRMS (ESI-TOF) *m/z* $[M+Na]^+$

Calcd for $[C_{23}H_{28}O_2+Na]^+$: 359.1982, found: 359.1980. FT-IR (ATR, neat): 2965, 2931, 1676, 1605, 1225, 1181, 737 cm^{-1}.

2,4-diethyl-1,5-bis(4-ethylphenyl)pentane-1,5-dione: (**Table 2.2, 1k**). Prepared from 1-(4-ethylphenyl) butan-1-one (0.088 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1k and syn-1k in (1:1.4) ratio was isolated as a yellow liquid (0.076 g, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.3 Hz, 4H), 7.62 (d, *J* = 8.3 Hz, 4H), 7.31 (d, *J* = 8.2 Hz, 4H), 7.07 (d, *J* = 8.2 Hz, 4H), 3.46 – 3.39 (m, 2H), 3.31 – 3.25 (m, 2H), 2.70 (q, *J* = 7.6 Hz, 4H), 2.61 (q, *J* = 7.6 Hz, 4H), 2.32 – 2.25 (m, 1H), 2.05 – 2.02 (m, 2H), 1.80– 1.67 (m, 4H), 1.63 – 1.58 (m, 1H), 1.56 – 1.47 (m, 4H), 1.27 (t, *J* = 7.6 Hz, 6H), 1.19 (t, *J* = 7.6 Hz, 6H), 0.85 (t, *J* = 7.5 Hz, 6H), 0.79 (t, *J* = 7.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 204.5, 203.5, 150.0, 149.8, 135.3, 135.0, 128.7, 128.4, 128.34, 128.0, 45.3, 45.0, 33.8, 29.0, 28.9, 27.2, 25.4, 15.3, 15.2, 11.9, 11.7. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{25}H_{32}O_2+H]^+$: 365.2475, found: 365.2460. FT-IR (ATR, neat): 2964, 2928, 1674, 1604, 1264, 1171, 734 cm^{-1}.

1,5-bis(4-ethylphenyl)-2,4-dipropylpentane-1,5-dione: (**Table 2.2, 1l**). Prepared from 1-(4-ethylphenyl) pentan-1-one (0.095 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1l and syn-1l in (1.25:1.) ratio was isolated as a yellow liquid (0.082g, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.3 Hz, 4H), 7.60 (d, *J* = 8.3 Hz, 4H), 7.30 (d, *J* = 8.2 Hz, 4H), 7.06 (d, *J* = 8.2 Hz, 4H), 3.53 – 3.46 (m, 2H), 3.37 – 3.30 (m, 2H), 2.71 (q, *J* = 7.6 Hz, 4H), 2.60 (q, *J* = 7.6 Hz, 4H), 2.29 – 2.22 (m, 1H), 2.05 – 2.01 (m, 2H), 1.86 – 1.83 (m, 1H), 1.77 – 1.68 (m, 2H), 1.66 – 1.56 (m, 3H), 1.46 – 1.36 (m, 4H), 1.34 – 1.16 (m, 19H), 0.83 (t, *J* = 7.3 Hz, 6H), 0.78 (t, *J* = 7.3 Hz,

6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 204.6, 149.7, 135.2, 135.0, 128.7, 128.4, 128.3, 128.0, 43.7, 43.4, 36.4, 34.5, 34.4, 29.0, 28.9, 20.7, 20.6, 15.2, 15.2, 14.2, 14.2. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{27}H_{36}O_2+H]^+$: 393.2788, found: 393.2772. FT-IR (ATR, neat): 2962, 2927, 1672, 1605, 1248, 1180, 735 cm^{-1}.

2,4-dimethyl-1,5-di(thiophen-2-yl)pentane-1,5-dione: (**Table 2.2, 1m**). Prepared from 1-(thiophen-2-yl)propan-1-one (0.070 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1m and syn-1m in (1.15:1) ratio was isolated as a yellow liquid (0.053 g, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 3.0 Hz, 2H), 7.66 (d, *J* = 4.9 Hz, 2H), 7.54 (d, *J* = 5.6 Hz, 2H), 7.44 (d, *J* = 3.0 Hz, 2H), 7.18 – 7.15 (m, 2H), 6.93 – 6.91 (m, 2H), 3.43 (sextet, *J* = 8.0 Hz, 2H), 3.31 (sextet, *J* = 8.0 Hz, 2H), 2.44 (dt, *J* = 14.0, 7.1 Hz, 1H), 2.00 (t, *J* = 8.0 Hz, 2H), 1.53 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.24 – 1.21 (m, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.3, 196.7, 144.1, 143.9, 134.1, 134.1, 132.4, 132.0, 128.50, 128.1, 40.6, 40.1, 37.9, 37.8, 19.3, 17.8. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{15}H_{16}O_2S_2+Na]^+$: 315.0484, found: 315.0463. FT-IR (ATR, neat): 3646, 2969, 2861, 1653, 1516, 1264, 1059, 727 cm^{-1}.

2,4-diethyl-1,5-di(thiophen-2-yl)pentane-1,5-dione: (**Table 2.2, 1n**). Prepared from 1-(thiophen-2-yl)butan-1-one (0.077 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1n and syn-1n in (1:1.3) ratio was isolated as a yellow liquid (0.054 g, 68%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 3.6 Hz, 2H), 7.65 (d, *J* = 4.9 Hz, 2H), 7.50 (d, *J* = 4.9 Hz, 2H), 7.33 (d, *J* = 3.7 Hz, 2H), 7.16 – 7.13 (m, 2H), 6.86 – 6.84 (m, 2H), 3.27 – 3.21 (m, 2H), 3.15 – 3.08 (m, 2H), 2.33 – 2.26 (m, 1H), 2.04 – 2.01 (m, 2H), 1.82 – 1.65 (m, 5H), 1.61 – 1.50 (m, 4H), 0.84 (t, *J* = 7.4 Hz, 12H). $^{13}C\{^1H\}$ NMR

(101 MHz, $CDCl_3$) δ 197.4, 196.5, 145.4, 144.9, 134.1, 134.1, 132.2, 132.0, 128.46, 128.1, 47.5, 47.3, 34.4, 34.4, 27.6, 25.6, 12.0, 11.9. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{17}H_{20}O_2S_2+Na]^+$: 343.0797, found: 343.0777. FT-IR (ATR, neat): 3647, 2971, 2862, 1653, 1516, 1247, 1064, 726 cm^{-1}.

2,4-dipropyl-1,5-di(thiophen-2-yl)pentane-1,5-dione: (**Table 2.2, 1o**). Prepared from 1-(thiophen-2-yl)pentan-1-one (0.084 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1o and syn-1o in (1:1.3) ratio was isolated as a yellow liquid (0.057 g, 66%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 3.2 Hz, 2H), 7.65 (d, *J* = 4.9 Hz, 2H), 7.50 (d, *J* = 4.9 Hz, 2H), 7.32 (d, *J* = 3.7 Hz, 2H), 7.16 – 7.13 (m, 2H), 6.85 – 6.83 (m, 2H), 3.34 – 3.28 (m, 2H), 3.21 – 3.14 (m, 2H),2.30 – 2.23 (m, 1H), 2.04 – 2.00 (m, 2H), 1.79 – 1.74 (m, 1H), 1.73 – 1.61 (m, 4H), 1.50 – 1.41(m, 4H), 1.37 – 1.28 (m, 4H), 1.24 – 1.14 (m, 4H), 0.84 (t, *J* = 7.3 Hz, 6H), 0.80 (t, *J* = 7.3 Hz, 12H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 197.5, 196.7, 145.3, 144.9, 134.1, 134.1, 132.2, 132.0, 128.5, 128.1, 46.0, 45.7, 36.8, 35.2, 35.0, 34.7, 20.8, 20.7, 14.2. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{19}H_{24}O_2S_2+Na]^+$: 371.1110, found: 371.1094. FT-IR (ATR, neat): 3647, 2979, 2872, 1653, 1517, 1247, 1059, 723 cm^{-1}.

1,5-bis(2,5-dimethoxyphenyl)-2,4-dimethylpentane-1,5-dione: (**Table 2.2, 1p**). Prepared from 1-(2,5-dimethoxyphenyl) propan-1-one (0.097 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1p and syn-1p in (1:1.3) ratio was isolated as a yellow liquid (0.072 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.06 (dd, *J* = 7.1, 3.2, 4H), 6.97 (dd, *J* = 9.0, 3.2, 1H), 6.92 – 6.86 (m, 3H), 6.77 (d, *J* = 9.0, 4H), 3.82 (s, 6H), 3.77 (s, 12H), 3.74 (s, 12H), 3.69 (s, 6H), 3.62 – 3.51 (m, 4H), 2.31 (m,

1H), 1.82 (m, 2H), 1.40 (m, 1H), 1.13 (d, *J* = 6.9, 6H), 1.10 (d, *J* = 6.9, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ= 207.38, 207.28, 154.06, 153.58, 153.47, 153.45, 152.47, 152.36, 151.86, 151.52, 131.06, 129.64, 129.15, 119.12, 118.79, 117.05, 116.99, 114.50, 114.43, 113.04, 112.84, 77.48, 77.16, 76.84, 56.21, 55.86, 43.15, 42.82, 36.78, 36.14, 18.62, 17.27. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{23}H_{28}O_6+H]^+$: 401.1959, found: 401.1938. FT-IR (ATR, neat): 2979, 2834, 1671, 1582, 1492, 1222, 1046, 730 cm^{-1}.

1,5-bis(2,5-dimethoxyphenyl)-2,4-diethylpentane-1,5-dione: (**Table 2.2, 1q**). Prepared from 1-(2,5-dimethoxyphenyl) butan-1-one (0.104 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1q and syn-1q in (1:1.6) ratio was isolated as a yellow liquid (0.081 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.07 (d, *J* = 3.2, 4H), 6.96 (d, *J* = 9.0, 3.2, 2H), 6.91 – 6.85 (m, 4H), 6.73 (s, 1H), 6.71 (s, 1H), 3.84 – 3.68 (m, 14H), 3.74 (s, 6H),3.58 (s, 6H), 3.51 – 3.44 (m, 2H), 2.21 (m, 1H), 1.94 – 1.90 (m, 2H), 1.69 (m, 4H), 1.56 (m, 1H), 1.43 (m, 4H), 0.88 (t, *J* = 7.4, 6H), 0.81 (t, *J* = 7.4, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 206.9, 206.7, 153.3, 152.6, 152.4, 130.2, 129.7, 119.0, 118.7, 114.50, 114.3, 113.1, 112.9, 56.1, 55.9, 55.8, 55.7, 49.8, 49.4, 32.2, 26.1, 24.9, 11.7, 11.7. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{25}H_{32}O_6+Na]^+$: 451.2091, found: 451.2072. FT-IR (ATR, neat): 2969, 2834, 1670, 1607, 1491, 1222, 1165, 729 cm^{-1}.

1,5-bis(2,5-dimethoxyphenyl)-2,4-dipropylpentane-1,5-dione: (**Table 2.2, 1r**). Prepared from 1-(2,5-dimethoxyphenyl) pentan-1-one (0.111 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1r and syn-1r in (1:2) ratio was isolated

as a yellow liquid (0.073 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.07 (d, *J* = 3.0, 4H), 6.96 (dd, *J* = 9.0, 3.2, 2H), 6.91 – 6.85 (m, 2H), 6.72 (s, 1H), 6.70 (s, 1H), 3.83 – 3.70 (m, 14H), 3.74 (s, 6H), 3.56 (s, 6H), 3.62 – 3.51 (m, 2H), 2.24 – 2.13 (m, 1H), 1.91 (m, 2H), 1.74 – 1.56 (m, 4H), 1.53 (m, 1H), 1.43 – 1.09 (m, 12H), 0.84 (t, *J* = 7.1, 6H), 0.78 (t, *J* = 7.2, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 207.0, 206.9, 153.5, 153.3, 152.6, 129.6, 119.1, 118.8, 114.5, 114.4, 113.0, 112.8, 56.1, 55.90, 55.83, 55.6, 48.2, 47.8, 35.4, 34.3, 33.0, 20.5, 20.50, 14.3, 14.3. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{27}H_{36}O_6+Na]^+$: 479.2404, found: 479.2397. FT-IR (ATR, neat): 2980, 2831, 1669, 1494, 1263, 1163, 731 cm^{-1}.

2,4-dimethyl-1,5-di-m-tolylpentane-1,5-dione: (**Table 2.2, 1s**). Prepared from 3'-methyl propiophenone (0.074 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1s and syn-1s in (1:1.17) ratio was isolated as a yellowish solid (0.067 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (s, 4H), 7.51 – 7.40 (m, 4H), 7.29 (dd, *J* = 4.5, 1.5, 4H), 7.18 – 7.14 (m, 2H), 7.11 (t, *J* = 7.5, 2H), 3.49 (h, *J* = 7.0, 2H), 3.37 (h, *J* = 7.0, 2H), 2.34 (s, 6H), 2.31 – 2.25 (m, 1H), 2.16 (s, 6H), 1.89 (t, *J* = 7.2, 2H), 1.38 (dt, *J* = 13.9, 7.0, 1H), 1.08 (dd, *J* = 11.5, 6.9, 12H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 204.84, 204.19, 138.44, 136.69, 133.98, 133.80, 129.06, 128.83, 128.72, 128.55, 125.77, 125.45, 38.65, 38.25, 37.71, 37.11, 21.53, 21.34, 18.96, 17.78. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{21}H_{24}O_2+Na]^+$: 303.1356, found: 303.1369. FT-IR (ATR, neat): 2979, 1678, 1601, 1584, 1261, 1160, 737 cm^{-1}.

1,5-bis(4-methoxyphenyl)-2,4-dimethylpentane-1,5-dione: (**Table 2.2, 1t**). Prepared from 4-methoxy propiophenone (0.082 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two

diastereomers anti-1t and syn-1t in (1:1.3) ratio was isolated as a yellow liquid (0.053 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.8 Hz, 4H), 7.73 (d, *J* = 8.8 Hz, 4H), 6.95 (d, *J* = 8.8 Hz, 4H), 6.75 (d, *J* = 8.8 Hz, 4H), 3.85 (s, 6H), 3.77 (s, 6H), 3.54 (sextet, *J* = 8.0 Hz, 2H), 3.48 – 3.37 (m, 2H), 2.38 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.96 (t, *J* = 8.0 Hz 2H), 1.43 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.16 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 203.1, 202.5, 163.6, 163.4, 130.8, 130.5, 129.6, 129.3, 113.95, 113.7, 55.5, 55.4, 38.1, 37.9, 37.8, 37.5, 18.9, 17.7. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{21}H_{24}O_4+Na]^+$: 363.1567, found: 363.1572. FT-IR (ATR, neat): 2931, 1669, 1598, 1574, 1246, 1142, 735 cm^{-1}.

2,2'-methylenebis(3,4-dihydronaphthalen-1(2H)-one): (**Table 2.2, 1u**).[5e] Prepared from 1-tetralone (0.073 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1u and syn-1u in (1.05:1) ratio was isolated as a yellow liquid liquid (0.051 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.00 (d, *J* = 7.9 Hz, 4H), 7.46 (t, *J* = 7.5 Hz, 4H), 7.29 (t, *J* = 8.4 Hz, 4H), 7.24 (d, *J* = 7.7 Hz, 4H), 3.05 (dq, *J* = 5.2, 3.3, 2.1 Hz, 8H), 2.87-2.76 (m, 4H), 2.72 (q, *J* = 6.7 Hz, 1H), 2.33 (ddq, *J* = 22.6, 13.7, 4.7 Hz, 4H), 2.03 (t, *J* = 6.6 Hz, 2H), 2.00 – 1.85 (m, 4H), 1.59 (dt, *J* = 13.6, 5.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 201.03, 200.51, 144.07, 144.03, 133.36, 132.67, 128.85, 127.55, 127.48, 126.70, 45.98, 44.97, 30.95, 30.10, 29.45, 29.26, 28.69, 28.53. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{21}H_{20}O_2+Na]^+$: 327.1356, found: 327.1352.

1,5-di([1,1'-biphenyl]-4-yl)-2,4-dimethylpentane-1,5-dione: (**Table 2.2, 1v**). Prepared from 4'-phenyl propiophenone (0.105 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1v and syn-1v in (1.5:1) ratio was isolated as a yellowish solid

(0.063 g, 58%). ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.15 (d, *J* = 8.4 Hz, 4H), 7.83 (d, *J* = 8.5 Hz, 4H), 7.74 (d, *J* = 8.0 Hz, 4H), 7.65 (d, *J* = 7.1 Hz, 4H), 7.54 – 7.44 (m, 12H), 7.44 – 7.32 (m, 8H), 3.67 (h, *J* = 7.0 Hz, 2H), 3.59 – 3.50 (m, 2H), 2.51 (dt, *J* = 14.1, 7.2 Hz, 1H), 2.06 (t, *J* = 7.2 Hz, 2H), 1.54 (dt, *J* = 13.9, 7.1 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 6H), 1.23 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ= 204.28, 203.57, 145.93, 145.76, 140.04, 139.81, 135.32, 135.02,129.23, 129.10, 129.01, 128.89, 128.36, 128.28, 127.55, 127.43, 127.32, 38.58, 38.35, 38.09, 19.04, 17.82. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{31}H_{28}O_2+H]^+$: 433.2162, found: 433.2172. FT-IR (ATR, neat): 2969, 2931, 1672, 1604, 1255, 1178, 732 cm^{-1}.

1,5-di([1,1'-biphenyl]-4-yl)-2,4-diethylpentane-1,5-dione: (**Table 2.2, 1w**). Prepared from 4'-phenyl butyrophenone (0.112 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-1w and syn-1w in (1:1.5) ratio was isolated as a yellowish solid (0.063 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.10 (d, *J* = 8.4 Hz, 4H), 7.73 (dd, *J* = 15.8, 8.4 Hz, 8H), 7.64 (d, *J* = 7.1 Hz, 4H), 7.50 – 7.43 (m, 6H), 7.43 – 7.38 (m, 8H), 7.37 – 7.32 (m, 6H), 3.58 – 3.46 (m, 2H), 3.41 – 3.30 (m, 2H), 2.38 (dt, *J* = 14.4, 7.5 Hz, 1H), 2.15 – 2.05 (m, 2H), 1.79 (m, 4H), 1.72 – 1.67 (m, 1H), 1.61 – 1.48 (m, 4H), 0.90 (t, *J* = 7.4 Hz, 6H), 0.85 (t, *J* = 7.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ= 204.56, 203.43, 145.80, 145.61, 139.96, 139.67, 136.21, 135.90, 129.05, 128.94, 128.76, 128.30, 128.20, 127.40, 127.36, 127.24, 127.14, 45.24, 34.50, 34.41, 27.31, 25.49, 11.91, 11.82. HRMS (ESI-TOF) *m/z* [M+H]+ Calcd for $[C_{33}H_{32}O_2+H]^+$: 461.2475, found: 461.2478. FT-IR (ATR, neat): 2962, 2926, 1671, 1602, 1264, 1186, 741 cm^{-1}.

2,4-dibenzyl-1,5-diphenylpentane-1,5-dione: (**Table 2.3, 2a**). [5b] Prepared from 1,3-diphenylpropan-1-one (0.105 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-2a and syn-2a in (1:1.3) ratio was isolated as a yellow liquid (0.067 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.85 (d, *J* = 7.1, 4H), 7.56 – 7.52 (m, 6H), 7.43 (t, *J* = 7.6, 4H), 7.35 (t, *J* = 6.8, 2H), 7.21 – 7.06 (m, 20H), 6.97 (d, *J* = 6.5, 4H), 3.78 (p, *J* = 8.0, 2H), 3.71 (p, *J* = 8.0, 2H), 3.03 (dd, *J* = 12, 8.0 Hz, 2H), 3.00 (dd, *J* = 12, 8.0 Hz, 2H), 2.70 (dd, *J* = 12, 8.0 Hz, 2H), 2.63 (dd, *J* = 12, 8.0 Hz, 2H), 2.40 (dt, *J* = 14.0, 7.1 Hz, 1H), 2.12 (t, *J* = 8.0 Hz, 2H), 1.74 (dt, *J* = 14.0, 7.1 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 203.9, 203.2, 139.3, 138.9, 137.3, 136.9, 133.2, 132.9, 129.0, 129.0, 128.8, 128.5, 128.5, 128.5, 128.4, 128.1, 126.4, 126.4, 46.0, 45.7, 39.9, 38.4, 34.6, 34.4. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{31}H_{28}O_2+Na]^+$: 455.1982, found: 455.1962.

2,4-dibenzyl-1,5-di-*p*-tolylpentane-1,5-dione: (**Table 2.3, 2b**). Prepared from 3-phenyl-1-(*p*-tolyl)propan-1-one (0.112 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-2b and syn-2b in (1:1.1) ratio was isolated as a yellow liquid (0.064 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 8.3, 4H), 7.41 (d, *J* = 8.3, 4H), 7.23 – 7.05 (m, 20H), 6.95 (d, *J* = 8.7, 8H), 3.73 (p, *J* = 8.0, 2H), 3.65 (p, *J* = 8.0, 2H), 3.01 (dd, *J* = 12, 8.0 Hz, 2H), 2.98 (dd, *J*=12, 8.0 Hz, 2H), 2.67 (dd, *J* = 12, 8.0 Hz, 2H), 2.61 (dd, *J* = 12, 8.0 Hz, 2H), 2.40 (s, 6H), 2.37 – 2.33 (m, 1H), 2.27 (s, 6H), 2.11–2.04 (m, 2H), 1.73 – 1.66 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 203.55, 202.79, 144.06, 143.60, 139.53, 139.12, 134.88, 134.48, 129.50, 129.12, 129.04, 128.63, 128.52, 128.49, 128.27, 126.40, 126.33, 45.94, 45.60, 39.91, 38.43, 34.58,

21.77, 21.62. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{33}H_{32}O_2+H]^+$: 461.2475, found: 461.2469. FT-IR (ATR, neat): 2980, 1674, 1606, 1249, 1180, 744 cm^{-1}.

2,4-dibenzyl-1,5-bis(4-ethylphenyl)pentane-1,5-dione: (**Table 2.3, 2c**). Prepared from 1-(4-ethylphenyl)-3-phenylpropan-1-one (0.120 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-2c and syn-2c in (1:1.05) ratio was isolated as a yellow liquid (0.068g, 56%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 4H), 7.46 (d, *J* = 8.0 Hz, 4H), 7.26 – 7.06 (m, 20H), 7.00 – 6.95 (m, 8H), 3.74 (p, *J* = 8.0 Hz, 2H), 3.67 (p, *J* = 8.0 Hz, 2H), 3.02 (dd, *J* = 12, 8.0 Hz, 2H), 2.99 (dd, *J* = 12, 8.0 Hz, 2H), 2.73 – 2.53 (m, 12H), 2.36 (dt, *J* = 14.0, 7.1 Hz, 1H), 2.08 (t, *J* = 8.0 Hz, 2H), 1.73 – 1.66 (m, 1H), 1.26 (t, *J* = 7.6 Hz, 6H), 1.16 (t, *J* = 7.6 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 203.5, 202.8, 150.2, 149.7, 139.5, 139.1, 135.0, 134.7, 129.0, 129.0, 128.7, 128.5, 128.5, 128.4, 128.3, 127.9, 126.4, 126.3, 45.9, 45.6, 39.8, 38.3, 34.8, 34.6, 29.0, 28.9, 15.3, 15.1. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{35}H_{36}O_2+Na]^+$: 511.2608, found: 511.2587. FT-IR (ATR, neat): 2925, 1674, 1605, 1264, 1180, 735 cm^{-1}.

2,4-bis(4-fluorobenzyl)-1,5-di-*p*-tolylpentane-1,5-dione: (**Table 2.3, 2d**). Prepared from 3-(4-fluorophenyl)-1-(p-tolyl)propan-1-one (0.121 g, 0.50 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 20/1) an inseparable mixture of two diastereomers anti-2d and syn-2d in (1:1) ratio was isolated as a yellow liquid (0.064 g, 52%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.74 (d, *J* = 8.2 Hz, 4H), 7.39 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 7.7 Hz, 4H), 7.01 – 6.78 (m, 20H), 3.69 (p, *J* = 8.0 Hz, 2H), 3.59 (p, *J* = 8.0 Hz, 2H), 2.96 (dd, *J* = 12, 8.0 Hz, 2H), 2.93 (dd, *J* = 12, 8.0 Hz, 2H), 2.66 (dd, *J* = 12, 8.0 Hz, 2H), 2.59 (dd, *J* = 12, 8.0 Hz, 2H), 2.66 – 2.59 (m, 4H), 2.41 (s, 6H), 2.38 – 2.30 (m, 1H), 2.27 (s, 6H), 2.04 (t, *J* = 8.0 Hz 2H),

1.70 – 1.63 (m, 1H). ^{19}F NMR (377 MHz, $CDCl_3$) δ = -116.9, - 116.8. Fluorine-decoupled $^{13}C\{^1H, ^{19}F\}$ NMR (101 MHz, $CDCl_3$) δ = 203. 44,202.56 144.33, 143.87, 135.11, 134.83, 134.66, 134.42, 130.46, 130.42, 129.60, 129.20, 129.04, 128.57, 128.25, 115.30, 45.99, 45.64, 39.25, 37.54, 34.92, 34.54, 21.78, 21.63. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{33}H_{30}F_2O_2+Na]^+$: 519.2106, found: 519.2092. FT-IR (ATR, neat): 2979, 1680, 1606, 1491, 1454, 1228, 1179, 972, 813 755 cm^{-1}.

Analytical data of mechanistic study

2,4-dimethyl-1,5-diphenylpentane-1,5-dione-2,3,3,4-*d*4: (**Scheme 2.4, 3a**). Prepared from propiophenone (0.067 g, 0.5 mmol) and CD_3OD (0.5 mL). After purification by column chromatography (eluting with hexane/EtOAc, 20/1)an inseparable mixture of two diastereomers anti-3a and syn-3a in (1:1.15) ratio was isolated as a yellow liquid (0.051 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.2 Hz, 4H), 7.77 (d, *J* = 8.1 Hz, 4H), 7.58 (t, *J* = 7.3 Hz, 2H), 7.54 – 7.42 (m, 6H), 7.32 (t, *J* = 7.7 Hz, 4H), 1.20 (s, 6H), 1.16 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 204.5, 204.0, 136.6, 136.3, 133.2, 133.0, 128.8, 128.7, 128.5, 128.3, 38.49, 38.34, 38.27, 38.07, 38.05, 37.88, 37.84, 37.64, 37.50, 37.47, 18.64, 17.53. HRMS (ESI-TOF) *m/z* $[M+Na]^+$ Calcd for $[C_{19}H_{16}D_4O_2+Na]^+$: 307.1607, found: 307.1597. FT-IR (ATR, neat): 2979, 2928, 1676, 1595, 1578, 1273, 1168, 702 cm^{-1}.

2-methyl-1-phenylprop-2-en-1-one: (**Scheme 2.4, 3b**). [13a] Prepared from propiophenone (0.067 g, 0.5 mmol). After purification by column chromatography (eluting with hexane/EtOAc, 100/1) the compound was isolated as a yellow liquid (0.067 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.0, 2H), 7.53 (t, *J* = 7.4, 1H), 7.43 (t, *J* = 7.5, 2H), 5.91 (s, 1H), 5.62 (s, 1H), 2.07 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 198.5, 143.9, 137.8, 132.1, 129.5, 128.3, 127.2, 18.7. HRMS (ESI-

TOF) *m/z* $[M+H]^+$ Calcd for $[C_{10}H_{10}O+H]^+$: 147.0804, found: 147.0809. FT-IR (ATR, neat): 2979, 1681, 1596, 1448, 1232, 1175, 974, 701 cm^{-1}.

2-methyl-1-phenylpropan-1-one: (**Scheme 2.4, 3c**).[4e] Prepared from propiophenone (0.067 g, 0.50 mmol) and MeOH (1 mL). After purification by column chromatography (eluting with hexane/EtOAc, 100/1) the compound was isolated as a yellow liquid (0.068 g, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 7.1, 2H), 7.55 (t, *J* = 7.3, 1H), 7.46 (t, *J* = 7.5, 2H), 3.56 (h, *J*=6.9, 1H), 1.22 (d, *J* = 6.9, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ = 204.71, 136.31, 132.94, 128.74, 128.45, 35.48, 19.28.

1-(4-aminophenyl)ethan-1-one: (**Scheme 2.4, 3d**). [13b] Prepared from 1-(4-nitrophenyl)ethan-1-one (0.0825 g, 0.50 mmol) and MeOH (1 mL) under optimised condition. After purification by column chromatography (eluting with hexane/EtOAc, 20/1) the compound was isolated as a yellow liquid (0.042 g, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 6.65 (d, *J* = 8.1 Hz, 2H), 4.12 (s, 2H), 2.50 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 196.59, 151.20, 130.94, 128.07, 113.86, 26.23.

2.4.4. Synthetic application of 1,5-diketones

General Procedure A for pyridine synthesis: An oven-dried sealed tube was charged with Co-por (1.5×10^{-2} mmol, 0.03 equiv.) and NaO^{t}Bu (2.5×10^{-1} mmol, 0.5 equiv.). Under an inert atmosphere, ketone (0.5 mmol, 1 equiv.), methanol (0.5 mL) and toluene (0.5 mL) were added to the reaction mixture and the system was purged with nitrogen gas. Then, the sealed tube was closed with PTFE stopper and the reaction mixture was stirred at 135° C for 24 h. The reaction mixture was cooled to room temperature followed by the addition of NH_4OAc (1 mmol) along with acetic acid (0.5 mL) and again heated at 90 °C for 6 h. The reaction mixture was cooled to room temperature and

concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the substituted pyridine products **32**, **33** and **34** in 85% (0.055 g), 78% (0.056 g) and 78% (0.086 g) yield.

General procedure B for pyridine synthesis: An oven-dried sealed tube was charged with 1,5-diketone (0.5 mmol, 1 equiv.), then hydroxylamine hydrochloride (1.5 mmol, 3 equiv.) and ethanol (1 mL) were added to it. The resulting mixture was heated at 90 ^{o}C for 4 h. The resulting reaction mixture was purified by column chromatography on silica gel with ethyl acetate/petroleum ether as eluent without any workup to give the desired product **32**, **33,** and **34** in 95% (0.0615 g), 95% (0.068 g) and 92% (0.101 g) yield.

General procedure C for pyridine synthesis: An oven-dried sealed tube was charged with Co-por (1.5×10^{-2} mmol, 0.03 equiv.) and NaO^{t}Bu (2.5×10^{-1} mmol, 0.5 equiv.). Under an inert atmosphere ketone (0.5 mmol, 1 equiv.), methanol (0.5 mL) and toluene (0.5 mL) were added to the reaction mixture and the system was purged with nitrogen gas. Then, the sealed tube was closed with PTFE stopper and the reaction mixture was stirred at 135^{o} C for 24 h. The reaction mixture was cooled to room temperature followed by the addition of $NH_2NH_2.H_2O$ (1.5 mmol) along with acetic acid (0.5 mL) and heated at 90 ^{o}C for 6 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (2 x 5 mL), and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the substituted pyridine products **32**, **33** and **34** in 82% (0.053 g), 78% (0.056 g) and 73% (0.080 g) yields respectively.

3,5-dimethyl-2,6-diphenylpyridine: (**Scheme 2.6, 4a**).[13c] Prepared from propiophenone (0.067 g, 0.50 mmol) through procedure **B**, after purification by column chromatography (eluting with hexane/EtOAc, 96/4) the compound was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 6.9, 4H), 7.50 (s, 1H), 7.44 (t, *J* = 7.3, 4H), 7.37 (t, *J* = 7.3, 2H), 2.38 (s, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 141.53, 140.31, 129.45, 129.36, 128.19, 127.92, 19.71. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{19}H_{17}N+H]^+$: 260.1434, found: 260.1418.

3,5-diethyl-2,6-diphenylpyridine: (**Scheme 2.6, 4b**).[13c] Prepared from butyrophenone (0.074 g, 0.5 mmol) through procedure **B**, after purification by column chromatography (eluting with hexane/EtOAc, 96/4) the compound was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.53 (d, *J* = 7.0, 4H), 7.39 (dt, *J* = 23.0, 7.1, 6H), 2.71 (q, *J* = 7.5, 4H), 1.20 (t, *J* = 7.5, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.48, 138.03, 135.91, 129.30, 128.23, 127.91, 25.41, 15.41. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{21}H_{21}N+H]^+$: 288.1747, found: 288.1725.

