Exploring New Directions in Hydrogen Transfer Chemistry

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This thesis is submitted for the degree of Doctor of Philosophy (PhD) at Cardiff University

November 2019

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SUMMARY

This thesis describes the development of new routes towards hydrogen transfer chemistry. Transfer hydrogenation is known concept in which hydrogen is transferred from one molecule to another without the use of molecular hydrogen. Borrowing hydrogen is a methodology which employs this concept and is known as hydrogen-autotransfer, as it combines a transfer hydrogenation process with a concurrent reaction on the *in situ* generated reactive intermediate. This is a great methodology as it doesn't require toxic and harmful alkylating agents for alkylation. Alcohols are generally used for this methodology which are benign and friendly starting materials producing water as the sole by-product making this process highly atom economic. In this thesis, several methodologies related to hydrogen transfer chemistry have been developed.

Initial research was focussed on tandem ruthenium catalysed hydrogen transfer and S_NAr chemistry whereby sacrificial additives are used to facilitate the formation of two different sets of compounds following dehydrogenative S_NAr chemistry. Several diaryl ethers and secondary amines are formed in good yields. The next project involved the development of a general iron-catalysed methylation using methanol as a C1 building block. The process exhibits a broad reaction scope with a variety of ketones, indoles, oxindoles, amines, and sulfonamides to undergo efficient methylation. This methodology was later applied to the *β*-methylation of alcohols which is described in a separate chapter in this thesis.

The oxindole framework is present in several pharmacologically active compounds. Hence the next part of this thesis involved the development of an efficient iron-catalysed *C*(3)-alkylation of oxindoles *via* the borrowing hydrogen approach. This process exhibits a broad reaction scope, allowing primary and secondary aliphatic alcohols to be utilised as alkylating agents with a range of substituted oxindoles. Finally, the last chapter explains a one-pot iron-catalysed conversion of allylic alcohols to *α*-methyl ketones using methanol as C1 building block.

ACKNOWLEDGEMENTS

Firstly, I would like to thank the Catalysis CDT for giving me the opportunity to carry out research at one of three possible top-class universities. My acceptance in the CDT wouldn't have been successful without Louis Morrill, my supervisor. I would like to thank him greatly for all his support and guidance during the past three years, making me a better and more independent student, which will surely be beneficial for my future. I also would like to thank my co-supervisor Professor Jonathan Williams who sadly passed away during my final year. My research followed on from what your group published, and hence you were an inspiration. Within the Cardiff chemistry department, I would like to thank Robert Jenkins for all his help with regards to NMR experiments and maintenance.

I would like to thank many group members for their support. Firstly, James and Imtiaz, with whom I spent most of my first and second year with. It was a pleasure to work with you in the lab. Secondly, all the members of lab 0.30 which include Alex, Ben A. and Deepak. I enjoyed the great times and good laughs we had during the past 2 years. I also enjoyed all the boardgame and poker sessions we had outside working hours. Since we have joint group meetings with the DLB group, I would like to thank Roddy, Andy, Tom and Will for all the great discussions and good times in and out of the lab. Although we didn't see much of each other during working hours, I enjoyed my time with them at the occasional run to the pub after work, and during weekly sessions of football.

During these three years, I have met several great people along the way, some of these include Micol, Toby, Filipa and Matt in 1.106. It was great to share a lab with you. I would also like to thank all the CDT members from my cohort, specifically Jon, Mark and Naomi. I enjoyed spending time with all of you, especially the UNO games we played during our train trips to Bristol and Bath in our MRes year.

From our research group in 1.106, I would like to thank Shyam for his support and advice. You were a great inspiration during my time in Cardiff. I would also like to thank Dan and Mubarak. It was a pleasure to work with you on joint projects and I hope that I have successfully nurtured you to become great chemists. Also, it was great having weekly football sessions with all three of you. I wish you all great success in your future endeavours.

Finally, I would like to thank Ben RB. You have been with me from the start of my PhD until the very end. I am extremely grateful for all your support. Thank you for all the great chemistry and other related discussions during the past 3 years. I couldn't have asked for a better friend.

I would also like to mention 3 good friends of mine back in Malta. Kurt, Malcolm and Clinton, it is always great to see you every time I come back to Malta on holiday.

The last people to thank are my grandparents, Arthur, Carmen, Cettina and Philip, and my parents Marisa and Tonio. Thank you for encouraging me to pursue my dreams. I wouldn't have made it this far without your help. I am forever grateful for your mental and financial support during the last four years and I wish to dedicate this thesis to all of you. I would also like to dedicate this to aunt Marie Claire, who passed away before I joined the 4-year CDT programme.

Ultimately, I would like to thank my wife Nicole who has continuously supported me during the past 10 years. I wouldn't have made it so far without her by my side. I am extremely grateful for everything you do for me. I enjoyed all the time and trips we had inside and outside of the UK. Thank you for motivating me when I needed it most and giving me the strength to get to the finish line.

LIST OF ABBREVIATIONS

AP	Affinity purification
API	Active pharmaceutical ingredient
ASAP	Atmospheric solids analysis probe
AA-ADH	*Aromatoleum aromaticum* alcohol dehydrogenase
BH	Borrowing hydrogen
[BMIM]PF_6	1-Butyl-3-methylimidazolium hexafluorophosphate
Bn	Benzyl
BOC	*N*-*tert*-Butoxycarbonyl
COD	Cyclooctadiene
CI	Chemical ionisation
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
DCC	*N*,*N*'-dicyclohextlcarbodiimide
Dcpb	1,4-bis(dicyclohexylphosphino)butane
Dcpe	1,2-bis(dicyclohexylphosphino)ethane
DFT	Density functional theory
DIPEA	*N*,*N*-Diisopropylethylamine
DMAC	*N*,*N*-dimethylacetamide
DMCC	Dimethylcarbamoyl chloride
DME	Dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	*N*,*N*-dimethylsulfoxide
DPEphos	Bis[(2-diphenylphosphino)phenyl] ether
Dppe	1,2-bis(diphenylphosphino)ethane
Dppf	1,1'-bis(diphenylphosphino)ferrocene
Dppp	1,1'-bis(diphenylphosphino)methane
EDG	Electron donating group
EI	Electron ionisation
ESI	Electrospray ionisation
Et	Ethyl

EWG	Electron withdrawing group
Fe-HMS	iron doped hexagonal mesoporous silica
H/D	Hydrogen/deuterium
HRMS	High resolution mass spectroscopy
Hz	Hertz
^{i}Pr	isopropyl
KHMDS	Potassium hexamethyldisilazide
Me	Methyl
MHz	Megahertz
mp	melting point
MPV	Meerwein-Pondorf-Verley
NaDH	Nicotinamide adenine dinucleotide
^{n}Bu	normal butyl
^{n}dec	normal decyl
^{n}Pr	normal propyl
NHC	Nucleophilic heterocyclic carbene
NMR	Nuclear magnetic resonance
NNN	Nitrogen-nitrogen-nitrogen
NNP	Nitrogen-nitrogen-phosphorus
NOESY	Nuclear Overhauser spectroscopy
NSI	Nanospray ionisation
Pet. ether	Petroleum ether
PCP	Phosphorus-carbon-phosphorus
Ph-AmDH	Phenylalanine amine dehydrogenase
PhMe	Toluene
PPy	4-pyrrolidinylpyridine
PNP	Phosphorus-nitrogen-phosphorus
RDS	Rate determining step
^{s}Bu	*sec*-butyl
S_N2	Bimolecular nucleophilic substitution
S_NAr	Nucleophilic aromatic substitution
SyADH	*Sphingobium yanoikuyae* alcohol dehydrogenase
^{t}Am	*tert*-amyl
TMSCl	trimethylsilyl chloride

TBSCl	*tert*-butyldimethylsilyl chloride
TeSADH	*Thermoanaerobacter ethanolicus* secondary alcohol dehydrogenase
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TON	Turnover number
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

LIST OF PUBLICATIONS

1. K. Polidano, B. G. Reed-Berendt, A. Basset, A. J. A. Watson, J. M. J. Williams and L. C. Morrill, *Org. Lett.*, 2017, **19**, 6716−6719.
2. K. Polidano, B. D. W. Allen, J. M. J. Williams and L. C. Morrill, *ACS Catal.*, 2018, **8**, 6440–6445.
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4. K. Polidano, J. M. J. Williams and L. C. Morrill, *ACS Catal.*, 2019, **9**, 8575-8580.
5. D. E. Latham, K. Polidano, J. M. J. Williams and L. C. Morrill, *Org. Lett.*, 2019, **21**, 7914-7918.
6. B. G. Reed-Berendt, K. Polidano and L. C. Morrill, *Org. Biomol. Chem.*, 2019, **17**, 1595–1607.

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Chapter 1: Introduction

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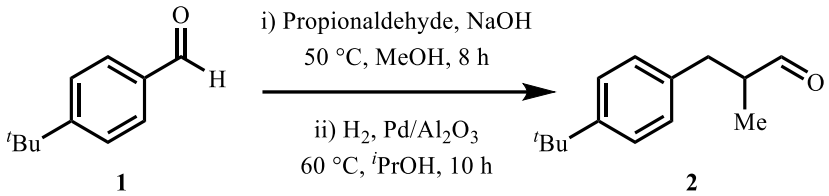
1.1. Hydrogenation and hydrogen transfer

Hydrogenation is a very important transformation both in the synthesis of fine chemicals and pharmaceuticals.[1,2] Almost every total synthesis report incorporates a hydrogenation process in the production of a target molecule.[3,4,5] Similarly, a great number of fine chemicals are produced on industrial scale *via* hydrogenation reactions using supported metal catalysts.[6] Some examples of these include the synthesis of amines, alcohols, aldehydes, diols and lactones. Diols are great building blocks for the manufacture of some heterocycles. 1,5-pentanediol is produced *via* the catalytic hydrogenation of glutaric acid by BASF on a 500 ton/annum scale.[6] Similarly, 1,4-bis(hydroxymethyl)cyclohexane, which is used in polyester films and fibres, is also manufactured *via* the hydrogenation of dimethyl terephthalate at 160-180 °C and at a pressure of 30-48 MPa.[7] Lilial (**2**), which is used as a perfume and in laundry powders, is manufactured by the aldol reaction of 4-*tert*-butylbenzaldehyde (**1**) with propionaldehyde,[8] followed by selective hydrogenation of the *α*,*β*-unsaturated intermediate.[9]



1 **2**

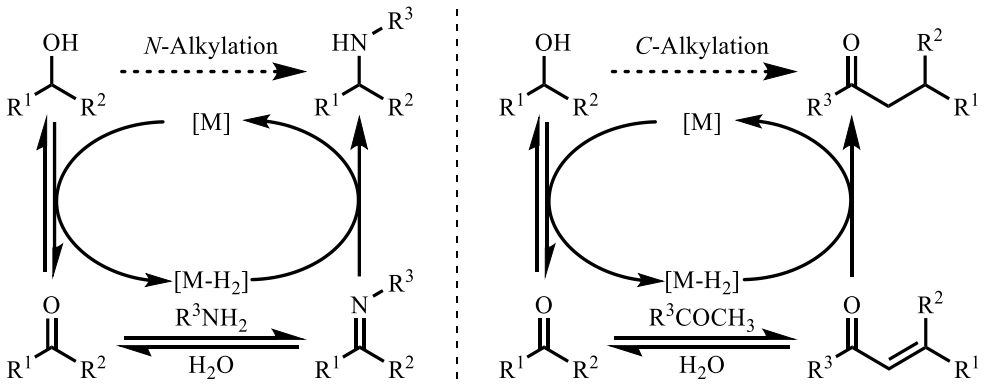
Scheme 1.1: Manufacture of Lilial

Hydrogenation of esters to form alcohols is very common in the fine chemicals industry. Benzyl alcohol, for example, is made from methyl benzoate using precious metal systems as catalysts,[10] whilst furfuryl alcohol has been made *via* vapour phase reduction of furfuraldehyde over a copper catalyst at 140 °C.[11] With regards to pharmaceutical synthesis, many examples exist that involves a hydrogenation process in the synthetic route. One example is the synthesis of ambroxol, where 4-acetamidophenol is catalytically reduced using rhodium catalysis, which subsequently undergoes reductive amination forming the desired compound.[12] All the above hydrogenation reports use molecular hydrogen as the hydrogen source. This does impose a health and safety hazard and therefore requires complex reaction setups. Transfer hydrogenation utilises hydrogen donors to achieve the desired transformation and hence avoids the use of molecular hydrogen by substituting this with readily available and inexpensive sacrificial additives.[13] The only drawback is that this process introduces waste by-products. It wasn't until the 1960s that transfer hydrogenation became an established field of chemistry. Many research groups in the world have explored this field in detail, some of which also developed some examples of asymmetric transfer

hydrogenation methodologies as well.[14] General hydrogenations result in the lowering of the oxidation level of the product relative to the starting material. As a research group, our goal is to develop hydrogen auto-transfer processes in which the oxidation level of the starting materials is the same as the desired products.

1.2. The borrowing hydrogen methodology

As stated previously, the concept of hydrogen transfer is very important for the synthesis of fine chemicals and pharmaceuticals. One methodology, which has applied the concept of hydrogen transfer to great effect, is the borrowing hydrogen methodology.[15,16,17] This process is referred to as hydrogen auto-transfer, as it combines a transfer hydrogenation process with a concurrent reaction on the *in situ* generated reactive intermediate. Transition metals are generally employed in this process together with alcohols as starting materials. This transformation occurs over three stages. A catalyst is used to oxidise the starting alcohol forming the more reactive carbonyl compound in a reversible manner. This is intercepted by a nucleophile forming another unsaturated intermediate *via* a condensation reaction. This step in the cycle must be faster than the alcohol dehydrogenation in order to drive the process forward. Finally, the catalyst uses the borrowed hydrogen to hydrogenate the new intermediate, forming the desired compound. This methodology is of great importance as it can be employed in the synthesis of C-C and C-N bonds either *via* the *C*-alkylation of carbonyl compounds or through the *N*-alkylation of amines as shown in Scheme 1.2.



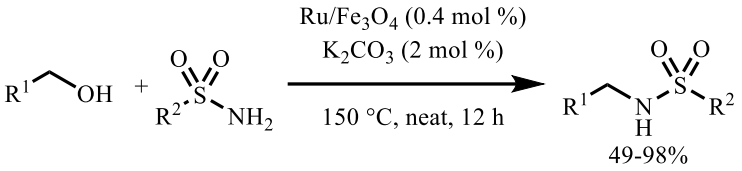
Scheme 1.2: The borrowing hydrogen methodology - *N*-alkylation (Left) and *C*-alkylation (Right)

Alkylation transformations are generally performed using toxic and harmful alkylating agents such as alkyl halides. This process generates large amount of waste since it releases high M_w halide leaving groups making it a low atom economic process. The borrowing hydrogen methodology avoids this problem since in most of the cases, H_2O is the main by-product, making this transformation highly atom economic. Furthermore, alkylation

reactions tend to suffer from poor selectivity. Borrowing hydrogen solves this problem and depending on the conditions, it is quite selective and thus prevents multi-alkylation from taking place. From the first report by Grigg and co-workers,[18] borrowing hydrogen has become a huge field in the literature and many reports have been published which employ either heterogeneous catalysis, biocatalysis or the most popular homogeneous catalysis.

1.3. Borrowing hydrogen chemistry *via* heterogeneous catalysis

Heterogenous catalysis is popular due to the ease of product and catalyst isolation, catalyst recycling, and operational handling. Prior to the process being referred to as 'borrowing hydrogen', the *N*-alkylation of amines was carried out using heterogeneous nickel catalysts back in the 1930s[19] and 1950s.[20] Within the field of borrowing hydrogen, there are some reports of heterogeneous type catalysts.[21] Some examples are briefly explained below. One the first examples in the 21st century was by Beller and co-workers. In 2009,[22] they reported the use of Ru/Fe_3O_4 (0.4 mol %) for the *N*-alkylation of sulfonamides (Scheme 1.3).

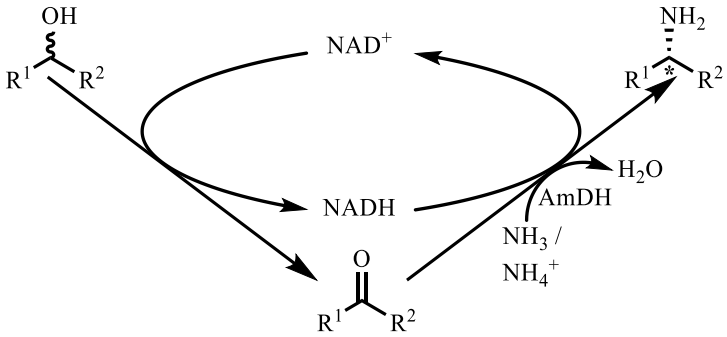


Scheme 1.3: Ruthenium-catalysed *N*-alkylation of sulfonamides

Together with K_2CO_3 (2 mol %), several sulfonamides undergo *N*-alkylation with a range of benzyl alcohols obtaining products with good yields and TONs between 100-225. They also include some mechanistic studies using d_7-benzyl alcohol to gain support for the proposed BH mechanism. Most recent publications include the work by Li and co-workers.[23] A recyclable bimetallic Cu-Ni catalyst supported over alumina was used to *N*-alkylate a variety of primary and secondary alcohols obtaining good yields for the respective products. Luque and co-workers also contributed to this field. In 2010,[24] they released a publication which involved the synthesis of a heterogenous iron catalyst (Fe-HMS, 0.39 wt %) and its application of the *N*-alkylation of amines using alcohols. This methodology was carried out in microwave conditions (300 W, 1-2 h) using DABCO (2.0 equiv.) as a base. Other examples of heterogeneously catalysed borrowing hydrogen reactions include the work by Ravasio and co-workers, and this involved the use of Cu/Al_2O_3 at 130 °C for the amination of alcohols.[25]

1.4. Biocatalytic borrowing hydrogen processes

The synthesis of α-chiral amines is of great interest to industry. Turner and co-workers have utilised biocatalysis to achieve the amination of alcohols at high conversions synthesising the corresponding products with high enantiomeric excess. Starting with enantiopure or racemic alcohols, their initial report involved the use of AA-ADH (*Aromatoleum aromaticum* alcohol dehydrogenase) and Ph-AmDH (phenylalanine amine dehydrogenase) in an ammonium chloride buffer (pH 8.7), to achieve the desired transformation with complete inversion of configuration forming enantiopure amines.[26]



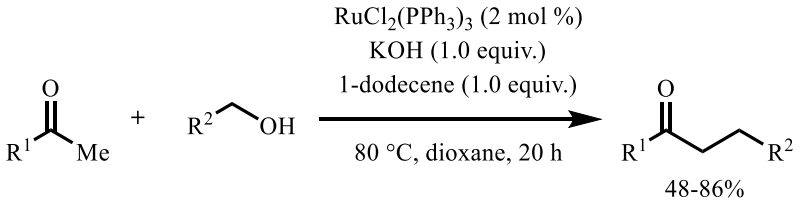
Scheme 1.4: Two-enzyme cascade for the *N*-alkylation of amines

This process had some limitations. One example was the requirement for a pair of ADHs to achieve alcohol dehydrogenation. This was addressed by the same group in another publication in 2017.[27] They managed to develop a second generation biocatalytic system for the enantioselective *N*-alkylation of amines, which involved the use of TeSADH as an enzyme. This was engineered to accept NADH as a cofactor. When this system was applied to the *N*-alkylation of amines with alcohols, several enantiopure amines were accessed. In the same year, the group further developed new biocatalytic methodologies for the same transformation. Similar to their previous report,[26] they combined two enzymes, an alcohol dehydrogenase (SyADH/TeSADH) and a reductive aminase (*Asp*RedAm), to successfully carry out a redox-neutral biocatalytic amination of alcohols.[28] This particular process works well at pH 9 accessing a diverse range of chiral secondary amines in great yields and high *ee* (> 97%) tolerating a great number of reducible functionalities in the process. Most recently this process has been extended to carboxylic acids as starting materials.[29] By incorporating a carboxylic acid reductase (CAR*sr*) and glucose/GDH as a catalyst recycler, a number of carboxylic acids were *in situ* reduced to aldehydes which can undergo enantioselective reductive amination forming chiral amines in good yields and high *ee*.

1.5. *C*-alkylation chemistry using precious metals *via* homogeneous catalysis

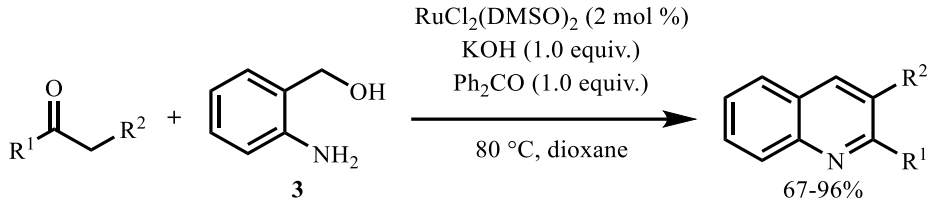
1.5.1. Ruthenium and osmium catalysis

The most common type of catalysis for typical borrowing hydrogen processes is homogeneous catalysis. Even though these types of catalysts are generally non-recyclable, they are usually more active for borrowing hydrogen transformations. When this process was first developed, ruthenium catalysts were at the forefront as they are stable and robust catalysts capable of withstanding high temperatures and harsh conditions. One of the first reports involving ruthenium chemistry was a patent reported in 1969,[30] and this showed the successful *C*-alkylation of ketones using alcohols utilizing a $Ru(acac)_3$ type complex in low loadings (0.2 mol %) in the presence of a hydroxide base (15 mol %). This process required an autoclave which was used at 145 °C to convert various ketones to their respective alkylated products. Following this result, the field was vastly opened for further investigation. In 2002, Chul and co-workers reported a regioselective *C*-alkylation of ketones using $RuCl_2(PPh_3)_3$ as their catalyst.[31] They managed to access a variety of alkylated products using a variety of benzyl and phenethyl alcohols with a range of acetophenones and alkyl type ketones in good to excellent yields (48-86%), as shown in Scheme 1.5. In this case they required a hydrogen accepter being 1-dodecene in order to prevent over-reduction of the desired product.



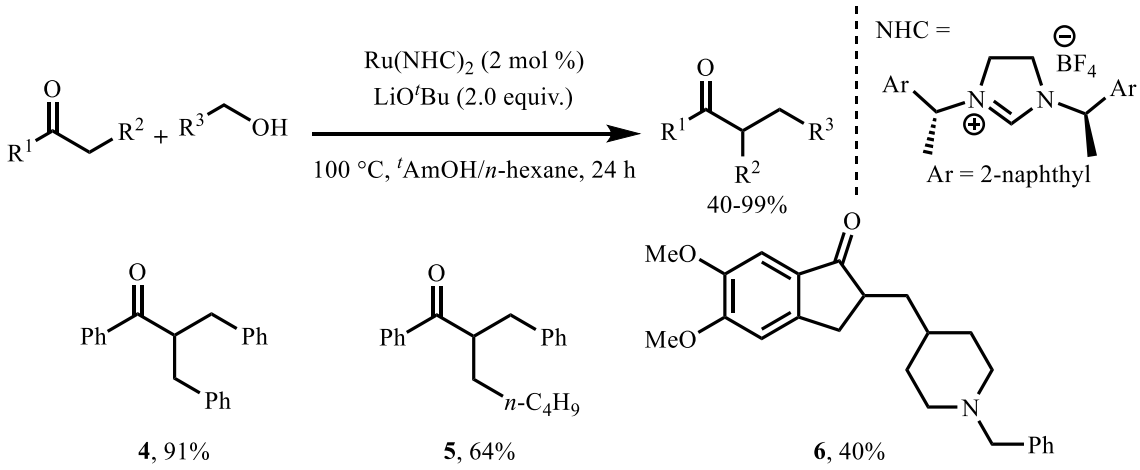
Scheme 1.5: $RuCl_2(PPh_3)_3$ catalysed C-alkylation

Building on these reports, Yus and co-workers in 2005,[32] disclosed another *C*-alkylation of ketones using $RuCl_2(DMSO)_2$ as their catalyst in similar conditions to Chul. Similar yields were obtained for this transformation. One representative example here is the incorporation of 2-aminobenzyl alcohol (**3**) as starting material. Together with benzophenone as hydrogen acceptor, the alkylated product forms, followed by a Friedländer quinoline synthesis as shown in Scheme 1.6.



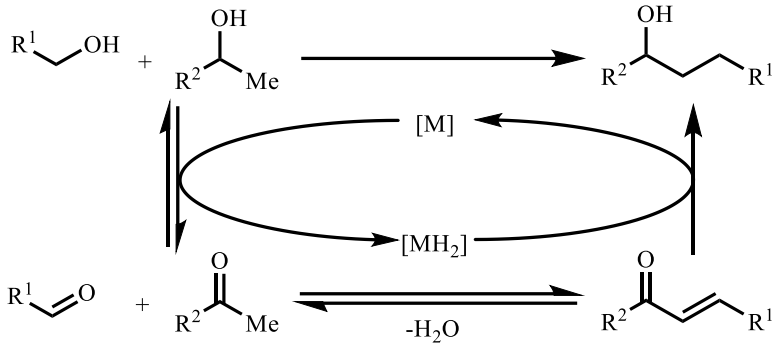
Scheme 1.6: Friedländer quinoline synthesis

All the above examples use benzyl alcohols as alkylating agents for *C*-alkylation chemistry. In 2014, Jiang and co-workers,[33] reported the use of pyridyl methanols for the *C*-alkylation of various acetophenones and cyclohexanone derivatives using [Ru(*p*-cymene)Cl_2]$_2$ (0.5 mol %), xantphos (1 mol %) and KO^{t}Bu (40 mol %) as base. As noticed by all the mentioned reports, the monoalkylation of acetophenones has been well-established; however, the *α*-alkylation of methylene ketones still proved to be challenging. This was until the report by Glorius and co-workers in 2016,[34] in which they optimised this process to work successfully using a nucleophilic heterocyclic carbene containing catalyst (2 mol %) under the conditions displayed in Scheme 1.7. They have applied this to variety of cyclic ketones, *α*-methyl and *α*-benzyl ketones, together with a range of both benzyl and *n*-alkyl alcohols as alkylating agents. Some representative examples include the benzylation and pentylation of 3-phenylpropiophenone (**4** and **5**); and the production of donepezil (**6**) which is used to help treat Alzheimer's disease. Within the same report, they also include a few examples of sequential dialkylation of acetophenones.



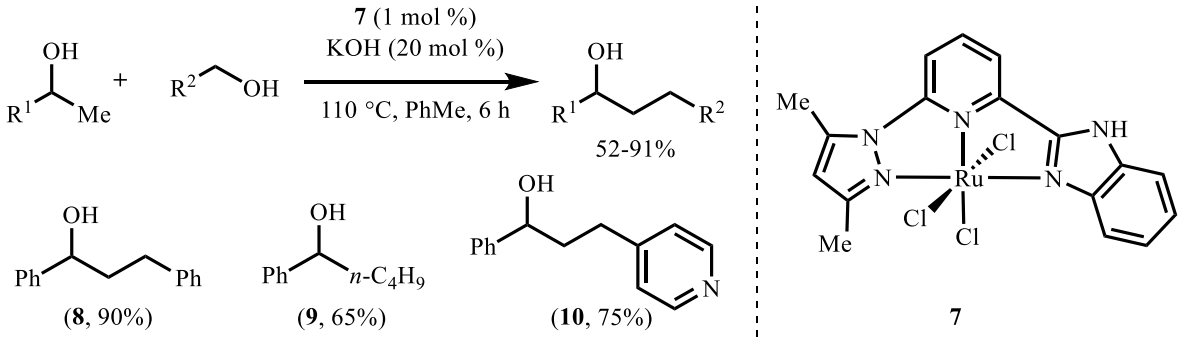
Scheme 1.7: Ru(NHC)$_2$ catalysed *α*-alkylation of *α*-methylene ketones

Another interesting BH transformation which has been well explored is the *β*-alkylation of alcohols, which involves the coupling of two different alcohols *via* a Guerbet type mechanism as shown in Scheme 1.8. A catalyst oxidises two alcohols forming two carbonyl compounds. These undergo a cross-aldol condensation reaction in the presence of base forming an *α*,*β*-unsaturated intermediate, which then gets globally hydrogenated forming the desired alcohol.



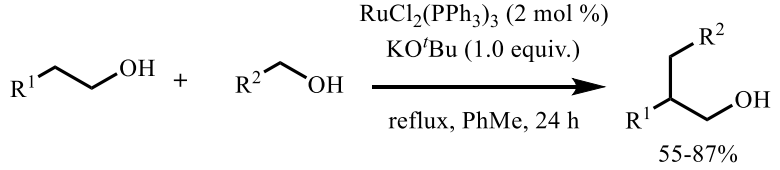
Scheme 1.8: Guerbet type alkylation of alcohols with alcohols

Chul and co-workers have reported this transformation to work using ruthenium catalysis using $RuCl_2(PPh_3)_3$ (5 mol %), KOH (3.0 equiv.) as base and 1-dodecene (5.0 equiv.) as a hydrogen acceptor accessing a range of alcohols in good yields.[35] They state that the presence of 1-dodecene aids in catalyst regeneration. In 2016, Yu and co-workers reported the same transformation to work using another ruthenium catalyst which contains an unsymmetrical pyridyl-based ligand bound to the metal centre (**7**).[36] Under their optimised conditions, a variety of secondary alcohols undergo successful alkylation using a variety primary benzyl and *n*-alkyl alcohols, as illustrated in Scheme 1.9.



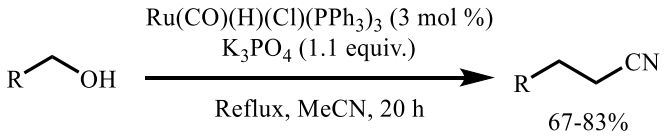
Scheme 1.9: Ruthenium-catalysed alkylation using unsymmetrical pyridyl-based *N*-heterocylic ligands

β-Alkyation of alcohols was only investigated for secondary alcohols, but in 2018, Johnson and co-workers[37] utilized similar conditions to Yu and co-workers[36] to carry out the *β*-alkylation of primary alcohols. Several phenethyl alcohols and *n*-alkyl alcohols proved to be compatible with the methodology, as shown in Scheme 1.10, together with some examples of different benzyl alcohols. Interestingly, despite furfuryl alcohol working well as the alkylating agent, 2-pyridinemethanol was completely unreactive for this transformation.



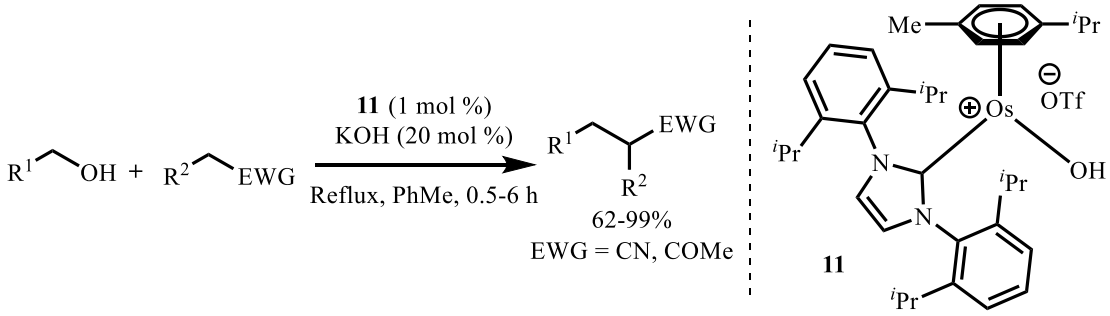
Scheme 1.10: $RuCl_2(PPh_3)_3$ catalysed C-alkylation of primary alcohols using primary alcohols

All the stated reports involve carbonyl compounds as intermediates. Substituted acetonitrile derivatives have also been applied to BH chemistry. In comparison to acetophenones (pK_a 24.4 in DMSO), acetonitrile is harder to deprotonate due to a higher pK_a value (31.3 in DMSO). The first report was back in 1981 by Tongpenyai and co-workers.[18] In this publication, they screened several precious metal catalysts for the alkylation of benzyl cyanide using alcohols, and after optimising their methodology, they tested a few *n*-alkyl alcohols obtaining good yields of the respective products. Inspired by this work, Ryu and co-workers pursued the alkylation of acetonitrile using homogeneous ruthenium catalysis ultimately forming a number of alkyl acetonitriles in good yields, as shown in Scheme 1.11.[38]



Scheme 1.11: Ruthenium-catalysed alkylation of acetonitrile using alcohols

Osmium chemistry has also found its use in BH catalysis. In 2013, Yus and co-workers synthesised a cationic osmium complex which was used to carry out both the alkylation of ketones and acetonitriles independently.[39] The process required a Dean-Stark apparatus to prevent the hydration of nitrile compounds. After presenting some examples demonstrating the scope of their methodology, they also propose a mechanistic cycle explaining how their catalyst works for the general transformation.

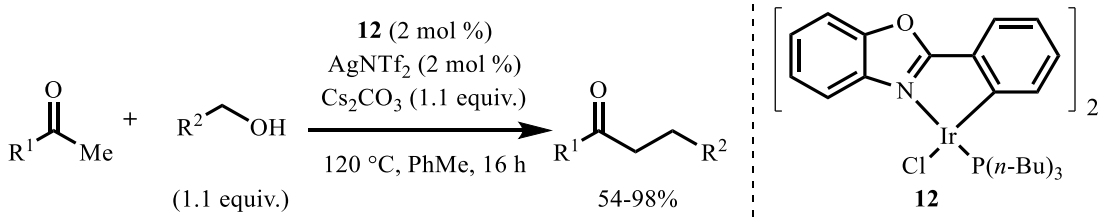


Scheme 1.12: Osmium-catalysed alkylation of ketones and phenylacetonitriles

1.5.2. Iridium catalysis

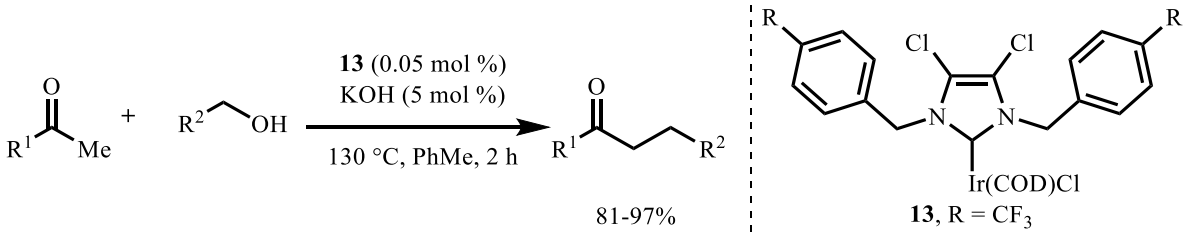
Iridium catalysis is also very popular in the field of BH chemistry. Specifically the commercial $[Ir(COD)Cl]_2$ (1 mol %) has been reported as an efficient catalyst for the α-alkylation of ketones using alcohols.[40] Ishii and co-workers utilized this catalyst to successfully effect this transformation using KOH (10 mol %) as base and PPh_3 (4 mol %) as a ligand. They carry out these reactions at 100 °C in the absence of solvent using excess alcohol in each case. Within the same report, they also carried out some validation of

intermediate studies in order to gain support on their proposed mechanism. In 2012, Zhao and co-workers employed the classical and commercial $[Cp^*IrCl_2]_2$ catalyst (1 mol %) for the same transformation obtaining good yields using a variety of benzyl and alkyl alcohols.[41] Two years later, Ding and co-workers developed another iridium catalyst which contained a benzoxazole backbone (**12**, 1 mol %) to achieve the same transformation. Interestingly, they required a silver salt additive for bimetallic catalysis obtaining higher yields. Similarly, both benzyl and *n*-alkyl alcohols were used as alkylating agents.[42]



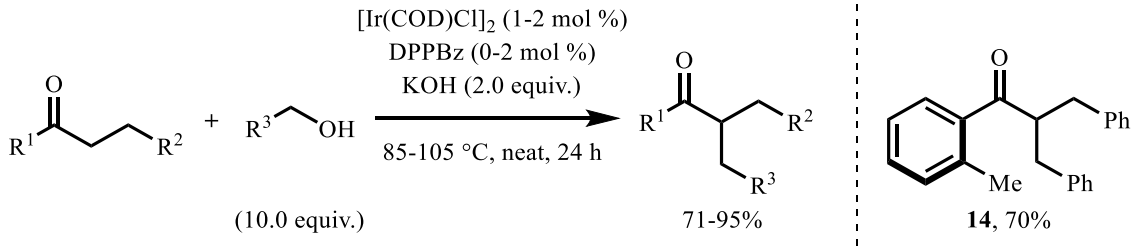
Scheme 1.13: *α*-alkylation of ketones with primary alcohols catalysed by iridium–CNP complex

Later, in the same year, the same group published another paper carrying out the same transformation using a benzothiazole version of the catalyst.[43] Recently, in 2018,[44] Gulcemal and co-workers have reported an Ir-NHC complex (**13**) for the *α*-alkylation of ketones with alcohols. After screening several Ir-NHC catalysts, they observed that their most active catalyst was one which contained an electron-poor NHC ligand, mainly for better yields, short reaction times and also better selectivity, preventing over-reduction of the product.



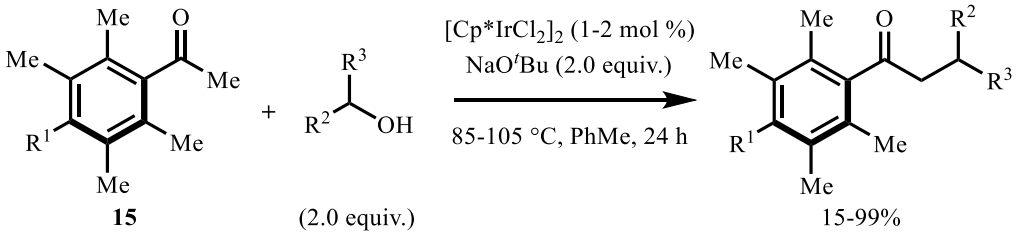
Scheme 1.14: IrNHC complex for the *α*-alkylation of ketones using alcohols

In 2015, Donohoe and co-workers reported the alkylation of *α*-branched ketones using primary alcohols.[45] Since this is particularly challenging, they have designed specific substrates that will prevent a *retro*-aldol reaction from occurring. When employing an *ortho*-substituted acetophenone derivative (**14**) as their model substrate under the conditions in Scheme 1.15, this facilitates the alkylation to work efficiently.



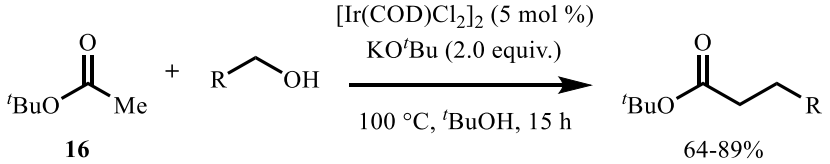
Scheme 1.15: Iridium-catalysed alkylation of *α*-branched ketones using alcohols

The more substitution present on the aromatic system, the better the outcome, as these starting materials have the aromatic ring out of conjugation with the carbonyl making it both easier to deprotonate, preventing reduction of the starting material. Under their optimised conditions, they explored a vast scope which include the use of multi-substituted acetophenone derivatives and cyclopropyl ketones as pro-nucleophiles accessing a variety of alkylated products in excellent yields. The same group, 2 years later, published another article which involved the alkylation of multi-substituted ketones using secondary alcohols (Scheme 1.16). At 85 °C, using $[Cp^*IrCl_2]_2$ as their catalyst, a range of substituted ketones, such as **15**, are alkylated using various secondary alcohols obtaining good-excellent yields of the respective products. In the same publication, they carried out some late stage functionalisation which first involved cleavage of the Ph* group *via* a *retro*-Friedel Crafts acylation reaction using bromine at low temperature, followed by the addition of an array of nucleophiles leading to derivatised products in good yields.



Scheme 1.16: Iridium-catalysed *C*-alkylation of ketones using secondary alcohols

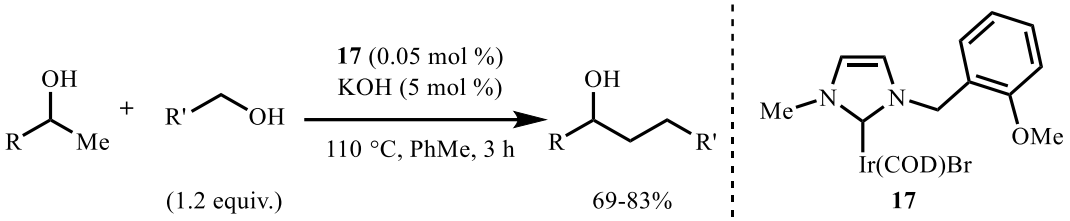
The above reports all use ketones as pro-nucleophiles. Using other carbonyl compounds, such as esters and amides, is much more challenging as the α-hydrogen is less acidic than that of ketones. The alkylation of general *tert*-butyl esters such as *tert*-butyl acetate (**16**), however, has been reported in 2010 by Ishii and co-workers as shown in Scheme 1.17. When diols are used as alkylating agents, diesters are obtained.



Scheme 1.17: Iridium-catalysed α-alkylation of acetates with primary alcohols

Iridium catalysis has also been employed in the β-alkylation of alcohols. One report in 2015 by Oro and co-workers incorporate an Ir-NHC type complex (**17**), shown in Scheme 1.18, carrying out this transformation obtaining good conversions (> 89%) of starting materials. When they test different substrates, it is noticeable that they obtained a mixture of alkylated ketone (minor) and product (major), as confirmed by GC analysis. This is due to the inability

of the catalyst to re-hydrogenate the more electron rich ketone. Due to this, they exclusively isolate products with an alcohol/ketone ratio > 98%.

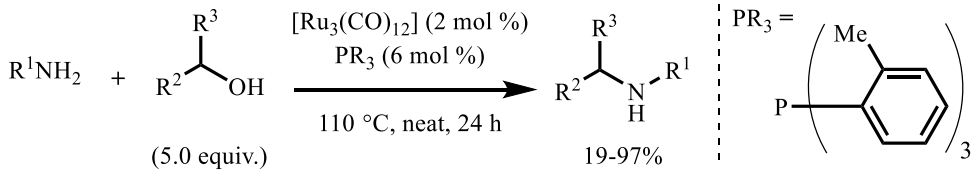


Scheme 1.18: Iridium-catalysed *β*-alkylation of alcohols using alcohols

1.6. *N*-alkylation chemistry using precious metals *via* homogeneous catalysis

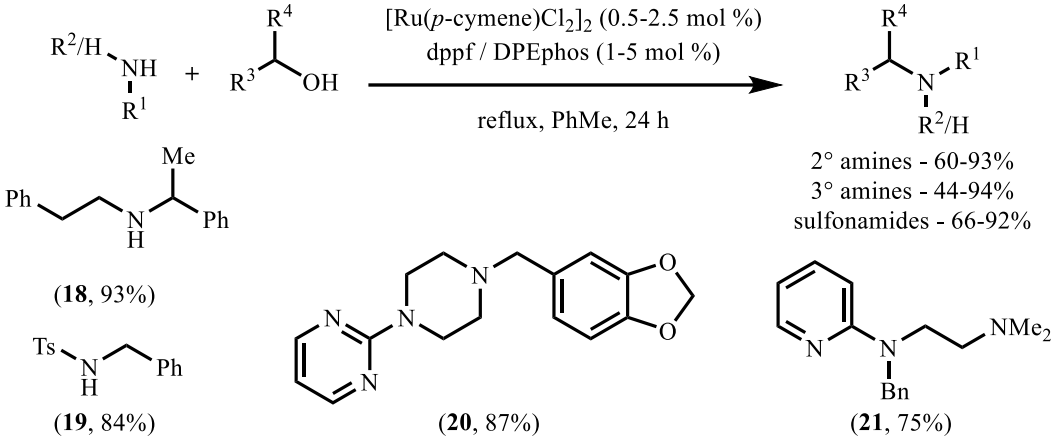
1.6.1. Ruthenium catalysis

N-Alkylation has been of interest for a long time as it is a great way in which C-N bonds are formed. Similar to *C*-alkylation chemistry, initial reports involved the application of ruthenium catalysis for *N*-alkylation chemistry. One of the first *N*-alkylation reports was by Beller and co-workers. In 2006,[46] this group used a commercial ruthenium complex, $Ru_3(CO)_{12}$, for the *N*-alkylation of *n*-hexylamine using alcohols. Their developed methodology was optimised using a bulky phosphine as a ligand to achieve the desired transformation for a variety primary and secondary alcohols as illustrated in Scheme 1.19.



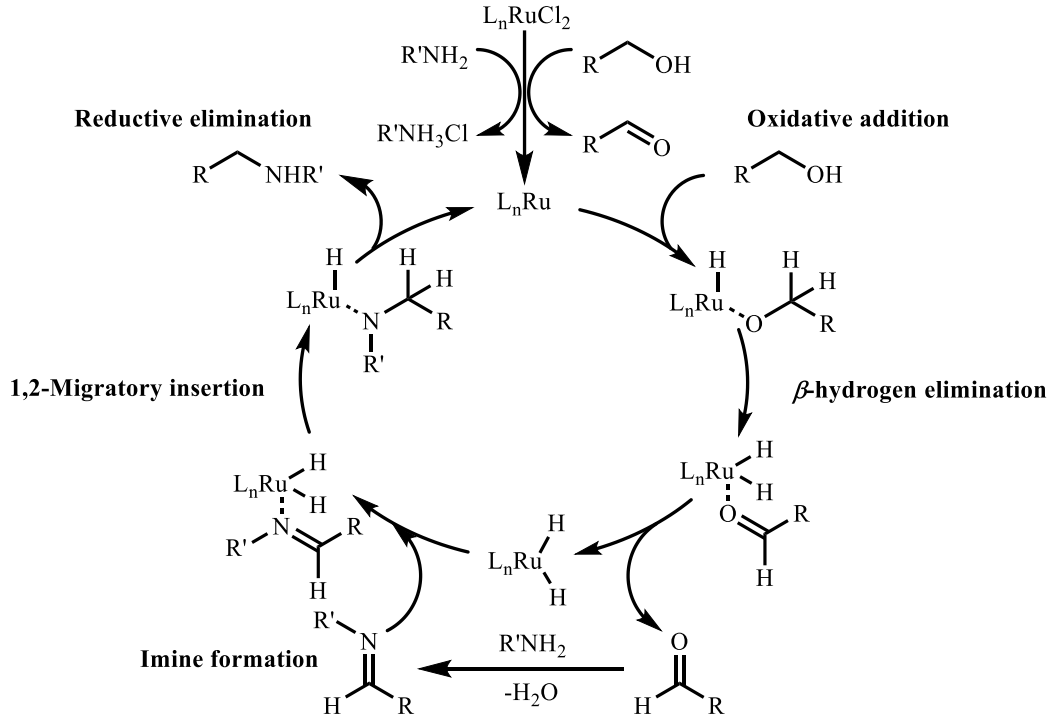
Scheme 1.19: Ruthenium-catalysed *N*-alkylation of amines using alcohols

Interestingly, when the starting amine was changed, conversion significantly decreased in comparison to their model substrate. Following this report, Williams and co-workers published an article in 2009 which dealt with the *N*-alkylation of primary and secondary amines, sulfonamides and *N*,*N*-dialkylation using diols.[47] They employed [Ru(*p*-cymene)Cl_2]$_2$ as their catalyst with dppf as a bidentate ligand for all their scope using both primary and secondary alcohols as alkylating agents accessing a range of alkylated amines and sulfonamides in excellent yields. They also apply this methodology for the synthesis of APIs such as piribedil (**20**), used as an anti-Parkinsonian agent, and tripelennamine (**21**), used to treat asthma and hay fever.



Scheme 1.20: Ruthenium-catalysed *N*-alkylation of amines and sulfonamides using alcohols

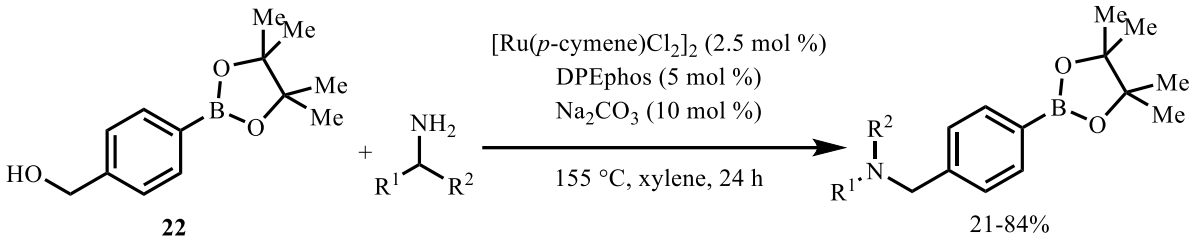
Following their scope, they also carried out some H/D cross-over studies to gain some support on a proposed mechanism for the transformation which is displayed in Scheme 1.21.



Scheme 1.21: Proposed mechanism for the *N*-alkylation of amines using alcohols

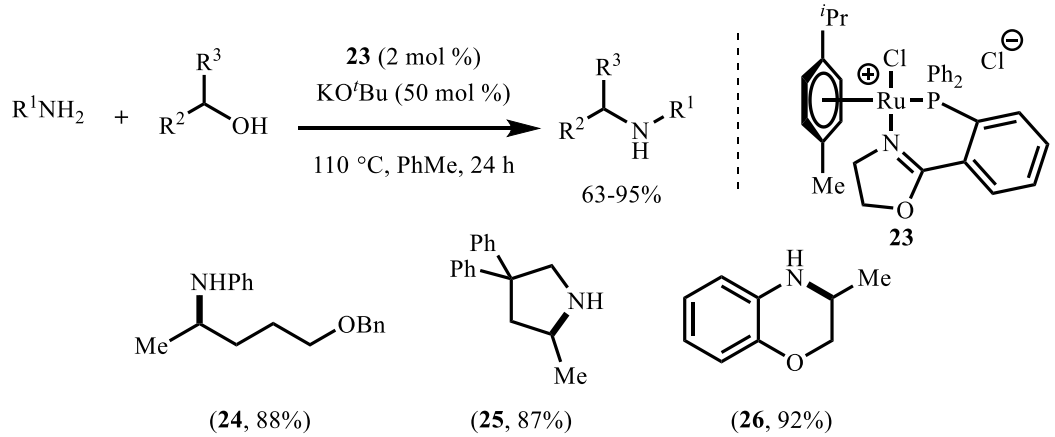
The mechanism proceeds as follows. The ruthenium precatalyst is activated using the starting amine and alcohol generating the corresponding ammonium chloride and aldehyde. The alcohol coordinates to the Ru(0) species *via* oxidative addition forming a Ru(II) alkoxo species which undergoes *β*-hydrogen elimination forming the intermediate aldehyde and a Ru(II) dihydride species. The aldehyde condenses with the amine starting material forming the corresponding imine, which coordinates to the Ru(II) dihydride species. A 1,2-migratory insertion occurs forming a Ru(II) amino species which reductively eliminates, releasing the product and the reforms the active catalytic species.

In the same year, the same group reported the conversion of alcohols into *N*-protected primary amines followed by *in situ* deprotection of sulfonyl, acetyl, BOC and silyl groups.[48] Each deprotection required the respective conditions to produce the desired amine in good yield. In 2011, Williams and co-workers repeated most of their previous scope[47] at 125 °C under microwave conditions facilitating the process to work in less than 3 hours.[49] The same group, in 2013,[50] also reported the same transformation forming secondary and tertiary amines using the same ruthenium catalyst together with DPEphos as a ligand. This time they utilised substrates having pendant boronate groups such as compound **22**. Their motivation for doing this is that boronate groups can be used in cross coupling reactions as well as in the construction of sensors for saccharides and anions.



Scheme 1.22: Synthesis of amines with pendant boronic esters by borrowing hydrogen catalysis

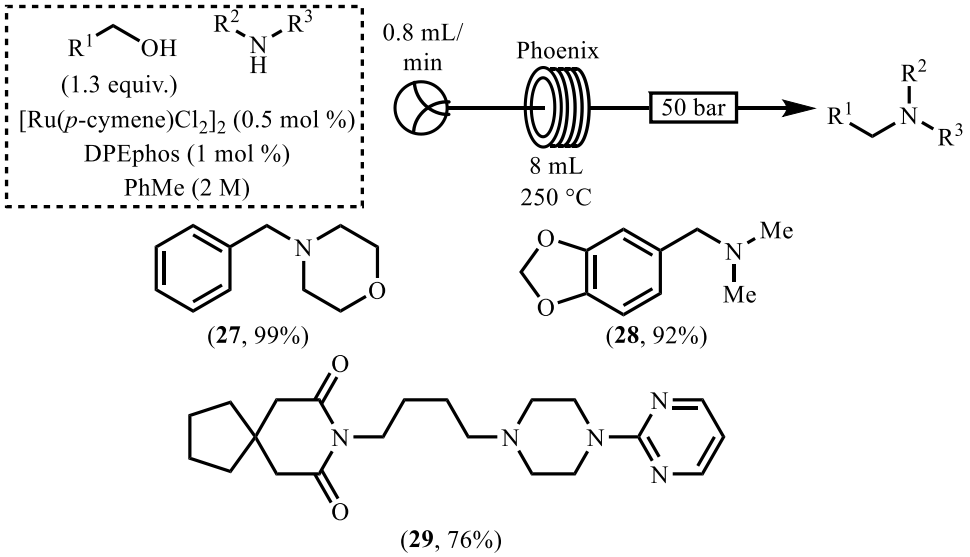
In 2014, the same transformation was also reported by Moasser and co-workers using the same catalyst under phosphine free conditions.[51] In 2016, Takacs and co-workers developed a range of ruthenium catalysts and applied them to the amination of alcohols.[52] After catalyst screening, catalyst **23** (2.0 mol %) proved to be optimal, and hence they explored a vast scope which included both intramolecular and intermolecular transformations, synthesising a range of compounds, some examples are showed in Scheme 1.23.



Scheme 1.23: Ruthenium-catalysed amination of alcohols

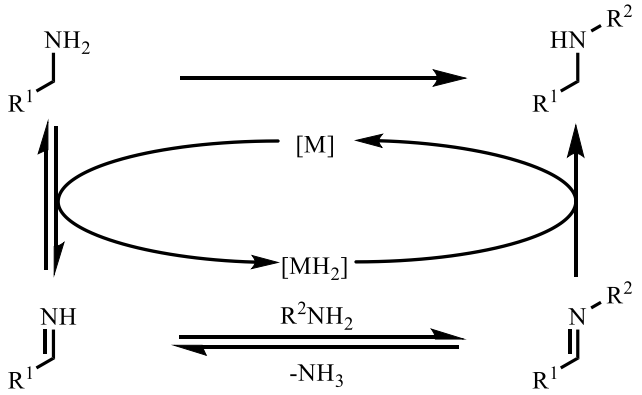
Most recently, it has become evident that known transformations are being carried out using enabling technologies. These include photochemistry, mechanochemistry, electrochemistry and flow chemistry. In 2019, a continuous flow method was developed for the *N*-alkylation

of amines using alcohols *via* a borrowing hydrogen approach.[53] The process was optimised using benzyl alcohol and morpholine as their starting materials, in a phoenix flow reactor which can accommodate high temperatures, as shown in Scheme 1.24. Ultimately, by employing Williams and co-workers' conditions,[47] Ley and co-workers managed to access a range of tertiary amines in good yields. They also applied this to the synthesis of buspirone (**29**), used to treat anxiety disorder.



Scheme 1.24: Ruthenium-catalysed borrowing hydrogen catalysis in flow

All the above *N*-alkylation examples involve alcohols as alkylating agents hence producing water as the by-product. Amines have also been used as alkylating agents. This produces ammonia as the by-product and proceeds according to the cycle illustrated in Scheme 1.25.



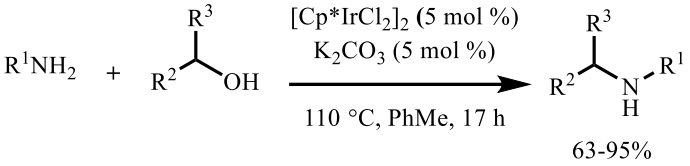
Scheme 1.25: *N*-alkylation of amines with amines

The cycle involves amine dehydrogenation by a catalyst forming an imine. A different amine nucleophile reacts with the imine releasing a molecule of ammonia and a more substituted imine. The new imine gets hydrogenated by the catalyst forming a new amine. In 2007, Beller and co-workers investigated the coupling of *n*-hexylamine and aniline using a range of known ruthenium complexes.[54] This process was unique and only worked for the Shvo

catalyst, giving 94% after 24 h. The process is compatible with a range of solvents from heptane to DMSO, all giving > 90% conversion to the alkylated amine.

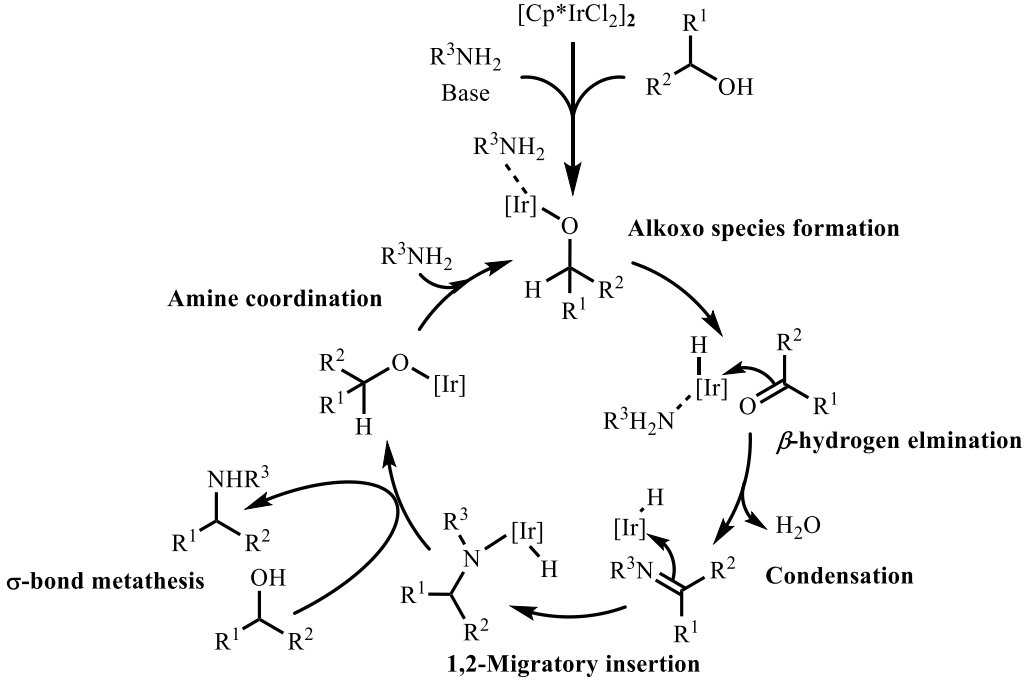
1.6.2. Iridium catalysis

The first iridium-catalysed *N*-alkylation was reported by Yamaguchi and co-workers in 2003.[55] This group were interested in the $[Cp^*IrCl_2]_2$ catalyst for this transformation. They screened several bases for the alkylation of aniline with benzyl alcohol and ultimately, they optimised the process to work under the conditions shown in Scheme 1.26.



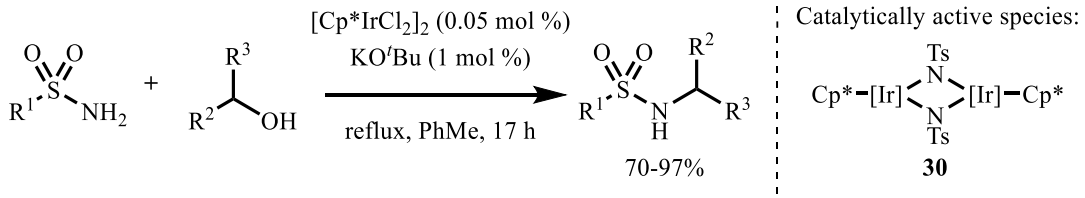
Scheme 1.26: Iridium-catalysed *N*-alkylation of amines using alcohols

Various primary and secondary alkyl and benzyl alcohols were tested for this methodology, all giving great product yields in the process. In 2008, they published a similar paper involving lower catalytic loadings of $[Cp^*IrCl_2]_2$ with a broader scope.[56] In this report, secondary amines work well with a range of alcohols giving tertiary amines in great yields. In order to gain information on a proposed mechanism, they carry out a reductive amination reaction using isopropanol as their hydrogen source, ultimately obtaining a 76% of their parent product. Hence, they proposed a mechanism, which is illustrated in Scheme 1.27.



Scheme 1.27: Proposed mechanism for the *N*-alkylation of amines with alcohols

Similar to Williams' work, this involves catalyst activation releasing an ammonium chloride. The alcohol coordinates to this active Ir(III) species which is subsequently followed by β-hydrogen elimination to form the transient carbonyl compound intermediate. The amine condenses with the carbonyl compound producing the corresponding imine and an iridium hydride species. The imine inserts into the iridium hydride bond releasing the final product. Finally, alcohol coordination restarts the cycle. In 2009, the same group disclosed the *N*-alkylation of carbamates and amides with alcohols.[57] The same catalyst was used, this time requiring high catalytic loadings (5 mol %) together with NaOAc to facilitate this *N*-alkylation process. In 2010, Yamaguchi and co-workers also investigated the *N*-alkylation of sulfonamides.[58] By re-optimising to KO^{t}Bu (1-30 mol %) as base, they have managed to *N*-alkylate *p*-toluenesulfonamide using a variety of alkyl and benzyl alcohols (Scheme 1.28). Interestingly, when they mix $[Cp^*IrCl_2]_2$ with $TsNH_2$ at rt using KO^{t}Bu as base, they isolate a dimer (**30**) which is their main catalytic species; as when substituted instead of their parent catalyst, they obtain 100% conversion to the product.



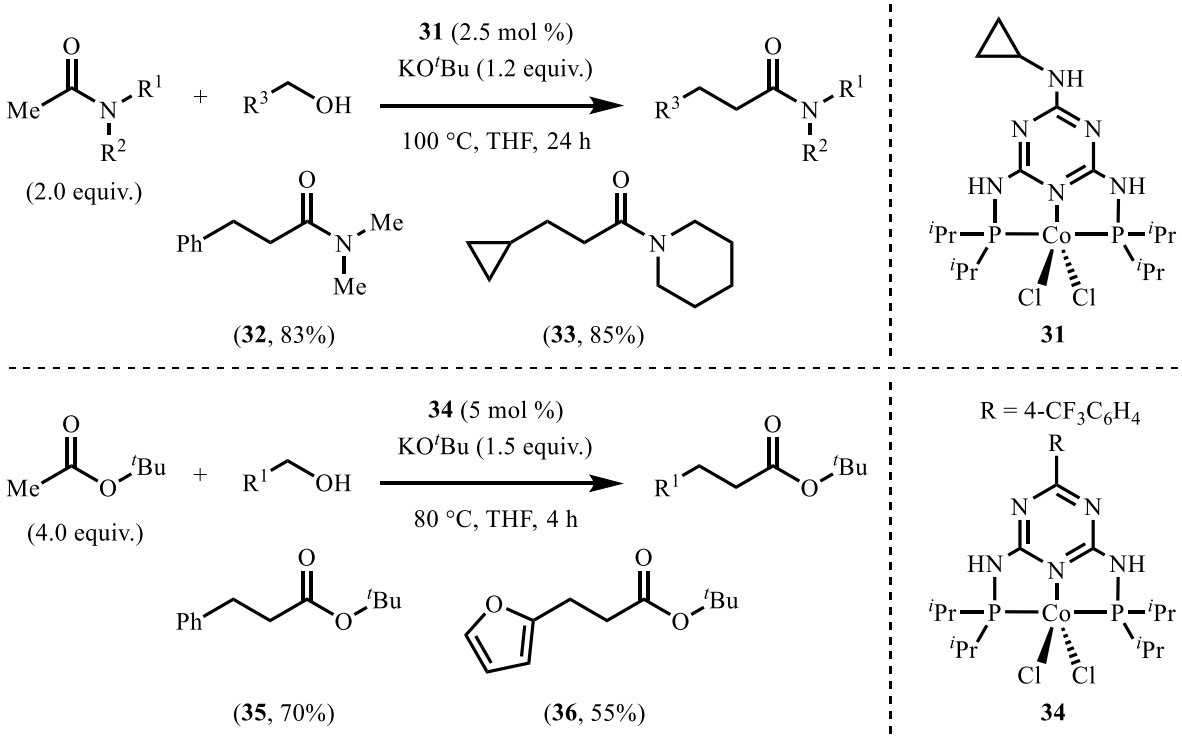
Scheme 1.28: Iridium-catalysed *N*-alkylation of sulfonamides

In 2010, the methodology developed by Yamaguchi and co-workers was re-optimised by Williams and co-workers to work in water and $[BMIM]PF_6$ as an ionic liquid.[59] In general, sulfonamides worked well in water whilst secondary amines worked considerably better in $[BMIM]PF_6$ for only 3 h of reactivity. The *N*-alkylation of ureas also became of interest, and in 2013, Xie and co-workers employed $[Cp^*IrCl_2]_2$ as their catalyst with NaOH (40 mol %) as base, to successfully alkylate a variety of ureas using benzyl and alkyl alcohols.[60] When alkyl alcohols were used as alkylating agents, these were used in excess and no other solvent was required for this transformation to proceed. A plausible mechanism was also proposed which was near-identical to what was proposed by Yamaguchi and co-workers.[55]

1.7. *C*-alkylation chemistry using earth-abundant metals *via* homogeneous catalysis

1.7.1. Cobalt catalysis

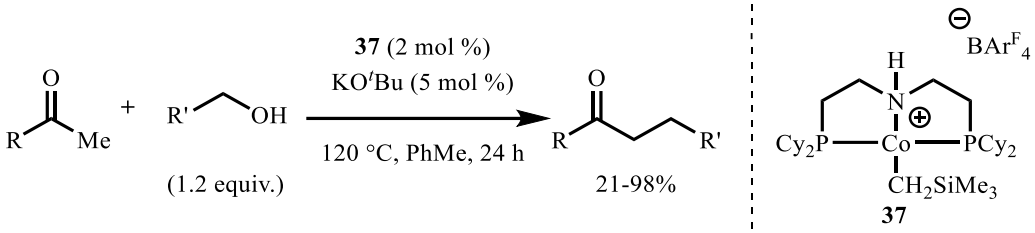
From 2010 onwards, research has been focussed on developing new catalysts for borrowing hydrogen which incorporate base metals[16,17] such as cobalt, manganese, nickel, iron and copper. The main reason for this is due to earth abundancy and price. From these four metals, cobalt is the least earth abundant metal, but despite this, many research groups have developed a variety of catalysts for borrowing hydrogen processes. One of the cobalt-catalysed reports for *C*-alkylation chemistry was published by Kempe and co-workers in 2016.[61] This report covered both the *C*-alkylation of esters and amides using a PNP type complex. In comparison to ketones as pro-nucleophiles, these are more challenging as the α-hydrogen is less acidic due to resonance stabilisation of amides. Esters also can easily undergo undesired side reactions. Despite this, both processes were optimised independently using different cobalt catalysts (**31** and **34**) leading to successful alkylation under the conditions stated in Scheme 1.29. Some examples are shown below. In the same publication, the research group also carried out some late stage derivatisation of the products.



Scheme 1.29: Cobalt-catalysed *C*-alkylation of amides and esters using alcohols

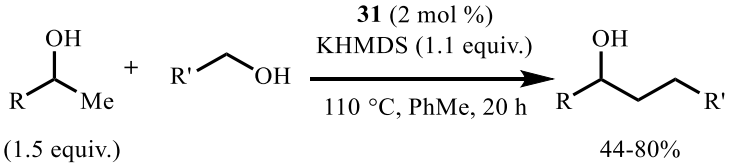
In 2017, Zheng and co-workers employed an ionic cobalt(II) PNP complex[62] which was originally developed by Hanson and co-workers,[63] for the α-alkylation of ketones using

alcohols. A variety of aryl ketones undergo *C*-alkylation with both benzylic and aliphatic alcohols, using **37** (2 mol %) and KO^{t}Bu (5 mol %), giving the products in high yields, as illustrated in Scheme 1.30.



Scheme 1.30: Cobalt-catalysed alkylation of ketones using alcohols

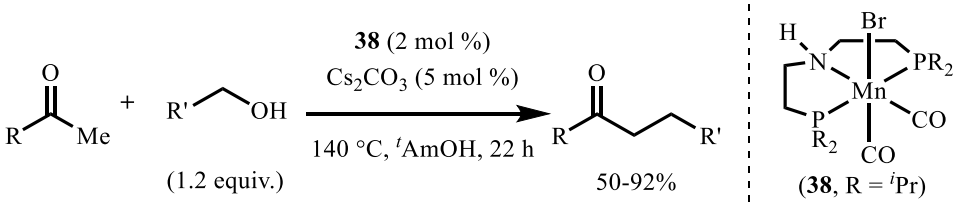
In 2017,[64] Kempe and co-workers, reported the *C*-alkylation of secondary alcohols using primary alcohols by employing a similar catalytic system to that which they reported previously. They managed to access higher and longer chain alcohols in good isolated yields under the conditions stated in Scheme 1.31. Interestingly, heterocoupling of aliphatic alcohols also worked well when employing this methodology.



Scheme 1.31: Cobalt-catalysed alkylation of secondary alcohols with primary alcohols

1.7.2. Manganese catalysis

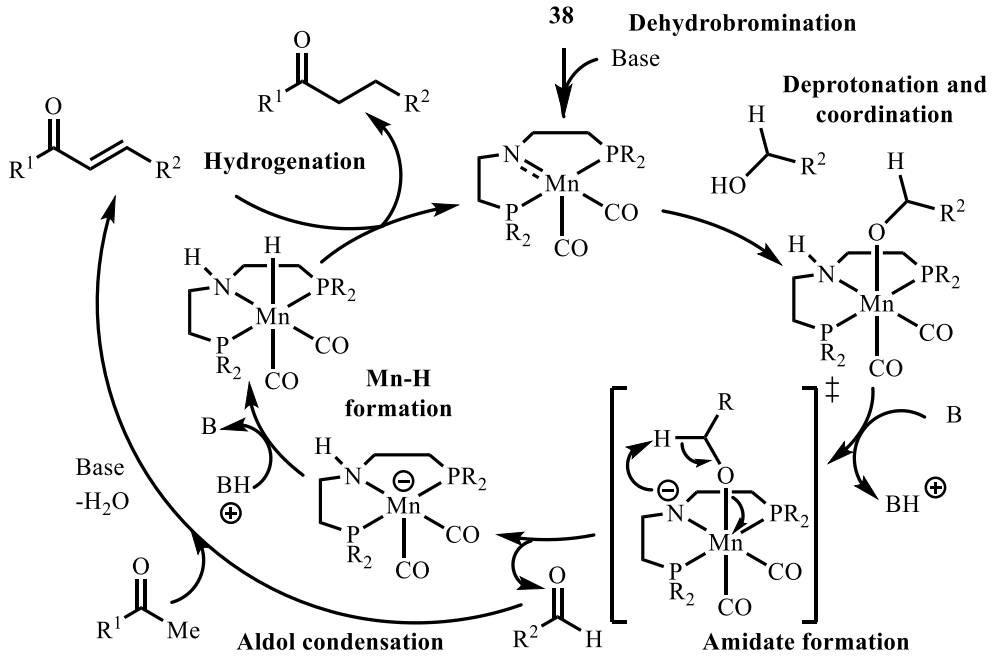
The first manganese catalysed *C*-alkylation was published by Beller and co-workers in 2016.[65] In this process, they developed a novel manganese PNP pincer complex for this transformation. They found that 2 mol % of **38** together with 5 mol % of Cs_2CO_3 was enough to give efficient alkylation using both benzyl and *n*-alkyl alcohols, as illustrated in Scheme 1.32.



Scheme 1.32: Manganese-catalysed alkylation of ketones using alcohols

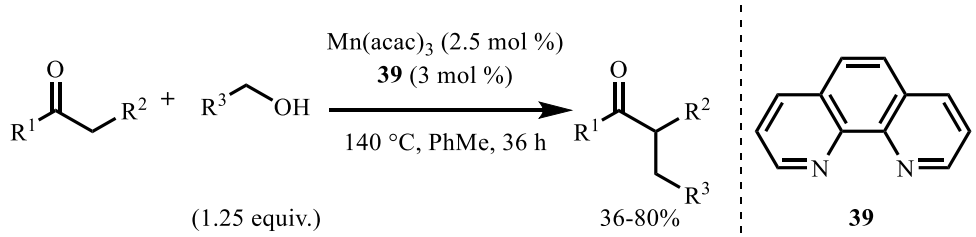
Notably, besides standard ketones, they also include the alkylation of some examples of oxindoles and some hormone derivatives. Finally, by taking benzyl alcohol-d_2, they carry out some H/D cross over study obtaining a 64/36 and a 67/33 H/D at the α and β positions respectively, gaining support on a plausible mechanism. As shown in Scheme 1.33, the cycle

begins *via* a base promoted dehydrobromination reaction followed by alkoxo species formation and re-protonation of the nitrogen atom. As observed from the transition state, base deprotonates the *N*-H bond resulting in the formation of an amidate which subsequently carries out an intramolecular deprotonation releasing the intermediate aldehyde. This then undergoes a base-mediated aldol condensation with the ketone pro-nucleophile generating an *α*,*β*-unsaturated species. The negatively charged manganese complex is re-protonated forming the manganese hydride species, which is used to hydrogenate the alkene bond forming the alkylated ketone, restarting the catalytic cycle.



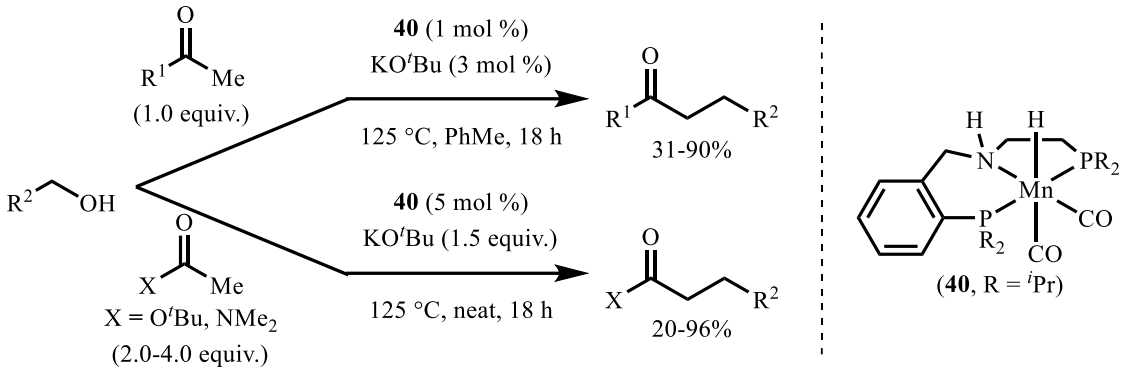
Scheme 1.33: Proposed mechanism for the manganese-catalysed alkylation of ketones using alcohols

In Beller's report,[65] there is only one example of the alkylation of *α*-methylene ketones, and this was when employing 1-tetralone as the pro-nucleophile. Banerjee and co-workers, in 2018,[66] disclosed the *C*-alkylation of *α*-methylene ketones using the cheap $Mn(acac)_3$ precatalyst (2.5 mol %) and 1,10-phenanthroline (3 mol %) as their ligand. Under their optimised conditions, shown in Scheme 1.34, alkylation was successful using an array of alcohols. Some H/D mechanistic studies are also reported in the same publication.



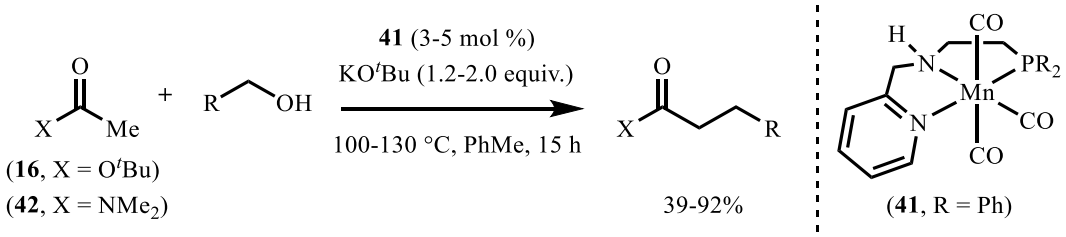
Scheme 1.34: Manganese-catalysed alkylation of *α*-methylene ketones using alcohols

In 2018, Milstein and co-workers also reported this same transformation with a different manganese PNP complex (**40**, 1 mol %).[67]



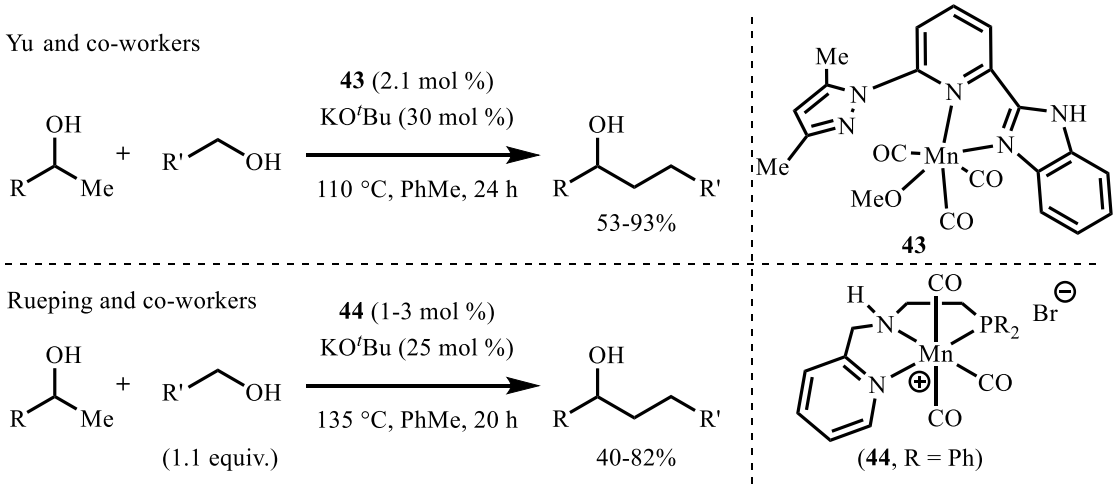
Scheme 1.35: Manganese-catalysed *C*-alkylation of ketones, esters and amides

In the same publication, as illustrated in Scheme 1.35, they also carried out the *C*-alkylation of *tert*-butyl acetate and *N*,*N*-dimethylacetamide, both in neat conditions, using higher catalyst loading, obtaining excellent yields of the respective products. Interestingly, when they investigated the alkylation of secondary alcohols with primary alcohols, they only obtained dehydrogenative coupling to give alkylated ketones. Within the same period, El-Sepelgy and co-workers reported same alkylation using an NNP type complex (**41**) under the conditions displayed in Scheme 1.36.[68]



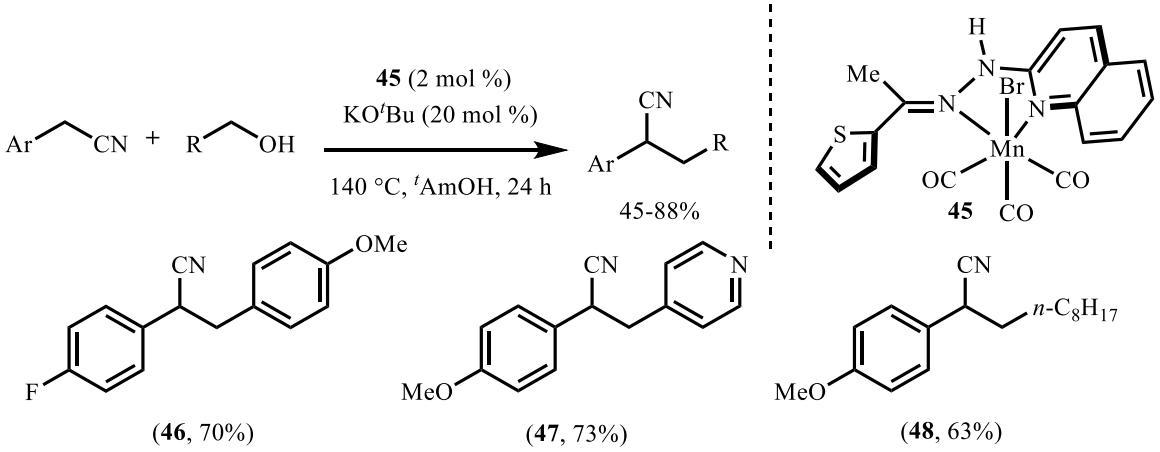
Scheme 1.36: Manganese NNP pincer catalysed *C*-alkylation of esters and amides

In 2018, two reports for the manganese-catalysed *β*-alkylation of secondary alcohols with primary alcohols were released, initially by Yu and co-workers who utilise a phosphine free catalyst (**43**),[69] followed by Rueping and co-workers who incorporate an NNP type complex (**44**).[70] Both reactions are illustrated in Scheme 1.37.



Scheme 1.37: Manganese-catalysed *β*-alkyation of secondary alcohols with primary alcohols

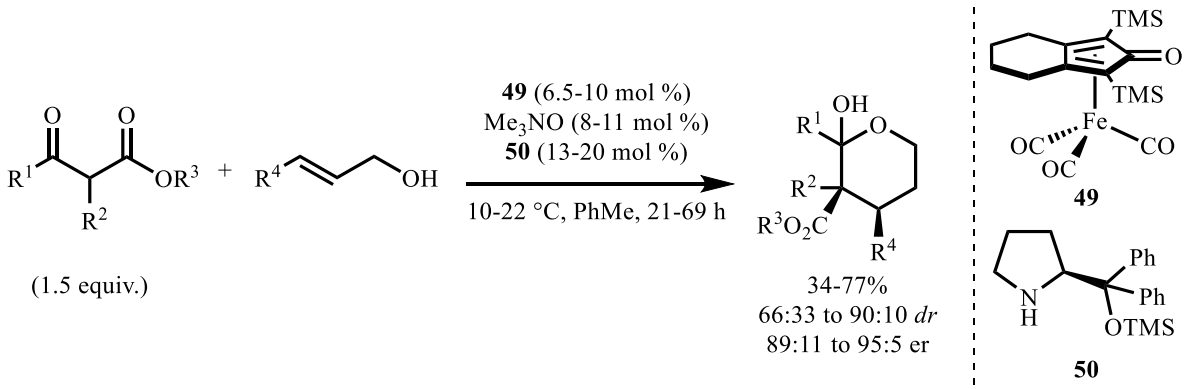
In 2018, Maji and co-workers reported the first manganese-catalysed *C*-alkylation of nitriles using primary alcohols, under the conditions displayed in Scheme 1.38.[71] They utilise a phosphine-free novel complex bearing a bidentate hydrazine ligand for this transformation (**45**). Interestingly, the catalyst precursor, $Mn(CO)_5Br$, gives slight conversion to the product but when the ligand is present, *in situ* generation of the catalyst results in efficient alkylation of nitriles using both various benzyl and alkyl alcohols. At the end of this publication, they also carry out various mechanistic experiments to gain support on a proposed mechanism.



Scheme 1.38: Manganese-catalysed *C*-alkylation of nitriles using alcohols

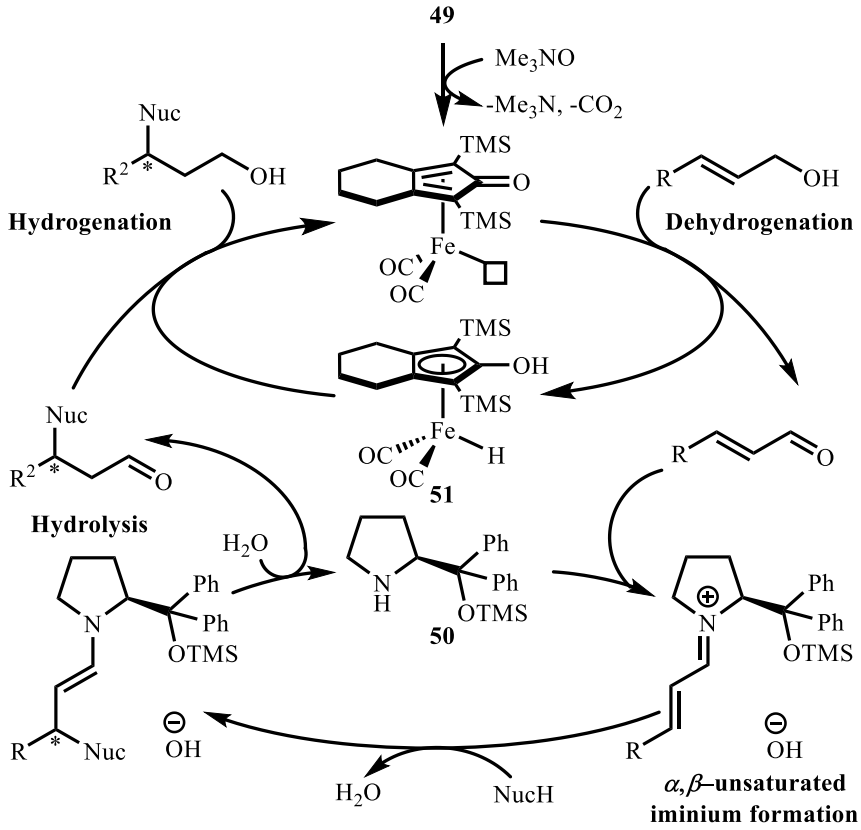
1.7.3. Iron catalysis

Both cobalt and manganese are earth abundant transition metals, however, the most earth abundant transition metal in the earth's crust is iron. From 2012, iron has become one of the most popular metals in borrowing hydrogen chemistry. In 2013, Quintard, Rodriguez and co-workers employed a (cyclopentadienone)iron carbonyl complex (**49**, 6.5-8 mol %) with Me_3NO (8-11 mol %), in conjunction with a secondary amine organocatalyst to carry out γ-functionalisation of allylic alcohols enantioselectively.[72] This process occurs at temperatures ranging from 10-22 °C using a typical Jørgensen-Hayashi organocatalyst (**50**) over long reaction times which attribute to the high enantioselectivities obtained. 1,3-*β*-Ketoesters are employed as nucleophiles accessing a range of tetrahydropyrans with excellent *er* and *dr*.



Scheme 1.39: Iron/amine catalysed γ-functionalisation of allylic alcohols

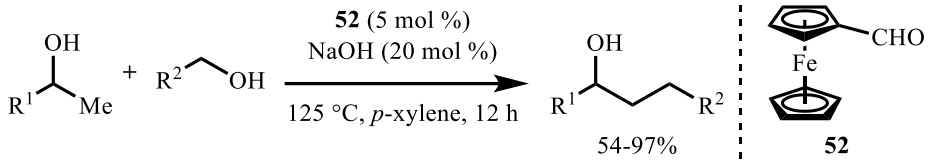
Following these results, they propose a mechanism which is illustrated in Scheme 1.40. Me_3NO is used to activate precatalyst **49** generating the active catalytic species having a vacant coordination site on the metal centre. This then oxidises the allylic alcohol starting material generating an iron-hydride species (**51**) together with an *α,β*-unsaturated aldehyde. This aldehyde condenses with **50** forming an *α,β*-unsaturated iminium species. A nucleophile adds in at the γ-position of the iminium intermediate forming an enamine which upon hydrolysis generates a γ-functionalised aldehyde. Hydrogenation of this aldehyde by the iron-hydride complex reforms the active species and releases the product.



Scheme 1.40: Iron/amine catalysed γ-functionalisation of allylic alcohols – proposed mechanism

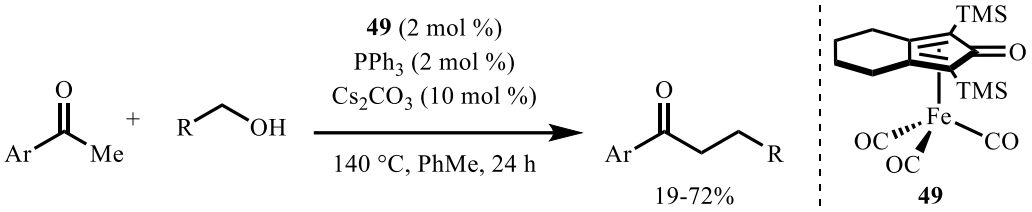
Sun and co-workers also reported the *β*-alkylation of secondary alcohols with primary alcohols,[73] where they use the commercial ferrocenecarboxaldehyde (**52**, 5 mol %) under the

conditions in Scheme 1.41. A variety of secondary alcohols undergo *C*-alkylation with primary alcohols forming the corresponding products in excellent yields. By testing various plausible intermediates, they gain more insight into a proposed mechanism.



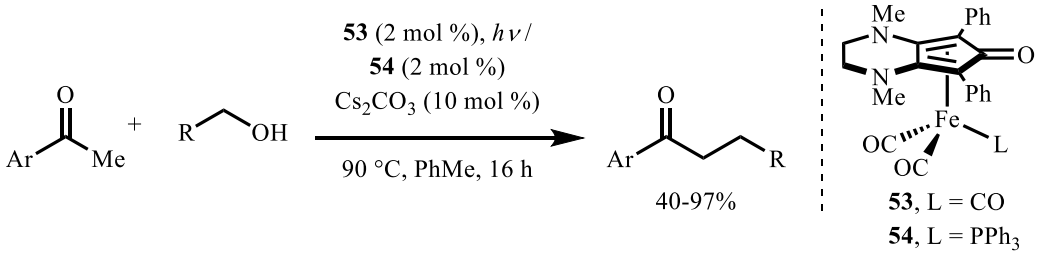
Scheme 1.41: Iron-catalysed *β*-alkylation of secondary alcohols with primary alcohols

The first iron-catalysed *α*-alkylation of ketones was reported by Darcel and co-workers in 2015.[74] **49** (2 mol %) again was utilised, together with PPh_3 (2 mol %) and Cs_2CO_3 (10 mol %) as base to form a variety of alkylated ketones in good yields. Surprisingly, when using methanol as an alkylating agent, no product formation was observed.



Scheme 1.42: Iron-catalysed *C*-alkylation of ketones using alcohols

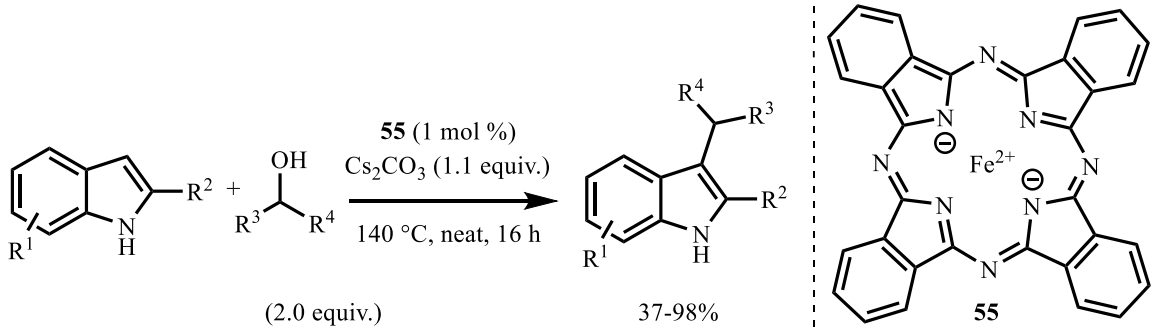
The methodology was further improved by Renaud and co-workers;[75] and this involved the incorporation of an electron-rich (cyclopentadienone)iron carbonyl complex (**53/54**, 2 mol %) as their iron precatalyst at 90 °C for 16 h.



Scheme 1.43: Improved iron-catalysed *C*-alkylation of ketones using alcohols

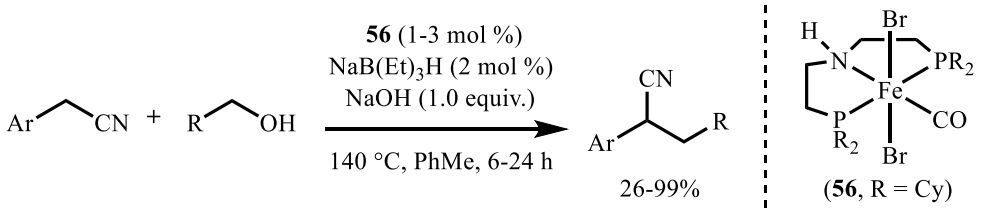
Interestingly, they state two methodologies for catalyst activation. The first involved photolytic activation of tricarbonyl complex **53** in the presence of UV light for 2 h; whilst the second involved thermal activation of the PPh_3 bound species (**54**). This research group also carried out DFT calculations for all the proposed catalytic steps proving that their catalyst is indeed superior to the standard Knölker type catalysts bearing silyl substituents.[74] In 2017, Piersanti and co-workers reported an iron-catalysed *C*(3)-alkylation of indoles using benzyl alcohols.[76] In this report the alkylation was carried out using a commercial iron(II) phthalocyanine compound (Scheme 1.44). By employing (**55**, 1 mol %) with Cs_2CO_3 (1.1 equiv.) as base, a number of substituted *C*(3)-alkylated indoles are accessed in good yields.

The following year, Renaud and co-workers also reported the same transformation[77] obtaining higher yields using similar conditions to their previous report.[75]



Scheme 1.44: Iron-catalysed *C*(3)-alkylation of indoles using alcohols

One of the latest reports involving *C*-alkylation was by wang and co-workers.[78] They disclosed the alkylation of a range of nitrile compounds using alcohols. In this case, they report an iron(II) PNP pincer complex (**56**, 1-3 mol %) for this transformation using $NaB(Et)_3H$ as an activator. At 130 °C in PhMe, this transformation was successful forming the desired products in excellent yields. Using NMR studies, they illustrate the formation of an iron-hydride species by forming their active catalyst *in situ*, thus gaining some support on a proposed mechanism.

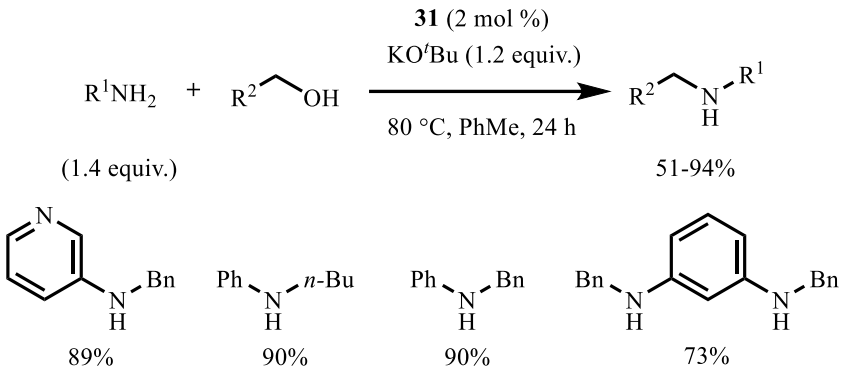


Scheme 1.45: Iron-catalysed *C*-alkylation of nitriles using alcohols

1.8. *N*-alkylation chemistry using earth-abundant metals *via* homogeneous catalysis

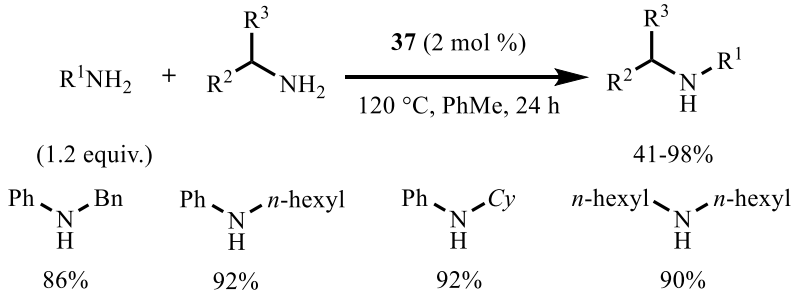
1.8.1. Cobalt catalysis

Kempe and co-workers, prior to publishing the *C*-alkylation of esters and amides, reported the application of the same Cobalt PNP pincer type complex,[61] for the *N*-alkylation of amines using alcohols.[79] In this report, a number of PNP pincer ligands were synthesised and were all screened for this transformation. Ultimately (**31**, 2 mol %) was enough to form the desired products in good yields using KO^tBu (1.2 equiv.) as base at a temperature of 80 °C. Within the same report, they disclose the selective sequential *N*-alkylation of benzene-1,3-diamine using two different alcohols, forming unsymmetrically alkylated diamines.



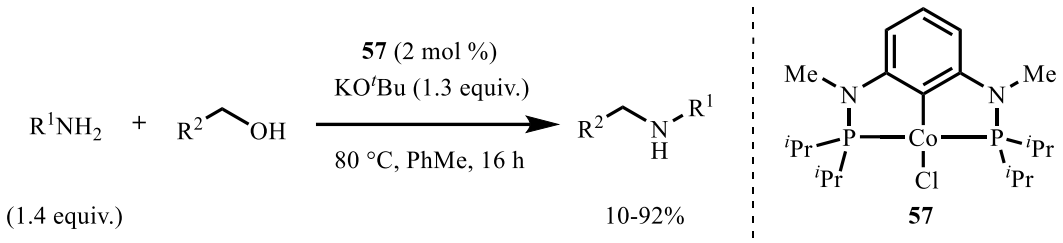
Scheme 1.46: Cobalt-catalysed *N*-alkylation of amines using alcohols

The following year, Zhang and co-workers also reported the *N*-alkylation of amines using alcohols.[80] In comparison to the work by Kempe and co-workers, no base was utilised and 4 Å molecular sieves were required, facilitating the formation of the intermediate imine more readily. A variety of aryl and *n*-alkyl amines undergo efficient alkylation using benzylic alcohols, *n*-alkyl alcohols and cyclohexanol as alkylating agents. The same group, in collaboration with Zheng and co-workers, reported the first base metal-catalysed *N*-alkylation of aryl amines with alkyl amines using **37** as their catalyst.[81] This promoted the *N*-alkylation of various anilines and diamines, with benzyl amines and both primary and secondary alkylamines, producing a range of secondary aryl amines in good yields as shown in Scheme 1.47. Additionally, the methodology was then employed to the homocoupling of primary aliphatic amines, and to the intramolecular synthesis of cyclic secondary amines.



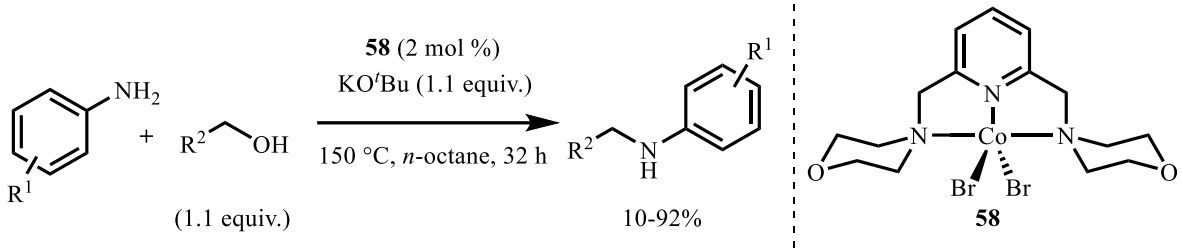
Scheme 1.47: Cobalt-catalysed *N*-alkylation of aryl amines using alkyl amines as alkylating agents

In 2016, Kempe and co-workers developed a cobalt PCP type complex and were the first group to apply this to catalysis.[82] After optimisation, 2 mol % of **55** efficiently promoted the *N*-alkylation of aryl amines with a range of primary benzyl and *n*-alkyl alcohols as alkylating agents. Typical standard conditions required the use of KO^{t}Bu (1.3 equiv.) as base with a reaction temperature of 80 °C. Notably, when they employed a similar complex to Hanson and co-workers,[63] no base was required as the catalyst already contains a basic trimethylsilyl methylene group bound to the metal centre. On the other hand, 3 Å MS were required in this case to achieve the desired transformation.



Scheme 1.48: Cobalt(II) PCP catalysed *N*-alkylation of amines using alcohols

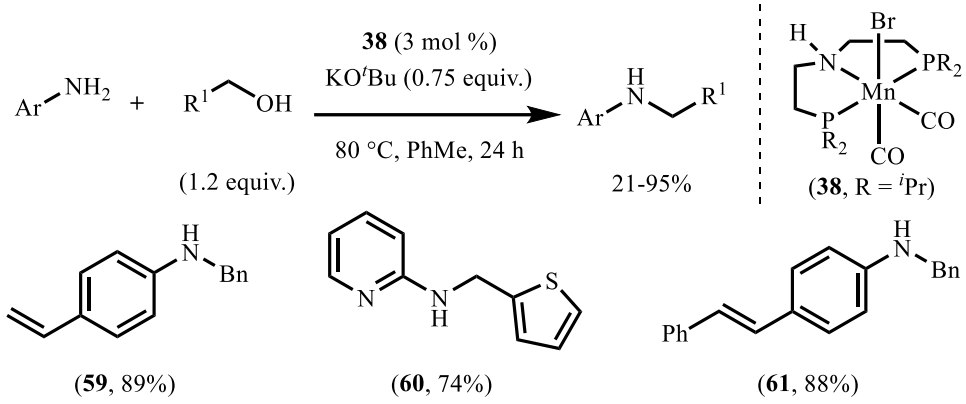
Most recently, Balaraman and co-workers have also developed an air-stable Cobalt type complex (**58**) for the *N*-alkylation of amines using alcohols (Scheme 1.49).[83] The process was carried out in *n*-octane at 150 °C, and this enabled the successful *N*-alkylation with substituted benzyl alcohols. When employing benzene-1,3-diamines as nucleophiles, they also undergo *N*,*N*'-dialkylation. Interestingly, when the same reaction is carried out using 4 Å MS, the corresponding imine is formed. In this report they also carried out some H/D cross-over studies to gain some validation on a proposed mechanism.



Scheme 1.49: Cobalt(II) *NNN* catalysed *N*-alkylation of amines using alcohols

1.8.2. Manganese catalysis

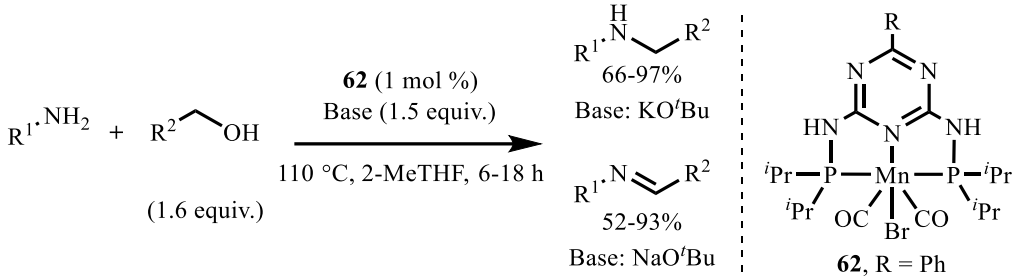
The first manganese-catalysed *N*-alkylation of amines with alcohols was reported by Beller and co-workers in 2016.[84] The same Mn(I) PNP pincer complex which they reported in their *C*-alkylation study[65] was utilised for this process.



Scheme 1.50: Manganese-catalysed *N*-alkylation of amines with alcohols

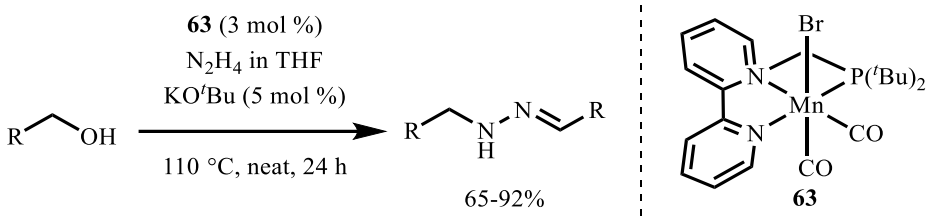
By incorporating **38** (3 mol %) and KO^{t}Bu (0.75 equiv.) as base, various alcohols have successfully been used to *N*-alkylate aryl amines at 80 °C, as shown in Scheme 1.50. *N*-

methylation occurs required higher temperature (100 °C) using methanol as solvent. In 2018, Kempe and co-workers developed a novel manganese PNP pincer complex (**62**)[85] having a similar framework to their cobalt catalyst which they utilised in both *C* and *N*-alkylation chemistry.[61,79] In this particular work (Scheme 1.51), different bases gave different products. Specifically, KO^{t}Bu (1.0 equiv.) favoured the formation of the *N*-alkylated amine whilst NaO^{t}Bu resulted in acceptorless dehydrogenative condensation forming the corresponding imine. Through mechanistic studies, they attributed this to coordinative interaction of K^+ ions with their catalyst. Interestingly, within their scope they also tolerate styrene-type functionalities, preferentially reducing the imine intermediate.



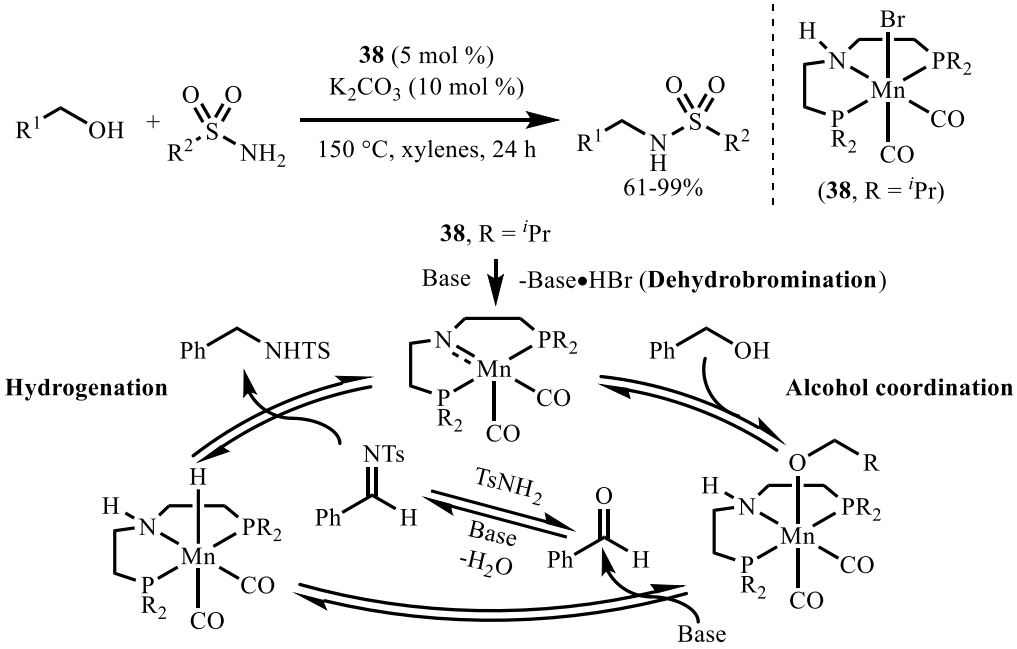
Scheme 1.51: Manganese-catalysed base-switchable synthesis of amines or imines *via* borrowing hydrogen

Milstein and co-workers have reported the first *N*-alkylation of hydrazine using alcohols as alkylating agents.[86] By employing a Mn(I) PNN pincer catalyst (**63**, 3 mol %) and KO^{t}Bu (5 mol %), a variety of benzyl and long chain *n*-alkyl alcohols undergo acceptorless dehydrogenative coupling forming *N*-hydrazones in excellent yields.



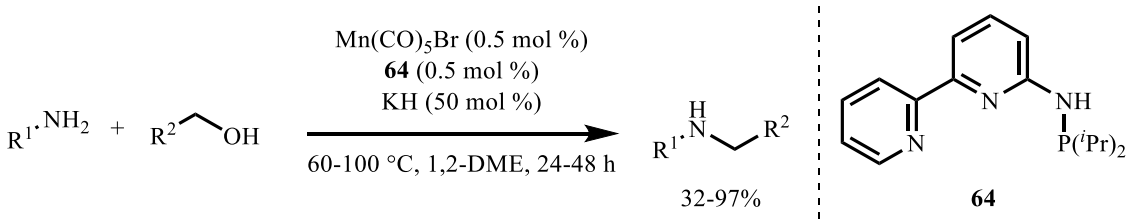
Scheme 1.52: Manganese-catalysed coupling of alcohols with hydrazine

In early 2019, our group has published the *N*-alkylation of sulfonamides using alcohols. By employing Beller's catalyst (**38**, 5 mol %) using catalytic base (K_2CO_3, 10 mol %), a range of sulfonamides undergo *N*-alkylation using both benzyl and *n*-alkyl alcohols. For alkyl alcohols, reactions were carried out in neat alcohol to obtain higher isolated yields. Finally, some mechanistic experiments were carried out to gain support on a proposed mechanism illustrated in Scheme 1.53.



Scheme 1.53: Manganese-catalysed *N*-alkylation of sulfonamides using alcohols

Most recently, Hultzsch and co-workers have also employed another manganese catalyst containing a bipyridine type framework.[87] They reported that the catalyst is prepared *in situ* with ligand **64**; and in the presence of KH (50 mol %) in 1,2-DME as solvent at 60-100 °C, *N*-alkylation is carried out efficiently using aryl amines as nucleophiles and both primary and secondary alcohols as alkylating agents, as illustrated in Scheme 1.54. Finally, they apply this to the synthesis of cinacalcet, which is used to treat tertiary hyperparathyroidism.

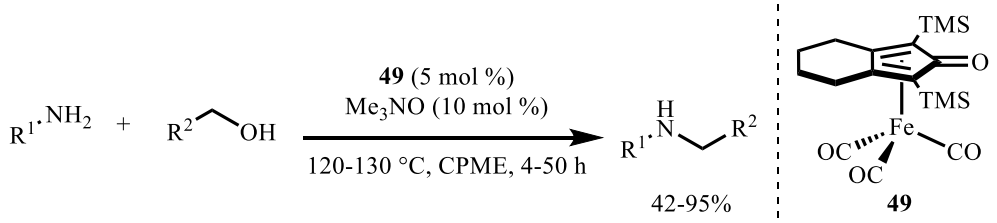


Scheme 1.54: *N*-alkylation of amines catalysed by a manganese NNP complex

1.8.3. Iron catalysis

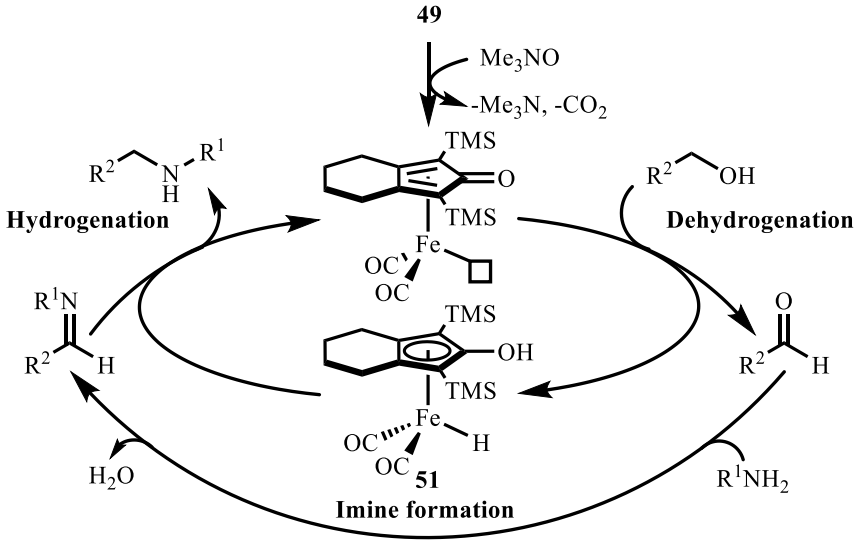
Prior to the work by Piersanti and co-workers,[76] Singh and co-workers had initially utilised the same iron(II) phthalocyanine complex (**55**) for *N*-alkylation of amines using alcohols, with NaO^{t}Bu (2.0 equiv.) at 100 °C for 24 h.[88] The majority of the work was carried out using aminobenzothiazoles and aminopyrimidines as their nucleophiles with various benzyl alcohols. In 2014, Feringa, Barta and co-workers disclosed the *N*-alkylation of amines using alcohols[89] using **49** as their catalyst, as displayed in Scheme 1.55. By incorporating CPME as their solvent, a range of aryl amines, benzyl amines and secondary amines undergo

successful *N*-alkylation with primary alcohols and diols, in the absence of base. Secondary alcohols gave low conversions, whilst diols resulted in the formation of multi-membered heterocycles. This methodology was applied to the synthesis of piridebil, and later was extended to the *N*-alkylation of amines using benzyl alcohols.[90] Interestingly MS were required as water scavengers giving enhanced yields.



