New Frontiers in Borrowing Hydrogen Catalysis

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Summary

This thesis describes the exploration and development of new reactions in borrowing hydrogen chemistry. Borrowing hydrogen (or hydrogen-autotransfer) is a sub-category of transfer hydrogenation chemistry, whereby a catalyst is employed to oxidise a starting material, (typically an alcohol) by dehydrogenation, yielding a metal hydride species and a reactive intermediate (typically a carbonyl). An *in situ* reaction is then performed on this reactive intermediate, and the metal catalyst returns the "borrowed" hydrogen to the resultant species, effecting an alkylation. This transformation provides many advantages over classical alkylation methods, but principally that it allows alkylations to be performed without the use of toxic or harmful materials. Alcohols are a typical reagent for these reactions, hence *via* borrowing hydrogen catalysis, alkylation can be effected with an environmentally benign, widely available alkylating agent. Furthermore, these reactions typically yield water as sole by-product, thus this transformation is highly atom economic.

Initial efforts described here were in the exploration of a new regime for enantioselective borrowing hydrogen catalysis. The second chapter describes how enamine and dienamine reactions were attempted, with limited success. Next, work was performed on a cleavage-S_NAr isomerisation reaction, effecting the formation of diaryl ethers, as presented in the third chapter. Multiple examples were formed in high yields.

Attention was then transferred to earth-abundant transition metal-catalysed borrowing hydrogen methods. The fourth chapter discusses a manganese-catalysed *N*-alkylation of sulfonamides. Sulfonamides are important moieties in biologically active molecules. A borrowing hydrogen method for efficient alkylation of sulfonamides with both benzylic and aliphatic alcohols of varied chain lengths was investigated. Multiple examples were formed in high yields. The final chapter discusses the work performed in the tandem reduction-*N*-methylation of nitroarenes, under manganese catalysis. The reduction of nitroarenes is a key reaction in the production of aniline derivatives. Several examples were formed in moderate yields.

Acknowledgements

First and foremost I'd like to thank Louis Morrill. Louis, I know you hate long rambling thanks, so I'll keep it simple – without you, doing a PhD wouldn't have been possible. Coming into your research group and meeting you changed my life. It has been a privilege and a pleasure to work with you these past 5 years.

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List of Abbreviations

Ac	Acetyl
AIDS	Acquired immune deficiency syndrome
API	Active pharmaceutical ingredient
Ar	Aryl
MeO-BIPHEP	2,2′-Bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl
Bn	Benzyl
Bz	Benzoyl
ca	*Circa*
CBz	Carboxybenzyl
cf.	*Conferatur*
COD	1,5-Cyclooctadiene
Cp*	Pentamethylcyclopentadiene
CPA	Chiral phosphoric acid
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutyl aluminium hydride
DMA	Dimethyl acetamide
DMEDA	*N,N‘*-Dimethylethylenediamine

DMF	Dimethylformamide
DMAP	*N,N*-Dimethyl-4-aminopyridine
DMSO	Dimethyl sulfoxide
dpePhos	Bis[(2-diphenylphosphino)phenyl] ether
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Ferrocenediyl-bis(diphenylphosphine)
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
ee	Enantiomeric excess
EWG	Electron-withdrawing group
FDA	Food and Drug Administration
GC	Gas chromatography
GCMS	Gas chromatography-mass spectrometry
HIV	Human immunodeficiency virus
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry
^{i}Bu	*iso*-butyl
^{i}Pr	*iso*-propyl
IR	Infra-red
LUMO	Lowest unoccupied molecular orbital
Mp	Melting point
MS	Mass spectrometry
NAD^{+}	Nicotinamide adenine dinucleotide
NADH	Nicotinamide adenine dinucleotide hydride

NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Nicotinamide adenine dinucleotide phosphate hydride
^{n}Bu	Normal butyl
Nf	Nonaflate, $CF_3(CF_2)_3SO_3^-$
NFSI	*N*-Fluorobenzenesulfonimide
NHC	Nucleophilic heterocyclic carbene
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Np	Naphthyl
^{n}Pr	Normal propyl
Nuc	Nucleophile
PCC	Pyridinium chlorochromate
PEEK	(Poly)ether-ether-ketone
PEG	(Poly)ethylene glycol
Ph	Phenyl
PHMS	(Poly)methylhydrosiloxane
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
PNP	Phosphorus-nitrogen-phosphorus
S_N	Nucleophilic substitution
S_N2	Bimolecular nucleophilic substitution
S_NAr	Aromatic nucleophilic substitution
^{t}Am	*tert*-Amyl
TBS	*tert*-Butyl dimethylsilane

^{t}Bu	*tert*-Butyl
THF	Tetrahydrofuran
THP	Tetrahydropyran
Tol	Tolyl
TON	Turn over number
Ts	Toluene sulfonyl
TSA	Toluene sulfonic acid
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. I. Khan, B. G. Reed-Berendt, R. L. Melen and L. C. Morrill, *Angew. Chemie - Int. Ed.*, 2018, **57**, 12356–12359.
3. B. G. Reed-Berendt, K. Polidano and L. C. Morrill, *Org. Biomol. Chem.*, 2019, **17**, 1595–1607.
4. B. G. Reed-Berendt and L. C. Morrill, *J. Org. Chem.*, 2019, **84**, 3715–3724.
5. W. I. Nicholson, A. C. Seastram, S. A. Iqbal, B. G. Reed-Berendt, L. C. Morrill and D. L. Browne, *ChemSusChem*, 2020, **13**, 131–135.
6. B. G. Reed-Berendt, N. Mast and L. C. Morrill, *European J. Org. Chem.*, 2020, **9**, 1136–1140.

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Chapter 1: Introduction

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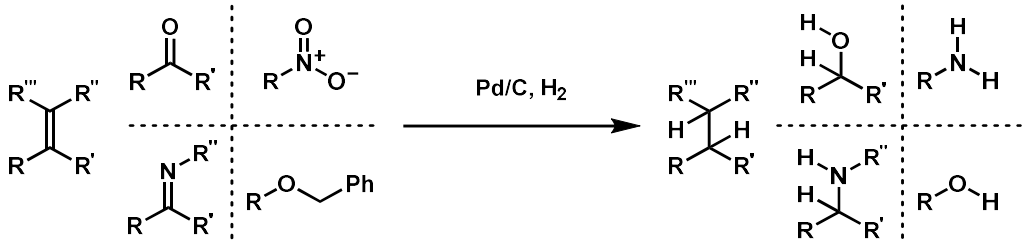
1.1. Hydrogenation chemistry

Hydrogenation is defined as "[a] chemical reaction between molecular hydrogen and an element or compound, ordinarily in the presence of a catalyst."[1] This reaction plays a key role in many aspects of organic and inorganic chemistry, with applications spanning food chemistry, pharmaceutical synthesis, and other chemical industries.[2-5] Examples include margarine production, the synthesis of enantioenriched pharmaceuticals, and the late-stage functionalisation of biologically relevant compounds. Classically, hydrogenation reactions are performed with a metal catalyst and appropriate hydrogen source. This approach may be split into two categories - direct hydrogenation (with molecular hydrogen), or transfer hydrogenation (with compounds or materials as hydrogen sources).

1.1.1. Direct hydrogenation

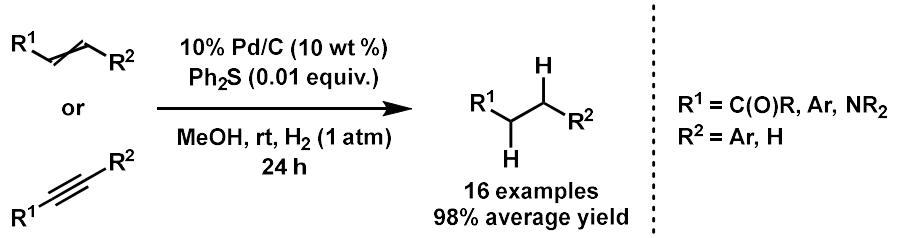
Direct hydrogenation typically employs the use of a hydrogen atmosphere or pressure, and a supported metal catalyst. An example of such reactions is the ubiquitous use of palladium on charcoal, with hydrogen gas[6] (scheme **1.1**).



Scheme 1.1 - Examples of reactions performed by palladium on charcoal

This catalytic system is capable of reducing a wide range of functional groups, from alkenes, carbonyl and imine compounds, to nitroarenes. Hydrogenation is also able to effect the cleavage of benzyl ethers and other moieties; a process known as hydrogenolysis. However, a consequence of this broad applicability is a loss of chemoselectivity in molecules where more than one reducible functional group is present. This is due to the high catalytic activity of this system, and can lead to the

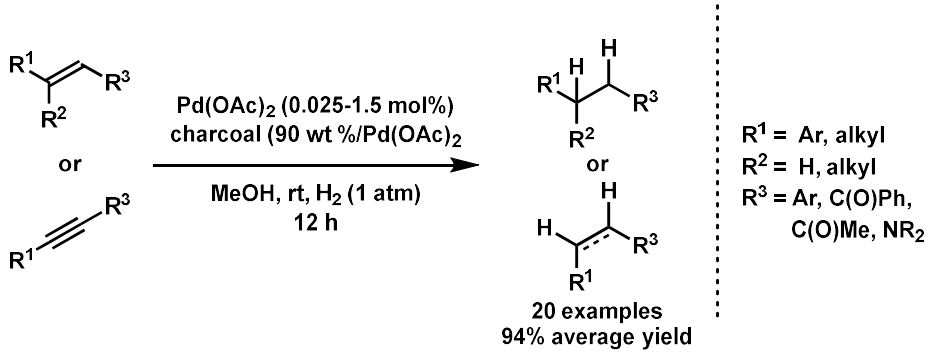
global reduction of a molecule containing multiple compatible functional groups. Much of the methodology in this field is therefore concerned with altering the reactivity of this catalytic system, to effect chemoselective reductions. While modified catalysts of this kind have been in use since the early 1950's, as in the case of the Lindlar catalyst,[7a] A good contemporary example in this context can be taken form the work of Sajiki and co-workers.[7b] Here, diphenylsulfide was employed as a catalyst poison, to strongly bind to the catalyst in order to attenuate the reactivity of the palladium catalyst (scheme **1.2**).



Scheme 1.2 - The use of Ph_2S as a catalyst poison for Pd/C

The authors reported 16 examples in 98% average yield. The chemoselectivity of this catalytic system was in the tolerance of other reducible functional groups, with examples of aldehydes, ketones, amides and esters left unreduced under the reaction conditions. Benzyl esters were also tolerated, without benzyl cleavage reported by the authors.

While many reductions classically use commercial palladium on charcoal, this widely available catalyst is pyrophoric, and activity may vary from batch to batch as particle size of the palladium, and its dispersion on charcoal vary, due to the methods of its preparation. Alternative strategies in the use of this catalyst have been employed in efforts to solve these problems. For instance, the work of Fouquet and co-workers[8] utilised palladium(II) acetate (as a solution in THF) and charcoal to form *in situ* palladium on charcoal, thus bypassing the pyrophoric nature, and reaction-to-reaction variance of the commercial catalyst, while still accessing the benefits of its use, namely it's high activity and surface area (scheme **1.3**).



Scheme 1.3 - *In situ* Pd/C formation

This reaction demonstrated multiple examples of the reduction of secondary and tertiary alkenes and alkynes, with 20 examples in 94% average yield. Examples of reducible functionalities, such as ketones and esters were reported without observed reduction of the undesired functionalities. Furthermore, the authors demonstrated the reduction of 5*α*-cholestan-3*β*-ol. Utilising this as a model substrate, the authors showed that, in comparison to commercially available samples of palladium on charcoal, this method produced a more reliable active hydrogenation catalyst.

Metals besides palladium are widely used in hydrogenation chemistry. Pertinent examples include Wilkinson's catalyst – a sixteen-electron rhodium species[9] (**1**), and Crabtree's catalyst – a sixteen-electron iridium species[10] as homogeneous hydrogenation catalysts (**2**, figure **1.1**).

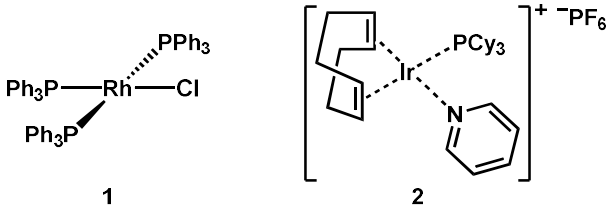
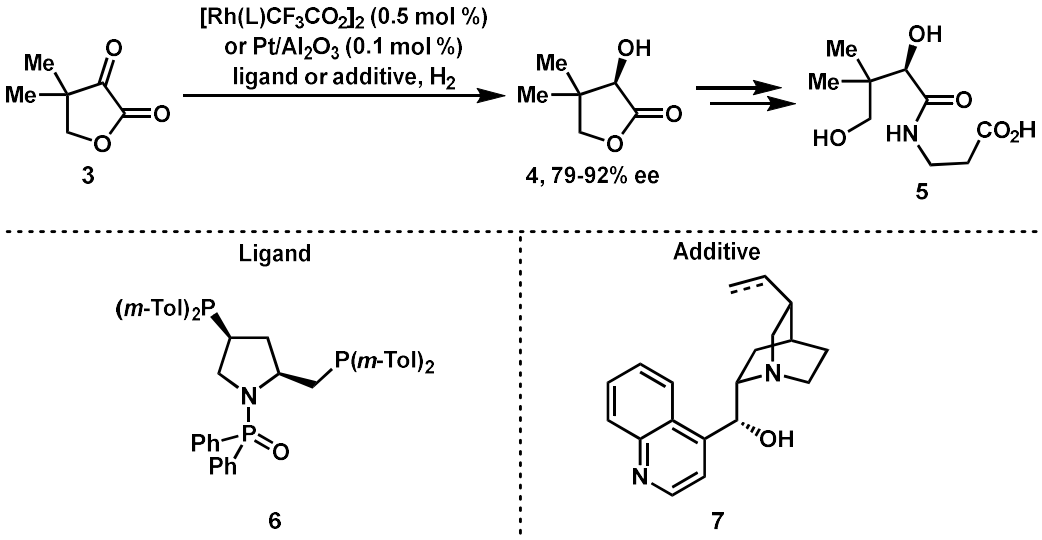


Figure 1.1 - Transition metal catalysts for direct hydrogenation

These molecules, and other homogenous catalysts with differing metals, have been the subject of great literature interest, especially where chiral ligands are utilised to effect enantioselective hydrogenation.[11] An example is in the synthesis (*R*)-pantothenic acid (vitamin B_5, **5**), *via* the key intermediate (*R*)-pantolactone (**4**).[12] Here, multiple studies demonstrated the use of homogeneous ruthenium or heterogeneous palladium catalysts with chiral ligands or additives, to perform the reduction of the intermediate keto-lactone **3** (scheme **1.4**).

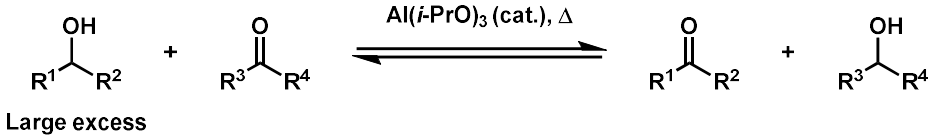


Scheme 1.4 - Methods for the synthesis of (*R*)-pantolactone

The use of such additives and ligands provided high enantiomeric excess of the target compound, demonstrating the broader application of such reductions in the synthesis of enantioenriched compounds. However, despite the broad use of these catalysts and the wide range of applications, the use of molecular hydrogen creates a significant safety issue. Transfer hydrogenation provides an alternative, complementary route towards such reductions, while increasing their safety profile significantly.

1.1.2. Transfer hydrogenation

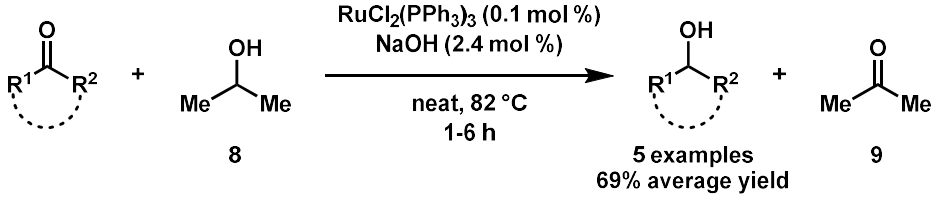
Transfer hydrogenation, by contrast to direct hydrogenation, uses an organic molecule as a hydrogen donor.[13] This has several key benefits, mainly that typical hydrogen donors provide a much safer alternative to hydrogen gas. In additions, many hydrogen donors are relatively inert compounds, which are easily handled, readily available, and typically yield simple organic waste products. A seminal example of transfer hydrogenation is the Meerwein–Pondorf–Verley (MPV) reduction,[14] where simple alcohols may be used as a hydrogen source for the reduction of carbonyl compounds (scheme **1.5**).



Scheme 1.5 - MPV reduction

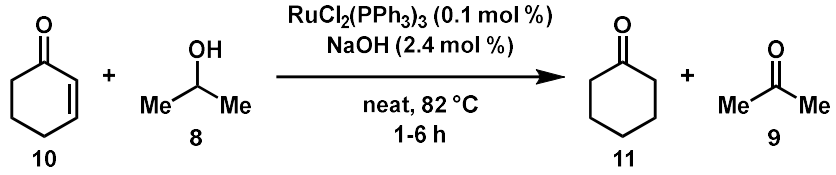
This reaction uses a widely available metal catalyst, and demonstrates applicability towards an array of aldehydes and ketones. Additionally, high chemoselectivity of carbonyl reduction can be observed under these reaction conditions. However, due to this reaction being readily reversible, large excesses of alcohol as reducing agent are required for this reaction to reach completion. Additionally, due to the Lewis acidic nature of the aluminium catalyst, potential side reactions under these conditions often occur. These include aldol condensations (where enolisable positions are available), Tishchenko reactions (with aldehydes), and other reactions at high temperature. Following this work, many other metals were demonstrated to induce the MPV reduction, and despite the drawbacks of early works, the reaction class as a whole finds broad applications in academia and chemical industry.[15]

Other approaches to this method involve the use of precious metal catalysis. The work of Bäckwall and co-workers[16] demonstrated a ruthenium-catalysed transfer hydrogenation of a small range of ketones with *iso*-propanol (scheme **1.6**).



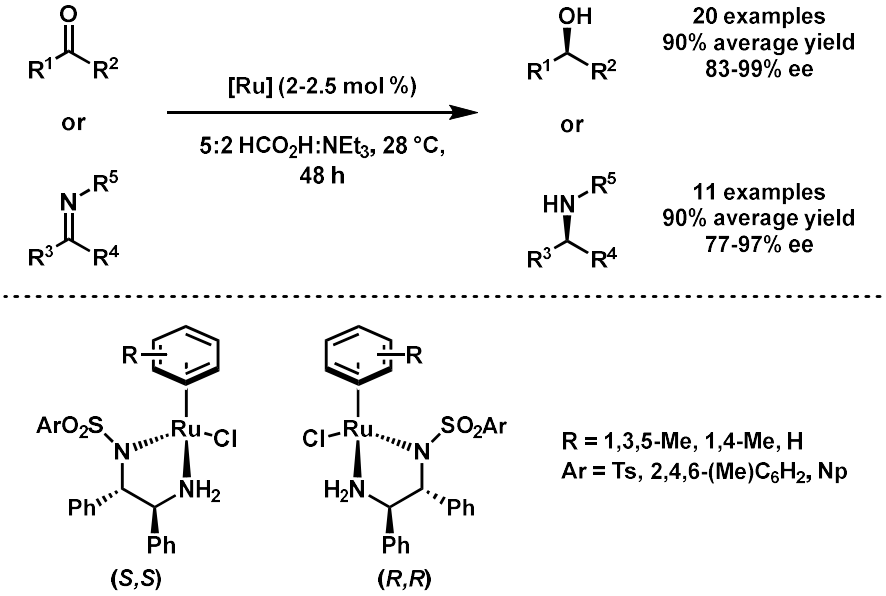
Scheme 1.6 - Ruthenium-catalysed transfer hydrogenation

While only demonstrating a few examples, this work demonstrated a significant reduction in temperature to 82 °C. However, poor selectivity for the reduction of carbonyls was observed in the presence of other functional groups – 2-cyclohexene-1-one as substrate resulted in exclusive 3,4-hydrogenation (scheme **1.7**).



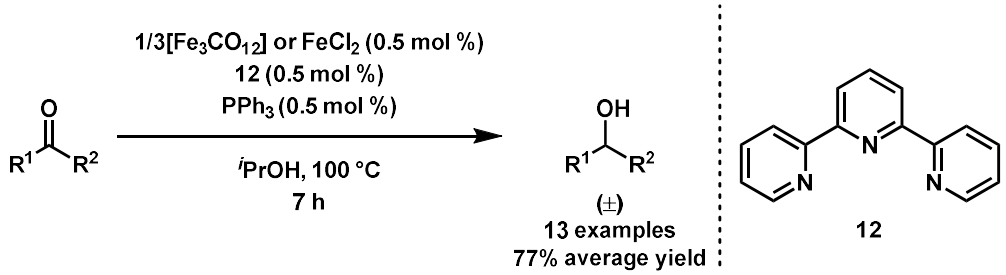
Scheme 1.7 - Selective 1,4- over 1,2-reduction

The extension of this work was to apply well-defined chiral catalysts towards transfer hydrogenation. Noyori and co-workers[17] demonstrated enantioselective transfer hydrogenation of ketones (scheme **1.8**). A wide range of compounds were prepared with 31 examples of enantioselective reductions of aldehydes and ketones, in 90% average yield. High enantiomeric excesses were observed with these catalysts, where the enantiomer of the product could be selected by the choice of ligand. Formic acid was utilised as hydrogen source in this reaction, producing CO_2 as sole by-product.



Scheme 1.8 - Asymmetric transfer hydrogenation

In order to reduce the reliance on precious metal catalysis, recent investigations describe transfer hydrogenation with earth-abundant metal catalysts, such as iron,[18] cobalt,[19] copper[20] and manganese.[21] A representative example can be found in the work of Beller and co-workers[22] (scheme **1.9**).



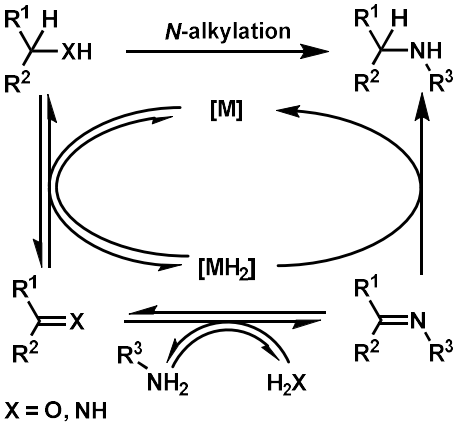
Scheme 1.9 - Iron-catalysed transfer hydrogenation

Here, an *in situ* formed iron catalyst effected the transfer hydrogenation of 13 acetophenone derivatives and aliphatic ketones, in 77% average yield. Both iron catalysts provide benefits over extant precious metal catalysts with regard to cost, and especially where iron(II) chloride is used, the low catalyst loading and wide availability of this species is notable.

This type of transformation can be further extended towards stereoselective catalysis.[18a,19b,20b,21d] Additionally, transfer hydrogenation can also be effected using borane catalysis[23] and frustrated Lewis pair[24] catalysis. However, a general limitation of transfer hydrogenation reactions is the requirement for (super)stoichiometric additives in the form of the reducing agents. Likewise, as these reactions are often reversible (where alcohols are used as reducing agents), large excesses of alcohol are required to drive this reaction to completion. This limits the atom economy of these reactions, and generates large amounts of waste. An alternative procedure, providing higher atom economy and less waste generation, is borrowing hydrogen catalysis.

1.2. The borrowing hydrogen principle

A related reaction to transfer hydrogenation is hydrogen autotransfer, or borrowing hydrogen.[25] This principle is illustrated below with the alkylation of amines (scheme **1.10**).



Scheme 1.10 - A generalised borrowing hydrogen catalytic cycle

Here, a metal catalyst that is capable of performing transfer hydrogenation of alcohols or amines is utilised to perform an *in situ* oxidation of the starting material (be that alcohol or amine), resulting in the corresponding unsaturated compound (i.e. an aldehyde or imine). An intermediate reaction – in this case a condensation reaction – can now be performed upon the *in situ* generated reactive intermediate with an external amine. This extrudes the sole by-product of this reaction (water or ammonia). The metal hydride species formed in the initial oxidation can now return the "borrowed" hydrogen from the initial oxidation to the formed imine, effecting reduction of the imine to product amine, and regenerating the metal catalyst, thus closing the catalytic cycle.

This formally redox-neutral process allows the use of simple alcohols or amines as alkylating agents, where the sole by-product is water or ammonia. Thus, these reactions are highly atom economic. This offers advantages over classical alkylating reagents, such as alkyl halides, as these reagents are both less atom economic, and significantly more toxic. The use of alcohols as alkylating agents by other routes would require stoichiometric activation, such as the Mitsunobu reaction.[26] Other examples include an array of Lewis or Brønsted acid-catalysed transformations.[27] However, these reactions can be prone to self-alkylation of the alcohol, and the reactivity of these methods is precluded to S_N-type reactions. By contrast, borrowing hydrogen catalysis allows access to a wide range of carbonyl chemistry, as opposed to being limited to substitution reactions. This route also provides access to this chemistry without the downsides of using aldehydes as starting materials.[28] Furthermore, this process avoids stoichiometric oxidation and reduction steps that would otherwise be required for a selective monoalkylation transformation (as in the case of reductive amination), and allows this complex reaction to occur in a one-pot fashion. The utility of alcohols as alkylating agents is also desirable, due to their wide abundance and commercial availability.

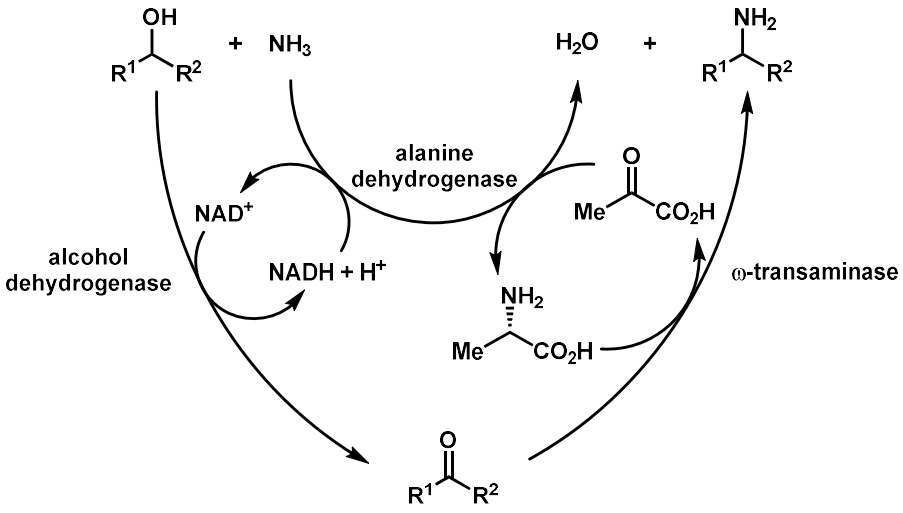
However, there are disadvantages associated with borrowing hydrogen chemistry. Typically these reactions require high temperatures that preclude the use of sensitive functional groups. Furthermore, reactions of this type are highly challenging to perform enantioselectively, with few examples published in the literature. Finally, typical metals required for this process are precious metals, such

as ruthenium, rhodium, osmium and iridium (though there have been recent attempts to explore the use of earth-abundant transition metals for this chemistry[29]).

Borrowing hydrogen chemistry can be widely split into 3 classes - biocatalytic, heterogeneous, and homogeneous reactions. While earlier examples date back to the early 1900's,[30] this introduction will cover the recent advancements and discoveries in borrowing hydrogen catalysis.

1.3. Biocatalytic borrowing hydrogen methods

Biocatalysis has received much attention in recent literature.[31] Several applications of this concept utilise the borrowing hydrogen principle, where a combination of enzymes allow the use of alcohols as alkylating agents. An early example can be taken from the work of Kroutil and co-workers.[32] Here, a network of 3 enzymes were used; an alcohol dehydrogenase, an alanine dehydrogenase, and a ω-transaminase. The action of these three enzymes in tandem effected the alkylation of amines with alcohols. The catalytic cycle for such enzymatic pathways is found below (scheme **1.11**).

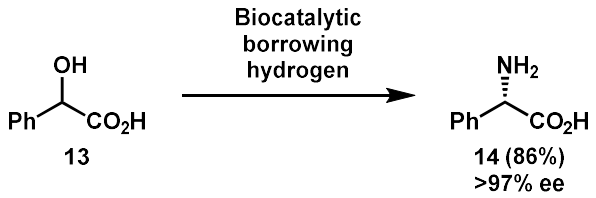


Scheme 1.11 - Biocatalytic borrowing hydrogen methodology

The alcohol dehydrogenase oxidises the alcohol to its corresponding carbonyl compound. This process consumes NAD^+ (nicotinamide adenine dinucleotide), and generates its reduced form (NADH), and a proton. The formed carbonyl compound

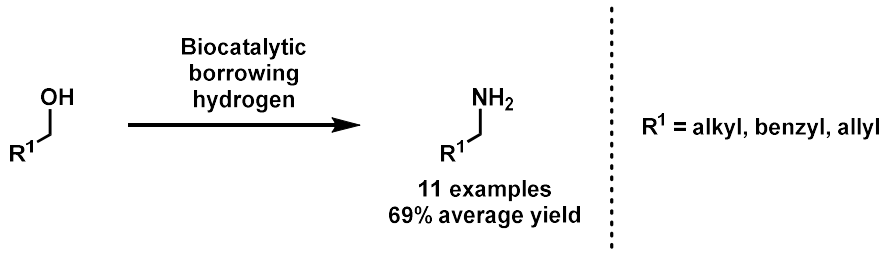
can now be aminated by alanine, *via* the ω-transaminase, producing the target amine product. This in turn generates pyruvate. The alanine dehydrogenase transforms pyruvate back into alanine, with the concurrent oxidation of NADH back to NAD^+. This consumes ammonia, and generates water as sole by-product.