2,6-di([1,1'-biphenyl]-4-yl)-3,5-diethylpyridine: (**Scheme 2.6, 4c**). Prepared from 4'-phenyl butyrophenone (0.112 g, 0.50 mmol) through procedure **B**, after purification by column chromatography (eluting with hexane/EtOAc, 95/5) the compound was isolated as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.2, 3.8, 12H), 7.60 (s, 1H), 7.45 (t, *J* = 7.6, 4H), 7.35 (t, *J* = 7.3, 2H), 2.79 (q, *J* = 7.5, 4H), 1.25 (t, *J* = 7.5, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ = 155.43, 141.14, 139.87, 137.73, 135.72, 129.73, 128.91, 127.41, 127.29, 127.02, 25.49, 15.54. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{33}H_{30}N+H]^+$: 440.2373, found: 440.2361. FT-IR (ATR, neat): 2979, 2883, 2283, 2067, 1487, 1435, 1385, 1263, 1155, 760, 736 cm^{-1}.

2.5. Reference

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CHAPTER 3

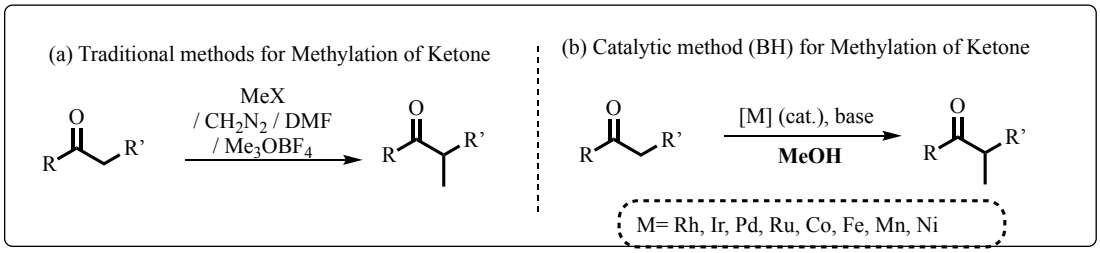
Ligand controlled ruthenium catalyzed borrowing hydrogen and interrupted borrowing hydrogen methodologies: Functionalization of ketones using methanol as a C1 source

3.1 Introduction

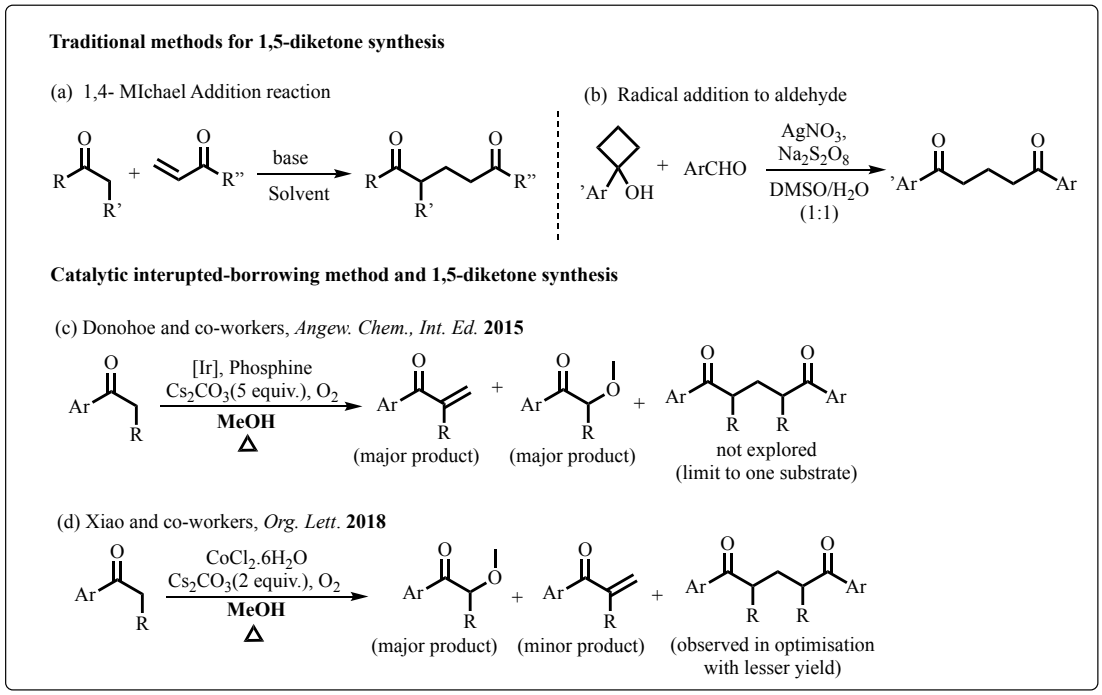
The development of green and sustainable transformations is a contemporary challenge in organic chemistry.[1] In this context, borrowing hydrogen (BH) or hydrogen auto transfer and interrupted-borrowing hydrogen (I-BH) approaches have become highly efficient tools in the field of organic synthesis.[1a,1c,1d,1f,2,3] These approaches provide a greener alternative to regular C-C bond forming reactions, as they generate only H_2 and/or H_2O as the by-products. It should be noted that traditional methods involve multistep synthesis and generate a stoichiometric amount of waste products.[4] The BH and I-BH methodologies allow the functionalization of alcohols in different C-C bond forming reactions. Methanol, the simplest, abundant, sustainable and affordable C-1 feedstock is gaining attention among all the alcohols.[2,3] As a vital chemical feedstock, methanol is used in a series of chemical processes including dehydrogenation process which results in the formation of formaldehyde in the presence of a metal catalyst. [2,3] In general, metal-catalysed dehydrogenation of methanol to formaldehyde in the presence of ketone can undergo reactions involving two competing pathways. It may end up in a α-methylated ketone using the BH method,[2] and 1,5-diketone or α-methoxymethylated ketones *via* the I-BH.[3]

α-Methylated ketones and 1,5-diketones are major starting materials for many compounds that are biologically and pharmaceutically active, and also for the synthesis of fine chemicals and natural products.[5] Conventionally, pre-functional reagents like Grignard reagents, methyl iodide or methyl sulphate or diazomethane are used to incorporate *methyl* group on the α-position of ketones. However, all these techniques are ecologically unfavourable owing to the employment of genotoxic and explosive chemicals (**Scheme 3.1.a**).[4a-d,6] The borrowing hydrogen (BH) technique has given an opportunity to incorporate the *methyl* group using methanol as an alternative reagent,

which generates only environment friendly by product H_2O. This methodology has been employed by different groups to make α-methylated ketones (**Scheme 3.1 b**).[2]



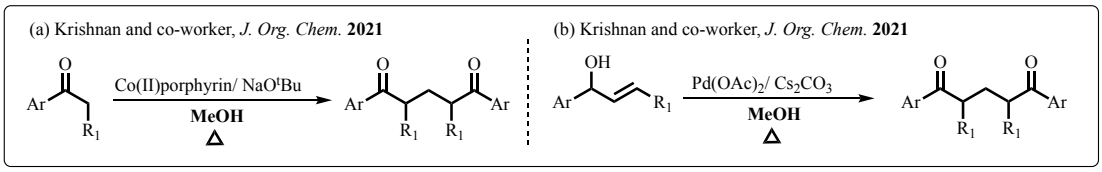
Scheme 3.1: Traditional and catalytic method for methylation of ketones



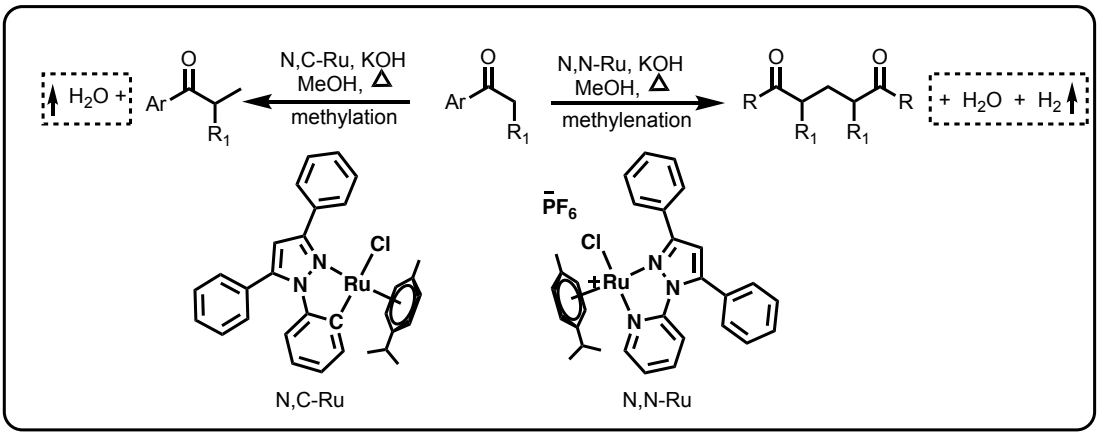
Scheme 3.2: Traditional and catalytic method for synthesis of 1,5-diketones

On the other hand 1,5-diketones were synthesized[4,7] by condensation of ketones with vinyl ketones (Michael addition),[4i] radical addition to alkenes,[4f,4g,4h] aldehydes,[4e] metal catalysed hydroacylation,[7a] and three component reactions.[7b] The synthesis of 1,5-diketones through environmentally benign methods are gaining more focus. In particular, the synthesis of 1,5-diketones from ketones/allyl alcohols and methanol using the interrupted-borrowing hydrogen approach has been explored by us and

others[3a-d] and has gained significant interest owing to its simplicity and wide substrate scope (**Scheme 3.2.c**, **Scheme 3.2.d** & **Scheme 3.3**).



Scheme 3.3: Our previous work methylenation of ketones (1,5-diketone synthesis)



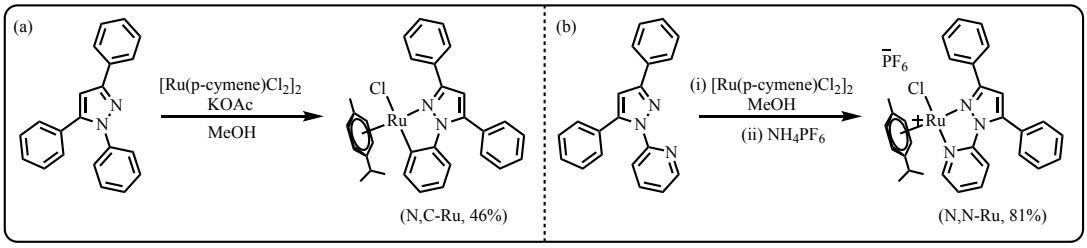
Scheme 3.4. Our approach, ligand switchable selective BH and I-BH products

Although, both BH and I-BH methodologies are reported individually for the synthesis of α-methylated ketones[2] and 1,5-diketones respectively,[3a-d] ligand controlled activation of BH and I-BH using same metal is scarcely reported. Herein, we report ligand controlled activation of methanol to produce BH and I-BH products namely α-methylated ketones and 1,5-diketones using ruthenium complexes. Thus, N,C-chelated ruthenium catalyst promotes the formation of BH products whereas N,N-chelated ruthenium catalyst assists the formation of I-BH product (**Scheme 3.4.**).

3.2 Results and discussion

Recently, we reported palladacycle catalysed N-alkylation and C-alkylation of amines and ketones, respectively, using alcohols as environmentally friendly reagents.[2e] As part of our continued interest in exploring methanol as a reagent, we turned our attention to

explore a ruthenocycle as a catalyst. For this study two different ruthenocycles were prepared, namely N,C-Ru and N,N-Ru complex.



Scheme 3.5. Synthesis of (a) N,C-Ru complex and (b) N,N-Ru complex

The N,C-Ru complex was obtained *via* a C-H bond activation on the N-phenyl ring of 1,3,5–triphenyl-1H-pyrazole moiety facilitated in presence of KOAc and dichloro (*p*-cymene)ruthenium(II)dimer (**Scheme 3.5.a**). The ^{1}H NMR analysis of the N,C-Ru complex showed an upfield shift for the pyrazole hydrogen and resonates at 6.50 ppm in comparison to the pyrazole hydrogen for the 1,3,5–triphenyl-1H-pyrazole which resonates at 6.84 ppm. We also observed downfield shift for the aromatic hydrogens of the substituted phenyl rings on pyrazole of N,C-Ru complex in comparison to the aromatic hydrogens for 1,3,5–triphenyl-1H-pyrazole. The N,N-Ru complex was obtained by coordinating pyridine and pyrazole nitrogens of the 2-(3,5-diphenyl-1H-pyrazol-1-yl)pyridine with (*p*-cymene) ruthenium (**Scheme 3.5.b**). NMR analysis for the N,N-Ru complex did not show any substantial change for the pyrazole hydrogen, however a slight downfield for the aromatic hydrogens were observed in comparison to the ligand. Molecular structures for both N,C-Ru and N,N-Ru complexes were confirmed using single crystal X-ray analysis. The N,C-Ru complex crystalize in a monoclinic system ($P2_1/c$), whereas the N,N-Ru complex crystalize in a triclinic system (P-1) (**Table 3.6.**). X-ray analysis also reveals that both N,C-Ru and N,N-Ru complexes were co-ordinated with nitrogen atom of the pyrazole ring.

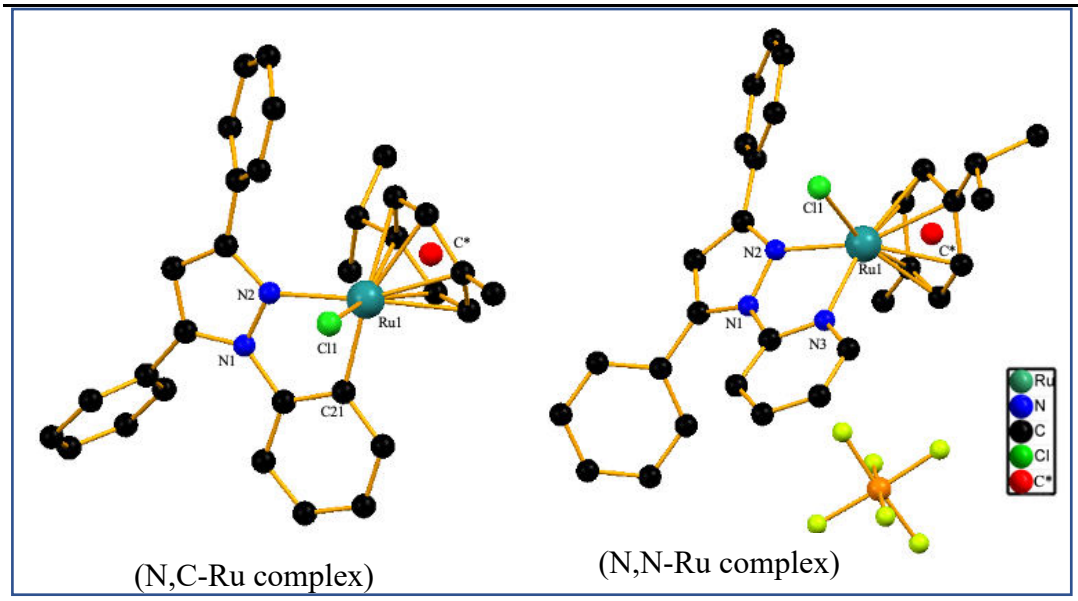


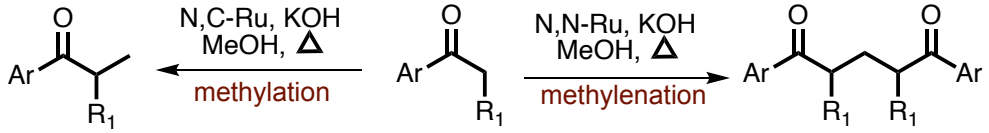
Figure 3.1. Molecular structure of N,C-Ru complex and N,N-Ru complex. Hydrogen atoms are omitted for clarity.

The Ru-N bond distances (Ru1—N2 2.081(2) Å for N,C-Ru complex; Ru1—N2 2.097(5) Å and Ru1—N3 2.086(5) Å for N,N-Ru complex) and Ru-Cl bond distances (Ru1—Cl1 (2.4283(7)) Å for N,C-Ru complex; 2.4060(13) Å for N,N-Ru complex) are comparable with reported[7d] cyclometalated ruthenium compounds (**Table 3.5.**). The observed distance Ru1—centroid(C*) distances 1.7040(3) Å for N,C-Ru complex; 1.6827(4) Å for N,N-Ru complex are also comparable with the literature reported [ref] complexes of similar types.

We commenced our initial investigation for methylation of propiophenone as a model system using N,C-chelated ruthenium catalyst (N,C-Ru). In a pressure tube, propiophenone (0.5 mmol), methanol (1 mL), N,C-Ru catalyst (1 mol%), and base (10 mol%) were heated to 70 °C for 24h (**Table 3.1**). Performing the reaction in a condition mentioned above for 24 hours using KO^{t}Bu as a base resulted in a 35% yield of α-methylated propiophenone (**Table 3.1**, entry **1**), confirmed by NMR analysis. Among the different bases screened (KO^{t}Bu, NaO^{t}Bu, LiO^{t}Bu, KOH, NaOH, LiOH, K_2CO_3,

Na_2CO_3) only KOH resulted in the desired product exclusively in high yield (**Table 3.1**, entries **1-8**). Thus, use of N,C-Ru catalyst (1 mol%), and KOH (20 mol %) in MeOH (1 mL) at 70 °C for 24 hours provide the optimum conditions in producing the desired α-methylated ketone (**1**) in 86% yield (**Table 3.1**, entry **9**). Notably, a further increase of base and catalyst loading had an adverse effect on the reaction, which produced 1,5-diketone, an I-BH product along with α-methylated ketone (**1a**) (**Table 3.1**, entries **10-12**). To our surprise, when we performed the reaction using N,N-Ru catalyst (**Table 3.1**, entry **13**) we observed the formation of 1,5-diketone as a major product instead of α-methylated ketone. Further optimization of different bases and the base loading demonstrated that use of N,N-Ru catalyst (1 mol%), KOH (50 mol %), and MeOH (1 mL) at 70 °C for 24 hours provided the desired 1,5-diketone (**2a**) in 78% yield (**Table 3.1**, entry **14**). Increase of reaction temperature showed adverse effect in product yield (**Table 3.1**, entries **21-22**,). Furthermore, when we screened different ruthenium sources such as $RuCl_3.H_2O$ and $[Ru(p\text{-cymene})Cl_2]_2$ as catalysts under the optimised conditions, we observed a low yield of α-methylated ketone along with 1,5-diketone (**Table 3.1**, entries **23-25**).

Table 3.1: Optimization table for the synthesis of α-methylated ketone & 1,5-diketone using N,C-Ru complex and N,N-Ru complex [a]



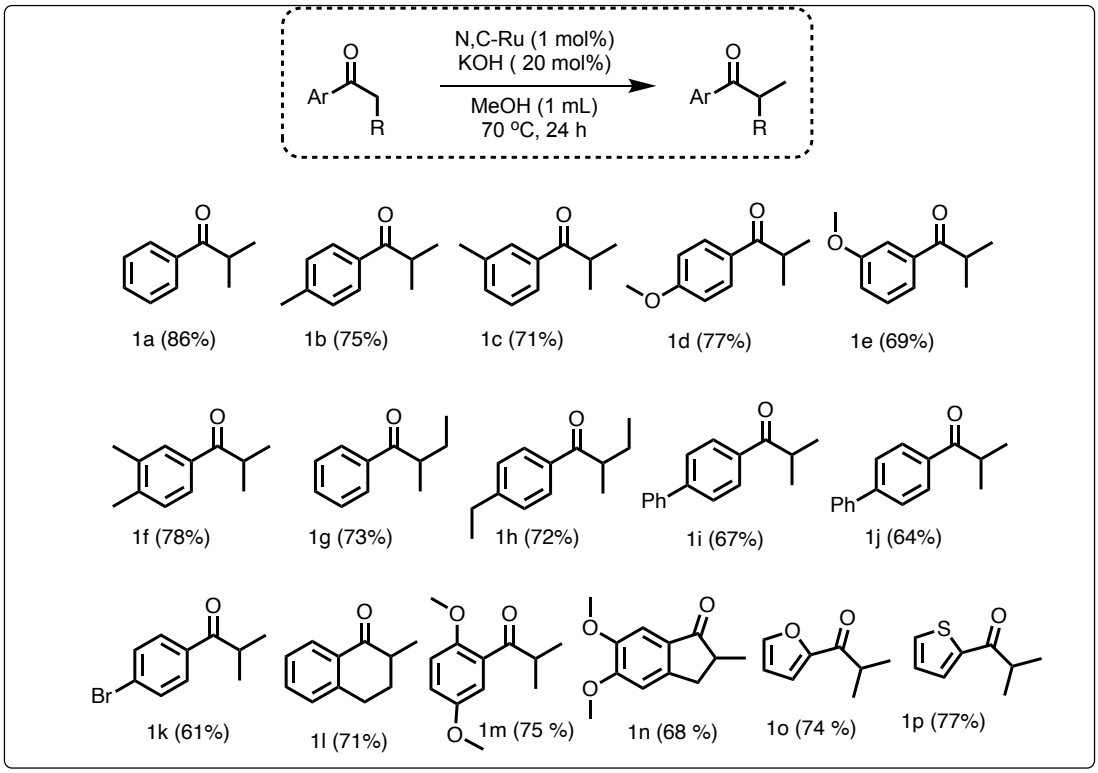
(X) (Y)

Entry	Catalyst (mol %)	Base (mol %)	T (°C) [c]	Yield (%)[b]	
				X	Y
1	N,C-Ru (1 mol%)	KO^{t}Bu (10 mol%)	70	35	ND

2	N,C-Ru (1 mol%)	NaO^{t}Bu (10 mol%)	70	30	ND
3	N,C-Ru (1 mol%)	LiO^{t}Bu (10 mol%)	70	32	ND
4	N,C-Ru (1 mol%)	KOH (10 mol%)	70	66	ND
5	N,C-Ru (1 mol%)	NaOH (10 mol%)	70	45	ND
6	N,C-Ru (1 mol%)	LiOH (10 mol%)	70	40	ND
7	N,C-Ru (1 mol%)	K_2CO_3 (10 mol%)	70	26	ND
8	N,C-Ru (1 mol%)	Na_2CO_3 (10 mol%)	70	24	ND
9	**N,C-Ru(1 mol%)**	**KOH (20 mol%)**	**70**	**86**	**Trace**
10	N,C-Ru (2 mol%)	KOH (20 mol%)	70	76	< 20
11	N,C-Ru (2 mol%)	KOH (50 mol%)	70	58	32
12	N,C-Ru (2 mol%)	KOH (75 mol%)	70	55	29
13	N,N-Ru (1 mol%)	KOH (20 mol%)	70	Trace	48
14	**N,N-Ru(1 mol%)**	**KOH (50 mol%)**	**70**	**Trace**	**78**
15	N,N-Ru (1 mol%)	KOH (75 mol%)	70	Trace	77
16	N,N-Ru (2 mol%)	KOH (50 mol%)	70	< 20	65
17	N,N-Ru (1 mol%)	NaOH (50 mol%)	70	Trace	62
18	N,N-Ru (1 mol%)	K_2CO_3 (50 mol%)	70	Trace	41
19	N,N-Ru (1 mol%)	Na_2CO_3 (50 mol%)	70	Trace	36
20	N,N-Ru (1 mol%)	KO^{t}Bu (50 mol%)	70	Trace	49
21	N,C-Ru (1 mol%)	KOH (20 mol%)	100	74	< 20
22	N,N-Ru (1 mol%)	KOH (50 mol%)	100	< 20	72
23	$RuCl_3.H_2O$(1 mol%)	KOH (50 mol%)	70	< 20	32
24	[Ru(*p*-cymene)Cl_2]$_2$	KOH (50 mol%)	70	< 20	31
25	[Ru(*p*-cymene)Cl_2]$_2$	KOH (20 mol%)	70	< 20	< 20

[a]Reaction conditions: propiophenone 0.5 mmol, base 0.1 mmol, catalyst 0.5x10^{-2} mmol, [b]All yields are isolated yields. [c]Reactions were performed at temperature 70-100 °C (oil bath temperature) for 24 h.

Table 3.2. Substrate scope for α-methylated ketones from aryl ketones [a]

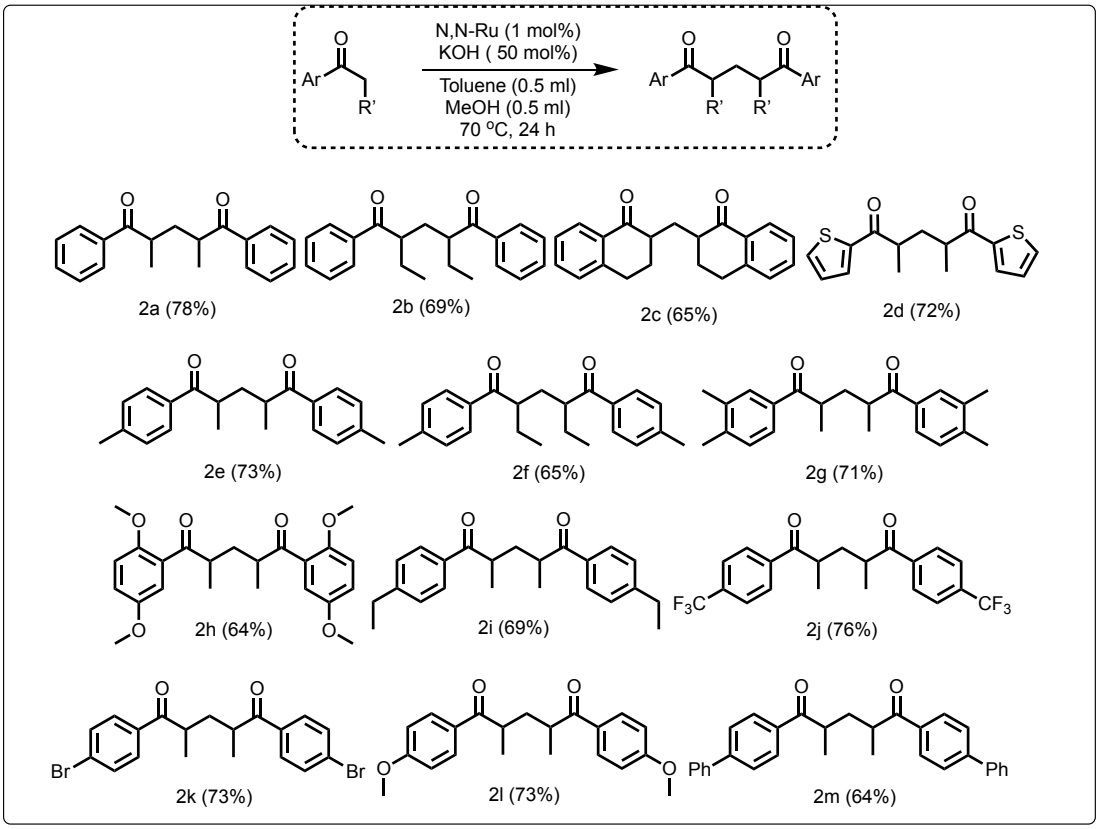


[a] Reaction conditions: ketone 0.5 mmol, catalyst 0.5x10^{-2}mmol and base 1x10^{-1} mmol. All yields are isolated yields.

Having identified the optimal conditions for both BH and I-BH methodologies, we first concentrated on screening substrate scope for BH reaction (**Table 3.2**). Using the optimal conditions mentioned above several aryl ketones with electron-donating substituents (*p,m*-CH_3, *p,m*-OCH_3, *p*-CH_2CH_3) were found to undergo the reaction to yield the corresponding α-methylated ketone products (**1b–1e, 1g** & **1h)** in 75%, 71%, 77%, 69%, 73% and 72% respectively (**Table 3.2**). Propiophenones with di-substitution such as 1-(3,4-dimethylphenyl)propan-1-one and 1-(2,5-dimethoxyphenyl)-propan-1-one tolerated this protocol yielding the desired product in 78% and 75%, respectively

(**1f** & **1m**). Aryl ketone with 4-bromo substituent produced the corresponding α-methylated ketone product (**1k**) in 61% isolated yield. Furthermore, biphenyl and heteroaryl (furyl and thiophene) ketones were found to be suitable to yield the desired products **1i, 1j, 1o,** & **1p** in 67%, 64%, 74%, & 77% respectively. Gratifyingly, alicyclic ketones were also active to yield the desired α-methylated ketone products (**1l**, **1n**) in 71% & 68% respectively. However, 4-CN and 4-NO_2 substituted aryl ketones under the optimised conditions produced a complex reaction mixture.

Table 3.3. Substrate scope for 1,5-diketones from mono aryl ketones[a]



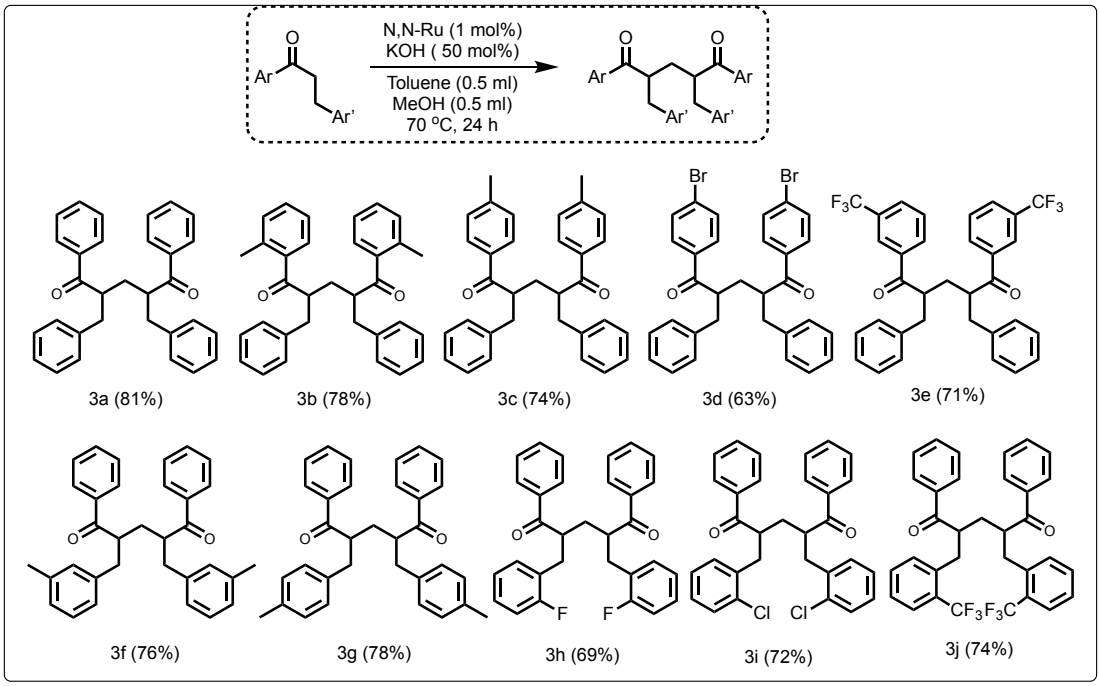
[a]Reaction conditions: ketone 0.5 mmol, catalyst $0.5x10^{-2}$ mmol and base $2.5x10^{-1}$ mmol. All yields are isolated yields.

With this success, we next turned our attention to explore the reactivity of methanol with ketone using an N,N-Ru catalyst. A mixture of propiophenone (0.5 mmol), KOH (50 mol%), N,N-Ru catalyst (1 mol %) and MeOH (1 mL) at 70 °C was heated in a pressure tube for 24 hours, providing the desired 1,5 diketone product (**2a**)

in good yield. NMR methods were used to analyse and identify the 1,5-diketone product, which was found to be a mixture of inseparable diastereomers. The scope of this I-BH approach using N,N-Ru catalyst was explored (**Table 3.3**). Under the optimised reaction conditions, different aryl ketones with electron-donating groups (*p*-CH_3, *p*-OCH_3, *p*-CH_2CH_3) produced good yields of 1,5-diketones (**2e**, **2f**, **2i** & **2l**). Substrates like butyrophenone, 3,5-dimethyl propiophenone, 1,4-dimethoxy propiophenone, and 4-phenyl propiophenone yielded the respective 1,5-diketones in 69%, 71%, 64%, and 64% respectively (**2b**, **2g**, **2h**, & **2m**).