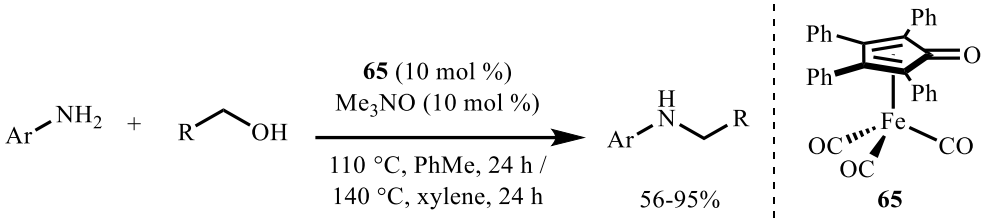
Scheme 1.55: Iron-catalysed *N*-alkylation of amines with alcohols

Their proposed cycle begins with CO de-coordination using Me_3NO forming the active catalytic species, by oxidising the CO to CO_2. This then dehydrogenates the starting alcohol forming the aldehyde and iron-hydride species. The aldehyde condenses with an amine forming an imine intermediate which then gets hydrogenated by the iron-hydride species forming the corresponding alkylated amine and the active catalytic species. This is illustrated in Scheme 1.56.



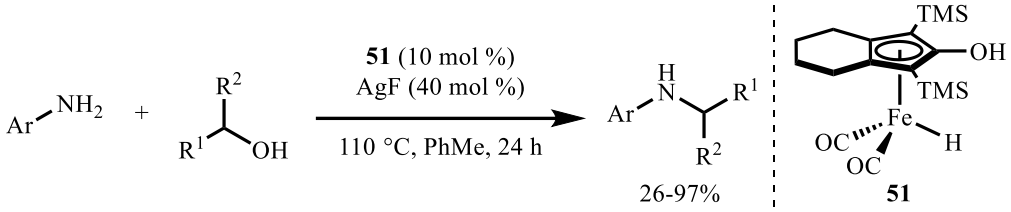
Scheme 1.56: Iron-catalysed *N*-alkylation of amines with alcohols – proposed mechanism

Wills and co-workers contributed to this field and synthesised a modified (cyclopentadienone)iron tricarbonyl complex for the same *N*-alkylation of amines, as displayed in Scheme 1.57.[91] Iron precatalyst (**65**, 10 mol %) and Me_3NO (10 mol %) were sufficient to achieve this transformation in excellent yields using benzyl alcohols, *n*-alkyl alcohols and cyclic secondary alcohols. Later, this same group synthesised various (cyclopentadienone)iron tricarbonyl complexes for *N*-alkylation reactions.[92]



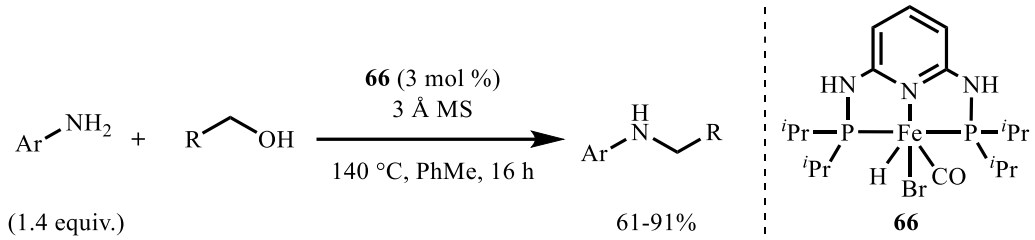
Scheme 1.57: C−N Bond Formation between alcohols and amines using an (cyclopentadienone)iron catalyst

Within the same timeframe, Zhao and co-workers established a more general approach to synthesise amines from secondary alcohols (Scheme 1.58).[93] In this case, an [Fe-H] type catalyst (**51**) was employed. Interestingly, they required AgF (40 mol %) as a Lewis acid in order to make their intermediate ketone more electrophilic facilitating imine formation to work more efficiently. Alkyl amines were also tested but were comparably less reactive.



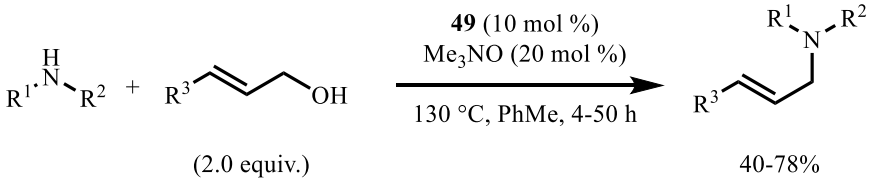
Scheme 1.58: Iron-catalysed *N*-alkylation aided by a Lewis acid

In 2016, Kirchner and co-workers developed an iron(II) PNP pincer complex (**66**, 3 mol %) for the *N*-alkylation of amines using alcohols (Scheme 1.59).[94] The addition of 3 Å MS as water scavengers and Lewis acids were required to force this transformation to proceed.



Scheme 1.59: *N*-Alkylation of amines catalysed by an Fe(II) PNP pincer complex

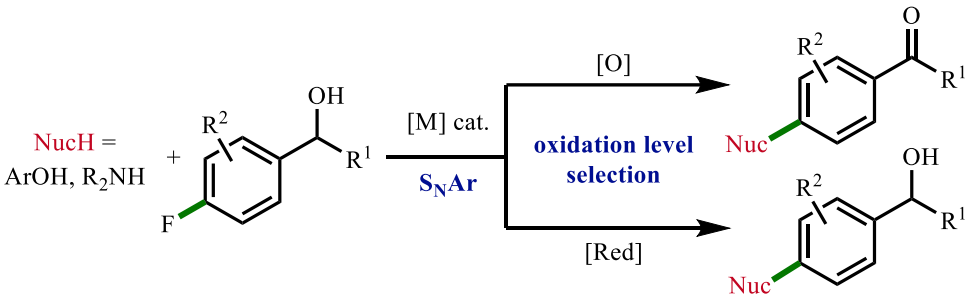
In the same year, Sundararaju and co-workers employed **49** for the amination of allylic alcohols (Scheme 1.60).[95] Even though this process can result in a number of side reactions, this process is particularly selective for 1,2-additon of the enal intermediate. Modest yields for products are obtained together with the tolerance of other reducible functionalities.



Scheme 1.60: Iron-catalysed *N*-alkylation using allylic alcohols

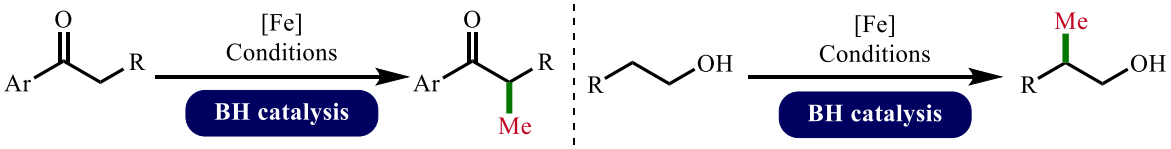
1.9. Aims and objectives

The aims of this PhD were to develop improved methodologies for the synthesis of C-C and C-N bonds using the borrowing hydrogen methodology. Williams and co-workers published a transformation which deals with the oxidation of benzylic allylic alcohols forming ketones which undergo nucleophilic aromatic substitution.[96] This process is quite limited as substrates require the use of sacrificial oxidants within the substrate itself. Hence, the aim here is to broaden this transformation's application to organic synthesis by using less specific and more readily available substrates together with the use of external sacrificial additives to promote the formation of the products. This would be done preferably using earth-abundant metal catalysts; however, some precious metal catalysts will be considered if they are compatible and more active for the transformation.



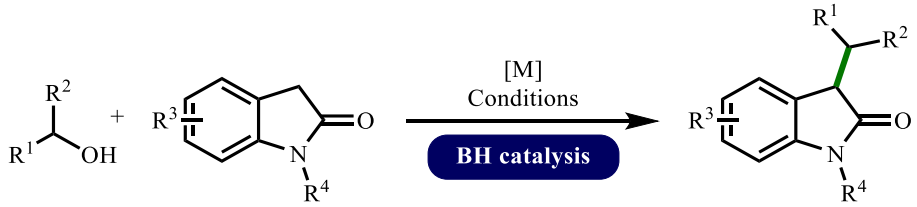
Scheme 1.61: Borrowing hydrogen S_NAr of alcohols

Methylation is a fundamental transformation in organic synthesis however employs toxic and harmful methylating agents. Since borrowing hydrogen methylation is common in the literature using precious metal systems,[97] and general alkylation is known using a variety of earth abundant systems,[17] the aim here is to develop an operationally simple methylation process for various classes of substrates using the most earth abundant transition metal, which is iron. Most reported iron precatalysts are bench stable and easy to scale up, and hence this process could have applications on an industrial level.



Scheme 1.62: Iron-catalysed borrowing hydrogen methylation

Other aims include the development of other alkylation processes using earth-abundant metals. It was proposed that by taking oxindoles as an example, these could be preferentially mono-alkylated at the *C*(3) position. Many pharmacological active compounds contain the oxindole framework[98] and hence if successful, this would also be beneficial in industry.



Scheme 1.63: Iron-catalysed alkylation of oxindoles

One-pot processes are of great interest as they reduce the number of individual steps required to achieve the desired product. By incorporating earth abundant metal catalysts, the aim here is to develop a hydrogen transfer protocol that would be used to carry out transformations that would conventionally require multi-step procedures. By doing this, waste is limited making the transformation more applicable. Finally, the last aim of this PhD is to provide mechanistic understanding of the proposed transformations through intermediate validation and kinetic analysis.

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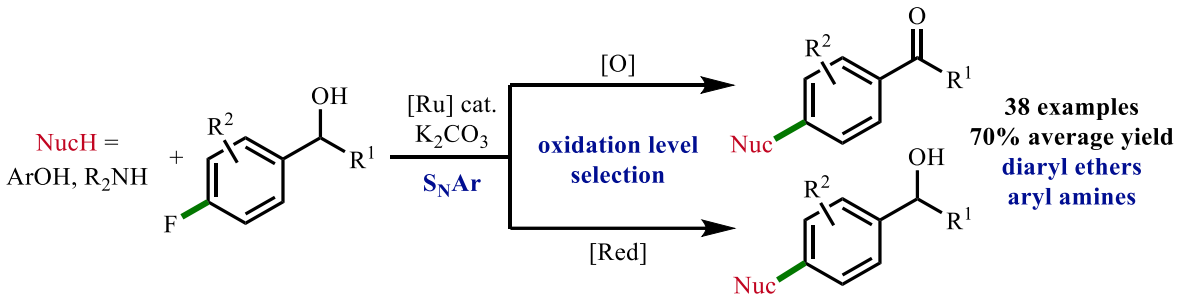
Chapter 2: Exploring tandem ruthenium catalysed hydrogen transfer and S_NAr chemistry

Table of contents

For the experimental section see chapter 7

2. Preface

This chapter discusses the merger of ruthenium-catalysed hydrogen transfer and S_NAr chemistry. A hydrogen-transfer strategy for the catalytic functionalisation of benzylic alcohols *via* electronic arene activation has been developed. Through this methodology, a diverse range of bespoke diaryl ethers and aryl amines were accessed in excellent isolated yields (38 examples, 70% average yield). Taking advantage of the hydrogen-transfer approach, the oxidation level of the functionalised products was selected by the choice of simple and inexpensive additives.



Publication: K. Polidano, B. G. Reed-Berendt, A. Basset, A. J. A. Watson, J. M. J. Williams and L. C. Morrill, *Org. Lett.*, 2017, **19**, 6716−6719.

Acknowledgements

Benjamin G. Reed-Berendt – A PhD student who finished the substrate scope for the isomerisation/S_NAr and epoxide synthesis part of the project.

Anais Basset – An exchange student who worked on the optimisation of the isomerisation/S_NAr part of the project.

Andrew J. A. Watson – A former PhD student at the University of Bath who was of great help during the preliminary investigations stage of this project.

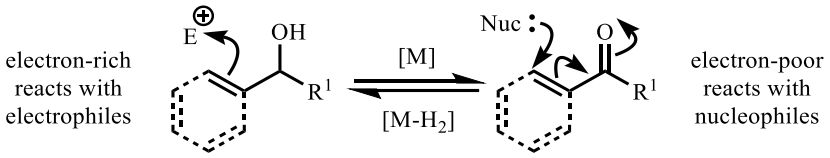
Jonathan M. J. Williams – CDT co-supervisor, University of Bath.

Louis C. Morrill – Supervisor, Cardiff University.

2.1. Introduction

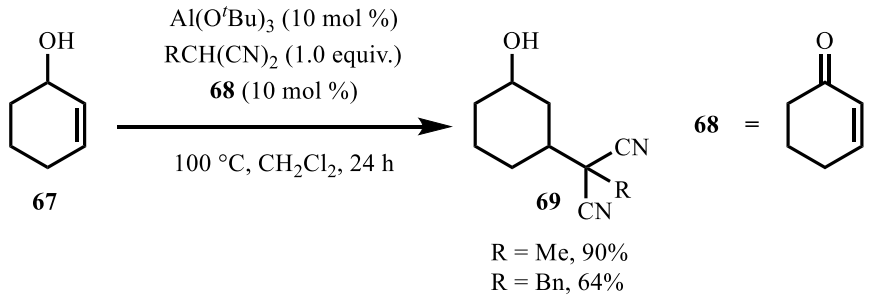
2.1.1. Remote electronic activation

As stated in Chapter 1, the most common and well reported transformations involving the borrowing hydrogen methodology are the *N*-alkylation of amines with alcohols and the *C*-alkylation of ketones, amides and esters with alcohols. We sought to investigate a different transformation. Hydrogen transfer has been well-explored throughout the past three decades[1] both using earth-abundant and precious metal catalysts. It is a powerful approach that can be employed to access the diverse reactivity of carbonyl compounds from alcohol starting materials. In this chapter, our interest was mainly focussed on employing the concept of remote electronic activation[2] in tandem with hydrogen transfer chemistry. Taking benzylic alcohols as an example; by altering the properties of an aromatic ring remotely, the ring would be able to react with nucleophiles rather than electrophiles or *vice versa*. One way in which this can be carried out is by utilising a catalyst which can promote hydrogen transfer as shown in Scheme 2.1.



Scheme 2.1: Remote electronic activation

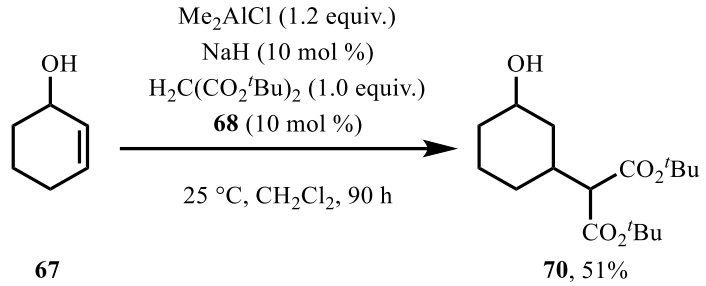
Jonathan M. J. Williams has contributed to this field. One of the initial publications employing the concept of remote electronic activation involved the indirect addition of nucleophiles to allylic alcohols as shown in Scheme 2.2.[3]



Scheme 2.2: Aluminium-catalysed indirect addition of malononitriles to allylic alcohols

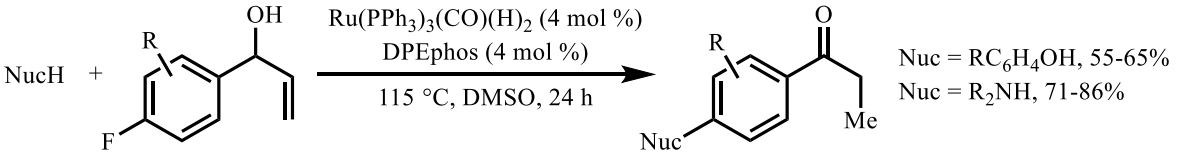
Using an aluminium catalyst, 2-cyclohexen-1-ol (**67**) is oxidised to 2-cyclohexen-1-one (**68**). Some of **68** is required prior to dehydrogenation to aid the transformation to take place. At this point this intermediate can undergo a 1,4-conjugate addition with methyl malononitrile and benzyl malononitrile independently in the presence of an alkoxide base leading to the formation of a 3-substituted cyclohexanone. The catalyst then transfers back the abstracted

hydrogen reducing this intermediate leading to the formation of the new alcohol (**69**). In the absence of catalyst, oxidation does not occur, and the starting allylic alcohol cannot undergo this transformation. In 2005, the same group reported a using a different pro-nucleophile, which was di-*tert*-butyl malonate.[4]



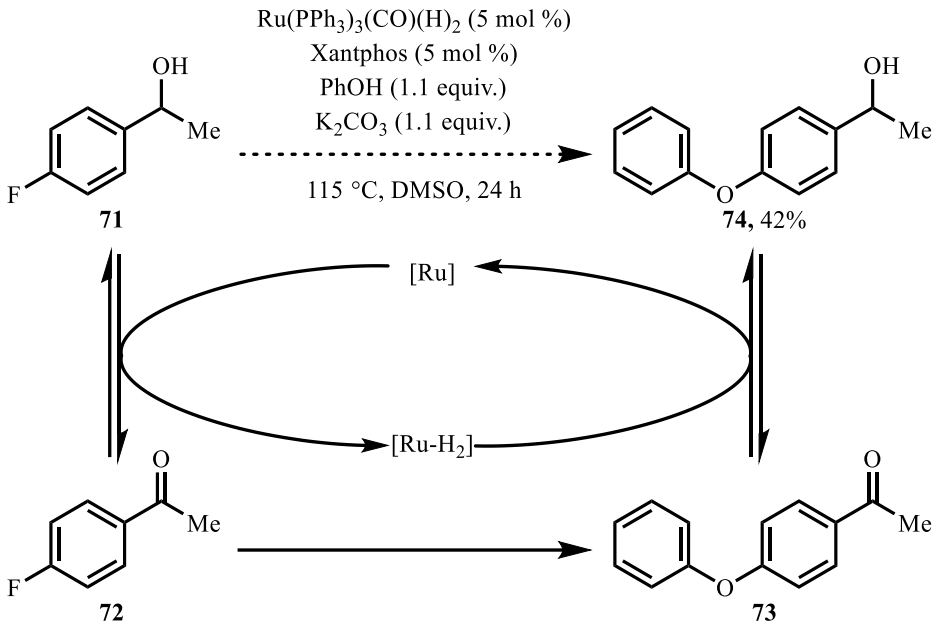
Scheme 2.3: Aluminium aided indirect addition of malonates to allylic alcohols

As shown in Scheme 2.3, the highest yield they obtained in this domino Oppenauer/Michael addition/MPV reaction was 51%. Unlike the malononitrile pro-nucleophiles, these malonates were giving reactivity problems and they could only achieve this by using super-stoichiometric amounts of dimethylaluminium chloride with the addition of catalytic NaH base. In 2013, Williams and co-workers developed a ruthenium-catalysed transfer hydrogenation/isomerisation of aryl allyl alcohols, generating acetophenones that are activated toward nucleophilic aromatic substitution.[5] Again, the concept of remote electronic activation is utilised in this transformation as the starting benzylic allylic alcohols cannot undergo nucleophilic aromatic substitution. Ultimately the transformation was optimised using the conditions illustrated in Scheme 2.4.



Scheme 2.4: Ruthenium-catalysed transfer hydrogenation/isomerisation/S_NAr of aryl allyl alcohols

This was followed by substrate scope varying both secondary amine and phenol nucleophiles obtaining tertiary amines and diaryl ethers respectively in good to excellent yields. Despite this successful work, this redox-neutral approach requires a sacrificial olefin hydrogen acceptor within the substrate thus significantly limiting its broader application in organic synthesis. In the same publication, a BH S_NAr of benzylic alcohols was investigated with a single NMR yield of 42% being obtained for the respective product, as shown in Scheme 2.5.

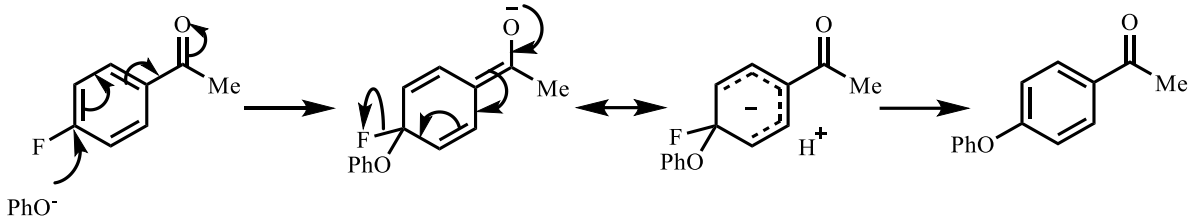


Scheme 2.5: Borrowing hydrogen S_NAr of alcohols

The BH S_NAr of alcohols was of interest to us as to the best of our knowledge, there were no other reports in the literature on this transformation. Thus, we envisaged making this process work by further investigations.

2.1.2. Nucleophilic aromatic substitution (S_NAr)

Nucleophilic aromatic substitution is a well-known process whereby a nucleophile substitutes a leaving group on an aromatic ring leading to the formation of a new compound.[6] S_NAr can only occur if the aromatic ring contains an electron-withdrawing group such as carbonyl derivatives and nitro groups. This is required in this class of reactions, as when nucleophiles attack at aromatic rings, movement of electrons results in the formation of a high energy Meisenheimer complex which is stabilised by resonance. When compared to S_N2 type reactions, the leaving group ability is reversed here as the C-X bond must be highly polarised for this reaction to proceed and hence fluoride is typically the best leaving group for this transformation.



Scheme 2.6: Classical S_NAr reaction - Meisenheimer complex and resonance forms

In our context, shown in Scheme 2.6, taking 4'-fluoroacetophenone as the electrophile and phenol as the nucleophile, for example; when phenol attacks the electropositive carbon atom, the Meisenheimer complex produced is stabilised by the *para*-substituted EWG and thus by movement of electrons, the mixture would release fluoride as the leaving group leading to the formation of 4'-phenoxyacetophenone.

2.1.3. Importance of diaryl ether moiety in biologically active compounds.

Through this S_NAr transformation, the compounds produced would all contain the diaryl ether moiety. This BH S_NAr transformation was pursued as the diaryl ether moiety is present in several biologically active compounds, and hence, this could have some potential applications. Some of these compounds are shown in Figure 2.1.

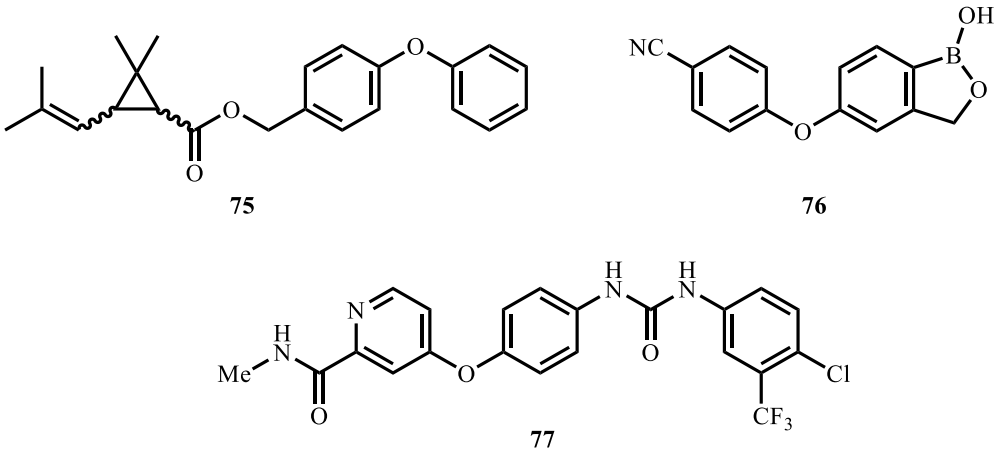
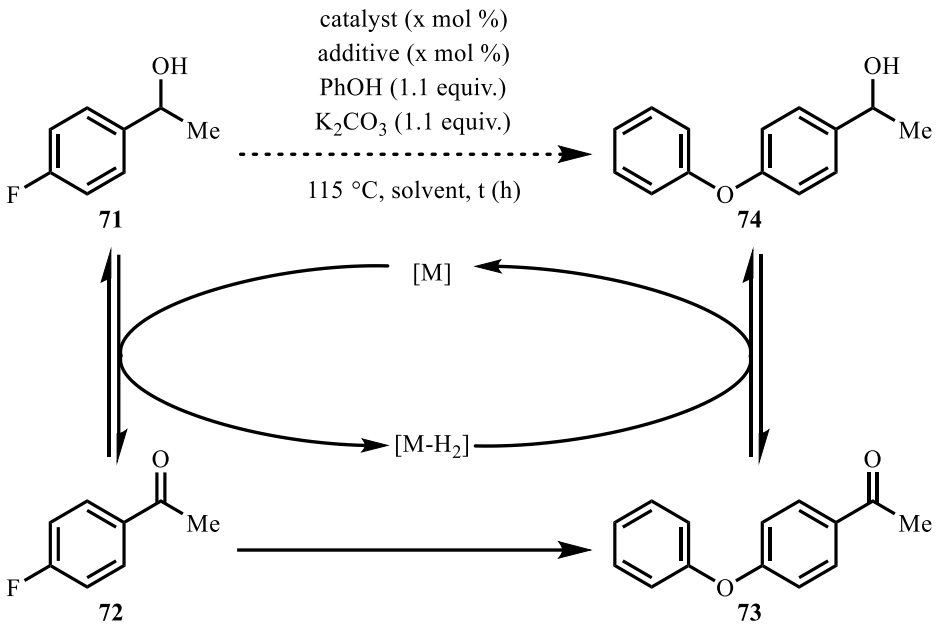


Figure 2.1: Biologically active compounds containing the diaryl ether moiety

Phenothrin (**75**) is a synthetic pyrethroid[7] used to for head lice treatment killing ticks and fleas. For children less than two years old, crisaborole (**76**) has been found to be non-steroidal topical medication used for the treatment atopic dermatitis.[8] Finally, sorafenib (**77**) is used for the treatment of advanced thyroid carcinoma and primary kidney and liver cancer.[9]

2.2. Results and discussion

2.2.1. Preliminary investigations



Scheme 2.7: Preliminary investigations on the BH S_NAr of alcohols

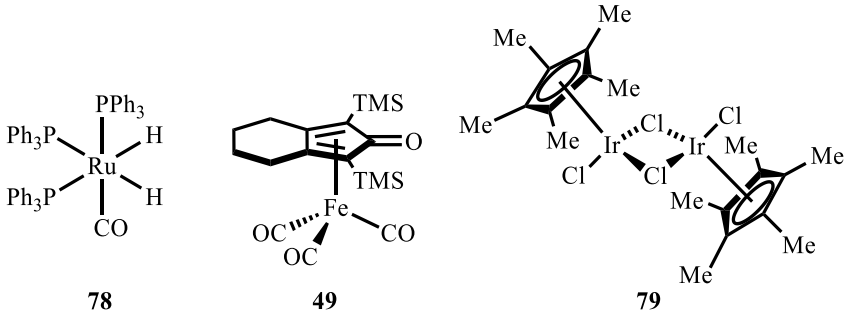


Figure 2.2: Known borrowing hydrogen catalysts

During these investigative tests carried out on the BH S_NAr of alcohols, all reactions were performed without the use of an internal standard and thus all results obtained (Table 2.1) were calculated by relative integrals of all the compounds involved.

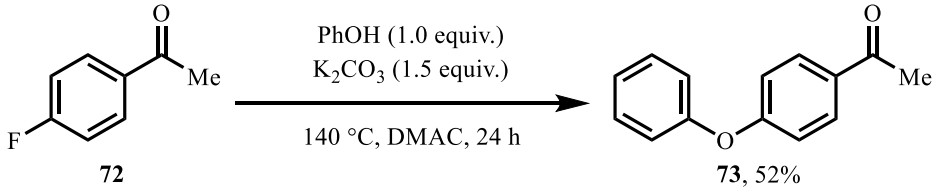
Table 2.1: BH S_NAr of alcohols - preliminary investigations

Entry[a]	Catalyst (loading)	Ligand/Additive (loading)	Time (h)	Solvent	71 (%)	72 (%)	73 (%)	74 (%)
1	**78 (5)**	xantphos (5)	24	DMSO	37	2	13	48
2	**49 (5)**	**Me_3NO (10)**	24	DMSO	98	1	1	0
3	**49 (5)**	**Me_3NO (10)**	24	DMAC	95	1	1	3
4	**49 (5)**	**Me_3NO (10)**	24	DMF	95	0	1	4
5	**79 (5)**	-	24	DMSO	69	11	17	3
6	**79 (5)**	-	24	Xylene	51	46	3	-
7	**79 (5)**	-	24	DMF	59	1	24	16
8	78 (5)	xantphos (5)	**48**	DMSO	3	2	38	58
9	78 (5)	xantphos (5)	**168**	DMSO	7	0	30	**63**
10	78 (5)	xantphos (5)	24	**DMAC**	60	4	8	28
11	78 (5)	xantphos (5)	24	**DMF**	62	4	20	14
12	**78 (10)**	**xantphos (10)**	24	DMSO	3	2	44	51

[a]Reactions performed using 0.4 mmol of alcohol **71**.

Initially we started by replicating the literature result, as shown in entry 1, obtaining a comparable NMR yield of **74** (48%). As this was successful, we further investigated this

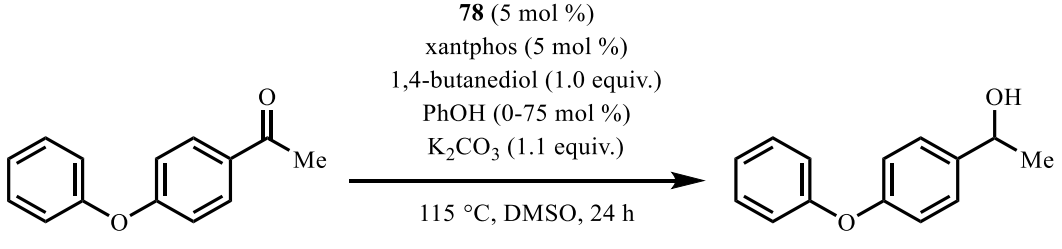
transformation. Ideally these types of transformations should be carried out using earth-abundant metals as they are cheaper and more readily available. Hence, some tests were carried out using a Knölker-type (cyclopentadienone)iron carbonyl complex (**49**) as catalyst (entries 2-4) with different polar aprotic solvents. These all gave recovered starting material with low conversion to **74** (0-4%) as observed in the crude ^{1}H NMR mixture (entries 4-6). This was possibly due to phenol being a catalyst poison. Other precious metal complexes such as $[Cp^*IrCl_2]_2$ (**79**) gave 16% conversion to **74** in DMF as solvent (entry 7), but still was inferior to the commercial $Ru(PPh_3)_3(CO)(H)_2$ catalyst (**78**) (entries 5-7). Clearly longer reaction times showed promise and the relative yield of **74** was increasing over time. Different polar aprotic solvents, such as DMF and DMAC, gave worse results whilst doubling the catalyst loading did not show a significant improvement. From these tests it was clear that the main problem is the final hydrogenation step. One plausible reason for incomplete reactivity was catalyst poisoning either by the nucleophile itself (phenol). Some tests were carried out to see if the phenol was a catalytic poison.[10] Intermediate **73** was readily synthesised by nucleophilic aromatic substitution of 4'-fluoroacetophenone (**72**) and phenol using K_2CO_3 in DMAC as solvent, as shown in Scheme 2.8.



72 **73**, 52%

Scheme 2.8: S_NAr reaction of 4'-fluoroacetophenone with phenol

With intermediate **73** in hand, it was reacted under the reported conditions using 1,4-butanediol as a sacrificial reducing agent, and different equivalents of phenol (10-75 mol %) to see if the transfer hydrogenation goes to completion (Scheme 2.9). From the trials shown in Table 2.2, it was concluded that phenol was not a catalyst poison as in all cases the ratio of **74/73** ranged from 80:20 to 83:17 with and without phenol additive. It was undoubtedly shown that the reaction does not go to completion.



73 **74**

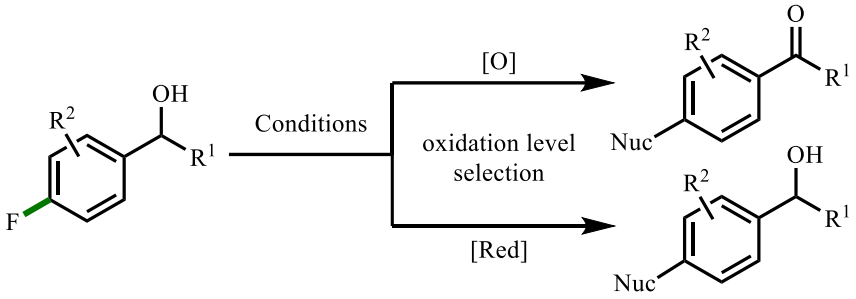
Scheme 2.9: Transfer hydrogenation of 4'-phenoxyacetophenone with 1,4-butanediol

Table 2.2: Transfer hydrogenation results

Entry[a]	Catalyst (loading)	Ligand/Additive (loading)	Phenol (mol %)	Time (h)	Solvent	73 (%)[b]	74 (%)[b]
1	78 (5)	xantphos (5)	-	24	DMSO	18	82
2	78 (5)	xantphos (5)	10	24	DMSO	18	82
3	78 (5)	xantphos (5)	25	24	DMSO	19	81
4	78 (5)	xantphos (5)	50	24	DMSO	17	83
5	78 (5)	Xantphos (5)	75	24	DMSO	20	80

[a]Reactions performed using 0.4 mmol of alcohol **71**. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

The main reason for this problem is that once the S_NAr has taken place, the phenoxy substituent affects the electronics of the acetophenone making it more electron rich and therefore harder to reduce. On the other hand, the positive outcome from these results was that we successfully demonstrated the use of sacrificial reductants to help shift the equilibrium forward towards the product. Through transfer hydrogenation we were able to manipulate the formation of the product. Similarly, the use of a sacrificial oxidant would undoubtedly shift the equilibrium to the substituted ketone as it will be used to abstract the hydrogen from the catalyst preventing the final hydrogenation from taking place. With these results in hand and taking inspiration from the work of Williams and co-workers, we envisaged developing a more general strategy for catalytic arene functionalisation *via* electronic activation of simple benzylic alcohols using inexpensive additives that serve as oxidants or reductants, as shown in Scheme 2.10.



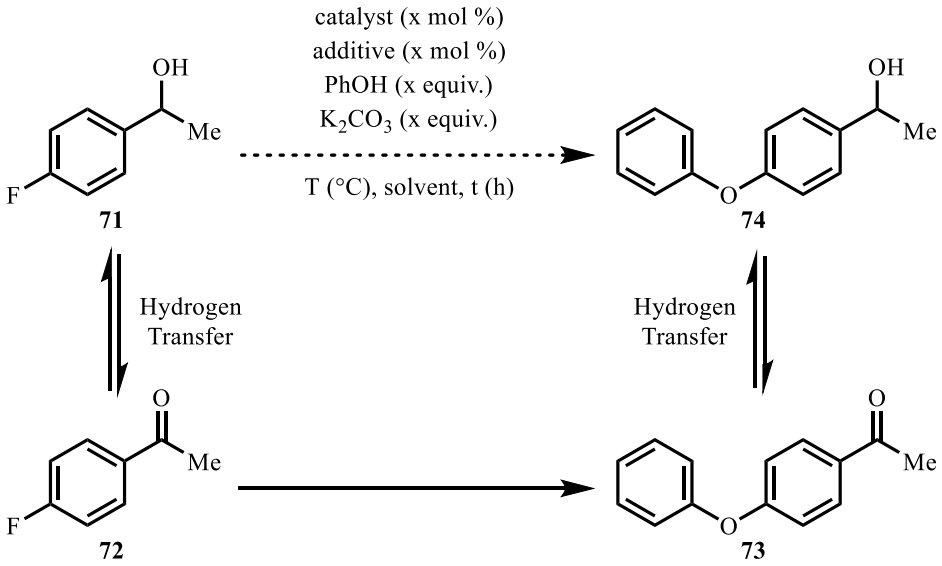
Scheme 2.10: Remote electronic activation of benzylic alcohols aided by oxidants and reductants

This approach removes the strict requirement for highly specialised aryl allyl alcohol substrates, significantly expanding the potential synthetic applications of this method. Within the literature, the use of oxidants for transfer hydrogenation processes is well-known. Some of these included the addition of ketones,[11] alkenes[12] and α,β-unsaturated compounds[13] as oxidants. Similarly, reductive processes have also been reported. Some examples included the use of alcohols,[14,15] diols[16,17] and formic acid[18,19] as reductants. We took advantage of the hydrogen transfer approach and hence it was anticipated that the oxidation level of the functionalised products could be selected as desired by the addition of an external oxidant or reductant, generating a diverse array of ketone and alcohol products.

2.2.2. Dehydrogenative and redox-neutral S_NAr

2.2.2.1. Optimisation of hydrogen-transfer S_NAr protocol

Prior to addition of oxidants and reductants, the overall reaction had to be optimised in a way that after the selected time, **71** and **72** would have disappeared from the reaction mixture. This was carried out to prevent re-formation of the starting alcohol when the reductant is added. The oxidant, on the other hand, if added at the start of the reaction, wouldn't hinder any dehydrogenation from taking place.



Scheme 2.11: Optimisation of the hydrogen transfer-S_NAr protocol

Therefore, to test our hypothesis, the optimisation of the hydrogen-transfer S_NAr was carried out using 1-(4-fluorophenyl)ethan-1-ol (**71**) as the model substrate. All the optimisation experiments were carried out in a sealed microwave vial. Each vial containing a magnetic stirrer bar was charged with phenol (x mmol, x equiv.), base (x mmol, x equiv.), ligand (x mol %), catalyst (x mol %), solvent (x mL) and 1-(4-fluorophenyl)-1-ethanol (51 µL, 56 mg, 0.4 mmol). The vial was sealed with a cap and left to react at 130 °C for 24 h. This was then cooled followed by the addition of 1,3,5-trimethylbenzene (56 µL, 48 mg, 0.4 mmol), H_2O (1 mL) and Et_2O (1 mL). In some cases, brine (1 mL) was added to aid layer separation. The mixture was then stirred for 5 minutes, the vial cap opened and left to settle for a further 5 minutes. The top layer was sampled and analysed using ^1H NMR. As shown in Figure 2.3, the reaction mixtures were analysed by comparing integrals of the α-methyl groups of the respective acetophenones (singlets) and alcohols (doublets) with 1,3,5-trimethylbenzene as internal standard. Table 2.3 shows the respective results from the optimisation.

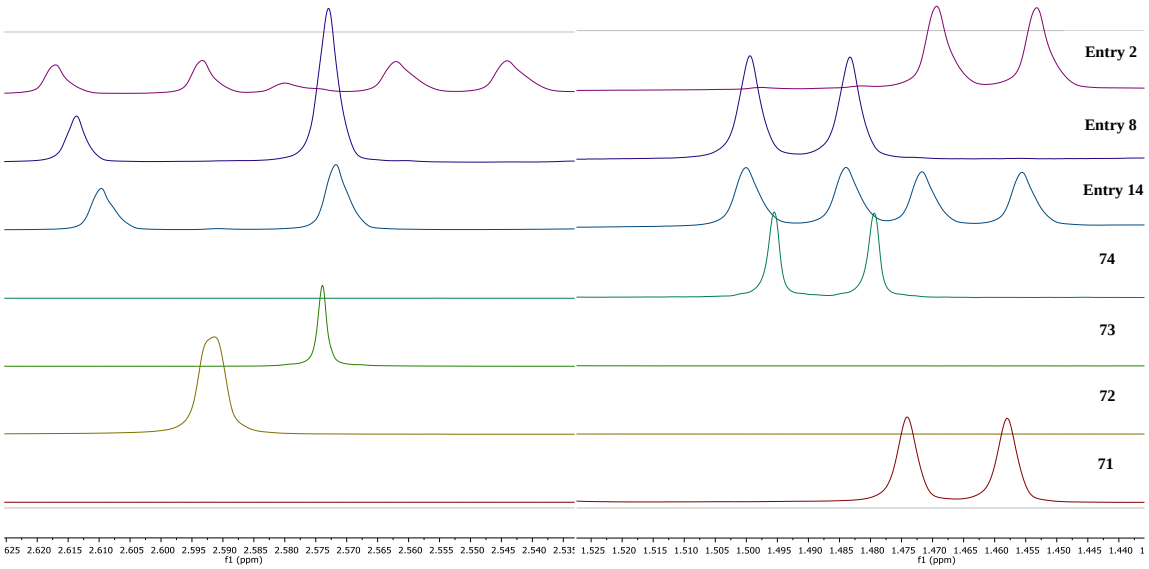


Figure 2.3: Stacked ^{1}H NMR (400 MHz, $CDCl_3$) spectra displaying the hydrogen transfer-S_NAr optimisation

Table 2.3: Hydrogen transfer-S_NAr optimisation table

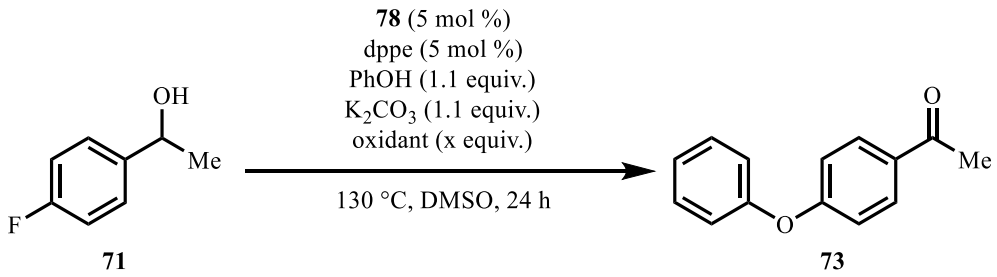
Entry[a]	Catalyst (5 mol%)	Ligand/ Additive (loading/ mol %)	Phenol equiv.	Base (eq.)	Solv. (Conc.)	T (°C)	71[b] %	72[b] %	73[b] %	74[b] %
1	-	-	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	98	-	-	-
2	**78**	-	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	23	2	38	25
3	**79**	-	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	29	1	37	3
4	**49**	Me_3NO (10)	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	95	-	-	-
5	78	**xantphos (5)**	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	7	1	35	33
6	78	**DPEphos (5)**	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	7	2	37	40
7	78	**dcpb (5)**	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	4	1	48	30
8	78	**dppe (5)**	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	0	1	62	28
9	78	**dppp (5)**	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	1	1	56	36
10	78	**dcpe (5)**	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	2	1	49	36
11	78 (**2.5 mol %**)	dppe (2.5)	1.1	K_2CO_3 (1.1 eq.)	DMSO (1 M)	130	63	1	25	7
12	78	dppe (5)	**1.5**	**K_2CO_3 (1.5 eq.)**	DMSO (1 M)	130	4	2	46	38
13	78	dppe (5)	1.1	**Cs_2CO_3 (1.1 eq.)**	DMSO (1 M)	130	2	2	44	34
14	78	dppe (5)	1.1	**Et_3N (1.1 eq.)**	DMSO (1 M)	130	43	26	10	3
15	78	dppe (5)	1.1	K_2CO_3 (1.1 eq.)	**DMAC (1 M)**	130	6	3	46	44
16	78	dppe (5)	1.1	K_2CO_3 (1.1 eq.)	**DMF (1 M)**	130	38	0	30	23
17	78	dppe (5)	1.1	K_2CO_3 (1.1 eq.)	**DMSO (0.5M)**	130	2	2	45	37

18	78	dppe (5)	1.1	K_2CO_3 (1.1 eq.)	**DMSO (2M)**	130	8	0	58	34
19	78	dppe (5)	1.1	K_2CO_3 (1.1 eq.)	**DMSO (1M)**	115	10	3	47	39
20	78	dppe (5)	1.1	K_2CO_3 (1.1 eq.)	**DMSO (1M)**	150	14	-	52	26
21[c]	78	dppe (5)	1.1	K_2CO_3 (1.1 eq.)	**DMSO (1M)**	130	<1	<1	52	34

[a]Reactions performed using 0.4 mmol of alcohol **71** and bench-grade DMSO. [b]Yield as determined by ^{1}H NMR analysis of crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. [c]16 h reaction time

As noted from entry 1 in Table 2.3, a background reaction with no catalyst was carried out, and this showed that the reaction fails in the absence of catalyst. When screening different catalysts such as $[Cp^*IrCl_2]_2$ (**79**) and the classic Knölker-type (cyclopentadienone)iron carbonyl complex (**49**); these were both inferior to $Ru(PPh_3)_3(CO)(H)_2$ (**78**) (entries 2-4); similar to the previous preliminary tests in Table 2.1. Different ligands were screened in conjunction with $Ru(PPh_3)_3(CO)(H)_2$ as the catalyst, and from these results (entries 5-10), dppe (1,2-bis(diphenylphosphino)ethane) was found to be the best ligand for undergoing tandem dehydrogenation and S_NAr. This was the best ligand as it probably had the best bite angle (85°)[20] for dehydrogenation facilitating the dihydride species to be *cis* to each other when bound to the metal centre. Halving the catalyst and ligand loading (entry 11) resulted in more unreacted starting material. Carbonate bases are common in S_NAr reactions.[21] 1.1 equiv. of K_2CO_3 was discovered to be optimal as more base (entry 12) resulted in the retention of **71** and **72**. Cs_2CO_3 and Et_3N gave considerably less reactivity in comparison to K_2CO_3 (entries 13-14). Different polar aprotic solvents such as DMAC and DMF were detrimental resulting in lower starting material conversion (entries 15-16). Doubling or halving the concentration was also worse whilst 130 °C was the optimal temperature for this process (entries 17-20). The reaction proceeded well at 16 h (entry 21), however, 24 h still demonstrated to be the optimal reaction time. From this optimisation table, entry 8 gave the best result, giving 62% of **73** and 28% of **74** with negligible amount of **71** and **72** being observed. At this point these conditions were used for oxidant and reductant screening.

2.2.2.2. Optimisation of dehydrogenative S_NAr protocol



Scheme 2.12: Optimisation of dehydrogenative S_NAr protocol

An almost identical procedure was carried out when screening oxidants. This required the same setup together with the addition of oxidant (x equiv.) prior to sealing the reaction vial. Table 2.4 shows the different oxidants that were screened together with the respective results.

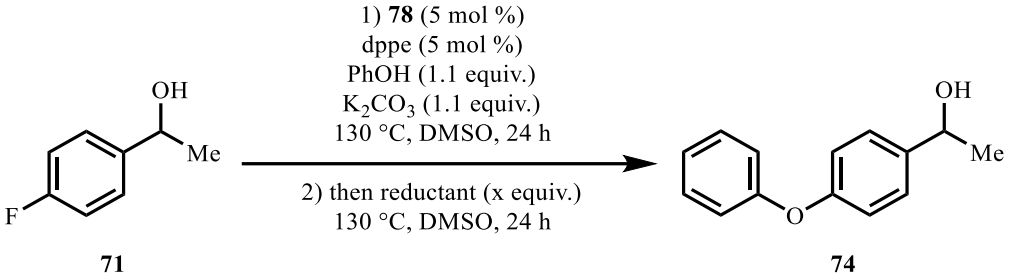
Table 2.4: Dehydrogenative S_NAr optimisation table

Entry [a]	Oxidant	Oxidant (equiv.)	73 (%)[b]	74 (%)[b]
1	Acetone	2	75	10
2	Acetone	5	**81 (79)**	5
3	Acetophenone	2	81	10
4	Acetophenone	5	**86**	6
5	2-Butanone	2	76	15
6	2-Butanone	5	**85**	5
7	Cyclohexanone	2	56	20
8	Cyclohexanone	5	69	21
9	3,3-Dimethylbutanone	2	67	18
10	3,3-Dimethylbutanone	5	71	15
11	3,3-Dimethylbut-1-ene	2	46	31
12	3,3-Dimethylbut-1-ene	5	51	29
13	1-hexene	2	53	33
14	1-hexene	5	55	26
15	3-Methyl-2-butanone	2	72	12
16	3-Methyl-2-butanone	5	**89**	10
17	4-Methyl-2-pentanone	2	72	17
18	4-Methyl-2-pentanone	5	**85**	8
19	Styrene	2	42	20
20	Styrene	5	23	15
21	Crotonitrile	2	54	10
22	Crotonitrile	5	54	10

[a]Reactions performed using 0.4 mmol of alcohol **71** and bench-grade DMSO. [b]Yield as determined by ^{1}H NMR analysis of crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

From the selected oxidants in Table 2.4, all the ketone oxidants gave the best ^{1}H NMR yield of 4'-phenoxyacetophenone (**73**). When the number of equivalents were increased from 2 to 5 equiv., in all cases the yield increased. Oxidants containing alkene moieties were detrimental to the process probably due to alkene coordination to the metal centre blocking any sites for dehydrogenation, hence preventing any catalysis from taking place. Styrene and crotonitrile oxidants resulted in a slurry type reaction mixture due to oxidant polymerisation taking place. The best results are shown in entries 2, 4, 6, 16 and 18 and from these, acetone (5.0 equiv., entry 2) was selected as the optimal oxidant, giving an 81% NMR yield of **73**, isolated to 79%. Employing acetone as the additive is quite attractive since it is cheap, and the only by-product is 2-propanol which can be removed by simple evaporation.

2.2.2.3. Optimisation of redox neutral S_NAr protocol



Scheme 2.13: Optimisation of redox neutral S_NAr protocol

In this case, a minor alteration was made to the procedure. After 24 h, the vial was cooled and charged with the reductant (x mmol, x equiv.) for an allotted time, stated in Table 2.5.

Table 2.5: Redox neutral S_NAr optimisation table

Entry[a]	Reductant	Reductant (equiv.)	Time (h)	73 (%)[b]	74 (%)[b]
1	1,4-Butanediol	2	24	12	52
2	Formic Acid	2	24	11	**74**
3	*Cis*-2-butene-1,4-diol	2	24	14	30
4	Isopropanol	2	24	37	44
5	Sodium Formate	2	24	11	**74**
6	Formic Acid	5	24	9	**82 (80)**
7	1,4-butane diol	5	24	8	50
8	Isopropanol	5	24	14	**73**
9	Sodium Formate	5	24	8	**73**
10	Formic Acid	5	1	29	56
11	Formic Acid	5	2	29	57
12	Formic Acid	5	3	27	58

[a]Reactions performed using 0.4 mmol of alcohol **71** and bench-grade DMSO. [b]Yield as determined by ^{1}H NMR analysis of crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

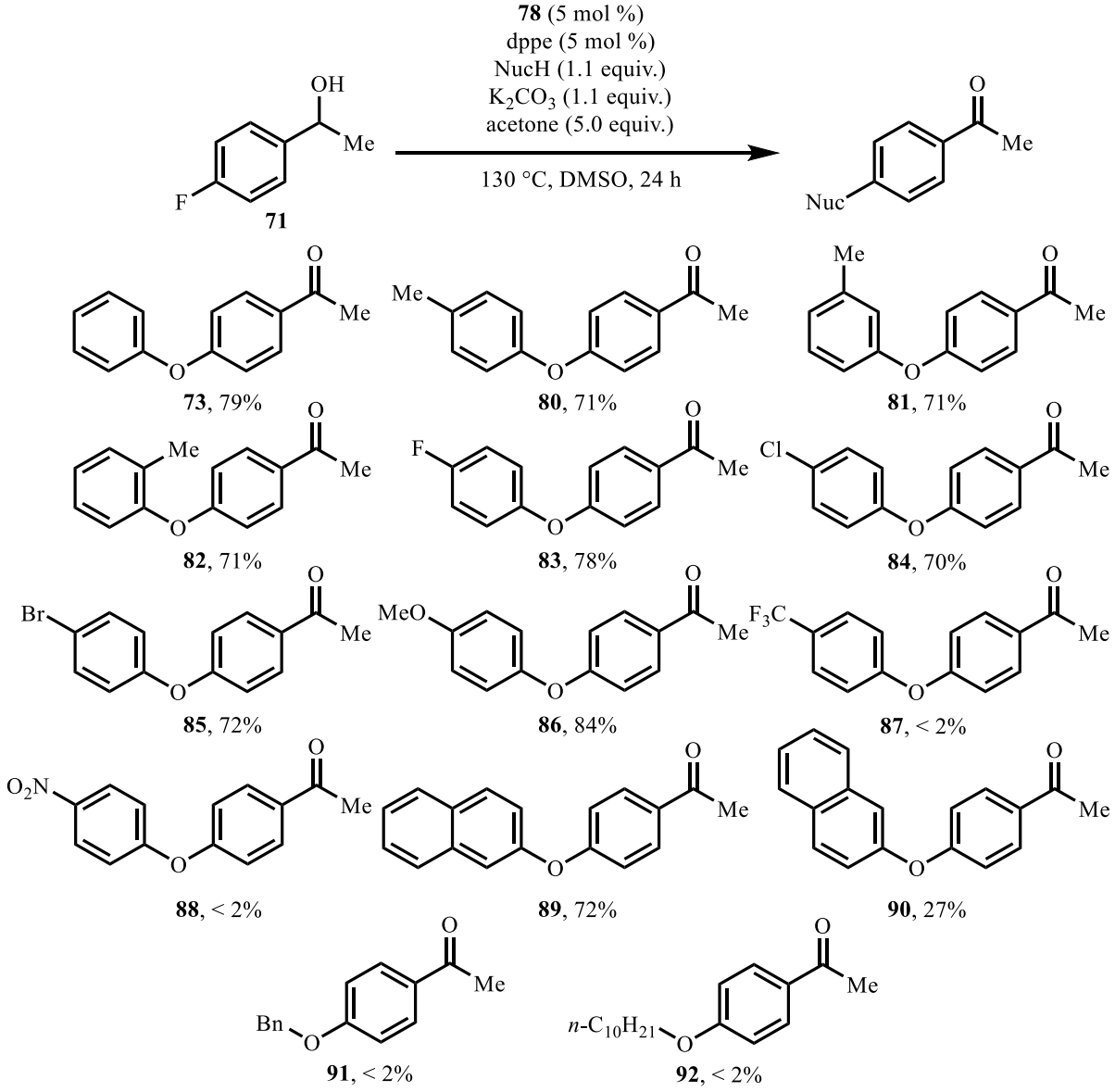
1,4-butanediol, formic acid, *cis*-2-butene-1,4-diol, 2-propanol and sodium formate (entries 1-5) were all screened as reductants, initially using 2.0 equiv. As expected, formic acid, 1,4-butanediol and sodium formate (entries 1, 2 and 5) gave good results with substantial transfer hydrogenation taking place to **74** leading to an NMR yield of 52, 74 and 74% respectively. Using *cis*-2-butene-1,4-diol and 2-propanol as additives resulted in a lower NMR yield of **74**. *Cis*-2-butene-1,4-diol is probably incompatible with our system as it would coordinate to the metal centre blocking any dehydrogenation sites; similar to 1-hexene in the oxidative S_NAr. In the case of 2-propanol, this is slightly harder to dehydrogenate. Several tests were then carried out using 5.0 equiv. of reductant (entries 6-9). From these results, formic acid was the optimal reductant giving an 82% NMR yield of **74**, which was successfully isolated to 80%. The advantage of using formic acid is that it only generates CO_2 as a by-product and hence makes isolations easier without any by-products. Finally, some experiments were carried out to see if the final reduction takes place within a shorter time period but from entry 12 alone, the result clearly shows that 3 h is not enough. Hence, we decided to stick with a

24 h reduction reaction to ensure near complete transfer hydrogenation. This redox neutral protocol would thus employ a two-step one-pot procedure consisting of 48 h total reaction time which is presented in Scheme 2.13.

2.2.3. Substrate scope

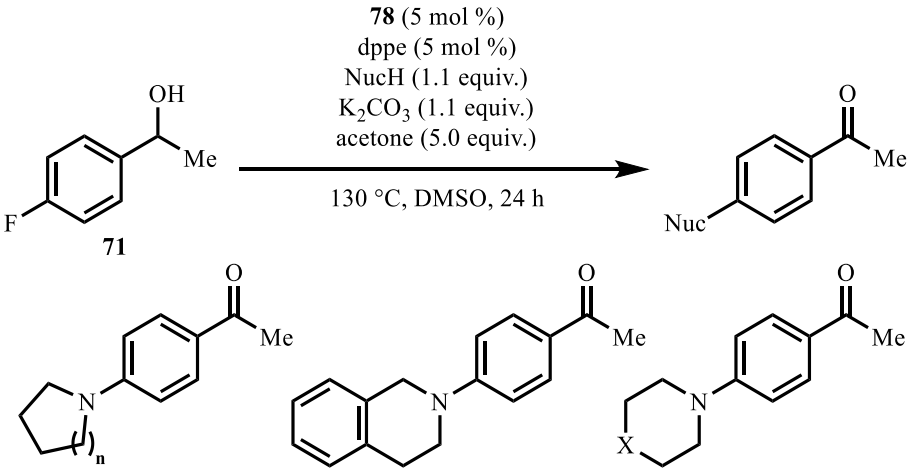
2.2.3.1. Scope of the dehydrogenative S_NAr protocol

Using the optimised conditions for the dehydrogenative S_NAr protocol (Table 2.3, entry 8; Table 2.4, entry 2), various aryl alcohols can be employed as the nucleophile accessing a range of substituted diaryl ether products in excellent yields (70-86%).

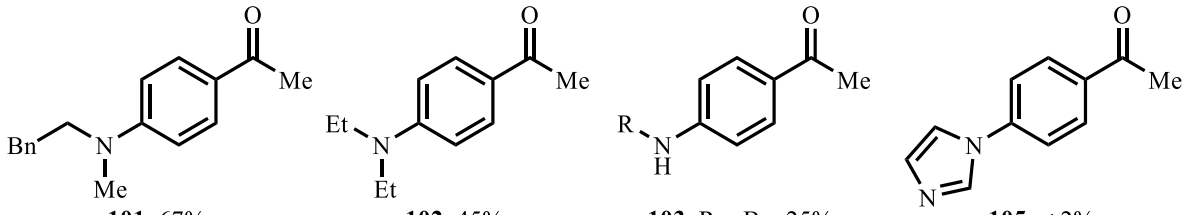


Scheme 2.14: Dehydrogenative S_NAr scope

Cresols, including a hindered *o*-cresol, were successfully tolerated (4-Me, 3-Me and 2-Me, **80-82**) with negligible loss of reactivity. Halo-substituted phenols such as 4-F, 4-Cl and 4-Br were all tolerated leading to excellent yields of the respective diaryl ethers (**83-85**, 70-78%). The transformation using these halo-containing nucleophiles is beneficial as they can be further functionalised through other reactions such as cross-coupling transformations.[22] Electron-donating groups such as 4-methoxyphenol provided a high isolated yield for the respective diaryl ether due to its enhanced nucleophilicity (**86**, 84%). Electron-withdrawing groups and weakly nucleophilic aryl alcohols such as 4-nitrophenol and 4-(trifluoromethyl)phenol resulted in no formation of the diaryl ether with mixtures of starting alcohol and acetophenone returned as observed from the corresponding ^{1}H NMR spectra of the crude NMR mixtures. 2-Naphthol is compatible with the reaction system giving 72% of **89** whilst 1-naphthol gave poor reactivity since it is a weak nucleophile, both sterically and electronically (**90**, 27%). Aliphatic alcohol nucleophiles, such as 1-decanol and benzyl alcohol, were completely unreactive in this protocol (**91-92**, < 2%) giving a complex mixture of products. As the pK_a of alkyl alcohols (~16) is higher when compared to phenol nucleophiles (~10), these were tested using stronger bases such as NaH and KO^{t}Bu, but still there was no trace of product in the respective mixtures. With thiophenol as a nucleophile, starting materials were returned due to catalyst poisoning by the nucleophile. Secondary amines were then investigated for the dehydrogenative S_NAr protocol.



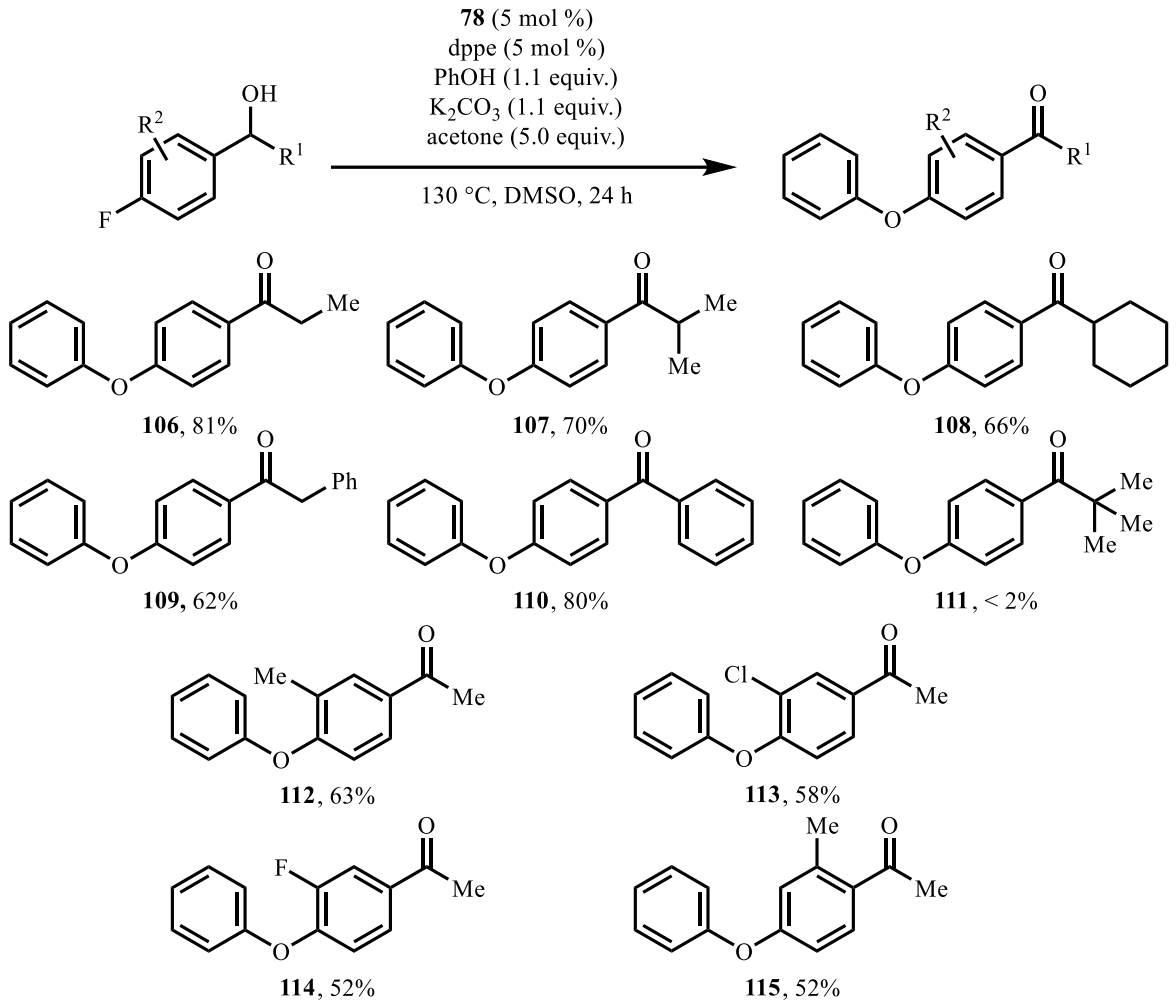
Scheme 2.15: Dehydrogenative S_NAr amine scope



101, 67% **102**, 45% **103**, R = Bn, 25% **104**, R = Ph, < 2% **105**, < 2%

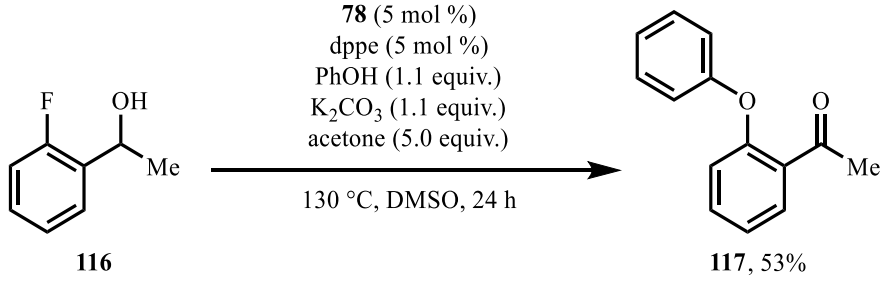
Figure 2.4: Dehydrogenative S_NAr amine scope - continued

5, 6 and 7-membered saturated heterocyclic amines (**93-95**) all worked well under the dehydrogenative S_NAr conditions giving 70, 83 and 66% respectively. Other strongly nucleophilic secondary amine nucleophiles such as 1,2,3,4-tetrahydroisoquinoline, morpholine, 4-phenylpiperazine, 4-methylpiperazine and 4-phenylpiperidine all were tolerated giving excellent yields of the corresponding products (**96-100**, 68-83%). The methodology has thus been demonstrated to work efficiently with phenols and cyclic secondary amine nucleophiles. *N*-Methylphenethylamine, being an acyclic secondary amine, works reasonably well (**101**, 67%) whilst diethyl amine, gave a synthetically useful yield (**102**, 45%) probably due to product volatility. Some limitations to this methodology are uncovered when employing primary aliphatic and aromatic amines such as benzyl amine (**103**, 25%) and aniline (**104**, < 2%). The main issue with these is their nucleophilicity. Another limitation to this methodology is when using heterocycles as nucleophiles. Imidazole was tested as a nucleophile (**105**, < 2%) but unfortunately hindered any possible reactivity from taking place. Ruthenium-imidazole complexes have been reported in the literature[23,24,25] and therefore a possible reason for their lack of reactivity would be coordination to the catalyst, and hence this changes the ruthenium centre's electronics and prevents any dehydrogenation from taking place. This result was expected as the reaction mixture turned black after a few minutes of reactivity. The scope of the fluoroarene was subsequently tested by reacting fluoroarenes containing different α-carbonyl functional groups with phenol as the model nucleophile. Different sterically hindered alcohols were readily synthesised by Grignard addition to 4-fluorobenzaldeyhde. Having all these in hand (R = Et, ^{i}Pr, Cy, Bn and Ph), they were tested for the methodology, and all proved to be compatible with the dehydrogenative S_NAr protocol giving good yields (**106-110**, 62-84%) of the respective diaryl ether products with minute loss of reactivity. It was only when an extremely bulky *tert*-butyl group was present that the reaction did not proceed (**111**, < 2%). Other fluoroarenes containing substituents on the fluoroarene itself were synthesised either by MeMgBr addition to aldehydes or reduction of the corresponding acetophenones with $NaBH_4$.



Scheme 2.16: Dehydrogenative S_NAr fluoroarene scope

These were also tested under the standard dehydrogenative conditions. As shown in Scheme 2.16, the results show that the methodology tolerates 2-Me, 3-Me, 3-F and 3-Cl (**112-115**, 52-63%) well with some loss of reactivity due to the increased steric encumbrance present in the starting alcohol. Since electron-withdrawing groups activate the ring towards S_NAr at the *ortho* and *para* positions, we wanted to demonstrate that this protocol works also at the *ortho* position. 1-(2-Fluorophenyl)ethan-1-ol (**116**) was synthesised and was tested for this methodology giving a moderate yield for 2'-phenoxyacetophenone (**117**, 53%) with some minor loss of reactivity.

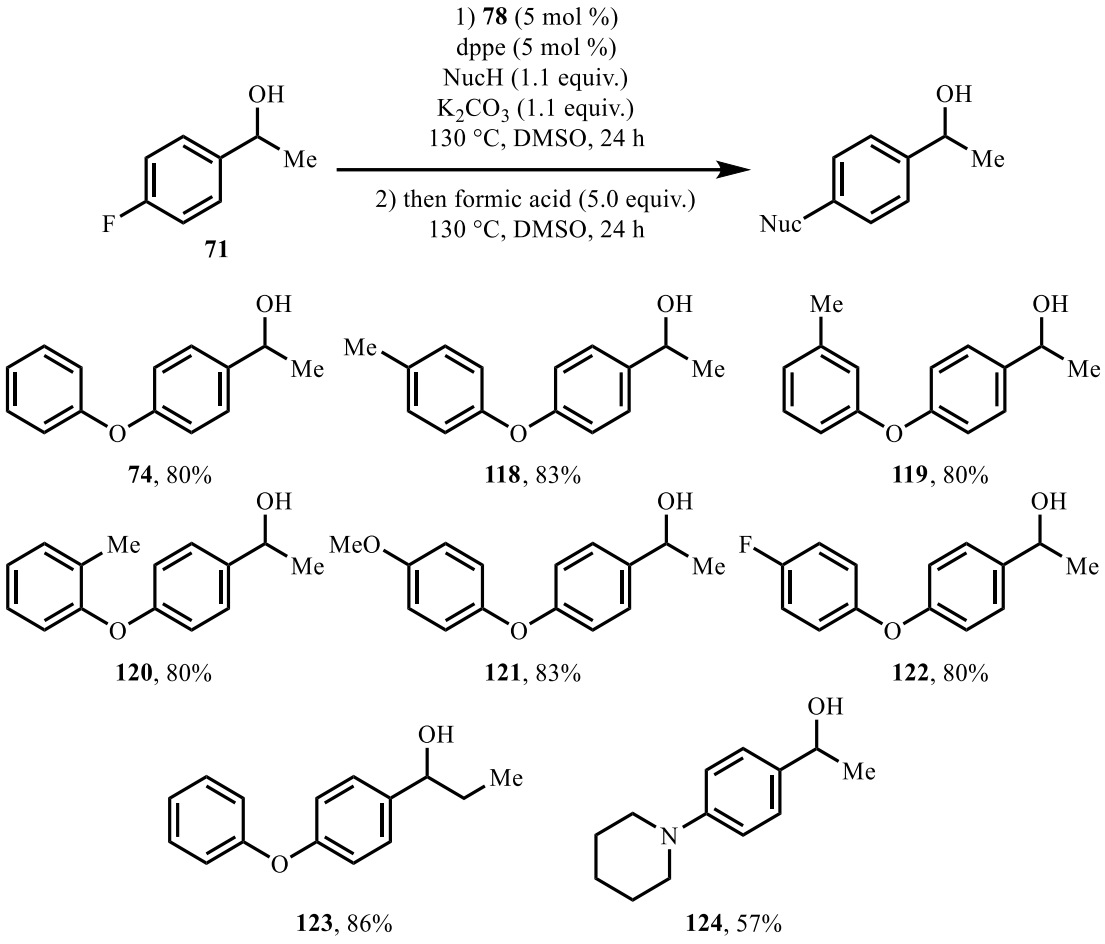


Scheme 2.17: Dehydrogenative S_NAr from 1-(2-fluorophenyl)ethan-1-ol

Other limitations to this methodology are electrophiles that have worse leaving groups, such as chloride (4-Cl, 2-Cl). Both did not show any sign of reactivity giving a mixture of starting alcohol and oxidised acetophenone as observed from the ^{1}H NMR spectrum of the crude reaction mixture.

2.2.3.2. Scope of redox-neutral S_NAr scope

Having successfully demonstrated the dehydrogenative S_NAr methodology to work for a variety of nucleophiles and fluoroarenes, the scope of the redox-neutral pathway was subsequently investigated using formic acid as the reductant as shown in Scheme 2.18.



Scheme 2.18: Redox neutral S_NAr scope

Some selected examples were investigated using this methodology. Cresols were successfully tolerated with negligible loss of reactivity (**118-120**, 80-83%). 4-Methoxyphenol and 4-fluorophenol worked extremely well, both giving 89% of the respective alcohol (**121-122**). When employing 1-(4-fluorophenyl)-propan-1-ol as the fluoroarene, redox-neutral S_NAr was successful obtaining the corresponding alcohol in an excellent yield (**123**, 86%). As stated in section 2.2.1, the main problem for the incomplete

reactivity of the BH S_NAr pathway is due to the increased electron-richness of the substituted intermediate. Bearing this in mind, when employing piperidine for the redox-neutral process, the tertiary amine is even more electron rich when compared to diaryl ether, but under these conditions, it is still able to be partially reduced obtaining a 57% yield of the respective alcohol (**124**).

2.3. Lignin depolymerisation - introduction

Recently, developing and applying catalysis for lignin depolymerisation has become of great interest in the literature.[26] Precious metal complexes are now known to be robust and stable catalysts for the valorisation of lignocellulosic biomass. The breakdown of lignocellulosic biomass, having a typical structure shown in Figure 2.5, is also a very useful tool, as doing so results in the generation of sustainable pathways to fuels and chemicals.

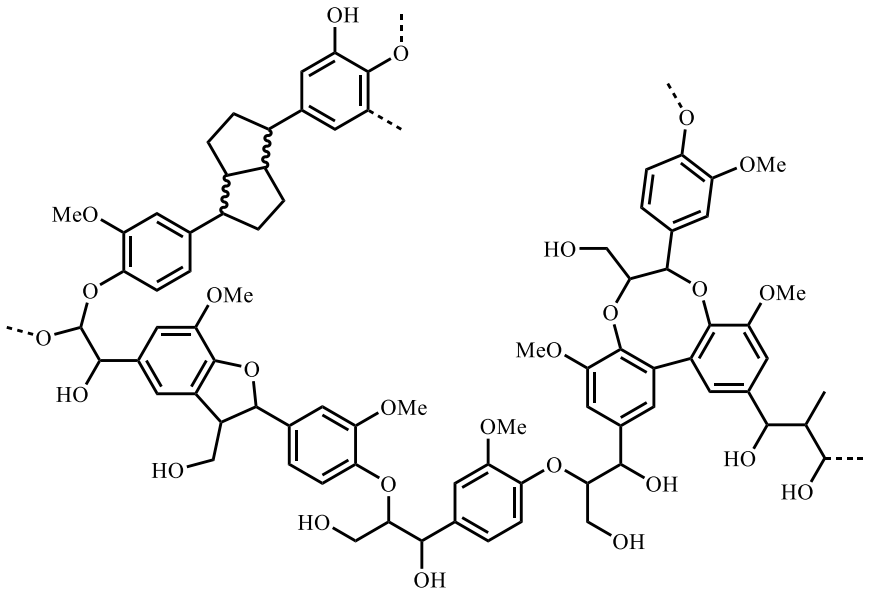
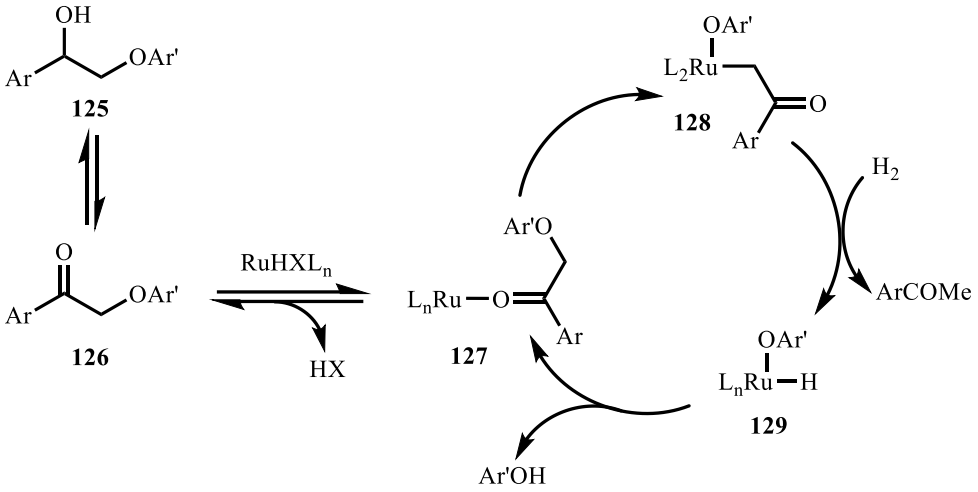


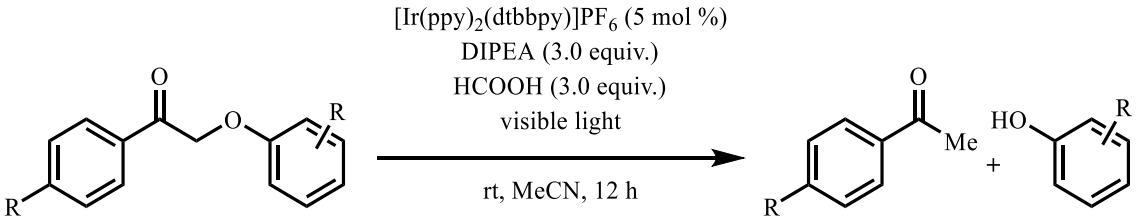
Figure 2.5: Lignocellulosic biomass

Cellulose, hemicellulose and lignin are the main constituents of lignocellulosic biomass. These are used in the manufacture of some soaps and pulps.[27] 2-Aryloxy-1-phenylethanols are compounds that are present in the backbone structure of ligninocellulose and its derivatives, and one way to break this down is to carry out a cleavage of the C-O bond present in this species. Ellman and co-workers were one of the few people who first applied ruthenium catalysis in lignin polymerisation. In 2010,[28] they utilised $Ru(PPh_3)_3(CO)(H)_2$ with xantphos as their catalytic system to successfully break down these compounds. Hence this generates acetophenones and phenols. They also provide a stepwise catalytic cycle for this transformation as illustrated in Scheme 2.19.



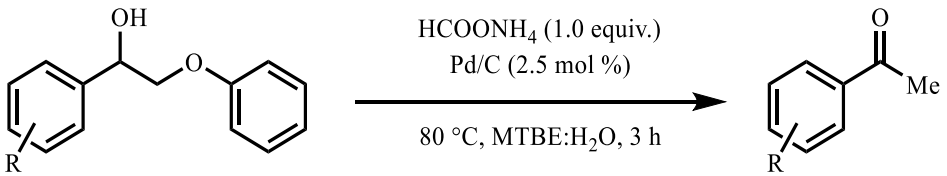
Scheme 2.19: Ruthenium catalysed C-O bond cleavage of 2-aryloxy-1-phenylethanols

The catalyst first dehydrogenates the starting alcohol (**125**) leading to the formation of 2'-aryloxyacetophenones (**126**). The carbonyl compound produced coordinates to the metal centre and C-O bond activation follows leading to the formation of an intermediate (**128**) having a metal-carbon and metal-oxygen bond. The hydrogen produced from the first step is used to undergo hydrogenolysis leading to the formation of a metal-hydride species (**129**) and the corresponding acetophenone. Reductive elimination results in phenol formation with catalyst regeneration. Leitner and co-workers[29] have also developed a similar catalytic system to Ellman involving a ruthenium triphos catalyst. Stephenson and co-workers, in 2014,[30] reported the same transformations a photochemical mediated C-O cleavage of 2-aryloxyacetophenones using an iridium catalyst generating the same products as shown in Scheme 2.20.



Scheme 2.20: Ir/visible light catalysed cleavage of 2-aryloxyacetophenones

Samec and co-workers have also used Pd/C with $HCOONH_4$ both as a base and a hydrogen donor with subsequent substrate scope giving acetophenones within 3 h, with yields greater than 90%.[31] Their parent example is shown in Scheme 2.21.



Scheme 2.21: Iridium catalysed C-O bond cleavage of 2-aryloxy-1-phenylethanols

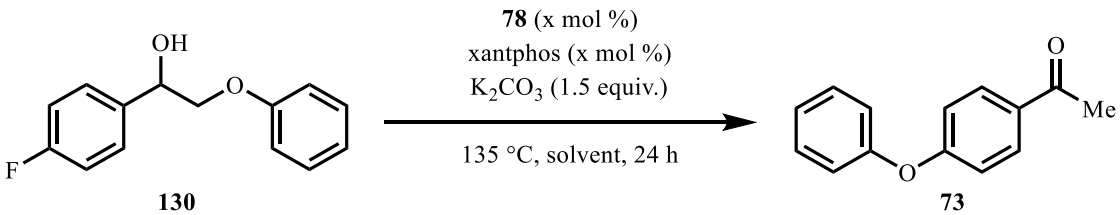
2.4. Isomerisation/S_NAr

In section 2.2.3, we have successfully functionalised benzylic alcohols to undergo dehydrogenative and redox-neutral S_NAr by the addition of simple and inexpensive additives being acetone and formic acid respectively. Despite the low cost of these additives and the ease of product isolation, an alternative approach with increased atom economy was sought. Inspired by lignin depolymerisation reports, we envisaged developing a one-pot isomerisation process of 2-aryloxy-1-arylethanols to diaryl ethers, which proceeds *via* transfer hydrogenation to generate fluoroarenes that would be electronically activated towards nucleophilic aromatic substitution with phenols as nucleophiles.

2.5. Results and discussion

2.5.1. Optimisation of isomerisation/S_NAr protocol

This optimisation was carried out by Anais Basset, a foreign exchange student, in Scheme 2.22. Initially she took 1-(4-fluorophenyl)-2-phenoxyethan-1-ol (**130**) as the model substrate with Bergman's conditions and noticed complete conversion of the starting alcohol after 24 h. The main difference from Bergman's conditions, which is a crucial requirement for this isomerisation/S_NAr transformation, is a base and a polar aprotic solvent. Like the dehydrogenative and redox-neutral S_NAr, these reactions were performed in sealed microwave vials. After extensive optimisation carried out by Anais Basset, shown in Table 2.6, it was discovered that the reaction proceeds best when using 2.5 mol % of $Ru(PPh_3)_3(CO)(H)_2$ (**78**) and 2.5 mol % of xantphos ligand, 1.5 equiv. of K_2CO_3 base at 135 °C in DMAC solvent (1 M) for 24 h. Lower catalyst loading and different solvents such as DMSO and DMAC worked worse compared to the stated optimised conditions (entry 6).



130 **73**

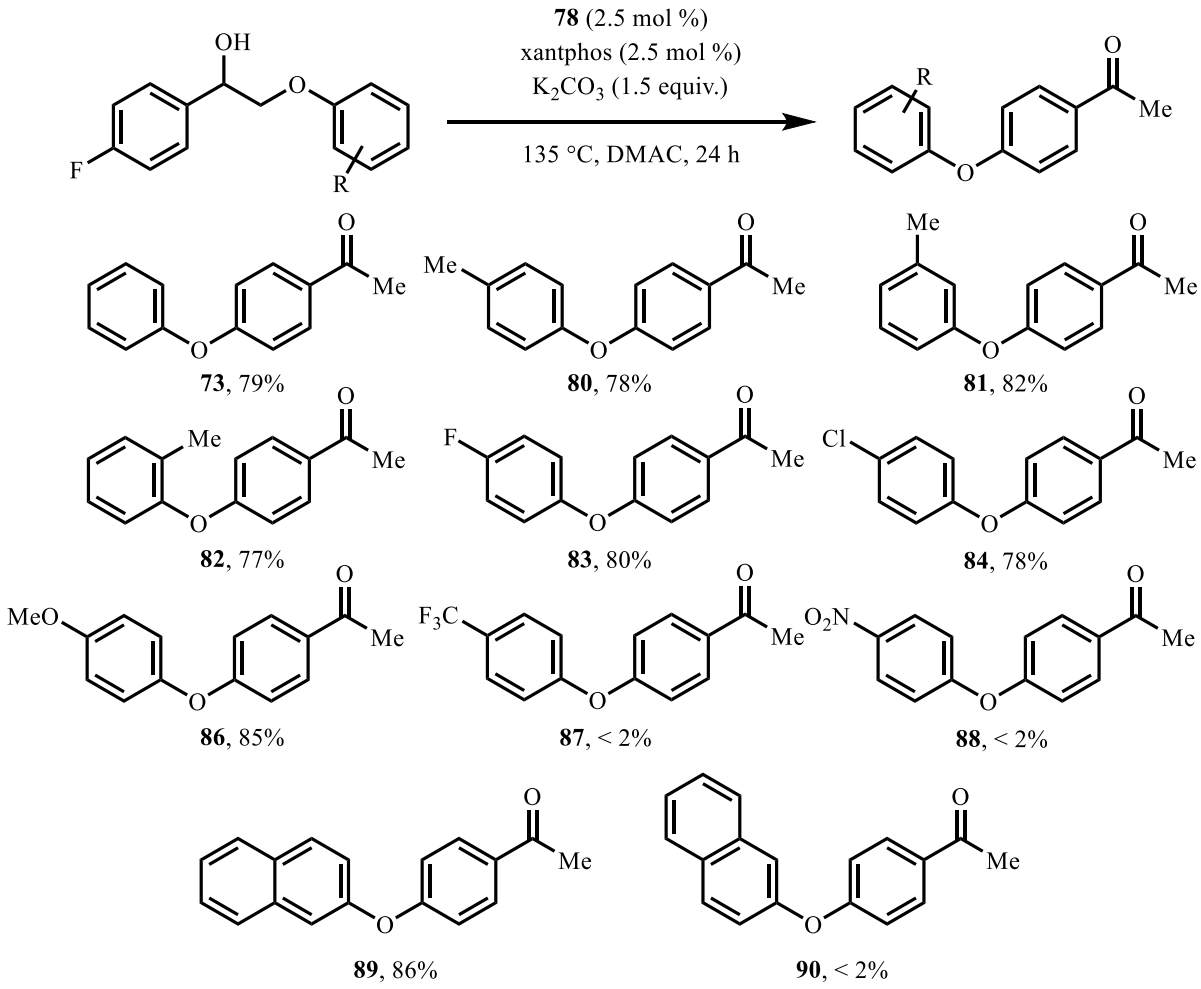
Scheme 2.22: Ruthenium-catalysed isomerisation/S_NAr of 2-aryloxy-1-phenylethanols

Table 2.6: Isomerisation/S_NAr optimisation table

Entry[a]	78 & xantphos (mol %)	Time (h)	Solvent (Conc.)	73 (%)[b]
1	5	24	DMF (0.4 M)	91
2	5	24	DMSO (0.4 M)	76
3	5	24	DMAC (0.4 M)	100
4	2.5	24	DMAC (0.4 M)	95
5	1	24	DMAC (0.4 M)	26
6	2.5	24	DMAC (1 M)	**100 (79)**
7	2.5	16	DMAC (1 M)	100

[a]Reactions performed using 1 mmol of alcohol **130**. [b]Yield as determined by ^{1}H NMR analysis of crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

2.5.2. Substrate scope of isomerisation/S_NAr protocol



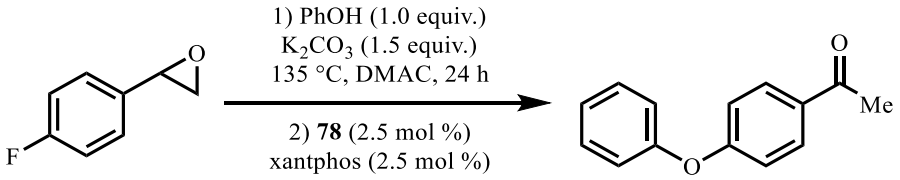
Scheme 2.23: Isomerisation/S_NAr substrate scope

After I successfully isolated the parent compound (**73**) in good yield, Benjamin Reed-Berendt, a PhD student in the group, continued the substrate scope for the isomerisation/S_NAr isolating compounds **80**-**86** and **89**. Similar to the dehydrogenative S_NAr (section 2.2.3.1), the methodology tolerates methyl groups around the ring including 1-(4-fluorophenyl)-2-(*o*-tolyloxy)ethan-1-ol, which contains a sterically hindered *o*-cresol substituent (4-Me, 3-Me and 2-Me, **80**-**82**), giving diaryl ether yields ranging from 77-82%.

Substrates containing 4-fluoro and 4-chlorophenoxy substituents gave excellent yields (**83-84**, 76-80%). Electron-donating groups (4-OMe) providing enhanced nucleophilicity gave 85% yield of the respective diaryl ether (**86**) whilst electron-withdrawing groups (4-NO_2, 4-CF_3) underwent C-O bond cleavage but no S_NAr (**87-88**, < 2%) as the phenols produced are weak nucleophiles. 2-Aryloxy-1-phenylethanol, having a 2-naphthol functionality, is a competent nucleophile giving 86% of the diaryl ether (**89**) whilst 1-naphthol gave no conversion (**90**, < 2%) since it is inadequate nucleophile both electronically and sterically.

2.5.3. One-pot diaryl synthesis from epoxide

Even though these alcohols are found in the backbone of lignocellulosic biomass, unfortunately, they are not commercially available, and require a two-step synthesis from commercially available 2-bromo-4'-fluoroacetophenone. An alternative to this would be carrying out the whole protocol from a commodity epoxide (**131**) which is commercially available form typical suppliers. The procedure was slightly modified from the isomerisation/S_NAr methodology, and Benjamin Reed-Berendt ultimately deciphered a two-step one-pot procedure whereby the phenol is added first in the present of K_2CO_3 (1.5 equiv.) and DMAC as solvent at 135 °C for 24 h to ring open the epoxide, followed by addition of $Ru(PPh_3)_3(CO)(H)_2$ (2.5 mol %) and xantphos (2.5 mol %) for a further 24 h under the same conditions leading to the formation of 4'-phenoxyacetophenone (**73**) in a moderate yield (59%).



131 **73**, 59%

Scheme 2.24: Ruthenium catalysed telescoped diaryl synthesis from epoxide

2.6. Conclusion

In conclusion, we have developed a general approach for the catalytic functionalisation of benzylic alcohols *via* electronic arene activation, accessing a diverse range of diaryl ethers and aryl amines in excellent isolated yields. We have developed three different methodologies, the first utilises the hydrogen transfer approach to select the oxidation level of the functionalised products *via* the addition of simple, inexpensive additives. The second

methodology is an application of the valorisation of lignocellulosic biomass whereby we have successfully isomerised 2-aryloxy-1-phenylethanols giving diaryl ethers in excellent yields. The last one employs isomerisation/S_NAr chemistry starting directly from a commodity epoxide.

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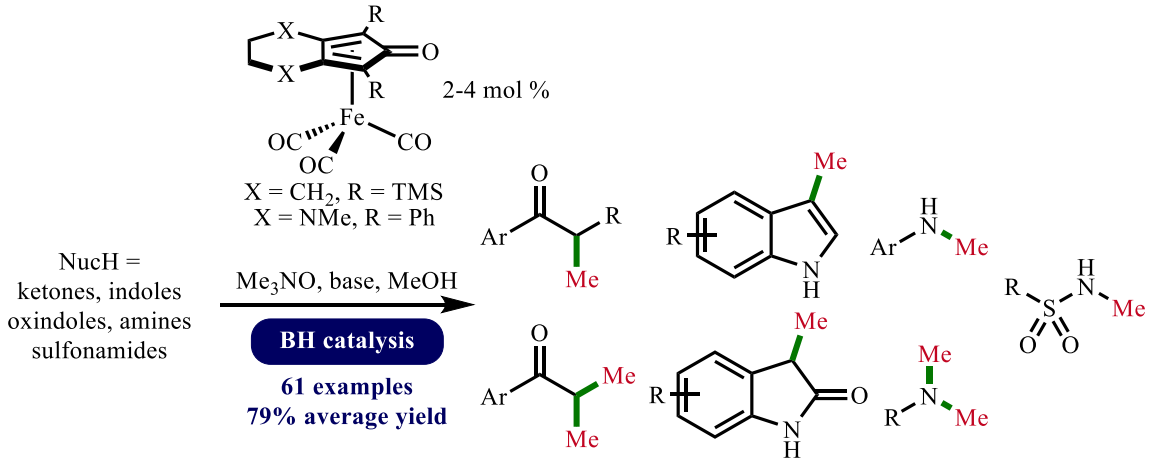
Chapter 3: Iron-catalysed methylation using the borrowing hydrogen approach

Table of contents

For the experimental section see chapter 8

3. Preface

This chapter discusses the development of a general iron-catalysed methylation using methanol as a C1 building block. This methodology has been developed *via* the borrowing hydrogen approach. It employs a Knölker-type (cyclopentadienone)iron carbonyl complex as precatalyst (2 mol %) and exhibits a broad reaction scope. A variety of ketones, indoles, oxindoles, amines, and sulfonamides undergo mono- or dimethylation in excellent isolated yields (61 examples, 79% average yield).



Publication: K. Polidano, B. D. W. Allen, J. M. J. Williams and L. C. Morrill, *ACS Catal.*, 2018, **8**, 6440–6445.

Acknowledgements

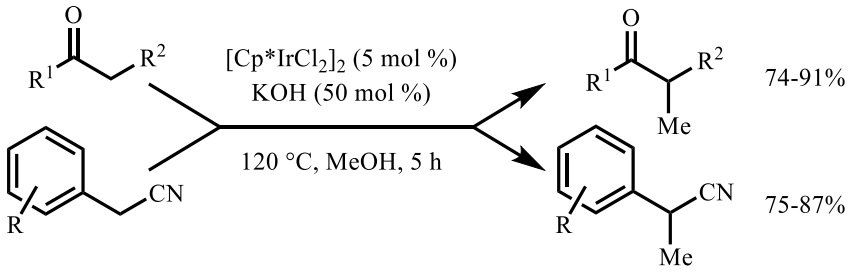
Benjamin. D. W. Allen – A post-doctorate research associate in the Morrill group who carried out the methylation of both primary and secondary amines.

Jonathan M. J. Williams – CDT co-supervisor, University of Bath.

Louis C. Morrill – Supervisor, Cardiff University.

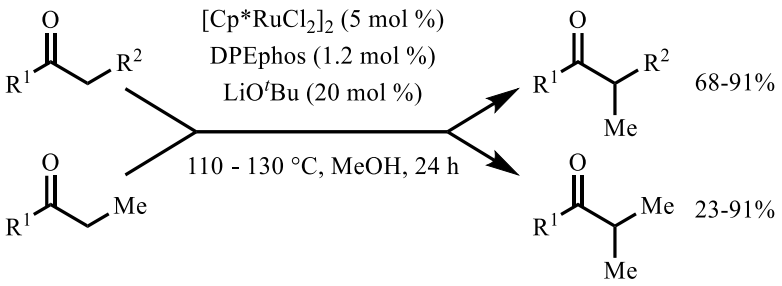
3.1. Introduction

Methylation is an essential transformation in synthetic chemistry that is commonly used for the synthesis of fine chemicals and pharmaceuticals.[1,2] The main drawback with conventional methylation procedures is that they commonly employ toxic and harmful methylating agents such as iodomethane and dimethyl sulphate.[3,4] Another drawback is that these traditional processes are not atom economic due to the release of high molecular weight leaving groups generating large amounts of toxic waste. During the last decade, methanol has become an attractive methylating agent as it is abundant and also biodegradable.[5] By utilising the borrowing hydrogen methodology together with methanol as the alkylating agent, methylation would become a highly atom economical process producing less waste, generating water as the sole by-product. When comparing benzyl and general *n*-alkyl alcohols, methanol is quite challenging to use for the BH methodology since the enthalpy of dehydrogenation is higher (ΔH (MeOH) = +84 kJ mol^{-1}) when compared to other alkyl alcohols such as ethanol (ΔH (EtOH) = +68 kJ mol^{-1}).[6] As stated in chapter 1, the first initial report for methylation using methanol was by Tonpenyai and co-workers back in 1981[7] where they successfully methylated aryl acetonitriles and aromatic amines using a rhodium catalytic system. Since then, a great number of reports have been published with respect to BH methylation. Some highlighted examples include the work by Obora and co-workers who employ the commercial $[Cp^*IrCl_2]_2$ for the methylation of acetophenone derivatives and benzyl cyanides (Scheme 3.1).[8] They also provide some examples of sequential alkylation-methylation using benzyl alcohols and methanol as alkylating agents.



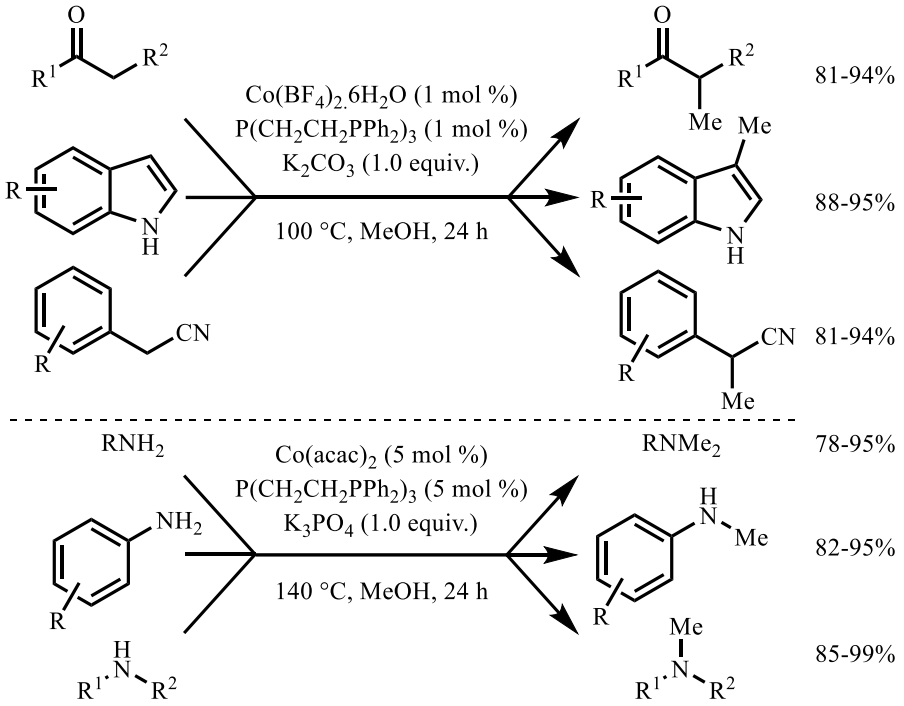
Scheme 3.1: Iridium-catalysed *C*-methylation of ketones and benzyl cyanides

In 2016, Seayad and co-workers reported a ruthenium-catalysed methylation of a range of acetophenones using methanol as solvent.[9] Interestingly, by temperature variation they also demonstrate some selective examples (mono vs dimethylation).



Scheme 3.2: Ruthenium-catalysed *C*-methylation of ketones

Prior to this project being published, Beller[10] and Sortais[11] reported the methylation of aromatic amines using manganese PNP pincer complexes. In Beller's work, several aromatic amines undergo *N*-methylation in good yields, some of which include the *N*-methylation of 4-aminostyrene and 4-aminostilbene without the reduction of the alkene moieties. Similarly, Liu and co-workers disclosed the cobalt-catalysed methylation of ketones, benzyl cyanides, indoles and amines in two separate publications,[12,13] as shown in Scheme 3.3.



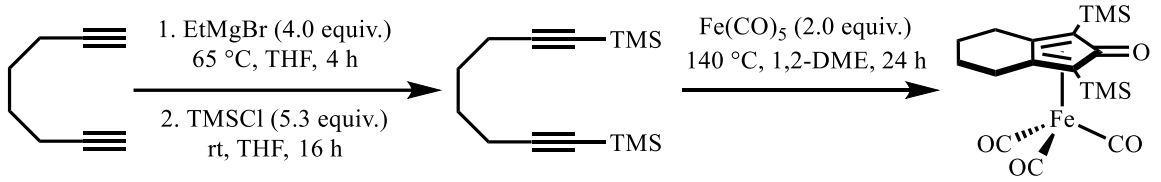
Scheme 3.3: Cobalt-catalysed methylation of ketones, indoles, nitriles and amines using methanol

Despite these reports, the use of iron catalysis in BH methylation remained an unsolved problem. Hence, we ventured to carry out methylation with methanol using iron catalysis, the most abundant transition metal in the earth's crust.

3.2. Results and discussion

3.2.1. Precatalyst synthesis and preliminary investigations

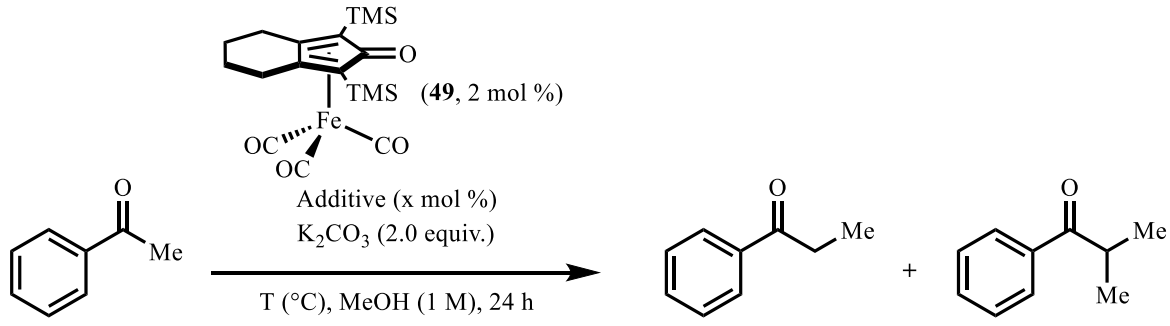
As stated in chapter 1, Darcel and co-workers[14] have successfully carried out the *C*-alkylation of ketones using alcohols involving a Knölker-type (cyclopentadienone)iron carbonyl complex as catalyst. In this publication they explicitly state that alkylation with equivalent amount of methanol does not occur. Despite this statement, iron-catalysed methylation was still pursued as it is a valuable transformation in synthesis. Initially the same general (cyclopentadienone)iron precatalyst (**49**) was screened using different conditions. This precatalyst was chosen for screening as it is a bench-stable organometallic complex which is easy to make on scale *via* two-step synthesis starting from a cheap starting material being 1,7-octadiyne. As shown in Scheme 3.4, 1,7-octadiyne (**132**) is treated with EtMgBr in THF followed by entrapment of the organolithium species with TMSCl to produce **133** in quantitative yield. After purification by distillation, this intermediate was heated in an ACE pressure tube with $Fe(CO)_5$ in 1,2-DME at 140 °C for 24 h, leading to the formation of **49** *via* a [2+2+2] cycloaddition reaction in good yield.[15]



132 **133,** 99% **49,** 66%

Scheme 3.4: Iron precatalyst synthesis

Following the synthesis of this precatalyst, the methylation of acetophenone (**134**) was investigated using solvent quantity methanol at different temperatures, K_2CO_3 (2.0 equiv.) as a base in a sealed microwave vial, as shown in Scheme 3.5. Table 3.1 shows the respective results for these investigative tests using 1,3,5-trimethylbenzene as an internal standard.



134 **135** **136**

Scheme 3.5: Preliminary investigations for acetophenone methylation

Table 3.1: Acetophenone methylation preliminary investigations

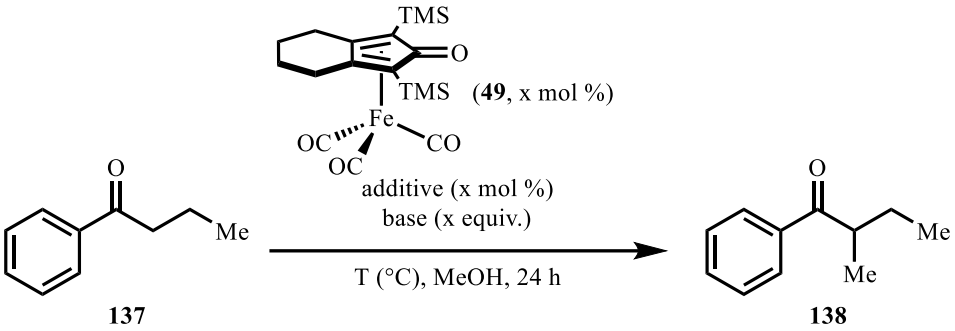
Entry[a]	Additive (mol %)	Temperature (°C)	134 (%)[b]	135 (%)[b]	136 (%)[b]
1	-	80	43	13	44
2	Me_3NO (4)	80	18	3	78
3	-	100	25	14	49
4	Me_3NO (4)	100	22	12	53
5	-	120	23	11	66
6	Me_3NO (4)	120	11	6	82

[a]Reactions performed using 1 mmol of ketone **134** and bench-grade MeOH [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

From these preliminary results, methylation in methanol does work giving both mono (**135**) and dimethylated (**136**) products. The presence of Me_3NO (entries 2, 4 and 6) as an additive is also beneficial for the transformation as it oxidises one of the CO ligands to CO_2, activating the catalyst, promoting the formation of **136** more easily. Following on from these trials, this transformation was further investigated through optimisation.

3.2.2. Optimisation of the iron-catalysed borrowing hydrogen methylation

We wanted to focus initially on monomethylation of ketones and thus the model substrate for optimisation was changed to *n*-butyrophenone (**137**), as illustrated in Scheme 3.6.



Scheme 3.6: Optimisation of the iron-catalysed methylation

All the optimisation experiments were carried out in a sealed microwave vial. Each vial containing a magnetic stirrer bar was charged with base (x mmol, x equiv.), additive (x mmol, x mol %) and [Fe] precatalyst **49** (x mg, x mmol, 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 was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL) and *n*-butyrophenone (**137**) (145 µL, 148 mg, 1.00 mmol). The mixture was left to react at a specified temperature for the specified time. This was then cooled followed by the addition of 1,3,5-trimethylbenzene (139 µL, 120 mg, 1.00 mmol), H_2O (2 mL) and EtOAc (2 mL). In some cases, brine (1 mL) was added to aid layer separation. The mixture was then stirred for 5 minutes, the vial cap opened and left to settle for a further 5 minutes. The

top layer was sampled and analysed by ^{1}H NMR spectroscopy. As shown in Figure 3.1, the reaction mixtures were analysed by comparing integrals of the terminal methyl groups of **137** and **138** with 1,3,5-trimethylbenzene as internal standard. Table 3.2 show the respective results from the optimisation.

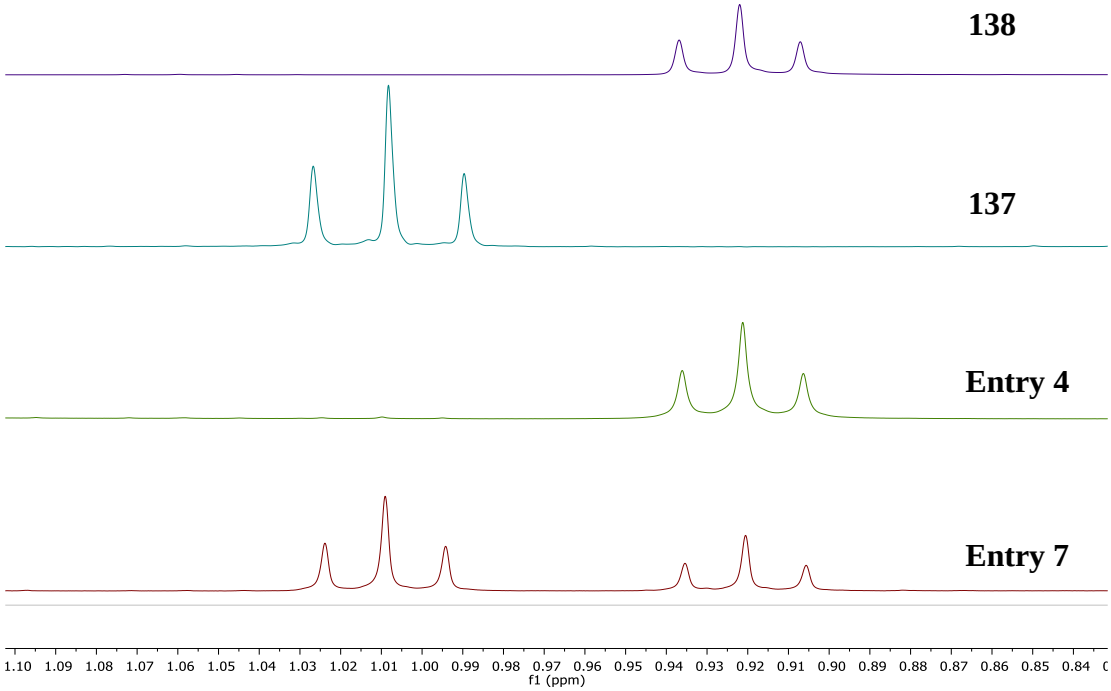


Figure 3.1: ^{1}H NMR (500 MHz, $CDCl_3$) spectra for the optimisation for the methylation of *n*-butyrophenone (**137**)

Table 3.2: Optimisation table for the methylation of *n*-butyrophenone

Entry[a]	Catalyst (mol %)	Additive (mol %)	Base (equiv.)	Solvent (Conc.)	T (°C)	137 (%)[b]	138 (%)[b]
1	-	-	K_2CO_3 (2)	MeOH (0.5 M)	80	98	< 2
2	49 (2)	-	K_2CO_3 (2)	MeOH (0.5 M)	80	44	55
3	49 (2)	Me_3NO (2)	K_2CO_3 (2)	MeOH (0.5 M)	80	7	92
4	**49 (2)**	**Me_3NO (4)**	**K_2CO_3 (2)**	**MeOH (0.5 M)**	**80**	**1**	**98 (88)**
5	49 (2)	Me_3NO (4)	K_2CO_3 (2)	**MeOH (1 M)**	80	3	93
6	49 (2)	Me_3NO (4)	K_2CO_3 (2)	**MeOH (0.2 M)**	80	1	94
7	49 (2)	**PPh_3 (4)**	K_2CO_3 (2)	MeOH (0.5 M)	80	59	37
8	49 (2)	Me_3NO (4)	K_2CO_3 (2)	MeOH (0.5 M)	**60**	7	88
9	49 (2)	Me_3NO (4)	K_2CO_3 (2)	MeOH (0.5 M)	**100**	1	94
10	49 (2)	Me_3NO (4)	**KOH** (2)	MeOH (0.5 M)	80	5	93
11	49 (2)	Me_3NO (4)	**NaOH** (2)	MeOH (0.5 M)	80	3	93
12	49 (2)	Me_3NO (4)	**KO^{t}Bu** (2)	MeOH (0.5 M)	80	1	91
13	49 (2)	Me_3NO (4)	**Cs_2CO_3** (2)	MeOH (0.5 M)	80	1	95
14	49 (2)	Me_3NO (4)	**LiO^{t}Bu** (2)	MeOH (0.5 M)	80	1	92
15	49 (2)	Me_3NO (4)	K_2CO_3 (**5**)	MeOH (0.5 M)	80	2	98
16	49 (2)	Me_3NO (4)	K_2CO_3 (**1**)	MeOH (0.5 M)	80	1	93
17	49 (2)	Me_3NO (4)	K_2CO_3 (**0.5**)	MeOH (0.5 M)	80	5	85
18	49 (2)	Me_3NO (4)	K_2CO_3 (**0.1**)	MeOH (0.5 M)	80	50	42
19	49 (**4**)	Me_3NO (4)	K_2CO_3 (2)	MeOH (0.5 M)	80	4	96
20	49 (**1**)	Me_3NO (4)	K_2CO_3 (2)	MeOH (0.5 M)	80	13	81
21	49 (2)	Me_3NO (4)	K_2CO_3 (2)	MeOH : PhMe (1:1) (0.5 M)	80	54	40

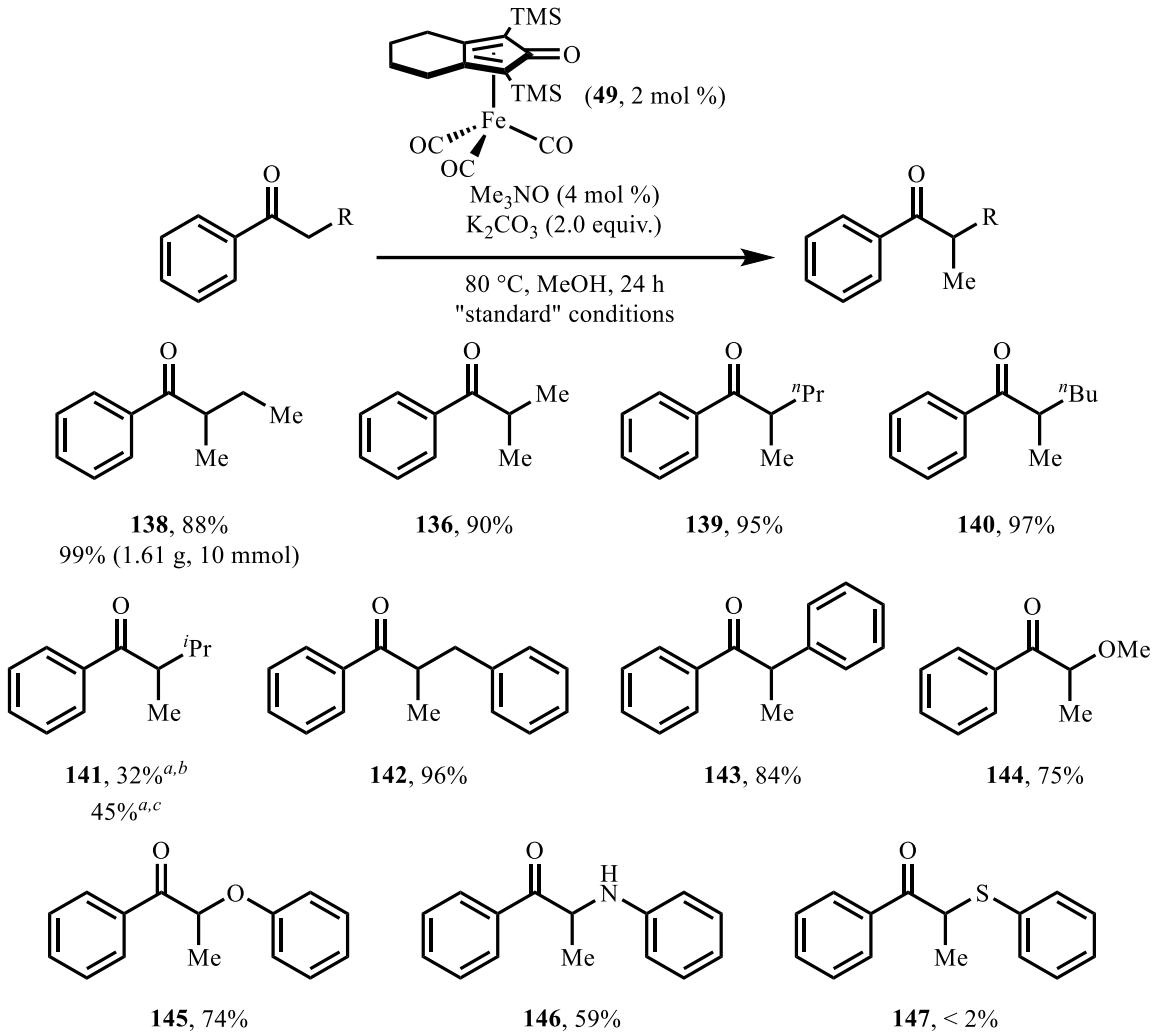
[a]Reactions performed using 1 mmol of ketone **137** and bench-grade MeOH. [**137**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

As shown in Table 3.2, a background for the reaction was immediately tested in the absence of catalyst (entry 1) using K_2CO_3 (2.0 equiv.), and this revealed complete starting material recovery after 24 h. In the presence of [Fe] precatalyst **49**, the reaction worked reasonably well giving 55% of **138** (entry 2). The addition of Me_3NO activator (2 mol %, entry 3) aided the transformation increasing the amount of **138** to 92%. Doubling the amount of activator (4 mol %, entry 4) with the same amount of K_2CO_3 (2.0 equiv.) increased the NMR yield of **138** to 98%, giving the optimal result, isolated to 88%. At double and half the concentration, the conversion was slightly less (entries 5-6), and substituting Me_3NO to PPh_3 (4 mol %, entry 7) resulted in a significant loss of conversion of **137** to **138**. PPh_3 has been reported to be a good additive for CO decoordination with respect to using other alcohols[16] as alkylating agents but clearly there is no synergic effect with MeOH. A higher and lower reaction temperature resulted in a lower NMR yield of **138** (entry 8-9). Employing Cs_2CO_3, hydroxide and alkoxide bases (entries 10-14) resulted in slightly lower conversions to **138**. 5.0 equiv. of K_2CO_3 gave the same NMR yield of **138** (entry 15) and thus we decided to persist with 2.0 equiv. of base. Utilising sub-stoichiometric and catalytic amounts of K_2CO_3 was considerably worse (entries 16-18), whilst doubling and halving the catalyst loading was lower than the optimal result of this transformation (entries 19-20). Finally, we wanted to demonstrate the effect of MeOH as solvent. In the presence of a 1:1 mixture of MeOH/PhMe, this solvent system was detrimental giving a 40% NMR yield of **138**, and hence this showed that the reaction only works well in MeOH. The reason for this is that the oxidation of MeOH is quite hard to carry out when compared to benzyl and other alkyl alcohols, since the enthalpy of dehydrogenation of MeOH is much higher. The equilibrium between MeOH and formaldehyde is shifted towards MeOH and thus an excess quantity of MeOH is required for significant dehydrogenation to form formaldehyde and subsequent alkylation.

