



**Exploring The Borrowing Hydrogen  
Methodology using Earth Abundant Metals**

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## Acknowledgement

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First and foremost, I will start by giving all my thanks to Allah (SWT), the lord of the universe, the ever-living and sustainer, the eternal possessor, the mighty, the giver and taker of life and the almighty Chemist, all successes are due to you my lord, without you by my side nothing would have been possible for me. You deserve all my thanks and gratitude. I would also give thanks to my sponsor and employer, Federal university Gusau, FUGUS for sponsoring my PhD through the tertiary education fund (TETFUND), I really appreciated it and I am indebted to you, much gratitude.

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## Abstract

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This thesis describes the development of new catalytic methodologies in borrowing hydrogen chemistry also known as hydrogen auto transfer, which is a sub-class of transfer hydrogenation chemistry. The main aim was to develop new catalytic methods *via* the borrowing hydrogen process using earth abundant metals like iron, manganese or cobalt. The second chapter of this thesis discusses the iron catalysed C(3)-alkylation of oxindole with alcohols via the borrowing hydrogen process using iron complex as the catalysts. Oxindole framework is found in many pharmacologically active compounds. It underwent selective C(3)-mono-alkylation with a wide range of simple aliphatic, benzylic and heteroaryl alcohols in good to excellent yield (28 examples, 79% average yield). The mechanistic study revealed the presence of reactive carbonyl intermediate and a metal hydride probing the borrowing catalytic process.

In chapter three, the first transition metal C-alkylation of aryl ketones with secondary alcohols using only base was discussed. The method employed a bulky and sterically hindered substrate as the ketone, establishing a route for the synthesis of  $\beta$ -substituted carbonyl compounds with different secondary alcohols, giving a wide range of products with good yield (23 examples, 65% average yield). From the mechanistic study it was proposed that the reaction proceeds via an Oppenauer-type oxidation of secondary alcohol followed by selective cross aldol-condensation and then the subsequent Meerwein-Ponndorf-Verley (MPV)-type reduction of the enone. In the final research chapter, chapter four, the enantioselective N-alkylation of amines with secondary alcohols was investigated and the desired products were obtained in an excellent yield albeit with no any e.e.

and the isomerization/alkylation reaction of epoxy styrene with primary alcohols was also investigated but no any meaningful results was obtained from the pilot study.

## List of Publications

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1. M. B. Dambatta<sup>†</sup>, K. Polidano, A. D. Northey, J. M. J. Williams and L. C. Morrill\*. Iron-Catalysed Borrowing Hydrogen C-Alkylation of Oxindoles with Alcohols. *ChemSusChem*, 2019, **12**, 2345–2349.
2. M. B. Dambatta<sup>†</sup>, J. Santos, R. R. Bolt, L. C. Morrill\*. Transition Metal  $\alpha$ -C-Alkylation of Ketones with Secondary Alcohols. *Tetrahedron*, 2020, **76**, 131571.
3. B. G. Reed-Berendt<sup>†</sup>, D. E. Latham<sup>†</sup>, M. B. Dambatta and L. C. Morrill\*. Borrowing Hydrogen for Organic Synthesis. *ACS Cent. Sci.* 2021, **7**, 570–585.

### Key:

<sup>†</sup>Primary author(s)

\*Primary investigator(supervisor)

## Abbreviations

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$\alpha$	Alpha
$\beta$	Beta
$\gamma$	Gamma
$\delta$	Delta
$\mu\text{L}$	Microlitre(s)
ACE	Ace (brand)
Aq	Aqueous
Ar	Aryl group (aromatic)
Atm	Atmosphere(s)
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Br	Broad
Bu	Butyl
Bz	Benzoyl
C	Celsius
c	Concentration
Cat.	Catalyst
cm	Centimetre(s)
Cp	Cyclopentadienyl
CPA	Chiral phosphoric acid
Cy	Cyclohexyl
D	Doublet
D	Deuterium
DFT	Density functional theory



DIBAL-H	Di-iso-butylaluminium hydride
dr	Diastereomeric ratio
EDW	Electron donating group
equiv.	Equivalent
Et	Ethyl
EWG	Electron withdrawing group
g	Gram (s)
h	Hour(s)
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
<i>i</i> or <i>l</i>	Iso
IPA	Isopropyl alcohol
IR	Infrared
<i>m</i>	Meta
m	Multiplet
Me	Methyl
Mes	Mesityl
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol	Mole(s)
mol %	Mole percentage
mp	Melting point

MVP	Merweein-Ponndof-Verley
<i>n</i> or <i>n</i>	normal
NMR	Nuclear magnetic resonance
<i>o</i>	Ortho
<i>p</i>	Para
P	Pressure
Ph	Phenyl
PNP	Phosphorus-Nitrogen-Phosphorus
Ppm	Part(s) per million
Pr	Propyl
q	Quartet
quint	Quintet
R	Alkyl
R <sub>f</sub>	Retardation factor
rt	Ambient (room) temperature
s	Singlet
sat.	Saturated
sept	Septet
sex	Sextet
SM	Starting material
T	Temperature
<i>t</i> or <i>t</i>	Tertiary
t	time
t	Triplet
TFA	Trifluoroacetic acid

TH	Transfer hydrogenation
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	Tosyl
TS	Transition state

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# Chapter One

## Introduction to Borrowing Hydrogen Methodology

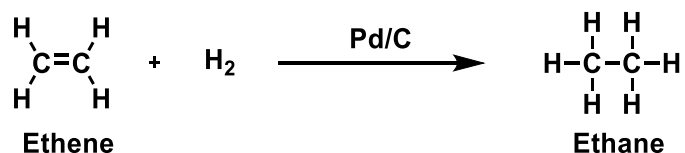
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### 1.1 Hydrogenation Chemistry

Hydrogenation is one of the most fundamental transformations in organic synthesis and this simply means a chemical reaction between molecular hydrogen and another compound(s), usually in the presence of a metal catalyst like palladium, nickel or platinum.<sup>1</sup> Hydrogenation reactions are extensively used to create commercial goods, for example in the food industry to make a large variety of manufactured goods, like spreads and shortenings, from liquid oils. This process also increases the chemical stability of products and yields semi-solid products like margarine. Hydrogenation is also used in coal processing where solid coal is converted to a liquid coal through the addition of hydrogen, which makes it available to be used as fuel.<sup>2-3</sup>

A common example of an hydrogenation reaction in organic chemistry is the addition reaction of molecular hydrogen onto an alkene. In this reaction, two hydrogen atoms are added across the double bond of an alkene, resulting in a saturated alkane. Hydrogenation of a double bond is a thermodynamically favorable reaction because it forms a more stable (lower energy) product. In other words, the energy of the product is lower than the energy of the reactant; thus it is exothermic. The heat released is called the heat of hydrogenation in this process, which is an indicator of a molecule's stability.<sup>4-5</sup> An example of the hydrogenation process is the addition of molecular hydrogen to ethene using

palladium metal as the catalyst to make saturated compound called ethane as shown in Scheme 1.



**Scheme 1:** Hydrogenation of ethene to ethane using palladium supported on carbon as catalyst

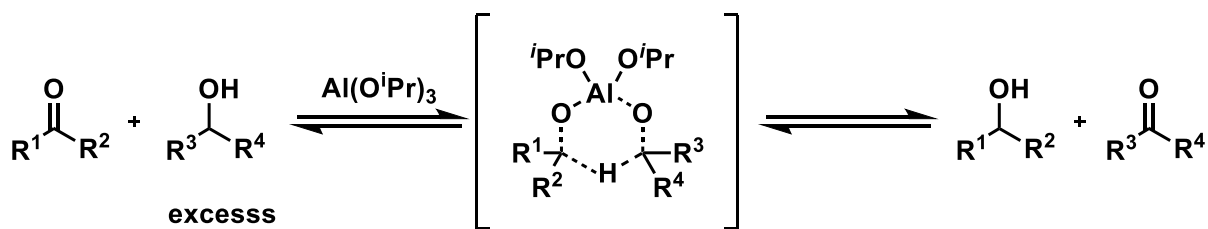
Hydrogenation can be classified into two main categories; namely the direct hydrogenation like in Scheme 1 above which involves the use of molecular hydrogen from an external source (hydrogen atmosphere or pressure) and the transfer hydrogenation reaction TH, which employs compounds or materials as the hydrogen source.

## 1.2 Transfer Hydrogenation

In transfer hydrogenation the addition of molecular hydrogen is from an alternative compound; a non-H<sub>2</sub> hydrogen source and this is a convenient and powerful method to access various hydrogenated compounds. It is an attractive alternative to direct hydrogenation. Transfer hydrogenation has numerous advantages over direct hydrogenation as it does not require eventually hazardous pressurised H<sub>2</sub> gas nor any elaborate experimental setups, most of the hydrogen donors are readily available, inexpensive, and easy to handle. And the major side product from the process can be recycled.<sup>6-12</sup> The transfer hydrogenations are divided according to the catalyst involved in the reaction, among which are the Meerwein-Ponndorf-Verley (MVP) reduction, late transition metal-catalysed reactions, organocatalytic reaction etc.



Transfer hydrogenation is more than a hundred years old, for example the MVP reduction was reported in 1925 and the first transfer hydrogenation reaction of carbonyl compounds discovered independently by Meerwein and Verley.<sup>13,14</sup> In this reduction, an aluminium alkoxide acts as the promoter for the reduction of the carbonyl compound to an alcohol while the secondary alcohol present in excess acts as the hydrogen donor, and the reaction proceeds through the formation of a six membered ring complex in the transition state. Both the carbonyl compound and the reducing alcohol are coordinated to the same metal centre as shown in Scheme 2 below.<sup>15-17</sup> Other metals were used for this kind of transformation in a similar pattern after 1925, for example in 1932 Winans and Adkins used supported nickel in the alkylation of aniline with alcohol,<sup>18</sup> and two decades later Pratt and Frazza achieved the same transformation using a different nickel catalyst.<sup>19</sup> Both of these transformation employed heterogeneous catalysts. The earliest example employing homogeneous catalysis came in 1981 and 1984 when Griggs and Wantanabe showed the N-alkylation of anilines and acetonitrile derivatives with alcohol using rhodium and ruthenium-based catalysts respectively.<sup>20-22</sup> In spite of these many examples of transfer hydrogenation, the term borrowing hydrogen has not come to use until in 2004 when Williams and co-workers coined it.<sup>23</sup>

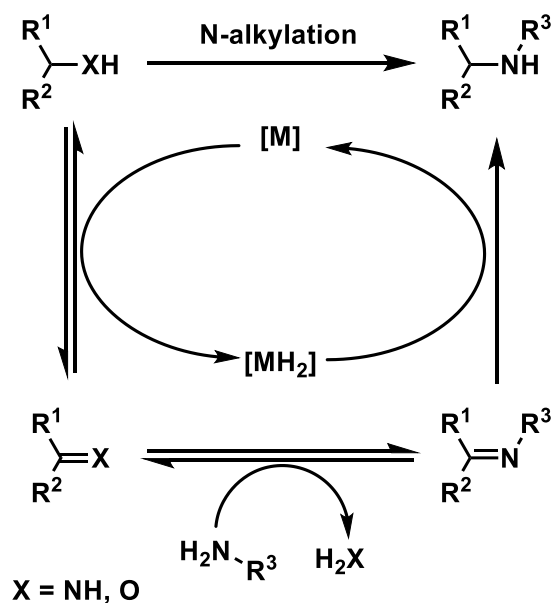


**Scheme 2:** MPV-reduction of alcohol via a cyclic transition state

It can be seen above in the reduction of ketone, that the hydrogen donor or source being the alcohol is needed in excess amount to drive the reaction to completion, and these reactions are often reversible. Therefore, this limits the atom economy of the process and leads to the generation of excess waste. Another alternative is the borrowing hydrogen methodology, a redox neutral process which provides less waste, high atom economy and is environmentally friendly.

### 1.3 Borrowing Hydrogen

Borrowing hydrogen or hydrogen auto transfer is under the categories of transfer hydrogenation with a different key step, where a pair of transfer hydrogenation is coupled with an intermediate reaction on the in situ generated reactive specie.<sup>24-</sup><sup>28</sup> Scheme 3 is the general pathway explaining the borrowing hydrogen process using an amine N-alkylation.



**Scheme 3:** General transition metal catalysed borrowing hydrogen process

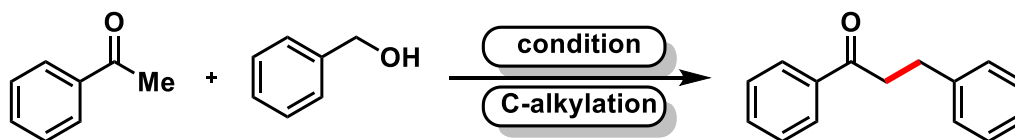
The process begins with the dehydrogenation of an alcohol or an amine using the transition metal, generating a reactive carbonyl or imine intermediate. This

intermediate further react with a nucleophile like an enolate generated in situ or an amine to form another intermediate, which can be reduced by the metal hydride [MH<sub>2</sub>] generated from the first oxidation step. This final reaction liberates the product and regenerate the metal catalyst, completing the catalytic cycle.<sup>29</sup>

#### 1.4 C-Alkylation Process

The reaction of acetophenone and benzyl alcohol to form dihydrochalcone will be used as a representative example to explain the C-alkylation processes in borrowing hydrogen methodology. Most of the early works on C-alkylation reactions employed mainly the precious metals catalysts. This is evident from the work of Chul Shim and co-workers demonstrating the alkylation of acetophenone with alcohols using a ruthenium catalyst in 2002.<sup>30</sup> Two years later, another work by Ishi and co-workers showed the same transformation using a homogeneous iridium catalyst,<sup>31</sup> followed shortly by a heterogeneous palladium catalysed reaction in the report of Cho.<sup>32</sup> In a similar manner, Yus and co-workers used nickel nanoparticles to achieve the same reaction.<sup>33</sup> Other reports utilised different transition metals to achieved similar result like osmium,<sup>34</sup> supported copper,<sup>35</sup> and rhodium.<sup>36</sup> One interesting work was demonstrated by Wang and co-workers where a rhodium catalyst was used in the alkylation of ketones and alcohols with alcohols, both giving alkylated ketones as the product. Here the alcohols were oxidised and further alkylated by the second alcohol in the process.<sup>37</sup> The use of earth abundant metal catalysts in homogeneous borrowing hydrogen was not widely investigated until Sortais and Darcel in 2015 and Beller and co-workers in 2016. Sortais and Darcel used an iron-based catalyst in the  $\alpha$ -alkylation of ketones with primary alcohols, extending the application of their method to the synthesis of 2-aminobenzyl alcohol through the Friedlander-type

annulation.<sup>38</sup> While Beller and co-workers employed the use of a manganese based catalyst, alkylating acetophenones and extending the strategy to even heterocyclic compounds such as oxindoles.<sup>39</sup> In another report by Zhang and co-workers, cobalt was used to demonstrate similarly the  $\alpha$ -alkylation of ketones with primary alcohols.<sup>40</sup> All these reports are shown in scheme 4 below, including some selected examples of compounds synthesised through the processes, probing the wide applicability of BH methods in its ability to tolerate other functional groups, its use in direct synthesis and modification of natural products.



Chul Shim, 2002  
 $\text{RuCl}_2(\text{PPh}_3)_2$  (2 mol %)  
 1-dodecene (1 equiv.)  
 $\text{KO}^t\text{Bu}$  (1 equiv.)  
 dioxane, 80 °C  
 20 h  
 82% yield

Ishii, 2004  
 $[\text{Ir}(\text{cod})\text{Cl}]_2$  (1 mol %)  
 $\text{PPh}_3$  (4 mol %)  
 $\text{KOH}$  (10 mol %)  
 neat, 100 °C  
 4 h  
 86% yield

Cho, 2005  
 $\text{Pd/C}$  (5 mol %)  
 1-decene (4 equiv.)  
 $\text{KOH}$  (3 equiv.)  
 dioxane, 100 °C  
 20 h  
 66% yield

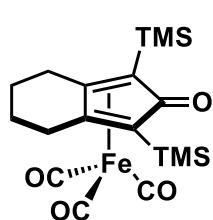
Yus, 2007  
 Ni NPs (1 equiv.)  
 THF, 76 °C  
 6 h  
 85% yield

Sortais & Darcel, 2015  
 $[\text{Fe}]$  1 (2 mol %)  
 $\text{PPh}_3$  (2 mol %)  
 $\text{Cs}_2\text{CO}_3$  (10 mol %)  
 toluene, 140 °C  
 24 h  
 60% yield

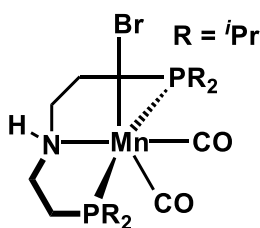
Bellar, 2016  
 $[\text{Mn}]$  2 (2 mol %)  
 $\text{Cs}_2\text{CO}_3$  (5 mol %)  
 $^t\text{amyl alcohol}$ , 140 °C  
 22 h  
 88% yield

Wang, 2016  
 $[\text{Rh}]$  3 (2 mol %)  
 $\text{Cs}_2\text{CO}_3$  (1.5 equiv.)  
 xylene, 150 °C  
 24 h  
 91% yield

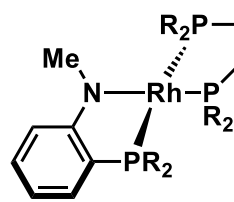
Zhang, 2017  
 $[\text{Co}]$  4 (2 mol %)  
 $\text{KO}^t\text{Bu}$  (5 mol %)  
 toluene, 120 °C  
 24 h  
 93% yield



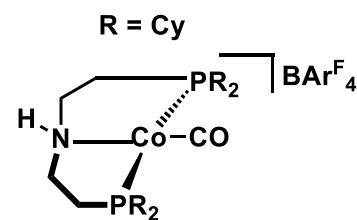
[Fe] 1



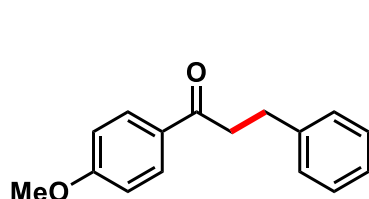
[Mn] 2



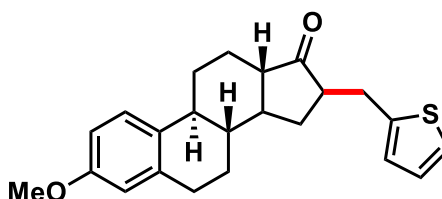
[Rh] 3



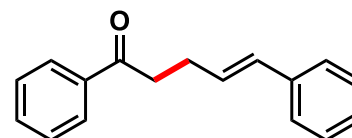
[Co] 4



Sortais & Darcel, 2015  
 $[\text{Fe}]$  1



Bellar, 2016  
 $[\text{Mn}]$  2

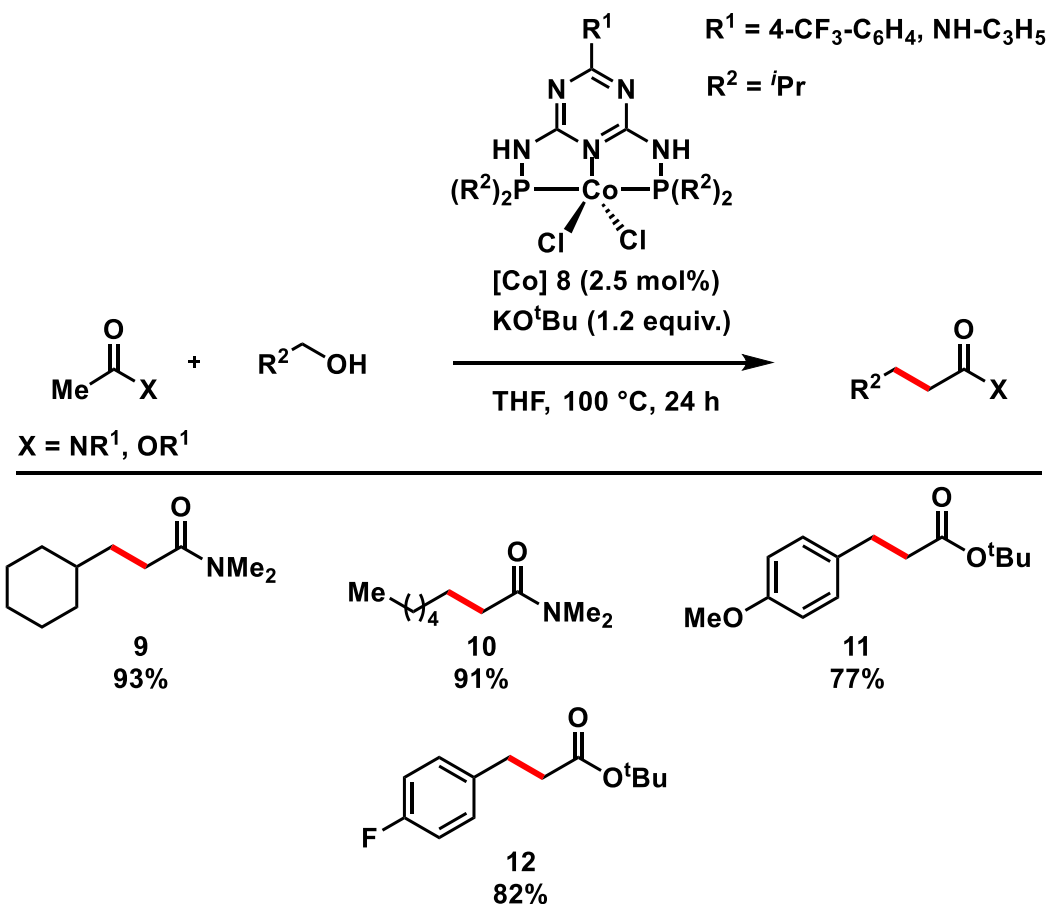


Zhang, 2017  
 $[\text{Co}]$  4

**Scheme 4:** Some catalytic synthesis of Dihydrochalcone via borrowing hydrogen

Other nucleophiles like the nitriles, esters and amides can also be functionalised in same way to ketones, for example nitriles being one of the building blocks in

organic synthesis can be alkylated through the borrowing hydrogen process.<sup>41</sup> For esters and amides, functionalizing the  $\alpha$ -position is difficult compared to that of ketones or aldehydes, because of the low acidity of the C-H of esters and amides and the fact that esters can easily undergo transesterification reaction in the presence of an alcohol. Despite these challenges, progress was made in the  $\alpha$ -alkylation of unactivated esters and amides with primary alcohols. For example, the works of Ishi and Huang demonstrated this transformation using iridium based catalysts.<sup>42-44</sup> The first earth-abundant-metal-catalysed process of  $\alpha$ -alkylation of unactivated esters and amides came in 2016 by Kempe using cobalt complex **8** shown in Scheme 5 with some selected examples.<sup>45</sup> Compounds including indoles,<sup>46,47</sup> oxindoles,<sup>48</sup> heteroarenes,<sup>49-51</sup> sulfones,<sup>52</sup> and thioamides<sup>53</sup> were all successfully functionalized in same manner. It is worth stating here that part of this thesis involved the C-alkylation of oxindole, a class of cyclic amide lactam, chapter two.



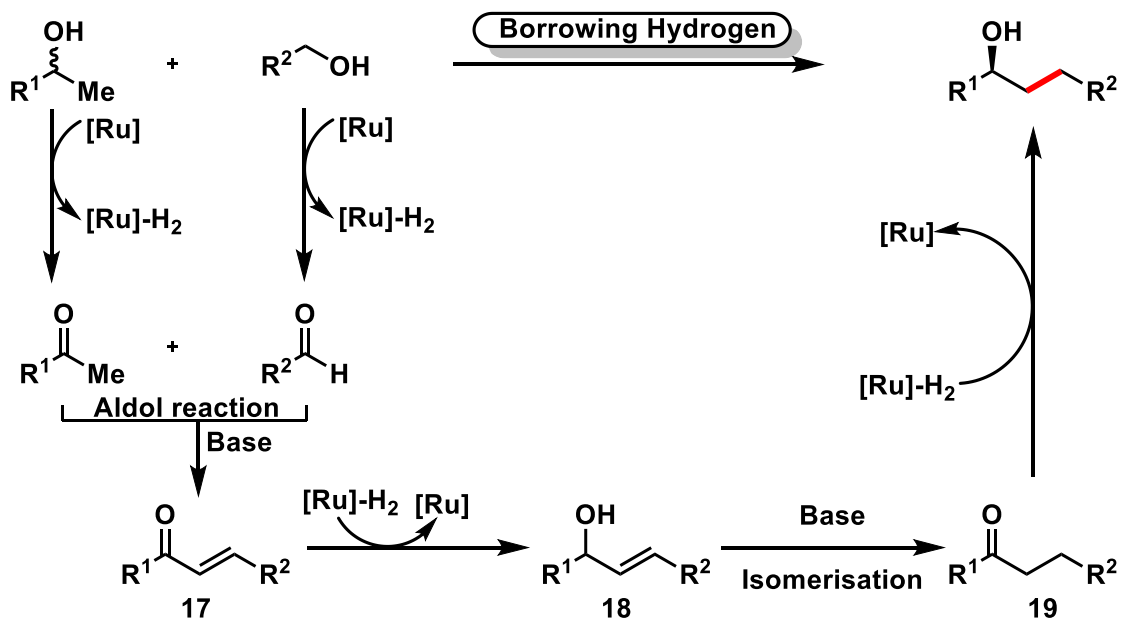
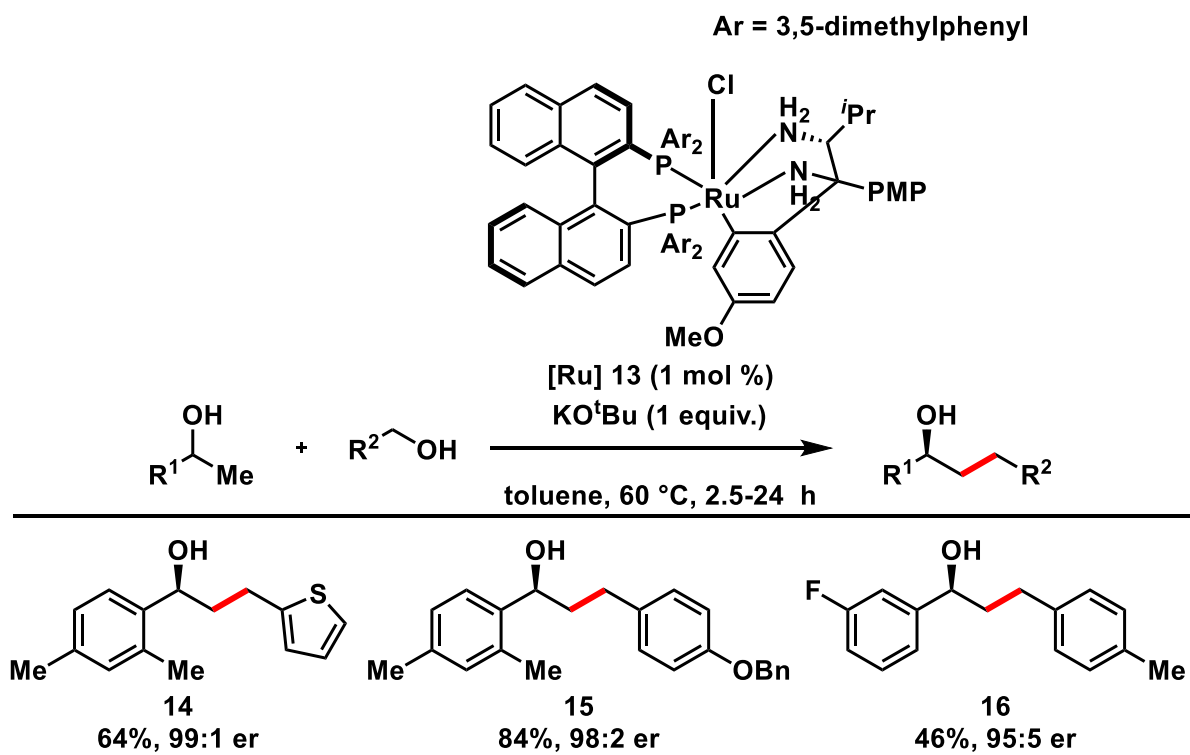
**Scheme 5:**  $\alpha$ -alkylation of esters and amides

Most of the early works in C-alkylation via BH focused on the use of primary alcohols as alkylating agents. The use of secondary alcohols was limited and proved to be notably difficult. This is due to possible competing self-condensation reactions from the ketone intermediate of the secondary alcohol and the substrate.<sup>54</sup> In 2017, Donohoe and coworkers made a breakthrough by addressing the issue of self-condensation reaction using sterically hindered substrates, in an iridium catalysed process.<sup>55,56</sup> Other metals used for such transformation are cobalt,<sup>57</sup> iron<sup>58</sup> and manganese.<sup>59</sup> Part of this thesis contained the transition-metal-free-alkylation of ketones using secondary alcohols, chapter three.

With respect to the enantioselective C-C bond formation reaction via BH, only few examples existed, most of them came in the last decade. One of the recent works

was that of Wang and co-workers in 2020, where a chiral ruthenium complex was employed to access chiral alcohols by asymmetric Guerbet reaction, giving the products with a very high ee of up to 98% as shown in Scheme 6 including the proposed mechanism with some of the examples of the products obtained **14-16** from the process.<sup>60</sup> From the Scheme 6 below, it was proposed in the mechanism that the first step involved the dehydrogenation of the two alcohols by the ruthenium catalyst to give the carbonyl compounds along with the ruthenium hydride species intermediate ( $[\text{Ru}]\text{-H}_2$ ). The carbonyl compound condensed in the presence of a base to an  $\alpha$ ,  $\beta$ -unsaturated ketone **17** intermediate followed by its reduction to allylic alcohol **18** intermediate by the ruthenium hydride. The alcohol underwent a base catalysed isomerisation to form ketone **19** which was finally reduced to the chiral alcohol product. It was believed that this final step determined the enantioselectivity of the reaction and by the chiral ruthenium catalyst **13** resembling the Noyori asymmetric hydrogenation.



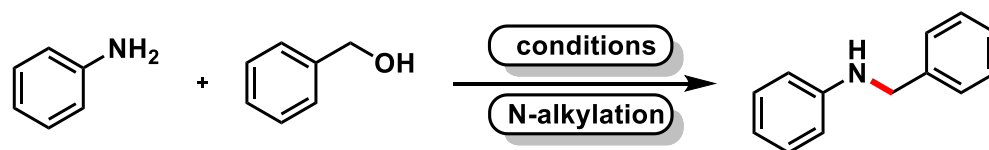


**Scheme 6:** Asymmetric Guerbet reaction; a route to accessing chiral that alcohol via BH process

### 1.5 N-Alkylation Process

The development of sustainable and user friendly methods for the formation of C-N bonds is paramount to organic chemistry.<sup>61</sup> This bond forming process gives a

class of compound called amines which are widely used in pharmaceuticals, agrochemicals, surfactants and are present in natural occurring compounds like the alkaloids.<sup>62</sup> In recent years the borrowing hydrogen have been developed as a more sustainable method in making amines from alcohols.<sup>63</sup> The earliest work was that of Winans and Adkins in 1932,<sup>7</sup> while the pioneering reports involving the use of homogeneous catalysts in N-alkylation of amines was demonstrated independently by Watanabe and Grigg in the 1980s,<sup>9-11</sup> as stated previously but from 2000 to date there has been tremendous progress in this area employing both heterogeneous and homogeneous catalysts based on mostly precious metals. The reaction of aniline and benzyl alcohol to form N-benzylaniline will be used as the archetypal hydrogen autotransfer reaction explaining the N-alkylation process with some selected examples, including few amines synthesised from the process demonstrating its diversity, all in Scheme 7 below.



Yamaguchi, 2003  
 $[\text{Cp}^*\text{IrCl}_2]_2$  (2.5 mol %)  
 $\text{K}_2\text{CO}_3$  (5 mol %)  
 toluene, 110 °C  
 17 h  
 93% yield

Williams, 2009  
 $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$  (2.5 mol %)  
 dppf (5 mol %)  
 toluene, 110 °C  
 24 h  
 80% yield

Satsuma, 2009  
 $\text{Ag}/\text{Al}_2\text{O}_3$  (4 mol % Ag)  
 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  (5 mol %)  
 o-xylenes, 144 °C  
 24 h  
 94% yield

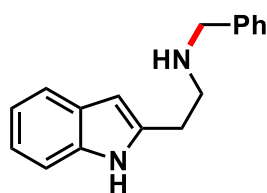
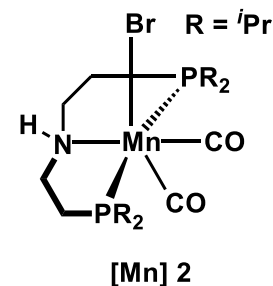
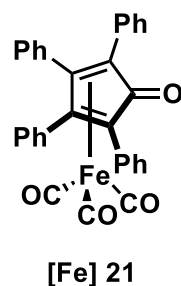
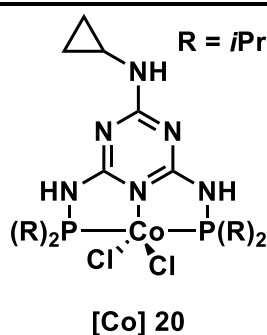
Raman & Yus, 2009  
 $\text{Fe}_3\text{O}_4$  (20 mol %)  
 $\text{KO}^t\text{Bu}$  (2 equiv.)  
 1,4-dioxane, 90 °C  
 7 days  
 88% yield

Sabater, 2010  
 $\text{Pd}/\text{MgO}$  (0.75 mol % Pd)  
 $\text{PhCF}_3$ , 180 °C  
 15 mins  
 79% yield

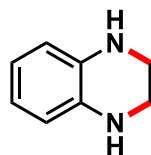
Kempe, 2015  
 $[\text{Co}] 17$  (2.5 mol %)  
 $\text{KO}^t\text{Bu}$  (1.2 equiv.)  
 toluene, 80 °C  
 24 h  
 62% yield

Wills, 2015  
 $[\text{Fe}] 18$  (2.5 mol %)  
 $\text{Me}_3\text{NO}$  (10 mol %)  
 toluene, 110 °C  
 48 h  
 95% yield

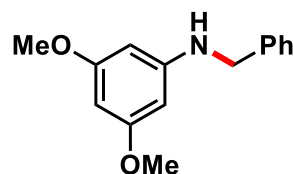
Bellar, 2016  
 $[\text{Mn}] 2$  (2 mol %)  
 $\text{KO}^t\text{Bu}$  (1 equiv.)  
 toluene, 80 °C  
 24 h  
 78% yield



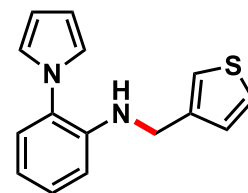
Williams, 2009  
 $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$



Feringa & Barta, 2014  
 $[\text{Fe}] 1$



Kempe, 2015  
 $[\text{Co}] 17$

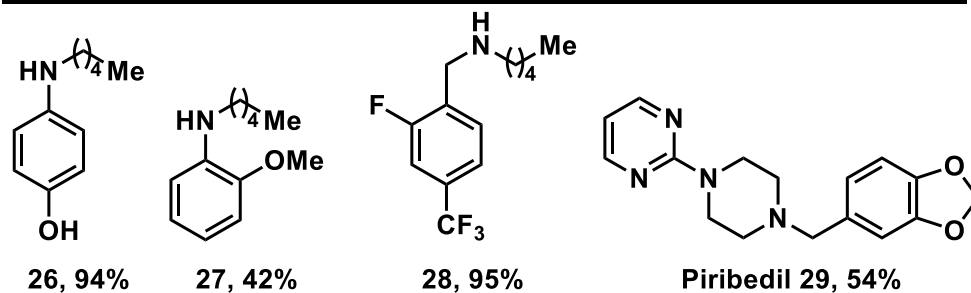
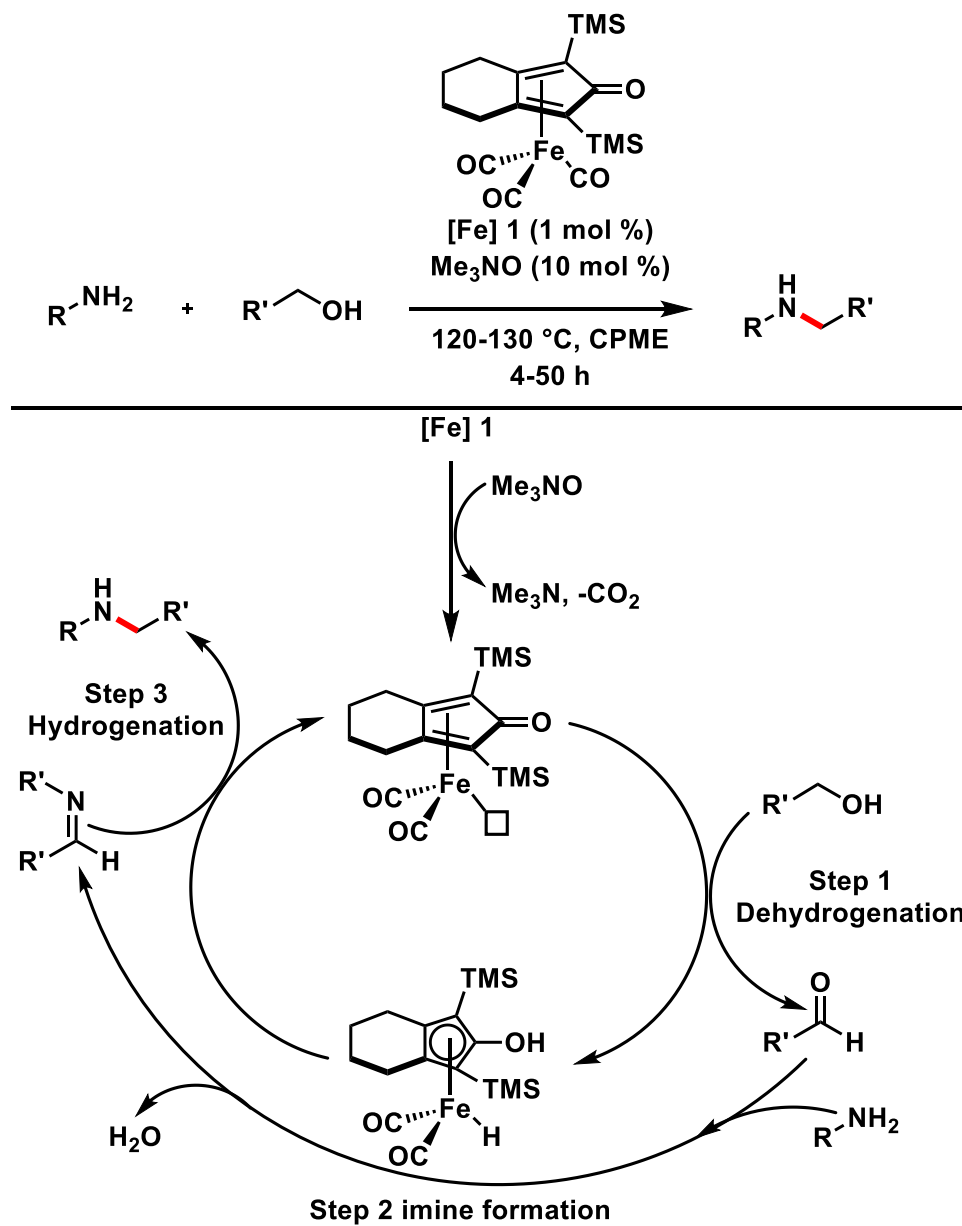


Bellar, 2016  
 $[\text{Mn}] 2$

**Scheme 7:** Selected methods for catalytic synthesis of N-Benzylaniline via Borrowing Hydrogen

The first example is the work of Yamaguchi and co-workers, who used iridium-cyclopentadienyl complex for benzylation of anilines with benzyl alcohol,<sup>64</sup> while Williams and co-workers performed same reaction using a ruthenium *p*-cymene

dichloride, both of which are homogeneous catalysis. The use of heterogeneous catalysts as an alternative to homogeneous catalysts were reported by Satsuma,<sup>65</sup> Ramon and Yus<sup>66</sup> and Sabater<sup>67</sup> between 2009 to 2010 using supported silver, magnetite and supported palladium. All showing the ability to catalyzed the reaction. It's a long-standing goal for researchers in chemical synthesis to have sustainable, eco-friendly, inexpensive methods for the synthesis of amines, and earth abundant metals provide that opportunity.<sup>68</sup> To this effect a significant breakthrough was accomplished in 2014 by Feringa and Barta in the alkylation of amines with alcohols using a Knolker iron complex **1** shown in Scheme 8 including the proposed reaction mechanism and some selected examples.