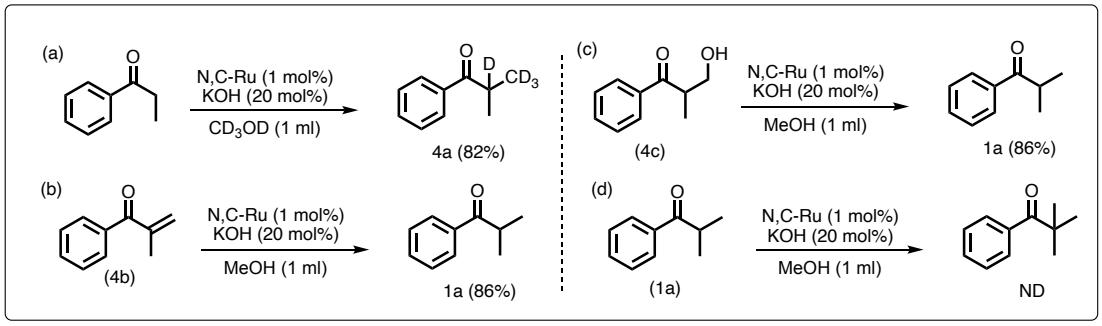
Notably, our approach tolerated alicyclic and hetero aryl ketones yielding the desired diastereomer product (**2c, 2d**) in 65% and 72% respectively. Propiophenones with electron-withdrawing groups (*p*-CF_3, *p*-Br) also react smoothly, providing the respective 1,5-diketones in 76% and 73 % respectively (**2j** & **2k**).

Table 3.4. Substrate scope for 1,5-diketones from di aryl ketones [a]



[a]Reaction conditions: ketone 0.5 mmol, catalyst $0.5x10^{-2}$ mmol and base $2.5x10^{-1}$ mmol. All yields are isolated yields.

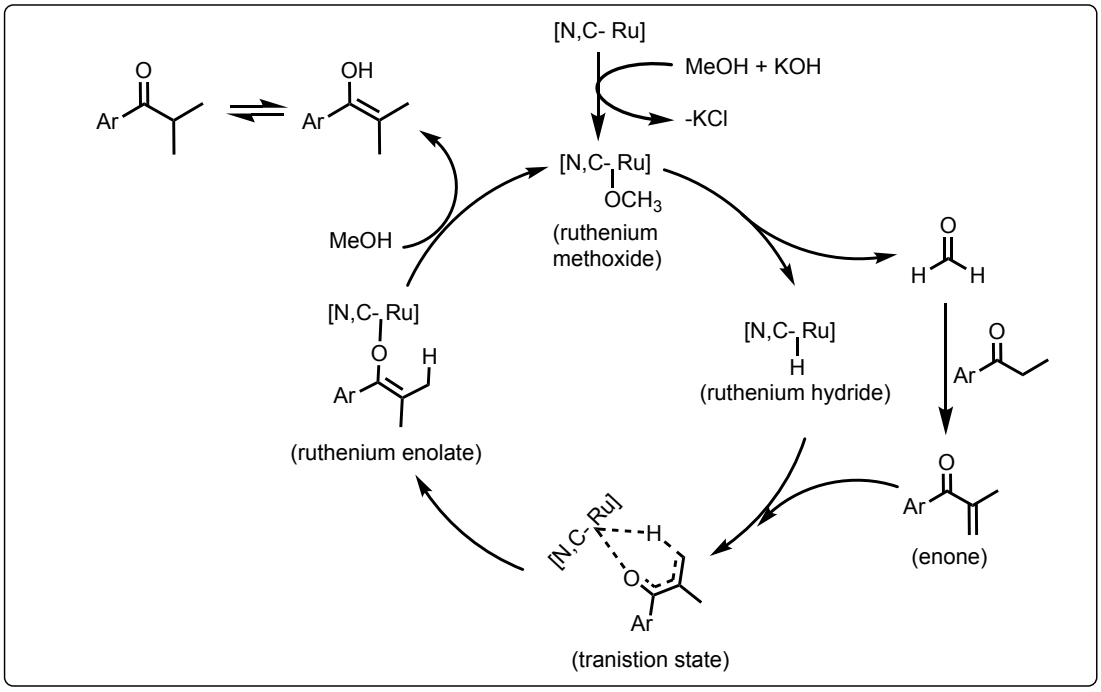
Prompted by these results, we next examined the reactivity of different 3-phenylpropiophenones (**Table 3.4.**). Under the optimized conditions, 3-phenyl-propiophenone formed the corresponding 1,5-diketone (**3a**) in 81% yield. 3-Phenylpropiophenones with electron-donating (*o*, *m*, *p*-CH_3) and electron-withdrawing (F, Cl, Br, CF_3) groups on both the aryls at 1- and 3-positions were well tolerated and resulted in the desired 1,5-diketones in good yield (**3b-3j**).



Scheme 3.6: Mechanistic studies for formation of α-methylated ketones

Control experiments were carried out to get insight into the possible reaction pathway for BH approach. (**Scheme 3.6**) From our experience and based on previous reports,[2] we anticipated that the in situ generated formaldehyde from MeOH undergoes aldol condensation with ketone generating β-hydroxy ketone (**4c**) and α,β-unsaturated ketone or enone (**4b**) as the possible intermediates in the course of the reaction. To validate our hypothesis, we screened compounds **4b** and **4c** as reactants under the optimised reaction conditions. Both compounds **4b** & **4c** produced α-methyl ketone (**1a**) in high yield. Reaction of propiophenone with CD_3OD instead of MeOH gave the deuterated methyl incorporated ketone compound **4a**, which clarifies that the hydride addition to enone intermediate was taking place to produce the desired α-methylated ketone where MeOH acts as a hydride source in the BH protocol. Use of **1a** as a starting material which has only one α-hydrogen under the optimized conditions did not yield any

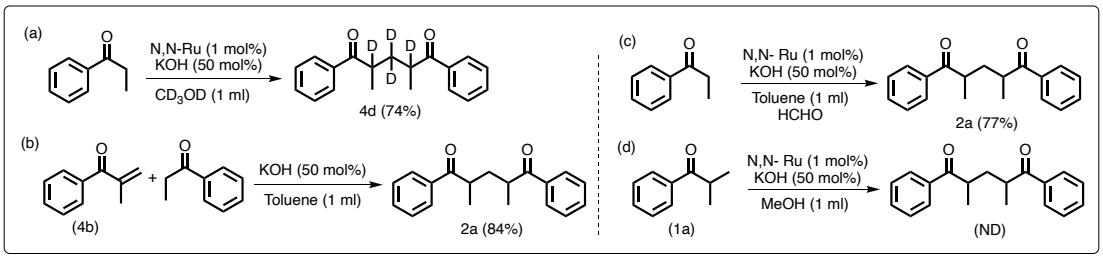
methylated product, suggesting that two α-hydrogens are essential for the formation of enone intermediate and subsequent product formation. Based on these findings, we propose a plausible reaction mechanism as shown in **Scheme 3.7**.



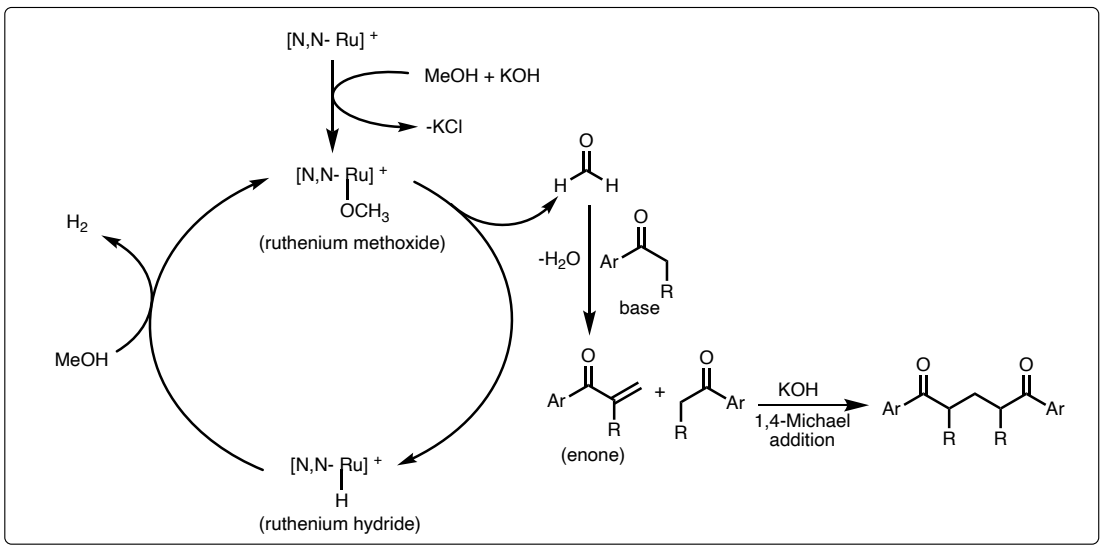
Scheme 3.7: Proposed mechanism for ligand controlled BH approach

Controlled reactions were also performed to understand the mechanism involved with I-BH approach (**Scheme 3.8**). We hypothesized that enone (**4b**) formed during the reaction reacts with propiophenone through Michael addition to yield the 1,5-diketone product. To confirm our hypothesis, we reacted the enone intermediate (**4b**) and propiophenone in the presence of a base, which produced the expected product in 84% yield (**Scheme 3.8.b**). Under the optimized experimental conditions, reaction of CD_3OD with propiophenone produced 1,5-diketone with deuterated methylene (-CD_2-) along with deuterium incorporation at the α-position. To validate the ligand controlled I-BH strategy produce formaldehyde during the reaction, we performed a reaction with propiophenone and paraformaldehyde instead of MeOH; as expected the desired 1,5-diketone (**2a**) was produced in 77% yield. No conversion was observed

under the optimised conditions with reaction of ketone (**1a**) which has one α-hydrogen, as it hinders the formation of the enone intermediate. These finding suggests that the *in situ* formed formaldehyde undergoes aldol condensation with ketone yielding the enone (**4b**), which subsequently reacts with another molecule of ketone through Michael addition to yield the 1,5-diketone product (**2a**). Based on these experiments, we proposed a plausible reaction mechanism as shown in **Scheme 3.9**. Although, the exact reason behind the ligand controlled selectivity observed is not known; as noticed in other complexes,[8] the electronic effect of the cationic N,N-Ru catalyst having both neutral donor ligand play a crucial role for the formation of the α,β-unsaturated ketone, by liberating H_2 gas without reversible hydrogenation.



Scheme 3.8. Mechanistic studies for formation of 1,5-diketones



Scheme 3.9. Proposed mechanism for ligand controlled I-BH approach.

Table 3.5. Selected bond distances and bond angles for N,C-Ru and N,N-Ru complexes

	N,C-Ru	**N,N-Ru**
Ru1—N2 (Å)	2.081(2)	2.097(5)
Ru1—Cl1 (Å)	2.4283(7)	2.4060(13)
Ru1—C21 (Å)	2.045(2)	-------
Ru1—N3 (Å)	-------	2.086(5)
Ru1—C* (Å)	1.7040(3)	1.6827(4)
N2-Ru-Cl1 (°)	87.63(6)	88.11(13)
N2-Ru-C* (°)	130.802(59)	130.497(138)
N2-Ru-C21(°)	76.96(9)	-------
C21-Ru-Cl1 (°)	88.33(7)	-------
C21-Ru-C* (°)	128.844(72)	-------
Cl1-Ru-C* (°)	127.693(22)	128.604(40)
N2-Ru-N3(°)	-------	75.58(18)
N3-Ru-Cl1 (°)	-------	84.79(14)
N3-Ru-C* (°)	-------	131.184(141)

Table 3.6. Crystal data and structure refinement data for N,C-Ru and N,N-Ru

Identification code	**N,C-Ru**	**N,N-Ru**
Empirical formula	$C_{31}H_{29}ClN_2Ru$	$C_{31}H_{31}Cl_3F_6N_3PRu$
Formula weight	566.08	797.98
Temperature/K	293(2)	297.8(3)
Crystal system	monoclinic	triclinic
Space group	$P2_1/c$	P-1
a/Å	17.20889(16)	11.5259(4)
b/Å	9.44674(7)	12.4813(4)
c/Å	15.71796(13)	13.9192(3)
α/°	90	107.232(3)
β/°	93.2002(9)	94.356(3)
γ/°	90	107.537(3)
Volume/Å^3	2551.25(4)	1793.36(10)
Z	4	2
ρ_{calc}g/cm^3	1.474	1.478
μ/mm^{-1}	6.098	6.514
F(000)	1160.0	804.0
Crystal size/mm^3	0.15 × 0.13 × 0.12	0.15 × 0.14 × 0.12
Radiation	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range for data collection/°	5.144 to 159.228	7.886 to 155.896
Index ranges	-21 ≤ h ≤ 21, -12 ≤ k ≤ 8,	-14 ≤ h ≤ 14, -15 ≤ k ≤ 15,

	$-20 \leq l \leq 19$	$-13 \leq l \leq 17$
Reflections collected	21094	24841
Independent reflections	5369 [R_{int} = 0.0544, R_{sigma} = 0.0335]	7351 [R_{int} = 0.1228, R_{sigma} = 0.0609]
Data/restraints/parameters	5369/0/319	7351/0/409
Goodness-of-fit on F^2	1.171	1.276
Final R indexes [I>=2σ (I)]	R_1 = 0.0410, wR_2 = 0.1338	R_1 = 0.0976, wR_2 = 0.2734
Final R indexes [all data]	R_1 = 0.0429, wR_2 = 0.1361	R_1 = 0.1036, wR_2 = 0.2816
Largest diff. peak/hole / e $Å^{-3}$	0.52/-1.25	2.75/-2.02

3.3. Conclusion

In summary, we have developed a ligand-controlled switchable catalytic system. Reaction of ketones with methanol in the presence of a N,C-Ru catalyst yielded the BH product whereas N,N-Ru catalyst produced the I-BH product. Both N,C-Ru and N,N-Ru catalysts exhibit excellent functional group compatibility; a variety of ketones especially aryl ketones were well-tolerated. The control reactions confirmed that the reaction proceeds through the formation of HCHO *via* β-hydride elimination of methanol, followed by the formation of a α-methylenated intermediate. The α-methylenated intermediate undergoes two competing transformations depending on the ligand attached to ruthenium. A methylated product is obtained using N,C-Ru catalyst through BH process, and a 1,5-diketone product through the I-BH methodology using the N,N-Ru catalyst.

3.4. Experimental section

3.4.1. General information

All reagents and solvents were obtained from commercial sources. Starting materials for the 1,5-diketone products (**3a**-**3j**) were synthesized using literature reported methods.[10] Solvents were purified according to standard procedures. All 400 MHz ^{1}H, 100 MHz ^{13}C, 376 MHz ^{19}F spectra were recorded on a spectrometer operating at 400 MHz. All ^{1}H and ^{13}C NMR spectra were referenced internally to solvent signals and ^{19}F NMR spectra were externally referenced to α,α,α-trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). High-resolution mass spectra (HRMS) were recorded using Bruker microTOF-QII mass spectrometer. Single-crystal X-ray diffraction data were collected on a Rigaku Oxford X-ray diffractometer using Cu-Kα radiation (1.54184 Å). SADABS absorption corrections were applied. The structures were solved and refined with SHELX suite of programs or Olex. All non- hydrogen atoms were refined with anisotropic displacement coefficients. The H atoms were placed at calculated positions and were refined as riding atoms. Crystallographic data for catalyst N,C-Ru and N,N-Ru and details of X-ray diffraction experiments and crystal structure refinements are given in **Table 3.6** (CCDC deposition no. 2156022-2156023). Diastereomeric ratio were determined from ^{1}H NMR. Diastereomers were identified as per the recent report.[3a]

3.4.2 Synthesis of ligands and catalysts

Synthesis of 1,3,5-triphenyl-1H-pyrazole: 1,3-Diphenylpropane-1,3-dione (2.00 g, 8.9 mmol) and phenyl hydrazine (1.16 g, 10.7 mmol) were taken in 100 mL round bottom flask. To this flask, 10 mL of methanol and 10 mL of acetic acid were added and the reaction mixture was refluxed for overnight. To the cooled reaction mixture, saturated sodium carbonate solution was added and the compound was extracted using

dichloromethane (3 × 10 mL). The solvent was removed under vacuum and the residue was purified by column chromatography using *n*-hexane: EtOAc (95:5) to afford the product, 1,3,5 –triphenyl-1H- pyrazole as a white solid. Yield = 2.42 g (92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.1 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.41 – 7.35 (m, 5H), 7.34 – 7.31 (m, 4H), 7.31 – 7.27 (m, 2H), 6.84 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.0, 144.6, 140.1, 132.9, 130.6, 129.1, 128.9, 128.8, 128.6, 128.5, 128.2, 127.6, 125.9, 125.5, 105.3. HRMS (ESI) calcd for $C_{21}H_{16}N_2$ ($[M+H]^+$) : 297.1386, found 297.1373.

Synthesis of 2-(3,5-diphenyl-1H-pyrazol-1-yl)pyridine: 1,3-Diphenylpropane-1,3-dione (2.00 g, 8.9 mmol) and 2-hydrazinopyridine (1.168 g, 10.7 mmol) were taken in 100 mL round bottom flask. To this flask, 10 mL of methanol and 10 mL of acetic acid were added and the reaction mixture was refluxed for overnight. To the cooled reaction mixture, saturated sodium carbonate solution was added and the compound was extracted using dichloromethane (3 × 10 mL). The solvent was removed under vacuum and the residue was purified by column chromatography using *n*-hexane:EtOAc (95:5) to afford the product, 2-(3,5-diphenyl-1H-pyrazol-1-yl)pyridine as a white solid. Yield = 2.27 g (86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 4.8 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 2H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.30 (m, 6H), 7.25 – 7.20 (m, 1H), 6.85 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.8, 152.5, 148.5, 145.2, 138.4, 132.8, 131.1, 128.8, 128.7, 128.4, 128.4, 126.1, 122.5, 119.1, 106.6. HRMS (ESI) calcd for $C_{20}H_{15}N_3$ ([M+Na]+) : 320.1158, found 320.1131.

Synthesis of N,C-ruthenacycle (N,C-Ru): An oven dried RB flask was charged with 1,3,5–triphenyl-1H-pyrazole (1.00 g, 3.37 mmol), KOAc (0.66 g, 6.74 mmol) and dichloro (*p*-cymene)ruthenium(II)dimer (1.03 g, 1.69 mmol). Under inert atmosphere,

5 mL dry methanol was added to the RB flask and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was subjected to celite filtration, followed by column chromatography using *n*-hexane/EtOAc (50:1) to obtain the desired N,C-Ru catalyst as a yellow powder. Bright yellow crystals were obtained by recrystallisation using dichloromethane and hexane. Yield = 0.88 g (46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 6.7 Hz, 2H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.61 – 7.53 (m, 3H), 7.53 – 7.47 (m, 3H), 7.44 (d, *J* = 8.3 Hz, 2H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.50 (s, 1H), 5.33 (d, *J* = 5.7 Hz, 1H), 4.76 (d, *J* = 5.9 Hz, 1H), 4.73 (d, *J* = 5.8 Hz, 1H). 4.53 (d, *J* = 5.7 Hz, 1H), 2.18 – 2.13 (m, 1H), 2.05 (s, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.3, 164.1, 155.8, 143.3, 142.8, 140.4, 133.7, 130.6, 130.5, 129.7, 129.6, 129.2, 129.0, 128.4, 125.7, 122.4, 114.5, 109.8, 96.7, 93.0, 88.6, 83.9, 81.6, 30.7, 23.1, 21.2, 18.9. HRMS (ESI) calcd for $C_{31}H_{29}N_2Ru$ ($[M\text{-}Cl]^+$) : 531.1377, found 531.1385.

Synthesis of Ruthenacycle of 2-(3,5-diphenyl-1H-pyrazol-1-yl)pyridine(N,N-Ru): An oven dried RB flask was charged with 2-(3,5-diphenyl-1H-pyrazol-1-yl)pyridine (1.00 g, 3.36 mmol) and dichloro(*p*-cymene) ruthenium(II) dimer (1.03 g, 1.68 mmol). Under inert atmosphere, 10 mL dry methanol was added to the RB flask and the reaction mixture was stirred at room temperature for 24 h. Then, 3 equiv. of NH_4PF_6 was added to the reaction mixture and stirred for another 1h. The obtained yellowish precipitate was washed with MeOH to get the desired N,N-Ru catalyst. The pure N,N-ruthenacycle is isolated as a yellow powder and recrystallized with dichloromethane and hexane, which affords bright yellow crystals. Yield = 1.94 g (81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, *J* = 5.7 Hz, 1H), 8.10 (dd, *J* = 6.3, 2.9 Hz, 2H), 7.76 – 7.57 (m, 7H), 7.54 – 7.45 (m, 3H), 6.83 (d, *J* = 8.2 Hz, 2H), 5.73 (d, *J* = 6.2 Hz, 1H), 5.25 – 5.14 (m, 2H),

5.10 (d, *J* = 6.1 Hz, 1H), 2.64 (p, *J* = 7.0 Hz, 1H), 2.17 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 159.9, 155.5, 148.7, 147.8, 140.9, 131.6, 131.3, 131.1, 130.1, 130.0, 129.4, 129.3, 127.3, 124.9, 113.7, 113.1, 106.5, 103.2, 85.7, 85.2, 84.3, 83.9, 31.2, 22.5, 21.5, 18.7. HRMS (ESI) calcd for $C_{30}H_{29}ClN_3Ru$ ($[M\text{-}PF_6]^+$) : 568.1093, found 568.1050.

3.4.3. General procedure for synthesis of α-methylated ketones

An oven-dried pressure tube was charged with N,C-ruthenacycle (0.5x 10^{-2} mmol), KOH (1x 10^{-1} mmol), ketone (0.5 mmol) and 1mL of MeOH in an open atmosphere then the tube was closed with a cap and the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature, the contents of the reaction mixture were dissolved in dichloromethane (15 mL), and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the corresponding methylated product in high purity.

3.4.4. General procedure for synthesis of 1,5 diketones

An oven-dried pressure tube was charged with N,N-ruthenacycle (0.5x 10^{-2} mmol), KOH (2.5x 10^{-1} mmol), with ketone (0.5 mmol) and 1mL of MeOH in an open atmosphere then the tube was closed with a cap and the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature, the contents of the reaction mixture were dissolved in dichloromethane (15 mL), and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the corresponding 1,5-diketones in high purity.

General procedure for gram scale synthesis of 1,5-diketone

An oven dried pressure tube was charged with N,N-ruthenacycle (10x 10^{-2}mmol), KOH (50x 10^{-1} mmol), propiophenone (1.34 g, 10 mmol) and 5mL of MeOH in an open atmosphere then the tube was closed with a cap and the reaction mixture was stirred at 70 °C for 24 h. The reaction mixture was cooled to room temperature, the contents of the reaction mixture were dissolved in dichloromethane (15 mL), and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the corresponding 1,5-diketone product in 0.966 g, 69% yield.

3.4.5. Analytical data for synthesized compounds:

2-methyl-1-phenylpropan-1-one:[9a] (**Table 3.2, 1a**) Prepared from propiophenone (0.067 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1), the product was isolated as a yellowish liquid (0.0636 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.56 (hept, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.7, 136.3, 132.9, 128.7, 128.4, 35.5, 19.3.

2-methyl-1-(*p*-tolyl)propan-1-one:[2f] (**Table 3.2, 1b**) Prepared from 4-methyl propiophenone (0.074 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.061 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 3.49 (hept, *J* = 6.9 Hz, 1H), 2.36 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.3, 143.6, 133.8, 129.4, 128.5, 35.3, 21.7, 19.3.

2-methyl-1-(*m*-tolyl)propan-1-one:[2g] (**Table 3.2, 1c**) Prepared from 3-methyl propiophenone (0.074 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.057 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.73 (m, 2H), 7.37 – 7.34 (m, 2H), 3.55 (hept, *J* = 6.9 Hz, 1H), 2.42 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.9, 138.5, 136.4, 133.7, 128.9, 128.6, 125.6, 35.5, 21.5, 19.3.

1-(4-methoxyphenyl)-2-methylpropan-1-one: [2f] (**Table 3.2, 1d**) Prepared from 4-methoxy propiophenone (0.082 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.0685 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 3.50 (hept, *J* = 6.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 203.2, 163.3, 130.6, 129.2, 113.8, 55.5, 35.0, 19.4.

1-(3-methoxyphenyl)-2-methylpropan-1-one: [2g] (**Table 3.2, 1e**) Prepared from 3-methoxy propiophenone (0.082 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.061 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 1H), 7.48 (s, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 3.84 (s, 3H), 3.52 (hept, *J* = 6.8 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.4, 159.9, 137.7, 129.6, 120.9, 119.2, 112.8, 55.5, 35.6, 19.3.

1-(3,4-dimethylphenyl)-2-methylpropan-1-one: (**Table 3.2, 1f**) Prepared from 3,4-dimethyl propiophenone (0.081 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.0687 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 3.53 (hept, *J* = 6.8 Hz, 1H), 2.30 (s, 6H), 1.20 (d, *J* = 6.9 Hz,

6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.5, 142.3, 136.9, 134.1, 129.8, 129.5, 126.1, 35.1, 20.0, 19.8, 19.3. HRMS (ESI) calcd for $C_{12}H_{16}O$ ($[M+Na]^+$) : 199.1093, found 199.1085.

2-methyl-1-phenylbutan-1-one:[2h] (**Table 3.2, 1g**) Prepared from butyrophenone (0.074 g, 0.5 mmol). After purification by column chromatography (n-hexane/EtOAc, 50/1) the product was isolated as yellowish liquid (0.059 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.41 (sextet, *J* = 6.8 Hz, 1H), 1.91-1.76 (m, 1H), 1.58-1.43 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.6, 136.9, 132.9, 128.7, 128.3, 42.2, 26.8, 16.9, 11.9.

1-(4-ethylphenyl)-2-methylbutan-1-one: (**Table 3.2, 1h**) Prepared from 4-ethyl butyrophenone (0.088 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.068 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H), 3.27 (sextet, *J* = 6.8 Hz, 1H), 2.57 (q, *J* = 7.6 Hz, 2H), 1.78-1.65 (m, 1H), 1.44-1.30 (m, 1H), 1.13 (t, *J* = 7.6 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.79 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.1, 149.7, 134.5, 128.5, 128.1, 41.9, 28.9, 26.7, 16.9, 15.2, 11.8. HRMS (ESI) calcd for $C_{13}H_{18}O$ ($[M+Na]^+$) : 213.1250, found 213.1252.

1-([1,1'-biphenyl]-4-yl)-2-methylpropan-1-one: [9b] (**Table 3.2, 1i**) Prepared from 4-phenyl propiophenone (0.105 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish solid (0.075 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 3.60

(hept, *J* = 6.8 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.2, 145.6, 140.1, 135.0, 129.1, 129.0, 128.3, 127.4, 127.4, 35.5, 19.3.

1-([1,1'-biphenyl]-4-yl)-2-methylbutan-1-one: [2e] (**Table 3.2, 1j**) Prepared from 4-phenyl butyrophenone (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish solid (0.076 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.0 Hz, 1H), 3.44 (sextet, *J* = 6.7 Hz, 1H), 1.95-1.80 (m, 1H), 1.60-1.46 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.2, 145.6, 140.1, 135.6, 129.1, 128.9, 128.3, 127.4, 127.4, 42.3, 26.8, 16.9, 11.9.

1-(4-bromophenyl)-2-methylpropan-1-one: [2g] (**Table 3.2, 1k**) Prepared from 4-bromo propiophenone (0.106 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.0689 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 3.49 (hept, *J* = 7.0 Hz, 1H), 1.21 (d, *J* = 6.8 Hz, 6H).$^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 203.5, 135.0, 132.0, 130.0, 128.0, 35.5, 19.2.

2-methyl-3,4-dihydronaphthalen-1(2*H*)-one:[9a] (**Table 3.2, 1l**) Prepared from 1-tetralone (0.073 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.057 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 1H), 7.45 (t, *J* = 6.8 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 3.10 – 2.92 (m, 2H), 2.65 – 2.54 (m, 1H), 2.24-2.15 (m, 1H), 1.95 – 1.83 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 201.0, 144.3, 133.2, 132.5, 128.8, 127.5, 126.7, 42.8, 31.5, 28.9, 15.6.

1-(2,5-dimethoxyphenyl)-2-methylpropan-1-one:[9c] (**Table 3.2, 1m**) Prepared from 2,5-dimethoxy propiophenone (0.097 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.078 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 3.2 Hz, 1H), 6.98 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.50 (hept, *J* = 6.8 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 207.9, 153.7, 152.2, 129.4, 118.8, 114.4, 113.0, 56.3, 55.9, 40.2, 18.7.

5,6-dimethoxy-2-methyl-2,3-dihydro-1*H*-inden-1-one:[9d] (**Table 3.2, 1n**) Prepared from 5,6-dimethoxy indanone (0.096 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.070 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.86 (s, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 3.30 (dd, *J* = 16.7, 7.3 Hz, 1H), 2.74 – 2.67 (m, 1H), 2.63 (dd, *J* = 16.7, 3.4 Hz, 1H), 1.29 (d, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 208.4, 155.6, 149.6, 148.8, 129.1, 107.5, 104.6, 56.3, 56.2, 42.3, 34.9, 16.8.

1-(furan-2-yl)-2-methylpropan-1-one: [2f] (**Table 3.2, 1o**) Prepared from 1-(furan-2-yl)propan-1-one (0.062 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.051 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.7 Hz, 1H), 7.19 (d, *J* = 3.9 Hz, 1H), 6.53 (dd, *J* = 3.5, 1.7 Hz, 1H), 3.33 (hept, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 193.8, 152.3, 146.3, 117.2, 112.2, 36.4, 18.9.

2-methyl-1-(thiophen-2-yl)propan-1-one:[9a] (**Table 3.2, 1p**) Prepared from 1-(thiophen-2-yl)propan-1-one (0.070 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the product was isolated as a yellowish liquid (0.059 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 3.8 Hz, 1H), 7.62 (d, *J* = 5.0

Hz, 1H), 7.15 – 7.10 (m, 1H), 3.39 (hept, *J* = 6.8 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 197.7, 143.7, 133.6, 131.7, 128.3, 37.3, 19.5.

2,4-dimethyl-1,5-diphenylpentane-1,5-dione:[9c] (**Table 3.3, 2a**) Prepared from propiophenone (0.067 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.25:1 ratio was isolated as a yellow liquid (0.0545 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.5 Hz, 4H), 7.78 (d, *J* = 7.5 Hz, 4H), 7.57 (t, *J* = 7.3 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 4H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 4H), 3.62 (sextet, *J* = 7.0 Hz, 2H), 3.51 (sextet, *J* = 7.0 Hz, 2H), 2.44 (dt, *J*=14.0, 7.1 Hz, 1H), 2.01 (t, *J* = 7.6 Hz, 2H), 1.49 (dt, *J* = 14.0, 7.1 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.17 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.5, 203.9, 136.6, 136.4, 133.2, 133.0, 128.9, 128.7, 128.6, 128.3, 38.7, 38.2, 37.4, 37.1, 18.8, 17.7.

2,4-diethyl-1,5-diphenylpentane-1,5-dione:[9c] (**Table 3.3, 2b**) Prepared from butyrophenone (0.074 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1:1.14 ratio was isolated as a yellow liquid (0.053 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.9 Hz, 4H), 7.70 (d, *J* = 7.9 Hz, 4H), 7.58 (t, *J* = 7.3 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 4H), 7.42 (t, *J* = 7.4 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 4H), 3.45 (p, *J* = 6.9 Hz, 2H), 3.31 (p, *J* = 6.8 Hz, 2H), 2.31 (dt, *J*=14.0, 7.1 Hz, 1H), 2.06 (t, *J* = 7.9 Hz, 2H), 1.81 – 1.66 (m, 5H), 1.57 – 1.46 (m, 4H), 0.86 (t, *J* = 7.4 Hz, 6H), 0.80 (t, *J* = 7.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.8, 203.9, 137.6, 137.3, 133.2, 133.0, 128.8, 128.6, 128.4, 128.2, 45.5, 45.1, 33.5, 33.2, 27.2, 25.4, 11.8, 11.7.

2,4-dimethyl-1,5-di-*p*-tolylpentane-1,5-dione:[3a] (**Table 3.3, 2c**) Prepared from 1-(*p*-tolyl)propan-1-one (0.074 g, 0.50 mmol). After purification by column chromatography

(*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.07:1 ratio was isolated as a yellow liquid (0.056 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 4H), 7.67 (d, *J* = 8.3 Hz, 4H), 7.29 (d, *J* = 7.9 Hz, 4H), 7.11 (d, *J* = 7.9 Hz, 4H), 3.58 (sextet, *J* = 6.8 Hz, 2H), 3.46 (sextet, *J* = 6.9 Hz, 2H), 2.42 (s, 6H), 2.41 – 2.36 (m, 1H), 2.33 (s, 6H), 1.98 (t, *J* = 7.1 Hz, 2H), 1.46 (dt, *J* = 13.9, 7.1 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.2, 203.6, 144.0, 143.8, 134.0, 133.8, 129.5, 129.3, 128.7, 128.4, 38.5, 38.0, 37.5, 37.2, 21.7, 21.6, 18.9, 17.7.