3.2.3. Substrate scope

3.2.3.1. Monomethylation of ketones

After successful optimisation, substrate scope followed. Initially the scalability of this process was demonstrated, by carrying out the same transformation on a 10 mmol scale. This reaction was carried out in an ACE pressure tube leading to the formation of **138** in 99% yield.

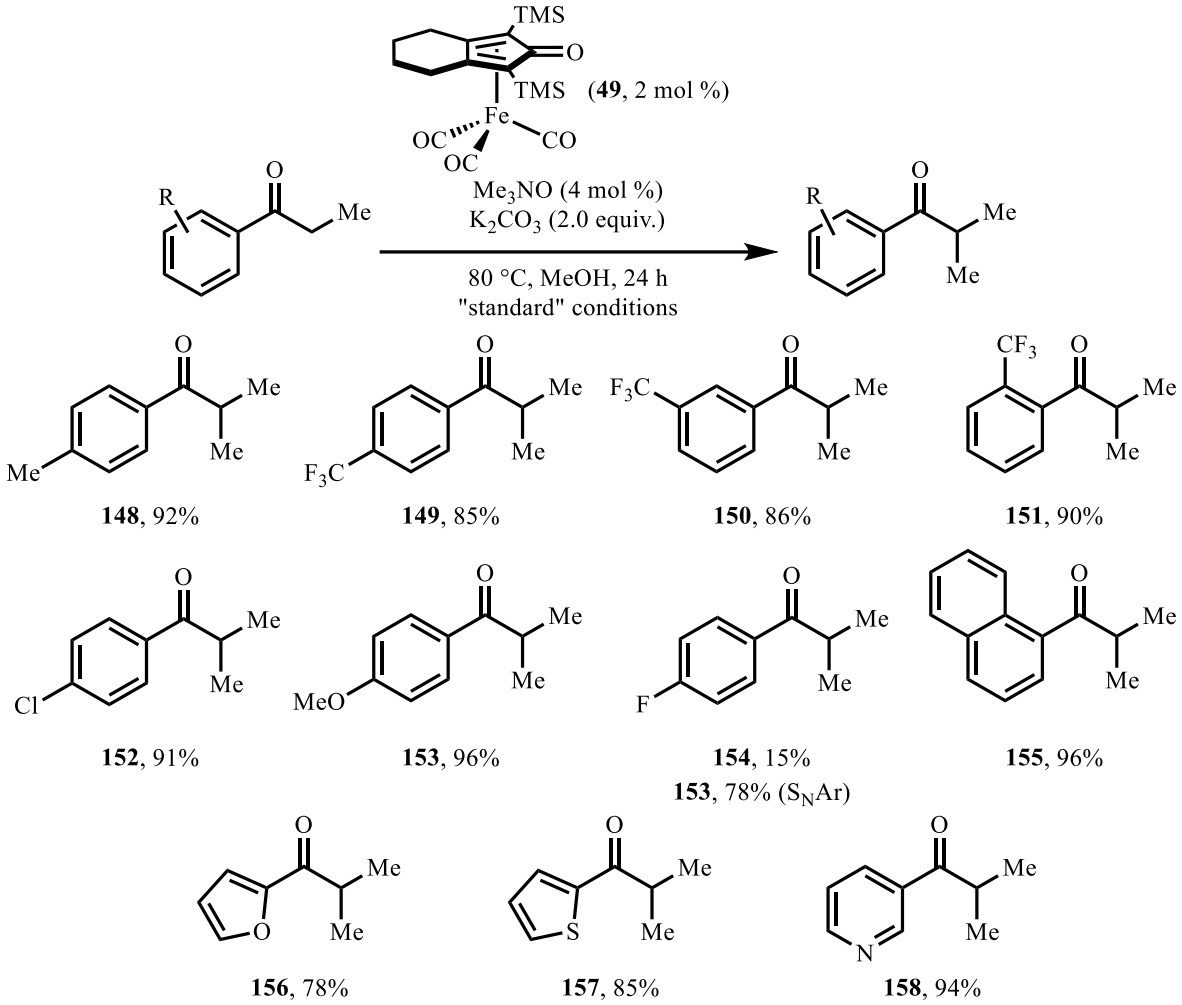


Scheme 3.7: Ketone scope – substituent variation at *α*-position

[a] ^{1}H NMR yield using 1,3,5-trimethylbenzene as internal standard, [b]Standard conditions. [c]72 h.

Within the methodology, acetophenone derivatives bearing *α*-alkyl functional group (R = Et, Me, ^{n}Pr, ^{n}Bu, Bn) all worked extremely well giving excellent yields of the corresponding *α*-methylated ketones (**136**, **138**, **139**, **140**, **142**, 88-97%). Unfortunately, when isovalerophenone was used as the starting material (R = ^{i}Pr), methylation was inefficient giving a 32% NMR yield of **141** using the standard conditions, and a 45% NMR yield when left running for 72 h. The presence of this terminal isopropyl group sterically encumbers any efficient methylation from taking place. When incorporating an *α*-phenyl and an *α*-heteroatom in the acetophenone derivative (R = Ph, OMe, OPh, NHPh), the methylation worked moderately well (**143**-**146**, 59-84%), since these groups provide some electron rich character making the corresponding substrates harder to deprotonate. Compound **146** resulted in a low yield as this resulted in hydrogenolysis of the C-N bond forming acetophenone and aniline which were both methylated as observed from the ^{1}H NMR spectrum of the crude mixture. When a thiophenoxy substituent (R = SPh) was present at the

α position, no product was formed (**147**, < 2%) presumably due to hydrogenolysis of the C-S bond forming thiophenol which is probably a catalyst poison preventing any catalysis from taking place. Thiophenol has been reported as a reagent for cross-coupling reactions,[17] however, iron catalysis incorporating Knölker type catalysts with thiophenol is still undiscovered, hence increasing the likelihood that these class of reagents poison the catalyst. Further ketone scope involved investigating the effect of substituents within the aryl unit (Scheme 3.8).



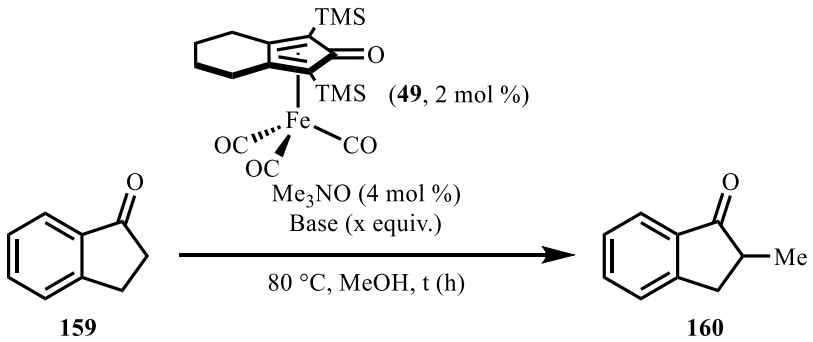
Scheme 3.8: Ketone scope - substituent variation within the aryl unit

Using the standard conditions, 4-Me is tolerated well giving 92% of the methylated product (**148**). Sterically encumbered groups were tolerated with negligible loss of reactivity giving excellent yields for 4-CF_3, 3-CF_3 and 2-CF_3 isobutyrophenones respectively (**149-151**, 85-90%). The presence of trifluoromethyl groups also aids the transformation to proceed more efficiently as the pK_a of the starting propiophenone is lowered making the starting material more acidic. Halide (4-Cl, **152**) and electron-donating groups (4-OMe, **153**) gave exceptional yields whilst when a 4-fluoro functional group was present within the aryl unit, this resulted in a methylation-S_NAr reaction giving 15% of **154** and 78% of **153**. Hindered

external aromatic systems (1-naphthyl) worked exceptionally well giving 96% of the methylated product (**155**) together with the toleration of heteroaryl functionalities such as 2-furanyl, 2-thiophenyl and 3-pyridyl ketones (**156-158**, 78-94%).

3.2.3.2. Methylation of cyclic ketones

When cyclic ketones such as 1-indanone (**159**) were subjected to the standard conditions, the NMR yield of the methylated product was quite low (**160**, 42%). The problem is that these ketones are much harder to deprotonate when compared to general acetophenone derivatives. With propiophenone for example, the bond can rotate to be in an anti-periplanar geometry relative to the carbonyl functional group thus facilitating easy deprotonation. In this case the cyclic ketone has restricted rotation and we anticipated a stronger base would be required for efficient deprotonation to form the respective enolate. With this in mind, a number of reactions were carried out with different bases to re-optimise the methylation of cyclic ketones using 1-indanone (**159**) as the model substrate.



Scheme 3.9: Methylation re-optimisation for 1-indanone

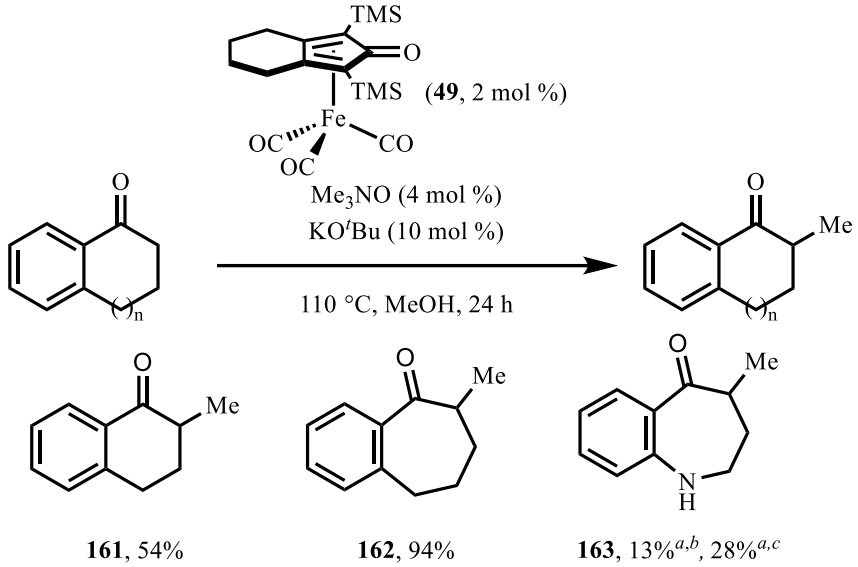
Table 3.3: Methylation re-optimisation table for cyclic ketones

Entry[a]	Base (equiv.)	Time (h)	160 (%)[b]
1	K_2CO_3 (2)	24	42
2	KO^{t}Bu (0.1)	24	**74 (66)**
3	LiO^{t}Bu (2)	24	42
4	K_2CO_3 (2)	72	63

[a]Reactions performed using 1 mmol of ketone **159** and bench-grade MeOH. [**159**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

As shown in Table 3.3, when employing KO^{t}Bu (2.0 equiv.) as base, this gave a complex mixture of products in the crude mixture, whilst when reducing base loading to 10 mol % (entry 2) this aided the methylation leading to a 74% NMR yield of **160**, which was successfully isolated to a 66% yield. LiO^{t}Bu was a worse base for the methylation (entry 3) and when applying the standard conditions for a longer period of time (72 h, entry 4) this still gave less conversion to the product when compared to 10 mol % of KO^{t}Bu. These

optimal conditions were repeated at 110 °C to see if it will go to completion but it gave the same NMR yield as entry 2. These conditions (entry 2) were then applied to the methylation of other cyclic ketones such as 1-tetralone and 1-benzosuberone.



161, 54% **162**, 94% **163**, 13%[a,b], 28%[a,c]

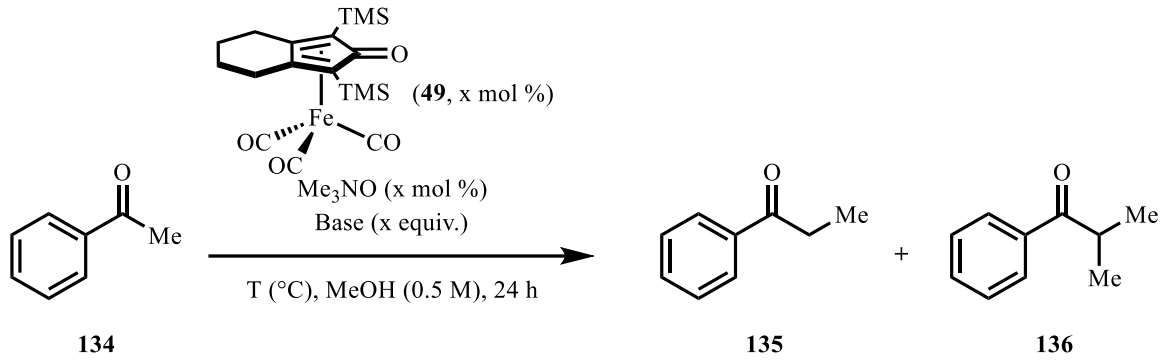
Scheme 3.10: Methylation of cyclic ketones

[a] ^{1}H NMR yield using 1,3,5-trimethylbenzene as internal standard, [b] 80 °C, [c] 110 °C.

Unfortunately, they gave low NMR yields at 80 °C, but when the temperature was increased to 110 °C, **161** and **162** were isolated to 54 and 94 % respectively. When 1,2,3,4-tetrahydro-5*H*-benzo[b]azepin-5-one was tested for methylation, this gave a 13% NMR yield at 80 °C and 28% NMR yield at 110 °C for **163**. From these results, it was very difficult to force this reaction to obtain a synthetically useful yield and therefore it was no longer pursued. Since general methylation seems to work with 2.0 equiv. of K_2CO_3 (**standard conditions**) and 10 mol % of KO^{t}Bu (**alternate conditions**), from this point forward, reactions were carried out in duplicate with both sets of conditions.

3.2.3.3. Dimethylation of ketones

Since we have successfully carried out mono-methylation of propiophenones, the next stage was to try to force dimethylation of acetophenones to work. By taking acetophenone (**134**, Scheme 3.11) as the model substrate, several different conditions were screened to see if dimethylation could be re-optimised. Table 3.4 shows all the corresponding results.



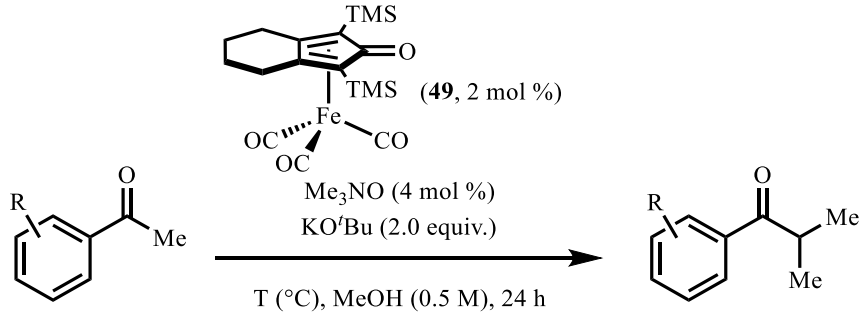
Scheme 3.11: Optimisation of the dimethylation of acetophenone

Table 3.4: Optimisation table for the dimethylation of acetophenone

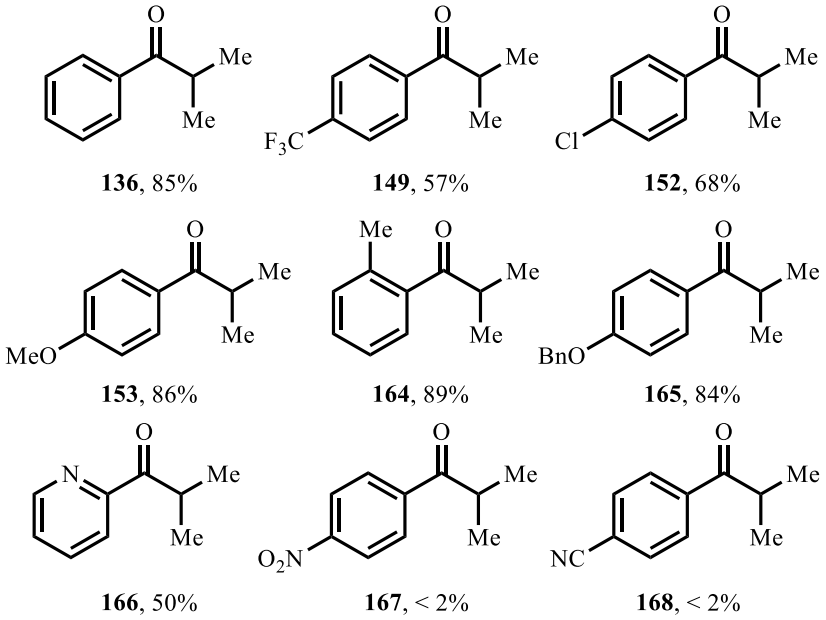
Entry[a]	47 (loading)	Me_3NO (loading)	Base (equiv.)	T (°C)	134[b] (%)	135[b] (%)	136[b] (%)
1	2	4	**K_2CO_3 (2)**	80	18	3	75
2	2	4	**KO^{t}Bu (0.1)**	80	33	12	55
3	2	4	**KO^{t}Bu (2)**	80	-	-	**99** (**85**)
4	2	4	**K_2CO_3 (3)**	80	15	5	80
5	**4**	**8**	K_2CO_3 (2)	80	15	6	73
6	2	4	K_2CO_3 (2)	**100**	16	4	77

[a]Reactions performed using 1 mmol of ketone **134** and bench-grade MeOH. [**134**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

Using the standard conditions (entry 1), dimethylation does not go to full conversion to **136**. The alternate conditions (entry 2) are also significantly worse giving only 55% of **136**. When 2.0 equiv. of KO^{t}Bu was employed, the dimethylation reaction went to completion giving a 99% NMR yield of **136**, isolated to an 85% yield. Increasing the number of equivalents of K_2CO_3, catalyst loading and temperature (entries 4-6) still resulted in incomplete dimethylation when compared to the conditions stated in entry 3. From all these results, the problem is the mono-methylation step. The problem is that the first deprotonation forms the least stable enolate and thus is even more reversible. With a stronger base, this process is even faster promoting the addition to formaldehyde to occur more efficiently. The scope for dimethylation was demonstrated to work for some examples of aryl substituted acetophenones as shown in Scheme 3.12.



Scheme 3.12: Dimethylation of acetophenones



136, 85% **149**, 57% **152**, 68%

153, 86% **164**, 89% **165**, 84%

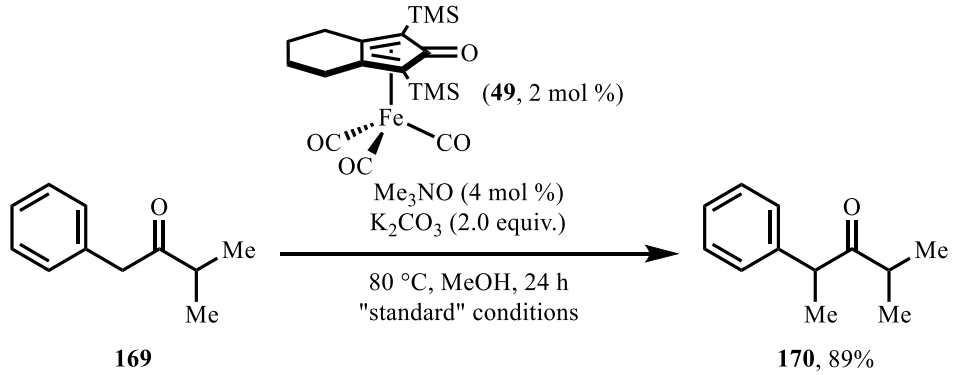
166, 50% **167**, < 2% **168**, < 2%

Figure 3.2: Dimethylation of acetophenones

With the aryl unit, electron withdrawing groups such as 4-CF_3 were tolerated obtaining a synthetically useful yield (**149**, 57%). 4-Cl, 4-OMe and 2-Me were all tolerated obtaining good overall yields of the respective isobutyrophenones (**152**, **153**, **164**, 68-89%). The formation of **165** with a yield of 84% demonstrated successful functional group tolerance bearing in mind the possibility of reduction of the benzyl group, which in this case did not occur. Finally, 2-acetylpyridine successfully underwent methylation obtaining a synthetically useful yield (**166**, 50%). 4-cyano and 4-nitroacetophenone were incompatible with this methodology as an extremely complex mixture was observed in the ^{1}H NMR spectrum of the crude mixture which could not be interpreted.

3.2.3.4. Mono vs dimethylation

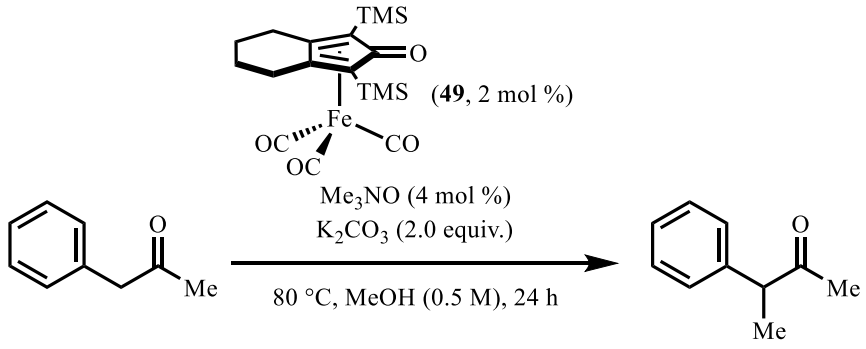
After successfully demonstrating mono-methylation and dimethylation independently, selective mono- and dimethylation was then investigated, by varying the conditions. Prior to these investigations, we tested 3-methyl-1-phenyl-2-butanone (**169**) for methylation. Using the standard conditions, this substrate successfully underwent methylation at the benzylic position.



169 **170**, 89%

Scheme 3.13: Methylation of 3-methyl-1-phenyl-2-butanone

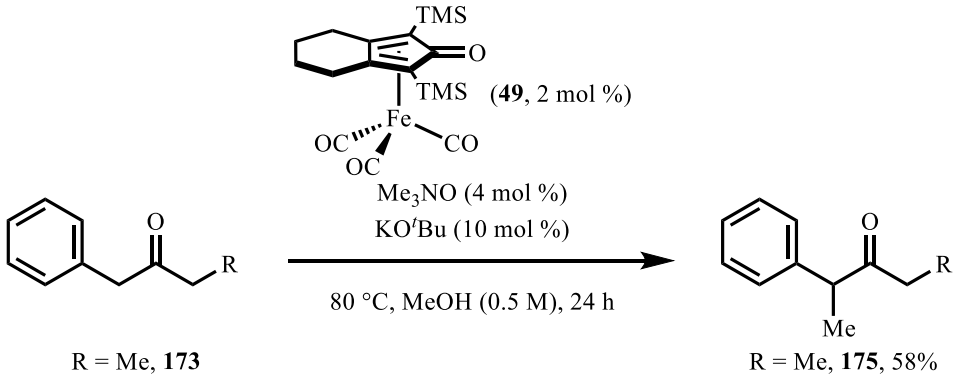
The selectivity trials commenced by choosing phenylacetone (**171**) as our model substrate. Using the standard conditions, phenylacetone undergoes mono-methylation (Scheme 3.14) at the most acidic position (benzylic position) giving a synthetically useful yield (**172**, 50%).



171 **172**, 50%

Scheme 3.14: Methylation of phenylacetone

From this result, it was anticipated that increasing temperature (110 °C) or changing base (KO^{t}Bu) would result in the formation of the dimethylated or trimethylated product, but unfortunately, using these conditions, the crude revealed a complex mixture of mono, di and trimethylated products which could not be isolated independently.



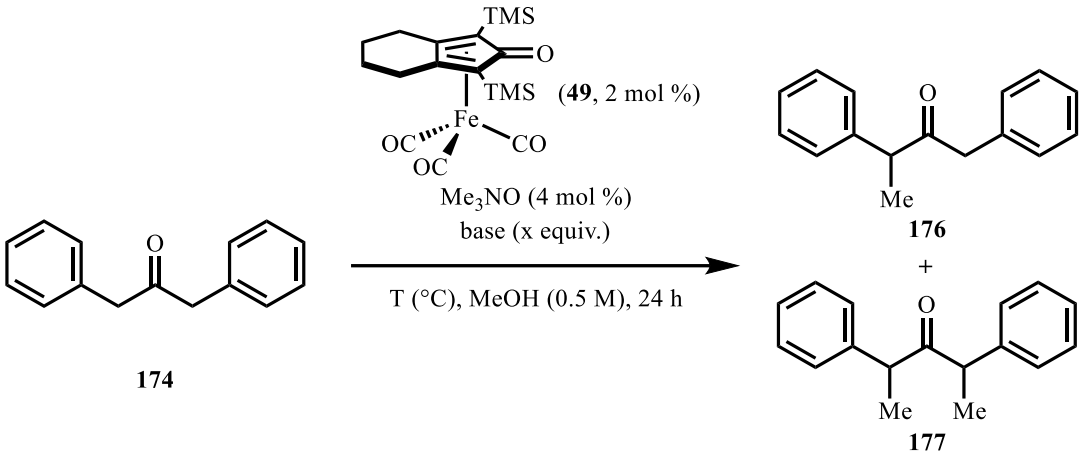
R = Me, **173**
R = Ph, **174**

R = Me, **175**, 58%
R = Ph, **176**, 57%

Scheme 3.15: Monomethylation of ketones

1-Phenyl-2-butanone (**173**) was then tested for selective mono-methylation. Using the standard conditions, a 71% NMR yield of **175** was obtained, whilst using the alternate conditions (10 mol % KO^{t}Bu), a 78% NMR yield of **175** was obtained, which was

successfully isolated in 58% yield. The remainder of the material in both cases was a mixture of **173** and **170**. Unfortunately, selective dimethylation could not be achieved under harsher conditions. Finally, we also attempted 1,3-diphenylacetone as the substrate. Mono-methylation was successful using 10 mol % KO^{t}Bu (**176**, 57%). Using different conditions, stated in Table 3.5, we couldn't force the reaction towards selective dimethylation. Any temperature higher than 130 °C resulted in loss of MeOH from the reaction vessel.



Scheme 3.16: Optimisation for dimethylation of 1,3-diphenylacetone

Table 3.5: Optimisation table for the dimethylation of 1,3-diphenylacetone

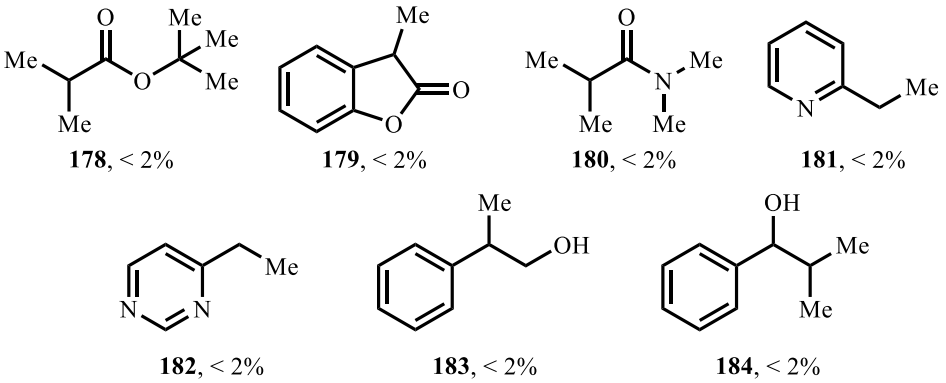
Entry[a]	Base (equiv.)	Temperature (°C)	174 (%)[b]	176 (%)[b]	177 (%)[b]
1	K_2CO_3 (2)	110	55	27	14
2	KO^{t}Bu (0.1)	110	30	**66 (57)**	-
3	K_2CO_3 (2)	130	23	51	10
4	KO^{t}Bu (0.1)	130	30	63	-

[a]Reactions performed using 1 mmol of ketone **174** and bench-grade MeOH. [**174**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

3.2.3.5. *α*-Methylation of esters, un-activated amides, methyl *N*-heteroaromatics and alcohols

We wanted to expand our methodology to see if methylation could be carried out on other classes of substrates. We started with the methylation of esters. Substrates that were tested were *tert*-butyl propionate and 2(3*H*)-benzofuranone. Unfortunately, in both cases, using the standard and alternate conditions, no starting materials and product peaks (**178**-**179**, < 2%) were present in the ^{1}H NMR spectrum of the crude reaction mixture, probably due to substrate decomposition. From this result, this class of substrate was not pursued any longer. We also investigated un-activated amides such as *N*,*N*-dimethylpropionamide. When we employed both the standard and alternate conditions independently, the crude result showed 33% of starting amide remaining with no trace of product formation (**180**, < 2%). The

methylation of methyl *N*-heteroaromatics[18] was unsuccessful when using 2-picoline and 4-methylpyrimidine as substrates (**181-182**, < 2%).



178, < 2% **179**, < 2% **180**, < 2% **181**, < 2%

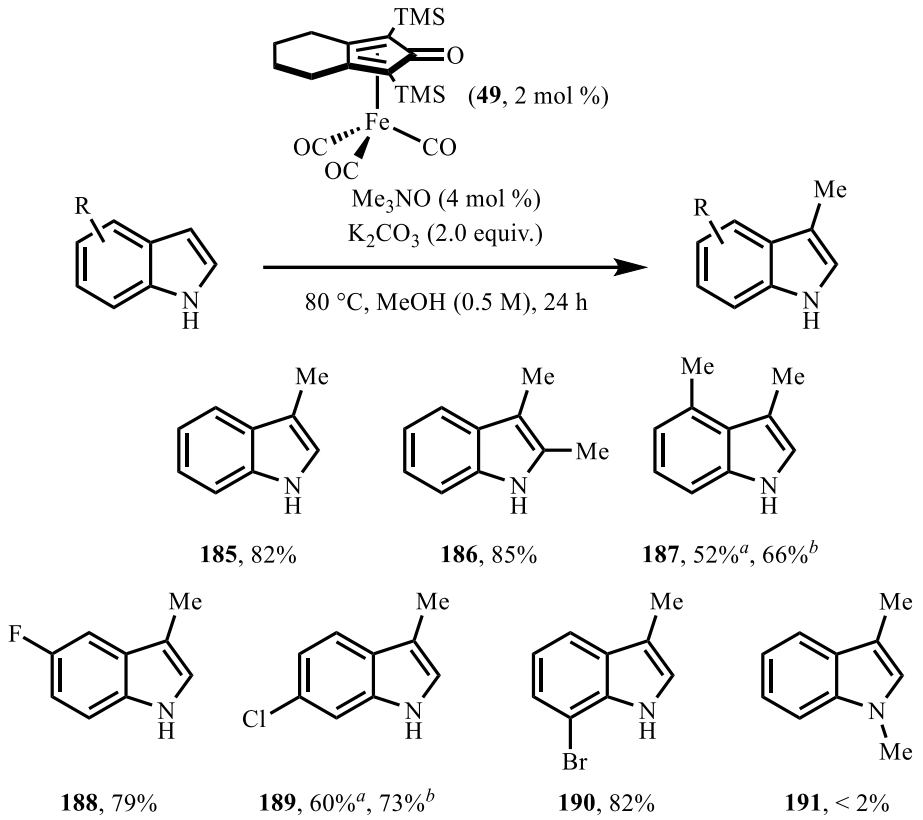
182, < 2% **183**, < 2% **184**, < 2%

Scheme 3.17: Unsuccessful methylation examples

A plausible explanation for complete substrate unreactivity here is that the pK_a of the α-proton is too high making it harder to deprotonate. Beta-methylation of alcohols is known with precious metals,[19,20] and both primary and secondary alcohols were also tested using this methodology. When 1-phenylethanol and 2-phenylethanol were used as substrates, the ^{1}H NMR spectrum of the crude reaction mixture revealed near complete starting material recovery with no trace of product formation (**183-184**, < 2%), which is likely due to no dehydrogenation taking place.

3.2.3.6. Indole and oxindole *C*(3)-methylation

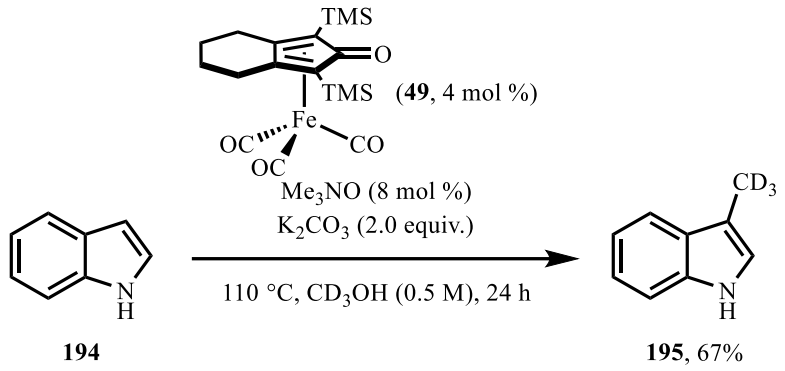
We sought to investigate other possible nucleophiles for iron-catalysed methylation. Heterocycles were of interest to us and hence, indoles were tested for this methodology. Iron-catalysed borrowing hydrogen alkylation of indoles has been widely explored,[21,22] all occurring at the *C*(3) position. When we reacted indole using the standard conditions, a 90% NMR yield of 3-methylindole (**185**) was obtained which was successfully isolated to an 82% yield. Using the alternate conditions (10 mol % KO^{t}Bu), a 57% NMR yield was obtained with starting material remaining. From these results, we decided to investigate the scope by testing various indoles having different substituents at each position in the heterocycle using the standard conditions (Scheme 3.18).



Scheme 3.18: *C*(3) methylation of indoles

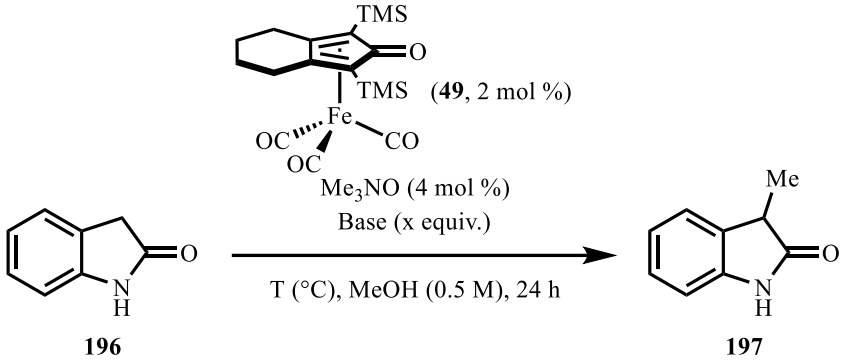
[a]Standard conditions. [b]48 h.

Using the standard conditions, 2-Me, 4-F and 7-Br indoles worked well obtaining excellent yields of the respective 3-methylindole (**186**, **188**, **190**, 79-85%). 4-Methylindole is a weaker nucleophile due to steric clashes with the adjacent methyl group and thus required 48 h for a good yield to be obtained (**187**, 66%). Similarly, 6-chloroindole is an electronically weak nucleophile and required doubling the reaction time (**189**, 73%). As shown for the borrowing hydrogen alkylation cycle of indoles,[21] the *N*-H proton must be present for the transformation to proceed. To confirm this hypothesis, *N*-methylindole was reacted under our standard conditions. This gave complete recovery of starting material with no product formation (**191**, < 2%) clearly justifying that the indole methylation is proceeding *via* a borrowing hydrogen mechanism. Through this methodology we envisioned synthesising a compound which can be utilised in the studies of metabolism kinetics.[23] This compound was d_3-skatole (**193**). This transformation was carried out in CD_3OD using indole (**194**) as the nucleophile.



Scheme 3.19: Synthesis of d^3-skatole

This process did not work well using the same conditions giving only a 53% NMR yield of the product, but when the catalyst loading was doubled, and the temperature was increased to 110 °C, this gave an 80% NMR yield of **195** isolated to a 67% yield. Oxindoles have also been reported for *C*(3)-alkylation and thus, we envisioned applicability of this methodology to methylate oxindoles at the most acidic position, the *C*(3) position. Using the standard conditions, only a 45% NMR yield of 3-methyl-2-oxindole (**197**) was obtained and hence this process was re-optimised by variation of bases and temperatures as shown in Table 3.6.



Scheme 3.20: *C*(3)-alkylation of oxindole re-optimisation

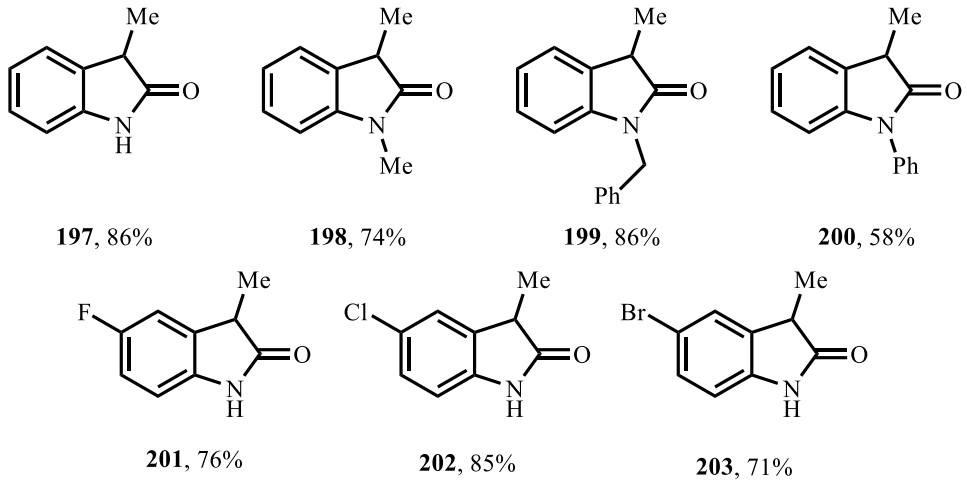
Table 3.6: Re-optimisation table for the *C*(3)-alkylation of oxindoles

Entry[a]	Base (equiv.)	Temperature (°C)	197 (%)[b]
1	K_2CO_3 (2)	80	45
2	KO^{t}Bu (0.1)	80	30
3	KO^{t}Bu (2)	80	32
4	K_2CO_3 (2)	110	**93 (86)**
5	KO^{t}Bu (0.1)	110	69
6	KO^{t}Bu (2)	110	78

[a]Reactions performed using 1 mmol of oxindole **196** and bench-grade MeOH. [**196**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

Changing the base to 10 mol % KO^{t}Bu (entry 2) and 2.0 equiv. of KO^{t}Bu (entry 3) was detrimental giving 30 and 32% NMR yields respectively, whilst increasing the temperature to 110 °C using the standard conditions gave the optimal result which was a 93% NMR yield isolated to 86% (entry 4). When trying 10 mol % KO^{t}Bu and 2.0 equiv. of KO^{t}Bu at 110 °C

(entries 5-6), the NMR yields were low compared to that of the conditions stated in entry 4. With low NMR yields, it was noticed that no oxindole (**196**) was present which was probably due to substrate decomposition. With the oxindole *C*(3)-methylation re-optimisation complete, the scope was investigated by testing the methodology for various substituted oxindoles at position *N*(1) and *C*(5), as displayed in Figure 3.3.



197, 86% **198**, 74% **199**, 86% **200**, 58%

201, 76% **202**, 85% **203**, 71%

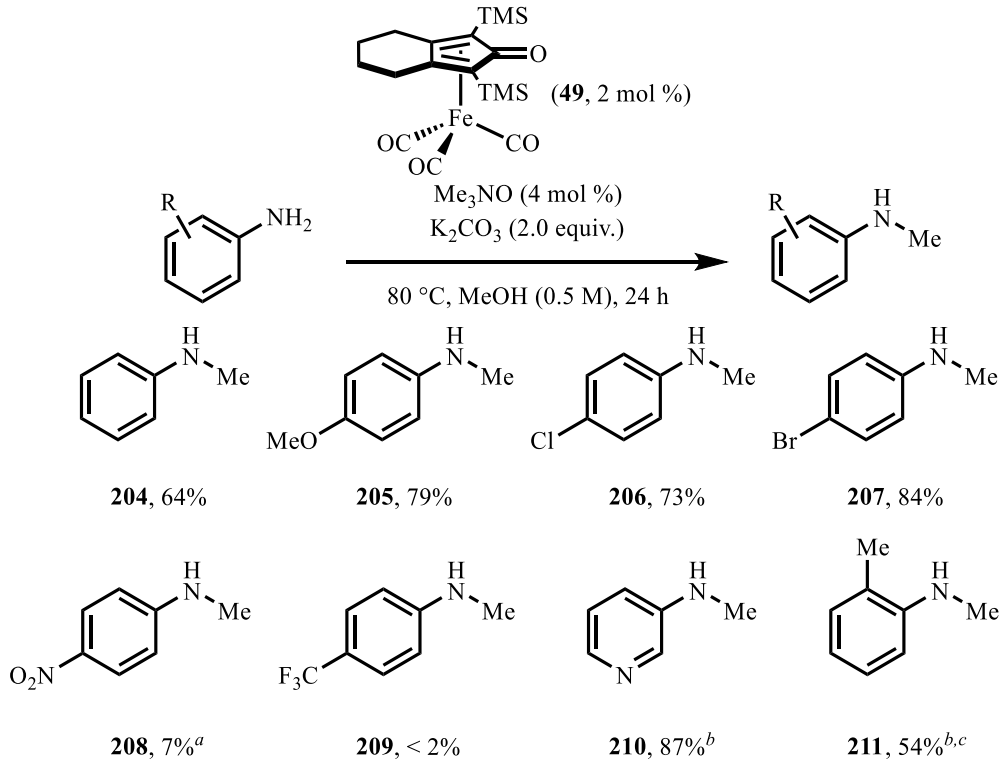
Figure 3.3: *C*(3)-methylation of oxindoles

N-Methyl (**198**) and *N*-benzyl (**199**) substituents worked really well giving 74 and 86% of the *C*(3)-methylated product respectively. The *N*-phenyl substrate gave 58% (**200**) with no starting material remaining probably due to starting material decomposition. 5-F, 5-Cl and 5-Br were successfully tolerated for *C*(3)-methylation giving excellent yields of the corresponding products (**201**-**203**, 71-85%).

3.2.3.7. *N*-monomethylation of aryl amines

As already stated in chapter 1, *N*-alkylation has already been explored using iron catalysts. In the publications reported Feringa and Barta, they have successfully reported the *N*-alkylation of aryl amines using alkyl alcohols[24] and the *N*-alkylation of primary and secondary amines using benzyl alcohols.[25] Compared to the *C*-alkylation of ketones, no base is required for this transformation as the amine condenses easily with the intermediate forming an imine species which is readily reduced to the corresponding amine. Using our developed methodology, we wanted to explore the iron-catalysed *N*-methylation of amines. This part of this chapter was exclusively carried out by Benjamin Allen, a PDRA in the group, who provided support on the project. Aniline was used as the model substrate. By incorporating the standard methylation conditions in the absence of base, no product formation was observed with complete starting material recovery, as observed from the ^{1}H

NMR spectrum of the crude mixture after 24 h. However, in the presence of base, aniline was completely converted into the product giving a 90% NMR yield of **204**, isolated in 64% yield. From these results, it was clear that base is required for methanol dehydrogenation since it is much harder to dehydrogenate methanol compared to benzyl alcohols. Since this transformation worked well using the standard conditions, Benjamin Allen moved to substrate scope, by testing various substituted anilines, as shown in Scheme 3.21.



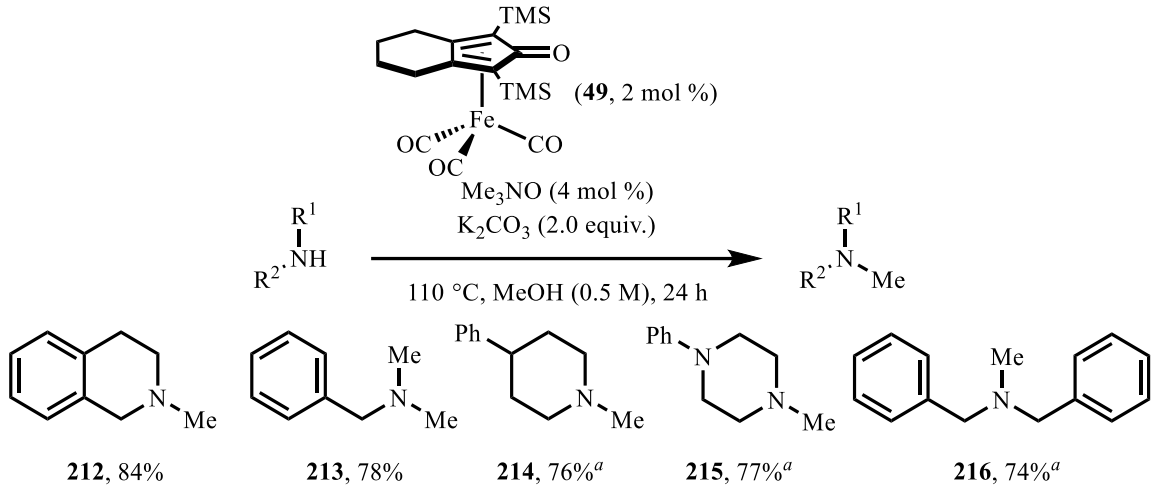
Scheme 3.21: *N*-methylation of aryl amines

[a]NMR yield, [b]110 °C, [c]96 h

Electron-donating and halo-substituted groups such as 4-MeO, 4-Cl and 4-Br all worked well with no significant loss of reactivity (**205-207**, 73-84%). Electron-poor anilines such as 4-nitroaniline, using the standard conditions, only gave 7% conversion to **208** while 4-(trifluorophenyl)aniline gave a complex mixture of products which could not be interpreted. Both substrates were no longer tested. 3-Aminopyridine, on the other hand, worked but required higher temperature (110 °C) for complete conversion since it is a weak nucleophile due to the inductive effect of the pyridyl nitrogen, giving an 87% yield of the respective methylated product (**210**). *O*-Toluidine, being a sterically hindered nucleophile, was initially tested using the standard conditions at 110 °C, giving only a 57% NMR yield. After 96 h of reactivity, a 66% NMR yield of **211** was obtained, successfully isolated to 54%. After having successfully demonstrated the methodology for the *N*-methylation of anilines, Benjamin Allen tested the *N*-methylation of aliphatic secondary amines in Scheme 3.22.

3.2.3.8. *N*-methylation of aliphatic secondary amines

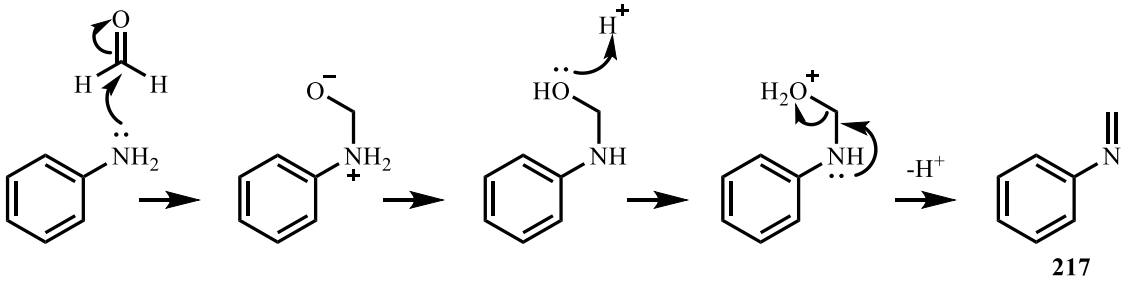
Benjamin Allen started with 1,2,3,4-tetrahydroisoquinoline, and this only gave 29% of the expected product using the standard conditions. Since starting material remained in the mixture, this was repeated at 110 °C giving 100% conversion to product (**212**) which was successfully isolated to an 84% yield. Similar to the *N*-methylation of aryl amines, base is also required for this transformation as in the absence of base, 100% staring material was retained as observed from ^{1}H NMR spectrum of the crude reaction mixture, confirming our hypothesis for methanol dehydrogenation.



Scheme 3.22: N-methylation of secondary amines

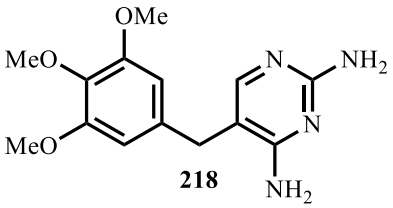
[a] **49** (4 mol %), Me_3NO (8 mol %)

At 110 °C, *N*-benzylmethylamine also worked well giving 78% of **213**. Unfortunately, when employing these re-optimised conditions, the *N*-methylation of 4-phenylpiperidine, 4-phenylpiperazine and dibenzylamine only gave 57, 57 and 66% NMR yields respectively; but when the catalyst loading and activator were doubled for these substrates, at 110 °C, the respective products were isolated to 76, 77 and 74% respectively (**214-216**). When aliphatic primary amines were subjected to these conditions in order to undergo dimethylation, in all cases, cyclohexylamine, *n*-hexylamine and benzylamine did not show any sign of product formation with starting material being recovered in all cases.



Scheme 3.23: Condensation of aniline with formaldehyde

As illustrated in Scheme 3.23, when anilines condense with formaldehyde, this results in the formation of an imine species (**217**) which is stabilised by conjugation of the aromatic ring. With primary aliphatic amines, this cannot occur and thus the alkylation is even more reversible making the process hard to push forward. Secondary amines, on the other hand, are nucleophilic enough that the condensation is faster and thus more iminium species is present in the mixture which can be reduced more easily. After obtaining these successful results, we wanted to test the applicability of this methodology towards active pharmaceutical ingredients. One API that caught our eye was trimethoprim (**218**) since it bears several NH_2 groups which all could be potentially methylated.



218

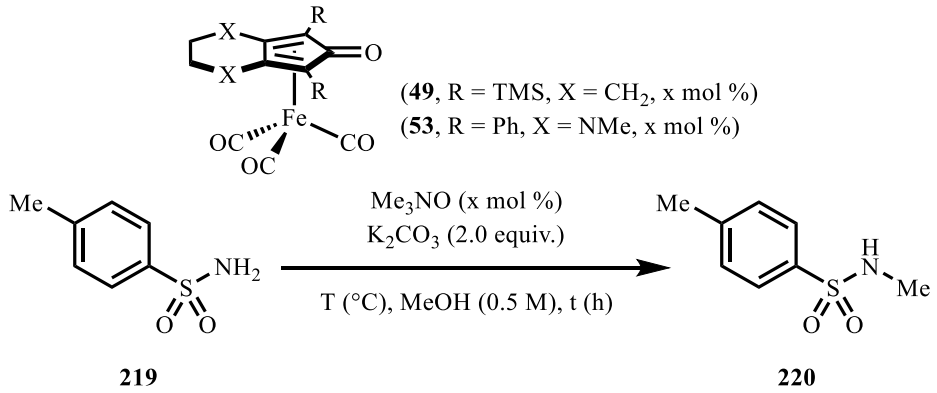
Figure 3.4: Trimethoprim

Under our standard conditions we thought that methylation could be possible but after careful analysis of the ^{1}H NMR spectrum of the crude reaction mixture, several NHC*H*$_3$ doublets were present in the mixture which probably meant that multiple methylation took place across both nitrogen atoms. Starting material was present in large amounts and hence, following this result, the methylation of this compound was aborted. Soon after this work was published, Renaud and co-workers published the *N*-methylation and *N*-ethylation of amines using iron catalysis.[26]

3.2.3.9. *N*-methylation of sulfonamides

So far, the iron-catalysed methylation methodology has been tested for electron-rich and slightly electron-poor nucleophiles. Since the majority of these were successful, we envisaged trying even more challenging substrates, such as the *N*-alkylation of amides, ureas, carbamates and sulfonamides. At first, one example from each class of substrates was tested. Benzamide, phenyl urea and *tert*-butyl carbamate were all incompatible with the methodology with no product formation in both cases. Benzamide and phenyl urea were completely recovered whilst *tert*-butyl carbamate was not present in the crude mixture due to possible substrate decomposition. *p*-Toluenesulfonamide (**219**), on the other hand revealed the formation of the respective product (**220**) with an NMR yield of 17% (Table

3.7, entry 1), and hence a minor re-optimisation was carried out to see if the reaction can be forced to go to completion.



219 **220**

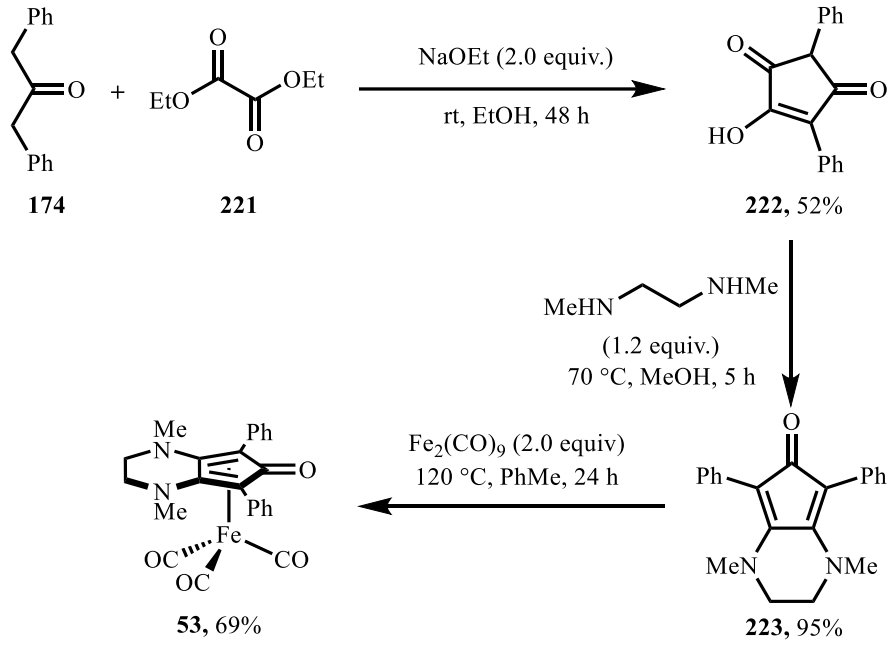
Scheme 3.24: Re-optimisation for the *N*-methylation of sulfonamides

Table 3.7: N-methylation of sulfonamides re-optimisation

Entry[a]	Catalyst (loading)	Me_3NO loading	T (°C)	t (h)	220 (%)[b]
1	49 (2)	4	80	24	17
2	49 (2)	4	110	24	19
3	49 (2)	4	80	72	28
4	49 (4)	8	110	24	44
5	53 (2)	4	110	24	16
6	**53 (4)**	**8**	110	24	**98 (92)**

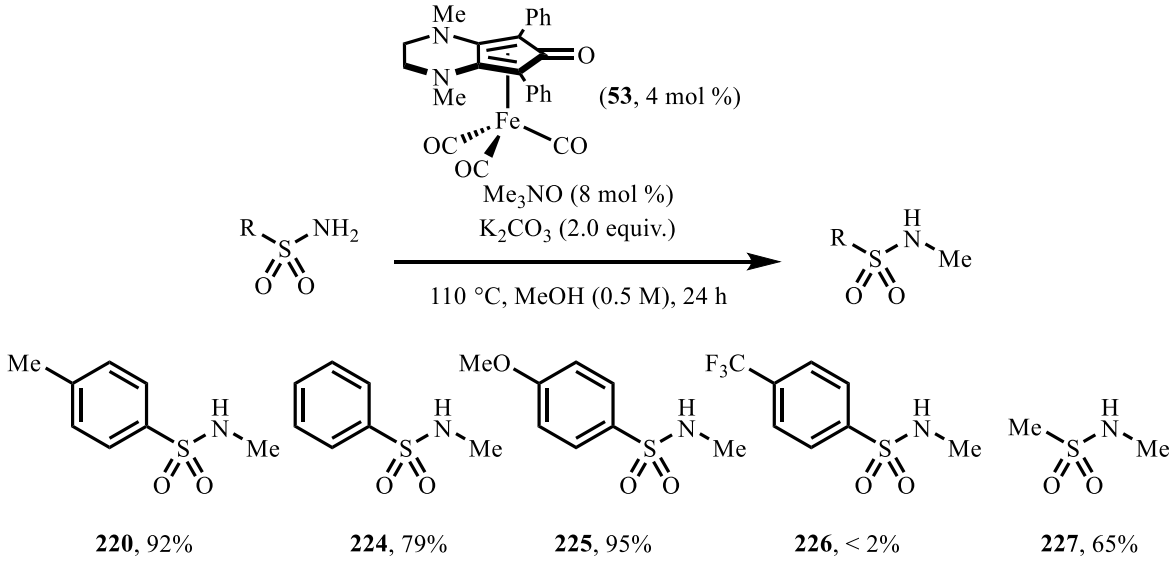
[a]Reactions performed using 1 mmol of sulfonamide **219** and bench-grade MeOH. [**219**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

At 110 °C, using the same catalytic system, this resulted in increased conversion to **220** but still was quite low (entry 2). Leaving the reaction for 3 days using the standard conditions resulted in a slight increment in conversion, whilst doubling the catalyst loading at 110 °C gave only 44% (entry 4). Since these extremely electron poor nucleophiles, a modification of the precatalyst was carried out. Most recently in the literature, Renaud and co-workers have demonstrated that the *C*-alkylation of ketones works even better than the report by Darcel and co-workers,[14] when using a more electron-rich (cyclopentadienone)iron tricarbonyl complex precatalyst.[27] The synthesis of this precatalyst involved three-steps, starting from 1,3-diphenylacetone (**174**) and diethyl oxalate (**221**) using sodium ethoxide as base. This undergoes double deprotonation and substitution furnishing **222**. By addition of *N,N'*-dimethylethylenediamine, this intermediate undergoes a double nucleophilic addition in quantitative yield leading to the formation of **223**. When this species is treated with $Fe_2(CO)_9$ in dry PhMe under a 24 h reflux, followed by alumina chromatography, the precatalyst (**53**) is furnished with a good yield (Scheme 3.25).



Scheme 3.25: (cyclopentadienone)iron carbonyl (**53**) synthesis

After having synthesised this precatalyst, it was tested for sulfonamide *N*-methylation. 2 mol % **53** with 4 mol % of Me_3NO gave a 16% NMR yield of **220** (Table 3.7, entry 5). This precatalyst worked and when catalyst loading was doubled, this led to full conversion to **220** (entry 6). The product was isolated in 92% yield. This particular precatalyst (**53**) is much more electron-rich than our parent precatalyst (**49**) and hence is the main reason that methylation of these electron poor nucleophiles was successful. After successful re-optimisation, a few other sulfonamides were tested giving ranged yields from 65-95% (**224**, **225**, **227**) as shown in Scheme 3.26. With 4-(trifluoromethyl)phenyl sulfonamide, an even more electron poor nucleophile, no conversion to product (**226**) was observed in the ^{1}H NMR spectrum of the crude reaction mixture.

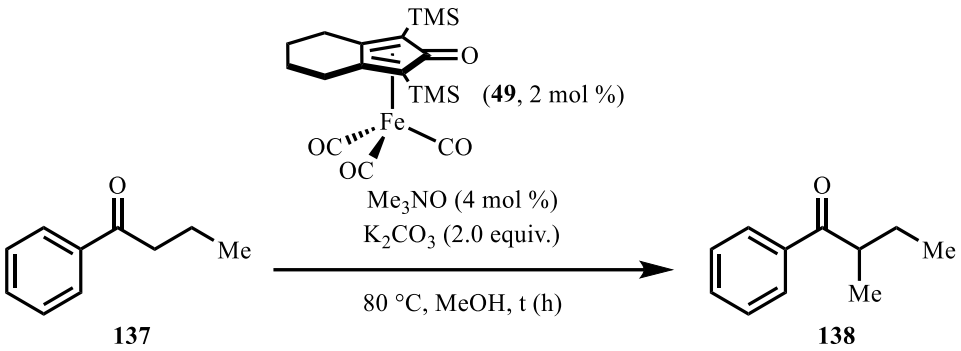


Scheme 3.26: *N*-methylation of sulfonamides

3.2.4. Mechanistic considerations

3.2.4.1. Kinetic studies

After having successfully demonstrated the methylation methodology to work for seven classes of substrates, kinetic studies were carried out to gain more insight on the kinetics of the process. Eight identical setups of the same transformation using **137** as the model substrate were carried out in parallel and these were stopped independently at the time points stated in Table 3.8. The same mini workup was carried out, and all were sampled and analysed using ^{1}H NMR spectroscopy after the addition of mesitylene as internal standard.



Scheme 3.27: Methylation of *n*-butyrophenone - time course experiments

Table 3.8: Time course experiments

Time (h)[a]	137 (%)[b]	138 (%)[b]
0.25	96	1
0.5	95	2
1	83	16
2	63	36
4	40	57
8	15	83
16	5	95
24	1	98

[a]Reactions performed using 1 mmol of ketone **137** and synthesis-grade MeOH. [**137**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

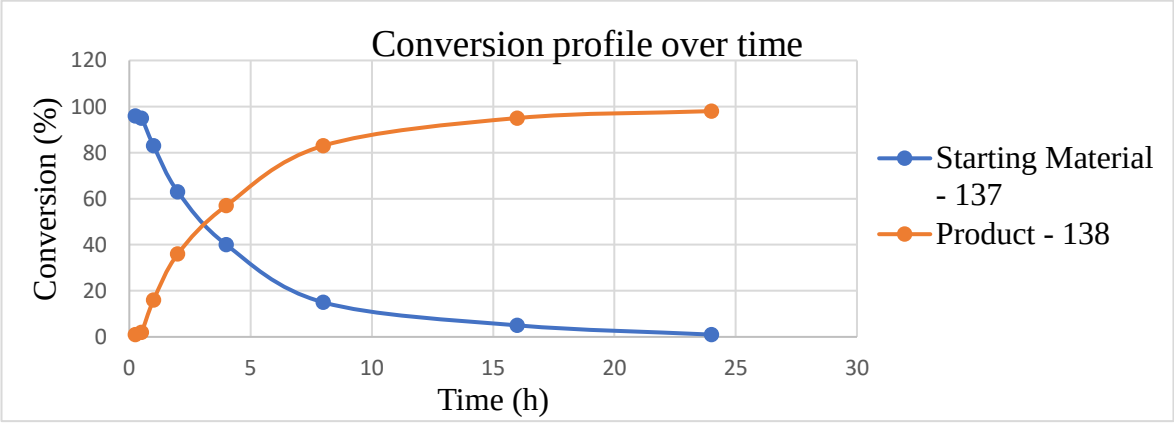


Figure 3.5: Conversion-Time graph for the methylation of *n*-butyrophenone

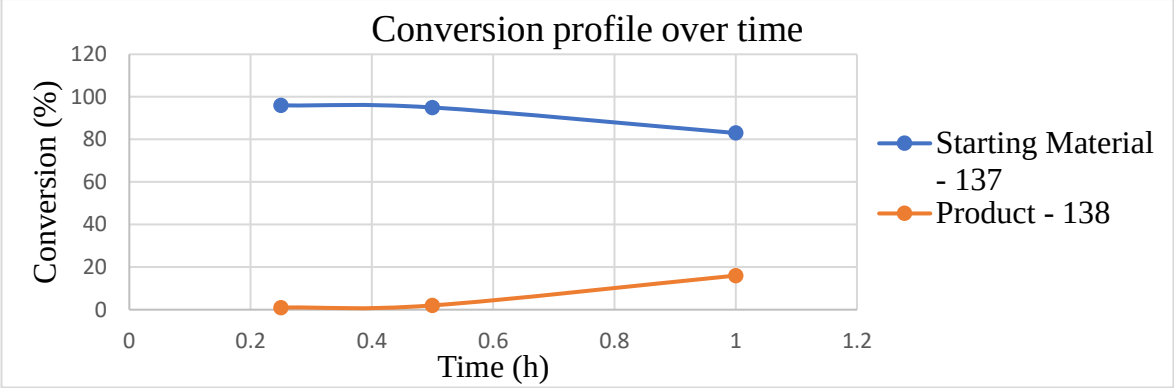
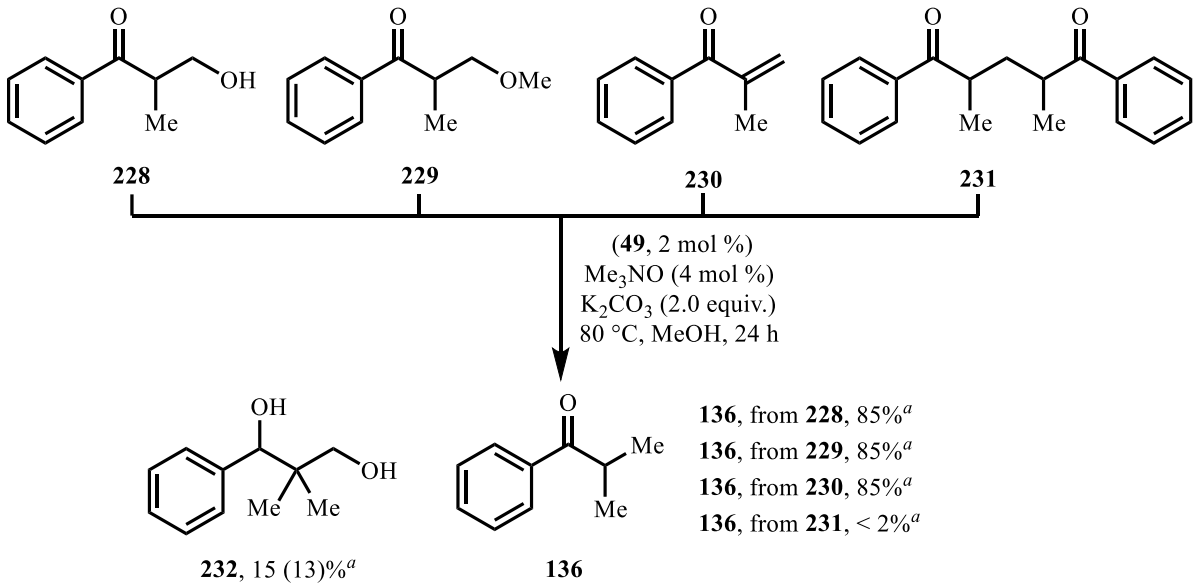


Figure 3.6: 0 min - 1 h expansion of the conversion time graph in Figure 3.5

As observed from Figure 3.5, the process takes between 30 minutes and 1 hour until it gradually proceeds. This time period was expanded, as illustrated in Figure 3.6. This may be attributed to an induction period due to catalyst activation, or due to the equilibration of the reaction temperature. The transformation then gradually proceeds leading to the final methylated product (**138**) in 98% NMR yield after 24 h.

3.2.4.2. Validation of plausible reaction intermediates

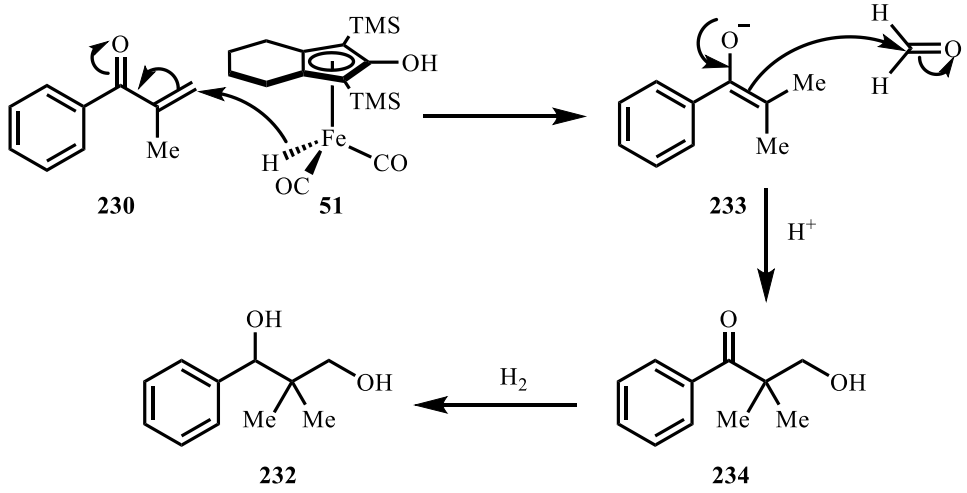
We became more interested on how the methylation works mechanistically. Selecting the methylation of propiophenone (**136**) as a representative example, several plausible intermediates were independently synthesised and subsequently probed using the standard conditions as shown in Scheme 3.28.



Scheme 3.28: Validation of plausible intermediates

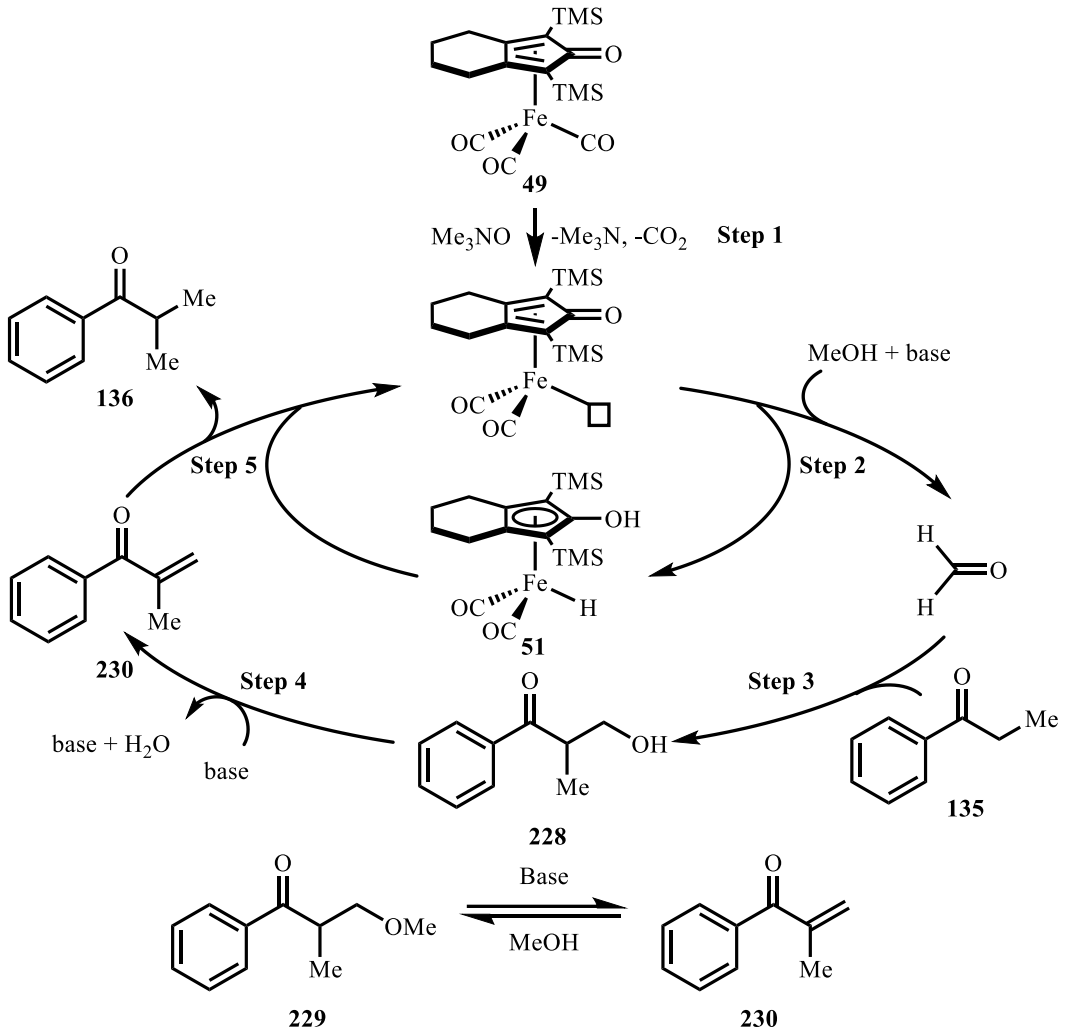
[a]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

Intermediates **228**, **229** and **230** all give 85% conversion to the product indicating that they are plausible intermediates in the mechanistic cycle whilst **231** gives no conversion (< 2%). The remaining mass balance in each case is diol **232**. An explanation for this diol formation is shown in Scheme 3.29.



Scheme 3.29: Mechanism explaining the formation of diol **232**

When the active catalytic species (**51**) delivers the hydride to **230** forming a tetra-substituted enolate **233**, this can then react with the unreacted formaldehyde leading to the formation of the *β*-hydroxy ketone **234**. Since the catalyst is still in its active form, the only place where the hydrogen can go is to *β*-hydroxy ketone **234**, where the carbonyl is reduced, forming diol **232**. With regards to the other plausible intermediates (**228** and **229**), the terminal OH and OMe groups are moderate leaving groups and this can undergo a base assisted elimination forming **230**. On the contrary, if **231** where to undergo an elimination reaction, the terminal group is a worse bad leaving group making this intermediate a non-productive pathway in the whole process. Another plausible explanation is that this compound is difficult to break down at 80 °C. When **228**, **229** and **230** were independently reacted in the absence of base, these gave 66%, 88% and 81% starting material recovery respectively as observed from the ^{1}H NMR spectrum of the crude reaction mixture, clearly indicating that the presence of base aids every step of the transformation. Furthermore, to help understand which step is rate-determining, we treated **228** using the standard conditions for 30 minutes of reactivity and this resulted in 85% conversion of the product, confirming that from **228** to the product, all the intermediate steps are fast. Hence, we concluded that the it is most likely that the RDS is the first dehydrogenation step, as the opposite hydrogenation of formaldehyde is extremely easy. From these results we propose the following catalytic cycle (Scheme 3.30).



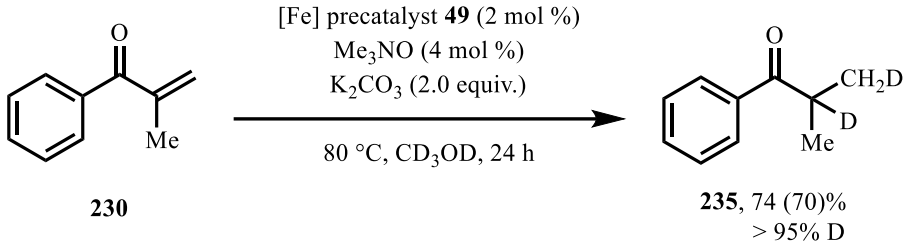
Scheme 3.30: Proposed mechanistic cycle for the methylation of propiophenone

The proposed mechanism begins with CO decoordination of the 18-electron iron precatalyst (**49**) by Me_3NO to form the active iron complex, which abstracts hydrogen from methanol in the presence of base to form the required transient reactive formaldehyde intermediate and the proposed 18-electron iron-hydride species (**51**). A subsequent aldol reaction with propiophenone generates *β*-hydroxy ketone **228** that undergoes a base-catalysed E1cB dehydration to form enone **230**, which may exist in equilibrium with **229**. Finally, reduction of enone **230** by the iron−hydride complex gives methylated product **136** with the regeneration of the active iron complex.

3.2.4.3. Evidence of iron-hydride species and methanol as methylating agent

To further justify that the methylation is actually occurring from methanol, a series of reactions were carried out employing CD_3OD as solvent using the standard reaction conditions, as illustrated in Scheme 3.31. Enone **230** was converted to **235** (74 (70)%, > 95%

D) providing evidence for the proposed iron-hydride species and that the hydrogen is actually coming from methanol. As noticed from Figure 3.7, an integral of 5.0 is obtained for the geminal dimethyl group.



230 **235**, 74 (70)%
> 95% D

Scheme 3.31: Hydrogenation of **230** with CD_3OD

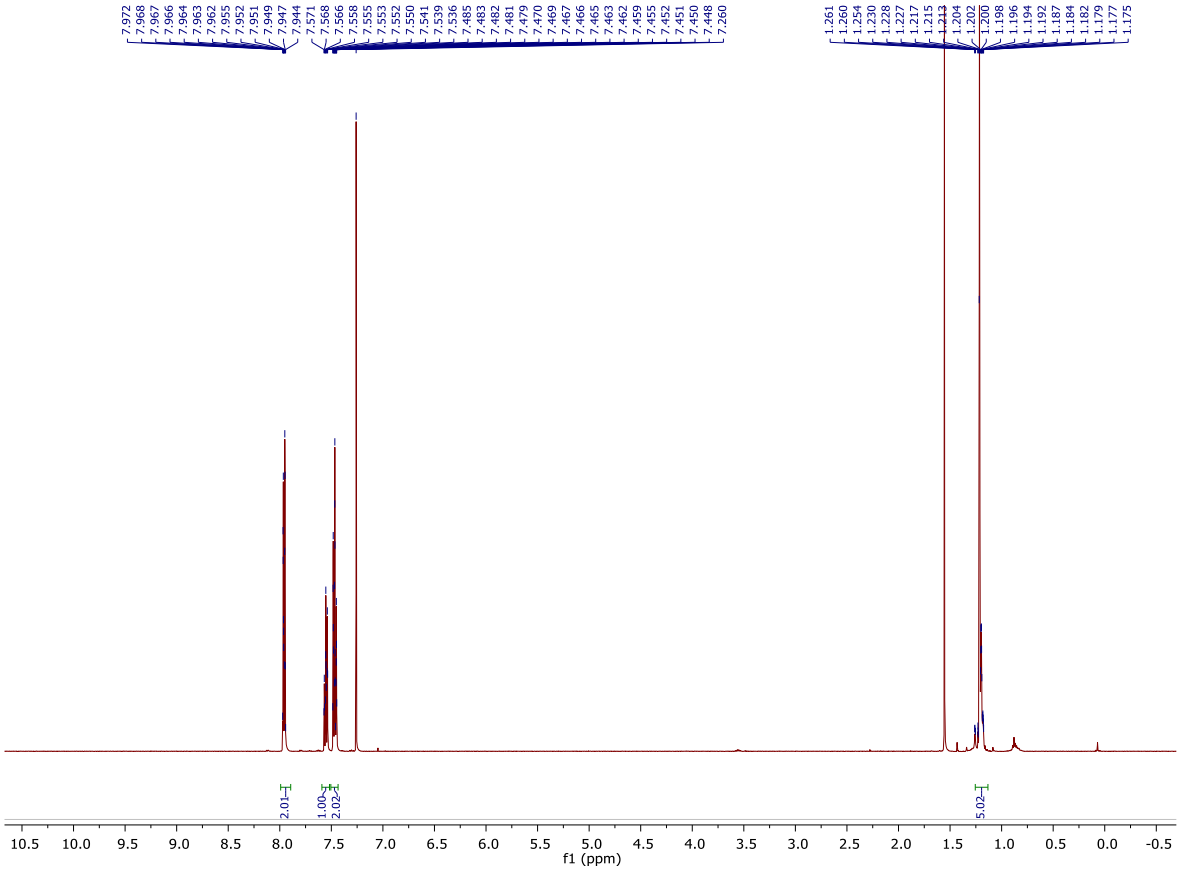
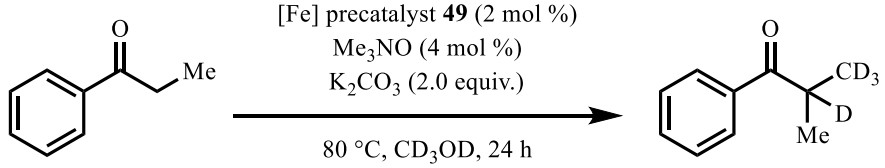


Figure 3.7: ^1H NMR (500 MHz, $CDCl_3$) spectrum of isolated compound **235**

Furthermore, propiophenone **135** was converted to **236** (95 (90)%, > 95% D), confirming that methanol is the source of the methyl group. In this case an integral of 3.0 was obtained or the geminal dimethyl group validating the presence of the C*D*$_3$ species.



135 **236**, 95 (90)%
> 95% D

Scheme 3.32: Methylation with CD_3OD

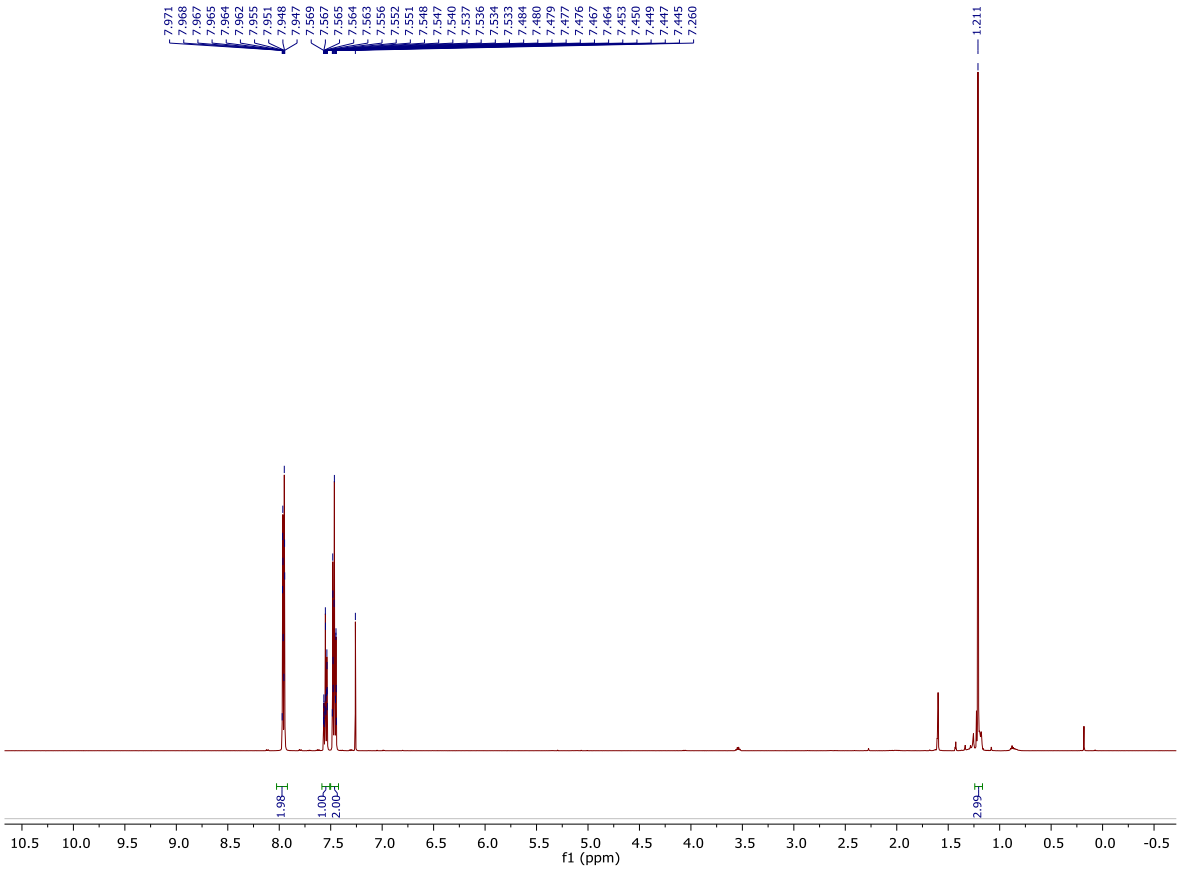
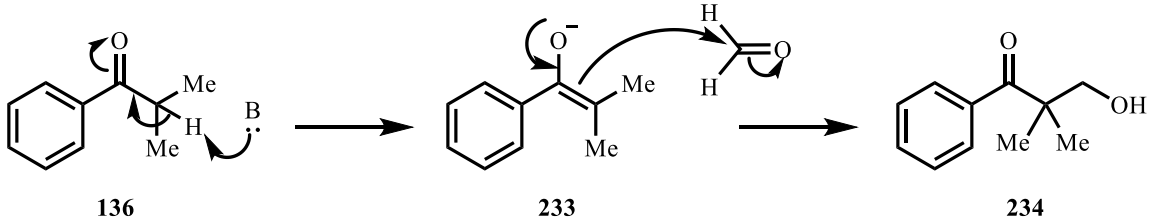


Figure 3.8: ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of isolated compound **236**

Following these deuterated experiments, Rueping and co-workers also published the same deuterated methylation transformation using manganese catalysis for a variety of different ketones.[28] As stated in section 3.1, ketone methylation using alkyl halides such as iodomethane can easily result in multi-alkylation reactions. The benefits of this borrowing hydrogen process are that multi-alkylation is avoided. There are two justifications of this statement. Firstly, the pK_a of general acetophenone derivatives increases relative to the number of substituents attached at the α-carbonyl position. Secondly, and most importantly, when a multi-substituted ketone such as isobutyrophenone (**136**) undergoes another aldol addition reaction to formaldehyde, this leads to β-hydroxy ketone **234**, as illustrated in Scheme 3.33. At this point there is no α-proton present for the E1cB elimination leading to a non-productive pathway.



136 **233** **234**

Scheme 3.33: Alkylation of isobutyrophenone (**136**)

3.3. Conclusion

In conclusion, a general and efficient iron-catalysed methylation procedure has been developed using methanol as a sustainable C1 building block *via* the borrowing hydrogen approach. A diverse array of ketones, indoles, oxindoles, amines, and sulfonamides undergo mono- or dimethylation in excellent isolated yields (61 examples, 79% average yield). Mechanistic experiments provided evidence for plausible reaction intermediates, an iron-hydride species, and methanol as the methylating agent in this catalytic process. This borrowing hydrogen process is highly atom economic and avoids the use of toxic and harmful methylating agents. The methodology is a simple one-pot procedure and can have potential applications in industry.

3.4. References

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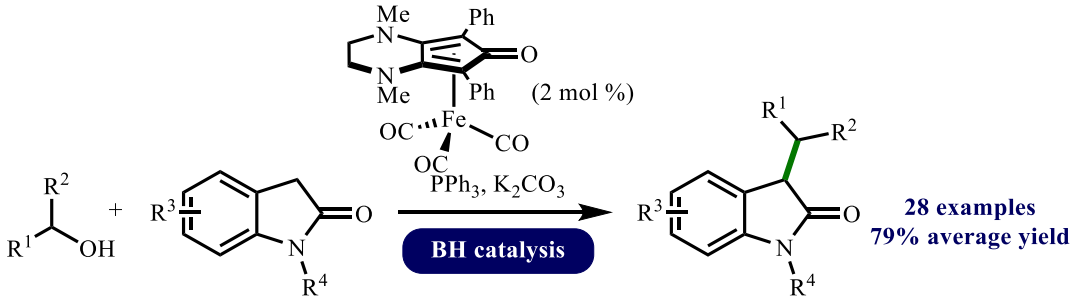
Chapter 4: Iron-catalysed borrowing hydrogen *C*-alkylation of oxindoles using alcohols

Table of contents

For the experimental section see chapter 9

4. Preface

This chapter discusses the development of a general and efficient iron-catalysed *C*(3)-alkylation of oxindoles *via* the borrowing hydrogen approach. This process employs a (cyclopentadienone)iron carbonyl complex as precatalyst and constitutes a broad reaction scope, allowing primary benzylic, *n*-alkyl, and secondary aliphatic alcohols to be utilised as alkylating agents. A range of substituted oxindoles undergo selective *C*(3)-alkylation in excellent isolated yields (28 examples, 79% average yield). Mechanistic experiments provided evidence for plausible reaction intermediates and provided support of a transfer hydrogenation process.



Publication: M. B. Dambatta, K. Polidano, A. D. Northey, J. M. J. Williams and L. C. Morrill, *ChemSusChem*, 2019, **12**, 2345–2349.

Acknowledgements

Mubarak B. Dambatta – A PhD student who carried out the optimisation, oxindole and alcohol substrate scope of the project.

Kurt Polidano – Responsible for catalyst synthesis, finished the substrate scope, worked on the barbituric acids and mechanistic studies section of this project.

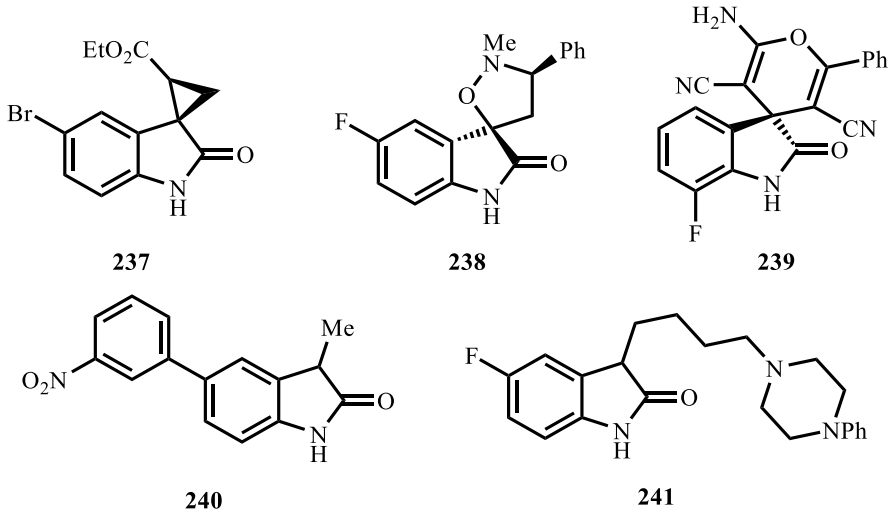
Alexander D. Northey – A supervised MChem student who discovered the project.

Jonathan M. J. Williams – CDT co-supervisor, University of Bath.

Louis C. Morrill – Supervisor, Cardiff University.

4.1. Introduction

In chapter 3, the *C*(3)-methylation of oxindoles was carried out using iron catalysis. This oxindole skeleton is very important as it exists in a variety of naturally occurring compounds.[1,2,3] Many of these compounds, which are either mono or disubstituted at the *C*(3) position, contain some form of pharmacological activity. Some of these include HIV-1 non-nucleoside reverse transcriptase inhibitors, such a **237**; compound **238** which possesses cytostatic activity against h460 cancer cells, compound **239** which possesses anti-inflammatory and analgesic activity; and receptor antagonists such as **240** and **241**, all shown in Figure 4.1. Hence we envisioned developing a green methodology for the general *C*(3)-alkylation of oxindoles as this could have some industrial application.



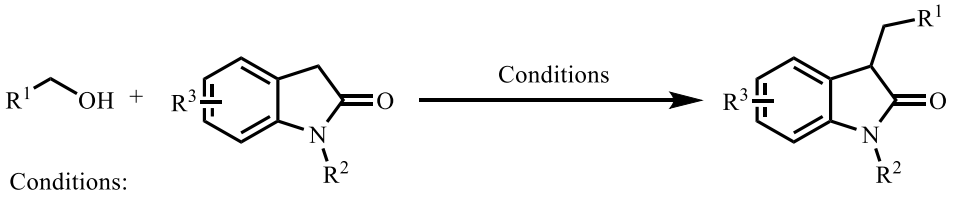
237 **238** **239**

240 **241**

Figure 4.1: Biologically active C(3)-substituted oxindoles

The general synthesis of these types of products would involve employing current alkylation methods such as using harmful and toxic alkylating agents, which not only produce a large amount of waste, but also exhibit poor selectivity. Similar to chapter 3, an alternative would be to utilise the borrowing hydrogen approach for the *C*(3)-alkylation of oxindoles as the process would be more highly atom economic producing water as the sole by-product. The *C*(3)-alkylation of oxindoles has been reported before. Some of the most recent *C*(3) oxindole alkylation reactions which employ heterogeneous catalysis, include the work by Shimizu and co-workers, who use a Pt/CeO_2 (1 mol %) catalyst to achieve this transformation in good to excellent yields using both benzyl and *n*-alkyl alcohols as alkylating agents.[4] Interestingly, no base was required for this transformation. Furthermore, Ohta and co-workers have also developed another catalytic system which employs 10% Pd/C

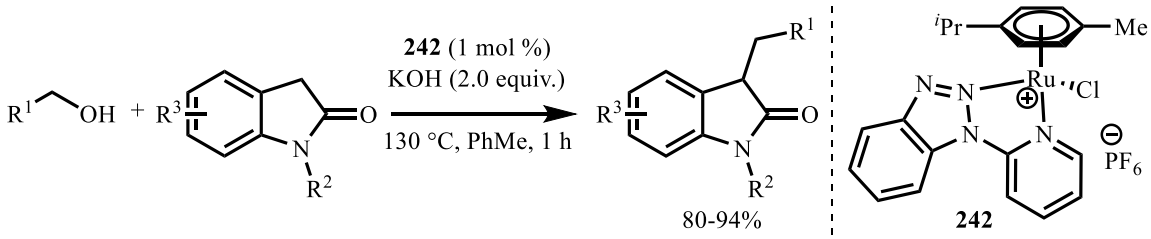
as catalyst for this same transformation.[5] In the same report several barbituric acids also undergo *C*-alkylation.



Shimizu and co-workers: Pt/CeO_2 (1 mol %), 170 °C, mesitylene, 24 h - 58-95%
Ohta and co-workers: Pd/C (10 mol %), KOH (20 mol %), 120 °C, dioxane, 24 h - 41-99%

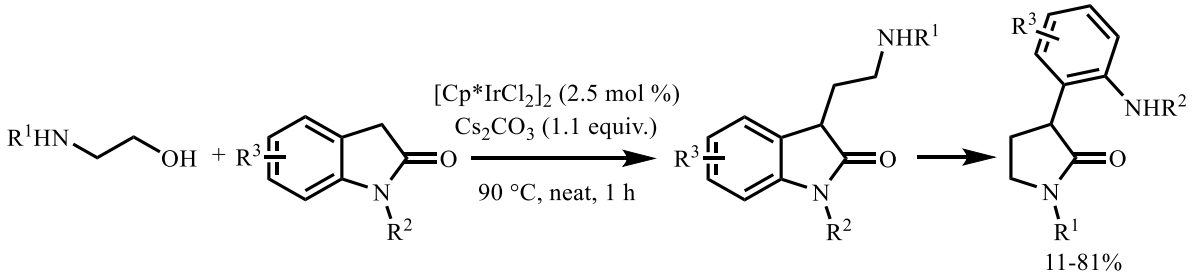
Scheme 4.1: *C*(3)-alkylation using alcohols using heterogeneous catalysis

With regards to homogeneous catalytic systems, most recent publications include the work by Wang and co-workers who employed a defined ruthenium complex for this transformation (Scheme 4.2).[6] The reaction works well for a variety of benzyl and *n*-alkyl alcohols, but interestingly, when the mixture is heated for a further 12 h under air atmosphere, this results in the C-H hydroxylation of the *C*(3) products.



Scheme 4.2: Ruthenium-catalysed *C*(3)-alkylation of oxindoles using alcohols

Another most recent highlight was the work by Piersanti and co-workers who use $[Cp^*IrCl_2]_2$ (2.5 mol %) for this transformation.[7] They only employ ethanolamines as alkylating agents. When using *N*-acetylprotected amines as alkylating agents, the process worked well. Surprisingly, when general ethanolamine and *N*-benzyl ethanolamine were used, this resulted in the formation of a transamidated product giving lactams (Scheme 4.3).



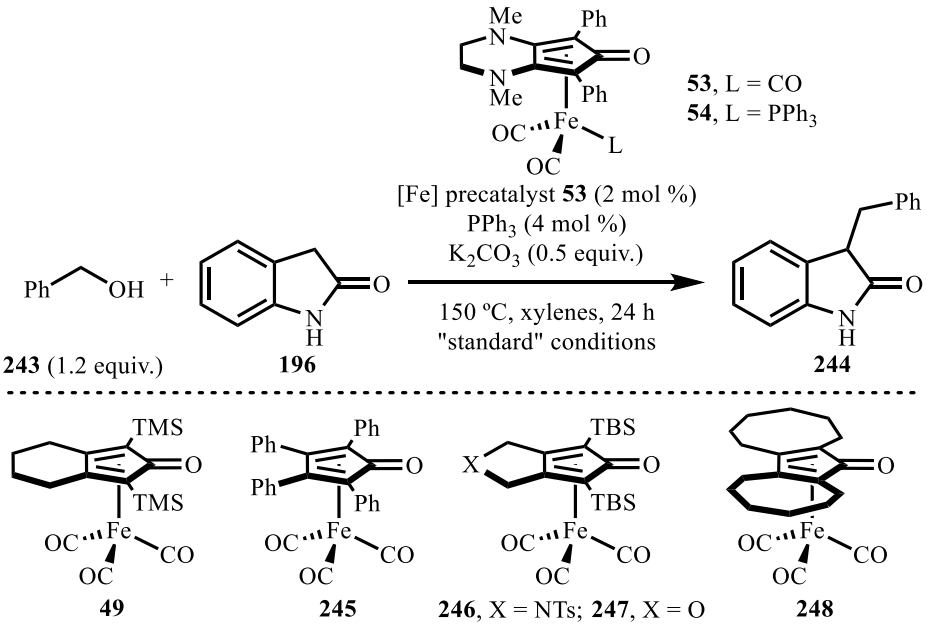
Scheme 4.3: Iridium-catalysed *C*(3)-alkylation of oxindoles using alcohols followed by lactamisation

Besides this, only random examples of oxindole alkylation using earth-abundant metals exist; these being part of a general *C*-alkylation study. (Chapter 1**,** section 1.7).[8] Hence the development of the *C*(3)-alkylation of oxindoles using earth-abundant metals was still of great importance; and so we pursued this transformation.

4.2. Results and discussion

4.2.1. Optimisation of iron catalysed oxindole *C*(3)-benzylation

We focussed on iron catalysis for the *C*(3)-alkylation of oxindoles, and initially a former MChem student, Alexander D. Northey, discovered the process to work with (cyclopentadienone)iron carbonyl complex **53** through the observation of three separate doublets of doublets corresponding to the 3 benzylic protons in the expected final compound (**244**), in the respective ^{1}H NMR spectrum of the crude reaction mixture of the initial investigation. Ultimately, it was Mubarak B. Dambatta who optimised this process, which is illustrated in Scheme 4.4.



Scheme 4.4: Optimisation of the iron-catalysed oxindole *C*(3)-alkylation

As shown in Table 4.1, the process has been optimised to work with 2 mol % of [Fe] precatalyst **53**, 4 mol % of PPh_3 as catalyst activator, using 50 mol % of K_2CO_3 as base, in xylenes at 150 °C for 24 h (entry 1). [Fe] precatalyst **49** gave 18% of **244**, though still incomparable to [Fe] precatalyst **53**, as it is unique for this transformation due to its electron rich framework. The PPh_3 version of this precatalyst also showed 95% conversion to **244**. There is no conversion in the absence of **53** (entry 2) and negligible conversion when employing [Fe] precatalysts **245**-**248**[9,10,11,12] (entries 6-9, 5% of **244**). The exclusion of PPh_3 (thermal activation, entry 10) or substitution with Me_3NO (entry 11) resulted in slightly lower conversion implying that PPh_3 is the best for catalyst activation with respect to this transformation. Substituting K_2CO_3 for Cs_2CO_3 (50 mol %, entry 12) and reducing the

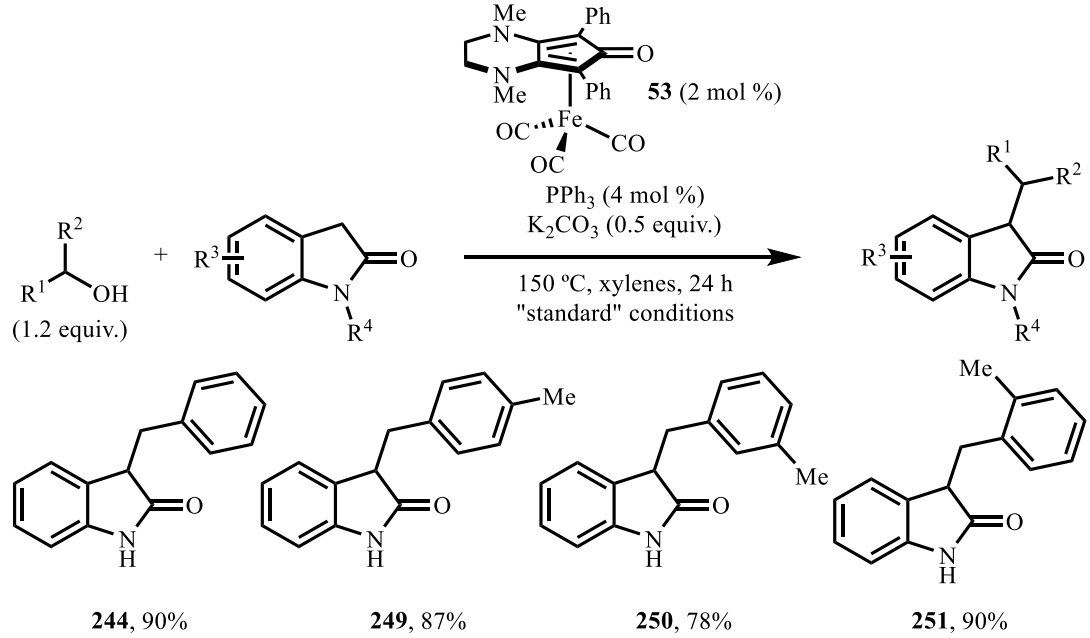
amount of K_2CO_3 to 10 mol % (entry 13) gave slightly reduced yield, whilst solvent swap to PhMe still gave good conversion (entry 14). Increasing the concentration, decreasing the temperature, time and catalyst loading independently all proved to be slightly detrimental to the process (entries 15-18). Despite these results, each of these factors improves the practicality of this alkylation procedure. Mubarak then explored the full scope of the transformation as illustrated in Scheme 4.5 and Figure 4.2.

Table 4.1: Optimisation table

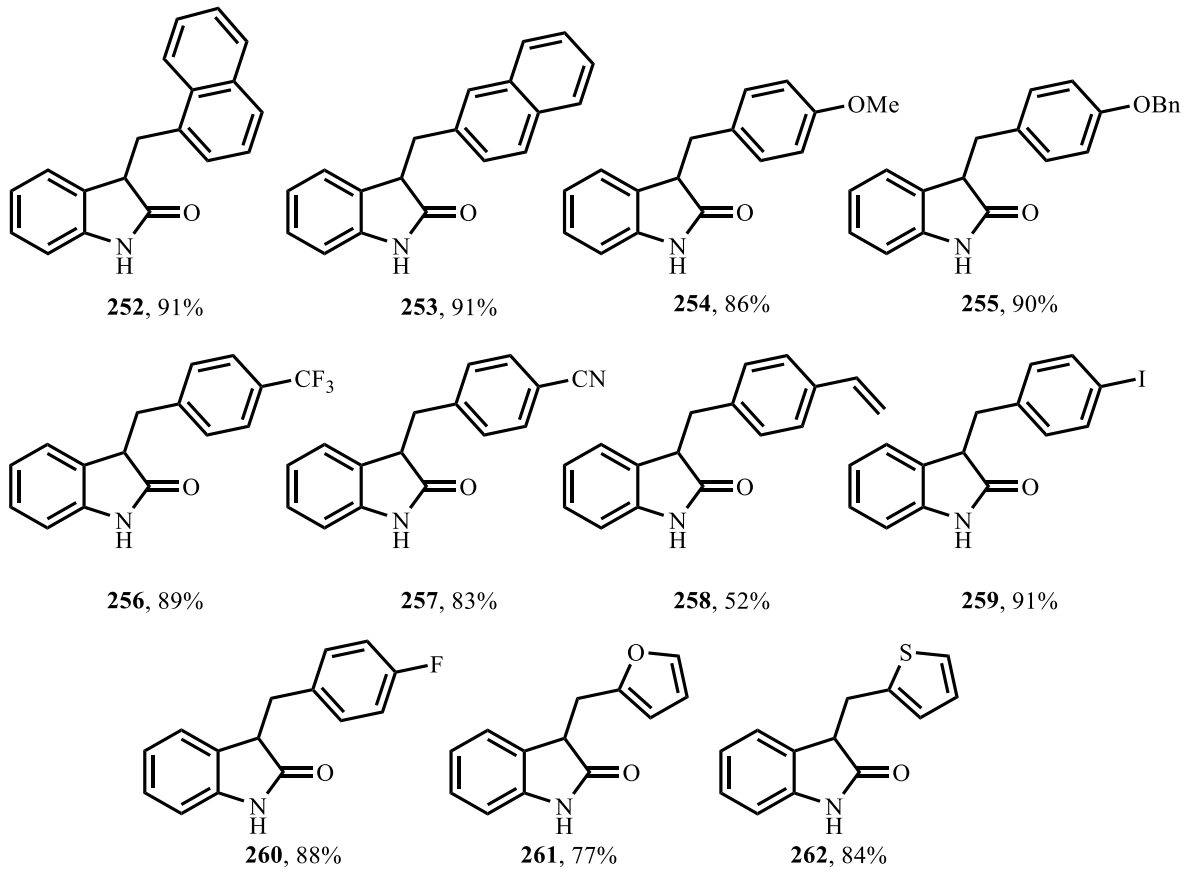
Entry[a]	Variation from 'standard' conditions	Yield[b] (%)
1	None	**97 (90)**
2	No [Fe] precatalyst **53**	< 2
3	No K_2CO_3	26
4	**54** (2 mol %) instead of **53** (No PPh_3)	95
5	**49** (2 mol %) instead of **53**	18
6	**245** (2 mol %) instead of **53**	5
7	**246** (2 mol %) instead of **53**	5
8	**247** (2 mol %) instead of **53**	5
9	**248** (2 mol %) instead of **53**	5
10	No PPh_3	90
11	Me_3NO (4 mol %) instead of PPh_3	92
12	Cs_2CO_3 (0.5 equiv.) instead of K_2CO_3	85
13	K_2CO_3 (0.1 equiv.)	88
14	PhMe instead of xylenes	91
15	[**196**] = 1 M	93
16	130 °C instead of 150 °C	86
17	t = 6 h	92
18	[Fe] precatalyst **53** (1 mol %), PPh_3 (2 mol %)	73

[a]Reactions performed with oxindole (**196**, 1 mmol) and bench-grade xylenes. [**196**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR spectroscopy of the crude mixture with 1,3,5-trimethylbenzene as internal standard. Isolated yield given in parentheses.

4.2.2. Substrate scope – Oxindole and alcohol scope



Scheme 4.5: Oxindole and benzyl alcohol scope



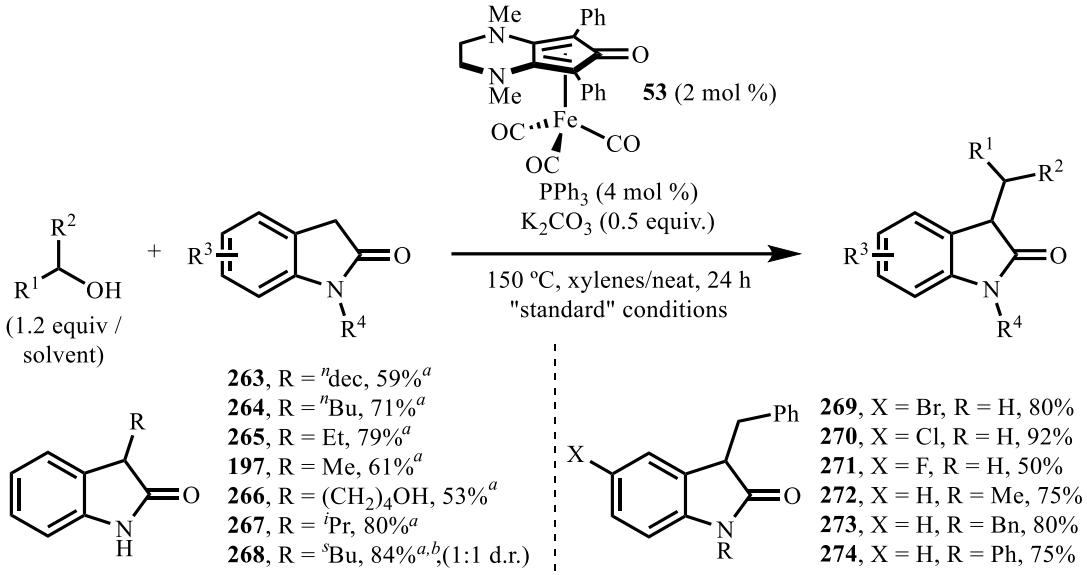
252, 91% **253**, 91% **254**, 86% **255**, 90%

256, 89% **257**, 83% **258**, 52% **259**, 91%

260, 88% **261**, 77% **262**, 84%

Figure 4.2: Oxindole and benzyl alcohol scope (continued)

Mubarak isolated compound **244**, compounds **249**-**254** and **259**-**262**. My role in this scope was to test benzyl alcohols containing reducible functionalities (**255**, **257**, **258**). From Scheme 4.5 and Figure 4.2, it can be noted that the process is quite versatile and many substituted benzyl alcohols can be used as alkylating agents. In general, the process tolerates alcohols containing sterically hindered units and extended aromatics successfully (**249**-**253**, 78-91%). Alcohols containing electron-donating groups (4-OMe, 4-OBn, **254**-**255**) and electron-withdrawing groups (4-CF_3, 4-CN, **256**-**257**) gave excellent yields of the final products. Despite 4-OBn, 4-CN and 4-vinyl (**258**, 52%) being reducible functionalities, the catalytic system was chemoselective, and these functional groups remained intact. The main reason for this is that in each case the α,β-unsaturated amide produced is much more electron poor and thus easier to reduce that the mentioned functional groups. Furthermore, despite having 1.2 equiv. of benzyl alcohol, it is much easier to hydrogenate the remaining benzaldehyde rather than a nitrile, benzyloxy or styrene functionality. Halo-substituted alcohols and heterocyclic methyl alcohols were also tolerated successfully (**259**-**262**, 77-91%).