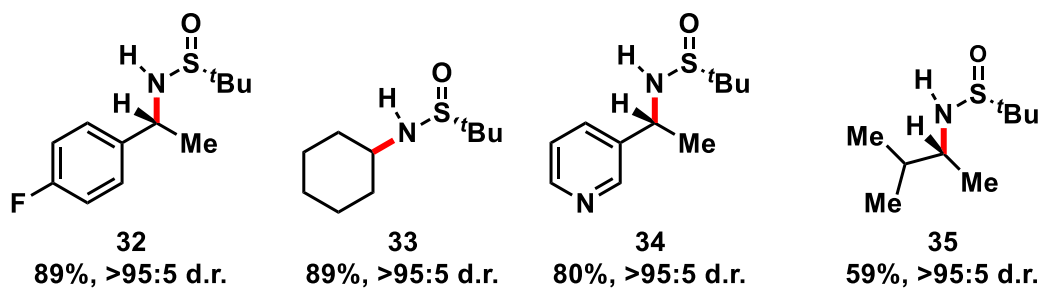
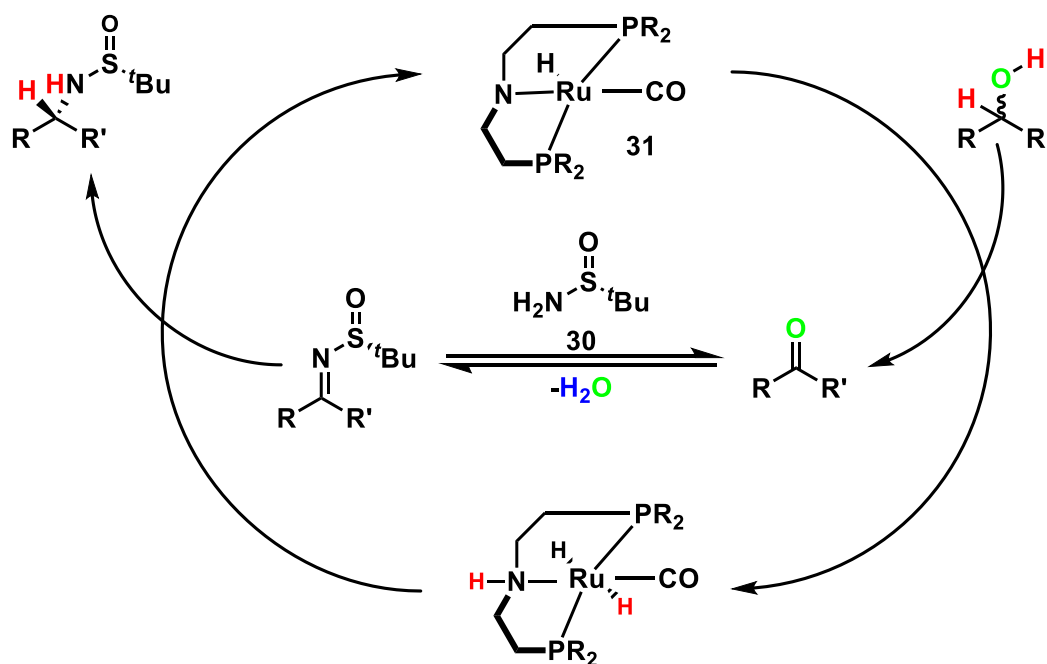
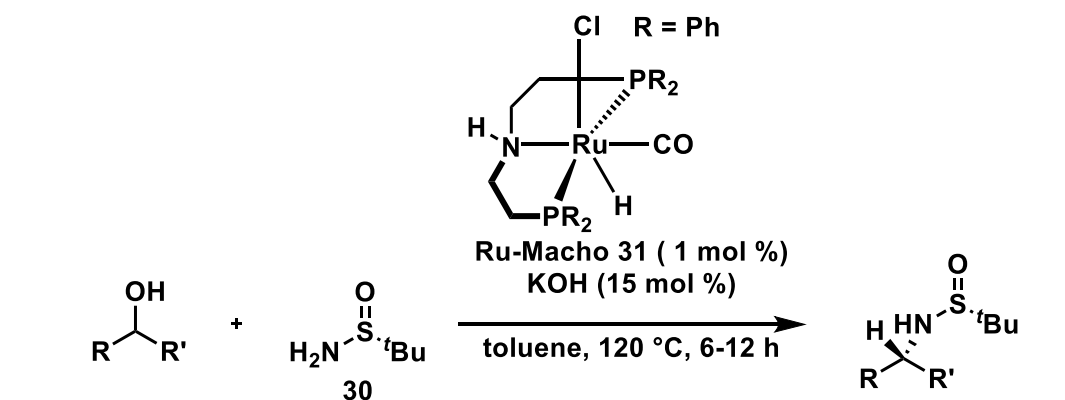
**Scheme 8:** alkylation of amines with alcohols using earth abundant metal complex of iron

From the Scheme above the catalytic cycle began with the CO de-coordination using the oxidant Me<sub>3</sub>NO to form the active catalyst and oxidised the CO to CO<sub>2</sub>. This active catalyst then oxidised the alcohol into aldehyde and iron hydride species, the aldehyde formed then condensed with an amine forming an imine intermediate which was further reduced by the iron hydride species to the corresponding alkylated amine and regenerating the active catalyst species. The selected examples show the application and efficiency of the method for example, product **26** gave the highest yield of all the substituted anilines products in just only 4 hours and this increased reactivity might be attributed to the presence of the phenolic moiety which likely catalysed the imine formation step while compound **27** gave the least yield and required a longer time and molecular sieve as the drying agent. This method demonstrated not only alkylation of anilines but also benzyl amines as shown in compound **28** and in the synthesis of N-aryl piperazine **29**, a drug for the treatment of Parkinson's diseases called piribedil with a yield of 54%. This process employed the use of a wide range of alcohols including diols that formed nitrogen heterocyclic compounds.<sup>69</sup> This work stimulated further developments in the use of earth abundant metal based catalysts as seen in the works of Kempe and co-workers<sup>70</sup> and that of Wills and co-workers<sup>71</sup> employing cobalt and iron based catalysts to achieve similar transformations. Subsequently, the group of Beller in 2016 increased the range of earth abundant metal based catalysts with a manganese pincer complex **2**, catalysing same reaction.<sup>72</sup>

#### 1.5.1 Diastereoselective N-alkylation

Extending the borrowing hydrogen methodology of N-alkylation of aniline to other nucleophiles is possible. For example, the N-alkylation of sulfonamides was

demonstrated with primary alcohols in many reports<sup>73-75</sup> while Dong & Guan in 2014 reported the diastereoselective N-alkylation of chiral non-racemic sulfonamide **30** with secondary alcohols using only 1 mol% of ruthenium based catalyst **31**.<sup>76</sup> The sulfonamide **30** is the nucleophile while the secondary alcohol gives the reactive electrophile as the intermediate. This method demonstrated high diastereoselective control and all the products were obtained with d.r of greater than 95:5. The method and some selected examples of compounds obtained (**32-35**) including the mechanism are shown in Scheme 9 below.



**Scheme 9:** diastereoselective N-alkylation of sulfonamide with secondary alcohols

It was proposed in the mechanism above that the racemic alcohol underwent oxidation by the Ru-pincer complex **31** to form the ketone intermediate and ruthenium hydride. The ketone formed condensed with sulfonamide **30** forming

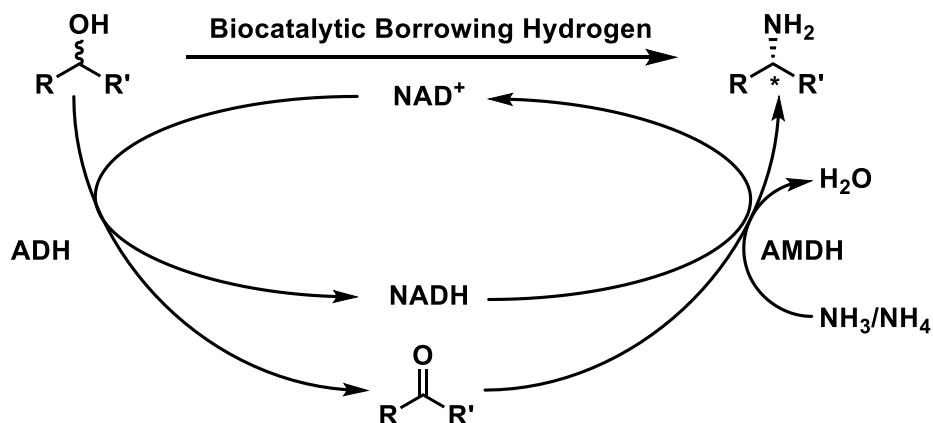


sulfinylimine intermediate which was further hydrogenated by the ruthenium hydride to generate the  $\alpha$ -chiral sulfinylamine with high and predictable diastereoselectivity.

Other examples show the enantioselective N-alkylation of amines with secondary alcohols, a good example was the work of Zhao and co-workers employing dual chiral catalysis of chiral phosphoric acid and chiral iridium catalyst, giving products with high e.e of up to 97%.<sup>77</sup> This was the basis for my third research work as explained in chapter four of this thesis.

### 1.5.2 Biocatalytic Borrowing Hydrogen

The synthesis of chiral amines is paramount to organic synthesis because of their importance in chemical industry and biocatalysis can be used to achieved that as shown recently as an alternative way for the development of enantioselective borrowing hydrogen reactions.<sup>78-79</sup> The earliest work was that of Kroutil and co-workers for the N-alkylation of amines with alcohols,<sup>80</sup> where three enzymes were used in the process, the first enzyme is used in the oxidation of secondary alcohol to ketone, the second one is used in the reductive amination of the ketone to the final chiral amine product while the third one is used for the regeneration of the co-factor. An advance study was carried out by Turner and co-workers in 2015, employing the use of only two enzymes; the AA-ADH (*Aromatoleum aromaticum*, alcohol dehydrogenase) and the Ph-AmDH (phenylalanine, amine dehydrogenase) in an ammonium chloride buffer (pH 8.7), as opposed to the previous report were they used three enzymes. Aqueous ammonia is used as the nucleophile, the amine donor, producing a good number of chiral amines with high a yield of up to 96% and enantiomeric excess of 99% as shown in Scheme 10 below.<sup>81</sup>



**Scheme 10:** Two-enzyme cascade for the hydrogen-borrowing amination of alcohols. The limitation of the method was the use of only aqueous ammonia as the nucleophile but this was later addressed in their subsequent work, employing primary amines as the nucleophile, where a good number of products were obtained with high ee in the process.<sup>82</sup>

### 1.6 Summary

From the works discussed and highlighted above, it is evident that borrowing hydrogen is an alternative method to the traditional alkylation reaction which employed the use of toxic alkyl halide in making C-C and C-N bond. The method is user and environmentally friendly and make use of alcohols which are relatively cheap and can be easily obtained from biodegradable materials. Only water or ammonia is produced as the by-product, making it an atom economic process. The earliest reports, employed the use of precious metals but in the last two decades, the attention has been on the earth abundant metals and most recently there are so many works done using them. Despite so many progresses made in the area so far, there is still need for more research or work towards milder reaction conditions like low temperature and catalyst loading. And secondly,

there are limited work on stereoselective borrowing hydrogen using earth abundant metals, this is an area where researchers have focused on recently.

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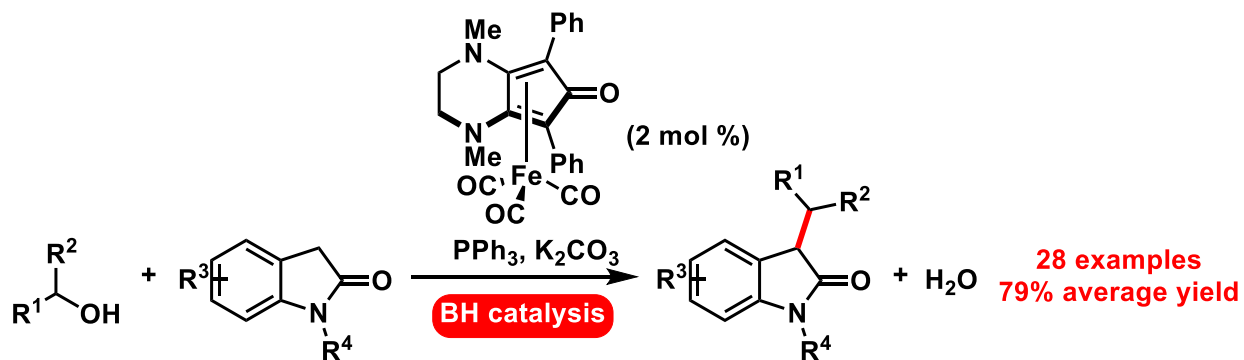


## Chapter Two

### Iron-catalyzed borrowing hydrogen C-alkylation of oxindoles with alcohols

#### 2.1 Preface

In this chapter the development of a general and efficient iron-catalyzed C-alkylation of oxindoles *via* the borrowing hydrogen approach using a (cyclopentadienone)iron carbonyl complex as precatalyst will be discussed. The method exhibited a broad reaction scope, allowing various classes of alcohols to be employed as alkylating agents, including primary and secondary aliphatic alcohols. A range of substituted oxindoles (28 examples) underwent selective C-alkylation in excellent isolated yields (average yield of 79%). The mechanistic experiments carried out provided evidence for plausible reaction intermediates and provided support for a transfer hydrogenation process.



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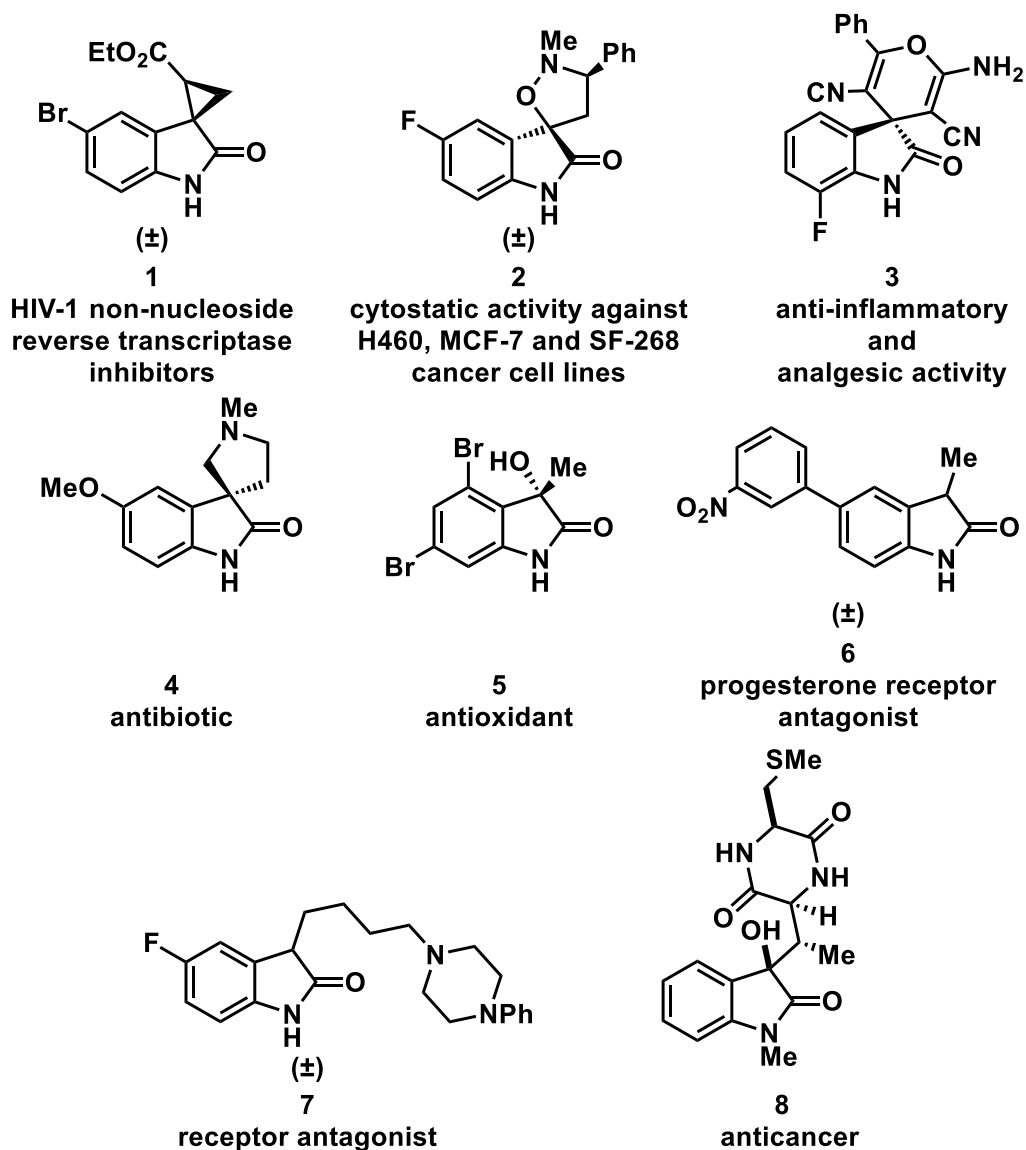
Alexander D. Northey: A former MChem student, who first observed the reaction

Kurt Polidano: A former PhD student who helped in making some barbituric acids

substrates and assisted in the mechanistic studies by preparing the intermediates and some precatalysts used for the study.

## 2.2 Introduction

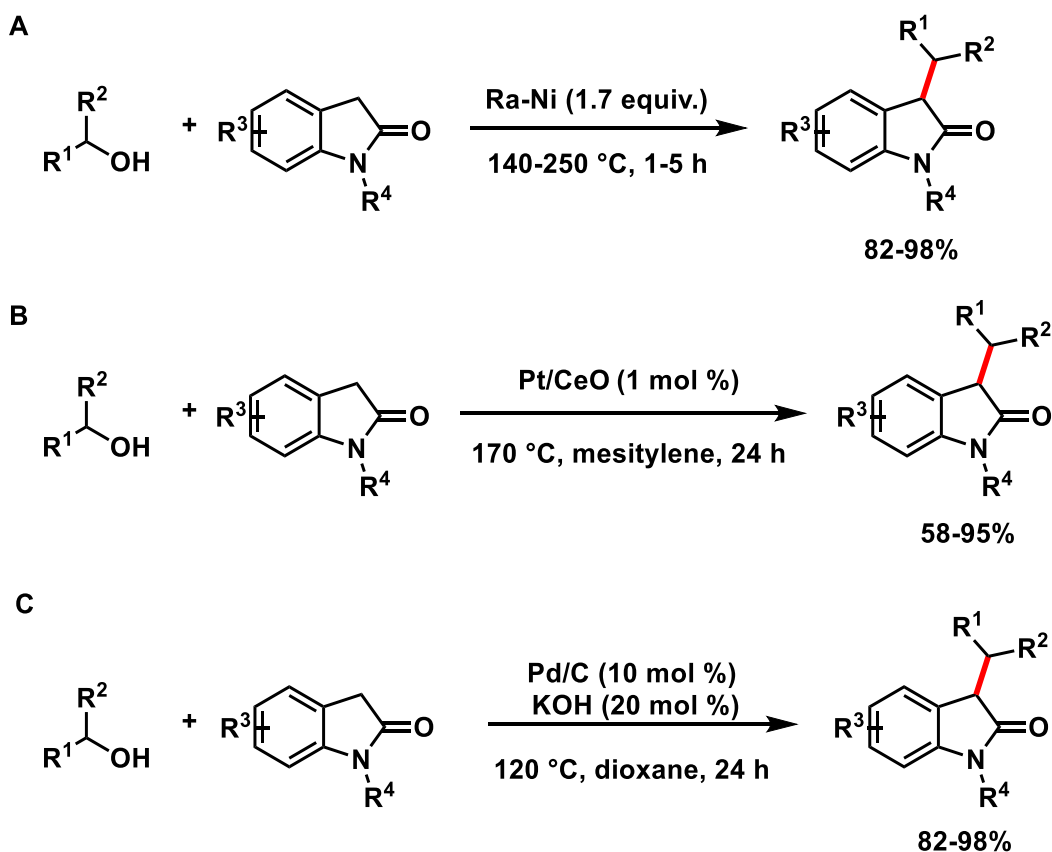
The oxindole skeleton is an important framework found in many bioactive natural products, mostly plants secondary metabolites. *C*(3)-mono- or di-substituted oxindoles have been shown to possess many pharmacological activities, and thus are employed in drug discovery research.<sup>1,2,3</sup> Some selected examples shown in Fig 1, include the HIV-1 non-nucleoside reverse transcriptase inhibitor **1**, the cytostatic anticancer agents **2** and **3**, which possess anti-inflammatory and analgesic activities. Others include the progesterone receptor anatagonists **6** and **7**, the antibiotic agent compound **4**<sup>4,5</sup> and the two 3-hydroxy-substituted oxindoles **5** and **8**, which are reported to have antioxidant and anticancer properties.<sup>6</sup> This encouraged and gave me the reason to develop a borrowing hydrogen methodology for the alkylation of oxindoles at *C*(3)-position that could have some industrial application in pharmaceutical companies.



**Fig 1:** Examples of biologically active C(3)-substituted oxindoles

The synthesis of these substituted unprotected oxindoles traditionally involves the use of alkyl halides, commonly used in stoichiometric amounts, which generates a lot of toxic waste to the environment. This method also has a poor selectivity resulting in mono and dialkylation products and competition between C- and N-alkylation.<sup>7</sup> Thus, there is need for a more efficient and environmentally friendly alternative method like borrowing hydrogen. The regioselective C(3)-alkylation of oxindoles with alcohols as alkylating agent using heterogeneous

catalysts through the borrowing hydrogen methodology has been reported.<sup>8,9,10</sup> For example, Volk and co-workers reacted oxindole with various primary and secondary alcohols by heating in an autoclave at 150–220 °C for 1–5 h in the presence of Raney nickel as the catalyst with good to excellent yield of 82–98% (Scheme 1A).<sup>8</sup> Shimizu and co-workers used 1 mol% of Pt/CeO<sub>2</sub> as the catalyst to achieve the same transformation in good to excellent yields using both benzyl and aliphatic alcohols as alkylating agents (Scheme 1B).<sup>9</sup> Interestingly, the nucleophiles were generated without the use of a base in both of these methods. Recently, Ohta and co-workers developed another catalytic system using 10 mol% of palladium supported on carbon (10 mol% Pd/C) in the presence of KOH (Scheme 1C) to give similar transformation.<sup>10</sup>

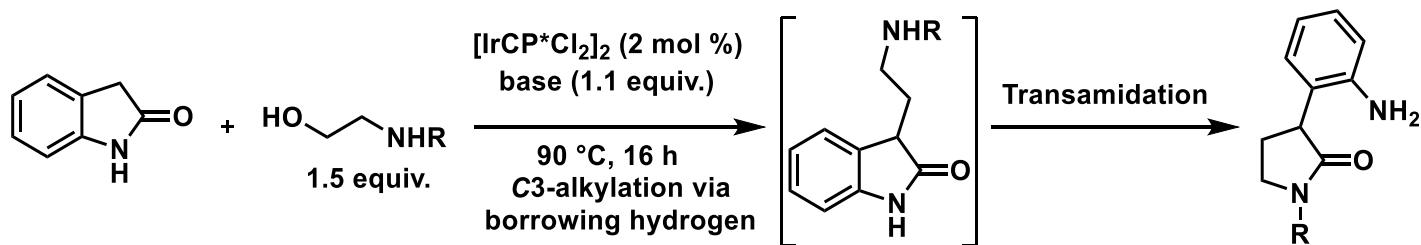


**Scheme 1A-C:** C(3)-alkylation of oxindoles with alcohols using heterogeneous catalysts

Apart from the heterogeneous catalysts, homogeneous precious metals complexes were also employed in the C(3)-alkylation of oxindoles. Among the earliest works, Griggs and co-workers used an iridium complex for the alkylation of both oxindole and N-methyl oxindole with a wide range of substituted benzyl and heteroaryl alcohols. Interestingly, the reactions were done under solvent free thermal and microwave conditions, giving an excellent yield of the products, up to 97%.<sup>11</sup>

Madsen and co-workers in similar transformation to that of Grigg and co-workers used a ruthenium complex precatalyst in the C(3)-alkylation of oxindoles with a range of aromatic, heteroaromatic, and aliphatic alcohols, furnishing products with good to excellent yields of 71-92%.<sup>12</sup>

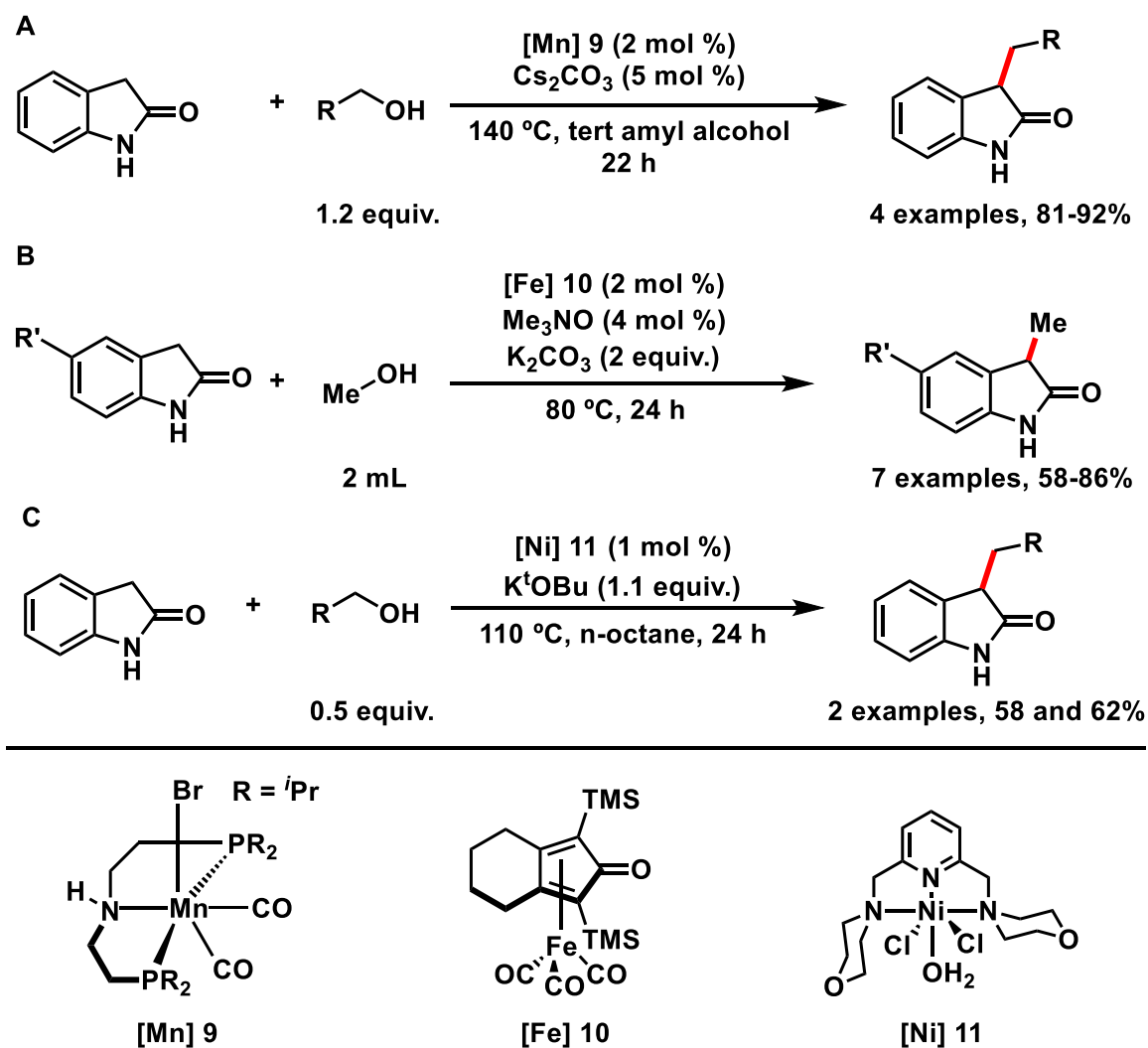
Recently, Piersanti and co-workers<sup>5</sup> showed that the alkylation of oxindole at the C(3) position produces an important intermediate which proceeds to a more useful compound, the  $\gamma$ -lactam by transamidation, that could be utilised in drug related synthesis (Scheme 2) using just 2 mol% of  $[\text{IrCP}^*\text{Cl}_2]_2$ , 1.1 equiv. of a base, and 1.5 equiv. of the alcohol, at 90 °C in 16 h. During the same period, Wang and co-workers showed that a ruthenium complex could be used to functionalise oxindoles at C(3) and also give 3-functionalised-3-hydroxy-2-oxindole with an excellent yield.<sup>13</sup>



**Scheme 2:** Synthesis of  $\gamma$ -lactam via borrowing hydrogen

With respect to the earth abundant metals complexes of iron, cobalt, and manganese, only a few examples were reported in the literature for the C(3)-alkylation of oxindole. For example, Beller and co-workers reported the C(3)-alkylation of oxindole with primary alcohols using manganese catalyst **9** and only four examples were described (Scheme 3A).<sup>14</sup> In another study by Morrill and co-workers using iron catalyst **10**, seven oxindoles were alkylated with methanol (Scheme 3B)<sup>15</sup> while only two examples were obtained from the work of Balaraman and co-workers using nickel catalyst **11** in the alkylation of unactivated amides and esters (Scheme 3C).<sup>16</sup> Therefore, there is need to develop a general borrowing hydrogen method using earth abundant metal preferably iron being the most abundant of all the earth abundant metals, for the C(3)-alkylation of oxindole. The rest of this chapter describes the results of the development of a new method for the selective mono-C(3)-alkylation of various oxindoles with both benzylic and simple aliphatic alcohols using a bench stable (cyclopentadienone)iron(0) carbonyl complex with just 2 mol%.





**Scheme 3A-C:** C(3)-alkylation of oxindoles with alcohols using earth abundant metal catalysts

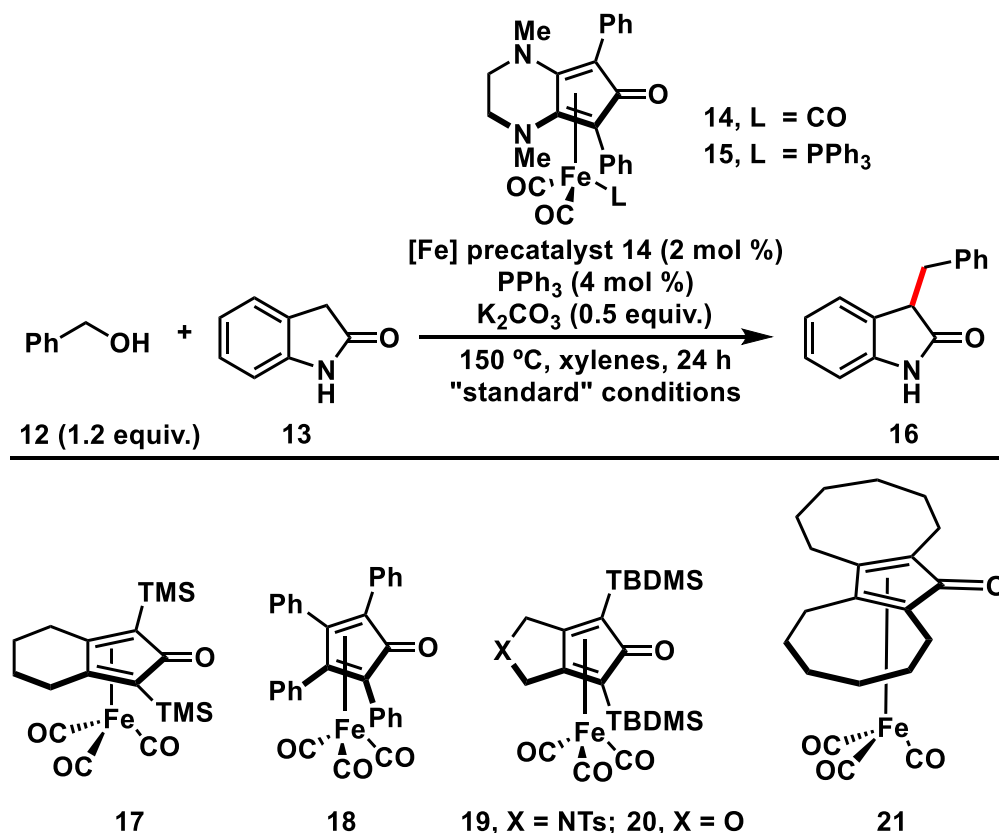
## 2.3 Results and discussion

### 2.3.1 Optimisation of iron catalysed oxindole C(3)-benzylation

The main aim of the group is to carry out new transformations using earth abundant metals with iron being the priority as the most abundant of all.

Therefore, the mono selective C(3)-alkylation of oxindole was investigated using iron precatalysts. This method was first discovered by observing the desired product **16** (Scheme 4) in a crude reaction mixture by <sup>1</sup>H NMR respectively.

Afterward, it was further optimised as shown in Table 1.



**Scheme 4:** Optimisation of the iron-catalysed C(3)-alkylation of oxindole

The research began with a BH system comprising of 2 mol% of bench-stable (cyclopentadienone)iron(0) carbonyl complex **14**, 4 mol% of PPh<sub>3</sub> as the activator of the iron precatalyst, 1.5 equiv. of K<sub>2</sub>CO<sub>3</sub> in 0.5M xylene at 150 °C for 24 h which enabled the C(3)-benzylation of oxindole with just 1.2 equiv. of benzyl alcohol as the alkylation agent, giving the desired product **16** in 97% NMR yield and an isolated yield of 90% (entry 1, Table 1). This method has proved to be a high-atom-economy process. Testing the system without [Fe] precatalyst **14** yielded zero product **16** (entry 2, Table 1) and only 26% of the desired product was observed when no base was used (entry 3, Table 1) signifying the need of the precatalyst for the process to occur and the importance of the base in the process. Precatalyst **15** gave 95% of the product based on <sup>1</sup>H NMR spectroscopy

(entry 4, Table 1), demonstrating it to be a viable catalytic intermediate in the plausible mechanism. Iron being the most abundant of earth abundant metals, we deemed it necessary to investigate other alternative iron complexes.

Unfortunately, complexes **17-21** did not give any useful yield (entries 5-9, Table 1) which signified that iron precatalysts **14** and **15** which contain a more electron-rich cyclopentadienone framework were specifically effective for this desired transformation. Absence of the PPh<sub>3</sub> activator affected the process as only 90% of **16** was obtained as compared to that of (entry 1) which gave 97%, indicating that the precatalyst **14** could be activated with the use of heat alone at 150 °C (entry 10, Table 1). Changing the activator PPh<sub>3</sub> to trimethyl-N-oxide (4 mol%), had a slight negative effect on the reaction (entry 11, Table 1). Using Cs<sub>2</sub>CO<sub>3</sub> instead of K<sub>2</sub>CO<sub>3</sub> resulted in lower yield of the product **16** with 85% obtained (entry 12, Table 1), while lowering the amount of K<sub>2</sub>CO<sub>3</sub> to 10 mol% (0.1 equiv.) produced good NMR yield of 88% of **16**, signifying that the base can be employed in catalytic amount (entry 13, Table 1). Other changes to the reaction conditions like using toluene as a solvent, increasing the concentration of the reaction medium, lowering the temperature to 130 °C and time to 16 h, all had a negative effect on the process (entry 14-17, Table 1). And lastly, using 1 mol% of precatalyst **14** and 2 mol% of PPh<sub>3</sub> activator reduced the efficiency of the process, with only 73% of **16** obtained as NMR yield (entry 18, Table 1).

**Table 1:** Optimisation of the iron-catalyzed C(3)-alkylation of oxindole

Entry <sup>a</sup>	Variation from 'standard' conditions	Yield <sup>b</sup> (%)
1	none	97 (90)
2	no [Fe] precatalyst <b>14</b>	< 2
3	no K <sub>2</sub> CO <sub>3</sub>	26
4	<b>15</b> (2 mol%) instead of <b>14</b> (No PPh <sub>3</sub> )	95
5	<b>17</b> (2 mol%) instead of <b>14</b>	18
6	<b>18</b> (2 mol%) instead of <b>14</b>	5
7	<b>19</b> (2 mol%) instead of <b>14</b>	5
8	<b>20</b> (2 mol%) instead of <b>14</b>	5
9	<b>21</b> (2 mol%) instead of <b>14</b>	5
10	no PPh <sub>3</sub> activator	90
11	Me <sub>3</sub> NO (4 mol%) instead of PPh <sub>3</sub>	92
12	Cs <sub>2</sub> CO <sub>3</sub> (0.5 equiv.) instead of K <sub>2</sub> CO <sub>3</sub>	85
13	K <sub>2</sub> CO <sub>3</sub> (0.1 equiv.)	88
14	toluene instead of xylenes	91
15	[ <b>10</b> ] = 1 M	93
16	130 °C instead of 150 °C	86
17	t = 6 h	92
18	[Fe] precatalyst <b>14</b> (1 mol%), PPh <sub>3</sub> (2 mol%)	73

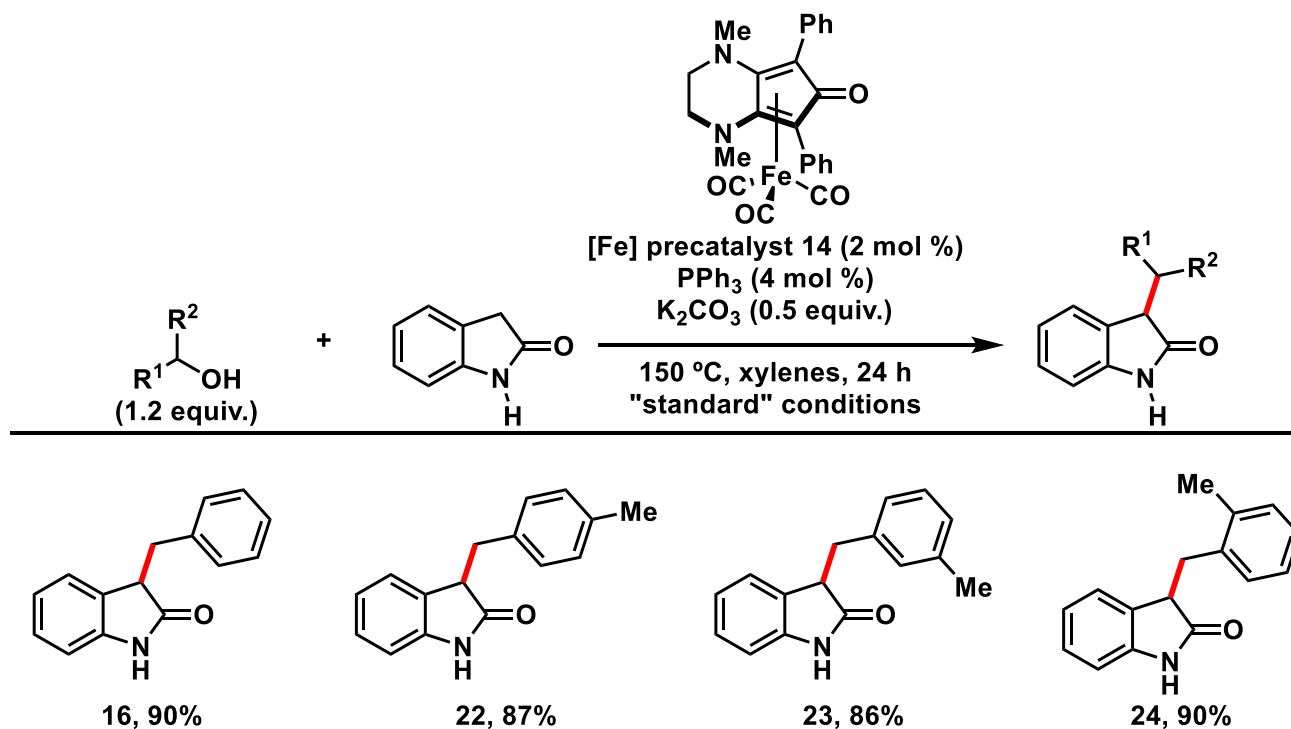
<sup>a</sup>Reactions performed with oxindole (**13**, 1 mmol) and bench-grade xylenes. [**10**] = 0.5 M. <sup>b</sup>Yield after 24 h as determined by <sup>1</sup>H NMR spectroscopy of the crude mixture with 1,3,5-trimethylbenzene as internal standard. Isolated yield given in parentheses.