2,4-diethyl-1,5-di-*p*-tolylpentane-1,5-dione: [3a] (**Table 3.3, 2d**) Prepared from 1-(*p*-tolyl)butan-1-one (0.081 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1:1.32 ratio was isolated as a yellow liquid (0.0.0545 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.3 Hz, 4H), 7.59 (d, *J* = 8.2 Hz, 4H), 7.28 (d, *J* = 8.0 Hz, 4H), 7.05 (d, *J* = 8.0 Hz, 4H), 3.41 (p, *J* = 7.1 Hz, 2H), 3.27 (p, *J* = 6.4 Hz, 2H), 2.41 (s, 6H), 2.31 (s, 6H), 2.29 – 2.20 (m, 1H), 2.07 – 1.99 (m, 2H), 1.80 – 1.65 (m, 4H), 1.65 – 1.57 (m, 1H), 1.55 – 1.44 (m, 4H), 0.84 (t, *J* = 7.5 Hz, 6H), 0.78 (t, *J* = 7.4 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.5, 203.5, 143.9, 143.6, 135.2, 134.9, 129.5, 129.2, 128.6, 128.3, 45.3, 44.9, 33.8, 33.5, 27.2, 25.4, 21.7, 21.6, 11.9, 11.7.

1,5-bis(3,4-dimethylphenyl)-2,4-dimethylpentane-1,5-dione:[3a] (**Table 3.3, 2e**) Prepared from 1-(3,4-dimethylphenyl) propan-1-one (0.081 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1:1.07 ratio was isolated as a yellow liquid (0.0.0595 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 4H), 7.52 – 7.47 (m, 4H), 7.25 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 3.57 (sextet, *J* = 7.0 Hz, 2H), 3.45 (sextet, *J* = 6.9 Hz, 2H), 2.40 (dt, *J* = 14.3, 7.3 Hz, 1H), 2.34 (s, 6H), 2.33 (s, 6H), 2.23 (s, 6H),

2.16 (s, 6H), 1.97 (t, *J* = 7.2 Hz, 2H), 1.46 (dt, *J* = 13.9, 7.1 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.6, 203.9, 142.7, 142.4, 137.2, 136.9, 134.6, 134.3, 130.0, 129.8, 129.7, 129.5, 126.3, 126.0, 38.5, 38.1, 37.9, 37.4, 20.1, 20.0, 19.9, 19.7, 19.0, 17.8.

1,5-bis(4-ethylphenyl)-2,4-dimethylpentane-1,5-dione:[3a] (**Table 3.3, 2f**) Prepared from 1-(4-ethylphenyl) propan-1-one (0.081 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) inseparable mixture of two diastereomers in 1.29:1 ratio was isolated as a yellow liquid (0.058 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 4H), 7.70 (d, *J* = 8.3 Hz, 4H), 7.32 (d, *J* = 8.3 Hz, 4H), 7.14 (d, *J* = 8.3 Hz, 4H), 3.59 (sextet, *J* = 7.0 Hz, 2H), 3.48 (sextet, *J* = 6.9 Hz, 2H), 2.72 (q, *J* = 7.6 Hz, 4H), 2.63 (q, *J* = 7.6 Hz, 4H), 2.46 – 2.39 (m, 1H), 1.99 (t, *J* = 8.0 Hz, 2H), 1.50 – 1.43 (m, 1H), 1.27 (t, *J* = 7.6 Hz, 6H), 1.22 – 1.18 (m,12H), 1.16 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.2, 203.6, 150.1, 149.9, 134.3, 134.1, 128.8, 128.5, 128.4, 128.1, 38.5, 38.1, 37.6, 37.3, 29.1, 28.9, 18.9, 17.7, 15.3, 15.2.

1,5-bis(4-methoxyphenyl)-2,4-dimethylpentane-1,5-dione:[3b] (**Table 3.3, 2g**) Prepared from 4-methoxy propiophenone (0.082 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.5:1 ratio was isolated as a yellow liquid (0.062 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.9 Hz, 4H), 7.73 (d, *J* = 8.6 Hz, 4H), 6.96 (d, *J* = 8.6 Hz, 4H), 6.75 (d, *J* = 8.6 Hz, 4H), 3.86 (s, 6H), 3.77 (s, 6H), 3.54 (sextet, *J* = 7.1 Hz, 2H), 3.42 (sextet, *J* = 6.8 Hz, 2H), 2.39 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.96 (t, *J* = 7.1 Hz 2H), 1.43 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.16 (d, *J* = 6.9 Hz, 6H), 1.13 (d, *J* = 6.8 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 203.1, 202.5, 163.6, 163.4, 130.8, 130.5, 129.5, 129.3, 113.9, 113.7, 55.5, 55.4, 38.1, 37.9, 37.8, 37.5, 18.9, 17.7.

1,5-bis(2,5-dimethoxyphenyl)-2,4-dimethylpentane-1,5-dione:[3a] (**Table 3.3, 2h**) Prepared from 1-(2,5-dimethoxyphenyl) propan-1-one (0.097 g, 0.50 mmol). After purification by column chromatography (n-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1:1.75 ratio was isolated as a yellow liquid (0.064 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 3.2 Hz, 2H), 7.05 (d, *J* = 3.2 Hz, 2H), 6.98 (d, *J* = 3.2 Hz, 1H), 6.95 (d, *J* = 3.2 Hz, 1H), 6.92 (d, *J* = 3.2 Hz, 1H), 6.89 (d, *J* = 3.2 Hz, 1H), 6.88 (s, 1H), 6.86 (s, 1H), 6.78 (s, 1H), 6.75 (s, 1H), 3.81 (s, 6H), 3.77 (s, 6H), 3.74 (s, 6H), 3.68 (s, 6H), 3.61 – 3.50 (m, 4H), 2.30 (dt, *J* = 13.8, 7.0 Hz, 1H), 1.81 (t, *J* = 7.2 Hz, 2H), 1.40 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.12 (d, *J* = 6.9 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 207.4, 207.3, 153.5, 153.4, 152.5, 152.4, 129.6, 129.1, 119.1, 118.8, 114.5, 114.4, 113.0, 112.8, 56.2, 55.9, 55.8, 55.8, 43.1, 42.8, 37.1, 36.8, 17.3.

2,2'-methylenebis(3,4-dihydronaphthalen-1(2H)-one):[9a] (**Table 3.3, 2i**) Prepared from 1-tetralone (0.073 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.14:1 ratio was isolated as a yellow liquid (0.0495 g, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.00 (d, *J* = 7.9 Hz, 4H), 7.46 (t, *J* = 7.5 Hz, 4H), 7.29 (t, *J* = 8.4 Hz, 4H), 7.24 (d, *J* = 7.7 Hz, 4H), 3.19-2.93 (m, 8H), 2.87-2.76 (m, 4H), 2.71 (dt, *J* = 14.9, 7.2 Hz, 1H), 2.42 – 2.25 (m, 4H), 2.03 (t, *J* = 6.6 Hz, 2H), 2.00 – 1.85 (m, 4H), 1.59 (dt, *J* = 13.6, 5.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ = 201.0, 200.5, 144.1, 144.0, 133.3, 132.7, 132.5, 128.8, 128.6, 127.5, 127.5, 126.7, 45.9, 44.9, 30.9, 30.1, 29.4, 29.2, 28.7, 28.5.

2,4-dimethyl-1,5-bis(4-(trifluoromethyl)phenyl)pentane-1,5-dione: (**Table 3.3, 2j**) Prepared from 4-trifluoromethyl propiophenone (0.101 g, 0.50 mmol). After purification by column chromatography (n-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers anti and syn in 1.05:1 ratio was isolated as a yellow solid

(0.079 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.0 Hz, 4H), 7.86 (d, *J* = 8.0 Hz, 4H), 7.78 (d, *J* = 8.0 Hz, 4H), 7.60 (d, *J* = 7.9 Hz, 4H), 3.60 (sextet, *J* = 6.1, 5.4 Hz, 2H), 3.50 (sextet, *J* = 6.9 Hz, 2H), 2.44 (dt, *J* = 13.8, 7.1 Hz, 1H), 2.04 (t, *J* = 7.0 Hz, 2H), 1.50 (dt, *J* = 13.8, 7.1 Hz, 1H), 1.23 (d, *J* = 6.9 Hz, 6H), 1.19 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H}{^{19}F} NMR (101 MHz, $CDCl_3$) 203.3, 202.7, 139.1, 138.8, 134.6, 134.6, 128.9, 128.5, 126.0, 125.8, 38.8, 38.7, 37.1, 36.6, 18.7, 17.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.07, -63.22. HRMS (ESI) calcd for $C_{21}H_{18}F_6O_2$ ([M+Na]$^+$): 439.1103, found 439.1133.

1,5-bis(4-bromophenyl)-2,4-dimethylpentane-1,5-dione: (**Table 3.3, 2k**) Prepared from 4-bromo propiophenone (0.106 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.265:1 ratio was isolated as a yellow solid (0.080 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.4 Hz, 4H), 7.64 (d, *J* = 8.5 Hz, 4H), 7.61 (d, *J* = 8.5 Hz, 4H), 7.46 (d, *J* = 8.3 Hz, 4H), 3.52 (sextet, *J* = 6.9 Hz, 2H), 3.40 (sextet, *J* = 6.9 Hz, 2H), 2.38 (dt, *J* = 14.1, 7.2 Hz, 1H), 1.98 (t, *J* = 7.1 Hz, 2H), 1.45 (dt, *J* = 13.8, 7.0 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 6H), 1.15 (d, *J* = 6.9 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 203.3, 202.7, 135.1, 134.9, 132.2, 132.0, 130.1, 129.7, 128.5, 128.5, 38.5, 38.2, 37.3, 36.9, 18.8, 17.6. HRMS (ESI) calcd for $C_{19}H_{18}Br_2O_2$ ([M+H]$^+$): 436.9746, found 436.9769.

2,4-dimethyl-1,5-di(thiophen-2-yl)pentane-1,5-dione:[3b] (**Table 3.3, 2l**) Prepared from 1-(thiophen-2-yl)propan-1-one (0.070 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.05:1 ratio was isolated as a yellow liquid (0.052 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 3.6 Hz, 2H), 7.65 (d, *J* = 4.9 Hz, 2H), 7.53 (d, *J* = 4.9 Hz, 2H), 7.43 (d, *J* = 3.6 Hz, 2H), 7.16 (t, *J* = 4.1 Hz, 2H), 6.91 (t, *J* = 4.1 Hz, 2H), 3.42

(sextet, *J* = 6.9 Hz, 2H), 3.30 (sextet, *J* = 6.9 Hz, 2H), 2.43 (dt, *J* = 14.0, 7.2 Hz, 1H), 1.99 (t, *J* = 7.3 Hz, 2H), 1.51 (dt, *J* = 13.9, 7.1 Hz, 1H), 1.22 (d, *J* = 4.1 Hz, 6H), 1.21 (d, *J* = 4.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 197.3, 196.7, 144.1, 143.9, 134.1, 134.1, 132.4, 132.0, 128.5, 128.1, 40.5, 40.1, 37.8, 37.8, 19.3, 17.8.

1,5-di([1,1'-biphenyl]-4-yl)-2,4-dimethylpentane-1,5-dione:[3b] (**Table 3.3, 2m**) Prepared from 4'-phenyl propiophenone (0.105 g, 0.50 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.11:1 ratio was isolated as a yellowish solid (0.069 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 4H), 7.83 (d, *J* = 8.3 Hz, 4H), 7.74 (d, *J* = 8.3 Hz, 4H), 7.65 (d, *J* = 7.3 Hz, 4H), 7.54 – 7.44 (m, 12H), 7.44 – 7.32 (m, 8H), 3.67 (sextet, *J* = 6.9 Hz, 2H), 3.54 (sextet, *J* = 6.9 Hz, 2H), 2.50 (dt, *J* = 14.1, 7.2 Hz, 1H), 2.05 (t, *J* = 7.2 Hz, 2H), 1.54 (dt, *J* = 14.0, 7.1 Hz, 2H), 1.25 (d, *J* = 6.9 Hz, 6H), 1.22 (d, *J* = 6.9 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ= 204.28, 203.57, 145.93, 145.76, 140.04, 139.81, 135.32, 135.02,129.23, 129.10, 129.01, 128.89, 128.36, 128.28, 127.55, 127.43, 127.32, 38.58, 38.35, 38.09, 37.26, 19.04, 17.82.

2,4-Dibenzyl-1,5-diphenylpentane-1,5-dione: [3a] (**Table 3.4, 3a**) Prepared from 1,3-diphenylpropan-1-one (0.105 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.11:1 ratio was isolated as a yellowish liquid (0.0875 g, 81%). ^{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), 3.04 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.99 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.70 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.63 (dd, *J* = 12.0, 8.0 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). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 203.9, 203.2, 139.3, 138.9, 137.3, 136.9, 133.2, 132.9, 129.0,

129.0, 128.8, 128.5, 128.5, 128.5, 128.5, 128.1, 126.5, 126.4, 46.0, 45.8, 39.9, 38.4, 34.6, 34.4.

2,4-Dibenzyl-1,5-di-o-tolylpentane-1,5-dione:[3b] (**Table 3.4, 3b**) Prepared from 3-phenyl-1-(*o*-tolyl)propan-1-one (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.28:1 ratio was isolated as a yellowish liquid (0.090 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 4H), 7.42 (d, *J* = 8.2 Hz, 4H), 77.25 – 7.20 (m, 6H), 7.20 – 7.16 (m, 3H), 7.15 – 7.11 (m, 6H), 7.11 – 7.04 (m, 5H), 6.99 – 6.92 (m, 8H), 3.74 (p, *J* = 6.9 Hz, 2H), 3.66 (p, *J* = 7.0 Hz, 2H), 3.02 (dd, *J* = 14.0, 8.0 Hz, 2H), 2.98 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.68 (dd, *J* = 14.0, 8.0 Hz, 2H), 2.61 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.40 (s, 6H), 2.34 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.27 (s, 6H), 2.08 (t, *J* = 7.1 Hz, 2H), 1.70 (dt, *J* = 13.7, 6.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 204.0, 203.3, 139.3, 138.8, 138.1, 138.0, 136.9, 133.2, 132.9, 129.8, 129.7, 128.8, 128.6, 128.5, 128.5, 128.4, 128.4, 128.1, 127.2, 127.1, 126.0, 46.0, 45.7, 39.7, 38.4, 21.4, 21.4.

2,4-Dibenzyl-1,5-di-p-tolylpentane-1,5-dione:[3a] (**Table 3.4, 3c**) Prepared from 3-phenyl-1-(*p*-tolyl)propan-1-one (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.20:1 ratio was isolated as a yellowish liquid (0.085 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 4H), 7.42 (d, *J* = 8.3 Hz, 4H), 7.23 (d, *J* = 8.0 Hz, 6H), 7.18 (d, *J* = 7.5 Hz, 4H), 7.14 (d, *J* = 7.3 Hz, 4H), 7.12 – 7.09 (m, 2H), 7.06 (d, *J* = 7.1 Hz, 4H), 6.99 – 6.93 (m, 8H), 3.75 (p, *J* = 7.3 Hz, 2H), 3.66 (p, *J* = 6.8 Hz, 2H), 3.03 (dd, *J* = 16.0, 8.0 Hz, 2H), 2.98 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.68 (dd, *J* = 13.7, 6.7 Hz, 2H), 2.61 (dd, *J* = 13.6, 6.6 Hz, 2H), 2.40 (s, 6H), 2.35 (dt, *J* = 14.0, 6.9 Hz, 1H), 2.27 (s, 6H), 2.08 (t, *J* = 7.1 Hz, 2H), 1.70 (dt, *J* = 13.7, 6.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 203.5, 202.8, 144.0, 143.6, 139.5, 139.1,

134.8, 134.4, 129.5, 129.3,129.3, 129.1, 129.0, 128.6, 128.5, 128.2, 126.4, 126.3, 45.9, 45.5, 39.9, 38.4, 34.9, 34.5, 21.7, 21.6.

2,4-dibenzyl-1,5-bis(4-bromophenyl)pentane-1,5-dione: (**Table 3.4, 3d**) Prepared from 1-(4-bromophenyl)-3-phenylpropan-1-one (0.144 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.13:1 ratio was isolated as a yellowish liquid (0.093 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 4H), 7.56 (d, *J* = 8.6 Hz, 4H), 7.30 (s, 8H), 7.21- 7.12 (m, 12H), 7.04 (d, *J* = 7.5 Hz, 4H), 6.96 (d, *J* = 7.3 Hz, 4H), 3.67 (p, *J* = 6.7 Hz, 2H), 3.59 (p, *J* = 7.1 Hz, 2H), 3.00 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.96 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.71 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.60 (dd, *J* = 16.0, 8.0 Hz, 2H), 2.38 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.13 (t, *J* = 7.1 Hz, 2H), 1.72 (dt, *J* = 13.4, 6.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 203.0, 202.0, 139.0, 138.5, 135.8, 135.3, 133.3, 133.0, 132.0, 131.7, 129.9, 129.4, 128.9, 128.6, 128.6, 128.4, 126.6, 126.6, 46.0, 45.7, 40.0, 38.5, 35.1, 34.1. HRMS (ESI) calcd for $C_{31}H_{26}Br_2O_2$ ([M+H]$^+$): 589.0372, found 589.0345.

2,4-Dibenzyl-1,5-bis(3-(trifluoromethyl)phenyl)pentane-1,5- dione:[3b] (**Table 3.4, 3e**) Prepared from 3-phenyl-1-(3-(trifluoromethyl)-phenyl)propan-1-one (0.139 g, 0.5 mmol). After purification by column chromatography (n-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.08:1 ratio was isolated as a yellowish liquid (0.1005 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 2H), 8.00 (d, *J* = 7.9 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.66 (s, 2H), 7.62 – 7.51 (m, 6H), 7.25 (t, *J* = 7.8 Hz, 2H), 7.20 – 7.15 (m, 6H), 7.15 – 7.09 (m, 6H), 7.05 (d, *J* = 6.9 Hz, 4H), 6.97 (d, *J* = 6.6 Hz, 4H), 3.76 – 3.61 (m, 4H), 3.00 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.96 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.78 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.62 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.45 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.21 (t, *J* = 7.1Hz, 2H), 1.79 (dt, *J* = 13.4, 6.4 Hz, 1H). ^{13}C{^{1}H}{^{19}F}

NMR (101 MHz, $CDCl_3$) δ 202.8, 201.8, 138.8, 138.3, 137.6, 137.1, 131.5, 131.2, 131.0, 130.8, 129.7, 129.7, 129.4, 129.4, 129.1, 128.9, 128.9, 128.7, 126.8, 126.7, 125.3, 124.7, 46.4, 46.0, 40.3, 38.8, 35.2, 34.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.64, −62.91.

2,4-Bis(3-methylbenzyl)-1,5-diphenylpentane-1,5-dione: [3b] (**Table 3.4, 3f**) Prepared from 1-phenyl-3-(m-tolyl) propan-1-one (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.25:1 ratio was isolated as a yellowish liquid (0.0874 g, 76%). ^1H 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), 3.00 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.96 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.66 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.57 (dd, *J* = 12.0, 8.0 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). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 204.0, 203.3, 139.3, 139.1, 138.8, 138.1, 138.0, 137.3, 136.9, 133.2, 132.9, 129.8, 129.7, 128.8, 128.6, 128.5, 128.5, 128.4, 128.1, 127.2, 127.1, 126.0, 45.9, 45.7, 39.7, 38.4, 34.6, 34.4, 21.4, 21.4.

2,4-Bis(4-methylbenzyl)-1,5-diphenylpentane-1,5-dione: [3b] (**Table 3.4, 3g**) Prepared from 1-phenyl-3-(*p*-tolyl) propan-1-one (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.32:1 ratio was isolated as a yellowish liquid (0.089 g, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.1 Hz, 4H), 7.55 (t, *J* = 6.6 Hz, 6H), 7.44 (t, *J* = 7.6 Hz, 4H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 4H), 7.01 (d, *J* = 7.9 Hz, 4H), 6.96 – 6.92 (m, 8H), 6.87 (d, *J* = 8.0 Hz, 4H), 3.77 (p, *J* = 6.9 Hz, 2H), 3.69 (p, *J* = 7.0 Hz, 2H), 3.00 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.96 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.65 (dd, *J* = 14.0,

8.0 Hz, 2H), 2.57 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.36 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.26 (s, 6H), 2.25 (s, 6H), 2.09 (t, *J* = 7.0 Hz, 2H), 1.70 (dt, *J* = 13.7, 6.7 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.0, 203.3, 137.3, 136.8, 136.2, 135.9, 135.8, 133.2, 132.9, 129.2, 129.2, 128.9, 128.9, 128.8, 128.8, 128.6, 128.5, 128.1, 46.0, 45.8, 39.3, 37.9, 34.4, 34.2, 21.1, 21.0.

2,4-Bis(2-fluorobenzyl)-1,5-diphenylpentane-1,5-dione:[3b] (**Table 3.4, 3h**) Prepared from 3-(2-fluorophenyl)-1-phenylpropan-1-one (0.114 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.34:1 ratio was isolated as a yellowish liquid (0.081 g, 69%). ^{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), 3.88 (p, *J* = 7.0 Hz, 2H), 3.80 (p, *J* = 7.2 Hz, 2H), 3.02 (dd, *J* = 14.0, 8.0 Hz, 2H), 2.98 (dd, *J* = 14.0, 8.0 Hz, 2H), 2.76 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.69 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.44 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.09 (t, *J* = 7.0 Hz, 2H), 1.68 – 1.60 (m, 1H). $^{13}C\{^{1}H\}\{^{19}F\}$ NMR (101 MHz, $CDCl_3$) δ 203.4, 202.8, 140.8, 139.8, 137.0, 136.6, 133.3, 133.0, 131.7, 131.6, 128.7, 128.5, 128.4, 128.3, 128.1, 126.1, 125.8, 124.1, 124.1, 115.3, 44.3, 44.0, 34.1, 33.8, 33.3, 32.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ −117.22, −117.33.

2,4-Bis(2-chlorobenzyl)-1,5-diphenylpentane-1,5-dione:[3b] (**Table 3.4, 3i**) Prepared from 3-(2-chlorophenyl)-1-phenylpropan-1-one (0.122 g, 0.5 mmol). After purification by column chromatography (n-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1.28:1 ratio was isolated as a yellowish liquid (0.09 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 4H), 7.43 (dd, *J* = 13.0, 7.4 Hz, 6H), 7.32 (t, *J* = 7.5 Hz, 4H), 7.25 (t, *J* = 7.3 Hz, 2H), 7.18 (d, *J* = 7.7 Hz, 2H), 7.14 – 7.03 (m, 6H), 7.01 – 6.87 (m, 12H), 3.95 (p, *J* = 6.8 Hz, 2H), 3.82 (p, *J* = 7.0 Hz, 2H), 2.98 (dd, *J* =

12.0, 8.0 Hz, 2H), 2.93 (dd, *J* = 14.0, 8.0 Hz, 2H), 2.79 (dd, *J* = 14.0, 8.0 Hz, 2H), 2.75 (dd, *J* = 14.0, 8.0 Hz, 2H), 2.38 (dt, *J* = 13.8, 6.9 Hz, 1H), 2.04 (t, *J* = 6.9 Hz, 2H), 1.56 (dt, *J* = 13.4, 6.5 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 203.8, 203.0, 137.2, 136.7, 136.6, 136.5, 134.0, 133.9, 133.3, 132.9, 132.0, 131.7, 129.6, 129.5, 128.6, 128.5, 128.4, 128.0, 126.8, 126.8, 43.4, 43.2, 37.8, 36.6, 34.8, 34.3.

1,5-Diphenyl-2,4-bis(2-(trifluoromethyl)benzyl)pentane-1,5- dione:[3b] (**Table 3.4, 3j**) Prepared from 1-phenyl-3-(2-(trifluoromethyl)- phenyl)propan-1-one (0.139 g, 0.5 mmol). After purification by column chromatography (n-hexane/EtOAc, 50/1) an inseparable mixture of two diastereomers in 1:1 ratio was isolated as a yellowish solid (0.105 g, 74%). 1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.2 Hz, 4H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.55 – 7.48 (m, 4H), 7.43 (d, *J* = 7.2 Hz, 4H), 7.39 (t, *J* = 7.7 Hz, 4H), 7.35-7.27 (m, 4H), 7.25 - 7.17 (m, 6H), 7.16 – 7.08 (m, 8H), 3.92 (p, *J* = 6.6 Hz, 2H), 3.76 (p, *J* = 7.3 Hz, 2H), 3.17 (dd, *J* = 16.0, 8.0 Hz, 2H), 3.11 (dd, *J* = 14.0, 8.0 Hz, 2H), 2.93 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.93 (dd, *J* = 12.0, 8.0 Hz, 2H), 2.48 (dt, *J* = 14.1, 7.1 Hz, 1H), 2.12 (t, *J* = 7.9 Hz, 2H), 1.64 (dt, *J* = 12.6, 6.3 Hz, 1H). $^{13}C\{^{1}H\}\{^{19}F\}$ NMR (101 MHz, $CDCl_3$) δ 203.9, 203.0, 137.5, 137.4, 137.3, 136.7, 133.3, 133.0, 132.1, 131.9, 131.8, 128.7, 128.5, 128.5, 128.0, 126.8, 126.7, 126.4, 126.3, 126.3, 126.0, 123.2, 44.8, 44.7, 36.7, 35.6, 35.3, 34.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −59.12, −59.14.

Control experiments:

2-methyl-1-phenylpropan-1-one-2,3,3,3-*d*$_4$:[2i] (**Scheme 3.6**, **4a**) Prepared from propiophenone (0.067 g, 0.5 mmol) and CD_3OD (1ml) using N,C-Ru catalyst under the optimised condition. After purification by column chromatography (*n*-hexane/EtOAc,

50/1) the compound was isolated as a yellowish liquid (0.062 g, 82%). HRMS (ESI) calcd for $C_{10}H_8D_4O$ ($[M+H]^+$): 153.1212, found 153.1211.

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.1/1)*100) = 90% D

Peak B: 100-((0/3)*100) = 100% D

2-methyl-1-phenylprop-2-en-1-one:[2f] (**Scheme 3.6, 4b**) Prepared from propiophenone (0.067 g, 0.5 mmol) and HCHO (6 equiv.) in toluene (1 mL) using N, N-Ru catalyst under optimised condition. After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the compound was isolated as a yellowish liquid (0.055 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 5.93 – 5.88 (m, 1H), 5.64 – 5.60 (m, 1H), 2.07 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 198.5, 143.8, 137.8, 132.1, 129.5, 128.3, 127.3, 18.8.

3-hydroxy-2-methyl-1-phenylpropan-1-one:[2f] (**Scheme 3.6, 4c**) A 50 mL round-bottom flask was charged with 5mL methanol, $NaHCO_3$ (50 mg, 0.6 mmol), 37% formaldehyde in H_2O (1.5 mL, 20.0 mmol) and propiophenone (1 mL, 1.0075 g, 7.5 mmol). The mixture was heated at 50 °C for 24 h. It was then cooled and acidified to pH 4 using conc. HCl. EtOAc (10 mL) was then added, and the mixture transferred to a separatory funnel. The organic layer was collected and the aqueous phase washed with EtOAc (2 x 10 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. After purification by column chromatography (*n*-hexane/EtOAc, 50/1) the compound was isolated as a yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.1 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz,

2H), 3.94 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.81 (dd, *J* = 8.0, 4.0 Hz, 1H), 3.71 – 3.62 (m, 1H), 1.24 (d, *J* = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 204.6, 136.2, 133.5, 128.8, 128.5, 64.7, 43.0, 14.7.

2,4-dimethyl-1,5-diphenylpentane-1,5-dione-2,3,3,4-*d*$_4$:[3a] (**Scheme 3.8, 4d**) Prepared from propiophenone (0.067 g, 0.5 mmol) and CD_3OD (1ml) using N,N-Ru catalyst under optimised condition. After purification by column chromatography (n-hexane/EtOAc, 50/1) the compound was isolated as a yellowish liquid (0.053 g, 74%).

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.52/4)*100) = 87% D

Peak B: 100-((0/4)*100) = 100% D

3.5. References

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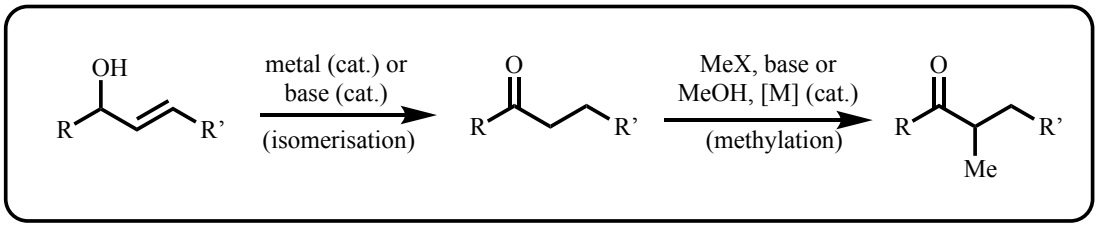
CHAPTER 4

Palladium-catalysed synthesis of α-methyl ketones from allylic alcohols and methanol

4.1 Introduction

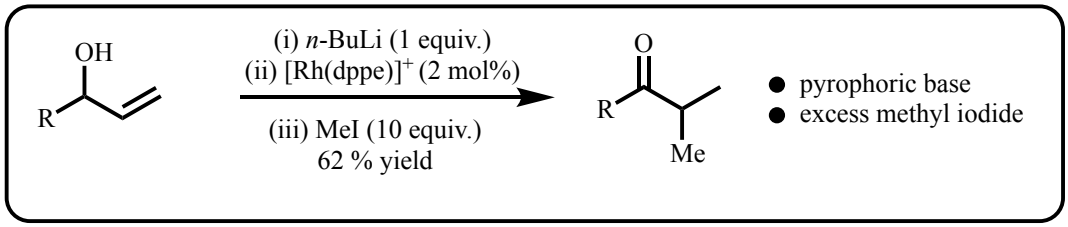
Allylic alcohols play an important role in organic synthesis as alkylating or allylating reagents.[1] Owing to the easy leaving nature of the hydroxyl group, they are used as reactants in the form of their esters, halides, sulfonates, carboxylates, *etc*.[2] Alternatively, allylic alcohols can be activated/protected using stoichiometric amounts of Lewis acids such as BEt_3 and $Ti(O\text{-}iPr)_4$. Unfortunately, these methods lead to the generation of large wastes which impact the reaction atom economy.[2] In many instances, allylic alcohols act as reagents, alternative to carbonyl compounds which can be obtained *via* simple metal-catalyzed redox isomerization.[3] Allylic alcohols also serve as enolate precursors to form new C-C bonds. However, in the absence of electrophiles they tautomerize to produce the respective carbonyl compounds.[3] Moreover, the enolate readily undergoes aldol and Mannich type reactions with electrophiles such as aldehydes and imines respectively.[2a,3e,4] In addition to the importance of allylic alcohols in organic synthesis another important aspect concerns the importance of the *methyl* substituent in the products. Thus, the *methyl* group is one of the chemical motifs occurring in many pharmaceutically and biologically active molecules.[5] 'Methyl' branches also act as desirable structural units with improved combustion characteristics for custom-made fuel elements.[6]



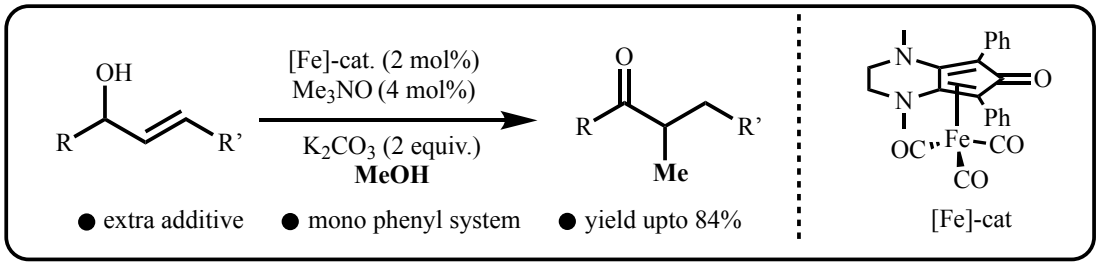
Scheme 4.1. Traditional two-step approach: allylic alcohols to α-methyl ketones

Traditionally, methyl iodide or methyl sulfate, and diazomethane, methyl formamide,[7] were used to incorporate the *methyl* group into the desired framework. However, all

these approaches are environmental unfriendly owing to the use of genotoxic and explosive reagents.[8] Methanol which can be derived from biomass[9] or through CO_2 hydrogenation[10] can act as a highly desired green methylating reagent. Therefore, use of methanol as a methylating reagent by hydrogen borrowing approach is gaining interest as it is a green and renewable C-1 source.[5b,11,12]



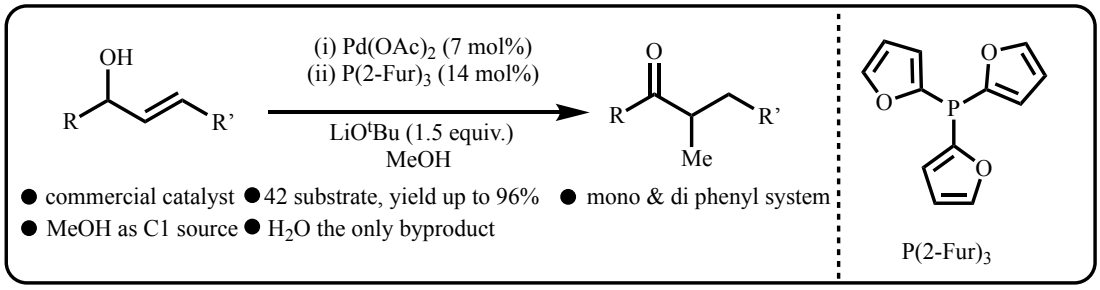
Scheme 4.2: Catalytic sequential approach: α-methyl ketones from allylic alcohols



Scheme 4.3: Catalytic one-pot approach:α-methyl ketones from allylic alcohols

Selective one-pot conversion of secondary allylic alcohols to α-methyl ketones[13] is a potentially beneficial reaction. The direct conversion of secondary allylic alcohols to α-methyl ketones has been documented by Motherwell and co-workers using a rhodium catalyst (**Scheme 4.2)**.[13a] This process involves use of *n*-BuLi to form an alkoxide followed by the isomerization of the allylic alkoxide and subsequent alkylation using excess methyl iodide (10 equiv). The limitations of this approach include the use of a pyrophoric base and super stoichiometric amount of methylating reagent. To overcome these drawbacks, recently Morrill and co-workers reported a homogeneous iron-complex based catalytic system (**Scheme 4.3**)[13b] for the direct one-pot conversion of

secondary allylic alcohols to α-methyl ketones using methanol. Despite being a one pot procedure, this method uses iron-complex which need to be synthesized. Furthermore, additional additive was used to activate the precatalyst during the course of the reaction.