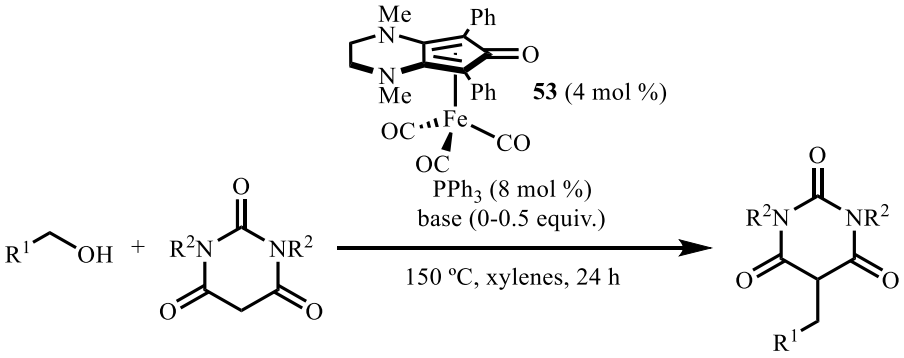


Scheme 4.6: Oxindole and alkyl alcohol scope

[a]Alcohol used as solvent, [b][Fe] precatalyst **53** (4 mol %), PPh_3 (8 mol %).

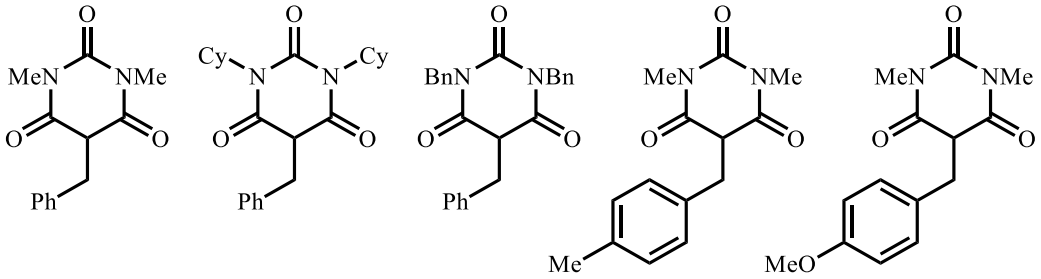
The methodology was also extended to primary and secondary alkyl alcohols (**197**, **263**-**268**, 53-84%. Since these are non-activated and thus harder to oxidise, solvent quantity amounts of alcohol were required to achieve good yields of the respective products. Under the optimised reactions conditions, a range of oxindoles also underwent efficient *C*(3)-benzylation (**269**-**274**, 50-92%).

4.2.3. Substrate scope – *C*-alkylation of barbituric acids



Scheme 4.7: *C*-alkylation of barbituric acids

Next, the alkylation of another class of activated amides was demonstrated, these being barbituric acids. Mubarak re-optimised the *C*-alkylation of barbituric acids, which in this case required double the catalyst loading in comparison to oxindoles. Mubarak also isolated **275** and **276** in good yield. **277**, **278** and **279** were purified my myself.



(**275**, 60%)[a] (**276**, 75%)[a] (**277**, 57%)[b] (**278**, 73%)[a] (**279**, 50%)[b]

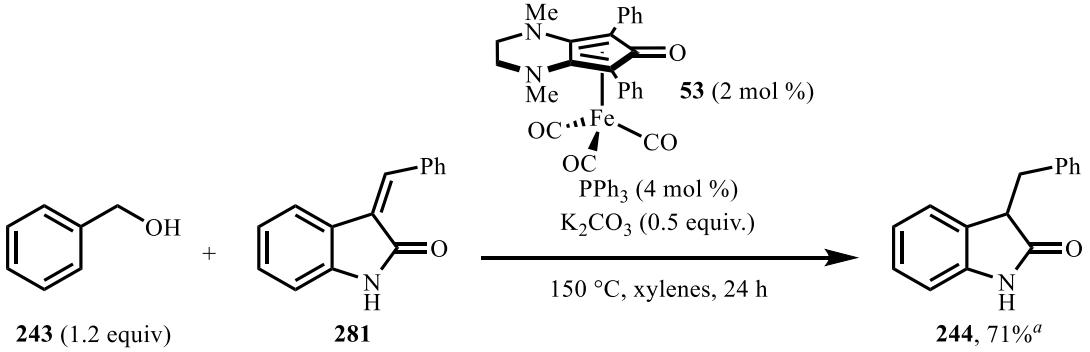
Figure 4.3: *C*-alkylation of barbituric acids

[a]0 equiv. K_2CO_3, [b]0.5 equiv. K_2CO_3

As shown in Figure 4.3, **275**, **276** and **278** are all alkylated in good yields. As noticed for these examples, base was not required since the barbituric acids are in equilibrium with the enol tautomer and hence can act as nucleophiles in the absence of base. On the other hand, **277** and **279** are more electron-rich and the addition of K_2CO_3 (50 mol %) helped facilitate the process.

4.2.4. Mechanistic studies

We wanted to gain more information on a proposed mechanism for this transformation. For this to be successful, we tried to synthesise several plausible intermediates which are present in Scheme 4.9. Ultimately the unsaturated amide, **281**, could only be synthesised *via* aldol condensation of **196** with benzaldehyde using piperidine as base. Compound **280** could not be synthesised as resulted in the formation of **281**.



243 (1.2 equiv) **281** **244**, 71%[a]

Scheme 4.8: Validation of plausible reaction intermediate (**281**)

[a]Yield after 24 h as determined by ^{1}H NMR spectroscopy of the crude mixture with 1,3,5-trimethylbenzene as internal standard

When tested under the standard conditions (Scheme 4.8), **281** gave a 71% NMR yield of **244**, shown in Figure 4.4, confirming that it is indeed a plausible intermediate in this transformation. When ^{1}H NMR spectrum of the crude reaction mixture was overlapped with

the pure ^{1}H NMR spectra of the **244** and **281**, as shown in Figure 4.5, this confirmed the formation of **244**.

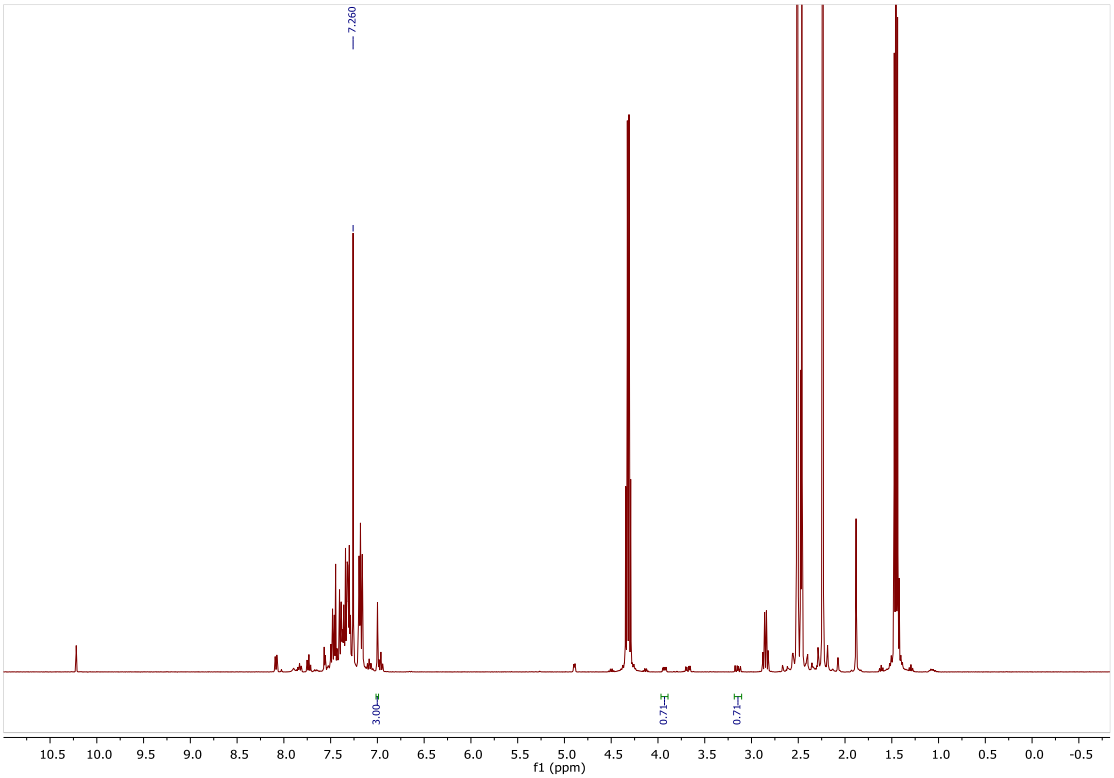


Figure 4.4: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of crude mixture showing the reactivity of **281**

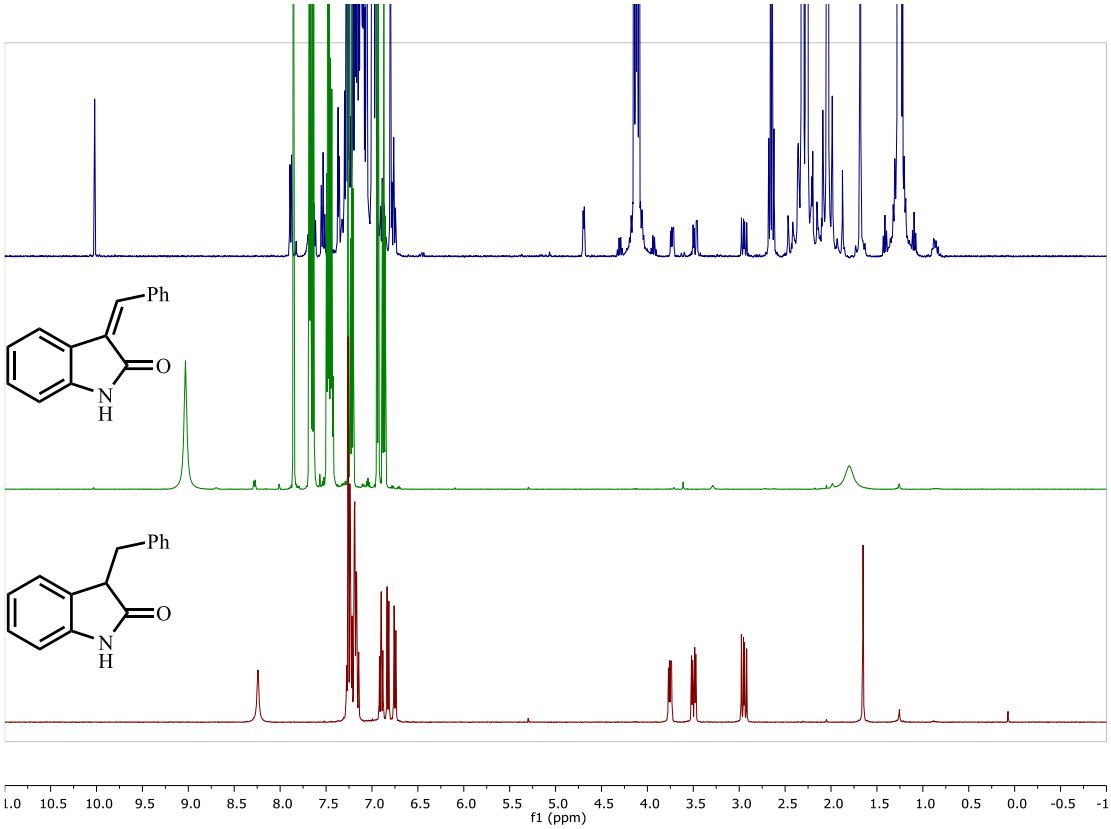
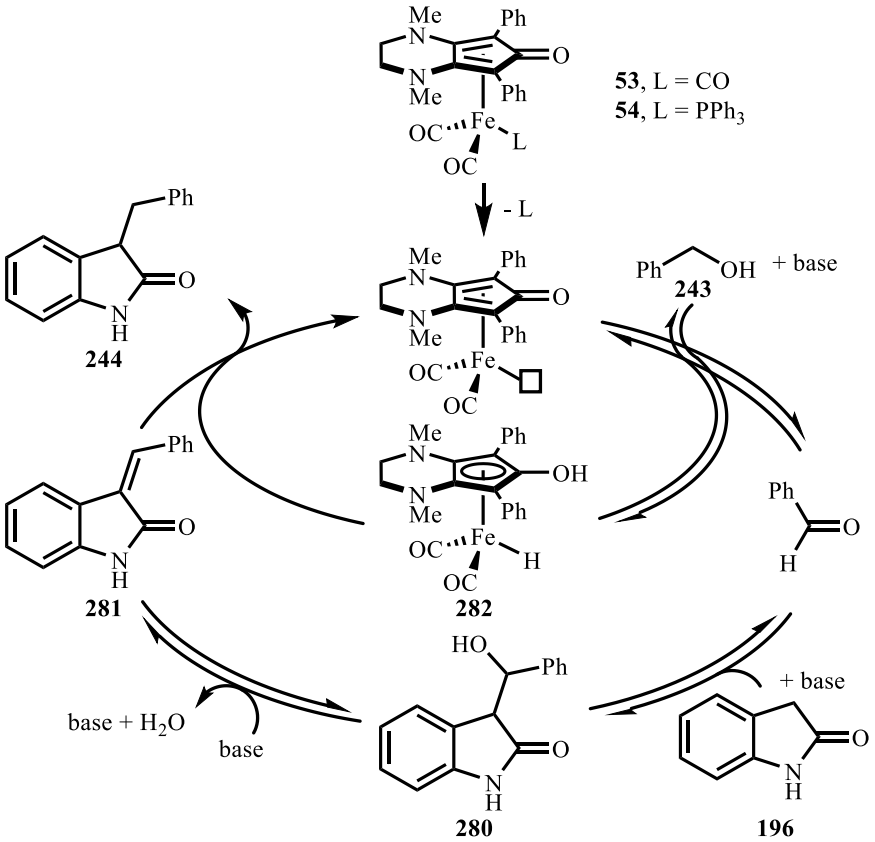


Figure 4.5: Overlap of ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of crude mixture with pure spectra of **244** and **281**

Hence, following this result, the following mechanistic cycle was proposed using the model transformation involving oxindole and benzyl alcohol as starting materials.



Scheme 4.9: Proposed mechanistic cycle for the *C*(3)-alkylation of oxindoles

Catalyst activation is carried out using PPh_3 forming the active catalytic species with a vacant coordination side ready for hydride abstraction. This active species dehydrogenates benzyl alcohol (**243**) with the aid of base generating benzaldehyde and an iron-hydride species (**282**), Benzaldehyde, in the presence of base, undergoes an aldol reaction with oxindole **196**, as a pro-nucleophile to form **280**. A rapid base catalysed condensation reaction follows forming *α*,*β*-unsaturated amide **281**. The unsuccessful synthesis of **280** also helps us gain support that this step in the proposed cycle is fast. Finally, the iron-hydride species returns the borrowed hydrogen, reducing **281**, forming the new alkylated product **244**.

4.3. Conclusion

In conclusion, an iron-catalysed *C*(3)-alkylation of oxindoles has been developed. The process utilises an air-stable (cyclopentadienone)iron type catalyst which is relatively easy to make on scale and hence could have some applications in industry. The transformation is compatible with a variety of primary benzyl, *n*-alkyl and secondary alcohols giving good to

excellent yields of the corresponding products. The process is a simple one-pot procedure and conditions can easily be varied to accommodate different starting materials, improving its practicality. Mechanistic studies provided evidence for plausible reaction intermediates and provided support of a transfer hydrogenation process.

4.4. References

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Chapter 5: Iron-catalysed borrowing hydrogen *β*-C(sp^3)-methylation of alcohols

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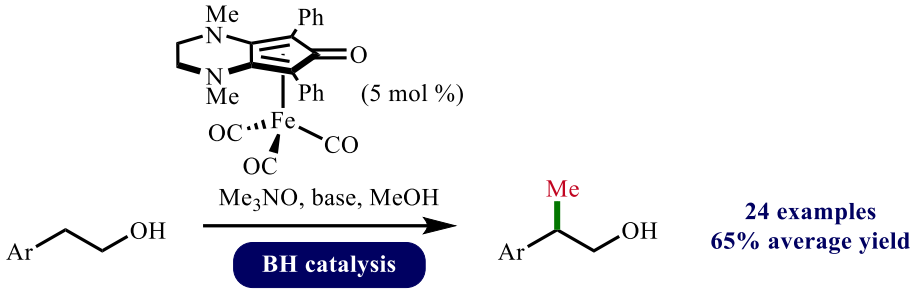
For the experimental section see chapter 10

5. Preface

This chapter discusses the development of an iron-catalysed *β*-*C*(sp^3)-methylation of primary alcohols using methanol as a C1 building block. The transformation is carried out *via* a borrowing hydrogen approach, and employs a well-defined bench stable (cyclopentadienone)iron(0) carbonyl complex as precatalyst (5 mol %). This process enables a diverse selection of substituted 2-arylethanols to undergo *β*-*C*(sp^3)-methylation in good to excellent isolated yields (24 examples, 65% average yield).



Publication: K. Polidano, J. M. J. Williams and L. C. Morrill, *ACS Catal.*, 2019, **9**, 8575-8580.

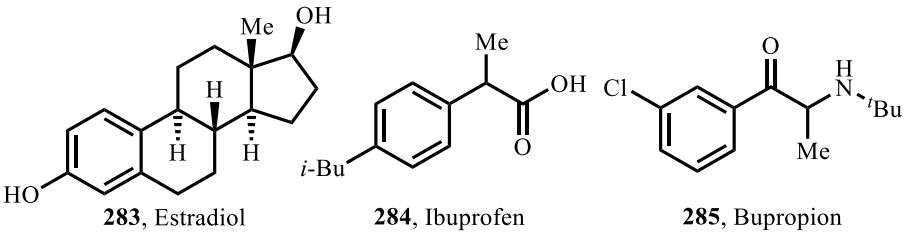
Acknowledgements

Jonathan M. J. Williams – CDT co-supervisor, University of Bath.

Louis C. Morrill – Supervisor, Cardiff University.

5.1. Introduction

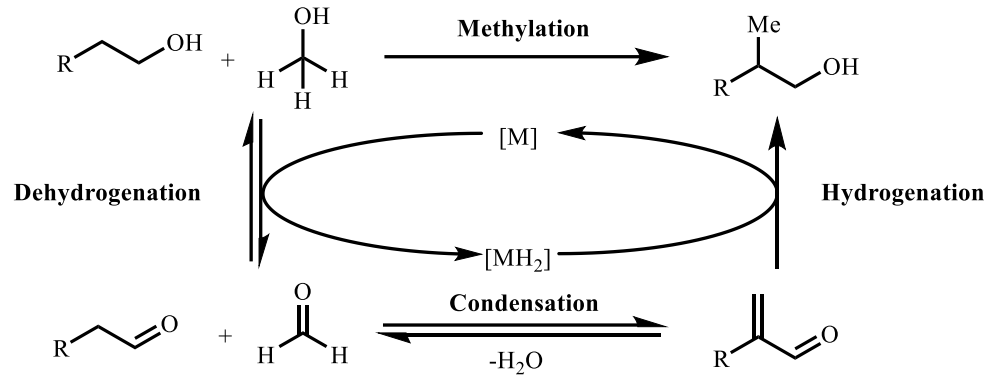
In chapter 3, we discussed the disclosure of an iron-catalysed methylation process for a variety of classes of substrates. Within the scope, we also investigated the *β*-methylation of alcohols but unfortunately these were incompatible with the parent catalytic system. *β*-Methylation of alcohols is of great interest as it is a well-known fact that methyl groups are widely present in a range of pharmaceutical compounds. Specifically, the *C*(sp^3)−Me motif is present in a significant portion of the "Top 200 Brand Name Drugs by Prescription in 2016".[1] Some of these are illustrated in Figure 5.1.



283, Estradiol **284**, Ibuprofen **285**, Bupropion

Figure 5.1: Examples of pharmaceutical products containing the C(sp^3)-Me motif

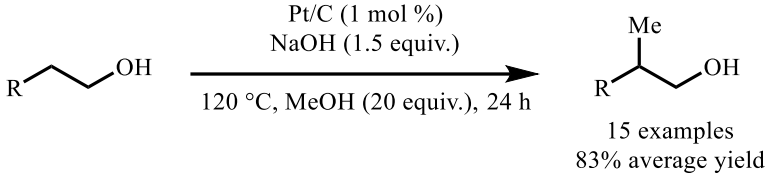
Therefore, there is the need to develop new methodologies for the methylation of *C*(sp^3)−H bonds.[2] As stated in chapter 2, methylation is typically carried out using harmful and toxic reagents such as diazomethane, dimethyl sulphate and iodomethane.[3,4] There is still the need to avoid using these toxic chemicals preventing the generation of large amounts of waste. We envisioned returning to re-investigate the *β*-methylation of alcohols, again using methanol as our alkylating agent, which would result in a highly atom economic process producing water as the sole by-product. The cycle of this transformation, referred to as the Guerbet mechanism, is displayed in Scheme 5.1.



Scheme 5.1: Guerbet cycle for *β*-methylation

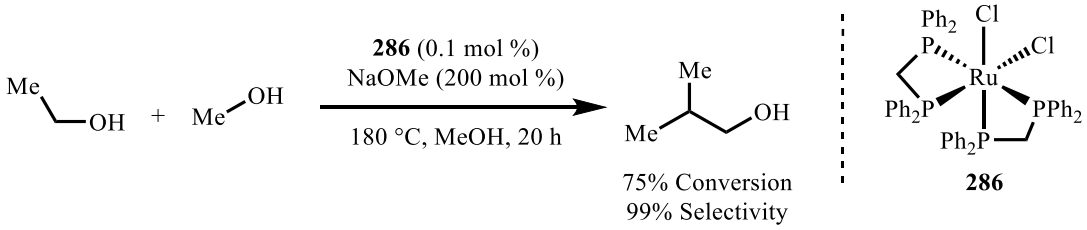
A metal catalyst is used to dehydrogenate methanol and another starting alcohol to form formaldehyde and another corresponding carbonyl compound. In the presence of base, these two carbonyl compounds will undergo a cross aldol condensation reaction to give an electron poor *α*,*β*-unsaturated intermediate. The hydridic metal complex can then return the borrowed

hydrogen and carry out global hydrogenation of this intermediate to form the alcohol containing the $C(sp^3)$–Me motif. There are some existing reports of *β*-methylation, and all these generally employ either a heterogeneous or homogeneous type precious metal catalytic system. With regards to heterogeneous systems, Liu and co-workers have successfully reported the use of yolk-structured microporous carbon nanotubes for this transformation.[5] Other reports of *β*-methylation which employs heterogeneous catalysis include the work by Shimizu and co-workers where they employ a metal/support catalytic system.[6] Their optimised system involved using Pt/C as the heterogeneous catalyst with 1.5 equiv. of NaOH as base, in an excess of methanol facilitating the successful methylation of *β*-aryl and alkyl alcohols in excellent yields (Scheme 5.2).



Scheme 5.2: *β*-methylation using Pt/C

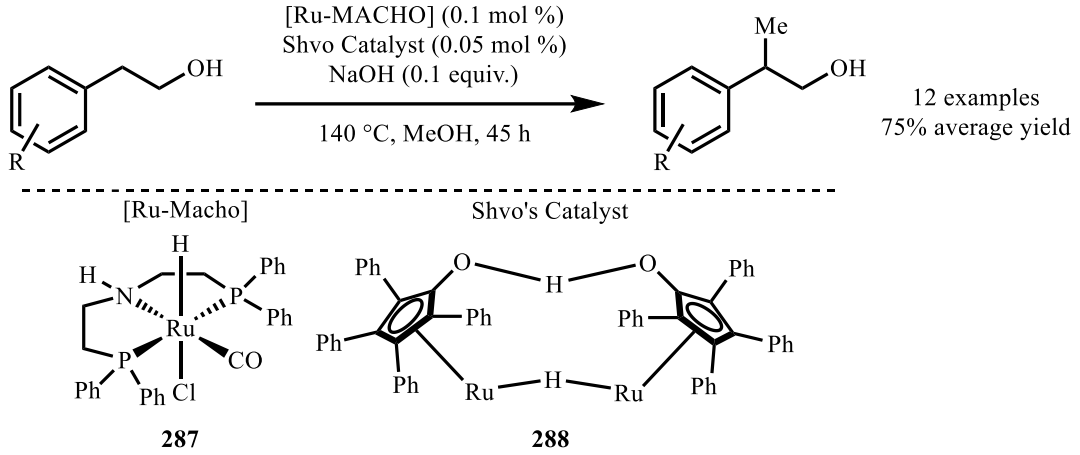
Within the same publication, they also undergo several kinetic experiments such as time course and kinetic isotope tests to help gain more support on the mechanism. They also state the catalyst can be recovered and recycled for 5 runs giving a TON of 3280 without significant loss of reactivity. In comparison to heterogeneous catalysis, the application of homogeneous catalysts for this transformation has been investigated to a greater degree. Within this field, Wass and co-workers have successfully shown the catalytic conversion of methanol/ethanol to isobutanol, which is a highly selective route to an advanced biofuel (Scheme 5.3).[7]



Scheme 5.3: Catalytic conversion of methanol/ethanol to isobutanol

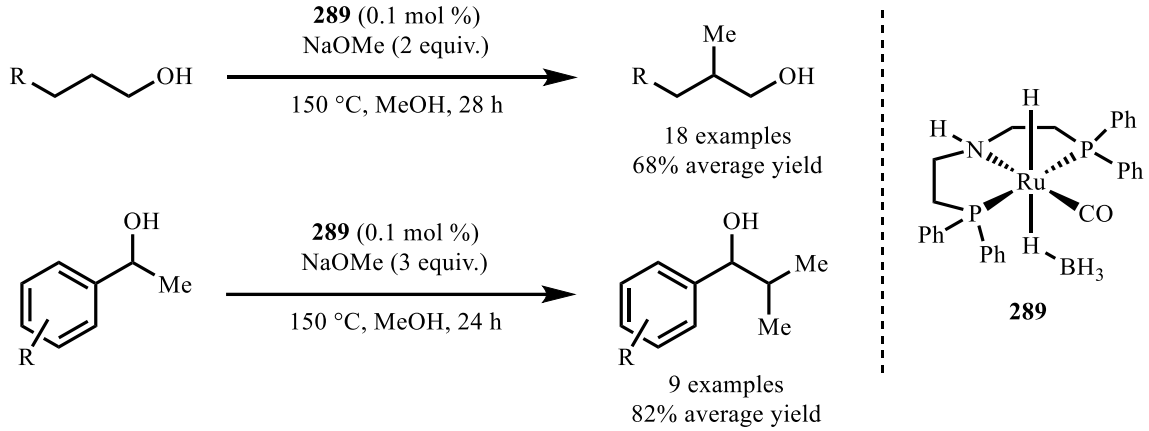
The process generally requires low catalytic loadings of a ruthenium precatalyst with dppm as a ligand, extremely high temperatures, and super-stoichiometric base for the reaction to proceed efficiently. The conversion of ethanol to 1-butanol has also been reported using manganese catalysis.[8] Beller and co-workers have also successfully reported this transformation using ruthenium catalysis.[9] In their report they utilise ruthenium metal complexes for *β*-methylation (Scheme 5.4). There are two major drawbacks here. Firstly,

they require both catalysts simultaneously for this to proceed as they state that catalyst **287** unfortunately is not able to dehydrogenate their starting phenethyl alcohol, whilst their co-catalyst (**288**) cannot undergo methanol dehydrogenation. The second drawback is that since a large amount of hydrogen is generated in their reactor, they are consistently required to release the pressure over 45 h to favour the dehydrogenation of both their alcohols and thus, obtain satisfactory conversions across a decent range of 2-arylethanols.



Scheme 5.4: Rutheniumcatalysed *β*-methylation of alcohols

Most recently, Leitner has disclosed a more efficient *β*-methylation process using a modified Ru-MaCHO having a pendant borohydride ligand (Scheme 5.5).[10] Using their optimised conditions, they have carried out a number of examples using different alcohols such as primary phenethyl alcohols, primary alkyl alcohols and secondary 1-phenylethanols in good yields.



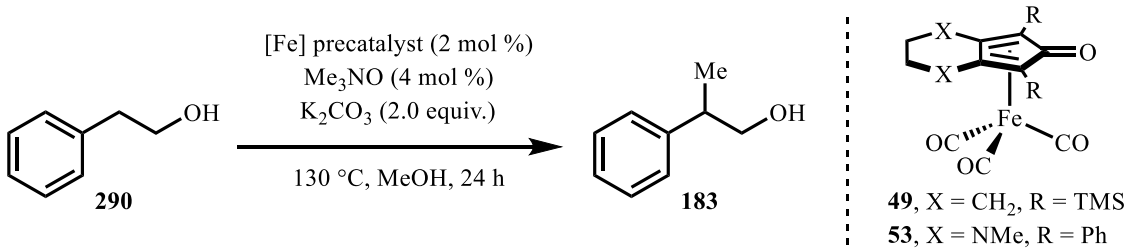
Scheme 5.5: Improved ruthenium-catalysed *β*-methylation of alcohols

Despite these reports, heterogeneous or homogeneous catalyst systems based on an earth-abundant first-row transition metal has not yet been reported for this process. In this report, a well-defined bench stable (cyclopentadienone)iron(0) carbonyl complex (5 mol %) has been employed for an operationally simple and efficient catalytic *β*-*C*(sp³)-methylation of various primary alcohols using methanol as the alkylating agent.

5.2. Results and discussion

5.2.1. Optimisation of iron catalysed *β-C*(sp3)-methylation

Initially similar conditions to the *α*-methylation of ketones[11] were applied to this transformation as shown in the scheme below. The temperature was increased from 80 to 130 °C as from chapter 3 we already obtained no conversion at 80 °C.



Scheme 5.6: *β*-methylation preliminary investigations

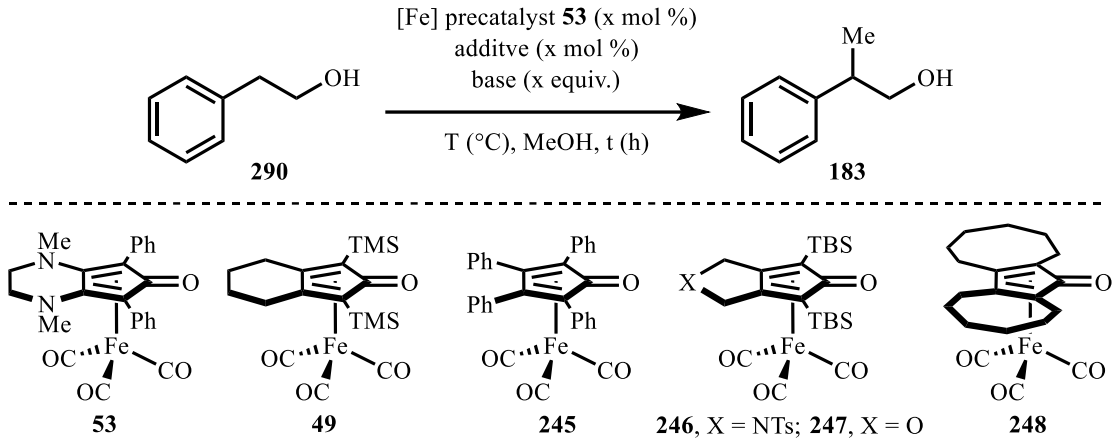
Table 5.1: *β*-methylation preliminary investigations

Entry[a]	Cat. Loading (mol %)	Additive (mol %)	Base (equiv)	290 (%)[b]	183 (%)[b]
1	**49** (2)	Me_3NO (4)	K_2CO_3 (2)	98	< 2
2	**53** (2)	Me_3NO (4)	K_2CO_3 (2)	31	64

[a]Reactions performed using 0.5 mmol of alcohol **290** and synthesis-grade MeOH. [**290**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

As shown in Table 5.1, (cyclopentadienone)iron carbonyl complex **53** having an electron rich backbone was clearly superior to the (cyclopentadienone)iron carbonyl complex **49** which was used in the standard conditions in the previous *α*-methylation of ketones.[11] Due to **53** being more electron-rich, it was expected that this precatalyst would be better, as it aids in increasing the rate of dehydrogenation. After this preliminary test, optimisation was then carried out. All the optimisation experiments were carried out in a sealed microwave vial. Each vial containing a magnetic stirrer bar was charged with base (x mmol, x equiv.), additive (x mmol, x mol %), [Fe] precatalyst **53** (x mg, x mmol, x mol %), MeOH (x mL) and 2-phenylethanol (60 µL, 61 mg, 0.5 mmol). The vial was sealed with a cap and the vial was heated to the appropriate temperature for 24 h. This was then cooled followed by the addition of 1,3,5-trimethylbenzene (70 µL, 60 mg, 0.5 mmol), sat. aq. NH_4Cl (0.5 mL), H_2O (0.5 mL) and EtOAc (1 mL). In some cases, brine (1 mL) was added to aid layer separation. The mixture was then stirred for 5 minutes, the vial cap opened and left to settle for a further 5 minutes. The top layer was sampled and analysed by ^{1}H NMR spectroscopy. As shown in Figure 5.2, the reaction mixtures were analysed by comparing integrals of benzylic protons

of **290** and **183** with 1,3,5-trimethylbenzene as internal standard. Table 5.2 show the respective results from the optimisation.



Scheme 5.7: Optimisation of the iron-catalysed *β*-C(sp³)-methylation

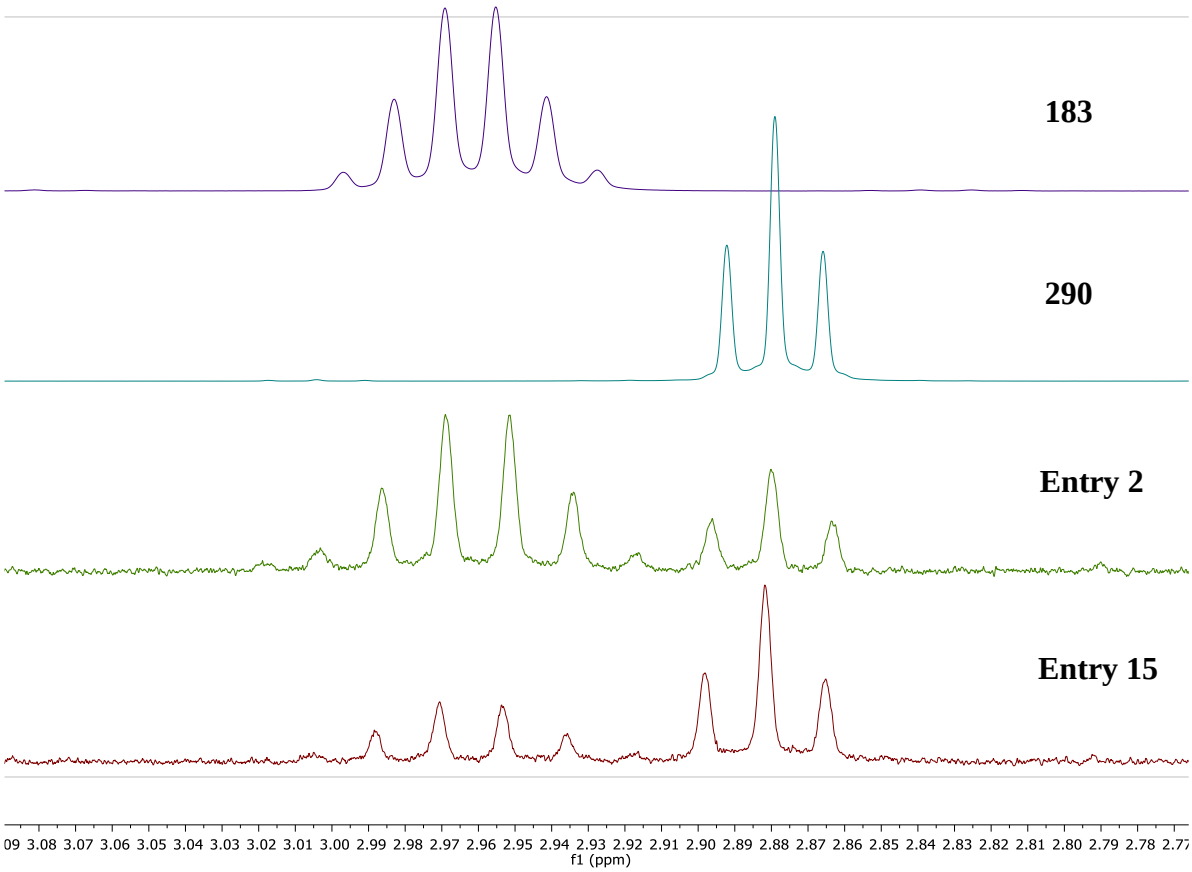


Figure 5.2: Stacked ^{1}H NMR (500 MHz, $CDCl_3$) spectra for the optimisation of the methylation of 2-phenylethanol (**290**)

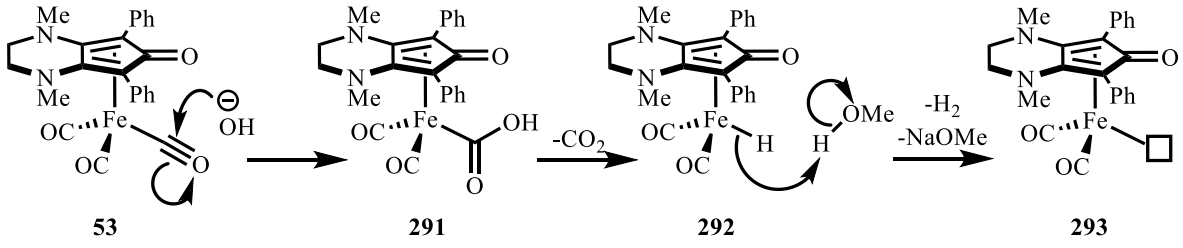
As shown in Table 5.2, a background reaction was immediately tested in the absence of precatalyst and activator (entry 1) using NaOH (2.0 equiv.), and this revealed complete starting material recovery after 24 h of reactivity. In the presence of [Fe] precatalyst **53** (5 mol%) and activator (10 mol %), the reaction worked well giving 85% of **183**, isolated to 75% (entry 2).

Table 5.2: Optimisation table for the iron-catalysed *β*-C(Sp3)-methylation

Entry[a]	Cat. loading (mol %)	Additive (mol %)	Base (equiv)	Solvent [290]	T (°C)	Time (h)	183 (%)[b]
1	-	-	NaOH (2)	MeOH (0.5 M)	130	24	< 2
2	**53 (5)**	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	24	**85 (75)**
3	**49 (5)**	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	24	< 2
4	**245 (5)**	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	24	< 2
5	**246 (5)**	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	24	< 2
6	**247 (5)**	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	24	< 2
7	**248 (5)**	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	24	< 2
8	53 (5)	-	NaOH (2)	MeOH (0.5 M)	130	24	81
9	53 (5)	**PPh_3 (10)**	NaOH (2)	MeOH (0.5 M)	130	24	76
10	53 (5)	Me_3NO (10)	-	MeOH (0.5 M)	130	24	< 2
11	53 (5)	Me_3NO (10)	**K_2CO_3** (2)	MeOH (0.5 M)	130	24	75
12	53 (5)	Me_3NO (10)	**KO*t*-Bu** (2)	MeOH (0.5 M)	130	24	80
13	53 (5)	Me_3NO (10)	**Cs_2CO_3** (2)	MeOH (0.5 M)	130	24	54
14	53 (5)	Me_3NO (10)	**KOH** (2)	MeOH (0.5 M)	130	24	75
15	53 (5)	Me_3NO (10)	NaOH **(0.2)**	MeOH (0.5 M)	130	24	54
16	53 (5)	Me_3NO (10)	NaOH **(4)**	MeOH (0.5 M)	130	24	66
17	**53 (10)**	Me_3NO (20)	NaOH (2)	MeOH (0.5 M)	130	24	73
18	**53 (2)**	Me_3NO (4)	NaOH (2)	MeOH (0.5 M)	130	24	62
19	53 (5)	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	**140**	24	79
20	53 (5)	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	**120**	24	64
21	53 (5)	Me_3NO (10)	NaOH (2)	**MeOH (1 M)**	130	24	69
22	53 (5)	Me_3NO (10)	NaOH (2)	**MeOH (0.25 M)**	130	24	57
23	53 (5)	Me_3NO (10)	NaOH (2)	**MeOH/PhMe (0.5 M)**	130	24	72
24	53 (5)	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	**6**	70
25	53 (5)	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	**48**	81
26[c]	53 (5)	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	24	34
27[d]	53 (5)	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	24	83
28[e]	53 (5)	Me_3NO (10)	NaOH (2)	MeOH (0.5 M)	130	24	84

[a]Reactions performed using **290** (0.5 mmol) and reagent grade MeOH. [**290**] = 0.5 M. [b]As determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses. [c]$MgSO_4$ (2.0 equiv.) added. [d]Activated molecular sieves (100 mg) added. [e][Fe] precatalyst **53** (2.5 mol %) added at start, second portion of [Fe] precatalyst **53** (2.5 mol %) added after 6 h.

Other [Fe] precatalysts (**49**,**245-248**)[12,13,14,15] gave no conversion demonstrating that [Fe] precatalyst **53** is unique for this transformation. In the absence of Me_3NO, and substituting this for PPh_3 (entries 8-9), gave a small decrease in conversion. This implies that hydroxide can be used to activate the precatalyst as shown in Scheme 5.8.



53 **291** **292** **293**

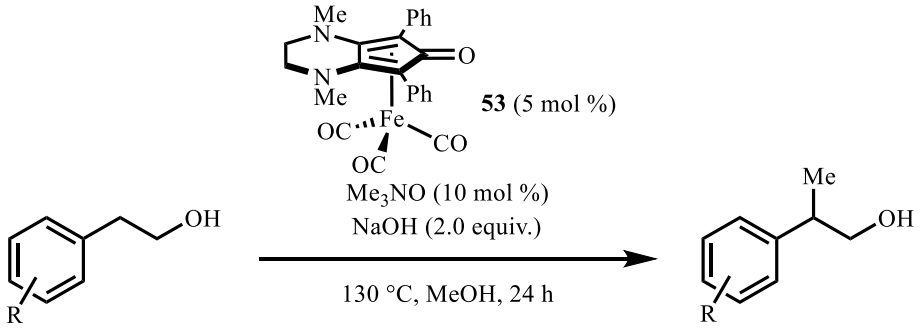
Scheme 5.8: Precatalyst activation using hydroxide

If the precatalyst is activated *via* the above scheme, Hieber's Method,[16] this would involve addition of hydroxide to a C≡O ligand to form the acid (**291**). Subsequent decarboxylation would yield an iron-hydride species (**292**) where in the presence of MeOH, it would undergo H_2 and NaOMe formation to generate the vacant coordination site on the metal centre (**293**).

Hence, the transformation works best when employing NaOH as base. In the absence of NaOH (entry 10), no conversion was observed, whilst substituting this base for others such as K_2CO_3 and KO^{t}Bu proved to be slightly worse (entries 10-14). Reducing or increasing the quantity of NaOH resulted in much lower conversion of **290** to **183** (entries 15-16). Lower catalyst loading resulted in lower conversion whilst double the catalyst loading still did not reach full conversion (entries 17-18). Raising or reducing the temperature was detrimental (entries 19-20), whilst a 0.5 M concentration proved to be optimal for this transformation (entries 21-23). At this stage of the optimisation, the transformation was achieved with an 85% NMR yield of the final product, and we wanted to see if we could push this to completion as not only would it be a better result but also make product isolations much simpler. It was observed that the reaction is 70% complete after 6 h whilst a lower NMR yield is obtained after 48 h which could imply the occurrence of product decomposition. Since we generate an equivalent of H_2O for every equivalent of starting material, we thought that this might affect the reversibility of the reaction reforming the starting material, so we carried out some experiments in the presence of $MgSO_4$ and activated molecular sieves (entries 26-27) as H_2O scavengers. Unfortunately, these modifications did not help in reaching full conversion, clearly showing that the presence of H_2O is not an issue in this transformation. Catalyst poisoning was also a possible issue, so an experiment was carried out which involved the addition of precatalyst **53** in portions, 2.5 mol % at the start for 6 h, and a further 2.5 mol % for 18 h (entry 28). An 84% NMR yield of **53** was obtained and this clearly showed that the catalyst was not getting poisoned. Ultimately, after this extensive optimisation, the conditions stated in entry 2 were selected.

5.2.2. Substrate scope - *β*-methylation of primary alcohols

Once we had these optimised conditions in hand, we pursued the scope of this *β*-methylation process by investigating a variety of primary and secondary alcohols.



Scheme 5.9: Substrate scope – *β*-methylation of primary alcohols

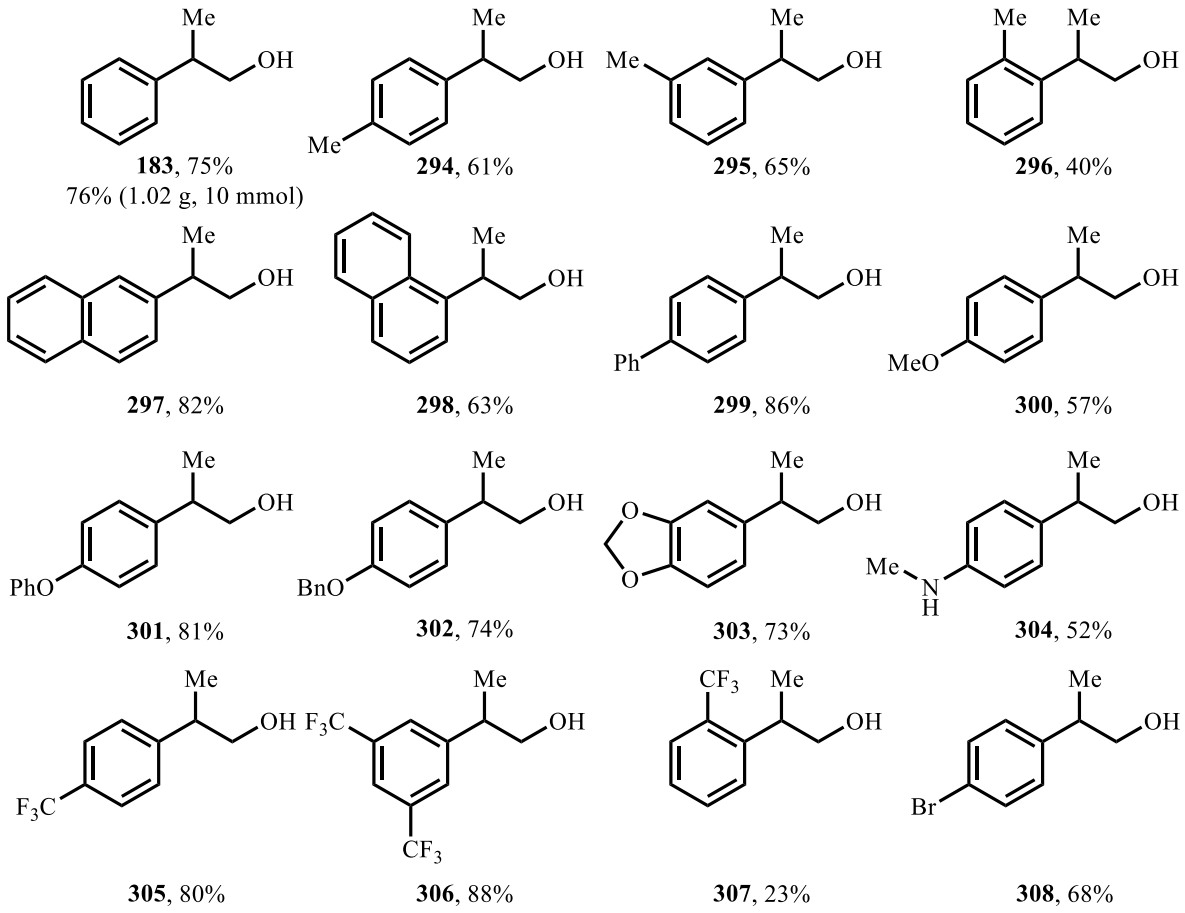
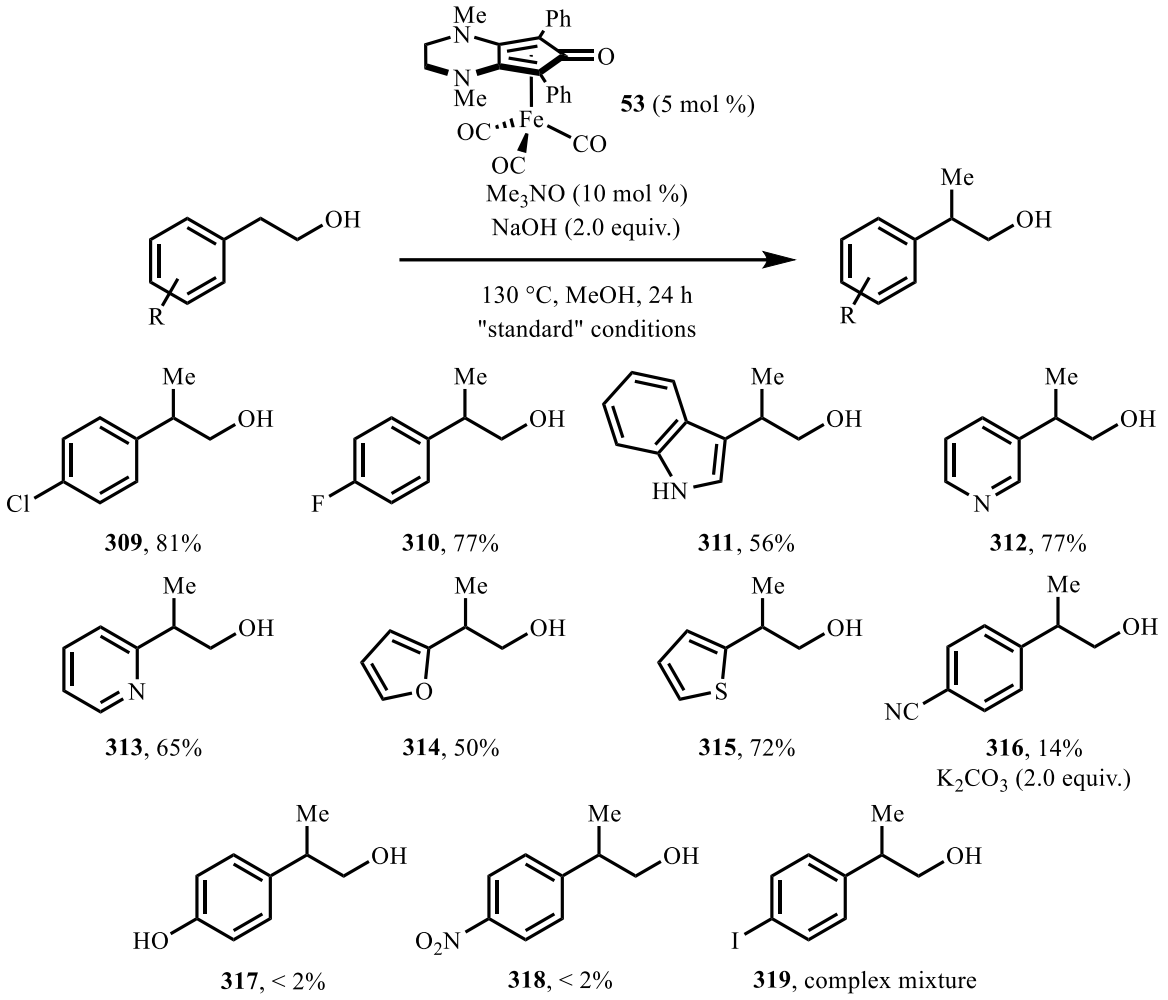


Figure 5.3: Substrate scope – *β*-methylation of primary alcohols

As shown in Figure 5.3, a diverse selection of substituted 2-arylethanols underwent efficient *β*-*C*(sp^3)-methylation, giving the corresponding methylated products in good to excellent isolated yields. The parent reaction works well on scale up giving 1.02 g of product on a 10 mmol scale. Within the aryl unit, the effect of steric hindrance was successfully investigated as a substrate containing a 2-Me substituent gave a synthetically useful yield (**294**, 40%). 3-Me, 4-Me (**294**-**296**, 61-65%) were also tolerated, together with extended aromatics (**297**-**298**, 63-82%). As expected, the more hindered 1-naphthaleneethanol underwent less efficient methylation in comparison to 2-naphthaleneethanol. Employing a 4-phenyl substituent gave an excellent yield of the respective product (**299**, 86%), and electron-donating aryl substituents (4-OMe, 4-OPh and 4-OBn) were successfully tolerated (**300**-**302**, 57-81%) together with an acetal-protected catechol motif (**303**, 73%). Even though this makes the benzylic proton less acidic, these were still successful. Interestingly, when we took 4-aminophenethyl alcohol as the starting material this underwent both *β*-*C*(sp^3)-methylation and *N*-methylation[17,18,19,20,21] obtaining **304** in a modest yield (52%). Substrates having electron-withdrawing functional groups (4-CF_3 and 3,5-$(CF_3)_2$) performed particularly well, better than electron-donating groups, giving products **305** and **306** in 80%

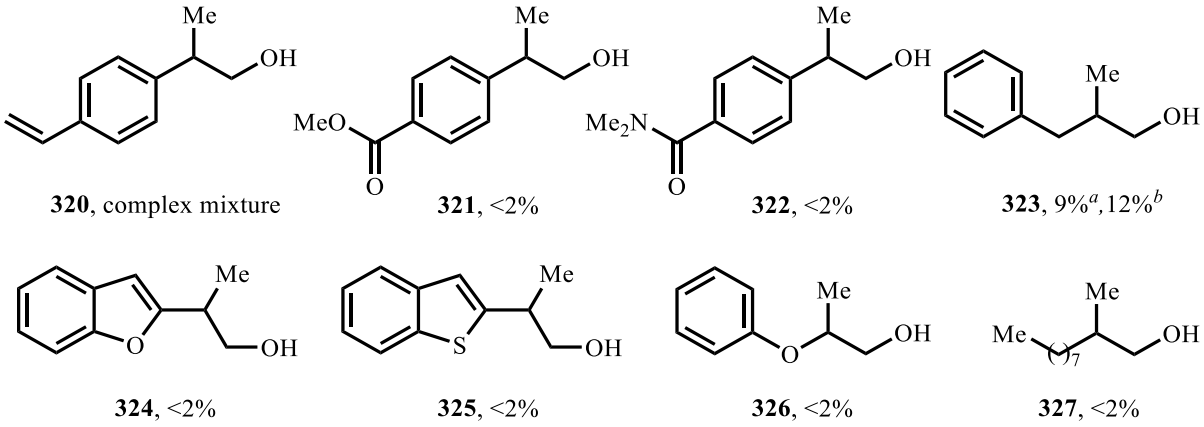
and 88% isolated yields, respectively. The main reason for such a big difference in yield may be attributed towards the increased acidity of the *in situ* generated aldehyde intermediates, making it more reactive towards aldol addition. Even though having 2-CF_3 provides some electron-withdrawing character, this did not work as well, since it also provides a steric effect (**307**, 23%) similar to **296**. Halogen-containing substrates such as 4-bromo, 4-chloro and 4-fluoro were all tolerated successfully giving excellent yields of the corresponding *β-C*(sp³)-methylated alcohols (**308**-**310**, 68-81%).



Scheme 5.10: Substrate scope – *β*-methylation of primary alcohols - continued

The incorporation of 4-Br is beneficial as it provides a functional handle for further transformations such as cross-coupling reactions.[22] Some examples of 2-heteroarylethanols also underwent successful *β-C*(sp³)-methylation. These included alcohols containing pyridyl, furan, thiophene and unprotected indole motifs, giving modest-good yields of the respective products (**311**-**315**, 50-72%). In the case of **314**, this gave a lower yield in comparison to **315**, probably due to product volatility. 4-Cyanophenethyl alcohol, gave a complex mixture under the standard conditions probably due to base hydrolysis of the nitrile group. Some product formation was observed in the ^{1}H NMR spectrum of the crude reaction

mixture when employing K_2CO_3 (2.0 equiv.) as base. Despite being a reducible substrate, it provided some functional group tolerance with a 14% isolated yield being obtained for the corresponding methylated compound (**316**). Unfortunately, when employing 4-hydroxy and 4-nitrophenethyl alcohols (**317**-**318**, <2%), no *β*-*C*(sp^3)-methylation was observed, with a complex ^{1}H NMR spectrum of the crude reaction mixture being obtained in each case. In the case of 4-iodophenethyl alcohol, the ^{1}H NMR spectrum of the crude reaction mixture revealed that the starting material underwent a reaction involving a hydride delivery to the C-I bond releasing iodide, and thus a mixture of **319** and **183** were obtained which weren't separable when analysing the crude by TLC.



320, complex mixture **321**, <2% **322**, <2% **323**, 9%[a],12%[b]

324, <2% **325**, <2% **326**, <2% **327**, <2%

Figure 5.4: Incompatible substrates for *β*-methylation

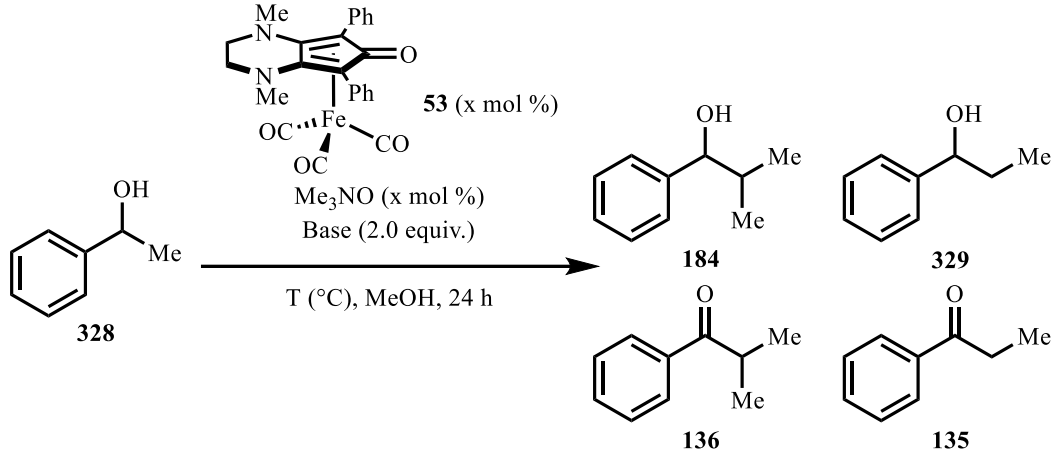
[a]Standard conditions, [b]KOtBu as base

When employing a 4-vinyl substrate (**320**), this did not show any functional group tolerance as the vinyl group got reduced due to the presence of a benzylic C*H*$_2$ quartet in the ^{1}H NMR spectrum of the crude reaction mixture. Some methylation was observed but again TLC did not show any separation between all the different components in the mixture. As noted from Scheme 5.1, the *α*,*β*-unsaturated intermediate contains a styrene moiety which easily gets reduced under these conditions. Therefore, it was expected that the process doesn't tolerate a 4-vinyl species since it is very similar to the intermediate. Other alcohols containing reducing functionalities such as an ester and an amide were also tested but both crudes revealed no aromatic signals which either meant substrate decomposition, hydrolysis or polymerisation (**321**-**322**, < 2%). From most of these results it was clear that the presence of an aryl group at the *β*-position proved to be crucial for this transformation. The requirement of a *β*-aryl group for high conversion is attributed towards the increased acidity of the corresponding *in situ* generated aldehyde intermediate. To gain confirmation on this statement, we subjected 3-phenylpropan-1-ol, having an extra methylene group between the phenyl and alcohol moieties, using our standard conditions. This gave a 9% NMR yield of

323 which was confirmed according to the data of this compound in the literature. The pK_a of the *β*-proton here is much higher, compared to the general 2-arylethanols and so, several experiments were carried out using other bases but ultimately, we couldn't improve upon a 12% NMR yield of **323** (KO^tBu, 2.0 equiv.). Enlightened by the success in the methylation of tryptophol, several 10 π heteroaromatics were synthesised for *β*-methylation, but these gave complex mixtures giving impure compounds post-isolation (**324**-**325**, < 2%). 1-decanol and 2-phenoxy-1-ethanol were also tested but gave full recovery of starting material in both cases, validating the requirement of a *β*-aryl group (**326**-**327**, < 2%).

5.2.3. Substrate scope - *β*-methylation of secondary alcohols

Since we were successful in achieving 24 examples for the *β*-methylation of primary alcohols, we then pursued to investigate the *β*-methylation of secondary alcohols. By employing 1-phenylethanol as our model substrate (Scheme 5.11), a few re-optimisation tests were carried out for the dimethylation of secondary alcohols, as shown in Table 5.3. In order to compare the conversion of starting material to product, the product for this transformation was synthesised *via* the reduction of **136** using $NaBH_4$.



Scheme 5.11: Re-optimisation of *β*-methylation of secondary alcohols

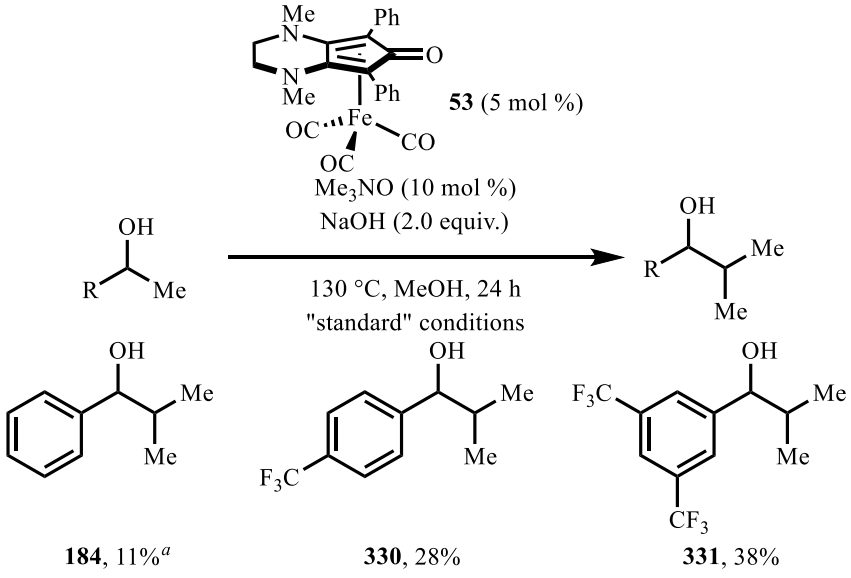
Table 5.3: Re-optimisation table for the *β*-methylation of secondary alcohols

Entry[a]	Cat. loading (mol %)	Additive (mol %)	Base (equiv)	328 (%)[b]	184 (%)[b]	329 (%)[b]	136 (%)[b]	135 (%)[b]
1	53 (5)	Me_3NO (10)	**NaOH (2)**	45	11	< 2	20	< 2
2	53 (5)	Me_3NO (10)	**K_2CO_3 (2)**	42	11	< 2	44	< 2
3	53 (5)	Me_3NO (10)	**KO^tBu (2)**	51	9	< 2	33	< 2
4	**53 (10)**	**Me_3NO (20)**	NaOH (2)	42	11	6	33	< 2

[a]Reactions performed using **328** (0.5 mmol) and reagent grade MeOH. [**328**] = 0.5 M. [b]As determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

Despite re-optimisation trials, the ^1H NMR yield of **184** could not be increased more than 11%. The main reason for this is that secondary alcohols are harder to oxidise and hence, the

corresponding acetophenone is also harder to reduce since these are more electron rich than the corresponding aldehydes. The formation of α-methyated ketones was observed in all cases clearly showing that the starting oxidation and final reduction are the main problems in this transformation. However, we hoped that by taking substrates having electron-withdrawing groups within the aryl unit (Scheme 5.12), these would lower the pK_a of the α-carbonyl ketone intermediate facilitating the process to work more efficiently.



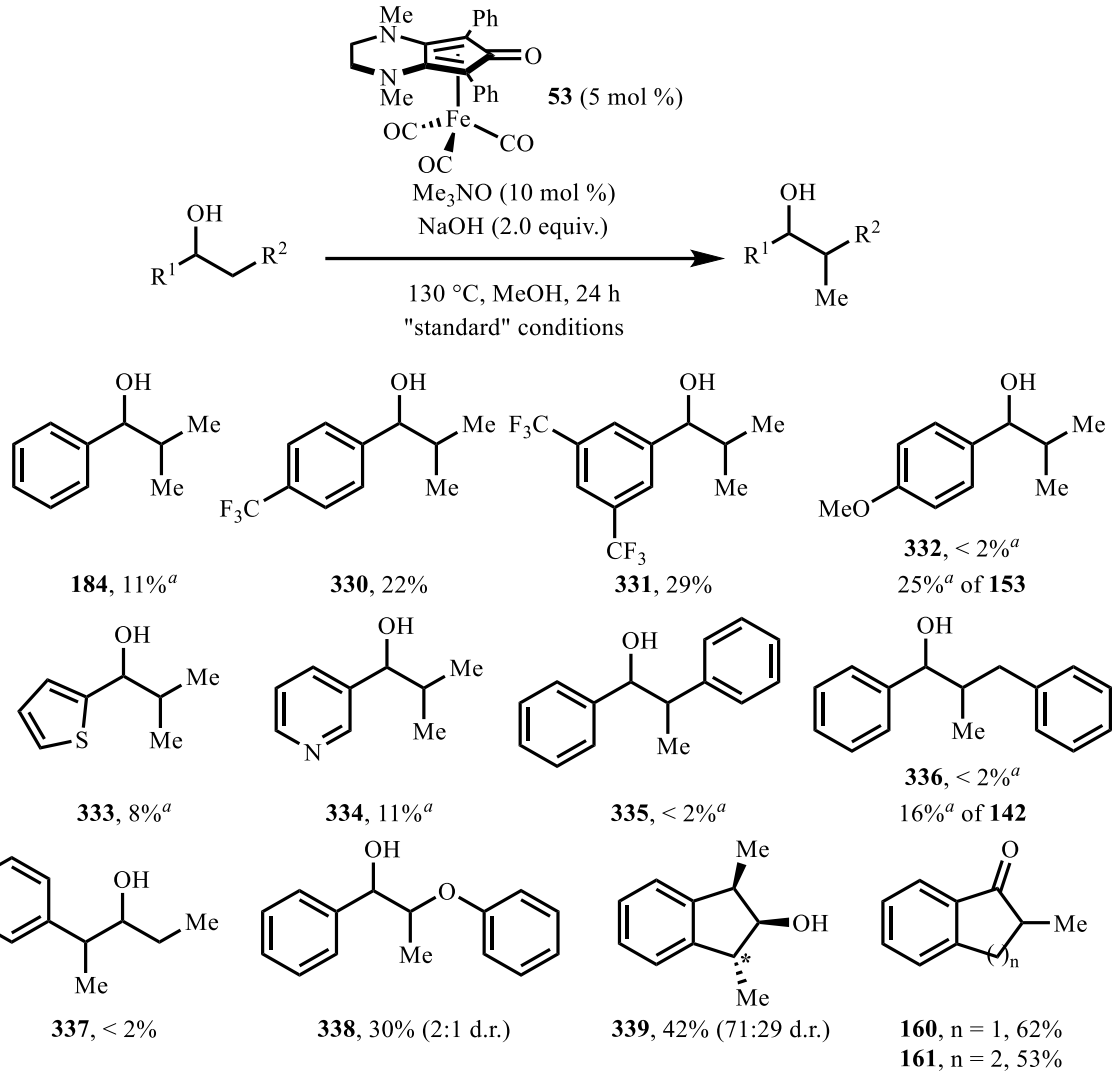
184, 11%[a] **330**, 28% **331**, 38%

Scheme 5.12: *β*-methylation of 1-arylethanols

[a]As determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard

From Scheme 5.12, clearly electron-withdrawing groups have an impact on this transformation. The product yield increased relative to the number of electron-withdrawing groups attached, confirming our hypothesis. Furthermore, we also investigated a range of 1-aryl-1-propanols. Substrates for compounds **332**-**334** and **336**-**337** were synthesised by Mubarak B. Dambatta, Daniel E. Latham and Benjamin G. Reed-Berendt, who all provided some support in the final stages of this project. Scheme 5.13 shows all the results for *β*-methylation of 1-aryl-1-propanols. Similar to 1-phenylethanol (**328**), the *β*-methylation of 1-phenyl-1-propanol also struggles to proceed since the catalytic system cannot dehydrogenate secondary alcohols efficiently. Electron-withdrawing substituents within the aryl unit also have the same effect producing the same compound in a low yield (**330**-**331**, 22-29%). On the contrary, the presence of electron-donating groups did not show any product formation (**332**, < 2%), although a small amount of α-methylated ketone **153** was present. ^{1}H NMR analysis of thiophene and pyridine containing substrates all revealed low NMR yields for the corresponding dimethylated products (**333**-**334**, < 2%), with starting material recovered in both cases. When *β*-phenyl and *β*-benzyl containing secondary alcohols were employed as substrates, no product formation was observed. However, when *β*-benzyl was used, the

presence of methylated ketone **142** was noted in the corresponding ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 5.13: *β*-methylation of 1-aryl-1-propanols

[a]As determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard

This clearly justifies the fact that the iron-hydrogen complex cannot reduce the electron-rich intermediate in these cases. All the above examples would generate ketone intermediates which would be stabilised by conjugation of the aromatic ring. When 1-benzyl-1-propanol was employed as substrate, complete starting material recovery was observed, with no formation of **337**. In this case, the intermediate produced is not stabilised by conjugation and hence, this is harder to form. Pleasingly, when 2-phenoxy-1-phenylethanol was employed as substrate, the electron-withdrawing nature of the phenoxy substituent at the *α*-position aided in oxidation of the starting material as well as methylation, since the *β*-proton is more acidic than the standard 1-phenyl-1-propanol (**328**). Despite this, the product (**338**) could only be obtained with a 30% isolated yield, 2:1 d.r. As we had some success with acyclic secondary alcohols, we then employed some benzylic cyclic secondary alcohols for the scope.

Interestingly 2-indanol underwent dimethylation producing **339** (42%, 71:29 d.r.) in a synthetically useful yield. In this transformation, 2 out of 3 possible diastereomers (Figure 5.5) could be obtained.

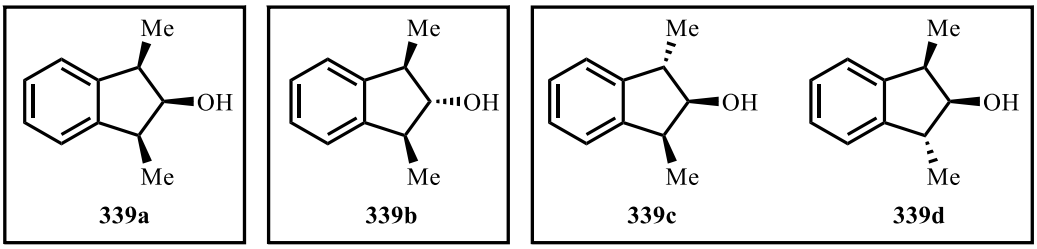


Figure 5.5: Possible diastereomers of **339**

When isolating both sets of compounds, it was immediately observed that we had **set 3** of diastereomers as the major set, due to inequivalent benzylic products and methyl groups. However, the minor set of diastereomers was determined using NOESY ^{1}H NMR spectroscopy as illustrated in Figure 5.7.

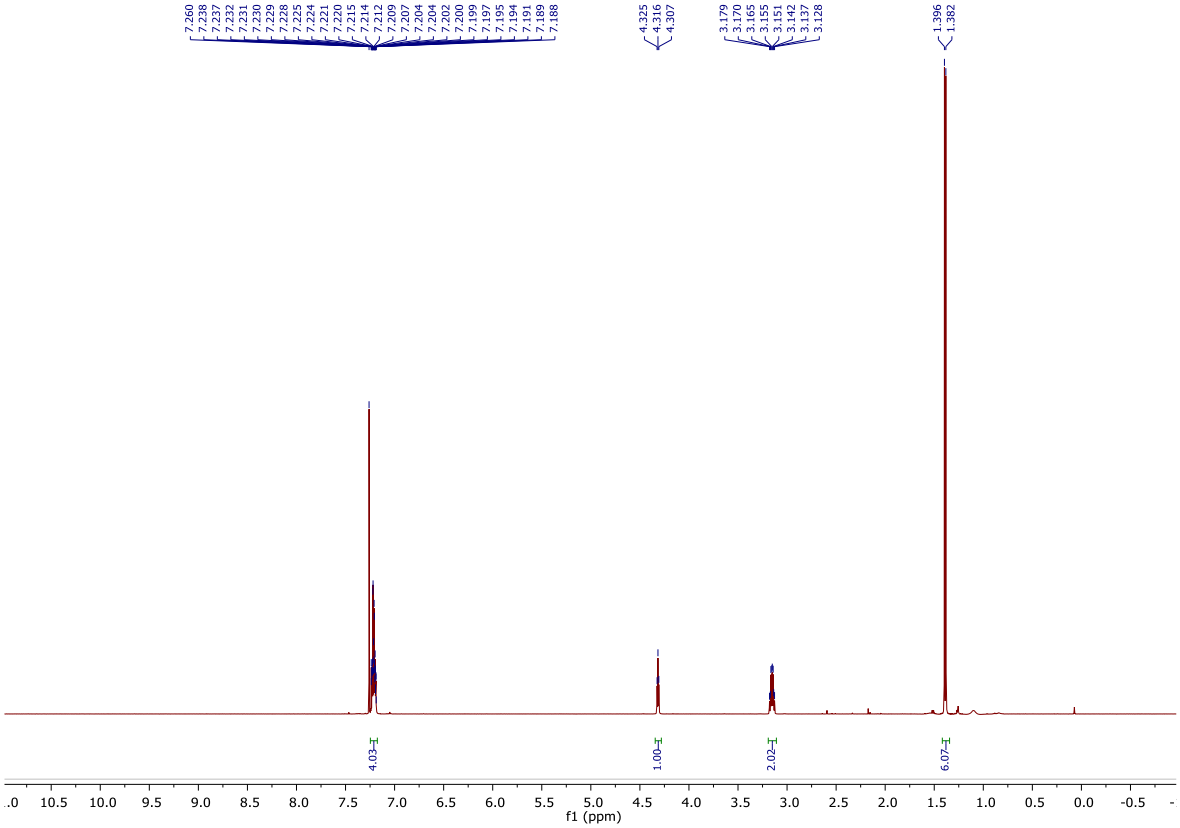


Figure 5.6: ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of pure **339a**

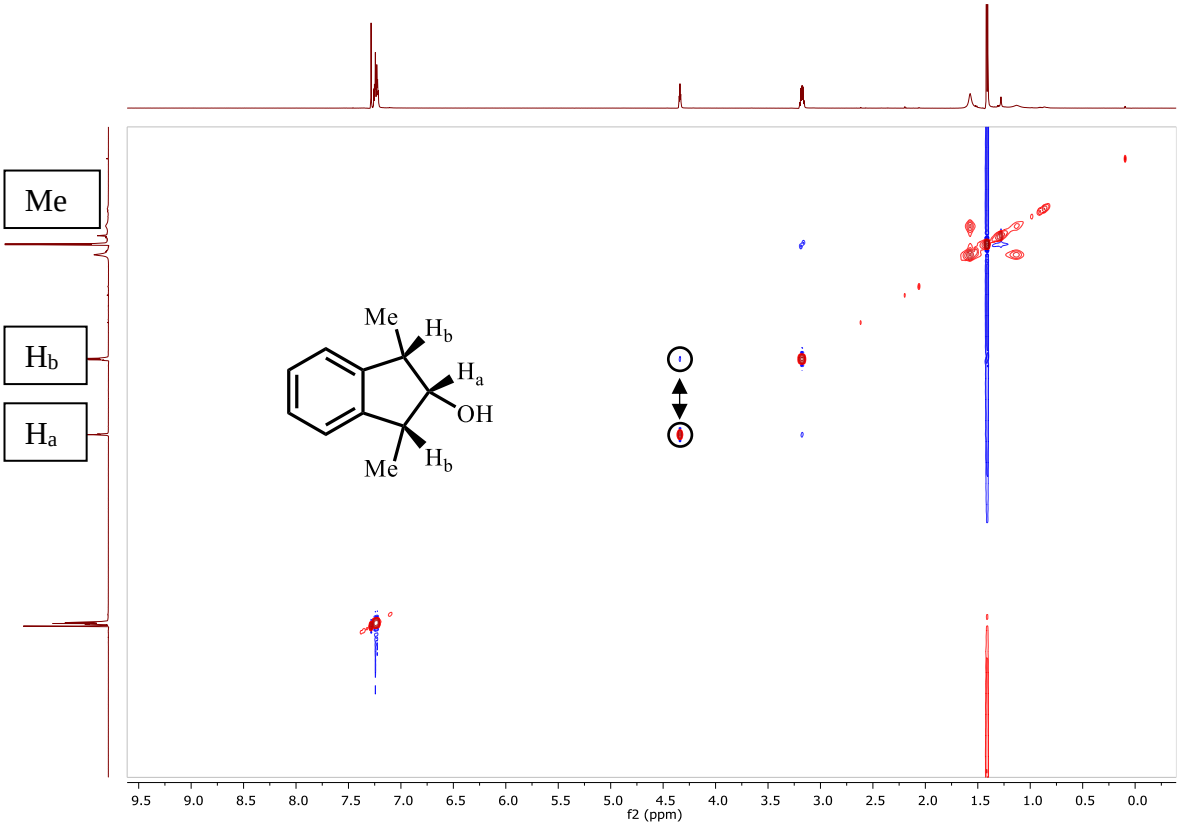


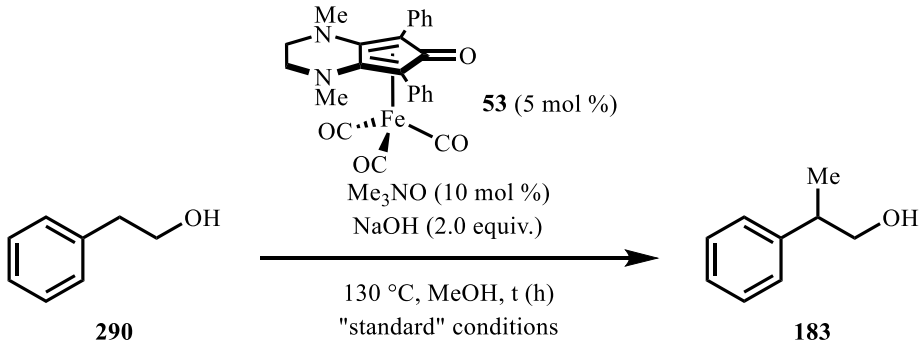
Figure 5.7: NOESY ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of **339**

We immediately noticed we had a symmetrical compound due to few peaks present in the ^{1}H NMR spectrum. By careful analysis of the NOESY ^{1}H NMR spectrum, it was confirmed that the C*H*OH proton in the product has a through space interaction with the neighbouring benzylic protons. There is not enough through space interaction with the methyl group clearly showing that the protons are all on the same face of the molecule. This was expected as hydride delivery would occur preferentially from the least hindered face, rather than the face composed of the *β*-methyl group. Hence, we had **set 1** as a minor set of diastereomers. Even though, the ketone produced *via* dehydrogenation is non-conjugated, the presence of the aromatic ring reduces the steric hindrance within the starting material and hence aids oxidation. Additionally, there are two activated benzylic positions within the starting material which can both easily undergo methylation, and the intermediate dimethylated ketone is not conjugated with the aromatic system, hence, it will be reduced to some extent. On the other hand, 1-indanol and 1-tetralol displayed dehydrogenative *α*-carbonyl methylation giving synthetically useful yields with no *β*-methylated alcohols being observed (**160**-**161**, 52-63%).

5.2.4. Mechanistic considerations

5.2.4.1. Kinetic studies

Similar to chapters 3 and 4, we wanted to carry out some mechanistic tests to understand in detail how the mechanism of this transformation proceeds. Eight identical setups of the same transformation using **290** as the model substrate were carried out in parallel and these were stopped independently at the time points stated in Table 5.4. The same mini workup was carried out, and all were sampled and analysed using ^{1}H NMR spectroscopy after the addition of mesitylene as internal standard.



Scheme 5.14: Methylation of 2-phenylethanol - time course experiments

Table 5.4: Time course experiments

Time (h)[a]	290 (%)[b]	183 (%)[b]
0.25	70	21
0.5	56	31
1	43	44
2	22	72
4	20	74
8	16	78
16	16	79
24	15	80

[a]Reactions performed using 0.5 mmol of alcohol **290** and synthesis-grade MeOH. [**290**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

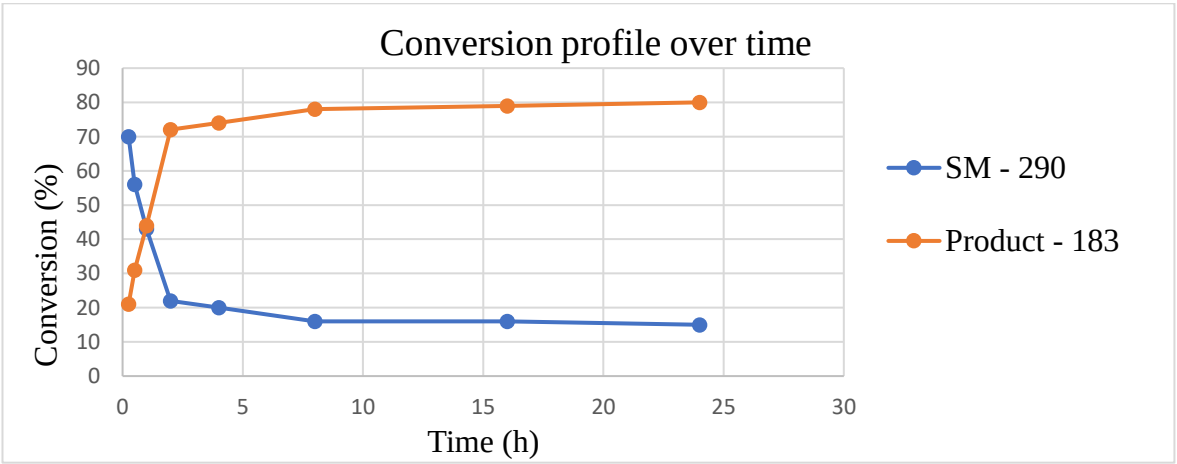
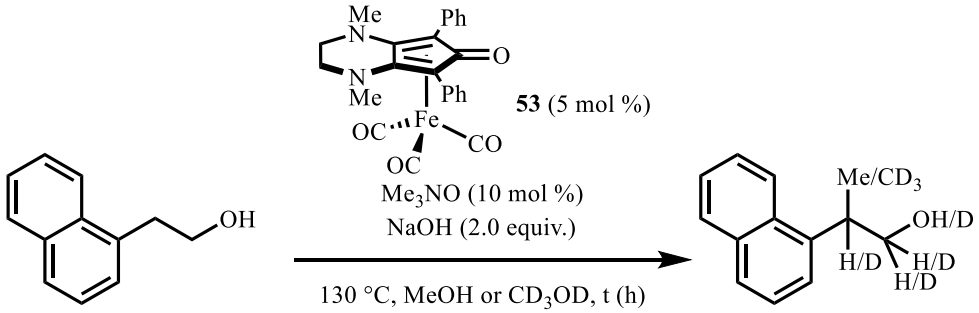


Figure 5.8: Conversion-Time graph for the methylation of 2-phenylethanol

As observed from Figure 5.8, the process is very fast. In contrast to the *α*-methylation of ketones, there is no induction period for catalyst activation here, since it is probably being thermally activated (130 °C). The process reaches 72% conversion of **183** after 2 h of reactivity. Beyond 2 h, the conversion to **183** reached a steady state, and slowly increased to 80% after 24 h. No aldehyde intermediates were observed, most likely because they are short lived species which rapidly hydrogenate to their corresponding alcohols. Following this result, a potential kinetic isotope effect was then investigated using MeOH and CD_3OD as solvents. From all the starting materials and corresponding products, all the aromatic peaks overlapped with each other. It was difficult to monitor these using the aliphatic ^1H NMR signals, but eventually 1-naphthaleneethanol showed different ArC(8)*H* signals, due to the steric encumbrance the *β*-methyl group in the product provides (**298**). The above reactions were repeated using 1-naphthaleneethanol as the starting material both with MeOH and CD_3OD; and were independently stopped at the time points stated in Table 5.5.



340 **341**

Scheme 5.15: Methylation with MeOH / CD_3OD

Table 5.5: Time course experiments

Time (h)[a]	340 (%)[b] in MeOH	341 (%)[b] in MeOH	340 (%)[b] in CD_3OD	341 (%)[b] in CD_3OD
0.25	85	8	84	8
0.5	79	13	79	12
1	68	27	75	16
2	49	44	66	25
4	36	59	63	26
8	35	60	63	27
16	34	62	63	28
24	33	63	63	28

[a]Reactions performed using 0.5 mmol of alcohol **340** and synthesis-grade MeOH. [**340**] = 0.5 M. [b]Yield after 24 h as determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

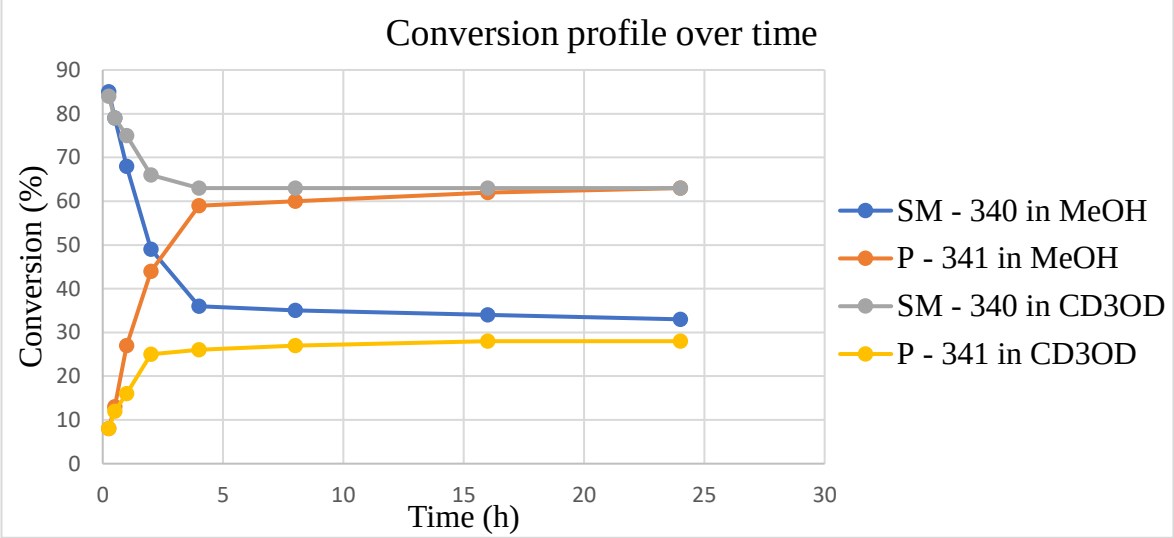
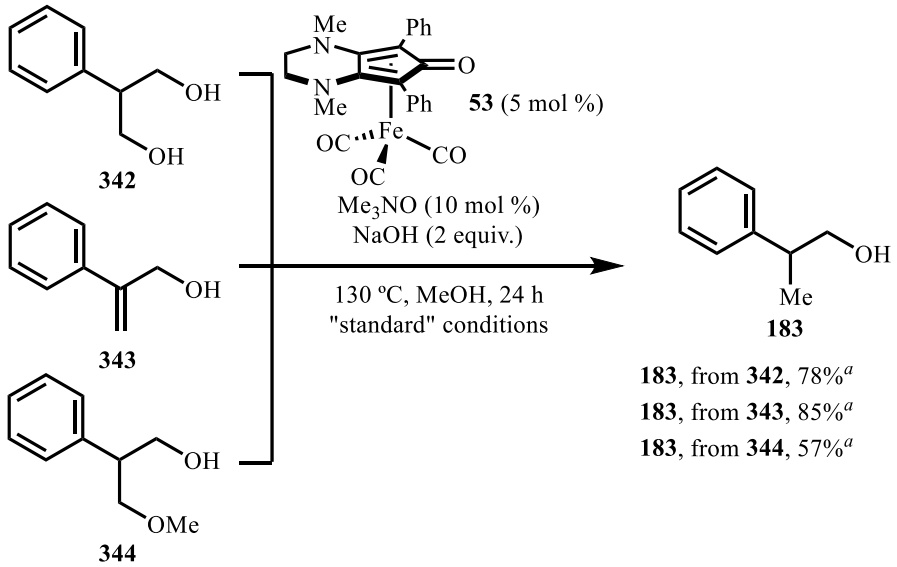


Figure 5.9: Conversion-Time graph for the methylation of 1-naphthaleneethanol using MeOH and CD_3OD

As shown in Table 5.5 and Figure 5.9, the first time points revealed the same conversion both using MeOH and CD_3OD, within experimental error. Therefore, we couldn't calculate any kinetic isotope effect for this process. The reaction with CD_3OD reaches a maximum of 28% conversion over 24 h in comparison to 63% with MeOH. This implies that the catalyst is getting poisoned with the large amount of D_2 which is generated after some hours of reactivity.

5.2.4.2. Validation of plausible reaction intermediates

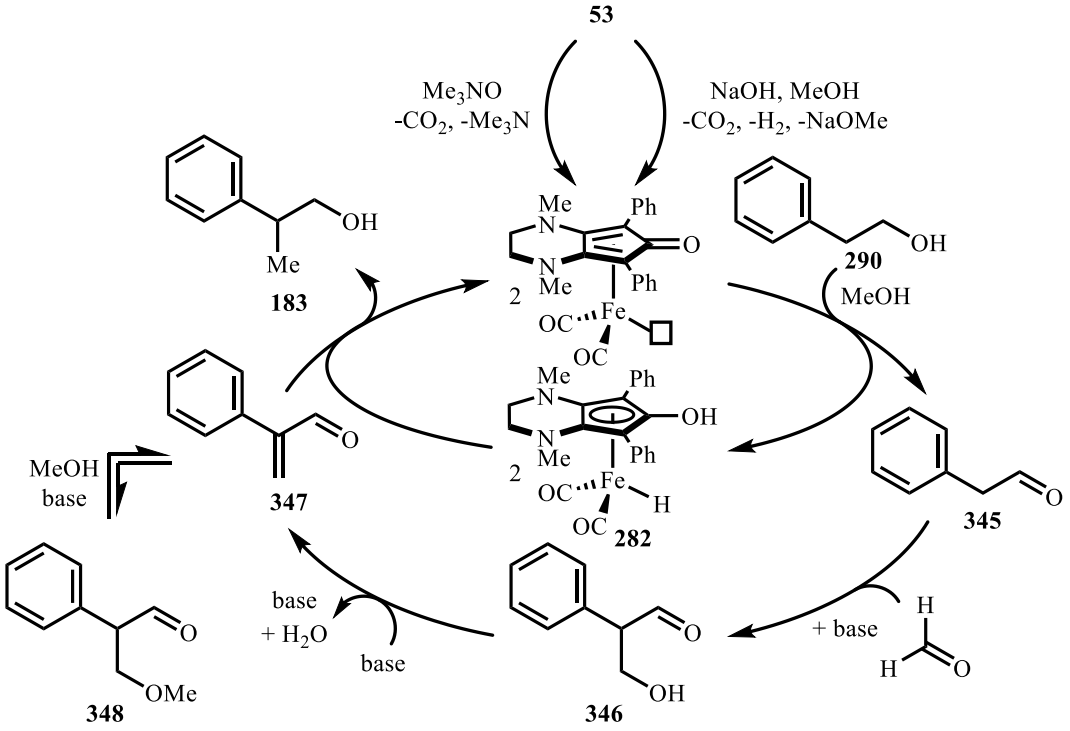


Scheme 5.16: Validation of plausible intermediates

[a]As determined by ^1H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard

With regards to mechanism, 2-phenylethanol was taken as the model substrate and several plausible intermediates relating to this starting material were synthesised (**342-344**). These

were then subjected to the standard conditions as shown in Scheme 5.16, all giving reasonable ^{1}H NMR yields confirming that they indeed are plausible intermediates within the cycle. As will be explained in Scheme 5.17, the synthesised intermediates are hydrogenated versions of some of the proposed intermediates within the cycle.



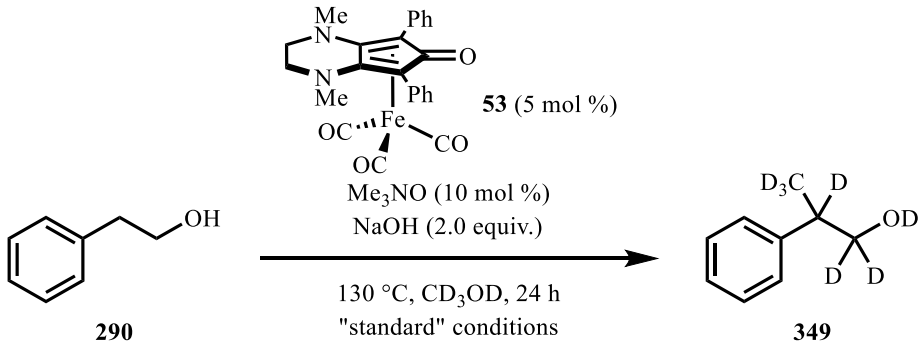
Scheme 5.17: Proposed reaction mechanism for *β*-methylation

The plausible mechanism begins as follows. Activation of precatalyst **53** by CO decoordination either using Me_3NO forming Me_3N and CO_2; or using NaOH releasing H_2 and NaOMe (Hieber's method). Each of these would generate a coordination site on the metal centre which would then dehydrogenate 2-phenylethanol (**290**) and MeOH generating phenylacetaldehyde (**345**) and formaldehyde respectively. Both aldehydes would then undergo an aldol reaction forming *β*-hydroxy aldehyde **346** that undergoes rapid base catalysed condensation forming enal **346** which is in equilibrium with the corresponding methyl ether **347**. Finally, global hydrogenation by the iron-hydrogen complex gives the final *β*-methylated product (**183**) and the regenerated active catalytic species. As stated previously, we have managed to purchase or synthesise hydrogenated versions of **346**, **347** and **348** which gave good conversions under our standard conditions. Unfortunately, after several attempts, **346** and **347** could not by synthesised. Compound **345**, which is commercially available, and **348**, which was synthesised, both gave complex ^{1}H NMR spectra of the respective crude mixtures, and no formation of **183** was observed. This is

probably due to their limited lifetime within the cycle and so when they are used from the start, they decompose rather than react under the standard conditions.

5.2.4.3. Employing CD_3OD as solvent

Finally, to gain further mechanistic insight, CD_3OD was employed as the solvent instead of MeOH under the standard conditions for the parent substrate (**290**). This unknown compound was isolated, and characterised using ^1H NMR spectroscopy with a drop of D_2O to promote deuterium exchange, as shown in Figure 5.10. This was overlapped with the pure ^1H NMR spectrum of **183**, in Figure 5.11 in order to confirm the shifts of the corresponding peaks, and hence calculate the corresponding percentage deuterium incorporations.



Scheme 5.18: Employing CD_3OD as solvent

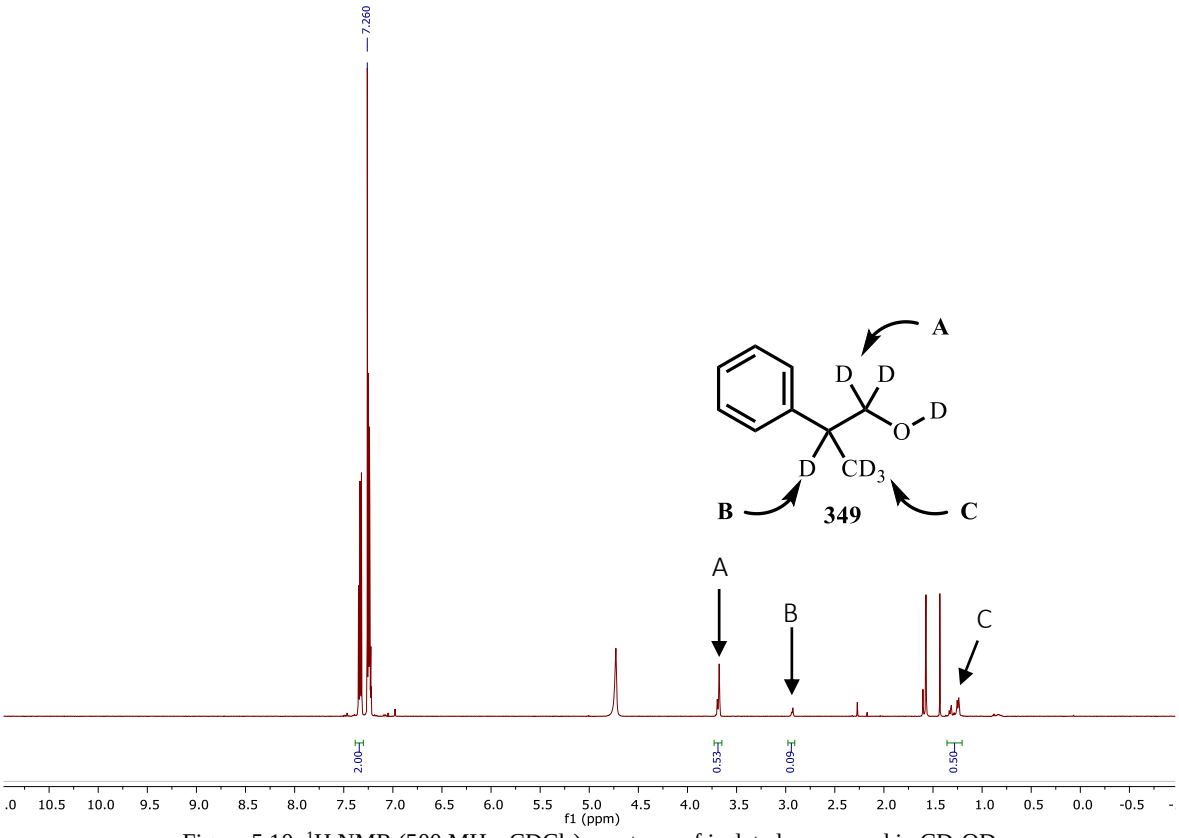


Figure 5.10: ^1H NMR (500 MHz, $CDCl_3$) spectrum of isolated compound in CD_3OD

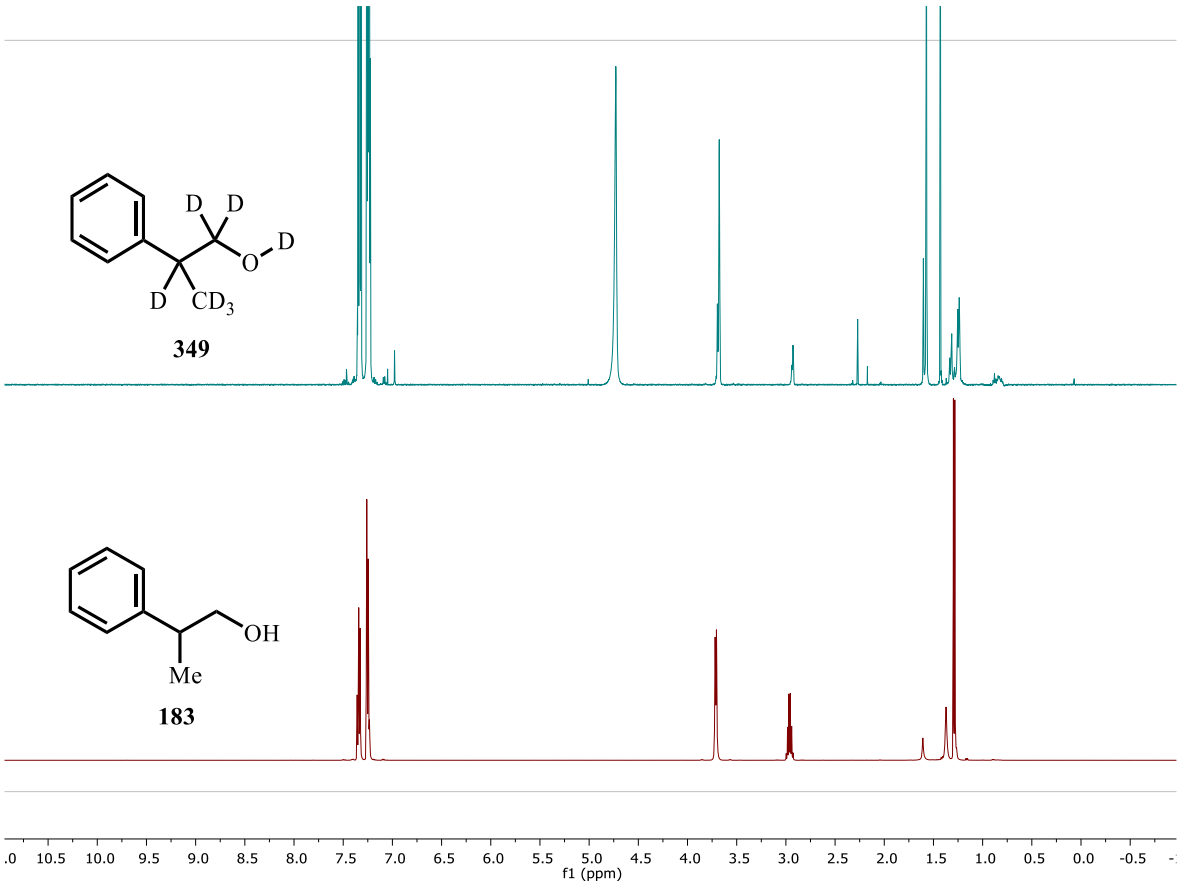


Figure 5.11: ^{1}H NMR (500 MHz, $CDCl_3$) Spectra overlap - CD_3OD (top), MeOH (bottom)

The percentage deuterium incorporation was calculated as follows for each peak represented in Figure 5.11.

Deuterium incorporation equation:

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

Peak A: 100-((0.53/2)*100) = 74% D

Peak B: 100-((0.09/1)*100) = 91% D

Peak C: 100-((0.50/3)*100) = 83% D

From these results, it was concluded that we had high deuterium incorporation at the α and β positions. Hence, we can confirm methanol as the methylating agent, and this helps us gain support for the presence of an iron hydride species and a borrowing hydrogen mechanism.

5.3. Conclusion

In conclusion, an operationally simple and efficient iron-catalysed *β*-C(sp^3)-methylation of primary alcohols has been developed. This process employs methanol as a C1 building block *via* the borrowing hydrogen approach together with a bench stable (cyclopentadienone)iron catalyst and is also the first report with a first-row transition metal for *β*-aryl alcohols. In general, an array of substituted 2-arylethanols have successfully undergone *β*-C(sp^3)-methylation efficiently, whilst some encouraging results have also been obtained with secondary alcohols.

5.4. References

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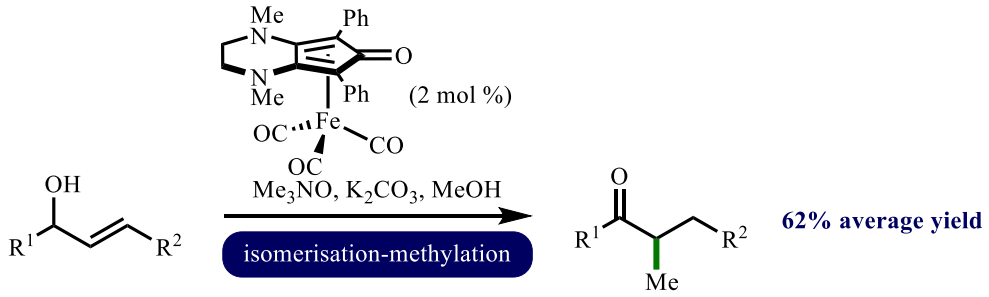
Chapter 6: One-pot conversion of allylic alcohols to *α*-methyl ketones *via* iron-catalysed isomerisation-methylation

Table of contents

For the experimental section see chapter 11

6. Preface

This chapter discusses the development of a methodology for a one-pot iron-catalysed conversion of allylic alcohols to *α*-methyl ketones. This process is referred to isomerisation-methylation and utilises a (cyclopentadienone)iron carbonyl complex as a precatalyst together with methanol as a C1 building block, accessing a range of methylated ketones in good isolated yields. (20 examples, 62% average yield).



Publication: D. E. Latham, K. Polidano, J. M. J. Williams and L. C. Morrill, *Org. Lett.*, 2019, **21**, 7914-7918.

Acknowledgements

Daniel E. Latham – A first year PhD student who finished the optimisation on this project together with the substrate scope.

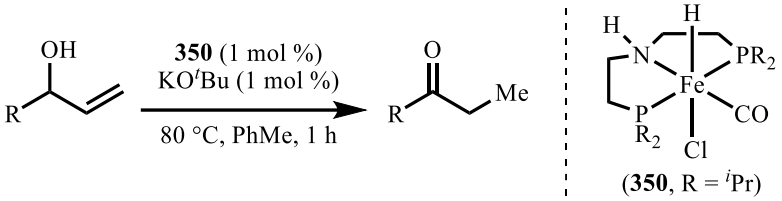
Kurt Polidano – Discovered the project, carried out initial optimisation studies together with final mechanistic investigations.

Jonathan M. J. Williams – CDT co-supervisor, University of Bath.

Louis C. Morrill – Supervisor, Cardiff University.

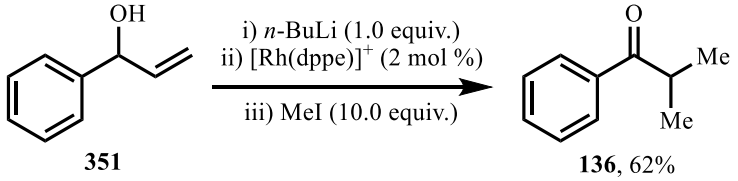
6.1. Introduction

Allylic alcohols are widely available useful compounds and have been used as building blocks in synthetic chemistry for a variety of transformations.[1] In terms of reactivity, one transformation which is of relevant importance is the isomerisation to form carbonyl compounds. This has been reported using quite a different array of catalysts. General isomerisation of allylic alcohols is also efficient, green, environmentally sustainable and can also be regarded as a highly atom economic process. Many reports using precious metal catalysts have been reported, some examples include the use of iridium,[2,3] rhodium,[4,5] palladium[6,7] and ruthenium.[8,9] Like general borrowing hydrogen processes, the utilisation of earth abundant metal catalysis has become increasingly common, even for allylic alcohol isomerisation. Specifically, there are several reports using nickel,[10] cobalt,[11] and iron.[12,13] Most recently, De Vries and co-workers have developed a methodology for the same transformation using a well-defined PNP pincer type iron catalyst.[14] In this report a variety of benzylic and *n*-alkyl allylic alcohols undergo efficient isomerisation forming propiophenones and alkyl ketones in excellent yields.



Scheme 6.1: Iron-catalysed isomerisation of allylic alcohols

Borrowing hydrogen methylation is a well-known transformation and has been carried out using a variety of precious metals[15] and first row transition metals.[16] This transformation is green, efficient and avoids the use of toxic and harmful methylating agents. As discussed in chapters 3 and 5, we have contributed to this field through the α-C(sp^3)-methylation of ketones[17] and the β-C(sp^3)-methylation of alcohols.[18] The one pot conversion of allylic alcohols to α-C(sp^3)-methylated ketones is known and this was reported in 1991[19] and 1999[20] by Motherwell and co-workers. In this report, *n*-BuLi is used to generate an alkoxide, which is isomerised using a rhodium catalyst, followed by entrapment of the enolate using iodomethane as illustrated in Scheme 6.2.

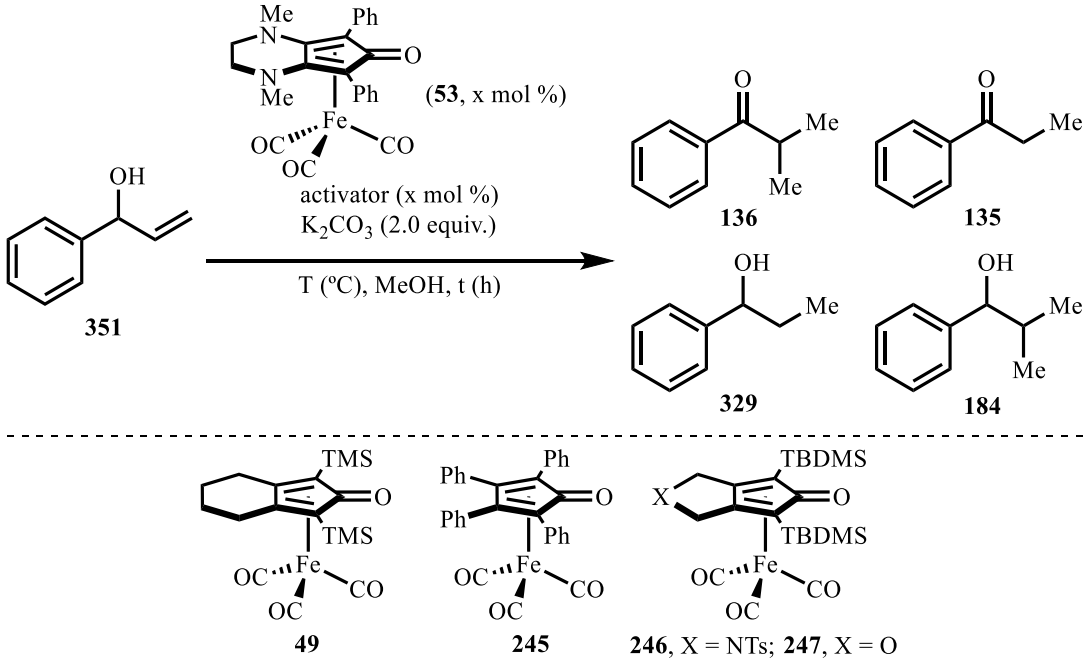


Scheme 6.2: Rhodium-catalysed isomerisation-methylation using iodomethane

This process however utilises a precious metal catalyst, a pyrophoric base and excess iodomethane as alkylating agent. Besides this report, no highly atom economic isomerisation-methylation process has yet been developed using earth-abundant transition metal catalysis. Hence, we pursued to make this transformation work using iron catalysis and methanol as a C1 building block.