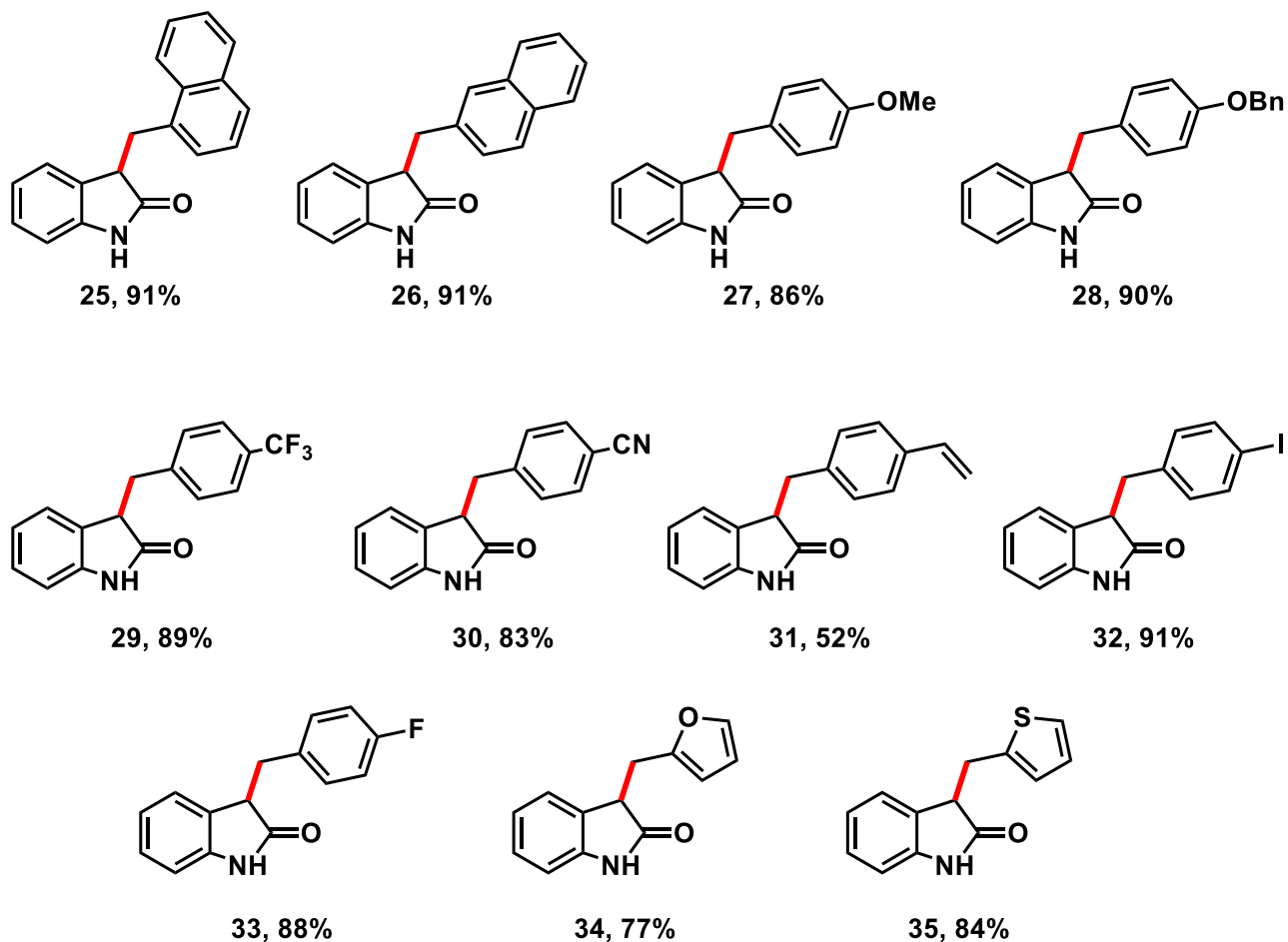
### 2.3.2 Substrate scope of oxindole and benzylic alcohols

With the optimised condition as shown above, the substrate scope for the alkylation of oxindole was explored starting with different kinds of benzylic alcohols, from substituted benzyl alcohols to heterocyclic methyl alcohols

(Scheme 5). From Scheme 5 below, it can be seen that different benzyl alcohols, with various kind of substituents, ranging from electron donating groups (products **22-24**, **27** and **28**) to electron withdrawing groups in products **29**, **30**, **32** and **33**, could be employed as alkylating agents with a yield of 83-91%. Alcohols with bulky aromatic groups like the naphthalene moiety could also be tolerated by the process (compound **25** and **26** both gave a 91% yield). Alcohols containing reducible functionalities (**28**, **30** and **31**) were well tolerated, indicating the applicability of the system to even challenging substrates and its chemo selectivity. Furthermore, heterocyclic methyl alcohols were also tolerated and used as alkylating agents in the process respectively (**34**, 77% and **35**, 84%)

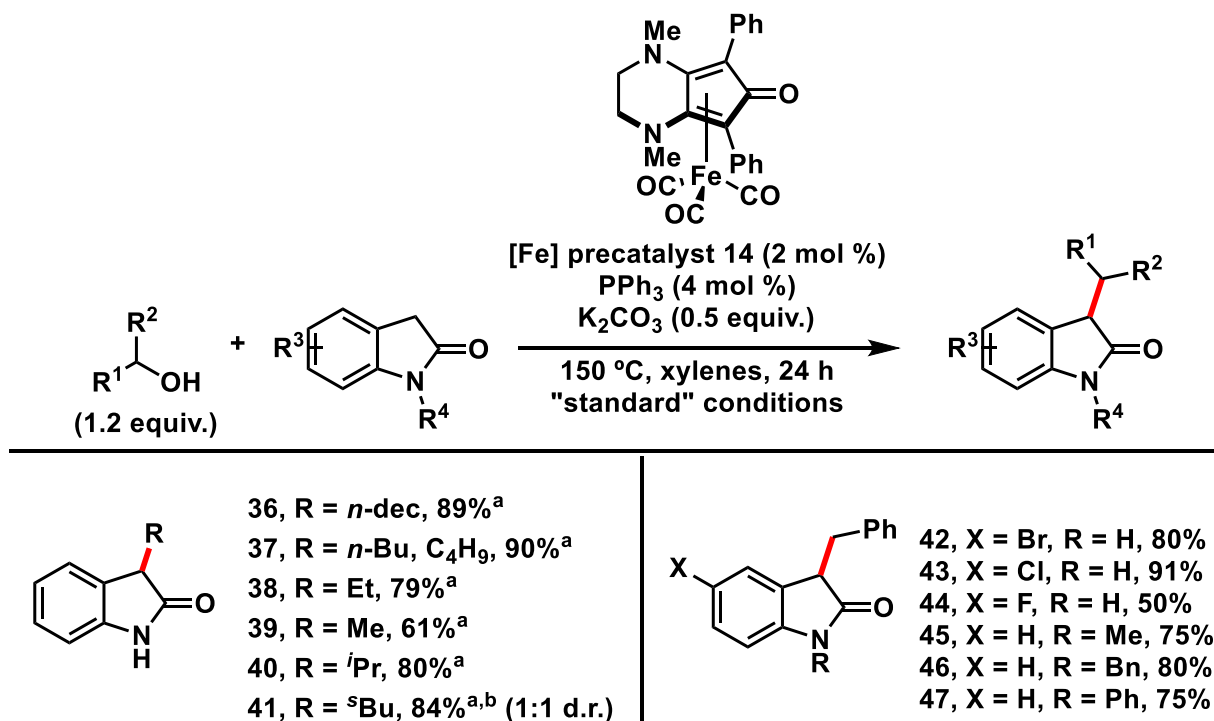
Scheme 5.





**Scheme 5:** Derivatives of oxindole showing the scope of tolerated benzylic alcohol

Non activated alcohols like simple primary and secondary aliphatic alcohols were also successfully employed as alkylating agents. They were used as solvents, giving a good yield 59-80% (**36-40**). Interestingly, 2-butanol, a secondary alcohol, gave a mixture of diastereomers with 1:1 d.r. (**41**) and a yield of 84% (Scheme 6). A few oxindoles, substituted either at C5 or at the N-position, were successfully alkylated with benzyl alcohol using the optimised condition with an excellent yield of up to 92% (**42-47**), showing the versatility of the process Scheme 6.



<sup>a</sup>Alcohol used as solvent, <sup>b</sup>[Fe] precatalyst **14** (4 mol%), PPh<sub>3</sub> (8 mol%).

**Scheme 6:** Oxindoles and alkyl alcohols scope

### 2.3.3 Substrate scope of C-alkylation of barbituric acids

Our BH method was further extended to the C-alkylation of barbituric acids, a class of activated amide that have been found to be competent nucleophiles in homogenous BH employing precious metals like ruthenium<sup>17</sup> and iridium.<sup>18</sup> When barbituric acid was subjected to the standard condition for the C-alkylation of oxindole, only 20% of the product was obtained (entry 1, Table 2), this process was then re-optimized after series of reactions using different bases the desired product was only obtained in less than 70% (entries 1-7, Table 2), while increasing the amount of pre-catalyst **14** (4 mol%) and its activator PPh<sub>3</sub> (8 mol%) obtaining 97% of the product (entry 8, Table 2) as compared to the oxindoles where only 2 mol% of the precatalyst was required.

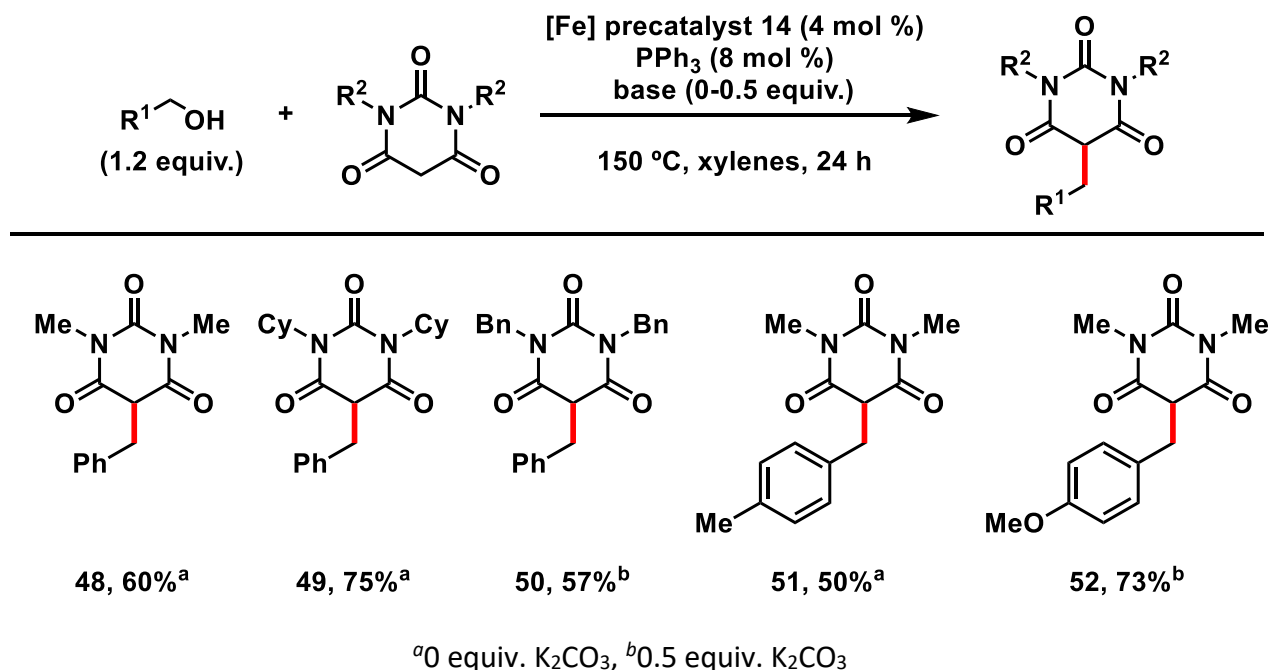
**Table 1:** Optimisation of the C-alkylation of barbituric acid with alcohols

Entry	Variation from 'standard' conditions	product <sup>a</sup> (%)	Barbituric acid (%) <sup>a</sup>
1	none	20	3
2	no K <sub>2</sub> CO <sub>3</sub>	20	52
3	NaOtBu (1.5eq)	26	8
4	NaOH (1.5eq)	34	2
5	KO <sup>t</sup> Bu (1.5eq)	33	7
6	KO <sup>t</sup> Bu (0.5eq)	39	-
7	K <sub>2</sub> CO <sub>3</sub> (0.1eq)	66	2
8	<b>14</b> (4 mol%), PPh <sub>3</sub> (8 mol%)	97	0

<sup>a</sup>Yield after 24 h as determined by <sup>1</sup>H NMR spectroscopy of the crude mixture with 1,3,5-trimethylbenzene as internal standard. Isolated yield given in parentheses

Interestingly, only two of the tested acids required the use of a base in the process. It should be noted that the non-requirement of a base is due to the fact that the barbituric acids are in equilibrium with the enol tautomer, hence act as nucleophiles. Good to moderate yields (50-75%) were obtained for compounds **48-52**, as shown in Scheme 7 below. The procedure is the first of its kind where an earth abundant metal was used in the alkylation of barbituric acids.



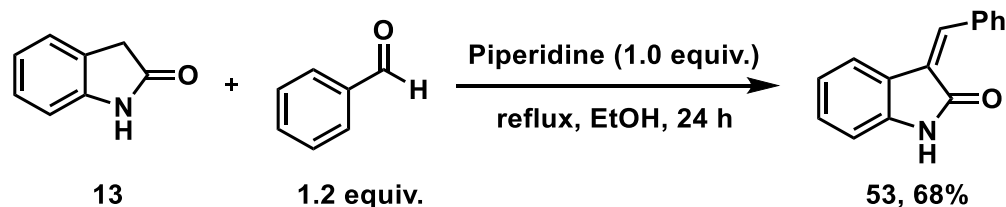


**Scheme 7:** C-alkylation of barbituric acid with alcohols

## 2.4.0 Mechanistic studies

### 2.4.1 Synthesis of plausible intermediate - 3-benzylideneindolin-2-one

To propose a mechanism for the process, attempts were made to synthesise some plausible intermediates. Only the unsaturated amide **53** was successfully synthesised, by aldol condensation of compound **13** with benzaldehyde using a base (Scheme 8).

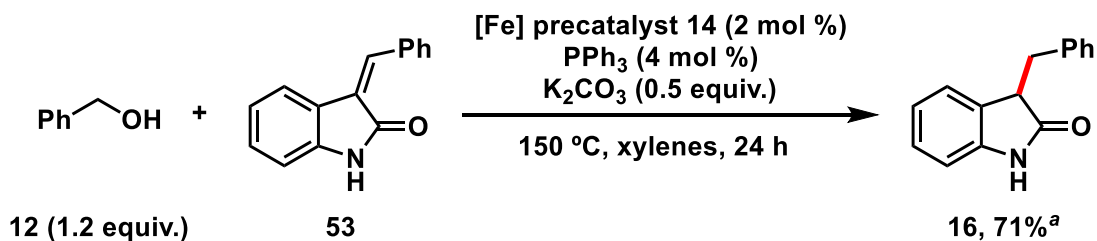


**Scheme 8:** Synthesis of compound **53**

A round-bottomed flask equipped with a magnetic stirrer bar was charged with oxindole (666 mg, 5.0 mmol), EtOH (20 mL), piperidine (494  $\mu$ L, 426 mg, 5.0 mmol)

and benzaldehyde (610  $\mu\text{L}$ , 637 mg, 6.0 mmol). The mixture was heated to reflux for 24 h. It was then cooled and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10-25% EtOAc in hexanes, 40 x 160 mm silica) gave the title compound as a yellow solid (758 mg, 68%); mp 158-160  $^{\circ}\text{C}$  (Lit. 164-166  $^{\circ}\text{C}$ );  $R_f = 0.30$  (eluent = 30% EtOAc in hexanes);  $\nu_{\text{max}} / \text{cm}^{-1}$  (film): 3186, 3150, 3078, 3021, 2832, 2357, 1705, 1607, 1460, 1327, 1231, 1202, 781, 689, 650, 550;  **$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )**  $\delta$ H: 6.87 (1H, t,  $J$  7.5, ArC(5)H), 6.94 (1H, d,  $J$  8.0, ArC(7)H), 7.22 (1H, t,  $J$  7.5, ArC(6)H), 7.40-7.52 (3H, m, ArC(3',4',5')H), 7.61-7.71 (3H, m, ArC(4)H, ArC(2',6')H), 7.86 (1H, s, CH=C), 9.03 (1H, br s, NH);  **$^{13}\text{C NMR}$  (500 MHz,  $\text{CDCl}_3$ )**  $\delta$ C: 110.3 (ArC(7)), 121.9 (C(3)=CHPh), 122.0 (ArC(5')), 123.2 (ArC(4')), 127.6 (ArC(3a)), 128.8 (ArC(3',5')), 129.5 (ArC(2',6')), 129.8 (ArC(4')), 130.0 (ArC(6)), 135.0 (ArC(1')), 137.7 (Ar'CH), 141.6 (ArC(7a)), 170.3 (C=O); HRMS (EI+) calculated for  $[\text{C}_{15}\text{H}_{11}\text{NO}]^+$  (M)+  $m/z$  : 221.0841, found 221.0845, (1.8 ppm).

Compound **53** was then subjected to the standard condition for the general C(3)-benzylation of oxindole and the desired product **16** was obtained in good yield up to 71% as shown in below in Scheme 9.

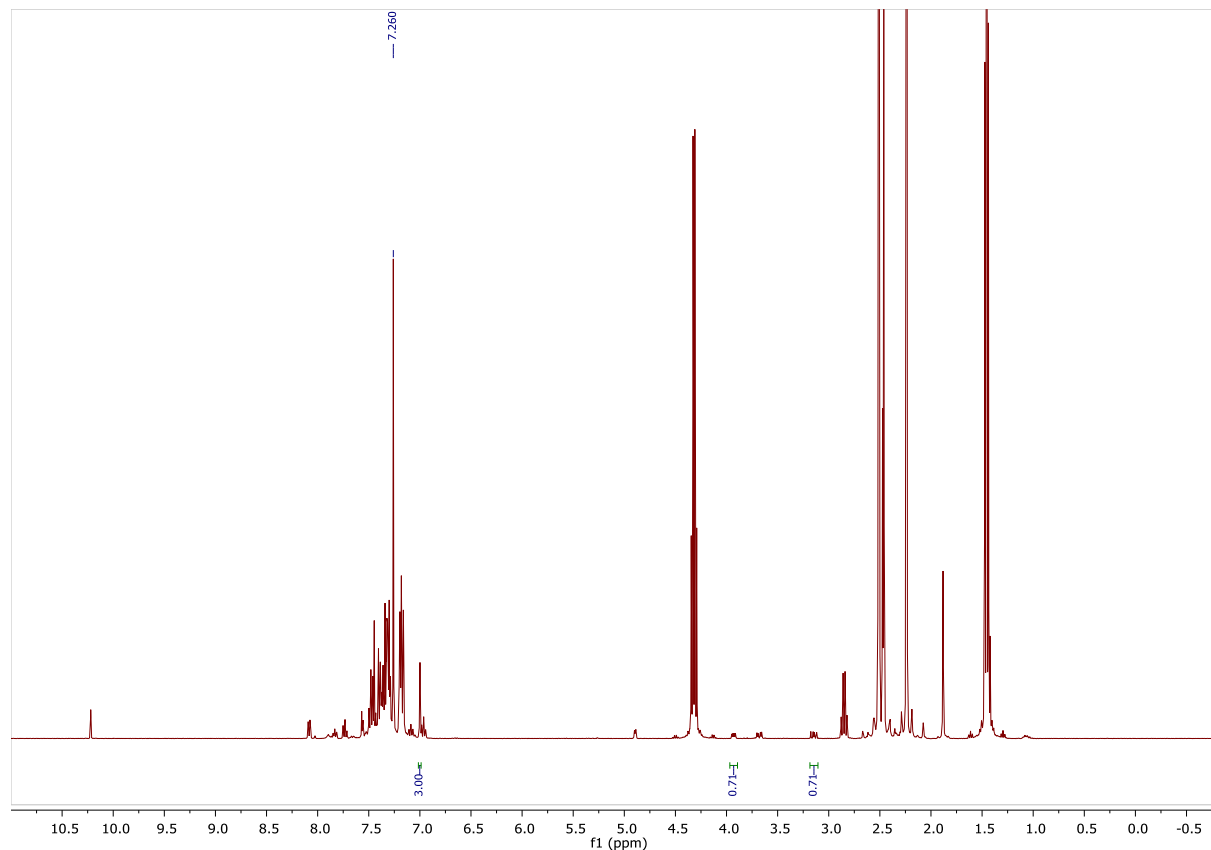


<sup>a</sup>Yield after 24 h as determined by  $^1\text{H NMR}$  spectroscopy of the crude mixture with mesitylene as internal standard

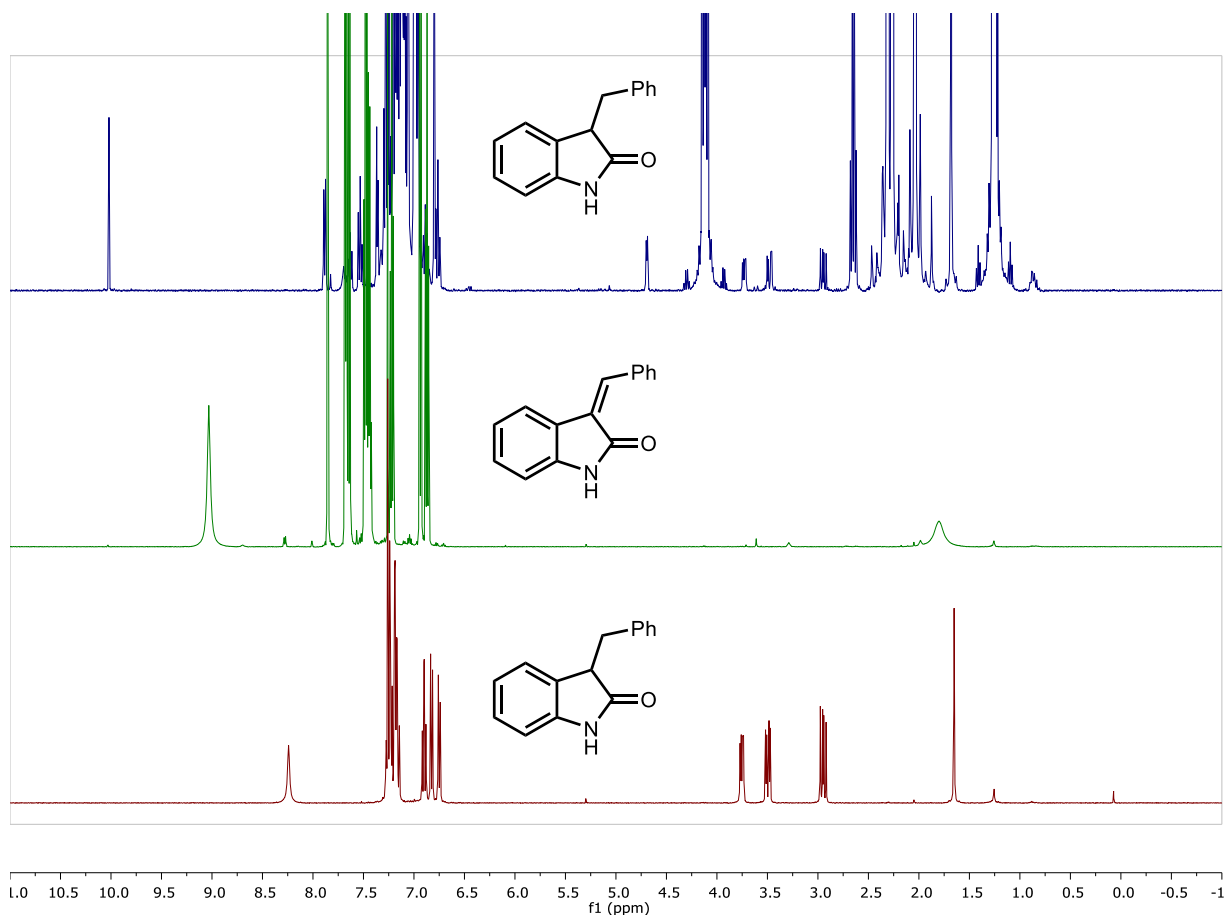
**Scheme 9:** Validation of plausible intermediate **53**

The reaction above in Scheme 9 confirmed that compound **53** is a plausible intermediate in the alkylation of oxindole. The  $^1\text{H NMR}$  spectrum also has

revealed its reactivity by giving the desired product **16** evident of the three doublet of doublets obtained which correspond the two benzylic hydrogens between 2.94-3.75ppm Fig 2.



**Figure 2:** <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) spectrum of crude mixture showing the reactivity of **53**. To further confirm the formation of compound **16** from compound **53**, the <sup>1</sup>H NMR spectrum of the crude reaction mixture (blue) obtained from the reaction of compound **53** (green) was overlapped with the <sup>1</sup>H NMR spectrum of the isolated pure product **16** as shown in Fig 3. The peaks in the region 2.49-3.75ppm are characteristic of the product. Thus, with the results obtained, a plausible mechanism was proposed as shown in Scheme 9.

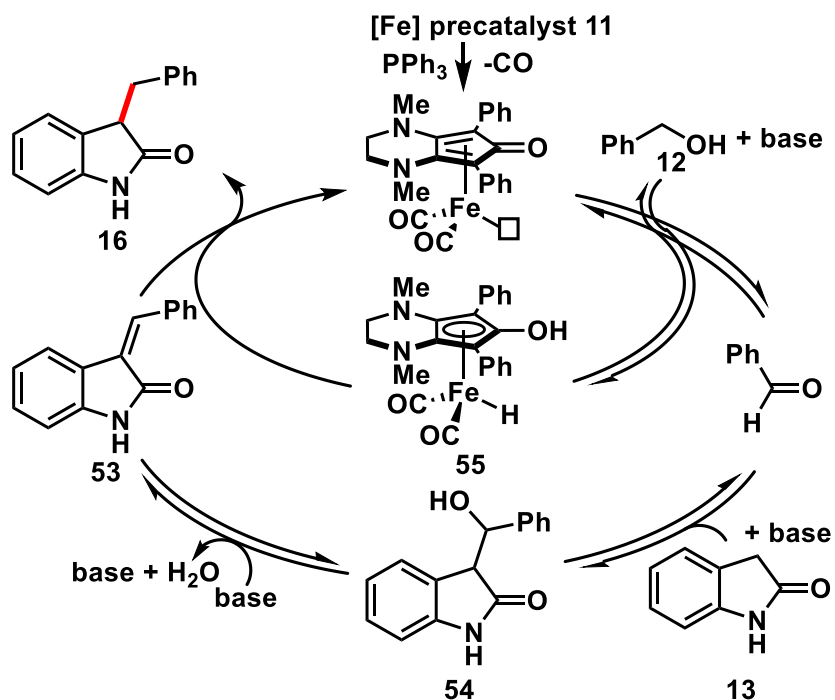


**Figure 3:** Overlap of  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) spectrum of crude mixture with pure spectra of **16** and **53**.

#### 2.4.2 Plausible mechanism

First the catalytic cycle starts by activation of the precatalyst **14** using the activator,  $\text{PPh}_3$  via de-coordination of a CO which created a vacant site for hydride abstraction. This catalyst then oxidised the benzyl alcohol **12** to a benzaldehyde intermediate in the presence a base, generating the reduced version of the catalyst **55**. With the aid of a base, oxindole **13** underwent an aldol reaction with the benzaldehyde to give the  $\beta$ -hydroxy amide intermediate **54** which subsequently underwent rapid base catalysed E1cB dehydration giving the  $\alpha$ ,  $\beta$ -unsaturated amide **53**, which was supported by the mechanistic experiment

above. Finally, the amide was reduced by the metal hydride **55** giving the product **16** and regenerating the active iron catalyst (Scheme 9).



**Scheme 9:** Proposed reaction mechanism for iron-catalysed C(3)-alkylation of oxindole

## 2.5 Conclusion

In conclusion, an iron-catalysed C(3)-alkylation of oxindoles has been developed with a variety of simple benzyl, *n*-alkyl, and secondary alcohols giving good to excellent yield (50-92%, average yield 79%). The process has other application as seen in the successful C(5)-alkylation of barbituric acids, which was the first earth abundant catalysed process for C(5)-alkylation of barbituric acids. A plausible mechanism was proposed validating the process as a borrowing hydrogen methodology.

## 2.6 Experimental

### 2.6.1. General Information

Unless stated otherwise, all reactions were performed using oven-dried 10 mL microwave vials equipped with Teflon-coated magnetic stirrer bars and sealed with an aluminium crimp cap. Dry solvents such as toluene, hexanes, diethyl ether and hexanes were obtained after passing these previously degassed solvents through activated alumina columns (Mbraun, SPS-800). All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Room temperature (rt) refers to 20-25 °C. Ice/water and CO<sub>2</sub>(s)/acetone baths were used to obtain temperatures of 0 °C and -78 °C respectively. All reactions involving heating were carried out using DrySyn blocks and contact thermometers. *In vacuo* refers to reduced pressure using a rotary evaporator.

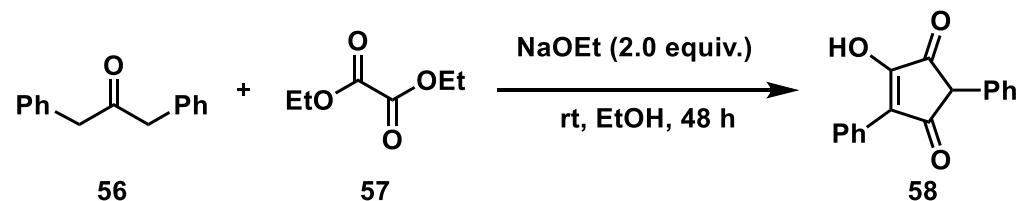
Analytical thin layer chromatography was carried out using aluminium plates coated with silica (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO<sub>4</sub> solution. Flash chromatography used Kieselgel (40-63 µm) silica in the solvent system stated. Melting points were recorded on a Gallenkamp melting point apparatus and corrected by linear interpolation of melting point standards benzophenone (47-49 °C), and benzoic acid (121-123 °C). Infrared spectra were recorded on a Shimadzu IR Affinity-1 Fourier Transform ATIR spectrometer as thin films using a Pike MIRacle ATR accessory. Characteristic peaks are quoted (ν<sub>max</sub> / cm<sup>-1</sup>). <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F NMR spectra were obtained on either a Bruker Avance 400 (<sup>1</sup>H NMR, 400 MHz; <sup>13</sup>C NMR, 101 MHz; <sup>19</sup>F NMR, 376 MHz) or a Bruker Avance 500 (<sup>1</sup>H NMR, 500 MHz, <sup>13</sup>C NMR, 126 MHz; <sup>19</sup>F NMR, 471 MHz) spectrometer at rt in

the solvent stated. Chemical shifts are reported in parts per million (ppm) not relative to TMS ( $^1\text{H}$ ,  $^{13}\text{C}$ ) but referenced using the residual solvent signal in  $^1\text{H}$  NMR and in  $^{13}\text{C}$  NMR spectra.  $^{19}\text{F}$  NMR spectra are reported in the absence of an internal standard reference. All coupling constants,  $J$ , are quoted in Hz. Multiplicities are reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, dt = doublet of triplets, tt = triplet of triplets and m = multiplet. The abbreviation Ph to denote phenyl, Ar to denote aromatic, br to denote broad. High resolution mass spectrometry (HRMS,  $m/z$ ) data was acquired either at Cardiff University on a Micromass LCT spectrometer or at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

#### 2.6.2. Synthesis of Precatalyst

The precatalyst was prepared via a 3-step synthesis as shown below:

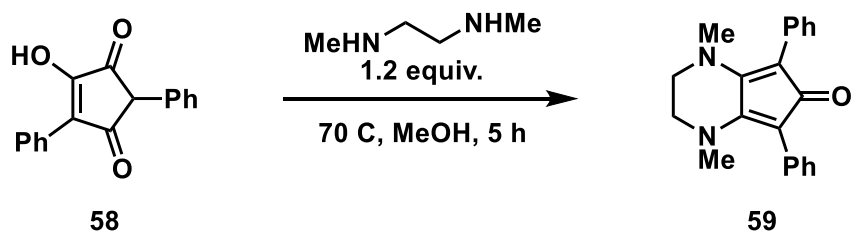
##### **Step 1:** Synthesis of 4-hydroxy-2,5-diphenylcyclopent-4-ene-1,3-dione



Under nitrogen, a flame dried Schlenk tube was charged with ethanol (20 mL) and metal sodium (920 mg, 40 mmol) at 0 °C. After complete dissolution, the solution was charged with 1,3-diphenylacetone (4.20 g, 20.0 mmol) and diethyl oxalate (2.70 mL, 2.92 g, 20 mmol). This was left to react at rt for 48 hours. The mixture was cooled to 0 °C and glacial acetic acid was carefully added dropwise until the colour turned yellow-orange. The reaction mixture was then poured into ice/water (100 mL) and the aqueous layer was acidified to pH 1 by careful

dropwise addition of concentrated sulfuric acid (96%). The yellow solid was filtered. The precipitate was dissolved in acetone (50 mL) and transferred to a conical flask. It was dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Purification by recrystallization yielded a yellow solid (2.75 g, 52%), mp 168-170 °C (dec) ( $\text{CHCl}_3$ /hexanes),  $R_f = 0.33$  (eluent = 100% EtOAc).  **$^1\text{H NMR}$  (500 MHz,  $(\text{CD}_3)_2\text{SO}$ )**  $\delta_{\text{H}}$ : 4.49 (1H, s), 7.19 (2H, d,  $J$  7.0), 7.28-7.46 (4H, m), 7.46-7.54 (2H, m), 7.98-8.10 (2H, m);  **$^{13}\text{C NMR}$  (126 MHz,  $(\text{CD}_3)_2\text{SO}$ )**  $\delta_{\text{C}}$ : 55.9, 127.4, 128.1, 128.2, 128.7, 128.8, 128.8, 128.8, 129.5, 134.4, 166.4, 196.8, 197.5. Spectroscopic data in accordance with that stated in the literature.<sup>1</sup>

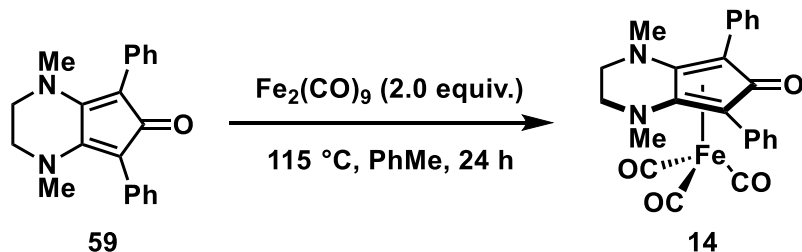
**Step 2:** Synthesis of 1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one



Under nitrogen, a flame dried round-bottomed flask was charged with 4-hydroxy-2,5-diphenylcyclopent-4-ene-1,3-dione (2.51 g, 9.50 mmol), methanol (15 mL) and *N,N'*-dimethylethylenediamine (1.23 mL, 1.00 g, 11.4 mmol). The mixture was heated under reflux for 5 h. It was then cooled and concentrated *in vacuo*, leading to the formation of the pure compound (2.86 g, 95%), mp 184-186 °C,  $R_f = 0.50$  (eluent = 5% MeOH in  $\text{CH}_2\text{Cl}_2$ ).  **$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{H}}$ : 2.84 (6H, s), 3.36 (4H, s), 7.12-7.19 (2H, m), 7.23-7.32 (8H, m);  **$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{C}}$ : 42.2, 50.1, 99.0, 125.6, 127.4, 131.2, 133.8, 151.0, 195.4. Spectroscopic data in accordance with that stated in the literature.<sup>19</sup>

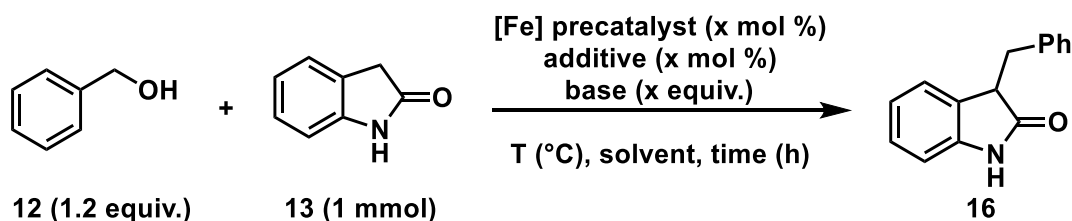


**Step 3:** Synthesis of the (1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one)tricarbonyliron



Under nitrogen, a flame dried Schlenk tube was charged with this 1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6H-cyclopenta[b]pyrazin-6-one (800 mg, 2.5 mmol), diiron nonacarbonyl (1.84 g, 5.0 mmol) and dry and degassed toluene (10 mL). The mixture was heated under reflux for 24 h. It was then cooled and transferred to a round-bottomed flask and washed several times with toluene (3 x 10 mL). The mixture was concentrated *in vacuo*. Purification by flash alumina chromatography surrounded by celite (0-1 % MeOH in  $\text{CH}_2\text{Cl}_2$ , 50 x 200 mm alumina) followed by precipitation (pentane/ $\text{Et}_2\text{O}$ ) gave an orange-yellow solid (800 mg, 69%), mp (198-201 °C)  $R_f = 0.46$  (eluent = 5% MeOH in  $\text{CH}_2\text{Cl}_2$ ).  **$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{H}}$ : 2.38 (6H, s), 2.87-2.97 (2H, m), 3.39-3.50 (2H, m), 7.29-7.35 (2H, m), 7.36-7.42 (4H, m), 7.51-7.58 (4H, m);  **$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{C}}$ : 41.6, 50.2, 71.1, 114.6, 128.0, 128.4, 131.9, 132.4, 165.8, 210.3. Spectroscopic data in accordance with that stated in the literature.<sup>19</sup>

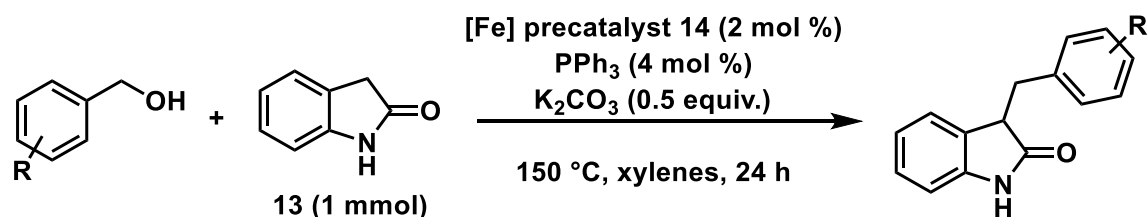
### 2.6.3 Optimization of Fe-catalyzed oxindole C(3)-benzylation



A 10 mL microwave vial equipped with a stirrer bar was charged with oxindole **13** (133 mg, 1.0 mmol), base (x equiv.), additive (x mol %) and precatalyst (x mol %) The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle repeated three times. Under nitrogen the vial was then charged with xylene (2 mL) and benzyl alcohol **12** (1.2 mmol, 1.2 equiv.). The mixture was left to react at 150 °C for 24 hours. It was then cooled, followed by the addition of mesitylene (139  $\mu$ L, 120 mg, 1.0 mmol), H<sub>2</sub>O (2 mL) and EtOAc (2 mL). Brine (1 mL) was added to aid layer separation. The mixture was stirred for 5 min, left to settle for a further 5 min, cap removed and the top layer was sampled and analysed using <sup>1</sup>H NMR with mesitylene as the internal standard.

### 2.6.3 Substrate Scope

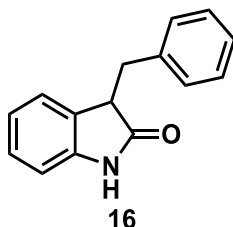
#### 2.6.3.1 General Procedure 1



A 10 mL microwave vial equipped with a stirrer bar was charged with substituted oxindole **13** (1.0 mmol), K<sub>2</sub>CO<sub>3</sub> (69.1 mg, 0.5 mmol, 0.5 equiv.), PPh<sub>3</sub> (10.5 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **14** (9.1 mg, 0.02 mmol, 2 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle repeated three times. Under nitrogen the vial was then charged with xylene (2 mL) and substituted benzyl alcohol **12** (1.2 mmol, 1.2 equiv.). The mixture was left to react at 150 °C for 24 hours. It was then cooled, washed with EtOAc (25 mL) and transferred to a separatory funnel filled

with brine (25 mL). The organic layer was collected and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*.

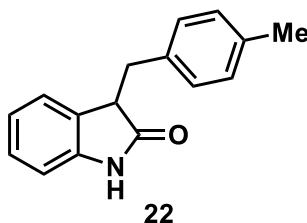
### 3-benzylindolin-2-one



The title compound was prepared according to general procedure 1 using benzyl alcohol **12** (124  $\mu\text{L}$ , 130 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol).