Initial work studied the racemisation of mandelic acid (**13**), and subsequent transformation into phenylglycine **14** (scheme **1.12**).



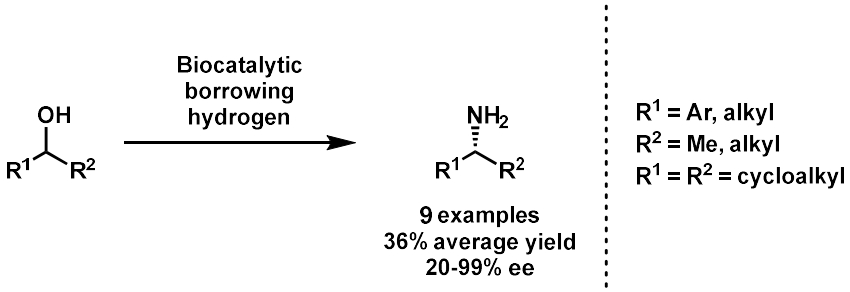
Scheme 1.12 - Dynamic kinetic resolution of acid 13

Phenylglycine was produced in an 86% yield, with greater than 97% enantiomeric excess. This work was then extended to examples of primary alcohols and diols,[33] which could be transformed into the corresponding amines or diamines (scheme **1.13**).



Scheme 1.13 - Scope of primary alcohols in biocatalytic borrowing hydrogen

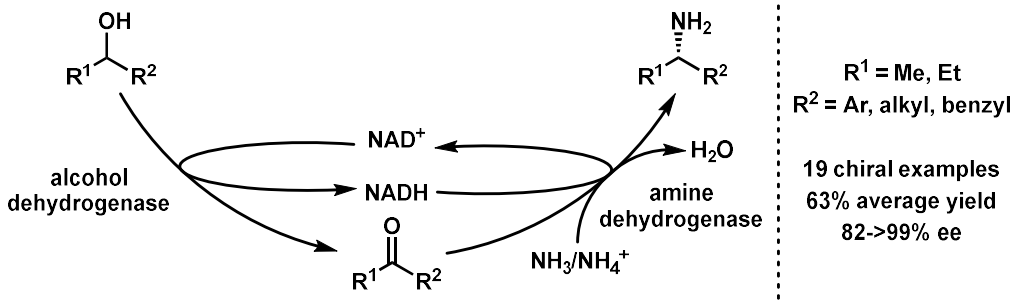
11 examples were reported with 69% average yield. This work was further applied to the amination of secondary alcohols[34] (scheme **1.14**).



Scheme 1.14 - The scope of early biocatalytic borrowing hydrogen

9 examples of enantioenriched amines were reported, in 36% average yield and a wide range of enantiomeric excesses. An example of high enantiomeric excess can be observed when (*S*)-4-phenylbutan-2-ol was employed as starting material, resulting in product (*S*)-4-phenylbutan-2-amine in 47% yield and 98% enantiomeric excess. However, the 36% average yield, small scope, and variance of enantioselectivity demonstrated by this method limited its further applications.

Further extensions of this method can be found in the work of Turner and co-workers.[35] Here, an alternative, smaller network of enzymes was used, resulting in the following catalytic cycle (scheme **1.15**).



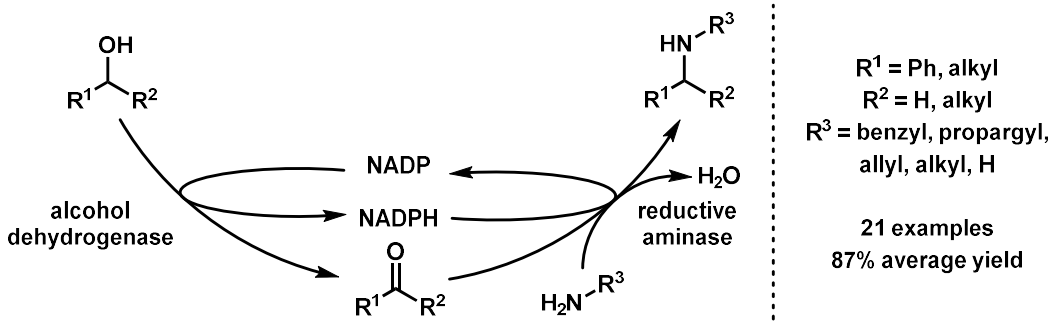
Scheme 1.15 - Smaller enzyme networks for biocatalytic borrowing hydrogen

As before, an alcohol dehydrogenase generates NADH from NAD^+. However, a more generic amine dehydrogenase was utilised here, which consumes ammonia and NADH to effect the desired amination, producing water and NAD^+, and closing the catalytic cycle.

A range of racemic and chiral secondary alcohols was used as starting materials. By altering which amine dehydrogenase was used, the authors demonstrated retention or inversion of stereochemistry where chiral alcohols were used, or enantioselective reactions where racemic secondary alcohols were used. The authors reported 19 examples with up to >99% enantiomeric excess, and 62% average yield.

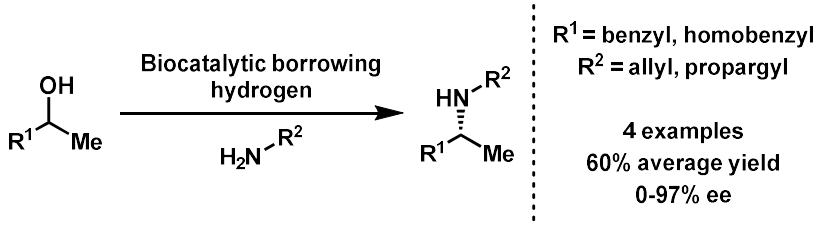
Turner and co-workers extended this method towards the use of primary amines, instead of ammonia as the amine source.[36] This was achieved with a reductive aminase enzyme, replacing the amine dehydrogenase, and an alteration of NAD^+ to NADP (nicotinamide adenine dinucleotide phosphate) to effect amination with

primary amines, following a similar catalytic cycle to that earlier discussed (scheme **1.16**).



Scheme 1.16 - Primary amines in biocatalytic borrowing hydrogen

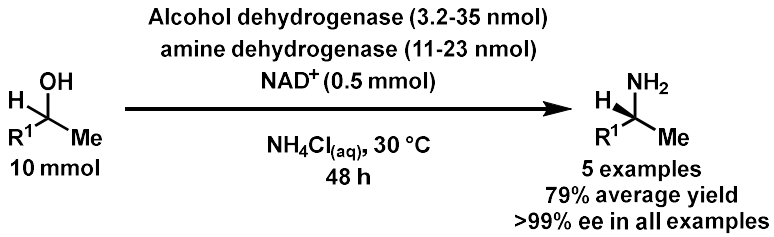
21 examples were reported, with 87% average yield. Both primary and secondary alcohols were used as alkylating agents, to yield the corresponding secondary amines. The authors also reported attempts towards an enantioselective variation of this method, by employing secondary alcohols and an alternative range of enzymes to effect this transformation (scheme **1.17**).



Scheme 1.17 - Enantioselective biocatalytic borrowing hydrogen with primary amines

4 products were reported, with 60% average yield. However, a wide range of enantioselectivities were also observed, limiting the further applications of this process.

A final example of this method can be found in the work of Mutti and co-workers,[37] which built on the earlier work of Turner and co-workers,[35] where alcohol dehydrogenase and amine dehydrogenase were used. However, a key modification presented in this work was to immobilise the enzymes on a porous glass support. This provided a heterogeneous approach to biocatalysis, with excellent results at nanomolar amounts of enzyme (scheme **1.18**).



Scheme 1.18 - Heterogeneous biocatalytic borrowing hydrogen

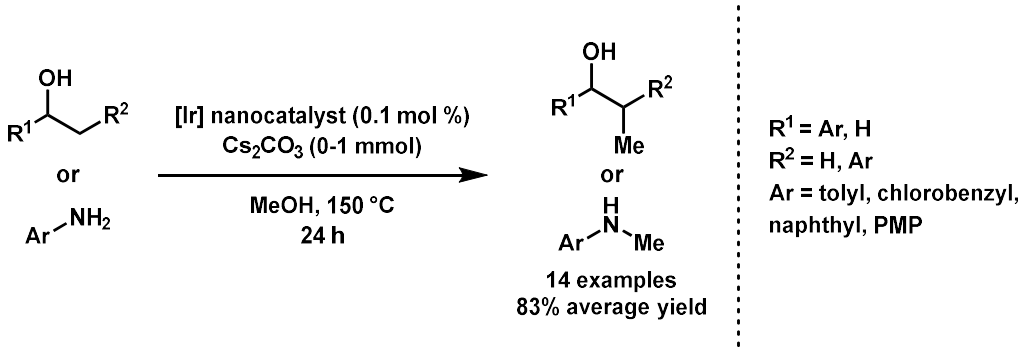
Despite being demonstrated in only 5 examples, this reaction proceeded with high enantiomeric excesses and good average yield, together with the low reaction temperature and catalyst loading, and high operating scale of the reaction. This demonstrated the potential for further applications of this method.

Overall, biocatalytic routes provide a low temperature route to borrowing hydrogen catalysis. However, the requirements for engineered enzymes in order to effect good substrate tolerance, and likewise the necessity for aqueous conditions limit the scope for further applications of biocatalytic borrowing hydrogen. However, these represent some excellent examples of enantioselective borrowing hydrogen catalysis.

1.4. Heterogeneous borrowing hydrogen methods

Heterogeneous borrowing hydrogen catalysis has been a field of much interest in recent years.[37] This is largely due to the attractive industrial prospects of heterogeneous catalysis, the ease of recycling and separating catalysts from reactants, and the operational simplicity of such methods. The majority of heterogeneous work has been undertaken with precious metal catalysts, 2 pertinent examples of which are discussed below.

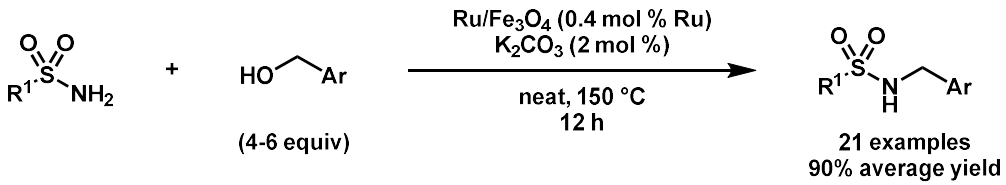
An example of heterogeneous iridium catalyst can be taken from the work of Obora and co-workers.[39] Here, iridium nanoparticles were used to effect methylation of a variety of nucleophiles, with methanol as methylating reagent and solvent for the reactions (scheme **1.19**).



Scheme 1.19 - Iridium nanoparticle-catalysed methylation with methanol

A range of primary and secondary alcohols were employed, resulting in the *β*-alkylation of these alcohols, in 83% average yield. The use of alcohol as substrates is notable, as they also have the potential to enter the borrowing hydrogen cycle. Despite this, no self-alkylation of the starting material was reported by the authors, demonstrating excellent selectivity. Anilines could also be employed, extending the substrate scope. Additionally, the authors reported TON's of up to 310,000 for the methylation of anilines. These values were achieved by reducing the catalyst loading to 10^{-4} mol %. This low catalyst loading demonstrated the high reactivity of this iridium catalyst, and showed great potential for further applications.

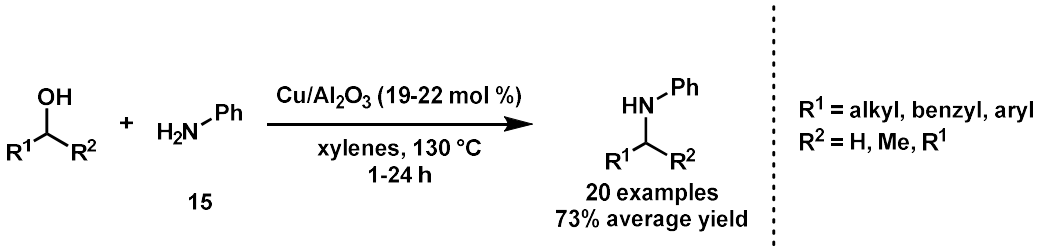
An example of heterogeneous ruthenium catalysis can be taken from the work of Beller and co-workers.[40] A supported ruthenium catalyst was employed to effect the alkylation of sulfonamides, using benzyl alcohols as alkylating reagent (scheme **1.20**).



Scheme 1.20 - Hetereogenous alkylation of sulfonamides with alcohols

An array of benzylic alcohols were reported to alkylate a range of aryl and alkyl sulfonamides, with 21 examples with 90% average yield, at 0.4 mol% ruthenium loadings. The authors also reported TON's within the range of 111-223 for this catalytic system. Once again, the low catalyst loading demonstrated the utility of borrowing hydrogen catalysis in this heterogeneous fashion.

Some work has been undertaken to perform heterogeneous borrowing hydrogen catalysis with earth-abundant metals.[41] A representative example can be found in the work of Zaccheria and co-workers,[41e] where a supported copper/alumina catalyst was used to effect the *N*-alkylation of aniline (**15**, scheme **1.21**).



Scheme 1.21 - Heterogeneous copper-catalysed amine *N*-alkylation

The authors report a range of alcohols, including secondary cyclic alcohols as alkylating agents, with 20 examples in 73% average yield. Alternative amines to aniline were not reported. Additionally, this transformation required high catalyst loadings, especially when compared to previously discussed homogeneous examples. This is a disadvantage in terms of the amount of catalyst required, however the use of an earth abundant catalyst is desirable.

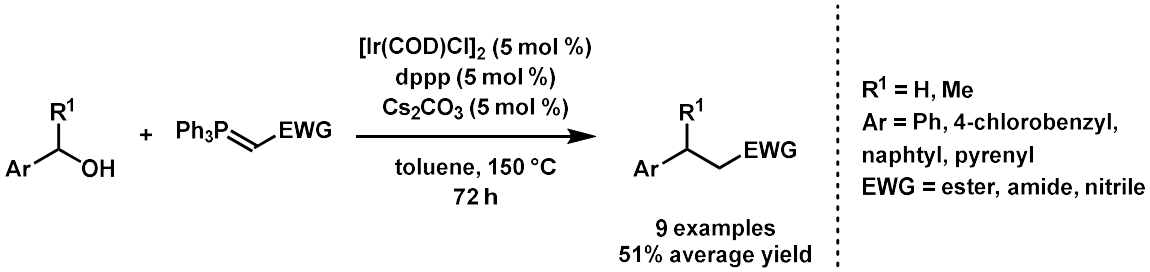
While heterogeneous catalysis has obvious power with regards to ease of separation of reagents and catalysts, homogeneous catalysis provides a complementary route, where commercially available materials can be used directly as catalysts.

1.5. Homogeneous borrowing hydrogen methods

Homogeneous catalysis represents the largest bulk of borrowing hydrogen work in recent years. The term was coined by Williams and co-workers in 2002,[42] but since this report the scope of this methodology has been extended to a wide range of precious and earth-abundant metal catalysis. The borrowing hydrogen chemistry of a selection of metals typical in the literature will be discussed.

1.5.1. Iridium-catalysed borrowing hydrogen methods

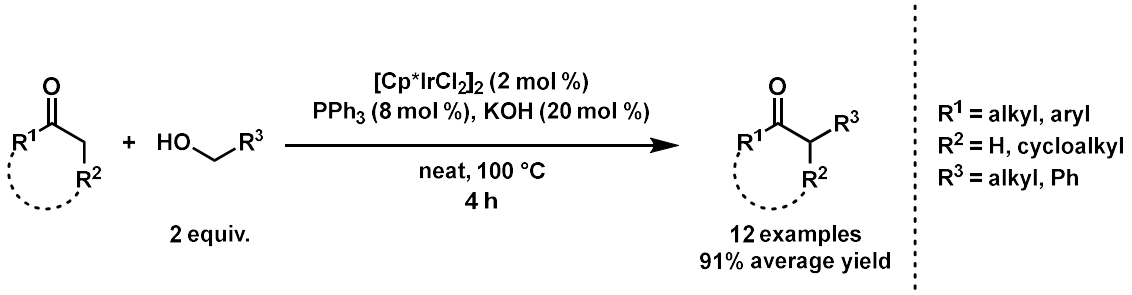
Early work in homogeneous borrowing hydrogen catalysis was reported by Williams and co-workers,[42] where a sixteen-electron iridium(I) pre-catalyst with dppp as ligand were used to effect an "indirect" Wittig reaction[43] of alcohols. This proceeded *via in situ* oxidation of alcohols, subsequent Wittig reaction, and reduction of the formed alkene (scheme **1.22**).



Scheme 1.22 - Iridium-catalysed indirect Wittig reaction of alcohols

Despite reporting 51% average yield, this work demonstrated the breadth of carbonyl chemistry available to borrowing hydrogen methodology, along with impressive tolerance of the catalyst to stoichiometrically generated triphenyl phosphine. However, a clear limitation of this work is that the catalyst was incapable of closing the catalytic cycle without the presence of an electron-withdrawing group; the formed alkene cannot be reduced without it, and thus the active catalytic species cannot be regenerated. Additionally, this procedure operated at high catalyst loading - 5 mol % iridium. Regardless, this early work not only coined the term "borrowing hydrogen", but also generated much interest in this area.

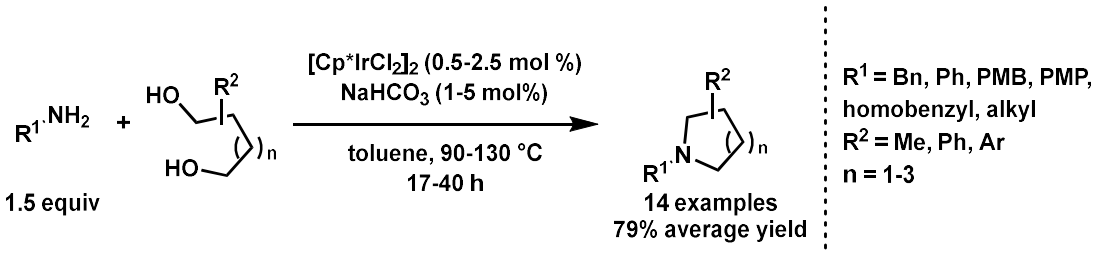
Alternative reactivity was described by Ishii and co-workers,[44] who reported the *C*-alkylation of ketones with alcohols, utilising the same iridium catalyst with triphenylphosphine as ligand, and potassium hydroxide as base (scheme **1.23**).



Scheme 1.23 - Iridium-catalysed *C*-alkylation of ketones

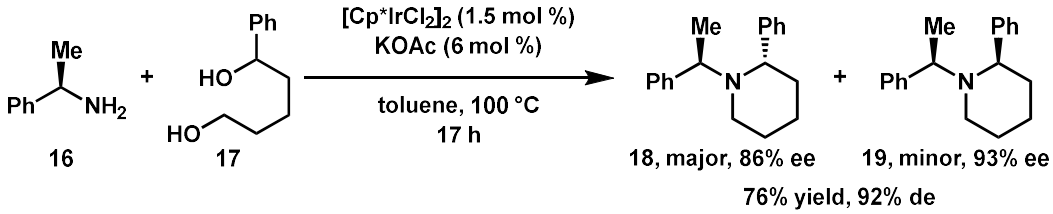
With lower iridium loading than the two previous examples (4 mol %), and shorter reaction times, this system demonstrated 12 examples in 91% average yield. This work represented an extension of iridium-catalysed borrowing hydrogen methodology towards *C*-alkylation processes.

Yamaguchi and co-workers continued to investigate this catalyst in *N*-alkylation processes, towards the synthesis of heterocycles.[45] Here, however, intramolecular systems were investigated, with diols as electrophiles, and primary amines as nucleophiles, to form saturated nitrogen heterocycles (scheme **1.24**).



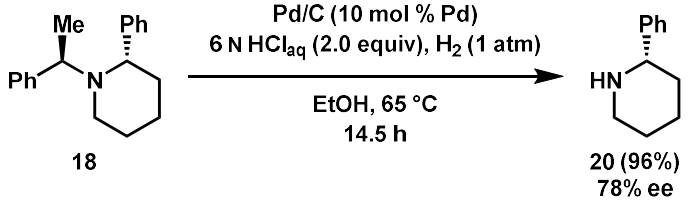
Scheme 1.24 - Intramolecular heterocycle formation with diols

Here, the authors report 14 examples of heterocyclic products with 1-5 mol % iridium, in 79% average yield. The heterocycles reported include pyrrolidines, piperidines, azepanes, indolines, tertrahydroisoquinolines, and morpholines. This approach provides significant benefits over more classical routes, which might take a dicarbonyl compound with stoichiometric reducing agents - namely a reduction in the amount of reagents used. The authors extended this work towards chiral heterocycle formation (scheme **1.25**).



Scheme 1.25 - Diasterospecific heterocycle formation

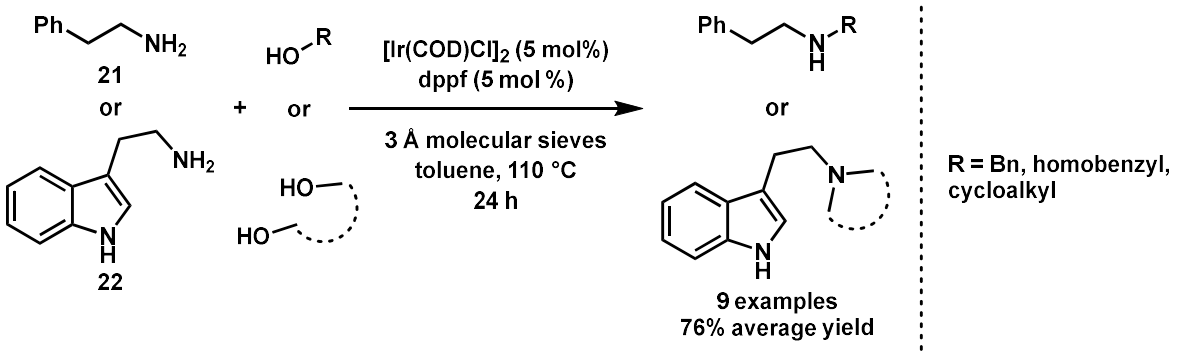
Here, a chiral amine is used to direct final hydride addition to a formed imine/iminium species, resulting in the formation of two chiral piperidine derivatives. The low enantiomeric excesses were attributed to racemisation of the auxiliary by isomerisation of the imine or iminium intermediates. The authors also demonstrated removal of the chiral 1-phenylethyl fragment by palladium-catalysed hydrogenation (scheme **1.26**).



Scheme 1.26 - Palladium-catalysed removal of the chiral auxhiliary

This allowed the authors to report (*S*)-2-phenylpiperidine **20** in a 96% yield, with 78% enantiomeric excess. Despite the relatively low enantiomeric excess of the final product, this is a good example of an approach towards stereoselective borrowing hydrogen.

Williams and co-workers extended this work towards the *N*-alkylation of tryptamine and phenethylamine with alcohols.[46] These molecules were selected due to the prevalence of these motifs in medicinal chemistry and drug molecules. A small range of alcohols were applied to both molecules (scheme **1.27**).

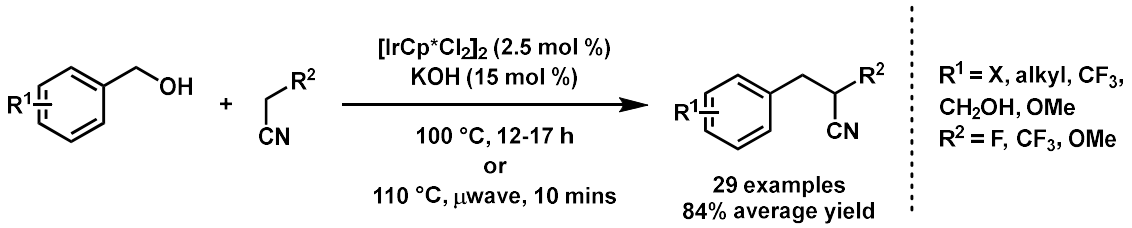


Scheme 1.27 - *N*-alkylation of tryptamine and phenethylamine

9 examples of the resulting compounds were isolated in 76% average yield. Several examples of diols were also applied as alkylating reagents to produce heterocyclic amines. This work bears much similarity to that of Yamaguchi and co-workers,[44] but demonstrated the use of an iridium(I) pre-catalyst, rather than an iridium(III) pre-catalyst.

Williams and co-workers reported further studies of iridium-catalysed borrowing hydrogen reactions.[47] Here the authors reported multiple reactions, including a Horner-Wadsworth-Emmons reaction (using phosphonates and allylic alcohols), the alkylation of nitroalkenes (with secondary alcohols as nucleophiles), Knoevenagel-type condensations (from 1,3-dicarbonyl compounds and alcohols), and the alkylation of *β*-ketonitriles (with alcohols as electrophiles). This work demonstrated the proof-of-concept that these reactions were compatible with borrowing hydrogen catalysis, but very few examples reported.

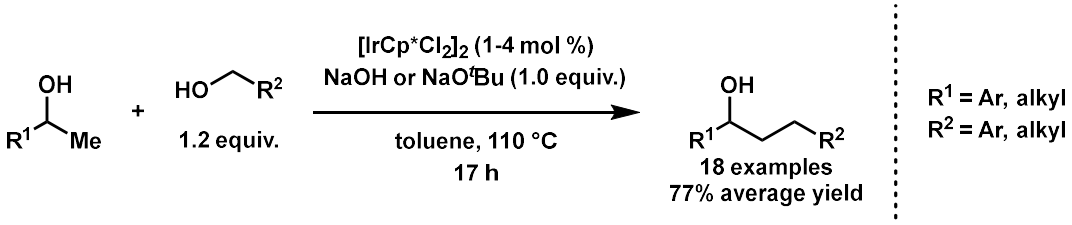
After this proof-of-concept work, Grigg and co-workers reported the alkylation of arylacetonitriles with benzyl alcohols.[48] Using standard batch chemistry, or microwave assistance, an iridium(III) pre-catalyst and catalytic base, an efficient alkylation was reported (scheme **1.28**).



Scheme 1.28 - Alkylation of arylacetonitriles with benzyl alcohols

With 5 mol % loading of iridium, this transformation was demonstrated with 29 examples, in 89% average yield. Furthermore, products arising from bis- and trisbenzyl alcohols were tolerated, and the corresponding products recovered in good yields. This reaction demonstrates the selectivity of reduction towards the formed phenylacrylonitrile, instead of reduction of the nitrile moiety itself. Grigg and co-workers later extended this procedure towards the *C*-alkylation of *N*-methyl barbituric acids.[49]

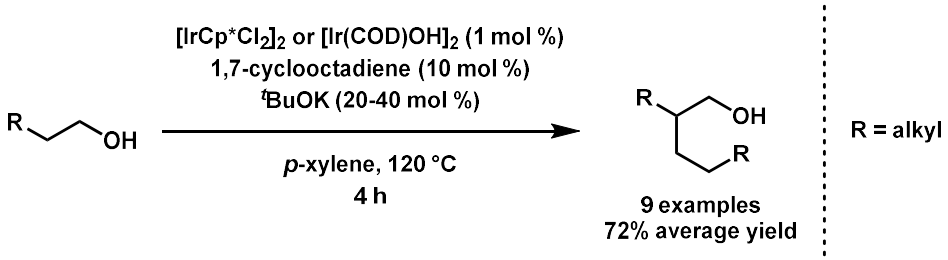
Yamaguchi and co-workers reported the *β*-alkylation of alcohols with alcohols, utilising $[IrCp^*Cl_2]_2$.[50] 18 examples were reported with 77% average yield (scheme **1.29**).



Scheme 1.29 - *β*-Alkylation of secondary alcohols with alcohols

Despite the similarity to previously reported *C*-alkylation work, this demonstrated the ability of both alcohols to be active in the catalytic cycle, allowing alcohols to be used as both the nucleophilic and electrophilic component in the reaction mixture. This reaction was also impressive for its selectivity – neither self-alkylation of either starting material, nor further alkylation of the product were observed.