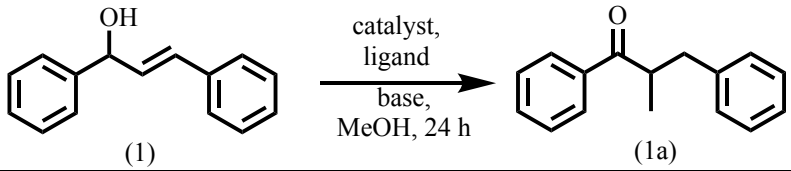
Scheme 4.4: Our current approach: isomerisation-methylation of allyl alcohol using $Pd(OAc)_2$ precatalyst (α-methyl ketones from allylic alcohols and methanol)

Recently, we have reported the synthesis of monomethylated amines, ketones and 1,5-diketones using methanol as a reagent.[11d,14] As part of our continuing efforts to use methanol as a reagent, here, we report a one-pot conversion of secondary allylic alcohols (both 1,3-diaryl propenols and 1-aryl propenols) to α-methyl ketones *via* isomerisation-methylation reactions using methanol as a C1 source and commercially available palladium acetate as a precatalyst (**Scheme 4.4**) to overcome the limitations of the above reports.

4.2: Results and discussion

The one-pot homogeneous Iron catalyzed conversion of secondary allylic alcohol to α-methylated ketone, using methanol as described above[13b] attracted our attention. Palladium catalyst act as a versatile metal source for allyl alcohols to form a variety of coupled products.[1d] On counting the above reports, we were intrigued by the possibility of one-pot conversion of secondary allylic alcohol to α-methylated ketone, using a palladium catalyst.

Table 4.1: Optimization for the synthesis of α-methylated ketone using allyl alcohol and methanol via isomerisation-methylation[a]

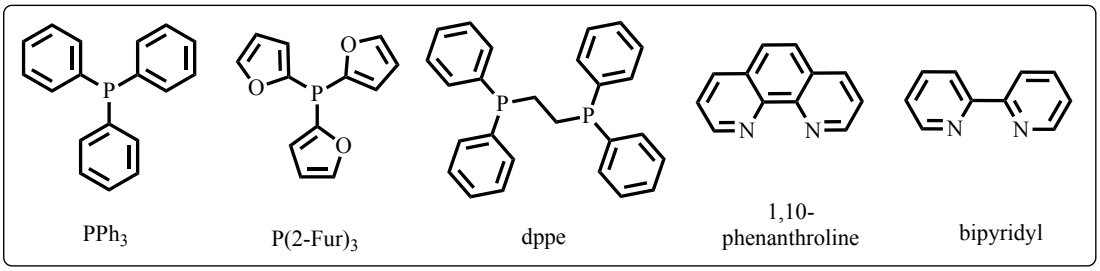


(1) (1a)

Entry	Catalyst (mol%)	Ligand (mol%)	Base (equiv.)	Conversi-on (%) [c]	Yield (%) [b]
1[d]	$Pd(OAc)_2$ (5)	PPh_3 (10)	LiO^{t}Bu (1)	96	26
2 [d]	$Pd(OAc)_2$ (5)	dppe (5)	LiO^{t}Bu (1)	98	30
3 [d]	$Pd(OAc)_2$ (5)	1,10-phenan throline (5)	LiO^{t}Bu (1)	98	Trace
4 [d]	$Pd(OAc)_2$ (5)	2,2'-bipyridyl (5)	LiO^{t}Bu (1)	98	Trace
5 [d]	$Pd(OAc)_2$ (5)	$P(2\text{-Fur})_3$ (10)	LiO^{t}Bu (1)	98	60
6 [d]	$Pd(OAc)_2$ (5)	$P(2\text{-Fur})_3$ (10)	LiO^{t}Bu (1.5)	>99	76
7 [d]	$Pd(OAc)_2$ (5)	$P(2\text{-Fur})_3$ (10)	LiO^{t}Bu (2)	>99	80
8 [d]	$Pd(OAc)_2$ (10)	$P(2\text{-Fur})_3$ (20)	LiO^{t}Bu (1.5)	>99	92
9[e]	$Pd(OAc)_2$ (10)	$P(2\text{-Fur})_3$ (20)	LiO^{t}Bu (1.5)	>99	97
10 [e]	**$Pd(OAc)_2$ (7)**	**$P(2\text{-Fur})_3$ (14)**	**LiO^{t}Bu (1.5)**	**>99**	**96**
11 [e]	$Pd(OAc)_2$ (3)	$P(2\text{-Fur})_3$ (6)	LiO^{t}Bu (1.5)	99	55
12 [e]	$Pd(OAc)_2$ (2)	$P(2\text{-Fur})_3$ (4)	LiO^{t}Bu (1.5)	99	49
13 [e]	$Pd(OAc)_2$ (7)	$P(2\text{-Fur})_3$ (14)	LiO^{t}Bu (0.5)	94	78
14 [e]	$Pd(OAc)_2$ (7)	$P(2\text{-Fur})_3$ (14)	LiO^{t}Bu (0.1)	90	10
15 [e]	$Pd(OAc)_2$ (7)	$P(2\text{-Fur})_3$ (14)	LiOH (1.5)	99	84
16 [e]	$Pd(OAc)_2$ (7)	$P(2\text{-Fur})_3$ (14)	NaO^{t}Bu (1.5)	99	40
17 [e]	$Pd(OAc)_2$ (10)	$P(2\text{-Fur})_3$ (20)	KO^{t}Bu (1.5)	99	36

18 [e]	$Pd(OAc)_2$ (10)	$P(2\text{-Fur})_3$ (20)	KOH (1.5)	99	44
19 [e]	$Pd(OAc)_2$ (10)	$P(2\text{-Fur})_3$ (20)	NaOH (1.5)	99	38
20 [e]	$PdCl_2$ (10)	$P(2\text{-Fur})_3$ (20)	LiO^tBu (1.5)	99	28
21 [e]	$PdCl_2$ (10)	1,10-phenan throline(5)	LiO^tBu (1.5)	99	Trace
22 [e]	$Pd_2(dba)_3$ (10)	$P(2\text{-Fur})_3$ (20)	LiO^tBu (1.5)	99	Trace

[a]Reaction conditions: 1,3-diphenylprop-2-en-1-ol 0.5 mmol, base 0.75 mmol, catalyst $3.5x10^{-2}$ mmol, ligand $7x10^{-2}$ mmol. [b]All yields are isolated yields. [c]All conversions are ^1H NMR conversions. Reactions were performed at [d]120 °C (oil bath temperature) & [e]130 °C (oil bath temperature) for 24 h. dppe-1,2-Bis(diphenylphosphino)ethane, $P(2\text{-Fur})_3$-Tri(2-furyl)phosphine.

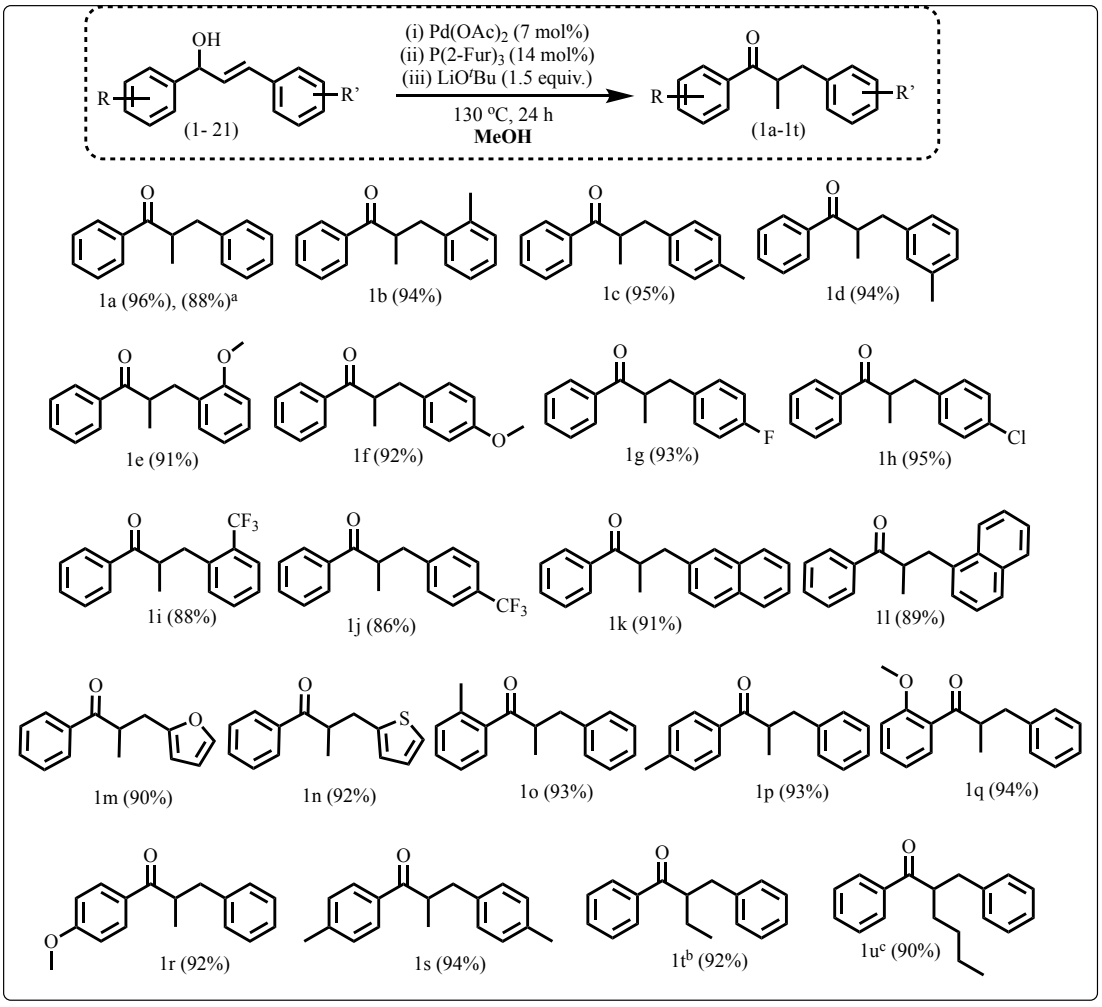


Scheme 4.5. Ligands used for this methylation of allyl alcohols

In this light, 1,3-diphenylprop-2-en-1-ol (**1**) was chosen as a model substrate to scrutinize the reaction parameters including catalyst, ligand, temperature and base (**Table 4.1**). Among the different monodentate and bidentate ligands (PPh_3, dppe, 1,10-phenanthroline, 2,2'-bipyridyl and $P(2\text{-Fur})_3$; **Scheme 4.5**) screened, a significant increase in yield was observed when we used $P(2\text{-Fur})_3$ as a ligand (**Table 4.1, entries 1-5**). Bases like LiOH, NaO^tBu, KO^tBu, KOH and NaOH gave a low yield of the desired product (**Table 4.1, entries 15-19**). Lowering the catalyst and base load gave a low yield of the desired α-methylated ketone product (**Table 4.1, entries 11-14**).

Furthermore, the reactivity of palladium sources such as $PdCl_2$ and $Pd_2(dba)_3$ as catalysts were studied under the optimized conditions, which resulted in a very low yield of the desired α-methyl ketone product (**Table 4.1, entries 20-22**). Use of 7 mol% of $Pd(OAc)_2$, 14 mol% of $P(2\text{-Fur})_3$ and 1.5 equiv of LiO^tBu in MeOH (1 mL) at 130 °C for 24 h produced the desired α-methylated ketone (**1a**) in 96% yield (**Table 4.1, entry 10**), which was confirmed by NMR and HRMS analysis.

Table 4.2. Substrate scope for α-methyl ketones starting from 1,3-diaryl propenols and methanol



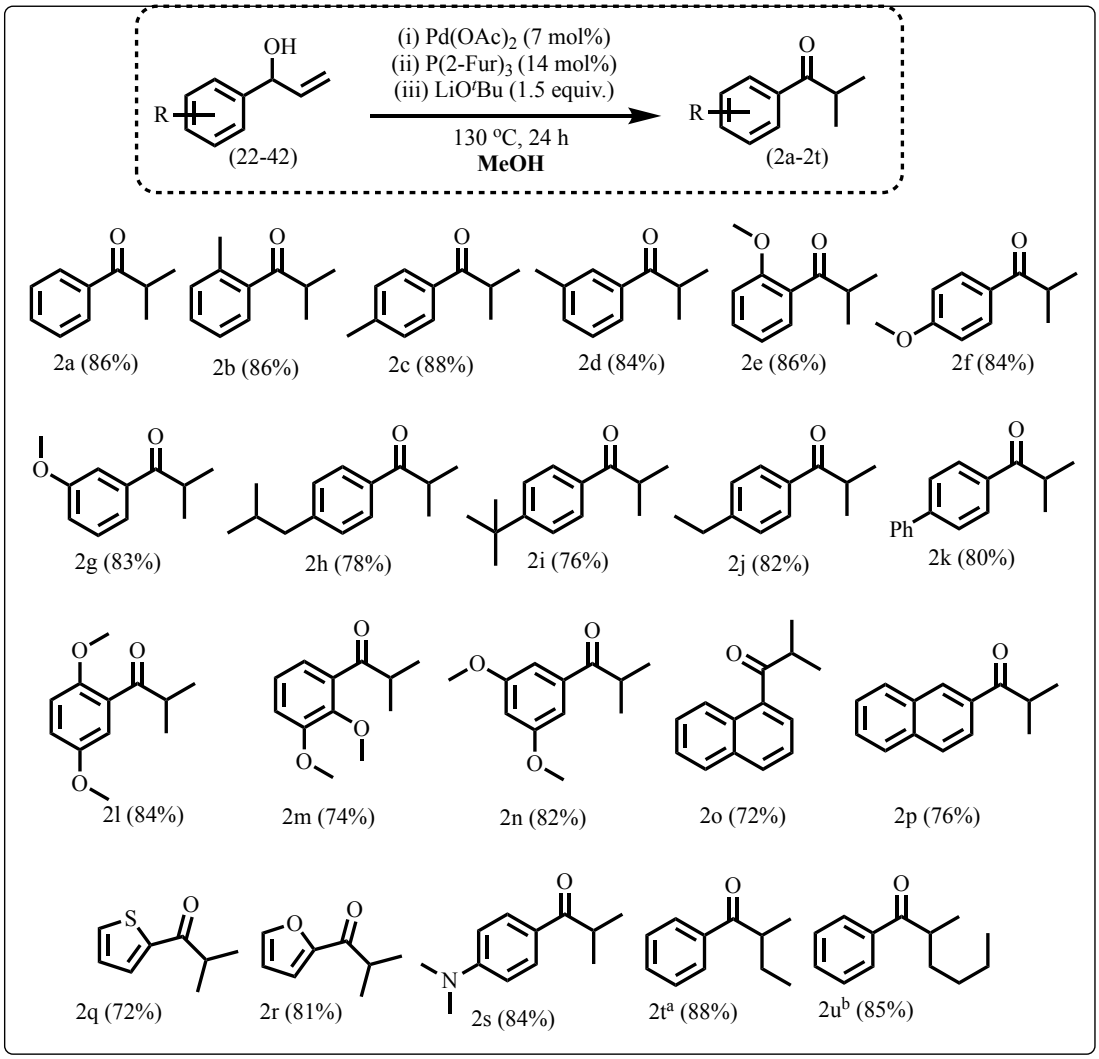
Reaction conditions: allylic alcohol 0.5 mmol, LiO^tBu 0.75 mmol, $Pd(OAc)_2$ $3.5x10^{-2}$

mmol, $P(2\text{-Fur})_3$ $7x10^{-2}$ mmol. All yields are isolated yields. [a]Yield of gram scale reaction. [b]Ethanol was used instead of MeOH. [c]*n*-Butanol was used instead of MeOH.

The substrate scope of the palladium-catalysed isomerisation-methylation of a variety of allylic alcohols is depicted in **Table 4.2**. Substrates with various aromatic substituents at the 1- and 3-positions of allylic alcohols provided the corresponding α-methylated ketones in good to excellent yields. Aryl substrates with electron-donating substituents (*o,p,m*- CH_3, *o,p*-OCH_3) at the 3-position of allylic alcohols, afforded the corresponding α-methylated ketone products **1b-1f** in high yields of 94%, 95%, 94%, 91%, and 92% respectively under the optimized conditions (**Table 4.2**). Our catalytic system was also well tolerated for aryl substrates with electron-withdrawing substituents (-F, -Cl, $-CF_3$) at the 3-position of allylic alcohols to yield the corresponding α-methylated ketone products **1g-1j** in very good yield of 93%, 95%, 88% and 86% respectively (**Table 4.2**). Furthermore, naphthyl and heteroaryls such as furyl and thiophene at the 3-position of allylic alcohols were found to be active enough to yield the desired products **1k-1n** in 91%, 89%, 90%, and 92% respectively (**Table 4.2**). Unfortunately, aryl substrates with chloro (*o* & *p*-Cl) and fluoro substituents (*o* & *p*-F) at the 1-position of allylic alcohol produced the dehalogenated α-methyl ketone, (in case of chloro) such as compound **1a** and nucleophilic aromatic substituted α-methyl ketones such as compounds **1q** & **1r** (in case of fluoro). Substrates bearing electron donating substituents ($-CH_3$, $-OCH_3$) on the aryl group at the 1-position of allylic alcohol under similar reaction conditions yielded the desired α-methyl ketones **1o-1s** in excellent yield of 93%, 93%, 94%, 92%, and 94% respectively (**Table 4.2**). To our surprise alcohols such as EtOH and *n*-butanol produced the desired products **1t-1u** in 92% and 90% respectively under the optimized conditions (**Table 4.2**). To check the

synthetic utility of our methodology, a gram scale reaction using substrate **(1)** was carried under the optimized reaction conditions, which produced the corresponding product **(1a)** in 88% yield. Aryl substrates with reducible functional groups (NO_2 and CN) at the 3-position of allylic alcohols gave a complex mixture.

Table 4.3. Substrate scope for α-methyl ketones starting from 1-aryl propenols and methanol

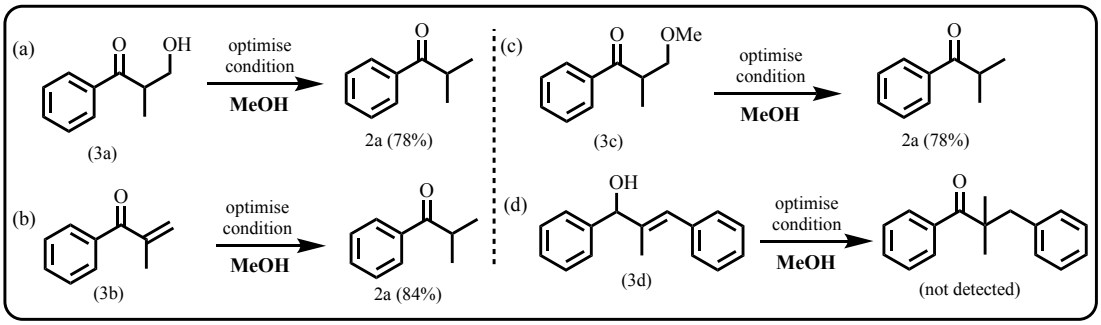


Reaction conditions: allylic alcohol 0.5 mmol, LiO^{t}Bu 0.75 mmol, $Pd(OAc)_2$ $3.5x10^{-2}$ mmol, $P(2\text{-Fur})_3$ $7x10^{-2}$ mmol. All yields are isolated yields. [a]Ethanol was used instead of MeOH. [b]*n*-Butanol was used instead of MeOH.

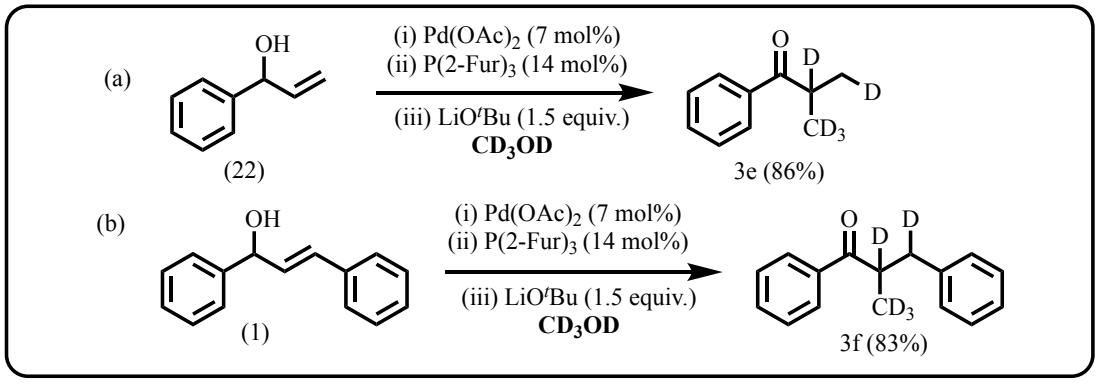
Encouraged by these results, we explored our catalytic protocol to achieve one-pot isomerisation-methylation of 1-aryl propenols (**Table 4.3**). Under the optimised conditions mentioned above, different electron-donating substituents (*o, m, p*-CH_3, *o, m, p*- OCH_3, *p*-^{i}Bu, *p*-^{t}Bu, *p*-C_2H_5) at the aryl group of allylic alcohols produced the desired α-methylated ketone products **2a-2j** in the range of 76% - 86% yield (**Table 4.3**). Notably, substrates with sterically demanding di-methoxy substituents at the aryl group were tolerated under the optimized conditions and provided the α-methylated ketone products **2l-2n** in 84%, 74%, and 82% respectively (**Table 4.3**). Apart from that biphenyl- and naphthyl-propenols also participated in the isomerisation-methylation process to yield the products **2k**, **2o** & **2p** in 80%, 72% & 76% respectively. Interestingly, hetero aryl-propenols also participated in the reaction to furnish the desired products **2q** & **2r** in 72% and 81% yields respectively (**Table 4.3**). Interestingly, amine substitution on the aryl group of allylic alcohol also gave the desired product **2s** in 84% yield. The scope of the reaction was further examined using ethanol and *n*-butanol. Under the optimized conditions, both ethanol and *n*-butanol gave the desired products **2t** & **2u** in 88% and 85% respectively. However, *o,&p*-Cl and *o,&p*-F aryl alcohols did not produce the desired products, instead, they yielded dehalaogenated (compound **2a**) and methoxylated (compound **2e** & **2f**) products respectively.

Control experiments were performed to understand the reaction pathway (**Scheme 4.6**). We anticipated β-hydroxy ketone (**3a**), enone (**3b**) (or) β-methoxy ketone (**3c**) as the possible intermediates formed during the reaction. [3a,4g] To verify this, we reacted compounds **3a, 3b** & **3c** under our optimized reaction conditions; which resulted in the corresponding α-methyl ketone products in good yield. This proves that the reaction sequence involves an aldol type reaction to generate intermediates **3a, 3b** or **3c** starting from allylic alcohol and *in situ* generated formaldehyde. Additional

experiments were performed using **3d** as the starting material. Under the optimised reaction conditions, they did not produce any methylated product, instead they got converted to the corresponding saturated ketones which suggests that the presence of α-hydrogen is essential for the formation of enone and subsequent product formation. When the reaction was performed by employing CD_3OD as a reagent, (**Scheme 4.7**) significant deuterium incorporation was observed at the α- and β- positions (**3e-3f**). Both compound **3e** & **3f** showed more than 50 % deuterium incorporation (55% for **3e** and 62 % for **3f**) at the β-positions respectively, which indicates the involvement of a palladium hydride species in the reaction mechanism that could be formed upon dehydrogenation of allylic alcohol or methanol.

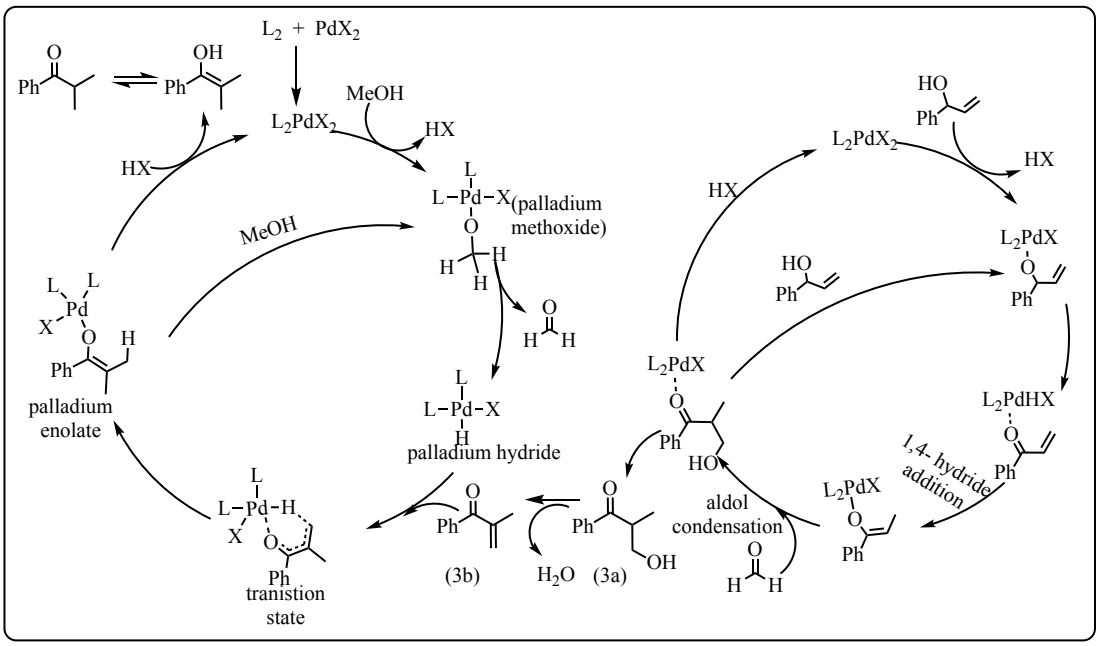


Scheme 4.6. Control experiments: Validation of possible reaction intermediates for methylation of allyl alcohols



Scheme 4.7. Validation of possible reaction intermediates *via* deuterated study for methylation of allyl alcohols

The 1,4-hydride addition from palladium hydride to the enone intermediate generates the enolate intermediate having the deuterium incorporation at the β-position. Based on the control experiments and from the literature reports,[1d,3a,4g] we propose a catalytic cycle for the direct methylation of allylic alcohols using methanol as a reagent (**Scheme 4.8**). The *in situ* generated palladium complex reacts with methanol and allylic alcohol in the presence of a base, which in turn can undergo β-hydride elimination to form the reactive formaldehyde along with the corresponding metal enolate precursor. The palladium enolate intermediate by reacting with formaldehyde can result in the formation of the corresponding aldol product (β-hydroxy ketone (**3a**)), which upon elimination will form the corresponding enone intermediate (unsaturated ketone (**3b**)). The resultant unsaturated ketone gets reduced by the palladium hydride in the presence of methanol to yield the corresponding α-methylated product.



Scheme 4.8. Proposed mechanism for methylation of allyl alcohols

4.3. Conclusion

In summary, we have developed a one-pot conversion of allylic alcohols to α-methyl ketones using a palladium-catalysed isomerization-methylation approach, having H_2O as the only by-product. A variety of allylic alcohols were converted to the corresponding α-methyl ketones in good to excellent isolated yields (up to 96%). Control experiments and the reactions studied using CD_3OD as a reagent reveal the involvement of a palladium hydride species and a palladium enolate species in the catalytic process.

4.4. Experimental section

4.4.1. General information

All reagents and solvents were obtained from commercial sources. All starting materials were synthesized according to literature procedures.[1,2] Solvents were purified according to standard procedures. All 400 MHz ^1H, 100 MHz ^{13}C, 376 MHz ^{19}F spectra were recorded on a spectrometer operating at 400 MHz. All ^1H and ^{13}C NMR spectra were referenced internally to solvent signals and ^{19}F NMR spectra were externally referenced to α,α,α- trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm). High-resolution mass spectra (HRMS) were recorded using Bruker microTOF-QII mass spectrometer.

General procedure for the synthesis of 1-aryl propenols: [13b]

An oven-dried Schlenk tube under N_2 atmosphere was charged with aldehyde (3.0 mmol) in dry THF (3 mL). Under inert atmosphere, vinyl magnesium bromide (3.6 mL, 3.6 mmol, 1 M in THF) at -78 °C, was added to the reaction mixture (drop wise) with continues stirring. Then the reaction mixture was stirred at room temperature for 12h. The reaction was quenched with sat. aq. NH_4Cl (2 mL) and the mixture was transferred to a separatory funnel and extracted using EtOAc (2x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture

was subjected to flash column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the allyl alcohol in high purity.

General procedure for the synthesis of 1,3-diary propenols: [14b]

An oven-dried RB Flask was charged with substituted acetophenone (2.5 mmol, 1.0 equiv) in methanol (10 mL) at 0 °C; to this solution aqueous NaOH (10%) was added (dropwise) and stirred at room temperature for 1 hour. Then, substituted benzaldehyde (2.5 mmol, 1.0 equiv) was added slowly to the reaction mixture and stirred at room temperature. Progress of the reaction was monitored by TLC. After complete consumption of the starting material, solvent was removed under vacuum and the residue was treated with H_2O (5 mL), EtOAc (15 mL). The organic layer was extracted with EtOAc (3 x 10 mL) and the combined organic fraction was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude mixture using silica-gel column chromatography yielded the desired α,β-unsaturated ketone. In next step sodium borohydride (3.0 mmol, 1.2 equiv) was added to the stirred solution of α,β-unsaturated ketone (2.5 mmol, 1.0 equiv) in MeOH: THF (10 mL, 1:1) at 0 °C and the reaction mixture was further stirred at room temperature. The solvent from the reaction mixture was evaporated in vacuum, and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the allylic alcohol in high purity.