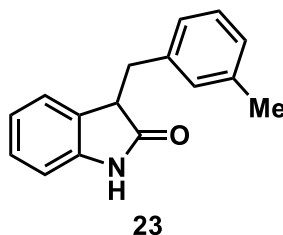
Purification by flash silica chromatography (eluent = 25% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a yellow solid (200 mg, 90%). mp 128-132  $^{\circ}\text{C}$  (Lit. 129-130 $^{\circ}\text{C}$ );<sup>20</sup>  $R_f$  = 0.20 (eluent = 20% EtOAc in hexanes);  **$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )**  $\delta_H$ : 2.94 (1H, dd,  $J$  13.6, 9.2,  $\text{CH}^A\text{H}^B$ ), 3.50 (1H, dd,  $J$  13.6, 4.4,  $\text{CH}^A\text{H}^B$ ), 3.75 (1H, dd,  $J$  9.2, 4.8, C(3) $H$ ), 6.75 (1H, d,  $J$  7.2, ArC(7) $H$ ), 6.83 (1H, d,  $J$  7.6, ArC(4) $H$ ), 6.90 (1H, t,  $J$  8.0, ArC(5) $H$ ), 7.13-7.31 (6H, m, Ar $H$ ), 8.24 (1H, br s, NH);  **$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )**  $\delta_C$ : 36.8 ( $\text{CH}_2$ ), 47.6 C(3)), 109.8 (ArC(7)), 122.2 (ArC(5)), 125.0 (ArC(4)), 126.8 (ArC(4')), 128.1 (ArC(6)), 128.5 (ArC(2',6')), 129.1 (ArC(1')), 129.6 (ArC(3',5')), 137.9 (ArC(3a)), 141.5(ArC(7a)), 179.5 (C=O). Spectroscopic data in accordance with the literature.<sup>20</sup>

### 3-(4-methylbenzyl)indolin-2-one



The title compound was prepared according to general procedure 1 using 4-methylbenzyl alcohol (147 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a pink solid (207 mg, 87%). mp 148-150 °C, (149-150°C);<sup>20</sup>  $R_f$  = 0.30 (eluent = 15% EtOAc in hexanes); **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta_H$ : 2.31 (3H, s), 2.91 (1H, dd,  $J$  14.0, 9.2), 3.45 (1H, dd,  $J$  13.6, 4.4), 3.73 (1H, dd,  $J$  9.2, 4.4), 6.80 (2H, dd,  $J$  17.6, 8.0), 6.91 (1H, dt,  $J$  7.6), 7.06 (4H, s), 7.16 (1H, t,  $J$  7.6), 8.15 (1H, br s); **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta_C$ : 21.2, 36.3, 47.6, 109.7, 122.2, 125.1, 128.0, 129.1, 129.2, 129.4, 134.8, 136.3, 141.4, 179.4. Spectroscopic data in accordance with the literature.<sup>20</sup>

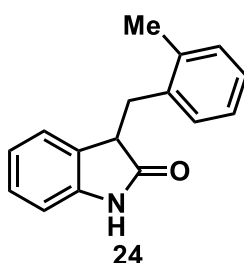
### 3-(3-methylbenzyl)indolin-2-one



The title compound was prepared according to general procedure 1 using 3-methylbenzyl alcohol (145  $\mu$ L, 147 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as an off-white solid (186 mg, 86%). mp 98-100 °C;  $R_f$  = 0.30 (eluent = 30% EtOAc in petroleum ether);  $\nu_{max}/cm^{-1}$  (film): 3132, 3065, 3024, 2914, 2820, 1697, 1613, 1468, 1337, 1300, 1227, 748, 694, 667, 617, 557; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta_H$ : 2.30 (3H, s, CH<sub>3</sub>), 2.88 (1H, dd,  $J$  13.6, 9.6, CH<sup>A</sup>H<sup>B</sup>), 3.46 (1H, dd,  $J$  13.6, 4.8, CH<sup>A</sup>H<sup>B</sup>), 3.73 (1H, dd,  $J$  9.2, 4.4, C(3)H), 6.74 (1H, d,  $J$  7.6, ArC(7)H), 6.81 (1H, d,  $J$  8.0, ArC(4)H), 6.89 (1H, dt,  $J$  14.4, 7.2, ArH), 6.97 (1H, d,  $J$  8.0, ArH), 7.03 (2H, d,  $J$  7.6, ArH), 7.09-7.21

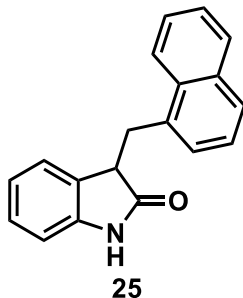
(2H, m, ArH), 7.87 (1H, br s, NH);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 21.5 (ArC(5)CH<sub>3</sub>), 36.8 (CH<sub>2</sub>), 47.7 C(3), 109.8 (ArC(7)), 122.2 (ArC(5)), 125.2 (ArC(4)), 126.1 (ArC(2')), 127.0 (ArC(3')), 128.1 (ArC(6)), 129.3 (ArC(1')), 130.2 (ArC(6')), 130.7 (ArC(4')), 136.7 (ArC(5')), 136.9 (ArC(3a)), 141.4 (ArC(7a)), 179.9 (C=O); HRMS (NSI<sup>+</sup>) calculated for [C<sub>16</sub>H<sub>16</sub>NO]<sup>+</sup> (M + H)<sup>+</sup> m/z: 238.1226, found 238.1229 (+1.1 ppm).

### 3-(2-methylbenzyl)indolin-2-one



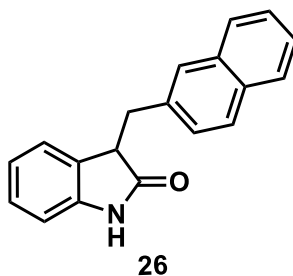
The title compound was prepared according to general procedure 1 using 2-methylbenzyl alcohol (145  $\mu\text{L}$ , 147 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a yellow solid (213 mg, 90%). mp 105-106 °C (Lit. 106-108 °C);<sup>17</sup>  $R_{\text{f}}$  = 0.33 (eluent = 20% EtOAc in hexanes);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.30 (3H, s) 2.81 (1H, dd,  $J$  13.6, 10.8), 3.52 (1H, dd,  $J$  14.0, 4.8), 3.71 (1H, dd,  $J$  10.8, 4.8), 6.54 (1H, d,  $J$  7.2), 6.80-6.91 (2H, m), 7.13-7.22 (5H, m), 8.63 (1H, br s);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 19.8, 34.4, 46.3, 109.8, 122.2, 125.2, 126.1, 127.0, 128.1, 129.3, 130.2, 130.7, 136.7, 136.9, 141.4, 179.8. Spectroscopic data in accordance with the literature.<sup>20</sup>

### 3-(naphthalen-1-ylmethyl)indolin-2-one



The title compound was prepared according to general procedure 1 using 1-naphthalenemethanol (190 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as pale a brown solid (248 mg, 91%). mp 135-138 °C;  $R_f$  = 0.33 (eluent = 20 % EtOAc in hexanes);  **$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{H}}$ : 3.06 (1H, dd,  $J$  14.0, 11.2), 3.89 (1H, dd,  $J$  11.2, 4.0), 4.13 (1H, dd,  $J$  14.0, 4.0, C(3) $H$ ), 6.81 (1H, d,  $J$  7.6), 6.81 (1H, t,  $J$  7.2), 6.88 (1H, d,  $J$  7.6), 7.16 (1H, t,  $J$  8.0), 7.31 (1H, d,  $J$  6.8), 7.44 (1H, t,  $J$  7.2), 7.49-7.62 (2H, m), 7.84 (2H, d,  $J$  7.6), 7.92 (1H, d,  $J$  8.0), 8.25 (1H, br s, NH);  **$^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{C}}$ : 35.1, 46.4, 109.6, 121.1, 123.8, 125.3, 125.6, 126.0, 126.5, 127.9, 128.0, 128.1, 129.1, 129.5, 131.8, 134.2, 134.4, 141.2, 179.3. Spectroscopic data in accordance with the literature.<sup>20</sup>

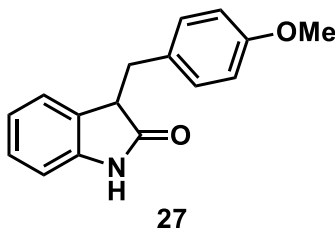
### 3-(naphthalen-2-ylmethyl)indolin-2-one



The title compound was prepared according to general procedure 1 using 2-naphthalenemethanol (190 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a cream solid (249 mg, 91%). mp 151-

153 °C;  $R_f = 0.38$  (eluent = 30 % EtOAc in hexanes);  $\nu_{\max}/\text{cm}^{-1}$  (film): 3175, 3136, 3073, 3024, 2905, 1694, 1614, 1472, 1337, 1310, 1236, 1148, 968, 820, 754, 735, 664, 583;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 3.12 (1H, dd,  $J$  13.6, 10.0,  $\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 3.65 (1H, dd,  $J$  14.0, 4.8,  $\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 3.88 (1H, dd,  $J$  10.0, 4.4, C(3)H), 6.78 (2H, t,  $J$  8.0, ArH), 6.87 (1H, t,  $J$  5.6, ArH), 7.14 (1H, t,  $J$  7.6, ArH), 7.33 (1H, dd,  $J$  8.4, 2.0, ArH), 7.39-7.51 (2H, m, ArH), 7.62 (1H, m, ArH), 7.69-7.82 (3H, m, ArH), 7.84 (1H, br s, NH);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 36.9 ( $\text{CH}_2$ ), 47.4 C(3), 109.7 (ArC(7)), 122.2 (ArC(5)), 125.1 (ArC(4)), 125.7 (ArC(2')), 126.1 (ArC(8')), 127.7 (ArC(7')), 127.8 (ArC(3')), 127.8 (ArC(6')), 128.1 (ArC(6)), 128.2 (ArC(4',5')), 129.1 (ArC(1')), 132.5 (ArC(2a')), 133.5 (ArC(6a')), 135.5 (ArC(3a)), 141.4 (ArC(7a)), 179.2 (C=O); HRMS ( $\text{ESI}^+$ ) calculated for  $[\text{C}_{19}\text{H}_{16}\text{NO}]^+$  (M + H) $^+$   $m/z$  : 274.1226, found 274.1230 (+1.3 ppm).

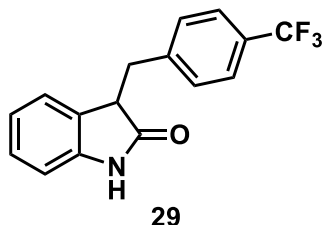
### 3-(4-methoxybenzyl)indolin-2-one



The title compound was prepared according to general procedure 1 using 4-methoxybenzyl alcohol (166 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a pink solid (218 mg, 86%). mp 111-114 °C (Lit. 110-111 °C);<sup>17</sup>  $R_f = 0.33$  (eluent = 15% EtOAc in petroleum ether);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.92 (1H, dd,  $J$  13.6, 7.6), 3.41 (1H, dd,  $J$  13.6, 4.4), 3.70 (1H, dd,  $J$  8.8, 4.4), 3.76 (3H, s), 6.75-6.83 (4H, m), 6.91 (1H, t,  $J$  6.4), 7.06 (2H, d,  $J$  8.8), 7.16 (1H, t,  $J$  6.8), 8.85 (1H, br s);  $^{13}\text{C NMR}$  (101 MHz,

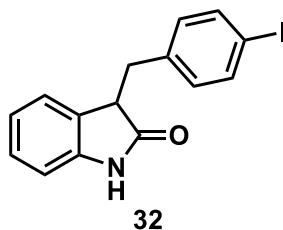
**CDCl<sub>3</sub>**)  $\delta_c$ : 35.9, 47.7, 55.3, 109.8, 113.9, 122.1, 150.0, 128.0, 129.2, 129.8, 130.5, 141.6, 158.4, 179.8. Spectroscopic data in accordance with the literature.<sup>20</sup>

### 3-(4-(trifluoromethyl)benzyl)indolin-2-one



The title compound was prepared according to general procedure 1 using 3-(4-trifluoromethyl) benzyl alcohol (164  $\mu$ L, 211 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a cream solid (259 mg, 89%). mp 128-130  $^{\circ}$ C; (Lit.112-113  $^{\circ}$ C);<sup>17</sup>  $R_f$  = 0.30 (eluent = 30% EtOAc in hexanes); **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta_H$ : 3.09 (1H, dd,  $J$  14.0, 8.4), 3.46 (1H, dd,  $J$  14.0, 4.8), 3.67 (1H, dd,  $J$  8.0, 4.4), 6.82 (2H, dd,  $J$  16.0, 7.6), 6.93 (1H, t,  $J$  7.6), 7.17 (1H, t,  $J$  8.0), 7.21-7.32 (2H, m), 7.41-7.53 (2H, m), 8.06 (1H, br, s); **<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)**  $\delta_F$ : -62.4; **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta_C$ : 36.3, 47.3, 110.1, 122.4, 124.3 (q,  $J$  272.2), 124.7, 125.4 (q,  $J$  3.5), 128.4, 128.5, 129.2 (q,  $J$  32.1), 129.9, 141.5, 141.9, 179.3. Spectroscopic data in accordance with the literature.<sup>20</sup>

### 3-(4-Iodobenzyl)indolin-2-one

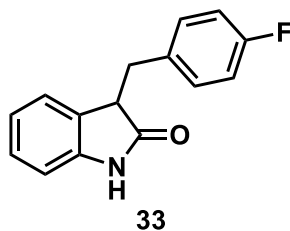


The title compound was prepared according to general procedure 1 using 4-iodobenzyl alcohol (281 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol).



Purification by flash silica chromatography (eluent = 15% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a cream solid (213 mg, 91%). Mp 153-155 °C;  $R_f = 0.35$  (eluent = 20% EtOAc in petroleum ether);  $\nu_{\max}/\text{cm}^{-1}$  (film): 3129, 3061, 3024, 2918, 2832, 1703, 1609, 1483, 1466, 1437, 1398, 1337, 1310, 1234, 1177, 1098, 1059, 1003, 775, 752, 658, 619;  **$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{H}}$ : 2.98 (1H, dd,  $J$  14.0, 8.5,  $\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 3.37 (1H, dd,  $J$  13.5, 4.5,  $\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 3.72 (1H, dd,  $J$  8.0, 4.5, C(3) $H$ ), 6.79 (1H, d,  $J$  8.0, ArC(7) $H$ ), 6.84-6.92 (3H, m, Ar $H$ ), 6.94 (1H, t,  $J$  7.5, ArC(5) $H$ ), 7.18 (1H, t,  $J$  8.0, ArC(6) $H$ ), 7.55 (2H, d,  $J$  8.5, ArC(3',5') $H$ ), 7.72 (1H, br s, NH);  **$^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{C}}$ : 36.1 ( $\text{CH}_2$ ), 47.3 C(3)), 92.3 (ArC(4')), 109.9 (ArC(7)), 122.3 (ArC(5)), 124.9 (ArC(4)), 128.3 (ArC(6)), 128.6 (ArC(1')), 131.6 (ArC(2',6')), 137.4 (ArC(3a)), 137.5 (ArC(3',5')), 141.4 (ArC(7a)), 178.9 (C=O); HRMS ( $\text{NSI}^+$ ) calculated for  $[\text{C}_{15}\text{H}_{13}\text{NOI}]^+$  ( $\text{M}+\text{H}$ ) $^+$   $m/z$ : 350.0036, found 350.0040 (+1.0 ppm).

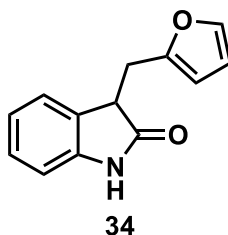
### 3-(4-fluorobenzyl)indolin-2-one



The title compound was prepared according to general procedure 1 using 4-fluorobenzyl alcohol (131  $\mu\text{L}$ , 151 mg 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as pale a yellow solid (213 mg, 88%). mp 128-130 °C (Lit. 151-152 °C);<sup>17</sup>  $R_f = 0.20$  (eluent = 20% EtOAc in petroleum ether);  **$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )**  $\delta_{\text{H}}$ : 3.02 (1H, dd,  $J$  14, 7.5), 3.41 (1H, dd,  $J$  14.0, 5.0), 3.72 (1H, dd,  $J$  7.5, 5.0), 6.79 (1H, d,  $J$  8.0), 6.85 (1H, d,  $J$  7.5),

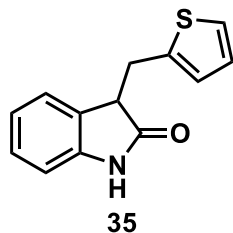
6.88-6.97 (3H, m), 7.04-7.13 (2H, m), 7.17 (1H, t, *J* 15.0), 7.71 (1H, br, s); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ<sub>F</sub>: -116.2; <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 35.8, 47.7, 109.9, 115.3 (d, *J* 21.2), 122.3, 124.8, 128.2, 128.8, 131.0 (d, *J* 16.2), 133.3 (d, *J* 3.2), 141.5, 161.9 (d, *J* 245), 179.5. Spectroscopic data in accordance with the literature.<sup>20</sup>

### 3-(furan-2-ylmethyl)indolin-2-one



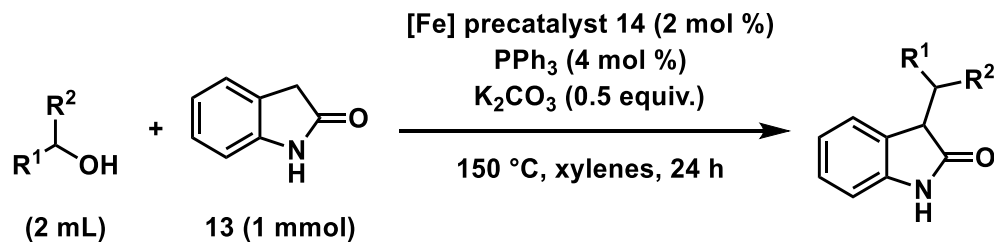
The title compound was prepared according to general procedure 1 using 2-hydroxymethyl furan (104 μL, 118 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a pale brown solid (164 mg, 77%). mp 142-147 °C (Lit. 146-147 °C);<sup>20</sup> R<sub>f</sub> = 0.52 (eluent = 30% EtOAc in petroleum ether); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 2.99 (1H, dd, *J* 14.5, 9.5), 3.48 (1H, dd, *J* 15.0, 4.0), 3.81 (1H, dd, *J* 9.0, 4.0), 6.03 (1H, s), 6.29 (1H, s), 6.79 (1H, d, *J* 7.0), 6.86 (1H, d, *J* 7.5), 6.94 (1H, t, *J* 8.5), 7.19 (1H, t, *J* 7.5), 7.34 (1H, s), 8.12 (1H, br s); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 29.2, 45.2, 107.5, 109.8, 110.5, 122.4, 124.9, 128.2, 128.9, 141.4, 141.7, 152.0, 179.2. Spectroscopic data in accordance with the literature.<sup>20</sup>

### 3-(thiophen-2-ylmethyl)indolin-2-one



The title compound was prepared according to general procedure 1 using 2-hydroxymethyl thiophene (114  $\mu\text{L}$ , 137 mg, 1.2 mmol) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a brown solid (192 mg, 84%). mp 152-153  $^{\circ}\text{C}$  (Lit. 154-155  $^{\circ}\text{C}$ );<sup>20</sup>  $R_f$  = 0.50 (eluent = 20% EtOAc in petroleum ether);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 3.35 (1H, dd,  $J$  15.0, 8.0), 3.60 (1H, dd,  $J$  15.0, 4.5), 3.75 (1H, dd,  $J$  7.5, 4.5), 6.75-6.83 (2H, m), 6.87 (1H, t,  $J$  4.0), 6.94-7.01 (2H, m), 7.09 (1H, d,  $J$  4.0), 7.19 (1H, t,  $J$  5.5), 7.57 (1H, br, s);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 30.9, 47.6, 109.7, 122.4, 124.4, 124.9, 126.6, 126.8, 128.4, 128.7, 139.7, 141.5, 178.4. Spectroscopic data in accordance with the literature.<sup>20</sup>

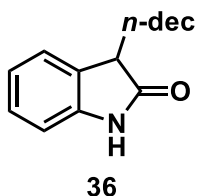
#### 2.6.3.2 General procedure 2



A 10 mL microwave vial equipped with a stirrer bar was charged with oxindole **13** (133 mg, 1.0 mmol),  $\text{K}_2\text{CO}_3$  (69.1 mg, 0.5 mmol, 0.5 equiv.),  $\text{PPh}_3$  (10.5 mg, 0.04 mmol, 4 mol %) and  $[\text{Fe}]$  precatalyst **11** (9.1 mg, 0.02 mmol, 2 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle repeated three times. Under nitrogen the vial was then charged with alcohol (2 mL). The mixture was left to react at 150  $^{\circ}\text{C}$  for 24 hours. It was then cooled, washed with EtOAc (25 mL) and transferred to a

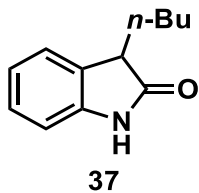
separatory funnel filled with brine (25 mL). The organic layer was collected and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*.

### 3-decylindolin-2-one



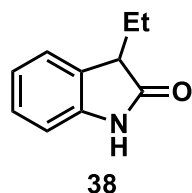
The title compound was prepared according to general procedure 2 using 1-decanol (2 mL) and oxindole **13** (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as pale yellow solid (112 mg, 59%). mp 70-71°C; R<sub>f</sub> = 0.29 (eluent = 20% EtOAc in petroleum ether);  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3177, 3065, 2911, 2851, 1697, 1616, 1470, 1344, 1319, 1223, 1173, 1152, 747, 718, 665, 584; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{H}}$ : 0.87 (3H, t, *J* 7.0, (CH<sub>3</sub>)), 1.17-1.47 (16H, m, 8 x (CH<sub>2</sub>)), 1.85-2.06 (2H, m, C(3)H(CH<sub>2</sub>)), 3.46 (1H, t, *J* 5.5, C(3)H), 6.88 (1H, d, *J* 7.5, ArC(4)H), 7.03 (1H, t, *J* 9.0, ArC(5)H), 7.17-7.25 (2H, m, ArH), 8.25 (1H, br s, NH); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{C}}$ : 14.3 (CH<sub>2</sub>CH<sub>3</sub>), 22.8 (CH<sub>2</sub>CH<sub>3</sub>), 25.9 (CH<sub>2</sub>CH<sub>2</sub>), 29.4 (CH<sub>2</sub>CH<sub>2</sub>), 29.5 (CH<sub>2</sub>CH<sub>2</sub>), 29.7 (CH<sub>2</sub>CH<sub>2</sub>), 29.7 (CH<sub>2</sub>CH<sub>2</sub>), 29.8 (CH<sub>2</sub>CH<sub>2</sub>), 30.7 (CH<sub>2</sub>CH<sub>2</sub>), 32.0 (CHCH<sub>2</sub>), 46.3 C(3), 109.8 (ArC(7)), 122.3 (ArC(5)), 124.3 (ArC(4)), 127.9 (ArC(6)), 130.1 (ArC(3a)), 141.7 (ArC(7a)), 180.8 (C=O); HRMS (**NSI**<sup>+</sup>) calculated for [C<sub>18</sub>H<sub>28</sub>NO]<sup>+</sup> (M + H)<sup>+</sup> m/z: 274.2165, found 274.2167 (+0.6 ppm).

### 3-butylindolin-2-one



The title compound was prepared according to general procedure 2 using 1-butanol (2 mL) and oxindole **13** (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a yellow solid (159 mg, 71%). mp 59-62°C;  $R_f = 0.62$  (eluent = 20% EtOAc in petroleum ether);  $\nu_{\max}/\text{cm}^{-1}$  (film): 3183, 3078, 2953, 2928, 2862, 1697, 1613, 1468, 1333, 1314, 1223, 1171, 1153, 1099, 795, 747, 702, 665, 583;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.88 (3H, t,  $J$  7.0, ( $\text{CH}_2\text{CH}_3$ )), 1.23-1.45 (4H, m, 2 x ( $\text{CH}_2$ )), 1.87-2.05 (2H, m, ( $\text{C}(3)\text{H}(\text{CH}_2)$ )), 3.47 (1H, t,  $J$  6.0, ), 6.88 (1H, d,  $J$  8.0), 7.03 (1H, t,  $J$  7.0), 7.17-7.25 (2H, m), 8.18 (1H, br s);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 14.0 ( $\text{CH}_2\text{CH}_3$ ), 22.9 ( $\text{CH}_2\text{CH}_3$ ), 28.0 ( $\text{CH}_2\text{CH}_2$ ), 30.4 ( $\text{C}(3)(\text{CH}_2)$ ), 46.2 ( $\text{C}(3)$ ), 109.8 ( $\text{ArC}(7)$ ), 122.4 ( $\text{ArC}(5)$ ), 124.3 ( $\text{ArC}(4)$ ), 127.9 ( $\text{ArC}(6)$ ), 130.1 ( $\text{ArC}(3a)$ ), 141.7 ( $\text{ArC}(7a)$ ), 180.8 ( $\text{C}=\text{O}$ ); HRMS ( $\text{NSI}^+$ ) calculated for  $[\text{C}_{12}\text{H}_{16}\text{NO}]^+$  ( $\text{M} + \text{H}$ ) $^+$   $m/z$ : 190.1226, found 190.1225 (-0.7 ppm).

### 3-ethylindolin-2-one

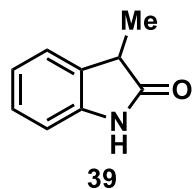


The title compound was prepared according to general procedure 2 using ethanol (2 mL) and oxindole **13** (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a cream solid (126 mg, 79%). mp 98-100 °C (Lit. 99-101°C);<sup>21</sup>  $R_f = 0.23$  (eluent = 20% EtOAc in petroleum ether);  $^1\text{H NMR}$  (400 MHz,

**CDCl<sub>3</sub>**)  $\delta_{\text{H}}$ : 0.93 (3H, t, *J* 7.2), 1.94-2.16 (2H, m), 3.46 (1H, t, *J* 5.6), 6.91 (1H, d, *J* 6.8), 7.03 (1H, t, *J* 8.0), 7.17-7.25 (2H, m), 9.01 (1H, br s); **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{C}}$ : 10.1, 23.7, 47.4, 109.9, 122.3, 124.2, 127.9, 129.7, 142.0, 181.1.

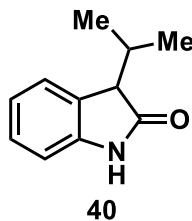
Spectroscopic data in accordance with the literature.<sup>21</sup>

### 3-methylindolin-2-one



The title compound was prepared according to general procedure 2 using methanol (2 mL) and oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a pale brown solid (90 mg, 61%). mp 117-119 °C, (Lit. 119-120°C);<sup>22</sup>  $R_{\text{f}}$  = 0.24 (eluent = 20% EtOAc in hexanes); **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{H}}$ : 1.51 (3H, d, *J* 7.6), 3.47 (1H, q, *J* 7.6), 6.89 (1H, d, *J* 7.6), 7.03 (1H, dt, *J* 8.3, 1.0), 7.16-7.26 (2H, m), 8.46 (1H, br s); **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{C}}$ : 15.4, 41.3, 109.9, 122.5, 123.9, 128.0, 131.4, 141.4, 181.8. Spectroscopic data in accordance with the literature.<sup>22</sup>

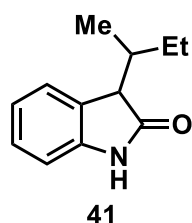
### 3-isopropylindolin-2-one



The title compound was prepared according to general procedure 2 using 2-propanol (2 mL) and oxindole **13** (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in petroleum ether, 30 x 150 mm silica)

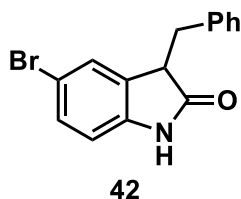
gave the title compound as an orange solid (140 mg, 80%). mp 102-106 °C (Lit. 102-106 °C);<sup>20</sup> R<sub>f</sub> = 0.36 (eluent = 20% EtOAc in petroleum ether); **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)** δ<sub>H</sub>: 0.93 (3H, d, *J* 6.8), 1.21 (3H, d, *J* 7.2), 2.43-2.57 (1H, m), 3.40 (1H, d, *J* 3.6), 6.88 (1H, d, *J* 8.0), 7.01 (1H, dt, *J* 7.6, 1.2), 7.17-7.25 (2H, m), 8.32 (1H, br s); **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)** δ<sub>C</sub>: 18.1, 20.0, 30.9, 52.3, 109.7, 122.2, 124.8, 128.0, 128.5, 142.1, 180.1. Spectroscopic data in accordance with the literature.<sup>20</sup>

### 3-(sec-butyl)indoline



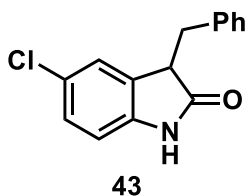
The title compound was prepared according to general procedure 2 using [Fe] precatalyst **14** (18.2 mg, 0.04 mmol, 4 mol %), PPh<sub>3</sub> (21 mg, 0.08 mmol, 8 mol %), 2-butanol (2 mL) and oxindole **13** (133 mg, 1.0 mmol); giving the crude product after work up (56:44 *dr*). Purification by flash silica chromatography (eluent = 15% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as an inseparable mixture of diastereomers, as a white solid (159 mg, 84%, 3:1 *dr*); mp 114-118 °C; R<sub>f</sub> = 0.30 (eluent = 20% EtOAc in petroleum ether); ν<sub>max</sub>/cm<sup>-1</sup> (film): 3158, 2957, 2928, 2870, 1703, 1663, 1620, 1487, 1466, 1333, 1227, 1018, 943, 743, 665, 625, 579; Data for mixture of diastereomers: **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ<sub>H</sub>: 0.78 (2H, d, *J* 6.5), 0.93 (1H, t, *J* 7.5), 0.98-1.08 (3H, m), 1.48-1.68 (2H, m), 2.15-2.32 (1H, m), 3.44-3.55 (1H, m), 6.86-6.92 (1H, m), 6.97-7.04 (1H, m), 7.16-7.25 (2H, m), 8.57-8.71 (1H, m); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ<sub>C</sub>: 12.3, 12.4, 15.1, 16.6, 25.8, 27.5, 37.5, 37.8, 50.7, 51.2, 109.6, 109.7, 122.1, 122.2, 124.4, 125.0, 127.8, 127.9, 128.1, 129.2, 142.0, 142.2, 180.0, 180.6; HRMS (**NSI**<sup>+</sup>) calculated for [C<sub>12</sub>H<sub>16</sub>NO]<sup>+</sup> (M + H)<sup>+</sup> m/z: 190.1226, found 190.1225 (-0.7 ppm).

### 3-benzyl-5-bromoindolin-2-one



The title compound was prepared according to general procedure 1 using benzyl alcohol **12** (124  $\mu$ L, 130 mg, 1.2 mmol) and 5-bromo-2-oxindole (212 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a yellowish brown solid (246 mg, 80%); mp 133-134  $^{\circ}$ C (Lit. 138-140  $^{\circ}$ C);<sup>21</sup>  $R_f$  = 0.20 (eluent = 20% EtOAc in hexanes);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.90 (1H, dd,  $J$  14.0, 9.5), 3.41 (1H, dd,  $J$  13.5, 4.5), 3.70 (1H, dd,  $J$  8.5, 4.5), 6.70 (1H, d,  $J$  8.0), 6.82 (1H, s), 7.12 (2H, d,  $J$  7.0), 7.16-7.30 (4H, m), 9.24 (1H, br s);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 36.6, 47.8, 111.3, 114.8, 127.1, 128.1, 128.6, 129.5, 131.0, 131.1, 137.2, 140.6, 179.4. Spectroscopic data in accordance with the literature.<sup>21</sup>

### 3-benzyl-5-chloroindolin-2-one

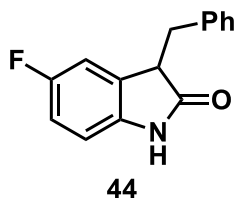


The title compound was prepared according to general procedure 1 using benzyl alcohol **12** (124  $\mu$ L, 130 mg, 1.2 mmol) and 5-chloro-2-oxindole (168 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a yellow solid (236 mg, 92%); mp 106-109  $^{\circ}$ C (Lit. 115-116  $^{\circ}$ C);<sup>21</sup>  $R_f$  = 0.26 (eluent = 20% EtOAc in hexanes);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.94 (1H, dd,  $J$  13.5, 9.0), 3.43 (1H, dd,  $J$  13.5, 4.5), 3.71 (1H, dd,  $J$  8.5, 4.5), 6.72 (2H, d,  $J$  8.5), 7.08-7.18 (3H, m), 7.18-7.26



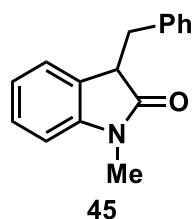
(3H, m), 8.39 (1H, br s);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 36.6, 47.9, 110.8, 125.3, 127.1, 127.5, 128.1, 128.6, 129.5, 130.8, 137.3, 140.2, 179.6. Spectroscopic data in accordance with the literature.<sup>21</sup>

### 3-benzyl-5-fluoroindolin-2-one



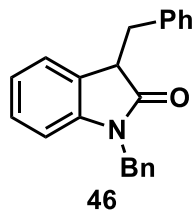
The title compound was prepared according to general procedure 1 using benzyl alcohol **12** (124  $\mu\text{L}$ , 130 mg, 1.2 mmol) and 5-fluoro-2-oxindole (151 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a pale brown solid (120 mg, 50%). mp 137-139  $^{\circ}\text{C}$ ;  $R_{\text{f}}$  = 0.26 (eluent = 20% EtOAc in hexanes);  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3080, 3026, 2918, 2872, 1715, 1672, 1628, 1479, 1252, 1206, 1159, 889, 866, 818, 777, 741, 692, 652;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.96 (1H, dd,  $J$  14.0, 9.5,  $\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 3.50 (1H, dd,  $J$  14.0, 4.5,  $\text{CH}^{\text{A}}\text{H}^{\text{B}}$ ), 3.76 (1H, dd,  $J$  9.0, 4.5, C(3)H), 6.50 (1H, d,  $J$  7.5, ArH), 6.75 (1H, dd,  $J$  8.5, 4.5, ArH), 6.88 (1H, dt,  $J$  9.0, 2.0, ArH), 7.19 (2H, d,  $J$  7.0, ArH), 7.22-7.33 (3H, m, ArH), 8.03 (1H, br s, NH);  $^{19}\text{F}$  NMR (376 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{F}}$ : 120.8;  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 36.6 (C(3)HCH<sub>2</sub>), 48.1 C(3)H, 110.2 (d,  $J$  8.2, ArC(7)), 113.0 (d,  $J$  25.0, ArC(4)), 114.5 (d,  $J$  23.7, ArC(6)), 127.1 ArC(4'), 128.6 ArC(2',6'), 129.5 ArC(3',5'), 130.7 (d,  $J$  8.4, ArC(3a)), 137.4 (d,  $J$  2.0, ArC(7a)), 158.8 (d,  $J$  240, ArC(5)), 179.3 (C=O); HRMS ( $\text{NSI}^+$ ) calculated for  $[\text{C}_{15}\text{H}_{13}\text{FNO}]^+$  (M + H)<sup>+</sup>  $m/z$ : 242.0976, found 242.0979 (+1.4 ppm).

### 3-benzyl-1-methylindolin-2-one



The title compound was prepared according to general procedure 1 using benzyl alcohol **12** (124  $\mu\text{L}$ , 130 mg, 1.2 mmol) and *N*-methyloxindole (147 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a yellow solid (177 mg, 75%); mp 61-63  $^{\circ}\text{C}$ ;  $R_f = 0.32$  (eluent = 20% EtOAc in hexanes);  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2922, 2851, 1697, 1609, 1495, 1466, 1452, 1370, 1354, 1339, 1262, 1157, 1121, 1084, 1018, 991, 748, 702, 623, 586, 540;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.90 (1H, dd,  $J$  14.0, 9.5), 3.18 (3H, s), 3.52 (1H, dd,  $J$  13.5, 4.5), 3.74 (1H, dd,  $J$  9.5, 4.5), 6.77 (2H, t,  $J$  7.0), 6.94 (1H, t,  $J$  6.5), 7.19 (2H, d,  $J$  7.0), 7.21-7.32 (4H, m);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 26.3, 37.0, 47.2, 108.0, 122.2, 124.7, 126.7, 128.1, 128.4, 128.5, 129.5, 138.1, 144.3, 177.2; HRMS ( $\text{NSI}^+$ ) calculated for  $[\text{C}_{16}\text{H}_{16}\text{NO}]^+$  ( $\text{M} + \text{H}$ ) $^+$   $m/z$ : 238.1226, found 238.1228 (+0.7 ppm).

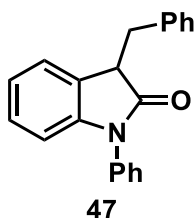
### 1,3-dibenzylindolin-2-one



The title compound was prepared according to general procedure 1 using benzyl alcohol **12** (124  $\mu\text{L}$ , 130 mg, 1.2 mmol) and *N*-benzyloxindole (223 mg, 1.2 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a white solid (253 mg, 80%); mp 95-97  $^{\circ}\text{C}$  (Lit. 97-98  $^{\circ}\text{C}$ );<sup>20</sup>  $R_f = 0.36$  (eluent = 20% EtOAc in hexanes);  $^1\text{H NMR}$  (400 MHz,

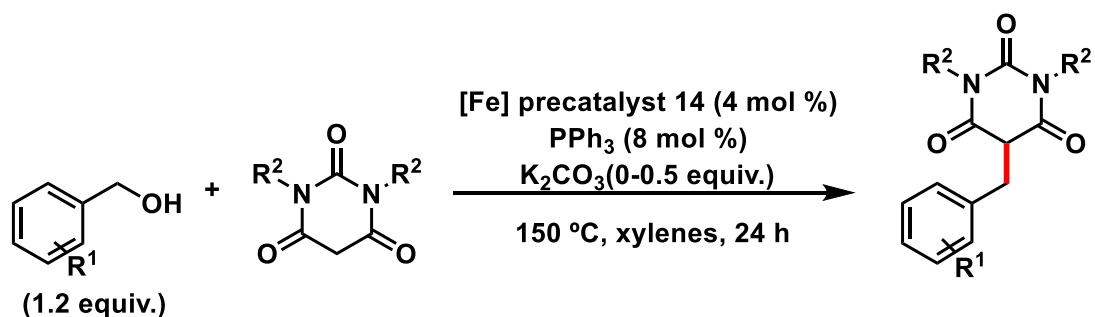
**CDCl<sub>3</sub>**)  $\delta_{\text{H}}$ : 3.13 (1H, dd, *J* 13.6, 8.0), 3.51 (1H, dd, *J* 13.6, 4.4), 3.85 (1H, dd, *J* 8.4, 4.4), 4.58 (1H, d, *J* 15.6), 5.03 (1H, d, *J* 15.6), 6.55 (1H, d, *J* 7.6), 6.94-6.99 (4H, m), 7.19-7.15 (3H, m), 7.17-7.25 (6H, m); **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{C}}$ : 36.6, 43.6, 47.2, 109.2, 122.2, 124.6, 126.8, 127.0, 127.4, 128.0, 128.3, 128.4, 128.8, 129.8, 135.7, 137.5, 143.5, 177.0. Spectroscopic data in accordance with the literature.<sup>20</sup>

### 3-benzyl-1-phenylindolin-2-one



The title compound was prepared according to general procedure 1 using benzyl alcohol **12** (124  $\mu\text{L}$ , 130 mg, 1.2 mmol) and 1-phenyloxindole (209 mg, 1.2 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as an off-white solid (223 mg, 75%); mp 87-89 °C;  $R_{\text{f}}$  = 0.26 (eluent = 20% EtOAc in hexanes);  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 3057, 3034, 1717, 1609, 1589, 1497, 1476, 1451, 1371, 1327, 1275, 1223, 1171, 1099, 1076, 1022, 754, 696; **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{H}}$ : 3.17 (1H, dd, *J* 14.0, 8.4), 3.52 (1H, dd, *J* 13.2, 4.4), 3.92 (1H, dd, *J* 8.4, 4.4), 6.64 (1H, d, *J* 7.6), 6.93-7.02 (2H, m), 7.11-7.17 (3H, m), 7.17-7.25 (5H, m), 7.38 (1H, t, *J* 6.8), 7.48 (2H, t, *J* 7.2); **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta_{\text{C}}$ : 37.2, 47.3, 109.2, 122.6, 124.8, 126.7, 126.8, 128.0, 128.1, 128.2, 128.3, 129.6, 129.7, 134.5, 137.3, 144.4, 176.5; HRMS (**NSI**<sup>+</sup>) calculated for [C<sub>21</sub>H<sub>18</sub>NO]<sup>+</sup>(M + H)<sup>+</sup> *m/z*: 300.1383, found 300.1384 (+0.4 ppm).

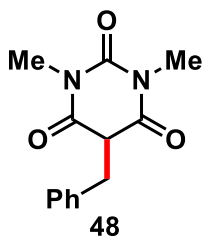
### 5-benzyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione



### 2.6.3.2 General Procedure 2

A 10 mL microwave vial equipped with a stirrer bar was charged with barbituric acid (1.0 mmol),  $\text{K}_2\text{CO}_3$  (0-0.5 equiv.),  $\text{PPh}_3$  (21.0 mg, 0.08 mmol, 8 mol %) and [Fe] precatalyst **14** (18.3 mg, 0.04 mmol, 4 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle repeated three times. Under nitrogen the vial was then charged with alcohol (1.2 mmol) and xylene (2 mL). The mixture was left to react at 150 °C for 24 h. It was then cooled, washed with EtOAc (25 mL) and transferred to a separatory funnel filled with brine (25 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*.

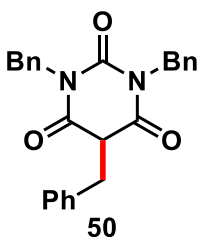
### 5-benzyl-1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione



The title compound was prepared according to general procedure 2 using *N,N*-dimethyl barbituric acid (156 mg, 1.0 mmol),  $\text{PPh}_3$  (21.0 mg, 0.08 mmol) and [Fe] precatalyst **14** (18.3 mg, 0.04 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as

an orange solid (147 mg, 60%). mp 110-112 °C;  $R_f = 0.23$  (eluent = 20% EtOAc in hexanes);  $\nu_{\max}/\text{cm}^{-1}$  (film): 2928, 2851, 1665, 1441, 1418, 1377, 1310, 1279, 1202, 1161, 1101, 1024, 995, 930, 849, 750, 706, 561;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 3.12 (6H, s, 2 x ( $\text{CH}_3$ )), 3.46 (2H, d,  $J$  4.8, ( $\text{C}(3)\text{HCH}_2$ )), 3.77 (1H, t,  $J$  4.8,  $\text{C}(3)\text{H}$ ), 7.03 (2H, dd,  $J$  7.2, 3.6,  $\text{ArC}(2',6')\text{H}$ ), 7.21-7.25 (3H, m,  $\text{ArH}$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 28.3 (2x  $\text{N}(\text{CH}_3)$ ), 38.0  $\text{C}(3)\text{HCH}_2$ , 50.9  $\text{C}(3)\text{H}$ , 128.0  $\text{ArC}(4')$ , 128.7  $\text{ArC}(3',5')$ , 129.0  $\text{ArC}(2',6')$ , 135.3  $\text{ArC}(1')$ , 151.1  $\text{MeN}(\text{C}=\text{O})\text{NMe}$ , 168.4  $\text{MeN}(2\text{x}\text{C}=\text{O})\text{NMe}$ ; HRMS ( $\text{NSI}^+$ ) calculated for  $[\text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_3]^+(\text{M} + \text{H})^+$   $m/z$ : 247.1077, found 247.1080 (+1.1 ppm).