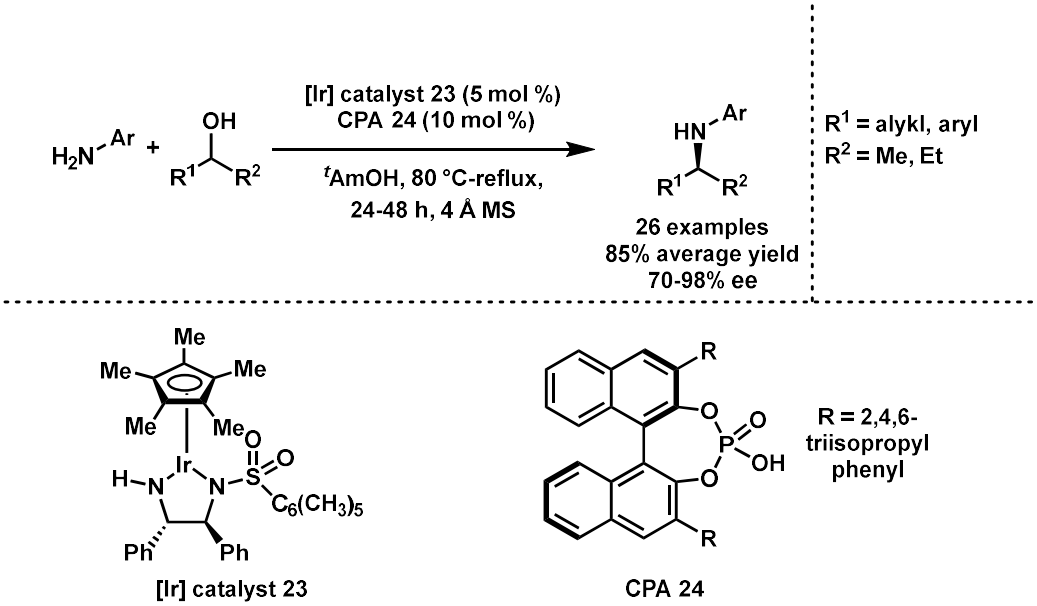
Ishii and co-workers described a similar transformation,[51] but in the form of the Guerbet reaction, a common method to convert low molecular weight alcohols into higher molecular weight products.[52] Here, aliphatic alcohols were employed to produce *β*-branched, dimeric alcohols (scheme **1.30**).



Scheme 1.30 - The Guerbet reaction *via* borrowing hydrogen catalysis

This work demonstrated 9 examples of Guerbet products with 72% average yield, with both alcohols acting as both electrophiles and nucleophiles in the catalytic cycle.

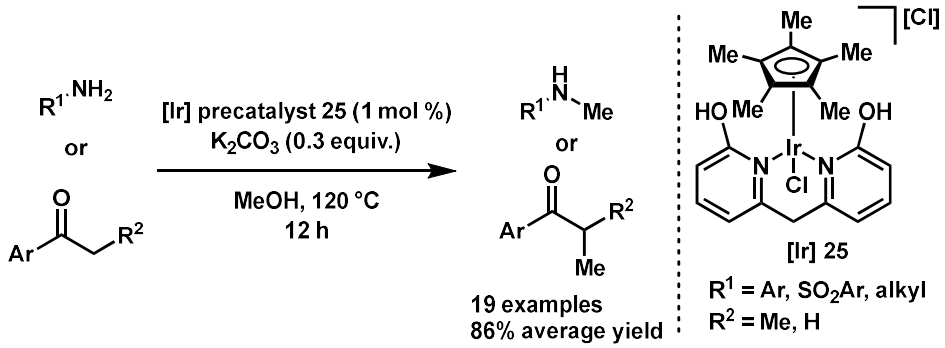
This concludes a summary of the types of reaction accessible by borrowing hydrogen chemistry, as illustrated *via* iridium catalysis. A selection of state-of-the-art iridium-catalysed borrowing hydrogen chemistry will now follow. An example from Zhao and co-workers[53] demonstrated enantioselective borrowing hydrogen, *via* dual catalysis with a chiral Brønsted acid (scheme **1.31**).



Scheme 1.31 - Enantioselective borrowing hydrogen synthesis of chiral seconary amines

Here, an enantioenriched chiral phosphoric acid (CPA) was used to perform face selective protonation of the imine intermediate, resulting in selective hydrogenation of the imine, based on the steric blocking of one face by the conjugate base of the CPA. An enantioenriched, sixteen-electron iridium(III) complex was also used to aid enantioselection. This transformation demonstrated 26 examples in 85% average yield and up to 98% enantiomeric excess. This work is one of the few examples of enantioselective borrowing hydrogen chemistry in the literature, performing a powerful stereoselective alkylation reaction from simple alcoholic starting materials.

Recent iridium-catalysed borrowing hydrogen literature involves developments towards alternative catalyst scaffolds and reactivity for challenging transformations. A good example can be taken from the work of Chen and co-workers[54] (scheme **1.32**).



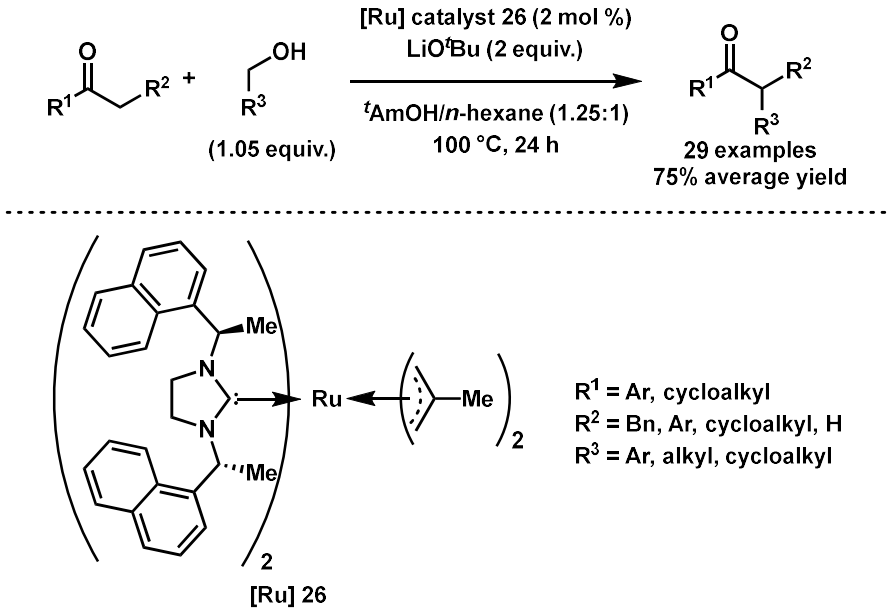
Scheme 1.32 - Iridium-catalysed methylation with methanol

Methylation of 19 examples of amines and ketones with methanol are reported in this work, with 86% average yield. This demonstrated the broad applicability of this iridium(III) pre-catalyst scaffold. Exclusive monomethylation was reported, and selective methylation with methanol is impressive, as it has multiple advantages over other methylation procedures, principally the low cost of the methylating reagent.

In summary, iridium can be utilised to perform a range of *N*- and *C*-alkylation processes, utilising a range of catalyst structures. The following section on ruthenium catalysis in borrowing hydrogen will focus more on pertinent examples in the literature.

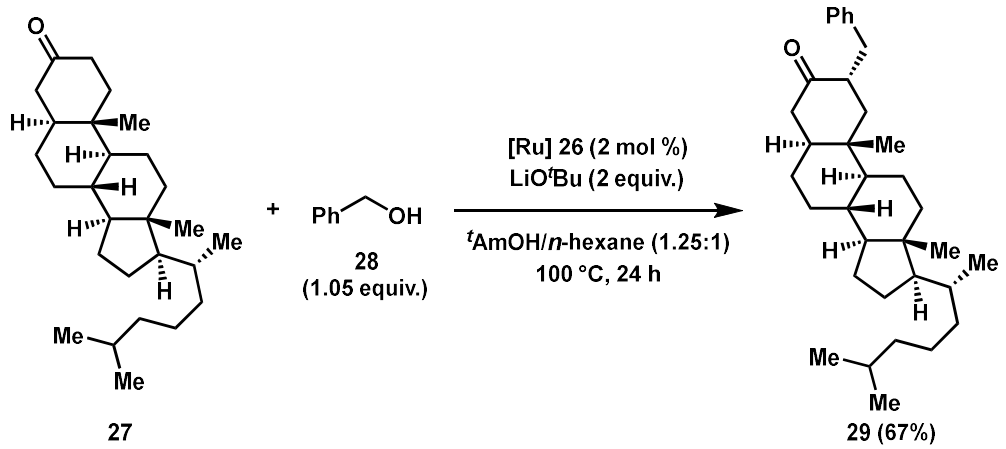
1.5.2. Ruthenium-catalysed borrowing hydrogen methods

While early reports in the field of ruthenium-catalysed borrowing hydrogen were made in 2004,[55] this reaction reports an indirect Wittig reaction (similar to previously discussed iridium chemistry).[42] A pertinent example of recent, more broadly applicable *C*-*C* bond forming reactions with ruthenium can be taken from the work of Glorius and co-workers (scheme **1.33**).[56]

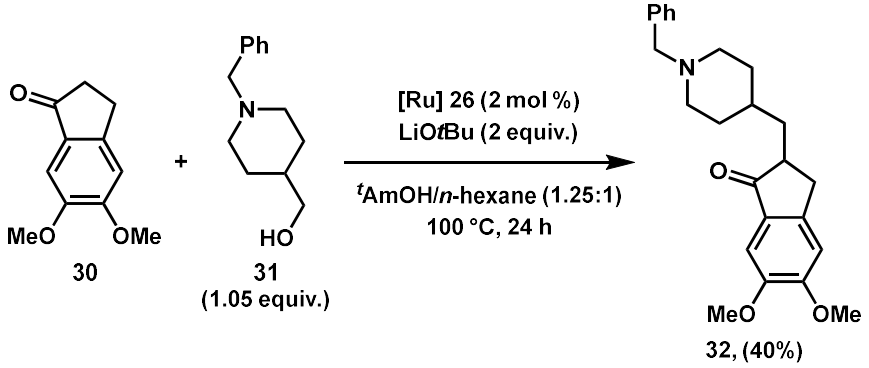


Scheme 1.33 - Ruthenium-catalysed alkylation of ketones

Here, a ruthenium(II) NHC precatalyst is employed to effect the alkylation of ketones The authors demonstrated 29 examples in high yields, including multiple examples on gram-scale. Base was employed to deprotonate both the alcohol starting material, to facilitate oxidation, and to deprotonate the ketone to render it more nucleophilic. The authors extended this work to the alkylation of cholestanone **27 (**to yield product **29** as a single diastereomer), and the synthesis of donepezil (**32**), a drug for the treatment of Alzheimer's disease[57] (schemes **1.34** and **1.35** respectively).



Scheme 1.34 - Cholestanone alkylation

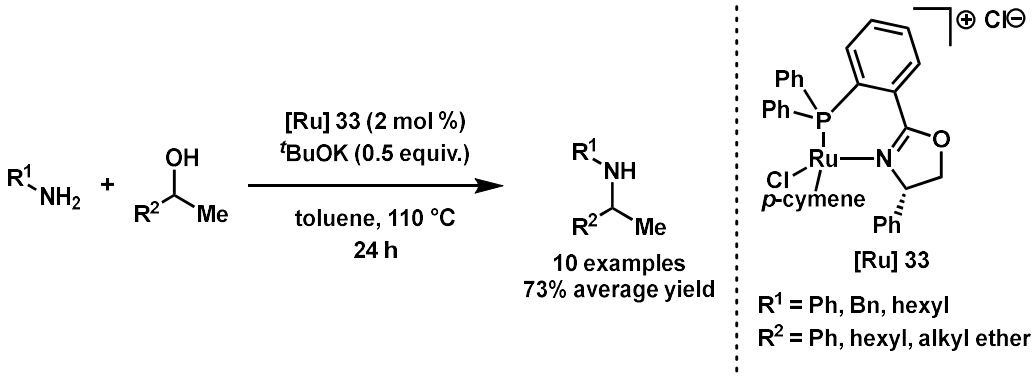


Scheme 1.35 - The synthesis of donepezil

Where product **29** was recovered in 67% yield, donepezil **32** was recovered in a modest 40% yield. However, this was an example of the synthesis of this drug molecule in a single step from commercially available materials. Additionally, a small range of di-alkylations were reported, from acetophenone derivatives. This work also reported a relatively low temperature of 100°C, in comparison the higher temperatures previously discussed. This low temperature, along with the broad

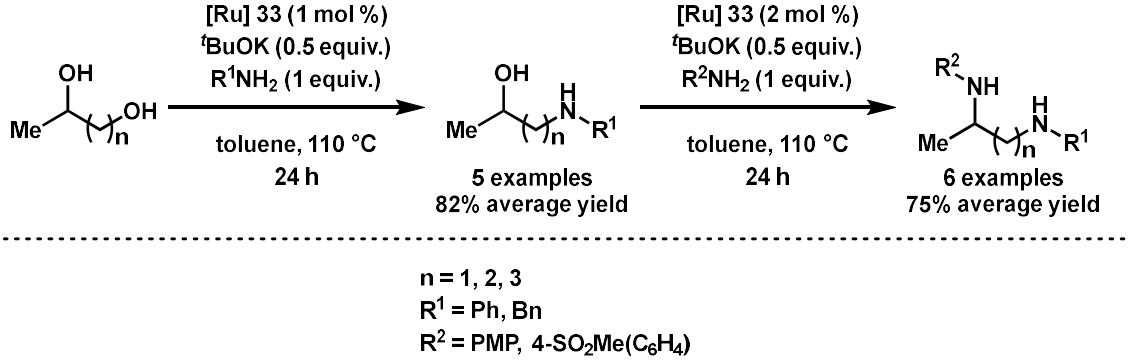
substrate scope, and demonstration of the tolerance of drug molecule synthesis and cholestanone alkylation, showed the potential for further synthetic utility of this work.

A recent example of *N*-alkylation with ruthenium catalysis can be found in the work of Marichev and Takacs.[58] An enantioenriched (99% ee of the ligand) chiral eighteen-electron ruthenium(II) complex (**33**) was employed to perform the alkylation of amines with secondary alcohols (scheme **1.36**).



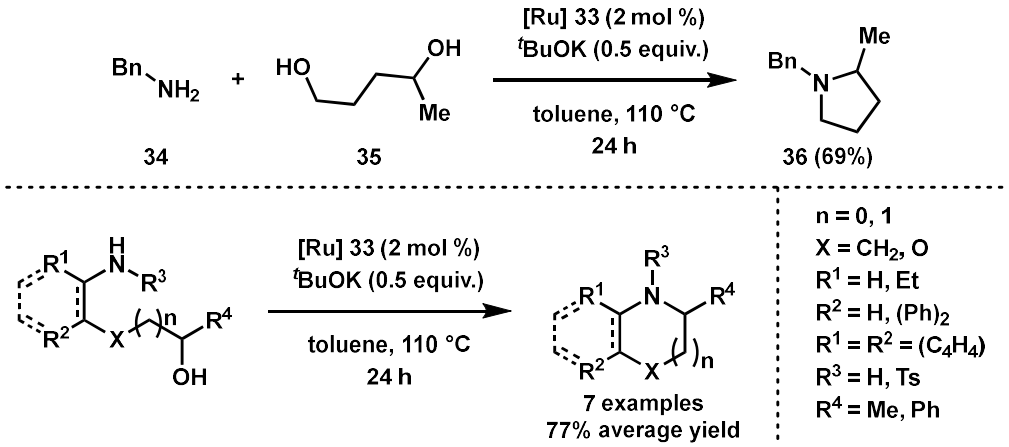
Scheme 1.36 - Alkylation of amines with secondary alcohols

While perhaps a more standard reaction, this transformation was then applied to sequential diamination of diols; where first a primary alcohol is alkylated, then a second alkylation with another amine can be effected (scheme **1.37**).



Scheme 1.37 - Sequential diamination of diols *via* ruthenium catalysis

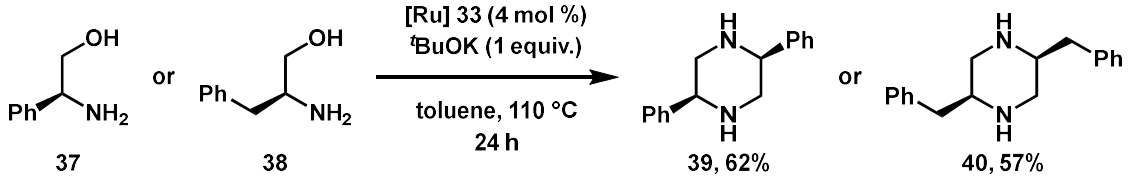
The lowered catalyst loading in the first step can be attributed to facile alkylation with primary alcohols, relative to the more difficult alkylation of secondary alcohols. This method was then applied towards heterocycle formation diols with a single amine nucleophile in an intermolecular fashion, as well as in an intramolecular fashion with 1,4 and 1,5 amino-alcohols (scheme **1.38**).



Scheme 1.38 - Heterocycle formation *via* borrowing hydrogen catalysis

While only 8 examples of products are reported here, such transformations demonstrated the applicability of this catalytic system towards a range of 5- and 6-memebered ring heterocycles, proceeding with high yields.

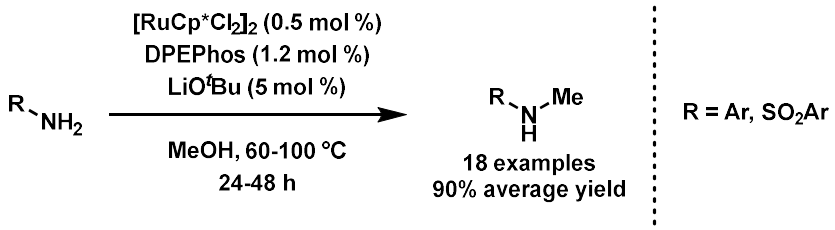
Finally, the authors demonstrated a cyclodimerisation of ethanolamines – taking (*S*)-phenylglycinol (**37**) and (*S*)-phenylalanol (**38**) to give the corresponding piperazines (scheme **1.39**).



Scheme 1.39 - Cyclodimerisation of ethanolamines towards chiral piperazines

This transformation demonstrated the tolerance of amino-acid derivatives, resulting in moderate yields in both examples. The tolerance of chiral moieties was also shown - no erosion of enantiopurity was reported by the authors, despite the high reaction temperatures, and potential for epimerisation. Further applications towards heterocycles were reported, but with poor yields and few examples.

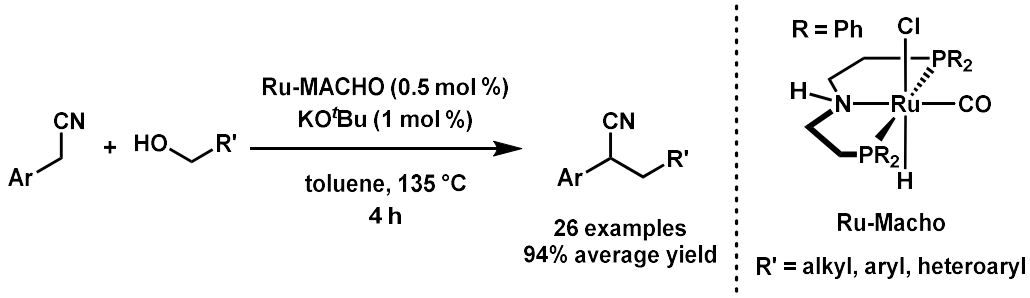
Other pertinent literature examples of ruthenium-catalysed borrowing hydrogen transformations can be taken from the work of Seayad and co-workers.[59] Here, the use of methanol as methylating reagent effects *N*-methylamine formation (scheme **1.40**).



Scheme 1.40 - Amine alkylation with methanol as methylating reagent

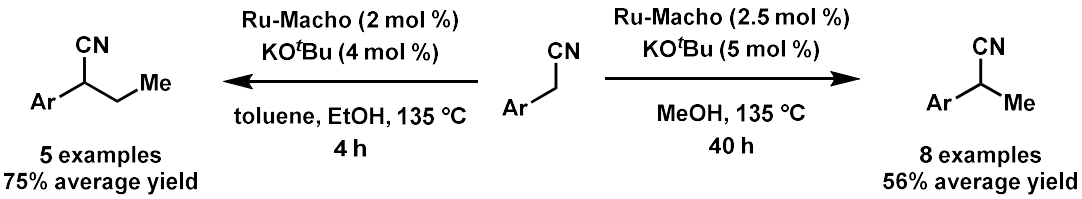
18 examples were demonstrated, with impressive tolerance of functional groups, and a few examples of selectivity for aniline over other amines, returning the examples in 90% average yield. Additionally, low catalyst loading was required for this transformation. Where aromatic amines (i.e. aniline derivatives) and sulfonamides were employed, this reaction generated exclusively monomethylated products. This work was extended towards a range of aliphatic amines, demonstrating dialkylation with the same catalytic system. However, alternative routes towards selective monomethylation of aliphatic amines were not discussed, and were not reported.

A final example of pertinent ruthenium chemistry can be found in the work of Thiyagarajan and Gunananthan.[60] Here, the authors reported the alkylation of benzyl nitriles with a range of alcohols, using a eighteen electron ruthenium(II) *PNP*-pincer precatalyst (scheme **1.41**).



Scheme 1.41 - Ruthenium-catalysed α–nitrile alkylation

26 examples were reported with 94% average yield, with relatively low reaction times, catalyst loading and using a catalytic amount of base. This reaction demonstrated particular applicability to long chain aliphatic alcohols, as opposed to the more classical benzylic alcohols utilised in this chemistry. Despite the high temperatures, these reactions were not ran under pressurised conditions. These conditions were then modified to demonstrate the ethylation and methylation of benzyl nitriles, by ethanol and methanol respectively (scheme **1.42**).



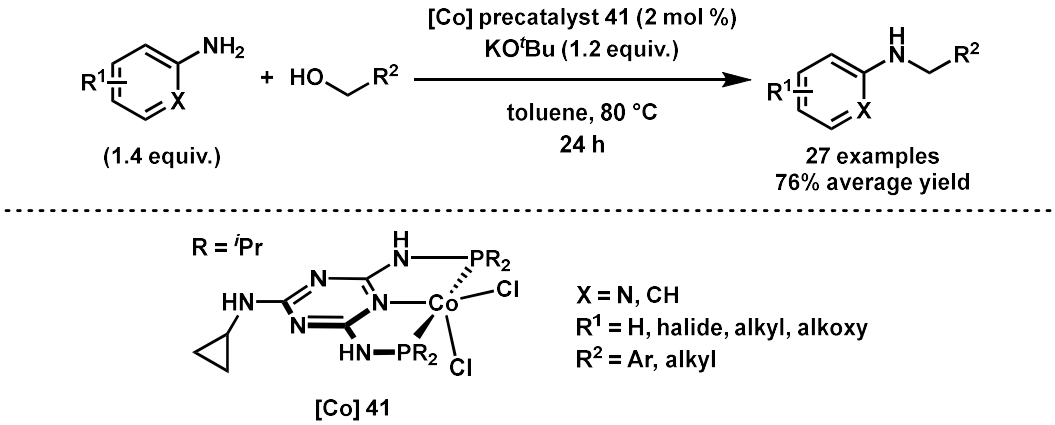
Scheme 1.42 - Ethylation and methylation *via* ruthenium catalysis

A small modification of conditions for ethylation was required, with four-fold catalyst and base loading. 5 examples were reported in 75% average yield. Similar modifications were required for methylation - performing the reaction in solvent methanol for 40 hours at five-fold catalyst and base loading. 8 examples of this transformation were reported, with 56% average yield. These reactions require some comment - the temperatures here are in significant excess of the boiling points of both alcohols used. This is especially surprising in the case of methylation; after 40 hours it would be unusual for any methanol to remain in an open system. The authors then went on to demonstrate that no secondary alcohols could be utilised as alkylating agents, and showed that this selectivity occurred even when both primary and secondary alcohols were present in the reaction mixture. This can be attributed to the greater steric and electronic barriers to successful reaction with secondary alcohols. Once again, this reaction demonstrated the tolerance of nitrile compounds towards these transfer hydrogenation conditions.

This concludes a summary of recent, pertinent ruthenium-catalysed borrowing hydrogen chemistry. However, recent work in the field of homogeneous borrowing hydrogen catalysis has involved a drive towards more earth abundant transition metal catalysis.[29] This introduction will now focus on three prominent metals for catalysis in this field - cobalt, manganese, and iron.

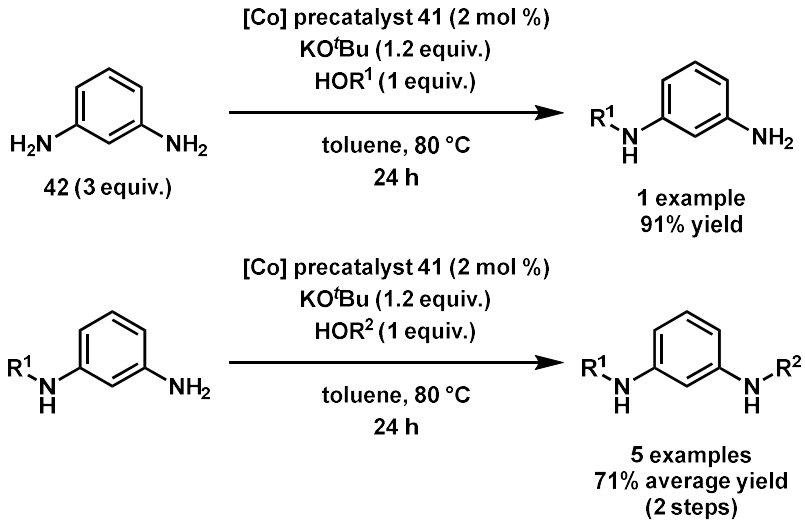
1.5.3. Cobalt-catalysed borrowing hydrogen methods

Early work in cobalt-catalysed borrowing hydrogen can be found in the work of Kempe and co-workers.[61] A seventeen-electron cobalt(II) *PNP*-pincer precatalyst was employed to perform the alkylation of amines with alcohols (scheme **1.43**).



Scheme 1.43 - Alkylations of amines with alcohols *via* cobalt catalysed borrowing hydrogen

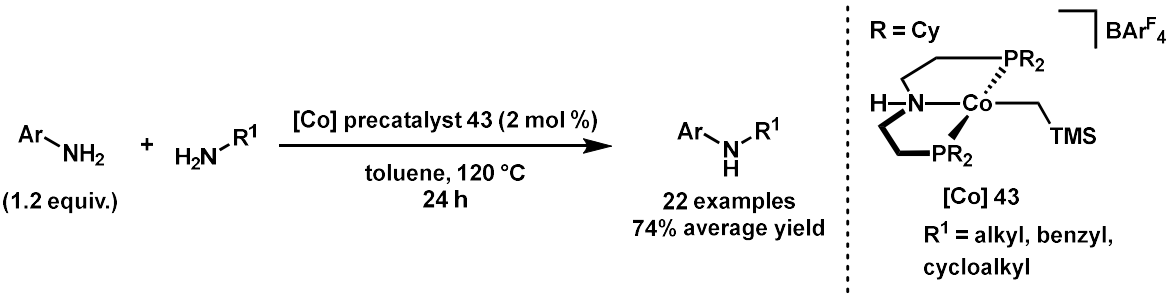
27 examples were reported, utilising a range of alcohols and amines. Notable substrates included anilines bearing halide substituents, which provide a functional handle for further elaboration.[62] A high average yield of 76% was reported, under the relatively low temperature of 80 °C. As before, this work shows selectivity towards monoalkylation, generating only secondary amines. The authors then extended this work towards the mono- and dialkylation of 1,3-diaminobenzene (**42**). By sequential addition of alcohol and catalyst, a range of inequivalent dialkylations, and one monoalkylation was reported in a reagent-controlled fashion. However, this work was not continued towards any one-pot dialkylations (scheme **1.44**).



Scheme 1.44 - Monoalkylation and sequential dialkylation of 1,3-diaminobenzene

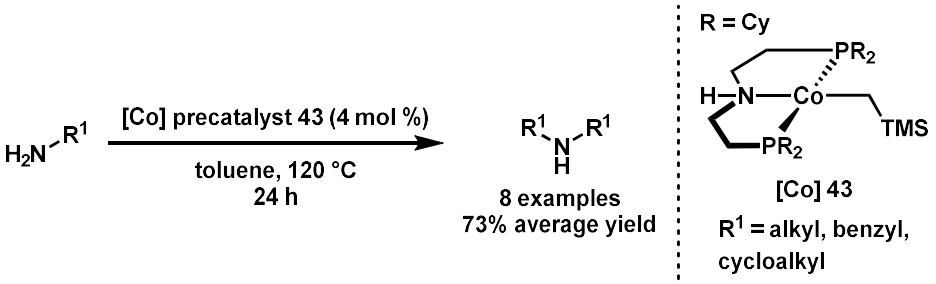
Regardless, this work demonstrated the utility and activity of cobalt catalysis in borrowing hydrogen, and inspired further work in the field of earth-abundant transition metal-catalysed borrowing hydrogen.

Other pertinent work in this field can be found in the work of Zheng, Zhang and co-workers.[63] Here, an alkylation of amines with amines was reported, with a fifteen-electron cobalt(II) pre-catalyst, where only ammonia was produced as a side product, in the same fashion that previous works produce water (scheme **1.45**).