4.4.2. General procedure for α-methylation of allyl alcohol

An oven-dried pressure tube was charged with $Pd(OAc)_2$ (3.5×10^{-2} mmol), $P(2\text{-Fur})_3$ (7×10^{-2} mmol) and LiO^tBu (7.5×10^{-1} mmol). Under an inert atmosphere allylic alcohol (0.5 mmol) and methanol (1 mL) were added to the reaction mixture and the system was purged with nitrogen gas for 1 minute. After closing the sealed tube with PTFE

stopper the reaction mixture was stirred at 130 ºC for 24 h. The reaction mixture was transferred to a round bottom flask after cooling it to room temperature, then the sealed tube was rinsed with CH_2Cl_2 (2 x 5 mL); the combined organic mixture was concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the desired α-methylated ketone product in high purity. (Note: All reactions were carried out in a 50 mL pressure tube made up of a material that can withstand the internal pressure).

Procedure for gram scale reaction

An oven-dried sealed tube was charged with $Pd(OAc)_2$ (3.5 x 10^{-1} mmol), P(2-Fur)$_3$ (7 x10^{-1} mmol) and LiO^tBu (7.5 mmol). Under inert atmosphere, 1,3-diphenylprop-2-en-1-ol (5 mmol, 1.05 g), methanol (5 mL) were added to the reaction mixture and the system was purged with nitrogen gas for 1 minute. Then the tube was closed with PTFE stopper and the reaction mixture was stirred at 130 ºC for 24 h. The reaction mixture was transferred to a round bottom flask after cooling it to room temperature, the sealed tube was rinsed with DCM (3 x 10 mL), the combined organic mixture was concentrated under vacuum. After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.986 g, 88%).

4.4.3. Analytical data for unreported allyl alcohols

1-(*o*-tolyl)prop-2-en-1-ol (Table 4.3, 23): Prepared from 2-methylbenzaldehyde (0.360 g, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc: 95:5), the compound was isolated as a yellowish liquid (0.364 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.2 Hz, 1H), 7.24 – 7.17 (m, 2H), 7.16 (d, *J* = 6.7 Hz, 1H), 6.10 – 5.98 (m, 1H), 5.42 (d, *J* = 5.4 Hz, 1H), 5.32 (d, *J* = 17.1 Hz, 1H), 5.21 (d, *J* =

10.3 Hz, 1H), 2.37 (s, 3H), 1.89 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.57, 139.51, 135.48, 130.65, 127.76, 126.44, 125.96, 115.35, 72.17, 19.24.

1-(2-methoxyphenyl)prop-2-en-1-ol (Table 4.3, 26): Prepared from 2-methoxybenzaldehyde (0.408 g, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc: 95:5), the compound was isolated as a yellowish liquid (0.374 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.20 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 6.23 – 6.04 (m, 1H), 5.42 (d, *J* = 9.8 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 3.86 (s, 3H), 2.88 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.83, 139.57, 130.85, 128.86, 127.54, 121.01, 114.61, 110.85, 71.68, 55.49.

1-(4-isobutylphenyl)prop-2-en-1-ol (Table 4.3, 29): Prepared from 4-isobutylbenzaldehyde (0.486 g, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc: 95:5), the compound was isolated as a yellowish liquid (0.422 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.13 – 5.98 (m, 1H), 5.35 (d, *J* = 18.4 Hz, 1H), 5.23 – 5.16 (m, 2H), 2.47 (d, *J* = 7.1 Hz, 2H), 1.86 (hept, 1H), 1.26 (s, 1H), 0.90 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.49, 140.49, 140.05, 129.46, 126.28, 115.01, 75.38, 45.25, 30.35, 22.49.

1-(4-(*tert*-butyl)phenyl)prop-2-en-1-ol (Table 4.3, 30): Prepared from 4-(tert-butyl) benzaldehyde (0.486 g, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc: 95:5), the compound was isolated as a yellowish liquid (0.479 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.13 – 5.97 (m, 1H), 5.36 (d, *J* = 17.1 Hz, 1H), 5.26 – 5.10 (m, 2H), 1.32 (s, 9H), 1.26 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.94, 140.40, 139.80, 126.22, 125.65, 115.03, 75.29, 34.68, 31.48.

1-(4-ethylphenyl)prop-2-en-1-ol (Table 4.3, 31): Prepared from 4-ethylbenzaldehyde (0.402 g, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc: 95:5), the compound was isolated as a yellowish liquid (0.399 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.13 – 5.94 (m, 1H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.25 – 5.12 (m, 2H), 2.65 (q, *J* = 7.6 Hz, 2H), 2.05 (s, 1H), 1.24 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.03, 140.42, 140.03, 128.21, 126.50, 115.01, 75.34, 28.68, 15.74.

1-([1,1'-biphenyl]-4-yl)prop-2-en-1-ol (Table 4.3, 32): Prepared from [1,1'-biphenyl]-4-carbaldehyde (0.546 g, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc: 95:5), the compound was isolated as a yellowish liquid (0.479 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.56 (m, 4H), 7.45 (t, *J* = 7.9 Hz, 4H), 7.36 (t, *J* = 7.3 Hz, 1H), 6.17 – 6.00 (m, 1H), 5.40 (d, *J* = 17.1 Hz, 1H), 5.30 – 5.19 (m, 2H), 2.05 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.70, 140.92, 140.86, 140.26, 128.91, 127.48, 127.25, 126.90, 115.43, 75.28.

1-(2,3-dimethoxyphenyl)prop-2-en-1-ol (Table 4.3, 34): Prepared from 2,3-dimethoxy benzaldehyde (0.498 g, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc: 95:5), the compound was isolated as a yellowish liquid (0.419 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.20 – 6.00 (m, 1H), 5.44 (d, *J* = 4.9 Hz, 1H), 5.33 (d, *J* = 17.1 Hz, 1H), 5.18 (d, *J* = 10.3 Hz, 1H), 3.87 (s, 3H), 3.87 (s, 3H), 2.74 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.77, 146.65, 140.37, 136.40, 124.39, 119.41, 114.61, 112.10, 71.45, 61.07, 55.93.

1-(3,5-dimethoxyphenyl)prop-2-en-1-ol (Table 4.3, 35): Prepared from 3,5-dimethoxy benzaldehyde (0.498 g, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc: 95:5), the compound was isolated as a yellowish

liquid (0.442 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 2H), 6.38 (s, 1H), 6.10 – 5.91 (m, 1H), 5.36 (d, *J* = 17.1 Hz, 1H), 5.20 (d, *J* = 10.3 Hz, 1H), 5.14 (d, *J* = 6.0 Hz, 1H), 3.79 (s, 6H), 2.09 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.09, 145.24, 140.04, 115.48, 104.25, 99.85, 75.51, 55.50.

1-(4-(dimethylamino)phenyl)prop-2-en-1-ol (Table 4.3, 40): Prepared from 4-(dimethyl amino)benzaldehyde (0.447 g, 3.0 mmol). After purification by column chromatography (*n*-hexane/EtOAc: 95:5), the compound was isolated as a yellowish liquid (0.414 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 6.15 – 5.95 (m, 1H), 5.34 (d, *J* = 17.1 Hz, 1H), 5.17 (d, *J* = 10.3 Hz, 1H), 5.13 (d, *J* = 5.6 Hz, 1H), 2.95 (s, 6H), 1.88 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.49, 140.61, 130.67, 127.59, 114.41, 112.72, 75.18, 40.77.

4.4.4. Analytical data for α-methyl ketone compounds

2-methyl-1,3-diphenylpropan-1-one:[11d] (**Table 4.2, 1a**) Prepared from 1,3-diphenylprop-2-en-1-ol (0.105 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.108 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.0 Hz, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.30 – 7.23 (m, 2H), 7.23 – 7.15 (m, 3H), 3.76 (sext, J = 6.9 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 203.88, 140.08, 136.60, 133.04, 129.21, 128.76, 128.50, 128.41, 126.32, 42.90, 39.52, 17.54.

2-methyl-1-phenyl-3-(*o*-tolyl)propan-1-one:[14c] (**1 Table 4.2, b**) Prepared from 1-phenyl-3-(o-tolyl)prop-2-en-1-ol (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.112 g, 94%). ^{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-(*p*-tolyl)propan-1-one:[14d] (**Table 4.2, 1c**) Prepared from 1-phenyl-3-(p-tolyl)prop-2-en-1-ol (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.113 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.14 – 7.04 (m, 4H), 3.73 (sext, *J* = 6.9 Hz, 1H), 3.14 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.66 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.31 (s, 3H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.97, 136.93, 136.56, 135.77, 133.02, 129.17, 129.08, 128.75, 128.42, 42.94, 39.01, 21.13, 17.42.

2-methyl-1-phenyl-3-(*m*-tolyl)propan-1-one: (**Table 4.2, 1d**) Prepared from 1-phenyl-3-(*m*-tolyl)prop-2-en-1-ol (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.112 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.07 – 6.97 (m, 3H), 3.76 (sext, *J* = 6.8 Hz, 1H), 3.16 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.67 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.33 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.91, 139.96, 138.00, 136.55, 133.00, 130.00, 128.72, 128.40, 128.36, 127.04, 126.19, 42.83, 39.36, 21.50, 17.46. HRMS (ESI): calcd for $C_{17}H_{18}O$ ($[M+Na]^+$): 261.1250, found: 261.1260.

3-(2-methoxyphenyl)-2-methyl-1-phenylpropan-1-one: (**Table 4.2, 1e**) Prepared from 3-(2-methoxyphenyl)-1-phenylprop-2-en-1-ol (0.120 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.116 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J*

= 7.7 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.23 – 7.17 (m, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 6.92 – 6.82 (m, 2H), 3.95 – 3.86 (m, 1H), 3.85 (s, 3H), 3.22 (dd, *J* = 13.3, 5.4 Hz, 1H), 2.64 (dd, *J* = 13.3, 8.6 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.31, 157.53, 136.64, 132.84, 131.41, 128.54, 128.47, 128.08, 127.69, 120.37, 110.23, 55.18, 40.42, 35.19, 16.74. HRMS (ESI): calcd for $C_{17}H_{18}O_2$ ($[M+Na]^+$): 277.1199, found: 277.1205.

3-(4-methoxyphenyl)-2-methyl-1-phenylpropan-1-one:[11d] (**Table 4.2, 1f**) Prepared from 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-ol (0.120 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.117 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.7 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 3.77 (s, 3H), 3.71 (sext, *J* = 7.0 Hz, 1H), 3.12 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.65 (dd, *J* = 13.8, 7.7 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.00, 158.11, 136.60, 133.00, 132.06, 130.12, 128.73, 128.38, 113.86, 55.31, 43.07, 38.61, 17.44.

3-(4-fluorophenyl)-2-methyl-1-phenylpropan-1-one:[14e] (**Table 4.2, 1g**) Prepared from 3-(4-fluorophenyl)-1-phenylprop-2-en-1-ol (0.114 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.113 g, 93%). ^{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), 7.14 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.93 (t, *J* = 8.7 Hz, 2H), 3.72 (sext, *J* = 7.0 Hz, 1H), 3.13 (dd, *J* = 13.8, 6.8 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.

3-(4-chlorophenyl)-2-methyl-1-phenylpropan-1-one:[14e] (**Table 4.2, 1h**) Prepared from 3-(4-chlorophenyl)-1-phenylprop-2-en-1-ol (0.122 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.123 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.20 (d, *J* = 6.8 Hz, 2H), 3.75 (sext, *J* = 6.6 Hz, 1H), 3.17 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.69 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.92, 140.08, 136.55, 133.07, 129.22, 128.77, 128.51, 128.42, 126.33, 42.89, 39.48, 17.54.

1-phenyl-3-(2-(trifluoromethyl)phenyl)propan-1-one: (**Table 4.2, 1i**) Prepared from 1-phenyl-3-(2-(trifluoromethyl)phenyl)prop-2-en-1-ol (0.139 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.129 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.1 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.37 (d, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 3.85 (sext, *J* = 7.1 Hz, 1H), 3.39 (dd, *J* = 14.3, 7.2 Hz, 1H), 2.97 (dd, *J* = 15.3, 6.8 Hz, 1H), 1.23 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (^{19}F- decoupled) (101 MHz, $CDCl_3$) δ 203.77, 138.75, 136.60, 133.15, 132.27, 131.73, 128.86, 128.76, 128.37, 126.55, 126.36, 124.87, 42.14, 35.88, 18.29. ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.09. HRMS (ESI): calcd for $C_{17}H_{15}F_3O$ ($[M+Na]^+$): 315.0967, found: 315.0959.

1-phenyl-3-(4-(trifluoromethyl)phenyl)propan-1-one: (**Table 4.2, 1j**) Prepared from 1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (0.139 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.125 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.45 (t, *J* = 7.6 Hz,

2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.77 (sext, *J* = 7.1 Hz, 1H), 3.24 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.78 (dd, *J* = 13.7, 7.2 Hz, 1H), 1.23 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (^{19}F- 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 -62.29. HRMS (ESI): calcd for $C_{17}H_{15}F_3O$ ($[M+H]^+$): 293.1148, found: 293.1142.

2-methyl-3-(naphthalen-2-yl)-1-phenylpropan-1-one: (**Table 4.2, 1k**) Prepared from 3-(naphthalen-2-yl)-1-phenylprop-2-en-1-ol (0.130 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.125 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.2 Hz, 2H), 7.44 (dt, *J* = 20.1, 6.9 Hz, 2H), 7.21 – 7.10 (m, 4H), 7.06 (t, *J* = 6.7 Hz, 1H), 3.80 (sext, *J* = 6.8 Hz, 1H), 3.12 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.65 (dd, *J* = 13.7, 7.7 Hz, 1H), 1.16 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.83, 140.13, 135.61, 133.85, 132.66, 129.90, 129.69, 129.24, 128.61, 128.52, 127.84, 126.83, 126.34, 124.33, 42.96, 39.62, 17.78. HRMS (ESI): calcd for $C_{20}H_{18}O$ ($[M+H]^+$): 275.1430, found: 275.1444.

2-methyl-3-(naphthalen-1-yl)-1-phenylpropan-1-one:[12b] (**Table 4.2, 1l**) Prepared from 3-(naphthalen-1-yl)-1-phenylprop-2-en-1-ol (0.130 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.122 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.72 – 7.60 (m, 3H), 7.54 (s, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 7.31 (q, *J* = 8.2 Hz, 4H), 7.24 (d, *J* = 8.4 Hz, 1H), 3.74 (sext, *J* = 6.9 Hz, 1H), 3.24 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.75 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.13 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.80, 137.60, 136.50, 133.61, 133.08, 132.22, 128.77, 128.42, 128.11, 127.71, 127.68, 127.63, 126.08, 125.45, 42.84, 39.55, 17.64.

3-(furan-2-yl)-2-methyl-1-phenylpropan-1-one:[14f] (**Table 4.2, 1m**) Prepared from 3-(furan-2-yl)-1-phenylprop-2-en-1-ol (0.100 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.096 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.1 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.31 – 7.27 (m, 1H), 6.24 (d, *J* = 3.1 Hz, 1H), 6.02 (d, *J* = 3.2 Hz, 1H), 3.87 (sext, *J* = 7.0 Hz, 1H), 3.15 (dd, *J* = 15.1, 6.5, 1H), 2.77 (dd, *J* = 15.1, 7.6 Hz, 1H), 1.23 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.35, 153.78, 141.35, 136.32, 133.12, 128.78, 128.46, 110.32, 106.63, 40.13, 31.75, 17.65.

2-methyl-1-phenyl-3-(thiophen-2-yl)propan-1-one:[14f] (**Table 4.2, 1n**) Prepared from 1-phenyl-3-(thiophen-2-yl)prop-2-en-1-ol (0.108 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.106 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.10 (d, *J* = 5.1 Hz, 1H), 6.91 – 6.85 (m, 1H), 6.84 – 6.75 (m, 1H), 3.77 (sext, *J* = 7.0 Hz, 1H), 3.38 (dd, *J* = 14.8, 6.7 Hz, 1H), 2.95 (dd, *J* = 14.8, 7.2 Hz, 1H), 1.26 (d, *J* = 6.7 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.

2-methyl-3-phenyl-1-(*o*-tolyl)propan-1-one:[14f] (**Table 4.2, 1o**) Prepared from 3-phenyl-1-(*o*-tolyl)prop-2-en-1-ol (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.111 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.8 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.20 – 7.14 (m, 2H), 7.11 (t, *J* = 8.7 Hz, 5H), 3.47 (sext, *J* = 7.0 Hz, 1H), 3.07 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.55 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.31 (s, 3H), 1.07

(d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.24, 140.08, 138.67, 137.83, 131.76, 130.90, 129.19, 128.48, 127.65, 126.30, 125.64, 46.39, 39.22, 20.83, 17.04.

2-methyl-3-phenyl-1-(*p*-tolyl)propan-1-one:[14f] (**Table 4.2, 1p**) Prepared from 3-phenyl-1-(*p*-tolyl)prop-2-en-1-ol (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.111 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.22 – 7.14 (m, 4H), 7.10 (dd, *J* = 12.6, 7.0 Hz, 3H), 3.64 (sext, *J* = 6.9 Hz, 1H), 3.08 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.60 (dd, *J* = 13.7, 7.9 Hz, 1H), 2.32 (s, 3H), 1.11 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.52, 143.84, 140.19, 134.01, 129.45, 129.21, 128.55, 128.47, 126.27, 42.71, 39.51, 21.73, 17.58.

1-(2-methoxyphenyl)-2-methyl-3-phenylpropan-1-one:[14g] (**Table 4.2, 1q**) Prepared from 1-(2-methoxyphenyl)-3-phenylprop-2-en-1-ol (0.120 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.119 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.30 – 7.22 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 3H), 7.01 – 6.88 (m, 2H), 3.85 (s, 3H), 3.73 (sext, *J* = 6.8 Hz, 1H), 3.17 (dd, *J* = 13.5, 5.7 Hz, 1H), 2.57 (dd, *J* = 13.6, 8.7 Hz, 1H), 1.10 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.33, 157.91, 140.43, 132.96, 130.25, 129.25, 129.05, 128.30, 126.05, 120.80, 111.44, 55.57, 47.33, 39.27, 16.40.

1-(4-methoxyphenyl)-2-methyl-3-phenylpropan-1-one:[14f] (**Table 4.2, 1r**) Prepared from 1-(4-methoxyphenyl)-3-phenylprop-2-en-1-ol (0.120 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.117 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2H), 7.29 – 7.22 (m, 2H), 7.22 – 7.13 (m, 3H), 6.91 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 3.70 (sext, *J* = 7.0 Hz, 1H), 3.15 (dd, *J* = 13.7, 6.3 Hz, 1H), 2.68 (dd, *J* = 13.7,

7.8 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.40, 163.46, 140.20, 130.65, 129.44, 129.17, 128.43, 126.22, 113.86, 55.52, 42.41, 39.58, 17.65.

2-methyl-1,3-di-*p*-tolylpropan-1-one:[14g] (**Table 4.2, 1s**) Prepared from 1,3-di-*p*-tolylprop-2-en-1-ol (0.119 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.118 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.09 – 7.04 (m, 4H), 3.69 (h, *J* = 6.9 Hz, 1H), 3.11 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.63 (dd, *J* = 13.7, 8.0 Hz, 1H), 1.17 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.49, 143.71, 137.01, 135.65, 134.02, 129.39, 129.11, 129.04, 128.51, 42.73, 39.04, 21.66, 21.07, 17.44.

2-benzyl-1-phenylbutan-1-one:[14h] (**Table 4.2, 1t**) Prepared from 1,3-diphenylprop-2-en-1-ol (0.105 g, 0.5 mmol) and EtOH (1ml). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.109 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (t, *J* = 6.7 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.26 – 7.12 (m, 5H), 3.69 (pent, *J* = 6.7 Hz, 1H), 3.11 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.78 (dd, *J* = 13.8, 6.7 Hz, 1H), 1.91 – 1.74 (m, 1H), 1.70 – 1.59 (m, 1H), 0.89 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.01, 140.19, 137.71, 132.95, 129.16, 128.69, 128.49, 128.28, 126.26, 49.87, 37.86, 25.41, 11.81.

2-benzyl-1-phenylhexan-1-one:[14i] (**Table 4.2, 1u**) Prepared from 1,3-diphenylprop-2-en-1-ol (0.105 g, 0.5 mmol) and *n*-butanol (1ml). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.120 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.24 – 7.11 (m, 5H), 3.73 (p, *J* = 7.2 Hz, 1H), 3.11 (dd, *J* = 13.6, 7.7 Hz, 1H), 2.78 (dd, *J* = 13.6, 6.5 Hz, 1H), 1.89 – 1.72 (m, 1H),

1.62 – 1.48 (m, 1H), 1.27 (dq, *J* = 9.0, 4.7, 4.1 Hz, 4H), 0.83 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.09, 140.05, 137.52, 132.85, 129.02, 128.57, 128.36, 128.16, 126.13, 48.32, 38.68, 32.13, 29.54, 23.74, 14.08.

2-methyl-1-phenylpropan-1-one:[11d] (**Table 4.3, 2a**) Prepared from 1-phenylprop-2-en-1-ol (0.067 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.064 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.56 (hept, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.71, 136.31, 132.94, 128.74, 128.45, 35.48, 19.28.

2-methyl-1-(*o*-tolyl)propan-1-one:[12f] (**Table 4.3, 2b**) Prepared from 1-(*o*-tolyl)prop-2-en-1-ol (0.074 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0697 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.1 Hz, 1H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.24 (d, *J* = 4.4 Hz, 2H), 3.34 (hept, *J* = 6.9 Hz, 1H), 2.42 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.35, 138.73, 137.51, 131.69, 130.67, 127.47, 125.62, 38.87, 20.82, 18.62.

2-methyl-1-(*p*-tolyl)propan-1-one:[13b] (**Table 4.3, 2c**) Prepared from 1-(*p*-tolyl)prop-2-en-1-ol (0.074 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.071 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 3.49 (hept, *J* = 6.9 Hz, 1H), 2.36 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.38, 143.72, 133.89, 129.50, 128.66, 35.40, 21.79, 19.42.

2-methyl-1-(*m*-tolyl)propan-1-one:[13b] (**Table 4.3, 2d**) Prepared from 1-(*m*-tolyl)prop-2-en-1-ol (0.074 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.068 g,

84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.74 (m, 2H), 7.36 – 7.33 (m, 2H), 3.55 (hept, *J* = 6.8 Hz, 1H), 2.41 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.95, 138.52, 136.39, 133.68, 128.98, 128.59, 125.63, 35.50, 21.54, 19.33.

1-(2-methoxyphenyl)-2-methylpropan-1-one:[12b] (**Table 4.3, 2e**) Prepared from 1-(2-methoxyphenyl) prop-2-en-1-ol (0.082 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0766 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.37 (m, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 3.47 (hept, *J* = 6.9 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.39, 157.76, 132.67, 130.03, 129.08, 120.75, 111.42, 55.60, 40.16, 18.64.

1-(4-methoxyphenyl)-2-methylpropan-1-one:[11d] (**Table 4.3, 2f**) Prepared from 1-(4-methoxyphenyl)prop-2-en-1-ol (0.082 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0748 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 3.50 (hept, *J* = 6.8 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.21, 163.35, 130.64, 129.18, 113.82, 55.51, 35.00, 19.38.

1-(3-methoxyphenyl)-2-methylpropan-1-one:[12i] (**Table 4.3, 2g**) Prepared from 1-(3-methoxyphenyl) prop-2-en-1-ol (0.082 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.074 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.48 (s, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 5.6 Hz, 1H), 3.84 (s, 3H), 3.52 (hept, *J* = 6.8 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.46, 159.98, 137.70, 129.65, 120.92, 119.26, 112.84, 55.50, 35.59, 19.30.

1-(4-isobutylphenyl)-2-methylpropan-1-one:[13b] (**Table 4.3, 2h**) Prepared from 1-(4-isobutylphenyl) prop-2-en-1-ol (0.095 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0797 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 3.54 (hept, *J* = 6.8 Hz, 1H), 2.52 (d, *J* = 7.2 Hz, 2H), 1.89 (hept, *J* = 6.8 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.40, 147.38, 134.01, 129.44, 128.43, 45.46, 35.30, 30.23, 22.45, 19.35.

1-(4-(*tert*-butyl)phenyl)-2-methylpropan-1-one:[15a] (**Table 4.3, 2i**) Prepared from 1-(4-(*tert*-butyl)phenyl)prop-2-en-1-ol (0.095 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0776 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 3.55 (hept, *J* = 6.8 Hz, 1H), 1.34 (s, 9H), 1.21 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.32, 156.60, 133.68, 128.43, 125.67, 35.32, 35.18, 31.22, 19.34.

1-(4-ethylphenyl)-2-methylpropan-1-one:[15b] (**Table 4.3, 2j**) Prepared from 1-(4-ethylphenyl)prop-2-en-1-ol (0.081 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0722 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 3.54 (hept, *J* = 6.8 Hz, 1H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.27 (d, *J* = 7.6 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.35, 149.84, 134.03, 128.69, 128.24, 35.35, 29.04, 19.36, 15.33.

1-([1,1'-biphenyl]-4-yl)-2-methylpropan-1-one:[13b] (**Table 4.3, 2k**) Prepared from 1-([1,1'-biphenyl]-4-yl)prop-2-en-1-ol (0.105 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 95:5), the compound was isolated as a yellowish liquid (0.0897 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.73 –

7.59 (m, 4H), 7.47 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 1H), 3.60 (hept, *J* = 6.8 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.24, 145.62, 140.09, 135.02, 129.08, 129.06, 128.30, 127.40, 127.39, 35.54, 19.34.

1-(2,5-dimethoxyphenyl)-2-methylpropan-1-one:[15c] (**Table 4.3, 2l**) Prepared from 1-(2,5-dimethoxyphenyl)prop-2-en-1-ol (0.097 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0874 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 3.2 Hz, 1H), 6.99-6.96 (m, 1H), 6.89-6.87 (m, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.50 (hept, *J* = 6.8 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.93, 153.67, 152.26, 129.43, 118.78, 114.40, 113.05, 56.29, 55.95, 40.18, 18.69.

1-(2,3-dimethoxyphenyl)-2-methylpropan-1-one:[15d] (**Table 4.3, 2m**) Prepared from 1-(2,3-dimethoxyphenyl)prop-2-en-1-ol (0.097 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.077 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 – 7.05 (m, *J* = 7.8 Hz, 1H), 7.02 – 6.93 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.35 (hept, *J* = 6.8 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.72, 152.87, 147.10, 134.84, 124.26, 120.35, 114.76, 61.81, 56.01, 40.39, 18.56.

1-(3,5-dimethoxyphenyl)-2-methylpropan-1-one: (**Table 4.3, 2n**) Prepared from 1-(3,5-dimethoxyphenyl)prop-2-en-1-ol (0.097 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0854 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 2.3 Hz, 2H), 6.63 (t, *J* = 2.3 Hz, 1H), 3.82 (s, 6H), 3.48 (hept, *J* = 6.8 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.35, 160.99, 138.31, 106.24, 105.02, 55.66, 35.62, 19.34. HRMS (ESI): calcd for $C_{12}H_{16}O_3$ ($[M+H]^+$): 209.1172, found: 209.1188.

2-methyl-1-(naphthalen-1-yl)propan-1-one:[13b] (**Table 4.3, 2o**) Prepared from 1-(naphthalen-1-yl)prop-2-en-1-ol (0.092 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0713 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.3 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 7.1 Hz, 1H), 7.64 – 7.45 (m, 3H), 3.52 (hept, *J* = 6.5 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.20, 136.98, 133.98, 131.77, 130.53, 128.45, 127.64, 126.48, 125.97, 125.72, 124.50, 39.68, 18.79.

2-methyl-1-(naphthalen-2-yl)propan-1-one:[13b] (**Table 4.3, 2p**) Prepared from 1-(naphthalen-2-yl)prop-2-en-1-ol (0.092 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0753 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.04 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.93 – 7.84 (m, 2H), 7.64 – 7.50 (m, 2H), 3.73 (hept, *J* = 6.8 Hz, 1H), 1.29 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.68, 135.61, 133.63, 132.73, 129.84, 129.66, 128.58, 128.45, 127.87, 126.82, 124.47, 35.54, 19.43.

2-methyl-1-(thiophen-2-yl)propan-1-one:[13b] (**Table 4.3, 2q**) Prepared from 1-(thiophen-2-yl)prop-2-en-1-ol (0.070 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0555 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 3.7 Hz, 1H), 7.63 (d, *J* = 4.9 Hz, 1H), 7.13 (t, *J* = 4.1 Hz, 1H), 3.39 (hept, *J* = 6.9 Hz, 1H), 1.24 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.66, 143.80, 133.57, 131.70, 128.20, 37.35, 19.57.

1-(furan-2-yl)-2-methylpropan-1-one:[12f] (**Table 4.3, 2r**) Prepared from 1-(furan-2-yl)prop-2-en-1-ol (0.062 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.056 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 1.7 Hz, 1H), 7.19 (d, *J* = 3.9 Hz, 1H),

6.53 (dd, *J* = 3.5, 1.7 Hz, 1H), 3.33 (hept, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.85, 152.29, 146.36, 117.26, 112.23, 36.37, 18.90.

1-(4-(dimethylamino)phenyl)-2-methylpropan-1-one:[14g] (**Table 4.3, 2s**) Prepared from 1-(4-(dimethylamino)phenyl)prop-2-en-1-ol (0.089 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.080 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 9.1 Hz, 2H), 6.64 (d, *J* = 9.1 Hz, 2H), 3.50 (hept, *J* = 6.7 Hz, 1H), 3.03 (s, 6H), 1.18 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.88, 153.37, 130.61, 124.09, 110.84, 40.15, 34.49, 19.64.

2-methyl-1-phenylbutan-1-one:[15e] (**Table 4.3, 2t**) Prepared from 1-phenylprop-2-en-1-ol (0.067 g, 0.5 mmol) and EtOH (1ml). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0714 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.41 (sext, *J* = 6.7 Hz, 1H), 1.90 – 1.77 (m, 1H), 1.55 – 1.43 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.65, 136.90, 132.92, 128.72, 128.36, 42.22, 26.79, 16.89, 11.91.

2-methyl-1-phenylhexan-1-one:[12f] (**Table 4.3, 2u**) Prepared from 1-phenylprop-2-en-1-ol (0.067 g, 0.5 mmol) and *n*-butanol (1ml). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0801 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 2H), 7.55 (t, *J* = 7.1 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 3.46 (sext, *J* = 6.8 Hz, 1H), 1.88 – 1.71 (m, 1H), 1.51 – 1.37 (m, 1H), 1.34 – 1.25 (m, 4H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.95 – 0.77 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.70, 136.91, 132.90, 128.72, 128.35, 40.67, 33.57, 29.73, 22.93, 17.36, 14.08.

Analytical data for mechanistic study:

3-hydroxy-2-methyl-1-phenylpropan-1-one:[12e] (**Scheme 4.6, 3a**) A 50 mL round-bottom flask was charged with 5mL methanol, $NaHCO_3$ (50 mg, 0.6 mmol), 37% formaldehyde in H_2O (1.5 mL, 20.0 mmol) and propiophenone (1 mL, 1.0075 g, 7.5 mmol). The mixture was heated at 50 °C for 24 h. It was then cooled and acidified to pH 4 using conc. HCl. EtOAc (10 mL) was then added, and the mixture transferred to a separatory funnel. The organic layer was collected and the aqueous phase washed with EtOAc (2 x 10 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (*n*-hexane/ EtOAc: 80:20) gave a colourless oil (0.750 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.1 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 3.94 (dd, *J* = 11.1, 7.0 Hz, 1H), 3.81 (dd, *J* = 11.1, 4.1 Hz, 1H), 3.71 – 3.62 (m, 1H), 1.24 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.62, 136.25, 133.47, 128.86, 128.55, 64.68, 43.04, 14.71.