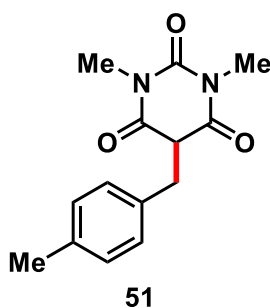
### 1,3,5-tribenzylpyrimidine-2,4,6(1H,3H,5H)-trione



The title compound was prepared according to general procedure 2 using 1,3-dibenzylpyrimidine-2,4,6(1H,3H,5H)-trione (308 mg, 1.0 mmol), benzyl alcohol (124  $\mu\text{L}$ , 130 mg, 1.2 mmol) and  $\text{K}_2\text{CO}_3$  (69 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 180 mm silica) gave the title compound as a white solid (227 mg, 57%); mp 105-108 °C (Lit. 110-112 °C);  $R_f = 0.48$  (eluent = 30% EtOAc in hexanes);  $\nu_{\max} / \text{cm}^{-1}$  (film): 3061, 3032, 2978, 1678, 1584, 1493, 1433, 1400, 1337, 1273, 1204, 1155, 1084, 1063, 1028, 745, 691, 604, 573, 500;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 3.47 (2H, d,  $J$  5.0,  $\text{CHCH}_2$ ), 3.79 (1H, t,  $J$  5.0,  $\text{CHCH}_2$ ), 4.90 (4H, s, 2x $\text{CH}_2\text{N}$ ), 6.82 (2H, d,  $J$  7.5, ( $\text{CHCH}_2$ ) $\text{ArC}(2,6)\text{H}$ ), 6.95 (2H, t,  $J$  7.5, ( $\text{CHCH}_2$ ) $\text{ArC}(3,5)\text{H}$ ), 7.12 (1H, t,  $J$  7.5,

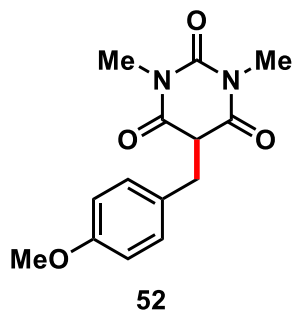
CHCH<sub>2</sub>ArC(4)H), 7.18-7.32 (10H, m, (2xNCH<sub>2</sub>)ArC(2-6)H); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δC: 37.2 (2xCH<sub>2</sub>N), 45.2 (CH<sub>2</sub>Ph), 50.5 (CHCH<sub>2</sub>), 127.5 (CHCH<sub>2</sub>ArC(4)), 128.0 (ArC), 128.6 (ArC), 128.7 (CHCH<sub>2</sub>ArC(3,5)), 129.0 (CHCH<sub>2</sub>ArC(2,6)), 129.3 (ArC(4')), 135.0 (CH<sub>2</sub>ArC(1)), 136.0 (2xNCH<sub>2</sub>ArC(1)), 151.0 (N-(C=O)-N), 168.0 (2xBnN-(C=O)); HRMS (ESI+) calculated for [C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub>]<sup>+</sup> (M+H)<sup>+</sup> m/z : 399.1709, found 399.1707, (-0.5 ppm).

### 1,3-dimethyl-5-(4-methylbenzyl)pyrimidine-2,4,6(1H,3H,5H)-trione



The title compound was prepared according to general procedure 2 using *N,N*-dimethyl barbituric acid (156 mg, 1.0 mmol) and 4-methylbenzyl alcohol (147 mg, 1.2 mmol). Purification by flash silica chromatography (eluent = 5-15% EtOAc in cyclohexane, 30 x 160 mm silica) gave the title compound as a yellow solid (189 mg, 73%); mp 94-97 °C; R<sub>f</sub> = 0.24 (eluent = 30% EtOAc in hexanes); ν<sub>max</sub> / cm<sup>-1</sup> (film): 3036, 2986, 2936, 1680, 1653, 1468, 1435, 1383, 1323, 1308, 1287, 1119, 1003, 866, 804, 764, 604, 548, 474; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δH: 2.28 (3H, s, ArC(4)CH<sub>3</sub>), 3.13 (6H, s, 2xNCH<sub>3</sub>), 3.42 (2H, d, *J* 4.5, CHCH<sub>2</sub>), 3.75 (1H, t, *J* 4.5, CHCH<sub>2</sub>), 6.91 (2H, d, *J* 7.5, ArC(2,6)H), 7.03 (2H, d, *J* 7.5, ArC(3,5)H); <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>) δC: 21.2 (ArC(4)CH<sub>3</sub>), 28.3 (2xNCH<sub>3</sub>), 37.7 (CHCH<sub>2</sub>), 50.9 (CHCH<sub>2</sub>), 128.9 (ArC), 129.4 (ArC), 132.1 (ArC), 137.6 (ArC), 151.2 (N-(C=O)-N), 168.5 (2xMeN-(C=O)); HRMS (EI+) calculated for [C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>]<sup>+</sup> (M)<sup>+</sup> m/z : 260.1161, found 260.1170, (+3.5 ppm).

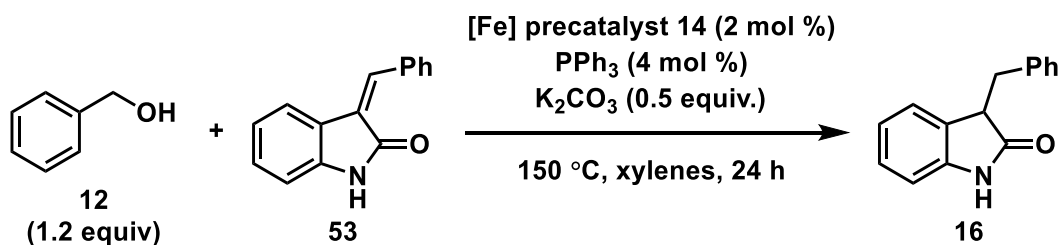
## 5-(4-methoxybenzyl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione



The title compound was prepared according to general procedure 2 using *N,N*-dimethyl barbituric acid (156 mg, 1.0 mmol), 4-methoxybenzyl alcohol (138 mg, 1.2 mmol), and  $K_2CO_3$  (69 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as an off-white solid (138 mg, 50%); mp 108-111 °C (Lit. 113 °C);<sup>11</sup>  $R_f = 0.16$  (eluent = 30% EtOAc in hexanes);  **$^1H$  NMR (500 MHz,  $CDCl_3$ )**  $\delta$ H: 3.14 (6H, s, 2xNCH<sub>3</sub>), 3.42 (2H, d, *J* 4.5, CHCH<sub>2</sub>), 3.74 (1H, t, *J* 4.5, CHCH<sub>2</sub>), 3.76 (3H, s, OCH<sub>3</sub>), 6.75 (2H, d, *J* 7.5, ArC(3,5)H), 6.95 (2H, d, *J* 8.0, ArC(2,6)H);  **$^{13}C$  NMR (126 MHz,  $CDCl_3$ )**  $\delta$ C: 28.4 (2xNCH<sub>3</sub>), 37.3 (CH<sub>2</sub>), 51.0 (CHCH<sub>2</sub>), 55.3 (OCH<sub>3</sub>), 114.1 (ArC(3,5)), 127.1 (ArC(1)), 130.1 (ArC(2,6)), 151.2 (N-(C=O)-N), 159.3 (ArC(4)), 168.5 (2xMeN-(C=O)). Spectroscopic data in accordance with that stated in the literature.<sup>23</sup>

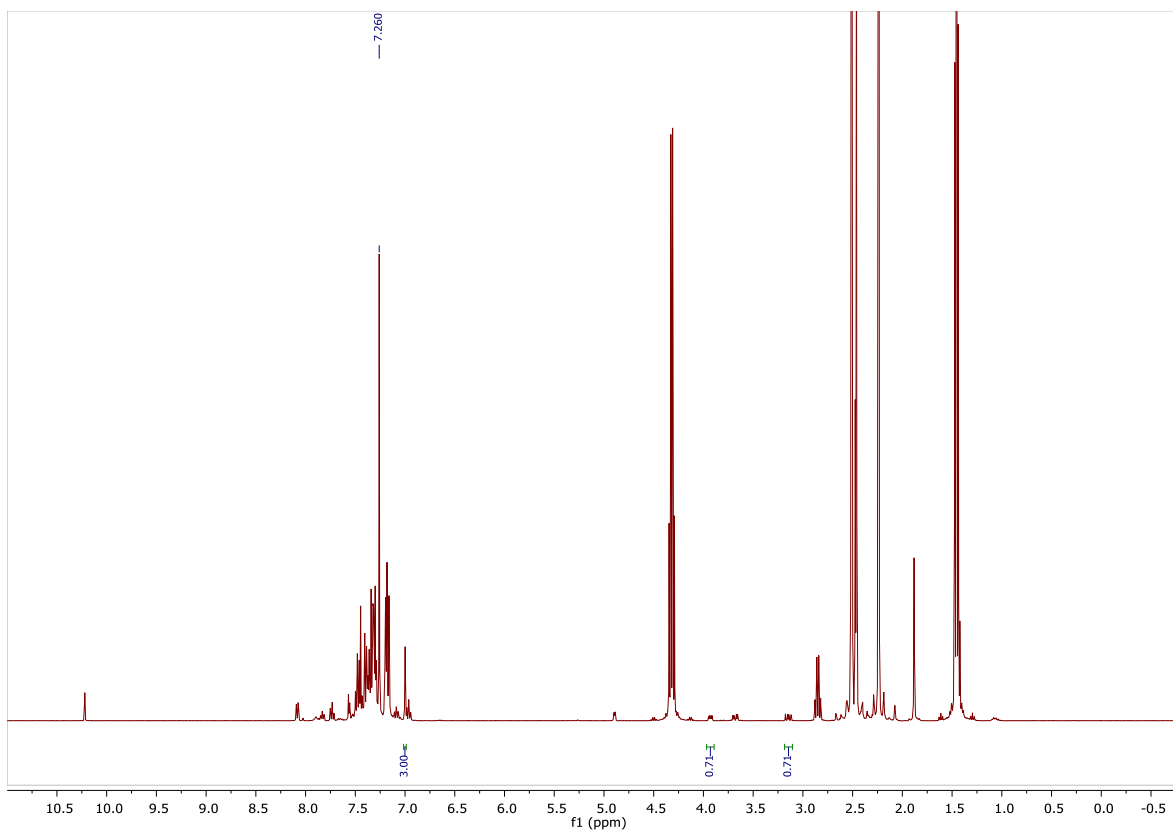
### 2.6.4 Mechanistic studies

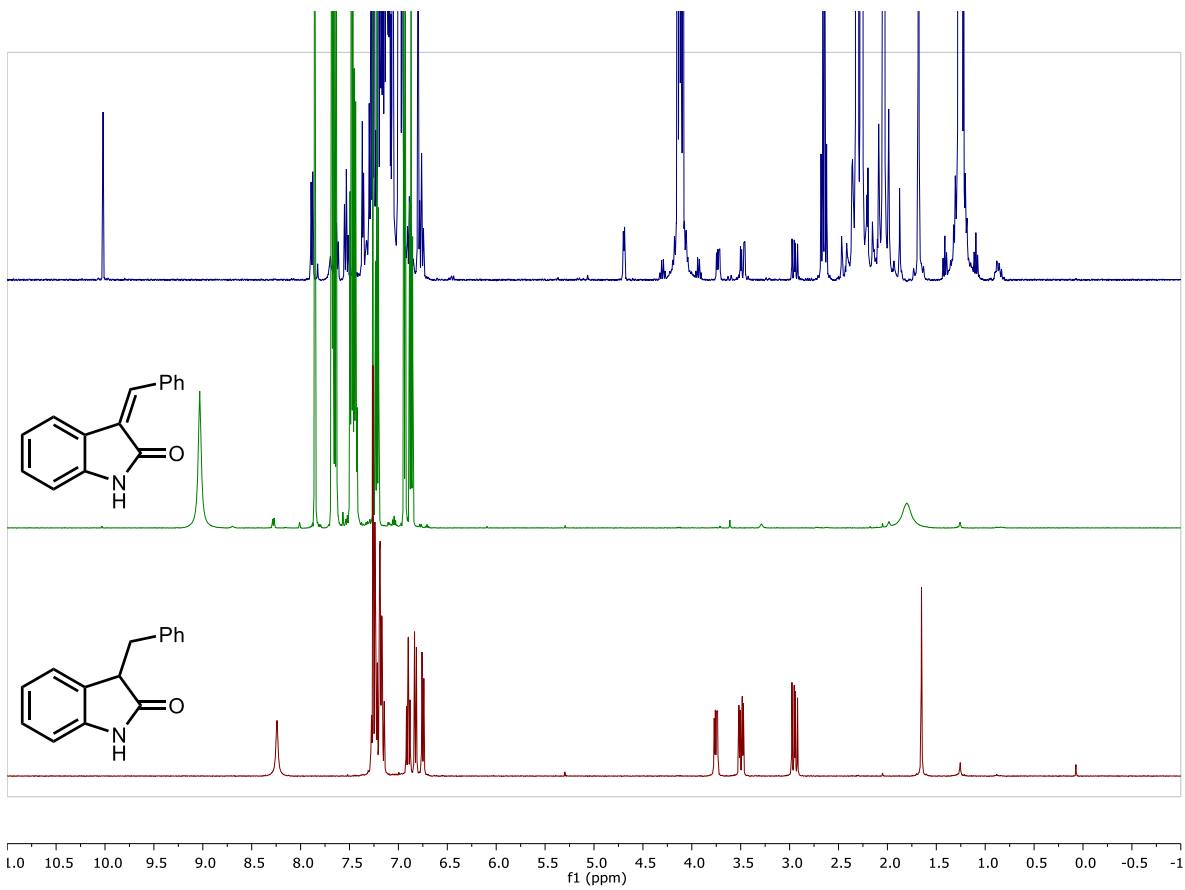
#### 2.6.4.1 Evidence supporting an $\alpha,\beta$ -unsaturated amide intermediate



A 10 mL microwave vial equipped with a stirrer bar was charged with 3-benzylideneindolin-2-one (221 mg, 1.0 mmol),  $K_2CO_3$  (69.1 mg, 0.5 mmol, 0.5 equiv.),  $PPh_3$  (10.5 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **14** (9.1 mg, 0.02 mmol, 2 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle repeated three times. Under nitrogen the vial was then charged with xylene (2 mL) and benzyl alcohol **12** (124  $\mu$ L, 130 mg, 1.2 mmol, 1.2 equiv.). The mixture was left to react at 150 °C for 24 hours. It was then cooled, followed by the addition of mesitylene (139  $\mu$ L, 120 mg, 1.0 mmol),  $H_2O$  (2 mL) and EtOAc (2 mL). Brine (1 mL) was added to aid layer separation. The mixture was stirred for 5 min, left to settle for a further 5 min, cap removed and the top layer was sampled and analysed using  $^1H$  NMR. The result gave **71%** NMR yield of 3-benzylindolin-2-one evident from the three doublets of doublets observed in the crude reaction mixture and the pure isolated product. These doublets are those of the three benzylic hydrogens ranging between 2.45ppm to 3.75ppm.







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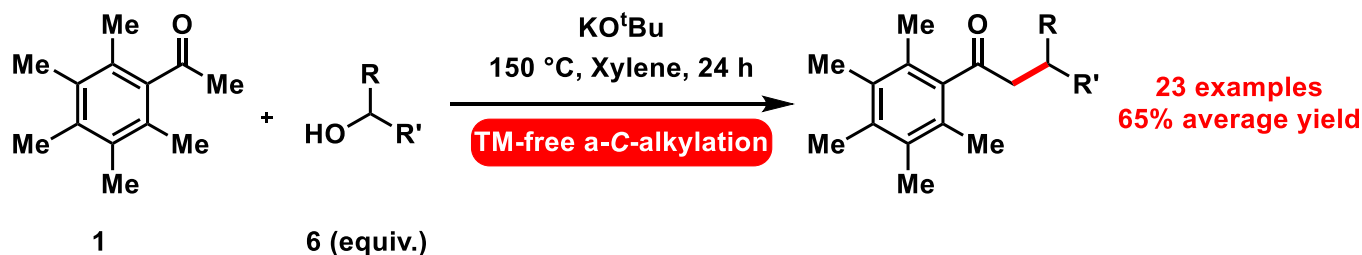
## Chapter Three

### Transition metal free $\alpha$ -C-alkylation of ketones using secondary alcohols

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#### 3.1 Preface

This chapter discusses the transition metal free selective  $\alpha$ -alkylation of ketone using secondary alcohols as a route to the synthesis of beta-substituted carbonyl compounds. The ketone substrate employed is a unique one, it has a group which prevent it from self condensation reaction and interestingly only base is required to facilitate the process with a large number of both aliphatic and benzylic secondary alcohols used as alkylating agents (23 examples, 65% average yield). The reaction was proposed to proceeds via an Oppenauer-type oxidation of the alcohol followed by selective cross aldol-condensation and the subsequent Meerwein-ponndorf-Verley (MPV)-type enone reduction.



**Publication:** M. B. Dambatta, J. Santos, R. R. Bolt, L. C. Morrill, *Tetrahedron*, **76**, 2020, 131571.

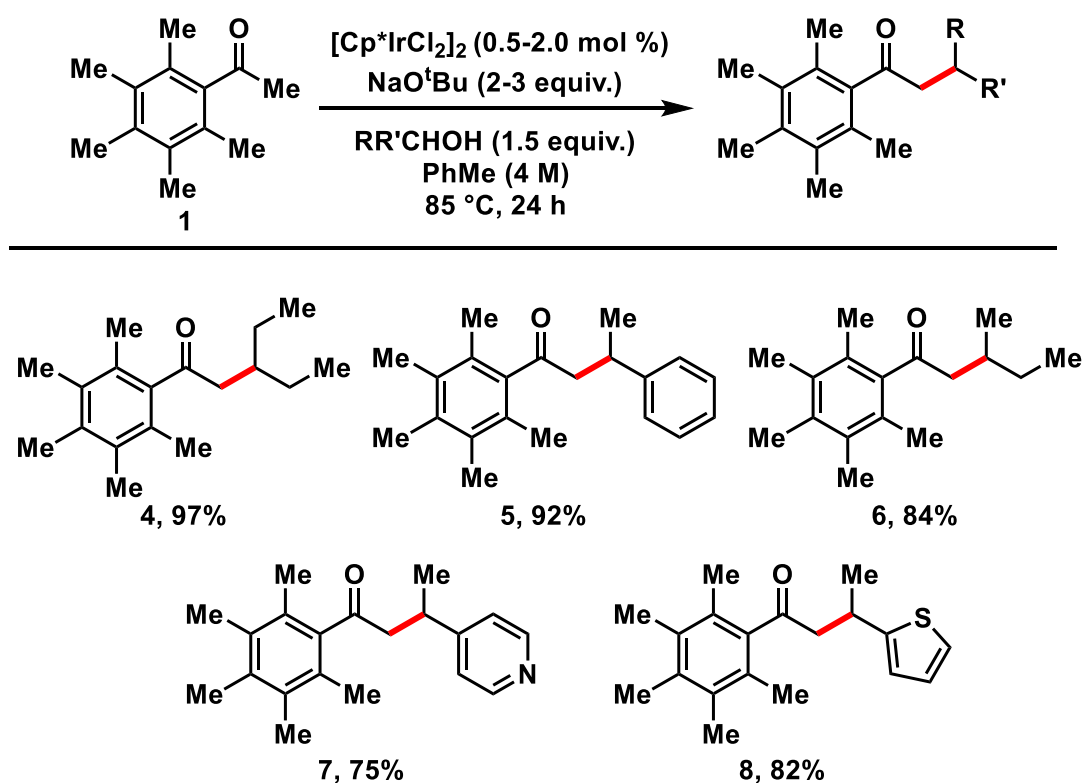
**Acknowledgement:** Joseph Santos an MChem student in our group who helped with some of the substrate scope and Robert Bolt a final year undergraduate student who also helped in making some substrate and alcohols scope.

### 3.2 Introduction

The use of borrowing hydrogen concept in C-C bond formation is now seen as an alternative to the use of toxic alkyl halide.<sup>1</sup> In this method, a metal catalyst is employed for the oxidation of an alcohol, which generates an *in-situ* intermediate that is attacked by an enolate or nucleophile to form an unsaturated intermediate. This intermediate is then reduced by metal hydride, generating water as the only by-product.<sup>2</sup> Ketones have proved to be versatile building blocks for the synthesis of numerous products like pharmaceutical and biological compounds, polymers and natural products.<sup>3</sup> The synthesis of these ketones either  $\alpha$ - or  $\beta$ -substituted traditionally involve the reaction of carbonyl compounds with a strong base like nBuLi or LDA and the subsequent addition of toxic alkyl halides.<sup>4</sup> This method suffers from many drawbacks among which are; the generation of chemical waste as stoichiometric amount of metal halide, over alkylation of the ketones and the possible homolytic coupling of the carbonyl compound making the method not to be an atom economical; making the whole process expensive.<sup>4</sup>

The alkylation of ketones with primary alcohols is well established using the borrowing hydrogen methodology unlike the secondary alcohols where only sporadic examples existed in the literature,<sup>5</sup> which may be as a result of possible competing ketone self-condensation reaction. The advances in using secondary alcohols as alkylating agent in the  $\alpha$ -alkylation of ketones comes from Donohoe and co-workers using an iridium catalyst.<sup>5</sup> They employed an aryl ketone as the carbonyl substrate which is sterically bulky and this has proved to be the key in

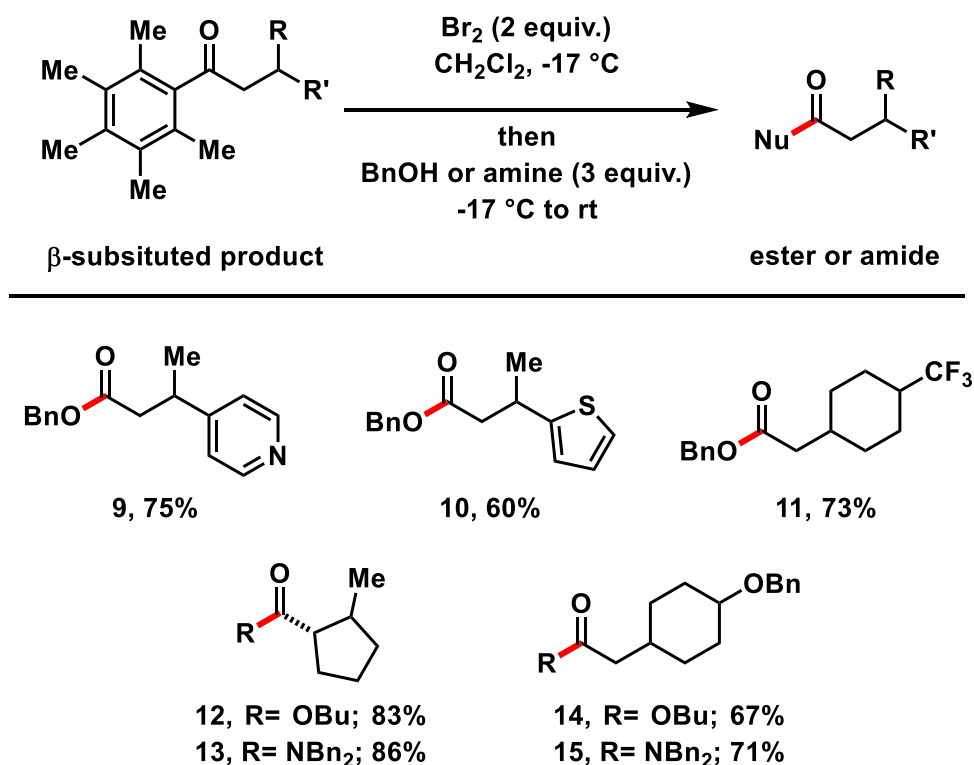
the transformation because the aryl group serve as a shield to the adjacent carbonyl group, thereby, preventing self condensation of the ketone.<sup>6</sup> Secondly, the success of their transformation can be seen from the slow release of the second ketone from the oxidation of secondary alcohol. This means it is not also available for self condensation since its concentration is low and whatever that is release is taken up by the aryl ketone substrate. The general method and some examples are shown in Scheme 1 below.



**Scheme 1:**  $\alpha$ -alkylation of aryl ketone with secondary alcohols

Another interesting achievement and application of their methodology is that by retro Friedel-Crafts acylation, the aryl group can be trapped with a nucleophile to form an ester or amide with a good to an excellent yield. Benzyl alcohol and amine were used as the nucleophiles. Some of the  $\beta$ -substituted products synthesised using the method were treated first with  $Br_2$  to form an acid bromide

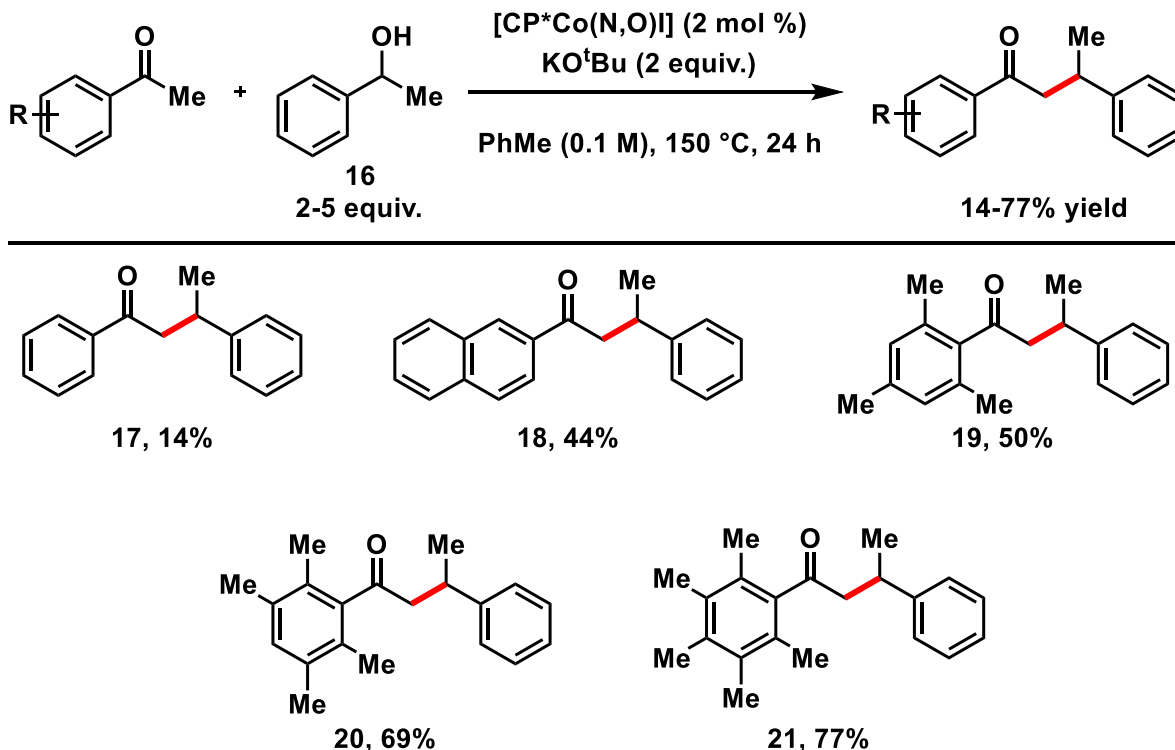
intermediate which further reacted with the nucleophiles to form the butyl ester and benzyl amides.<sup>5</sup> some of the products **9-15** obtained from the strategy shown in Scheme 2.



**Scheme 2:** selected  $\beta$ -branched esters and amide by retro Friedel craft acylation of aryl substituted ketones

In another development by Sundararaju and co-workers the same transformation was reported albeit with the use of a base metal. A well-defined and high-valence complex  $\text{Cp}^*\text{Co(III)}$  was employed as the catalyst in the process with a wide range of secondary alcohols, both symmetrical and unsymmetrical, cyclic and acyclic ones. The applicability of the process is seen in the number of products synthesized (30 examples), a few of them are highlighted in Scheme 3. This system to the best of my knowledge this was the first catalytic  $\alpha$ -alkylation of aryl ketone employing an earth abundant metal.<sup>7</sup>



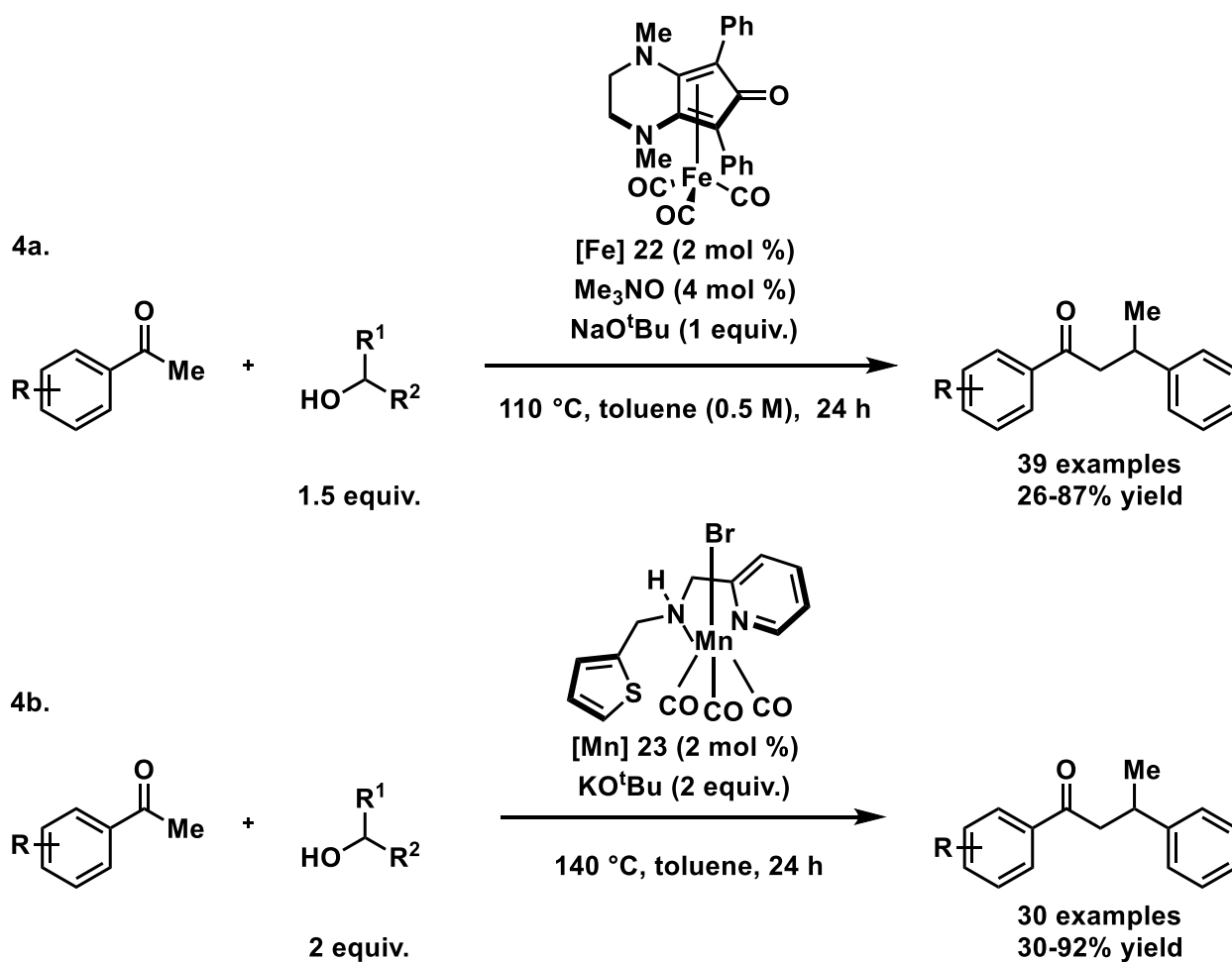


**Scheme 3:** alkylation of aryl ketone with phenyl ethanol and the effect of substitution

Another aspect that was highlighted by the report was that the steric hindrance around the carbonyl group is necessary for the success of the process. Aryl group with less substitutions gave a very low yield. And as the substitution pattern increases the yield increases also from the acetophenone product with 14% to the pentamethyl acetophenone product with 77% under same conditions as shown in Scheme 3.<sup>7</sup>

Furthermore, to the little progress made in the synthesis of  $\beta$ -substituted carbonyl compounds, the interest in finding more and better sustainable methods has increased. In this regard, Renaud and co-workers reported a work aimed at addressing the issue of the use of an expensive iridium metal catalyst and the relatively high reaction condition reported by Donohoe and Sundaraju respectively. In the attempt they used a phosphine-free

diaminocyclopentadienone iron tricarbonyl complex **22** in the process. The method yielded a wide range of products with a moderate and good yield to excellent one (26%-87%) Scheme 4a.<sup>8</sup> At same time the group of Maji reported similar transformation using manganese(I) complex **23** making 30 good examples from aryl ketone and different secondary alcohols with a yield of up to 93% Scheme 4b.<sup>9</sup> It is worth mentioning that both of these methods used phosphine free ligands.

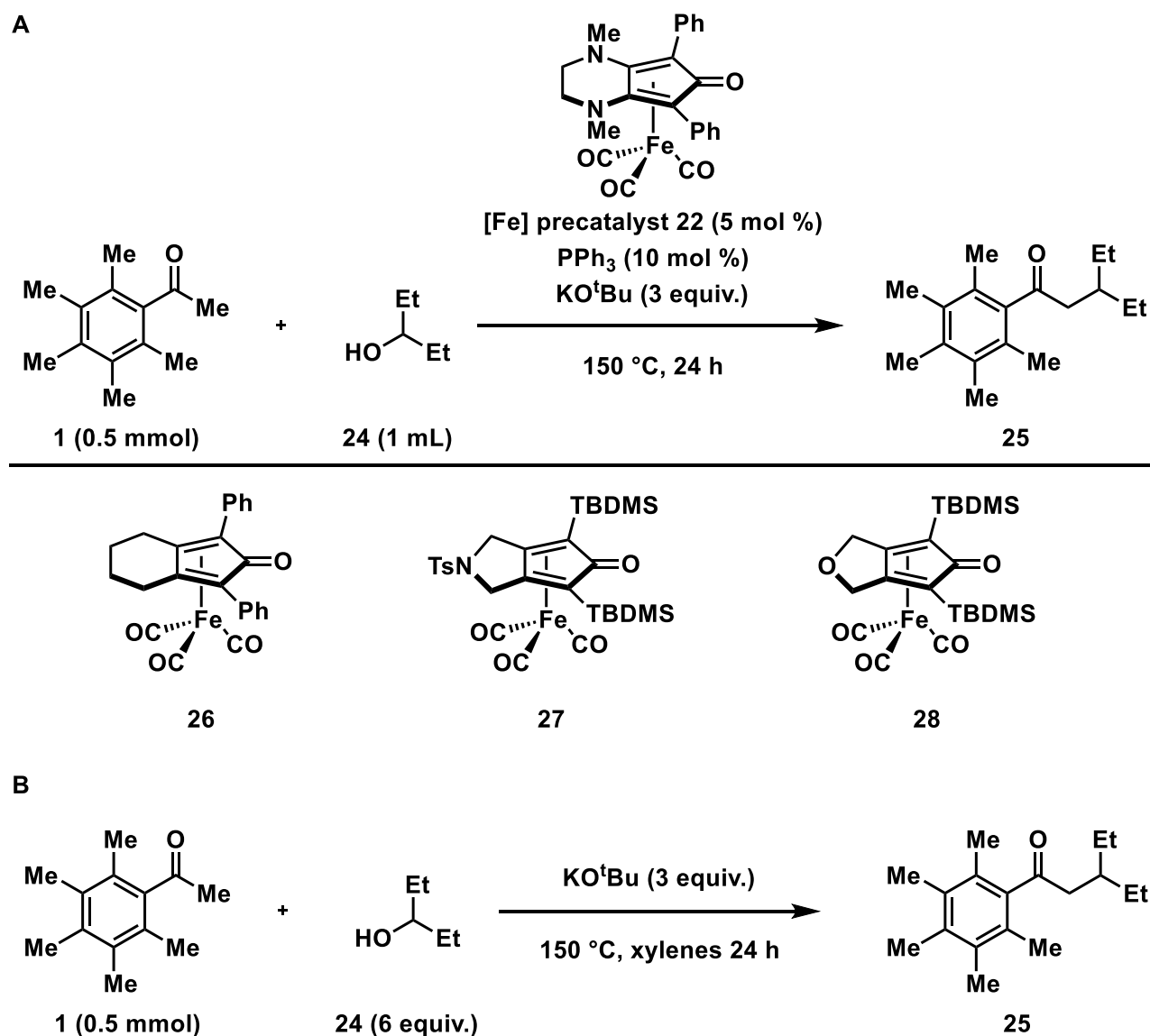


**Scheme 4:** α-alkylation of ketone with secondary alcohols

## 3.2 Results and discussion

### 3.2.1 Optimisation of $\alpha$ -alkylation of aryl-ketone with secondary alcohol

The main aim initially was to optimized the reaction with one of the iron precatalysts as shown in scheme 5A and all the precatalysts performed moderately very well but interestingly the transformation was achieved at last without the use of the metal catalyst in scheme 5B.



**Scheme 5A-B:**  $\alpha$ -alkylation pentamethylacetophenone **1** with 3-pentanol **24**

The optimization began with 5 mol% of iron precatalyst **22**, 3 equivalents of KO<sup>t</sup>Bu as the base and in excess of the secondary alcohol **24** at 150 °C for 24h. All the iron precatalysts **22**, **26**, **27** and **28** gave good to excellent yield of the product **25** between 74-95% (entries 1-4) with precatalyst **26** giving the highest of all with 95% (entry 2, Table 1). The effect of the amount of the precatalyst was checked and that of the activator but there was no significant different even at 2 mol% of the precatalyst and 4 mol% of the activator PPh<sub>3</sub> (entries 5-7). On running a control reaction in the absence of any of the iron precatalysts, fortunately, a significant background reaction was discovered entry 8 with 92% as the yield Table 1.

**Table 1:** α-alkylation of pentamethyl acetophenone **1** with 3-pentanol **3**

Entry	Cat. Loading (mol %)	Additive (mol %)	Base (eq.)	Solvent (Conc.)	T (°C)	<b>1</b> (%)	<b>25</b> (%)
1	Precatalyst <b>22</b> (5)	PPh <sub>3</sub> (10)	KO <sup>t</sup> Bu (3eq)	0.5	150	-	86
2	Precatalyst <b>26</b> (5)	PPh <sub>3</sub> (10)	KO <sup>t</sup> Bu (3eq)	0.5	150	-	95
3	Precatalyst <b>27</b> (5)	PPh <sub>3</sub> (10)	KO <sup>t</sup> Bu (3eq)	0.5	150	5	87
4	Precatalyst <b>28</b> (5)	PPh <sub>3</sub> (10)	KO <sup>t</sup> Bu (3eq)	0.5	150	21	74
5	Precatalyst <b>26</b> (4)	PPh <sub>3</sub> (8)	KO <sup>t</sup> Bu (3eq)	0.5	150	2	93
6	Precatalyst <b>26</b> (3)	PPh <sub>3</sub> (6)	KO <sup>t</sup> Bu (3eq)	0.5	150	2	92
7	Precatalyst <b>26</b> (2)	PPh <sub>3</sub> (4)	KO <sup>t</sup> Bu (3eq)	0.5	150	2	96
8	-	-	KO <sup>t</sup> Bu (3eq)	0.5	150	2	92

Reactions performed using 0.5 mmol of ketone **53** and bench-grade 3-pentanol, Yield after 24 h as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard

With the result obtained above, the base metal free alkylation reaction was further optimized with a model reaction as shown in Scheme 5B, which comprises of the aryl ketone **1** (0.5 mmol), 6 equiv. of 3-pentanol as the secondary alcohol

and 3 equiv. of KO<sup>t</sup>Bu as the base in 1 M xylene at 150 °C for 24 h. This system efficiently and selectively gave the expected alkylated product **25** in more than 98% NMR yield as determined (entry 1). From here the effect of other alkoxides bases was investigated and they both gave same results (entries 2 and 3). But other non alkoxides inorganic bases like the KOH, NaOH and K<sub>2</sub>CO<sub>3</sub> returned almost all the starting ketone with little product of just 5% (entries 4-6). Reducing the amount of the alcohol from 6 equiv. to 1 equiv. affect the yield of the product significantly (entries 7-9) and so also decreasing the reaction temperature, where no any product was observed at 85 °C (entries 10-12). Reducing the reacting time affect the yield but lowering the amount of base to 1 equiv. does not affect the yield of the product significantly (entries 15 and 16). All these results are shown below in Table 2.