Scheme 1.45 - Amine cross coupling *via* borrowing hydrogen catalysis

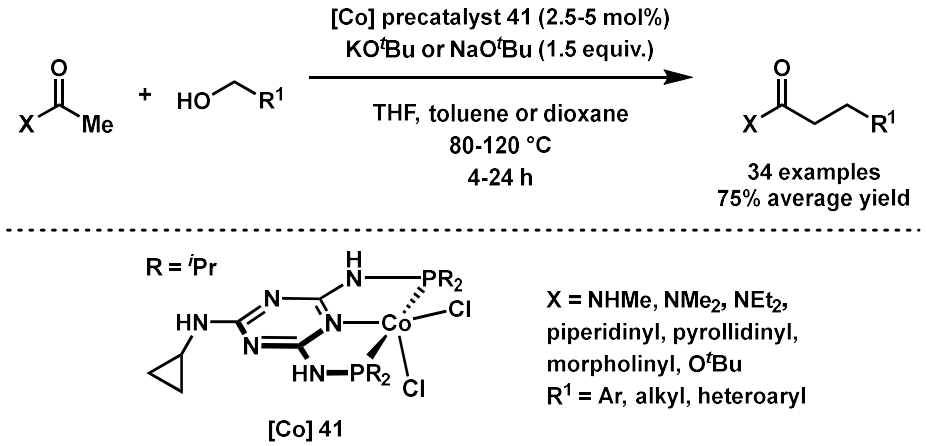
This reaction was reported with 22 examples in 74% average yield. Despite the risk of homocoupling of the aliphatic amines, the formation of dialkyl amines only occurred in selected examples, demonstrating high selectivity for aniline nucleophiles. *α*-branched amines were also tolerated as alkylating reagents, despite the increased steric bulk about the corresponding imine electrophile. Inspired by the observed side reaction, the authors demonstrated the self-alkylation of aliphatic amines under cobalt catalysis (scheme **1.46**).



Scheme 1.46 - Amine self-alkylation *via* borrowing hydrogen catalysis

By increasing catalyst loading, self-alkylation was reported with selected examples in 73% average yield. This transformation was selective for the production of secondary amines, with no tertiary amine formation reported by the authors. Despite the production of ammonia being less desirable than water, this reaction demonstrates both the compatibility of the cobalt catalyst with ammonia, and provides a complementary route for borrowing hydrogen alkylation, without the use of alcohols.

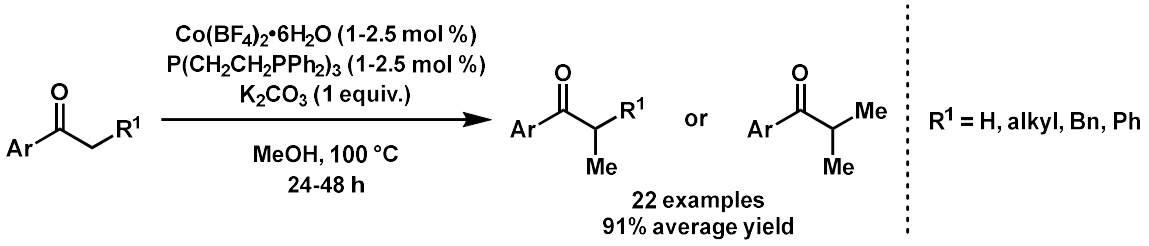
Other pertinent, recent work in cobalt-catalysed borrowing hydrogen chemistry can be found again in the work of Kempe and co-workers.[64] Utilising the same cobalt *PNP*-pincer precatalyst as in previous work,[61] the authors reported the *C*-alkylation of amides and esters, in contrast to classical ketone alkylation (scheme **1.47**).



Scheme 1.47 - Cobalt-catalysed alkylation of amides and esters *via* borrowing hydrogen

Here, a wide range of amides and esters were employed as nucleophiles, and shown to be active under a range of conditions. Thirty-four examples were reported, with 75% average yield. The authors reported neither the decomposition of products – despite the high reaction temperatures – nor the *N*-alkylation of amides where secondary amides were utilised as substrates. The authors also performed the derivatisation of a selection of the formed *C*-alkylated amides, demonstrating the further synthetic utility of such products.

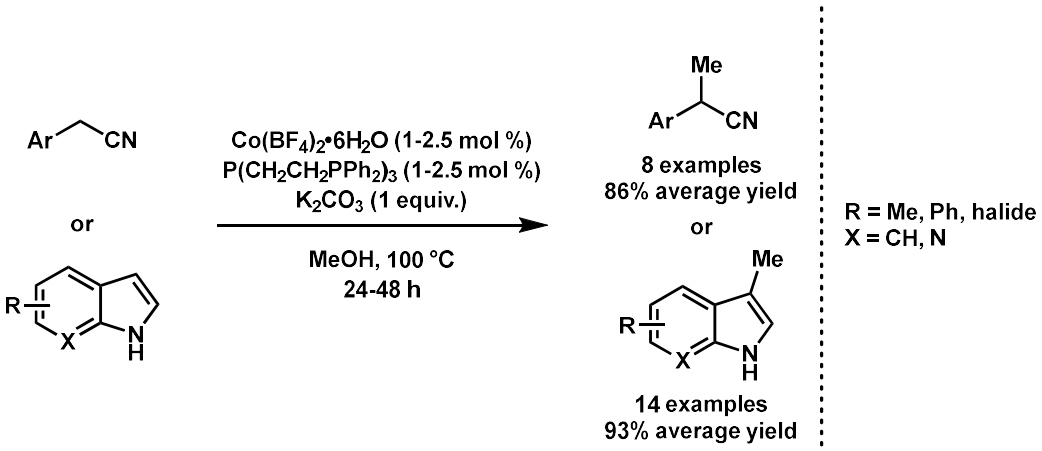
Liu and co-workers[65] demonstrated the utility of cobalt catalysis towards the methylation of a wide range of nucleophilic compounds with methanol. First, a wide range of *α*-aryl ketones was demonstrated in this reaction, with mono- and dimethylation being reported, depending upon the substitution at the *α*-ketone carbon (scheme **1.48**).



Scheme 1.48 - Cobalt-catalysed *C*-methylation of ketones with methanol

22 examples were reported, including those bearing a variety of functional groups, such as halides, vinyl moieties, and electron-withdrawing groups on the arene ring. These compounds were isolated in 91% average yield. Where R^1 was a hydrogen atom, exclusive dimethylation was reported, and when other moieties were present; exclusive monomethylation was reported. Notably, the active catalyst was formed *in situ* from a commercially available cobalt(II) salt, and tetradentate phosphine ligand. This is in contrast to the cobalt-catalysed works discussed previously, all of which utilised a preformed precatalyst. This work therefore demonstrated the applicability of a more simple catalytic system, requiring fewer synthetic steps from commercially available materials.

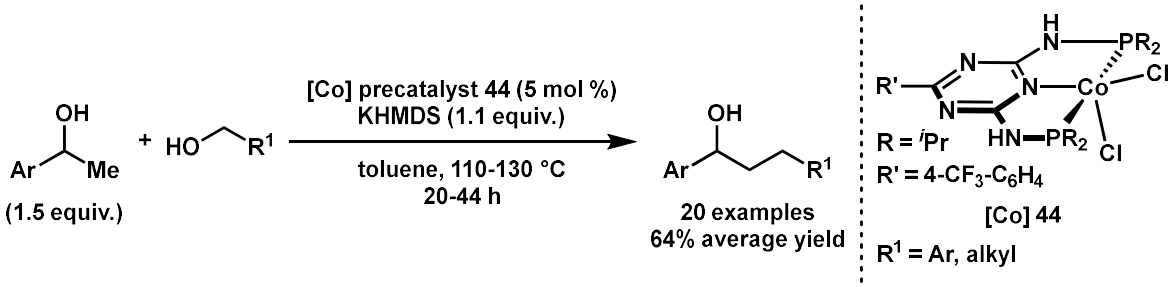
The authors extended this work towards the *C*-alkylation of nitriles, and the *C*2-alkylation of indoles (scheme **1.49**). Here, 8 examples of *α*-nitrile alkylation were reported in 86% average yield, and 14 examples of indole alkylation were reported in 93% average yield.



Scheme 1.49 - Cobalt-catalysed *C*-alkylation of nitriles and indoles

In the case of nitrile alkylation, once again this reaction was selective to monomethylation, and no reduction of the nitrile moiety was reported. In addition, the methylation of indoles showed complete selectivity for *C*2-alkylation, with no *N*-alkylation reported. That such a breadth of reactivity was possible with a simple cobalt salt and phosphine ligand was an important demonstration of alternative approaches to earth abundant metal-catalysed borrowing hydrogen, despite the long reaction times found in this work.

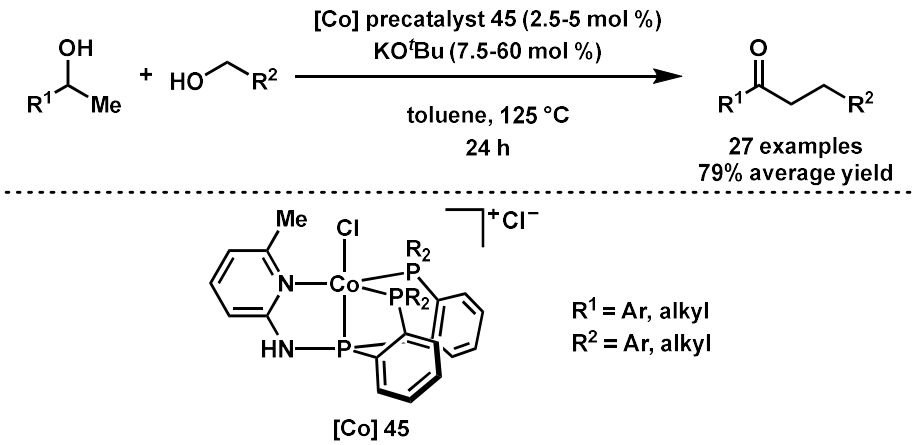
Final examples of pertinent methodology in cobalt-catalysed borrowing hydrogen can be found in the work of Kempe and co-workers.[66] A cobalt *PNP*-pincer precatalyst was utilised to effect the *β*-alkylation of secondary aromatic alcohols with primary alcohols (scheme **1.50**).



Scheme 1.50 - Alkylation of alcohols with alcohols *via* cobalt catalysis

A wide range of alcohols were reported in this transformation, with 20 examples in 64% average yield. As before, no self-condensation of either the secondary alcohol or primary alcohol was reported, nor was there further reaction of the product alcohols, demonstrating excellent selectivity for primary alcohols as alkylating reagents. However, this transformation required high reaction times, and a superstoichiometric amount of a strong base.

This work was extended by Ding and co-workers.[67] Utilising an alternative seventeen-electron cobalt(II) precatalyst, the authors demonstrated a similar reaction to that of Kempe and co-workers,[63] but with an acceptorless dehydrogenation step to yield *α*-alkylated ketones from alcohol starting materials (scheme **1.51**).



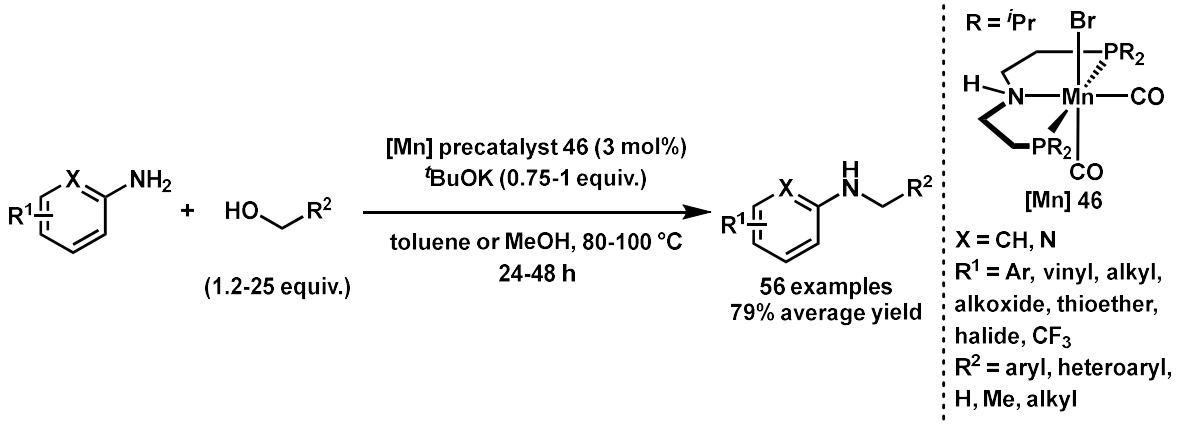
Scheme 1.51 - Oxdiation-methylation of secondary alcohols with alcohols

The authors cite the structure of cobalt catalyst **45** as enabling this oxidative process, resulting in 27 examples in 79% average yield. This demonstrated the ability of cobalt catalysis to perform acceptorless dehydrogenation (a reaction involving dehydrogenation and the release of hydrogen gas),[68] and also provided a complementary route towards the product ketones, in contrast to other approaches that require ketone starting materials. Furthermore, there was no report of self-alkylation processes of either starting material or product, demonstrating high selectivity towards the desired transformation.

Cobalt catalysis provides an earth-abundant transition metal-catalysed route towards traditional borrowing hydrogen chemistry. This metal shows excellent activity towards a variety of the alkylation processes typical in this literature, as demonstrated above. Cobalt catalysis demonstrates a wide range of phosphine and *PNP*-pincer based catalysts. This has some similarities with the types of catalyst found in the literature for manganese-catalysed borrowing hydrogen chemistry.

1.5.4. Manganese-catalysed borrowing hydrogen methods

Borrowing hydrogen methods utilising manganese catalysis were pioneered by Beller and co-workers.[69] Taking an eighteen-electron manganese(I) *PNP*-pincer complex, a wide range of anilines were alkylated with alcohols (scheme **1.52**).



Scheme 1.52 - Manganese-catalysed *N*-alkylation with alcohols

Reporting 42 examples in 78% average yield, this transformation was shown to have a broad substrate scope. Both benzylic and aliphatic alcohols were employed in this

reaction, yielding the corresponding *N*-benzyl and *N*-alkyl alcohols. This work reported complete selectivity for monoalkylation, with only secondary amines reported as products. Aliphatic amines, however, were not reported as nucleophiles in this work. Methanol was also used to effect the *N*-methylation of anilines, reporting 14 examples. In this case, excess methanol was used as a cosolvent. Beller and co-workers then extended this work towards the synthesis of compounds similar to that of the Alzheimer's drug, resveratrol[70] (**47**, figure **1.2**).

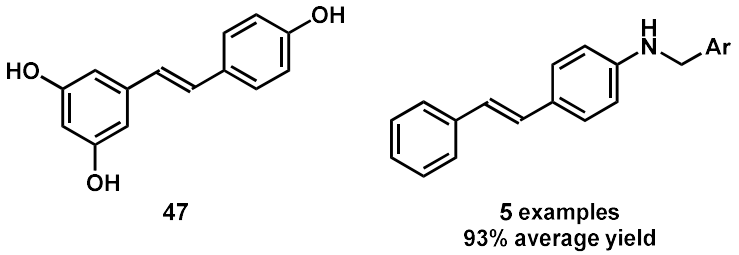
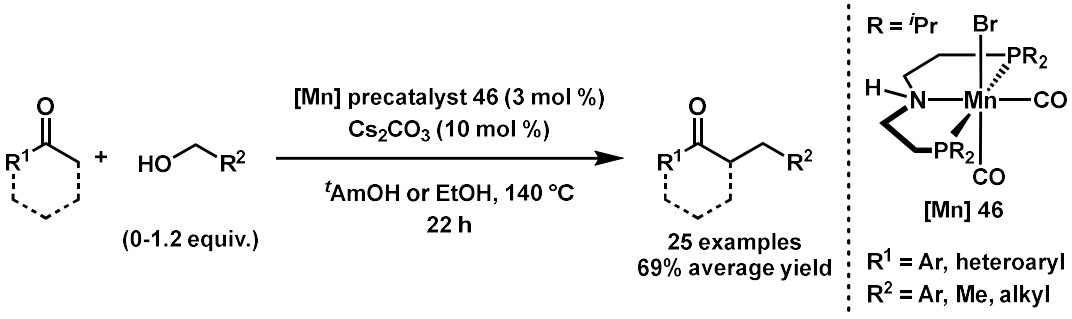


Figure 1.2 - Resveratrol and synthesised compounds

Taking (*E*)-aminostilbene as starting material, the authors report selected derivatives in high yields under standard conditions. This transformation showed the potential applicability of manganese catalysis towards natural products and API's, especially as the alkene moiety was left untouched by the reaction conditions. Furthermore, the relatively low temperature of this work demonstrated the reactivity of this manganese catalyst.

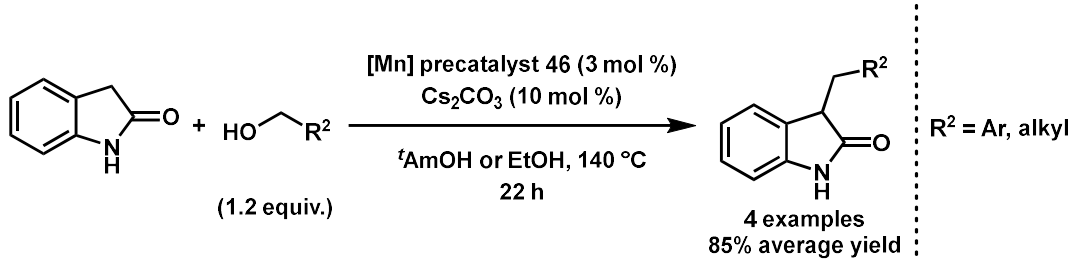
Beller and co-workers in the same year reported the alkylation of ketones with alcohols, *via* manganese catalysis.[71] Here, acetophenone derivatives were used as nucleophiles, with a range of benzylic and aliphatic alcohols as alkylating agents (scheme **1.53**).



Scheme 1.53 - α-alkylation of ketones with primary alcohols

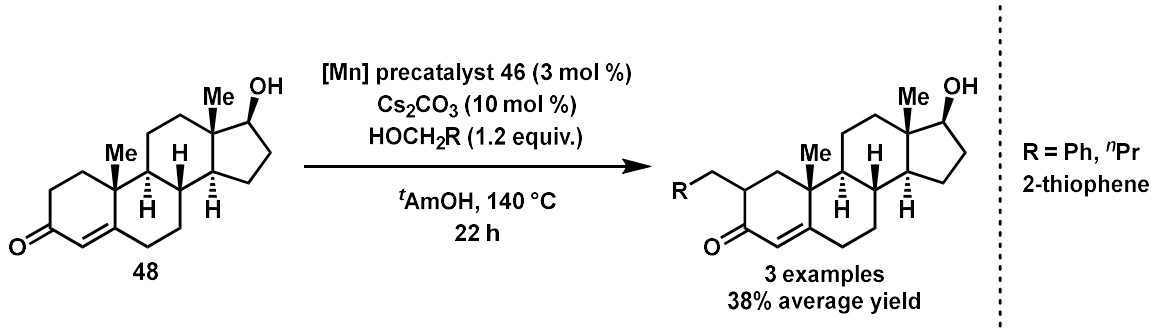
Twenty-five examples were reported in 69% average yield. This scope demonstrated good tolerance of heteroaromatic ketones and alcohols, and an

example of an allylic alcohol in the form of cinnamyl alcohol, generating the corresponding *γ*-ketoalkene in 22% yield. Despite the low yield, the tolerance of an allyl alcohol in these harsh reaction conditions is notable. However, aliphatic ketones were not reported as alkylating agents. Beller and co-workers also extended this work towards oxindole *C*-alkylation (scheme **1.54**).



Scheme 1.54 - Oxindole alkylation with primary alcohols

Four examples were reported, demonstrating this proof-of-concept transformation in high average yield. As before, this transformation shows complete selectivity for both *C*-alkylation over *N*-alkylation, and monoalkylation. The authors went on to perform the alkylation of biologically active compounds, for example testosterone (**48**) as substrates in this transformation (scheme **1.55**).

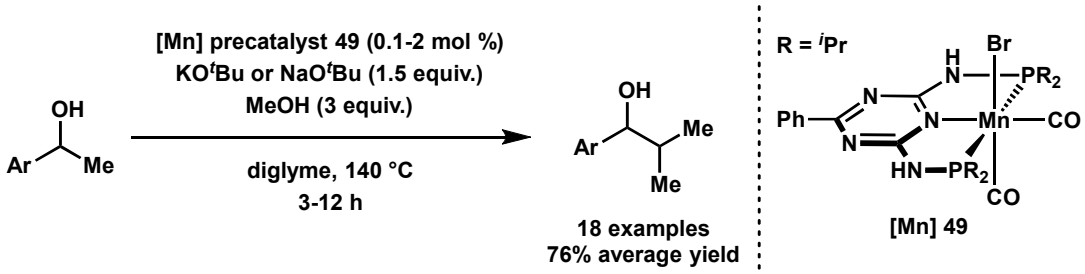


Scheme 1.55 - Steroid alkylation *via* borrowing hydrogen catalysis

Despite the low yields in the alkylation of testosterone, these reactions demonstrated the applicability of this transformation towards the late-stage functionalisation of API's, as this procedure is moderately tolerant of the functionality and stereochemistry of the starting materials - the low yield of this transformation suggests that this tolerance is only partial. However, the authors do not comment on the remaining 62% of resultant material.

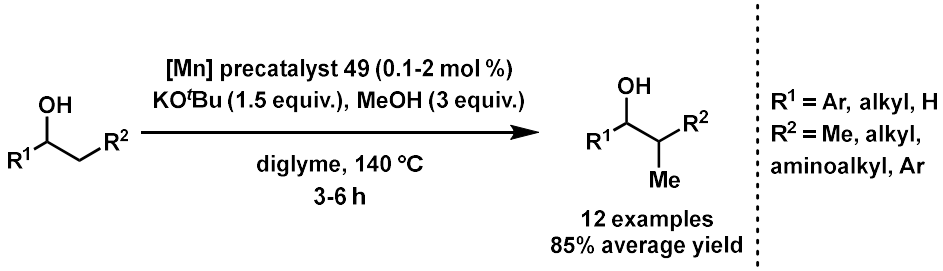
Recent developments in manganese-catalysed borrowing hydrogen catalysis have been to explore more active manganese complexes, or more functional-group

tolerant catalysts. A good example of this can be found in the work of Kempe and co-workers,[72] where manganese precatalyst **49** was employed to perform the *β*-methylation of alcohols with methanol. Initial efforts were made in the dialkylation of 1-arylethanols (scheme **1.56**).



Scheme 1.56 - Dimethylation of 1-arylethanols *via* manganese catalysis

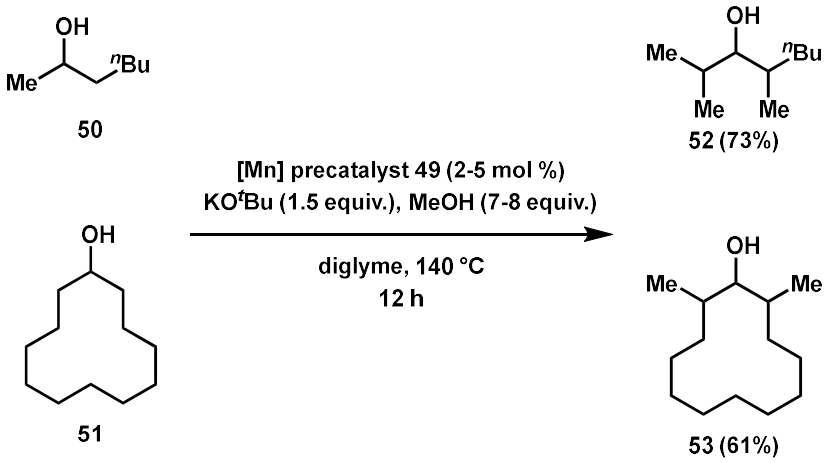
Eighteen examples of *β*-branched alcohols were isolated in 76% average yield. As discussed before, this transformation highlighted the ability of the catalyst to react simultaneously with multiple species that are active in the catalytic cycle. Likewise, despite the risks of the alcohol starting material undergoing self-alkylation reactions, the authors reported complete selectivity for methanol as alkylating reagent. This transformation was also performed with as low as 0.1 mol % catalyst loading, in short reaction times, demonstrating the high activity of catalyst **49**. Notable substrates included those with heteroaromatic functionalities, a ferrocene derivative, and a variety of other substrates bearing halide moieties. This work was extended towards the *β*-alkylation of *β*-branched alcohols, such that only monomethylation was possible (scheme **1.57**).



Scheme 1.57 - β-methylation of alcohols with methanol

This extension of the substrate scope demonstrated the tolerance of other alcohols, including several primary alcohols as substrates. Here, no further alkylation of the product alcohol was observed, despite the potential for such reactivity. This once again demonstrated the selectivity of this transformation towards methanol as

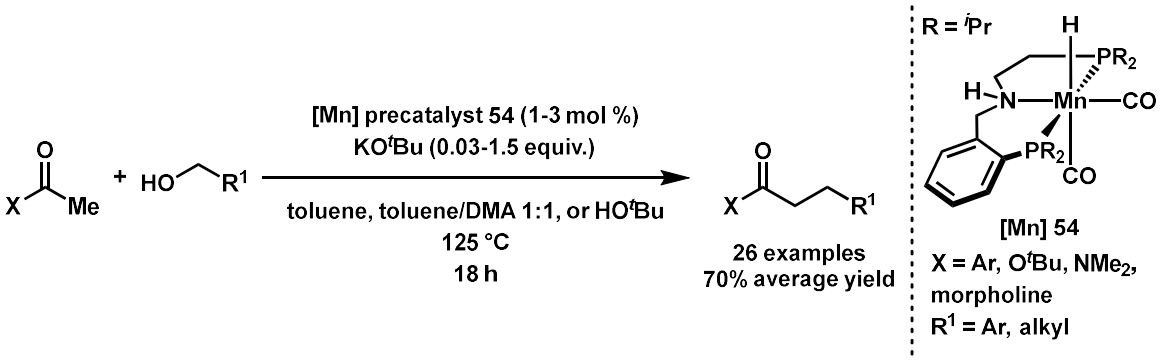
methylating reagent. As before, desirable low reaction times were reported, however in a few cases catalyst loading was increased for efficient reactivity. A final extension of this work was the application of this transformation to the polymethylation of secondary alcohols (scheme **1.58**).



Scheme 1.58 - Polymethylation of secondary alcohols

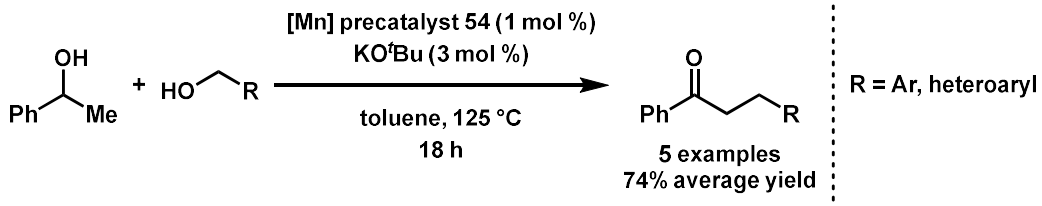
This transformation required higher catalyst loading, and an increase in the equivalents of methanol. However, this polyalkylation, followed by reduction of the corresponding sterically encumbered ketone intermediates, demonstrated the potential for broader applicability of this manganese catalyst for the *β*-methylation of sterically encumbered alcohols. Compared to more traditional routes, this reaction avoids the use of toxic aryl halides, however it requires high temperatures, excess methylating reagent, and metal catalyst.

Other pertinent examples of manganese-catalysed borrowing hydrogen can be taken from that of Milstein and co-workers.[73] The authors demonstrated first the *α*-alkylation of a wide range of carbonyl compounds (scheme **1.59**).



Scheme 1.59 - α-alkylation of carbonyl compounds with alcohols

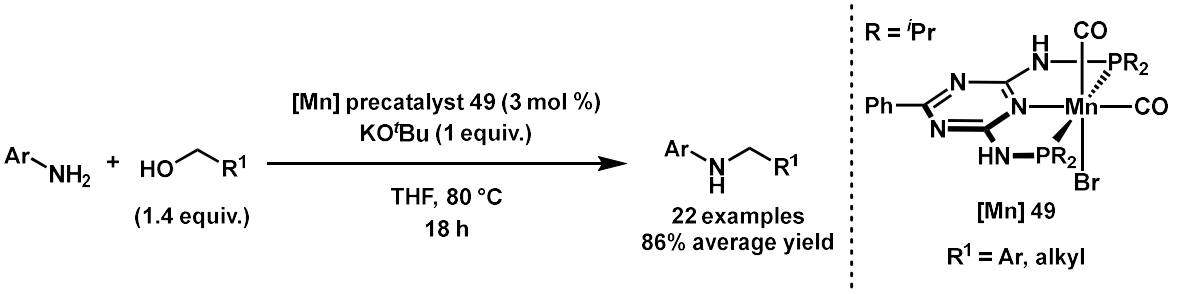
Despite the similarity to the work of Beller and co-workers,[69] this work demonstrated the *C*-alkylation of amide and carbonate functionalities, highlighting the wider applicability of this chemistry, and its tolerance of these functional groups. A wide array of alcohols were reported as alkylating reagents in this transformation, resulting in 26 examples in 70% average yield. The authors then tested the scope of the catalyst towards acceptorless dehydrogenation reactions.[68] Taking alcohols in the place of carbonyl compounds as starting materials, the tandem *β*-alkylation - oxidation of alcohols was reported (scheme **1.60**).