6.2. Results and discussion

6.2.1. Preliminary investigations and optimisation



Scheme 6.3: Optimisation of iron catalysed isomerisation-methylation protocol

All the preliminary optimisation experiments were carried out in a sealed microwave vial. Each vial containing a magnetic stirrer bar was charged with K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv), additive (x mmol, x mol %), [Fe] precatalyst **53** (x mg, x mmol, x mol %), MeOH (1 mL) and 1-phenylprop-2-ene-1-ol (**351**) (67 mg, 0.5 mmol). The mixture was left to react at a specified temperature for the specified time. This was then cooled followed by the addition of 1,3,5-trimethylbenzene (70 µL, 60 mg, 0.5 mmol), H_2O (1 mL) and EtOAc (1 mL). In some cases, brine (1 mL) was added to aid layer separation. The mixture was then stirred for 5 minutes, the vial cap opened and left to settle for a further 5 minutes. The top layer was sampled and analysed by ^{1}H NMR spectrscopy with 1,3,5-trimethylbenzene as internal standard. Figure 6.1 shows the respective stacked spectra of the optimisation. Table 6.1 shows my contribution to this optimisation table. For a detailed optimisation table, the data can be found in the supporting information for this published report.[21]

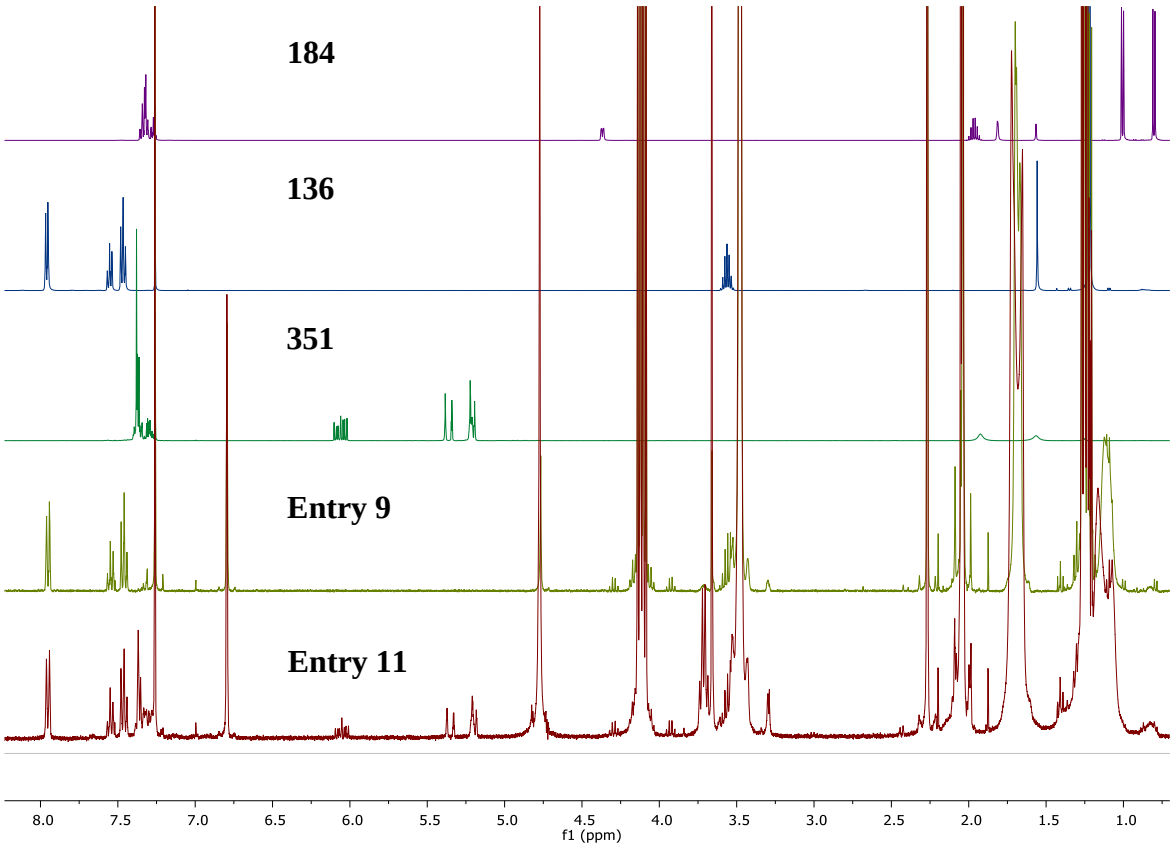


Figure 6.1: Stacked ^{1}H NMR (500 MHz, $CDCl_3$) spectra for the iron catalysed isomerisation-methylation

Table 6.1: Optimisation table for the isomerisation-methylation protocol

Entry[a]	Catalyst (mol %)	Activator (mol %)	T (°C)	Time (h)	351[b] (sM)	136[b] (P)	135[b] (NM)	329[b] RSM	184[b] RP
1	49 (5)	Me_3NO (10)	80	24	100	< 2	< 2	< 2	< 2
2	53 (5)	Me_3NO (10)	80	24	91	9	< 2	< 2	< 2
3	246 (5)	Me_3NO (10)	80	24	90	3	< 2	< 2	< 2
4	247 (5)	Me_3NO (10)	80	24	88	2	< 2	< 2	< 2
5	49 (5)	Me_3NO (10)	120	24	82	11	< 2	< 2	< 2
6	53 (5)	Me_3NO (10)	120	24	< 2	77	< 2	< 2	11
7	246 (5)	Me_3NO (10)	120	24	83	10	< 2	< 2	< 2
8	**53 (2)**	Me_3NO (4)	120	24	58	32	< 2	< 2	< 2
9	53 (2)	Me_3NO (4)	**130**	24	< 2	**88 (76)**	< 2	< 2	4
10	53 (2)	Me_3NO (4)	**110**	24	71	17	< 2	< 2	< 2
11	53 (2)	**PPh_3 (4)**	130	24	31	59	2	< 2	< 2
12	**53 (3)**	Me_3NO (6)	130	24	< 2	83	10	< 2	7
13	**53 (4)**	Me_3NO (8)	130	24	< 2	79	12	< 2	11
14	53 (2)	Me_3NO (4)	130	**2**	76	13	5	< 2	3
15	53 (2)	Me_3NO (4)	130	**4**	25	61	< 2	< 2	4
16	53 (2)	Me_3NO (4)	130	**6**	< 2	89	< 2	< 2	4
17	53 (2)	Me_3NO (4)	130	**8**	< 2	89	< 2	< 2	4

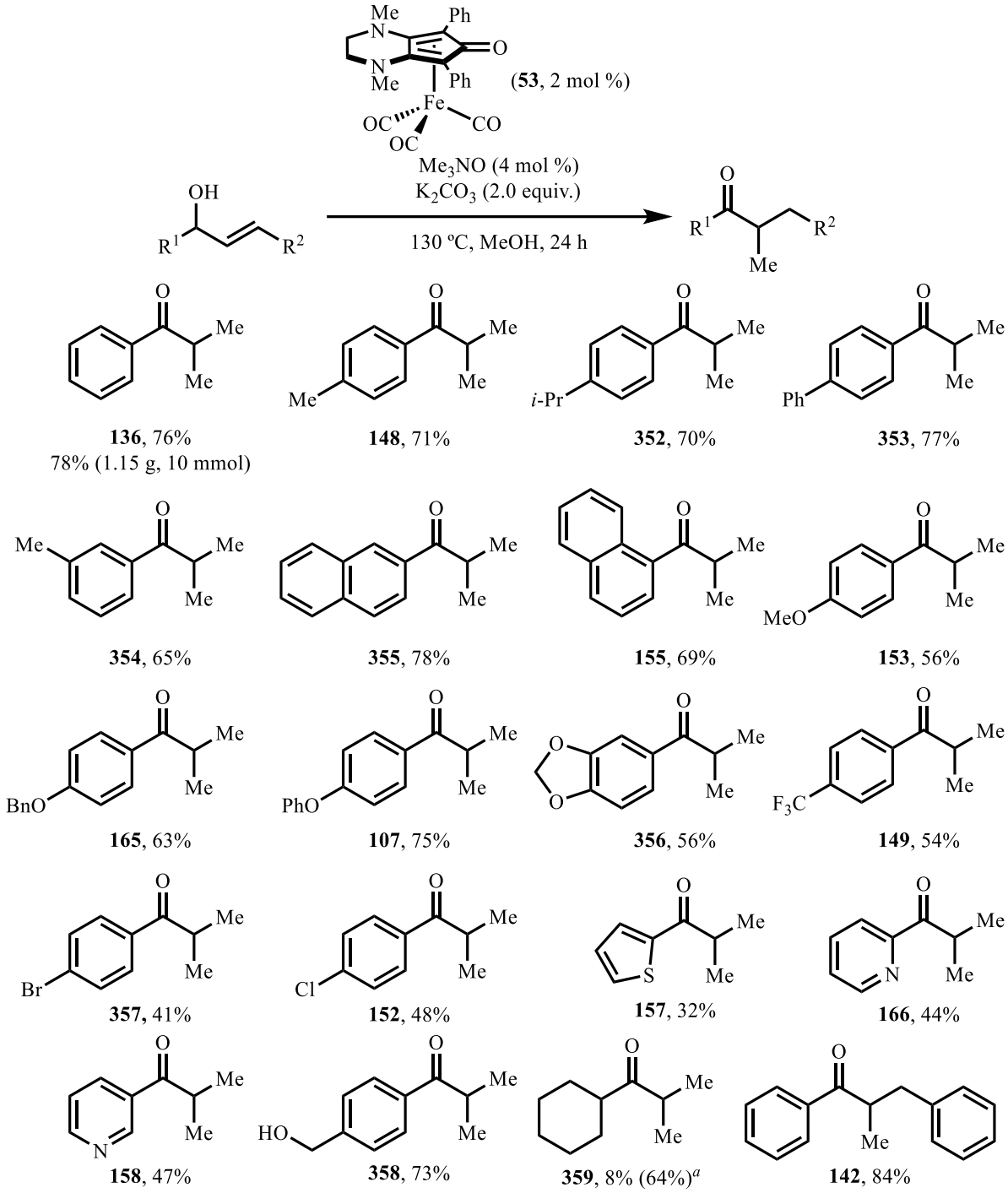
[a]Reactions performed using 0.5 mmol of allylic alcohol **351** and bench-grade MeOH. [**351**] = 0.5 M. [b]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard. Isolated yield given in parentheses.

Initial optimisation studies using K_2CO_3 (2.0 equiv.) as base and a range of iron precatalysts (**49**,**53**,**246**,**247**) demonstrated that the process gives negligible conversion at similar conditions stated in our α-C(sp^3)-methylated ketones[17] (entries 1-4). This clearly shows that the activation barrier for isomerisation of **352** to **136** is higher than that of the general

methylation process which we have published previously. At 120 °C (entries 5-7), product formation was observed using [Fe] precatalyst **53** and hence, isomerisation requires substantially higher temperature to proceed. The high temperature also aided the formation of **184** *via* hydrogenation of **136**. Reducing the catalyst loading to 2 mol % while maintaining the temperature at 120 °C (entry 8); in order to prevent overreduction of **136**, resulted in loss of conversion. When the temperature was increased to 130 °C using 2 mol % of [Fe] precatalyst **53**, this gave the optimal result of 88% of **136** isolated to 76%, with only 4% of **184** (entry 9). Lowering the temperature to 110 °C proved to be detrimental with only 17% product formation (entry 10). As shown in chapter 2, the use of PPh_3 (entry 11) did not favour the α-C(sp^3)-methylation of ketones. This was also evident in this transformation giving only 59% of **136**. When we tried to push this transformation to completion by increasing the catalyst loading to 3 and 4 mol % respectively (entries 12 and 13), this revealed the increased formation of **184** without improving conversion to our desired product. Finally, we wanted to see if the transformation required a shorter reaction time. We anticipated that by setting up various reactions at different time points, we would be able to see at what time the side-product **184** would start forming. However, under our standard conditions (entry 9), the side-product starts forming after 2 h of reactivity. Even though, the transformation reaches its maximum possible conversion after 6 h of reactivity, all reactions for substrate scope were carried out for 24 h to increase the chances of less reactive substrates to react. The project was then passed on to Daniel E. Latham who carried out the substrate scope on all aryl containing compounds.

6.2.2. Substrate scope

In general, a variety of aryl allylic alcohols undergo good-excellent isomerisation-methylation, all shown in Scheme 6.4. The process works well on a 10 mmol scale giving a 78% isolated yield of **136**. Surprisingly, **359** was formed in a 64% NMR yield, isolated in 8% yield due to volatility issues. The substrate for **359** was synthesised by Daniel E. Latham. Non-aromatic ketones are harder to oxidise as the intermediate is not stabilised by conjugation unlike acetophenone derived compounds and hence this was a surprising result.

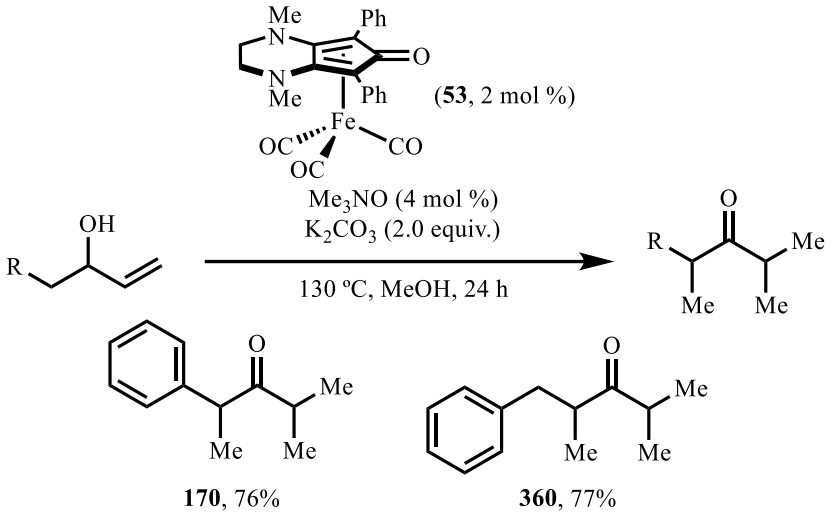


Scheme 6.4: Scope of isomerisation-methylation

[a]^{1}H NMR yield after 24 h as determined using 1,3,5-trimethylbenzene as internal standard

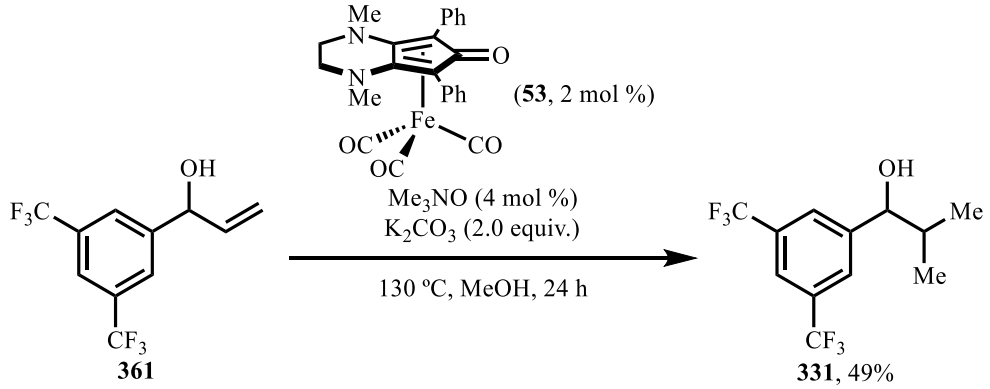
We also managed to synthesise some variants of allylic alcohols having two possible sites for methylation. Interestingly, isomerisation of the allylic alcohol worked well followed by double methylation at both possible sites, as shown in Scheme 6.5. Daniel E. Latham isolated **170** in 76% yield while I successfully isolated **360** in 77% yield, with negligible amounts of monomethylated products observed in the respective ^{1}H NMR spectra of the crude reaction mixtures. As explained in chapter 3, we were unsuccessful in carrying out selective

dimethylation of *α,α'*-alkyl ketones. In this case, this worked due to the presence of a more active catalyst, having an electron-rich framework in the reaction mixture.



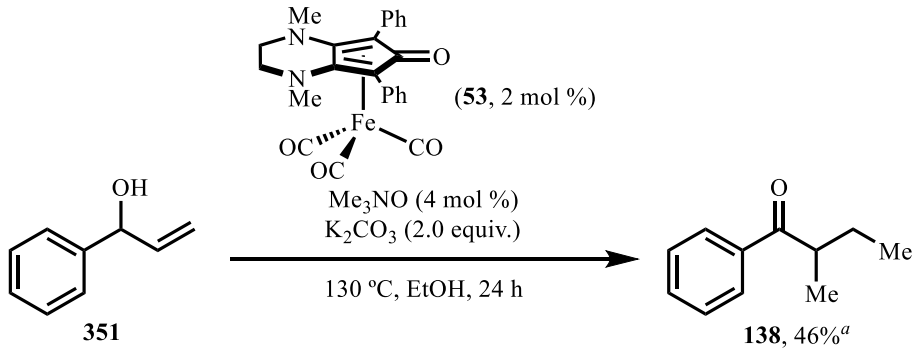
Scheme 6.5: Isomerisation-dimethylation of ketones

As shown in the optimisation studies we were avoiding over-reduction to our desired product. Scheme 6.6 shows a synthesised substrate containing electron-withdrawing groups. This promoted a formal hydromethylation of allylic alcohols.



Scheme 6.6: Hydromethylation of allylic alcohols

In this result, Daniel showed that having highly electron-withdrawing groups on the aryl unit (**361**), clearly demonstrates the ease of hydrogenation to form the methylated alcohol (**331**).



Scheme 6.7: Isomerisation-ethylation of allylic alcohols

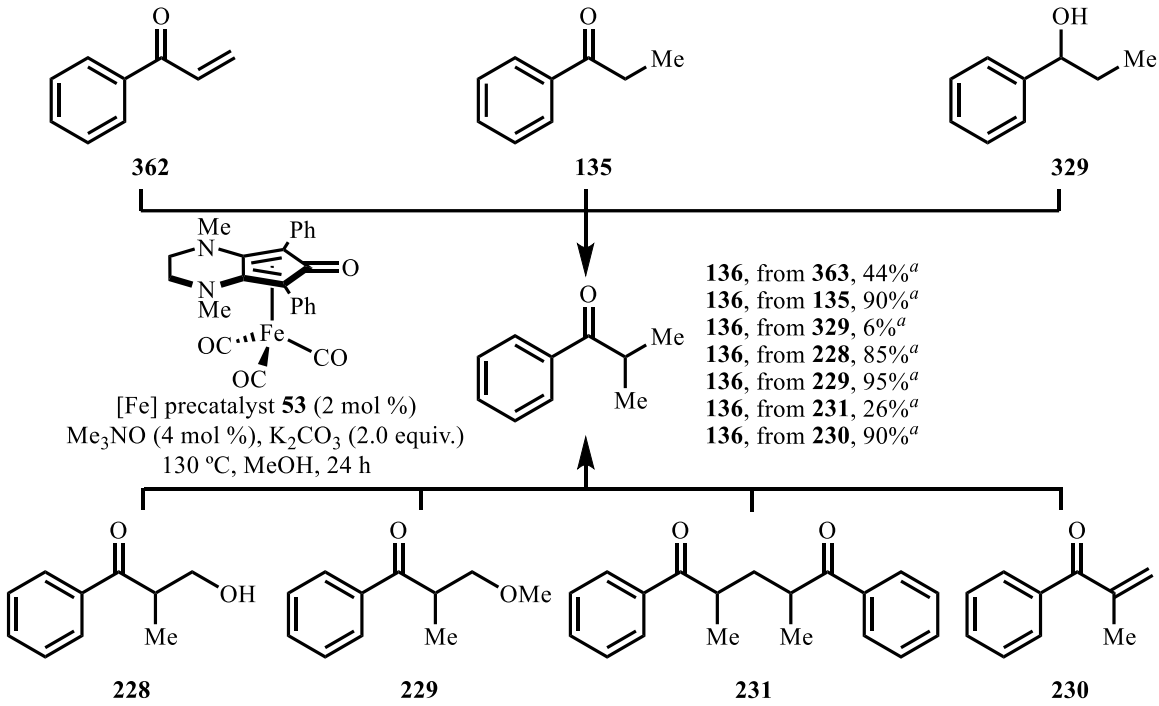
[a]^{1}H NMR yield after 24 h as determined using 1,3,5-trimethylbenzene as internal standard

Furthermore, Daniel has also provided one example of an α-ethylated ketone (**138**) using ethanol as the alkylating agent with **351** as starting material obtaining a 46% NMR yield of the product (Scheme 6.7) as compared with literature reported spectra.

6.2.3. Mechanistic considerations

6.2.3.1. Validation of plausible reaction intermediates

Similar to the α-C(sp^3)-methylation of ketones, we wanted to understand the mechanism of this transformation. Several intermediates were synthesised and tested under our standard conditions. Scheme 6.8 illustrates the corresponding tests.

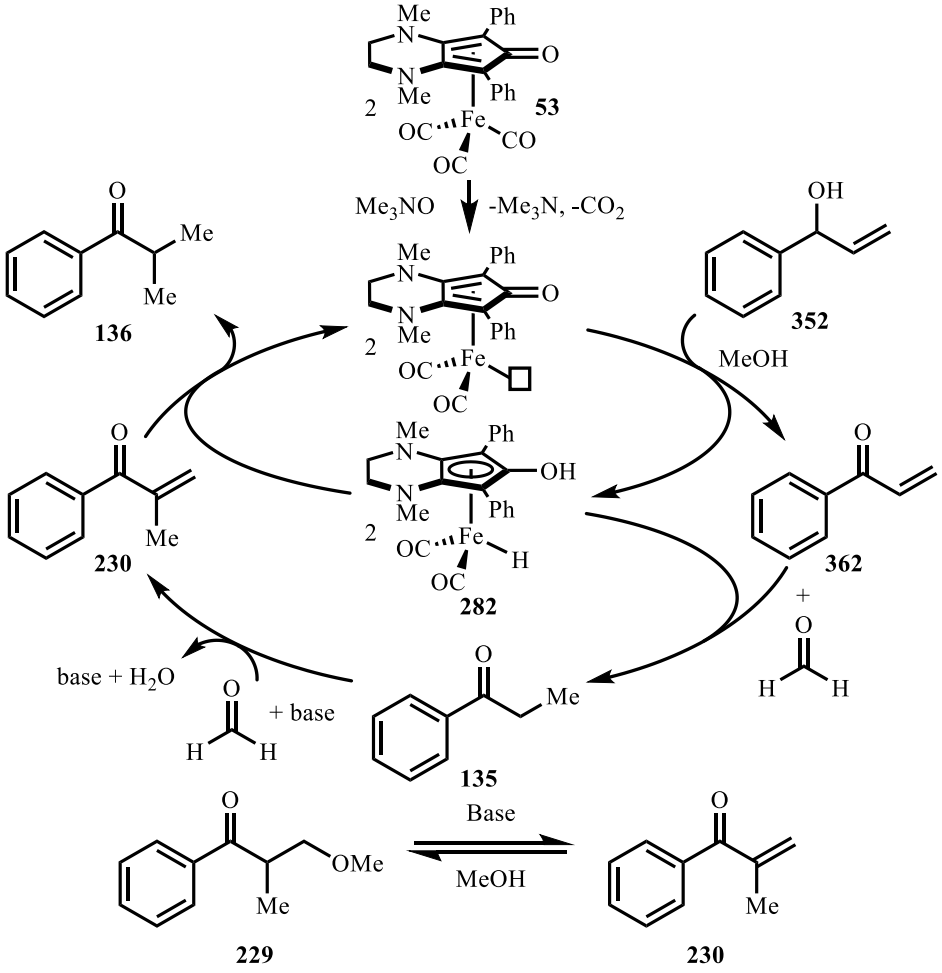


Scheme 6.8: Validation of plausible reaction intermediates

[a]Yield after 24 h as determined by ^{1}H NMR analysis of the crude reaction mixture with 1,3,5-trimethylbenzene as the internal standard.

When compared to the general α-C(sp^3)-methylation of ketones,[17] this transformation is slightly more complicated. **362**, synthesised by Daniel E. Latham, would be formed from the oxidation of 1-phenylprop-2-ene-1-ol. This gave only 44% conversion to **136** as there is probably some degree of decomposition taking place. Reduction of **362** the leads to propiophenone (**135**). **329** would be formed by transfer hydrogenation of **135**. Similar to the α-C(sp^3)-methylation of ketones,[17] β-hydroxyketone **228**, methyl ether **229**, diketone **231** and enone **230** are all plausible intermediates. These intermediates (**228**-**231**) were all

synthesised according to procedures stated in chapter 3 and were employed again for this project. When all these intermediates were subjected to our standard conditions, each one gave conversion to **136** indicating that they are all likely reaction intermediates. From these results, we propose the following catalytic cycle (Scheme 6.9).

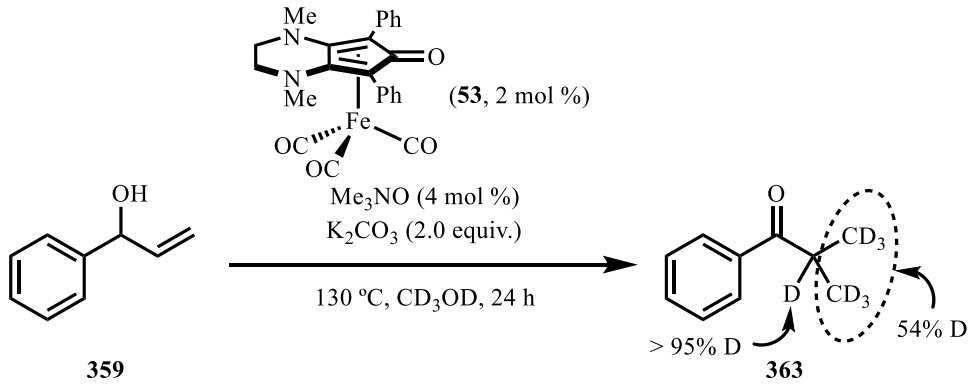


Scheme 6.9: Proposed reaction mechanism

Me_3NO forms the active catalytic species by de-coordinating one of the CO ligands, forming CO_2 a vacant coordination site on the metal centre. This active species oxidises **352** forming enone **362** which undergoes alkene hydrogenation by the iron-hydrogen complex (**282**) forming **135**. MeOH is also dehydrogenated in the presence of base by the active species forming formaldehyde. **135** undergoes subsequent aldol addition to formaldehyde forming *β*-hydroxy ketone **228** followed by a base mediated condensation producing enone **230** which is in equilibrium with methyl ether **229**. Finally, hydrogenation of enone **230** by the iron-hydrogen complex gives product **136** together with the regeneration of the active catalytic species.

6.2.3.2. Employing CD_3OD as solvent

The standard transformation was then repeated using CD_3OD to gain more support on the mechanism, as displayed in Scheme 6.10.



Scheme 6.10: Employing CD_3OD as solvent

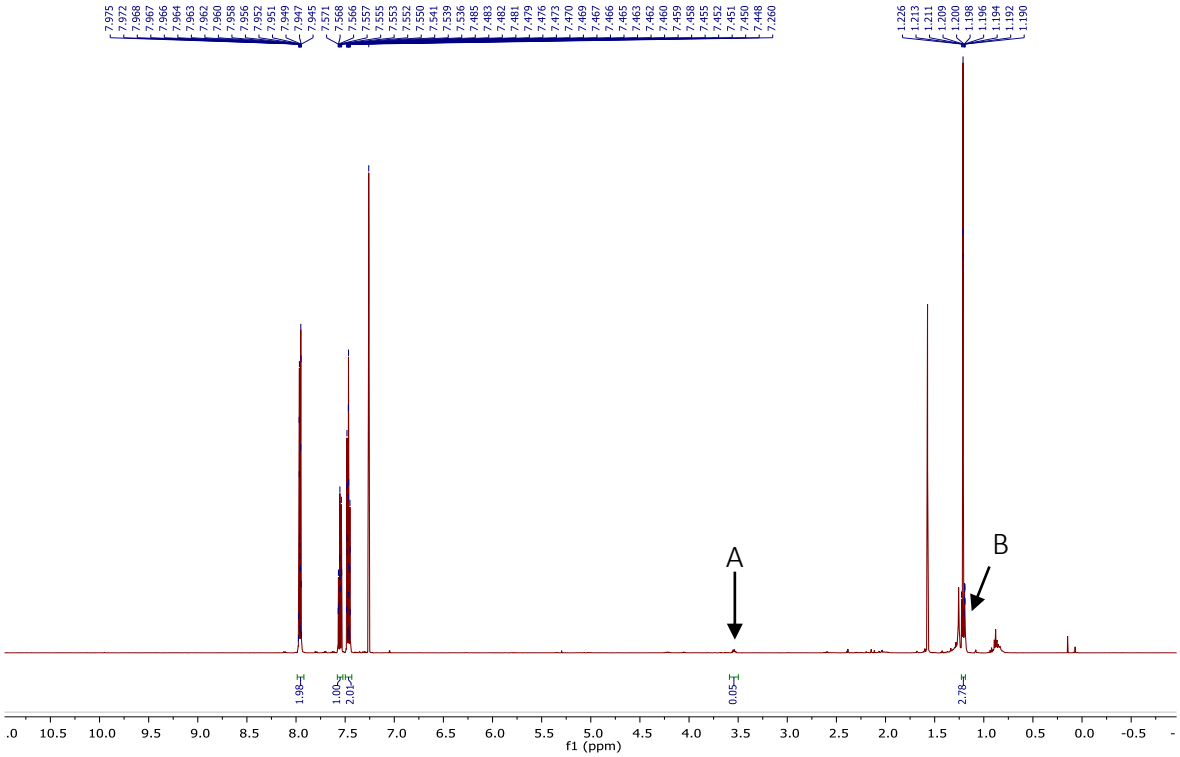


Figure 6.2: ^1H NMR (500 MHz, $CDCl_3$) spectrum of the reaction when employing CD_3OD as solvent

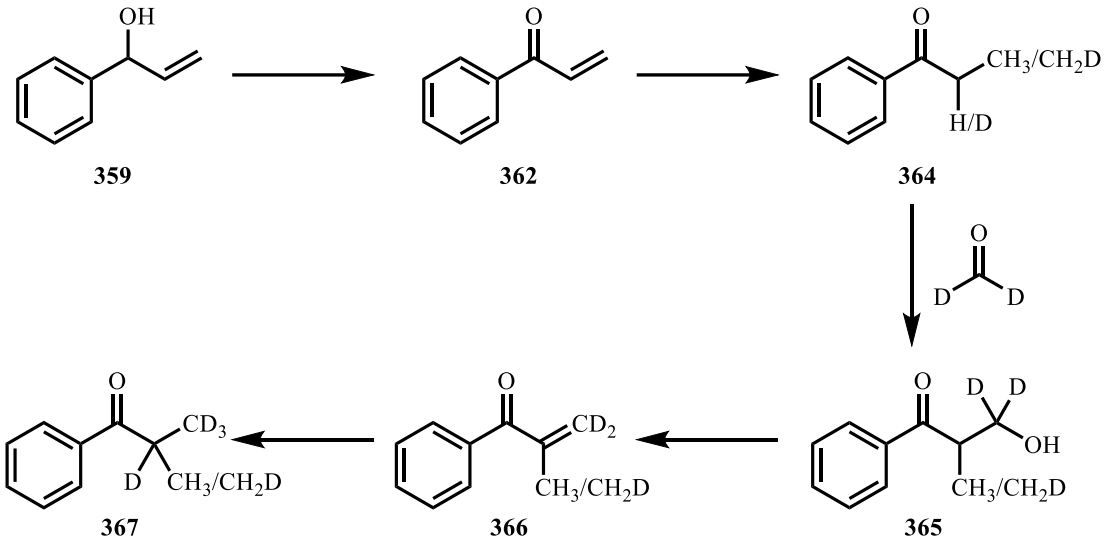
Deuterium incorporation equation: % D = 100-((peak integral/equivalent protons)*100)

Peak A: 100-((0.05/1)*100) = 95% D

Peak B: 100-((2.78/6)*100) = 54% D

As noticed from Figure 6.2, the spectrum is quite complex. Hence, we rationalised why we don't get high deuterium incorporation at both methyl groups. From the mechanism displayed in Scheme 6.9, when the redox isomerisation is carried out, propiophenone is theoretically obtained with low deuterium incorporation as when **359** is dehydrogenated to

form the enone, **362** is immediately hydrogenated using same H_2. There would be some deuterium incorporation from CD_3OD but as observed from the result in Figure 6.2, there is less chance of this occurring. From section 6.2.3.1, it was shown that enone **362** gives 44% of **136**. This is because it is a short-lived species and hence the hydrogenation to form **135** is quite fast. As illustrated in Scheme 6.11, when CD_3OD is converted to formaldehyde-d_2, the aldol product **365** would then undergo a base mediated condensation to form **366** having a CD_2 species present. Since formaldehyde-d_2 is our electrophile, this CD_2 must always be present in this transformation. The final reduction is where it gets more complicated. It really depends on how much deuterium was incorporated in the hydrogenation of **362** to **364**. The D_2-hydrogeration from **366** to **367** is more likely to occur since more CD_3OD is present that substrate **359**, and hence the formation of **367** would be the likely outcome.



Scheme 6.11: Stepwise formation of **368**

From Figure 6.2, we have also proven that the proton at the α-carbonyl position is highly deuterated giving > 95% D. Hence, this is also evidence for the likelihood of an α-CD_3 species present. Theoretically 3-4 atoms from 6 possible atoms would be deuterated giving a range of 50-67% D. We are within that range and have obtained 54% D over 6 atoms which helps us gain support for our proposed mechanism as well.

6.3. Conclusion

An operationally simple and efficient one-pot transformation for the isomerisation-methylation of allylic alcohols to α-C(sp^3)-methylated ketones has been developed. This process utilises methanol as a C1 building block, iron catalysis to promote this transformation and exhibits a good substrate scope, which is significantly better and greener

to previous synthetic methods. Mechanistic experiments provided evidence for plausible reaction intermediates, an iron-hydride species, and methanol as the methylating agent in this catalytic process.

6.4. References

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Experimental – 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_2(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 F_{254} silica) and visualisation was achieved using ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ 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).

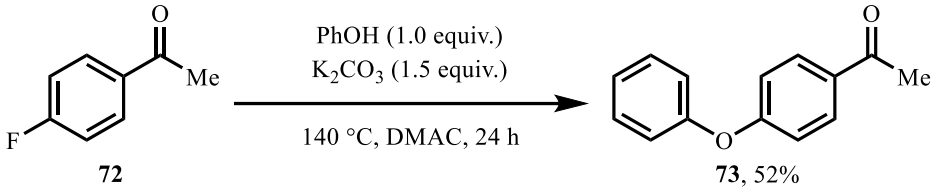
Infrared spectra were recorded on a Shimadzu IR Affinity-1 Fourier Transform ATIR spectrometer as thin films using a Pike MIRacle ATR accessory. Characteristic peaks are quoted (ν_{max} / cm^{-1}). ^{1}H, ^{13}C, ^{19}F NMR spectra were obtained on either a Bruker Avance 400 (^{1}H NMR, 400 MHz; ^{13}C NMR, 101 MHz; ^{19}F NMR, 376 MHz) or a Bruker Avance 500 (^{1}H NMR, 500 MHz, ^{13}C NMR, 126 MHz; ^{19}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}H, ^{13}C) but referenced using the residual solvent signal in ^{1}H NMR and in ^{13}C NMR spectra. ^{19}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, sept = septet, oct = octet, dt = doublet of triplets, dq = doublet of quartets, tt = triplet of triplets, ddd = doublet of doublet of doublets, m = multiplet and multiples thereof. 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.

Chapter 7: Experimental

Exploring tandem ruthenium catalysed hydrogen transfer and S_NAr chemistry

Table of contents

7.1. Synthesis of 1-(4-phenoxyphenyl)ethan-1-one – NMR studies

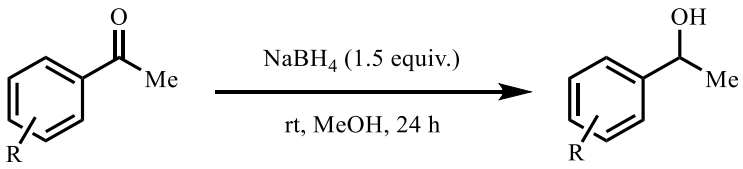


72 **73**, 52%

Under nitrogen, a flame dried round-bottomed equipped a magnetic stirrer bar was charged with phenol (659 mg, 7.0 mmol) and K_2CO_3 (1.2 g, 8.4 mmol). DMAC (7 mL) was then added followed by the addition of 4'-fluoroacetophenone (0.9 mL, 1.0 g, 7.0 mmol). The mixture was heated at 140 °C for 24 h. The reaction was then cooled, diluted with water and the organic layer extracted with Et_2O (100 mL). The organic layer was collected. The aqueous layer was washed with Et_2O (2 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by recrystallization gave the title compound as a yellow solid (823 mg, 52%); mp 51-54 °C, (hexanes) (Lit. 45-47 °C);[1] R_f = 0.43 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3059, 2994, 1672, 1572, 1414, 1360, 1244, 1161, 1111, 957, 847, 799, 768, 696, 575, 501; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.57 (3H, s, C*H*$_3$), 6.97-7.03 (2H, m, ArC(3,5)*H*), 7.04-7.10 (2H, m, ArC(2',6')*H*), 7.17-7.23 (1H, m, ArC(4')*H*), 7.36-7.44 (2H, m, ArC(3',5')*H*), 7.91-7.97 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 26.6 (*C*H$_3$), 117.4 (Ar*C*(3,5)), 120.3 (Ar*C*(2',6')), 124.8 (Ar*C*(4')), 130.2 (Ar*C*(3',5')), 130.7 (Ar*C*(2,6)), 132.1 (Ar*C*(1)), 155.7 (Ar*C*(1')), 162.1 (Ar*C*(4)), 196.9 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{14}H_{13}O_2]^+$ $(M+H)^+$ m/z : 213.0916, found 213.0921, (+2.3 ppm).

7.2. Substrate synthesis

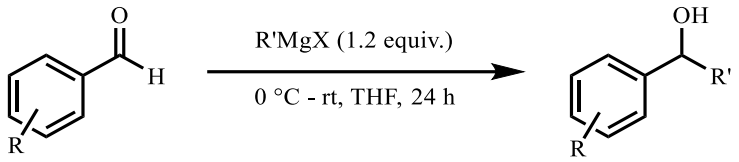
7.2.1. General procedure 1



A flame dried round-bottomed flask equipped with a magnetic stirrer bar was charged with the requisite acetophenone (1 equiv.), methanol (0.4 M) and $NaBH_4$ (1.5 equiv.). The reaction mixture was stirred at rt for 24 h. The reaction mixture cooled to 0 °C and quenched with sat. aq. NH_4Cl and H_2O. It was transferred to a separatory funnel followed by the addition of EtOAc and H_2O. The organic layer was collected, and the aqueous phase washed

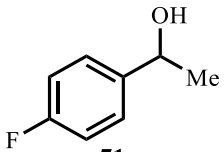
with EtOAc (x 2). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

7.2.2. General procedure 2



A flame dried round-bottomed flask equipped with a magnetic stirrer bar was charged with the requisite aldehyde (1 equiv.) and dry THF. The mixture was cooled to 0 °C and to this solution was added dropwise the appropriate Grignard reagent (1.2 equiv.). The reaction mixture was stirred at rt for 24 h. The reaction mixture cooled to 0 °C and quenched with sat. aq. NH_4Cl and H_2O. It was transferred to a separatory funnel followed by the addition of EtOAc and H_2O. The organic layer was collected, and the aqueous phase washed with EtOAc (x 2). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

1-(4-fluorophenyl)ethan-1-ol



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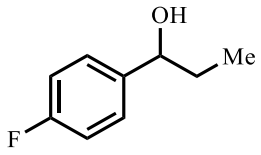
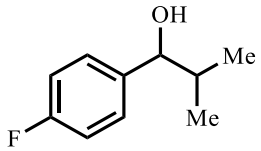
The title compound was prepared according to general procedure 1 using 4'-fluoroacetophenone (11.0 mL, 12.5 g, 90.6 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 50 x 150 mm silica) gave the title compound as a colourless oil (10.6 g, 83%), R_f = 0.30 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.48 (3H, d, *J* 6.5, CHC*H*$_3$), 1.77 (1H, br s, O*H*), 4.90 (1H, q, *J* 6.5, *CH*CH$_3$), 6.98-7.08 (2H, m, ArC(3,5)*H*), 7.30-7.39 (2H, m, ArC(2,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -115.3; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 25.4 (CH*C*H$_3$), 69.9 (*C*HCH$_3$), 115.4 (d, *J* 21.3, Ar*C*(3,5)), 127.2 (d, *J* 8.1, Ar*C*(2,6)), 141.7 (d, *J* 3.1, Ar*C*(1)), 162.3 (d, *J* 245.2, Ar*C*(4)). Spectroscopic data in accordance with that stated in the literature.[2]

1-(4-fluorophenyl)propan-1-ol



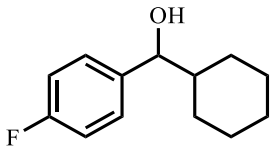
The title compound was prepared according to general procedure 2 using 4'-fluorobenzaldehyde (1.0 mL, 1.2 g, 9.3 mmol) and EtMgBr (3.7 mL, 11.2 mmol, 3 M in Et_2O). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 50 x 130 mm silica) gave the title compound as a pale-yellow oil (1.4 g, 98%), R_f = 0.38 (eluent = 20% EtOAc in hexanes). ν_{max} / cm^{-1} (film) 3343, 2970, 1604, 1508, 1221, 1155, 1011, 972, 827, 528, 538; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.90 (3H, t, *J* 7.5, C*H*$_3$CH$_2$), 1.66-1.88 (3H, m, CH$_3$C*H*$_2$, O*H*), 4.59 (1H, dt, *J* 6.6, 3.4, C*H*OH), 6.99-7.07 (2H, m, ArC(3,5)*H*), 7.28-7.34 (2H, m, ArC(2,6)*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -115.3; **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 10.2 (CH$_2$*C*H$_3$), 32.1 (*C*H$_2$CH$_3$), 75.5 (*C*HOH), 115.3 (d, *J* 21.4, Ar*C*(3,5)), 127.7 (d, *J* 8.0, Ar*C*(2,6)), 140.4 (d, *J* 3.0, Ar*C*(1)), 162.3 (d, *J* 246.0, Ar*C*(4)); HRMS (**CI$^+$**) calculated for $[C_9H_{10}OF]^+$ $(M-H)^+$ m/z : 153.0721, found 153.0720, (-0.8 ppm).

1-(4-fluorophenyl)-2-methylpropan-1-ol



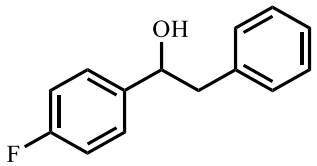
The title compound was prepared according to general procedure 2 using 4'-fluorobenzaldehyde (1.0 mL, 1.2 g, 9.3 mmol) and *i*PrMgCl (5.6 mL, 11.2 mmol, 2 M in Et_2O). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 40 x 150 mm silica) gave the title compound as a yellow oil (639 mg, 41%), R_f = 0.46 (eluent = 20% EtOAc in hexanes). ν_{max} / cm^{-1} (film) 3375, 2965, 2876, 1601, 1506, 1219, 1155, 1028, 1009, 841, 818, 773, 579, 542; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 0.79 (3H, d, *J* 6.8, CH(C*H*$_3$)(CH$_3$), 0.99 (3H, d, *J* 6.8, CH(CH$_3$)(C*H*$_3$), 1.92 (1H, oct, *J* 6.8, C*H*(CH$_3$)$_2$,), 4.36 (1H, d, *J* 6.8, C*H*OH), 6.97-7.07 (2H, m, ArC(3,5)*H*), 7.25-7.32 (2H, m, ArC(2,6)*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -115.4; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.3 (CH(*C*H$_3$)(CH$_3$), 19.0 (CH(CH$_3$)(*C*H$_3$), 35.5 (*C*H(CH$_3$)$_2$), 79.5 (*C*HOH), 115.1 (d, *J* 21.3, Ar*C*(3,5)), 128.2 (d, *J* 8.1, Ar*C*(2,6)), 139.4 (d, *J* 3.2, Ar*C*(1)), 162.3 (d, *J* 245.4, Ar*C*(4)); HRMS (**NSI$^+$**) calculated for $[C_{10}H_{12}OF]^+$ $(M-H)^+$ m/z : 167.0878, found 167.0882, (+2.6 ppm)

Cyclohexyl(4-fluorophenyl)methanol



The title compound was prepared according to general procedure 2 using 4'-fluorobenzaldehyde (1.0 mL, 1.2 g, 9.3 mmol) and CyMgCl (8.6 mL, 11.2 mmol, 1.3 M in THF/PhMe). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 50 x 150 mm silica) gave the title compound as a yellow oil (1.5 g, 76%); R_f = 0.54 (eluent: 20 % EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3362, 2920, 2851, 1605, 1512, 1450, 1219, 1152, 1078, 1013, 835, 565, 529; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 0.82-1.30 (5H, m, Cy*H*), 1.30-1.42 (1H, m, Cy*H*), 1.51-1.84 (5H, m, Cy*H*, O*H*), 1.91-2.01 (1H, m, Cy*H*), 4.36 (1H, d, *J* 7.2, C*H*OH), 6.97-7.06 (2H, m, ArC(3,5)*H*), 7.22-7.30 (2H, m, ArC(2,6)*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -115.4; **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 26.1 (Cy*C*), 26.2 (Cy*C*), 26.5 (Cy*C*), 28.9 (Cy*C*), 29.3 (Cy*C*), 45.2 (Cy*C*H), 78.8 (*C*HOH), 115.1 (d, *J* 21.3, Ar*C*(3,5)), 128.3 (d, *J* 8.0, Ar*C*(2,6)), 139.4 (d, *J* 3.1, Ar*C*(1)), 162.2 (d, *J* 246.0, Ar*C*(4)); HRMS (**CI$^+$**) calculated for $[C_{13}H_{16}OF]^+$ $(M-H)^+$ m/z : 207.1191, found 207.1193, (+1.1 ppm).

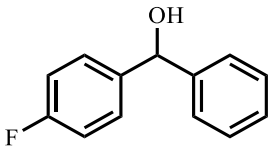
1-(4-fluorophenyl)-2-phenylethan-1-ol



The title compound was prepared according to general procedure 2 using 4'-fluorobenzaldehyde (1.0 mL, 1.2 g, 9.3 mmol) and BnMgCl (8.0 mL, 11.2 mmol, 2 M in THF). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 40 x 150 mm silica) gave the title compound as a yellow solid (1.2 g, 61%); mp 45-48 °C (Lit. 43-44 °C);[3] R_f = 0.40 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3343, 2909, 1599, 1512, 1452, 1223, 1161, 1051, 995, 820, 731, 691, 544; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.92-3.06 (2H, m, CH_2), 4.89 (1H, dd, *J* 8.0, 5.2, C*H*OH), 6.98-7.07 (2H, m, ArC(3,5)*H*), 7.14-7.20 (2H, m, ArC(2,6)*H*), 7.21-7.27 (1H, m, ArC(4')*H*), 7.27-7.35 (4H, m, ArC(2',3',5',6')*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -115.0; **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 46.3 (*C*H_2), 74.8 (*C*HOH), 115.3 (d, *J* 21.4, Ar*C*(3,5)), 126.8 (Ar*C*(4')), 127.7 (d, *J* 8.1, Ar*C*(2,6)), 128.7 (Ar*C*(2',6')), 129.6 (Ar*C*(3',5')), 137.8 (Ar*C*(1')), 139.6 (d, *J* 3.1, Ar*C*(1)),

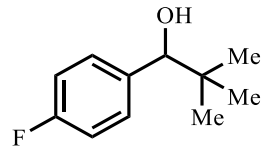
162.3 (d, *J* 246.2 Hz, Ar*C*(4)); HRMS (**NSI**$^+$) calculated for $[C_{14}H_{12}OF]^+$ $(M\text{-}H)^+$ m/z : 215.0878, found 215.0880, (+1.1 ppm).

(4'-Fluorophenyl)(phenyl)methanol



The title compound was prepared according to general procedure 1 using 4'-fluorobenzophenone (1.0 g, 5.0 mmol) and $NaBH_4$ (284 mg, 7.50 mmol). Purification by flash silica chromatography (eluent = 10-30 % EtOAc in hexanes, 50 x 130 mm silica) gave the title compound as a white solid (920 mg, 91%); mp 45-48 °C (Lit. 42-43 °C);[4] R_f = 0.40 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3383, 3300, 3022, 1601, 1508, 1491, 1449, 1227, 1159, 1036, 1013, 851, 814, 723, 694, 646, 563; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.22 (1H, d, *J* 3.5, O*H*), 5.83 (1H, d, *J* 3.5, C*H*OH), 6.98-7.06 (2H, m, ArC(3,5)*H*), 7.26-7.39 (7H, m, ArC(2,6,2',3', 4', 5', 6')*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -115.1; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 75.8 (*C*HOH), 115.4 (d, *J* 21.5, Ar*C*(3,5)), 126.6 (Ar*C*), 127.9 (Ar*C*(4')), 128.4 (d, *J* 8.2, Ar*C*(2,6)), 128.7 (Ar*C*), 139.7 (d, *J* 3.2, Ar*C*(1)), 143.8 (Ar*C*(1')), 162.3 (d, *J* 246.0, Ar*C*(4)); HRMS (**CI**$^+$) calculated for $[C_{13}H_{10}OF]^+$ $(M\text{-}H)^+$ m/z : 201.0721, found 201.0720, (-0.6 ppm).

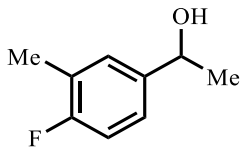
1-(4-fluorophenyl)-2,2-dimethylpropan-1-ol



The title compound was prepared according to general procedure 2 using 4'-fluorobenzaldehyde (1.0 mL, 1.2 g, 9.3 mmol) and ^{t}BuMgCl (6.6 mL, 11.2 mmol, 1.7 M in THF). Purification by flash silica chromatography (eluent = 4% EtOAc in hexanes, 40 x 150 mm silica) gave the title compound as an off-white solid (417 mg, 25%); mp 38-41 °C; R_f = 0.58 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3412, 2968, 2951, 2901, 2872, 1601, 1506, 1477, 1366, 1225, 1157, 1042, 1001, 837, 831, 768, 592, 546; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 0.91 (9H, s, C(C*H*$_3$)$_3$), 4.39 (1H, s, C*H*OH), 6.96-7.05 (2H, m, ArC(3,5)*H*), 7.23-7.32 (2H, m, ArC(2,6)*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -115.6; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 25.9 (C(*C*H$_3$)$_3$), 35.8 (*C*(CH$_3$)$_3$), 81.9 (*C*HOH), 114.5 (d, *J*

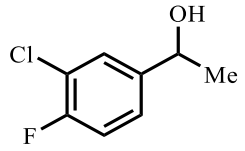
21.2, Ar*C*(3,5)), 129.2 (d, *J* 7.9, Ar*C*(2,6)), 137.9 (d, *J* 3.2, Ar*C*(1)), 162.2 (d, *J* 245.4, Ar*C*(4)); HRMS (**NSI$^+$**) calculated for $[C_{11}H_{14}OF]^+$ $(M\text{-}H)^+$ m/z : 181.1034, found 181.1038, (+2.1 ppm).

1-(4-fluoro-3-methylphenyl)ethan-1-ol



The title compound was prepared according to general procedure 2 using 4'-fluoro-3'-methylbenzaldehyde (967 mg, 7.0 mmol) and MeMgBr (2.8 mL, 8.4 mmol, 3 M in Et_2O). Purification by flash silica chromatography (eluent = 10-25% EtOAc in hexanes, 40 x 140 mm silica) gave the title compound as a pale yellow oil (1.0 g, 94%); R_f = 0.34 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3337, 2970, 1503, 1371, 1248, 1209, 1146, 1115, 928, 876, 818, 756, 604, 440; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 1.47 (3H, d, *J* 6.4, C*H*CH_3), 1.74 (1H, d, *J* 3.6, O*H*), 2.28 (3H, d, *J* 2.0, ArC(3)C*H*$_3$), 4.85 (1H, dq, *J* 6.4, 3.2, C*H*OH), 6.92-7.01 (1H, m, ArC(5)*H*), 7.11-7.17 (1H, m, ArC(6)*H*), 7.20 (1H, dd, *J* 7.5, 2.4, ArC(2)*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -119.6; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 14.7 (d, *J* 3.5, ArC(3)*C*H_3), 25.4 (CH*C*H_3), 70.0 (*C*HOH), 115.0 (d, *J* 22.4, Ar*C*(5)), 124.4 (d, *J* 8.1, Ar*C*(6)), 124.9 (d, *J* 17.4, Ar*C*(3)CH_3), 128.7 (d, *J* 5.2, Ar*C*(2)), 141.3 (d, *J* 3.5, Ar*C*(1)), 160.8 (d, *J* 244.3, Ar*C*(4)); HRMS (**NSI$^+$**) calculated for $[C_9H_{10}OF]^+$ $(M\text{-}H)^+$ m/z : 153.0721, found 153.0725, (+2.5 ppm).

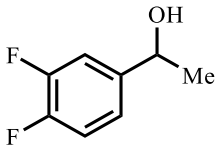
1-(3-chloro-4-fluorophenyl)ethan-1-ol



The title compound was prepared according to general procedure 1 using 3'-chloro-4'-fluoroacetophenone (690 mg, 4.0 mmol) and $NaBH_4$ (227 mg, 6.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 110 mm silica) gave the title compound as a pale-yellow oil (669 mg, 96%); R_f = 0.34 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3321, 2982, 1499, 1248, 1090, 1074, 916, 818, 708, 677, 513, 466; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.48 (3H, d, *J* 6.5, CHC*H*$_3$), 1.79 (1H, d, *J* 3.5, O*H*), 4.83-4.92 (1H, m, C*H*OH), 7.11 (1H, t, *J* 8.5, ArC(5)*H*), 7.20-7.25 (1H, m, ArC(6)*H*), 7.43

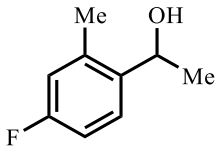
(1H, dd, *J* 7.0, 2.0, ArC(2)*H*); **^{19}F NMR (471 MHz, CDCl$_3$)** δ_F: -117.6; **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 25.4 (CH*C*H$_3$), 69.3 (*C*HOH), 116.5 (d, *J* 21.0, Ar*C*(5)), 120.9 (d, *J* 17.8, Ar*C*(3)Cl), 125.1 (d, *J* 7.2, Ar*C*(6)), 127.7 (Ar*C*(2)), 142.8 (d, *J* 3.8, Ar*C*(1)), 157.3 (d, *J* 248.5, Ar*C*(4)); HRMS (**CI$^+$**) calculated for $[C_8H_{10}N^{35}ClF]^+$ $[M+NH_4-H_2O]^+$ m/z : 174.0480, found 174.0481, (+0.4 ppm).

1-(3,4-difluorophenyl)ethan-1-ol



The title compound was prepared according to general procedure 1 using 3',4'-difluoroacetophenone (401 µL, 500 mg, 3.2 mmol) and $NaBH_4$ (182 mg, 4.8 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 100 mm silica) gave the title compound as a colourless oil (478 mg, 94%); R_f = 0.28 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3325, 2982, 1610, 1517, 1433, 1371, 1277, 1150, 1117, 876, 818, 778, 629; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 1.47 (3H, d, *J* 6.4, CHC*H*$_3$), 1.79 (1H, d, *J* 3.6, O*H*), 4.88 (1H, dq, *J* 3.6, 6.4, C*H*OH), 7.03-7.17 (2H, m, Ar*H*), 7.17-7.25 (1H, m, Ar*H*); **^{19}F NMR (377 MHz, CDCl$_3$)** δ_F: -140.0 (d, *J* 21.1, ArC(*F*)), -137.6 (d, *J* 21.1, ArC(*F*)); **^{13}C NMR (101 MHz, CDCl$_3$)** δ_C: 25.5 (CH*C*H$_3$), 69.5 (d, *J* 1.2, *C*HOH), 114.5 (d, *J* 17.7, Ar*C*), 117.3 (d, *J* 17.3 Hz, Ar*C*), 121.4 (dd, *J* 6.4, 3.6, Ar*C*(6)), 143.0 (m, Ar*C*(1)), 148.9 (dd, *J* 82.1, 12.8, Ar*C*), 151.3 (dd, *J* 83.0, 12.7, Ar*C*); HRMS (**CI$^+$**) calculated for $[C_8H_7OF_2]^+$ $(M-H)^+$ m/z : 157.0470, found 157.0470, (-0.3 ppm).

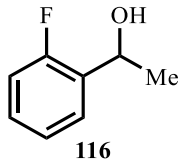
1-(4-fluoro-2-methylphenyl)ethan-1-ol



The title compound was prepared according to general procedure 2 using 4'-fluoro-2'-methylbenzaldehyde (967 mg, 7.0 mmol) and MeMgBr (2.8 mL, 8.4 mmol, 3 M in Et_2O). Purification by flash silica chromatography (eluent = 10-25% EtOAc in hexanes, 40 x 140 mm silica) gave the title compound as a pale-yellow oil (1.0 g, 93%), R_f = 0.34 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3325, 2982, 1614, 1589, 1495, 1447, 1269, 1244, 1150, 1113, 1074, 1003, 953, 889, 860, 816, 584, 480; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H:

1.45 (3H, d, *J* 6.4, C*H*CH$_3$), 1.67 (1H, d, *J* 3.6, O*H*), 2.34 (3H, s, ArC(2)C*H*$_3$), 5.10 (1H, dq, *J* 6.4, 3.6, C*H*OH), 6.84 (1H, dd, *J* 9.6, 2.8, ArC(3)*H*), 6.91 (1H, dt, *J* 8.4, 2.8, ArC(5)*H*), 7.47 (1H, dd, *J* 8.8, 6.0, ArC(6)*H*); **^{19}F NMR (377 MHz, CDCl$_3$)** δ_F: -116.4; **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 19.1 (d, *J* 1.4, ArC(2)*C*H$_3$), 24.2 (CH*C*H$_3$), 66.5 (*C*HOH), 113.0 (d, *J* 20.8, Ar*C*), 117.0 (d, *J* 21.0, Ar*C*), 126.4 (d, *J* 8.4, Ar*C*(6)), 136.8 (d, *J* 7.7, Ar*C*(2)CH$_3$), 139.6 (d, *J* 3.0, Ar*C*(1)), 161.8 (d, *J* 245.2, Ar*C*(4)); HRMS (**NSI$^+$**) calculated for $[C_9H_{10}OF]^+$ $(M-H)^+$ m/z : 153.0721, found 153.0725, (+2.5 ppm).

1-(2-fluorophenyl)ethan-1-ol



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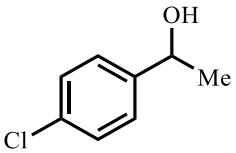
The title compound was prepared according to general procedure 2 using 2'-fluorobenzaldehyde (1.0 mL, 1.2 g, 9.5 mmol) and MeMgBr (3.8 mL, 11.4 mmol, 3M in Et$_2$O). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 40 x 130 mm silica) gave the title compound as a pale-yellow oil (1.1 g, 84%); R_f = 0.42 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3321, 2978, 1616, 1585, 1487, 1452, 1222, 1179, 1074, 1009, 901, 824, 750. 484; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.53 (3H, d, *J* 6.5, CHC*H*$_3$), 1,87 (1H, d, *J* 4.5, O*H*), 5.17-5.25 (1H, m, C*H*OH), 7.02 (1H, ddd, *J* 10.6, 8.2, 1.2, ArC(3)*H*), 7.15 (1H, dt, *J* 7.5, 1.5, Ar*H*), 7.21-7.28 (1H, m, Ar*H*), 7.49 (1H, dt, *J* 7.5, 1.5, Ar*H*); **^{19}F (377 MHz, CDCl$_3$)** δ_F: -120.0; **^{13}C NMR (101 MHz, CDCl$_3$)** δ_C: 24.1 (d, *J* 0.8, CH*C*H$_3$), 64.7 (d, *J* 3.1, *C*HOH), 115.4 (d, *J* 21.9, Ar*C*(3)), 124.4 (d, *J* 3.4, Ar*C*(5)), 126.8 (d, *J* 4.5, Ar*C*), 128.9 (d, *J* 8.4, Ar*C*), 132.8 (d, *J* 13.3, Ar*C*(1)), 159.9 (d, *J* 246.0, Ar*C*(2)); HRMS (**CI$^+$**) calculated for $[C_8H_{13}ONF]^+$ $(M+NH_4)^+$ m/z : 158.0976, found 158.0979, (+2.1 ppm).

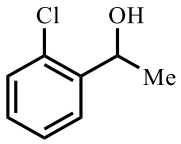
1-(4-chlorophenyl)ethan-1-ol



The title compound was prepared according to general procedure 2 using 4'-chlorobenzaldehyde (2.0 g, 14.0 mmol) and MeMgBr (7.0 mL, 21.0 mmol, 3 M in Et$_2$O). Purification by flash silica chromatography (eluent = 10-30% EtOAc in hexanes, 50 x 150

mm silica) gave the title compound as a pale yellow oil (1.9 g, 85%), R_f = 0.30 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.48 (3H, d, *J* 6.0, CHC*H*$_3$), 1.78 (1H, br s, O*H*), 4.89 (1H, q, *J* 6.5, C*H*OH), 7.32 (4H, s, ArC(2,3,4,5)*H*); **^{13}C NMR (125 MHz, $CDCl_3$)** δ_C: 25.3 (CH*C*H$_3$), 69.7 (*C*HCH$_3$), 126.9 (Ar*C*), 128.6 (Ar*C*), 133.0 (Ar*C*(4)), 144.3 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[5]

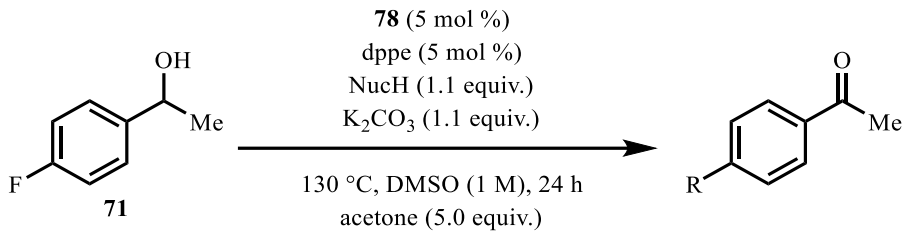
1-(2-chlorophenyl)ethan-1-ol



The title compound was prepared according to general procedure 2 using 2'-chlorobenzaldehyde (1.0 mL, 1.3 g, 8.9 mmol) and MeMgBr (3.6 mL, 10.8 mmol, 3 M in Et_2O). Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 50 x 140 mm silica) gave the title compound as a pale-yellow oil (1.28 g, 92%); R_f = 0.46 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3318, 2978, 1477, 1435, 1200, 1132, 1094, 1047, 1032, 1007, 899, 748, 691, 606, 461; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.50 (3H, d, *J* 6.5, CHC*H*$_3$), 1.97 (1H, br s, O*H*), 5.30 (1H, q, *J* 6.5, C*H*OH), 7.20 (1H, dt, *J* 7.5, 1.5, Ar*H*), 7.27-7.35 (2H, m, Ar*H*), 7.60 (1H, dd, *J* 7.5, 1.5, Ar*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 23.6 (CH*C*H$_3$), 67.1 (*C*HOH), 126.5 (Ar*C*), 127.3 (Ar*C*), 128.5 (Ar*C*), 129.5 (Ar*C*), 131.8 (Ar*C*), 143.2 (Ar*C*); HRMS (**CI$^+$**) calculated for $[C_8H_{13}{}^{35}ClON]^+$ $(M+NH_4)^+$ m/z : 174.0680, found 174.0680, (-0.1 ppm).

7.3. Scope of dehydrogenative and redox neutral S_NAr protocol

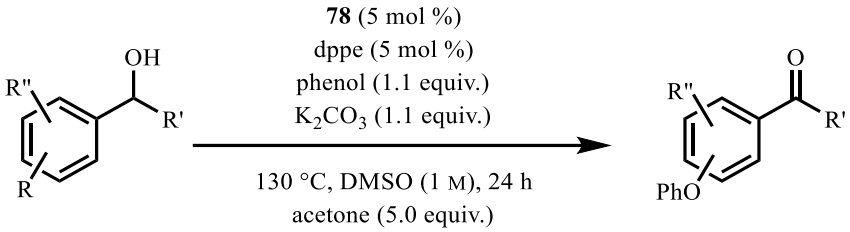
7.3.1. General procedure 3 – Nucleophile scope



A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with $Ru(PPh_3)_3(CO)(H_2)$ (18.3 mg, 0.02 mmol, 5.0 mol %), dppe (8.0 mg, 0.02 mmol, 5.0 mol %), nucleophile (0.44 mmol, 1.1 equiv.) and K_2CO_3 (61 mg, 0.44 mmol). To this mixture was added DMSO (0.4 mL), acetone (147 µL, 116 mg, 2.0 mmol) and 1-(4'-

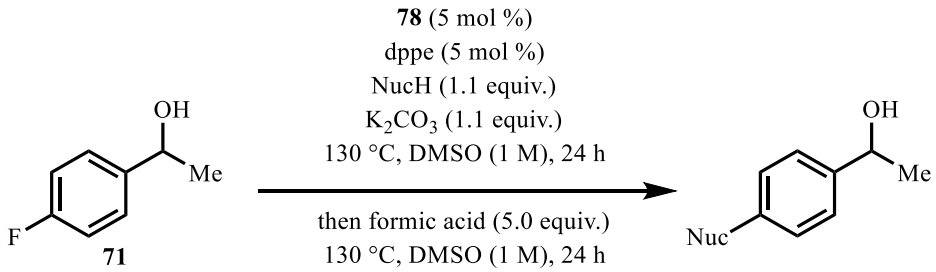
fluorophenyl)ethan-1-ol (51 µL, 56 mg, 0.4 mmol). The vial was sealed with a cap and left to react at 130 °C for 24 h. After cooling, the reaction mixture was transferred to a separatory funnel and the vial washed with EtOAc (25 mL) and H_2O (25 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

7.3.2. General procedure 4 – Fluoroarene scope



A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with $Ru(PPh_3)_3(CO)(H)_2$ (18.3 mg, 0.02 mmol, 5.0 mol %), dppe (8.0 mg, 0.02 mmol, 5.0 mol %), phenol (41 mg, 0.44 mmol, 1.1 equiv.) and K_2CO_3 (61 mg, 0.44 mmol, 1.1 equiv.). To this mixture was added DMSO (0.4 mL), acetone (147 µL, 116 mg, 2.0 mmol) and fluoroarene (0.4 mmol). The vial was sealed with a cap and left to react at 130 °C for 24 h. After cooling, the reaction mixture was transferred to a separatory funnel and the vial washed with EtOAc (25 mL) and H_2O (25 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

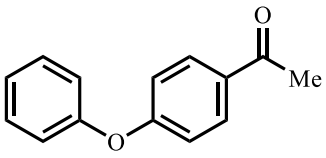
7.3.3. General procedure 5 – Redox neutral S_NAr scope



A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with $Ru(PPh_3)_3(CO)(H)_2$ (18.3 mg, 0.02 mmol, 5.0 mol %), dppe (8.0 mg, 0.02 mmol, 5.0 mol %), requisite nucleophile (0.44 mmol) and K_2CO_3 (61 mg, 0.44 mmol). To this mixture was added DMSO (0.4 mL) and 1-(4'-fluorophenyl)ethan-1-ol (51 µL, 56. mg, 0.4 mmol). The vial was sealed with a cap and left to react at 130 °C for 24 h. After cooling, formic acid (75

µL, 92.0 mg, 2.0 mmol) was then added to the reaction mixture. The reaction was then heated for a further 24 h at 130 ˚C. The reaction mixture was transferred to a separatory funnel and the vial washed with EtOAc (25 mL) and H_2O (25 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

1-(4-phenoxyphenyl)ethan-1-one



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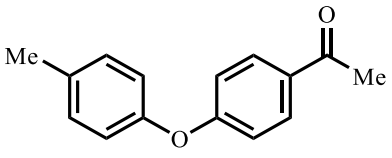
The title compound was prepared according to general procedure 3 using phenol (41 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 160 mm silica) gave the title compound as an off-white solid (67 mg, 79%). Spectroscopic data in accordance with that stated previously.

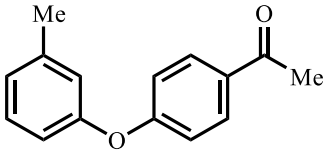
1-(4-(*p*-tolyloxy)phenyl)ethan-1-one



80

The title compound was prepared according to general procedure 3 using *p*-cresol (48 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a white solid (78 mg, 86%); mp 51-54 °C (Lit. 46-47 °C);[6] R_f = 0.48 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 1676, 1587, 1576, 1497, 1416, 1242, 1163, 961, 833, 820, 586, 544; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.37 (3H, s, ArC(4')*H*$_3$), 2.57 (3H, s, C*H*$_3$), 6.93-7.01 (4H, m, ArC(3,5,2',6')*H*), 7.16-7.23 (2H, m, ArC(3',5')*H*), 7.88-7.96 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 20.9 (ArC(4')*C*H$_3$), 26.6 (CO*C*H$_3$), 117.0 (Ar*C*(2',6')), 120.3 (Ar*C*(3,5)), 130.7 (Ar*C*(2,6,3',5')), 131.8 (Ar*C*(1)), 134.5 (Ar*C*(4')), 153.2 (Ar*C*(1')), 162.6 (Ar*C*(4)), 196.9 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{15}H_{15}O_2]^+$ $(M+H)^+$ m/z : 227.1067, found 227.1068, (+0.6 ppm).

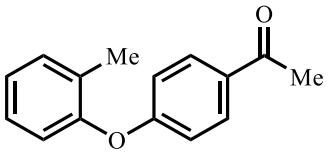
1-(4-(*m*-tolyloxy)phenyl)ethan-1-one



81

The title compound was prepared according to general procedure 3 using *m*-cresol (46 µL, 48 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a white solid (64 mg, 71%); mp 50-53 °C; R_f = 0.50 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2924, 2855, 1670, 1599, 1572, 1503, 1483, 1416, 1354, 1273, 1252, 1240, 1167, 934, 820, 791, 588, 575; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.36 (3H, s, ArC(3')H_3), 2.57 (3H, s, CH_3), 6.84-6.91 (2H, m, Ar*H*), 6.95-7.05 (3H, m, Ar*H*), 7.23-7.31 (1H, m, Ar*H*), 7.90-7.96 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 21.5 (Ar*C*H_3), 26.6 (CO*C*H_3), 117.3 (Ar*C*), 117.4 (Ar*C*(3,5)), 120.9 (Ar*C*), 125.4 (Ar*C*), 129.9 (Ar*C*), 130.7 (Ar*C*(2,6)), 131.9 (Ar*C*(1)), 140.5 (Ar*C*(3')CH_3), 155.6 (Ar*C*(1')), 162.3 (Ar*C*(4)), 196.9 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{15}H_{15}O_2]^+$ $(M+H)^+$ m/z : 227.1067, found 227.1068, (+0.6 ppm).

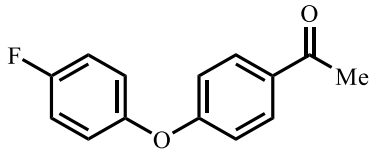
1-(4-(*o*-tolyloxy)phenyl)ethan-1-one



82

The title compound was prepared according to general procedure 3 using *o*-cresol (45 µL, 48 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a colourless oil (64 mg, 71%); R_f = 0.33 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 1676, 1603, 1576, 1501, 1485, 1358, 1233, 1159, 1109, 1040, 957, 874, 839, 777, 752, 581; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.19 (3H, s, ArC(2')CH_3), 2.56 (3H, s, COCH_3), 6.86-6.93 (2H, m, ArC(3,5)*H*), 6.99 (1H, d, *J* 8.0, ArC(6')*H*), 7.16 (1H, dt, *J* 7.5, 1.0, Ar*H*), 7.20-7.26 (1H, m, Ar*H*), 7.29 (1H, d, *J* 7.0, Ar*H*), 7.88-7.96 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 16.3 (ArC(2')*C*H_3), 26.6 (CO*C*H_3), 116.2 (Ar*C*(3,5)), 121.2 (Ar*C*), 125.5 (Ar*C*), 127.7 (Ar*C*), 130.6 (Ar*C*(2')CH_3), 130.9 (Ar*C*(2,6)), 131.6 (Ar*C*(1)), 132.0 (Ar*C*), 153.2 (Ar*C*(1')), 162.5 (Ar*C*(4)), 196.9 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{15}H_{15}O_2]^+$ $(M+H)^+$ m/z : 227.1067, found 227.1067, (+0.2 ppm).

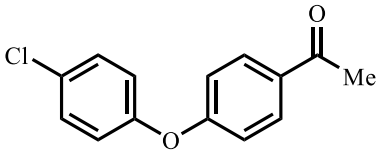
1-(4-(4-fluorophenoxy)phenyl)ethan-1-one



83

The title compound was prepared according to general procedure 3 using 4-fluorophenol (49 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound (71 mg, 78%) as a white solid; mp 67-70 °C (Lit. 67-69 °C);[6] R_f = 0.43 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 1664, 1603, 1591, 1576, 1495, 1416, 1354, 1248, 1215, 1188, 1163, 954, 880, 843, 812, 586, 546, 496; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.57 (3H, s, COCH_3), 6.93-7.00 (2H, m, ArC(3,5)*H*), 7.00-7.13 (4H, m, ArC(2',3',4',5')*H*), 7.90-7.97 (2H, m, ArC(2,6)*H*); **^{19}F NMR (376 MHz, $CDCl_3$)** δ_F: -118.1; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 26.6 (CO*C*H_3), 116.9 (d, *J* 23.4, Ar*C*(3',5')), 117.0 (Ar*C*(3,5)), 121.9 (d, *J* 8.4, Ar*C*(2',6')), 130.8 (Ar*C*(2,6)), 132.1 (Ar*C*(1)), 151.3 (d, *J* 2.8, Ar*C*(1')), 159.8 (d, *J* 244.0 Hz, Ar*C*(4')), 162.3 (Ar*C*(4)), 196.8 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{14}H_{12}O_2F]^+$ $(M+H)^+$ m/z : 231.0816, found 231.0817, (+0.5 ppm).

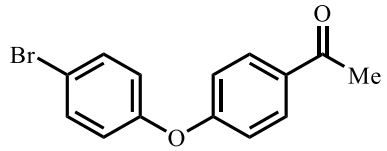
1-(4-(4-chlorophenoxy)phenyl)ethan-1-one



84

The title compound was prepared according to general procedure 3 using 4-chlorophenol (57 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as an off-white solid (69 mg, 70%); mp 69-72 °C (Lit. 63-64 °C);[6] R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2957, 2924, 2851, 1672, 1601, 1584, 1481, 1356, 1246, 1167, 1082, 1009, 961, 843, 820, 588, 577, 515, 486; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.58 (3H, s, CH_3), 6.96-7.04 (4H, m, ArC(3,5,2',6')*H*), 7.32-7.39 (2H, m, ArC(3',5')*H*), 7.91-7.98 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 26.6 (CO*C*H_3), 117.5 (Ar*C*), 121.5 (Ar*C*), 129.9 (Ar*C*(4')), 130.2 (Ar*C*), 130.8 (Ar*C*), 132.4 (Ar*C*(1)), 154.3 (Ar*C*(1')), 161.4 (Ar*C*(4)), 196.8 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{14}H_{12}O_2{}^{35}Cl]^+$ $(M+H)^+$ m/z : 247.0520, found 247.0522, (+0.7 ppm).

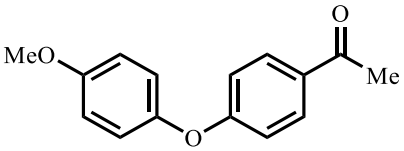
1-(4-(4-bromophenoxy)phenyl)ethan-1-one



85

The title compound was prepared according to general procedure 3 using 4'-bromophenol (76 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a white solid (84 mg, 72%); mp 78-81 °C (Lit. 74-75 °C);[6] R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 1670, 1597, 1580, 1479, 1354, 1163, 1069, 1007, 843, 826, 816, 594, 578, 501, 486; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.58 (3H, s, CH_3), 6.92-7.03 (4H, m, ArC(3,5,2',6')*H*), 7.47-7.53 (2H, m, ArC(3',5')*H*), 7.92-7.98 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 26.6 (CO*C*H_3), 117.4 (Ar*C*(4')), 117.6 (Ar*C*), 121.9 (Ar*C*), 130.8 (Ar*C*), 132.5 (Ar*C*(1)), 133.2 (Ar*C*), 154.9 (Ar*C*(1')), 161.5 (Ar*C*(4)), 196.8 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{14}H_{12}O_2{}^{79}Br]^+$ $(M+H)^+$ m/z : 291.0021, found 291.0025, (+1.4 ppm).

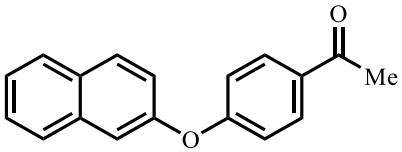
1-(4-(4-methoxyphenoxy)phenyl)ethan-1-one



86

The title compound was prepared according to general procedure 3 using 4'-methoxyphenol (55 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound (81 mg, 84%) as an off-white solid; mp 59-62 °C (Lit. 58-59 °C);[6] R_f = 0.35 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3003, 2957, 1670, 1597, 1503, 1350, 1194, 1161, 1103, 1030, 841, 827, 818, 594, 581, 511; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.56 (3H, s, COCH_3), 3.83 (3H, s, ArC(4')OCH_3), 6.89-6.97 (4H, m, Ar*H*), 6.98-7.06 (2H, m, Ar*H*), 7.88-7.95 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 26.6 (CO*C*H_3), 55.8 (O*C*H_3), 115.3 (Ar*C*), 116.5 (Ar*C*), 121.8 (Ar*C*), 130.7 (Ar*C*(2,6)), 131.6 (Ar*C*(1)), 148.7 (Ar*C*), 156.9 (Ar*C*), 163.1 (Ar*C*(4)), 196.9 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{15}H_{15}O_3]^+$ $(M+H)^+$ m/z : 243.1016, found 243.1018, (+0.9 ppm).

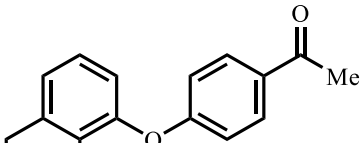
1-(4-(naphthalen-2-yloxy)phenyl)ethan-1-one



89

The title compound was prepared according to general procedure 3 using 2-naphthol (63 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 2% EtOAc in pet. ether (40-60 ^{o}C), 30 x 150 mm silica) gave the title compound as an off-white solid (76 mg, 72%); mp 74-77 °C (Lit. 68-72 °C);[7] R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3055, 1676, 1593, 1570, 1501, 1354, 1261, 1229, 1163, 1013, 959, 833, 797, 772, 583; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.59 (3H, s, C*H*$_3$), 7.03-7.09 (2H, m, Ar*H*), 7.23-7.28 (1H, m, Ar*H*), 7.43-7.54 (3H, m, Ar*H*), 7.73-7.79 (1H, m, Ar*H*), 7.83-7.92 (2H, m, Ar*H*), 7.93-8.00 (2H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 26.6 (CO*C*H$_3$), 116.3 (Ar*C*), 117.7 (Ar*C*(3,5)), 120.5 (Ar*C*), 125.5 (Ar*C*), 126.9 (Ar*C*), 127.4 (Ar*C*), 128.0 (Ar*C*), 130.4 (Ar*C*), 130.8 (Ar*C*(2,6)), 130.9 (Ar*C*), 132.2 (Ar*C*), 134.4 (Ar*C*), 153.3 (Ar*C*(1')), 162.1 (Ar*C*(4)), 196.9 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{18}H_{15}O_2]^+$ $(M+H)^+$ m/z : 263.1067, found 263.1069, (+0.9 ppm).

1-(4-(naphthalen-1-yloxy)phenyl)ethan-1-one

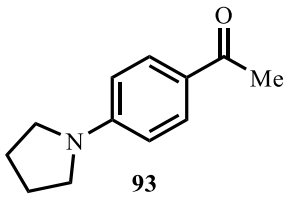


90

The title compound was prepared according to general procedure 3 using 1-naphthol (63 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 50% CH_2Cl_2 in hexanes, 30 x 150 mm silica) gave the title compound as a brown oil (29 mg, 27%); R_f = 0.45 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2990, 1676, 1589, 1503, 1416, 1248, 953, 866, 831, 762, 583, 478; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.57 (3H, s, C*H*$_3$), 6.97-7.05 (2H, m, ArC(3,5)*H*), 7.10-7.15 (1H, m, Ar*H*), 7.43-7.51 (2H, m, Ar*H*), 7.51-7.57 (1H, m, Ar*H*), 7.74 (1H, d, *J* 8.4, Ar*H*), 7.88-7.97 (3H, m, Ar*H*), 8.01 (1H, d, *J* 8.4, Ar*H*); **^{13}C NMR (100 MHz, $CDCl_3$)** δ_C: 26.6 (*C*H$_3$), 116.0 (Ar*C*), 117.0 (Ar*C*(3,5)), 122.0 (Ar*C*), 125.1 (Ar*C*), 126.0 (Ar*C*), 126.5 (Ar*C*), 127.0 (Ar*C*), 127.2 (Ar*C*), 128.1 (Ar*C*), 130.8 (Ar*C*(2,6)), 132.0 (Ar*C*), 135.2 (Ar*C*), 151.3 (Ar*C*(1')), 162.8 (Ar*C*(4)), 196.8 (*C*=O);

HRMS (**NSI**$^+$) calculated for $[C_{18}H_{15}O_2]^+$ $(M+H)^+$ m/z : 263.1067, found 263.1068, (+0.9 ppm).

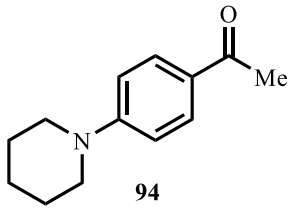
1-(4-(pyrrolidin-1-yl)phenyl)ethan-1-one



93

The title compound was prepared according to general procedure 3 using pyrrolidine (37 µL, 31 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 110 mm silica) gave the title compound as a yellow solid (53 mg, 70%); mp 127-131 °C (Lit. 126-127 °C);[8] R_f = 0.33 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2970, 2912, 2851, 1651, 1587, 1526, 1393, 1348, 1277, 1184, 1157, 955, 820, 594; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 1.98-2.09 (4H, m, C*H*$_2$CH$_2$NCH$_2$C*H*$_2$), 2.51 (3H, s, C*H*$_3$), 3.32-3.42 (4H, m, C*H*$_2$NC*H*$_2$), 6.48-6.56 (2H, m, ArC(3,5)*H*), 7.83-7.90 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 25.5 (*C*H$_2$CH$_2$NCH$_2$*C*H$_2$), 26.0 (CO*C*H$_3$), 47.7 (*C*H$_2$NC*H*$_2$), 110.8 (Ar*C*(3,5)), 125.0 (Ar*C*(1)), 130.8 (Ar*C*(2,6)), 151.1 (Ar*C*(4)), 196.5 (*C*=O); HRMS (**NSI**$^+$) calculated for $[C_{12}H_{16}ON]^+$ $(M+H)^+$ m/z : 190.1226, found 190.1225, (-0.7 ppm).

1-(4-(piperidin-1-yl)phenyl)ethan-1-one

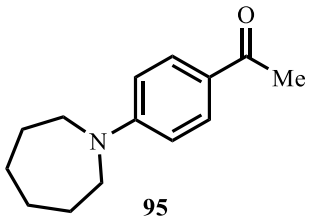


94

The title compound was prepared according to general procedure 3 using piperidine (43 µL, 38 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 110 mm silica) gave the title compound as an off-white solid (68 mg, 83%); mp 86-90 °C (Lit. 86 °C);[9] R_f = 0.40 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2999, 2938, 2922, 2847, 1653, 1587, 1545, 1427, 1385, 1356, 1223, 1123, 912, 820, 582; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 1.60-1.73 (6H, m, C*H*$_2$C*H*$_2$CH$_2$NCH$_2$C*H*$_2$), 2.51 (3H, s, C*H*$_3$), 3.31-3.40 (4H, m, C*H*$_2$NC*H*$_2$), 6.81-6.89 (2H, m, ArC(3,5)*H*), 7.81-7.89 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 24.5 (*C*H$_2$CH$_2$CH$_2$NCH$_2$CH$_2$), 25.5

($CH_2CH_2NCH_2CH_2$), 26.2 ($COCH_3$), 48.7 (CH_2NCH_2), 113.4 (Ar*C*(2,6)), 130.6 (Ar*C*(3,5)), 126.8 (Ar*C*(1)), 154.6 (Ar*C*(4)), 196.5 (*C*=O); HRMS (**NSI**$^+$) calculated for $[C_{13}H_{18}ON]^+$ $(M+H)^+$ m/z : 204.1383, found 204.1383, (+0.0 ppm).

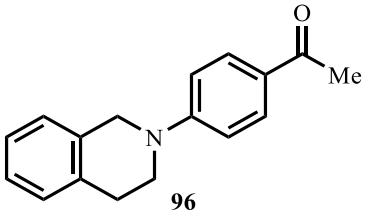
1-(4-(azepan-1-yl)phenyl)ethan-1-one



95

The title compound was prepared according to general procedure 3 using hexamethyleneimine (50 µL, 44 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 30 x 100 mm silica) gave the title compound (58 mg, 66%) as a yellow solid; mp 44-47 °C (Lit. 40-42 °C);[10] R_f = 0.38 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 1.51-1.59 (4H, m, $CH_2CH_2CH_2NCH_2CH_2CH_2$), 1.74-1.86 (4H, m, $CH_2CH_2NCH_2CH_2$), 2.49 (3H, s, CH_3), 3.53 (4H, t, *J* 6.0, CH_2NCH_2), 6.62-6.69 (2H, m, ArC(3,5)*H*), 7.81-7.88 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 26.0 (CH_3), 27.0 ($CH_2CH_2CH_2NCH_2CH_2CH_2$), 27.5 ($CH_2CH_2NCH_2CH_2$), 49.5 ($CH_2NCH_2$), 110.2 (Ar*C*(3,5)), 124.9 (Ar*C*(1)), 131.0 (Ar*C*(2,6)), 152.5 (Ar*C*(4)), 196.3 (*C*=O); Spectroscopic data in accordance with that stated in the literature.[10]

1-(4-(3,4-dihydroisoquinolin-2(1*H*)-yl)phenyl)ethan-1-one

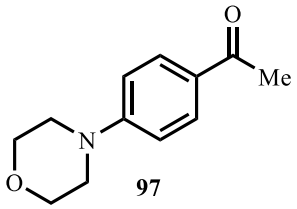


96

The title compound was prepared according to general procedure 3 using 1,2,3,4-tetrahydroisoquinoline (55 µL, 59 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 120 mm silica) gave the title compound as an off-white solid (69 mg, 68%); mp 101-104 °C (Lit. 105 °C);[11] R_f = 0.33 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.53 (3H, s, CH_3), 3.00 (2H, t, *J* 6.0, $ArCH_2CH_2N$), 3.68 (2H, t, *J* 6.0, $ArCH_2CH_2N$), 4.54 (2H, s, $ArCH_2N$), 6.84-6.92 (2H, m, ArC(3,5)*H*), 7.16-7.25 (4H, m, ArC(2',3',4',5')*H*), 7.88-7.95 (2H, m,

ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 26.2 (*C*H$_3$), 29.2 (*C*H$_2$CH$_2$N), 44.9 (CH$_2$*C*H$_2$N), 49.1 (Ar'*C*H$_2$N), 112.0 (Ar*C*(3,5)), 126.6 (Ar*C*), 126.6 (Ar*C*(1)), 126.6 (Ar*C*), 126.9 (Ar*C*), 128.3 (Ar*C*), 130.7 (Ar*C*(2,6)), 133.8 (Ar*C*), 135.2 (Ar*C*), 153.2 (Ar*C*(4)), 196.6 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[11]

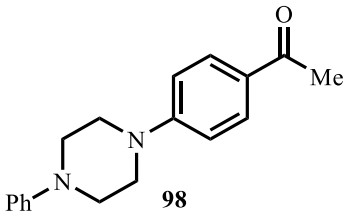
1-(4-morpholinophenyl)ethan-1-one



97

The title compound was prepared according to general procedure 3 using morpholine (38 µL, 38 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-20% EtOAc in hexanes, 30 x 120 mm silica) gave the title compound as an off-white solid (67 mg, 82%); mp 95-98 °C (Lit. 97 °C);[9] R_f = 0.13 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2961, 2913, 2851, 1655, 1591, 1549, 1514, 1385, 1362, 1238, 1115, 930, 816, 602, 584; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 2.53 (3H, s, C*H*$_3$), 3.26-3.35 (4H, m, C*H*$_2$NC*H*$_2$), 3.82-3.90 (4H, m, C*H*$_2$OC*H*$_2$), 6.83-6.91 (2H, m, ArC(3,5)*H*), 7.85-7.93 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ_C: 26.3 (CO*C*H$_3$), 47.7 (N(*C*H$_2$)$_2$), 66.7 (O(*C*H$_2$)$_2$), 113.4 (Ar*C*(3,5)), 128.3 (Ar*C*(1)), 130.5 (Ar*C*(2,6)), 154.4 (Ar*C*(4)), 196.7 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{12}H_{16}O_2N]^+$ $(M+H)^+$ m/z : 206.1176, found 206.1176, (+0.2 ppm).

1-(4-(4-phenylpiperazin-1-yl)phenyl)ethan-1-one

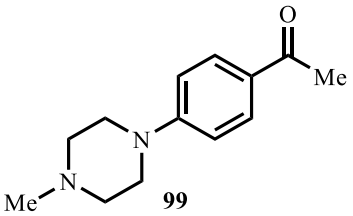


98

The title compound was prepared according to general procedure 3 using *N*-phenylpiperazine (67 µL, 71 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 30 x 120 mm silica) gave the title compound as an off-white solid (85 mg, 76%), mp 181-184 °C; R_f = 0.25 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2839, 1663, 1593, 1576, 1358, 1227, 1158, 943, 808, 756; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 2.54 (3H, s, C*H*$_3$), 3.31-3.39 (4H, m, NC*H*$_2$), 3.49-

3.56 (4H, m, NCH_2), 6.88-6.95 (3H, m, ArC(3,5,4')*H*), 6.95-7.01 (2H, m, ArC(2',6')*H*), 7.27-7.35 (2H, m, ArC(3',5')*H*), 7.87-7.94 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 26.3 (*C*H_3), 47.6 (N(*C*H_2)$_2$), 49.2 (N(*C*H_2)$_2$), 113.7 (Ar*C*(3,5)), 116.5 (Ar*C*(2',6')), 120.5 (Ar*C*(4')), 128.1 (Ar*C*(1)), 129.4 (Ar*C*(3',5')), 130.6 (Ar*C*(2,6)), 151.1 (Ar*C*(1')), 154.2 (Ar*C*(4)), 196.7 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{18}H_{21}ON_2]^+$ $(M+H)^+$ m/z : 281.1650, found 281.1648, (+0.6 ppm).

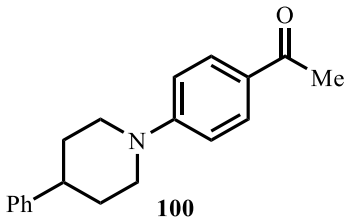
1-(4-(4-methylpiperazin-1-yl)phenyl)ethan-1-one



99

The title compound was prepared according to general procedure 3 using *N*-methylpiperazine (49 µL, 44 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5% Et_3N in EtOAc, 30 x 100 mm silica) gave the title compound as an orange-yellow solid (63 mg, 72%); mp 93-96 °C; R_f = 0.34 (eluent = 10% Et_3N in EtOAc); ν_{max} / cm^{-1} (film) 2990, 2932, 2839, 2778, 2745, 1653, 1591, 1508, 1454, 1371, 1358, 1283, 1233, 1157, 1007, 920, 822, 592; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.35 (3H, s, NCH_3), 2.52 (3H, s, COCH_3), 2.53-2.58 (4H, m, CH_3N(CH_2)$_2$), 3.33-3.41 (4H, m, ArN(CH_2)$_2$), 6.84-6.91 (2H, m, ArC(3,5)*H*), 7.84-7.91 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 26.3 (CO*C*H_3), 46.3 (N*C*H_3), 47.4 (ArN(*C*H_2)$_2$), 54.9 ((*C*H_2)$_2$NCH_3), 113.6 (Ar*C*(3,5)), 127.8 (Ar*C*(1)), 130.5 (Ar*C*(2,6)), 154.3 (Ar*C*(4)), 196.7 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{13}H_{19}ON_2]^+$ $(M+H)^+$ m/z : 219.1492, found 219.1493, (+0.5 ppm).

1-(4-(4-phenylpiperidin-1-yl)phenyl)ethan-1-one

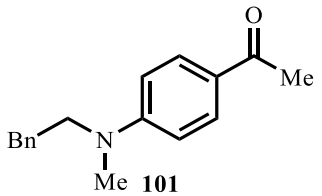


100

The title compound was prepared according to general procedure 3 using 4-phenylpiperidine (71 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 120 mm silica) gave the title compound as a white solid (98 mg, 83%); mp 150-153 °C; R_f = 0.35 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film)

1655, 1593, 1514, 1385, 1362, 1273, 1213, 1190, 1007, 924, 820, 756, 702, 584; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 1.84 (2H, dq, *J* 12.4, 4.1, 2xCHC*H*^{A}CH^{B}CH$_2$N), 1.92-2.02 (2H, m, 2xCHCH^{A}C*H*^{B}CH$_2$N), 2.53 (3H, s, C*H*$_3$), 2.75 (1H, tt, *J* 12.4, 3.6, CH$_2$C*H*(Ar)CH$_2$), 2.99 (2H, dt, *J* 12.4, 2.4, CH$_2$C*H*^{A}H^{B}N), 3.99-4.10 (2H, m, 2xCH$_2$CH^A*H*^{B}N), 6.88-6.96 (2H, m, ArC(3,5)*H*), 7.19-7.25 (3H, m, Ar*H*), 7.28-7.36 (2H, m, Ar*H*), 7.85-7.92 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ_C: 26.2 (CO*C*H$_3$), 32.9 (*C*H$_2$CH$_2$NCH$_2$*C*H$_2$), 42.7 (Ar*C*H(CH$_2$)), 48.6 (*C*H$_2$N*C*H$_2$), 113.7 (Ar*C*(3,5)), 126.6 (Ar*C*(4')), 126.9 (Ar*C*), 127.3 (Ar*C*(1)), 128.7 (Ar*C*), 130.6 (Ar*C*(2,6)), 145.6 (Ar*C*(1')), 154.3 (Ar*C*(4)), 196.9 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{19}H_{22}ON]^+$ $(M+H)^+$ m/z : 280.1696, found 280.1695, (-0.3 ppm).

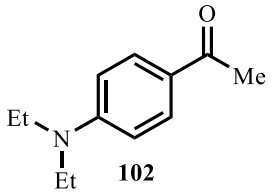
1-(4-(methyl(phenethyl)amino)phenyl)ethan-1-one



101

The title compound was prepared according to general procedure 3 using *N*-methylphenethylamine (64 µL, 60 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 140 mm silica) gave the title compound as an off-white solid (67 mg, 67%); mp 111-114 °C; R_f = 0.34 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2993, 2913, 1655, 1589, 1548, 1391, 1356, 1290, 1194, 951, 820, 750, 608, 592, 494; **^{1}H NMR (400 MHz, CDCl$_3$)** δ_H: 2.52 (3H, s, COC*H*$_3$), 2.85-2.92 (2H, m, ArC*H*$_2$CH$_2$N), 2.93 (3H, s, NC*H*$_3$), 3.61-3.69 (2H, m, ArCH$_2$C*H*$_2$N), 6.63-6.70 (2H, m, ArC(3,5)*H*), 7.16-7.26 (3H, m, Ar*H*), 7.27-7.35 (2H, m, Ar*H*), 7.84-7.92 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 26.1 (CO*C*H$_3$), 33.3 (Ar*C*H$_2$CH$_2$N), 38.9 (N*C*H$_3$), 54.5 (ArCH$_2$*C*H$_2$N), 110.6 (Ar*C*(3,5)), 125.5 (Ar*C*(1)), 126.6 (Ar*C*(4')), 128.8 (Ar*C*), 128.9 (Ar*C*), 130.9 (Ar*C*(2,6)), 139.2 (Ar*C*(1')), 152.2 (Ar*C*(4)), 196.5 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{16}H_{20}ON]^+$ $(M+H)^+$ m/z : 254.1539, found 254.1543, (+0.5 ppm).

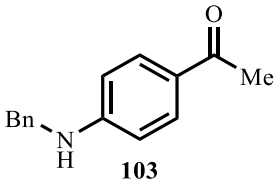
1-(4-(diethylamino)phenyl)ethan-1-one



102

The title compound was prepared according to general procedure 3 using diethylamine (46 µL, 32 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 30 x 120 mm silica) gave the title compound as a yellow solid (34 mg, 45%); mp 45-48 °C (Lit. 41.5-44.5 °C);[12] R_f = 0.36 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2972, 2922, 2868, 1651, 1585, 1524, 1404, 1356, 1267, 1190, 1157, 1070, 951, 818, 791, 592, 565; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 1.20 (6H, t, *J* 7.1, 2xC*H*$_3$CH$_2$N), 2.49 (3H, s, COC*H*$_3$), 3.42 (4H, q, *J* 7.1, 2xCH$_3$C*H*$_2$N), 6.62 (2H, d, *J* 8.8, ArC(3,5)*H*), 7.81-7.88 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 12.6 ((*C*H$_3$CH$_2$)$_2$N), 26.0 (CO*C*H$_3$), 44.6 ((CH$_3$*C*H$_2$)$_2$N), 110.1 (Ar*C*(3,5)), 124.7 (Ar*C*(1)), 130.9 (Ar*C*(2,6)), 151.2 (Ar*C*(4)), 196.2 (*C*=O); HRMS (**ESI$^+$**) calculated for $[C_{12}H_{18}NO]^+$ $(M+H)^+$ m/z : 192.1388, found 192.1385, (-1.6 ppm).

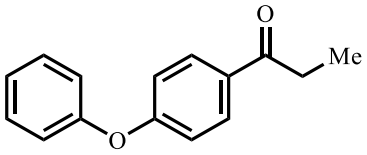
1-(4-(benzylamino)phenyl)ethan-1-one



103

The title compound was prepared according to general procedure 3 using benzylamine (48 µL, 47 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a yellow solid (24 mg, 25%); mp 92-95 °C; R_f = 0.30 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3350, 3063, 3024, 1645, 1585, 1564, 1530, 1356, 1279, 1263, 1179, 947, 837, 741, 694; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.50 (3H, s, COC*H*$_3$), 4.41 (2H, d, *J* 4.0, PhC*H*$_2$NH), 4.58 (1H, br s, N*H*), 6.57-6.63 (2H, m, ArC(3,5)*H*), 7.27-7.40 (5H, m, ArC(1'-5')*H*), 7.78-7.86 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 26.1 (CO*C*H$_3$), 47.7 (Ph*C*H$_2$N), 111.7 (Ar*C*(3,5)), 127.1 (Ar*C*(1)), 127.5 (Ar*C*), 127.7 (Ar*C*(4')), 128.9 (Ar*C*), 130.9 (Ar*C*(2,6)), 138.4 (Ar*C*(1')), 152.1 (Ar*C*(4)), 196.5 (*C*=O); HRMS (**AP$^+$**) calculated for $[C_{15}H_{16}NO]^+$ $(M+H)^+$ m/z : 226.1232, found 226.1232, (+0.0 ppm).

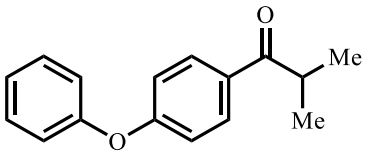
1-(4-phenoxyphenyl)propan-1-one



106

The title compound was prepared according to general procedure 4 using 1-(4-fluorophenyl)-1-propanol (62 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 4% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as an off-white solid; (73 mg, 81%); mp 41-44 °C (Lit. 39-40 °C);[13] R_f = 0.68 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3059, 2978, 2932, 1676, 1584, 1487, 1414, 1248, 1221, 1167, 953, 868, 847, 793, 762, 694, 500; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.22 (3H, t, *J* 7.3, CH_2CH_3), 2.97 (2H, q, *J* 7.3, CH_2CH_3), 6.97-7.03 (2H, m, ArC(3,5)*H*), 7.04-7.10 (2H, m, ArC(2',6')*H*), 7.20 (1H, t, *J* 7.3, ArC(4')*H*), 7.36-7.42 (2H, m, ArC(3',5')*H*), 7.92-7.98 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 8.5 (CH_2CH_3), 31.7 (CH_2CH_3), 117.4 (Ar*C*(3,5)), 120.3 (Ar*C*(2',6')), 124.7 (Ar*C*(4')), 130.2 (Ar*C*(3',5')), 130.4 (Ar*C*(2,6)), 131.8 (Ar*C*(1)), 155.7 (Ar*C*(1')), 161.9 (Ar*C*(4)), 199.6 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{15}H_{15}O_2]^+$ $(M+H)^+$ m/z : 227.1067, found 227.1067, (+0.2 ppm).

2-methyl-1-(4-phenoxyphenyl)propan-1-one

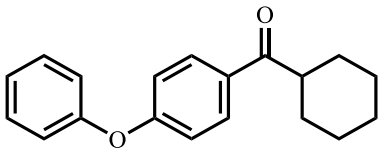


107

The title compound was prepared according to general procedure 4 using 1-(4-fluorophenyl)-2-methylpropan-1-ol (67 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1-5% Et_2O in hexanes, 30 x 160 mm silica) gave the title compound as a colourless oil (67 mg, 70%), R_f = 0.72 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3063, 2974, 2928, 1678, 1584, 1487, 1381, 1217, 1155, 976, 874, 843, 752, 689, 490; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_C: 1.21 (6H, d, *J* 6.8, $CH(CH_3)_2$), 3.52 (1H, sept, *J* 6.8, $CH(CH_3)_2$), 6.97-7.04 (2H, m, ArC(3,5)*H*), 7.04-7.11 (2H, m, ArC(2',6')*H*), 7.16-7.24 (1H, m, ArC(4')*H*), 7.35-7.44 (2H, m, ArC(3',5')*H*), 7.91-7.99 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 19.4 ($CH(CH_3)_2$), 35.2 ($CH(CH_3)_2$), 117.5 (Ar*C*(3,5)), 120.3 (Ar*C*(2',6')), 124.7 (Ar*C*(4')), 130.2 (Ar*C*(3',5')), 130.7 (Ar*C*(2,6)), 130.9 (Ar*C*(1)), 155.7

(Ar*C*(1')), 161.9 (Ar*C*(4)), 203.2 (*C*=O); HRMS (**NSI**$^+$) calculated for $[C_{16}H_{17}O_2]^+$ $(M+H)^+$ m/z : 241.1223, found 241.1223, (+0.0 ppm).

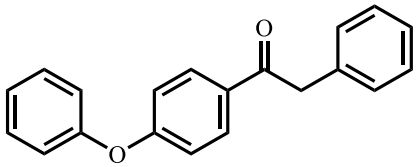
Cyclohexyl(4-phenoxyphenyl)methanone



108

The title compound was prepared according to general procedure 4 using cyclohexyl(4-fluorophenyl)methanol (83 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1-5% Et_2O in hexanes, 30 x 160 mm silica) gave the title compound as an off-white solid (74 mg, 66%), mp 56-59 °C, R_f = 0.72 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3059, 2924, 2855, 1670, 1584, 1485, 1234, 1206, 1157, 974, 872, 746, 690, 500; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 1.18-1.54 (5H, m, Cy*H*), 1.67-1.79 (1H, m, Cy*H*), 1.80-1.93 (4H, m, Cy*H*), 3.22 (1H, tt, *J* 11.2, 3.2, COC*H*), 6.97-7.03 (2H, m, ArC(3,5)*H*), 7.04-7.10 (2H, m, ArC(2',6')*H*), 7.16-7.23 (1H, m, ArC(4')*H*), 7.35-7.43 (2H, m, ArC(3',5')*H*), 7.90-7.97 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 26.0 (Cy*C*), 26.1 (Cy*C*), 29.6 (COCH(*C*H_2)$_2$), 45.6 (CO*C*H(CH_2)$_2$), 117.5 (Ar*C*(3,5)), 120.2 (Ar*C*(2',6')), 124.7 (Ar*C*(4')), 130.2 (Ar*C*(3',5)), 130.6 (Ar*C*(2,6)), 131.0 (Ar*C*(1)), 155.7 (Ar*C*(1')), 161.8 (Ar*C*(4)), 202.6 (*C*=O); HRMS (**ESI**$^+$) calculated for $[C_{19}H_{21}O_2]^+$ $(M+H)^+$ m/z : 281.1542, found 281.1545, (+1.1 ppm).

1-(4-phenoxyphenyl)-2-phenylethan-1-one

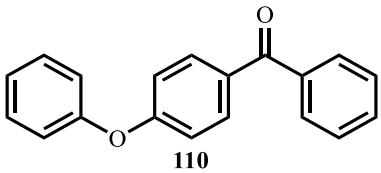


109

The title compound was prepared according to general procedure 4 using 1-(4-fluorophenyl)-2-phenylethan-1-ol (86 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 2-5% Et_2O in hexanes, 30 x 160 mm silica) gave the title compound as a white solid (71 mg, 62%); mp 88-91 °C; R_f = 0.66 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3051, 2884, 1674, 1605, 1574, 1254, 1198, 1165, 989, 816, 723, 694, 561, 503; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 4.24 (2H, s, COCH_2Ph), 6.95-7.02 (2H, m, ArC(3,5)*H*), 7.03-7.10 (2H, m, ArC(2',6')*H*), 7.16-7.23 (1H, m, ArC(4')*H*), 7.13-7.29 (3H,

m, Ar*H*), 7.29-7.36 (2H, m, Ar*H*), 7.36-7.43 (2H, m, Ar*H*), 7.96-8.03 (2H, m, ArC(2,6)*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ_C: 45.5 (CO*C*H$_2$Ph), 117.4 (Ar*C*(3,5)), 120.4 (Ar*C*(2',6')), 124.8 (Ar*C*), 127.0 (Ar*C*), 128.8 (Ar*C*), 129.5 (Ar*C*), 130.2 (Ar*C*), 131.1 (Ar*C*(2,6)), 131.3 (Ar*C*(1)), 134.9 (Ar*C*), 155.5 (Ar*C*(1')), 162.2 (Ar*C*(4)), 196.4 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{20}H_{17}O_2]^+$ $(M+H)^+$ m/z : 289.1223, found 289.1225, (+0.7 ppm).

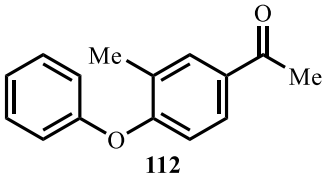
(4-phenoxyphenyl)(phenyl)methanone



110

The title compound was prepared according to general procedure 4 using (4-fluorophenyl)(phenyl)methanol (81 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a white solid (87 mg, 80%); mp 77-80 °C (Lit. 74-75 °C);[6] R_f = 0.66 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3034, 1649, 1584, 1489, 1310, 1285, 1246, 1074, 939, 847, 799, 733, 691, 677, 627, 501; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 7.03 (2H, d, *J* 8.5, ArC(3,5)*H*), 7.10 (2H, d, *J* 7.5, ArC(2',6')*H*), 7.21 (1H, t, *J* 7.5, ArC(4')*H*), 7.41 (2H, t, *J* 8.0, ArC(3',5')*H*), 7.48 (2H, t, *J* 7.5, ArC(3'',5'')*H*), 7.58 (1H, t, *J* 7.5, ArC(4''*H*), 7.75-7.80 (2H, m, ArC(2'',6'')*H*), 7.82 (2H, d, *J* 8.5, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 117.3 (Ar*C*(3,5)), 120.3 (Ar*C*(2',6')), 124.7 (Ar*C*(4')), 128.4 (Ar*C*(3'',5'')), 129.9 (Ar*C*(2'',6'')), 130.2 (Ar*C*(3',5')), 132.1 (Ar*C*(1)), 132.3 (Ar*C*(4'')), 132.6 (Ar*C*(2,6)), 138.1 (Ar*C*(1'')), 155.7 (Ar*C*(1')), 161.8 (Ar*C*(4)), 195.5 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{19}H_{15}O_2]$ $(M+H)^+$ m/z : 275.1067, found 275.1068, (+0.5 ppm).

1-(3-methyl-4-phenoxyphenyl)ethan-1-one

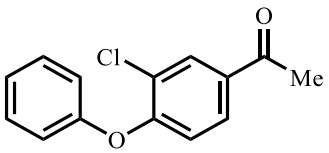


112

The title compound was prepared according to general procedure 4 using 1-(4-fluoro-3-methyl)ethan-1-ol (62 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1-5% Et$_2$O in hexanes, 30 x 160 mm silica) gave the title compound as a pale-yellow oil (57 mg, 63%); R_f = 0.54 (eluent = 20% EtOAc in hexanes);

ν_{max} / cm^{-1} (film) 3059, 2918, 1678, 1582, 1485, 1356, 1287, 1252, 1236, 1198, 1128, 961, 847, 741, 691, 592, 575; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.35 (3H, s, ArC(3)H_3), 2.57 (3H, s, COCH_3), 6.81 (1H, d, *J* 8.4, ArC(5)*H*), 6.95-7.04 (2H, m, ArC(2',6')*H*), 7.11-7.19 (1H, m, ArC(4')*H*), 7.33-7.41 (2H, m, ArC(3',5')*H*), 7.70-7.77 (1H, m, ArC(6)*H*), 7.86-7.90 (1H, m, ArC(2)*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 16.4 (ArC(3)CH_3), 26.6 (COCH_3), 117.0 (Ar*C*(5)), 119.3 (Ar*C*(2',6')), 124.0 (Ar*C*(4')), 128.1 (Ar*C*(6)), 129.1 (Ar*C*(3)CH_3), 130.1 (Ar*C*(3',5')), 131.9 (Ar*C*(2)), 132.3 (Ar*C*(1)), 156.4 (Ar*C*(4)), 159.8 (Ar*C*(1')), 197.3 (*C*=O); HRMS (**NSI$^+$**) calculated $[C_{15}H_{15}O_2]^+$ $(M+H)^+$ m/z : 227.1067, found 227.1066, (-0.2 ppm).

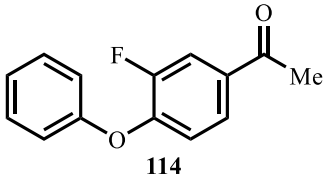
1-(3-chloro-4-phenoxyphenyl)ethan-1-one



113

The title compound was prepared according to general procedure 4 using 1-(3'-chloro-4'-fluorophenyl)ethan-1-ol (70 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1% EtOAc in hexanes, 30 x 160 mm silica) gave the title compound as a pale-yellow oil (58 mg, 58%); R_f = 0.52 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 1682, 1582, 1481, 1356, 1250, 1192, 1161, 881, 781, 687, 573, 502; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.57 (3H, s, COCH_3), 6.89 (1H, d, *J* 9.0, ArC(5)*H*), 7.02-7.09 (2H, m, ArC(2',6')*H*), 7.18-7.24 (1H, m, ArC(4')*H*), 7.37-7.44 (2H, m, ArC(3',5')*H*), 7.77 (1H, dd, *J* 8.5, 2.0, ArC(6)*H*), 8.08 (1H, d, *J* 2.0, ArC(2)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 26.6 (COCH_3), 118.1 (Ar*C*(5)), 119.7 (Ar*C*(2',6')), 124.9 (Ar*C*(4')), 125.0 (Ar*C*(3)), 128.4 (Ar*C*(6)), 130.3 (Ar*C*(3',5')), 131.3 (Ar*C*(2)), 133.0 (Ar*C*(1)), 155.5 (Ar*C*), 157.4 (Ar*C*), 195.8 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{14}H_{12}O_2{}^{35}Cl]^+$ $(M+H)^+$ m/z : 247.0520, found 247.0522, (+0.7 ppm).

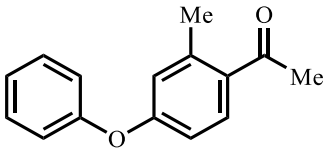
1-(3-fluoro-4-phenoxyphenyl)ethan-1-one



114

The title compound was prepared according to general procedure 4 using 1-(3',4'-difluorophenyl)ethan-1-ol (63 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1% EtOAc in hexanes, 30 x 170 mm silica) gave the title compound as a colourless oil (48 mg, 52%); R_f = 0.50 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3073, 1684, 1587, 1506, 1485, 1425, 1273, 1194, 903, 849, 745, 687, 592, 542; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.58 (3H, s, COC*H*$_3$), 6.94-7.02 (1H, m, Ar*H*), 7.02-7.09 (2H, m, Ar*H*), 7.15-7.23 (1H, m, Ar*H*), 7.34-7.43 (2H, m, Ar*H*), 7.65-7.71 (1H, m, Ar*H*), 7.75-7.83 (1H, m, Ar*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -130.9; **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 26.6 (CO*C*H$_3$), 117.0 (d, *J* 19.1, Ar*C*(2)), 119.1 (Ar*C*(2',6')), 119.4 (d, *J* 1.2, Ar*C*(6)), 124.7 (Ar*C*(4')), 125.4 (d, *J* 3.4, Ar*C*(5)), 130.2 (Ar*C*(3',5')), 133.2 (d, *J* 4.9, Ar*C*(1)), 149.3 (d, *J* 11.4, Ar*C*(4)), 153.3 (d, *J* 251.2, Ar*C*(3)F), 155.8 (Ar*C*(1')), 195.9 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{14}H_{12}O_2F]^+$ $(M+H)^+$ m/z : 231.0816, found 231.0817, (+0.5 ppm).