**Table 2:** Metal free  $\alpha$ -alkylation of pentamethyl acetophenone with 3-pentanol

Entry	variation from "standard" conditions	25 (%) <sup>a</sup>	1 (%)
1	none	>98	-
2	NaO <sup>t</sup> Bu (3 equiv.) instead of KO <sup>t</sup> Bu	>98	-
3	NaO <sup>t</sup> Am (3 equiv.) instead of KO <sup>t</sup> Bu	>98	-
4	KOH (3 equiv.) instead of KO <sup>t</sup> Bu	-	>98
5	NaOH (3 equiv.) instead of KO <sup>t</sup> Bu	5	92
6	K <sub>2</sub> CO <sub>3</sub> (3 equiv.) instead of KO <sup>t</sup> Bu	-	>98
7	<b>24</b> (4 equiv.)	77	14
8	<b>24</b> (2 equiv.)	17	73
9	<b>24</b> (1 equiv.)	6	89
10	130 °C	47	35
11	110 °C	7	89
12	85 °C	-	96

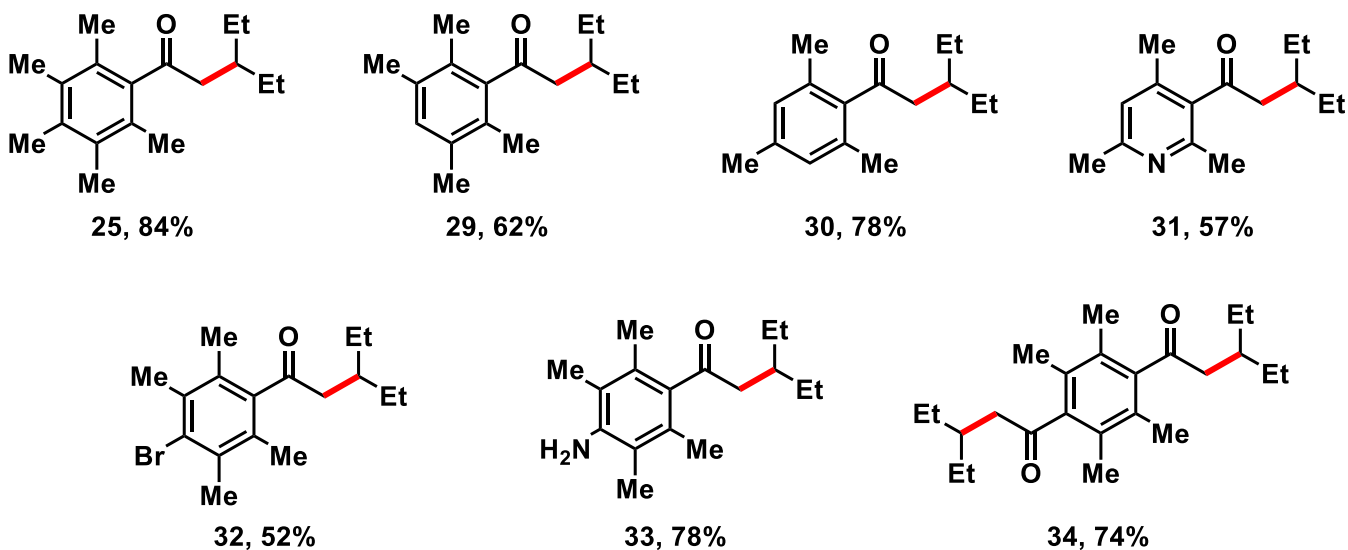
<b>13</b>	reaction time = 16 h	95	3
<b>14</b>	reaction time = 8 h	42	56
<b>15</b>	KO <sup>t</sup> Bu (2 equiv.)	92	3
16	<b>KO<sup>t</sup>Bu (1 equiv.)</b>	<b>91 (84)<sup>b</sup></b>	<b>5</b>

<sup>a</sup>Yield as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. <sup>b</sup>Isolated yield given in parentheses.

### 3.2.2 Scope of aryl ketones with 3-pentanol

Having established the reaction condition after optimization, the scope of the  $\alpha$ -C-alkylation of ketones with secondary alcohols was explored with different aryl methyl ketones and 3-pentanol **24** as the alkylating agent. The aryl ketones served as the nucleophiles while the 3-pentanol **24** served as the electrophile giving the expected products as the  $\beta$ -substituted carbonyl compounds in good to excellent yields (**25**, **29-34**, 52-84% isolated yield) Scheme 6A. Interestingly, a symmetrical diketones underwent dialkylation under the same conditions giving the desired product **34** in good yield 74%. As clearly stated and indicated even in the previous reports that the 2,6-substitution pattern in the aryl ketones is necessary to prevent the self-condensation of the ketones,<sup>5,6,7</sup> when 1-Naphthyl moiety was used instead of the aryl groups with the right substitution pattern as in **35**, Scheme 6B a complex mixture was observed which indicated the formation of many undesired products from different types of condensation reactions. Using ethyl aryl ketone does not give the desired product as all the starting material was recovered **36** Scheme 6B.

A



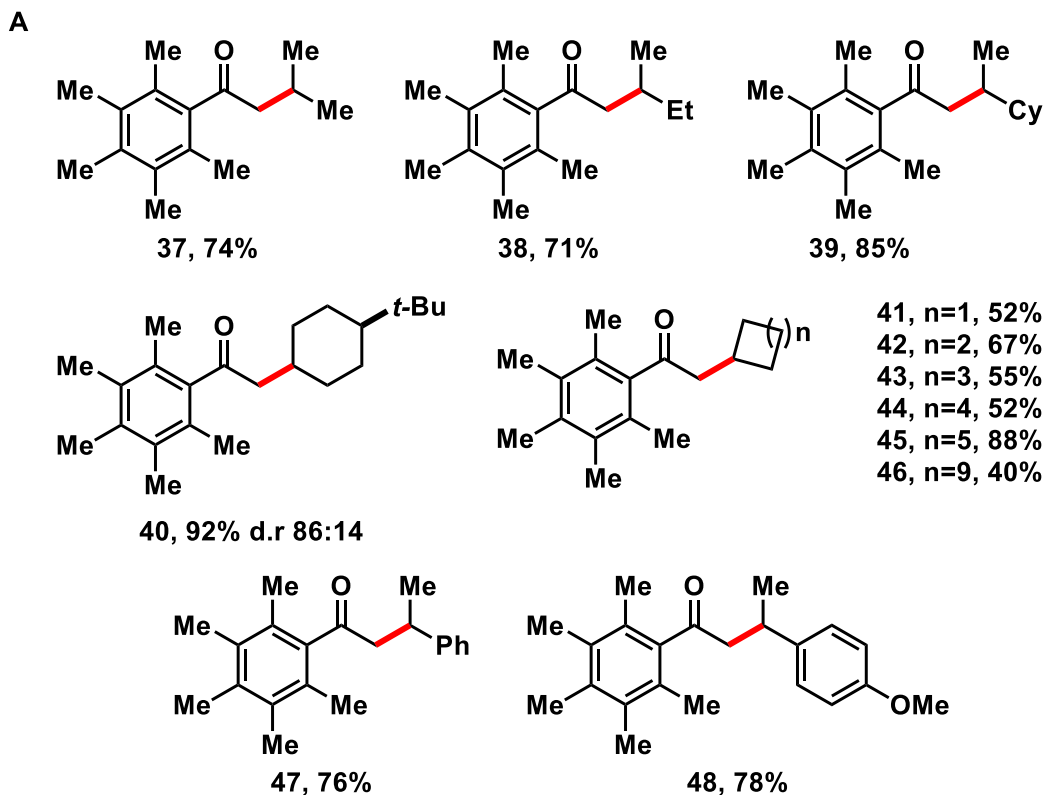
B

Scheme 6A-B: Aryl ketone scope with 3-pentanol **24**

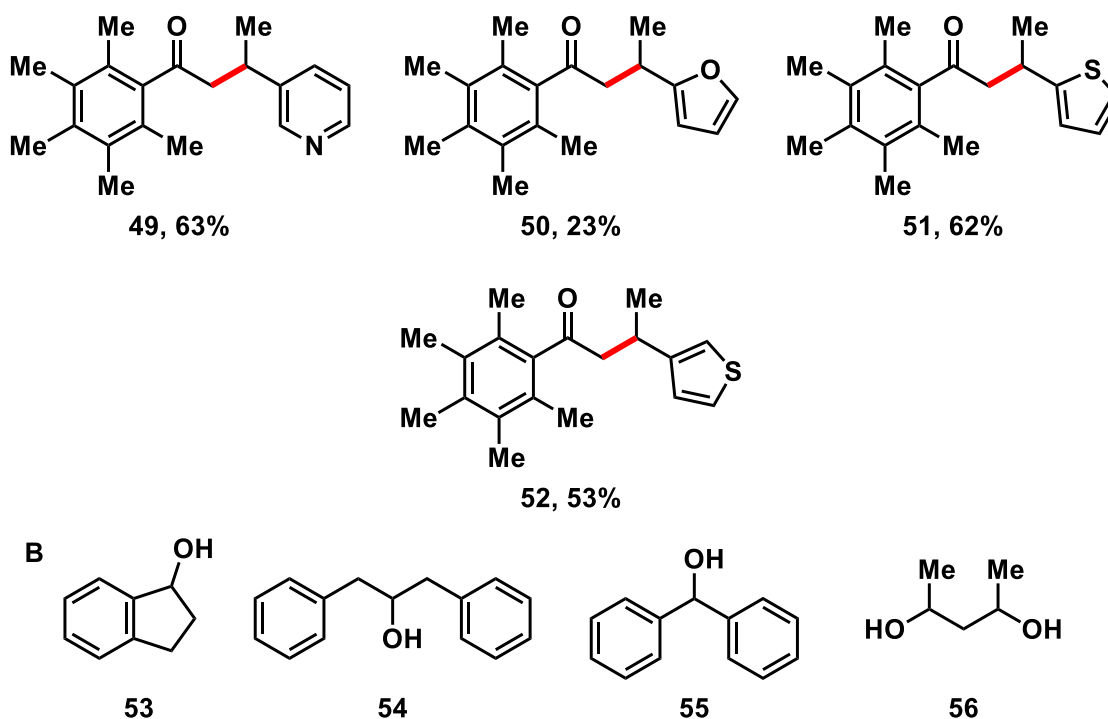
## 3.2.3 Scope of pentamethyl acetophenone with secondary alcohols

After exploring the aryl ketones scope we then explored the alcohols scope with pentamethyl acetophenone. Different secondary alcohols were used ranging from acyclic and cyclic aliphatic alcohols to even heteroaryls alcohols giving moderate to good isolated yield of 23-92% with an average yield of 63%, compounds **37-52** scheme 7A. Among the cyclic alcohol, 4-(*t*-butyl)cyclohexan-1-ol gave a mixture of diastereomers with a dr of 86:14 and a combined yield of 92% **65**. When sterically incumbent alcohols were used, all the starting materials were recovered indicating the effect of sterics around the hydroxyl group making it difficult for oxidation to the corresponding carbonyl to occur (**53-55**) and using pentan-2,4-

diol **56** also did not give the desired transformation resulted in complete recovery of the starting materials Scheme 7B. The number and different classes of secondary alcohols explored has shown the wide application of this method.





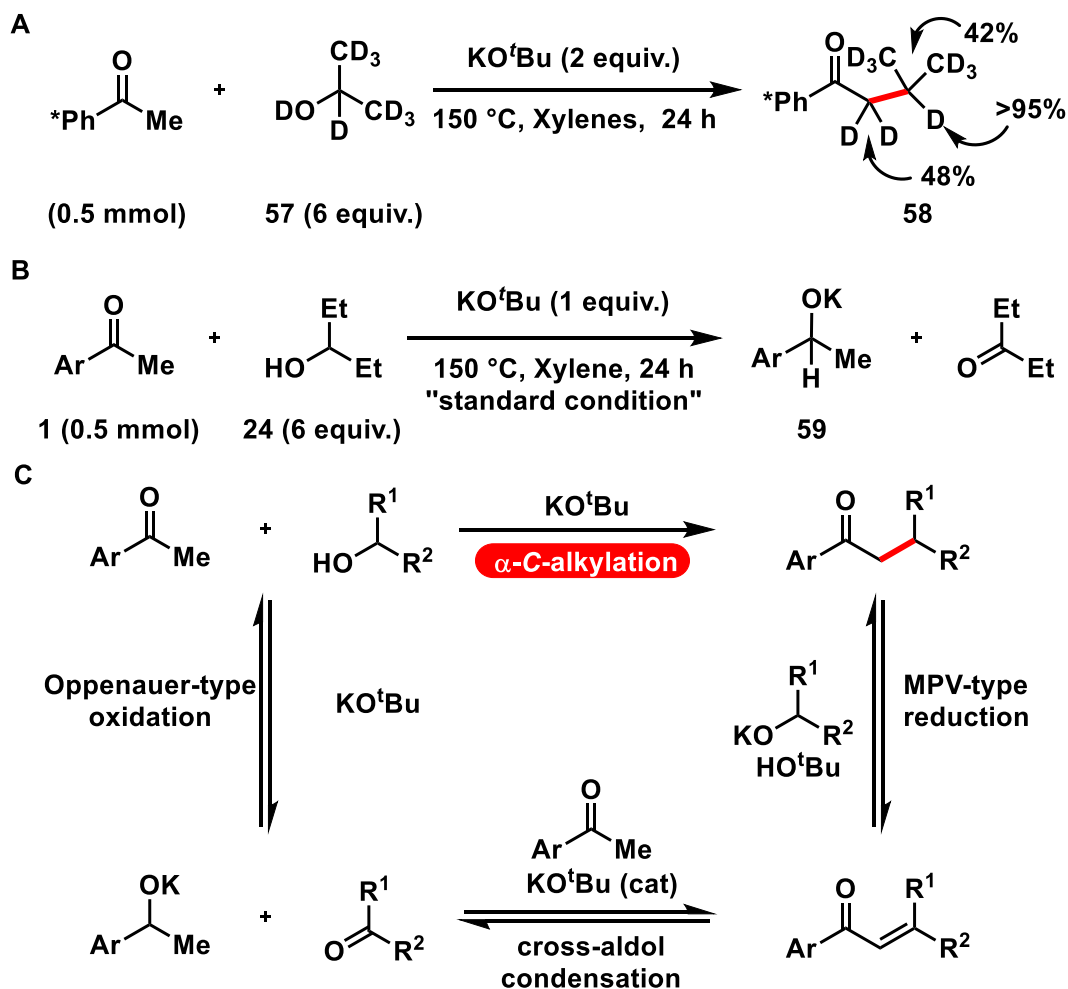


**Scheme 7A-B:** scope of pentamethyl acetophenone **1** with secondary alcohols

### 3.2.4 Proposed Plausible Reaction Mechanism

The title compound **58** was prepared according to general procedure 2 using 3 equiv. of isopropanol-d<sub>8</sub> **57** and 0.5 mmol of pentamethylacetophenone under the standard reaction conditions Scheme 8A, after the completion of the reaction and following the purification, 72% of **58** was obtained. From the <sup>1</sup>H spectrum of pure **58**, the deuterium incorporation was calculated using the deuterium incorporation equation. From the result obtained, a deuterium incorporation at the α, β and γ-positions of 46%, >95% and 42% was seen in compound **57** respectively. The >95% deuterium incorporation observed at the β-position provided evidence for the MPV-type reduction of the enone intermediate which is in line with what has been reported recently in the literature<sup>6</sup> while the H/D scrambling at the α and γ positions resulted from the acid-base equilibria Scheme 8A below. Furthermore, to confirm the suspected MPV-type reduction ketone **1**

and alcohol **24** were subjected to the standard reaction condition and after careful observation traces of the secondary alcohol **59** was observed, which was generated through the MPV-type reduction of ketone **1** and this has supported the initial Oppenauer-type oxidation of the alcohol **24**, Scheme 8B. Following these two observations and that reported in the literature,<sup>8</sup> it was believed that the reaction started with an Oppenauer-type oxidation of the alcohol followed by a selective cross-aldol condensation to form enone which was further reduced through the MPV-type reduction to the final product as expected in Scheme 8C below.



**Scheme 8A-C:** Proposed reaction mechanism

### 3.3 Experimental

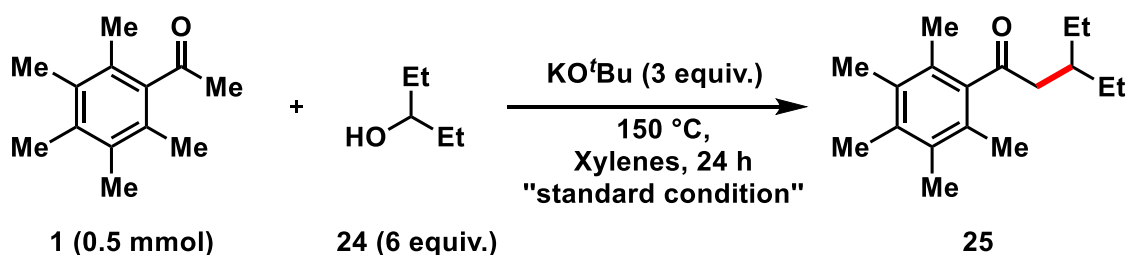
#### 3.3.1 General Information

Unless stated otherwise, all reactions were performed using oven-dried 10 mL microwave vials equipped with Teflon-coated magnetic stirrer bars and sealed with an aluminium crimp cap. Dry solvents such as toluene, hexanes, diethyl ether and hexanes were obtained after passing these previously degassed solvents through activated alumina columns (Mbraun, SPS-800). All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Room temperature (rt) refers to 20-25 °C. Ice/water and CO<sub>2</sub>(s)/acetone baths were used to obtain temperatures of 0 °C and -78 °C respectively. All reactions involving heating were carried out using DrySyn blocks and contact thermometers. *In vacuo* refers to reduced pressure using a rotary evaporator.

Analytical thin layer chromatography was carried out using aluminium plates coated with silica (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO<sub>4</sub> solution. Flash chromatography used Kieselgel (40-63 µm) silica in the solvent system stated. Melting points were recorded on a Gallenkamp melting point apparatus and corrected by linear interpolation of melting point standards benzophenone (47-49 °C), and benzoic acid (121-123 °C). Infrared spectra were recorded on a Shimadzu IR Affinity-1 Fourier Transform ATIR spectrometer as thin films using a Pike MIRacle ATR accessory. Characteristic peaks are quoted (ν<sub>max</sub> / cm<sup>-1</sup>). <sup>1</sup>H, <sup>13</sup>C, <sup>19</sup>F NMR spectra were obtained on either a Bruker Avance 400 (<sup>1</sup>H NMR, 400 MHz; <sup>13</sup>C NMR, 101 MHz; <sup>19</sup>F NMR, 376 MHz) or a Bruker Avance 500 (<sup>1</sup>H NMR, 500 MHz, <sup>13</sup>C NMR, 126 MHz; <sup>19</sup>F NMR, 471 MHz) spectrometer at rt in

the solvent stated. Chemical shifts are reported in parts per million (ppm) not relative to TMS ( $^1\text{H}$ ,  $^{13}\text{C}$ ) but referenced using the residual solvent signal in  $^1\text{H}$  NMR and in  $^{13}\text{C}$  NMR spectra.  $^{19}\text{F}$  NMR spectra are reported in the absence of an internal standard reference. All coupling constants,  $J$ , are quoted in Hz. Multiplicities are reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, dt = doublet of triplets, tt = triplet of triplets and m = multiplet. The abbreviation Ph to denote phenyl, Ar to denote aromatic, br to denote broad. High resolution mass spectrometry (HRMS,  $m/z$ ) data was acquired either at Cardiff University on a Micromass LCT spectrometer or at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

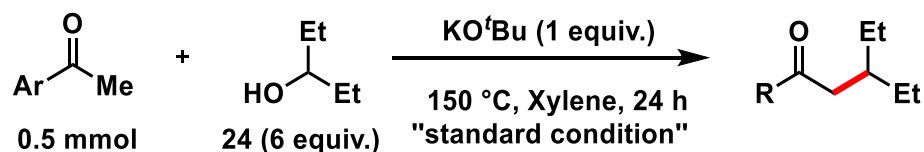
### 3.3.2 Reaction Optimization and Characterization Data



A 10 mL microwave vial equipped with a stirrer bar was charged with pentamethyl acetophenone **1** (95.2 mg, 0.5 mmol) and base (3 equiv.). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle repeated three times. Under nitrogen the vial was then charged with xylenes (0.5 mL) and 3-pentanol **24** (3.0 mmol, 6 equiv.). The mixture was stirred at 150 °C for 24 h. It was then cooled, followed by the addition of mesitylene (70  $\mu\text{L}$ , 60 mg, 0.5 mmol), H<sub>2</sub>O (2 mL) and EtOAc (2 mL). In some cases, brine (0.5 mL) was added to aid layer separation. The mixture was

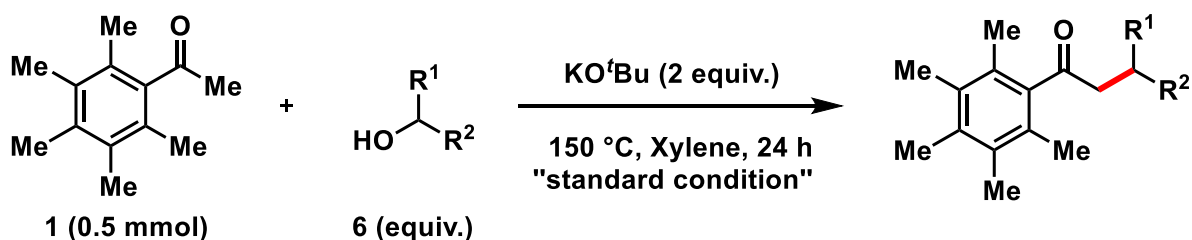
stirred for 5 min, left to settle for a further 5 min, cap was removed and the top layer was sampled and analysed using  $^1\text{H}$  NMR.

### 3.3.3 General Procedure 1



A 10 mL microwave vial equipped with a stirrer bar was charged with Ketone (0.5 mmol) and  $\text{KO}^t\text{Bu}$  (56.1 mg, 0.5 mmol, 1 equiv.) The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle was repeated three times. Under nitrogen the vial was then charged with xylenes (0.5 mL) and **24** 3-pentanol (3.0 mmol, 6 equiv.). The mixture was left to react at 150 °C for 24 h. It was then cooled, washed with EtOAc (25 mL) and transferred to a separatory funnel filled with brine (25 mL). The organic layer was collected and the aqueous phase was washed with EtOAc (2 x 25 mL). The organics were combined, dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude product.

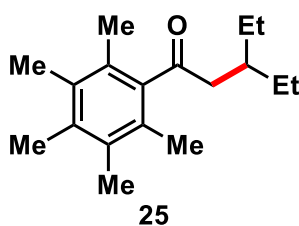
### 3.3.4 General procedure 2



A 10 mL microwave vial equipped with a stirrer bar was charged with pentamethylacetophenone **1** (95.2 mg, 0.5 mmol) and  $\text{KO}^t\text{Bu}$  (112 mg, 1.0 mmol, 2 equiv.). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle was repeated three times.

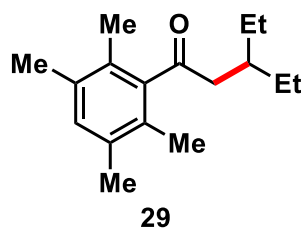
Under nitrogen the vial was then charged with secondary alcohol (3.0 mmol, 6 equiv.). The mixture was left to react at 150 °C for 24 h. It was then cooled, washed with EtOAc (25 mL) and transferred to a separatory funnel filled with brine (25 mL). The organic layer was collected and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to give the crude product.

### 3-ethyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one



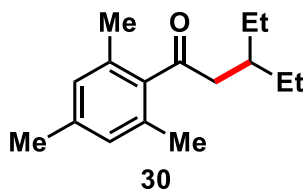
The title compound was prepared according to general procedure 1 using pentamethylacetophenone (95.2 mg, 0.5 mmol) and 3-pentanol **24** (325  $\mu$ L, 265 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as an off white solid (109 mg, 84%), mp 46–48 °C (Lit. 46–47 °C),<sup>1</sup>  $R_f$  = 0.38 (eluent = 2% EtOAc in petroleum ether); **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta_H$ : 0.89 (6H, t,  $J$  7.2, 2x(CH<sub>3</sub>)), 1.34–1.51 (4H, m, 2x(CH<sub>2</sub>)CH), 1.98–2.06 (1H, m, CH(CH<sub>2</sub>)<sub>2</sub>), 2.11 (6H, s, ArC(3,5)2x(CH<sub>3</sub>)), 2.18 (6H, s, ArC(2,6)2x(CH<sub>3</sub>)), 2.23 (3H, s, ArC(4)CH<sub>3</sub>), 2.62 (2H, d,  $J$  6.4, C=O(CH<sub>2</sub>)CH); **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta_C$ : 11.0 (CH<sub>2</sub>(2xCH<sub>3</sub>)), 16.1 (ArC(3,5)2xCH<sub>3</sub>), 16.8 (ArC(4)CH<sub>3</sub>), 17.2 (ArC(2,6)2xCH<sub>3</sub>), 25.7 (CH(2xCH<sub>2</sub>)), 35.2 ((C=O)CH<sub>2</sub>CH), 49.7 ((C=O)CH<sub>2</sub>), 127.4 (ArC(3,5)), 133.2 (ArC(2,6)), 135.4 (ArC(4)), 141.1 (ArC(1)), 211.6 (C=O). Spectroscopic data in accordance with the literature.<sup>5</sup>

### 3-ethyl-1-(2,3,5,6-tetramethylphenyl)pentan-1-one



The title compound was prepared according to general procedure 1 using 2,3,5,6-tetramethylacetophenone (88.2 mg, 0.5 mmol) and 3-pentanol **24** (325  $\mu$ L, 265 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a white solid (75 mg, 62%), mp 42–45 °C,  $R_f$  = 0.29 (eluent = 2% EtOAc in petroleum ether);  $\nu_{\max}/\text{cm}^{-1}$  (film): 2962.7, 2933.7, 2875, 2358.9, 1697.4, 1469.8, 1458.2, 1377.2, 1006.8, 867.9, 713.7;  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.90 (6H, t,  $J$  7.6,  $2\times(\text{CH}_3)$ ), 1.34–1.50 (4H, m,  $2\times(\text{CH}_2)$ ), 1.96–2.04 (1H, m,  $\text{CH}(\text{CH}_2)_2$ ), 2.07 (6H, s,  $\text{ArC}(3,5)2\times(\text{CH}_3)$ ), 2.20 (6H, s,  $\text{ArC}(2,6)2\times(\text{CH}_3)$ ), 2.62 (2H, d,  $J$  6.2,  $\text{C}=\text{O}(\text{CH})\text{CH}$ ), 6.94 (1H, s,  $\text{ArC}(4)\text{H}$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 11.0 ( $\text{CH}_2(2\times\text{CH}_3)$ ), 16.0 ( $\text{ArC}(3,5)2\times\text{CH}_3$ ), 19.6 ( $\text{ArC}(2,6)2\times\text{CH}_3$ ), 25.7 ( $\text{CH}(2\times\text{CH}_2)$ ), 35.2 ( $(\text{C}=\text{O})\text{CH}_2\text{CH}$ ), 49.4 ( $(\text{C}=\text{O})\text{CH}_2$ ), 128.0 ( $\text{ArC}(3,5)$ ), 131.4 ( $\text{ArC}(2,6)$ ), 134.5 ( $\text{ArC}(4)$ ), 143.2 ( $\text{ArC}(1)$ ), 211.4 ( $\text{C}=\text{O}$ ); HRMS ( $\text{ES}^+$ ) calculated for  $[\text{C}_{17}\text{H}_{27}\text{O}]^+$  ( $\text{M}+\text{H}$ ) $^+$  :  $m/z$  247.2062, found 247.2067 (+2.0 ppm).

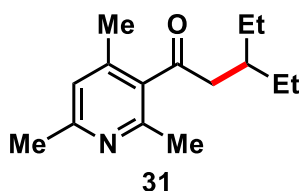
### 3-ethyl-1-mesitylpentan-1-one



The title compound was prepared according to general procedure 1 using 2,4,6-trimethylacetophenone (81.1 mg, 0.5 mmol) and 3-pentanol **24** (325  $\mu$ L, 265 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a yellow oil (90

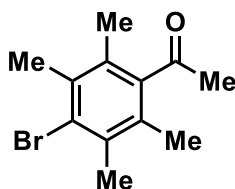
mg, 78%),  $R_f = 0.28$  (eluent = 2% EtOAc in petroleum ether);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.89 (6H, t,  $J$  7.6), 1.33–1.46 (4H, m), 1.94–2.03 (1H, m), 2.20 (6H, s), 2.30 (3H, s), 2.64 (2H, d,  $J$  6.4), 6.83 (2H, s);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 11.0, 19.3, 21.2, 25.8, 35.6, 49.0, 128.7, 132.6, 138.3, 140.2, 210.6. Spectroscopic data in accordance with the literature.<sup>6</sup>

### 3-ethyl-1-(2,4,6-trimethylpyridin-3-yl)pentan-1-one



The title compound was prepared according to general procedure 1 using 3-acetyl-2,4,6-trimethylpyridine (82.0 mg, 0.5 mmol) and 3-pentanol **24** (325  $\mu\text{L}$ , 265 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a pale yellow oil (66 mg, 57%),  $R_f = 0.23$  (eluent = 20% EtOAc in petroleum ether);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.89 (6H, t,  $J$  7.2), 1.37–1.44 (4H, m), 1.93–2.01 (1H, m), 2.19 (3H, s), 2.42 (3H, s), 2.48 (3H, s), 2.66 (2H, d,  $J$  6.4), 6.82 (1H, s);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 10.9, 18.9, 22.7, 24.3, 25.8, 35.8, 49.1, 122.5, 135.3, 142.8, 152.0, 157.7, 208.8. Spectroscopic data in accordance with the literature.<sup>5</sup>

### 1-(4-bromo-2,3,5,6-tetramethylphenyl)ethan-1-one

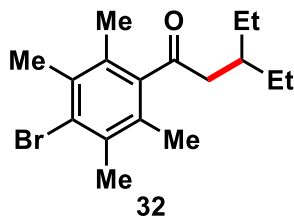


To a solution of 1-bromo-2,3,5,6-tetramethyl benzene (1.25 g, 8.4 mmol) and acetyl chloride (660  $\mu\text{L}$ , 9.3 mmol) in DCM (50 mL) was cooled in an ice bath. Then



AlCl<sub>3</sub> (1.4 g, 10.5 mmol) was added portion wise over 10 mins. The resulting mixture was warmed to RT and stirred for 8h and then poured onto crushed ice (100 g). After the ice had melted, the layers were separated and the aqueous layer was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The combined organics were washed with brine, dried in MgSO<sub>4</sub>, filtered and concentrated in vacuo. Purification by flash silica chromatography (eluent = 5% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a cream solid (1.6 g, 75%), mp 89–96 °C (Lit. 99–101 °C),<sup>1</sup> R<sub>f</sub> = 0.36 (eluent = 10% EtOAc in petroleum ether); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 2.17 (6H, s, ArC(3,5)2xCH<sub>3</sub>), 2.39 (6H, s, ArC(2,6)2xCH<sub>3</sub>), 2.45 (3H, s, C=O(CH<sub>3</sub>)); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 17.8 (ArC(3,5)2xCH<sub>3</sub>), 20.6 (ArC(2,6)2xCH<sub>3</sub>), 32.9 (C=O(CH<sub>3</sub>)), 128.9 (ArC(3,5)), 129.5 (ArC(4)), 134.9 (ArC(2,6)), 142.2 (ArC(1)), 208.9 (C=O). Spectroscopic data in accordance with the literature.<sup>5</sup>

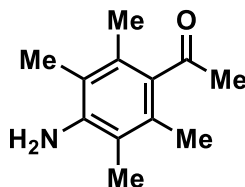
### 1-(4-bromo-2,3,5,6-tetramethylphenyl)-3-ethylpentan-1-one



The title compound was prepared according to general procedure 1 using 4-bromo-2,3,5,6-tetramethylacetophenone (127 mg, 0.5 mmol) and 3-pentanol **24** (325 μL, 265 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a brown solid (85 mg, 52%), mp 56–59 °C (Lit. 52–53 °C),<sup>1</sup> R<sub>f</sub> = 0.36 (eluent = 2% EtOAc in petroleum ether); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 0.89 (6H, t, *J* 7.5), 1.35–1.47 (4H, m), 1.97 (1H, m), 2.07 (2H, s), 2.15 (4H, s), 2.20 (2H, s), 2.39 (4H, s), 2.61 (2H, dd, *J* 13.0, 6.5); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 10.9, 17.8, 20.6, 25.7, 35.2,

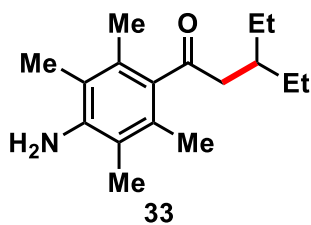
49.5, 129.2, 134.5, 134.9, 142.2, 210.6. Spectroscopic data in accordance with the literature.<sup>5</sup>

### 1-(4-amino-2,3,5,6-tetramethylphenyl)ethan-1-one



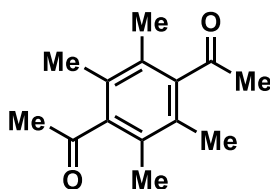
To a 20 mL microwave vial equipped with a stirrer bar was added the 1-(2,3,5,6-tetramethyl-4-nitrophenyl) ethan-1-one (553 mg, 2.5 mmol), CaCl<sub>2</sub>·2H<sub>2</sub>O (368 mg, 2.5 mmol), Zn dust (2.16 g, 33.0 mmol) and EtOH-H<sub>2</sub>O (4:1, 10 mL) sequentially. The reaction vessel was sealed with a microwave vial cap and heated in a pre-heated oil bath for 16hr. After cooling to room temperature, the mixture was concentrated in vacuo to dryness, then re-dissolved in DCM (30 mL) and washed with 1M aq. NaOH (30 mL). The aq. Layer was extracted with DCM (2 x 20 mL), and the combined organics dried in MgSO<sub>4</sub> and concentrated in vacuo to afford the amine as a pale pink solid (415 mg, 87%), mp 133–137 °C (Lit. 136–138 °C),<sup>1</sup> R<sub>f</sub> = 0.17 (eluent = 30% EtOAc in petroleum ether); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 2.08 (6H, s, ArC(3,5)2xCH<sub>3</sub>), 2.14 (6H, s, ArC(2,6)2xCH<sub>3</sub>), 2.44 (3H, s, C=O(CH<sub>3</sub>)), 3.67 (2H, s, NH<sub>2</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ<sub>C</sub>: 13.1 (ArC(3,5)2xCH<sub>3</sub>), 17.1 (ArC(2,6)2xCH<sub>3</sub>), 33.6 (C=O(CH<sub>3</sub>)), 118.3 (ArC(4)), 128.1 (ArC(3,5)), 134.6 (ArC(2,6)), 143.0 (ArC(1)), 210.2 (C=O). Spectroscopic data in accordance with the literature.<sup>5</sup>

### 1-(4-amino-2,3,5,6-tetramethylphenyl)-3-ethylpentan-1-one



The title compound was prepared according to general procedure 1 using 4-amino-2,3,5,6-tetramethylacetophenone (95.7 mg, 0.5 mmol) and 3-pentanol **24** (325  $\mu$ L, 265 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a milk colour solid (102 mg, 78%), mp 61–65 °C (Lit. 65–67 °C),<sup>1</sup>  $R_f$  = 0.29 (eluent = 20% EtOAc in petroleum ether); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta_H$ : 0.88 (6H, t, *J* 7.6), 1.33–1.49 (4H, m), 1.93–2.02 (1H, m), 2.07 (6H, s), 2.11 (6H, s), 2.61 (2H, d, *J* 6.0), 3.65 (2H, s); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta_C$ : 10.9, 13.1, 17.0, 25.7, 35.4, 50.2, 118.3, 128.2, 134.6, 142.9, 211.9. Spectroscopic data in accordance with the literature.<sup>5</sup>

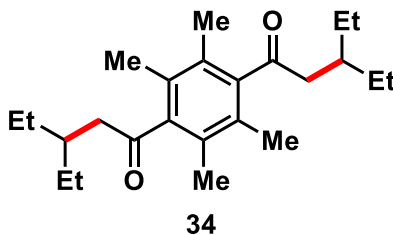
### 1,1'-(2,3,5,6-tetramethyl-1,4-phenylene)bis(ethan-1-one)



To a solution of 2,3,5,6-tetramethylbenzene (1.0 g, 7.45 mmol) and acetyl chloride (2.3 mL, 32 mmol) in CS<sub>2</sub> (30 mL) at room temperature was added aluminium chloride (6.8 g, 50.7 mmol) portion wise over 5 min. Following the addition, the mixture was heated to 55 °C and stirred at this temperature for 2 h. The mixture was cooled to room temperature and carefully poured into cold H<sub>2</sub>O (100 mL). The layers were separated and the organic layer washed with sat. aq. NaHCO<sub>3</sub> (50 mL). The aqueous layer was extracted with DCM (3 x 50 mL) and the combined organic extracts were washed with brine, dried in MgSO<sub>4</sub>, filtered and concentrated in vacuo. Purification by flash silica chromatography (eluent = 5% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as an off white solid (866 mg, 54%), mp 180–184 °C (Lit. 186–189 °C)<sup>1</sup>  $R_f$  = 0.26 (eluent = 5%

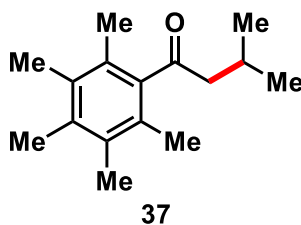
EtOAc in petroleum ether);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 2.10 (12H, s,  $\text{ArC}(2,3,5,6)4\times\text{CH}_3$ ), 2.45 (6H, s,  $\text{C}=\text{O}(2\times\text{CH}_3)$ );  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 16.3 ( $\text{ArC}(2,3,5,6)4\times\text{CH}_3$ ), 32.8 ( $\text{ArC}(1,4)2\times\text{C}=\text{O}(2\times\text{CH}_3)$ ), 128.6 ( $\text{ArC}(2,3,5,6)$ ), 143.4 ( $\text{ArC}(1,4)$ ), 209.2  $2\times(\text{C}=\text{O})$ . Spectroscopic data in accordance with the literature.<sup>5</sup>

### 1,1'-(2,3,5,6-tetramethyl-1,4-phenylene)bis(3-ethylpentan-1-one)



The title compound was prepared according to general procedure 1 using 4-acetyl-2,3,5,6-tetramethylacetophenone (109 mg, 0.5 mmol) and 3-pentanol **24** (650  $\mu\text{L}$ , 529 mg, 6.0 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a pale brown solid (133 mg, 74%), mp 142–145  $^{\circ}\text{C}$  (Lit. 145–147  $^{\circ}\text{C}$ ),<sup>1</sup>  $R_{\text{f}}$  = 0.43 (eluent = 5% EtOAc in petroleum ether);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.90 (12H, t,  $J$  7.2), 1.38–1.48 (8H, m), 1.90–2.01 (2H, m), 2.07 (12H, s), 2.59 (4H, d,  $J$  6.0);  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 10.9, 16.2, 25.7, 35.2, 49.3, 128.8, 143.3, 210.8. Spectroscopic data in accordance with the literature.<sup>5</sup>

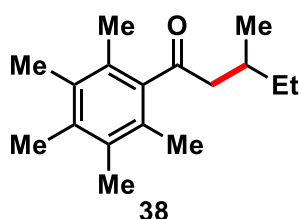
### 3-methyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



The title compound was prepared according to general procedure 2 using 2-propanol (230  $\mu\text{L}$ , 180 mg, 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in

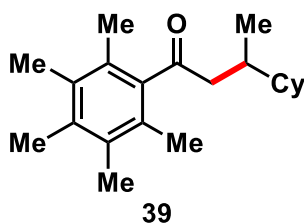
petroleum ether, 30 x 150 mm silica) gave the title compound as an off white solid (87 mg, 74%), mp 61–62 °C (Lit. 71–72 °C),<sup>3</sup>  $R_f$  = 0.21 (eluent = 2% EtOAc in petroleum ether); **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**  $\delta_H$ : 1.04 (6H, d,  $J$  7.0), 2.12 (6H, s), 2.19 (6H, s), 2.24 (3H, s), 2.29–2.38 (1H, m), 2.59 (2H, d,  $J$  6.5); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)**  $\delta_C$ : 16.1, 16.8, 17.1, 22.9, 23.4, 54.6, 127.4, 133.1, 135.4, 140.9, 211.3. Spectroscopic data in accordance with the literature.<sup>7</sup>

### 3-methyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-1-one



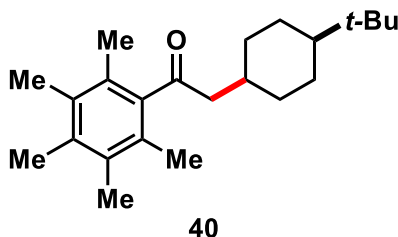
The title compound was prepared according to general procedure 2 using 2-butanol (275  $\mu$ L, 222 mg, 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as an off white solid (87 mg, 71%), mp 75–77 °C (Lit. 70–71 °C),<sup>1</sup>  $R_f$  = 0.23 (eluent = 2% EtOAc in petroleum ether); **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**  $\delta_H$ : 0.92 (3H, t,  $J$  7.6), 1.03 (3H, d,  $J$  6.8), 1.19–1.29 (1H, m), 1.41–1.50 (1H, m), 2.00–2.08 (1H, m), 2.11 (6H, s), 2.18 (6H, s), 2.23 (3H, s), 2.51 (1H, dd,  $J$  19.2, 8.0), 2.68 (1H, dd,  $J$  18.8, 5.2); **<sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)**  $\delta_C$ : 11.5, 16.1, 16.8, 17.2, 19.7, 29.5, 29.6, 52.7, 127.4, 133.2, 135.4, 141.0, 211.5. Spectroscopic data in accordance with the literature.<sup>5</sup>

### 3-cyclohexyl-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



The title compound was prepared according to general procedure 2 using 1-cyclohexylethanol (415  $\mu\text{L}$ , 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as an off white solid (128 mg, 85%), mp 82–86  $^{\circ}\text{C}$ ,  $R_f$  = 0.25 (eluent = 2% EtOAc in petroleum ether);  $\nu_{\text{max}}/\text{cm}^{-1}$  (film): 2966.5, 2918.3, 2850.8, 238.9, 1691.6, 1558.5, 1541.1, 1506.4, 1444.7, 1377.2, 1311.6, 1111.0;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 1.00 (3H, d,  $J$  7.0), 1.02–1.28 (5H, m), 1.58–1.78 (5H, m), 2.11 (6H, s), 2.13–2.15 (1H, m), 2.19 (6H, s), 2.23 (3H, s), 2.49 (1H, dd,  $J$  9.5, 19.0), 2.75 (1H, dd,  $J$  3.5, 19.0);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 16.1, 16.8, 16.9, 17.2, 26.8, 26.9, 29.2, 30.4, 32.8, 42.9, 50.4, 127.4, 133.2, 135.3, 141.1, 211.7; HRMS ( $\text{ES}^+$ ) calculated for  $[\text{C}_{21}\text{H}_{33}\text{O}_2]^+$  ( $\text{M}+\text{H}$ ) $^+$  :  $m/z$  301.2531, found 301.2540 (+3.0 ppm)

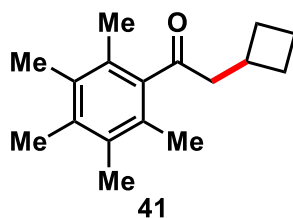
**2-((1*s*,4*s*)-4-(tert-butyl)cyclohexyl)-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one**



The title compound was prepared according to general procedure 1 using pentamethyl acetophenone **1** (95.2 mg, 0.5 mmol) and 4-(tert-butyl)cyclohexan-1-ol (469 mg) giving the crude product after work up (86: 14 *dr*). Purification by flash silica chromatography (eluent = 1 % EtOAc in petroleum ether, 35 x 200 mm silica) gave the compound as an inseparable mixture of diastereomers, as a white solid (151 mg, 92%, 86:14 *dr*), mp 74–77  $^{\circ}\text{C}$  (Lit. 75–77  $^{\circ}\text{C}$ ),<sup>1</sup>  $R_f$  = 0.35 (2% EtOAc in petroleum ether); Data for mixture of diastereoisomers,  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 0.82 (9H, s), 0.85–0.87 (2H, m), 0.99–1.09 (3H, m), 1.54–1.60 (4H, m),

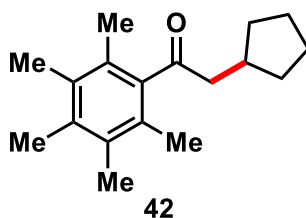
1.70–1.80 (2H, m), 2.11 (6H, s), 2.19 (6H, s), 2.24 (3H, s), 2.54–2.58 (1H, m), 2.74 (2H, d,  $J$  7.0),  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 16.1, 16.8, 17.1, 22.1, 26.9, 27.3, 27.4, 27.6, 27.7, 31.0, 32.7, 32.7, 33.9, 47.8, 48.1, 48.4, 53.3, 54.4, 127.4, 127.5, 133.2, 133.3, 135.3, 135.4, 141.0, 141.1, 211.4. Spectroscopic data in accordance with that stated in the literature.<sup>5</sup>

### 2-cyclobutyl-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one



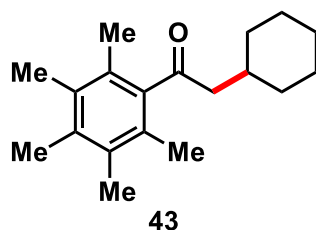
The title compound was prepared according to general procedure 1 using pentamethyl acetophenone **1** (95.2 mg, 0.5 mmol) and cyclobutanol (235  $\mu\text{L}$ ). Purification by flash silica chromatography (eluent = 1% EtOAc in petroleum ether, 35 x 200 mm silica) gave the title compound as a white solid (63 mg, 52%), mp 48–52  $^{\circ}\text{C}$ ,  $R_{\text{f}}$  = 0.22 (2% EtOAc in petroleum ether);  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  (film) 2952, 2922, 2860, 1691, 1654, 1469, 1409, 1360, 1314, 1263, 1132, 1100, 1068, 936, 792, 731, 702;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 1.34–1.39 (4H, m), 1.69–1.75 (2H, m), 2.10 (6H, s), 2.18 (6H, s), 2.23 (3H, s), 2.67 (2H, t,  $J$  7.5);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 14.1, 16.1, 16.8, 17.3, 22.7, 23.1, 45.8, 127.5, 133.2, 135.4, 141.0, 212.3; HRMS ( $\text{ES}^+$ ) calculated for  $[\text{C}_{17}\text{H}_{25}\text{O}]^+$  ( $\text{M}+\text{H}$ ) $^+$  :  $m/z$  245.1900, found 245.1906 (+2.5ppm).