Scheme 1.60 - Oxidation-methylation of alcohols *via* acceptorless dehydrogenation

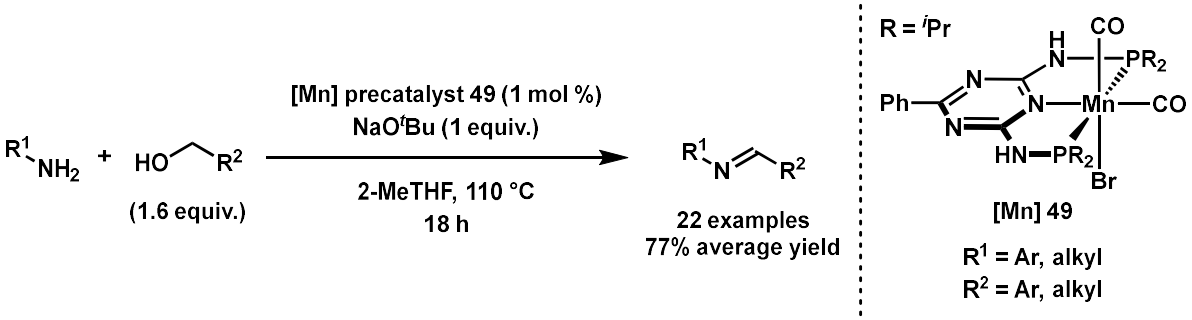
Despite only 5 examples being reported, this work demonstrated the efficacy of manganese catalysis towards such reactivity, as the resulting compounds were isolated in 74% average yield. This one-pot procedure still removed the requirement for stoichiometric oxidation that such a transformation would otherwise necessitate. This reaction bears similarity to the previously discussed *β*-methylation work of Kempe and co-workers,[72] however the manganese catalyst employed in this instance did not perform the terminal reduction of the generated ketone.

A final example of manganese catalysis is found in the work of Kempe and co-workers.[74] Manganese precatalyst **49** was applied again, but with application towards amine *N*-alkylation (scheme **1.61)**.



Scheme 1.61 - Manganes-catalysed borrowing hydrogen for the alkylation of amines

22 examples of *N*-alkylated anilines were synthesised in 86% average yield. However, only anilines were tolerated by this reaction - no aliphatic amines were reported. This reaction has distinct similarity to the work of Beller and co-workers,[69] but required much reduced reaction times and lower temperatures. Additionally, this work demonstrated the tolerance of this catalytic system towards amines, as this is the same catalyst used in the previously discussed *β*-methylation work.[72] The authors extended this work towards the formation of imines; it was found that under different reaction conditions, and by simply switching base, exclusive selectivity for the corresponding imine could be observed (scheme **1.62**).



Scheme 1.62 - Manganese-catalysed imine formation

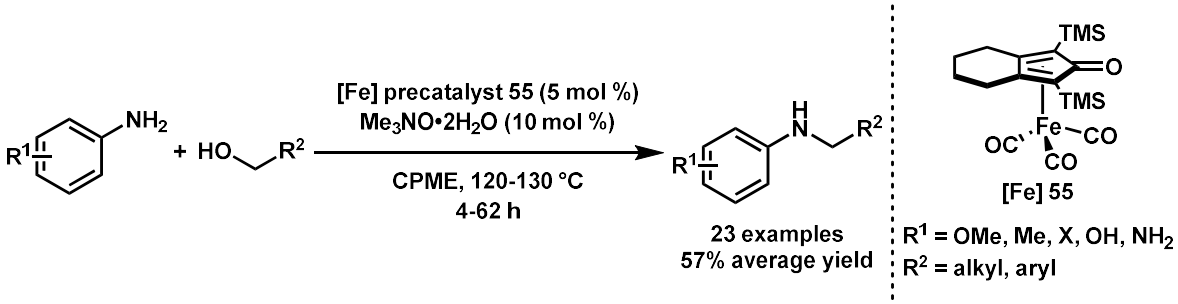
Under altered reaction conditions and decreased catalyst loading, 22 examples of *N*-phenyl aldimines were synthesised with 77% average yield. Here, aliphatic amines were tolerated, in contrast to the amine alkylation process discussed above. This could be due to the lack of selectivity for monoalkylation of aliphatic amines, although the authors did not discuss this result. This reaction further demonstrated the applicability of manganese catalysts towards acceptorless dehydrogenation reactions.[68]

Manganese catalysis provides a complementary route towards that offered by cobalt catalysis. Catalysis in this field utilises *PNP*-pincer ligand systems, and the catalysts typical in the literature also find use in acceptorless dehydrogenation reactions.

However, there are transformations that might require alternative catalysts to the two previously mentioned. Another common earth-abundant transition metal in borrowing hydrogen chemistry is iron.

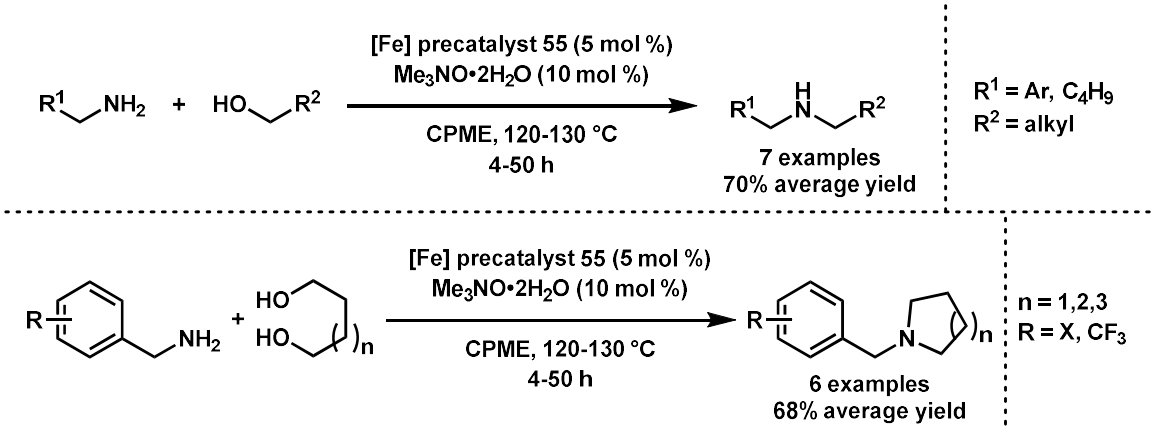
1.5.5. Iron-catalysed borrowing hydrogen methods

An early example of the utility of iron catalysis for borrowing hydrogen can be taken from the work of Barta and co-workers.[75] Here, a eighteen-electron iron(0) precatalyst (derived from the Shvo catalyst, and initially employed in hydrogenations by Casey)[76] was employed in the borrowing hydrogen method (scheme **1.63**).



Scheme 1.63 - Iron catalysed alkylation of anilines with alcohols

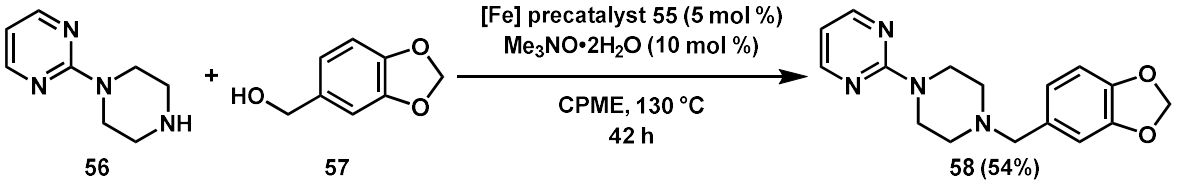
Trimethylamine *N*-oxide was used as an activator here, to remove a carbonyl ligand *via* oxidation, and liberate the active, sixteen-electron catalyst. Despite the modest average yield of 57%, 23 examples were reported. The authors also discussed a range of incompatible substrates; namely those bearing an electron-withdrawing group in the *para*-position. To further the scope of this work, the authors studied the alkylation of aliphatic and benzylic amines, and the use of diols and alkylating agents towards the synthesis of saturated heterocycles (scheme **1.64**).



Scheme 1.64 - *N*-alkylation of benzyl and alkyl amines with alcohols and diols

In this fashion, a variety of *N*-alkylated amines were demonstrated, with 7 examples of benzylic amines alkylation, and 6 examples of heterocycle formation with 68% average yield. Despite the few examples, the alkylation of benzylamines with *n*-pentanol is notable, as the authors reported no dialkylation occurring. Likewise, the high observed yields for pyrrolidines, piperidines and azepanes demonstrated the tolerance of these diols, despite the propensity for complicated side reactions to occur.

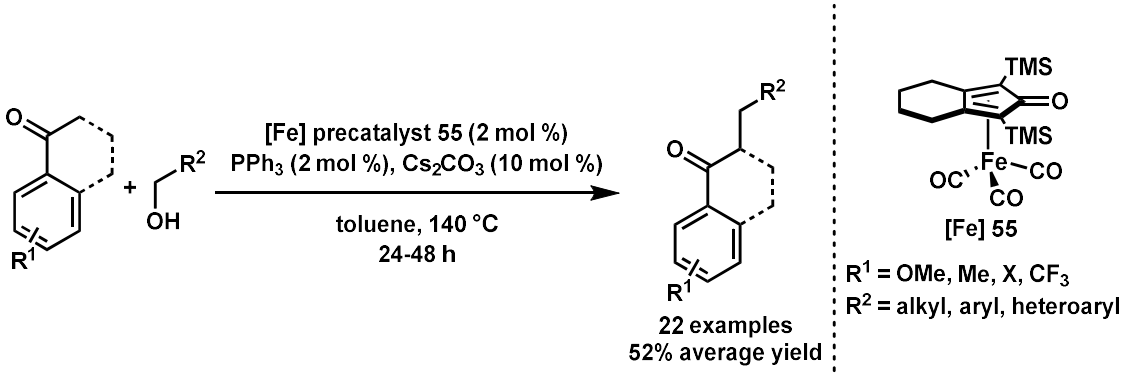
This work was further extended towards the synthesis of an active pharmaceutical compound. The drug molecule, Piribedil[77] (**58**), which finds use in the treatment of Parkinson's disease, was synthesised from the requisite amine (**56**) and alcohol (**57**, scheme **1.65**).



Scheme 1.65 - The synthesis of Piribedil *via* borrowing hydrogen catalysis

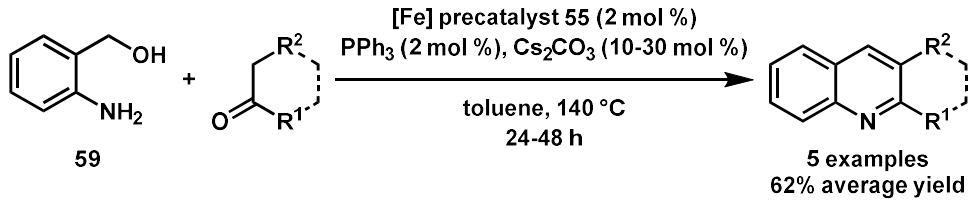
The authors made reference to the limited allowed level of noble metal catalysts in the synthesis of pharmaceutically active intermediates, and how the use of this iron catalyst would enable higher catalyst loading to be utilised, due to the increased exposure limits of iron relative to other metals in such processes.[78] Furthermore, this transformation allowed **58** to be synthesised from commercially available materials in 54% overall yield, demonstrating the potential for further synthetic utility of this transformation.

An example of the *α*-alkylation of ketones with alcohols using iron catalysis can be taken from the work of Darcel and co-workers.[79] The same iron catalyst as above ([Fe] **55**) was employed with acetophenone derivatives, to form the corresponding chain-extended ketones (scheme **1.66**).



Scheme 1.66 - Iron catalysed alkylation of ketones *via* borrowing hydrogen

Here, the authors employ triphenylphosphine as activator, in contrast to previously discussed work.[75] The triphenylphosphine can undergo ligand exchange with a carbon-monoxide ligand (although this process will be relatively slow, as catalyst **55** is a high-spin d8 complex) to yield a more exchange-labile complex. Caesium carbonate was also employed as a base, to activate the ketone as a nucleophile. Despite the 52% average yield, the authors reported 22 examples, demonstrating the tolerance of the catalytic system for a range of functional groups, including substrates bearing halogens and heteroaromatic moieties. This further demonstrated the breadth of chemistry compatible with this iron catalyst. The authors then extended this work towards a modified Freidländer annulation.[80] utilising 2-aminobenzyl alcohol (**59**) in the place of the more typical 2-amino benzaldehydes (scheme **1.67**).

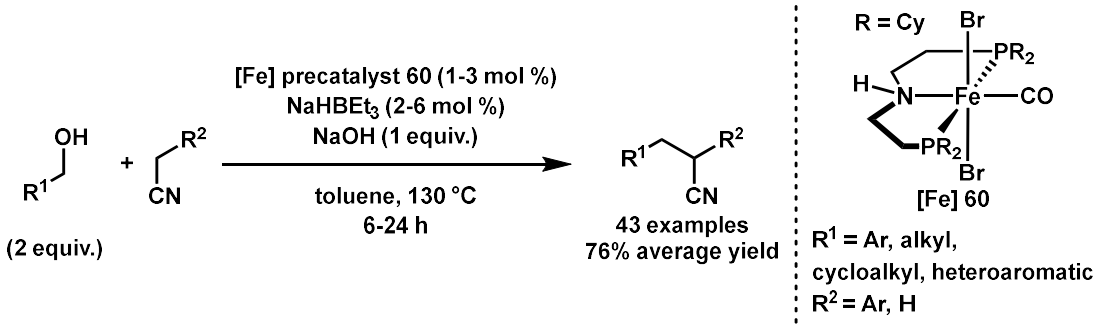


Scheme 1.67 - Modified Friedländer annulation

Five examples of quinolones were demonstrated in moderate yields. Notably, this reaction demonstrates the ability of this iron catalyst to perform acceptorless

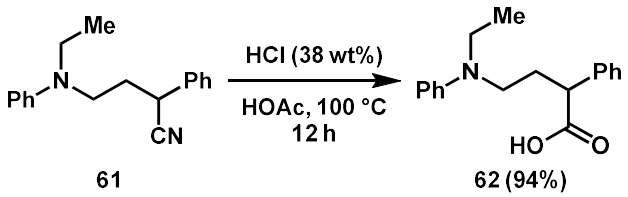
dehydrogenation reactions,[67] as this reaction is formally an oxidative process from the alcoholic starting material.

Further examples of the utility of iron catalysis in borrowing hydrogen can be demonstrated by the *α*-alkylation of nitriles, performed by Wang and co-workers.[80] An eighteen-electron iron *PNP*-precatalyst (**60**) was utilised in the alkylation of benzyl nitriles and acetonitrile with alcohols (scheme **1.68**).



Scheme 1.68 - Iron catalysed α-alkylation of nitriles with alcohols

Forty-three examples were reported in this transformation, with 76% average yield. Triethyl sodium borohydride was used as activator for [Fe] precatalyst **60**, to generate an iron hydride species. Interesting examples of electrophiles employed included benzyl alcohols bearing halogens, and simple aliphatic alcohols, such as decanol or cyclopropyl methanol. A variety of heteroaromatic alcohols were also successfully tolerated. As before, it can be observed that nitriles were tolerated well by this catalyst, despite their propensity to act as ligands for the metal catalyst, or as targets for transfer hydrogenations. Acidic hydrolysis of one of product **61** was also performed, to demonstrate the synthesis of aminobutyric acid (**62**, scheme **1.69**).

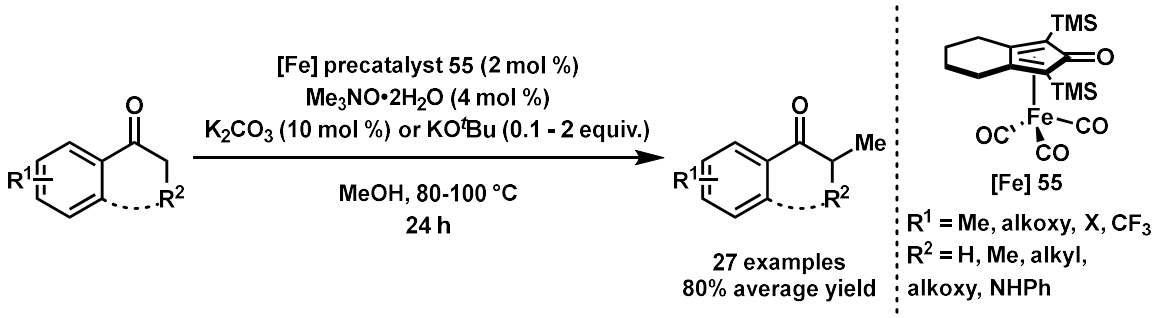


Scheme 1.69 - Acid hydrolysis of γ-amino butryonitrile

Hydrolysis proceeded smoothly, returning target compound **62** in 94% isolated yield.

An example of broadly applicable work in iron-catalysed borrowing hydrogen chemistry can be found in the work of Morrill and co-workers.[82] Here, methanol was

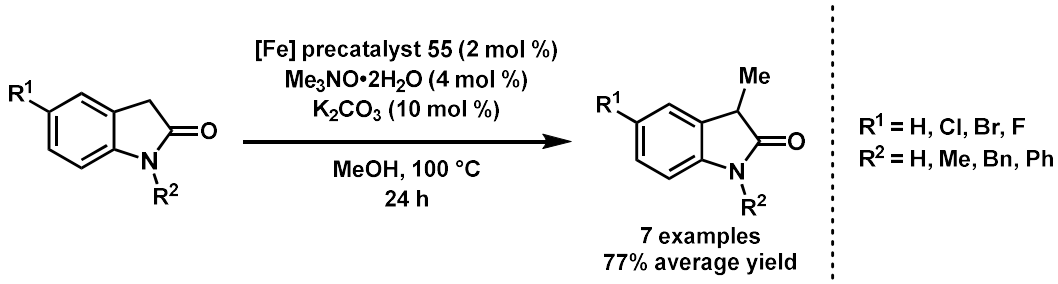
employed as a methylating reagent and solvent, to methylate a wide variety of nucleophiles. Acetophenone derivatives were demonstrated as efficient nucleophiles in this work (scheme **1.70**).



Scheme 1.70 - Iron catalysed methylation of ketones

Twenty-seven examples were demonstrated, including those bearing heteroatoms, and electron-withdrawing moieties with an average yield of 80%. Where R^2 = H, exclusive dimethylation was observed. Additionally, the methylation of butyrophenone was performed on a 10 mmol scale, resulting in a 99% isolated yield, and demonstrating the scalability of this procedure.

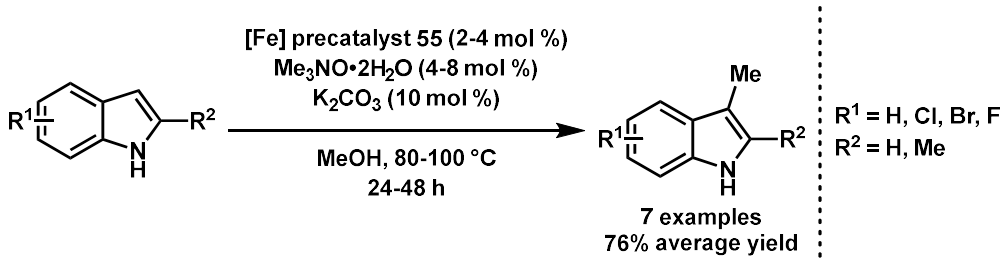
Oxindoles were then demonstrated as nucleophiles (scheme **1.71**).



Scheme 1.71 - Iron catalysed methylation of oxindoles

Seven examples of oxindoles were reported as nucleophiles, yielding the corresponding 3-methyloxindoles in high average yield. Tolerance of a range of substrates bearing halogens was reported, and likewise no *N*-methylation was reported even where R^2 = H, demonstrating the selectivity of this transformation towards *C*-alkylation.

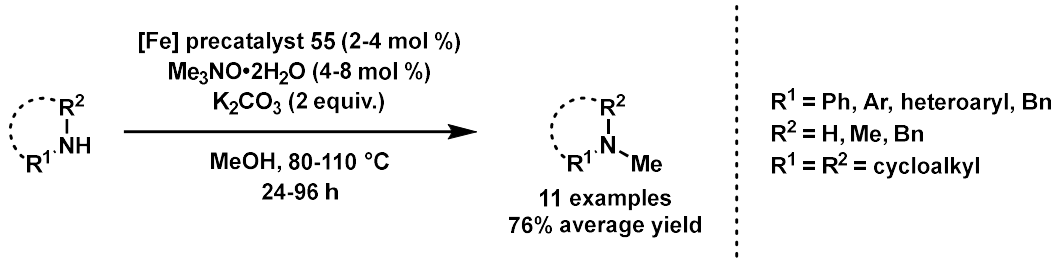
Indoles were next demonstrated as nucleophiles (scheme **1.72**).



Scheme 1.72 - Iron catalysed methylation of indoles

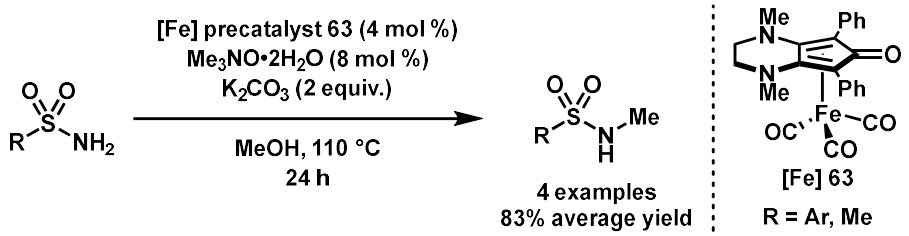
Indole nucleophiles were employed, with 7 examples in 76% average yield. Once again, this reaction showed exclusive selectivity for *C*-methylation at the 3-position, with no *N*-methylation or methylation in the 2-position reported. Additionally, it was shown that extant 2-functionalisation did not inhibit the alkylation, despite the increased steric bulk of the nucleophile.

A variety of *N*-methylation processes were then demonstrated in this transformation (scheme **1.73**).



Scheme 1.73 - Primary and secondary amine methylation

First, a selection of amines were utilised in this procedure, with 11 examples reported for methylation, with 76% average yield. Both primary and secondary amines were tolerated, however primary aliphatic amines were not reported as nucleophiles. This procedure was then extended towards sulfonamide methylation. However, due to the lower nucleophilicity of sulfonamides, an alteration of conditions was employed with an alternative catalyst scaffold (scheme **1.74**).



Scheme 1.74 - Iron catalysed methylation of sulfonamides with methanol

Utilising the eighteen electron iron(0) pre-catalyst developed by Renaud and co-workers (inspired by the earlier catalysts designed by Wills and co-workers),[83] the authors were able to methylate 4 examples of sulfonamides in 83% average yield. This procedure was reported only with sulfonamides bearing electron-donating groups, or with electron-neutral substrates. The authors reported that, when a sulfonamide bearing an electron-withdrawing group was employed, no conversion was observed to the product. This demonstrates a limitation of this work. Despite earlier reports by Deng and co-workers,[84] who reported the alkylation of sulfonamides with iron(II) chloride, this example remains the only iron-catalysed alkylation of sulfonamides performed with a well-defined iron complex, demonstrating the compatibility of iron cyclopentadienyl complexes with electron-deficient nucleophiles.

This concludes the pertinent examples in the field of iron-catalysed borrowing hydrogen chemistry. As can be seen, the tricarbonylcyclopentadieneone ligand donor set is extremely prevalent in this work. While providing a complementary approach to earth-abundant borrowing hydrogen catalysis, iron is also the second most abundant metal in the earth's crust,[85] providing some benefits over the other common metals. However, it should be noted that iron carbonyl compounds are extremely toxic, due to their ability to release carbon monoxide.

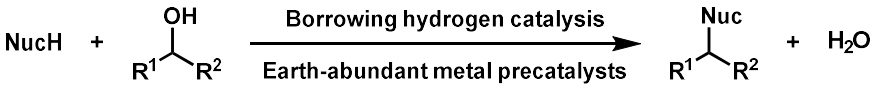
There are other metals that can be utilised for earth-abundant transition metal borrowing hydrogen catalysis, such as nickel[86] and copper.[87] However, such examples are similar to the majority of the work discussed above. While these provide another complementary route, these reactions are less noteworthy, due to their similarity.

1.6. Summary and outlook

In summary, the borrowing hydrogen principle enables a powerful route towards a variety of alkylations. These reactions provide distinct advantages over other alkylative processes, due to their selectivity, high yielding nature, atom economy, and ability to use commercially available alcohols as alkylating reagents. However, high temperatures and long reaction times are typically required. Furthermore, while the extant literature towards earth-abundant transition metal-catalysed borrowing hydrogen shows promise in wider applicability, further research is needed to synthesise catalysts that are able to compete with rare-earth transition metal catalysis. Such rare-earth metal catalysts are often more active, requiring lower reaction temperatures and catalyst loadings compared to their earth-abundant counterparts. However, these metals are difficult to obtain due to their poor natural abundance, and as a consequence are expensive, and less sustainable in the future of this area.

1.7. Aims and objectives

The aims of this PhD were as follows: to research and develop new borrowing hydrogen reactions. The reactions to be investigated utilised precious, or earth-abundant transition metal catalysts (scheme **1.75**).



Scheme 1.75 - Aims and objectives

The objectives were to add reactions to the array of available chemistry for the functionalisation of alcohols. This was be done by the investigation of new borrowing hydrogen reactions, and thus adding to the range of borrowing hydrogen reactions that could be performed. Likewise, extant precious metal-catalysed reactions were transferred to an earth-abundant metal-catalysed route. This helps to provide

greener, more environmentally-friendly alternatives to existing transformations, as well as providing more options and methods for performing specific transformations.

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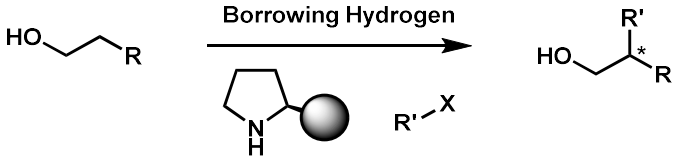
Chapter 2: Investigations into Stereoselective Borrowing Hydrogen Chemistry

Table of Contents

2. Preface

This chapter discusses investigations of stereoselective borrowing hydrogen *via* enamine catalysis. A range of classical enamine reactions were investigated from alcohol starting materials instead of aldehydes, with the aims of demonstrating the combination of borrowing hydrogen chemistry and enamine catalysis. Attempts were also extended in dienamine catalysis.



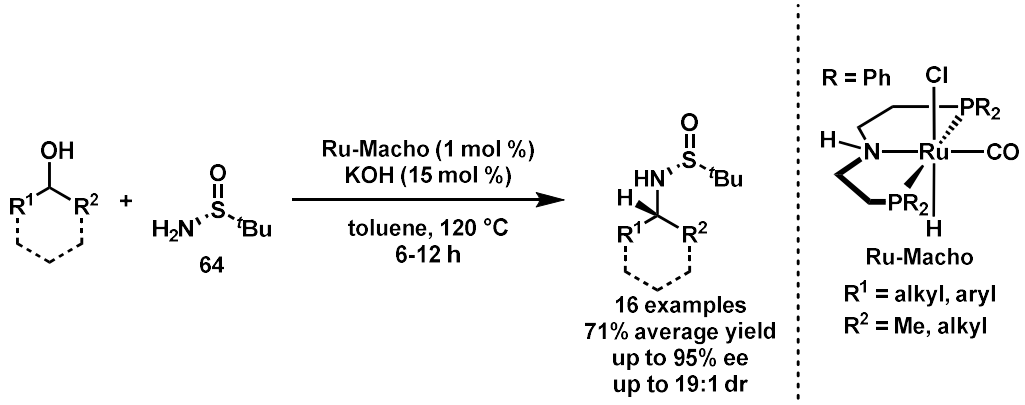
2.1. Introduction

2.1.1. Methods for stereoselective borrowing hydrogen transformations

As discussed in Chapter 1, borrowing hydrogen provides an array of advantages, compared to classical alkylation processes.[1] However, despite the obvious power of stereoselective transformations *via* borrowing hydrogen, there are few published examples of stereoselective processes in the literature. Among the known processes, there are several extant strategies – processes providing diastereoselectivity, processes with chiral catalysts or ligand scaffolds, or processes that proceed *via* dual catalysis.