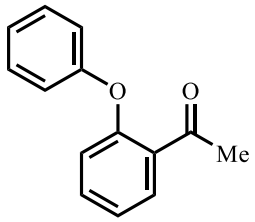
1-(2-methyl-4-phenoxyphenyl)ethan-1-one



115

The title compound was prepared according to general procedure 4 using 1-(4'-fluoro-2'-methyl)ethan-1-ol (62 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes, 30 x 160 mm silica) gave the title compound as a colourless oil (47 mg, 52%); R_f = 0.60 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2974, 2916, 1674, 1589, 1562, 1489, 1449, 1354, 1234, 1202, 1165, 1124, 974, 773, 694, 579, 490; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.53 (3H, s, ArC(2)C*H*$_3$), 2.56 (3H, s, COC*H*$_3$), 6.78-6.85 (2H, m, Ar*H*), 7.02-7.09 (2H, m, Ar*H*), 7.15-7.22 (1H, m, Ar*H*), 7.35-7.43 (2H, m, Ar*H*), 7.70-7.76 (1H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 22.4 (ArC(2)*C*H$_3$), 29.4 (CO*C*H$_3$), 114.6 (Ar*C*), 120.2 (Ar*C*), 121.1 (Ar*C*), 124.5 (Ar*C*), 130.1 (Ar*C*), 132.0 (Ar*C*(1)), 132.3 (Ar*C*), 142.3 (Ar*C*(2)CH$_3$), 155.8 (Ar*C*(1')), 160.4 (Ar*C*(4)), 199.9 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{15}H_{15}O_2]^+$ $(M+H)^+$ m/z : 227.1067, found 227.1066, (-0.2 ppm).

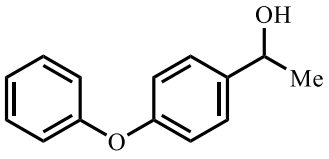
1-(2-phenoxyphenyl)ethan-1-one



117

The title compound was prepared according to general procedure 4 using 1-(2'-fluorophenyl)ethan-1-ol (56 mg, 0.44 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 1% EtOAc in hexanes, 30 x 170 mm silica) gave the title compound as a colourless oil (45 mg, 53%); R_f = 0.66 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3073, 1676, 1597, 1570, 1474, 1445, 1287, 1219, 1153, 872, 754, 691, 596, 496; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.65 (3H, s, COC*H*$_3$), 6.91 (1H, dd, *J* 8.0, 1.0, Ar*H*), 6.99-7.04 (2H, m, Ar*H*), 7.12-7.20 (2H, m, Ar*H*), 7.34-7.40 (2H, m, Ar*H*), 7.40-7.46 (1H, m, Ar*H*), 7.85 (1H, dd, *J* 8.0, 2.0, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 31.7 (CO*C*H$_3$), 119.0 (Ar*C*(2',6')), 119.4 (Ar*C*), 123.6 (Ar*C*), 124.0 (Ar*C*), 130.2 (Ar*C*(3',5')), 130.6 (Ar*C*(1)), 130.6 (Ar*C*), 133.8 (Ar*C*), 156.5 (Ar*C*(1')), 156.6 (Ar*C*(2)), 199.1 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{14}H_{13}O_2]^+$ $(M+H)^+$ m/z : 213.0910, found 213.0909, (-0.5 ppm).

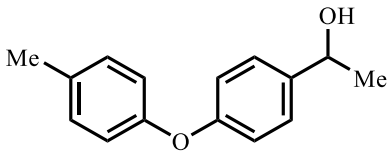
1-(4-phenoxyphenyl)ethan-1-ol



74

The title compound was prepared according to general procedure 5 using phenol (41 mg, 0.44 mmol) and K_2CO_3 (60.8 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a pale-yellow oil (68 mg, 80%); R_f = 0.28 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 1.51 (3H, d, *J* 6.4, CHC*H*$_3$), 1.75 (1H, br s, O*H*), 4.90 (1H, q, *J* 6.4, C*H*OH), 6.96-7.04 (4H, m, ArC(3,5,2',6')*H*), 7.06-7.14 (1H, m, ArC(4')*H*), 7.29-7.38 (4H, m, ArC(2,6,3',5')*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 25.3 (*C*H$_3$), 70.1 (*C*HOH), 119.0 (Ar*C*(2',6')), 119.0 (Ar*C*(3,5)), 123.4 (Ar*C*(4')), 127.0 (Ar*C*(2,6)), 129.9 (Ar*C*(3',5')), 140.8 (Ar*C*(1)), 156.7 (Ar*C*(1')), 157.4 (Ar*C*(4)). Spectroscopic data in accordance with that stated in the literature.[14]

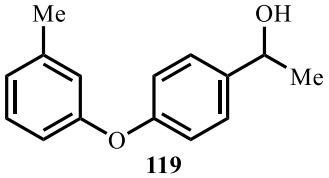
1-(4-(*p*-tolyloxy)phenyl)ethan-1-ol



118

The title compound was prepared according to general procedure 5 using *p*-cresol (48 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 100 mm silica) gave the title compound as a pale yellow oil (76 mg, 83%); R_f = 0.28 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3343, 3034, 2970, 1599, 1499, 1233, 1206, 1084, 1011, 870, 814, 492; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.50 (3H, d, *J* 6.5, CHC*H*$_3$), 1.74 (1H, d, *J* 3.5, O*H*), 2.34 (3H, s, ArC(4')*H*$_3$), 4.89 (1H, dq, *J* 6.5, 3.5, C*H*OH), 6.91 (2H, d, *J* 8.5, ArC(2',6')*H*), 6.96 (2H, d, *J* 8.5, ArC(3,5)*H*), 7.14 (2H, d, *J* 8.5, ArC(3',5')*H*), 7.32 (2H, d, *J* 8.5, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 20.8 (ArC(4')*C*H$_3$), 25.3 (CH*C*H$_3$), 70.1 (*C*HOH), 118.4 (Ar*C*(3,5)), 119.2 (Ar*C*(2',6')), 126.9 (Ar*C*(2,6)), 130.4 (Ar*C*(3',5')), 133.1 (Ar*C*(4')), 140.3 (Ar*C*(1)), 154.9 (Ar*C*(1')), 157.3 (Ar*C*(4)); HRMS (**NSI$^+$**) calculated for $[C_{15}H_{16}O_2Na]^+$ $(M+Na)^+$ m/z : 251.1043, found 251.1045, (+1.0 ppm).

1-(4-(*m*-tolyloxy)phenyl)ethan-1-ol

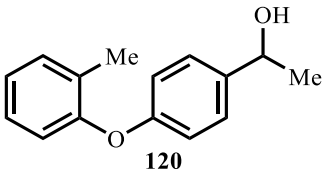


119

The title compound was prepared according to general procedure 5 using *m*-cresol (46 µL, 48 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 100 mm silica) gave the title compound as a pale-yellow oil (73 mg, 80%); R_f = 0.28 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3337, 2974, 1607, 1584, 1504, 1483, 1086, 1070, 1007, 935, 779, 687, 542, 442; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 1.51 (3H, d, *J* 6.4, CHC*H*$_3$), 1.76 (1H, d, *J* 3.2, O*H*). 2.33 (3H, s, ArC(5')*H*$_3$), 4.90 (1H, dq, *J* 6.4, 3.2, C*H*OH), 6.77-6.85 (2H, m, Ar*H*), 6.89-6.95 (1H, m, Ar*H*), 6.95-7.02 (2H, m, ArC(3,5)*H*), 7.21 (1H, t, *J* 8.0, ArC(5')*H*), 7.31-7.38 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 21.5 (ArC(3')*C*H$_3$), 25.3 (*C*HCH$_3$), 70.1 (*C*HOH), 116.1 (Ar*C*), 119.0 (Ar*C*), 119.6 (Ar*C*), 124.2 (Ar*C*), 127.0 (Ar*C*), 129.6 (Ar*C*), 140.0

(Ar*C*(3')CH_3), 140.6 (Ar*C*(1)), 156.8 (Ar*C*(1')), 157.3 (Ar*C*(4)); HRMS (**NSI**$^+$) calculated for $[C_{15}H_{15}O_2]^+$ $(M-H)^+$ m/z : 227.1078, found 227.1082, (+2.0 ppm).

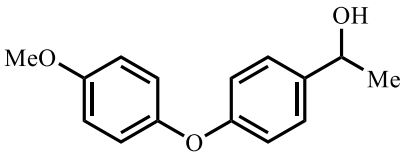
1-(4-(*o*-tolyloxy)phenyl)ethan-1-ol



120

The title compound was prepared according to general procedure 5 using *o*-cresol (45 µL, 48 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 30 x 100 mm silica) gave the title compound as a pale-yellow oil (71 mg, 78%); R_f = 0.28 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3325, 2970, 1605, 1582, 1504, 1483, 1233, 1180, 878, 835, 756, 540, 442; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 1.50 (3H, d, *J* 6.4, CHC*H*$_3$), 1.82 (1H, br s, O*H*), 2.24 (3H, s, ArC(6')*H*$_3$), 4.88 (1H, q, *J* 6.4, C*H*OH), 6.84-6.93 (3H, m, Ar*H*), 7.07 (1H, dt, *J* 7.8, 1.2, Ar*H*), 7.13-7.21 (1H, m, Ar*H*), 7.23-7.28 (1H, m, Ar*H*), 7.28-7.34 (2H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 16.3 (ArC(2')*C*H_3), 25.2 (CH*C*H_3), 70.1 (*C*HOH), 117.4 (Ar*C*), 119.9 (Ar*C*), 124.2 (Ar*C*), 127.0 (Ar*C*), 127.3 (Ar*C*), 130.1 (Ar*C*(2')CH_3), 131.6 (Ar*C*), 139.8 (Ar*C*(1)), 154.5 (Ar*C*), 157.4 (Ar*C*); HRMS (**NSI**$^+$) calculated for $[C_{15}H_{16}O_2Na]^+$ $(M+Na)^+$ m/z : 251.1043, found 251.1045, (+1.0 ppm).

1-(4-(4-methoxyphenoxy)phenyl)ethan-1-ol

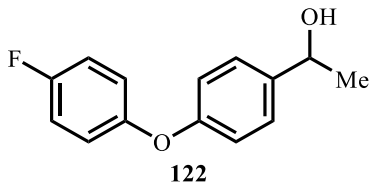


121

The title compound was prepared according to general procedure 5 using 4'-methoxyphenol (55 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-20% EtOAc in hexanes, 30 x 100 mm silica) gave the title compound as an off-white solid (87 mg, 89%); mp 51-54 °C; R_f = 0.17 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3271, 2970, 2839, 1605, 1501, 1229, 1072, 1007, 899, 880, 847, 831; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.49 (3H, d, *J* 6.5, CHC*H*$_3$), 1.72 (1H, br s, O*H*), 3.81 (3H, s, OC*H*$_3$), 4.88 (1H, q, *J* 6.5, C*H*OH), 6.85-6.95 (4H, m, Ar*H*), 6.95-7.01 (2H, m, Ar*H*), 7.28-7.34 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 25.3 (CH*C*H_3), 55.8 (O*C*H_3), 70.1 (*C*HOH),

115.0 (Ar*C*), 117.7 (Ar*C*), 120.9 (Ar*C*), 126.9 (Ar*C*(2,6)), 140.0 (Ar*C*(1)), 150.3 (Ar*C*), 156.1 (Ar*C*), 158.0 (Ar*C*); HRMS (**ASAP$^+$**) $[C_{15}H_{15}O_3]^+$ $(M-H)^+$ m/z : 243.1016, found 243.1012, (-1.5 ppm).

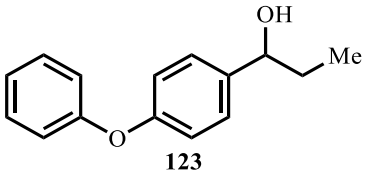
1-(4-(4-fluorophenoxy)phenyl)ethan-1-ol



122

The title compound was prepared according to general procedure 5 using 4-fluorophenol (49 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 5-15% EtOAc in hexanes, 30 x 120 mm silica) gave the title compound as an off-white solid (83 mg, 89%); mp 51-54 °C; R_f = 0.22 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3402, 3310, 2974, 2961, 1611, 1497, 1364, 1254, 1211, 1188, 1084, 1063, 1005, 899, 847, 824, 768, 552, 540, 494; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 1.50 (3H, d, *J* 6.4, CHC*H*$_3$), 1.74 (1H, br s, O*H*), 4.90 (1H, q, *J* 6.4, C*H*OH), 6.91-7.07 (6H, m, ArC(3,5,2',3',4',5')*H*), 7.30-7.37 (2H, m, ArC(2',6')*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -120.0; **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 25.3 (CH*C*H$_3$), 70.1 (*C*HOH), 116.4 (d, *J* 23.4, Ar*C*(3',5')), 118.4 (Ar*C*(3,5)), 120.6 (d, *J* 8.2, Ar*C*(2',6')), 127.1 (Ar*C*(2,6)), 140.7 (Ar*C*(1)), 153.0 (d, *J* 2.5, Ar*C*(1')), 157.1 (Ar*C*(4)), 158.9 (d, *J* 242.7, Ar*C*(4')); HRMS (**CI$^+$**) calculated for $[C_{14}H_{17}O_2NF]^+$ $(M+NH_4)^+$ m/z : 250.1238, found 250.1239, (+0.5 ppm).

1-(4-phenoxyphenyl)propan-1-ol

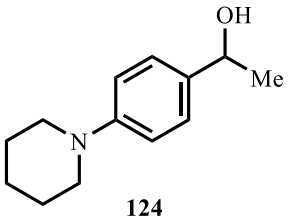


123

The title compound was prepared according to general procedure 5 using phenol (41 mg, 0.44 mmol) as the nucleophile and 1-(4-fluorophenyl)propan-1-ol (51 µL, 56 mg, 0.4 mmol) as the fluoroarene. Purification by flash silica chromatography (eluent = 2-20% EtOAc in hexanes, 30 x 120 mm silica) gave the title compound as a pale yellow oil (79 mg, 86%); R_f = 0.22 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3354, 2970, 2924, 2880, 1589, 1506, 1487, 1227, 1196, 1163, 872, 746, 691, 538, 494; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 0.93 (3H, t, *J* 7.2, CH_2CH_3), 1.68-1.92 (3H, m, CH_2CH_3, O*H*), 4.55-4.64 (1H, m, C*H*OH),

6.96-7.04 (4H, m, ArC(3,5,2',6')*H*), 7.07-7.14 (1H, m, ArC(4')*H*), 7.28-7.38 (4H, m, ArC(2,6,3',5')*H*); **^{13}C NMR (101 MHz, CDCl$_3$)** δ_C: 10.3 (CH_2CH_3), 32.0 (CH_2CH_3), 75.7 (*C*HOH), 118.9 (Ar*C*(3,5)), 119.0 (Ar*C*(2',6')) 123.4 (Ar*C*(4')), 127.6 (Ar*C*(2,6)), 129.9 (Ar*C*(3',5')), 139.6 (Ar*C*(1)), 156.7 (Ar*C*(1')), 157.4 (Ar*C*(4)); HRMS (**NSI$^+$**) calculated for $[C_{15}H_{15}O_2]^+$ $(M-H)^+$ m/z : 227.1078, found 227.1079, (+0.6 ppm).

1-(4-(piperidin-1-yl)phenyl)ethan-1-ol

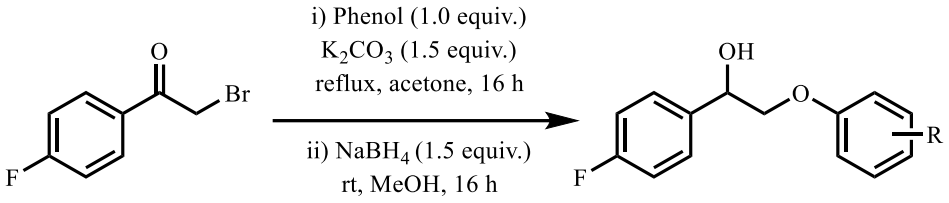


124

The title compound was prepared according to general procedure 5 using piperidine (43 µL, 38 mg, 0.44 mmol) as the nucleophile. Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 120 mm silica) gave the title compound as an off-white solid (46 mg, 57%); mp 60-63 °C; R_f = 0.21 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3246, 2972, 2932, 2851, 2828, 1609, 1508, 1454, 1233, 1132, 1094, 1067, 1013, 1005, 907, 866, 827, 814, 554; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.48 (3H, d, *J* 6.5, CHC*H*$_3$), 1.52-1.62 (2H, m, C*H*$_2$CH$_2$CH$_2$NCH$_2$CH$_2$), 1.66 (1H, br s, O*H*), 1.67-1.74 (4H, m, C*H*$_2$CH$_2$NCH$_2$C*H*$_2$), 3.15 (4H, t, *J* 5.5, CH$_2$C*H*$_2$NC*H*$_2$CH$_2$), 4.83 (1H, q, *J* 6.5, C*H*OH), 6.92 (2H, d, *J* 9.0, ArC(3,5)*H*), 7.26 (2H, d, *J* 8.5, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 24.3 (*C*H$_2$CH$_2$CH$_2$NCH$_2$CH$_2$), 24.8 (CH*C*H$_3$), 25.8 (*C*H$_2$CH$_2$NCH$_2$*C*H$_2$), 50.7 (CH$_2$*C*H$_2$N*C*H$_2$CH$_2$), 70.1 (*C*HCH$_3$), 116.5 (Ar*C*(3,5)), 126.3 (Ar*C*(2,6)), 136.4 (Ar*C*(1)), 151.7 (Ar*C*(4)); HRMS (**EI$^+$**) calculated for $[C_{13}H_{19}NO]^+$ $(M)^+$ m/z : 205.1467, found 205.1465, (-1.0 ppm).

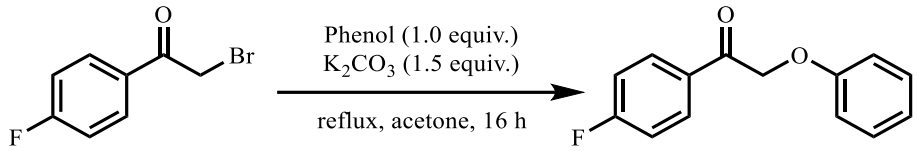
7.4. Substrate synthesis – Isomerisation/S$_N$Ar protocol

7.4.1. General procedure 6



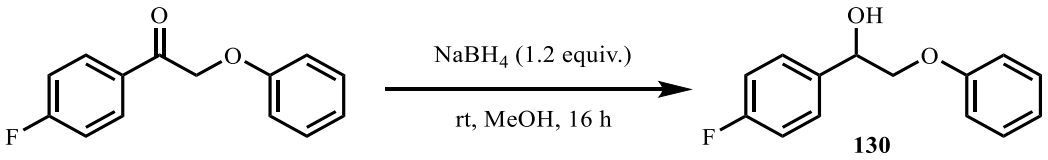
A round-bottomed flask equipped with a magnetic stirrer bar was charged with 2-bromo-4'-fluoroacetophenone (2.2 g, 10.0 mmol), a substituted phenol (10.0 mmol), and potassium carbonate (2.1 g, 15.0 mmol). Acetone (100 mL) was then added to the mixture and the reaction was stirred and heated to reflux for 16 h. The reaction was then filtered, and the filtrate concentrated *in vacuo*. The crude 2-aryloxyacetophenone was used for the next step without further purification. The resulting mixture was dissolved in methanol (80 mL), and a magnetic stirrer was added to the flask. The reaction was then cooled to 0 ˚C, and the solution was charged with sodium borohydride (416 mg, 15.0 mmol) portion wise. The reaction mixture was stirred at rt for 16 h. The reaction mixture cooled to 0 °C and quenched with sat. aq. NH_4Cl and H_2O. It was transferred to separatory funnel followed by the addition of EtOAc and H_2O. The organic layer was collected, and the aqueous phase washed with EtOAc (x 2). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

1-(4-fluorophenyl)-2-phenoxyethan-1-one



A round-bottomed flask equipped with a magnetic stirrer bar was charged with K_2CO_3 (9.6 g, 69 mmol), phenol (4.3 g, 46.0 mmol) and acetone (200 mL) To this mixture was added dropwise a solution of 2-bromo-4'-fluoroacetophenone (10.0 g, 46.0 mmol) in acetone (50 mL) over 30 min at RT. The resulting suspension was heated under reflux for 4 h. It was then cooled, filtered and concentrated *in vacuo*. Purification by recrystallisation gave the title compound as a yellow solid (7.21 g, 68%); mp 89-92 °C (pet. ether (40-60 °C); R_f = 0.53 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3059, 2899, 1699, 1587, 1497, 1431, 1248, 1221, 1159, 1094, 980, 837, 750, 685, 550, 511; **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 5.21 (2H, s, C(O)C*H*$_2$O), 6.94 (2H, d, *J* 8.0, ArC(3,5)*H*), 6.99 (1H, t, *J* 7.6, ArC(4)*H*), 7.17 (2H, m, ArC(2',6')*H*), 7.29 (2H, m, ArC(3',5')*H*), 8.06 (2H, m, ArC(2,6)*H*); **^{19}F NMR (377 MHz, $CDCl_3$)** δ_F: -103.4; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 71.0 (*C*H_2), 114.9 (Ar*C*(2',6')), 116.2 (d, *J* 22.1, Ar*C*(3,5)), 121.9 (Ar*C*(4')), 129.8 (Ar*C*(3',5')), 131.1 (Ar*C*(1)), 131.2 (d, *J* 9.5, Ar*C*(2,6)), 158.0 (Ar*C*(1')), 166.3 (d, *J* 256.5, Ar*C*(4)), 193.5 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{14}H_{12}O_2F]^+$ $(M+H)^+$ m/z : 231.0816, found 231.0816, (+0.2 ppm).

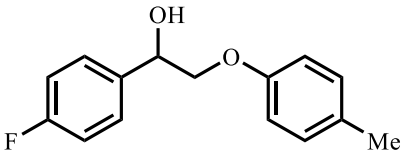
1-(4-fluorophenyl)-2-phenoxyethan-1-ol



130

A round-bottomed equipped with a magnetic stirrer bar was charged with 1-(4'-fluorophenyl)-2-phenoxyethan-1-one (6.5 g, 28.2 mmol) and methanol (300 mL). The solution was cooled to 0 °C and was charged with $NaBH_4$ (1.2 g, 33.8 mmol). The reaction was left to react at rt for 16 h and was then cooled to 0 °C and quenched with sat. aq. NH_4Cl (200 mL) and H_2O (100 mL). It was transferred to separatory funnel followed by the addition of EtOAc (200 mL) and H_2O (100 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 200 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by recrystallization gave the title compound as a white solid (5.1 g, 77%), mp 53-56 °C (hexanes); R_f = 0.35 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3237, 3067, 2938, 2878, 1599, 1585, 1510, 1497, 1456, 1225, 1152, 1078, 1042, 870, 752, 691, 592; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 3.98 (1H, dd, *J* 9.5, 9.0, OC*H*^{A}CH^B), 4.09 (1H, dd, *J* 3.0, 10.0, OCH^{A}C*H*^{B}), 5.11 (1H, dd, *J* 9.0, 3.0, C*H*OH), 6.89-6.95 (2H, m, ArC(2',6')*H*), 6.95-7.02 (1H, m, ArC(4')*H*), 7.04-7.10 (2H, m, ArC(3,5)*H*), 7.27-7.33 (2H, m, ArC(3,5)*H*), 7.40-7.47 (2H, m, ArC(2,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -114.1; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 72.1 (O*C*H$_2$), 73.3 (*C*HOH), 114.7 (Ar*C*(2',6')), 115.6 (d, *J* 21.5, Ar*C*(3,5)), 121.6 (Ar*C*(4')), 128.1 (d, *J* 8.2, Ar*C*(2,6)), 129.7 (Ar*C*(3',5')), 135.5 (d, *J* 3.2, Ar*C*(1)), 158.4 (Ar*C*(1')), 162.7 (d, *J* 247.0, Ar*C*(4)); HRMS (**EI$^+$**) calculated for $[C_{14}H_{13}FO_2]^+$ $(M)^+$ m/z : 232.0901, found 232.0900, (+0.4 ppm).

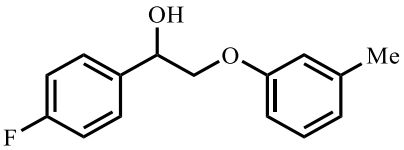
1-(4-fluorophenyl)-2-(*p*-tolyloxy)ethan-1-ol



The title compound was prepared according to general procedure 6 using *p*-cresol (1.1 g, 10 mmol). Purification by flash silica chromatography (eluent = 5-10 % EtOAc in hexanes, 60 x 150 mm silica) gave the title compound (1.8 g, 71%) as an off-white solid; mp 65-68 °C; R_f = 0.33 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3422, 2922, 2832, 1602, 1504, 1217, 1155, 1105, 1036, 1013, 870, 821, 729; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.29 (3H, s,

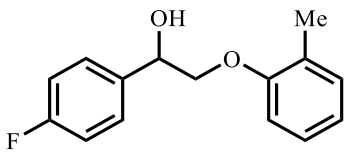
C*H*$_3$), 2.80 (1H, d, *J* 2.5, O*H*), 3.90-3.98 (1H, m, OC*H*^{A}CH^B), 4.06 (1H, dd, *J* 9.5, 3.0, OCH^{A}C*H*^{B}), 5.05-5.13 (1H, m, C*H*OH), 6.78-6.85 (2H, m, ArC(2',6')*H*), 7.03-7.12 (4H, m, ArC(3,5,3',5')*H*), 7.39-7.46 (2H, m, ArC(2,6)*H*); **^{19}F NMR (471 MHz, CDCl$_3$)** δ_F: -114.2; **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 20.6 (*C*H$_3$), 72.1 (O*C*H$_2$), 73.5 (1H, d, *J* 1.0, *C*HOH), 114.6 (Ar*C*(2',6')), 115.6 (d, *J* 21.4, Ar*C*(3,5)), 128.1 (d, *J* 8.2, Ar*C*(2,6)), 130.2 (Ar*C*(3',5')), 130.8 (Ar*C*(4')), 135.5 (d, *J* 3.2, Ar*C*(1)), 156.3 (Ar*C*(1')), 162.7 (d, *J* 247.0, Ar*C*(4)); HRMS (**EI$^+$**) calculated for $[C_{15}H_{15}FO_2]^+$ $[M]^+$ m/z : 246.1056, found 246.1068, (+4.9 ppm).

1-(4-fluorophenyl)-2-(*m*-tolyloxy)ethan-1-ol



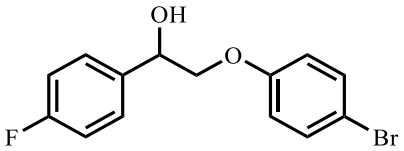
The title compound was prepared according to general procedure 6 using *m*-cresol (1.1 mL, 1.1 g, 10 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 50 x 170 mm silica) gave the title compound (1.5 g, 61%) as a white solid; mp 84-87 °C; R_f = 0.33 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3285, 3206, 2922, 2868, 1601, 1582, 1508, 1485, 1454, 1288, 1260, 1234, 1221, 1155, 1107, 1084, 1053, 920. 878, 853, 831, 772, 731, 691, 606, 575, 542, 525; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 2.33 (3H, s, C*H*$_3$), 2.79 (1H, d, *J* 2.0, O*H*), 3.96 (1H, t, *J* 9.0, OC*H*^{A}CH^B), 4.07 (1H, dd, *J* 9.5, 3.0, OCH^{A}C*H*^{B}), 5.06-5.34 (1H, m, C*H*OH), 6.69-6.77 (2H, m, Ar*H*), 6.80 (1H, d, *J* 7.5, Ar*H*), 7.03-7.12 (2H, m, Ar*H*), 7.17 (1H, t, *J* 8.0, Ar*H*), 7.39-7.47 (2H, m, ArC(2,6)*H*); **^{19}F NMR (471 MHz, CDCl$_3$)** δ_F: -114.1; **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 21.6 (*C*H$_3$), 72.1 (O*C*H$_2$), 73.3 (*C*HOH), 111.7 (Ar*C*), 115.6 (Ar*C*), 115.6 (d, *J* 21.5, Ar*C*(3,5)), 122.4 (Ar*C*), 128.1 (d, *J* 8.2, Ar*C*), 129.5 (Ar*C*), 135.6 (d, *J* 3.2, Ar*C*(2,6)), 139.9 (Ar*C*), 158.4 (ArC(1')), 162.7 (d, *J* 247, Ar*C*(4)); HRMS (**EI$^+$**) calculated for $[C_{15}H_{15}FO_2]^+$ $(M)^+$ m/z : 246.1056, found 246.1051, (-2.0 ppm).

1-(4-fluorophenyl)-2-(*o*-tolyloxy)ethan-1-ol



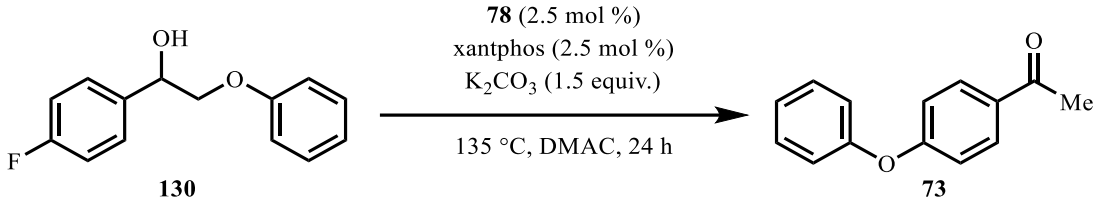
The title compound was prepared according to general procedure 6 using *o*-cresol (1.0 mL, 1.1 g, 10 mmol). Purification by flash silica chromatography (eluent = 5-7% EtOAc in hexanes, 50 x 170 mm silica) gave the title compound (1.5 g, 60%) as a pale-yellow oil; R_f = 0.33 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3385, 3028, 2928, 2860, 1603, 1589, 1510, 1491, 1462, 1437, 1184, 1157, 1121, 1036, 835, 750, 714, 608, 579; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.25 (3H, s, C*H*$_3$), 2.77 (1H, br s, O*H*), 4.00 (1H, t, *J* 8.5, OC*H*^{A}CH^B), 4.10 (1H, dd, *J* 9.5, 3.5, OCH^{A}C*H*^{B}), 5.14 (1H, dd, *J* 8.5, 3.5, C*H*OH), 6.79 (1H, d, *J* 8.0, ArC(3,5)*H*), 6.90 (1H, t, *J* 7.5, Ar*H*), 7.08 (1H, t, *J* 9.0, Ar*H*), 7.11-7.18 (2H, m, Ar*H*), 7.40-7.48 (2H, m, ArC(2,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -114.2; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 16.4 (*C*H$_3$), 72.2 (O*C*H$_2$), 73.4 (*C*HOH), 111.4 (Ar*C*), 115.6 (d, *J* 21.4, Ar*C*(3,5)), 121.3 (Ar*C*), 126.9 (Ar*C*(2')CH$_3$), 127.0 (Ar*C*), 128.2 (d, *J* 8.2, Ar*C*(2,6)), 131.0 (Ar*C*), 135.7 (d, *J* 3.2, Ar*C*(1)), 156.5 (Ar*C*(1')), 162.7 (d, *J* 247, Ar*C*(4)); HRMS (**EI$^+$**) calculated for $[C_{15}H_{15}FO_2]^+$ $(M)^+$ m/z : 246.1056, found 246.1057, (+0.4 ppm).

2-(4-bromophenoxy)-1-(4-fluorophenyl)ethan-1-ol



The title compound was prepared according to general procedure 6 using 4-bromophenol (1.7 g, 10 mmol). Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 60 x 150 mm silica) gave the title compound (2.3 g, 74%) as an off-white solid; mp 71-74 °C; R_f = 0.27 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.74 (1H, d, *J* 2.5, O*H*), 3.91-3.99 (1H, m, OC*H*^{A}CH^B), 4.03 (1H, dd, *J* 9.5, 3.0, OCH^{A}C*H*^{B}), 5.05-5.15 (1H, m, C*H*OH), 6.76-6.84 (2H, m, ArC(2',6')*H*), 7.03-7.13 (2H, m, ArC(3,5)*H*), 7.34-7.46 (4H, m, ArC(2,6,3',5')*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -113.8; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 72.0 (O*C*H$_2$), 73.5 (d, *J* 1.0, *C*HOH), 113.7 (Ar*C*(4')), 115.7 (d, *J* 21.5, Ar*C*(3,5)), 116.5 (Ar*C*(3',5')), 128.1 (d, *J* 8.2, Ar*C*(2,6)), 132.5 (Ar*C*(2',6')), 135.3 (d, *J* 3.2, Ar*C*(1)), 157.5 (Ar*C*(1')), 162.8 (d, *J* 247.0, Ar*C*(4)); HRMS (**EI$^+$**) calculated for $[C_{14}H_{12}FO_2{}^{79}Br]^+$ $(M)^+$ m/z : 310.0005, found 310.0003, (-0.6 ppm).

7.5. Substrate scope – Isomerisation protocol



130 **73**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with $Ru(PPh_3)(CO)(H)_2$ (23 mg, 0.025 mmol, 2.5 mol %), xantphos (14.5 mg, 0.025 mmol, 2.5 mol %), K_2CO_3 (207 mg, 1.5 mmol, 1.5 equiv.), DMAC (1 mL) and 1-(4-fluorophenyl)-2-phenoxyethanol (232 mg, 1.0 mmol). The vial was sealed with a cap and left to react at 135 ^oC for 24 h. After cooling, the reaction mixture was transferred to a separatory funnel and the vial washed with EtOAc (25 mL) and H_2O (25 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica column chromatography (eluent = 5% EtOAc in hexanes, 30 x 150 mm silica) gives the title compound as a white solid (168 mg, 79%); R_f = 0.43 (eluent = 20% EtOAc in hexanes). Spectroscopic data in accordance with that reported previously.

7.6. References

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Chapter 8: Experimental

Iron-catalysed methylation using the borrowing hydrogen approach

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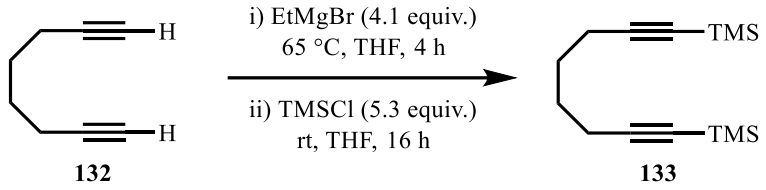
8.1. (cyclopentadienone)iron carbonyl precatalyst synthesis

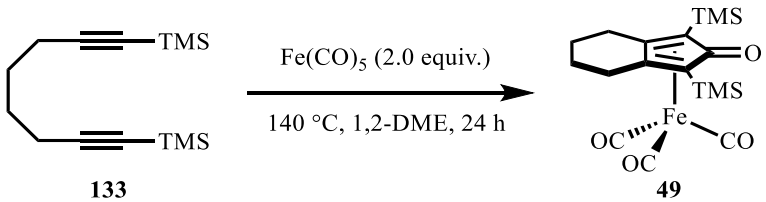
1,8-bis(trimethylsilyl)octa-1,7-diyne



132 **133**

The title compound was prepared according to a procedure stated in the literature.[1] A three-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with THF (13 mL) and EtMgBr (34 mL, 102.0 mmol, 3 M in Et_2O). The solution was heated to 60 °C and a solution of 1,7-octadiyne (3.3 mL, 2.6 g, 25.0 mmol) in THF (36 mL) was then added dropwise. It was stirred at 65 °C for 3 h and then cooled to rt. Trimethylsilyl chloride (16.7 mL, 14.4 g, 132.0 mmol, 5.3 equiv.) was then added dropwise and the suspension was left to stir at rt for 16 h. The cloudy white precipitate was quenched with sat. aq. NH_4Cl (5 mL) and water (50 mL). Hexane (50 mL) was added and the mixture was transferred to a separatory funnel. The organic phase was collected, the aqueous was washed with hexanes (3 x 15 mL). The organics were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by Kugelrohr distillation (200 °C at 10 mbar) yielded a pale-yellow oil (6.2 g, 99%); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.15 (18H, s, 2xSi(C*H*$_3$)$_3$), 1.59-1.65 (4H, m, CH_2(C*H*$_2$)$_2$$CH_2$), 2.20-2.30 (4H, m, 2xC*H*$_2$C≡CSi(CH$_3$)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 0.31 (2xSi(*C*H$_3$)$_3$), 19.5 (CH_2(*C*H$_2$)$_2$$CH_2$), 27.8 (2x*C*H$_2$C≡C), 84.8 (2x*C*≡CSi(CH$_3$)$_3$), 107.2 (2xC≡*C*Si(CH$_3$)$_3$). Spectroscopic data in accordance with that stated in the literature.[2]

Tricarbonyl(1,3-bis(trimethylsilyl)-4,5,6,7-tetrahydro-2*H*-inden-2-one)iron

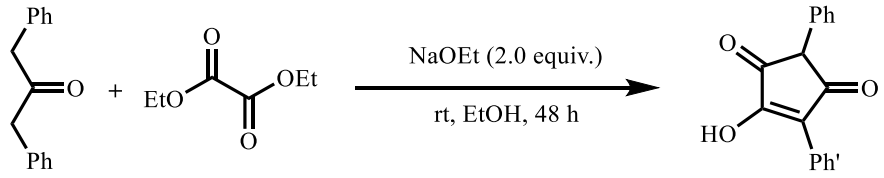


133 **49**

The title compound was prepared according to a procedure stated in the literature.[1] An ACE pressure containing a magnetic stirrer was charged with 1,8-bis(trimethylsilyl)octa-1,7-diyne (2.0 g, 8.0 mmol), iron pentacarbonyl (2.1 mL, 3.1 g, 16.0 mmol) and 1,2-dimethoxyethane (67 mL). This was then heated in an oil bath at 140 °C for 24 h. It was then cooled and concentrated *in vacuo*. The remaining solid residue was dissolved in boiling hexane (20 mL) and vacuum filtered while hot, removing any iron impurities. The filtrate

was then cooled and the formed yellow crystals were filtered off yielding the title compound (2.2 g, 66% yield); mp 133-135 °C; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.27 (18H, s, 2xSi(C*H*-$_3$)$_3$), 2.47-2.65 (4H, m, $CH_2(CH_2)_2CH_2$), 1.73-1.92 (4H, m, 2xCH_2C≡CSi(CH_3)$_3$); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: -0.1 (2xSi(*C*H_3)$_3$), 22.6 ($CH_2(CH_2)_2CH_2$), 24.9 ($CH_2(CH_2)_2CH_2$), 71.9 (2x*C*-Si(CH_3)$_3$), 111.2 (2xCH_2-*C*≡C), 181.4 (C-(*C*=O)-C), 209.2 (Fe(*C*O)$_3$). Spectroscopic data in accordance with that stated in the literature.[2]

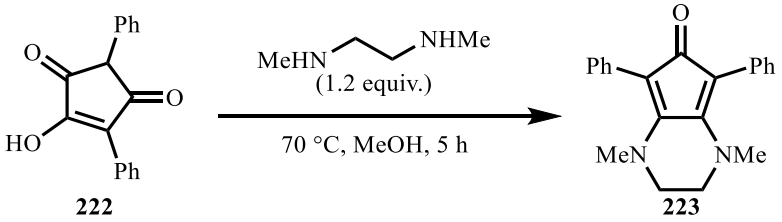
4-hydroxy-2,5-diphenylcyclopent-4-ene-1,3-dione



174 **221** **222**

The title compound was prepared according to a procedure stated in the literature.[3] Under nitrogen, a flame dried Schlenk tube equipped with a magnetic stirrer bar was charged with ethanol (20 mL) and metallic sodium (920 mg, 40.0 mmol) at 0 °C. After complete dissolution, the solution was charged with 1,3-diphenylacetone (4.0 g, 20.0 mmol) and diethyl oxalate (2.7 mL, 2.9 g, 20.0 mmol). This was left to stir at rt for 48 h. 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 $MgSO_4$, filtered and concentrated *in vacuo*. Purification by recrystallisation yielded a yellow solid (2.8 g, 52%); mp 168-170 °C (dec) ($CHCl_3$/hexanes), R_f = 0.33 (eluent = 100% EtOAc); **^{1}H NMR (500 MHz, $(CD_3)_2SO$)** δ_H: 4.49 (1H, s, C*H*), 7.19 (2H, d, *J* 7.0, ArC(2',6')*H*), 7.28-7.46 (4H, m, ArC(4,3',4',5')*H*), 7.46-7.54 (2H, m, ArC(3,5)*H*), 8.06-8.10 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $(CD_3)_2SO$)** δ_H: 55.9 (*C*H), 127.4 (Ar*C*(4')), 128.1 (Ar*C*), 128.2 (Ar*C*(3,5)), 128.7 (Ar*C*(2',6')), 128.8 (Ar*C*(2,6)), 128.8 (Ar*C*(4)), 128.8 (Ar*C*(3',5')), 129.5 (Ar*C*(1)), 134.4 (Ar*C*(1')), 166.4 (*C*OH) (Ar*C*), 196.8 (*C*=O), 197.5 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[3]

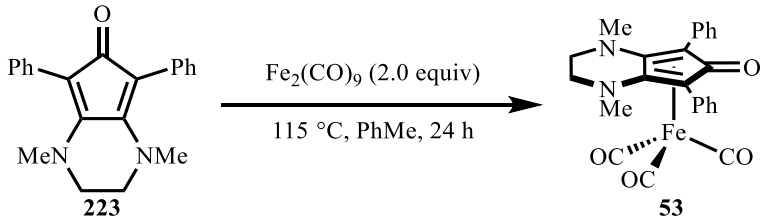
1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6*H*-cyclopenta[b]pyrazin-6-one



222 **223**

The title compound was prepared according to a procedure stated in the literature.[3] Under nitrogen, a flame dried round-bottomed equipped a magnetic stirrer bar was charged with 4-hydroxy-2,5-diphenylcyclopent-4-ene-1,3-dione (2.5 g, 9.5 mmol), methanol (15 mL) and *N*,*N*'-dimethylethylenediamine (1.2 mL, 1.0 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 (2.9 g, 95%); mp 184-186 °C; R_f = 0.50 (eluent = 5% MeOH in CH_2Cl_2); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.84 (6H, s, 2xNC*H*$_3$), 3.36 (4H, s, N(C*H*$_2$)$_n$N), 7.12-7.19 (2H, m, 2xArC(4)*H*), 7.23-7.32 (8H, m, 2xArC(2,3,5,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 42.2 (2xN*C*H$_3$), 50.1 (N(*C*H$_2$)$_2$N), 99.0 (2x*C*-Ar), 125.6 (2xAr*C*(4)), 127.4 (2xAr*C*(2,6)), 131.2 (2xAr*C*(3,5)), 133.8 (2xAr*C*(1)), 151.0 (2xN*C*=CPh), 195.4 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[3]

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



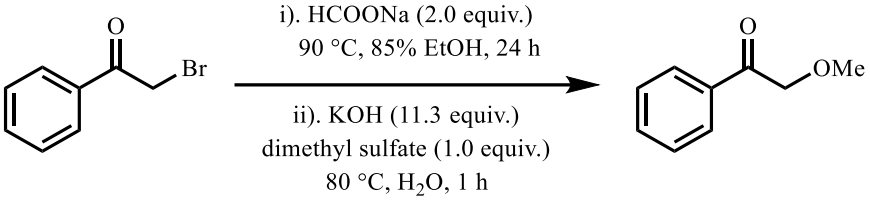
223 **53**

The title compound was prepared according to a procedure stated in the literature.[3] Under nitrogen, a flame dried Schlenk tube equipped with a magnetic stirrer bar was charged with 1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6*H*-cyclopenta[b]pyrazin-6-one (800 mg, 2.5 mmol), diiron nonacarbonyl (1.8 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 (eluent = 0-1% MeOH in CH_2Cl_2, 50 x 200 mm alumina) followed by precipitation (pentane/Et_2O) gave an orange-yellow solid (800 mg, 69%), mp 199-201 °C; R_f = 0.46 (eluent = 5% MeOH in CH_2Cl_2); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.38 (6H, s, 2xNC*H*$_3$),

2.87-2.97 (2H, m, NC*H*$_2$), 3.39-3.50 (2H, m, NC*H*$_2$), 7.29-7.35 (2H, m, 2xArC(4)*H*), 7.36-7.42 (4H, m, 2xArC(3,5)*H*), 7.51-7.58 (4H, m, 2xArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 41.6 (2xN*C*H$_3$), 50.2 (2xN*C*H$_2$), 71.1 (2x*C*=CNCH$_3$), 114.6 (2xC=*C*NCH$_3$), 128.0 (Ar*C*(4)), 128.4 (Ar*C*(3,5)), 131.9 (Ar*C*(1)), 132.4 (Ar*C*(2,6)), 165.8 (C-(*C*=O)-C), 210.3 (Fe(*C*O)$_3$). Spectroscopic data in accordance with that stated in the literature.[3]

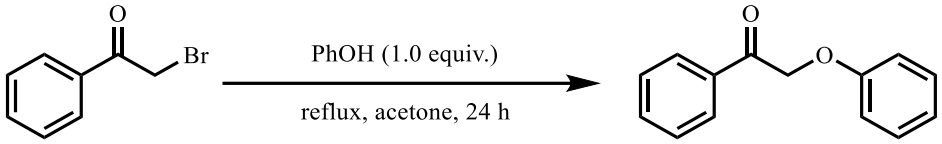
8.2. Substrate synthesis

2-methoxy-1-phenylethan-1-one



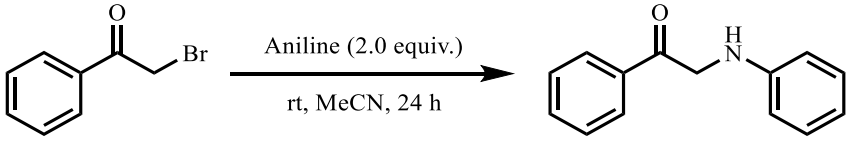
A round-bottomed flask equipped with a magnetic stirrer bar was charged with 2-bromoacetophenone (2.0 g, 10.0 mmol), sodium formate (1.4 g, 20.0 mmol) and 85% ethanol (50 mL). This was heated under reflux for 24 h. H_2O (100 mL) and EtOAc (100 mL) were then added to the suspension. The mixture was transferred to a separatory funnel, the organic layer was collected, and the aqueous phase washed with EtOAc (2 x 100 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. This was used for the next step without further purification. The flask containing this crude mixture (1.3 g) was charged with KOH (636 mg, 11.3 mmol) and water (5.4 mL). The suspension was cooled to 0 °C and charged with dimethyl sulfate (1.0 mL, 10.2 mmol). The mixture was heated to 80 °C for 1 h. It was then cooled followed by the addition of $CHCl_3$ (50 mL). The organic layer was collected, and the aqueous phase washed with $CHCl_3$ (2 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 0.5% EtOAc in pet. ether (40-60 °C), 50 x 180 mm silica) gave the title compound as a colourless oil (290 mg, 19%); R_f = 0.08 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 3.51 (3H, s, C*H*$_3$), 4.71 (2H, s, C*H*$_2$), 7.43-7.51 (2H, m, ArC(3,5)*H*), 7.55-7.62 (1H, m, ArC(4)*H*), 7.90-7.98 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 59.6 (*C*H$_3$), 75.4 (*C*H$_2$), 127.9 (Ar*C*(2,6)), 128.9 (Ar*C*(3,5)), 133.7 (Ar*C*(4)), 134.8 (Ar*C*(1)), 196.2 (*C*=O); Spectroscopic data in accordance with that stated in the literature.[4]

2-phenoxy-1-phenylethan-1-one



A round-bottomed flask equipped with a magnetic stirrer bar was charged with K_2CO_3 (2.1 g, 15.0 mmol), phenol (941 mg, 10.0 mmol) and acetone (25 mL) To this mixture was added dropwise a solution of 2-bromoacetophenone (2.0 g, 10.0 mmol) in acetone (25 mL) over 30 min at rt. The resulting suspension was heated under reflux for 24 h. It was then cooled, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 50 x 150 mm silica) gave the title compound as a white solid (1.7 g, 80%); mp 59-61 °C; (Lit. 60-61 °C);[5] R_f = 0.33 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3067, 2901, 1709, 1603, 1576, 1503, 1450, 1433, 1304, 1252, 1225, 1175, 1094, 976, 876, 748, 691, 665, 507; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 5.28 (2H, s, C*H*$_2$), 6.91-6.97 (2H, m, ArC(2',6')*H*), 6.99 (1H, t, *J* 7.5, ArC(4')*H*), 7.26-7.33 (2H, m, ArC(3',5')*H*), 7.51 (2H, t , *J* 7.5, ArC(3,5)*H*), 7.62 (1H, t, *J* 7.5, ArC(4)*H*), 7.98-8.04 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 70.9 (*C*H$_2$), 114.9 (Ar*C*(2',6')), 121.8 (Ar*C*(4')), 128.3 (Ar*C*(3,5)), 129.0 (Ar*C*(2,6)), 129.7 (Ar*C*(3',5')), 134.0 (Ar*C*(4)), 134.7 (Ar*C*(1)), 158.1 (Ar*C*(1')), 194.7 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{14}H_{13}O_2]^+$ $(M+H)^+$ m/z : 213.0910, found 213.0909, (-0.5 ppm).

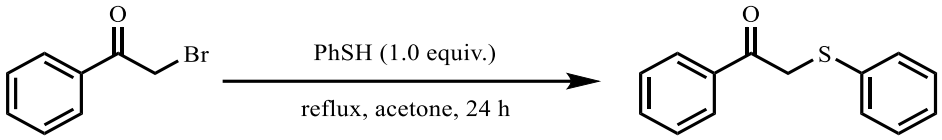
1-phenyl-2-(phenylamino)ethan-1-one



A round-bottomed flask equipped with a magnetic stirrer bar was charged with 2-bromoacetophenone (2.0 g, 10.0 mmol) and acetonitrile (20 mL). This mixture was then cooled in an ice bath followed by dropwise addition of aniline (1.8 mL, 1.9 g, 20.0 mmol). The mixture was left to react at rt for 24 h. The aniline hydrobromide was then filtered off and the filtrate concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 2% EtOAc in pet. ether (40-60 °C), 50 x 140 mm silica) gave the title compound as a yellow solid (1.7 g, 81%); mp 95-98 °C (Lit. 91-92 °C);[6] R_f = 0.36 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 4.63 (2H, s, C*H*$_2$), 4.94 (1H, br s, N*H*), 6.69-6.80 (3H, m, ArC(2',4',6')*H*), 7.19-7.28 (2H, m, ArC(3',5')*H*), 7.49-7.57 (2H, m, ArC(3,5)*H*), 7.60-7.67 (1H, m, ArC(4)*H*), 8.00-8.06 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126**

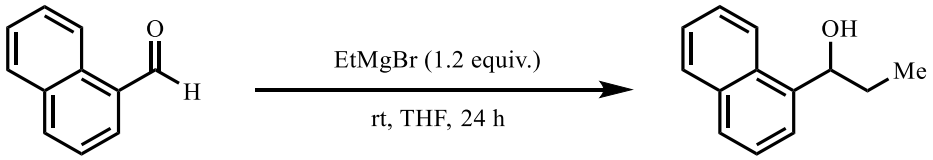
MHz, $CDCl_3$) δ_C: 50.5 (*C*H_2), 113.2 (Ar*C*(2',6')), 118.0 (Ar*C*(4')), 127.9 (Ar*C*(2,6)), 129.0 (Ar*C*(3,5)), 129.5 (Ar*C*(3',5')), 134.0 (Ar*C*(4)), 135.1 (Ar*C*(1)), 147.2 (Ar*C*(1')), 195.2 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[7]

1-phenyl-2-(phenylthio)ethan-1-one



A round-bottomed flask equipped with a magnetic stirrer bar was charged with K_2CO_3 (2.1 g, 15.0 mmol), 2-bromoacetophenone (2.0 g, 10.0 mmol) and acetone (50 mL). This mixture was then cooled in an ice bath followed by the dropwise addition of thiophenol (1.0 mL, 1.1 g, 10.0 mmol). The resulting suspension was heated under reflux for 24 h. It was then cooled, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% EtOAc in pet. ether (40-60 °C), 50 x 150 mm silica) gave the title compound as a white solid (2.1 g, 94%); mp 53-55 °C (Lit. 53-54 °C);[8] R_f = 0.40 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 4.28 (2H, s, C*H*$_2$), 7.20-7.25 (1H, m, ArC(4')*H*), 7.26-7.32 (2H, m, ArC(3',5')*H*), 7.36-7.42 (2H, m, ArC(2',6')*H*), 7.43-7.51 (2H, m, ArC(3,5)*H*), 7.55-7.62 (1H, m, ArC(4)*H*), 7.91-7.99 (2H, m. ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 41.3 (*C*H_2), 127.2 (Ar*C*(4')), 128.8 (Ar*C*(2,3,5,6)), 129.2 (Ar*C*(3',5')), 130.7 (Ar*C*(2',6')), 133.6 (Ar*C*(4)), 134.9 (Ar*C*(1)), 135.5 (Ar*C*(1')), 194.2 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[7]

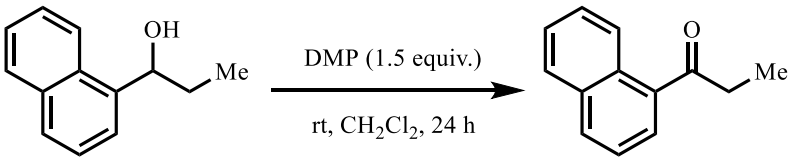
1-(naphthalen-1-yl)propan-1-ol



A round-bottomed flask equipped with a magnetic stirrer bar was charged with 1-naphthaldehyde (1.4 mL, 1.6 g, 10.0 mmol) and dry THF (16 mL). The mixture was cooled to 0 °C and EtMgBr (4.0 mL, 12.0 mmol, 3 M in Et_2O) was then added dropwise. The reaction was left to stir for 24 h and then was quenched by the addition of sat. aq. NH_4Cl (10 mL) and H_2O (10 mL). EtOAc (50 mL) was then added and the organic layer was then separated, and the aqueous layer washed with EtOAc (2 x 50 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*.

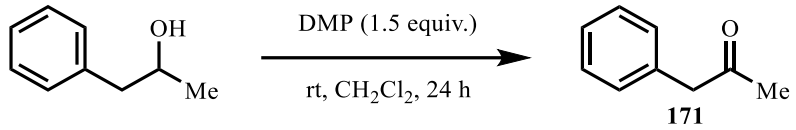
Purification by flash silica chromatography (eluent = 5-10% EtOAc in pet. ether (40-60 °C), 50 x 150 mm silica) gave a pale-yellow oil (1.7 g, 93%); R_f = 0.20 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3061, 3032, 2976, 2930, 1709, 1599, 1493, 1450, 1119, 1030, 762, 737, 696, 536; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.04 (3H, t, *J* 7.0, CH_2CH_3), 1.78 (1H, br s, O*H*), 1.88-2.10 (2H, m, CH_2CH_3), 5.42 (1H, dd, *J* 7.5, 5.0, C*H*OH), 7.44-7.56 (3H, m, ArC(3,6,7)*H*), 7.65 (1H, d, *J* 7.0, ArC(2)*H*), 7.78 (1H, d, *J* 7.0, ArC(4)*H*), 7.84-7.91 (1H, m, ArC(8)*H*), 8.13 (1H, d, *J* 8.5, ArC(5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 10.7 (CH_2CH_3), 31.2 (CH_2CH_3), 72.8 (*C*HOH), 123.0 (Ar*C*(2)), 123.4 (Ar*C*(5)), 125.5 (Ar*C*(3)), 125.6 (Ar*C*(6)), 126.1 (Ar*C*(7)), 128.0 (Ar*C*(4)), 129.0 (Ar*C*(8)), 130.7 (Ar*C*(8a)), 134.0 (Ar*C*(4a)), 140.4 (Ar*C*(1)); HRMS (**CI$^+$**) calculated for $[C_{13}H_{18}ON]^+$ $(M+NH_4)^+$ m/z : 204.1383, found 204.1381, (-0.9 ppm).

1-(naphthalen-1-yl)propan-1-one



A 250 round-bottomed flask equipped with a magnetic stirrer bar was charged with 1-(naphthalen-1-yl)propan-1-ol (1.6 g, 8.7 mmol) and CH_2Cl_2 (80 mL). The mixture was cooled to 0 °C and Dess-Martin Periodinane (5.5 g, 13.1 mmol) was added portion wise. This was left to stir at rt for 16 h. The mixture was quenched with a 1:1 mixture of 10 wt% $Na_2S_2O_3$ / sat. aq. $NaHCO_3$), and then transferred to a separatory funnel. The organic layer was separated, and the aqueous phase was washed with CH_2Cl_2 (2 x 80 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% EtOAc in pet. ether (40-60 °C), 50 x 150 mm silica) gave the title compound as a colourless oil (1.5 g, 96%); R_f = 0.42 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3049, 2974, 2936, 2899, 2876, 1678, 1593, 1572, 1506, 1460, 1410, 1377, 1333, 1228, 1177, 1107, 934, 797, 770, 631, 571; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.29 (3H, t, *J* 7.5, CH_2CH_3), 3.09 (2H, q, *J* 7.5, CH_2CH_3), 7.45-7.63 (3H, m, ArC(3,6,7)*H*), 7.86 (2H, 2d, *J* 8.0, 9.0, ArC(4,5)*H*), 7.98 (1H, d, *J* 8.0, ArC(2)*H*), 8.56 (1H, d, *J* 8.5, ArC(8)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 8.8 (CH_2CH_3), 35.5 (CH_2CH_3), 124.5 (Ar*C*), 125.9 (Ar*C*), 126.5 (Ar*C*), 127.2 (Ar*C*), 127.9 (Ar*C*), 128.5 (Ar*C*), 130.3 (Ar*C*), 132.4 (Ar*C*), 134.1 (Ar*C*), 136.4 (Ar*C*), 205.5 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{13}H_{13}O]^+$ $(M+H)^+$ m/z : 185.0966, found 185.0966, (+0.0 ppm).

1-phenyl-propan-2-one



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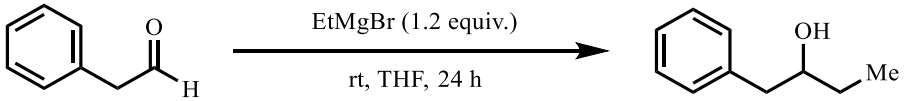
A round-bottomed flask equipped with a magnetic stirrer bar was charged with 1-phenyl-2-propanol (1.4 mL, 1.4 g, 10.0 mmol) and CH_2Cl_2 (100 mL). The mixture was to 0 °C and Dess-Martin Periodinane (6.4 g, 15.0 mmol) was added portion wise. This was left to stir at rt for 16 h. The mixture was quenched with a 1:1 mixture of 10 wt% $Na_2S_2O_3$ / sat. aq. $NaHCO_3$), and then transferred to a separatory funnel. The organic layer was separated, and the aqueous phase was washed with CH_2Cl_2 (2 x 80 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10% Et_2O in pet. ether (40-60 °C), 50 x 140 mm silica) gave the title compound as a colourless oil (1.2 g, 90%); R_f = 0.22 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.15 (3H, s, C*H*$_3$), 3.70 (2H, s, C*H*$_2$), 7.17-7.24 (2H, m, ArC(2,6)*H*), 7.26-7.30 (1H, m, ArC(4)*H*), 7.31-7.37 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 29.4 (*C*H$_3$), 51.2 (*C*H$_2$), 127.2 (Ar*C*(4)), 128.9 (Ar*C*(3,5)), 129.5 (Ar*C*(2,6)), 134.4 (Ar*C*(1)), 206.5 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[9]

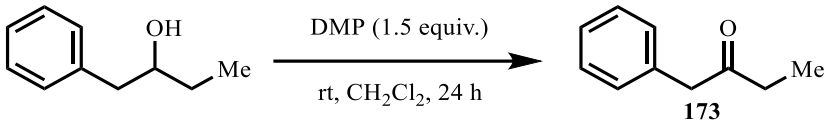
1-phenyl-2-butanol



A round-bottomed flask equipped with a magnetic stirrer bar was charged with phenylacetaldehyde (1.2 mL, 1.2 g, 10.0 mmol) and dry THF (16 mL). The mixture was cooled to 0 °C and EtMgBr (4.0 mL, 12.0 mmol, 3 M in Et_2O) was then added dropwise. The reaction was left to stir for 24 h and then was quenched by the addition of sat. aq. NH_4Cl (10 mL) and H_2O (10 mL). EtOAc (50 mL) was then added and the organic layer was then separated. The aqueous layer was washed with EtOAc (2 x 50 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 50 x 180 mm silica) gave the title compound as a pale yellow oil (656 mg, 44%); R_f = 0.48 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3368, 3038, 2963, 2932, 2872, 1493, 1454, 1113, 1078, 1013, 974, 737, 698, 534; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.00 (3H, t, *J* 7.5, CH_2CH_3), 1.42-1.66 (3H, m, C*H*$_2$CH$_3$, O*H*), 2.65 (1H, dd, *J* 13.5, 8.5 ArC*H*^{A}H^B), 2.84 (1H, dd, *J* 13.5, 4.5, ArCH^A*H*^{B}), 3.71-7.80 (1H, m, C*H*OH), 7.19-7.27 (3H, m, ArC(2,4,6)*H*),

7.28-7.36 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 10.2 (CH_2CH_3), 29.7 (CH_2CH_3), 43.7 ($PhCH_2$), 74.2 (*C*HOH), 126.6 (Ar*C*(4)), 128.8 (Ar*C*(2,6)), 129.6 (Ar*C*(3,5)), 138.7 (Ar*C*(1)); HRMS (**CI$^+$**) calculated for $[C_{10}H_{18}ON]^+$ $(M+NH_4)^+$ m/z : 168.1383, found 168.1385, (+1.2 ppm).

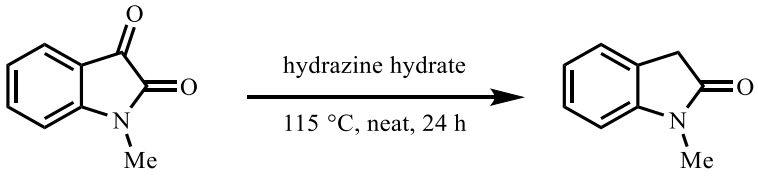
1-phenyl-propan-2-one



173

A round-bottomed flask equipped with a magnetic stirrer bar was charged with 1-phenyl-2-butanol (500 mg, 3.3 mmol) and CH_2Cl_2 (35 mL). The mixture was cooled to 0 °C and Dess-Martin periodinane (2.1 g, 5.0 mmol) was added portion wise. This was left to stir at rt for 16 h. The mixture was quenched with a 1:1 mixture of 10 wt% $Na_2S_2O_3$ / sat. aq. $NaHCO_3$ (25 mL), and then transferred to a separatory funnel. The organic layer was separated, and the aqueous phase was washed with CH_2Cl_2 (2 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% Et_2O in pet. ether (40-60 °C), 40 x 160 mm silica) gave the title compound as a colourless oil (490 mg, 99%); R_f = 0.21 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3034, 2974, 2936, 1709, 1495, 1452, 1412, 1352, 1105, 1034, 733, 698; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.03 (3H, t, *J* 7.5, CH_2CH_3), 2.48 (2H, q, *J* 7.5, CH_2CH_3), 3.69 (2H, s, $PhCH_2$), 7.18-7.23 (2H, m, ArC(2,6)*H*), 7.23-7.30 (1H, m, ArC(4)*H*), 7.30-7.36 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 7.9 (CH_2CH_3), 35.4 (CH_2CH_3), 50.0 ($PhCH_2$), 127.1 (Ar*C*(4)), 128.8 (Ar*C*(2,6)), 129.5 (Ar*C*(3,5)), 134.6 (Ar*C*(1)), 209.1 (*C*=O); HRMS (**CI$^+$**) calculated for $[C_{10}H_{16}ON]^+$ $(M+NH_4)^+$ m/z : 166.1226, found 166.1223, (-2.1 ppm).

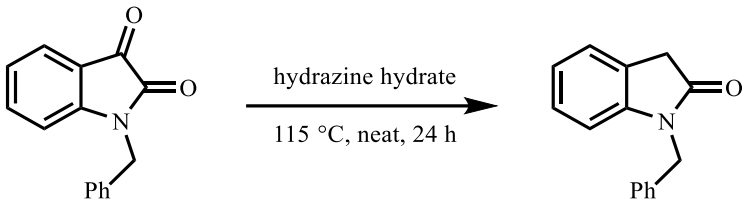
1-methylindolin-2-one



The title compound was prepared according to a modified procedure stated in the literature.[10] A round-bottomed flask equipped a magnetic stirrer bar was charged with *N*-methyl isatin (1.6 g, 10.0 mmol) and hydrazine hydrate 50-60% in H_2O (30 mL) and was left to react at 115 °C for 16 h. It was then cooled and filtered. Purification by flash silica chromatography

(eluent = 10% EtOAc in hexanes, 50 x 160 mm silica) gave the title compound as an off-white solid (901 mg, 61%); mp 86-88 °C (Lit. 82-84 °C);[11] R_f = 0.18 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 3.21 (3H, s, NC*H*$_3$), 3.52 (2H, s, C*H*$_2$), 6.82 (1H, d, *J* 7.5, ArC(7)*H*), 7.04 (1H, dt, *J* 7.5, 1.0, ArC(5)*H*), 7.24 (1H, d, *J* 8.0, ArC(4)*H*), 7.26-7.32 (1H, m, ArC(6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 26.3 (N*C*H$_3$), 35.9 (*C*H$_2$), 108.2 (Ar*C*(7)), 122.5 (Ar*C*(5)), 124.4 (Ar*C*(4)), 124.6 (Ar*C*(3a)), 128.0 (Ar*C*(6)), 145.4 (Ar*C*(7a)), 175.2 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[12]

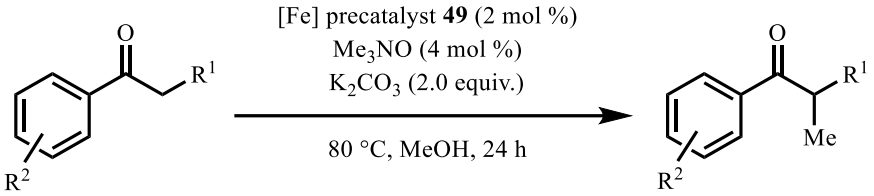
1-benzylindolin-2-one



The title compound was prepared according to a modified procedure stated in the literature.[13] A round-bottomed flask equipped a magnetic stirrer bar was charged with *N*-benzyl isatin (2.4 g, 10.0 mmol) and hydrazine hydrate 50-60% in H_2O (30 mL) and was left to react at 115 °C for 16 h. It was then cooled followed by the addition of EtOAc (75 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 75 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 50 x 150 mm silica) gave the title compound as an off-white solid (1.9 g, 86%); mp 63-65 °C (Lit. 62-64 °C);[14] R_f = 0.30 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 3.63 (2H, s, ArC*H*$_2$CO), 4.92 (2H, s, Ar'C*H*$_2$N), 6.72 (1H, d, *J* 7.5, ArC(7)*H*), 7.01 (1H, dt, *J* 7.5, 1.0, ArC(5)*H*), 7.12-7.20 (1H, m, ArC(6)*H*), 7.22-7.29 (2H, m, ArC(4)*H*, ArC(4')*H*), 7.29-7.35 (4H, m, ArC(2',3',5',6')*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 35.9 (*C*H$_2$(C=O)), 43.9 (N*C*H$_2$), 109.2 (Ar*C*), 122.5 (Ar*C*), 124.5 (Ar*C*), 124.6 (Ar*C*(3a)), 127.4 (Ar*C*), 127.7 (Ar*C*), 127.9 (Ar*C*), 128.9 (Ar*C*), 136.0 (Ar*C*), 144.5 (Ar*C*(7a)), 175.2 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[13]

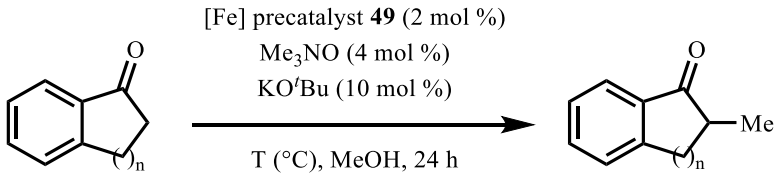
8.3. Scope of iron catalysed borrowing hydrogen methylation

8.3.1. General procedure 1 – Monomethylation of ketones



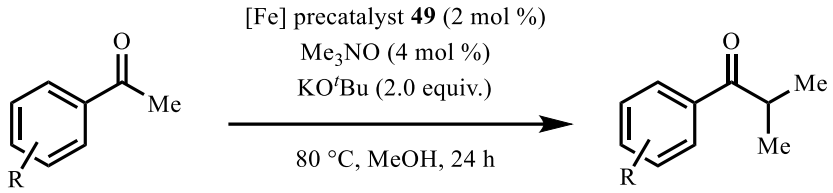
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.0 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 mg, 0.02 mmol, 2 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL) and ketone (1.0 mmol). The mixture was left to react at 80 °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 $MgSO_4$, filtered and concentrated *in vacuo*.

8.3.2. General procedure 2 – Monomethylation of cyclic ketones



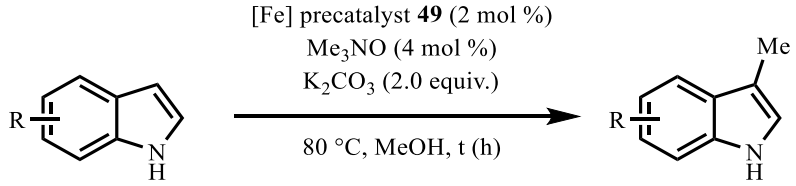
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with KO^tBu (11.2 mg, 0.1 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 mg, 0.02 mmol, 2 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL) and ketone (1.0 mmol). The mixture was left to react at 80 or 110 °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 $MgSO_4$, filtered and concentrated *in vacuo*.

8.3.3. General procedure 3 – Dimethylation of acetophenones



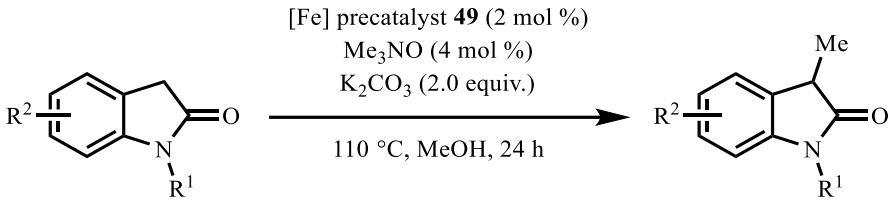
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with KO^{t}Bu (224 mg, 2.0 mmol), ketone (1.0 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 mg, 0.02 mmol, 2 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL). The mixture was left to react at 80 °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 $MgSO_4$, filtered and concentrated *in vacuo*.

8.3.4. General procedure 4 – *C*(3)-methylation of indoles



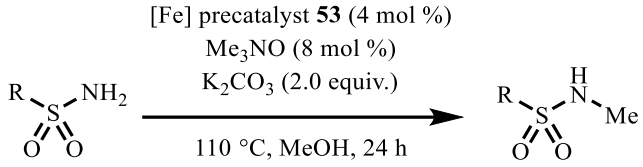
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.0 mmol), indole (1.0 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 mg, 0.02 mmol, 2 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL). The mixture was left to react at 80 °C for 24 or 48 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 $MgSO_4$, filtered and concentrated *in vacuo*.

8.3.5. General procedure 5 – *C*(3)-methylation of oxindoles



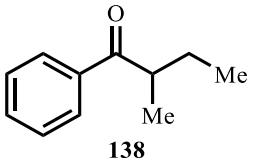
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.0 mmol), oxindole (1.0 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 mg, 0.02 mmol, 2 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL). The mixture was left to react at 110 °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 $MgSO_4$, filtered and concentrated *in vacuo*.

8.3.6. General procedure 6 – *N*-methylation of sulfonamides



A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.0 mmol), substituted sulfonamide (1.0 mmol), $Me_3NO.2H_2O$ (8.9 mg, 0.08 mmol, 8 mol %) and [Fe] precatalyst **53** (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 was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL). The mixture was left to react at 110 °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 $MgSO_4$, filtered and concentrated *in vacuo*.

2-methyl-1-phenylpropan-1-one



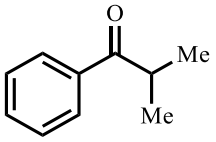
138

The title compound was prepared according to general procedure 1 using *n*-butyrophenone (145 µL, 148 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a yellow oil (144 mg, 88%); R_f = 0.47 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.92 (3H, t, *J* 7.5, $CH_2C\mathit{H}_3$), 1.19 (3H, d, *J* 7.0, $CH(C\mathit{H}_3)(C_2H_5)$), 1.44-1.55 (1H, m, $(C\mathit{H}^ACH^B)CH_3$), 1.78-1.90 (1H, m, $(CH^AC\mathit{H}^B)CH_3$), 3.40 (1H, sext, *J* 7.0, $C\mathit{H}(CH_3)(C_2H_5)$), 7.43-7.50 (2H, m, ArC(3,5)*H*), 7.52-7.59 (1H, m, ArC(4)*H*), 7.91-7.99 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 11.9 ($CH_2\mathit{C}H_3$), 16.9 ($(CH)(\mathit{C}H_3)(C_2H_5)$), 26.8 ($\mathit{C}H_2CH_3$), 42.3 ($(\mathit{C}H)(CH_3)(C_2H_5)$), 128.4 (Ar*C*(2,6)), 128.7 (Ar*C*(3,5)), 132.9 (Ar*C*(4)), 137.0 (Ar*C*(1)), 204.6 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[15]

10 mmol Scale

An ACE pressure tube was charged with K_2CO_3 (2.76 g, 20.0 mmol), $Me_3NO.2H_2O$ (44.5 mg, 0.4 mmol) and [Fe] precatalyst **49** (83.7 mg, 0.2 mmol). The vessel was closed with a suba seal 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 MeOH (20 mL) and *n*-butyrophenone (1.45 mL, 1.48 g, 10.0 mmol). It was sealed with the appropriate screw top cap, placed behind a blast shield, and the mixture was left to react at 80 °C for 24 h. It was then cooled, washed with EtOAc (50 mL) and transferred to a separatory funnel filled with brine (50 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 1% Et_2O in pet. ether (40-60 °C), 50 x 150 mm silica) gave a yellow oil (1.61 g, 99%). Spectroscopic data in accordance with that stated previously.

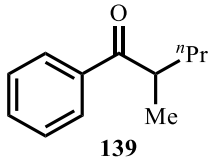
2-methyl-1-phenylpropan-1-one



136

The title compound was prepared according to general procedure 1 using propiophenone (133 µL, 134 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (133 mg, 90%); R_f = 0.40 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.22 (6H, d, *J* 7.0, $CH(C\mathit{H}_3)_2$), 3.56 (1H, sept, *J* 7.0, $C\mathit{H}(CH_3)_2$), 7.42-7.51 (2H, m, ArC(3,5)*H*), 7.51-7.60 (1H, m, ArC(4)*H*), 7.92-7.98 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.3 ($CH(\mathit{C}H_3)_2$), 35.5 ($\mathit{C}H(CH_3)_2$), 128.4 (Ar*C*(2,6)), 128.7 (Ar*C*(3,5)), 132.9 (Ar*C*(4)), 136.4 (Ar*C*(1)), 204.6 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[16]

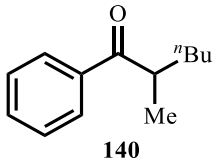
2-methyl-1-phenylpentan-1-one



139

The title compound was prepared according to general procedure 1 using valerophenone (166 µL, 162 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (168 mg, 95%); R_f = 0.49 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.90 (3H, d, *J* 7.0, $CH_2CH_2C\mathit{H}_3$), 1.19 (3H, d, *J* 7.0, $CH(C\mathit{H}_3)(C_3H_7)$), 1.27-1.48 (3H, m, $(C\mathit{H}^ACH^B)C\mathit{H}_2CH_3$), 1.72-1.85 (1H, m, $(CH^AC\mathit{H}^B)CH_2CH_3$), 3.48 (1H, sext, *J* 6.5, $C\mathit{H}(CH_3)(C_3H_7)$), 7.42-7.50 (2H, m, ArC(3,5)*H*), 7.51-7.59 (1H, m, ArC(4)*H*), 7.91-7.99 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 14.3 ($CH_2CH_2\mathit{C}H_3$), 17.3 ($CH(\mathit{C}H_3)(C_3H_7)$), 20.7 ($CH_2\mathit{C}H_2CH_3$), 36.0 ($\mathit{C}H_2CH_2CH_3$), 40.5 ($\mathit{C}H(CH_3)(C_3H_7)$, 128.4 (Ar*C*(2,6)), 128.7 (Ar*C*(3,5)), 132.9 (Ar*C*(4)), 136.9 (Ar*C*(1)), 204.7 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[17]

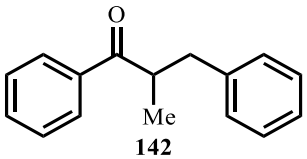
2-methyl-1-phenylhexan-1-one



140

The title compound was prepared according to general procedure 1 using hexanophenone (176 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (184 mg, 97%); R_f = 0.49 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2959, 2928, 2870, 2857, 1676, 1595, 1460, 1445, 1377, 1229, 1202, 968, 791, 702, 689; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.83-0.91 (3H, m, $CH_2CH_2CH_3$), 1.20 (3H, d, *J* 6.5, $CH(CH_3)(C_4H_9)$), 1.23-1.36 (4H, m, $CH_2CH_2CH_3$), 1.38-1.50 (1H, m, $(CH^ACH^B)C_3H_7$), 1.75-1.87 (1H, m, $(CH^ACH^B)C_3H_7$), 3.46 (1H, sext, *J* 6.5, $CH(CH_3)(C_4H_9)$), 7.42-7.50 (2H, m, ArC(3,5)*H*), 7.52-7.60 (1H, m, ArC(4)*H*), 7.92-8.00 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 14.1 ($CH_2CH_2CH_2CH_3$), 17.4 ($CH(CH_3)(C_4H_9)$), 23.0 ($CH_2CH_2CH_2CH_3$), 29.8 ($CH_2CH_2CH_2CH_3$), 33.6 ($CH_2CH_2CH_2CH_3$), 40.7 ($CH(CH_3)(C_4H_9)$), 128.4 (ArC(2,6)), 128.7 (ArC(3,5)), 132.9 (ArC(4)), 136.9 (ArC(1)), 204.7 (C=O); HRMS (**ASAP$^+$**) calculated for $[C_{13}H_{19}O]^+$ $(M+H)^+$ m/z : 191.1436, found 191.1438, (+1.0 ppm).

2-methyl-1,3-diphenylpropan-1-one

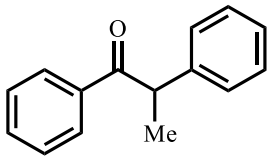


142

The title compound was prepared according to general procedure 1 using 3-phenylpropiophenone (210 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 4% EtOAc in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (216 mg, 96%); R_f = 0.40 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3061, 3030, 2970, 2936, 1678, 1593, 1576, 1493, 1449, 1373, 1229, 1179, 972, 739, 696; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.20 (3H, d, *J* 7.0, $CHCH_3$), 2.69 (1H, dd, *J* 13.5, 7.5, CH^AH^BPh), 3.17 (1H, dd, *J* 13.5, 6.5, CH^AH^BPh), 3.69-3.81 (1H, m, $CHCH_3$), 7.14-7.23 (3H, m, ArC(2',4',6')*H*), 7.23-7.30 (2H, m, ArC(3',5')*H*), 7.41-7.48 (2H, m, ArC(3,5)*H*), 7.51-7.58 (1H, m, ArC(4)*H*), 7.89-7.96 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.5 ($CHCH_3$), 39.5 (CH_2Ph), 42.9 ($CHCH_3$), 126.3 (ArC), 128.4 (ArC), 128.5 (ArC), 128.8 (ArC), 129.2 (ArC), 133.0 (ArC), 136.6 (ArC(1)), 140.1 (ArC(1')), 203.9 (C=O);

HRMS (**ASAP$^+$**) calculated for $[C_{16}H_{17}O]^+$ $(M+H)^+$ m/z : 225.1279, found 225.1279, (+0.0 ppm).

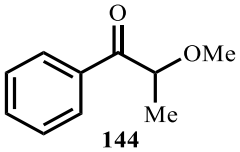
1,2-diphenylpropan-1-one



143

The title compound was prepared according to general procedure 1 using deoxybenzoin (196 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 4% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow solid (177 mg, 84%); mp 49-51 °C (Lit. 44-46 °C);[18] R_f = 0.38 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.54 (3H, d, *J* 7.0, CHC*H*$_3$), 4.69 (1H, q, *J* 7.0, C*H*CH$_3$), 7.16-7.24 (1H, m, ArC(4')*H*), 7.26-7.33 (4H, m, ArC(2',3',5',6')*H*) 7.34-7.42 (2H, m, ArC(3,5)*H*), 7.44-7.51 (1H, m, ArC(4)*H*), 7.91-7.99 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.6 (CH*C*H$_3$), 48.0 (*C*HCH$_3$), 127.0 (Ar*C*(4')), 127.9 (Ar*C*), 128.6 (Ar*C*), 128.9 (Ar*C*), 129.1 (Ar*C*), 132.9 (Ar*C*(4)), 136.6 (Ar*C*(1)), 141.6 (Ar*C*(1')), 200.5 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[19]

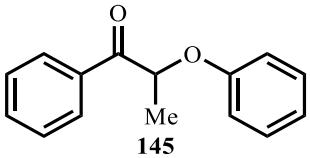
2-methoxy-1-phenylpropan-1-one



144

The title compound was prepared according to general procedure 1 using 2-methoxyacetophenone (150 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 10% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a pale yellow oil (123 mg, 75%); R_f = 0.40 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3065, 2978, 2932, 2830, 1692, 1595, 1447, 1227, 1209, 1123, 1111, 959, 866, 791, 698, 662; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.48 (3H, d, *J* 7.0, CHC*H*$_3$), 3.38 (3H, s, OC*H*$_3$), 4.62 (1H, q, *J* 7.0, C*H*CH$_3$), 7.43-7.50 (2H, m, ArC(3,5)*H*), 7.54-7.61 (1H, m, ArC(4)*H*), 8.02-8.06 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.6 (CH*C*H$_3$), 57.4 (O*C*H$_3$), 80.4 (*C*HCH$_3$), 128.0 (Ar*C*(2,6)), 128.0 (Ar*C*(3,5)), 133.5 (Ar*C*(4)), 135.0 (Ar*C*(1)), 200.7 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{10}H_{13}O_2]^+$ $(M+H)^+$ m/z : 165.0916, found 165.0912, (-2.4 ppm).

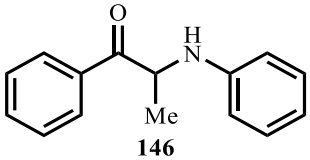
2-phenoxy-1-phenylpropan-1-one



145

The title compound was prepared according to general procedure 1 using 2-phenoxy-1-phenylethan-1-one (212 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a white solid (166 mg, 74%); mp 77-79 °C (Lit. 79-80 °C);[20] R_f = 0.47 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3061, 3011, 2936, 1688, 1585, 1495, 1452, 1238, 1221, 1130, 959, 930, 883, 799, 745, 700, 689, 658, 507; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.71 (3H, d, *J* 7.0, CHC*H*$_3$), 5.48 (1H, q, *J* 7.0, C*H*CH$_3$), 6.83-6.90 (2H, m, ArC(2',6')*H*), 6.90-6.96 (1H, m, ArC(4')*H*), 7.19-7.27 (2H, m, ArC(3',5')*H*), 7.43-7.51 (2H, m, ArC(3,5)*H*), 7.54-7.62 (1H, m, ArC(4)*H*), 8.04-8.11 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.9 (CH(*C*H$_3$)), 76.7 (*C*H(CH$_3$)), 115.3 (Ar*C*(2',6')), 121.6 (Ar*C*(4')), 128.9 (Ar*C*(2,6)), 129.0 (Ar*C*(3,5)), 129.7 (Ar*C*(3',5')), 133.8 (Ar*C*(4)), 134.3 (Ar*C*(1)), 157.6 (Ar*C*(1')), 199.1 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{15}H_{15}O_2]^+$ $(M+H)^+$ m/z : 227.1072, found 227.1070, (-0.9 ppm).

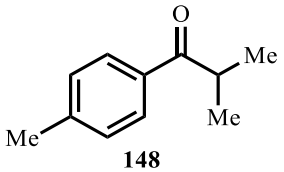
1-phenyl-2-(phenylamino)ethan-1-one



146

The title compound was prepared according to general procedure 1 using 1-phenyl-2-(phenylamino)ethan-1-one (211 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1-10% EtOAc in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow solid (132 mg, 59%); mp 94-97 °C (Lit. 94-95 °C);[21] R_f = 0.33 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.49 (3H, d, *J* 7.0, CHC*H*$_3$), 4.71 (1H, br s, N*H*), 5.13 (1H, q, *J* 7.0, C*H*CH$_3$), 6.65-6.70 (2H, m, ArC(2',6')*H*), 6.70-6.76 (1H, m, ArC(4')*H*), 7.14-7.22 (2H, m, ArC(3',5')*H*), 7.48-7.55 (2H, m, ArC(3,5)*H*), 7.58-7.65 (1H, m, ArC(4)*H*), 7.99-8.05 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.7 (CH*C*H$_3$), 53.5 (*C*HCH$_3$), 113.6 (Ar*C*(2',6')), 118.0 (Ar*C*(4')), 128.6 (Ar*C*(2,6)), 129.0 (Ar*C*(3,5)), 129.5 (Ar*C*(3',5')), 133.8 (Ar*C*(4)), 134.8 (Ar*C*(1)), 146.7 (Ar*C*(1')), 200.8 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[22]

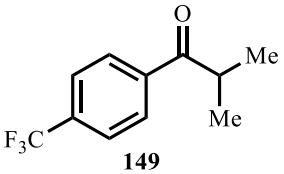
2-methyl-1-(p-tolyl)propan-1-one



148

The title compound was prepared according to general procedure 1 using 4-methylpropiophenone (149 µL, 148 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (150 mg, 92%), R_f = 0.40 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3038, 2968, 2930, 2868, 1678, 1605, 1466, 1379, 1229, 1207, 1155, 982, 827, 745, 592; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.21 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 2.41 (3H, s, ArC(4)C*H*$_3$), 3.54 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.26 (2H, d, *J* 8.0, ArC(3,5)*H*), 7.86 (2H, d, *J* 8.0, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.4 (CH(*C*H$_3$)$_2$), 21.8 (ArC(4)*C*H$_3$), 35.4 (*C*H(CH$_3$)$_2$), 128.6 (Ar*C*), 129.4 (Ar*C*), 133.8 (Ar*C*(1)), 143.6 (Ar*C*(4)), 204.3 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{11}H_{15}O]^+$ $(M+H)^+$ m/z : 163.1123, found 163.1122, (-0.6 ppm).

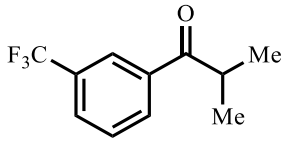
2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-one



149

The title compound was prepared according to general procedure 1 using 4-(trifluoromethyl)propiophenone (202 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (183 mg, 85%); R_f = 0.42 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.28 (6H, d, *J* 6.5, CH(C*H*$_3$)$_2$), 3.55 (1H, sept, *J* 6.5, C*H*(CH$_3$)$_2$), 7.73 (2H, d, *J* 9.0, ArC(3,5)*H*), 8.05 (2H, d, *J* 8.5, ArC(2,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -63.1; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.1 (CH(*C*H$_3$)$_2$), 36.0 (*C*H(CH$_3$)$_2$), 123.8 (q, *J* 273.0, ArC(4)*C*F$_3$), 125.8 (q, *J* 3.8, Ar*C*(3,5)), 128.8 (Ar*C*(2,6)), 134.3 (q, *J* 32.8, Ar*C*(4)), 139.1 (Ar*C*(1)), 203.6 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[23]

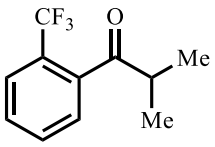
2-methyl-1-(3-(trifluoromethyl)phenyl)propan-1-one



150

The title compound was prepared according to general procedure 1 using 3-(trifluoromethyl)propiophenone (168 µL, 202 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (187 mg, 86%); R_f = 0.38 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.24 (6H, d, *J* 6.5, CH(C*H*$_3$)$_2$), 3.56 (1H, sept, *J* 6.5, C*H*(CH$_3$)$_2$), 7.62 (1H, t, *J* 8.0, ArC(5)*H*), 7.81 (1H, d, *J* 8.0, ArC(4)*H*), 8.13 (1H, d, *J* 7.5, ArC(6)*H*), 8.20 (1H, s, ArC(2)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -62.8; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.1 (CH(*C*H$_3$)$_2$), 35.7 (*C*H(CH$_3$)$_2$), 123.9 (q, *J* 273.0, *C*F$_3$), 125.3 (q, *J* 3.8, Ar*C*(4)), 129.4 (q, *J* 3.7, Ar*C*(2)), 129.4 (Ar*C*(6)), 131.4 (q, *J* 32.8, Ar*C*(3)), 131.6 (Ar*C*(5)), 136.9 (Ar*C*(1)), 203.2 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[24]

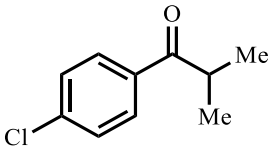
2-methyl-1-(2-(trifluoromethyl)phenyl)propan-1-one



151

The title compound was prepared according to general procedure 1 using 2-(trifluoromethyl)propiophenone (167 µL, 202 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 5% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a pale yellow oil (194 mg, 90%); R_f = 0.27 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.19 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 3.18 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.40 (1H, d, *J* 7.5, ArC(3)*H*), 7.55 (1H, t, *J* 7.5, ArC(5)*H*), 7.60 (1H, t, *J* 7.5, ArC(4)*H*), 7.71 (1H, d, *J* 8.0, ArC(2)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -58.0; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.3 (CH(*C*H$_3$)$_2$), 40.8 (*C*H(CH$_3$)$_2$), 123.7 (q, *J* 274.2, *C*F$_3$), 127.0 (q, *J* 4.9, Ar*C*(3)), 127.3 (Ar*C*(5)), 127.5 (q, *J* 32.3, Ar*C*(2)), 130.0 (Ar*C*), 131.8 (Ar*C*), 140.0 (q, *J* 2.1, Ar*C*(1)), 208.5 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[24]

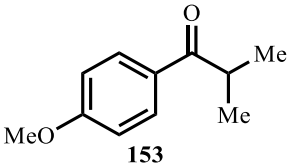
1-(4-chlorophenyl)-2-methylpropan-1-one



152

The title compound was prepared according to general procedure 1 using 4-chloropropiophenone (169 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (167 mg, 91%); R_f = 0.42 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.21 (6H, d, *J* 6.5, CH(C*H*$_3$)$_2$), 3.50 (1H, sept, *J* 6.5, C*H*(CH$_3$)$_2$), 7.40-7.47 (2H, m, ArC(3,5)*H*), 7.86-7.93 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.2 (CH(*C*H$_3$)$_2$), 35.5 (*C*H(CH$_3$)$_2$), 129.1 (Ar*C*), 129.9 (Ar*C*), 134.6 (Ar*C*(1)), 139.3 (Ar*C*(4)), 203.3 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[25]

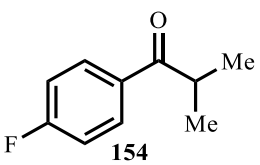
1-(4-methoxyphenyl)-2-methylpropan-1-one



153

The title compound was prepared according to general procedure 1 using 4'-methoxypropiophenone (175 µL, 164 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a colourless oil (171 mg, 96%); R_f = 0.20 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.21 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 3.52 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 3.87 (3H, s, OC*H*$_3$), 6.91-6.96 (2H, m, ArC(3,5)*H*), 7.92-7.98 (2H, m, ArC(2,6)*H*), **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.4 (CH(*C*H$_3$)$_2$), 35.1 (*C*H(CH$_3$)$_2$), 55.6 (O*C*H$_3$), 113.9 (Ar*C*(3,5)), 129.3 (Ar*C*(1)), 130.7 (Ar*C*(2,6)), 163.4 (Ar*C*(4)), 203.2 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[26]

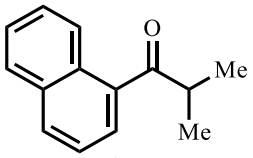
1-(4-fluorophenyl)-2-methylpropan-1-one



154

The title compound was prepared according to general procedure 1 using 4-fluoropropiophenone (139 μL, 152 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1-10% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (26 mg, 15%); R_f = 0.38 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.21 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 3.51 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.09-7.18 (2H, m, ArC(3,5)*H*), 7.94-8.03 (2H, m, ArC(2,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -105.9; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.3 (CH(*C*H$_3$)$_2$), 35.5 (*C*H(CH$_3$)$_2$), 115.8 (d, *J* 21.8, Ar*C*(3,5)), 131.1 (d, *J* 9.2, Ar*C*(2,6)), 132.7 (d, *J* 3.2, Ar*C*(1)), 165.7 (d, *J* 254.6, Ar*C*(4)), 203.3 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[27]

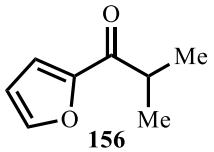
2-methyl-1-(naphthalen-1-yl)propan-1-one



155

The title compound was prepared according to general procedure 1 using 1-(naphthalen-1-yl)propan-1-one (184 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 4% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (190 mg, 96%); R_f = 0.40 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} 3048, 2968, 2928, 2870, 1678, 1595, 1506, 1466, 1383, 1227, 1186, 1159, 1082, 1055, 941, 797, 772, 633; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.25 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 3.52 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.45-7.61 (3H, m, Ar*H*), 7.74 (1H, dd, *J*, 7.0, 1.0, Ar*H*), 7.84-7.91 (1H, m, Ar*H*), 7.96 (1H, d, *J* 8.0, Ar*H*), 8.29 (1H, d, *J* 8.0, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.8 (CH(*C*H$_3$)$_2$), 39.8 (*C*H(CH$_3$)$_2$), 124.5 (Ar*C*), 125.8 (Ar*C*), 126.0 (Ar*C*), 126.6 (Ar*C*), 127.7 (Ar*C*), 128.5 (Ar*C*), 130.6 (Ar*C*), 131.8 (Ar*C*), 134.1 (Ar*C*), 137.1 (Ar*C*), 209.2 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{14}H_{15}O]^+$ $(M+H)^+$ m/z : 199.1123, found 199.1122, (-0.5 ppm).

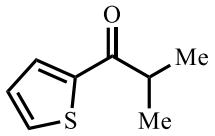
1-(furan-2-yl)-2-methylpropan-1-one



156

The title compound was prepared according to general procedure 1 using 2-propionylfuran (124 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 4% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (107 mg, 78%); R_f = 0.22 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3127, 2974, 2936, 2876, 1668, 1566, 1460, 1396, 1383, 1252, 1153, 1988, 1016, 988, 908, 883, 851, 756, 731, 596; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.21 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 3.33 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 6.53 (1H, dd, *J* 3.5, 2.0, ArC(4)*H*), 7.19 (1H, dd, *J* 3.5, 1.0, ArC(3)*H*), 7.58 (1H, dd, *J* 2.0, 2.0, ArC(5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.9 (CH(*C*H$_3$)$_2$), 36.4 (*C*H(CH$_3$)$_2$), 112.2 (Ar*C*(4)), 117.2 (Ar*C*(3)), 146.3 (Ar*C*(5)), 152.3 (Ar*C*(2)), 193.8 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_8H_{11}O_2]^+$ $(M+H)^+$ m/z : 139.0759, found 139.0758, (-0.7 ppm).

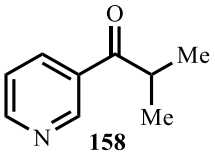
2-methyl-1-(thiophen-2-yl)propan-1-one



157

The title compound was prepared according to general procedure 1 using 2-propionylthiophene (125 µL, 140 mg, 1 mmol). Purification by flash silica chromatography (eluent = 5% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (132 mg, 85%); R_f = 0.33 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3092, 2972, 2930, 2870, 1657, 1516, 1464, 1414, 1233, 1225, 1049, 934, 831, 718; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.25 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 3.40 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.14 (1H, dd, *J* 5.0, 3.5, ArC(4)*H*), 7.63 (1H, dd, *J* 5.0, 1.5, ArC(3)*H*), 7.73 (1H, dd, *J* 4.0, 1.0, ArC(5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.6 (CH(*C*H$_3$)$_2$), 37.3 (*C*H(CH$_3$)$_2$), 128.2 (Ar*C*(4)), 131.7 (Ar*C*(3)), 133.5 (Ar*C*(5)), 143.8 (Ar*C*(2)), 197.6 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_8H_{11}OS]^+$ $(M+H)^+$ m/z : 155.0531, found 155.0531, (+0.0 ppm).

2-methyl-1-(pyridin-3-yl)propan-1-one

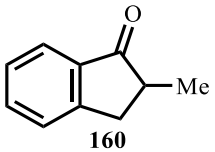


158

The title compound was prepared according to general procedure 1 using 3-propionylpyridine (135 mg, 1.0 mmol). Purification by flash silica chromatography (eluent

= 30% EtOAc in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (140 mg, 94%); R_f = 0.20 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3042, 2970, 2928, 2872, 1686, 1584, 1462, 1416, 1231, 1043, 1024, 978, 822, 723, 702, 619; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.25 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 3.52 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.43 (1H, ddd, *J* 8.0, 5.0, 1.0, ArC(5)*H*), 8.23 (1H, m, ArC(4)*H*), 8.77 (1H, dd, *J* 3.5, 1.5, ArC(4)*H*), 9.16 (1H, d, *J* 2.0, ArC(2)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.0 (CH(*C*H$_3$)$_2$), 36.1 (*C*H(CH$_3$)$_2$), 123.8 (Ar*C*(5)), 131.5 (Ar*C*(1)), 135.9 (Ar*C*(6)), 149.9 (Ar*C*(4)), 153.4 (Ar*C*(2)), 203.3 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_9H_{12}ON]^+$ $(M+H)^+$ m/z : 150.0913, found 150.0909, (-2.9 ppm).

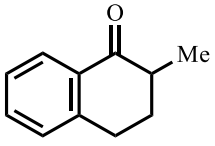
2-methyl-2,3-dihydro-1*H*-inden-1-one



160

The title compound was prepared according to general procedure 2 at 80 °C using 1-indanone (132 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in pet. ether (40-60 °C), 30 x 170 mm silica) gave the title compound as a pale yellow oil (96 mg, 66%); R_f = 0.27 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.32 (3H, d, *J* 7.5, CHC*H*$_3$), 2.67-2.78 (2H, m, CHC*H*$_2$), 3.36-3.45 (1H, m, C*H*CH$_3$), 7.34-7.40 (1H, m, ArC(5)*H*), 7.42-7.49 (1H, m, ArC(3)*H*), 7.59 (1H, dt, *J* 1.5, 7.5, ArC(4)*H*), 7.76 (1H, d, *J* 7.5, ArC(6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 16.4 (CH*C*H$_3$), 35.1 (*C*H$_2$), 42.1 (*C*HCH$_3$), 124.1 (Ar*C*(4)), 126.7 (Ar*C*(3)), 127.5 (Ar*C*(6)), 134.8 (Ar*C*(5)), 136.5 (Ar*C*(1)), 153.6 (Ar*C*(2)), 209.6 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[28]

2-methyl-3,4-dihydronaphthalen-1(2*H*)-one

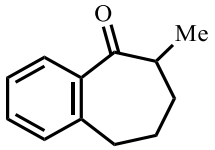


161

The title compound was prepared according to general procedure 2 at 110 °C using 1-tetralone (133 µL, 146 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 3% Et_2O in pet. ether (40-60 °C), 30 x 160 mm silica) gave the title compound as a colourless oil (87 mg, 54%); R_f = 0.34 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)**

δ_H: 1.28 (3H, d, *J* 7.0, CHC*H*$_3$), 1.83-1.95 (1H, m, CH(C*H*^{A}CH^B)), 2.20 (1H, dq, *J* 13.5, 4.5, CH(CH^{A}C*H*^{B})), 2.54-2.65 (1H, m, C*H*CH$_3$), 2.92-3.11 (2H, m, ArC*H*$_2$), 7.23 (1H, d, *J* 7.5, ArC(5)*H*), 7.30 (1H, t, *J* 7.5, ArC(3)*H*), 7.45 (1H, dt, *J* 7.5, 1.5, ArC(4)*H*), 8.04 (1H, dd, *J* 7.5, 1.5, ArC(2)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 15.6 (CH*C*H$_3$), 29.0 (Ar*C*H$_2$), 31.5 (CH*C*H$_2$), 42.8 (*C*HCH$_3$), 126.6 (Ar*C*), 127.5 (Ar*C*), 128.8 (Ar*C*), 133.2 (Ar*C*), 132.5 (Ar*C*(1)), 144.3 (Ar*C*(6)), 201.0 (*C*=O); Spectroscopic data in accordance with that stated in the literature.[29]

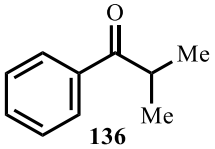
6-methyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulen-5-one



162

The title compound was prepared according to general procedure 2 at 110 °C using 1-benzosuberone (150 µL, 160 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 4% Et$_2$O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a pale yellow oil (163 mg, 94%); R_f = 0.38 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.23 (3H, d, *J* 6.5, CHC*H*$_3$), 1.56-1.65 (1H, m, C*H*), 1.66-1.77 (1H, m, C*H*), 1.86-1.96 (1H, m, C*H*), 2.01-2.13 (1H, m, C*H*), 2.86-2.97 (2H, m, C*H*CH$_3$, C(9)*H*^{A}), 2.97-3.07 (1H, m, C(9)*H*^{B}), 7.19-7.23 (1H, m, Ar*H*), 7.25-7.31 (1H, m, Ar*H*), 7.38 (1H, dt, *J* 7.5, 1.5, Ar*H*), 7.67 (1H, dd, *J* 8.0, 1.5, Ar*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 16.6 (CH*C*H$_3$), 25.7 (CH$_2$*C*H$_2$CH$_2$), 32.1 (CH*C*H$_2$), 33.8 (Ar*C*H$_2$), 44.3 (*C*HCH$_3$), 126.5 (Ar*C*), 128.6 (Ar*C*), 129.9 (Ar*C*), 131.4 (Ar*C*), 139.8 (Ar*C*), 142.0 (Ar*C*), 208.0 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[29]

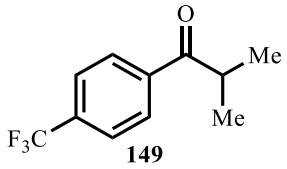
2-methyl-1-phenylpropan-1-one



136

The title compound was prepared according to general procedure 3 using acetophenone (117 µL, 120 mg, 1 mmol). Purification by flash silica chromatography (eluent = 1% Et$_2$O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (126 mg, 85%); R_f = 0.40 (eluent = 5% EtOAc in hexanes). Spectroscopic data in accordance with that stated previously.

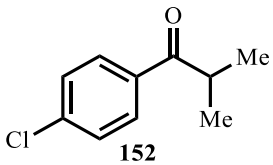
2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-one



149

The title compound was prepared according to general procedure 3 using 4-(trifluoromethyl)acetophenone (188 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 0.5% Et_2O in pet. ether (40-60 °C), 30 x 170 mm silica) gave a yellow oil (125 mg, 57%); R_f = 0.42 (eluent = 5% EtOAc in hexanes). Spectroscopic data in accordance with that stated previously.

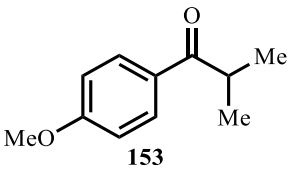
1-(4-chlorophenyl)-2-methylpropan-1-one



152

The title compound was prepared according to general procedure 3 using 4-chloroacetophenone (130 µL, 154 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 0.5% Et_2O in pet. ether (40-60 °C), 30 x 200 mm silica) gave a yellow oil (124 mg, 68%); R_f = 0.42 (eluent = 5% EtOAc in hexanes). Spectroscopic data in accordance with that stated previously.

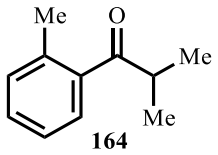
1-(4-methoxyphenyl)-2-methylpropan-1-one



153

The title compound was prepared according to general procedure 3 using 4-methoxyacetophenone (150 mg, 1 mmol). Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave a colourless oil (154 mg, 86%), R_f = 0.20 (eluent = 5% EtOAc in hexanes). Spectroscopic data in accordance with that stated previously.

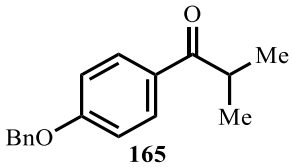
2-methyl-1-(*o*-tolyl)propan-1-one



164

The title compound was prepared according to general procedure 3 using 2-methylacetophenone (131 µL, 134 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 2% Et_2O in hexanes, 30 x 150 mm silica) gave the title compound as a yellow oil (144 mg, 89%); R_f = 0.56 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3022, 2970, 2932, 2868, 1686, 1458, 1381, 1223, 970, 943, 779, 737, 638; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.17 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 2.41 (3H, s, ArC(2')C*H*$_3$), 3.34 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.21-7.26 (2H, m, Ar*H*), 7.34 (1H, dt, *J* 7.0, 1.0, Ar*H*), 7.48-7.53 (1H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.7 (CH(*C*H$_3$)$_2$), 20.9 (ArC(2)*C*H$_3$), 38.9 (*C*H(CH$_3$)$_2$), 125.6 (Ar*C*(5)), 127.5 (Ar*C*), 130.7 (Ar*C*), 131.7 (Ar*C*), 137.5 (Ar*C*), 138.8 (Ar*C*), 209.4 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{11}H_{15}O]^+$ $(M+H)^+$ m/z : 163.1123, found 163.1123, (+0.0 ppm).

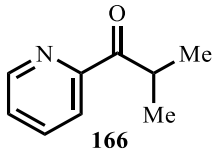
1-(4-(benzyloxy)phenyl)-2-methylpropan-1-one



165

The title compound was prepared according to general procedure 3 using 4-benzyloxyacetophenone (226 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 0.5-2% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as an off-white solid (214 mg, 84%); mp 44-46 °C; R_f = 0.29 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3057, 3034, 2982, 2940, 2880, 1665, 1599, 1566, 1506, 1452, 1379, 1225, 1157, 1003, 974, 924, 845, 756, 696, 640, 519; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.21 (6H, d, *J* 6.5, CH(C*H*$_3$)$_2$), 3.52 (1H, sept, *J* 6.5, C*H*(CH$_3$)$_2$), 5.14 (2H, s, PhC*H*$_2$O), 6.98-7.05 (2H, m, ArC(3,5)*H*), 7.30-7.37 (1H, m, ArC(4')*H*), 7.37-7.46 (4H, m, ArC(2',3',5',6')*H*), 7.92-7.98 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.4 (CH(*C*H$_3$)$_2$), 35.1 (*C*H(CH$_3$)$_2$), 70.3 (Ph*C*H$_2$O), 114.7 (Ar*C*(3,5)), 127.6 (Ar*C*(2',6')), 128.4 (Ar*C*(4')), 128.8 (Ar*C*(3',5')), 129.5 (Ar*C*(1)), 130.7 (Ar*C*(2,6)), 136.4 (Ar*C*(1')), 162.5 (Ar*C*(4)), 203.2 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{17}H_{19}O_2]^+$ $(M+H)^+$ m/z : 255.1385, found 255.1386, (+0.4 ppm).

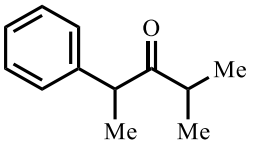
2-methyl-1-(pyridin-2-yl)propan-1-one



166

The title compound was prepared according to general procedure 3 using 2-acetylpyridine (112 µL, 121 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 4% Et_2O in hexanes, 30 x 170 mm silica) gave a colourless oil (75 mg, 50%); R_f = 0.60 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3049, 2970, 2934, 2874, 1695, 1582, 1460, 1344, 1221, 997, 982, 812, 743, 702, 613; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.21 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 4.11 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.45 (1H, ddd, *J* 7.5, 4.5, 1.0, Ar*H*), 7.83 (1H, dt, *J* 7.5, 1.5, Ar*H*), 8.04 (1H, dt, *J* 8.0, 1.0, Ar*H*), 8.66-8.70 (1H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.8 (CH(*C*H$_3$)$_2$), 34.4 (*C*H(CH$_3$)$_2$), 122.6 (Ar*C*), 127.0 (Ar*C*), 137.0 (Ar*C*)), 149.0 (Ar*C*(3)), 153.1 (Ar*C*(1)), 205.9 (*C*=O); HRMS (**EI$^+$**) calculated for $[C_9H_{11}NO]^+$ $(M)^+$ m/z : 149.0841, found 149.0841, (+0.0 ppm).

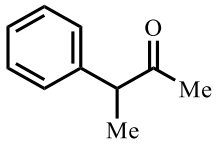
2-methyl-4-phenylpentan-3-one



170

The title compound was prepared according to general procedure 1 using 3-methyl-1-phenyl-2-butanone (168 µL, 162 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a yellow oil (144 mg, 81%); R_f = 0.47 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3028, 2968, 2930, 2870, 1707, 1601, 1487, 1466, 1449, 1379, 1125, 1092, 1059, 1015, 974, 752, 719, 694, 509; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.91 (3H, d, *J* 6.5, CH(C*H*$_3$)(CH$_3$)), 1.08 (3H, d, *J* 7.0, CH(CH$_3$)(C*H*$_3$)), 1.38 (3H, d, *J* 7.0, PhCH(C*H*$_3$)), 2.68 (1H, sept, *J* 7.0, C*H*(CH$_3$)$_2$), 3.92 (1H, q, *J* 7.0, PhC*H*(CH$_3$)), 7.18-7.27 (3H, m, ArC(2,4,6)*H*), 7.28-7.36 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.3 (CH(*C*H$_3$)(CH$_3$), 18.4 (CH(CH$_3$)(*C*H$_3$), 19.4 (PhCH(*C*H$_3$)), 39.3 (*C*H(CH$_3$)$_2$), 51.3 (Ph*C*H(CH$_3$)), 127.2 (Ar*C*(4)), 128.1 (Ar*C*(2,6)), 129.0 (Ar*C*(3,5)), 140.9 (Ar*C*(1)), 214.8 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{12}H_{17}O]^+$ $(M+H)^+$ m/z : 177.1279, found 177.1280, (+0.6 ppm).

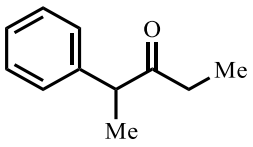
3-phenylbutan-2-one



172

The title compound was prepared according to general procedure 1 using 1-phenylpropan-2-one (134 µL, 134 mg, 1 mmol). Purification by flash silica chromatography (eluent = 2-3% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a pale yellow oil (74 mg, 50%); R_f = 0.33 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.39 (3H, d, *J* 7.0, CHC*H*$_3$), 2.05 (3H, s, COC*H*$_3$), 3.74 (1H, q, *J* 7.0, C*H*CH$_3$), 7.18-7.24 (2H, m, ArC(2,6)*H*), 7.24-7.29 (1H, m, ArC(4)*H*), 7.30-7.38 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.4 (CH*C*H$_3$), 28.5 (CO*C*H$_3$), 53.9 (*C*HCH$_3$), 127.3 (Ar*C*(4)), 128.0 (Ar*C*(2,6)), 129.1 (Ar*C*(3,5)), 140.7 (Ar*C*(1)), 209.0 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[9]

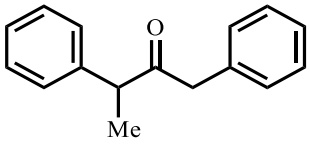
2-phenylpentan-3-one



175

The title compound was prepared according to general procedure 2 at 80 °C using 1-phenyl-2-butanone (149 µL, 148 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 1-2% Et_2O in pet. ether (40-60 °C), 30 x 200 mm silica) gave the title compound as a colourless oil (94 mg, 58%); R_f = 0.42 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3030, 2974, 2932, 1713, 1493, 1454, 1377, 1348, 1126, 1072, 957, 756, 702, 546; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.97 (3H, t, *J* 7.0, CH$_2$C*H*$_3$), 1.39 (3H, d, *J* 7.0, CHC*H*$_3$), 2.28-2.47 (2H, m, C*H*$_2$CH$_3$), 3.76 (1H, q, *J* 7.0, C*H*CH$_3$), 7.18-7.23 (2H, m, ArC(2,6)*H*), 7.23-7.28 (1H, m, ArC(4)*H*), 7.29-7.36 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 8.1 (CH$_2$*C*H$_3$), 17.7 (CH*C*H$_3$), 34.4 (*C*H$_2$CH$_3$), 52.8 (*C*HCH$_3$), 127.2 (Ar*C*(4)), 128.0 (Ar*C*(2,6)), 129.0 (Ar*C*(3,5)), 141.1 (Ar*C*(1)), 211.7 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{11}H_{15}O]^+$ $(M+H)^+$ m/z : 163.1117, found 163.1114, (-2.1 ppm).