2-methyl-1-phenylprop-2-en-1-one:[12e] (**Scheme 4.6, 3b**) and **3-methoxy-2-methyl-1-phenylpropan-1-one:**[12e] (**Scheme 4.6, 3c**) A 50 mL round-bottomed flask was charged with 5ml methanol, 0.5 N NaOH (20 mL, 10.0 mmol), 37% formaldehyde in H_2O (1.0 mL, 13.2 mmol) and 1ml propiophenone (1.0075 g, 7.5 mmol). The mixture was left to react at rt for 24 h. It was then cooled and acidified to pH 4 using conc. HCl. EtOAc (10 mL) was then added, and the mixture transferred to a separatory funnel. The organic layer was collected and the aqueous phase washed with EtOAc (2 x 10 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (*n*-hexane/ EtOAc: 99:1-80:20) gave 2-methyl-1-phenylprop-2-en-1-one (*n*-hexane/ EtOAc: 98:2), as a colourless oil (0.378 g, 34%), and 3-methoxy-2-methyl-1- phenylpropan-1-one (*n*-hexane/ EtOAc: 80:20), as

a colourless oil (0.507 g, 38%). **Data for 2-methyl-1-phenylprop-2-en-1-one:** (**Scheme 4.6, 3b**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 2H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 5.93 – 5.88 (m, 1H), 5.64 – 5.60 (m, 1H), 2.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.53, 143.87, 137.83, 132.14, 129.54, 128.27, 127.28, 18.77. **Data for 3-methoxy-2-methyl-1-phenylpropan-1-one:** (**Scheme 4.6, 3c**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.9 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 3.83 – 3.72 (m, 2H), 3.45 (h, *J* = 5.2 Hz, 1H), 3.31 (s, 3H), 1.20 (d, *J* = 5.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.85, 136.73, 133.14, 128.72, 128.48, 75.06, 59.20, 41.33, 14.95.

2-methyl-1,3-diphenylprop-2-en-1-ol: (**Scheme 4.6, 3d**) Prepared from propiophenone (0.40 g, 3 mmol) and benzaldehyde (0.318 g, 3 mmol) according to procedure in **Method-2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.6 Hz, 2H), 7.41 – 7.29 (m, 7H), 7.27 – 7.22 (m, 1H), 6.80 (s, 1H), 5.29 (s, 1H), 1.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.16, 139.66, 137.59, 129.17, 128.55, 128.53, 128.27, 127.74, 126.68, 126.60, 126.08, 79.61, 14.19.

2-methyl-1-phenylpropan-1-one-2,3,3,3-*d*4:[13b] (**Scheme 4.7, 3e**) Prepared from 1-phenylprop-2-en-1-ol (0.067 g, 0.5 mmol) and CD_3OD (1mL). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.0578 g, 86%).

Deuterium incorporation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.12/1)*100) = 88% D

Peak B: 100-((2.71/6)*100) = 55% D

1-phenyl-2-(phenylmethyl-*d*)propan-1-one-2,3,3,3-*d*4 : (**Scheme 4.7, 3f**) Prepared from 1,3-diphenylprop-2-en-1-ol (0.105 g, 0.5 mmol) and CD_3OD (1mL). After

purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a yellowish liquid (0.095 g, 83%). HRMS (ESI): calcd for $C_{16}H_{11}D_5O$ ($[M+Na]^+$): 252.1407, found: 252.1428.

Deuterium incorporation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.07/1)*100) = 93% D

Peak B: 100-((0.75/2)*100) = 62.5% D.

Peak C: 100-((0.34/3)*100) = 89% D

4.5. References

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CHAPTER 5

Ruthenium catalyzed one-pot sequential synthesis of substituted pyridines from allyl alcohols and methanol *via* isomerization-methylenation

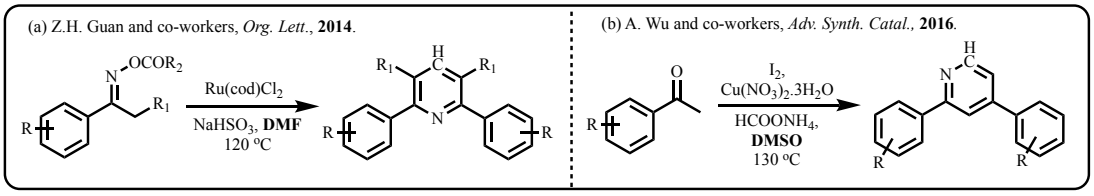
5.1. Introduction

One-pot multicomponent reactions have emerged as a powerful and efficient tool in organic synthesis for new bond formation. This strategy offers significant advantages over conventional multistep synthesis due to their flexible, convergent, and atom economic nature.[1] This strategy also represents as one of the environmentally friendly processes by reducing the number of steps, energy consumption, and waste production. In this context, borrowing hydrogen (BH) and interrupted borrowing hydrogen (I-BH) strategy received special attention as these protocols uses alcohols as the alkyl sources.[2,3] Among all alcohols, methanol received special attention as an alternate green C1 source utilizing BH and I-BH methods over the traditional methylating reagents due to its low-cost, abundance and environmentally friendly by-products.[3] One of the most significant transformations in organic chemistry is the direct methylenation or methylation of C-H bonds.[3] However, the utilisation of these in situ formed C-methylenation intermediates to create heterocyclic systems in a single pot is scarily reported,[4] due to the of suitable methods which can hinder the over reduction of the C-methylenation intermediates.[3a-3d, 5]

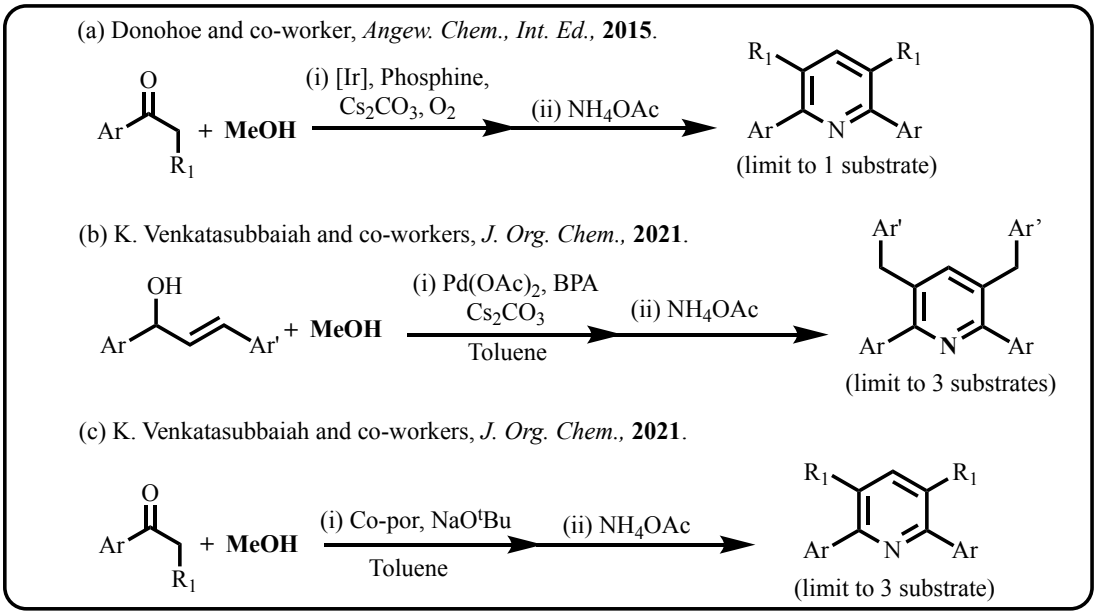
Among various heterocycles, pyridines and their benzo-/hetero-fused analogues play prominent role due to their diverse applications in agrochemical, pharmaceutical and material science.[6] Many pyridine derivatives were found in natural products,[7] for example nicotinic acid and pyridoxine as part of Vitamin B3 and Vitamin B6 respectively. Polysubstituted pyridines[8] with aryl substituents are essential functional moieties that have found useful applications as chemo sensors,[9] molecular electronics[10] and pharmaceuticals.[11] In particular, symmetrical pyridines exhibit high biological activity.[12] The diverse bioactivities of these pyridine derivatives have persistently attracted the attention of the scientific community for more than 140 years. Owing to

the growing importance of pyridines, various methods, such as condensation of amines and carbonyl compounds,[6d,13] transition metal catalysed cycloaddition reactions,[14] and cyclo-isomerization reactions[15] have been established for the synthesis of pyridines (**Scheme 5.1**). However, these methods are mainly focused on versatile unsymmetrical substituted pyridines; whereas protocol for the synthesis of valuable symmetrical pyridines has been less explored.[16] The search for new strategies that offer alternate methods to access highly functionalized symmetrical pyridine derivatives under mild reaction conditions using naturally abundant precursors are always in demand.

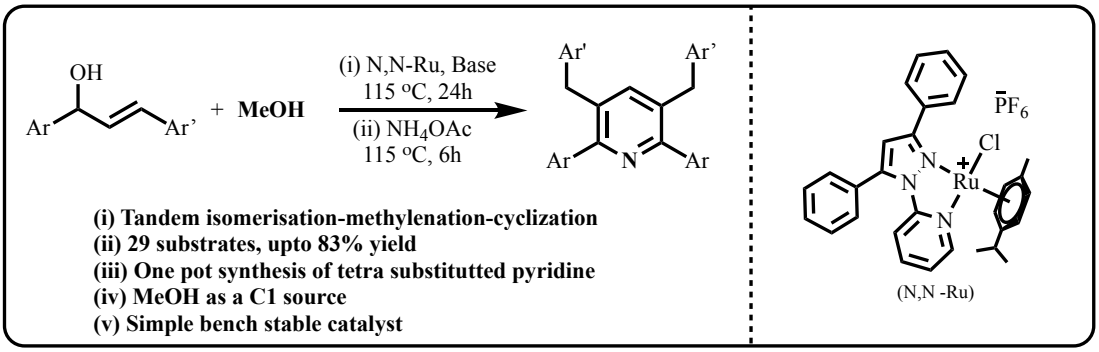
Allyl alcohols act as structural building blocks in organic synthesis because they operate as an excellent source of the corresponding ketone or enolate source *via* redox isomerisation.[17] The redox isomerisation process is an atom economical process and avoids the employment of any stoichiometric quantity of hazardous and expensive reagents. Utilising this process allyl alcohols are also employed in tandem-isomerisation functionalisation reaction for the production of C-C and C-heteroatom bonds. However, there have been only three reports for the synthesis of tetra substituted pyridines from ketones or allyl alcohols using methanol as a C1 source. Donohoe and co-workers[3i] for the first-time, reported the synthesis of one symmetrical and two unsymmetrical tetra substituted pyridines from ketones utilizing methanol as a C1 source, catalyzed by an Ir-complex (**Scheme 5.2.a**). Recently, we reported a palladium BINOL phosphoric system[3g] and Cobalt porphyrin system[3c] for the synthesis of 1,5-diketones, from allyl alcohols and ketones respectively utilising methanol *via* I-BH method. We further showed a limited scope for the synthesis of pyridines through a sequential manner (**Scheme 5.2.b & c**). In this chapter, we report ruthenium catalysed one pot sequential synthesis of substituted symmetrical pyridines utilising methanol as a C1 source through I-BH approach (**Scheme 5.3**).



Scheme 5.1. Catalytic synthesis of pyridine utilising methylating reagents



Scheme 5.2. Catalytic synthesis of pyridine utilising methanol as a C1 source



Scheme 5.3. Our approach, ruthenium catalysed tetra substituted pyridine synthesis from allyl alcohol utilising methanol as a C1 source

5.2. Results and discussion:

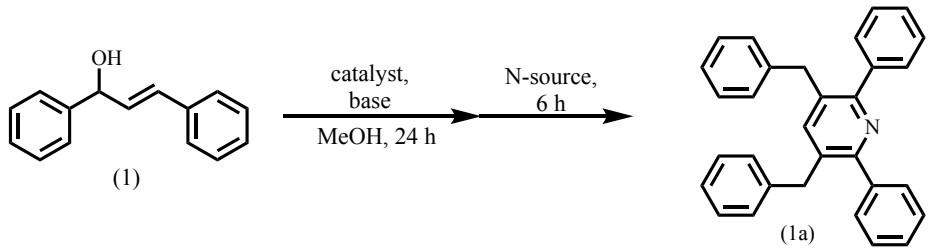
Recently, we reported a ligand-controlled ruthenium catalyzed borrowing hydrogen and interrupted borrowing hydrogen methodologies, where the reaction of ketones with methanol in the presence of N,N-Ru catalyst produced the I-BH product.[18]

To explore the catalytic activity of our N,N- Ru catalyst we examined it further for the synthesis of tetrasubstituted symmetrical pyridines through isomerisation-methylenation of allyl alcohol followed by sequential addition of ammonium acetate in one-pot.

1,3-Diphenylprop-2-en-1-ol (**1**) was chosen as a model substrate to evaluate the reaction parameters such as catalyst, base, temperature and nitrogen source for the synthesis of symmetrical pyridine in a one-pot sequential manner (**Table 5.1**). Following our recent study[18] of I-BH protocol, we started the reaction with 1 mol% of N,N-Ru catalyst, with 0.5 equivalent of KOH at 100 ^{o}C for 24h, followed by adding two equivalent of ammonium acetate and stirring the reaction mixture for additional 6h. To our delight, this conditions resulted 35% of the tetra substituted pyridine(**1a**) (**Table 5.1,** entry **1**). Further study reveal that KOH turned out to be the effective base among the different base studied (KOH, NaOH, LiOH, NaO^{t}Bu, KO^{t}Bu, K_2CO_3 and Na_2CO_3) (**Table 5.1,** entries **1-7**). Changing the temperature to 115 °C and the base to 1.5 equivalent provide the symmetrical pyridine in 81% (**Table 5.1,** entry **11**). Conducting the reaction at 120 °C resulted in a lower yield of the desired symmetrical pyridine product (**Table 5.1**, entry **12**). The increase in catalyst and base loading showed an adverse effect on product yield (**Table 5.1**, entries **13-14**). Among different nitrogen sources screened, ammonium acetate is found to be the best choice (**Table 5.1**, entries **15-17**). Furthermore, the reactivity of different ruthenium metal sources such as $RuCl_3.\ H_2O$ and $[RuCl_2(p\text{-cymen})]_2$ as catalysts were studied under the optimized conditions, which resulted in a lower yield of the desired pyridine product (**Table 5.1,** entries **18-19**). Use of 1mol% of N,N-Ru catalyst, 1.5 equiv of KOH and 2 equiv of ammonium acetate in MeOH (1 mL) at 115 °C for 30 h produced the desired pyridine

(**1a**) in 81% yield (**Table 5.1,** entry **11**). The pyridine formation was confirmed using NMR and HRMS analysis.

Table 5.1. Optimisation table for the synthesis of tetra substituted pyridine through a ruthenium catalysed isomerisation-methylenation process[a]



Entry	Catalyst (mol%)	Base (equiv.)	Nitrogen Source (equiv.)	Temperature (°C) [c]	Yield (%) [b]
1	N,N-Ru (1)	KOH (0.5)	NH_4OAc (2 equiv.)	100 °C	35
2	N,N-Ru (1)	NaOH (0.5)	NH_4OAc (2 equiv.)	100 °C	27
3	N,N-Ru (1)	LiOH (0.5)	NH_4OAc (2 equiv.)	100 °C	22
4	N,N-Ru (1)	KO^{t}Bu (0.5)	NH_4OAc (2 equiv.)	100 °C	Trace
5	N,N-Ru (1)	NaO^{t}Bu (0.5)	NH_4OAc (2 equiv.)	100 °C	Trace
6	N,N-Ru (1)	K_2CO_3 (0.5)	NH_4OAc (2 equiv.)	100 °C	Trace
7	N,N-Ru (1)	Na_2CO_3 (0.5)	NH_4OAc (2 equiv.)	100 °C	Trace
8	N,N-Ru (1)	KOH (1)	NH_4OAc (2 equiv.)	100 °C	54
9	N,N-Ru (1)	KOH (1.5)	NH_4OAc (2 equiv.)	100 °C	61
10	N,N-Ru (1)	KOH (1.5)	NH_4OAc (2 equiv.)	110 °C	69
11	**N,N-Ru (1)**	**KOH (1.5)**	**NH_4OAc (2 equiv.)**	**115 °C**	**81**
12	N,N-Ru (1)	KOH (1.5)	NH_4OAc (2 equiv.)	120 °C	72
13	N,N-Ru (1)	KOH (2)	NH_4OAc (2 equiv.)	115 °C	80
14	N,N-Ru (2)	KOH (1.5)	NH_4OAc (2 equiv.)	115 °C	65
15	N,N-Ru (1)	KOH (1.5)	NH_4OAc (3 equiv.)	115 °C	81
16	N,N-Ru (1)	KOH (1.5)	$NH_2OH.HCl$ (2 equiv.)	115 °C	75
17[d]	N,N-Ru (1)	KOH (1.5)	$NH_2NH_2.H_2O$ (2 equiv.)	115 °C	74
18	$RuCl_3.xH_2O$ (1)	KOH (1.5)	NH_4OAc (2 equiv.)	115 °C	27

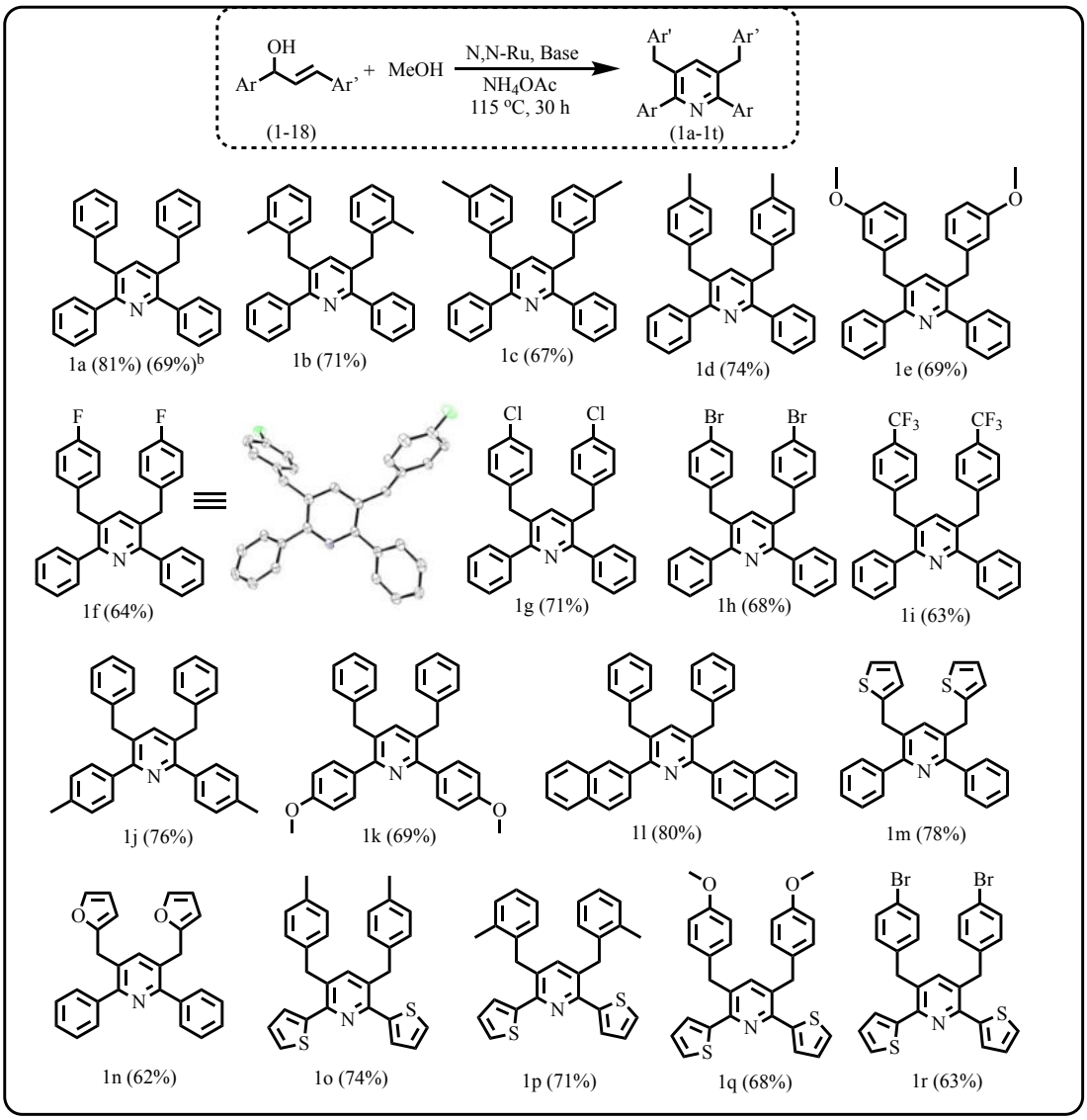
19	[Ru(p-cymene) Cl_2]$_2$ (0.5)	KOH (1.5)	NH_4OAc (2 equiv.)	115 °C	31

[a]Reaction conditions: 1,3-diphenylprop-2-en-1-ol (0.5 mmol), base, catalyst. [b]All yields are isolated yields. [c]Reactions were performed at temperature100-120 °C (oil bath temperature) for 30 h. [d]0.5 mL Acetic acid was added after 24 h along with nitrogen source.

Having the optimised conditions in hand, the scope of the ruthenium-catalysed isomerisation-methylenation of a variety of allylic alcohols were explored (**Table 5.2**). Substrates with diverse aromatic substituents at the 1- and 3-positions of allylic alcohols provided the corresponding symmetrical pyridines in good yield. Aryl units at the 3-position of allyl alcohol having *o,m,p*-CH_3 and *m,p*-OCH_3 substituents, were tolerated and afforded the corresponding tetra substituted pyridine products **1b-1e** in good yields 1b (71%), 1c (67%), 1d (74%) and 1e (69%) under the optimized conditions (**Table 5.2**). Aryl substrates with electron-withdrawing substituents (-F, -Cl, -Br, -CF_3) at the 3-position of allylic alcohols performed well under this catalytic system giving the corresponding tetra substituted pyridine products **1f-1i** in good yield of 64%, 71%, 68% and 63% respectively (**Table 5.2**). To our delight compound **1f** crystallized in a triclinic system (P-1) which was analysed using single crystal X-ray crystallography. Heteroaryl such as thiophene and furyl at the 3-position of allylic alcohols were found to be active enough to yield the desired pyridine products **1m & 1n** in 78%, and 62% respectively (**Table 5.2**). Furthermore, substrates bearing naphthyl group and *p*-CH_3 and *p*-OCH_3 substituents on the aryl group at the 1-position of allylic alcohol under similar reaction conditions yielded the desired tetra substituted pyridines **1j-1l** in good yield of 76%, 69% and 80% respectively (**Table 5.2**). To our surprise allyl alcohol having thiophene group at the 1-position also showed good activity under the reaction conditions. Thio

allyl alcohols with electron-donating and electron-withdrawing substituents on the aryl group at the 3-position yielded the corresponding pyridine products **1o-1r** in good yields of 74%, 71%, 68%, 63% and 60% respectively (**Table 5.2**). Unfortunately, allyl alcohols having aryl substrates with -NO_2 and -CN groups gave a complex mixture.

Table 5.2. Substrate scope for tetra substituted pyridines from 1,3-diaryl propenols and methanol[a]

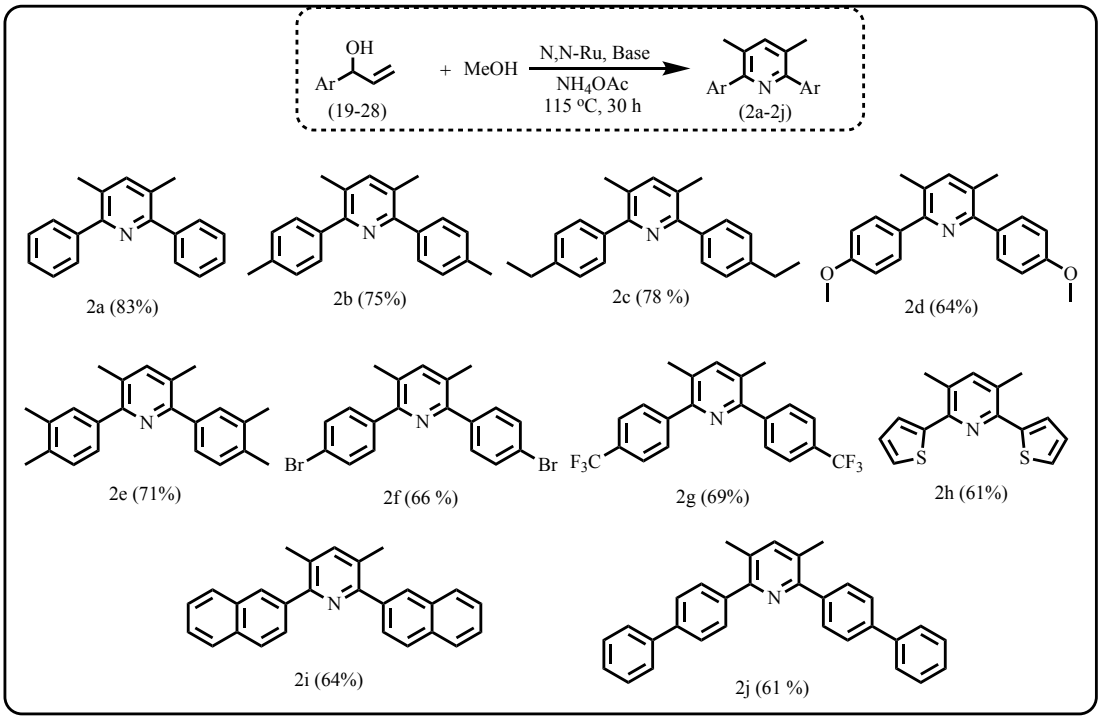


[a]Reaction conditions: allyl alcohol 0.5 mmol, KOH 1.5 equiv., N,N-Ru catalyst 0.5 x 10^{-2}. All yields are isolated yields. [b]Isolated yield of the gram scale reaction.

To check the synthetic utility of our methodology, a gram scale reaction was carried out using 1,3-Diphenylprop-2-en-1-ol (**1**) which produced the corresponding pyridine product **1a** in 69% yield.

Further, we extended our catalytic protocol to achieve isomerisation-methylenation of variety of 1-aryl propenols (**Table 5.3**). Under the optimised conditions mentioned above, different electron-donating substituents (*p*-CH_3, *p*-C_2H_5, *p*-OCH_3) at the aryl group of allylic alcohols produced the desired pyridine products **2a-2d** in good yields 2a (83%), 2b (75%), 2c (78%) and 2d (64%) (**Table 5.3**). Our catalytic system also showed good activity towards the aryl substrates with electron-withdrawing substituents (*p*-Br, *p*-CF_3) at the aryl group of allylic alcohol to yield the corresponding tetra substituted pyridine products **2f & 2g** in good yield of 74% and 69% respectively (**Table 5.3**).

Table-5.3. Substrate scope for tetra substituted pyridines from 1-aryl propenols and methanol[a]

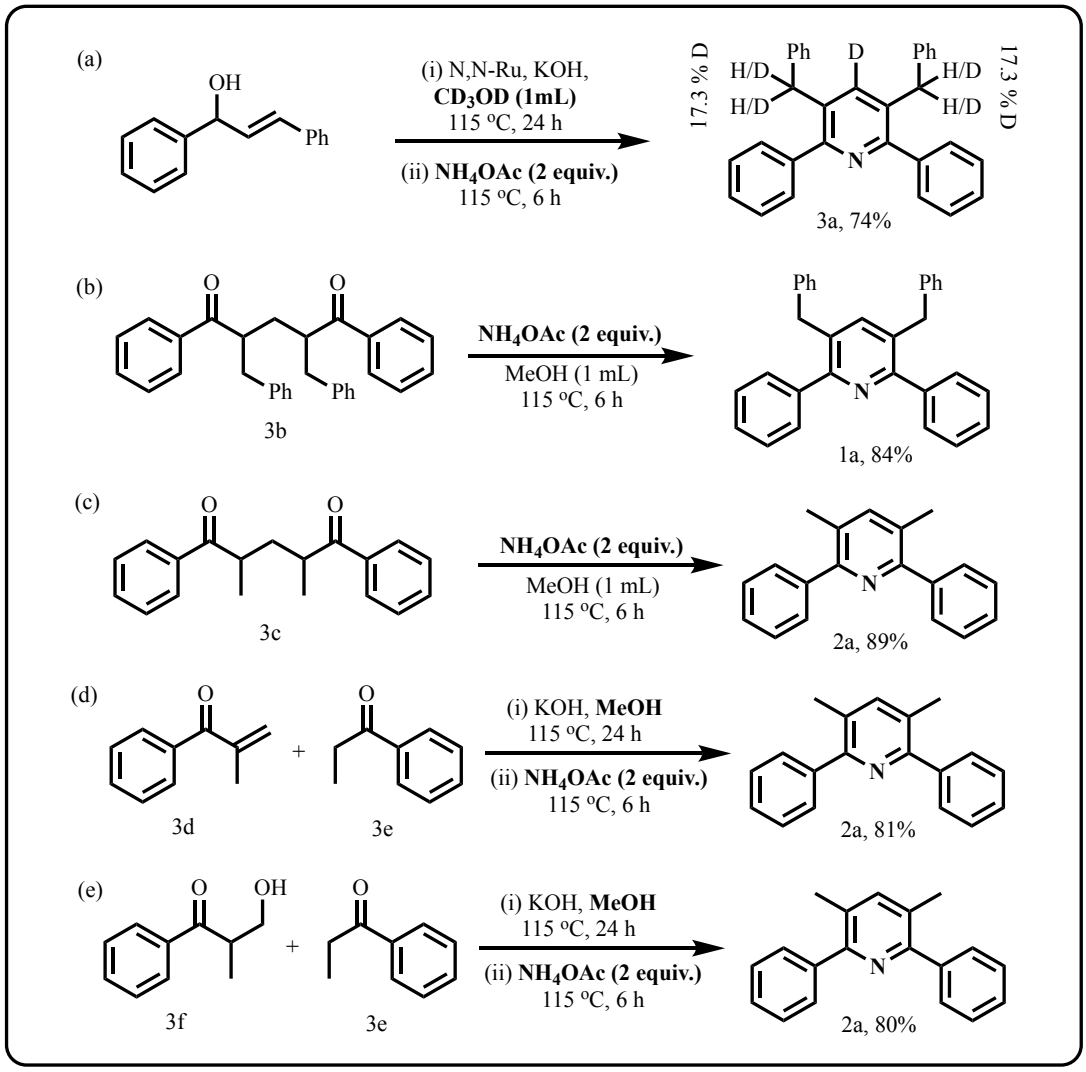


[a]Reaction conditions: allyl alcohol 0.5 mmol, KOH 1.5 equiv., N,N-Ru catalyst 0.5 x 10^{-2}. All yields are isolated yields.

Notably, sterically demanding di-methyl substituted aryl group was tolerated under the optimized conditions and provided the pyridine product **2e in** 71% yield (**Table 5.3**). Apart from that biphenyl- and naphthyl-propenols were also participated in the isomerisation-methylation process to yield the products **2i** & **2j** in 64% & 61% respectively. Interestingly, hetero aryl-propenol also participated in the reaction to furnish the desired product **2h** in 61% yield (**Table 5.3**).

Control experiments were performed to understand the mechanism involved in this reaction (**Scheme 5.4**). From the literature studies,[3c, g, i] we realised that the reaction proceeds *via* 1,5-diketone. To test this, we reacted 1,5-diketones (**3b** and **3c)** with ammonium acetate which resulted in to the pyridine products **1a** & **2a** in 86 % and 89% yield respectively. It is established that allyl alcohol generates saturated ketone or enolate precursor in the presence of metal catalyst *via* redox isomerisation. We believe that saturated ketone under goes I-BH protocol in the presence of MeOH to generate α-methylene intermediate, which further generates 1,5-diketone through Michael addition and subsequently reacts with ammonium acetate to produce the desired pyridine product. To confirm this hypothesis we reacted the expected I-BH intermediates **3d** & **3f** with saturated ketone **3e** under the optimised conditions without using N,N-Ru catalyst. As expected the desired pyridine product was observed, which confirms the formation of 1,5-diketone product. To get more insight, isotope labelled experiment was performed utilising 1,3-Diphenylprop-2-en-1-ol (**1**) and deuterated methanol under the optimised conditions which resulted the pyridine product **3a** in 74% yield. A 100% D in the pyridine ring of 3a, demonstrating that the methylene bridge is produced by an I-BH protocol using methanol, and 34.5% D in the side chain, indicating that redox

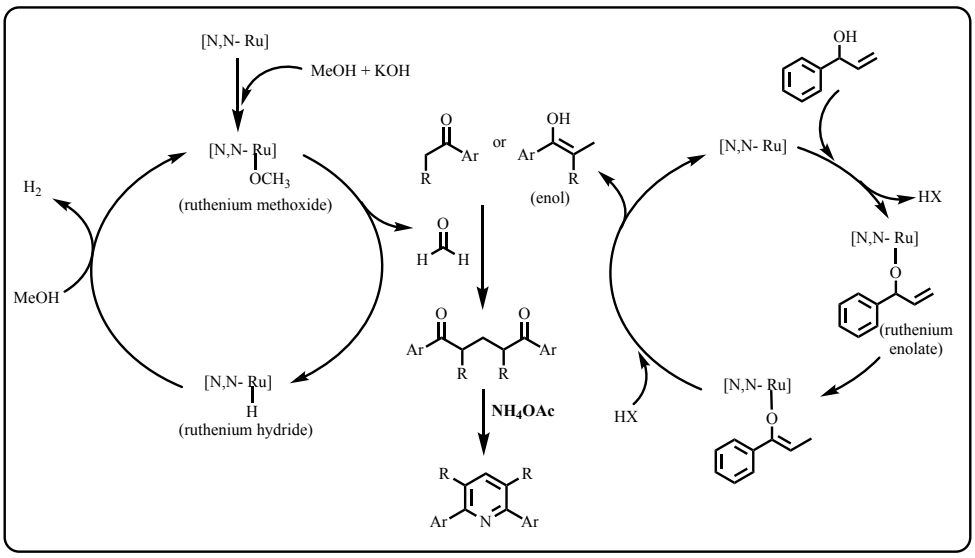
isomerisation of allyl alcohol occurs *via* a 1,4-hydride addition from metal hydride species.