2.1.1.1. Diastereoselective borrowing hydrogen transformations

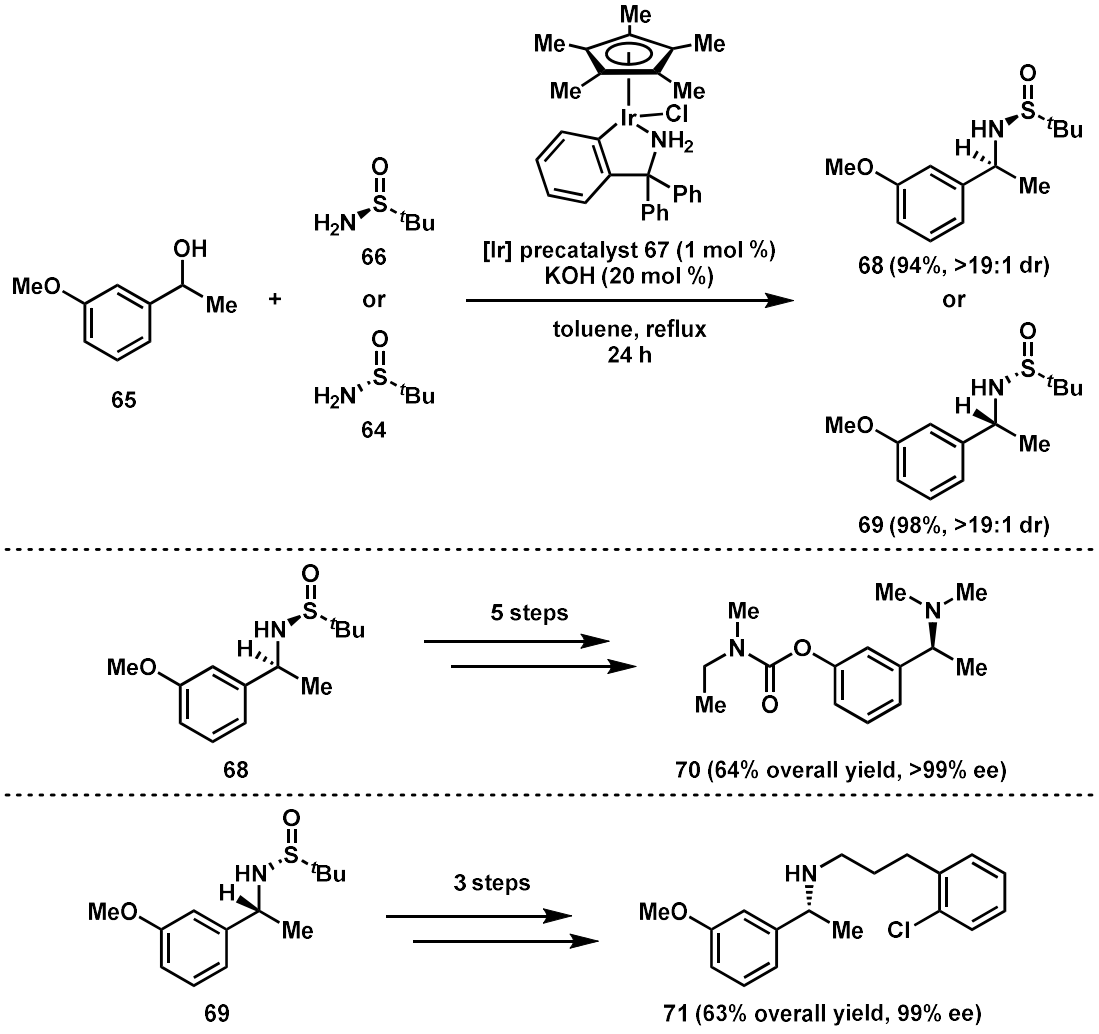
Chiral auxiliaries provide a powerful route to diastereoselective reactions, in a variety of chemical transformations.[2] A pertinent example of their use in borrowing hydrogen chemistry can be taken from the work of Dong and co-workers.[3] (*R*)-2-methylpropanesulfinamide (**64**, >99% ee) was used as a chiral auxiliary to effect diastereoselective alkylation of sulfinamides with secondary alcohols, under ruthenium catalysis by eighteen-electron precatalyst, Ru-Macho (scheme **2.1**).



Scheme 2.1 - Diastereoselective alkylation of sulfinamides with alcohols

Sixteen examples were reported with 71% average yield. Good diastereomeric ratios were observed, from 7:3 up to 19:1. Additionally, this reaction demonstrated good tolerance of heteroaromatic moieties. The authors observed no epimerisation of the sulfinamide, despite the high reaction temperatures.

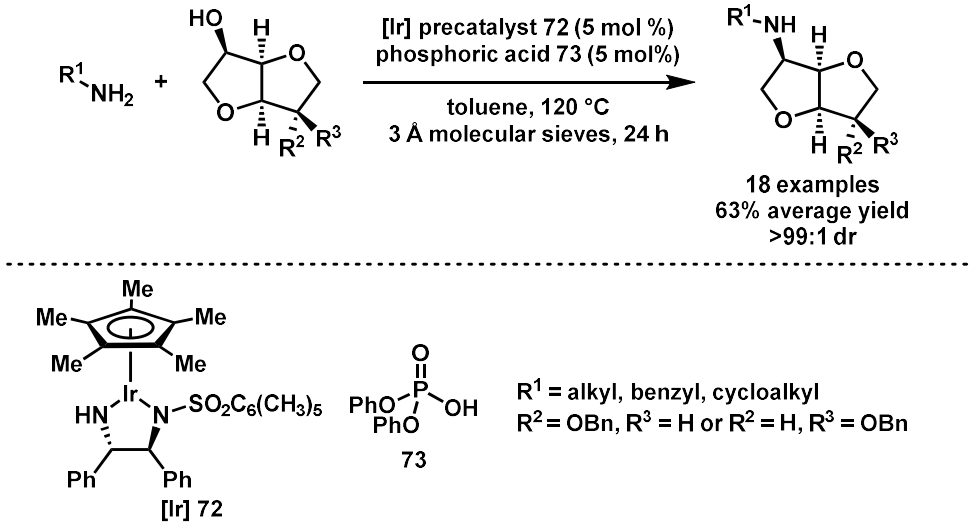
Xia and co-workers[4] who provided an extension of this work with an alternative catalyst, and also demonstrated the synthesis of some pharmaceutically relevant compounds, using an eighteen-electron iridium pre-catalyst (**67**, scheme **2.2**).



Scheme 2.2 - Synthesis and derivitisation of enantioenriched *N*-alkyl sulfinamides 68 and 69

(*S*)-rivastigmine (**70**)[5] and calcimimetic compound known as NPS R-568 (**71**)[6] were synthesised *via* removal of the auxiliary and further elaboration, resulting in 64 and 63% overall yield respectively, with 99% enantiomeric excess or greater. This demonstrated the wider applications of borrowing hydrogen chemistry towards such pharmaceutically relevant intermediates, especially in stereoselective approaches.

Other routes for diastereocontrol include utilising chiral starting materials. This approach was first demonstrated by Popowcyz and co-workers.[7] Bioderived isohexides were mono-protected, and employed as starting materials to effect diastereoselective borrowing hydrogen *N*-alkylation of primary amines (scheme **2.3**).

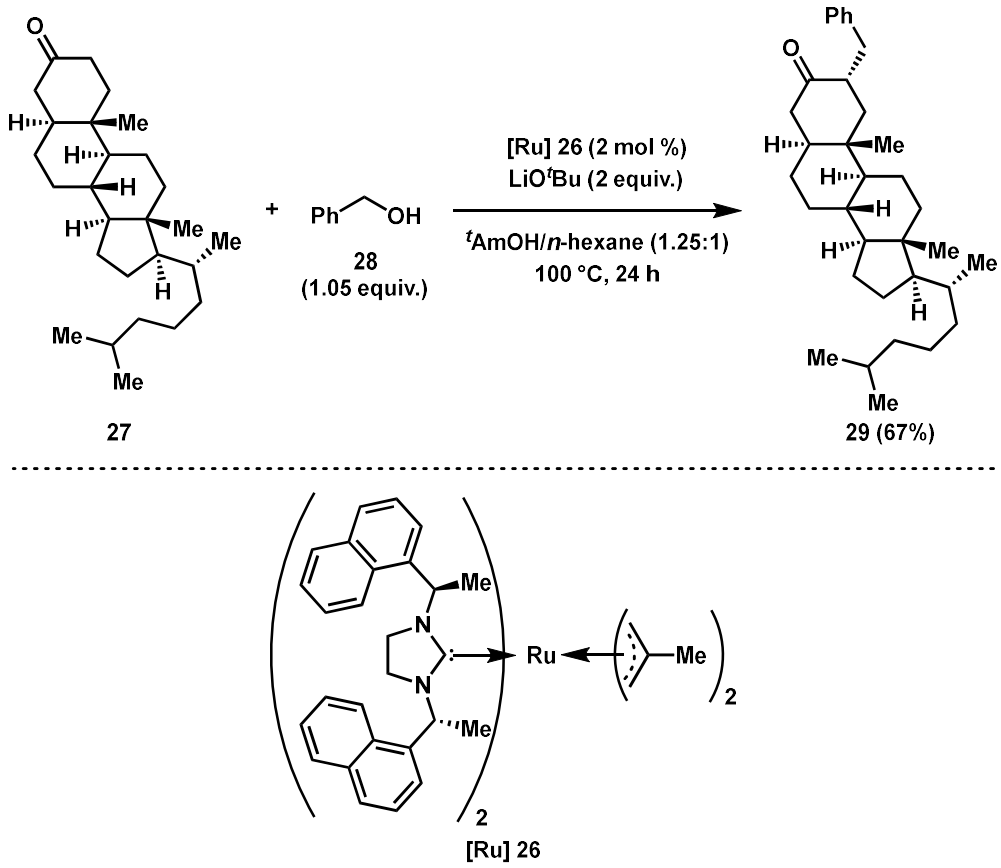


Scheme 2.3 - Iridium-catalysed diastereoselective alkylation of amines *via* borrowing hydrogen

With the use of molecular sieves to sequester water, the authors reported multiple examples with 63% average yield, and >99:1 diastereomeric ratios in all cases. This is an interesting examples of both substrate and catalyst control, where the authors demonstrated that achiral catalysts give poorer diastereoselectivity.

Popowcyz and co-workers also extended this work towards regioselective alkylation, while retaining diastereoselectivity;[8] this was achieved with unprotected isohexides as starting material, and regioselectivity observed based upon the stereochemistry of the isohexide starting material.

A final example can be found in the work of Glorius and co-workers,[9] where the alkylation of cholestanone **28** was demonstrated *via* ruthenium catalysis. Alkylated compound **29** was isolated in 67% yield, as a single stereoisomer, as determined by an NOE experiment in NMR spectroscopy (scheme **2.4**).



Scheme 2.4 - Ruthenium-catalysed cholestanone alkylation

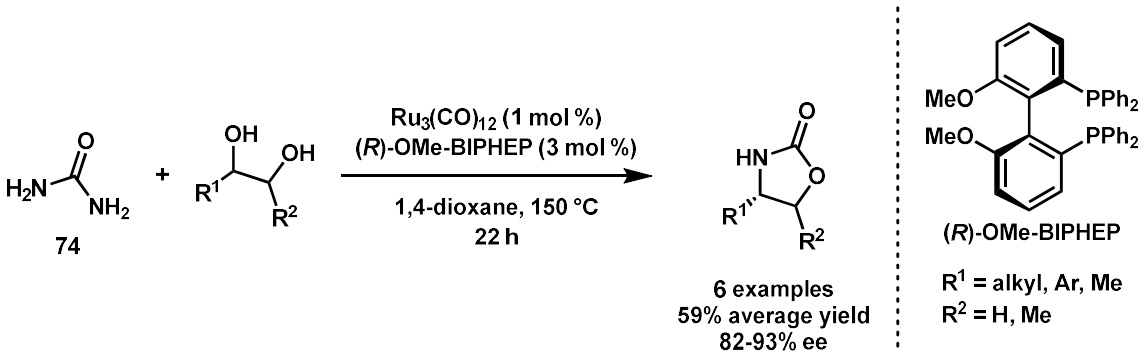
In summary, diastereoselective reactions in borrowing hydrogen can achieve good results, however there are few general examples of such methodologies, especially in *C*-*C* bond forming processes. Furthermore, such examples where chiral auxiliaries are used require further chemical transformations to remove the auxiliary, to yield an enantioenriched product. Transformations that can provide enantioselectivity in the absence of auxiliaries are therefore highly desirable, as these provide a shorter, more efficient route towards enantioenriched products.

2.1.1.2. Transformations with enantioenriched metal catalysts

The use of chiral ligands and chiral precatalysts has found many applications in enantioselective processes, whether in the production of API's, fine chemical industry, or wider academic research.[10] Given the wide applicability and potential

of such chemistry, several applications have been reported in borrowing hydrogen methodology.

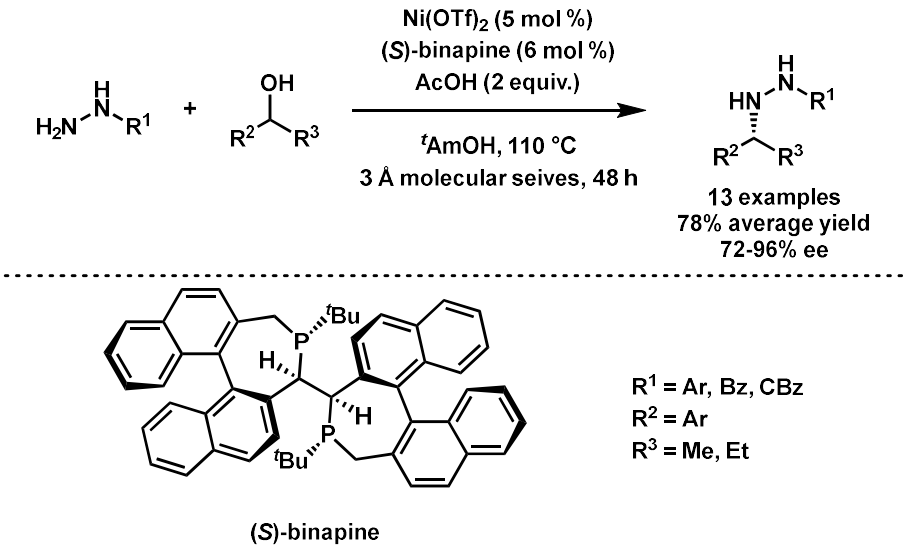
Beller and co-workers[11] reported the use of triruthenium(0) dodecacarbonyl as ruthenium source, and (*R*)-OMe-BIPHEP as chiral ligand in the enantioselective formation of oxazolidin-2-ones, with urea and 1,2-diols as starting materials (scheme **2.5**).



Scheme 2.5 - Enantioselective oxazolidin-2-one formation *via* borrowing hydrogen catalysis

Six examples were demonstrated in up to 93% enantiomeric excess and 59% average yield. While the small number of examples limits the applicability of this reaction, this is nonetheless an unusual example of heterocycle formation in borrowing hydrogen chemistry, especially where enantioselective catalysis is concerned. However, the stereochemical configuration of the less hindered alcohol cannot be controlled by this catalyst system.

Another example of chiral ligands can be taken from the work of Zhou and co-workers.[12] Here, nickel(II) triflate was employed as catalyst, with (*S*)-binapine as chiral ligand, to effect the enantioselective *N*-alkylation of acylhydrazines (scheme **2.6**).



Scheme 2.6 - Enantioselective *N*-alkylation of acylhydrazines

This work reports 13 examples in 78% average yield, with up to 96% enantiomeric excess. A simple nickel salt was used in this case, rendering this example more accessible, compared to precious metal-catalysed approaches that require the formation of a metal pre-catalyst.

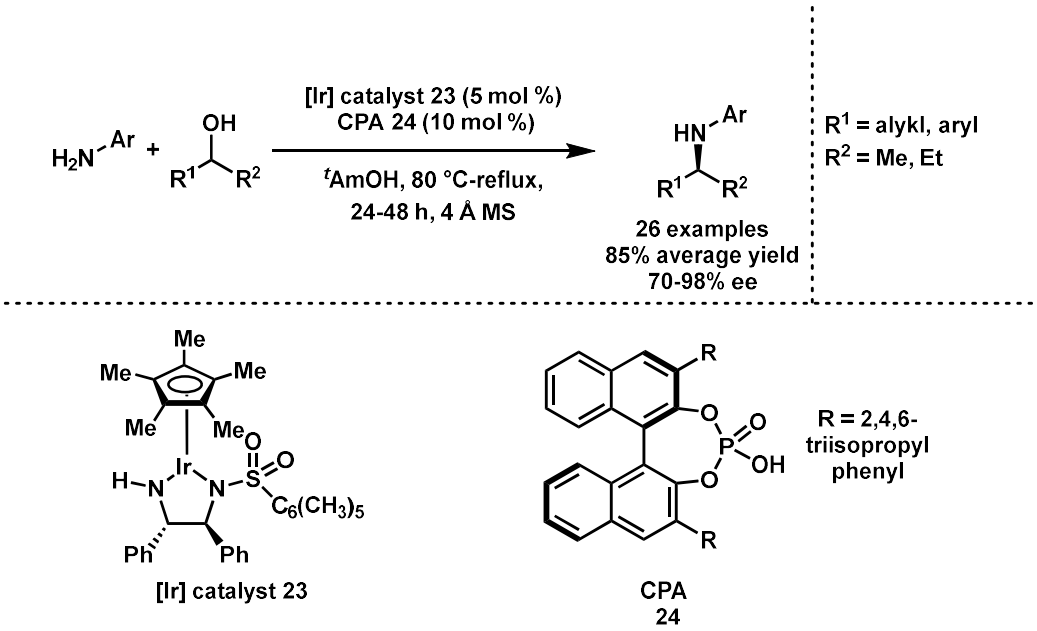
The approach of chiral catalysts in stereoselective borrowing hydrogen reactions provides powerful, single-step routes towards enantioenriched products. However, there are other routes to effect stereoselective borrowing hydrogen, namely approaches that utilise dual catalysis.

2.1.1.3. Transformations *via* dual catalytic systems

Dual catalytic processes are another approach to stereoselective borrowing hydrogen reactions. These transformations require an external catalyst to effect stereoinduction. As the borrowing hydrogen principle provides access to carbonyl chemistry, organocatalysis[13] is often employed as the enantioselective component of these dual catalytic approaches.

An example of organocatalysis in borrowing hydrogen chemistry was reported by Zhao and co-workers.[14] Here, a typical borrowing hydrogen reaction for the

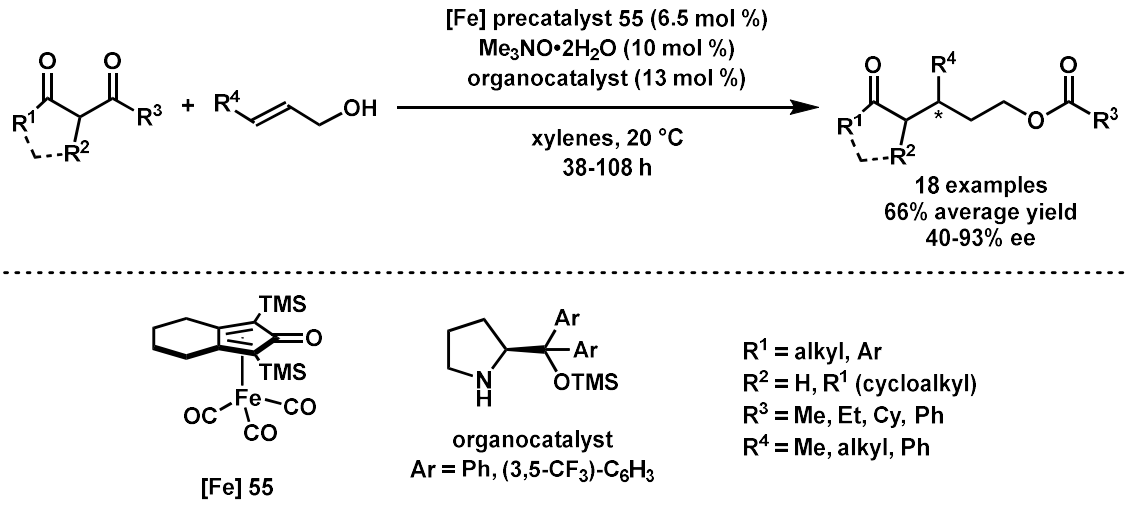
alkylation of amines with secondary alcohols is performed, with a sixteen-electron iridium catalyst. However, a key modification is employed; a chiral phosphoric acid (CPA) is used, to effect Brønsted acid catalysis (scheme **2.7**).



Scheme 2.7 - Enantioselective borrowing hydrogen synthesis of chiral secondary amines

The authors reported 26 examples in 85% average yield, with enantiomeric excesses ranging from 70-98%. The authors attributed asymmetric induction to the protonation of the key imine intermediate, and the interaction between the formed protonated iminium and the conjugate base of the CPA, leading to the selective steric blocking of one face of the imine, and enantioselective induction.

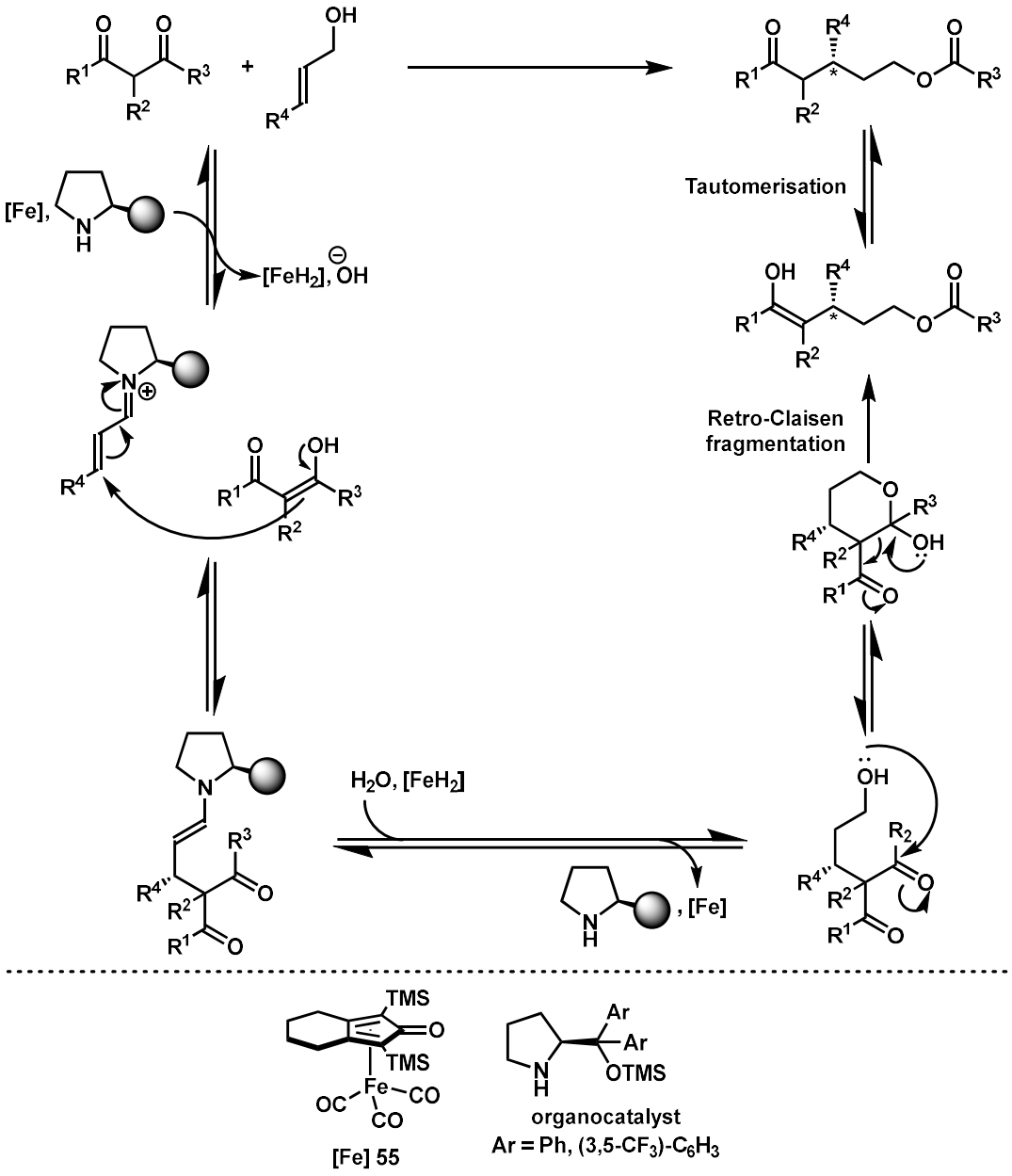
Other pertinent examples can be taken from the work of Rodriguez and Quintard, and co-workers.[15] These authors have reported multiple studies, combining borrowing hydrogen chemistry with secondary amine organocatalysis.[16] A pertinent example was the combination of the Knölker iron precatalyst (**55**) with a chiral diarylsilylprolinol organocatalyst (also known as a Jørgensen-Hiyashi catalyst), to effect the formation of enantioenriched 3,5-difunctionalised pentyl esters (scheme **2.8**).[15b]



Scheme 2.8 - Borrowing hydrogen-iminium dual catalysis

The combination of 1,3-diketones and allylic alcohols was utilised to synthesise the desired products with 18 examples in 66% average yield, and 40-93% enantiomeric excess. The reaction mechanism, as presented by the authors, is shown below (scheme **2.9**). While there are a range of values reported for enantiomeric excesses, this reaction demonstrated another organocatalytic method for enantioselective borrowing hydrogen catalysis. The authors further extended this work to synthesise an odorant, and two fragments of pharmaceuticals with high cytotoxic activity.

The mechanism of this reaction bears some consideration for this thesis. The mechanism begins with iron-catalysed dehydrogenation, transforming the allylic alcohol into an enal intermediate, and generating an iron hydride intermediate. This is sequestered by the amine organocatalyst, and condensation generates a key iminium intermediate. The catalyst then induces stereoselective 1,4-addition of the nucleophile to the starting material, generating a stereocentre in the product. Hydrolysis of the resulting enamine forms a corresponding aldehyde, which is reduced by the iron hydride species. The returned alcohol can now undergo a retro-Claisen reaction, and final tautomerisation yields the observed product.



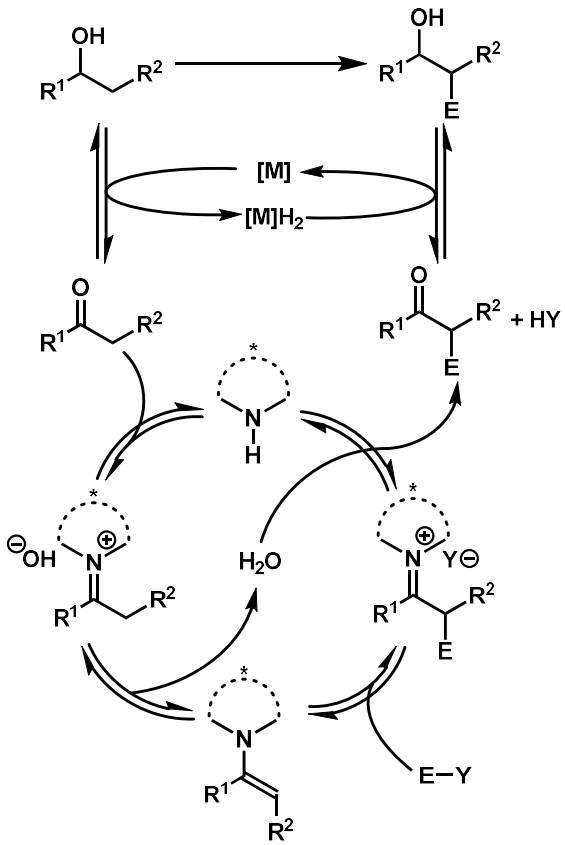
Scheme 2.9 - Postulated mechanism of dual catalytic borrowing hydrogen

This transformation showed the tolerance of borrowing hydrogen for such multi-step, complex reactions, but also demonstrated the compatibility of secondary amine organocatalysts with borrowing hydrogen catalysis, especially with (cyclopentadieneone)iron(0) catalysts.

Despite the potential for a wide range of organocatalytic reactions in tandem with borrowing hydrogen, wider examples beyond those described are lacking in the literature. Further research and investigations are required to bring this powerful combination into wider use.

2.2. Aims and objectives

Taking inspiration from this work, a similar reactive mode was investigated. Where the work of Rodriguez and Quintard[15] used iminium activation (A LUMO-lowering activation mode), investigations in enamine catalysis (A HOMO-raising activation mode) were undertaken, as this type of transformation is still unreported in the literature. A representative scheme for such a postulated reaction is shown below (scheme **2.10**).



Scheme 2.10 - Postulated mechanism for dual borrowing hydrogen-enamine catalysis

Borrowing hydrogen catalysis would initiate the reaction with dehydrogenation of the starting alcohol, generating an intermediate carbonyl compound. This could then undergo condensation, and deprotonation to form the corresponding enamine. If the secondary amine organocatalyst used is a chiral catalyst, then this can be done with control of the conformation and configuration of the enamine. The resulting species would now be a nucleophilic enamine, which can attack an electrophile, a step

where enantioselection could also occur with a chiral organocatalyst. After nucleophilic attack, a resulting functionalised iminium species would be returned. Hydrolysis by water would then regenerate the secondary amine organocatalyst, and returns a functionalised carbonyl compound. This carbonyl compound could now be reduced by the originally formed metal hydride species, regenerating the metal catalyst, returning the product functionalised alcohol, and closing the catalytic cycle.

While this reaction would provide all the usual benefits of borrowing hydrogen chemistry, this route also provides multiple advantages over typical enantioselective enamine catalysis. As these reactions are typically performed with aldehydes as starting materials, a comparison of the products of an enantioselective enamine reaction, and the proposed enantioselective enamine-borrowing hydrogen reaction is shown below (figure **2.1**).