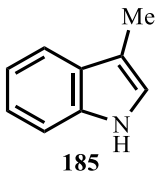
1,3-diphenylbutan-2-one



176

The title compound was prepared according to general procedure 2 at 80 °C using 1,3-diphenylacetone (210 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a colourless oil (127 mg, 57%); R_f = 0.36 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3061, 3032, 2976, 2930, 1709, 1599, 1493, 1450, 1119, 1030, 762, 737, 696, 536; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.37 (3H, d, *J* 7.0, PhCH(C*H*$_3$)), 3.57-3.67 (2H, m, PhC*H*$_2$), 3.81-3.90 (1H, q, *J* 7.0, PhC*H*(CH_3)), 7.01-7.09 (2H, m, Ar*H*), 7.16-7.25 (3H, m, Ar*H*), 7.25-7.31 (3H, m, Ar*H*), 7.31-7.38 (2H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.8 (PhCH(*C*H_3)), 48.2 (Ph*C*H_2), 52.2 (Ph*C*H(CH_3)), 127.0 (Ar*C*), 127.4 (Ar*C*), 128.2 (Ar*C*), 128.7 (Ar*C*), 129.1 (Ar*C*), 129.6 (Ar*C*), 134.5 (Ar*C*), 140.5 (Ar*C*), 208.2 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{16}H_{17}O]^+$ $(M+H)^+$ m/z : 225.1279, found 225.1280, (+0.4 ppm).

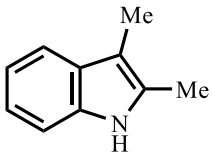
3-methyl-1*H*-indole



185

The title compound was prepared according to general procedure 4 using indole (117 mg, 1.0 mmol) for 24 h. Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave the title compound as a white solid (108 mg, 82%), mp 96-98 °C (Lit. 91-93 °C);[30] R_f = 0.58 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.35 (3H, d, *J* 1.0, ArC(3)C*H*$_3$), 6.96-6.99 (1H, m, ArC(2)*H*), 7.10-7.16 (1H, m, ArC(5)*H*), 7.17-7.23 (1H, m, ArC(6)*H*), 7.32-7.38 (1H, m, ArC(7)*H*), 7.56-7.62 (1H, m, ArC(4)*H*), 7.86 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 9.8 (ArC(3)*C*H_3), 111.1 (Ar*C*(7)), 111.8 (Ar*C*(3)CH_3), 119.0 (Ar*C*(4)), 119.2 (Ar*C*(5)), 121.7 (Ar*C*(2)), 122.0 (Ar*C*(6)), 128.4 (Ar*C*(3a)), 136.4 (Ar*C*(7a)). Spectroscopic data in accordance with that stated in the literature.[31]

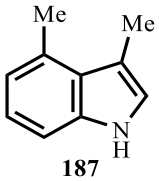
2,3-dimethyl-1*H*-indole



186

The title compound was prepared according to general procedure 4 using 2-methylindole (131 mg, 1.0 mmol) for 24 h. Purification by flash silica chromatography (eluent = 3% Et_2O in pet. ether (40-60 °C), 30 x 160 mm silica) gave the title compound as a white solid (123 mg, 85%); mp 109-111 °C (Lit. 104-106 °C);[32] R_f = 0.60 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.23 (3H, d, *J* 0.5, ArC(3)C*H*$_3$), 2.37 (3H, s, ArC(2)C*H*$_3$), 7.04-7.15 (2H, m, Ar*H*), 7.23-7.28 (1H, m, Ar*H*), 7.44-7.50 (1H, m, Ar*H*), 7.67 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 8.6 (ArC(3)*C*H$_3$), 11.7 (ArC(2)*C*H$_3$), 107.3 (Ar*C*), 110.1 (Ar*C*), 118.1 (Ar*C*), 119.1 (Ar*C*), 121.0 (Ar*C*), 129.6 (Ar*C*(4a)), 130.7 (Ar*C*), 135.3 (Ar*C*(7a)). Spectroscopic data in accordance with that stated in the literature.[32]

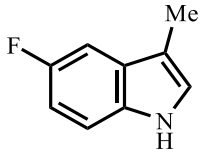
3,4-dimethyl-1*H*-indole



187

The title compound was prepared according to general procedure 4 using 4-methylindole (124 µL, 131 mg, 1.0 mmol) for 48 h. Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 200 mm silica) gave the title compound as a white solid (96 mg, 66%); mp 112-115 °C (Lit. 117-118 °C);[33] R_f = 0.70 (eluent = 20% EtOAc in hexanes). ν_{max} / cm^{-1} (film) 3375, 3053, 2955, 2916, 1572, 1503, 1443, 1335, 1248, 1065, 980, 797, 773, 746, 517; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.52 (3H, d, *J* 1.0, ArC(3)C*H*$_3$), 2.73 (3H, s, ArC(4)C*H*$_3$), 6.82 (1H, d, *J* 7.0, Ar*H*), 6.89-6.93 (1H, m, ArC(2)*H*), 7.01-7.08 (1H, m, Ar*H*), 7.17 (1H, d, *J* 8.0, Ar*H*), 7.81 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 13.2 (*C*H$_3$), 20.2 (*C*H$_3$), 109.1 (Ar*C*), 112.7 (Ar*C*(3)CH$_3$), 120.7 (Ar*C*), 121.9 (Ar*C*), 122.1 (Ar*C*), 126.7 (Ar*C*), 131.4 (Ar*C*), 136.9 (Ar*C*); HRMS (**ASAP$^+$**) calculated for $[C_{10}H_{12}N]^+$ $(M+H)^+$ m/z : 146.0970, found 146.0970, (+0.0 ppm).

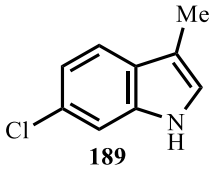
5-fluoro-3-methyl-1*H*-indole



188

The title compound was prepared according to general procedure 4 using 5-fluoroindole (135 mg, 1.0 mmol) for 24 h. Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 200 mm silica) gave the title compound as a white solid (117 mg, 79%); mp 83-85 °C (Lit. 82-83 °C);[34] R_f = 0.48 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3402, 2974, 2920, 2864, 1580, 1481, 1445, 1342, 1283, 1225, 1180, 1165, 1088, 932, 856, 826, 791, 671, 604, 484; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.30 (3H, d, *J* 1.0, ArC(3)CH_3), 6.93 (1H, dt, *J* 9.0, 2.5, Ar*H*), 6.99-7.09 (1H, m, Ar*H*), 7.21 (1H, dd, *J* 9.5, 2.5, Ar*H*), 7.25 (1H, dd, *J* 9.0, 4.5, Ar*H*), 7.86 (1H, br s, N*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -125.2; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 9.8 (ArC(3)*C*H_3), 103.9 (d, *J* 23.2, Ar*C*), 110.3 (d, *J* 26.5, Ar*C*), 111.6 (d, *J* 9.6, Ar*C*(7)), 112.1 (d, *J* 4.8, Ar*C*(3)CH_3), 123.5 (Ar*C*), 128.8 (d, *J* 9.6, Ar*C*(4a)), 132.9 (Ar*C*(7a)), 157.9 (d, *J* 234.5, Ar*C*(5)); HRMS (**ASAP$^+$**) calculated for $[C_9H_9NF]^+$ $(M+H)^+$ m/z : 150.0719, found 150.0717, (-1.3 ppm).

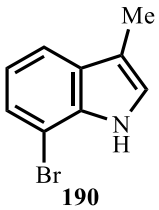
6-chloro-3-methyl-1*H*-Indole



189

The title compound was prepared according to general procedure 4 using 6-chloroindole (152 mg, 1.0 mmol) for 48 h. Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 200 mm silica) gave the title compound as a white solid (99 mg, 60%), mp 118-120 °C (Lit. 118-119 °C);[34] R_f = 0.74 (eluent = 20% EtOAc in hexanes). ν_{max} / cm^{-1} (film) 3410, 3399, 2974, 2928, 2864, 1665, 1597, 1454, 1321, 1223, 1159, 1090, 976, 905, 845, 804, 741, 696; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.31 (3H, d, *J* 1.0, ArC(3)CH_3), 6.94-6.98 (1H, m, ArC(2)*H*), 7.09 (1H, dd, *J* 8.5, 2.0, ArC(5)*H*), 7.33 (1H, d, *J* 2.0, ArC(7)*H*), 7.47 (1H, d, *J* 8.5, ArC(4)*H*), 7.86 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 9.7 (ArC(3)*C*H_3), 111.0 (Ar*C*), 112.1 (Ar*C*(3)CH_3), 119.9 (Ar*C*), 120.0 (Ar*C*), 122.3 (Ar*C*(2)), 127.1 (Ar*C*), 128.0 (Ar*C*), 136.7 (Ar*C*); HRMS (**ASAP$^+$**) calculated for $[C_9H_9N^{35}Cl]^+$ $(M+H)^+$ m/z : 166.0419, found 166.0422, (-1.2 ppm).

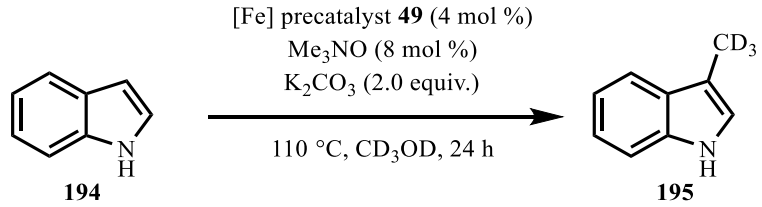
7-bromo-3-methyl-1*H*-indole



190

The title compound was prepared according to general procedure 4 using 7-bromoindole (196 mg, 1.0 mmol) for 24 h. Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 160 mm silica) gave the title compound as a yellow solid (173 mg, 82%); mp 46-48 °C; R_f = 0.70 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3383, 2967, 2909, 2857, 1549, 1487, 1435, 1323, 1198, 1078, 1043, 881, 799, 773, 735, 573; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.33 (3H, d, *J* 1.0, ArC(3)C*H*$_3$), 7.01 (1H, t, *J* 8.0, ArC(5)*H*), 7.02-7.05 (1H, m, ArC(2)*H*), 7.34 (1H, d, *J* 7.5, Ar*H*), 7.53 (1H, d, *J* 8.0, Ar*H*), 8.07 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 10.0 (ArC(3)*C*H$_3$), 104.7 (Ar*C*(7)), 113.1 (Ar*C*(3)CH$_3$), 118.2 (Ar*C*), 120.4 (Ar*C*), 122.3 (Ar*C*), 124.3 (Ar*C*), 129.6 (Ar*C*(4a)), 135.1 (Ar*C*(7a)); HRMS (**ASAP$^+$**) calculated for $[C_9H_8N^{79}Br]^+$ $(M)^+$ m/z : 208.9840, found 208.9845, (+2.4 ppm).

3-(methyl-*d*$_3$)-1*H*-indole

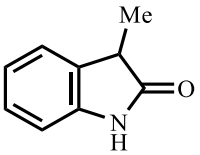


194 **195**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.0 mmol), indole (117 mg, 1.0 mmol), $Me_3NO.2H_2O$ (8.8 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (16.8 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 was repeated three times. Under nitrogen the vial was then charged with CD_3OD (2 mL). The mixture was left to react at 110 °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 $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 200 mm silica) gave a white solid (91 mg, 67%, >95% D); mp 86-88 °C (lit. 93 °C);[35] R_f = 0.58 (eluent = 20% EtOAc in

hexanes); ν_{max} / cm^{-1} (film) 3399, 3051, 2220, 2118, 2062, 1609, 1595, 1452, 1420, 1335, 1248, 1084, 1005, 739, 608, 496, 419; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 6.98 (1H, d, *J* 2.0, Ar*H*), 7.09-7.16 (1H, m, Ar*H*), 7.16-7.23 (1H, m, Ar*H*), 7.35 (1H, dt, *J* 8.0, 1.0, Ar*H*), 7.59 (1H, d, *J* 8.0, Ar*H*), 7.87 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 9.03 (sept, *J* 19.3, *C*D_3), 111.1 (Ar*C*), 111.8 (Ar*C*), 119.0 (Ar*C*), 119.2 (Ar*C*), 121.7 (Ar*C*), 122.0 (Ar*C*), 128.4 (Ar*C*), 136.4 (Ar*C*); HRMS (**EI$^+$**) calculated for $[C_9H_6D_3N]^+$ $(M)^+$ m/z : 134.0923, found 134.0922, (-0.7 ppm).

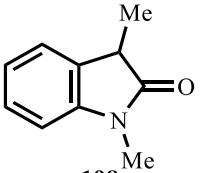
3-methylindolin-2-one



197

The title compound was prepared according to general procedure 5 using 2-oxindole (133 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in pet. ether (40-60 °C), 30 x 170 mm silica) gave the title compound as a yellow solid (125 mg, 86%); mp 106-108 °C (Lit. 107-109 °C);[36] R_f = 0.12 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3152, 3092, 2963, 2868, 1699, 1670, 1620, 1474, 1333, 1227, 1209, 746, 664, 554, 490, 444; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.50 (3H, d, *J* 8.0, CHC*H*$_3$), 3.47 (1H, q, *J* 8.0, C*H*CH_3), 6.89 (1H, d, *J* 7.5, ArC(7)*H*), 7.04 (1H, m, ArC(5)*H*), 7.21 (2H, m, ArC(4,6)*H*), 8.22 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.4 (CH*C*H_3), 41.1 (*C*HCH_3), 109.8 (Ar*C*(7)), 122.5 (Ar*C*(5)), 124.0 (Ar*C*(4)), 128.0 (Ar*C*(6)), 131.4 (Ar*C*(3a)), 141.3 (Ar*C*(7a)), 181.3 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_9H_{10}NO]^+$ $(M+H)^+$ m/z : 148.0757, found 148.0753, (-2.6 ppm).

1,3-dimethylindolin-2-one

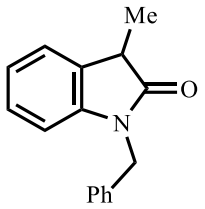


198

The title compound was prepared according to general procedure 5 using 1-methylindolin-2-one (147 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 170 mm silica) gave a white solid (119 mg, 74%); mp 53-55 °C (lit. 54-55 °C);[37] R_f = 0.30 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3395, 3046, 2970, 2936,

2899, 1699, 1609, 1489, 1452, 1375, 1341, 1308, 1258, 1126, 1088, 982, 748, 696, 604, 540, 488; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.48 (3H, d, *J* 8.0, CHC*H*$_3$), 3.21 (3H, s, NC*H*$_3$), 3.43 (1H, q, *J* 8.0, C*H*CH$_3$)), 6.82 (1H, d, *J* 7.5, Ar*H*), 7.06 (1H, dt, *J* 7.5, 1.0, Ar*H*), 7.24 (1H, d, *J* 7.0, Ar*H*), 7.26-7.31 (1H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.4 (CH*C*H$_3$), 26.3 (N*C*H$_3$), 40.6 (*C*HCH$_3$), 108.0 (Ar*C*), 122.5 (Ar*C*), 123.6 (Ar*C*), 127.9 (Ar*C*), 130.7 (Ar*C*(3a)), 144.1 (Ar*C*(7a)), 178.7 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{10}H_{12}NO]^+$ $(M+H)^+$ m/z : 162.0913, found 162.0910, (-2.1 ppm).

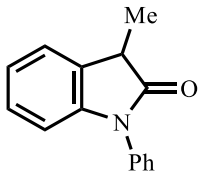
1-benzyl-3-methylindolin-2-one



199

The title compound was prepared according to general procedure 5 using 1-benzylindolin-2-one (223 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 180 mm silica) gave the title compound as a yellow solid (204 mg, 86%) mp 116-118 °C (lit. 119-120 °C);[38] R_f = 0.44 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.54 (3H, d, *J* 7.5, CHC*H*$_3$), 3.54 (1H, q, *J* 7.5, C*H*CH$_3$), 4.86-4.96 (2H, m, PhC*H*$_2$N), 6.72 (1H, d, *J* 7.5, Ar*H*), 7.02 (1H, t, *J* 7.0, Ar*H*), 7.15 (1H, t, *J* 7.5, Ar*H*), 7.22-7.27 (2H, m, Ar*H*), 7.27-7.34 (4H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.7 (CH*C*H$_3$), 40.7 (*C*HCH$_3$), 43.8 (*C*H$_2$), 109.1 (Ar*C*), 122.5 (Ar*C*), 123.7 (Ar*C*), 127.4 (Ar*C*), 127.7 (Ar*C*), 127.9 (Ar*C*), 128.9 (Ar*C*), 130.8 (Ar*C*(3a)), 136.1 (Ar*C*), 143.2 (Ar*C*(7a)), 178.9 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[38]

3-methyl-1-phenylindolin-2-one

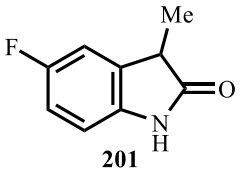


200

The title compound was prepared according to general procedure 5 using 1-phenyloxindole (209 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 180 mm silica) gave the title compound as an off-white solid (130 mg, 58%), mp 70-72 °C (Lit. 70-71 °C);[39] R_f = 0.46 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film)

3061, 2982, 2934, 1707, 1612, 1591, 1497, 1460, 1371, 1296, 1231, 1204, 1173, 760, 706, 648, 586, 492, 446; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.60 (3H, d, *J* 7.5, CHC*H*$_3$), 3.63 (1H, q, *J* 7.5, C*H*CH$_3$), 6.82 (1H, d, *J* 7.5, Ar*H*), 7.10 (1H, t, *J* 7.5, Ar*H*), 7.20 (1H, t, *J* 7.5, Ar*H*), 7.31 (1H, d, *J* 7.0, Ar*H*), 7.37-7.45 (3H, m, Ar*H*), 7.48-7.56 (2H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.9 (CH*C*H$_3$), 40.9 (*C*HCH$_3$), 109.4 (Ar*C*), 123.0 (Ar*C*), 123.9 (Ar*C*), 126.7 (Ar*C*), 127.9 (Ar*C*), 128.1 (Ar*C*), 129.7 (Ar*C*), 130.6 (Ar*C*(3a)), 134.7 (Ar*C*), 144.1 (Ar*C*(7a)), 178.1 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{15}H_{14}NO]^+$ $(M+H)^+$ m/z : 224.1070, found 224.1071, (+0.5 ppm).

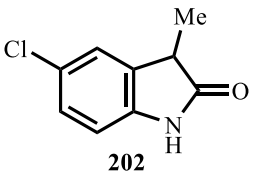
5-fluoro-3-methylindolin-2-one



201

The title compound was prepared according to general procedure 5 using 5-fluoro-2-oxindole (151 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 160 mm silica) gave the title compound as a yellow solid (126 mg, 76%); mp 180-182 °C (Lit. 180-182 °C);[40] R_f = 0.10 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.50 (3H, d, *J* 7.5, CHC*H*$_3$), 3.47 (1H, q, *J* 7.5, C*H*CH$_3$), 6.82 (1H, dd, *J* 8.5, 4.0, ArC(7)*H*), 6.91 (1H, dt, *J* 8.5, 2.5, ArC(6)*H*), 6.96 (1H, dd, *J* 8.0, 2.0, ArC(4)*H*), 8.64 (1H, br s, N*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: 120.9; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.3 (CH*C*H$_3$), 41.6 (d, *J* 1.9, *C*HCH$_3$), 110.2 (d, *J* 8.2, Ar*C*(7)), 112.0 (d, *J* 24.7, Ar*C*), 114.3 (d, *J* 23.6, Ar*C*), 133.2 (d, *J* 8.2, Ar*C*(3a)), 137.1 (d, *J* 2.1, Ar*C*(7a)), 159.3 (d, *J* 240.7, Ar*C*(5)), 180.9 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[40]

5-chloro-3-methylindolin-2-one

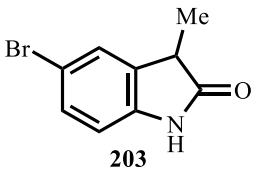


202

The title compound was prepared according to general procedure 5 using 5-chloro-2-oxindole (168 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 160 mm silica) gave the title compound as a yellow solid (153 mg,

85%); mp 194-196 °C (Lit. 199-201 °C);[41] R_f = 0.12 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3372, 3198, 2967, 2872, 1722, 1670, 1622, 1477, 1439, 1373, 1315, 1225, 1171, 876, 847, 718, 629, 573, 446; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.49 (3H, d, *J* 7.5, CHC*H*$_3$), 3.47 (1H, q, *J* 7.5, C*H*CH$_3$), 6.83 (1H, d, *J* 8.5, ArC(7)*H*), 7.16-7.22 (2H, m, ArC(4,6)*H*), 8.62 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.3 (CH*C*H$_3$), 41.3 (*C*HCH$_3$), 110.7 (Ar*C*), 124.5 (Ar*C*), 127.9 (Ar*C*), 128.0 (Ar*C*(3a)), 133.0 (Ar*C*), 139.8 (Ar*C*(7a)), 180.8 (*C*=O); HRMS (**ASAP**$^+$) calculated for $[C_9H_9NO^{35}Cl]^+$ $(M+H)^+$ m/z : 182.0373, found 182.0372, (-0.5 ppm).

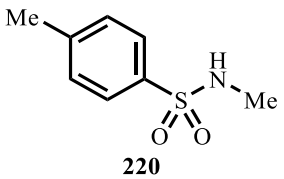
5-bromo-3-methylindolin-2-one



203

The title compound was prepared according to general procedure 5 using 5-bromo-2-oxindole (240 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 180 mm silica) gave the title compound as a yellow solid (180 mg, 71%); mp 188-190 °C (Lit. 186-187 °C);[42] R_f = 0.12 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3204, 2965, 2934, 2870, 1722, 1663, 1614, 1472, 1231, 1215, 1165, 816, 706, 629, 550; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.49 (3H, d, *J* 7.5, CHC*H*$_3$), 3.47 (1H, q, *J* 7.5, C*H*CH$_3$), 6.75-6.82 (1H, m, ArC(7)*H*), 7.31-7.37 (2H, m, ArC(4,6)*H*), 8.62 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.3 (CH*C*H$_3$), 41.3 (*C*HCH$_3$), 111.3 (Ar*C*(7)), 115.2 (Ar*C*(5)), 127.3 (Ar*C*), 130.9 (Ar*C*), 133.4 (Ar*C*(3a)), 140.3 (Ar*C*(7a)), 180.8 (*C*=O); HRMS (**ASAP**$^+$) calculated for $[C_9H_9NO^{79}Br]^+$ $(M+H)^+$ m/z : 225.9868, found 225.9868, (+0.0 ppm).

***N*,4-dimethylbenzenesulphonamide**

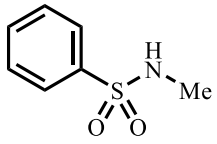


220

The title compound was prepared according to general procedure 6 using *p*-toluenesulfonamide (171 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes) gave an off-white solid (170 mg, 92%); mp 73-75 °C (lit. 75-76

°C);[43] R_f = 0.25 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 2.43 (3H, s, ArC(4)CH_3), 2.65 (3H, d, *J* 5.5, NCH_3), 4.35-4.45 (1H, m, N*H*), 7.29-7.35 (2H, m, ArC(3,5)*H*), 7.72-7.78 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 21.6 (ArC(4)*C*H$_3$), 29.4 (N*C*H$_3$), 127.4 (Ar*C*(2,6)), 129.8 (Ar*C*(3,5)), 135.8 (Ar*C*(4)), 143.6 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[44]

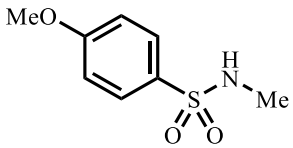
_N_-methylbenzenesulphonamide



224

The title compound was prepared according to general procedure 6 using benzenesulfonamide (157 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in pet. ether (40-60 °C), 30 x 220 mm silica) gave a pale-yellow oil (135 mg, 79%); R_f = 0.61 (eluent = 50% EtOAc in hexanes); **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 2.67 (3H, d, *J* 5.0, NCH_3), 4.36 (1H, br s, N*H*), 7.50-7.56 (2H, m, ArC(3,5)*H*), 7.57-7.62 (1H, m, ArC(4)*H*), 7.84-7.90 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 29.5 (N*C*H$_3$), 127.3 (Ar*C*(3,5)), 129.3 (Ar*C*(2,6)), 132.9 (Ar*C*(4)), 138.9 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[44]

4-methoxy-_N_-methylbenzenesulphonamide

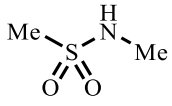


225

The title compound was prepared according to general procedure 6 using *p*-methoxybenzenesulfonamide (187 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 15-25% EtOAc in pet. ether (40-60 °C)) gave an off-white solid (192 mg, 95%); mp 94-96 °C (lit. 94-95 °C);[43] R_f = 0.14 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3279, 3096, 2986, 2947, 2849, 1595, 1574, 1493, 1466, 1416, 1321, 1304, 1256, 1157, 1126, 1090, 1072, 1015, 835, 557; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 2.64 (3H, d, *J* 3.5, NCH_3), 3.87 (3H, s, OCH_3), 4.36 (1H, br s, N*H*), 6.95-7.02 (2H, m, ArC(3,5)*H*), 7.77-7.83 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 29.4 (N*C*H$_3$), 55.8

(OCH_3), 114.4 (Ar*C*(3,5)), 129.5 (Ar*C*(2,6)), 130.5 (Ar*C*(1)), 163.1 (Ar*C*(4)); HRMS (**NSI$^+$**) calculated for $[C_8H_{12}O_3NS]^+$ $(M+H)^+$ m/z : 202.0532, found 202.0532, (-0.2 ppm).

_N_-methylmethanesulphonamide



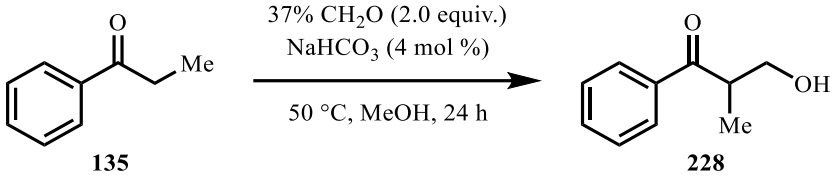
227

The title compound was prepared according to general procedure 6 using methanesulphonamide (95 mg, 1.0 mmol). Purification by flash silica chromatography (eluent = 40% EtOAc in pet. ether (40-60 °C)) gave a pale brown oil (71 mg, 65%); R_f = 0.21 (eluent = 50% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.82 (3H, s, NC*H*$_3$), 2.94 (3H, s, O_2SC*H*$_3$), 4.38 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 29.5 (N*C*H_3), 39.0 (O_2S*C*H_3). Spectroscopic data in accordance with that stated in the literature.[45]

8.4. Mechanistic studies

8.4.1. Synthesis of plausible intermediates

3-hydroxy-2-methyl-1-phenylpropan-1-one



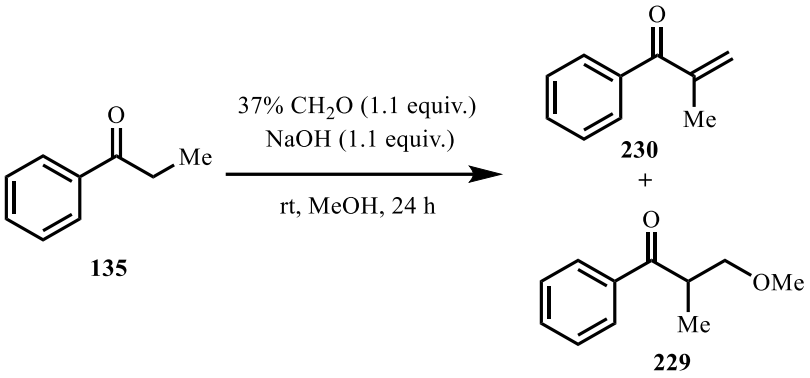
135 **228**

A round-bottomed flask equipped with a magnetic stirrer bar was charged with methanol (20 mL), $NaHCO_3$ (100 mg, 1.2 mmol), 37% formaldehyde in H_2O (4.5 mL, 60.0 mmol) and propiophenone (4.0 mL, 4.0 g, 30.0 mmol). The mixture was heated at 50 °C for 24 h. It was then cooled and acidified to pH 4 using conc. HCl. Et_2O (30 mL) was then added, and the mixture transferred to a separatory funnel. The organic layer was collected, and the aqueous phase washed with Et_2O (2 x 30 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 50 x 160 mm silica) gave a colourless oil (2.7 g, 56%); R_f = 0.16 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3414, 3061, 2970, 2932, 2868, 1676, 1597, 1447, 1238, 1209, 1026, 968, 793, 702, 687**; ^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.25 (3H, d, *J* 7.0, CHC*H*$_3$), 2.31 (1H, br s, O*H*), 3.62-3.72 (1H, m, C*H*CH_3), 3.77-3.86 (1H, m,

C*H*^{A}H^{B}OH), 3.89-3.98 (1H, m, CH^{A}*H*^{B}OH), 7.45-7.52 (2H, m, ArC(3,5)*H*), 7.55-7.62 (1H, m, ArC(4)*H*), 7.94-8.00 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 14.7 (CHC*H*$_3$), 43.0 (C*H*CH$_3$), 64.7 (C*H*$_2$OH), 128.6 (Ar*C*(3,5)), 128.9 (Ar*C*(2,6)), 133.5 (Ar*C*(4)), 136.2 (Ar*C*(1)), 204.6 (*C*=O); HRMS (**ASAP$^+$**) calculated for $[C_{10}H_{13}O_2]^+$ $(M+H)^+$ m/z : 165.0916, found 165.0914, (-1.2 ppm).

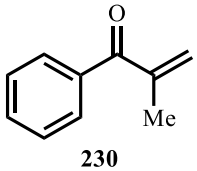
2-methyl-1-phenylprop-2-en-1-one

3-methoxy-2-methyl-1-phenylpropan-1-one



A round-bottomed flask equipped with a magnetic stirrer bar was charged with methanol (10 mL), 0.5 N NaOH (66 mL, 33.0 mmol), 37% formaldehyde in H_2O (2.5 mL, 33.0 mmol) and propiophenone (4.0 mL, 4.0 g, 30.0 mmol). The mixture was left to react at rt for 24 h. It was then cooled and acidified to pH 4 using conc. HCl. Et_2O (30 mL) was then added, and the mixture transferred to a separatory funnel. The organic layer was collected, and the aqueous phase washed with Et_2O (2 x 30 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 1-10% Et_2O in hexanes, 50 x 160 mm silica) gave 2-methyl-1-phenylprop-2-en-1-one; R_f = 0.42 (eluent = 5% EtOAc in hexanes); as a colourless oil (1.3 g, 29%); and 3-methoxy-2-methyl-1-phenylpropan-1-one; R_f = 0.54 (eluent = 20% EtOAc in hexanes); as a colourless oil (1.9 g, 35%).

2-methyl-1-phenylprop-2-en-1-one

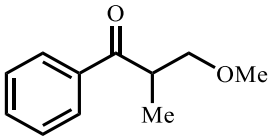


230

^{1}H NMR (500 MHz, CDCl$_3$) δ_H: 2.08 (3H, m, C*H*$_3$), 5.62 (1H, m, C*H*^{A}H^{B}), 5.93 (1H, m, CH^{A}*H*^{B}), 7.39-7.47 (2H, m, ArC(3,5)*H*), 7.49-7.57 (1H, m, ArC(4)*H*), 7.70-7.77 (2H, m,

ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.8 (*C*H_3), 127.2 (*C*H_2), 128.3 (Ar*C*(3,5)), 129.5 (Ar*C*(2,6)), 132.1 (Ar*C*(4)), 137.9 (Ar*C*(1)), 143.9 (*C*=CH_2), 198.5 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[46]

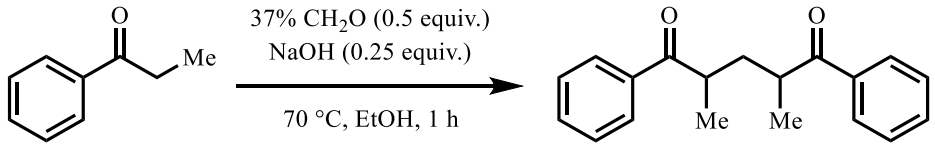
3-methoxy-2-methyl-1-phenylpropan-1-one



229

ν_{max} / cm^{-1} (film) 3065, 2982, 2940, 2880, 2833, 1680, 1593, 1450, 1387, 1217, 1190, 1105, 978, 945, 793, 702, 685, 648; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.21 (3H, d, *J* 7.0, CHC*H*$_3$), 3.32 (3H, s, OC*H*$_3$), 3.42-3.50 (1H, m, C*H*CH$_3$), 3.72-3.84 (2H, m, C*H*$_2$OCH$_3$), 7.43-7.51 (2H, m, ArC(3,5)*H*), 7.53-7.60 (1H, m, ArC(4)*H*), 7.95-8.00 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.0 (CH*C*H$_3$), 41.4 (*C*HCH$_3$), 59.2 (O*C*H$_3$), 75.1 (*C*H$_2$), 128.5 (Ar*C*(3,5)), 128.7 (Ar*C*(2,6)), 133.1 (Ar*C*(4)), 136.8 (Ar*C*(1)), 202.9 (*C*=O); HRMS (**NSI$^+$**) calculated for $[C_{11}H_{15}O_2]^+$ $(M+H)^+$ m/z : 179.1067, found 179.1065, (-0.9 ppm).

2,4-dimethyl-1,5-diphenylpentane-1,5-dione



135 **231**

A three-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with ethanol (12 mL), NaOH (250 mg, 6.3 mmol) and propiophenone (3.3 mL, 3.3 g, 25.0 mmol). The mixture was heated to 70 °C followed by dropwise addition of 37% formaldehyde (1 mL, 12.6 mmol) over a period of 5 min. This was heated for a further 60 min at 70 °C. The mixture was quenched with sat. aq. NH_4Cl (10 mL) and water (10 mL). Et_2O (50 mL) was added and the mixture was transferred to separatory funnel. The organic layer was collected, and the aqueous phase washed with Et_2O (2 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% Et_2O in hexanes, 40 x 150 mm silica) gave a colourless oil (2.6 g, 74%) as an inseparable mixture of diastereomers (55:45 d.r.); R_f = 0.15 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3059, 2972, 2934, 2874, 1676, 1593, 1578, 1443, 1379, 1238, 1217, 972, 791, 698, 685.

Selected data for diastereomer 1

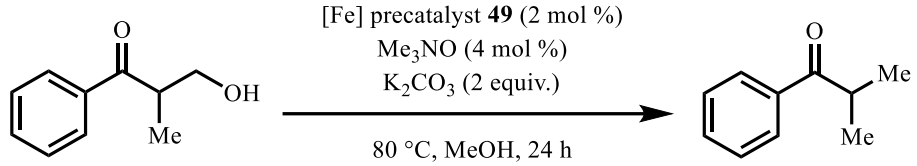
^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.22 (6H, d, *J* 7.0, CHC*H*$_3$), 2.01 (2H, t, *J* 7.0, C*H*$_2$), 3.50 (2H, sext, *J* 7.0, 2xC*H*CH$_3$), 7.30-7.37 (4H, m, 2xArC(3,5)*H*), 7.44-7.49 (2H, m, 2xArC(4)*H*), 7.75-7.81 (4H, m, 2xArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.9 (2xCH*C*H$_3$), 37.4 (*C*H$_2$), 38.7 (2x*C*HCH$_3$), 128.3 (2xAr*C*(3,5)), 128.7 (2xAr*C*(2,6)), 133.1 (2xAr*C*(4)), 136.6 (2xAr*C*(1)), 204.5 (2x*C*=O).

Selected data for diastereomer 2

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.18 (6H, d, *J* 7.0, CHC*H*$_3$), 1.46-1.52 (1H, m, C*H*^{A}H^B), 2.41-2.47 (1H, m, CH^A*H*^{B}), 3.62 (2H, sext, *J* 7.0, 2xC*H*CH$_3$), 7.48-7.54 (4H, m, 2xArC(3,5)*H*), 7.55-7.62 (2H, m, 2xArC(4)*H*), 8.02-8.09 (4H, m, 2xArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.7 (2xCH*C*H$_3$), 37.1 (*C*H$_2$), 38.3 (2x*C*HCH$_3$), 128.6 (2xAr*C*(3,5)), 128.9 (2xAr*C*(2,6)), 133.2 (2xAr*C*(4)), 136.4 (2xAr*C*(1)), 204.0 (2x*C*=O).

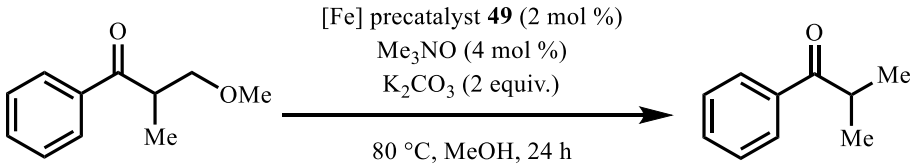
HRMS (**NSI$^+$**) calculated for $[C_{19}H_{21}O_2]^+$ $(M+H)^+$ m/z : 281.1536, found 281.1536, (+0.0 ppm).

8.4.2. Validation of plausible intermediates



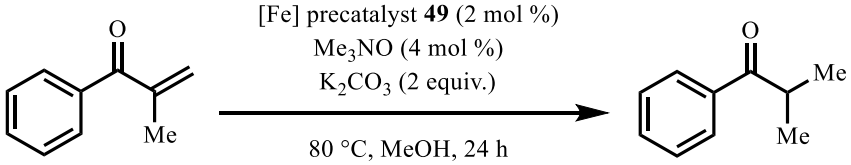
228 **136**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.00 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 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 was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL) and 3-hydroxy-2-methyl-1-phenylpropan-1-one (**228**) (164 mg, 1.00 mmol). The mixture was left to react at 80 °C for 24 h. It was then cooled followed by the addition of mesitylene (139 µL, 120 mg, 1.00 mmol), EtOAc (2 mL) and H_2O (2 mL). The mixture was stirred for 5 min, the cap removed, left to settle for a further 5 min. The top layer was sampled and analysed using ^{1}H NMR. This revealed 85% of **136**.



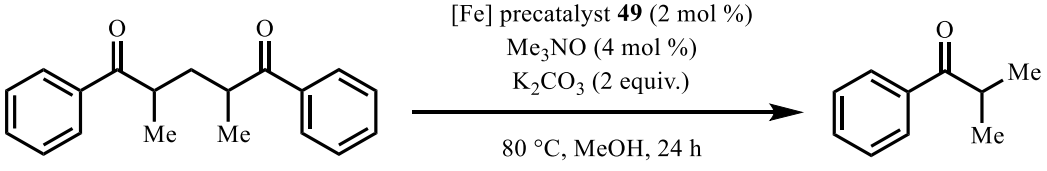
229 **136**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.00 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 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 was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL) and 3-methoxy-2-methyl-1-phenylpropan-1-one (**229**) (178 mg, 1.00 mmol). The mixture was left to react at 80 °C for 24 h. It was then cooled followed by the addition of mesitylene (139 µL, 120 mg, 1.00 mmol), EtOAc (2 mL) and H_2O (2 mL). The mixture was stirred for 5 min, the cap removed, left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 85% of **136**.



230 **136**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.00 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 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 was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL) and 2-methyl-1-phenylprop-2-en-1-one (**230**) (146 mg, 1.00 mmol). The mixture was left to react at 80 °C for 24 h. It was then cooled followed by the addition of mesitylene (139 µL, 120 mg, 1.00 mmol), EtOAc (2 mL) and H_2O (2 mL). The mixture was stirred for 5 min, the cap removed, left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 85% of **136**.

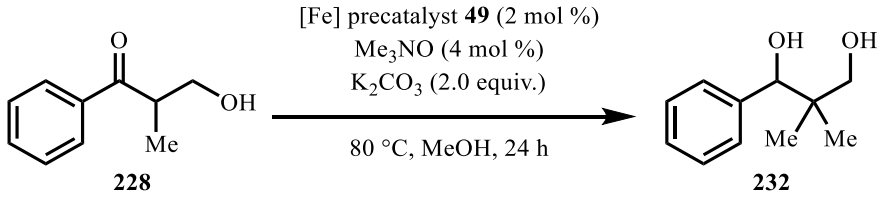


231 **136**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.00 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 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 was repeated three times. Under nitrogen the vial was then charged with MeOH (2 mL) and 2,4-dimethyl-1,5-diphenylpentane-1,5-dione (**231**) (280 mg, 1.00 mmol). The mixture was left to react at 80 °C for 24 h. It was then cooled followed by the addition of mesitylene (139 µL, 120 mg, 1.00 mmol), EtOAc (2 mL) and H_2O (2 mL). The mixture was stirred for 5 min, the cap removed, left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 0% of **136**.

8.4.3. Synthesis of diol

2,2-dimethyl-1-phenylpropane-1,3-diol

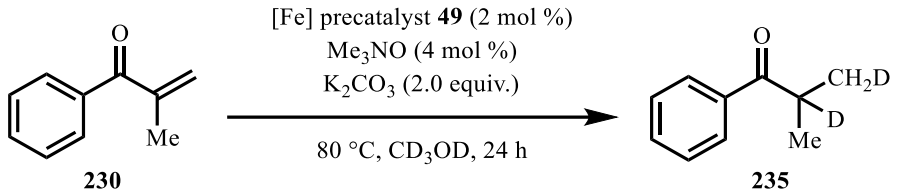


228 **232**

A 20 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (553 mg, 4.0 mmol), $Me_3NO.2H_2O$ (8.9 mg, 0.08 mmol, 4 mol %) and [Fe] precatalyst **49** (16.7 mg, 0.04 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 was repeated three times. Under nitrogen the vial was then charged with MeOH (4 mL) and 3-hydroxy-2-methyl-1-phenylpropan-1-one (2.0 mmol). The mixture was left to react at 80 °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 organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-20% EtOAc in pet. ether (40-60 °C), 30 x 150 mm silica) gave an off-white solid (51 mg, 13%), mp 76-78 °C (lit. 76-78 °C);[47] R_f = 0.18 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3342, 3225, 2963, 2928, 2893, 1472, 1449, 1360, 1024, 984, 735, 700, 650, 505; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.85 (3H, s, C*H*$_3$), 0.88 (3H, s, C*H*$_3$), 2.70 (2H, br s, 2xO*H*), 3.51 (1H, d, *J* 10.5, C*H*^{A}H^B), 3.58 (1H, d, *J* 11.0, CH^A*H*^{B}), 4.65 (1H, s, C*H*OH), 7.26-7.37 (5H, m, ArC(2,3,4,5,6)*H*). **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.2 (*C*H$_3$), 22.9 (*C*H$_3$), 39.3 (*C*(CH$_3$)$_2$), 72.3 (*C*H$_2$), 82.4 (*C*HOH),

127.7 (Ar*C*(4)), 127.7 (Ar*C*(3,5)), 127.9 (Ar*C*(2,6)), 141.6 (Ar*C*(1)); HRMS (**CI**$^+$) calculated for $[C_{11}H_{20}O_2N]^+$ $(M+NH_4)^+$ m/z : 198.1489, found 198.1485, (-1.8 ppm).

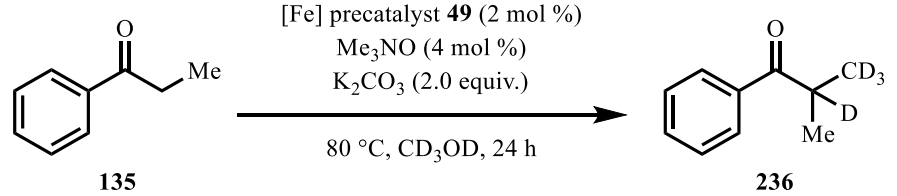
2-methyl-1-phenylpropan-1-one-2,3-*d*$_2$



230 **235**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.0 mmol), 2-methyl-1-phenylprop-2-en-1-one (146 mg, 1.0 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 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 was repeated three times. Under nitrogen the vial was then charged with CD_3OD (2 mL). The mixture was left to react at 80 °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 $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C)) gave a colourless oil (105 mg, 70%); R_f = 0.40 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3061, 2970, 2928, 2870, 1676, 1601, 1578, 1449, 1265, 1171, 997, 899, 773; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.16-1.24 (5H, m, C(C*H*$_3$)(C*H*$_2$D)), 7.43-7.50 (2H, m, ArC(3,5)*H*), 7.52-7.59 (1H, m, ArC(4)*H*), 7.93-7.99 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.9 (m, *C*D$_3$), 19.2 (*C*H$_2$D), 35.0 (m, *C*DCH$_2$D), 128.4 (Ar*C*(3,5)), 128.7 (Ar*C*(2,6)), 132.9 (Ar*C*(4)), 136.4 (Ar*C*(1)), 204.7 (*C*=O); HRMS (**EI**$^+$) calculated for $[C_{10}H_{10}D_2O]^+$ $(M)^+$ m/z : 150.1014, found 150.1013, (-0.7 ppm).

2-methyl-1-phenylpropan-1-one-2,3,3,3-*d*$_4$



135 **236**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (276 mg, 2.0 mmol), propiophenone (133 µL, 134 mg, 1.0 mmol), $Me_3NO.2H_2O$ (4.4 mg, 0.04

mmol, 4 mol %) and [Fe] precatalyst **49** (8.4 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 was repeated three times. Under nitrogen the vial was then charged with CD_3OD (2 mL). The mixture was left to react at 80 °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 $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 2% Et_2O in pet. ether (40-60 °C), 30 x 150 mm silica) gave a yellow oil (137 mg, 90%); R_f = 0.40 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3063, 2970, 2932, 2872, 1678, 1597, 1578, 1447, 1277, 1175, 988, 762, 689; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.20-1.30 (3H, m, C*H*$_3$), 7.39-7.47 (2H, m, ArC(3,5)*H*), 7.48-7.56 (1H, m, ArC(4)*H*), 7.89-7.96 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.5 (m, *C*D$_3$), 19.1 (*C*H$_3$), 34.9 (m, *C*D(CH$_3$)), 128.4 (Ar*C*(3,5)), 128.7 (Ar*C*(2,6)), 132.9 (Ar*C*(4)), 136.4 (Ar*C*(1)), 204.7 (*C*=O); HRMS (**EI**$^+$) calculated for $[C_{10}H_8D_4O]^+$ $(M)^+$ m/z : 152.1139, found 152.1139, (+0.0 ppm).

8.5. References

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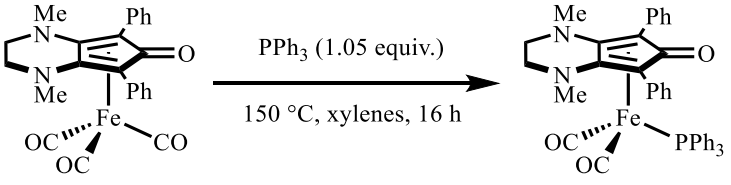
Chapter 9: Experimental

Iron-catalysed borrowing hydrogen *C*-alkylation of oxindoles using alcohols

Table of contents

9.1. (cyclopentadienone)iron carbonyl precatalyst synthesis

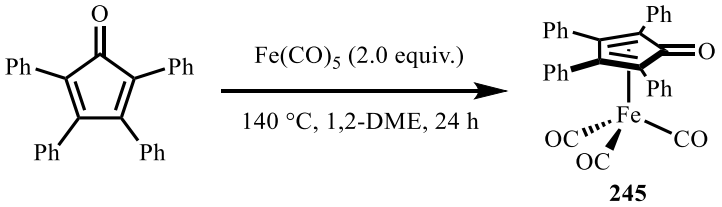
(1,4-dimethyl-5,7-diphenyl-1,2,3,4-tetrahydro-6*H*-cyclopenta[b]pyrazin-6-one) triphenylphosphine dicarbonyl iron



53 **54**

The title compound was prepared according to a procedure stated in the literature.[1] Under nitrogen, a flame dried Schlenk tube equipped with a magnetic stirrer bar was charged with [Fe] precatalyst **53** (171 mg, 0.38 mmol), PPh_3 (104 mg, 0.40 mmol) and dry and degassed xylenes (12.5 mL). The mixture was heated to 150 °C for 16 h. It was then cooled and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10-50 % EtOAc in hexanes, 30 x 200 mm silica) gave the title compound as an orange solid (104 mg, 40%); R_f = 0.50 (eluent = 30% EtOAc in hexanes, 30 x 150 mm silica); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 2.46 (6H, s, 2xNC*H*$_3$), 3.28-3.42 (4H, m, 2xNC*H*$_2$), 6.88-6.96 (6H, m, Ar*H*), 7.02 (4H, t, *J* 8.0, Ar*H*), 7.08-7.20 (11H, m, Ar*H*), 7.69 (4H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 40.3 (2xN*C*H$_3$), 47.2 (2xN*C*H$_2$), 71.4 (d, *J* 2.1, Ar*C*), 108.7 (d, *J* 2.0, Ar*C*), 126.1 (Ar*C*), 127.6 (Ar*C*), 127.6 (d, *J* 8.9, Ar*C*), 129.1 (d, *J* 2.1, Ar*C*), 130.9 (Ar*C*), 133.4 (d, *J* 10.5, Ar*C*), 133.7 (d, *J* 39.1, Ar*C*), 134.1 (Ar*C*), 161.0 (d, *J* 5.3, C=O), 217.1 (d, *J* 8.2, Fe(*C*O)$_2$). Spectroscopic data in accordance with that stated in the literature.[1]

(2,3,4,5-Tetraphenylcyclopentadienone)iron tricarbonyl



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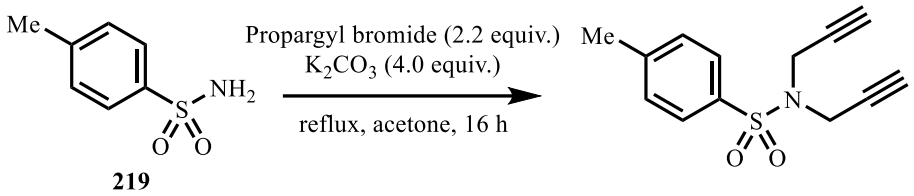
The title compound was prepared according to a modified procedure stated in the literature.[2] Under nitrogen, an ACE pressure tube equipped with a magnetic stirrer bar was charged with tetraphenylcyclopentadienone (1.5 g, 4.0 mmol) and 1,2-dimethoxyethane (12 mL). To this solution was then added iron pentacarbonyl (1.1 mL, 1.6 g, 8.0 mmol). The vessel was sealed and was heated to 140 °C for 24 h. It was then cooled and filtered to remove any iron particles and concentrated *in vacuo*. Purification by recrystallisation gave the title compound

as a dark-yellow solid (824 mg, 39%); mp 184-187 °C (hexanes); R_f = 0.14 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 7.10-7.30 (8H, m, Ar*H*), 7.23-7.35 (8H, m, Ar*H*), 7.50-7.65 (4H, m, Ar*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 82.5 (Ar*C*), 104.0 (Ar*C*), 127.9 (Ar*C*), 128.1 (Ar*C*), 128.1 (Ar*C*), 128.7 (Ar*C*), 130.0 (Ar*C*), 130.3 (Ar*C*), 130.9 (Ar*C*), 131.8 (Ar*C*), 169.8 (*C*=O), 208.5 (Fe(*C*O)$_3$). Spectroscopic data in accordance with that stated in the literature.[2]

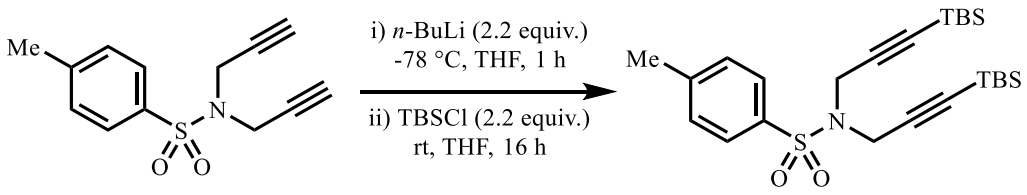
4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide



219

The title compound was prepared according to a procedure stated in the literature.[3] A round-bottomed flask equipped a magnetic stirrer bar was charged with *p*-toluenesulfonamide (5.5 g, 32.0 mmol), K_2CO_3 (13.3 g, 96.0 mmol) and acetone (290 mL). To this suspension was then added and propargyl bromide (7.8 mL, 70.4 mmol, 80 wt% in PhMe). The mixture was left to react at reflux for 16 h. It was then cooled, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 50 x 160 mm silica) gave the title compound as an off-white solid (6.8 g, 87%), mp 55-57 °C; R_f = 0.18 (eluent = 10% EtOAc in hexanes). **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.15 (2H, t, *J* 2.0, 2xC≡C*H*), 2.42 (3H, s, ArC(4)CH_3), 4.16 (4H, d, *J* 2.0, N(CH_2)$_2$), 7.30 (2H, d, *J* 8.0, ArC(3,5)*H*), 7.72 (2H, d, *J* 8.5, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 21.7 (ArC(4)*C*H$_3$), 36.3 (N(*C*H$_2$)$_2$), 74.2 (2xC≡*C*H), 76.3 (2x*C*≡CH) 128.0 (Ar*C*(2,6)), 129.7 (Ar*C*(3,5)), 135.3 (Ar*C*(4)), 144.1 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[3]

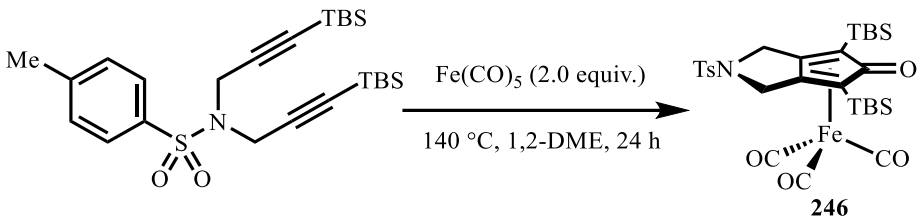
***N*,*N*-bis(3-(*tert*-butyldimethylsilyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide**



The title compound was prepared according to a procedure stated in the literature.[3] A flame dried round-bottomed flask equipped a magnetic stirrer bar was charged with 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (3.0 g, 12.0 mmol) and dry THF (25 mL). The

solution was cooled down to – 78 °C and *n*-BuLi (12 mL, 26.4 mmol, 2.2 M in hexanes) was then added dropwise. This was left stirring at - 78°C for 10 min and at rt for 1 h. To this solution was then added TBSCl (4.0 g, 26.4 mmol) portionwise and the mixture was left stirring at rt for 16 h. The mixture was quenched with sat. aq. NH_4Cl (10 mL). Et_2O (25 mL) was then added and the organic phase was collected. The aqueous phase was washed with Et_2O (2 x 25 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 0-2% Et_2O in hexanes, 50 x 180 mm silica) gave the title compound as an orange solid (1.22 g, 22%); mp 71-74 °C; R_f = 0.5 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: -0.01 (12H, s, 2xSi(C*H*$_3$)$_2$(C(CH$_3$)$_3$), 0.84 (18H, s, 2xSi(CH$_3$)$_2$(C(C*H*$_3$)$_3$), 2.41 (3H, s, ArC(4)C*H*$_3$), 4.19 (4H, s, N(C*H*$_2$)$_2$), 7.28 (2H, m, ArC(3,5)*H*), 7.69 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: -4.6 (2xSi(*C*H$_3$)$_2$(C(CH$_3$)$_3$), 16.6 (2xSi(CH$_3$)$_2$(*C*(CH$_3$)$_3$), 21.8 (ArC(4)*C*H$_3$), 26.2 (2xSi(CH$_3$)$_2$(C(*C*H$_3$)$_3$), 37.4 (N(*C*H$_2$)$_2$, 89.8 (2xNCH$_2$*C*≡C), 98.2 (2xNCH$_2$C≡*C*), 128.1 (Ar*C*(2,6)), 129.9 (Ar*C*(3,5)), 135.3 (Ar*C*(4)), 143.9 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[3]

(2,4-bis(*tert*-butyldimethylsilyl)-7-*N*-tosyl-bicyclo[3.3.0]hepta-1,4-dien-3-one)iron tricarbonyl



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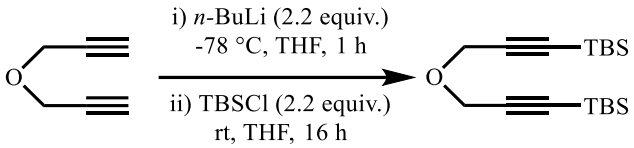
The title compound was prepared according to a procedure stated in the literature.[3] Under nitrogen, an ACE pressure tube was charged with *N*,*N*-bis(3-(tert-butyldimethylsilyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (700 mg, 1.5 mmol) and 1,2-dimethoxyethane (12 mL). To this solution was then added iron pentacarbonyl (389 µL, 576 mg, 2.9 mmol). The vessel was sealed and was heated to 140 °C for 24 h. It was then cooled and filtered to remove any iron particles and concentrated *in vacuo*. Purification by flash neutral alumina chromatography (eluent = 5% EtOAc in hexanes, 50 x 180 alumina) followed by recrystallisation gave the title compound as a yellow solid (794 mg, 84%); mp 209-212 °C (dec); R_f = 0.32 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 0.05 (6H, s, Si(C*H*$_3$)$_2$), 0.33 (6H, s, Si(C*H*$_3$)$_2$), 0.91 (18H, s, 2xSiC(C*H*$_3$)$_3$), 2.44 (3H, s, ArC(4)C*H*$_3$), 4.38 (4H, s, N(C*H*$_2$)$_2$), 7.35 (2H, d, *J* 8.0, ArC(3,5)*H*), 7.77 (2H, d, *J* 8.0,

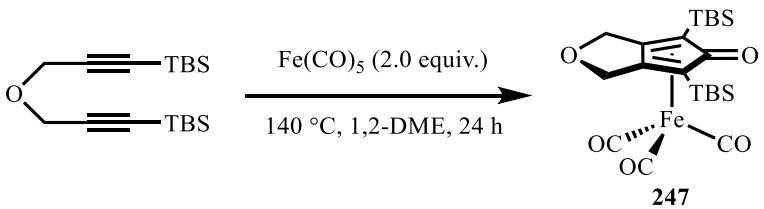
ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: -5.2 (2xSi*C*H_3), -4.8 (2xSi*C*H_3), 18.8 (2xSi*C*$(CH_3)_3$), 21.7 (ArC(4)*C*H_3), 27.4 (2xSiC(*C*$H_3)_3$), 49.5 (N(*C*$H_2)_2$, 69.8 (2xNCH_2-*C*≡C), 112.6 (2xNCH_2-C≡*C*), 127.4 (Ar*C*(2,6)), 130.3 (Ar*C*(3,5)), 133.9 (Ar*C*(4)), 144.7 (Ar*C*(1)), 180.6 (C-*C*=O-C), 207.2 (Fe(*C*O)$_3$); Spectroscopic data in accordance with that stated in the literature.[3]

(Oxybis(prop-1-yne-3,1-diyl))bis(*tert*-butyldimethylsilane)



The title compound was prepared according to a procedure stated in the literature.[3] A flame dried round-bottomed flask equipped a magnetic stirrer bar was charged with propargyl ether (2.0 mL, 1.8 g, 19.4 mmol) and dry THF (40 mL). The solution was cooled down to – 78 °C and *n*-BuLi (20 mL, 42.7 mmol, 2.13 M in hexanes) was then added dropwise. This was left stirring at - 78°C for 10 min and at rt for 1 h. To this solution was then added TBSCl (6.4 g, 42.7 mmol) portionwise, and the mixture was left stirring for 16 h. The mixture was quenched with sat. aq. NH_4Cl (10 mL). Et_2O (25 mL) was then added and the organic phase was collected. The aqueous phase was washed with Et_2O (2 x 25 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 0-10% Et_2O in hexanes, 50 x 200 mm silica) gave a yellow oil (1.6 g, 25%); R_f = 0.77 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 0.12 (12H, s, 2xSi(C*H*$_3)_2$(C(C$H_3)_3$), 0.94 (18H, s, 2xSi(C$H_3)_2$(C(C*H*$_3)_3$), 4.27 (4H, s, 2xOC*H*$_2$). **^{13}C NMR (126 MHz, $CDCl_3$)**, δ_C: -4.6 (2xSi(*C*$H_3)_2$(C(C$H_3)_3$), 16.6 (2xSi(C$H_3)_2$(*C*(C$H_3)_3$), 26.2 (2xSi(C$H_3)_2$(C(*C*$H_3)_3$), 57.2 (2xO*C*H_2), 90.5 (2xCH_2*C*≡C), 101.3 (2xCH_2C≡*C*). Spectroscopic data in accordance with that stated in the literature.[3]

(2,4-bis(*tert*-butyldimethylsilyl)-7-oxy-bicyclo[3.3.0]hepta-1,4-dien-3-one)iron tricarbonyl



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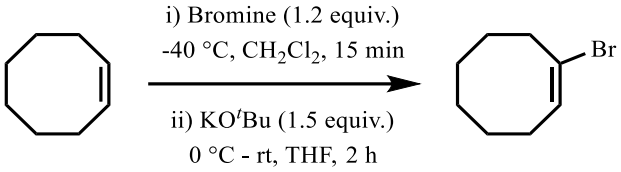
The title compound was prepared according to a procedure stated in the literature.[3] Under nitrogen, an ACE pressure tube equipped with a magnetic stirrer bar was charged with (oxybis(prop-1-yne-3,1-diyl))bis(*tert*-butyldimethylsilane) (968 mg, 3.0 mmol) and 1,2-dimethoxyethane (24 mL). To this solution was then added iron pentacarbonyl (789 µL, 968 mg, 6.0 mmol). The vessel was sealed and was heated to 140 °C for 24 h. It was then cooled and filtered to remove any iron particles and concentrated *in vacuo*. Purification by flash neutral alumina chromatography (eluent = 2% EtOAc in hexanes, 50 x 180 alumina) gave the title compound as a yellow solid (1.2g, 86%); mp 98-100 °C; R_f = 0.17 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.06 (6H, s, Si(C*H*$_3$)$_2$), 0.37 (6H, s, Si(C*H*$_3$)$_2$), 0.95 (18H, s, 2xSiC(C*H*$_3$)$_3$), 4.74 (4H, dd, *J* 31.5, 12.0, 2xOC*H*$_2$); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: -5.2 (2xSi*C*H$_3$), -4.8 (2xSi*C*H$_3$), 18.8 (2xSi*C*(CH$_3$)$_3$), 27.4 (2xSiC(*C*H$_3$)$_3$), 68.1 (2xO*C*H$_2$), 68.9 (2xOCH$_2$-*C*≡C), 114.0 (2xOCH$_2$-C≡*C*), 182.0 (C-*C*=O-C), 207.9 (Fe(*C*O)$_3$). Spectroscopic data in accordance with that stated in the literature.[3]

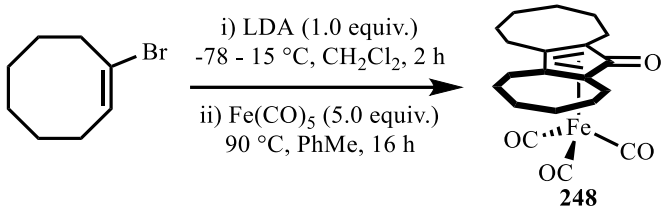
(*E*)-1-bromocyclooct-1-ene



The title compound was prepared according to a modified procedure stated in the literature.[5] Under nitrogen, a three-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with cyclooctene (16.6 mL, 13.8 g, 125.0 mmol) and CH_2Cl_2 (50 mL). The solution was cooled to -40 °C and was charged with Br_2 until the solution changed to yellow. Excess Br_2 (2 mL) was then added and the mixture was quenched with 10% aq. $Na_2S_2O_3$ (50 mL). The mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with CH_2Cl_2 (2 x 100 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo* giving *trans*-1,2-dibromocyclooctane (33.7 g, 99%). This was used for the next step without further purification. In a separate three-necked flask, KO^{t}Bu (21.0 g, 188.0 mmol) was suspended in dry THF (40 mL). To this suspension was then added a solution of *trans*-1,2-dibromocyclooctane (24.0 g, 89.0 mmol) in dry THF (50 mL) at 0 °C. The mixture was stirred for 2 h at rt and was then quenched with sat. aq. NH_4Cl (50 mL). The mixture was concentrated *in vacuo* until the THF was completely evaporated. The residue was dissolved in CH_2Cl_2 (50 mL) and the organic layer was collected. The aqueous layer was washed with CH_2Cl_2 (2 x 50 mL). The

organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by distillation (85-90 °C at 10 mbar) gave the title compound as a pale-yellow oil (15.3 g, 91%); R_f = 0.77 (eluent = 100% hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.46-1.58 (6H, m, C*H*$_2$), 1.60-1.68 (2H, m, C*H*$_2$), 2.06-2.13 (2H, m, C*H*$_2$), 2.57-265 (2H, m, C*H*$_2$), 6.03 (1H, t, *J* 8.5, *H*C=CBr); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 25.6 (*C*H$_2$), 26.5 (*C*H$_2$), 27.6 (*C*H$_2$), 28.8 (*C*H$_2$), 30.0 (*C*H$_2$), 35.3 (*C*H$_2$), 124.9 (*C*Br), 131.8 (*C*=CBr). Spectroscopic data in accordance with that stated in the literature.[4]

[bis(hexamethylene)cyclopentadienone]iron tricarbonyl



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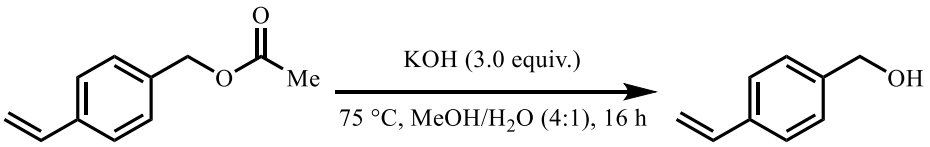
The title compound was prepared according to a modified procedure stated in the literature.[5] Under nitrogen, a flame-dried three-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with dry THF (12 mL). It was cooled to -78 °C followed by the addition of diisopropylamine (4.1 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 °C for 20 min and then heated up to -20 °C. After 10 min, the mixture was gradually left to heat up to 15 °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 $MgSO_4$ and concentrated *in vacuo*. The crude mixture (850 mg, 7.9 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 $Fe(CO)_5$ (5.5 mL, 8.2 g, 41.6 mmol). The mixture was heated to 90 °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. (243 mg, 2%); mp 153-155 °C (Lit. 156 °C);[5] R_f = 0.17 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.35-2.00 (18H, m, 9x C*H*$_2$), 2.39-2.51 (2H, m, C*H*$_2$), 2.56-2.65 (2H, m, C*H*$_2$), 2.72-2.82 (2H, m, C*H*$_2$); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 23.6 (2x*C*H$_2$), 23.9 (2x*C*H$_2$), 25.9 (2x*C*H$_2$), 26.4 (2x*C*H$_2$), 29.0 (2x*C*H$_2$),

31.5 (2x*C*H_2), 85.7 (2x*C*=C), 102.6 (2xC=*C*), 171.6 (*C*=O), 209.5 (Fe(*C*O)$_3$). Spectroscopic data in accordance with that stated in the literature.[Error! Bookmark not defined.]

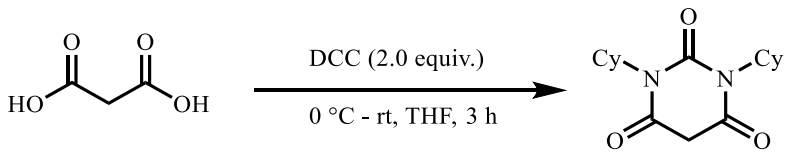
9.2. Substrate synthesis

(4-vinylphenyl)methanol



A round-bottomed flask equipped with a magnetic stirrer bar was charged with 4-vinylbenzyl acetate (705 mg, 4.0 mmol), KOH (673 mg, 12.0 mmol), MeOH (3.6 mL) and H_2O (0.9 mL). The mixture was heated to 75 °C for 16 h. It was then cooled, diluted with EtOAc (10 mL) and transferred to a separatory funnel filled with brine (15 mL). The organic phase was collected. The aqueous phase was washed with EtOAc (2 x 25 mL). The organics were combined, washed with sat. aq. NH_4Cl, dried over $MgSO_4$, filtered and concentrated *in vacuo.* Purification by flash silica chromatography (eluent = 30% Et_2O in hexanes, 30 x 150 mm silica) gave the title compound as a colourless oil (402 mg, 75%); R_f = 0.20 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.72 (1H, br s, O*H*), 4.68 (2H, s, CH_2OH), 5.25 (1H, d, *J* 11.0, CH=CH^AH^B), 5.76 (1H, d, *J* 18.0, CH=CH^AH^B), 6.72 (1H, dd, *J* 17.5, 11.0, C*H*=CH_2), 7.33 (2H, d, *J* 7.0, ArC(2,6)*H*), 7.41 (2H, d, *J* 7.5, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 65.3 (*C*H_2OH), 114.0 (CH=*C*H_2), 126.5 (Ar*C*(3,5)), 127.3 (Ar*C*(2,6)), 136.6 (*C*H=CH_2), 137.2 (Ar*C*(4)), 140.5 (Ar*C*(1)). Spectroscopic data in accordance with that stated the literature.[6]

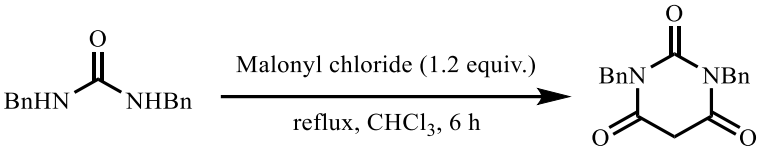
1,3-dicyclohexylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione



A round-bottomed flask equipped with a magnetic stirrer bar was charged with malonic acid (2.1 g, 20.0 mmol) and THF (25 mL). The solution was cooled to 0 °C followed by the addition of a solution of *N,N'*-dicyclohexylcarbodiimide (8.3 g, 40.0 mmol) in THF (25 mL) over a period of 30 min. The mixture was left to warm up to rt and was left stirring for a total of 3 h. The urea was filtered off and the filtrate was concentrated *in vacuo*. Purification by

recrystallisation gave the title compound as an off-white solid (3.2 g, 54%); mp 200-203 °C (ethanol) (Lit. 201-203 °C);[7] R_f = 0.44 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.14-1.27 (2H, m, C*H*), 1.34 (4H, qt, *J* 13.0, 3.5, C*H*), 1.53-1.70 (6H, m, C*H*), 1.77-1.88 (4H, m, C*H*), 2.24 (4H, qd, *J* 12.5, 3.5, C*H*), 3.59 (2H, s, (C=O)CH_2(C=O)), 4.58 (2H, tt, *J* 12.5, 3.5, 2xNC*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 25.3 ((CH$_2$)$_2$-*C*H$_2$-(CH$_2$)$_2$), 26.5 ((*C*H$_2$)$_2$-CH$_2$-(*C*H$_2$)$_2$), 29.3 (2xNCH-*C*H$_2$), 41.1 (C=O)*C*H$_2$(C=O), 55.5 (2xN*C*H), 151.4 (N-(*C*=O)-N), 165.2 (*C*=O)CH$_2$(*C*=O). Spectroscopic data in accordance with the literature.[8]

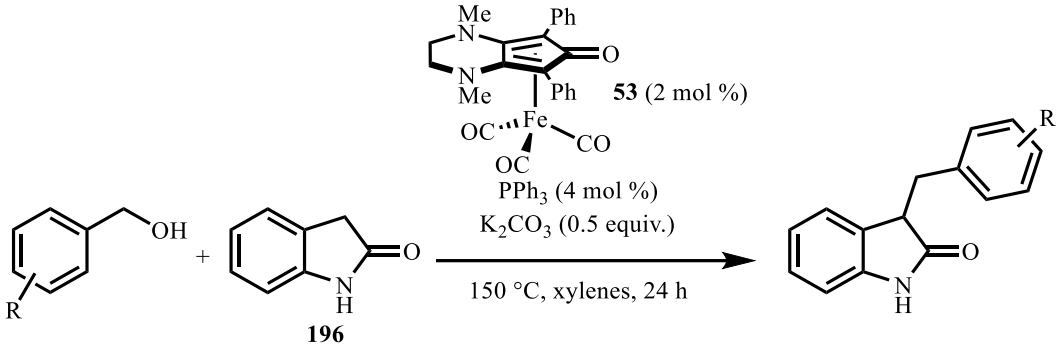
1,3-dibenzylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione



A 50 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with 1,3-dibenzyl urea (1.2 g, 5.0 mmol), $CHCl_3$ (15 mL) and malonyl chloride (580 µL, 846 mg, 6.0 mmol). The mixture was heated to reflux for 6 h. It was then cooled and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 35 x 140 mm silica) gave the title compound as a yellow solid (1.0 g, 68%); mp 142-145 °C (Lit. 146-147 °C);[9] R_f = 0.27 (eluent = 40% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 3.68 (2H, s, (C=O)CH_2(C=O)), 5.04 (4H, s, 2xCH_2N), 7.27-7.35 (6H, m, ArC(2,4,6)*H*), 7.38-7.46 (4H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 39.9 ((C=O)*C*H$_2$(C=O)), 45.3 (2x*C*H$_2$N), 128.2 (2xAr*C*(4)*H*), 128.7 (2xAr*C*), 129.3 (2xAr*C*), 136.1 (2xAr*C*(1)), 151.7 (N-*C*=O-N), 164.5 (2xCH$_2$-*C*=O). Spectroscopic data in accordance with that stated in the literature.[9]

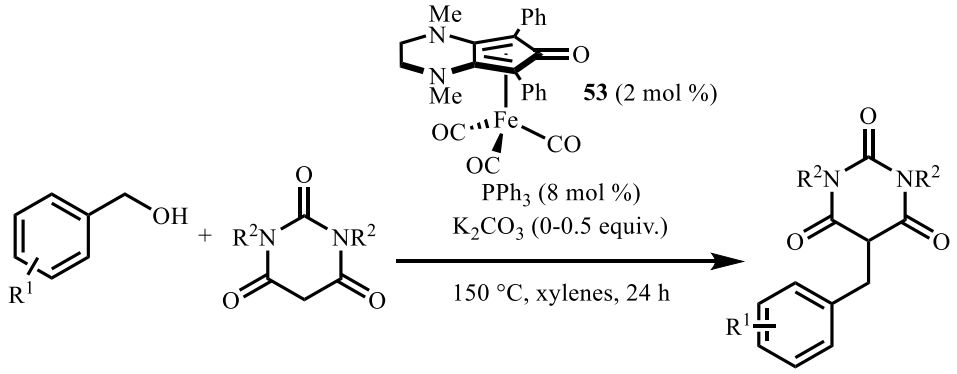
9.3. Scope of the iron catalysed oxindole C-benzylation

9.3.1. General procedure 1



A 10 mL microwave vial equipped with a stirrer bar was charged with oxindole (133 mg, 1.0 mmol), K_2CO_3 (69 mg, 0.5 mmol), PPh_3 (10.5 mg, 0.04 mmol, 4 mol %) and [Fe] precatalyst **53** (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 (1.2 mmol, 1.2 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 $MgSO_4$, filtered and concentrated *in vacuo*.

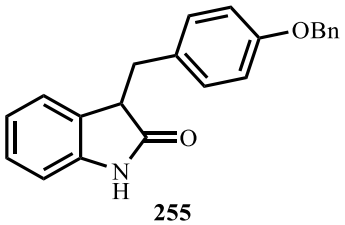
9.3.2. General procedure 2



A 10 mL microwave vial equipped with a stirrer bar was charged with barbituric acid (1.0 mmol), K_2CO_3 (0-0.5 equiv.), PPh_3 (21.0 mg, 0.08 mmol, 8 mol %) and [Fe] precatalyst **53** (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 $MgSO_4$, filtered and concentrated *in vacuo*.

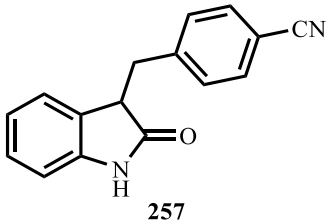
3-(4-(benzyloxy)benzyl)indolin-2-one



255

The title compound was prepared according to general procedure 1 using 4-benzyloxybenzyl alcohol (257 mg, 1.2 mmol). Purification by flash silica chromatography (eluent = 20-35% EtOAc in hexanes, 30 x 170 mm silica) gave the title compound as a pink solid (294 mg, 90%); mp 139-141 °C; R_f = 0.20 (eluent = 30% EtOAc in hexanes); ν_{max} / cm $^{-1}$ (film): 3184, 3130, 3084, 3034, 2895, 2847, 1697, 1618, 1512, 1468, 1234, 1175, 1013, 810, 735, 584; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.93 (1H, dd, *J* 14.0, 9.0, C*H*^{A}H^B), 3.42 (1H, dd, *J* 13.5, 4.5, CH^A*H*^{B}), 3.71 (1H, dd, *J* 8.5, 4.5, C(3)*H*), 5.02 (2H, s, OC*H*$_2$), 6.80 (2H, d, *J* 7.5, Ar*H*), 6.86 (2H, d, *J* 8.5, ArC(3',5')*H*), 6.91 (1H, t, *J* 7.5, Ar*H*), 7.07 (2H, d, *J* 8.0, ArC(2',6')*H*), 7.16 (1H, t, *J* 7.5, Ar*H*), 7.32 (1H, t, *J* 7.0, Ar*H*), 7.35-7.45 (4H, m, Ar*H*), 7.88 (1H, br s, N*H*); **^{13}C NMR (500 MHz, $CDCl_3$)** δ_C: 35.9 (CH*C*H$_2$), 47.8 (*C*HCH$_2$), 70.1 (O*C*H$_2$), 109.8 (Ar*C*), 114.8 (Ar*C*(3',5')), 122.1 (Ar*C*), 125.0 (Ar*C*), 127.6 (Ar*C*), 128.0 (Ar*C*), 128.1 (Ar*C*), 128.7 (Ar*C*), 129.2 (Ar*C*), 130.1 (Ar*C*), 130.6 (Ar*C*(2',6')), 137.1 (Ar*C*), 141.5 (Ar*C*(7a)), 157.7 (Ar*C*(4')), 179.6 (*C*=O); HRMS (**ESI$^+$**) calculated for $[C_{22}H_{20}NO_2]^+$ $(M+H)^+$ m/z : 330.1494, found 330.1493, (-0.3 ppm).

3-(4-cyanobenzyl)indolin-2-one

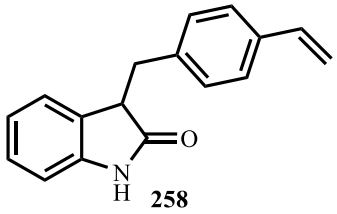


257

The title compound was prepared according to general procedure 1 using 4-(hydroxymethyl)benzonitrile (160 mg, 1.2 mmol). Purification by flash silica chromatography (eluent = 20-35% EtOAc in hexanes, 30 x 180 mm silica) gave the title compound as an off-white solid (208 mg, 83%); mp 132-134 °C; R_f = 0.10 (eluent = 30%

EtOAc in hexanes); ν_{max} / cm $^{-1}$ (film): 3184, 3132, 3086, 3034, 2895, 2843, 2226, 1703, 1616, 1472, 1412, 1337, 1234, 1175, 1103, 835, 756, 652, 583; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 3.17 (1H, dd, *J* 13.5, 7.5, C*H*^{A}H^B), 3.45 (1H, dd, *J* 13.5, 5.0, CH^A*H*^{B}), 3.78 (1H, dd, *J* 8.0, 5.0, C(3)*H*), 6.80 (1H, d, *J* 7.5, ArC(7)*H*), 6.89 (1H, d, *J* 7.5, ArC(4)*H*), 6.97 (1H, t, *J* 7.5, ArC(5)*H*), 7.19 (1H, t, *J* 7.5, ArC(6)*H*), 7.25 (2H, d, *J* 8.0, ArC(2',6')*H*), 7.50 (2H, d, *J* 8.5, ArC(3',5')*H*), 7.98 (1H, br s, N*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 36.5 (*C*H$_2$), 47.0 (Ar*C*(3)), 110.0 (Ar*C*(7)), 110.8 (Ar*C*(4')), 118.9 (*C*≡N), 122.5 (Ar*C*(5)), 124.7 (Ar*C*(4)), 128.1 (Ar*C*(3a)), 128.6 (Ar*C*(6)), 130.4 (Ar*C*(2',6')), 132.2 (Ar*C*(3',5'), 141.4 (Ar*C*(1')), 143.2 (Ar*C*(7a)), 178.6 (*C*=O); HRMS (**ESI$^+$**) calculated for $[C_{16}H_{13}N_2O]^+$ $(M+H)^+$ m/z : 249.1028, found 249.1030, (0.8 ppm).

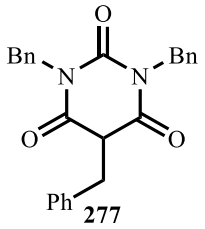
3-(4-vinylbenzyl)indolin-2-one



258

The title compound was prepared according to general procedure 1 using (4-vinylphenyl)methanol (161 mg, 1.2 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 160 mm silica) gave the title compound as an off-white solid (130 mg, 52%); mp 104-106 °C; R_f = 0.33 (eluent = 40% EtOAc in hexanes); ν_{max} / cm $^{-1}$ (film): 3169, 3132, 3073, 3019, 2889, 2832, 1701, 1616, 1510, 1466, 1339, 1236, 988, 907, 839, 764, 748, 662, 584, 490; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 2.96 (1H, dd, *J* 13.5, 9.0, C(3)H-C*H*^{A}H^B), 3.47 (1H, dd, *J* 13.5, 4.5, C(3)H-CH^A*H*^{B}), 3.75 (1H, dd, *J* 9.5, 5.0, C(3)*H*), 5.21 (1H, d, *J* 11.0, CH=C*H*^{A}H^B), 5.71 (1H, d, *J* 17.5, CH=CH^A*H*^{B}), 6.68 (1H, dd, *J* 17.5, 11.0, C*H*=CH$_2$), 6.81 (2H, t, *J* 8.0, Ar*H*), 6.91 (1H, t, *J* 7.5, Ar*H*), 7.07-7.21 (3H, m, Ar*H*), 7.29 (2H, d, *J* 8.0, Ar*H*), 8.25 (1H, br s, N*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 36.5 (CH*C*H$_2$), 47.5 *C*(3)H), 109.7 (Ar*C*), 113.6 (CH=*C*H$_2$), 122.2 (Ar*C*), 125.0 (Ar*C*), 126.3 (Ar*C*), 128.1 (Ar*C*), 129.0 (Ar*C*), 129.8 (Ar*C*), 136.1 (Ar*C*), 136.7 (Ar*C*), 137.5 (*C*H=CH$_2$), 141.3 (Ar*C*(7a)), 179.0 (*C*=O); HRMS (**ESI$^+$**) calculated for $[C_{17}H_{16}NO]^+$ $(M+H)^+$ m/z : 250.1232, found 250.1227, (-2.0 ppm).

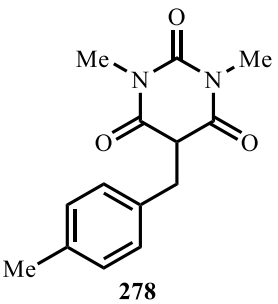
1,3,5-tribenzylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione



277

The title compound was prepared according to general procedure 2 using 1,3-dibenzylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (308 mg, 1.0 mmol), benzyl alcohol (124 µL, 130 mg, 1.2 mmol) and K_2CO_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);[10] R_f = 0.48 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 3061, 3032, 2978, 1678, 1584, 1493, 1433, 1400, 1337, 1273, 1204, 1155, 1084, 1063, 1028, 745, 691, 604, 573, 500; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 3.47 (2H, d, *J* 5.0, CHC*H*$_2$), 3.79 (1H, t, *J* 5.0, C*H*CH$_2$), 4.90 (4H, s, 2xC*H*$_2$N), 6.82 (2H, d, *J* 7.5, (CHCH$_2$)ArC(2,6)*H*), 6.95 (2H, t, *J* 7.5, (CHCH$_2$)ArC(3,5)*H*), 7.12 (1H, t, *J* 7.5, CHCH$_2$ArC(4)*H*), 7.18-7.32 (10H, m, (2xNCH$_2$)ArC(2-6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 37.2 (2x*C*H$_2$N), 45.2 (*C*H$_2$Ph), 50.5 (*C*HCH$_2$), 127.5 (CHCH$_2$Ar*C*(4)), 128.0 (Ar*C*), 128.6 (Ar*C*), 128.7 (CHCH$_2$Ar*C*(3,5)), 129.0 (CHCH$_2$Ar*C*(2,6)), 129.3 (Ar*C*(4')), 135.0 (CH$_2$Ar*C*(1)), 136.0 (2xNCH$_2$Ar*C*(1)), 151.0 (N-(*C*=O)-N), 168.0 (2xBnN-(*C*=O)); HRMS (**ESI$^+$**) calculated for $[C_{25}H_{23}N_2O_3]^+$ $(M+H)^+$ m/z : 399.1709, found 399.1707, (-0.5 ppm).

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

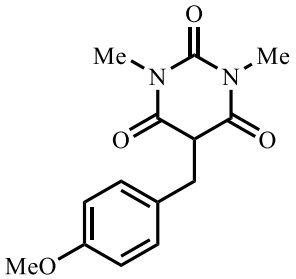


278

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_f = 0.24 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film): 3036, 2986, 2936, 1680, 1653,

1468, 1435, 1383, 1323, 1308, 1287, 1119, 1003, 866, 804, 764, 604, 548, 474; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.28 (3H, s, Ar*C*(4)C*H*$_3$), 3.13 (6H, s, 2xNC*H*$_3$), 3.42 (2H, d, *J* 4.5, CHC*H*$_2$), 3.75 (1H, t, *J* 4.5, C*H*CH$_2$), 6.91 (2H, d, *J* 7.5, ArC(2,6)*H*), 7.03 (2H, d, *J* 7.5, ArC(3,5)*H*); **^{13}C NMR (500 MHz, $CDCl_3$)** δ_C: 21.2 (ArC(4)*C*H$_3$), 28.3 (2xN*C*H$_3$), 37.7 (CH*C*H$_2$), 50.9 (*C*HCH$_2$), 128.9 (Ar*C*), 129.4 (Ar*C*), 132.1 (Ar*C*), 137.6 (Ar*C*), 151.2 (N-(*C*=O)-N), 168.5 (2xMeN-(*C*=O)); HRMS (**EI**$^+$) calculated for $[C_{14}H_{16}N_2O_3]^+$ $(M)^+$ 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

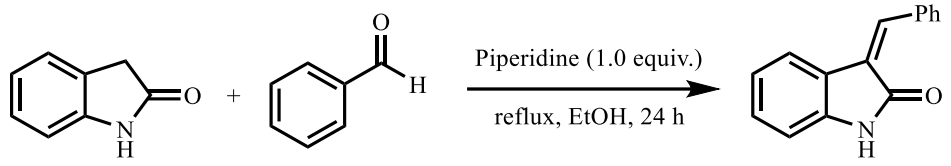


279

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);[11] R_f = 0.16 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 3.14 (6H, s, 2xNC*H*$_3$), 3.42 (2H, d, *J* 4.5, CHC*H*$_2$), 3.74 (1H, t, *J* 4.5, C*H*CH$_2$), 3.76 (3H, s, OC*H*$_3$), 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, $CDCl_3$)** δ_C: 28.4 (2xN*C*H$_3$), 37.3 (*C*H$_2$), 51.0 (*C*HCH$_2$), 55.3 (O*C*H$_3$), 114.1 (Ar*C*(3,5)), 127.1 (Ar*C*(1)), 130.1 (Ar*C*(2,6)), 151.2 (N-(*C*=O)-N), 159.3 (Ar*C*(4)), 168.5 (2xMeN-(*C*=O)). Spectroscopic data in accordance with that stated in the literature.[11]

9.4. Mechanistic invesitgations

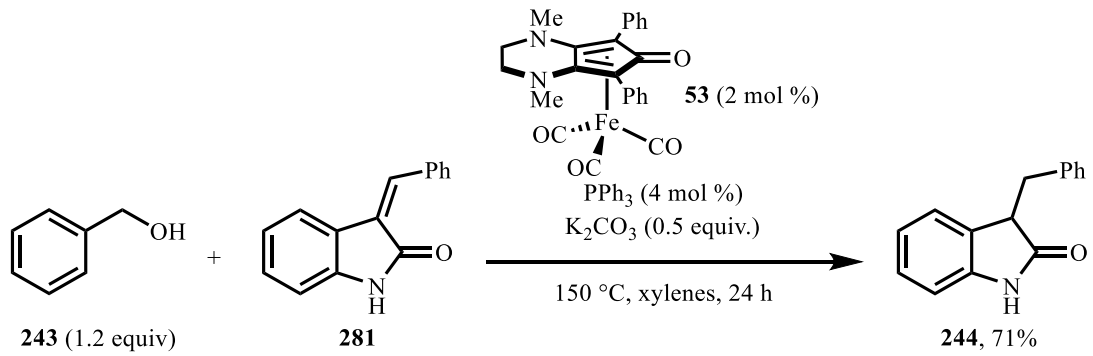
9.4.1. Synthesis of plausible intermediate - 3-benzylideneindolin-2-one



196 **281**

A round-bottomed flask equipped with a magnetic stirrer bar was charged with oxindole (666 mg, 5.0 mmol), EtOH (20 mL), piperidine (494 µL, 426 mg, 5.0 mmol) and benzaldehyde (610 µL, 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 °C (Lit. 164-166 °C);[12] R_f = 0.30 (eluent = 30% EtOAc in hexanes); ν_{max} / cm $^{-1}$ (film): 3186, 3150, 3078, 3021, 2832, 2357, 1705, 1607, 1460, 1327, 1231, 1202, 781, 689, 650, 550; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_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, C*H*=C), 9.03 (1H, br s, N*H*); **^{13}C NMR (500 MHz, $CDCl_3$)** δ_C: 110.3 (Ar*C*(7)), 121.9 (*C*(3)=CHPh), 122.0 (Ar*C*(5')), 123.2 (Ar*C*(4')), 127.6 (Ar*C*(3a)), 128.8 (Ar*C*(3',5')), 129.5 (Ar*C*(2',6')), 129.8 (Ar*C*(4')), 130.0 (Ar*C*(6)), 135.0 (Ar*C*(1')), 137.7 (Ar'*C*H), 141.6 (Ar*C*(7a)), 170.3 (*C*=O); HRMS (**EI$^+$**) calculated for $[C_{15}H_{11}NO]^+$ $(M)^+$ m/z : 221.0841, found 221.0845, (1.8 ppm).

9.4.2. Validation of plausible reaction intermediate



243 (1.2 equiv) **281** **244**, 71%

A 10 mL microwave vial equipped with a stirrer bar was charged with 3-benzylideneindolin-2-one (**281**) (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 **53** (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 (124 µL, 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 µL, 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 ^{1}H NMR. This revealed 71% of **244**.

9.5. References

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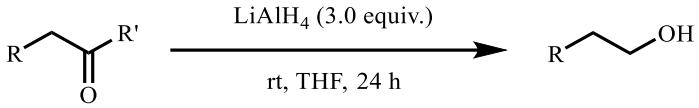
Chapter 10: Experimental

Iron-catalysed borrowing hydrogen *β-C*(sp3)-methylation of alcohols

Table of contents

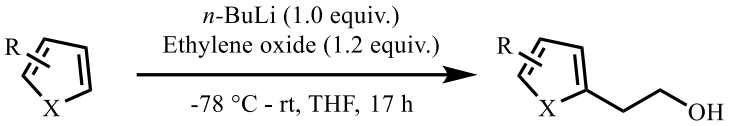
10.1. Substrate synthesis

10.1.1. General procedure 1



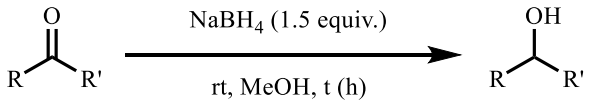
Under nitrogen, a round-bottomed flask equipped a magnetic stirrer bar was charged with $LiAlH_4$ (342 mg, 9.0 mmol) and dry THF (10 mL). The suspension was cooled to 0 °C and was then charged with a solution of carboxylic acid or ethyl ester (3.0 mmol) in dry THF (5 mL). The mixture was left to stir at 0 °C for 10 minutes and at rt for 24 h. The mixture was quenched with H_2O (1 mL), 2 M NaOH (2 mL) and H_2O (3 mL). $MgSO_4$ was added and the suspension was filtered. The filtrate was then concentrated *in vacuo*.

10.1.2. General procedure 2



Under nitrogen, a flame dried round-bottomed flask equipped with a magnetic stirrer bar was charged with heterocycle (1.0 equiv.), THF and *n*-BuLi (1.0 equiv.). The solution was cooled to -15 °C and charged with a solution of ethylene oxide in THF (1.2 equiv.) dropwise. The mixture was left to stir for 1 h at -15 °C, and 16 h at rt. It was then quenched with sat. aq. NH_4Cl and H_2O. The mixture was washed with EtOAc and transferred to a separatory funnel filled with brine. The organic layer was collected, the aqueous layer was washed with EtOAc (x2). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

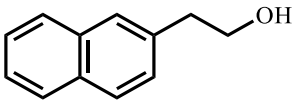
10.1.3. General procedure 3



A round-bottomed flask equipped with a magnetic stirrer bar was charged with ketone (1.0 equiv.) and MeOH. The solution was cooled to 0 °C and was then charged with $NaBH_4$ (340 mg, 9.0 mmol) portion wise. The mixture was left stirring for the specified time at rt. The mixture was quenched with sat. aq. NH_4Cl and H_2O. EtOAc was added and the mixture was transferred to a separatory funnel. The organic layer was collected. The aqueous phase was

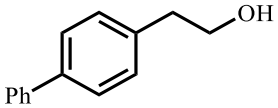
washed EtOAc (x2). The organics were combined, dried over $MgSO_4$ filtered and concentrated *in vacuo*.

2-(naphthalen-2-yl)ethan-1-ol



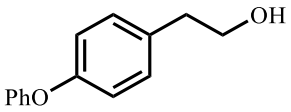
The title compound was prepared according to general procedure 1 using 2-naphthaleneacetic acid (559 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a white solid (438 mg, 86%); mp 68-70 °C (Lit. 65-66 °C);[1] R_f = 0.53 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3285, 3053, 3013, 2940, 2868, 1597, 1504, 1368, 1043, 1020, 827, 743, 731, 484; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.46 (1H, br s, O*H*), 3.04 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.95 (2H, t, *J* 6.5, C*H*$_2$OH), 7.37 (1H, dd, *J* 8.0, 2.0, Ar*H*), 7.41-7.51 (2H, m, Ar*H*), 7.69 (1H, s, ArC(1)*H*), 7.76-7.86 (3H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 39.5 (*C*H$_2$CH$_2$OH), 63.7 (*C*H$_2$OH), 125.6 (Ar*C*), 126.2 (Ar*C*), 127.5 (Ar*C*), 127.6 (Ar*C*), 127.6 (Ar*C*), 127.8 (Ar*C*), 128.4 (Ar*C*), 132.4 (Ar*C*), 133.7 (Ar*C*), 136.1 (Ar*C*); HRMS (**EI$^+$**) calculated for $[C_{12}H_{12}O]^+$ $(M)^+$ m/z : 172.0888, found 172.0892, (+2.3 ppm).

2-([1,1'-biphenyl]-4-yl)ethan-1-ol



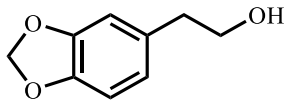
The title compound was prepared according to general procedure 1 using 4-biphenylacetic acid (637 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 10-20% EtOAc in hexanes, 30 x 170 mm silica) gave the title compound as a white solid (330 mg, 56%); mp 96-98 °C (Lit. 96-97.5 °C);[2] R_f = 0.53 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3240, 3063, 3032, 2941, 2874, 1520, 1487, 1404, 1368, 1121, 1059, 1045, 1013, 822, 758, 745, 685, 581; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.43 (1H, br s, O*H*), 2.93 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.92 (2H, t, *J* 6.5, C*H*$_2$OH), 7.28-7.38 (3H, m, Ar*H*), 7.44 (2H, t, *J* 7.0, Ar*H*), 7.56 (2H, d, *J* 7.0, Ar*H*), 7.59 (2H, d, *J* 7.5, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 39.0 (*C*H$_2$CH$_2$OH), 63.8 (*C*H$_2$OH), 127.2 (Ar*C*), 127.3 (Ar*C*), 127.5 (Ar*C*), 128.9 (Ar*C*), 129.6 (Ar*C*), 137.7 (Ar*C*), 139.6 (Ar*C*), 141.1 (Ar*C*); HRMS (**EI$^+$**) calculated for $[C_{14}H_{14}O]^+$ $(M)^+$ m/z : 198.1045, found 198.1045, (+0.0 ppm).

2-(4-phenoxyphenyl)ethan-1-ol



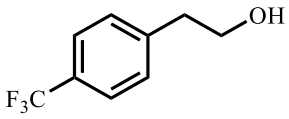
The title compound was prepared according to general procedure 1 using 4-phenoxyphenylacetic acid (685 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 35 x 130 mm silica) gave the title compound as a colourless oil (300 mg, 47%); R_f = 0.16 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3327, 3059, 3030, 2936, 2870, 1587, 1504, 1487, 1229, 1161, 1045, 1015, 868, 829, 750, 692, 507; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.41 (1H, br s, O*H*), 2.86 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.87 (2H, t, *J* 6.5, C*H*$_2$OH), 6.94-6.99 (2H, m, ArC(3,5)*H*), 6.98-7.03 (2H, m, ArC(2',6')*H*), 7.06-7.13 (1H, m, ArC(4')*H*), 7.16-7.22 (2H, m, ArC(2,6)*H*), 7.29-7.38 (2H, m, ArC(3',5')*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 38.6 (*C*H$_2$CH$_2$OH), 63.9 (*C*H$_2$OH), 118.9 (Ar*C*(2',6')), 119.2 (Ar*C*(3,5)), 123.3 (Ar*C*(4')), 129.9 (Ar*C*(3',5')), 130.4 (Ar*C*(2,6)), 133.4 (Ar*C*(1)), 156.0 (Ar*C*), 157.5 (Ar*C*); HRMS (**ESI$^+$**) calculated for $[C_{14}H_{13}O]^+$ $((M-H_2O)+H)^+$ m/z : 197.0966, found 197.0971, (+2.5 ppm).

2-(benzo[d][1,3]dioxol-5-yl)ethan-1-ol



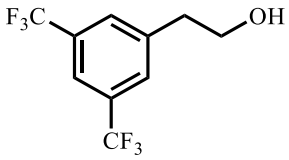
The title compound was prepared according to general procedure 1 using 3,4-(methylenedioxy)phenylacetic acid (541 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 10-15% EtOAc in *n*-pentane, 30 x 180 mm silica) gave the title compound as a pale yellow oil (294 mg, 59%); R_f = 0.50 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3341, 2941, 2882, 2779, 1501, 1483, 1441, 1242, 1184, 1034, 924, 810; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.39 (1H, br s, O*H*), 2.79 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.82 (2H, t, *J* 6.5, C*H*$_2$OH), 5.93 (2H, s, OC*H*$_2$O), 6.68 (1H, d, *J* 8.0, ArC(5)*H*), 6.72 (1H, s, ArC(2)*H*), 6.76 (1H, d, *J* 8.0, ArC(6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 39.0 (*C*H$_2$CH$_2$OH), 63.9 (*C*H$_2$OH), 101.0 (O*C*H$_2$O), 108.5 (Ar*C*), 109.5 (Ar*C*), 122.1 (Ar*C*(6)), 132.3 (Ar*C*(1)), 146.3 (Ar*C*), 147.9 (Ar*C*); HRMS (**EI$^+$**) calculated for $[C_9H_{10}O_3]^+$ $(M)^+$ m/z : 166.0630, found 166.0638, (+4.8 ppm).

2-(4-(trifluoromethyl)phenyl)ethan-1-ol



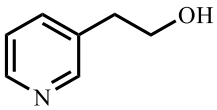
The title compound was prepared according to general procedure 1 using 4-(trifluoromethyl)phenylacetic acid (613 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a colourless oil (428 mg, 75%); R_f = 0.33 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.41 (1H, br s, O*H*), 2.93 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.90 (2H, t, *J* 6.5, CH$_2$OH), 7.36 (2H, d, *J* 8.0, ArC(3,5)*H*), 7.57 (2H, d, *J* 8.0, ArC(2,6)*H*); **^{19}F NMR (471 MHz, CDCl$_3$)** δ_F: -62.4; **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 39.1 (*C*H$_2$CH$_2$OH), 63.4 (*C*H$_2$OH), 124.4 (q, *J* 272.0, *C*F$_3$), 125.6 (q, *J* 3.8, Ar*C*(3,5)), 129.0 (q, *J* 32.5, Ar*C*(4)), 129.5 (Ar*C*(2,6)), 143.0 (m, Ar*C*(1)). Spectroscopic data in accordance with that stated the literature.[3]

2-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol



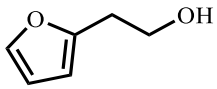
The title compound was prepared according to general procedure 1 using 2-(3,5-bis(trifluoromethyl)phenyl)acetic acid (817 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 5-15% EtOAc in *n*-pentane, 30 x 180 mm silica) gave the title compound as a white solid (459 mg, 59%); mp 54-56 °C (Lit. 54-56 °C);[2] R_f = 0.63 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3343, 2965, 2920, 1624, 1379, 1271, 1157, 1111, 1030, 899, 837, 704, 683; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.47 (1H, br s, O*H*), 3.00 (2H, t, *J* 6.0, C*H*$_2$CH$_2$OH), 3.94 (2H, t, *J* 6.0, CH$_2$OH), 7.71 (2H, s, ArC(2,6)*H*), 7.76 (1H, s, ArC(4)*H*); **^{19}F NMR (471 MHz, CDCl$_3$)** δ_F: -62.8; **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 38.7 (*C*H$_2$CH$_2$OH), 62.9 (*C*H$_2$OH), 120.7 (sept, *J* 3.9, Ar*C*(4)), 123.5 (q, *J* 273.0, 2x*C*F$_3$), 129.4 (m, Ar*C*(2,6)), 131.8 (q, *J* 33.1, Ar*C*(3,5)), 141.6 (m, Ar*C*(1)); HRMS (**EI$^+$**) calculated for $[C_{10}H_8OF_6]^+$ $(M)^+$ m/z : 258.0479, found 258.0477, (-0.8 ppm).

2-(pyridin-3-yl)ethan-1-ol



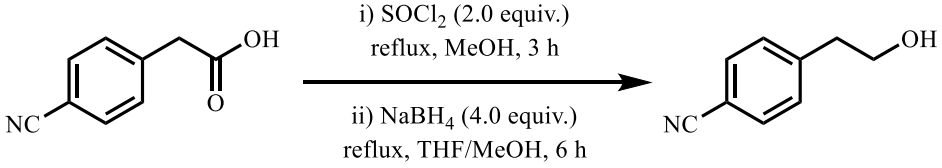
The title compound was prepared according to general procedure 1 using ethyl-3-pyridylacetate (456 µL, 496 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 5% MeOH in CH_2Cl_2, 30 x 150 mm silica) gave the title compound as a pale-yellow oil (247 mg, 66%); R_f = 0.17 (eluent = 50% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.87 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.88 (2H, t, *J* 6.5, CH$_2$OH), 7.23 (1H, ddd, *J* 7.5, 4.5, 1.0, ArC(5)*H*), 7.57 (1H, ddd, *J* 8.0, 2.5, 1.5, ArC(6)*H*), 8.44 (1H, dd, *J* 5.0, 1.5, ArC(4)*H*), 8.50 (1H, d, *J* 2.5, ArC(1)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 36.4 (*C*H$_2$CH$_2$OH), 63.3 (*C*H$_2$OH), 123.6 (Ar*C*(5)), 134.4 (Ar*C*(1)), 136.7 (Ar*C*(2)), 148.0 (Ar*C*), 150.4 (Ar*C*). Spectroscopic data in accordance with that stated in the literature.[3]

2-(furan-2-yl)ethan-1-ol



The title compound was prepared according to general procedure 2 using furan (1.5 mL, 1.4 g, 20.0 mmol), THF (20 mL) and ethylene oxide (8.0 mL, 24.0 mmol, 3.0 M in THF). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 40 x 100 mm silica) gave the title compound as a yellow oil (859 mg, 38%); R_f = 0.41 (eluent = 25% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.59 (1H, m, O*H*), 2.91 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.84-3.92 (2H, m, CH$_2$OH), 6.10-6.13 (1H, m, ArC(2)*H*), 6.31 (1H, dd, *J* 9.0, 1.5, ArC(4)*H*), 7.34 (1H, dd, *J* 2.0, 1.0, ArC(5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 31.7 (*C*H$_2$CH$_2$OH), 61.3 (*C*H$_2$OH), 106.7 (Ar*C*(5)), 110.4 (Ar*C*(4)), 141.7 (Ar*C*(3)), 153.0 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[3]

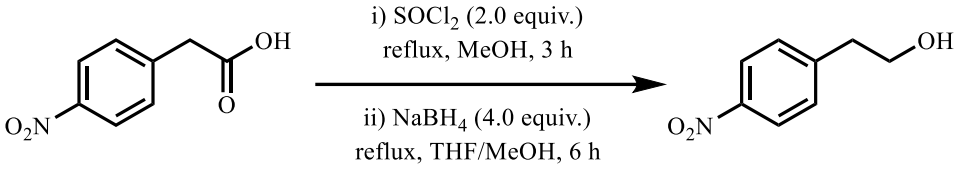
2-(4-cyanophenyl)ethan-1-ol



A round-bottomed flask equipped with a magnetic stirrer bar was charged with 2-(4-cyanophenyl)acetic acid (645 mg, 4.0 mmol) and MeOH (8 mL). The was cooled to 0 °C followed by dropwise addition of $SOCl_2$ (584 µL, 952 mg, 8.0 mmol). The mixture was

heated to reflux for 3 h. It was then cooled and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL), washed with sat. aq. $NaHCO_3$ (25 mL), H_2O (10 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then dissolved in THF (10 mL), cooled to 0°C and was charged with portion wise addition of $NaBH_4$ (605 mg, 16.0 mmol). The suspension was heated to reflux and was charged with MeOH (1 mL). The mixture was left to react at reflux for 6 h. It was then cooled to rt and poured into ice-water (30 mL). This biphasic mixture was transferred to a separatory funnel and washed with EtOAc (30 mL). The organic phase was collected. The aqueous phase was washed with EtOAc (2 x 30 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 20-40% EtOAc in hexanes, 35 x 210 mm silica) gave the title compound as a white solid (371 mg, 63%); mp 55-57 °C; ν_{max} / cm^{-1} (film) 3510, 2957, 2878, 2795, 2237, 1605, 1503, 1404, 1317, 1177, 1069, 1047, 1009, 849, 826, 557; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.42 (1H, br s, O*H*), 2.93 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.86-3.94 (2H, m, C*H*$_2$OH), 7.32-7.38 (2H, m, ArC(2,6)*H*), 7.58-7.63 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 39.3 (*C*H$_2$CH$_2$OH), 63.1 (*C*H$_2$OH), 110.5 (Ar*C*(4)), 119.1 (*C*≡N), 129.9 (Ar*C*(2,6)), 132.4 (Ar*C*(3,5)), 144.6 (Ar*C*(1)); HRMS (**EI$^+$**) calculated for $[C_9H_9NO]^+$ $(M)^+$ m/z : 147.0684, found 147.1685, (+0.7 ppm).

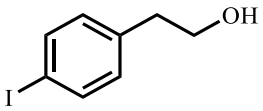
2-(4-nitrophenyl)ethan-1-ol



A round-bottomed flask equipped with a magnetic stirrer bar was charged with 4-nitrophenyl acetic acid (2.7 g, 15.0 mmol) and MeOH (30 mL). The was cooled to 0 °C followed by dropwise addition of $SOCl_2$ (3.6 g, 2.2 mL, 30.0 mmol). The mixture was heated to reflux for 3 h. It was then cooled and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 mL), washed with sat. aq. $NaHCO_3$ (30 mL), H_2O (30 mL), brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was then dissolved in THF (30 mL), cooled to 0°C and was charged with portion wise addition of $NaBH_4$ (2.3 g, 60.0 mmol). The suspension was heated to reflux and was charged with MeOH (1 mL). The mixture was left to react at reflux for 6 h. It was then cooled to rt and poured into ice-water (30 mL). This biphasic mixture was transferred to a separatory funnel and washed with EtOAc (30 mL).

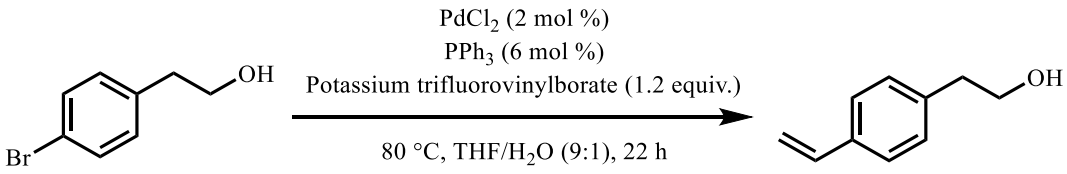
The organic phase was collected. The aqueous phase was washed with EtOAc (2 x 30 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 0-2% MeOH in CH_2Cl_2, 40 x 150 mm silica) gave the title compound as an orange solid (1.7 g, 68%); mp 65-67 °C (Lit. 64 °C);[4] R_f = 0.30 (eluent = 50% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.47 (1H, br s, O*H*), 2.98 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.93 (2H, t, *J* 6.0, C*H*$_2$OH), 7.41 (2H, d, *J* 7.5, ArC(2,6)*H*), 8.17 (2H, d, *J* 7.5, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 39.0 (*C*H$_2$CH$_2$OH), 63.0 (*C*H$_2$OH), 123.8 (Ar*C*(3,5)), 130.0 (Ar*C*(2,6)), 146.9 (Ar*C*(1)), 146.9 (Ar*C*(4)). Spectroscopic data in accordance with that stated in the literature.[3]

2-(4-iodophenyl)ethan-1-ol



The title compound was prepared according to general procedure 1 using 4-iodophenylacetic acid (786 mg, 3.0 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in pet. ether (40-60 °C), 30 x 200 mm silica) gave the title compound as a white solid (485 mg, 65%); mp 50-52 °C (Lit. 48-49 °C);[5] R_f = 0.50 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3375, 3318, 2953, 2930, 2862, 1479, 1364, 1045, 1005, 833, 795, 503; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.37 (1H, br s, O*H*), 2.81 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.84 (2H, t, *J* 6.5, C*H*$_2$OH), 6.99 (2H, d, *J* 7.5, Ar*H*), 7.63 (2H, d, *J* 7.0, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 38.8 (*C*H$_2$CH$_2$OH), 63.5 (*C*H$_2$OH), 91.8 (Ar*C*(4)), 131.2 (Ar*C*), 137.7 (Ar*C*), 138.4 (Ar*C*(1)); HRMS (**EI$^+$**) calculated for $[C_8H_9OI]^+$ $(M)^+$ m/z : 247.9698, found 247.9704, (+2.4 ppm).