### 2-cyclopentyl-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one



The title compound was prepared according to general procedure 2 using cyclopentanol (273  $\mu$ L, 258 mg, 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a white solid (83 mg, 67%), mp 68–70  $^{\circ}$ C, (Lit. 51–52  $^{\circ}$ C),<sup>1</sup>  $R_f$  = 0.24 (eluent = 2% EtOAc in petroleum ether);  **$^1$ H NMR (400 MHz,  $CDCl_3$ )**  $\delta_H$ : 1.11–1.20 (2H, m), 1.55–1.65 (4H, m), 1.92–2.00 (2H, m), 2.12 (6H, s), 2.18 (6H, s), 2.23 (3H, s), 2.34–2.46 (1H, m), 2.73 (2H, d,  $J$  6.8);  **$^{13}$ C NMR (101 MHz,  $CDCl_3$ )**  $\delta_C$ : 16.1, 16.8, 17.3, 25.1, 32.9, 34.8, 52.1, 127.4, 133.2, 135.4, 141.0, 211.9. Spectroscopic data in accordance with the literature.<sup>5</sup>

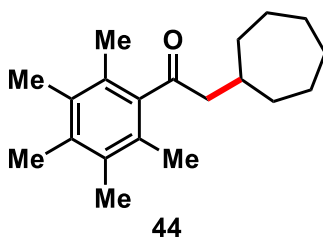
### 2-cyclohexyl-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one



The title compound was prepared according to general procedure 2 using cyclohexanol (317  $\mu$ L, 300 mg, 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a white solid (75 mg, 55%), mp 114–115  $^{\circ}$ C (Lit. 110–112  $^{\circ}$ C),<sup>1</sup>  $R_f$  = 0.21 (eluent = 2% EtOAc in petroleum ether);  **$^1$ H NMR (500 MHz,  $CDCl_3$ )**  $\delta_H$ : 0.95–1.03 (2H, m), 1.14–1.22 (1H, m), 1.32–1.41 (2H, m), 1.66–1.73 (3H, m), 1.85–1.88 (2H, m), 2.02–2.08 (1H, m), 2.11 (6H, s), 2.18 (6H, s), 2.23 (3H, s), 2.57 (2H, d,  $J$  6.5);  **$^{13}$ C NMR (126 MHz,  $CDCl_3$ )**  $\delta_C$ : 16.1, 16.8, 17.1, 26.3, 26.5, 32.5, 33.9, 53.4, 127.4, 133.2, 135.4, 140.9, 211.2. Spectroscopic data in accordance with the literature.<sup>5</sup>

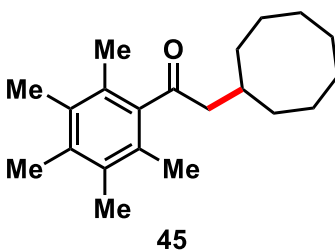
### 2-cycloheptyl-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one





The title compound was prepared according to general procedure 2 using cycloheptanol (361  $\mu\text{L}$ , 343 mg, 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a white solid (75 mg, 52%), mp 97–99  $^{\circ}\text{C}$ ,  $R_f$  = 0.20 (eluent = 2% EtOAc in petroleum ether);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 1.23–1.30 (2H, m), 1.46–1.56 (4H, m), 1.59–1.69 (4H, m), 1.81–1.86 (2H, m), 2.10 (6H, s), 2.18 (6H, s), 2.20–2.22 (1H, m), 2.23 (3H, s), 2.62 (2H, d,  $J$  6.5);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 16.1, 16.8, 17.2, 26.5, 28.4, 34.2, 35.1, 54.1, 127.5, 133.2, 135.4, 146.9, 211.4. Spectroscopic data in accordance with the literature.<sup>8</sup>

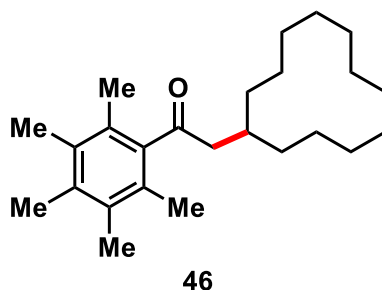
### 2-cyclooctyl-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one



The title compound was prepared according to general procedure 2 using cyclooctanol (397  $\mu\text{L}$ , 384.6 mg, 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a white solid (132 mg, 88%), mp 98–99  $^{\circ}\text{C}$ ,  $R_f$  = 0.20 (eluent = 2% EtOAc in petroleum ether);  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  (film) 2908, 2849, 1696, 1469, 1444, 1387, 1356, 1305, 1133, 920, 696;

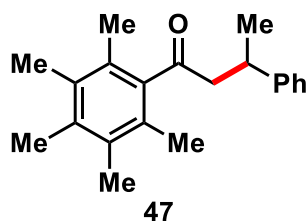
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ<sub>H</sub>: 1.34–1.40 (2H, m), 1.49–1.68 (10H, m), 1.72–1.78 (2H, m), 2.10 (6H, s), 2.18 (6H, s), 2.23 (3H, s), 2.27–2.33 (1H, m), 2.62 (2H, d, *J* 6.0); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ<sub>C</sub>: 16.1, 16.8, 17.2, 25.4, 26.3, 27.3, 32.2, 32.6, 54.2, 127.5, 133.2, 135.4, 141.0, 211.4. HRMS (**ES**<sup>+</sup>) calculated for [C<sub>21</sub>H<sub>33</sub>O]<sup>+</sup> (M+H)<sup>+</sup> : m/z 301.2531, found 301.2535 (+1.3 ppm).

### 2-cyclododecyl-1-(2,3,4,5,6-pentamethylphenyl)ethan-1-one



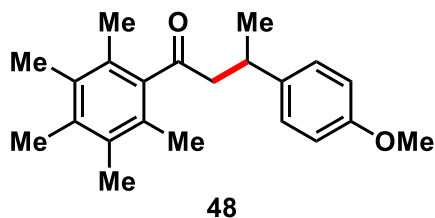
The title compound was prepared according to general procedure 2 using cyclododecanol (553 mg, 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a white solid (71 mg, 40%), mp 128–134 °C, R<sub>f</sub> = 0.19 (eluent = 2% EtOAc in petroleum ether); ν<sub>max</sub>/cm<sup>-1</sup> (film): 2927.9, 2860.4, 2843.1, 2357.0, 1734.0, 1697.4, 1685.8, 1447.7, 1440.8, 1309.7, 1244.1, 1124.5, 1105.2, 935.5, 711.7; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ<sub>H</sub>: 1.34–1.44 (22H, m), 2.11 (6H, s), 2.18 (6H, s), 2.23 (4H, s), 2.60 (2H, d, *J* 6.50); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ<sub>C</sub>: 16.1, 16.8, 17.3, 21.0, 21.9, 23.4, 23.5, 23.5, 24.0, 24.2, 24.3, 24.8, 29.1, 29.2, 29.4, 51.3, 127.5, 133.2, 135.3, 141.1, 211.6; HRMS (**ES**<sup>+</sup>) calculated for [C<sub>25</sub>H<sub>41</sub>O]<sup>+</sup> (M+H)<sup>+</sup> : m/z 357.3157, found 357.3159 (+0.6 ppm)

### 1-(2,3,4,5,6-pentamethylphenyl)-3-phenylbutan-1-one



The title compound was prepared according to general procedure 2 using neat 1-phenylethanol (362  $\mu\text{L}$ , 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 1% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as an off white solid (86.1 mg, 60%), mp 69–74  $^{\circ}\text{C}$  (Lit. 70–71  $^{\circ}\text{C}$ ),<sup>1</sup>  $R_f$  = 0.30 (eluent = 2% EtOAc in petroleum ether);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 1.39 (3H, d,  $J$  7.0), 2.00 (6H, s), 2.16 (6H, s), 2.22 (3H, s), 2.98 (1H, dd,  $J$  5.5, 7.5), 3.05 (1H, dd,  $J$  6.8, 8.0), 3.55 (1H, sext,  $J$  7.0), 7.19 (1H, tt, 7.0), 7.25–7.31 (4H, m);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 16.1, 16.8, 17.0, 22.5, 34.3, 53.9, 126.3, 127.2, 127.5, 128.6, 133.2, 135.5, 140.6, 146.8, 211.2. Spectroscopic data in accordance with the literature.<sup>5</sup>

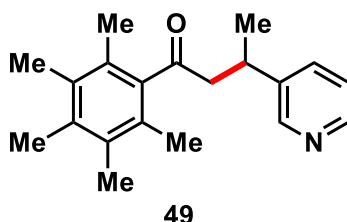
### 3-(4-methoxyphenyl)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



The title compound was prepared according to general procedure 1 using pentamethyl acetophenone **1** (95.2 mg, 0.5 mmol) and 1-(4-methoxyphenyl)ethan-1-ol (457 mg). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 35 x 150 mm silica) gave the title compound as a white solid (126 mg, 78%), mp 90–94  $^{\circ}\text{C}$ ,  $R_f$  = 0.18 (3% EtOAc in petroleum ether);  $\nu_{\text{max}}$  /  $\text{cm}^{-1}$  (film) 2964, 2932, 2860, 1689, 1610, 1512, 1512, 1364, 1303, 1243, 1176, 1105, 1032, 831;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 1.35 (3H, d,  $J$  7.0), 1.99 (6H, s),

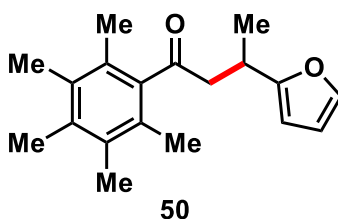
2.16 (6H, s), 2.22 (3H, s), 2.91 (1H, dd, *J* 7.5, 5.5), 2.99 (1H, dd, *J* 7.5, 6.0), 3.47–3.54 (1H, m), 3.79 (3H, s), 6.83 (2H, d, *J* 8.5), 7.17 (2H, d, *J* 8.5); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ<sub>c</sub>: 16.0, 16.8, 17.1, 22.7, 33.5, 54.2, 55.4, 113.9, 127.5, 128.1, 133.2, 135.5, 139.0, 140.6, 158.1, 210.3; HRMS (ES<sup>+</sup>) calculated for [C<sub>22</sub>H<sub>29</sub>O<sub>2</sub>]<sup>+</sup> (M+H)<sup>+</sup>: *m/z* 325.1987, found 325.1975 (-3.5ppm).

### 1-(2,3,4,5,6-pentamethylphenyl)-3-(pyridin-3-yl)butan-1-one



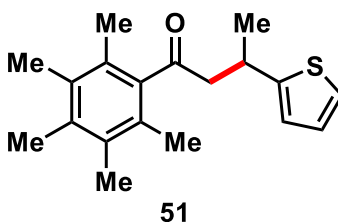
The title compound was prepared according to general procedure 1 using pentamethyl acetophenone **1** (95.2 mg, 0.5 mmol) and 1-(pyridin-3-yl) ethan-1-ol (369 mg). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 35 x 200 mm silica) gave the title compound as a white solid (92 mg, 62%), mp 85–88 °C (Lit. 89–91 °C),<sup>1</sup> *R*<sub>f</sub> = 0.30 (10% EtOAc in petroleum ether); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>H</sub>: 1.40 (3H, d, *J* 7.0), 1.97 (6H, s), 2.15 (6H, s), 2.21 (3H, s), 2.92–3.07 (2H, m), 3.58 (1H, sext, *J* 6.8), 7.22 (1H, dd, *J* 7.6, 5.2), 7.58 (1H, dt, 3.6, 2.0), 8.47 (1H, dd, *J* 4.8, 1.6), 8.53 (1H, dd, *J* 10.4, 2.0); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ<sub>c</sub>: 16.0, 16.8, 17.1, 22.1, 32.1, 53.5, 123.5, 127.4, 133.3, 134.8, 135.7, 140.2, 141.8, 147.9, 149.2, 209.6. Spectroscopic data in accordance with that stated in the literature.<sup>5</sup>

### 3-(furan-2-yl)-1-(2,3,4,5,6-pentamethylphenyl)butan-1-one



The title compound was prepared according to general procedure 1 using pentamethyl acetophenone **1** (95.2 mg, 0.5 mmol) and 1-(furan-2-yl) ethanol (336 mg). Purification by flash silica chromatography (eluent = 1% EtOAc in petroleum ether, 35 x 200 mm silica) gave the title compound as a white solid (32 mg, 23%), mp 58–60 °C,  $R_f = 0.17$  (2% EtOAc in petroleum ether);  $\nu_{\max} / \text{cm}^{-1}$  (film) 2980, 2924, 2359, 1697, 1558, 1541, 1506, 1456, 1150, 1072;  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{H}}$ : 1.39 (3H, d,  $J$  7.0), 2.06 (6H, s), 2.17 (6H, s), 2.22 (3H, s), 2.81 (1H, dd,  $J$  19.0, 8.0), 3.13 (1H, dd,  $J$  19.0, 5.0), 3.58–3.65 (1H, m), 6.03 (1H, dt  $J$  3.5, 3.0), 6.27 (1H, dd,  $J$  1.5, 3.0), 7.29 (1H, dd,  $J$  1.5, 0.5);  $^{13}\text{C NMR}$  (126 MHz,  $\text{CDCl}_3$ )  $\delta_{\text{C}}$ : 16.1, 16.8, 19.4, 28.1, 51.2, 104.1, 110.1, 126.8, 133.2, 135.6, 140.4, 141.0, 159.3, 209.2; HRMS ( $\text{ES}^+$ ) calculated for  $[\text{C}_{19}\text{H}_{25}\text{O}_2]^+$  ( $\text{M}+\text{H}$ ) $^+$  :  $m/z$  285.1674, found 285.1672 (-0.7 ppm).

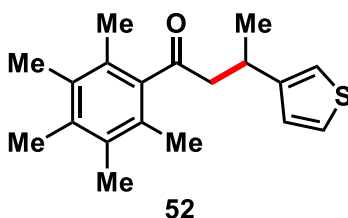
### 1-(2,3,4,5,6-pentamethylphenyl)-3-(thiophen-2-yl)butan-1-one



The title compound was prepared according to general procedure 1 using pentamethyl acetophenone (95.2 mg, 0.5 mmol) and 1-(thiophen-2-yl)ethan-1-ol (385 mg). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 35 x 200 mm silica) gave the title compound as a white solid (93 mg, 62%), mp 76–78 °C (Lit. 77–78 °C),<sup>1</sup>  $R_f = 0.17$  (2% EtOAc in petroleum ether);

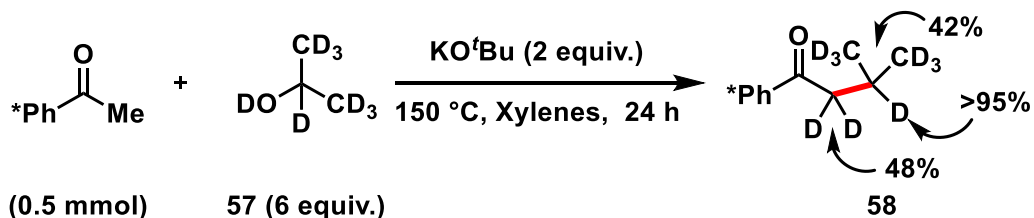
**<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ<sub>H</sub>: 1.47 (3H, d, *J* 6.9), 2.04 (6H, s), 2.17 (6H, s), 2.23 (3H, s), 2.95 (1H, dd, *J* 7.7, 19.0), 3.09 (1H, dd, *J* 5.5, 19.0), 3.83–3.92 (1H, m), 6.88–6.93 (2H, m), 7.13 (1H, d, *J* 5.0); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ<sub>C</sub>: 16.7, 17.0, 23.3, 30.0, 54.8, 122.9, 123.2, 126.7, 127.5, 133.2, 135.6, 140.3, 150.8, 209.7. Spectroscopic data in accordance with that stated in the literature.<sup>5</sup>

**1-(2,3,4,5,6-pentamethylphenyl)-3-(thiophen-3-yl)butan-1-one**

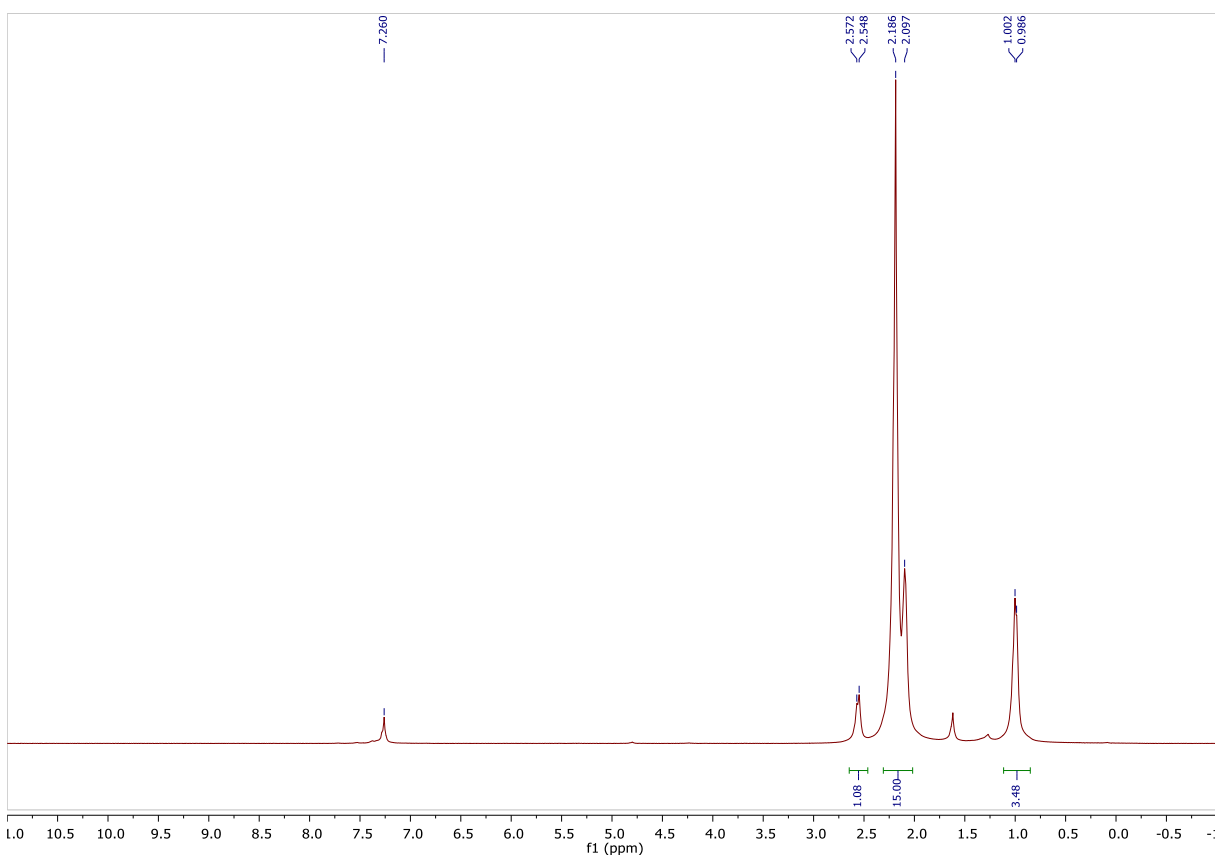


The title compound was prepared according to general procedure 2 using 1-(thiophen-3-yl) ethan-1-ol (385 mg, 3.0 mmol) and pentamethylacetophenone **1** (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as yellow solid (80 mg, 53%), mp 69–74 °C, *R*<sub>f</sub> = 0.32 (eluent = 5% EtOAc in petroleum ether); *v*<sub>max</sub>/cm<sup>-1</sup> (film): 2954.9, 2868.2, 2343.5, 1697.4, 1456.3, 1386.8, 1348.2, 1319.3, 1300.0, 1278.8, 1120.6, 1068.6, 923.9, 800.5, 781.2, 650.0; **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δ<sub>H</sub>: 1.40 (3H, d, *J* 7.0), 2.02 (6H, s), 2.18 (6H, s), 2.24 (3H, s), 2.96 (1H, dd, *J* 8.0, 19.0), 3.03 (1H, dd, *J* 6.0, 19.0), 3.69 (1H, sext, *J* 6.4), 7.03 (2H, d, *J* 4.0), 7.25–7.27 (1H, m,); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δ<sub>C</sub>: 16.0, 16.8, 16.9, 22.0, 29.7, 53.8, 119.6, 125.5, 126.9, 127.5, 133.2, 135.5, 140.5, 147.5, 211.1; HRMS (**ES**<sup>+</sup>) calculated for [C<sub>19</sub>H<sub>25</sub>OS]<sup>+</sup> (**M+H**)<sup>+</sup> : *m/z* 301.1446, found 301.1450 (+1.2 ppm).

### 3.3.5 Mechanistic study



The title compound **58** was prepared according to general procedure 2 using isopropanol-d8 **57** (230  $\mu\text{L}$ , 180 mg, 3.0 mmol) and pentamethylacetophenone (95.2 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 2% EtOAc in petroleum ether, 30 x 150 mm silica) gave the title compound as a white solid (86 mg, 72%), mp 61–62  $^\circ\text{C}$ ,  $R_f$  = 0.44 (eluent = 2% EtOAc in petroleum ether)



**Fig 1:** Proton NMR of pure product **58**

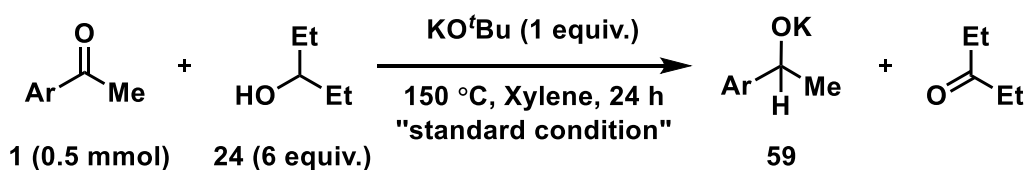
Deuterium incorporation equation:

$$\% \text{ D} = 100 - ((\text{peak integral} / \text{equivalent protons}) * 100)$$

$\alpha$ -position =  $100 - ((1.08/2) * 100) = 46\% \text{ D}$

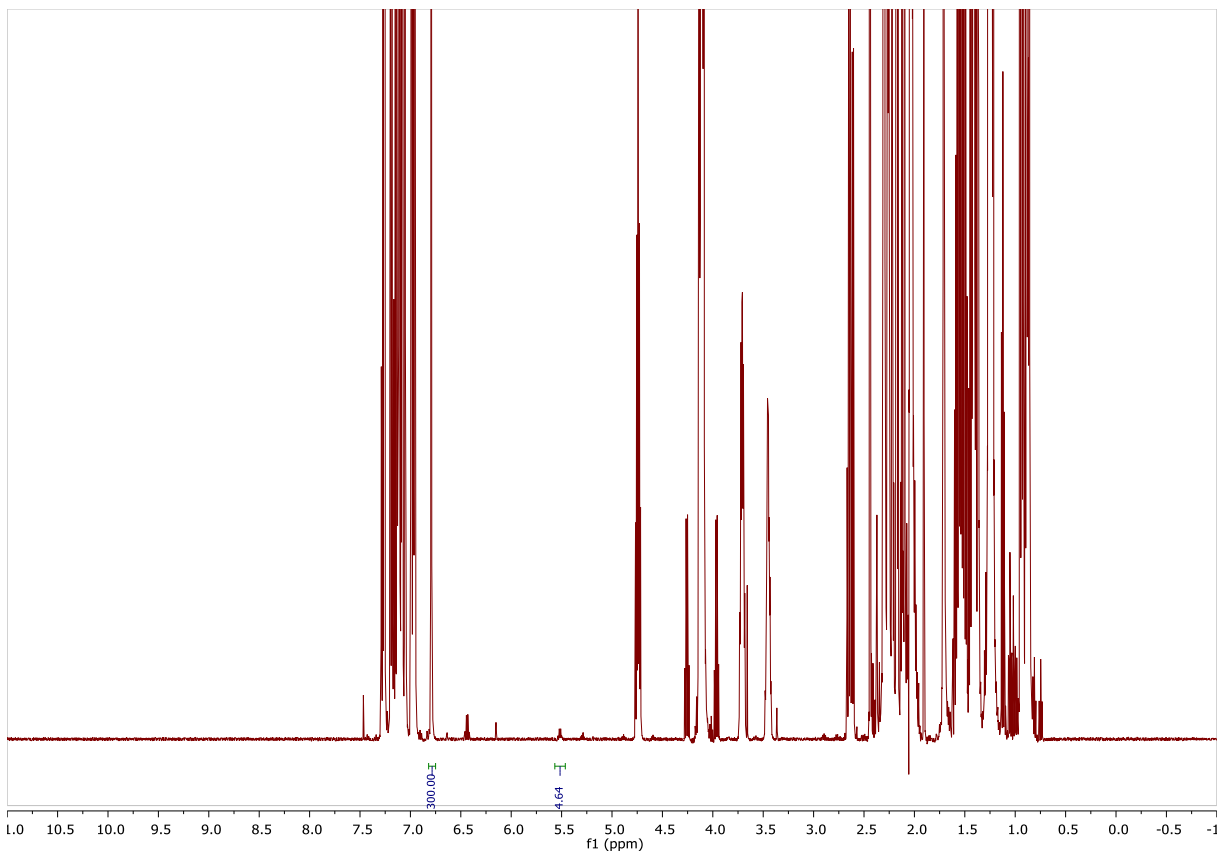
$\beta$ -position =  $100 - ((0/1) * 100) = 100\% \text{ D}$

$\gamma$ -position =  $100 - ((3.48/6) * 100) = 42\% \text{ D}$



A 10 mL microwave vial equipped with a stirrer bar was charged with ketone **1** (95.2 mg, 0.5 mmol) and base (1 equiv.). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle repeated three times. Under nitrogen the vial was then charged with xylenes (0.5 mL) and **24** (3.0 mmol, 6 equiv.). The mixture was stirred at 150 °C for 24 h. It was then cooled, followed by the addition of mesitylene (70  $\mu\text{L}$ , 60 mg, 0.5 mmol), H<sub>2</sub>O (2 mL), EtOAc (2 mL) and brine (0.5 mL) was added to aid layer separation. The mixture was stirred for 5 min, left to settle for a further 5 min, the cap was removed and the top layer was sampled and analysed using <sup>1</sup>H NMR with 1,3,5-trimethylbenzene as the internal standard and trace quantity of the secondary alcohol **59** about 5% was observed in this case which would have been generated *via* the MPV-type reduction of the aromatic ketone Fig 2.





**Fig 2:** Crude mixture evidence of MPV-type reduction of the aromatic ketone

## Reference

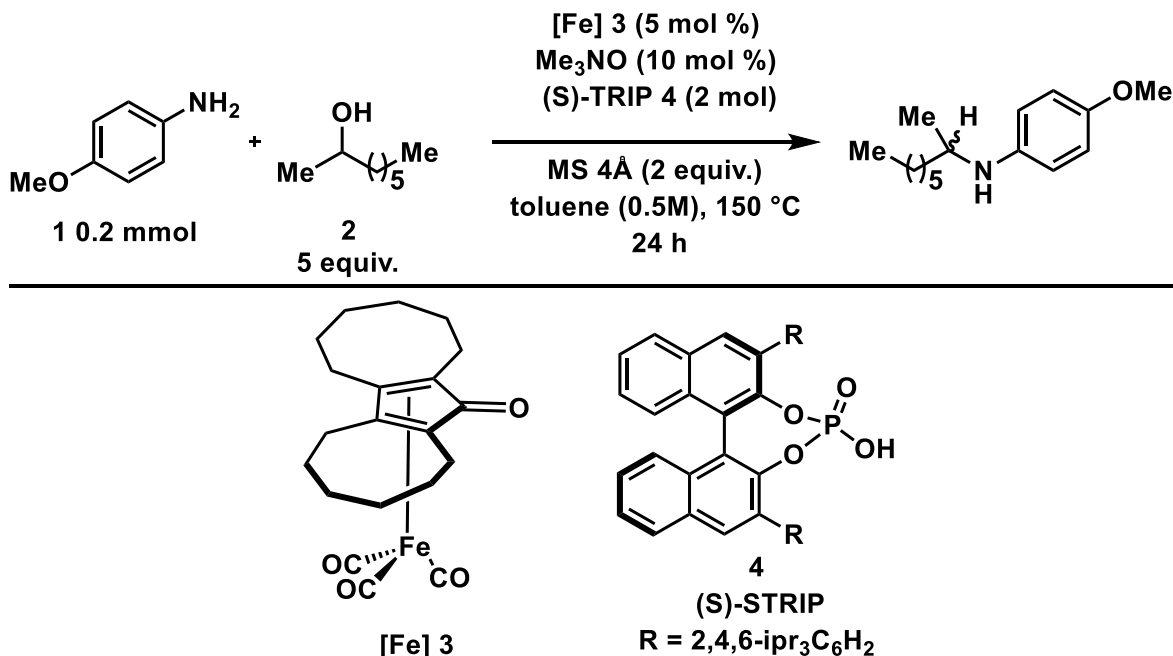
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3. O. Junzo, *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000.
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## Chapter Four

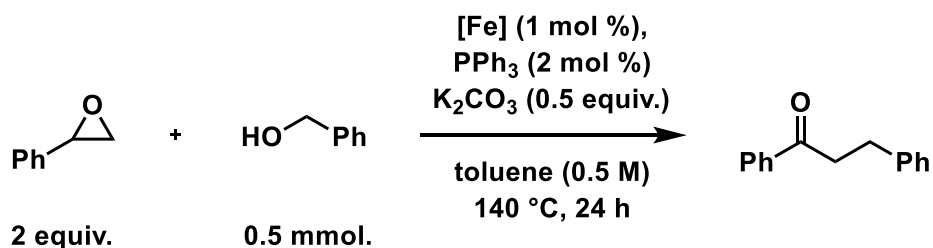
### Further Investigation into Borrowing Hydrogen Methodologies

#### 4.1 Preface

This chapter discusses two investigations in the borrowing hydrogen methodology; the first is the investigation into the enantioselective C-N alkylation of amines with secondary alcohols using dual catalysis of transition metal and chiral phosphoric acid. In this investigation the desired product was produced almost with no ee while the second investigation looked into the alkylation of epoxides using primary alcohols, which unfortunately gave a number of undesired products.



Enantioselective C-N alkylation of amines with secondary alcohols



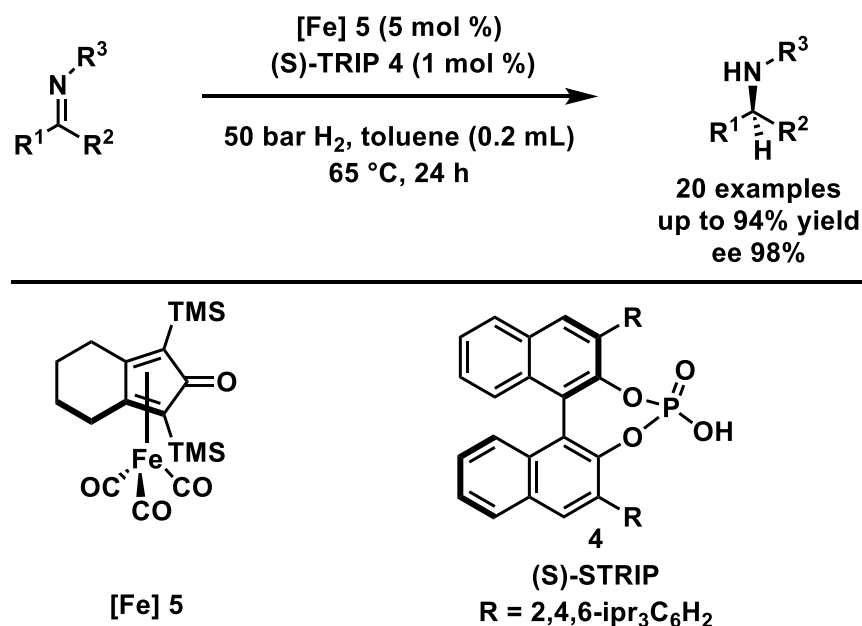
Alkylation of epoxide using primary alcohols

## 4.2 Introduction

Enantiomerically pure amines are among the building blocks of drugs and are also integral part of many other numerous bioactive compounds like herbicides and insecticide.<sup>1</sup> The development of efficient methods for the synthesis of these amines is a topic of interest in organic chemistry & catalysis. To this effect asymmetric hydrogenation has become the prime technology for this transformation.<sup>2</sup> All the known catalytic systems for such transformations employed the use of precious transition metals in combination with specific chiral phosphine ligands for the enantioselectivity. In an attempt to find a better way of making chiral amines with earth abundant metals, Beller and co-workers used a different approach with iron hydrogenation catalyst and a chiral Brønsted acid for the reduction of various imine to amines with excellent enantioselectivity.<sup>3</sup>

Their catalytic system comprises of Knölker type iron complex **5** and TRIP **4** as the chiral phosphoric acid which successfully reduced various aromatic ketimines efficiently. The yield obtained was moderately high up to 93% with excellent enantioselectivity of ee up to 98%. The system tolerated a number of electron donating and withdrawing groups on the benzene ring of the many substrates in their examples, the general method is shown below in scheme 1. Heteroaromatic imines were also reduced effectively with ee of 91-98%. Moreover, the reduction of aliphatic imines occurred with a good enantioselectivity and an ee of 67-83%.

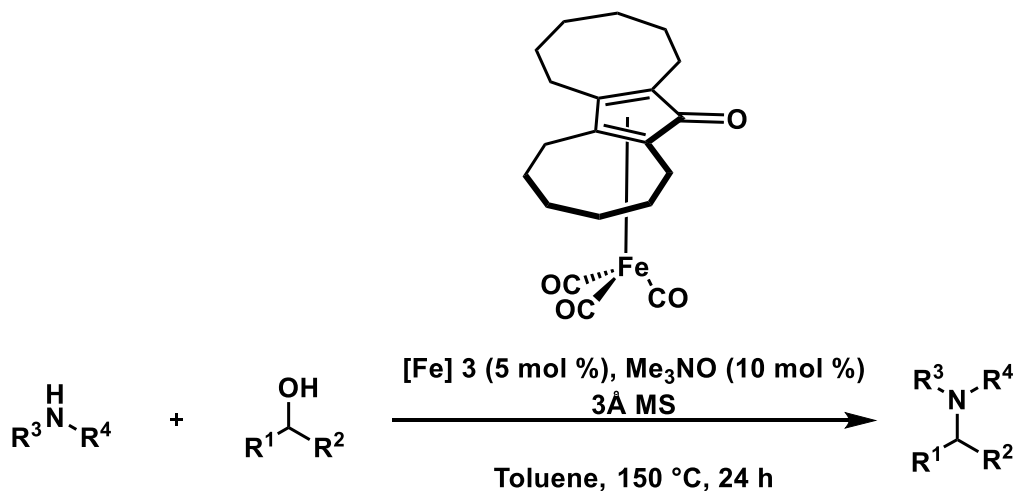
This is a good strategy that avoids the use of precious metals catalyst and chiral ligands shown in Scheme 1 below.<sup>3</sup>



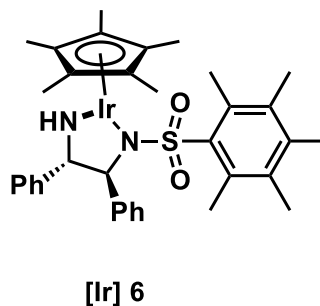
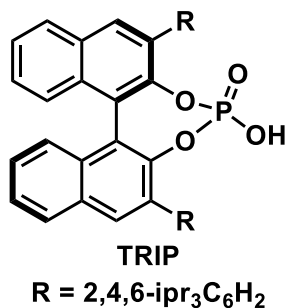
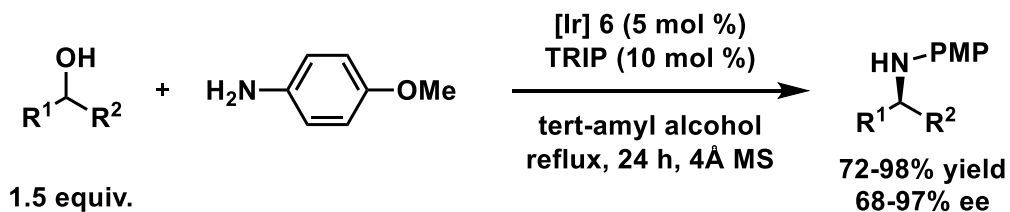
**Scheme 1:** Asymmetric hydrogenation of Imine

In 2019, Genneri and co-workers reported the iron catalysed amination of secondary alcohols using a stable cyclopentadienone iron complex **3**. In their study a large number of alcohols successfully underwent amination with amines giving the desired products with up to 99% NMR yield<sup>4</sup> Scheme 2a. With the exploration of catalytic asymmetric reduction of ketimines in the synthesis of chiral amines using reductants such as the one reported by Bellar and co-workers<sup>3</sup> with H<sub>2</sub> as the reductant in cooperative catalysis. Zhao reported an alternative way of making these amines using the borrowing hydrogen methodology in cooperation with acids.<sup>5</sup> This method provides access to enantioselective synthesis of chiral amines using alcohols as both alkylating agent and the hydrogen source. After extensive optimization using different iridium complexes, different acid additives ranging from achiral toluene sulfonic acid to chiral phosphoric acids, non-polar to

polar solvent, a cooperative catalytic system comprising of an iridium complex **6**, chiral phosphoric acid (TRIP) **4** and tert-amyl alcohol was found to give the desired product in good to excellent yield with high enantiomeric excess, furnishing amines in good yield and ee of up to 97% as shown in Scheme 2b.