Figure 2.1 - A comparison of products from enamine and enamine-borrowing hydrogen catalysis

Firstly, one of the main drawbacks of enamine catalysis is the formation of an epimerisable stereocentre, due to the acidity of the hydrogen atoms on the *α*-ketone carbon. This results in acid or base sensitivity of the product's stereocentre. The proposed route would instead render these hydrogen atoms *β*-alcohol, and therefore of much lower acidity, preventing epimerisation under basic or acidic conditions. This proposed route would also prevent the necessity for stoichiometric reductions, which would otherwise be required to access such enantioenriched alcohols. Secondly, due to the instability of aldehydes, and their tendency to undergo reactions such as auto-oxidation in air,[17] a common strategy in the literature is to further functionalise these compounds. This can be done to assess their enantiopurity *via* chiral HPLC, store them, or otherwise manipulate them to avoid the difficulties of handling chiral aldehydes. Once again, that the product of the proposed dual catalytic route is an alcohol, allows these manipulations to be avoided. Finally, it is common to make the aldehyde starting materials *via* oxidation of an alcohol precursor. Thus, the proposed dual catalytic system would also

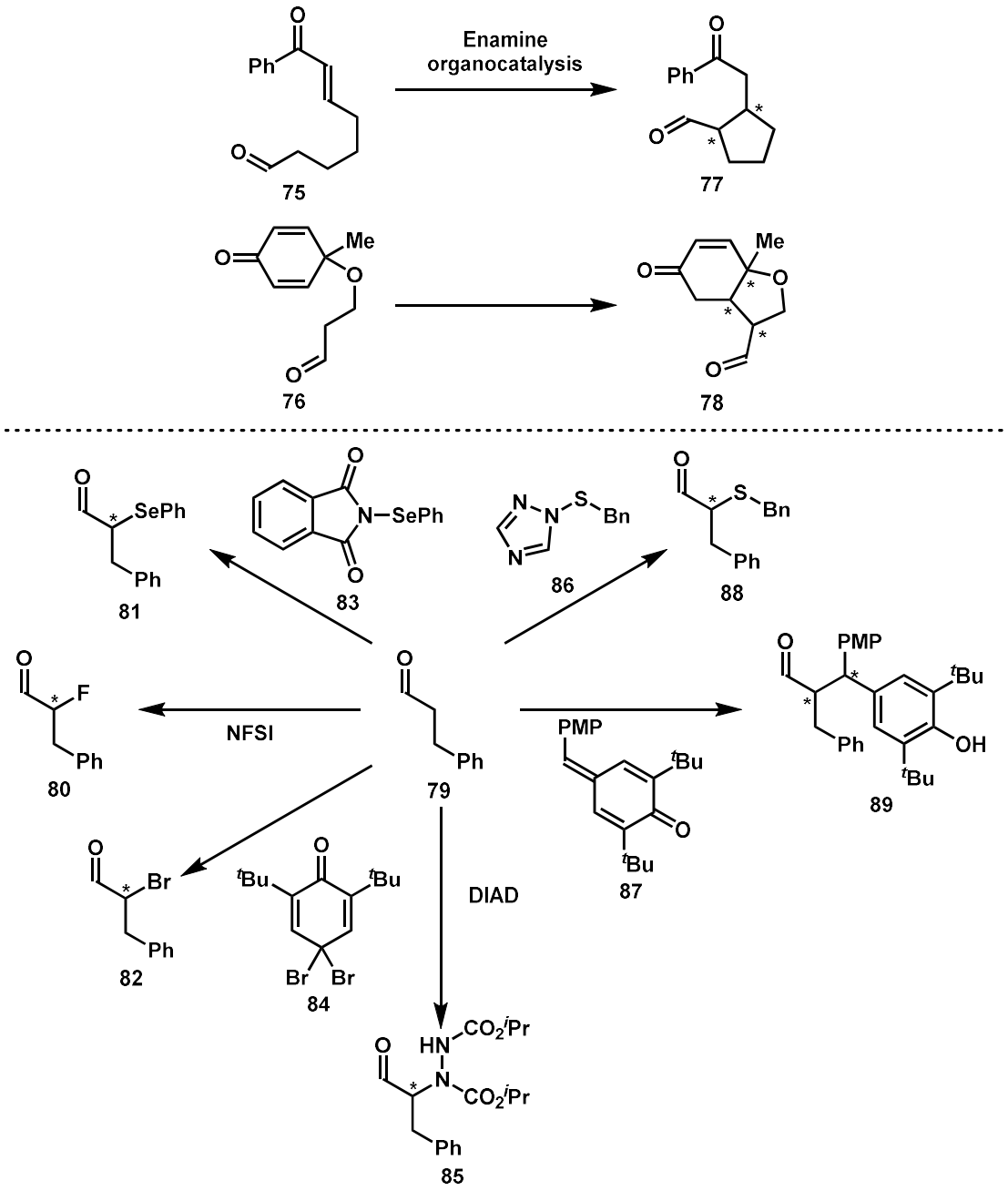
prevent the requirement for a stoichiometric oxidation step, reducing the number of steps in the synthesis of enantioenriched compounds.

However, there are potential challenges with borrowing hydrogen-enamine dual catalysis, which were considered during these investigations. First, the leaving group of the electrophile must be one that is compatible with the metal catalyst employed for the borrowing hydrogen cycle. Should this leaving group poison the catalyst, then the reaction will be unable to proceed. Secondly, the compatibility of the electrophile itself with the metal catalyst should be considered, for the same reasons discussed above. Finally, the formed iminium species is a highly electrophilic species, and is therefore a target for hydrogen transfer by the borrowing hydrogen catalyst. This would result in a cessation of organocatalysis, and hence any further reactivity would result from enolate chemistry. This in turn would result in no enantioselective catalysis occurring. Thus, the organocatalytic reaction occurring should be complete in a very short time, as this would limit the presence of the iminium species present in the reaction mixture at any given point during the reaction. With these challenges in mind, investigations into dual enamine-borrowing hydrogen catalysis were begun.

2.3. Results and discussion

2.3.1. Investigations into borrowing hydrogen-enamine catalysis

Initial investigations into dual catalytic borrowing hydrogen-enamine catalysis began with selecting reactions from the enamine catalysis literature. These reactions were selected in line with the considerations highlighted above - namely that either a fast intramolecular reaction, or an intermolecular reaction, was required. Intermolecular reactions from the works of Hayashi[17] and List,[18] as well as a selection of intramolecular reactions from the works of Jørgensen[19-22] and Cordova[23] were selected for investigation (scheme **2.11**).



Scheme 2.11 - Selected organicatalytic reactions for further investigation in dual catalysis

The selected reactions included two intermolecular cyclisations *via* enamine catalysis, then a short range of selected intermolecular reactions, including a wide range of *C*-heteroatom bond forming reactions, such as selenation, sulfuration, bromination and fluorination reactions. These were selected for their short reaction time, which was assumed to mean high rate, fast reactions.

With the targeted reactions in hand, synthesis of the required intermolecular substrates for a borrowing hydrogen reaction was undertaken, as well as the synthesis of the required electrophiles for intramolecular reactions.

2.3.1.1. Synthesis of the intermolecular substrates

The targeted borrowing hydrogen substrates are shown below (figure **2.2**):

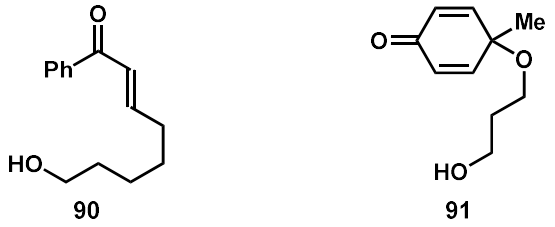
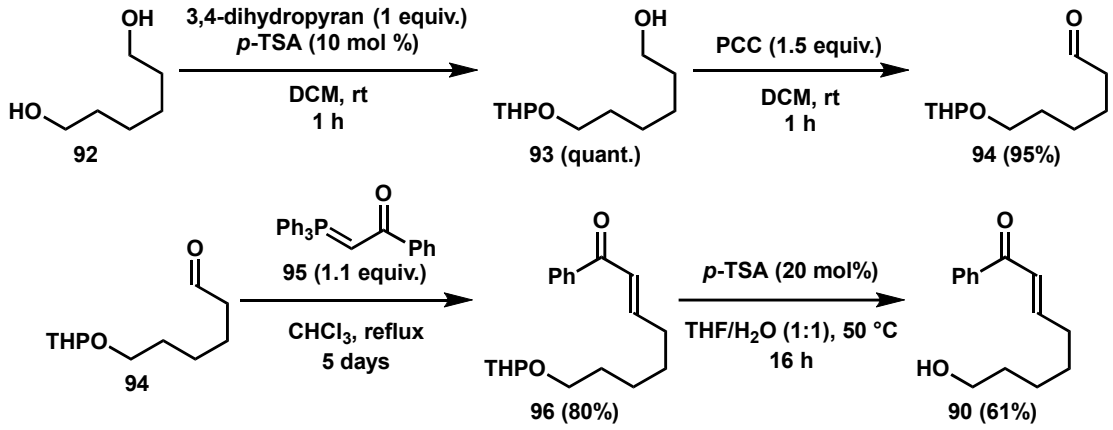


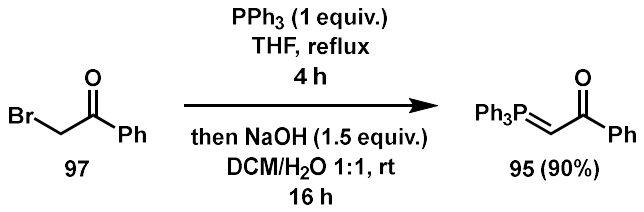
Figure 2.2 - Targeted intermolecular substrates

The synthesis of substrate **90** was performed by the following route (scheme **2.12**).



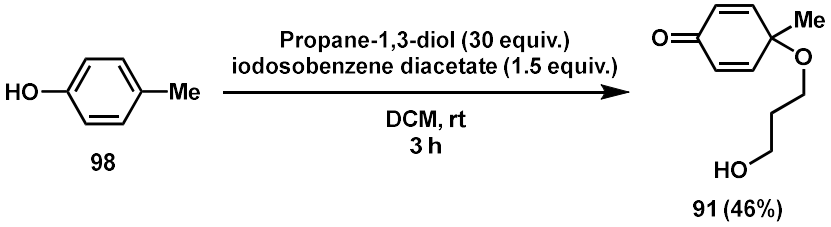
Scheme 2.12 - Synthesis of intermolecular substrate 90

First, hexane-1,6-diol (**92**) was monoprotected with 3,4-dihydropyran and catalytic acid, to form **93** in quantitative yield. Next, pyridinium chlorochromate oxidation was employed, returning aldehyde **94** in 95% yield. This was then subjected to a Wittig reaction with phosphanyl ylide **95**, resulting in the generation of the product **96** in 80% yield as an exclusively (*E*)-alkene. THP deprotection returns the target compound in 61% yield, representing a 46% overall yield. Phosphanyl ylide **95** was itself synthesised in a 2-step procedure, starting from 2-bromoacetophenone (**97**, scheme **2.13**).



Scheme 2.13 - Synthesis of phosphanyl ylide 95

The synthesis of substrate **91** was performed in one step, utilising a hypervalent iodine species known as PIDA (scheme **2.14**).



Scheme 2.14 - Synthesis of intermolecular substrate 91

With excess propane-1,3-diol as nucleophile, and PIDA acting as Lewis acid activator, substrate **91** was produced from *p*-creosol **98** in 46% yield.

2.3.1.2. Synthesis of electrophiles

The targeted electrophiles for borrowing hydrogen-enamine catalysis are shown below (figure **2.3**):

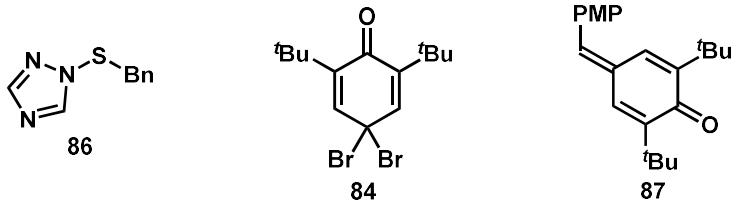
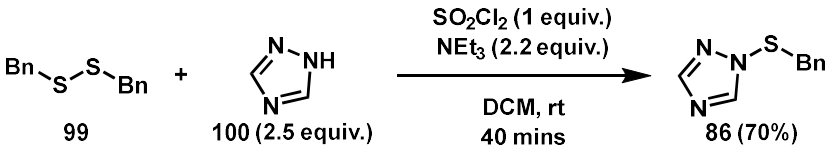


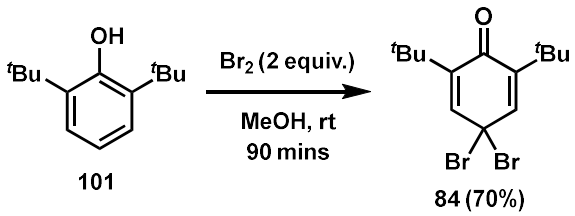
Figure 2.3 - Targeted intermolecular electrophiles to be sythesised

Electrophile **86** was synthesised from dibenzyl disulfide and 1,2,4-triazole (scheme **2.15**).



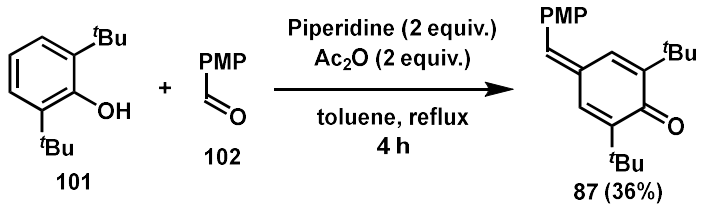
Scheme 2.15 - Synthesis of electrophile 86

With sulfuryl chloride as activator, the target benzylthiotriazole was isolated in 70% yield. Brominating reagent **84** was then synthesised, from 2,6-di-*tert*-butylphenol (**101**) and bromine (scheme **2.16**).



Scheme 2.16 - Synthesis of brominating reagent 84

Direct bromination yields the target compound **84** in 70% yield. *Para*-quinone methide **87** was then synthesised under Lewis base activation (scheme **2.17**).



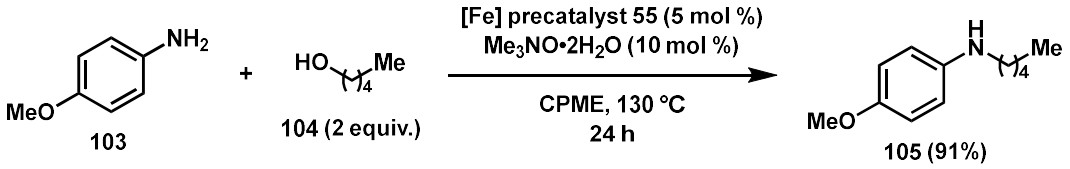
Scheme 2.17 - Synthesis of *para*-quinone methide 87

2,6-Di-*tert*-butylphenol (**101**) was once again employed here, with *para*-methoxybenzalydehyde (**102**) and piperidine as Lewis base, yielding the target quinone methide **87** in 36% yield. With the materials required to test our hypothesis in hand, a final stage of screening was performed.

2.3.1.3. Control reactions

Despite the range of reactions selected for screening, it was necessary to devise a way to assess whether the organocatalytic reactions were compatible with borrowing hydrogen catalysts. From the works of Rodriguez and Quintard,[15] it was known that diarylsilylprolinol organocatalysts were compatible with iron catalyst **55**. The intramolecular substrates were not considered plausible substrates for compatibility issues, as they contain functional groups commonly utilised in borrowing hydrogen chemistry. However, there are many functional groups in the proposed electrophile list that could present issues for easily oxidised metal catalysts, such as the iron precatalyst **55** desired for these reactions. A

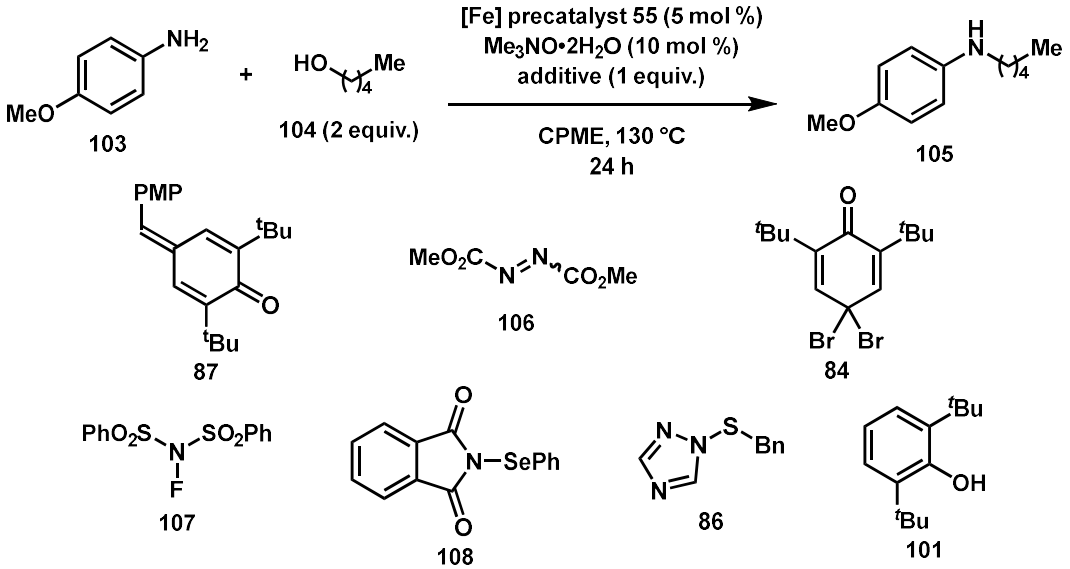
representative example from the work of Feringa and co-workers,[23] where *para*-anisidine (**103**) was alkylated *via* borrowing hydrogen catalysis with *n*-pentanol (**104**), was selected from the literature as a control reaction (scheme **2.18**).



Scheme 2.18 - Selected borrowing hydrogen control reaction

This reaction would be utilised to study the targeted electrophiles or products, which could be potential catalyst poisons. By adding a stoichiometric electrophile to this reaction system, the compatibility of these compounds with the borrowing hydrogen system could be assessed. If the addition of electrophile precludes the formation of the product, or the formation of pentanal (as observed by ^{1}H NMR spectroscopy), then this electrophile can be deemed incompatible with the borrowing hydrogen system, as it disrupts the action of the iron catalyst.

The targeted electrophiles, or compounds that represent their products, were all screened in this fashion. Table **2.1** shows the results of this testing.



Entry	Additive	Outcome
1	**87**	Yellow solution results, 84% yield of product **105** observed by ^{1}H NMR spectroscopy, **87** returned
2	**106**	Gas evolution and black solution observed, starting materials and **106** not returned, complex reaction mixture by ^{1}H NMR spectroscopy

3	**84**	Yellow solution results, no reaction observed, starting materials returned, **84** not returned
4	**107**	Black solution observed, starting materials and **107** not returned, complex reaction mixture by ^{1}H NMR spectroscopy
5	**108**	Orange solution observed, starting materials and **108** not returned, complex reaction mixture by ^{1}H NMR spectroscopy
6	**86**	Yellow solution observed, starting materials and **86** not returned, complex reaction mixture by ^{1}H NMR spectroscopy
7	**101**	Yellow solution observed, >98% yield of product **105** observed by ^{1}H NMR spectroscopy, **101** returned

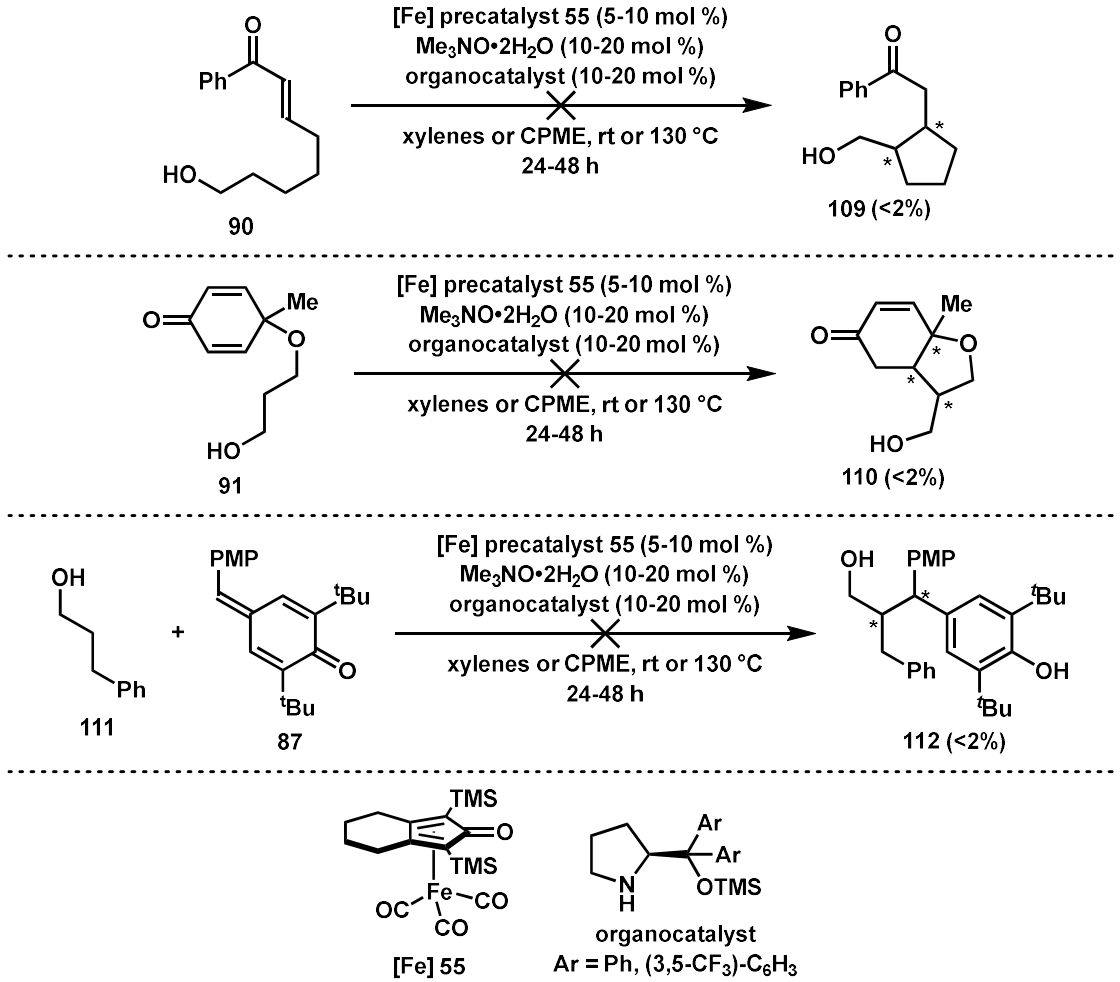
Table 2.1 - Electrophile and representative product material screening

When employed in the reaction, electrophile **87** did not inhibit the reaction to any extensive degree, returning both the electrophile, and the furnished product. By contrast, DIAD (**106**) resulted in extensive gas evolution, and the presumed decomposition of reaction components to a complex mixture, observed by the ^{1}H NMR spectrum of the crude reaction mixture. Brominating reagent **84** resulted in the cessation of the desired reaction, and decomposition of the reagent in question. NFSI (**107**) resulted in the formation of a complex mixture by ^{1}H NMR spectroscopy of the crude reaction mixture, and the loss of both products and additive. Electrophiles **108** and **86** also resulted in the loss of material, and formation of a complex mixture. Finally, additive **101**, which was used to mimic the desired reaction product and side product of electrophiles **87** and **84** respectively, did not impede reaction formation, and survived the reaction conditions as well.

With these results, it was demonstrated that many of these electrophiles are incompatible. However, it appears that both *para*-quinone methide **87**, and the phenol formed in its product, are compatible with these reactions. Therefore, this electrophile, and the targeted intramolecular substrates can be tested in a borrowing hydrogen reaction.

2.3.1.4. Borrowing hydrogen-enamine reaction screening

With the targeted materials in hand, screening in borrowing hydrogen reactions was undertaken. A scheme to summarise the results of these screenings is shown below (scheme **2.19**).



Scheme 2.19 - Attempted borrowing hydrogen-enamine catalysis

First, a range of low temperature reactions were screened, to assess whether these reactions would occur under such conditions. Using the reaction conditions of Rodriguez and Quintard[15b] for inspiration, these reactions were investigated by ^{1}H NMR spectroscopy after 48 hours of stirring at room temperature. All reactions were screened with varied loading of metal catalyst (and activator) and the organocatalyst, to explore systems with both high and low catalyst loadings. In addition, both toluene (from the work of Rodriguez and Quintard)[15b] and CPME (from the work of Feringa)[23] were employed as solvents, to assess the solvent effect on such a reaction. However, despite the range of conditions screened at low temperatures, no desired product was observed in the ^{1}H NMR spectra of the crude reaction mixtures. Greater than 95% starting material was returned in all reactions.

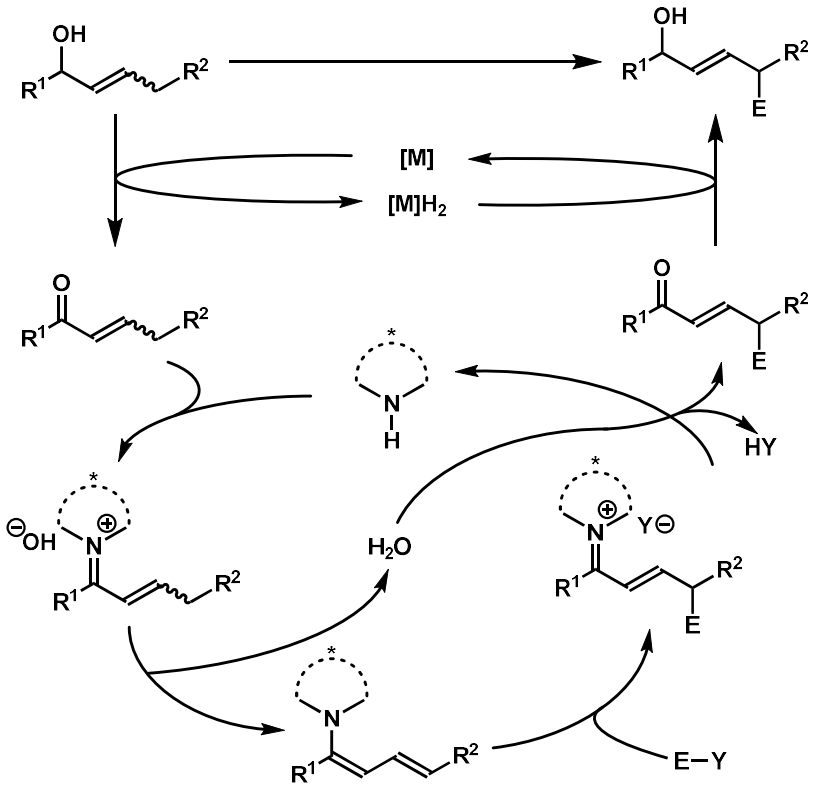
Next, a series of high temperature reactions was attempted, employing conditions inspired by those found in the work of Feringa and co-workers;[23] 130 °C for 24

hours. It was posited that the enhanced temperature would result in a less enantioselective process, however a proof-of-concept for borrowing hydrogen enamine catalysis would still be an important step in the progression of dual catalytic systems. Once again, no target compound was observed by ^{1}H NMR spectroscopy of the crude reaction mixtures. However, despite the high temperatures, starting materials were returned in every case. Trace aldehyde was observed in these higher temperature reactions, but evidently any resulting reactions were non-productive.

It was hypothesised that there were two primary issues with the current reactions. Firstly, that the alcohol oxidation step was limiting in both high and low temperature reactions, and a more reactive alcohol was required. Secondly, it was thought that in order for the completion of the reaction, a way to sequester the alcohol in the product was essential, as this would prevent the product from participating further in the reaction. The proposed route was to investigate dual catalysis *via* borrowing hydrogen-dienamine catalysis.

2.3.2. Investigations into borrowing hydrogen-dienamine catalysis

By contrast to enamine catalysis, which requires an aliphatic alcohol as substrate, dienamine catalysis requires an *α,β*-unsaturated carbonyl system, to access the corresponding dienamine, and effect *γ*-functionalisation of this system.[24] When transferred to borrowing hydrogen, such reactions would have allylic alcohols as substrates. This would be beneficial due to the greater ease of oxidation of allylic alcohols, due to their electron-rich nature, and the stability gained through the formation of a conjugated system. The general scheme for desired borrowing hydrogen-dienamine catalysis is as follows (scheme **2.20**):



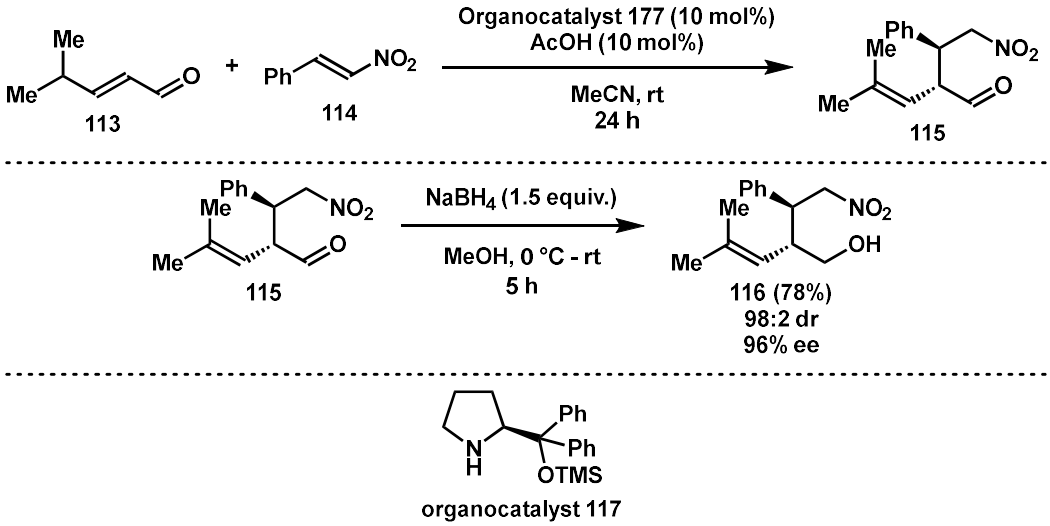
Scheme 2.20 - Postulated mechanism for dual borrowing hydrogen-dienamine catalysis

Initial oxidation would convert the starting allylic alcohol to the corresponding *α,β*-unsaturated carbonyl compound. Condensation with the secondary amine organocatalyst, and deprotonation, would result in the formation of the dienamine. The dienamine could now attack the electrophile from the *γ*-position, effecting *γ*-functionalisation, and returning an *α,β*-unsaturated iminium species. Hydrolysis of this species would return the functionalised *α,β*-unsaturated carbonyl compound, which could be reduced to the target *δ*-functionalised allylic alcohol.