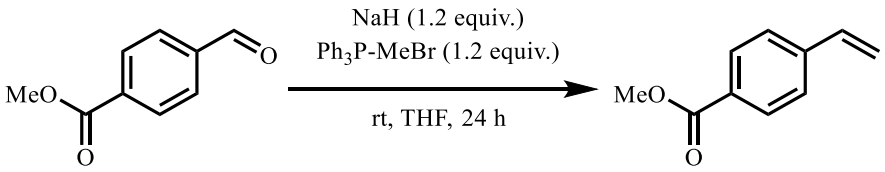
2-(4-vinylphenyl)ethan-1-ol



A 50 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with Cs_2CO_3 (4.9 g, 15.0 mmol), PPh_3 (78.9 mg, 0.3 mmol), $PdCl_2$ (17.7 mg, 0.1 mmol) and potassium trifluorovinylborate (804 mg, 6.0 mmol). To the mixture was then added 2(4-bromophenyl)ethan-1-ol (1.1 g, 5.0 mmol) and solution of THF and H_2O (9:1, 10 mL). The mixture was heated at 80 °C for 22 h. It was then cooled, diluted with THF, dried over

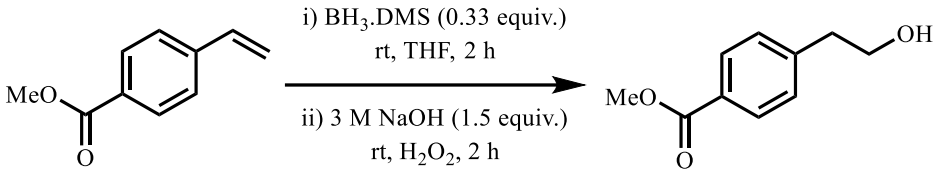
$MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 35 x 100 mm silica) gave the title compound as a pale yellow oil (609 mg, 82%); R_f = 0.53 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3321, 3088, 3005, 2936, 2874, 1630, 1508, 1406, 1113, 1045, 1016, 991, 905, 847, 829, 556; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.40 (1H, br s, O*H*), 2.87 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.86 (2H, t, *J* 6.5, C*H*$_2$OH), 5.22 (1H, dd, *J* 10.5, 1.0, CH=C*H*^{A}H^B), 5.72 (1H, dd, *J* 17.5, 1.0, CH=CH^A*H*^{B}), 6.70 (1H, dd, *J* 17.5, 10.5, C*H*=CH$_2$), 7.20 (2H, d, *J* 8.0, ArC(2,6)*H*), 7.37 (2H, d, *J* 8.0, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 39.1 (*C*H$_2$CH$_2$OH), 63.8 (*C*H$_2$OH), 113.6 (CH=*C*H$_2$), 126.6 (Ar*C*), 129.3 (Ar*C*), 136.1 (Ar*C*), 136.6 (*C*H=CH$_2$), 138.3 (Ar*C*); HRMS (**EI$^+$**) calculated for $[C_{10}H_{12}O]^+$ $(M)^+$ m/z : 148.0888, found 148.0885, (-2.0 ppm).

Methyl 4-vinylbenzoate



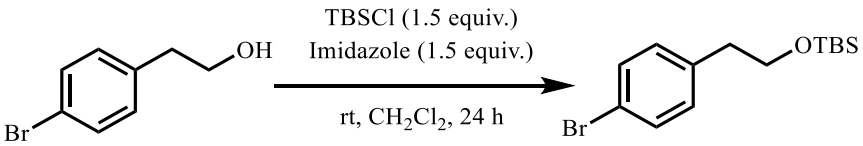
A round-bottomed flask equipped with a magnetic stirrer bar was charged with methyltriphenylphosphonium iodide (4.9 g, 12.0 mmol) and dry THF (40 mL). The suspension was then cooled to 0 °C and charged with NaH (480 mg, 12.0 mmol, 60% suspension in mineral oil). The suspension was left stirring for 30 mins at rt and was then charged with methyl 4-formylbenzoate (1.6 g, 10.0 mmol). The mixture was left to react for 24 h at rt and was quenched with H_2O (5 mL). The mixture was transferred to a separatory filled with brine (50 mL) and EtOAc (50 mL). The organic layer was collected. The aqueous layer was washed with EtOAc (2 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% Et_2O in hexanes, 40 x 160 mm silica) gave the title compound as a white solid (1.1 g, 70%); mp 32-34 °C (Lit. 33-34 °C);[6] R_f = 0.53 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 3.91 (3H, s, OC*H*$_3$), 5.38 (1H, dd, *J* 11.0, 1.0, CH=C*H*^{A}H^B), 5.86 (1H, dd, *J* 18.0, 1.0, CH=CH^A*H*^{B}), 6.75 (1H, dd, *J* 17.5, 11.0, C*H*=CH$_2$), 7.44-7.48 (2H, m, ArC(3,5)*H*), 7.97-8.02 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 52.2 (O*C*H$_3$), 116.6 (*C*H$_2$), 126.3 (Ar*C*(3,5)), 129.4 (Ar*C*(1)), 130.0 (Ar*C*(2,6)), 136.2 (*C*H=CH$_2$), 142.1 (Ar*C*(4)), 167.0 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[7]

Methyl 4-(2-hydroxyethyl)benzoate



Under nitrogen, a round-bottomed flask equipped with a magnetic stirrer bar was charged with methyl 4-vinylbenzoate (487 mg, 3.0 mmol) and dry THF (3 mL). The solution was cooled to 0 °C and was then charged with borane-dimethyl sulphide complex (0.5 mL, 1.0 mmol, 2 M in THF). The reaction was warmed to room temperature and was left stirring for 2 h. H_2O (2 mL) was added to dilute the solution followed by dropwise addition of 3 M NaOH (1.5 mL) and 30% w/w H_2O_2 (2.5 mL). The mixture was allowed to stir for another 2 h at rt and was then extracted with CH_2Cl_2 (25 mL). The organic layer was collected. The aqueous phase was washed with CH_2Cl_2 (2 x 25 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10-50% EtOAc in hexanes, 30 x 160 mm silica) gave the title compound as a colourless oil (139 mg, 26%); R_f = 0.10 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.40 (1H, br s, O*H*), 2.93 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.87-3.93 (5H, m, OC*H*$_3$, C*H*$_2$OH), 7.28-7.33 (2H, m, ArC(2,6)*H*), 7.96-8.01 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 39.3 (*C*H$_2$CH$_2$OH), 52.2 (O*C*H$_3$), 63.4 (*C*H$_2$OH), 128.6 (Ar*C*(4)), 129.2 (Ar*C*), 130.0 (Ar*C*), 144.2 (Ar*C*(1)), 167.2 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[8]

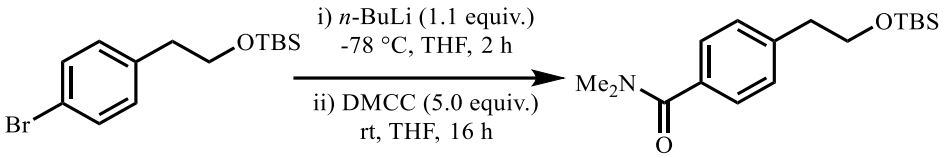
(4-bromophenethoxy)(*tert*-butyl)dimethylsilane



A round-bottomed flask equipped with a magnetic stirrer bar was charged with 4-bromophenethyl alcohol (2.1 mL, 3.0 g, 15.0 mmol) and dry CH_2Cl_2 (40 mL). The mixture was then charged with TBSCl (3.4 g, 22.5 mmol) and imidazole (1.5 g, 22.5 mmol). The mixture was left stirring for 24 h. The imidazolium hydrochloride was filtered, and the filtrate concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 2% Et_2O in hexanes, 40 x 120 mm silica) gave the title compound as a colourless oil (4.7 g, 99%); R_f = 0.23 (eluent = 100% hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: -0.03 (6H, s, Si(C*H*$_3$)$_2$), 0.86 (9H, s, Si(C(C*H*$_3$)$_3$))), 2.76 (2H, t, *J* 7.0, C*H*$_2$CH$_2$O), 3.78 (2H, t, *J* 7.0, C*H*$_2$O), 7.05-

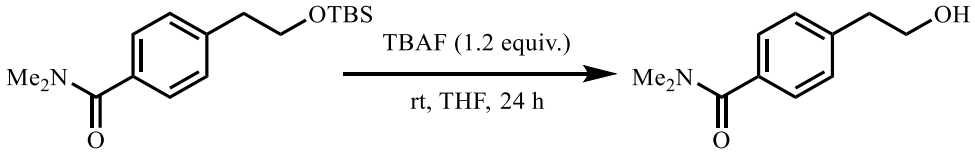
7.11 (2H, m, ArC(2,6)*H*), 7.37-7.42 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: -5.29 (Si(*C*H_3)$_2$), 18.5 (Si(*C*(CH$_3$)$_3$))), 26.0 ((Si(C(*C*H$_3$)$_3$))), 39.1 (*C*H_2CH_2O), 64.2 (*C*H_2O), 120.0 (Ar*C*(4)), 131.1 (Ar*C*), 131.4 (Ar*C*), 138.5 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[9]

4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-*N*,*N*-dimethylbenzamide



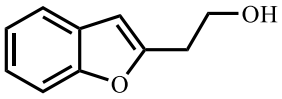
Under nitrogen, a 100 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with (4-bromophenethoxy)(*tert*-butyl)dimethylsilane (1.6 g, 5.0 mmol) and dry THF (50 mL). The solution was cooled to -78 °C followed by the addition of *n*-BuLi (2.3 mL, 5.5 mmol, 2.35 M in hexanes). The mixture was kept at -78 °C for 2h and was then charged with a solution of dimethylcarbamyl chloride (2.3 mL, 2.7 g, 25.0 mmol). The mixture was kept at -78 °C for 30 min and left stirring at rt for 16 h. H_2O (2 mL) was added and the mixture was transferred to a separatory funnel filled with brine. The organic layer was collected. The aqueous phase was washed with EtOAc (2 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 2-50% EtOAc in hexanes, 35 x 170 mm silica gave the title compound as a pale yellow oil (370 mg, 24%); R_f = 0.10 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 2949, 2934, 2893, 2862, 1638, 1612, 1491, 1470, 1389, 1252, 1092, 1078, 866, 833, 810, 772, 563; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: -0.03 (6H, s, Si(C*H*$_3$)$_2$), 0.85 (9H, s, Si(C(C*H*$_3$)$_3$))), 2.83 (2H, t, *J* 7.0, C*H*$_2$CH$_2$O), 2.98 (3H, br s, NC*H*$_3$), 3.10 (3H, br s, NC*H*$_3$), 3.80 (2H, t, *J* 7.0, C*H*$_2$O), 7.20-7.25 (2H, m, Ar*H*), 7.31-7.36 (2H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: -5.3 (Si(*C*H$_3$)$_2$), 18.5 (Si(*C*(CH$_3$)$_3$))), 26.0 (Si(C(*C*H$_3$)$_3$))), 35.5 (NCH$_3$), 39.5 (*C*H_2CH_2O), 39.7 (NCH$_3$), 64.3 (*C*H_2O), 127.2 (Ar*C*), 129.2 (Ar*C*), 134.2 (Ar*C*), 141.1 (Ar*C*), 171.9 (*C*=O); HRMS (**ESI$^+$**) calculated for [$C_{17}H_{30}NO_2Si$]$^+$ (M+H)$^+$ m/z : 308.2046, found 308.2053, (+2.3 ppm).

4-(2-hydroxyethyl)-*N*,*N*-dimethylbenzamide



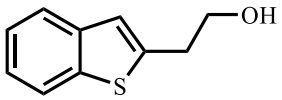
A 25 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-*N*,*N*-dimethylbenzamide (365 mg, 1.2 mmol), THF (6 mL) and TBAF (1.4 mL, 1.44 mmol, 1 M in THF). The mixture was left stirring at rt for 24 h and was then concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% MeOH in Et_2O, 30 x 100 mm silica gave the title compound as a pale-yellow oil (209 mg, 91%); R_f = 0.26 (eluent = 100% EtOAc); ν_{max} / cm^{-1} (film) 3393, 2934, 2859, 1603, 1566, 1489, 1449, 1395, 1269, 1086, 1047, 1020, 831, 754, 563; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.59 (1H, br s, O*H*), 2.89 (2H, t, *J* 6.5, CH_2CH_2OH), 2.99 (3H, br s, NCH_3), 3.11 (3H, br s, NCH_3), 3.86 (2H, t, *J* 6.5, CH_2OH), 7.22-7.29 (2H, m, Ar*H*), 7.34-7.40 (2H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 35.5 (NCH_3), 39.2 (*C*H_2CH_2OH), 39.8 (NCH_3), 63.6 (*C*H_2OH), 127.6 (Ar*C*), 129.1 (Ar*C*), 134.7 (Ar*C*), 140.4 (Ar*C*), 171.7 (*C*=O); HRMS (**ESI$^+$**) calculated for $[C_{11}H_{16}NO_2]^+$ $(M+H)^+$ m/z : 194.1181, found 194.1183, (+1.0 ppm).

2-(benzofuran-2-yl)ethan-1-ol



The title compound was prepared according to general procedure 2 using benzofuran (1.7 mL, 1.8 g, 15.0 mmol) and ethylene oxide (7.2 mL, 18.0 mmol, 2.5 M in THF). Purification by flash silica chromatography (eluent = 10-15% EtOAc in *n*-pentane, 50 x 150 mm silica) gave the title compound as a yellow oil (1.1 g, 47%); R_f = 0.57 (eluent = 50% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.73 (1H, br s, O*H*), 3.05 (2H, t, *J* 6.0, CH_2CH_2OH), 3.99 (2H, t, *J* 6.0, CH_2OH), 6.51 (1H, s, ArC(3)*H*), 7.20 (1H, t, *J* 7.5, Ar*H*), 7.24 (1H, t, *J* 7.5, Ar*H*), 7.43 (1H, d, *J* 8.0, Ar*H*), 7.51 (1H, d, *J* 7.5, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 32.2 (*C*H_2CH_2OH), 60.9 (*C*H_2OH), 103.8 (Ar*C*(3)), 111.0 (Ar*C*(7)), 120.6 (Ar*C*), 122.8 (Ar*C*), 123.7 (Ar*C*), 128.8 (Ar*C*(3a)), 154.9 (Ar*C*), 156.1 (Ar*C*). Spectroscopic data in accordance with that stated in the literature.[10]

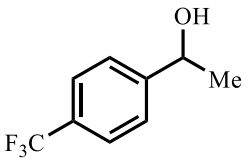
2-(benzo[b]thiophen-2-yl)ethan-1-ol



The title compound was prepared according to general procedure 2 using thianaphthalene (2.0 g, 15.0 mmol) and (7.2 mL, 18.0 mmol, 2.5 M in THF). Purification by flash silica chromatography (eluent = 10-20% EtOAc in *n*-pentane, 50 x 150 mm silica) gave the title

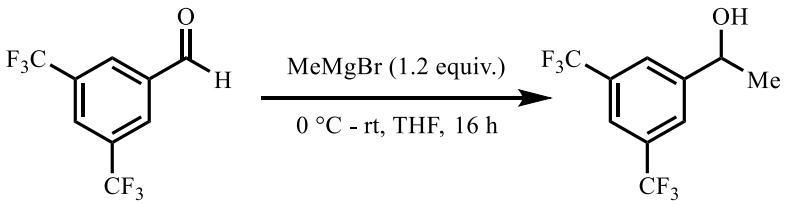
compound as a white solid (2.1 g, 80%); mp 84-86 °C (Lit. 795-80.5 °C);[11] R_f = 0.60 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3281, 3063, 2870, 1456, 1435, 1414, 1364, 1155, 1065, 1047, 1020, 880, 837, 739, 725; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.66 (1H, br s, O*H*), 3.16 (2H, t, *J* 6.5, C*H*$_2$CH$_2$OH), 3.95 (2H, q, *J* 5.5, C*H*$_2$OH), 7.11 (1H, s, ArC(3)*H*), 7.28 (1H, t, *J* 7.5, Ar*H*), 7.33 (1H, t, *J* 7.5, Ar*H*), 7.70 (1H, d, *J* 7.5, Ar*H*), 7.78 (1H, d, *J* 7.5, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 34.3 (*C*H$_2$CH$_2$OH), 63.2 (*C*H$_2$OH), 122.3 (Ar*C*), 122.4 (Ar*C*), 123.0 (Ar*C*), 123.9 (Ar*C*), 124.4 (Ar*C*), 139.7 (Ar*C*), 140.2 (Ar*C*), 142.0 (Ar*C*). HRMS (**EI$^+$**) calculated for $[C_{10}H_{10}OS]^+$ $(M)^+$ m/z : 178.0452, found 178.0450, (-1.1 ppm).

1-(4-(trifluoromethyl)phenyl)ethan-1-ol



The title compound was prepared according to general procedure 3 using 4'-(trifluoromethyl)acetophenone (753 mg, 4.0 mmol), $NaBH_4$ (227 mg, 6.0 mmol) and MeOH (10 mL) for 3 h. Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 30 x 110 mm silica) gave the title compound as a colourless oil (569 mg, 75%); R_f = 0.28 (eluent = 10% EtOAc in *n*-pentane); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.51 (3H, d, *J* 6.5, CHC*H*$_3$), 1.87 (1H, d, *J* 3.0, O*H*), 4.97 (1H, dq, *J* 6.5, 3.0, C*H*OH), 7.46-7.52 (2H, m, ArC(2,6)*H*), 7.58-7.64 (2H, m, ArC(3,5)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -62.5; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 25.6 (CH*C*H$_3$), 70.0 (*C*HCH$_3$), 124.3 (q, *J* 272.0, *C*F$_3$), 125.6 (q, *J* 3.8, Ar*C*(3,5)), 125.8 (Ar*C*(2,6)), 129.8 (q, *J* 32.4, Ar*C*(4)), 149.8 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[12]

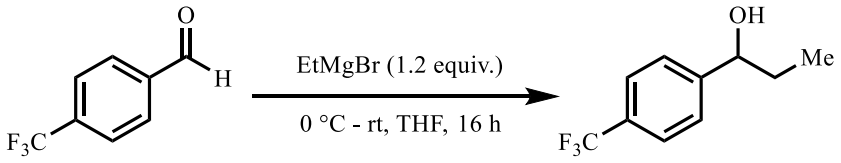
1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol



A flame dried round-bottomed flask equipped with a magnetic stirrer bar was charged with 3',5'-bis(trifluoromethyl)benzaldehyde (660 µL, 969 mg, 4.0 mmol) and THF (6 mL). The solution was cooled to 0 °C and was then charged with MeMgBr (1.6 mL, 4.8 mmol, 3 M in

Et_2O). The mixture was then left to reach rt and was left to stir for 16 h. The mixture was quenched with sat aq. NH_4Cl (2 mL) and H_2O (5 mL). EtOAc (25 mL) was added and the mixture was transferred to a separatory funnel. The organic layer was collected. The aqueous layer was washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% EtOAc in *n*-pentane, 30 x 150 mm silica) gave the title compound as a white solid (420 mg, 41%); mp 72-75 °C (Lit. 74 °C);[13] R_f = 0.41 (eluent = 10% EtOAc in *n*-pentane); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.55 (3H, d, *J* 6.5, CHC*H*$_3$), 1.99 (1H, br s, O*H*), 5.05 (1H, q, *J* 6.5, C*H*CH$_3$), 7.79 (1H, s, ArC(4)*H*), 7.82-7.87 (2H, s, ArC(2,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -62.5; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 25.8 (CH*C*H$_3$), 69.4 (*C*HCH$_3$), 121.5 (m, Ar*C*(4)), 123.5 (q, *J* 271.0, *C*F$_3$), 125.8 (m, Ar*C*(2,6)), 131.9 (q, *J* 33.3, Ar*C*(3,5)), 148.3 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[14]

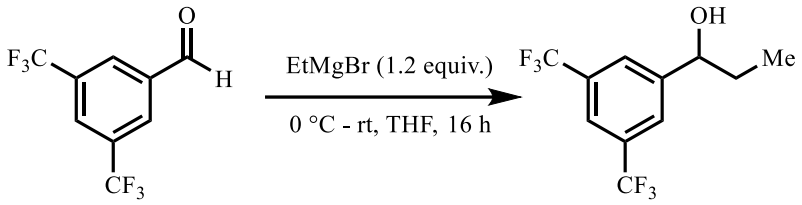
1-(4-(trifluoromethyl)phenyl)propan-1-ol



A flame dried round-bottomed flask equipped with a magnetic stirrer bar was charged with 4-(trifluoromethyl)benzaldehyde (410 µL, 522 mg, 3.0 mmol) and THF (6 mL). The solution was cooled to 0 °C and was then charged with EtMgBr (1.2 mL, 3.6 mmol, 3 M in Et_2O). The mixture was then left to reach rt and was left to stir for 16 h. The mixture was quenched with sat aq. NH_4Cl (2 mL) and H_2O (5 mL). EtOAc (25 mL) was added and the mixture was transferred to a separatory funnel. The organic layer was collected. The aqueous layer was washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a colourless oil (344 mg, 56%); R_f = 0.38 (eluent = 10% EtOAc in *n*-pentane); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.93 (3H, t, *J* 7.5, C*H*$_3$), 1.70-1.87 (2H, m, C*H*$_2$), 1.89-1.94 (1H, m, O*H*), 4.69 (1H, dt, *J* 6.5, 3.5, C*H*OH), 7.46 (2H, d, *J* 8.0, ArC(2,6)*H*), 7.61 (2H, d, *J* 8.0, ArC(3,5)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -62.5; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 10.0 (*C*H$_3$), 32.2 (*C*H$_2$), 75.4 (*C*HOH), 124.3 (q, *J* 272.0, *C*F$_3$), 125.5 (q, *J* 3.8, Ar*C*(3,5)), 126.4 (Ar*C*(2,6)), 129.8

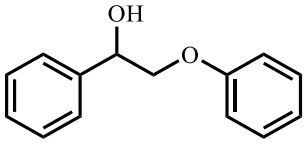
(q, *J* 32.4, Ar*C*(4)), 148.6 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[15]

1-(3',5'-bis(trifluoromethyl)phenyl)propan-1-ol



A flame dried round-bottomed flask equipped with a magnetic stirrer bar was charged with 3,5-(bistrifluoromethyl)benzaldehyde (494 µL, 726 mg, 3.0 mmol) and THF (6 mL). The solution was cooled to 0 °C and was then charged with EtMgBr (1.2 mL, 3.6 mmol, 3 M in Et_2O). The mixture was then left to reach rt and was left to stir for 16 h. The mixture was quenched with sat aq. NH_4Cl (2 mL) and H_2O (5 mL). EtOAc (25 mL) was added and the mixture was transferred to a separatory funnel. The organic layer was collected. The aqueous layer was washed with EtOAc (2 x 25 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a white solid (349 mg, 43%); mp 94-96 °C; R_f = 0.55 (eluent = 10% EtOAc in *n*-pentane); ν_{max} / cm^{-1} (film) 3277, 3192, 1626, 1464, 1382, 1350, 1275, 1159, 1113, 1049, 982, 937, 901, 862, 843, 739, 704, 683, 671; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.97 (3H, t, *J* 7.5, C*H*$_3$), 1.75-1.87 (2H, m, C*H*$_2$), 2.03 (1H, d, *J* 3,5, O*H*), 4.78 (1H, dt, *J* 6.5, 3.5, C*H*OH), 7.79 (1H, s, ArC(4)*H*), 7.82 (2H, s, ArC(2,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -62.8; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 9.9 (*C*H$_3$), 32.4 (*C*H$_2$), 74.8 (*C*HOH), 121.5 (m, Ar*C*(4)), 123.5 (q, *J* 273, *C*F$_3$), 126.3 (m, Ar*C*(2,6)), 131.8 (q, *J* 33.4, Ar*C*(3,5)), 147.2 (Ar*C*(1)); HRMS (**EI**$^+$) calculated for $[C_{11}H_{10}OF_6]^+$ $(M)^+$ m/z : 272.0636, found 272.0627 (-3.3 ppm).

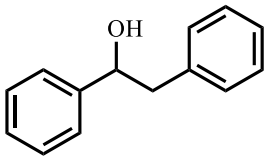
2-phenoxy-1-phenylethan-1ol



The title compound was prepared according to general procedure 3 using 2-phenoxy-1-phenylethan-1-one (1.3 g, 6.0 mmol) and MeOH (15 mL) for 16 h. Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 40 x 120 mm silica) gave the title compound as a white solid (1.2 g, 91%); mp 61-63 °C (Lit. 62-64 °C);[16] R_f = 0.36 (eluent =

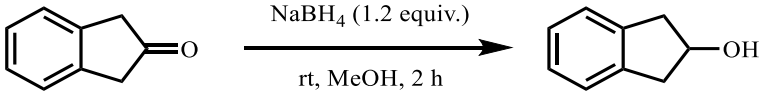
20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.81 (1H, s, O*H*), 4.02 (1H, dd, *J* 9.5, 9.0, C*H*^{A}H^{B}), 4.12 (1H, dd, *J* 9.5, 3.0, CH^{A}*H*^{B}), 5.14 (1H, dd, *J* 9.0, 3.0, C*H*OH), 6.90-6.96 (2H, m, ArC(2',6')*H*), 6.96-7.02 (1H, m, ArC(4')*H*), 7.27-7.33 (2H, m, ArC(3',5')*H*), 7.32-7.38 (1H, m, ArC(4)*H*), 7.38-7.44 (2H, m, ArC(3,5)*H*), 7.44-7.40 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 72.7 (*C*HOH), 73.4 (*C*H_2), 114.8 (Ar*C*(2',6')), 121.4 (Ar*C*(4')), 126.4 (Ar*C*), 128.3 (Ar*C*(4)), 128.7 (Ar*C*), 129.7 (Ar*C*), 139.8 (Ar*C*(1)), 158.5 (Ar*C*(1')); Spectroscopic data in accordance with that stated in the literature.[16]

1,2-diphenylethan-1-ol



The title compound was prepared according to general procedure 3 using deoxybenzoin (2.0 g, 10.0 mmol) and MeOH (25 mL) for 16 h. Purification by recrystallisation gave the title compound as a white solid (1.9 g, 95%); mp 62-64 °C (hexanes) (Lit. 65-66 °C);[17] R_f = 0.25 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.87 (1H, s, O*H*), 2.89 (1H, dd, *J* 13.5, 8.5, C*H*^{A}H^{B}), 2.95, (1H, dd, *J* 13.5, 5.0, CH^{A}*H*^{B}), 4.80 (1H, dd, *J* 8.5, 5.5, C*H*OH), 7.05-7.30 (10H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 46.2 (*C*H_2), 75.5 (*C*HOH), 126.0 (Ar*C*), 126.8 (Ar*C*), 127.7 (Ar*C*), 128.5 (Ar*C*), 128.6 (Ar*C*), 129.6 (Ar*C*), 138.2 (Ar*C*), 143.9 (Ar*C*). Spectroscopic data in accordance with that stated in the literature.[17]

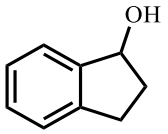
2,3-dihydro-1*H*-inden-2-ol



A 50 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with 2-indanone (661 mg, 5.0 mmol) and MeOH (25 mL). The solution was cooled to 0 °C and was charged with $NaBH_4$ (227 mg, 6.0 mmol). The mixture was left stirring for 2 h at rt. The mixture was quenched with sat. aq. NH_4Cl (2 mL) and H_2O (5 mL). EtOAc (25 mL) was added and the mixture was transferred to a separatory funnel. The organic layer was collected. The aqueous phase was washed EtOAc (2 x 25 mL). The organics were combined, dried over $MgSO_4$ filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 50% EtOAc in hexanes, 30 x 110 mm silica) gave the title

compound as a white solid (592 mg, 88%); mp 67-69 °C (Lit. 67-68 °C);[18] R_f = 0.07 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3260, 2932, 1479, 1458, 1423, 1341, 1308, 1269, 1198, 1032, 1020, 051, 926, 735, 542, 417; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.63 (1H, d, *J* 5.0, O*H*), 2.92 (2H, dd, *J* 16.5, 3.0, 2xC*H*^{A}H^B), 3.22 (2H, dd, *J* 16.5, 6.0, 2xCH^A*H*^{B}), 4.66-4.76 (1H, m, C*H*OH), 7.14-7.21 (2H, m, Ar*H*), 7.21-7.29 (2H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 42.8 (2x*C*H$_2$), 73.3 (*C*HOH), 125.1 (Ar*C*), 126.8 (Ar*C*), 140.9, (Ar*C*(1,2)); HRMS (**EI$^+$**) calculated for $[C_9H_{10}O]^+$ $(M)^+$ m/z: 134.0732, found 134.0732, (+0.0 ppm).

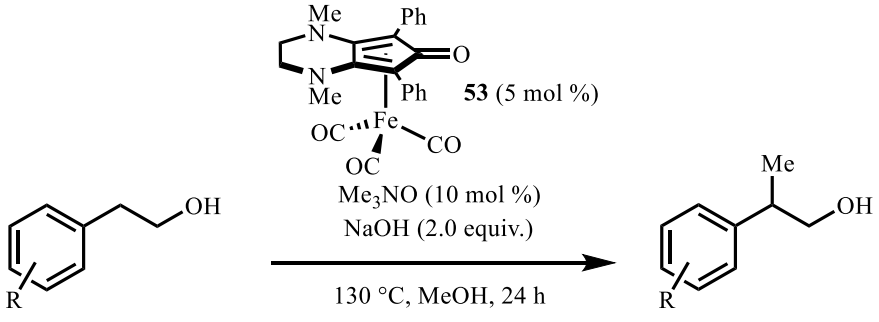
2,3-dihydro-1*H*-inden-1-ol



The title compound was prepared according to general procedure 3 using 1-indanone (925 mg, 7.0 mmol) and MeOH (20 mL) for 24 h. Purification by flash silica chromatography (eluent = 20% Et_2O in cyclohexane, 30 x 110 mm silica) gave the title compound as a white solid (780 mg, 83%); mp 51-53 °C (Lit. 52 °C);[19] R_f = 0.12 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.73 (1H, d, *J* 6.5, O*H*), 1.90-2.00 (1H, m, CHC*H*^{A}H^B), 2.45-2.55 (1H, m, CHCH^A*H*^{B}), 2.78-2.88 (1H, m, Ar-C*H*^{A}H^B), 3.07 (1H, ddd, *J* 16.0, 8.5, 5.0, Ar-CH^A*H*^{B}), 5.25 (1H, q, *J* 6.5, C*H*OH), 7.21-7.30 (3H, m, Ar*H*), 7.39-7.45 (1H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 29.9 (*C*H$_2$CH$_2$CHOH), 36.1 (*C*H$_2$CHOH), 76.6 (*C*HOH), 124.3 (Ar*C*), 125.0 (Ar*C*), 126.8 (Ar*C*), 128.5 (Ar*C*), 143.3 (Ar*C*), 145.1 (Ar*C*). Spectroscopic data in accordance with that stated in the literature.[20]

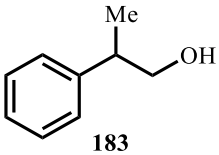
10.2. Substrate scope

10.2.1. General procedure 4



A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with NaOH (40 mg, 1.0 mmol), $Me_3NO.2H_2O$ (5.6 mg, 0.1 mmol, 10 mol %), [Fe] precatalyst **53** (11.4 mg, 0.025 mmol, 5 mol %), MeOH (1 mL) and alcohol (0.5 mmol). The vial was sealed with a cap and was left to stir at 130 °C for 24 h. It was then cooled, treated with sat. aq. NH_4Cl (0.5 mL) and H_2O (0.5 mL), washed with EtOAc (15 mL) and transferred to a separatory funnel filled with brine (15 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 15 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

2-phenylpropan-1-ol



183

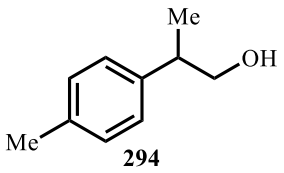
The title compound was prepared according to general procedure 4 using 2-phenylethanol (60 µL, 61 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (51 mg, 75%); R_f = 0.28 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.29 (3H, d, *J* 7.0, CHC*H*$_3$), 2.96 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.71 (2H, d, *J* 7.0, C*H*$_2$), 7.21-7.27 (3H, m, ArC(2,4,6)*H*), 7.30-7.37 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.7 (CH*C*H$_3$), 42.6 (*C*HCH$_3$), 68.9 (*C*H$_2$OH), 126.8 (Ar*C*(4)), 127.6 (Ar*C*(2,6)), 128.8 (Ar*C*(3,5)), 143.8 (Ar*C*(1)); Spectroscopic data in accordance with that stated in the literature.[21]

10 mmol Scale

An ACE pressure tube rated at 150 PSI was charged with NaOH (800 mg, 20.0 mmol), $Me_3NO.2H_2O$ (111 mg, 1.0 mmol) and [Fe] precatalyst **53** (228 mg, 0.5 mmol). The vessel was charged with MeOH (20 mL) and 2-phenylethanol (1.2 mL, 1.2 g, 10.0 mmol). It was sealed with the appropriate screw top cap, placed in an oil bath behind a blast shield, and the mixture was left to react at 130 °C for 24 h. It was then cooled and charged with sat aq. NH_4Cl (10 mL), EtOAc (20 mL) and H_2O (10 mL). The mixture was transferred to a separatory funnel filled with brine (50 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 50 mL). The organics were combined, dried over $MgSO_4$,

filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-10% EtOAc in pet. ether (40-60 °C), 40 x 220 mm silica) gave a colourless oil (1.02 g, 76%). Spectroscopic data in accordance with that reported previously.

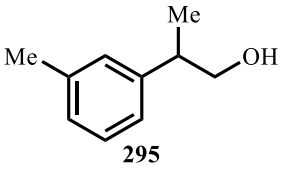
2-(*p*-tolyl)propan-1-ol



294

The title compound was prepared according to general procedure 4 using 4-methylphenethyl alcohol (70 µL, 68 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (46 mg, 61%); R_f = 0.47 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3335, 3019, 2963, 2920, 2864, 1514, 1449, 1034, 1011, 816, 721, 556, 527. **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.26 (3H, d, *J* 7.0, CHC*H*$_3$), 1.30 (1H, br s, O*H*), 2.33 (3H, s, ArC(4)C*H*$_3$), 2.92 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.68 (2H, d, *J* 7.0, C*H*$_2$), 7.14 (4H, s, ArC(2,3,4,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.8 (CH*C*H$_3$), 21.1 (ArC(4)*C*H$_3$), 42.4 (*C*HCH$_3$), 68.9 (*C*H$_2$), 127.5 (Ar*C*), 129.5 (Ar*C*), 136.4 (Ar*C*), 140.7 (Ar*C*); HRMS (**EI$^+$**) calculated for $[C_{10}H_{14}O]^+$ $(M)^+$ m/z : 150.1045, found 150.1047, (+1.3 ppm).

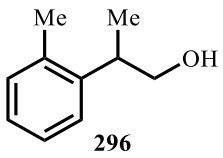
2-(*m*-tolyl)propan-1-ol



295

The title compound was prepared according to general procedure 4 using 2-(*m*-tolyl)-1-ethanol (68 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (49 mg, 65%); R_f = 0.53 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3329, 3015, 2961, 2928, 2868, 1491, 1460, 1383, 1030, 1011, 756, 723, 451; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.27 (3H, d, *J* 7.0, CHC*H*$_3$), 1.29 (1H, t, *J* 6.0, O*H*), 2.35 (3H, s, ArC(3)C*H*$_3$), 2.93 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.70 (2H, t, *J* 6.0, C*H*$_2$), 7.01-7.09 (3H, m, Ar*H*), 7.19-7.25 (1H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.8 (CH*C*H$_3$), 21.6 (ArC(3)*C*H$_3$), 42.5 (*C*HCH$_3$), 68.9 (*C*H$_2$), 124.6 (Ar*C*), 127.6 (Ar*C*), 128.4 (Ar*C*), 128.7 (Ar*C*), 138.4 (Ar*C*), 143.7 (Ar*C*); HRMS (**EI$^+$**) calculated for $[C_{10}H_{14}O]^+$ $(M)^+$ m/z : 150.1045, found 150.1045, (+0.0 ppm).

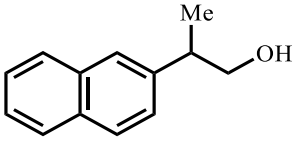
2-(*o*-tolyl)propan-1-ol



296

The title compound was prepared according to general procedure 4 using 2-(*o*-tolyl)-1-ethanol (68 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (30 mg, 40%); R_f = 0.43 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.25 (3H, d, *J* 7.0, CHC*H*$_3$), 1.38 (1H, br s, O*H*), 2.37 (3H, s, ArC(2)C*H*$_3$), 3.27 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.70 (1H, dd, *J* 11.0, 6.5, C*H*^{A}H^B-OH), 3.76 (1H, dd, *J* 11.0, 7.0, CH^A*H*^{B}-OH), 7.09-7.24 (4H, m, ArC(3,4,5,6)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 17.7 (CH*C*H$_3$), 19.8 (ArC(2)*C*H$_3$), 37.3 (*C*HCH$_3$), 68.2 (*C*H$_2$), 125.6 (Ar*C*(6)), 126.4 (Ar*C*), 126.5 (Ar*C*), 130.7 (Ar*C*(3)), 136.6 (Ar*C*(1)), 141.8 (Ar*C*(2)). Spectroscopic data in accordance with that stated in the literature.[21]

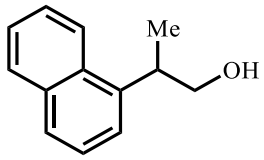
2-(naphthalen-1-yl)propan-2-ol



297

The title compound was prepared according to general procedure 4 using 2-(naphthalen-2-yl)ethan-2-ol (83 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a white solid (77 mg, 82%); mp 64-66 °C (Lit. 60 °C);[22] R_f = 0.40 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3279, 3051, 2968, 2916, 2851, 1597, 1504, 1452, 1369, 1032, 1007, 853, 816, 741, 478; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.35 (1H, br s, O*H*), 1.38 (3H, d, *J* 7.0, CHC*H*$_3$), 3.14 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.80 (2H, d, *J* 6.5, C*H*$_2$), 7.39 (1H, d, *J* 7.5, Ar*H*), 7.46 (2H, quint, *J* 7.5, Ar*H*), 7.69 (1H, s, ArC(1)*H*), 7.76-7.88 (3H, m, Ar*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 17.7 (CH*C*H$_3$), 42.7 (*C*HCH$_3$), 68.7 (*C*H$_2$), 125.7 (Ar*C*), 125.9 (Ar*C*), 126.2 (Ar*C*), 126.2 (Ar*C*), 127.8 (Ar*C*), 127.8 (Ar*C*), 128.5 (Ar*C*), 132.6 (Ar*C*), 133.7 (Ar*C*), 141.2 (Ar*C*(2)); HRMS (**EI$^+$**) calculated for $[C_{13}H_{14}O]^+$ $(M)^+$ m/z : 186.1045, found 186.1045, (+0.0 ppm).

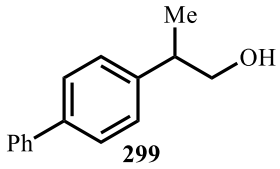
2-(naphthalen-1-yl)propan-1-ol



298

The title compound was prepared according to general procedure 4 using 2-(naphthalen-1-yl)ethan-1-ol (83 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (59 mg, 63%); R_f = 0.40 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.40 (1H, br s, O*H*), 1.45 (3H, d, *J* 6.5, CHCH_3), 3.78-4.02 (3H, m, CH_2), 7.43 (1H, d, *J* 7.0, Ar*H*), 7.45-7.58 (3H, m, Ar*H*), 7.76 (1H, d, *J* 8.0, Ar*H*), 7.88 (1H, d, *J* 8.0, Ar*H*), 8.16 (1H, d, *J* 8.5, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.0 (CH*C*H_3), 36.5 (*C*HCH$_3$), 68.3 (*C*H_2), 123.2 (Ar*C*), 123.2 (Ar*C*), 125.7 (Ar*C*), 125.7 (Ar*C*), 126.2 (Ar*C*), 127.2 (Ar*C*), 129.1 (Ar*C*), 132.1 (Ar*C*), 134.2 (Ar*C*), 139.7 (Ar*C*). Spectroscopic data in accordance with that stated in the literature.[21]

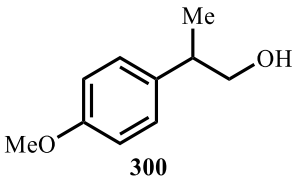
2-([1,1'-biphenyl]-4-yl)propan-1-ol



299

The title compound was prepared according to general procedure 4 using 2-([1,1'-biphenyl]-4-yl)ethan-1-ol (99 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 220 mm silica) gave the title compound as an off-white solid (91 mg, 86%); mp 64-66 °C; R_f = 0.63 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3269, 3055, 3028, 2972, 2941, 2901, 2859, 1707, 1485, 1362, 1329, 1256, 1229, 1180, 1030, 1003, 833, 816, 760, 727, 689, 673; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.32 (3H, d, *J* 7.0, CHCH_3), 3.02 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.76 (2H, d, *J* 7.0, CH_2), 7.30-7.37 (3H, m, Ar*H*), 7.41-7.47 (2H, m, Ar*H*), 7.54-7.61 (4H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.8 (CH*C*H$_3$), 42.3 (*C*HCH$_3$), 68.9 (*C*H_2), 127.2 (Ar*C*), 127.3 (Ar*C*), 127.5 (Ar*C*), 128.0 (Ar*C*), 128.9 (Ar*C*), 139.8 (Ar*C*), 141.1 (Ar*C*), 142.9 (Ar*C*); HRMS (**AP$^+$**) calculated for $[C_{15}H_{15}]^+$ ((M-H_2O)+H)$^+$ m/z : 195.1174, found 195.1173, (-0.5 ppm).

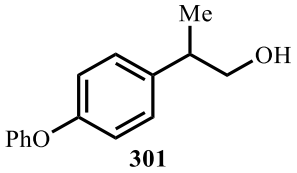
2-(4-methoxyphenyl)propan-1-ol



300

The title compound was prepared according to general procedure 4 using 4-methoxyphenethyl alcohol (76 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (48 mg, 57%); R_f = 0.33 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.25 (3H, d, *J* 7.0, CHC*H*$_3$), 1.30 (1H, br s, O*H*), 2.91 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.60-3.72 (2H, m, C*H*$_2$), 3.80 (3H, s, OC*H*$_3$), 6.88 (2H, d, *J* 8.0, ArC(3,5)*H*), 7.16 (2H, d, *J* 8.0, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.9 (CH*C*H$_3$), 41.7 (*C*HCH$_3$), 55.4 (O*C*H$_3$), 69.0 (*C*H$_2$), 114.2 (Ar*C*(3,5)), 128.5 (Ar*C*(2,6)), 135.7 (Ar*C*(1)), 158.5 (Ar*C*(4)). Spectroscopic data in accordance with that stated in the literature.[21]

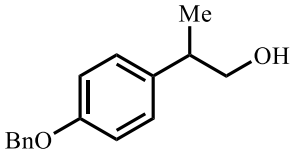
2-(4-phenoxyphenyl)propan-1-ol



301

The title compound was prepared according to general procedure 4 using 2-(4-phenoxyphenyl)ethan-1-ol (107 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 20% EtOAc in hexanes, 20 x 220 mm silica) gave the title compound as a colourless oil (92 mg, 81%); R_f = 0.20 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3327, 3036, 2961, 2920, 2870, 1587, 1504, 1489, 1234, 1198, 1167, 1036, 1009, 868, 835, 754, 691; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.28 (3H, d, *J* 7.0, CHC*H*$_3$), 1.32 (1H, br s, O*H*), 2.95 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.64-3.75 (2H, m, C*H*$_2$), 6.96-7.00 (2H, m, ArC(3,5)*H*), 6.99-7.03 (2H, m, ArC(2',6')*H*), 7.07-7.13 (1H, m, ArC(4')*H*), 7.17-7.23 (2H, m, ArC(2,6)*H*), 7.30-7.37 (2H, m, ArC(3',5')*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.9 (CH*C*H$_3$), 41.9 (*C*HCH$_3$), 68.9 (*C*H$_2$OH), 118.9 (Ar*C*(2',6')), 119.2 (Ar*C*(3,5)), 123.3 (Ar*C*(4)), 128.8 (Ar*C*(2,6)), 129.9 (Ar*C*(3',5')), 138.6 (Ar*C*(1)), 156.1 (Ar*C*), 157.4 (Ar*C*); HRMS (**ESI$^+$**) calculated for $[C_{15}H_{15}O]^+$ $((M-H_2O)+H)^+$ m/z : 211.1123, found 211.1128, (+2.4 ppm).

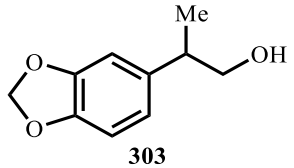
2-(4-(benzyloxy)phenyl)propan-1-ol



302

The title compound was prepared according to general procedure 4 using 4-benzyloxyphenethyl alcohol (114 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a white solid (90 mg, 74%); mp 52-54 °C; R_f = 0.33 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3256, 3034, 2980, 2963, 2882, 1611, 1508, 1447, 1379, 1242, 1179, 1013, 1001, 833, 731, 694, 546; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.25 (3H, d, *J* 6.5, CHC*H*$_3$), 1.29 (1H, br s, O*H*), 2.91 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.60-3.73 (2H, m, C*H*$_2$), 5.05 (2H, s, C*H*$_2$OAr), 6.95 (2H, d, *J* 8.0, ArC(3,5)*H*), 7.16 (2H, d, *J* 8.0, ArC(2,6)*H*), 7.32 (1H, t, *J* 7.5, ArC(4')*H*), 7.39 (2H, t, *J* 7.5, ArC(3',5')*H*), 7.43 (2H, d, *J* 7.5, ArC(2',6')*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.9 (CH*C*H$_3$), 41.7 (*C*HCH$_3$), 69.0 (*C*H$_2$OH), 70.2 (Ar'-*C*H$_2$O), 115.1 (Ar*C*(3,5)), 127.6 (Ar*C*), 128.1 (Ar*C*(4')), 128.6 (Ar*C*(2,6)), 128.7 (Ar*C*), 136.0 (Ar*C*), 137.2 (Ar*C*), 157.8 (Ar*C*(4)); HRMS (**EI$^+$**) calculated for $[C_{16}H_{18}O_2]^+$ $(M)^+$ m/z : 242.1307 found 242.1312, (+2.1 ppm).

2-(benzo[d][1,3]dioxol-5-yl)propan-1-ol

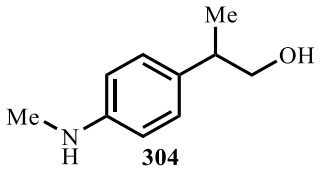


303

The title compound was prepared according to general procedure 4 using 2-(benzo[d][1,3]dioxol-5-yl)ethan-1-ol (83 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 20% Et_2O in *n*-pentane, 20 x 220 mm silica) gave the title compound as a pale-yellow oil (66 mg, 73%); ν_{max} / cm^{-1} (film) 3360, 2961, 2874, 1501, 1483, 1439, 1240, 1186, 1011, 935, 916, 860, 806, 637; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.23 (3H, d, *J* 7.0, CHC*H*$_3$), 1.33 (1H, br s, O*H*), 2.89 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.56-3.74 (2H, m, C*H*$_2$OH), 5.94 (2H, s, OC*H*$_2$O), 6.70 (1H, d, *J* 8.0, ArC(5)*H*), 6.74 (1H, s, ArC(2)*H*), 6.77 (1H, d, *J* 8.0, ArC(6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.9 (CH*C*H$_3$), 42.3 (*C*HCH$_3$), 68.9 (*C*H$_2$OH), 101.0 (O*C*H$_2$O), 107.7 (Ar*C*), 108.5 (Ar*C*), 120.7 (Ar*C*(6)), 137.7

(Ar*C*(1)), 146.4 (Ar*C*), 148.0 (Ar*C*); HRMS (**EI**$^+$) calculated for $[C_{10}H_{12}O_3]^+$ $(M)^+$ m/z : 180.0786, found 180.0789, (+1.7 ppm).

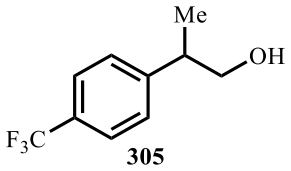
2-(4-(methylamino)phenyl)propan-1-ol



304

The title compound was prepared according to general procedure 4 using 4-aminophenethyl alcohol (69 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 20-50% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a pale-yellow oil (43 mg, 52%); R_f = 0.08 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3404, 3347, 2961, 2920, 2876, 2805, 1612, 1522, 1315, 1256, 1180, 1034, 1015, 1003, 820; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.23 (3H, d, *J* 7.0, CHC*H*$_3$), 2.79-2.90 (4H, m, C*H*CH$_3$, NC*H*$_3$), 3.58-3.70 (2H, m, C*H*$_2$), 6.58-6.64 (2H, m, ArC(3,5)*H*), 7.04-7.10 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.9 (CH*C*H$_3$), 31.0 (NH*C*H$_3$), 41.7 (*C*HCH$_3$), 69.0 (*C*H$_2$), 112.9 (Ar*C*(3,5)), 128.4 (Ar*C*(2,6)), 132.0 (Ar*C*(1)), 148.3 (Ar*C*(4)); HRMS (**EI**$^+$) calculated for $[C_{10}H_{15}NO]^+$ $(M)^+$ m/z : 165.1154, found 165.1152, (-1.2 ppm).

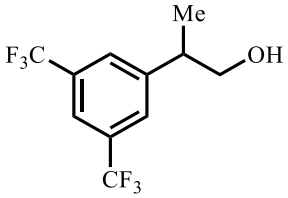
2-(4-(trifluoromethyl)phenyl)propan-1-ol



305

The title compound was prepared according to general procedure 4 using 4-(trifluoromethyl)phenethyl alcohol (76 µL, 95 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 15% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (82 mg, 80%); R_f = 0.43 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.30 (3H, d, *J* 7.0, CHC*H*$_3$), 1.34 (1H, br s, O*H*), 3.03 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.75 (2H, d, *J* 6.5, C*H*$_2$), 7.36 (2H, d, *J* 7.5, ArC(3,5)*H*), 7.59 (2H, d, *J* 8.0, ArC(2,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -62.4; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.6 (CH*C*H$_3$), 42.5 (*C*HCH$_3$), 68.5 (*C*H$_2$), 124.4 (q, *J* 272, *C*F$_3$), 125.7 (q, *J* 3.8, Ar*C*(3,5)), 128.0 (Ar*C*(2,6)), 129.1 (q, *J* 32.5, Ar*C*(4)), 148.2 (m, Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[21]

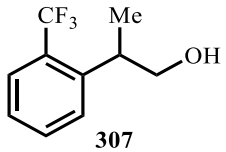
2-(3,5-bis(trifluoromethyl)phenyl)propan-1-ol



306

The title compound was prepared according to general procedure 4 using 2-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol (136 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 20% Et_2O in *n*-pentane, 20 x 140 mm silica) gave the title compound as a colourless oil (119 mg, 88%); ν_{max} / cm^{-1} (film) 3337, 2976, 2930, 2882, 1470, 1381, 1344, 1273, 1165, 1119, 1076, 1030, 978, 893, 847, 721, 704, 679; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.34 (3H, d, *J* 7.5, CHC*H*$_3$), 1.42 (1H, br s, O*H*), 3.11 (1H, sext, *J* 7.0, C*H*CH_3), 3.71-3.85 (2H, m, C*H*$_2$), 7.70 (2H, s, ArC(2,6)*H*), 7.76 (1H, s, ArC(4)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -62.8; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.5 (CH*C*H_3), 42.3 (*C*HCH_3), 68.0 (*C*H_2), 120.8 (sept, *J* 3.8, Ar*C*(4)), 123.5 (q, *J* 273.0, 2x*C*F_3), 127.9 (m, Ar*C*(2,6)), 131.8 (q, *J* 33.1, Ar*C*(3,5)), 146.8 (Ar*C*(1)); HRMS (**EI$^+$**) calculated for $[C_{11}H_{10}OF_6]^+$ $(M)^+$ m/z : 272.0636, found 272.0627, (-3.3 ppm).

2-(2-(trifluoromethyl)phenyl)propan-1-ol

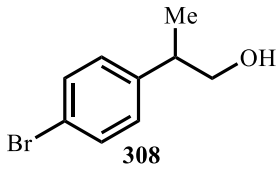


307

The title compound was prepared according to general procedure 4 using 2-(trifluoromethyl)phenethyl alcohol (79 µL, 95 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 15% Et_2O in *n*-pentane, 20 x 210 mm silica) gave the title compound as a colourless oil (23 mg, 23%); R_f = 0.16 (eluent = 20% Et_2O in *n*-pentane); ν_{max} / cm^{-1} (film) 3021, 2953, 2880, 1605, 1456, 1312, 1157, 1109, 1059, 1038, 770, 743, 652, 515; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.30 (3H, d, *J* 7.0, CHC*H*$_3$), 1.37 (1H, br s, O*H*), 3.42 (1H, dsext, *J* 7.0, 1.0, C*H*CH_3), 3.69-3.77 (1H, m, C*H*^{A}H^B), 3.78-3.86 (1H, m, CH^A*H*^{B}), 7.32 (1H, t, *J* 7.5, Ar*H*), 7.46 (1H, d, *J* 7.5, Ar*H*), 7.54 (1H, d, *J* 7.5, Ar*H*), 7.65 (1H, d, *J* 7.5, Ar*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -58.5; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.7 (CH*C*H_3), 37.6 (m, *C*HCH_3), 68.2 (*C*H_2OH), 124.7 (q, *J* 274.0, *C*F_3), 126.1 (q, *J* 5.9, Ar*C*(3)), 126.5 (Ar*C*), 127.8 (Ar*C*), 129.0 (q, *J* 29.2, Ar*C*(2)), 132.2 (m, Ar*C*), 143.3 (m,

Ar*C*(1)); HRMS (**EI**$^+$) calculated for $[C_{10}H_{11}OF_3]^+$ $(M)^+$ m/z : 204.0762, found 204.0763, (+0.5 ppm).

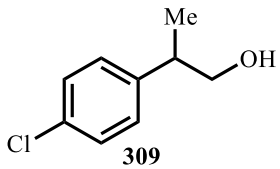
2-(4-bromophenyl)propan-1-ol



308

The title compound was prepared according to general procedure 4 using 2-(4-bromophenyl)ethan-1-ol (70 µL, 101 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (73 mg, 68%); R_f = 0.60 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3321, 2963, 2922, 2874, 1487, 1449, 1406, 1076, 1038, 1007, 816, 714, 550, 519; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.26 (3H, d, *J* 7.0, CHC*H*$_3$), 2.92 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.64-3.73 (2H, m, C*H*$_2$), 7.09-7.15 (2H, m, Ar*H*), 7.42-7.48 (2H, m, Ar*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 17.6 (CH*C*H$_3$), 42.1 (*C*HCH$_3$), 68.6 (*C*H$_2$), 120.5 (Ar*C*(4)), 129.4 (Ar*C*), 131.8 (Ar*C*), 142.9 (Ar*C*(1)); HRMS (**EI**$^+$) calculated for $[C_9H_{11}O^{79}Br]^+$ $(M)^+$ m/z : 213.0993, found 213.0995, (+0.9 ppm).

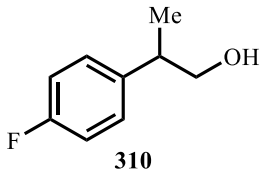
2-(4-chlorophenyl)propan-1-ol



309

The title compound was prepared according to general procedure 4 using 4-chlororophenethyl alcohol (68 µL, 78 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (69 mg, 81%); R_f = 0.40 (eluent = 30% EtOAc in hexanes); **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.26 (3H, d, *J* 7.0, CHC*H*$_3$), 1.31 (1H, br s, O*H*), 2.94 (1H, sext, 7.0, C*H*CH$_3$), 3.63-3.75 (2H, m, C*H*$_2$), 7.18 (2H, d, *J* 8.0, Ar*H*), 7.30 (2H, d, *J* 8.0, Ar*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 17.7 (CH*C*H$_3$), 42.0 (*C*HCH$_3$), 68.7 (*C*H$_2$), 128.9 (Ar*C*), 129.0 (Ar*C*), 132.5 (Ar*C*(4)), 142.4 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[21]

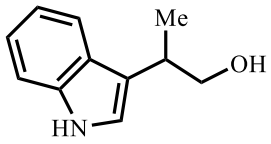
2-(4-fluorophenyl)propan-1-ol



310

The title compound was prepared according to general procedure 4 using 4-fluorophenethyl alcohol (63 µL, 70 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (60 mg, 77%); R_f = 0.37 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3327, 2961, 2930, 2876, 1601, 1512, 1221, 1159, 1034, 1011, 827, 550, 527; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.26 (3H, d, *J* 7.0, CHC*H*$_3$), 1.30 (1H, br s, O*H*), 2.94 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.62-3.74 (2H, m, C*H*$_2$), 7.02 (2H, t, *J* 8.5, ArC(3,5)*H*) 7.20 (2H, dd, *J* 8.0, 5.5, ArC(2,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -116.6; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.9 (CH*C*H$_3$), 41.8 (*C*HCH$_3$), 68.8 (*C*H$_2$), 115.5 (d, *J* 21.0, Ar*C*(3,5)), 129.0 (d, *J* 7.9, Ar*C*(2,6)), 139.5 (d, *J* 5.4, Ar*C*(1)), 161.8 (d, *J* 244.0, Ar*C*(4)); HRMS (**EI$^+$**) calculated for $[C_9H_{11}OF]^+$ $(M)^+$ m/z : 154.0794, found 154.0791, (-1.9 ppm).

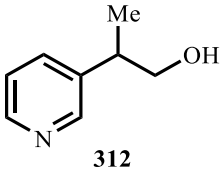
2-(1*H*-indol-3-yl)propan-1-ol



311

The title compound was prepared according to general procedure 4 using tryptophol (81 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 25% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a pale-yellow oil (49 mg, 56%); R_f = 0.13 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3545, 3402, 3283, 3055, 2963, 2926, 2870, 1454, 1341, 1221, 1090, 1020, 1005, 731; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.38 (1H, br s, O*H*), 1.41 (3H, d, *J* 7.0, CHC*H*$_3$), 3.32 (1H, sext, *J* 6.5, C*H*CH$_3$), 3.76-3.89 (2H, m, C*H*$_2$), 7.07 (1H, s, ArC(2)*H*), 7.13 (1H, t, *J* 7.5, Ar*H*), 7.21 (1H, t, *J* 7.5, Ar*H*), 7.38 (1H, d, *J* 8.0, Ar*H*), 7.67 (1H, d, *J* 8.0, Ar*H*), 8.05 (1H, br s, N*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.4 (CH*C*H$_3$), 34.1 (*C*HCH$_3$), 68.1 (*C*H$_2$), 111.4 (Ar*C*(7)), 118.2 (Ar*C*(3)), 119.4 (Ar*C*), 119.6 (Ar*C*), 121.3 (Ar*C*), 122.4 (Ar*C*), 126.9 (Ar*C*), 136.7 (Ar*C*); HRMS (**EI$^+$**) calculated for $[C_{11}H_{13}NO]^+$ $(M)^+$ m/z : 175.0997, found 175.1001, (+2.3 ppm).

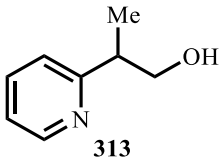
2-(pyridin-3-yl)propan-1-ol



312

The title compound was prepared according to general procedure 4 using 3-(2-hydroxyethyl)pyridine (62 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 60-70% EtOAc in hexanes, 20 x 180 mm silica) gave the title compound as a colourless oil (53 mg, 77%); R_f = 0.17 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3225, 2967, 2920, 2870, 1580, 1476, 1425, 1047, 1016, 810, 714, 635; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.31 (3H, d, *J* 7.0, CHC*H*$_3$), 2.99 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.70-3.79 (2H, m, C*H*$_2$), 7.23-7.28 (1H, m, Ar*H*), 7.55-7.60 (1H, m, Ar*H*), 8.47 (1H, dd, *J* 5.0, 2.0, ArC(4)*H*), 8.50 (1H, d, *J* 2.0, ArC(2)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.4 (CH*C*H$_3$), 40.2 (*C*HCH$_3$), 68.3 (*C*H$_2$), 123.7 (Ar*C*), 135.1 (Ar*C*), 139.4 (Ar*C*(1)), 148.1 (Ar*C*), 149.5 (Ar*C*); HRMS (**EI$^+$**) calculated for $[C_8H_{11}NO]^+$ $(M)^+$ m/z : 137.0841, found 137.0836, (-3.6 ppm).

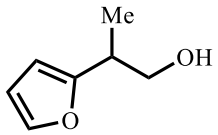
2-(pyridin-2-yl)propan-1-ol



313

The title compound was prepared according to general procedure 4 using 2-(2-hydroxyethyl)pyridine (62 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 30-50% EtOAc in hexanes, 20 x 180 mm silica) gave the title compound as a colourless oil (40 mg, 65%); R_f = 0.17 (eluent = 50% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3269, 2972, 2926, 2870, 1593, 1570, 1476, 1439, 1150, 1045, 1018, 997, 783, 750, 629, 557, 536; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.33 (3H, d, *J* 7.0, CHC*H*$_3$), 3.08 (1H, dquint, *J* 7.0, 4.0, C*H*CH$_3$), 3.84 (1H, dd, *J* 11.0, 6.5, C*H*^{A}H^B), 3.94 (1H, dd, *J* 10.5, 4.0, CH^A*H*^{B}), 7.16 (1H, ddd, *J* 7.5, 5.0, 1.0, Ar*H*), 7.20 (1H, d, *J* 7.5, ArC(6)*H*), 7.65 (1H, dt, *J* 7.5, 2.0, Ar*H*), 8.50 (1H, ddd, *J* 5.0, 2.0, 1.0, ArC(3)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.3 (CH*C*H$_3$), 42.0 (*C*HCH$_3$), 67.3 (*C*H$_2$), 121.7 (Ar*C*), 122.3 (Ar*C*), 137.0 (Ar*C*), 148.7 (Ar*C*), 165.1 (Ar*C*(1)); HRMS (**AP$^+$**) calculated for $[C_8H_{12}NO]^+$ $(M+H)^+$ m/z : 138.0919, found 138.0922, (+2.2 ppm).

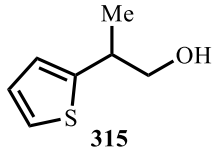
2-(furan-2-yl)propan-1-ol



314

The title compound was prepared according to general procedure 4 using 2-(furan-2-yl)ethan-1-ol (56 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 210 mm silica) gave the title compound as a colourless oil (31 mg, 50%); R_f = 0.42 (eluent = 25% EtOAc in hexanes); **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.27 (3H, d, *J* 7.0, CHC*H*$_3$), 3.05 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.68-7.78 (2H, m, C*H*$_2$), 6.09 (1H, dt, *J* 3.5, 1.0, ArC(5)*H*), 6.31 (1H, dd, *J* 3.5, 2.0, ArC(4)*H*), 7.34 (1H, dd, *J* 2.0, 1.0, ArC(3)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 15.3 (CH*C*H$_3$), 36.3 (*C*HCH$_3$), 66.8 (*C*H$_2$), 105.3 (Ar*C*), 110.2 (Ar*C*), 141.5 (Ar*C*(3)), 157.6 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[23]

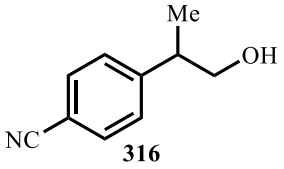
2-(thiophen-2-yl)propan-1-ol



315

The title compound was prepared according to general procedure 4 using 2-thiopheneethanol (56 µL, 64 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 20 x 200 mm silica) gave the title compound as a colourless oil (51 mg, 72%); R_f = 0.47 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3356, 2963, 2934, 2874, 2835, 1611, 1512, 1458, 1300, 1244, 1177, 1032, 1018, 1001, 827, 806, 559, 538; **^{1}H NMR (500 MHz, CDCl$_3$)** δ_H: 1.36 (3H, d, *J* 7.0, CHC*H*$_3$), 1.51 (1H, br s, O*H*), 3.26 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.63-3.78 (2H, m, C*H*$_2$), 6.87-6.93 (1H, m, ArC(5)*H*), 6.94-7.02 (1H, m, ArC(4)*H*), 7.20 (1H, d, *J* 5.0, ArC(3)*H*); **^{13}C NMR (126 MHz, CDCl$_3$)** δ_C: 18.7 (CH*C*H$_3$), 38.3 (*C*HCH$_3$), 69.1 (*C*H$_2$), 123.7 (Ar*C*), 124.0 (Ar*C*), 127.0 (Ar*C*), 147.5 (Ar*C*(1)); HRMS (**EI$^+$**) calculated for $[C_7H_{10}OS]^+$ $(M)^+$ m/z : 142.0452, found 142.0450, (-1.4 ppm).

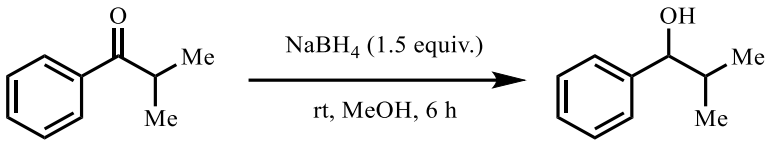
2-(4-cyanophenyl)propan-1-ol



316

The title compound was prepared according to general procedure 4 using 2-(4-cyanophenyl)ethan-1-ol (74 mg, 0.5 mmol) and K_2CO_3 (138 mg, 1.0 mmol) as base Purification by flash silica chromatography (eluent = 15% Et_2O in *n*-pentane, 20 x 220 mm silica) gave the title compound as a colourless oil (11 mg, 14%); R_f = 0.20 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3404, 2961, 2934, 2878, 2228, 1607, 1504, 1414, 1070, 1040, 1011, 974, 883, 563; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.29 (3H, d, *J* 7.0, CHC*H*$_3$), 3.02 (1H, sext, *J* 7.0, C*H*CH$_3$), 3.68-3.80 (2H, m, C*H*$_2$), 7.32-7.29 (2H, m, ArC(2,6)*H*), 7.57-7.65 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.5 (CH*C*H$_3$), 42.8 (*C*HCH$_3$), 68.3 (*C*H$_2$OH), 110.7 (Ar*C*(4)), 119.2 (*C*≡N), 128.6 (Ar*C*(2,6)), 132.6 (Ar*C*(3,5)), 149.9 (Ar*C*(1)); HRMS (**EI$^+$**) calculated for $[C_{10}H_{11}NO]^+$ $(M)^+$ m/z : 161.0841, found 161.0841, (+0.0 ppm).

2-methyl-1-phenylpropan-1-ol

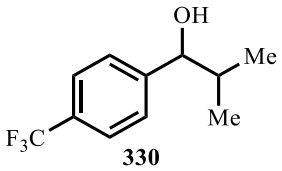


136 **184**

A round-bottomed flask equipped with a magnetic stirrer bar was charged with isobutyrophenone (750 µL, 741 mg, 5.0 mmol) and MeOH (12.5 mL). The solution was cooled to 0 °C and was charged with $NaBH_4$ (284 mg, 7.5 mmol). The solution was left to stir at rt for 6 h and was quenched with sat. aq. NH_4Cl (2 mL) and H_2O (5 mL). EtOAc (50 mL) was added and the mixture was transferred to a separatory funnel filled with brine (25 mL). The organic layer was collected, the aqueous phase was washed with EtOAc (2 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 30 x 120 mm silica) gave the title compound as a colourless oil (630 mg, 84%); R_f = 0.38 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.80 (3H, d, *J* 7.0, C*H*$_3$), 1.00 (3H, d, *J* 7.0, C*H*$_3$), 1.81 (1H, d, *J* 1.5, O*H*), 1.96 (1H, oct, *J* 7.0, C*H*(CH$_3$)$_2$), 4.37 (1H, dd, *J* 6.5, 1.5, C*H*OH), 7.22-7.38 (5H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.4 (*C*H$_3$), 19.2

(*C*H_3), 35.4 (*C*H(CH_3)$_2$), 80.2 (*C*HOH), 126.7 (Ar*C*), 127.6 (Ar*C*(4)), 128.3 (Ar*C*), 143.8 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[24]

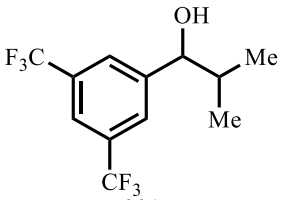
2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol



330

The title compound was prepared according to general procedure 4 using 1-(4-(trifluoromethyl)phenyl)ethan-1-ol (95 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in cyclohexane, 20 x 190 mm silica) gave the title compound as a colourless oil (31 mg, 28%); R_f = 0.52 (eluent = 10% EtOAc in *n*-pentane); ν_{max} / cm^{-1} (film) 3389, 2972, 2930, 2874, 1616, 1470, 1418, 1319, 1161, 1119, 1067, 1013, 837, 793, 611; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.84 (3H, d, *J* 6.5, C*H*$_3$), 0.97 (3H, d, *J* 6.5, C*H*$_3$), 1.88 (1H, br s, O*H*), 1.97 (1H, oct, *J* 6.5, C*H*(CH_3)$_2$), 4.48 (1H, d, *J* 6.5, C*H*OH), 7.44 (2H, d, *J* 8.0, ArC(2,6)*H*), 7.60 (2H, d, *J* 8.0, ArC(3,5)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -62.4; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.9 (*C*H_3), 19.0 (*C*H_3), 35.5 (*C*H(CH_3)$_2$), 79.3 (C*H*OH), 124.3 (q, *J* 272.0, *C*F_3), 125.3 (q, *J* 3.8, Ar*C*(3,5)), 127.0 (Ar*C*(2,6)), 129.7 (q, *J* 32.4, Ar*C*(4)), 147.6 (m, Ar*C*(1)); HRMS (**EI**$^+$) calculated for $[C_{11}H_{13}OF_3]^+$ $(M)^+$ m/z : 218.0918, found 218.0914, (-1.4 ppm).

1-(3,5-bis(trifluoromethyl)phenyl)-2-methylpropan-1-ol

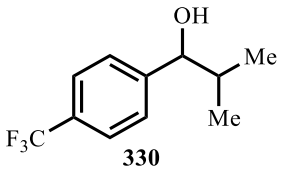


331

The title compound was prepared according to general procedure 4 using 1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol (129 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in cyclohexane, 20 x 190 mm silica) gave the title compound as a white solid (55 mg, 38%); mp 51-53 °C; R_f = 0.14 (eluent = 5% EtOAc in cyclohexane); ν_{max} / cm^{-1} (film) 3389, 3325, 2972, 2926, 2895, 2855, 1472, 1379, 1329, 1275, 1159, 1117, 1103, 1034, 901, 847, 827, 710, 679, 664; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 0.89 (3H, d, *J* 7.0, C*H*$_3$), 0.95 (3H, d, *J* 6.5, C*H*$_3$), 1.90-2.08 (2H**,** m, C*H*(CH_3)$_2$, O*H*), 4.59 (1H, d, *J* 6.0, C*H*OH), 7.79 (3H, s, ArC(2,4,6)*H*); **^{19}F NMR (471 MHz, $CDCl_3$)** δ_F: -

62.8; **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 17.3 (*C*H_3), 19.0 (*C*H_3), 35.5 (*C*HOH), 78.5 (*C*HCH_3), 121.4 (m, Ar*C*(4)), 123.5 (q, *J* 273.0, *C*F_3), 126.8 (Ar*C*(2,6)), 131.5 (q, *J* 33.3, Ar*C*(3,5)), 146.2 (Ar*C*(1)); HRMS (**EI**$^+$) calculated for $[C_{12}H_{12}OF_6]^+$ $(M)^+$ m/z : 286.0792, found 286.0783, (-3.1 ppm).

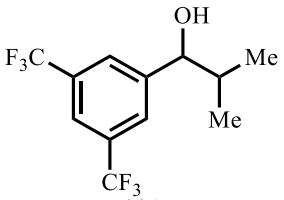
2-methyl-1-(4-(trifluoromethyl)phenyl)propan-1-ol



330

The title compound was prepared according to general procedure 4 using 1-(4-(trifluoromethyl)phenyl)propan-1-ol (102 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in cyclohexane, 20 x 190 mm silica) gave the title compound as a colourless oil (24 mg, 22%); R_f = 0.52 (eluent = 10% EtOAc in *n*-pentane). Spectroscopic data in accordance with that stated previously.

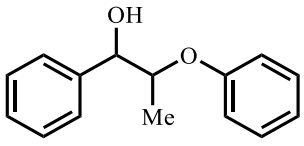
1-(3,5-bis(trifluoromethyl)phenyl)-2-methylpropan-1-ol



331

The title compound was prepared according to general procedure 4 using 1-(3,5-bis(trifluoromethyl)phenyl)propan-1-ol (136 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5% EtOAc in cyclohexane, 20 x 190 mm silica) gave the title compound as a white solid (40 mg, 28%); mp 51-53 °C; R_f = 0.14 (eluent = 5% EtOAc in cyclohexane). Spectroscopic data in accordance with that stated previously.

2-phenoxy-1-phenylpropan-1-ol



338

The title compound was prepared according to general procedure 4 using 2-phenoxy-1-phenylethan-1-ol (107 mg, 0.5 mmol). After workup, the crude revealed a 2:1 *dr*.

Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 20 x 220 mm silica) gave the title compound as a colourless oil (36 mg, 30%, 56:44 *dr*); R_f = 0.44 (eluent = 20% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3557, 3433, 3063, 3036, 2982, 2920, 1597, 1584, 1491, 1449, 1229, 1173, 1063, 993, 937, 883, 748, 692, 505;

Selected data for major diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.20 (3H, d, *J* 6.0, CHC*H*$_3$), 2.51 (1H, d, *J* 3.0, O*H*), 4.59 (1H, dq, *J* 6.0, 3.5, C*H*CH$_3$), 5.06 (1H, t, *J* 3.0, C*H*OH), 6.92-7.02 (3H, m, ArC(2',6')*H*), 7.27-7.41 (5H, m, ArC(2,3,4,5,6)*H*), 7.41-7.46 (2H, m, ArC(3',5')*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 13.0 (CH*C*H$_3$), 75.2 (*C*HOH), 77.9 (*C*HCH$_3$), 116.4 (Ar*C*(2',6')), 121.5 (Ar*C*(4')), 126.4 (Ar*C*(2,6)), 127.8 (Ar*C*(4)), 128.5 (Ar*C*(3,5)), 129.8 (Ar*C*(3',5')), 140.1 (Ar*C*(1)), 157.5 (Ar*C*(1')).

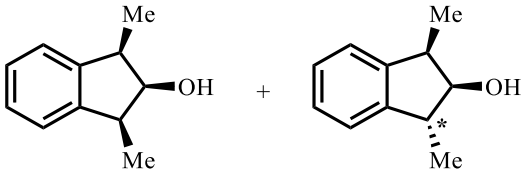
Selected data for minor diastereomer:

^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.13 (3H, d, *J* 6.0, CHC*H*$_3$), 3.05 (1H, d, *J* 2.0, O*H*), 4.45 (1H, dq, *J* 7.5, 6.0, C*H*CH$_3$), 4.71 (1H, dd, *J* 7.5, 2.5, C*H*OH), 6.92-7.02 (3H, m, ArC(2',6')*H*), 7.27-7.41 (5H, m, ArC(2,3,4,5,6)*H*), 7.41-7.46 (2H, m, ArC(3',5')*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.6 (CH*C*H$_3$), 78.3 (*C*HOH), 79.0 (*C*HCH$_3$), 116.4 (Ar*C*(2',6')), 121.6 (Ar*C*(4')), 127.5 (Ar*C*(2,6)), 128.4 (Ar*C*(4)), 128.6 (Ar*C*(3,5)), 129.8 (Ar*C*(3',5')), 139.9 (Ar*C*(1)), 157.7 (Ar*C*(1')).

HRMS (**EI$^+$**) calculated for $[C_{15}H_{16}O_2]^+$ $(M)^+$ m/z : 228.1150, found 228.1156, (+2.6 ppm).

(1*R*,2*S*,3*S*)-1,3-dimethyl-2,3-dihydro-1*H*-inden-2-ol

(1*R*,3*R*)-1,3-dimethyl-2,3-dihydro-1*H*-inden-2-ol



339a **339c-d**

The title compounds were prepared according to general procedure 2 using 2-indanol (67 mg, 0.5 mmol) giving the crude products after work up (71:29 *dr*). Purification by flash silica chromatography (eluent = 5-10% EtOAc in *n*-pentane, 20 x 140 mm silica) gave **339a** as a white solid (7 mg, 9%); mp 105-107 °C; R_f = 0.39 (eluent = 10% EtOAc in *n*-pentane); and **339c-d** as a colourless oil (27 mg, 33%); R_f = 0.35 (eluent = 10% EtOAc in *n*-pentane).

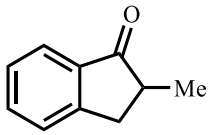
Data for **339a**:

ν_{max} / cm^{-1} (film) 3291, 3071, 3017, 2065, 2930, 2870, 2839, 1474, 1373, 1323, 1240, 1144, 1034, 1016, 962, 876, 768, 758, 712; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.39 (6H, d, *J* 7.0, 2xCHC*H*$_3$), 3.15 (2H, dq, *J* 7.0, 3.6, 2xC*H*CH_3), 4.32 (1H, t, *J* 3.6, C*H*OH), 7.17-7.25 (4H, m, 4xAr*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 12.0 (2xCH*C*H_3), 43.7 (2x*C*HCH_3), 80.2 (*C*HOH), 123.5 (Ar*C*(3,6)), 126.9 (Ar*C*(4,5)), 145.3 (Ar*C*(1,2)); HRMS (**EI**$^+$) calculated for $[C_{11}H_{14}O]^+$ $(M)^+$ m/z : 162.1045, found 162.1044, (-0.6 ppm).

Data for **339c-d**:

ν_{max} / cm^{-1} (film) 3358, 3021, 2961, 2930, 2870, 1477, 1450, 1375, 1103, 1098, 1061, 1011, 972, 752, 498, 461; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.25 (3H, d, *J* 7.0, CHC*H*$_3$), 1.31 (3H, d, *J* 7.0, CHC*H*$_3$), 3.05-3.13 (1H, m, C*H*CH_3), 3.23-3.33 (1H, m, C*H*CH_3), 4.10 (1H, t, *J* 6.0, C*H*OH), 7.16-7.23 (4H, m, 4xAr*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 13.3 (CH*C*H_3), 17.1 (CH*C*H_3), 42.0 (*C*HCH_3), 45.8 (*C*HCH_3), 82.4 (*C*HOH), 124.0 (Ar*C*(3,6)), 124.1 (Ar*C*(3,6)), 127.1 (Ar*C*(4,5)), 127.1 (Ar*C*(4,5)), 144.9 (Ar*C*(1,2)), 145.2 (Ar*C*(1,2)); HRMS (**EI**$^+$) calculated for $[C_{11}H_{14}O]^+$ $(M)^+$ m/z : 162.1045, found 162.1045, (+0.0 ppm).

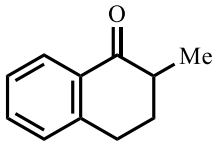
2-methyl-2,3-dihydro-1*H*-inden-1-one



160

The title compound was prepared according to general procedure 4 using 1-indanol (67 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5% Et_2O in *n*-pentane, 30 x 120 mm silica) gave the title compound as a colourless oil (46 mg, 62%); R_f = 0.27 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.32 (3H, d, *J* 7.0, CHC*H*$_3$), 2.67-2.77 (2H, m, Ar-C*H*$_2$), 3.35-3.45 (1H, m, C*H*CH_3), 7.34-7.40 (1H, m, ArC(3)*H*), 7.42-7.49 (1H, m, ArC(5)*H*), 7.59 (1H, dt, *J* 1.5, 7.5, ArC(4)*H*), 7.76 (1H, d, *J* 7.5, ArC(2)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 16.4 (CH*C*H_3), 35.1 (CH*C*H_2), 42.1 (*C*HCH_3), 124.1 (Ar*C*), 126.7 (Ar*C*), 127.5 (Ar*C*), 134.8 (Ar*C*), 136.5 (Ar*C*(1)), 153.6 (Ar*C*(6)), 209.6 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[25]

2-methyl-3,4-dihydronaphthalen-1(2*H*)-one



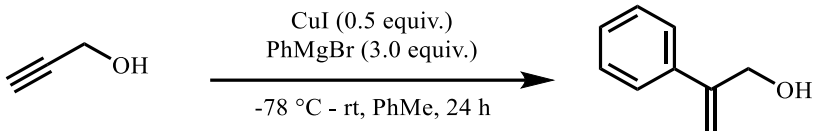
161

The title compound was prepared according to general procedure 2 using 1-tetralol (74 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5% Et_2O in *n*-pentane, 30 x 120 mm silica) gave the title compound as a colourless oil (43 mg, 53%); R_f = 0.34 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.28 (3H, d, *J* 7.0, CHC*H*$_3$), 1.83-1.95 (1H, m, CH(C*H*^{A}CH^B)), 2.20 (1H, dq, *J* 13.5, 4.5, CH(CH^{A}C*H*^{B})), 2.54-2.65 (1H, m, C*H*CH$_3$), 2.92-3.11 (2H, m, ArC*H*$_2$), 7.23 (1H, d, *J* 7.5, ArC(5)*H*), 7.30 (1H, t, *J* 7.5, ArC(3)*H*), 7.45 (1H, dt, *J* 7.5, 1.5, ArC(4)*H*), 8.04 (1H, dd, *J* 7.5, 1.5, ArC(2)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 15.6 (CH*C*H$_3$), 29.0 (Ar*C*H$_2$), 31.5 (CH*C*H$_2$), 42.8 (*C*HCH$_3$), 126.6 (Ar*C*), 127.5 (Ar*C*), 128.8 (Ar*C*), 133.2 (Ar*C*), 132.5 (Ar*C*(1)), 144.3 (Ar*C*(6)), 201.0 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[26]

10.3. Mechanistic investigations

10.3.1. Synthesis of plausible intermediates

2-phenylprop-2-en-1-ol

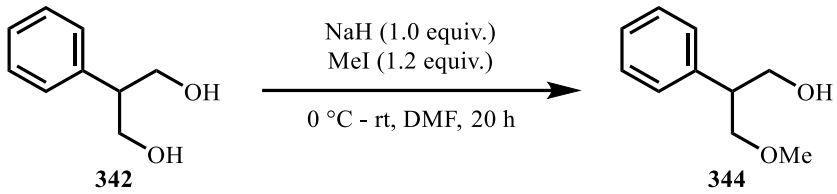


343

The title compound was prepared according to a procedure stated in the literature.[27] Under nitrogen, a three-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with copper(I) iodide (1.9 g, 10.0 mmol) and dry toluene (25 mL). The suspension was cooled to -78 °C followed by the addition of propargyl alcohol (1.2 mL, 1.1 g, 20.0 mmol). To this solution was then added a fresh prepared solution of phenylmagnesium bromide (60 mL, 60.0 mmol, 1 M in THF). The mixture was left to gradually warm up to room temperature and left stirring for 16 h. Sat. aq. NH_4Cl (10 mL), H_2O (20 mL) and EtOAc (50 mL) were then added. The mixture was transferred to a separatory funnel and the organic layer was collected. The aqueous layer was washed with EtOAc (2 x 50 mL). The organics

were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-25% EtOAc in hexanes, 35 x 170 mm silica) gave the title compound as a colourless oil (1.2 g, 45%); R_f = 0.28 (eluent = 20% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.56-1.66 (1H, m, O*H*), 4.55 (2H, d, *J* 6.0, C*H*$_2$OH), 5.36 (1H, q, *J* 1.5, C=C*H*^{A}H^B), 5.48 (1H, q, *J* 1.5, C=CH^A*H*^{B}), 7.28-7.33 (1H, m, ArC(4)*H*), 7.33-7.39 (2H, m, Ar*H*), 7.43-7.48 (2H, m, Ar*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 65.2 (*C*H$_2$OH), 112.8 (C=*C*H$_2$), 126.2 (Ar*C*), 128.1 (Ar*C*(4)), 128.7 (Ar*C*), 138.6 (Ar*C*(1)), 147.4 (*C*=CH$_2$). Spectroscopic data in accordance with that stated in the literature.[28]

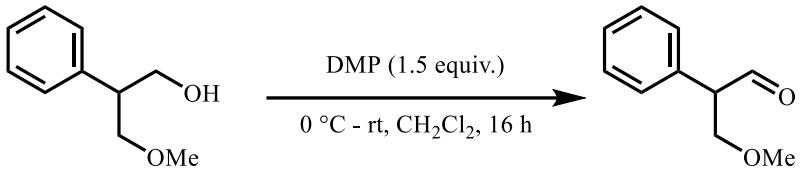
3-methoxy-2-phenylpropan-1-ol



342 **344**

A round-bottomed flask equipped with a magnetic stirrer bar was charged with 2-phenylpropane-1,3-diol (1.5 g, 10.0 mmol) and dry DMF (20 mL). The solution was cooled to 0 °C and was then charged with NaH (400 mg, 10.0 mmol, 60% suspension in mineral oil). After 30 min at this temperature, MeI (747 µL, 1.70 g, 12.0 mmol) was added. The flask was sealed with a cap and the mixture was left to stir at rt for 20 h. The mixture was quenched with sat aq. NH_4Cl (10 mL), H_2O (10 mL) and was then transferred to a separatory funnel filled with EtOAc (50 mL). The organic layer was collected. The aqueous phase was washed with EtOAc (2 x 50 mL). The organics were combined, washed with brine (5 x 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 30-70% EtOAc in hexanes, 35 x 110 mm silica) gave the title compound as a colourless oil (749 mg, 45%), R_f = 0.24 (eluent = 30% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3408, 3032, 2930, 2874, 2826, 1495, 1450, 1194, 1117, 1090, 1028, 756, 700; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.44 (1H, t, *J* 6.0, O*H*), 3.12-3.24 (1H, m, Ph-C*H*), 3.39 (3H, s, OC*H*$_3$), 3.65-3.79 (2H, m, C*H*$_2$OCH$_3$), 3.80-3.91 (1H, m, C*H*^{A}H^B), 3.94-4.03 (1H, m, CH^A*H*^{B}), 7.18-7.28 (3H, m, ArC(2,4,6)*H*), 7.29-7.36 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 47.8 (Ph-*C*H), 59.3 (O*C*H$_3$), 66.8 (*C*H$_2$OH), 76.6 (*C*H$_2$OCH$_3$), 127.2 (Ar*C*(4)), 128.1 (Ar*C*), 128.8 (Ar*C*) 139.7 (Ar*C*(1)); HRMS (**EI$^+$**) calculated for $[C_{10}H_{14}O_2]^+$ $(M)^+$ m/z : 166.0994, found 166.0992, (-1.2 ppm).

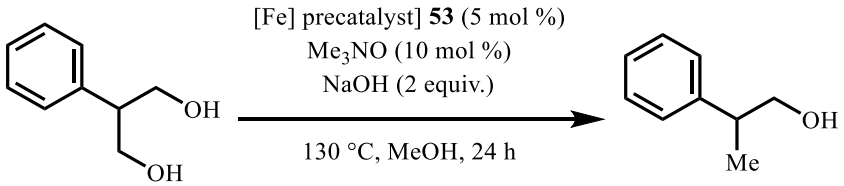
3-methoxy-2-phenylpropanal



344 **348**

A round-bottomed flask equipped with a magnetic stirrer bar was charged with 3-methoxy-2-phenylpropan-1-ol (889 mg, 5.3 mmol) and CH_2Cl_2 (50 mL). The solution was cooled to 0 °C followed by portionwise addition of Dess-Martin periodinane (3.4 g, 8.0 mmol). This was left to react at rt for 16 h. The mixture was quenched with a 1:1 mixture of 10 wt% $Na_2S_2O_3$ / sat. aq. $NaHCO_3$), and then transferred to a separatory funnel. The organic layer was separated, and the aqueous phase was washed with CH_2Cl_2 (2 x 50 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5-10% Et_2O in *n*-pentane, 30 x 150 mm silica) gave the title compound as a colourless oil (546 mg, 63%); ν_{max} / cm^{-1} (film) 3036, 2988, 2934, 2895, 2820, 1721, 1495, 1454, 1192, 1107, 955, 758, 700; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 3.36 (3H, s, OC*H*$_3$), 3.73 (1H, dd, *J* 9.5, 5.5, C*H*^{A}H^{B}OCH$_3$), 3.82-3.89 (1H, m, Ar-C*H*), 4.04 (1H, dd, *J* 9.5, 7.5, CH^A*H*^{B}OCH$_3$), 7.20-7.25 (2H, m, ArC(2,6)*H*), 7.29-7.35 (1H, m, ArC(4)*H*), 7.35-7.41 (2H, m, ArC(3,5)*H*), 9.76 (1H, dd, *J* 2.0, 0.5, *H*(C=O)); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 59.0 (*C*HCH$_2$), 59.3 (O*C*H$_3$), 72.0 (*C*H$_2$), 128.1 (Ar*C*(4)), 129.1 (Ar*C*), 129.2 (Ar*C*), 134.1 (Ar*C*(1)), 199.8 (*C*=O); HRMS (**EI$^+$**) calculated for $[C_{10}H_{12}O_2]^+$ $(M)^+$ m/z : 164.0837, found 164.0837, (+0.0 ppm).

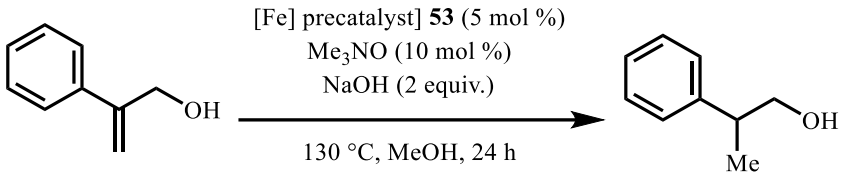
10.3.2. Validation of plausible reaction intermediates



342 **186**

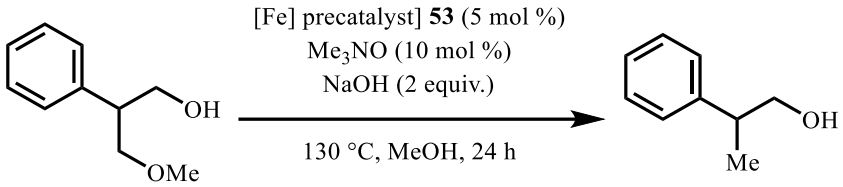
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with NaOH (40 mg, 1.0 mmol), Me_3NO (5.6 mg, 0.05 mmol, 10 mol %), [Fe] precatalyst **53** (11.4 mg, 0.025 mmol, 5 mol %), MeOH (1 mL) and 2-phenylpropane-1,3-diol (**342**) (76 mg, 0.5 mmol). The vial was sealed with a cap and was left to react at 130 °C for 24 h. It was then cooled, treated with mesitylene (70 µL, 60.1 mg, 0.5 mmol), EtOAc (1 mL), sat. aq. NH_4Cl (0.5 mL) and H_2O (0.5 mL). Brine (0.5 mL) was added to aid layer separation. The mixture was stirred

for 5 min and left to settle for a further 5 min. The top layer was sampled and analysed using ^{1}H NMR. This revealed 78% of **186**.



343 **186**

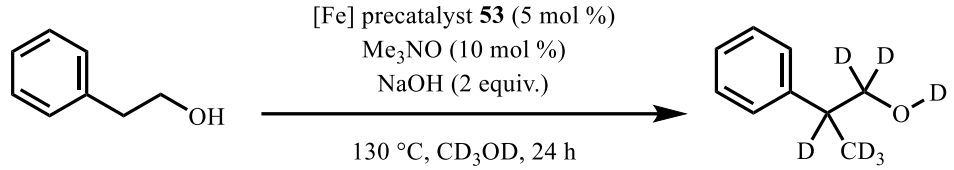
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with NaOH (40 mg, 1.0 mmol), Me_3NO (5.6 mg, 0.05 mmol, 10 mol %), [Fe] precatalyst **53** (11.4 mg, 0.025 mmol, 5 mol %), MeOH (1 mL) and 2-phenylprop-2-en-1-ol (**343**) (67 mg, 0.5 mmol). The vial was sealed with a cap and was left to react at 130 °C for 24 h. It was then cooled, treated with mesitylene (70 µL, 60 mg, 0.5 mmol), EtOAc (1 mL), sat. aq. NH_4Cl (0.5 mL) and H_2O (0.5 mL). Brine (0.5 mL) was added to aid layer separation. The mixture was stirred for 5 min and left to settle for a further 5 min. The top layer was sampled and analysed using ^{1}H NMR. This revealed 85% of **186**.



344 **186**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with NaOH (40 mg, 1.0 mmol), Me_3NO (5.6 mg, 0.05 mmol, 10 mol %), [Fe] precatalyst **53** (11.4 mg, 0.025 mmol, 5 mol %), MeOH (1 mL) and 3-methoxy-2-phenylpropan-1-ol (**344**) (83 mg, 0.5 mmol). The vial was sealed with a cap and was left to react at 130 °C for 24 h. It was then cooled, treated with mesitylene (70 µL, 60.1 mg, 0.5 mmol), EtOAc (1 mL), sat. aq. NH_4Cl (0.5 mL) and H_2O (0.5 mL). Brine (0.5 mL) was added to aid layer separation. The mixture was stirred for 5 min and left to settle for a further 5 min. The top layer was sampled and analysed using ^{1}H NMR. This revealed 57% of **186**.

10.3.3. Employing CD_3OD as solvent



290 **349**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with NaOH (40 mg, 1.0 mmol), $Me_3NO.2H_2O$ (5.6 mg, 0.05 mmol, 10 mol %), [Fe] precatalyst **53** (11.4 mg, 0.025 mmol, 5 mol %), CD_3OD (1 mL) and 2-phenylethanol (60 µL, 61 mg, 0.5 mmol). The vial was sealed with a cap and was left to stir at 130 °C for 24 h. It was then cooled, treated with sat. aq. NH_4Cl (0.5 mL) and H_2O (0.5 mL), washed with EtOAc (15 mL) and transferred to a separatory funnel filled with brine (15 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 15 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 20% Et_2O in *n*-pentane, 20 x 220 mm silica) gave a colourless oil (43 mg, 60%). The product was subjected to D_2O exchange by placing a drop of D_2O in the NMR tube with $CDCl_3$ as solvent.

10.4. References

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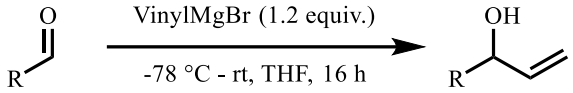
Chapter 11: Experimental

One-pot conversion of allylic alcohols to *α*-methyl ketones *via* iron-catalysed isomerisation-methylation

Table of contents

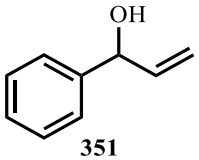
11.1. Substrate synthesis

11.1.1. General procedure 1



Under nitrogen, a flame dried round-bottomed flask equipped with a magnetic stirrer bar was charged with the requisite aldehyde (1 equiv.) and dry THF. The mixture was cooled to -78 °C, and to this solution was added vinylmagnesium bromide (1.2 equiv., 1 M in THF). The reaction mixture was stirred at rt for 16 h. The reaction mixture cooled to 0 °C and quenched with sat. aq. NH_4Cl and H_2O. It was transferred to separatory funnel followed by the addition of EtOAc and H_2O. The organic layer was collected, and the aqueous phase washed with EtOAc (x 2). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

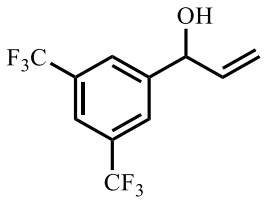
1-phenylprop-2-en-1-ol



351

The title compound was prepared according to general procedure 1 using benzaldehyde (1.9 mL, 2.0 g, 18.8 mmol), dry THF (20 mL) and vinylmagnesium bromide (22.6 mL, 22.6 mmol). Purification by flash silica chromatography (eluent = 5-10 % EtOAc in hexanes, 40 x 120 mm silica) gave the title compound (2.0 g, 80%) as a pale-yellow oil; R_f = 0.19 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (400 MHz, $CDCl_3$)** δ_H: 1.92 (1H, br s, O*H*), 5.17-5.25 (2H, m, C*H*(CH=C*H*^{A}H^B), 5.36 (1H, dt, *J* 17.2, 1.2, CH(CH=CH^A*H*^{B}), 6.06 (1H, ddd, *J* 17.1, 10.2, 6.1 Hz, CH(C*H*=CH_2), 7.26-7.41 (5H, m, Ar*H*); **^{13}C NMR (101 MHz, $CDCl_3$)** δ_C: 75.4 (*C*HOH), 115.2 (CH=*C*H_2), 126.4 (Ar*C*(2,6)), 127.8 (Ar*C*(4)), 128.6 (Ar*C*(3,5)), 140.2 (*C*H=CH_2), 142.6 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[1]

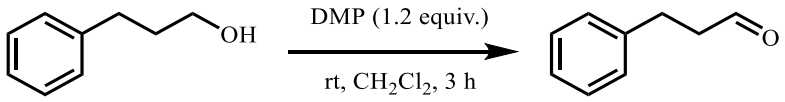
1-(3,5-bis(trifluoromethyl)phenyl)prop-2-en-1-ol



361

The title compound was prepared according to general procedure 1 using 3,5-bis(trifluoromethyl)benzaldehyde (660 μL, 968 mg, 4.0 mmol), THF (4 mL) and vinylmagnesium bromide (4.8 mL, 4.8 mmol). Purification by flash silica chromatography (eluent = 10% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a colourless oil (741 mg, 69%); R_f = 0.22 (eluent = 10% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 422, 602, 665, 681, 708, 827, 847, 901, 962, 1038, 1117, 1163, 1273, 1327, 1379, 1470, 1624, 2893, 2972, 3319, 3385; **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.18 (1H, br s, O*H*), 5.30-5.36 (2H, m, C*H*OH, CH=C*H*^{A}H^B), 5.44 (1H, dt, *J* 18.0, 1.0, CH=CH^A*H*^{B}), 6.00 (1H, ddd, *J* 17.0, 10.5, 6.5, C*H*OH), 7.80 (1H, s, ArC(4)*H*), 7.85 (2H, s, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 74.5 (*C*HOH), 117.6 (CH=*C*H_2), 121.7 (m, Ar*C*(4)), 123.6 (q, *J* 273.0, *C*F_3), 126.6 (m, Ar*C*(2,6)), 131.9 (q, *J* 33.3, Ar*C*(3,5)), 139.1 (*C*H=CH_2), 145.0 (Ar*C*(1)); HRMS (**EI$^+$**) calculated for $[C_{11}H_8OF_6]^+$ $(M)^+$ m/z : 270.0479, found 270.0481, (0.7 ppm).

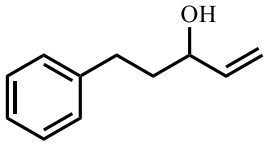
Hydrocinnamaldehyde



A round-bottomed flask equipped with a magnetic stirrer bar was charged with 3-phenyl-1-propanol (680 μL, 681 mg, 5.0 mmol) and CH_2Cl_2 (25 mL). The solution was cooled to 0 °C and was charged with Dess-Martin periodinane (2.5 g, 6.0 mmol). The suspension was allowed to stir at rt for 3 h. Sat. aq. $NaHCO_3$ (15 mL) and CH_2Cl_2 (15 mL) were added to the mixture and the suspension was filtered. The filtrate was washed with sat. aq. $NaHCO_3$ (50 mL). The organic layer was collected, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 5% EtOAc in hexanes, 30 x 70 mm silica) gave the title compound as a colourless oil (527 mg, 79%); R_f = 0.27 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 2.76-2.82 (2H, m, PhC*H*$_2$), 2.97 (2H, t, *J* 7.6, C*H*$_2$(C=O)), 7.17-7.24 (3H, m, ArC(2,4,6)*H*), 7.27-7.33 (2H, m, ArC(3,5)*H*), 9.83 (1H, t, *J* 1.4, H(*C*=O); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 28.3 (Ph*C*H_2), 45.4

($PhCH_2\mathit{C}H_2$), 126.5 (Ar*C*(4)), 128.4 (Ar*C*(2,6)), 128.8 (Ar*C*(3,5)), 140.5 (Ar*C*(1)), 201.7 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[2]

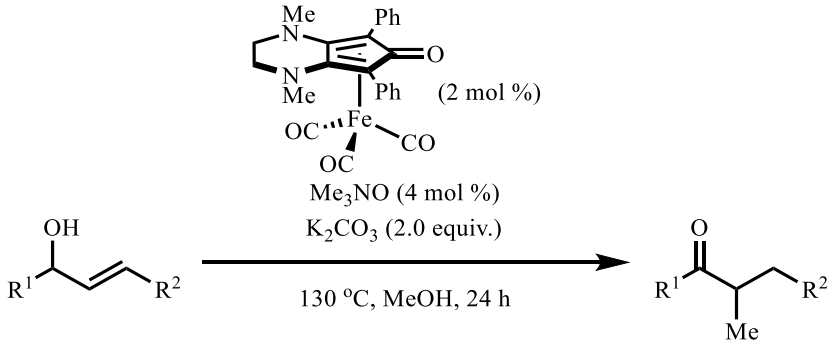
5-phenylpent-1-en-3-ol



The title compound was prepared according to general procedure 1 using hydrocinnamaldehyde (521 µL, 531 mg, 4.0 mmol). Purification by flash silica chromatography (eluent = 7% EtOAc in hexanes, 30 x 150 mm silica) gave the title compound as a colourless oil (431 mg, 66%); R_f = 0.20 (eluent = 10% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.53 (1H, br s, O*H*), 1.80-1.93 (2H, m, $PhCH_2C\mathit{H}_2$), 2.65-2.80 (2H, m, $PhC\mathit{H}_2$), 4.14 (1H, q, *J* 6.5, C*H*OH), 5.14 (1H, dt, *J* 10.5, 1.5, CH=CH^AH^B), 5.25 (1H, dt, *J* 17.5, 1.5, CH=CH$^A\mathit{H}^B$), 5.91 (1H, ddd, *J* 17.5, 10.5, 6.5, C*H*=CH_2), 7.17-7.23 (3H, m, ArC(2,4,6)*H*), 7.26-7.31 (2H, m, ArC(3,5)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 31.8 ($PhCH_2\mathit{C}H_2$), 38.7 ($Ph\mathit{C}H_2$), 72.6 (*C*HOH), 115.1 (CH=*C*H_2), 126.0 (Ar*C*(4)), 128.5 (Ar*C*(2,6)), 128.6 (Ar*C*(3,5)), 141.1 (*C*H=CH_2), 142.0 (Ar*C*(1)). Spectroscopic data in accordance with that stated in the literature.[3]

11.2. Substrate scope

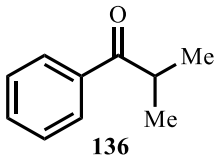
11.2.1. General procedure 2



A 10 mL microwave vial equipped with a stirrer bar was charged with K_2CO_3 (138 mg, 1.0 mmol), allylic alcohol (0.5 mmol), $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %) and [Fe] precatalyst **53** (4.6 mg, 0.01 mmol, 2 mol %). The vial was charged with MeOH (1 mL) before being sealed with a cap. The mixture was left to react at 130 °C for 24 h. The reaction was diluted with EtOAc (1 mL) and quenched with H_2O (1 mL) before being transferred to

a separatory funnel filled with brine (25 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 10 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

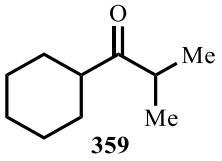
2-methyl-1-phenylpropan-1-one



136

The title compound was prepared according to general procedure 1 using 1-phenylprop-2-en-1-ol (67 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 5-10% EtOAc in hexanes, 20 x 150 mm silica) gave the title compound as a pale-yellow oil (56 mg, 76%); R_f = 0.40 (eluent = 5% EtOAc in hexanes); **^{1}H NMR (500 MHz, $CDCl_3$)** δ_H: 1.22 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 3.56 (1H, hept, *J* 7.0, C*H*(CH$_3$)$_2$), 7.43-7.50 (2H, m, ArC(3,5)*H*), 7.52-7.58 (1H, m, ArC(4)*H*), 7.92-7.98 (2H, m, ArC(2,6)*H*); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 19.3 (CH(*C*H$_3$)$_2$), 35.5 (*C*H(CH$_3$)$_2$), 128.4 (Ar*C*(2,6)), 128.7 (Ar*C*(3,5)), 132.9 (Ar*C*(4)), 136.4 (Ar*C*(1)), 204.6 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[4]

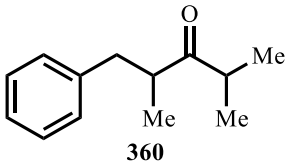
1-cyclohexyl-2-methylpropan-1-one



359

The title compound was prepared according to general procedure 1 using 1-cyclohexylprop-2-en-1-ol (70 mg, 0.5 mmol) giving a 64% NMR yield. Purification by flash silica chromatography (eluent = 2% EtOAc in hexanes) gave the title compound as a colourless oil (6 mg, 8%); R_f = 0.60 (eluent = 20% EtOAc in hexanes); **^{1}H NMR ($CDCl_3$, 500 MHz)** δ_H: 1.06 (6H, d, *J* 7.0, CH(C*H*$_3$)$_2$), 1.15-1.40 (9H, m, C*H*$_2$C*H*$_2$C*H*$_2$,C*H*$_2$C*H*), 1.63-1.71 (1H, m, C*H*), 2.46-2.55 (1H, m, C*H*(C=O)), 2.75 (1H, hept, 7.0, C*H*(CH$_3$)$_2$); **^{13}C NMR (126 MHz, $CDCl_3$)** δ_C: 18.6 (CH(*C*H$_3$)$_2$), 25.9 (*C*H$_2$), 26.0 (*C*H$_2$), 28.8 (*C*H$_2$), 39.1 (*C*H(CH$_3$)$_2$), 49.2 (*C*H(CH$_2$)$_2$), 218.0 (*C*=O). Spectroscopic data in accordance with that stated in the literature.[5]

2,4-dimethyl-1-phenylpentan-3-one

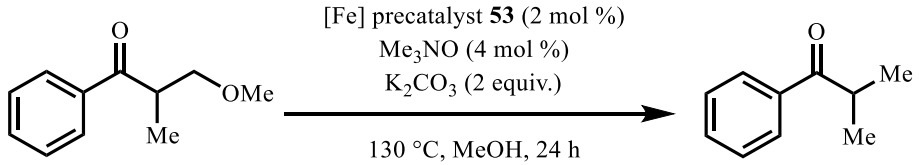


360

The title compound was prepared according to general procedure 2 using (81 mg, 0.5 mmol). Purification by flash silica chromatography (eluent = 0.5-1% EtOAc in hexanes) gave the title compound as a pale yellow oil (73 mg, 77%); R_f = 0.31 (eluent = 5% EtOAc in hexanes); ν_{max} / cm^{-1} (film) 3024, 2972, 2934, 2874, 1711, 1491, 1456, 1379, 1013, 745, 700; **^{1}H NMR (CDCl$_3$, 500 MHz)** δ_H: 0.88 (3H, d, *J* 7.0, CH(C*H*$_3$)(CH$_3$)), 1.01 (3H, d, *J* 7.0, CH(CH$_3$)(C*H*$_3$)), 1.08 (3H, d, *J* 6.5, CHC*H*$_3$), 2.46-2.62 (2H, m, C*H*CH$_3$, C*H*(CH$_3$)$_2$), 2.91-3.05 (2H, m, PhC*H*$_2$), 7.11-7.15 (2H, m, ArC(2,6)*H*), 7.16-7.20 (1H, m, ArC(4)*H*), 7.23-7.29 (2H, m, ArC(3,5)*H*); **^{13}C NMR (CDCl$_3$, 126 MHz)** δ_C: 17.3 (CH(*C*H$_3$)(CH$_3$), 17.9 (CH(CH$_3$)(*C*H$_3$), 18.1 (CH*C*H$_3$), 39.7 (Ph*C*H$_2$), 40.5 (*C*H(CH$_3$)$_2$), 46.7 (*C*HCH$_3$), 126.3 (Ar*C*(4)), 128.5 (Ar*C*(2,6)), 129.1 (Ar*C*(3,5)), 140.1 (Ar*C*(1)); HRMS calculated for $[C_{13}H_{17}]^+$ $((M-H_2O)+H)^+$ m/z : 173.1330, found 173.1331, (+0.6 ppm).

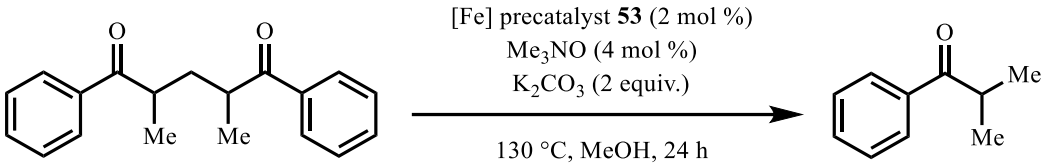
11.3. Mechanistic investigations

11.3.1. Validation of plausible reaction intermediates



229 **136**

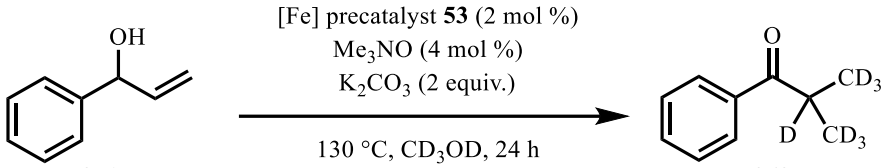
A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (138 mg, 1.0 mmol), $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %) and [Fe] precatalyst **53** (4.6 mg, 0.01 mmol, 2 mol %). The vial was sealed with a cap and was placed under vacuum. After 5 minutes it was flushed with nitrogen and the cycle was repeated three times. Under nitrogen the vial was then charged with MeOH (1 mL) and 3-methoxy-2-methyl-1-phenylpropan-1-one (**229**) (89 mg, 0.5 mmol). The mixture was left to react at 130 °C for 24 h. It was then cooled followed by the addition of mesitylene (70 µL, 60 mg, 0.50 mmol), EtOAc (1 mL) and H_2O (1 mL). The mixture was stirred for 5 min, the cap removed, left to settle for a further 5 min. The top layer was sampled and analysed using ^{1}H NMR. This revealed 95% of **136**.



231 **136**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (138 mg, 1.00 mmol), $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %) and [Fe] precatalyst **53** (4.6 mg, 0.01 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 was repeated three times. Under nitrogen the vial was then charged with MeOH (1 mL) and 2,4-dimethyl-1,5-diphenylpentane-1,5-dione (**231**) (190 mg, 0.5 mmol). The mixture was left to react at 130 °C for 24 h. It was then cooled followed by the addition of mesitylene (70 µL, 60 mg, 0.50 mmol), EtOAc (1 mL) and H_2O (1 mL). The mixture was stirred for 5 min, the cap removed, left to settle for a further 5 min. The top layer was sampled and analysed using ^1H NMR. This revealed 26% of **136**.

11.3.2. Employing CD_3OD as solvent



351 **363**

A 10 mL microwave vial equipped with a magnetic stirrer bar was charged with K_2CO_3 (138 mg, 1.0 mmol), $Me_3NO.2H_2O$ (2.2 mg, 0.02 mmol, 4 mol %), [Fe] precatalyst **53** (4.6 mg, 0.01 mmol, 2 mol %), CD_3OD (1 mL) and 1-phenylprop-2-en-1-ol (67 mg, 0.5 mmol). The vial was sealed with a cap and was left to stir at 130 °C for 24 h. It was then cooled, treated with sat. aq. NH_4Cl (0.5 mL) and H_2O (0.5 mL), washed with EtOAc (15 mL) and transferred to a separatory funnel filled with brine (15 mL). The organic layer was collected, and the aqueous phase washed with EtOAc (2 x 15 mL). The organics were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (eluent = 20% Et_2O in *n*-pentane, 20 x 220 mm silica) gave the title compound as a colourless oil (23 mg, 30%).

11.4. References

1. K. Hayashi, H. Tanimoto, H. Zhang, T. Morimoto, Y. Nishiyama and K. Kakiuchi, *Org. Lett.*, 2012, **14**, 5728-5731.
2. J. Liano, Z. Zhang, X. Tang, W. Wu, W. Guo and H. Jiang, *J. Org. Chem.*, 2015, **80**, 8903–8909.
3. G. A. Molander and L. Jean-Gérard, *J. Org. Chem.*, 2009, **74**, 1297–1303.
4. L.-J. Gu, C. Jin and H.-T. Zhang, *Chem. Eur. J.*, 2015, **21**, 8741–8744.
5. R. A. Swyka, W. G. Shuler, B. J. Spinello, W. Zhang, C. Lan and M. J. Krische, *J. Am. Chem. Soc.*, 2019, **141**, 6864–6868.