**Scheme 2 a:** Amination of secondary alcohol

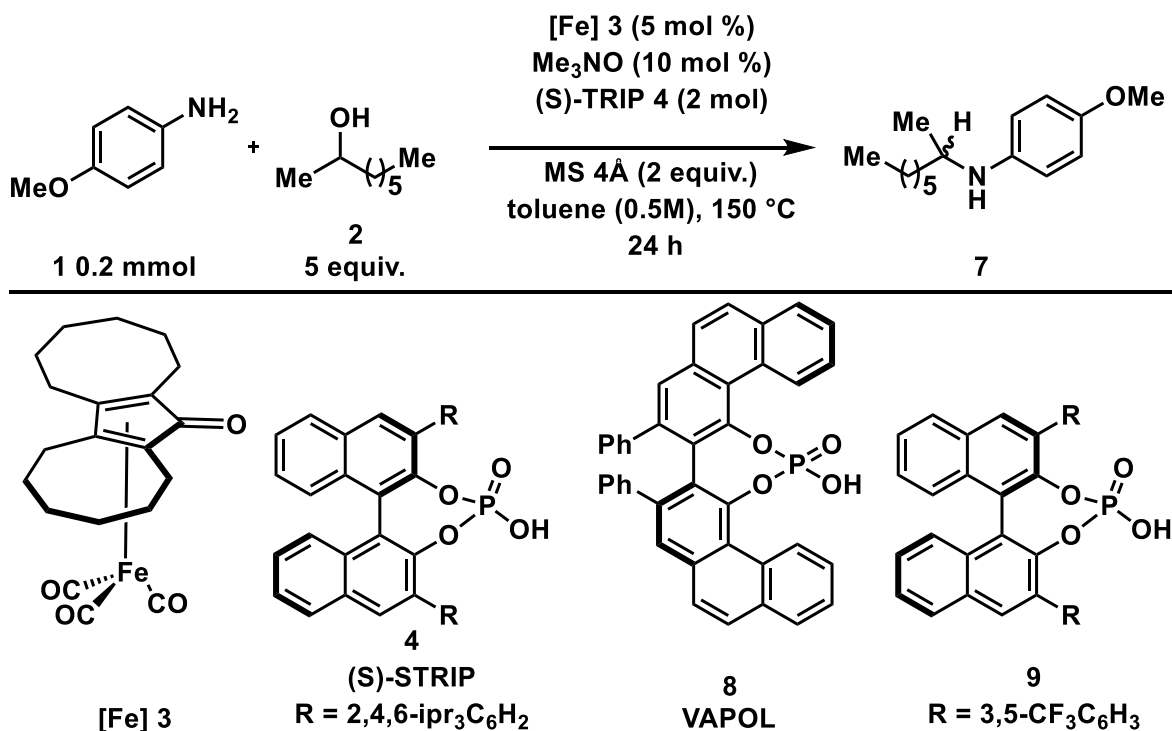


**Scheme 2 b:** Enantioselective amination of alcohols

With the existing reports in the literature from the reduction of ketimines to chiral amines, through the amination of secondary alcohols and to the enantioselective amination of alcohols to chiral amines, there was not any report where the amination of alcohols was carried out using earth abundant metals enantioselectively. For this reason, we aimed at doing the transformation reported by Zhao and co<sup>5</sup> using the cyclopentadienone iron complex **3** as the catalyst used in the study reported by Gennari and co-workers in the amination of secondary alcohols.<sup>4</sup>

### 4.3 Optimization of the reaction

We begin our investigation with 0.2 mmol of p-anisidine (**1**), 5 equiv. of 2-octanol **2**, 5 mol% of iron complex **3** as the precatalyst and 2 mol% of the (S)-TRIP **4** as the acid in toluene as shown in Scheme 3, this is the model reaction for the transformation.



**Scheme 3:** Enantioselective amination of secondary alcohols

From the model reaction above, **7** was produced in 70% yield albeit without any ee (entry 1). Other chiral phosphoric acids **8** and **9** were tested but did not give the desired product (entry 2 and 3). While doing the reaction without any CPA gave the product in an increased yield of 82% (entry 4), showing the other effect of CPA in slowing down the reaction. The use of molecular sieve or any other drying agent is necessary as no product was observed in its absence (entry 5), signifying the need to remove the water as it was formed so as to avoid the reaction from proceeding in the opposite direction. While the absence of base diminished the yield to 50%, probably the  $K_2CO_3$  was acting as a drying agent (entry 6) but the absence of both TRIP and base gave an increased yield of 75% (entry 7) both with zero ee. From here the effect of temperature was checked, decreasing the temperature from 150 °C to 130 °C, 110 °C and then to 90 °C, (entries 8-10). An excellent yield was obtained at 130° of 95% (entry 8) and the least was seen at 90° of 48% (entry 10), still with no enantioselectivity. The concentration of the reaction medium was then decreased, from 0.5M to 0.25M, and 85% of the product was seen without any ee in (entry 11). All the results are shown in Table 1 below.

**Table 1:** Result of Optimization Reaction

Entry	Cat. Loading (mol %)	Activator (mol %)	CPA (mol %)	Additive MS	Base (equiv.)	Solvent (Conc.)	T (°C)	1 (%)	7 (%)	ee (%)
1	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP <b>4</b> (2)	80 mg	K <sub>2</sub> CO <sub>3</sub> (2)	(0.5 M)	150	-	70	14



<b>2</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	<b>VAPOI 8 (2)</b>	80 mg	K <sub>2</sub> CO <sub>3</sub> (2)	(0.5 M)	150	7	-	-
<b>3</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	<b>CPA 9 (2)</b>	80 mg	K <sub>2</sub> CO <sub>3</sub> (2)	(0.5 M)	150	-	-	-
<b>4</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	-	80 mg	K <sub>2</sub> CO <sub>3</sub> (2)	(0.5 M)	150	-	82	0
<b>5</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (2)	-	K <sub>2</sub> CO <sub>3</sub> (2)	(0.5 M)	150	-	-	-
<b>6</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (2)	80 mg	-	(0.5 M)	150	-	50	0
<b>7</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	-	80 mg	-	(0.5 M)	150	-	75	0
<b>8</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (2)	80 mg	-	(0.5 M)	<b>130</b>	-	95	0
<b>9</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (2)	80 mg	-	(0.5 M)	<b>110</b>	-	78	0
<b>10</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (2)	80 mg	-	(0.5 M)	<b>90</b>	-	48	0
<b>11</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (2)	80 mg	-	<b>(0.25M)</b>	110	-	85	0

Yield after 24 h as determined by <sup>1</sup>H NMR spectroscopy of the crude mixture with 1,3,5-trimethylbenzene as internal standard and the ee was obtained by HPLC analysis

At this point the Bellar's reaction condition<sup>3</sup> was tested with our iron catalyst **3** at 65 °C in 1M of toluene but ended up with only 56% of the starting material **1** without any product (entry 1, Table 2). This result was comparable to the previous one obtained in (entry 10, Table 1), confirming that the reaction occurs at a relatively higher temperature. Little ee of 2% was seen when using the Zao's condition<sup>5</sup> employing iron complex **3** giving 48% of the product (entry 2). Lowering the amount of the TRIP and the temperature does not give any meaningful outcome of the product in terms of the yield and the ee (entries 3 and 4). The best result so far was obtained when the concentration of the reaction was reduced to 0.2M and using 5 mol% of the TRIP **4** in (entry 5) giving an ee of 6% and a yield of 77%. Exploring different drying agents did not yield the desired

ee in spite of the good yields observed at different temperatures (entries 6-13).

All the results are shown in Table 2 below.

**Table 2:** Result of Further Optimization Reaction

Entry	Cat. Loading (mol %)	Activator (mol %)	CPA (mol %)	Additive MS	Solvent (Conc.)	T (°C)	1 (%)	7 (%)	ee (%)
1	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP <b>4</b> (1)	80 mg	(1.0 M)	65	56	-	-
2	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP <b>4</b> (10)	100 mg	(0.4 M)	110	-	48	2
3	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	<b>TRIP (5)</b>	80 mg	(0.4 M)	110	-	11	2
4	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	80 mg	(0.4 M)	<b>90</b>	-	7	1
5	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	80 mg	<b>(0.2 M)</b>	110	-	77	6
6	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	<b>MgSO<sub>4</sub></b> <b>(2)</b>	(0.4 M)	110	-	73	4
7	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	MgSO <sub>4</sub> (2)	<b>(0.2 M)</b>	110	-	79	4
8	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	<b>CaCl<sub>2</sub></b> <b>(2)</b>	(0.2 M)	110	-	-	-
9	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	<b>Al<sub>2</sub>O<sub>3</sub></b> <b>(2)</b>	(0.2 M)	110	-	89	2
10	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	<b>SiO<sub>2</sub></b> <b>(2)</b>	(0.2 M)	110	-	81	3
11	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	Al <sub>2</sub> O <sub>3</sub> (2)	(0.4 M)	<b>90</b>	-	35	0
12	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	Al <sub>2</sub> O <sub>3</sub> (2)	(0.4 M)	<b>65</b>	81	-	-

<b>13</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	SiO <sub>2</sub> (2)	(0.4 M)	<b>90</b>	-	75	1
<b>14</b>	[Fe] <b>3</b> (5)	Me <sub>3</sub> NO (10)	TRIP (5)	SiO <sub>2</sub> (2)	(0.4 M)	<b>65</b>	86	-	-

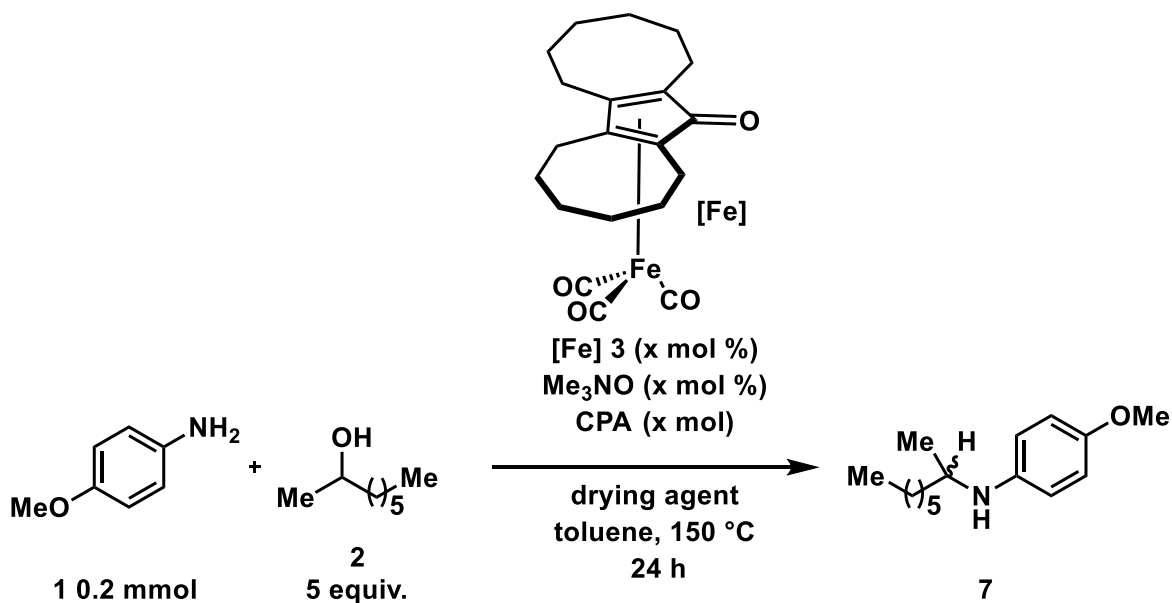
Yield after 24 h as determined by <sup>1</sup>H NMR spectroscopy of the crude mixture with 1,3,5-trimethylbenzene as internal standard and the ee was obtained by HPLC analysis

#### 4.4 Conclusion

After extensive optimization, the desired compound was obtained in good to excellent yield but without any meaningful ee. The best result obtained in terms of the yield of the product **7** was 95% while with respect to the ee was 6%. From the result obtained it was evident that temperature plays a very significant role in the reaction and the presence of drying agent too. The choice of the chiral phosphoric acid was also vital and the concentration of the reaction medium.

#### 4.5 Experimental

##### 4.5.1 Optimization of enantioselective amination of secondary alcohol

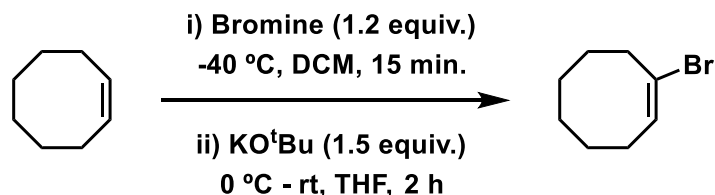


A 10 mL microwave vial equipped with a stirrer bar was charged with p-anisidine **1** (25.0 mg, 0.2 mmol),  $K_2CO_3$  (55.0 mg, 2 equiv.), drying agent (x equiv.) and precatalyst **3** (x mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle repeated three times. Under nitrogen the vial was then charged with toluene (x mL) and 2-octanol **2** (159.0  $\mu$ L, 5 equiv.). The mixture was left to react at 110 °C for 24 hours. It was then cooled, followed by the addition of mesitylene (28  $\mu$ L, 0.2 mmol),  $H_2O$  (2 mL) and EtOAc (2 mL). Brine (1 mL) was added to aid layer separation. The mixture was stirred for 5 min, left to settle for a further 5 min, cap removed and the top layer was sampled and analysed using  $^1H$  NMR with mesitylene as the internal standard. The ee was determined by HPLC analysis of the pure sample of the product obtained after purification of the crude mixture by flash silica chromatography (eluent = 5% EtOAc in petroleum ether, 30 x 150 mm silica). The HPLC instrument used for this experiment is shown below in Figure 1.



**Fig 1:** HPLC apparatus used to measure enantiomeric excess of pure products

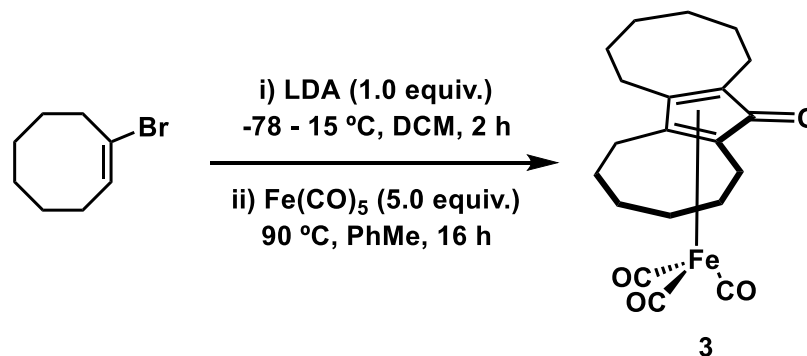
### (E)-1-bromocyclooct-1-ene



The title compound was prepared according to a modified procedure stated in the literature.<sup>6</sup> Under nitrogen, a three-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with cyclooctene (8.3 mL, 6.9 g, 62.5 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (30 mL). The solution was cooled to -40 °C and was charged with Br<sub>2</sub> until the solution changed to yellow. Excess Br<sub>2</sub> (1 mL) was then added and the mixture was quenched with 10% aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (30 mL). The mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 50 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo* giving *trans*-1,2-dibromocyclooctane (16.5 g, 98%). This was used for the next step without further purification. In a separate three-necked flask, KO<sup>t</sup>Bu (11.5 g, 94.0 mmol) was suspended in dry THF (30 mL). To this suspension was then added a solution of *trans*-1,2-dibromocyclooctane (12.0 g, 44.5 mmol) in dry THF (40 mL) at 0 °C. The mixture was stirred for 2hr at rt and was then quenched with sat. aq. NH<sub>4</sub>Cl (40 mL). The mixture was concentrated *in vacuo* until the THF was completely evaporated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) and the organic layer was collected. The aqueous layer was washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 25 mL). The organics were combined, dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by distillation (85-90 °C at 10 mbar) gave the title compound as a pale-yellow oil (7.3 g, 89%); R<sub>f</sub> = 0.77 (eluent = 100% hexanes); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δH: 1.46-1.58 (6H, m, CH<sub>2</sub>), 1.60-1.68 (2H, m, CH<sub>2</sub>), 2.06-2.13 (2H, m, CH<sub>2</sub>), 2.57-2.65 (2H, m, CH<sub>2</sub>), 6.03 (1H, t, J

8.5, HC=CBr);  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta\text{C}$ : 25.6 ( $\text{CH}_2$ ), 26.5 ( $\text{CH}_2$ ), 27.6 ( $\text{CH}_2$ ), 28.8 ( $\text{CH}_2$ ), 30.0 ( $\text{CH}_2$ ), 35.3 ( $\text{CH}_2$ ), 124.9 (CBr), 131.8 (C=CBr). Spectroscopic data in accordance with that stated in the literature.<sup>7</sup>

**[bis(hexamethylene)cyclopentadienone]iron tricarbonyl**



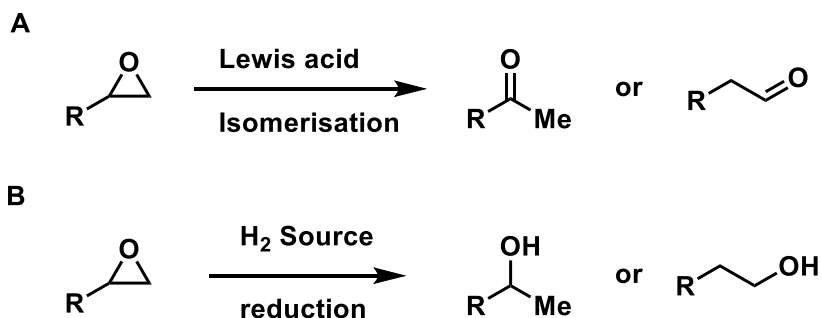
The title compound was prepared according to a modified procedure stated in the literature.<sup>6</sup> Under nitrogen, a flame-dried three-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with dry THF (10 mL). It was cooled to  $-78\text{ }^\circ\text{C}$  followed by the addition of diisopropylamine (4.1 mL, 2.9 g, 29.0 mmol) and *n*-BuLi (12.3 mL, 26.4 mmol, 2.15 M in hexanes). After 10 min, the mixture was charged with (*E*)-1-bromocyclooct-1-ene (5.0 g, 26.4 mmol). The mixture was left to stir at  $-78\text{ }^\circ\text{C}$  for 20 min and then heated up to  $-20\text{ }^\circ\text{C}$ . After 10 min, the mixture was gradually left to heat up to  $15\text{ }^\circ\text{C}$  and was left at this temperature for 90 min. It was then poured into a cold solution of 3N HCl. The solution was extracted with hexanes and the combined extracts were washed several times with water in order to remove the THF. The organic layer was dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The crude mixture (815 mg, 7.5 mmol) was then transferred to an ACE pressure tube equipped with a magnetic stirrer bar followed by the addition of dry toluene (8 mL) and  $\text{Fe}(\text{CO})_5$  (5.0 mL, 7.4 g, 37.5 mmol). The mixture was heated to  $90\text{ }^\circ\text{C}$  for 16 h. The mixture was filtered over celite and the filtrate concentrated *in vacuo*. Purification by flash silica

chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound an off-white solid. (970 mg, 24%); mp 153-155 °C (Lit. 156 °C);<sup>5</sup> Rf = 0.17 (eluent = 30% EtOAc in hexanes); **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)** δH: 1.35-2.00 (18H, m, 9xCH<sub>2</sub>), 2.39-2.51 (2H, m, CH<sub>2</sub>), 2.56-2.65 (2H, m, CH<sub>2</sub>), 2.72-2.82 (2H, m, CH<sub>2</sub>); **<sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>)** δC: 23.6 (2xCH<sub>2</sub>), 23.9 (2xCH<sub>2</sub>), 25.9 (2xCH<sub>2</sub>), 26.4 (2xCH<sub>2</sub>), 29.0 (2xCH<sub>2</sub>), 31.5 (2xCH<sub>2</sub>), 85.7 (2xC=C), 102.6 (2xC=C), 171.6 (C=O), 209.5 (Fe(CO)<sub>3</sub>). Spectroscopic data in accordance with that stated in the literature.<sup>7</sup>

#### 4.6 Alkylation of epoxide

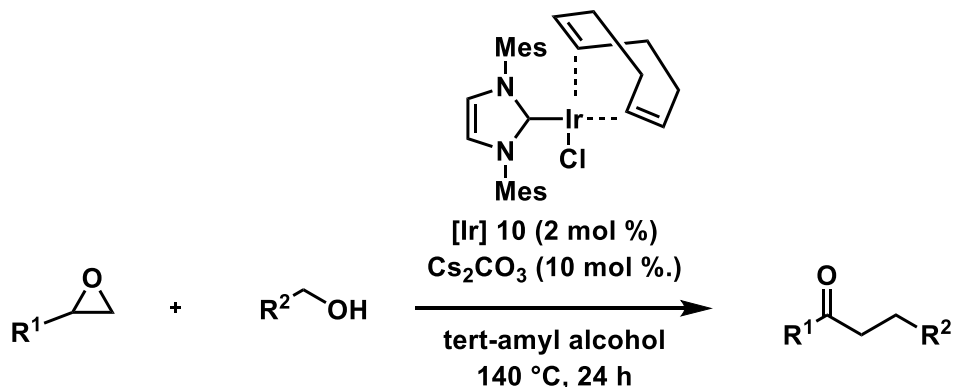
Ketones are versatile intermediates that are widely used in the organic synthesis of valuable compounds like pharmaceuticals, polymers and natural products.<sup>8</sup> And one of the numerous methods for the synthesis of either  $\alpha$ - or  $\beta$ -branched ketones is the transition-metal (TM) catalysed alkylation of ketones with alcohols through the borrowing hydrogen (BH) methodology. This has many advantages over the conventional methods<sup>9</sup> because of the use of readily available and inexpensive alcohols as both alkylating agents and hydrogen source in the BH strategy offers a greener and more sustainable alternative to the conventional alkylating methods, avoiding the use of mutagenic alkyl halides or excessive amounts of a strong base.<sup>10</sup> On the other hand, epoxides are also useful intermediates that can be transformed into various valuable organic molecules like the ketones through ring opening reaction by acid catalysed isomerisation, commonly called the Meinwald rearrangement Scheme 4a.<sup>11</sup> Another important transformation of epoxide is the reductive ring opening to either primary or secondary alcohols Scheme 4b. The traditional ring opening of epoxide involves the use of excess or stoichiometric amount of strong reducing agents like NaBH<sub>4</sub>

which result in selective formation of secondary alcohols.<sup>12</sup> Heterogenous catalysts like supported Pd were reported to reduced different epoxides selectively into either primary alcohols or secondary alcohols when aryl and alkyl epoxides were used.<sup>13,14</sup>



**Scheme 4:** A) Meinwald rearrangement to ketone and aldehyde. B) Reduction of epoxide to primary and secondary alcohol

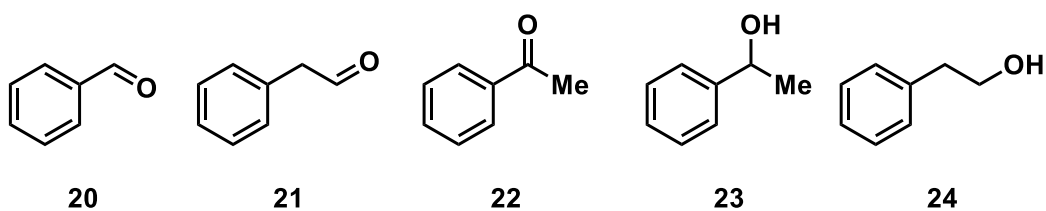
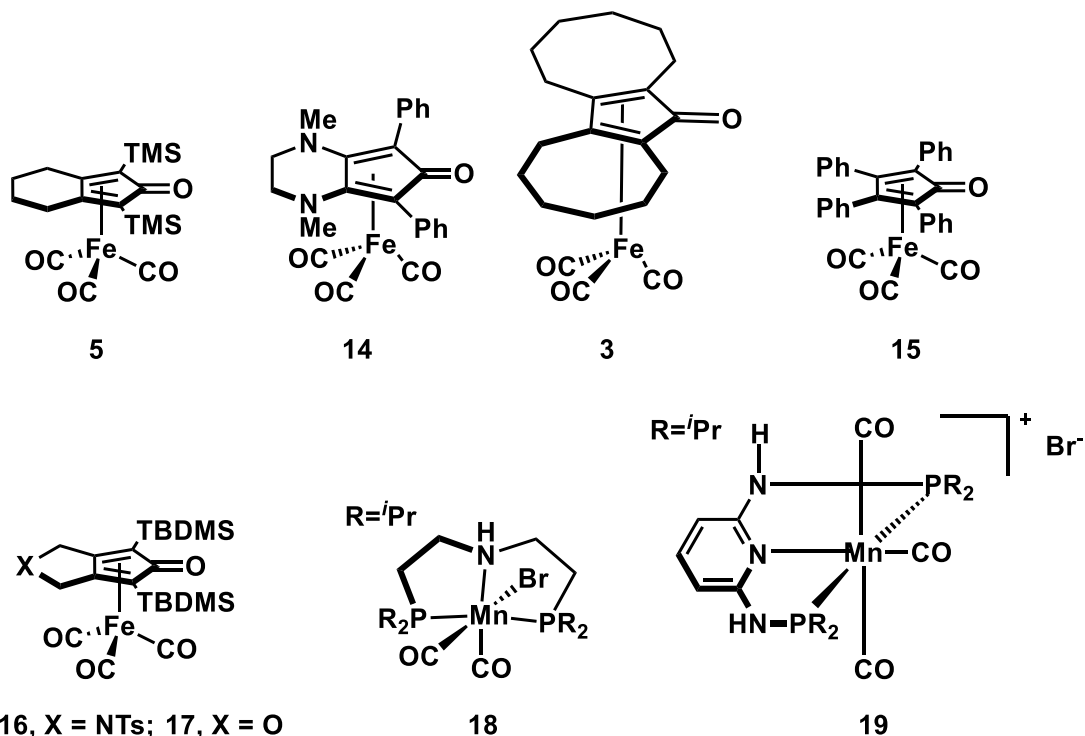
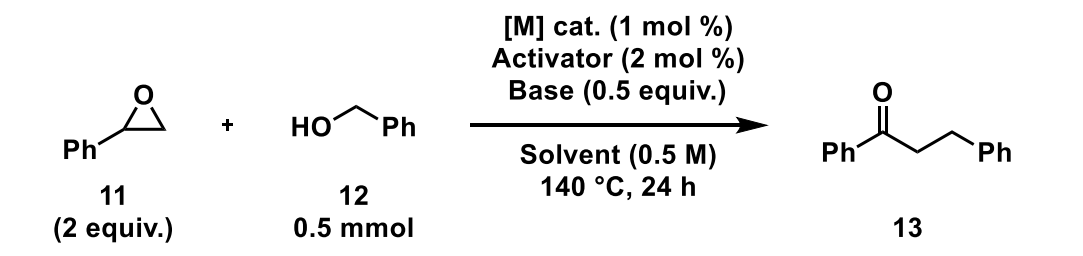
Recently, Gulcemal and co-workers reported the one pot selective ring opening of terminal epoxide/alkylation reaction, in their report a number of terminal epoxides were successfully ring opened selectively and reacted further with primary alcohols to give  $\alpha$ -alkylated ketones as the products using an iridium catalyst **10**.<sup>15</sup> This was the first borrowing hydrogen methodology where alkylated ketones were synthesised from epoxides and alcohols Scheme 5 below.



**Scheme 5:** One pot selective ring opening/alkylation of epoxide via borrowing hydrogen



At the beginning of our investigation our intention was to use an earth abundant metal as the catalyst to do the ring opening/alkylation of epoxides and that the report of Gulcemal was not known. Thus, we decided to explore the different earth abundant metal catalysts to see whether they would enable the one-pot selective ring opening of terminal epoxides, leading to either secondary alcohol or ketone that could be subsequently alkylated by primary alcohol to give  $\alpha$ -branched ketones through borrowing hydrogen methodology Scheme 6.



### Scheme 6: Isomerisation/Alkylation of Epoxystyrene

Epoxy styrene and benzyl alcohol were chosen for this study and the results obtained are shown in the Table 3 below.

**Table 3: Optimization of the reaction**

Entry	Cat. Loading	Additive	Base	Solvent	T	11	12	20	13	23	24
	(mol %)	(mol %)	(equiv.)	(Conc.)	(°C)	(%)	(%)	(%)	(%)	(%)	(%)

1	[Fe] <b>5</b> (1)	PPh <sub>3</sub> (2)	Cs <sub>2</sub> CO <sub>3</sub> (0.5)	(0.5 M)	140	-	35	22	-	-	18
2	[Fe] <b>14</b> (1)	PPh <sub>3</sub> (2)	Cs <sub>2</sub> CO <sub>3</sub> (0.5)	(0.5 M)	140	-	23	35	-	-	27
3	[Fe] <b>3</b> (1)	PPh <sub>3</sub> (2)	Cs <sub>2</sub> CO <sub>3</sub> (0.5)	(0.5 M)	140	-	27	22	-	-	27
4	[Fe] <b>15</b> (1)	PPh <sub>3</sub> (2)	Cs <sub>2</sub> CO <sub>3</sub> (0.5)	(0.5 M)	140	-	25	33	-	-	28
5	[Fe] <b>16</b> (1)	PPh <sub>3</sub> (2)	Cs <sub>2</sub> CO <sub>3</sub> (0.5)	(0.5 M)	140	-	35	16	-	-	30
6	[Fe] <b>147</b> (1)	PPh <sub>3</sub> (2)	Cs <sub>2</sub> CO <sub>3</sub> (0.5)	(0.5 M)	140	-	35	29	-	-	25
7	[Mn] <b>18</b> (1)	PPh <sub>3</sub> (2)	Cs <sub>2</sub> CO <sub>3</sub> (0.5)	(0.5 M)	140	80	46	-	-	-	3
8	[Mn] <b>19</b> (1)	PPh <sub>3</sub> (2)	Cs <sub>2</sub> CO <sub>3</sub> (0.5)	(0.5 M)	140	38	55	8	-	-	2

Yield after 24 h as determined by <sup>1</sup>H NMR spectroscopy of the crude mixture with 1,3,5-trimethylbenzene as internal standard

A model reaction was chosen comprising of 1.0 mmol of epoxystyrene **11** and 0.5 mmol of the benzyl alcohol **12**, using 1 mol% of the precatalyst, 2 mol% of activator, 0.5 equivalent of a base in 0.5M toluene at 140 °C. Eight iron and manganese complexes were selected for the study in the synthesis of dihydrochalcone **13** from benzyl alcohol **12** and epoxystyrene **11**. None of the reactions gave the desired product **13** unfortunately. Reaction conducted with

iron complexes gave primary alcohol **24** (entries 1-6, 18-30%). Oxidation of benzyl alcohol **12** was also observed in entries 1-6 giving benzaldehyde **20** in 16-35% yield unlike with the manganese catalysts **18** and **19** where only 8% of benzaldehyde **20** was seen with catalyst **19** (entry 8). No meaningful oxidation of the benzyl alcohol to benzaldehyde **20** was also observed with the manganese catalysts (entries 7 and 8). The starting epoxystyrene was only recovered when manganese catalysts were employed as seen in entries 7 and 8 (38 and 80%). Compounds **21**, **22** and **23** were not observed at all which were assumed to be part of the possible intermediates or products of the reaction. All the results are shown in Table 3 above and Scheme 4.

#### 4.7 Conclusion

At the end of the pilot investigation no meaningful amount of the desired product was obtained after screening eight different catalysts, iron based and manganese based. It was observed that other intermediates were formed but only the primary alcohol **24** from Table 3 entry 5 is of interest, and thus makes it the only result worth building on because alcohols are deemed to be good starting materials in organic synthetic and therefore any method that leads to their formation is worth looking at especially if it is from a substrate that has the ability to give different products.

## Reference

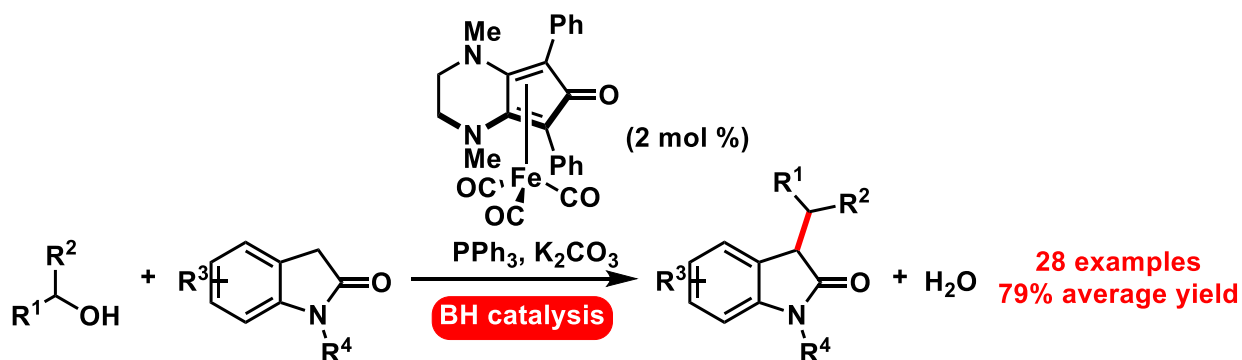
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## Chapter Five

### Summary, Conclusion and Recommendation

#### 5.1 Summary

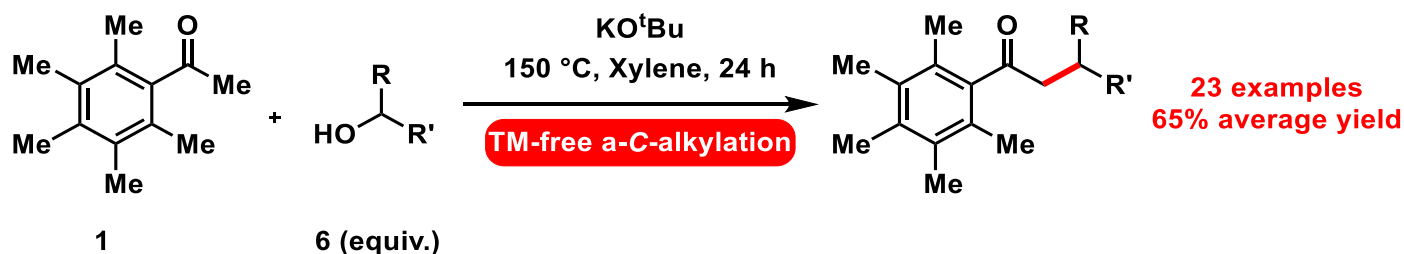
Four different projects using borrowing hydrogen methodology were investigated and reported in this thesis. Two out of the four projects were successfully while two did not actually lead to the desired outcome. The first project was the iron-catalyzed borrowing hydrogen C-alkylation of oxindoles with alcohols, where an oxindole under went C3-alkylation with a wide range of alcohols, from benzylic to simple primary and secondary alcohols, giving products with a good to an excellent yield (79%, average yield with 28 examples) Scheme 1. After some mechanistic investigation a reaction mechanism was proposed to go via the borrowing hydrogen process, which proved the formation of many intermediates like the aldehyde, the metal hydride and the  $\alpha$ ,  $\beta$ -unsaturated compounds. This method was extended to barbituric acids and became the first iron catalysed alkylation of the barbituric acids via the borrowing hydrogen.



**Scheme 1:** Iron-catalyzed C(3)-alkylation of oxindole

Secondly, a transition metal free alkylation of aryl ketone with secondary alcohols was studied, the ketone under went mono- $\alpha$ -alkylation selectively with many

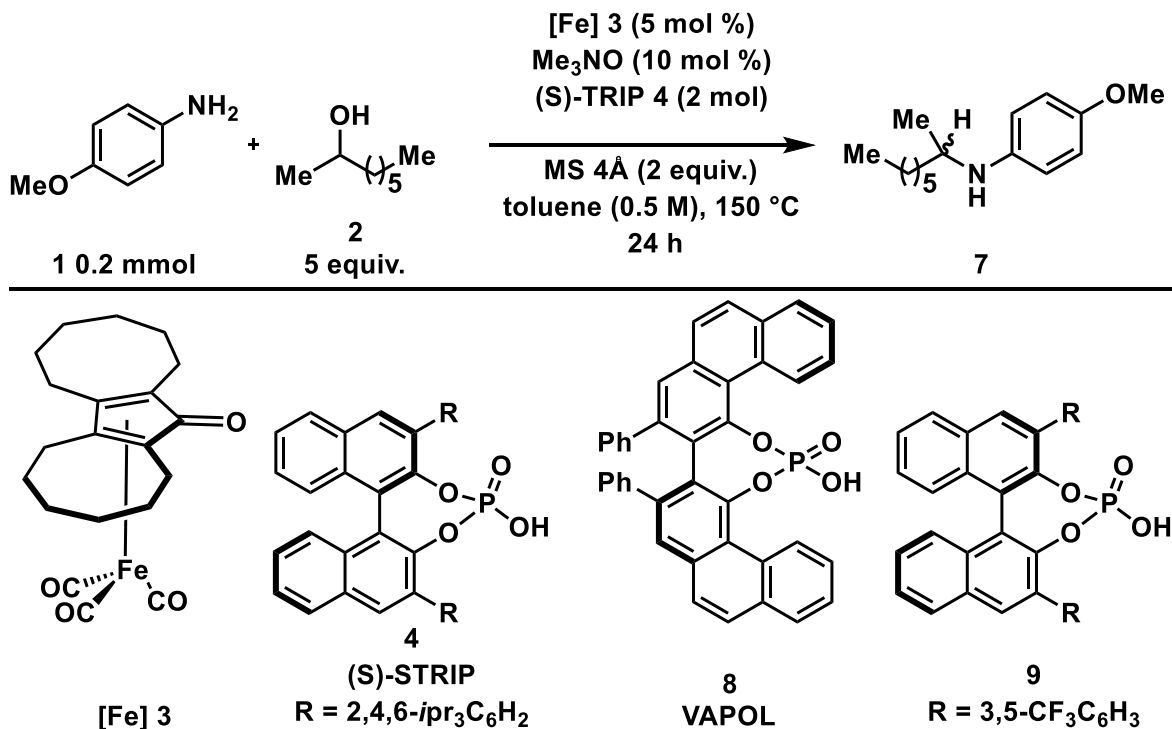
secondary alcohols, giving good yield of the products (23 examples, 66% average yield). The method employed the use of KO<sup>t</sup>Bu as the base and has provided a strategy to the synthesis of  $\beta$ -substituted carbonyl compounds Scheme 2 below.



**Scheme 2:** Transition metal free  $\alpha$ -alkylation of aryl ketone with secondary alcohols

After the mechanistic investigation using the deuterium labelling experiment, the reaction was proposed to proceed via an Oppenauer-type oxidation of the secondary alcohol and subsequent MVP-type reduction of the enone intermediate to the corresponding product.

The third project was the investigation into the enantioselective amination of secondary alcohols using iron complex as the catalyst in cooperation with chiral phosphoric acid CPA, where different CPAs were incorporated but with no any success at the end, only the racemates of the product were obtained in good to excellent yield at the end of the study, Scheme 3.



**Scheme 3:** Enantioselective amination of secondary alcohols

And lastly, the fourth project which was a pilot study for the isomerisation/alkylation of epoxystyrene project which did not give the much desired product but fortunately enough a primary alcohol was obtained in a moderate yield. This could be a foundation for more comprehensive research employing the earth abundant metal like iron.

## 5.2 Conclusion

It can be concluded that at the end of my PhD work I was able to developed two catalytic methods for C-alkylation processes; one was the borrowing hydrogen method using an earth abundant metal iron and alcohol as the alkylating agent and the second was the transition metal free alkylation of ketone with secondary alcohol, a method which served as a synthetic route to  $\beta$ -substituted carbonyl compound. While the third project in the area of stereoselective borrowing



hydrogen which involved the enantioselective amination of alcohols did not give the desired outcome, only racemates were obtained but the result has opened a door into further studies in that area and the fourth project, the isomerisation/alkylation of epoxystyrene *via* the borrowing hydrogen also yielded no expected outcome albeit with a little result that could be study further extensively as regioselective ring opening of epoxide.

### 5.3 Recommendation

In spite of the many works reported in the last two decades in the area of borrowing hydrogen, there is still limited applications of earth abundant metals of the first row in assymmetric reactions and also there is no biocatalytic borrowing hydrogen methods for C-alkylation process, an area that needs to be studied extensively. Furthermore, collective targets should be on milder reaction conditions, lower reaction time and catalyst loadings. And more effort should be given to design of new and more active catalysts based on earth abundant metals and the incorporation of borrowing hydrogen methodologies in a dual catalytic system especially with the chiral phosphoric acids which proved to be useful in stereoselective reactions.