Scheme 5.4. Mechanistic study for formation of substituted pyridines

Based on the previous reports [3c, g, i] and control experiments studied, we propose a plausible reaction mechanism for the isomerisation-methylenation of allyl alcohol to synthesize tetra substituted pyridine (**Scheme 5.5**). We hypothesise that the initial step involves the formation of methoxide species, which then proceed *via* a β-hydride elimination to generate the reactive formaldehyde, simultaneously allylic alcohol undergoes a redox isomerisation to obtain the corresponding enolate or ketone precursor. The metal hydride species reacts with another molecule of MeOH to generate

the metal methoxide species with the liberation of H_2 gas. Ketone or enolate precursor produced by allyl alcohol reacts with *in situ* generated formaldehyde to give the corresponding aldol product (β- hydroxy ketone (**3f**)), further *via* elimination it generates the enone intermediate (α,β-unsaturated ketone (**3e**)). The enone intermediate by reacting with another molecule of ketone or enolate generates the corresponding 1,5-diketone, which upon sequential addition with ammonium acetate leads to the formation of the desired tetra substituted pyridine product.



Scheme 5.5. Proposed mechanism for formation of substituted pyridines

Table 5.4. Crystal data and structure refinement data for compound 1f

Identification code	Compound **1f**
Empirical formula	$C_{31}H_{23}F_2N$
Formula weight	447.50
Temperature/K	100.00(10)
Crystal system	triclinic
Space group	P-1
a/Å	9.4134(5)

b/Å	10.6542(7)
c/Å	12.1372(7)
α/°	90.043(5)
β/°	104.592(5)
γ/°	106.186(5)
Volume/Å^3	1128.00(12)
Z	2
ρ_{calc}g/cm^3	1.318
μ/mm^{-1}	0.087
F(000)	468.0
Crystal size/mm^3	0.12 × 0.12 × 0.12
Radiation	Mo Kα (λ = 0.71073)
2Θ range for data collection/°	6.748 to 60.876
Index ranges	-12 ≤ h ≤ 13, -13 ≤ k ≤ 13, -16 ≤ l ≤ 16
Reflections collected	19511
Independent reflections	5470 [R_{int} = 0.0995, R_{sigma} = 0.0676]
Data/restraints/parameters	5470/0/307
Goodness-of-fit on F^2	1.055
Final R indexes [I>=2σ (I)]	R_1 = 0.0776, wR_2 = 0.2082
Final R indexes [all data]	R_1 = 0.0931, wR_2 = 0.2202
Largest diff. peak/hole / e Å^{-3}	0.80/-0.34

5.3. Conclusion

In conclusion, an operationally simple and efficient catalytic protocol was developed using a ruthenium catalyst which involves one-pot isomerisation-methylenation of allyl alcohol using methanol, followed by sequential addition of ammonium acetate to generate tetra substituted pyridines. A variety of secondary allylic alcohols were transformed to tetra substituted symmetrical pyridines (up to 83% isolated yield) with good yields and excellent functional group tolerance. The participation of the enone intermediate, metal hydride species formed by β-hydride elimination of methanol and metal enolate precursor is confirmed by the control reactions and deuterated study. This reactive enone intermediate generates the corresponding 1,5-diketone by coupling with another molecule of ketone, which leads to the formation of the desired tetra substituted pyridine product by successive addition of ammonium acetate.

5.4. Experimental section

5.4.1. General information

All reagents and solvents were obtained from commercial sources. All the starting materials were synthesized according to literature procedures.[18,19] Solvents were purified according to standard procedures. All 400 MHz ^{1}H, 100 MHz ^{13}C, 376 MHz ^{19}F spectra were recorded on a spectrometer operating at 400 MHz. All ^{1}H and ^{13}C NMR spectra were referenced internally to solvent signals and ^{19}F NMR spectra were externally referenced to α,α,α-trifluorotoluene in $CDCl_3$ (δ = -63.73 ppm).

General procedure for the synthesis of mono phenyl allyl alcohols:[19]

An oven-dried Schlenk tube under N_2 atmosphere was charged with aldehyde (3.0 mmol) in dry THF (3 mL). Under inert atmosphere, vinyl magnesium bromide (3.6 mL, 3.6 mmol, 1 M in THF) at -78 °C, was added to the reaction mixture (drop wise) with continues stirring. Then the reaction mixture was stirred at room temperature for 12h.

The reaction was quenched with sat. aq. NH_4Cl (2 mL) and the mixture was transferred to a separatory funnel and extracted using EtOAc (2x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the allyl alcohol in high purity. All the mono phenyl allyl alcohols were synthesized according to this procedure .

General procedure for the synthesis of bi-phenyl allyl alcohols:[20]

An oven-dried RB Flask was charged with substituted acetophenone (2.5 mmol, 1.0 equiv) in methanol (10 mL) at 0 °C; to this solution aqueous NaOH (10%) was added dropwise and stirred at room temperature for 1 hour. Then, substituted benzaldehyde (2.5 mmol, 1.0 equiv) was added slowly to the reaction mixture and stirred at room temperature. Progress of the reaction was monitored by TLC. After complete consumption of the starting material, solvent was removed under vacuum and the residue was treat with H_2O (5 mL), EtOAc (15 mL). The organic layer was extracted with EtOAc (3 x 10 mL) and the combined organic mixture was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude mixture using silica-gel column chromatography yielded the desired α,β-unsaturated ketone. In next step sodium borohydride (3.0 mmol, 1.2 equiv) was added to the stirred solution of α,β-unsaturated ketone (2.5 mmol, 1.0 equiv) in MeOH: THF (10 mL, 1:1) at 0 °C and the reaction mixture was further stirred at room temperature. The solvent from the reaction mixture was evaporated in vacuum, and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using *n*-hexane and ethyl acetate mixtures to afford the allyl alcohol in high purity. All the diphenyl allyl alcohols were synthesized according to this procedure .

5.4.2. General procedure for pyridine synthesis

An oven-dried pressure tube was charged with N,N-ruthenacycle (0.5x 10^{-2} mmol), KOH (1.5 mmol), allyl alcohol (0.5 mmol) and 1mL of MeOH in an open atmosphere, then the tube was closed with the cap and the reaction mixture was stirred at 115 °C for 24 h. The reaction mixture was cooled to room temperature followed by the addition of NH_4OAc (1 mmol) and further heated at 115 °C for another 6 h. The reaction mixture was cooled to room temperature, the contents of the reaction mixture were dissolved in dichloromethane (15 mL), and concentrated under vacuum. The crude mixture was subjected to column chromatography using *n*-hexane and ethyl acetate mixtures to afford the corresponding symmetrical pyridines in high purity.

Procedure for gram scale synthesis of pyridine:

An oven-dried pressure tube was charged with N,N-ruthenacycle (2.5x 10^{-2} mmol), KOH (7.5 mmol), allyl alcohol (2.5 mmol) and 5mL of MeOH in an open atmosphere then the tube was closed with a cap and the reaction mixture was stirred at 115 °C for 24 h. The reaction mixture was cooled to room temperature followed by the addition of NH_4OAc (5 mmol) and further heated at 115 °C for another 6 h. The reaction mixture was cooled to room temperature, the contents of the reaction mixture were dissolved in dichloromethane (3 x 15mL), and concentrated under vacuum. The crude mixture was subjected to column chromatography on silica gel using n-hexane and ethyl acetate mixtures to afford the symmetrical pyridine compound was isolated as a light-yellow solid (0.71 g, 69%).

5.4.3. Analytical data for pyridine compounds

3,5-dibenzyl-2,6-diphenylpyridine: (Table 5.2, 1a)[3g] Prepared from 1,3-diphenylprop-2-en-1-ol (0.105 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow

solid (0.083 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 4H), 7.42 – 7.35 (m, 7H), 7.26 – 7.22 (m, 4H), 7.19 (d, *J* = 7.2 Hz, 2H), 7.00 (d, *J* = 7.0 Hz, 4H), 4.03 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.71, 140.55, 140.18, 132.58, 129.41, 128.88, 128.61, 128.26, 128.07, 126.30, 38.29. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{31}H_{25}N+H]^+$: 412.2060, found: 412.2060.

3,5-bis(2-methylbenzyl)-2,6-diphenylpyridine: (Table 5.2, 1b) Prepared from (*E*)-1-phenyl-3-(*o*-tolyl)prop-2-en-1-ol (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.078 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.8 Hz, 4H), 7.45 – 7.36 (m, 6H), 7.13 – 7.05 (m, 6H), 7.02 (s, 1H), 6.90 (d, *J* = 7.1 Hz, 2H), 3.94 (s, 4H), 2.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.30, 140.39, 139.9, 138.48, 136.37, 132.06, 130.36, 129.44, 129.30, 128.29, 128.17, 126.58, 126.15, 36.14, 19.57. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{33}H_{29}N+H]^+$: 440.2373: found 440.2397.

3,5-bis(3-methylbenzyl)-2,6-diphenylpyridine: (Table 5.2, 1c) Prepared from (*E*)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-ol (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.073 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.7 Hz, 4H), 7.43 – 7.36 (m, 7H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.00 (d, *J* = 7.4 Hz, 2H), 6.80 (d, *J* = 7.6 Hz, 4H), 3.99 (s, 4H), 2.28 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.49, 141.41, 140.42, 139.98, 138.19, 132.73, 129.64, 129.44, 128.48, 128.25, 128.12, 127.03, 125.92, 38.15, 21.53. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{33}H_{29}N+H]^+$: 440.2373: found 440.2358.

3,5-bis(4-methylbenzyl)-2,6-diphenylpyridine: (Table 5.2, 1d) Prepared from (*E*)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-ol (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow

solid (0.081 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.8 Hz, 4H), 7.43 – 7.38 (m, 6H), 7.37 (s, 1H), 7.07 (d, *J* = 7.9 Hz, 4H), 6.90 (d, *J* = 8.0 Hz, 4H), 4.00 (s, 4H), 2.33 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.75, 156.53, 142.14, 141.21, 140.19, 137.50, 135.75, 132.76, 129.41, 129.28, 128.72, 128.23, 128.03, 37.80, 21.14. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{33}H_{29}N+H]^+$: 440.2373: found 440.2361.

3,5-bis(3-methoxybenzyl)-2,6-diphenylpyridine: (Table 5.2, 1e) Prepared from (*E*)-3-(3-methoxyphenyl)-1-phenylprop-2-en-1-ol (0.120 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 95:5), the compound was isolated as a light yellow solid (0.081 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.2 Hz, 4H), 7.46 – 7.37 (m, 7H), 7.19 (t, *J* = 7.9 Hz, 2H), 6.75 (d, *J* = 8.3 Hz, 2H), 6.64 (d, *J* = 7.5 Hz, 2H), 6.56 (s, 2H), 4.03 (s, 4H), 3.74 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.75, 142.14, 141.13, 140.20, 132.33, 129.53, 129.37, 128.23, 128.02, 121.23, 114.42, 111.70, 55.17, 38.26. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{33}H_{29}NO_2+H]^+$: 472.2271: found 472.2286.

3,5-bis(4-fluorobenzyl)-2,6-diphenylpyridine: (Table 5.2, 1f) Prepared from (*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-ol (0.114 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 95:5), the compound was isolated as a light yellow solid (0.071 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m, 4H), 7.43 – 7.36 (m, 6H), 7.30 (s, 1H), 6.93 (d, *J* = 7.1 Hz, 8H), 4.00 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.51 (d, *J* = 244.6 Hz), 156.77, 140.79, 139.98, 136.04 (d, *J* = 3.2 Hz), 132.59, 130.24 (d, *J* = 7.9 Hz), 129.28, 128.31, 128.17, 115.39 (d, *J* = 21.3 Hz), 37.51. ^{19}F NMR (376 MHz, $CDCl_3$) δ -116.40. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{31}H_{23}F_2N+H]^+$: 448.1871, found: 448.1894.

3,5-bis(4-chlorobenzyl)-2,6-diphenylpyridine: (Table 5.2, 1g) Prepared from (*E*)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-ol (0.122 g, 0.5 mmol). After purification by

column chromatography (*n*-hexane/ EtOAc: 95:5), the compound was isolated as a light yellow solid (0.085 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 4H), 7.43 – 7.36 (m, 6H), 7.28 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 4H), 6.90 (d, *J* = 8.4 Hz, 4H), 3.99 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.91, 140.81, 139.93, 138.85, 132.22, 132.21, 130.18, 129.27, 128.73, 128.36, 128.24, 37.69.

3,5-bis(4-bromobenzyl)-2,6-diphenylpyridine: (Table 5.2, 1h) Prepared from (*E*)-3-(4-bromophenyl)-1-phenylprop-2-en-1-ol (0.144 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 95:5), the compound was isolated as a light yellow solid (0.096 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.6 Hz, 4H), 7.44 – 7.37 (m, 6H), 7.30 (s, 1H), 7.21 (d, *J* = 8.4 Hz, 4H), 6.89 (d, *J* = 8.4 Hz, 4H), 3.99 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.69, 141.12, 139.42, 138.72, 132.48, 132.26, 130.17, 129.32, 128.76, 128.38, 37.65.

2,6-diphenyl-3,5-bis(4-(trifluoromethyl)benzyl)pyridine: (Table 5.2, 1i) Prepared from (*E*)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (0.139 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.166 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 8H), 7.43 – 7.38 (m, 6H), 7.29 (s, 1H), 7.08 (d, *J* = 8.1 Hz, 4H), 4.10 (s, 4H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.11, 144.38, 140.87, 139.68, 131.93, 129.27, 129.16, 128.44, 128.40, 125.57, 125.54, 38.15. ^{19}FNMR (376 MHz, $CDCl_3$) δ -62.28.

3,5-dibenzyl-2,6-di-*p*-tolylpyridine: (Table 5.2, 1j) Prepared from (*E*)-3-phenyl-1-(*p*-tolyl)prop-2-en-1-ol (0.112 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.083 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 4H), 7.36 (s, 1H), 7.27 – 7.18 (m, 10H), 7.01 (d, *J* = 7.0 Hz, 4H), 4.03 (s, 4H), 2.39 (s, 6H). ^{13}C NMR (101 MHz,

$CDCl_3$) δ 156.51, 141.39, 140.66, 137.85, 137.07, 132.30, 129.34, 128.91, 128.87, 128.59, 126.25, 38.23, 21.42. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{33}H_{29}N+H]^+$: 440.2373: found 440.2364.

3,5-dibenzyl-2,6-bis(4-methoxyphenyl)pyridine: (Table 5.2, 1k)[3i] Prepared from (*E*)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-ol (0.120 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.081 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.2 Hz, 4H), 7.44 (s, 1H), 7.24 (d, *J* = 7.4 Hz, 4H), 7.20 (d, *J* = 7.1 Hz, 2H), 6.99 (d, *J* = 7.1 Hz, 4H), 6.94 (d, *J* = 7.9 Hz, 4H), 4.03 (s, 4H), 3.83 (s, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 160.07, 155.43, 140.17, 133.04, 131.01, 128.83, 128.73, 128.51, 127.34, 126.47, 113.81, 55.47, 38.16. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{33}H_{29}NO_2+H]^+$: 472.2271: found 472.2256.

3,5-dibenzyl-2,6-di(naphthalen-2-yl)pyridine: (Table 5.2, 1l) Prepared from (*E*)-1-(naphthalen-2-yl)-3-phenylprop-2-en-1-ol (0.130 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.102 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.92 (d, *J* = 8.5 Hz, 2H), 7.90 – 7.86 (m, 2H), 7.84 – 7.80 (m, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.54 – 7.49 (m, 5H), 7.31 (s, 1H), 7.29 (d, *J* = 7.2 Hz, 3H), 7.23 (t, *J* = 7.1 Hz, 2H), 7.07 (d, *J* = 7.5 Hz, 4H), 4.14 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.77, 141.53, 140.61, 137.64, 133.16, 133.06, 132.79, 128.88, 128.66, 128.47, 127.93, 127.76, 127.43, 126.35, 126.30, 126.19, 38.45. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{39}H_{29}N+H]^+$: 512.2373, found: 512.2396.

2,6-diphenyl-3,5-bis(thiophen-2-ylmethyl)pyridine: (Table 5.2, 1m) Prepared from (*E*)-1-phenyl-3-(thiophen-2-yl)prop-2-en-1-ol (0.108 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a

light yellow solid (0.082 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.54 (d, *J* = 7.7 Hz, 4H), 7.44 – 7.37 (m, 6H), 7.16 (d, *J* = 5.2 Hz, 2H), 6.92 (dd, *J* = 5.1, 3.5 Hz, 2H), 6.68 (d, *J* = 3.4 Hz, 2H), 4.19 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.67, 143.39, 140.65, 139.71, 132.18, 129.34, 128.34, 128.28, 127.03, 125.57, 124.30, 32.82. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{27}H_{21}NS_2+H]^+$: 424.1188, found: 424.1188.

3,5-bis(furan-2-ylmethyl)-2,6-diphenylpyridine: (Table 5.2, 1n) Prepared from (*E*)-3-(furan-2-yl)-1-phenylprop-2-en-1-ol (0.100 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.060 g, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, 6H), 7.46 – 7.38 (m, 6H), 7.35 (s, 1H), 6.31 (d, *J* = 4.9 Hz, 2H), 5.95 (d, *J* = 3.1 Hz, 2H), 4.02 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.85, 153.85, 141.76, 140.40, 140.03, 129.85, 129.33, 128.29, 128.13, 110.43, 106.94, 31.37.

3,5-bis(4-methylbenzyl)-2,6-di(thiophen-2-yl)pyridine: (Table 5.2, 1o) Prepared from (*E*)-1-(thiophen-2-yl)-3-(*p*-tolyl)prop-2-en-1-ol (0.115 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.083 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, 6H), 7.29 (d, *J* = 3.7 Hz, 2H), 7.06 (s, 1H), 7.05 (d, *J* = 3.8 Hz, 1H), 7.04 (d, *J* = 3.7 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 4H), 4.19 (s, 4H), 1.58 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.39, 144.30, 142.59, 138.23, 131.95, 130.53, 129.59, 128.25, 127.87, 126.98, 120.54, 38.25. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{29}H_{25}NS_2+H]^+$: 452.1501, found: 452.1508.

3,5-bis(2-methylbenzyl)-2,6-di(thiophen-2-yl)pyridine: (Table 5.2, 1p) Prepared from (*E*)-1-(thiophen-2-yl)-3-(*o*-tolyl)prop-2-en-1-ol (0.115 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.080 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d,

J = 5.0 Hz, 2H), 7.31 (d, *J* = 3.4 Hz, 2H), 7.14 (d, *J* = 4.0 Hz, 4H), 7.09 – 7.03 (m, 4H), 6.87 (d, *J* = 7.4 Hz, 2H), 6.83 (s, 1H), 4.13 (s, 4H), 2.13 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.87, 144.72, 141.35, 137.31, 136.49, 130.49, 129.86, 129.15, 128.00, 127.89, 126.96, 126.86, 126.42, 36.97, 19.57. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{29}H_{25}NS_2+H]^+$: 452.1501, found: 452.1488.

3,5-bis(4-methoxybenzyl)-2,6-di(thiophen-2-yl)pyridine: (Table 5.2, 1q) Prepared from (*E*)-3-(4-methoxyphenyl)-1-(thiophen-2-yl)prop-2-en-1-ol (0.123 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.082 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 5.0 Hz, 2H), 7.41 – 7.35 (m, 2H), 7.20 (s, 1H), 7.10 – 7.03 (m, 2H), 6.98 (d, *J* = 8.4 Hz, 4H), 6.81 (d, *J* = 8.4 Hz, 4H), 4.17 (s, 4H), 3.79 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.36, 148.73, 143.26, 142.94, 131.58, 131.10, 129.85, 128.31, 127.84, 114.30, 55.38, 37.94. HRMS (ESI-TOF) *m/z* $[M+H]^+$ Calcd for $[C_{29}H_{25}NO_2S_2+H]^+$: 484.1399, found: 484.1411.

3,5-bis(4-bromobenzyl)-2,6-di(thiophen-2-yl)pyridine: (Table 5.2, 1r) Prepared from (*E*)-3-(4-bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-ol (0.147 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.091 g, 63%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 6.0 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 4H), 7.31 (d, *J* = 3.7 Hz, 2H), 7.07 (s, 1H), 7.05 (dd, *J* = 5.1, 3.7 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 4H), 4.19 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.33, 143.94, 142.66, 138.19, 131.96, 130.54, 129.80, 128.31, 127.86, 127.16, 120.57, 38.23.

3,5-dimethyl-2,6-diphenylpyridine: (Table 5.3, 2a)[16c] Prepared from 1-phenylprop-2-en-1-ol (0.067 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.054 g,

83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 6.9 Hz, 4H), 7.49 (s, 1H), 7.44 (t, *J* = 7.3 Hz, 4H), 7.40 – 7.35 (m, 2H), 2.39 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.85, 141.28, 140.72, 129.32, 129.25, 128.17, 127.78, 19.74.

3,5-dimethyl-2,6-di-*p*-tolylpyridine: (Table 5.3, 2b)[16d] Prepared from 1-(*p*-tolyl)prop-2-en-1-ol (0.074 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.054 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.1 Hz, 4H), 7.46 (s, 1H), 7.23 (d, *J* = 7.9 Hz, 4H), 2.39 (s, 6H), 2.37 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.68, 141.37, 137.70, 137.52, 129.27, 129.01, 128.82, 21.40, 19.79.

2,6-bis(4-ethylphenyl)-3,5-dimethylpyridine: (Table 5.3, 2c)[21] Prepared from 1-(4-ethylphenyl) prop-2-en-1-ol (0.081 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.068 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.1 Hz, 4H), 7.48 (s, 1H), 7.28 – 7.24 (m, 4H), 2.69 (q, *J* = 7.6 Hz, 4H), 2.39 (s, 6H), 1.26 (t, *J* = 7.6 Hz, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.65, 143.95, 141.52, 137.72, 129.35, 129.13, 127.68, 28.81, 19.79, 15.73.

2,6-bis(4-methoxyphenyl)-3,5-dimethylpyridine: (Table 5.3, 2d)[3g] Prepared from 1-(4-methoxyphenyl)prop-2-en-1-ol (0.082 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.052 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 4H), 7.45 (s, 1H), 6.97 (d, *J* = 8.8 Hz, 4H), 3.84 (s, 6H), 2.38 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.30, 155.27, 141.46, 133.09, 130.59, 128.77, 127.28, 113.51, 55.37, 19.81.

2,6-bis(3,4-dimethylphenyl)-3,5-dimethylpyridine: (Table 5.3, 2e)[16d] Prepared from 1-(3,4-dimethylphenyl)prop-2-en-1-ol (0.081 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light

yellow solid (0.056 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.40 (s, 2H), 7.32 (d, *J* = 7.7 Hz, 2H), 7.20 (d, *J* = 7.7 Hz, 2H), 2.39 (s, 6H), 2.33 (s, 6H), 2.32 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.91, 141.05, 138.43, 136.32, 136.06, 130.60, 129.21, 128.78, 126.69, 19.98, 19.81, 19.69.

2,6-bis(4-bromophenyl)-3,5-dimethylpyridine: (Table 5.3, 2f)[16d] Prepared from 1-(4-bromophenyl)prop-2-en-1-ol (0.106 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.069 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 4H), 7.48 (s, 1H), 7.45 (d, *J* = 8.5 Hz, 4H), 2.36 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.75, 141.65, 139.32, 131.37, 130.99, 129.59, 122.23, 19.69.

3,5-dimethyl-2,6-bis(4-(trifluoromethyl)phenyl)pyridine: (Table 5.3, 2g)[16d] Prepared from 1-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (0.101 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.068 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 8H), 7.56 (s, 1H), 2.40 (s, 6H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.69, 143.91, 141.78, 130.22, 129.90, 129.68, 125.30, 19.58. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.47.

3,5-dimethyl-2,6-di(thiophen-2-yl)pyridine: (Table 5.3, 2h)[16d] Prepared from 1-(thiophen-2-yl)prop-2-en-1-ol (0.070 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 97:3), the compound was isolated as a light yellow solid (0.041 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 4.3 Hz, 2H), 7.41 (d, *J* = 5.1 Hz, 2H), 7.37 (s, 1H), 7.13 (dd, *J* = 5.1, 3.7 Hz, 2H), 2.56 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.21, 145.83, 143.02, 127.72, 127.46, 127.35, 126.49, 20.92.

3,5-dimethyl-2,6-di(naphthalen-2-yl)pyridine: (Table 5.3, 2i)[16d] Prepared from 1-(naphthalen-2-yl)prop-2-en-1-ol (0.092 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 96:4), the compound was isolated as a light yellow

solid (0.057 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 2H), 7.95 – 7.87 (m, 6H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.58 (s, 1H), 7.53 – 7.48 (m, 4H), 2.47 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.82, 141.59, 137.95, 133.29, 133.04, 129.75, 128.57, 128.48, 127.84, 127.79, 127.45, 126.26, 126.17, 19.86.

2,6-di([1,1'-biphenyl]-4-yl)-3,5-dimethylpyridine: (Table 5.3, 2j) Prepared from 1-([1,1'-biphenyl]-4-yl)prop-2-en-1-ol (0.105 g, 0.5 mmol). After purification by column chromatography (*n*-hexane/ EtOAc: 95:5), the compound was isolated as a light yellow solid (0.062 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 8H), 7.64 (d, *J* = 7.1 Hz, 4H), 7.57 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 4H), 7.36 (t, *J* = 7.3 Hz, 2H), 2.46 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.24, 150.56, 141.02, 140.89, 137.01, 129.90, 128.92, 127.49, 127.32, 127.03, 19.84.

Analytical data for mechanistic study:

2,6-diphenyl-3,5-bis(phenylmethyl-*d*$_2$)pyridine-4-*d*: (Scheme 5.3, 3a) Prepared from 1,3-diphenylprop-2-en-1-ol (0.105 g, 0.5 mmol) and CD_3OD (1ml). After purification by column chromatography (*n*-hexane/ EtOAc: 98:2), the compound was isolated as a light yellow solid (0.095 g, 83%).

Deuterium incorporation equation:

% D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0/1)*100) = 100% D

Peak B: 100-((2.62/4)*100) = 34.5% D.

5.5 Reference

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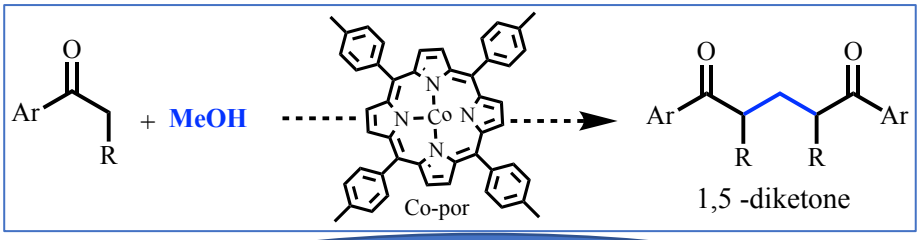
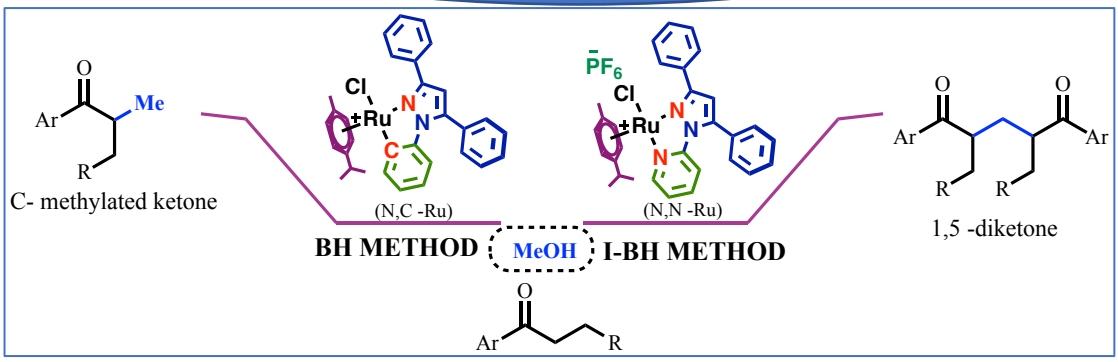
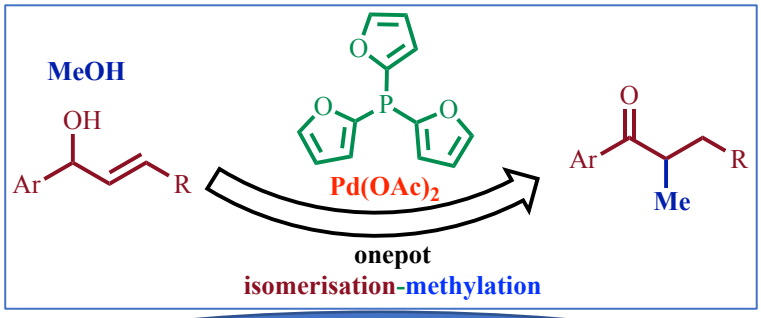
This thesis focused on the catalyst design, synthesis and its application to the activation of methanol as a green C1 source *via* the borrowing hydrogen(BH) or the interrupted borrowing hydrogen(I-BH) strategy for the formation of C-C bonds. My thesis work has been organized in to four chapters. The first chapter describes a unique approach for the activation of methanol to synthesize 1,5 diketones using simple cobalt(II)porphyrin. The developed approach is based on the activation and utilisation of methanol as a C1 source with a wide range of ketones *via* an I-BH protocol to yield 1,5-diketones as well as H_2 and H_2O as byproducts. Mechanistic study and deuterium-labelling study supports the activation of MeOH *via* an I-BH pathway in this protocol. The second chapter describes a unique ligand selective protocol for the activation of methanol as a C1 source to synthesize α-methylated ketones and 1,5-diketones utilising N,C−Ru and N,N−Ru catalyst respectively. Mechanistic study reveal that, in situ formed formaldehyde reacting with a ketone generates an enone intermediate, which undergoes two competing reactions, methylated product is obtained using the N,C−Ru catalyst through the BH method, and 1,5-diketone product obtained through the I-BH method using the N,N−Ru catalyst. Third chapter describes about the one-pot isomerization and methylation of allyl alcohols to synthesize α-methylated ketones catalyzed by commercially available $Pd(OAc)_2$. This protocol is based on the tandem isomerization and methylation of a variety of 1,3-diaryl propenols and 1-aryl propenols utilizing methanol as C1 source *via* BH method. The isotopic labelling experiments reveal the involvement of a palladium hydride species and a palladium enolate species in the catalytic process. Further, mechanistic study and the isotopic labelling studies reveals the involvement of BH pathway in this isomerization-methylation reaction. This final chapter describes a one-pot isomerization and methylenation of allyl alcohols, followed by a sequential addition protocol to synthesize symmetrical pyridines. This protocol was catalyzed by N,N-Ru catalyst for the isomerization- methylenation of allyl alcohol utilizing MeOH as a C1 source through I-BH strategy. A wide variety of 1,3-diaryl propenols and 1-

aryl propenols provides the desired pyridine products in good yield. Mechanistic study confirms the formation of 1,5-diketone from allyl alcohol and MeOH *via* a methylenated intermediate, which upon reaction with NH_4OAc produced the desired pyridine.



Functionalisation of ketones using MeOH as a C1 source





Functionalisation of allyl alcohols using MeOH as a C1 source