However, in this proposed mechanism, an issue can be predicted. All formed *α,β*-unsaturated carbonyl compounds, including both iminium species, are potential targets for a 1,4-reduction by the formed metal hydride. Routes that could minimise the presence of this species would be preferential. Additionally, while distant functionalisation is an important transformation, the original target of this work was *β*-alcohol functionalisation. Reactions that could solve or attenuate these problems were sought.

Inspiration was drawn from the work of Chen and co-workers.[25] Here, the authors used (*E*)-4-methylpent-2-enal (**113**) as a starting material. The geminal-dimethyl

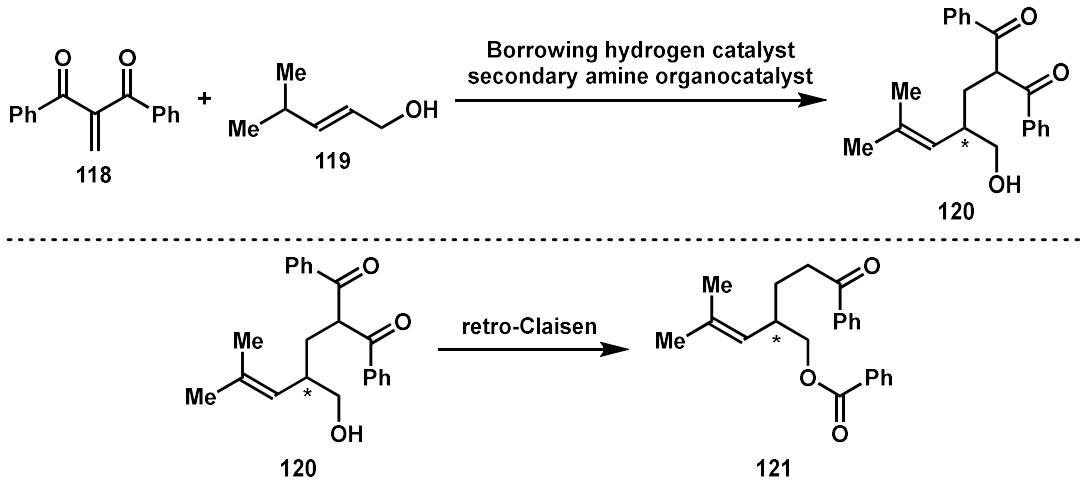
group provided high steric encumbrance, preventing *γ*-functionalisation, and resulting in exclusively *α*-functionalisation occurring (scheme **2.21**).



Scheme 2.21 - Trapped enamine reactivity in dienamine catalysis

This reaction, therefore, is an excellent candidate for transfer to borrowing hydrogen conditions. Not only would this reaction reach the target of *β*-alcohol functionalisation, but also it is possible that the geminal-dimethyl group would provide sufficient steric bulk to prevent transfer hydrogenation, and 1,4-reduction. Additionally, the intermediate products would have only an aldehyde or iminium as a site for reduction. This mode of trapped enamine reactivity therefore provides a route to combat the earlier discussed issues with dienamine catalysis in borrowing hydrogen.

However, this reaction does not remove the alcohol from the product. This was discussed earlier as a key approach for these reactions to succeed. An additional reaction was designed with this in mind. Using an electrophile that could undergo a retro-Claisen reaction in the same fashion as the product described in the work of Rodriguez and Quintard,[15b] the alcohol could theoretically be sequestered in the same way. The following reaction was proposed (scheme **2.22**):

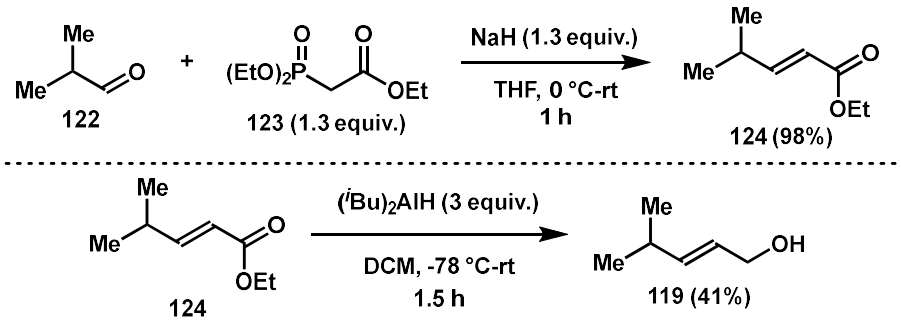


Scheme 2.22 - Posutlated retro-Claisen substrate and desired reactivity

Thus, two more reactions had been identified for testing - both utilising the same allylic alcohol, but with either *β*-nitrostyrene **114** or enedione **118** as electrophile. The targeted alcohol **119** and Michael acceptor **118** were then synthesised.

2.3.2.1. Synthesis of substrates

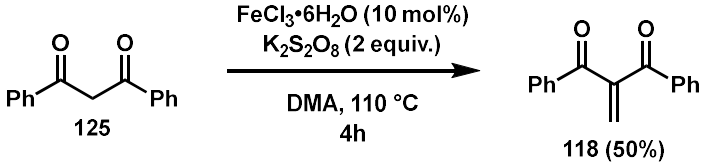
Alcohol **119** was synthesised in two steps. First, *iso*-butyraldehyde **122** was subjected to a Horner-Wadsworth-Emmons reaction with ethyl 2-diethoxyphosphorylacetate and sodium hydride as base. This returned intermediate acrylate **124** in 98% yield (scheme **2.23**).



Scheme 2.23 - Synthesis of alcohol 119

Acrylate **124** was then subjected DIBAL-H reduction, yielding the target alcohol **119** in 41% yield, and 40% overall yield.

Michael acceptor **118** was also synthesised. Utilising catalytic iron(III) chloride, with potassium persulfate as co-oxidant, DMA was utilised to furnish the target Michael acceptor in 50% yield (scheme **2.24)**.

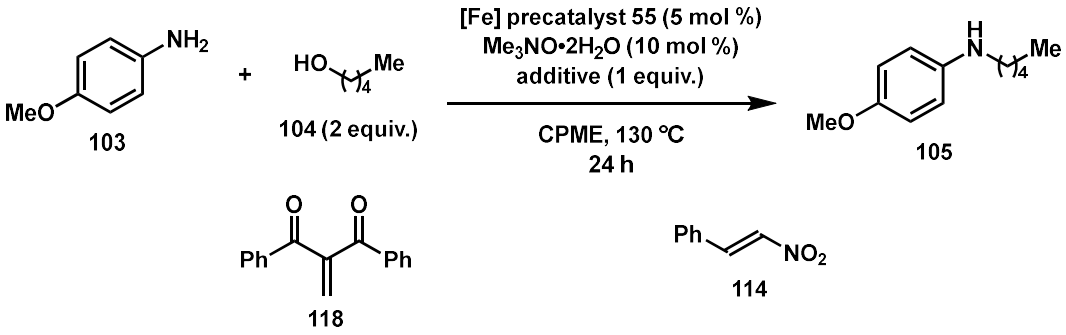


Scheme 2.24 - Synthesis of Michael acceptor 118

With both targeted substrates in hand, a second round of reaction screening was undertaken.

2.3.2.2. Control reactions

As before, a small range of control reactions were undertaken, to assess the compatibility of these reactants with one another. The same control reaction was used as above, with the results shown in the table below (table **2.2**).



Entry	Additive	Outcome
1	**118**	70% yield of product **105** observed by ^{1}H NMR spectroscopy, **118** returned
2	**114**	50% yield of product **105** observed by ^{1}H NMR spectroscopy, **114** not returned.

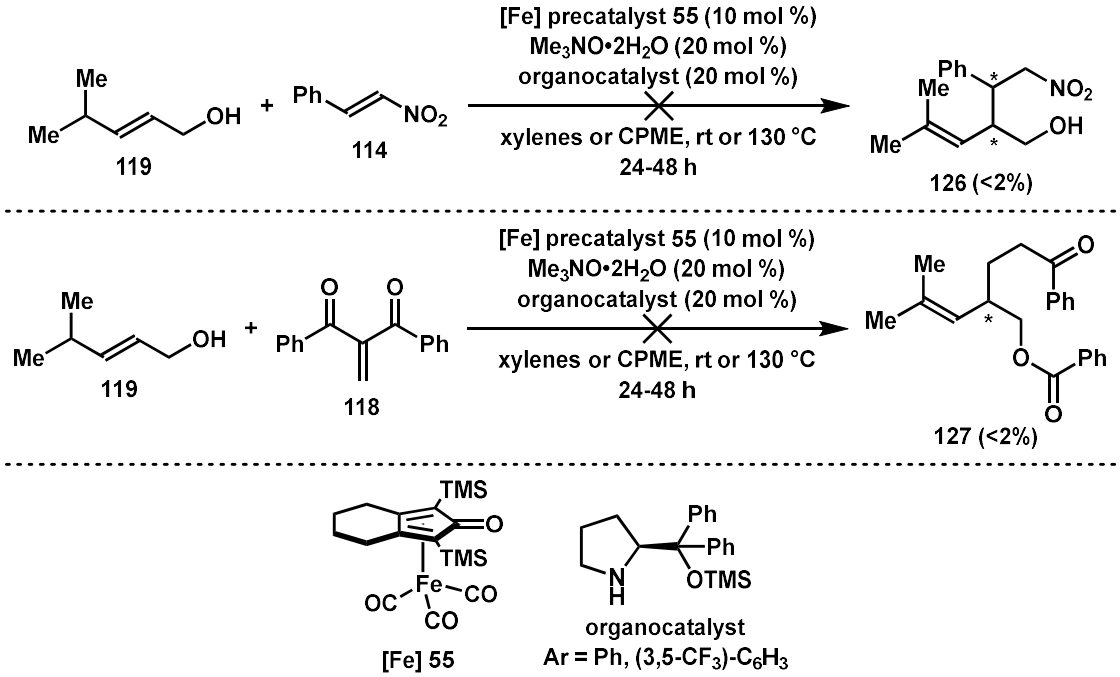
Table 2.2 - Electrophile screening

Enedione **118** survived the reaction conditions well, and provided only slight inhibition in the formation of the product. However, *β*-nitrostyrene **114** both reduced the amount of product observed by a significant margin, and was not recovered from

the reaction. Despite this result, it was decided to take both electrophiles forward, and subject them to potential borrowing hydrogen reactions as before.

2.3.2.3. Borrowing hydrogen-dienamine reaction screening

With the desired starting material and electrophiles in hand, these reactions were subjected to a similar set of conditions to the enamine reactions screened previously. However, no reactions with lower than 10 mol % metal catalyst loading, and 20 mol % organocatalyst and activator loading were attempted. A scheme summarising all attempts is shown below (scheme **2.25**).



Scheme 2.25 - Attempted borrowing hydrogen-dienamine catalysis

Once again, early attempts were run at room temperature, for 48 hours, in either xylenes or cyclopentyl methyl ether. These efforts showed similar results to before - no product could be observed by the ^{1}H NMR of the crude reaction mixtures, and starting materials were returned. However, even at room temperature these reactions returned trace amounts of aldehyde; a promising result for future work.

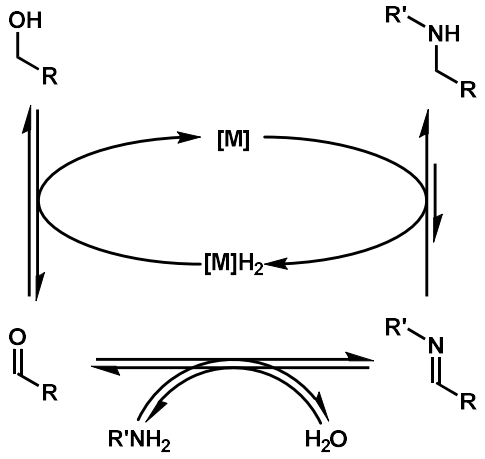
Further reactions were then attempted at the elevated temperature conditions, to assess whether there was a thermal barrier to this transformation occurring that

could be surpassed. Here, some small differences were observed. In the high temperature case, the *β*-nitrostyrene was not returned, but both starting material **119** and its corresponding aldehyde were returned. The aldehyde was only observed in trace amounts, and no product was returned in this reaction. Once again, the second reaction, with enedione **118**, returned only starting materials, and the observation of trace aldehyde. No product was observed under these conditions.

It was at this point investigations into this project were halted, in favour of more productive projects that could be pursued.

2.3.3. Discussion of potential issues

While it is evident that this work was unsuccessful, it is worthwhile to consider what caused this. One of the principles of borrowing hydrogen chemistry is that the intermediate reaction must be of a compatible rate with that of the transfer hydrogenation reaction (scheme **2.26**).

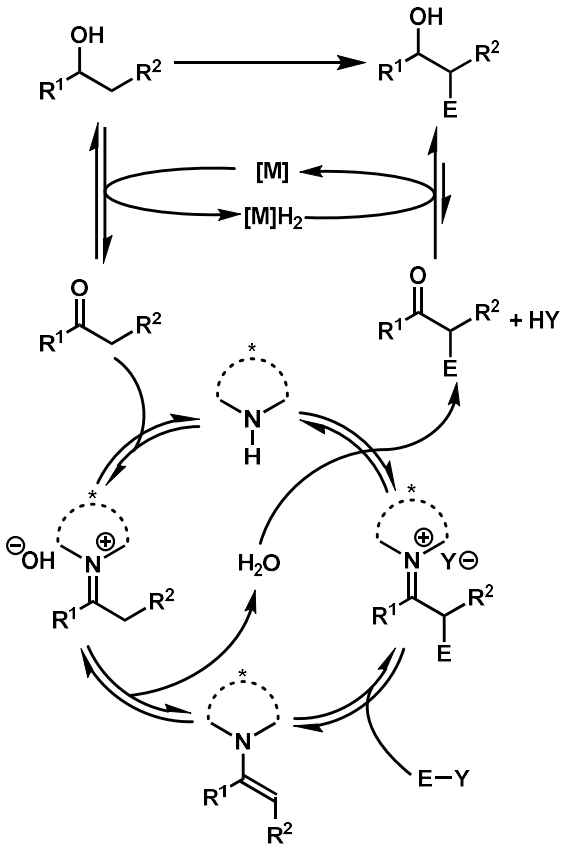


Scheme 2.26 - A generic scheme for borrowing hydrogen

That is to say that, if the initial oxidation is fast, then likewise is the reduction of the formed carbonyl species. The intermediate reaction (amine condensation, in this instance) must therefore be competitive with the reduction of the formed carbonyl compound. If this is not achieved, then the intermediate reaction would be unable to sequester the carbonyl compound before reduction, preventing the forward

reaction. Likewise, if the reduction of the formed imine is hindered by some means, then this leads to this compound being a more persistent species in the reaction mixture, leading to a greater propensity for hydrolysis to occur, regenerating both amine and aldehyde. However, the final reductive step of this reaction is functionally irreversible, in all known borrowing hydrogen reactions. This can act as a driving force, allowing the rest of the material to be converted *via* Le Chatelier's principle (excepting side reactions removing material from the reaction).

However, the general scheme for the postulated borrowing hydrogen-enamine chemistry is significantly more complex (scheme **2.10**).



Scheme 2.10 - Postulated mechanism for dual borrowing hydrogen-enamine catalysis

Here, the same concerns with regards to competitive secondary amine condensation and hydrogenation/dehydrogenation are true. However, it would also be necessary, for good reactivity, for the entire enamine cycle to be complete in a comparable time to the borrowing hydrogen hydrogenation/dehydrogenation reaction. Additionally, the problem of attempting to control enamine reactivity under this regime would be challenging, as each step is once again in equilibrium. It is

unknown whether the desired iminium species was ever formed, as it was never visible by the ^{1}H NMR of the crude reaction mixture. If it is assumed that these iminium compounds were forming, it is plausible that enamines are formed also. However, it could be that such species more readily react with water to return the iminium species, or the intermediate carbonyl compound, than with the electrophile to progress the reaction. One possible approach to this would be to attempt to sequester water from the reaction by the action of molecular sieves or other desiccants, however water is required to regenerate the secondary amine organocatalyst.

2.4. Future work

For future work, several approaches to enable this reaction can be envisioned. A proof of concept enamine reaction should be completed first, utilising a simple, achiral secondary amine, such as pyrrolidine or piperidine. This would allow good conditions that enable such a reaction to be developed without concerns for enantioselectivity. Additionally, such reactions would allow a more thorough understanding to be gained of the challenges discussed earlier, such as the control of equilibria, and the assessment of stability and compatibility of typical electrophiles with borrowing hydrogen.

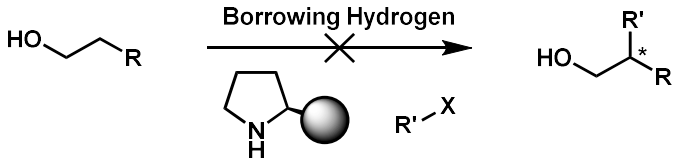
Other possible routes could include the use of more basic reaction mixtures, which could drive the formation of enamines from formed iminium compounds. However, this would lead to a background reaction occurring *via* enolate chemistry, which could lead to false-positives in the results of such reactions.

Further works should also explore the ability of other borrowing hydrogen catalysts to tolerate secondary amine organocatalysts. No other metals, or alternative catalysts of the same metal were screened in this work, as the literature precedent with the chosen iron catalyst demonstrated mild reaction conditions and high enantioselectivity. However, an understanding of how different catalysts perform under the desired, low temperature conditions would be valuable in the progression

of the field towards this reaction, and others that require low temperature for enantioinduction.

2.5. Summary

In summary, a range of enamine and dienamine chemistry was investigated in tandem with borrowing hydrogen chemistry. No promising results were observed, and investigations into this project were ceased for the favour of other investigations. The success of this mode of reactivity is dependent on the fine control of multiple equilibria, which was evidently not achieved. This transformation requires significantly more time and research than was attempted by this initial screening. Therefore, this project failed the aims and objectives of this thesis, but generated much useful data, supporting and suggesting further avenues of research in the field of borrowing hydrogen-enamine dual catalysis.



Scheme 2.27 - Attemped borrowing hydrogen-enamine catalysis

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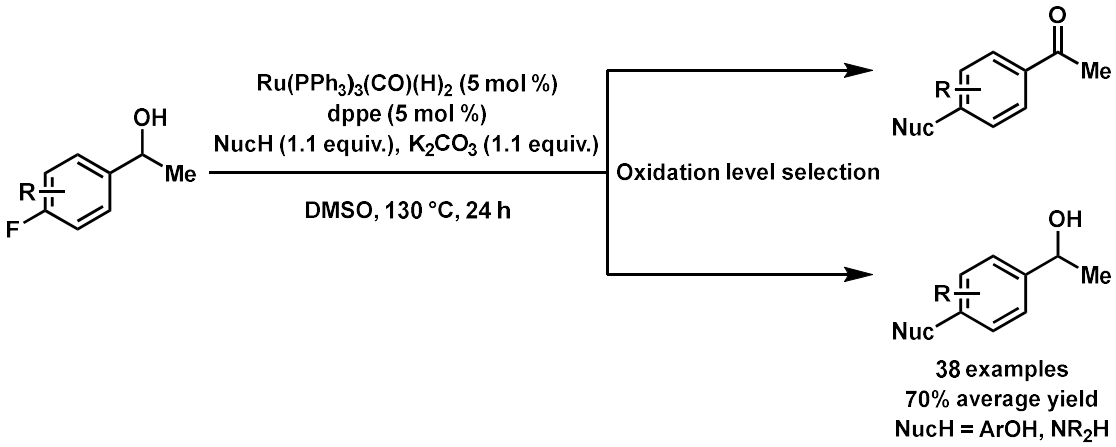
Chapter 3: Exploring Tandem Ruthenium-Catalysed Hydrogen Transfer and S_NAr Chemistry

Table of Contents

3. Preface

This chapter discusses the development of a procedure for ruthenium-catalysed cleavage, and tandem S_NAr reaction. This work was performed as part of a wider publication on the use of tandem ruthenium-catalysed hydrogen transfer and S_NAr chemistry. Herein, 38 examples were reported, in 70% average yield, with diaryl ethers and aryl amines synthesised. This work was then extended towards a ruthenium-catalysed oxidation-isomerisation, to generate the ketone products of the scheme below.



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.

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Kurt Polidano – Responsible for the optimisation and substrate scope investigation of the hydrogen transfer-S_NAr reaction, parts of the optimisation of the oxidative cleavage-S_NAr reaction, and synthesis of the model substrate in this part. Kurt Polidano reported 38 examples for this transformation in 70% average yield.

Benjamin G. Reed-Berendt – Responsible for parts of the optimisation of the oxidative cleavage-S_NAr reaction, and the synthesis of substrates, and the substrate scope investigation of the oxidative cleavage-S_NAr reaction.

Anaïs Basset – Responsible for parts of the optimisation of the oxidative cleavage-S_NAr reaction.

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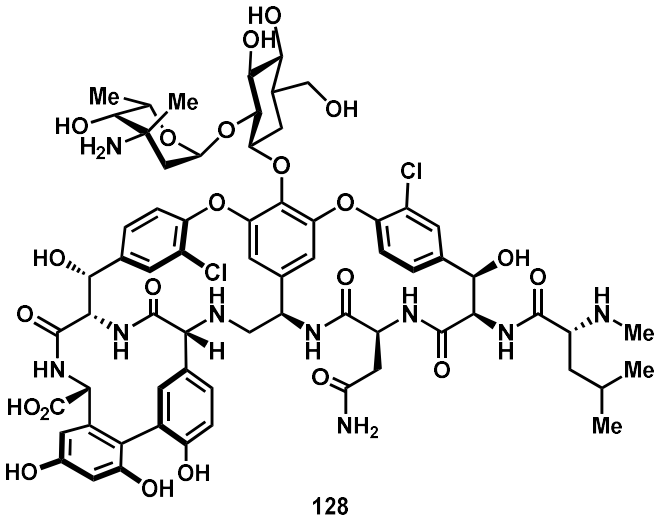
Louis C. Morrill – Supervisor of Benjamin G. Reed-Berendt and Kurt Polidano, Cardiff University.

3.1. Background

3.1.1. The importance of diaryl ethers

The diaryl ether moiety is common in the structure of many biologically active natural products,[1] as well as wider use as a structural motif in biological chemistry, such as in macrocyclic peptides,[2] and with applications in the synthesis of polymers.[3] Examples of such compounds include the drug vancomycin (**128**),[1a] used as an antibiotic against Gram-positive bacteria; the aristogins,[2e] a group of diaryl ethers from the plant *Aristolochia* genus which is used in traditional Chinese medicine; and poly(aryl-ether-ether-ketones) (PEEKs),[3b,c,d] which are thermoplastics with multiple applications in electronic, medical, and aerospace industries (scheme **3.1**).



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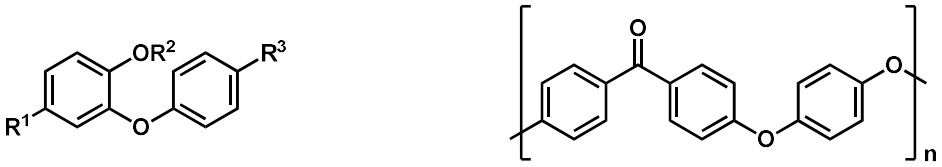
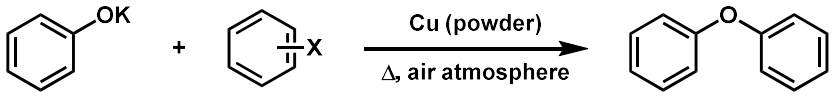


Figure 3.1 - Diaryl ether examples

Methods for the synthesis of diaryl ethers are therefore an important, topic of interest in the literature.[4] These can be widely separated into metal-catalysed methods, and other methods.

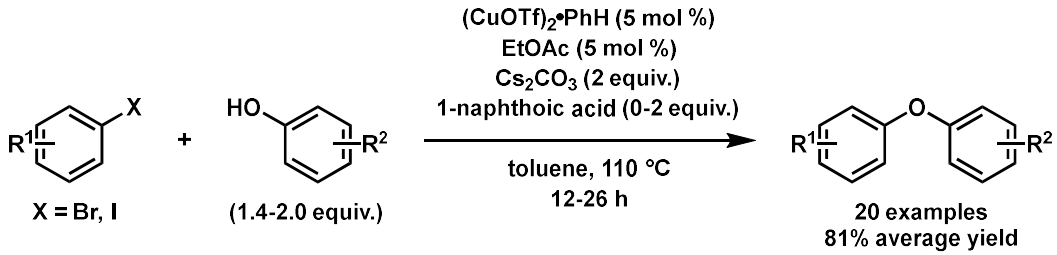
3.1.2. Transition metal-catalysed synthesis of diaryl ether compounds

An example of the methods for synthesis of diaryl ethers is the Ullmann ether synthesis.[5] This seminal discovery reacted aryl halides with potassium phenoxide and a copper powder under high temperatures in air, to yield the corresponding diaryl ethers (scheme **3.2**).



Scheme 3.2 - The Ullmann ether synthesis

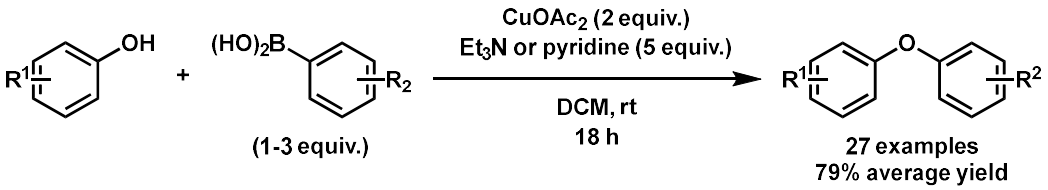
However, this reaction required temperatures in excess of 200 °C, demonstrated poor functional group tolerance, and required stoichiometric copper metal. Recent work has been undertaken to make this reaction more tolerant to sensitive functional groups, and able to proceed under milder conditions.[6] Buchwald and co-workers reported the use of catalytic copper(I) triflate with a wide range of phenols and aryl halides, returning diaryl ethers in high average yields[7] (scheme **3.3**).



Scheme 3.3 - Copper(I) triflate-catalysed biaryl ether formation

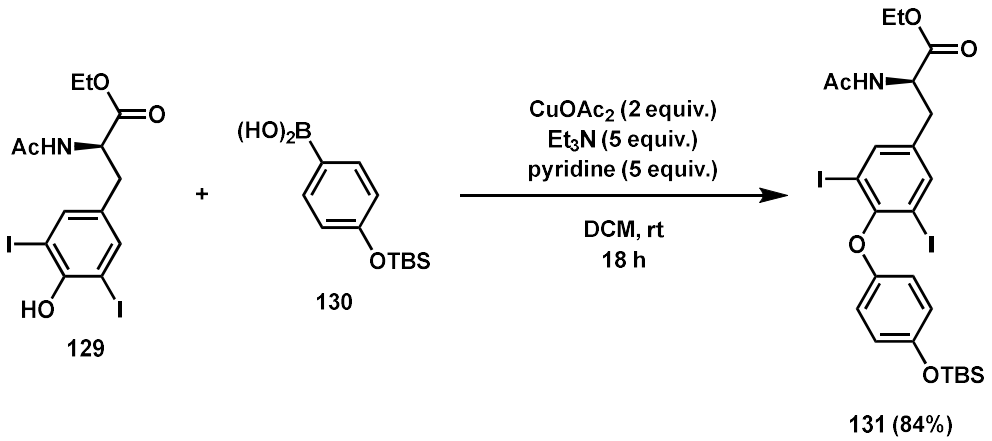
The authors demonstrated a broad scope, tolerant of many functionalities. The arylhalide component was tolerant of *ortho*-methyl and -acid functional groups, as well as *para*-nitrile and -ketone moieties. The phenol component was tolerant of *ortho*-alkyl substituents, and demonstrated a *para*-chloride substituent, providing a functional handle for further elaboration.[8] Furthermore, this reaction demonstrated a reduction (to 110 °C) in the previously discussed high reaction temperatures. The authors proposed that the reaction proceeded *via* a phenoxide cuprate, oxidative addition and reductive elimination to liberate the formed ether, and return a copper(I) species.

Other reactions have been developed, to provide complementary routes that do not require the use of aryl iodides. Evans and co-workers used boronic acids with phenols and stoichiometric copper salts, to synthesise diaryl ethers.[9] This reaction proceeded under mild conditions, with a broad scope (scheme **3.4**).



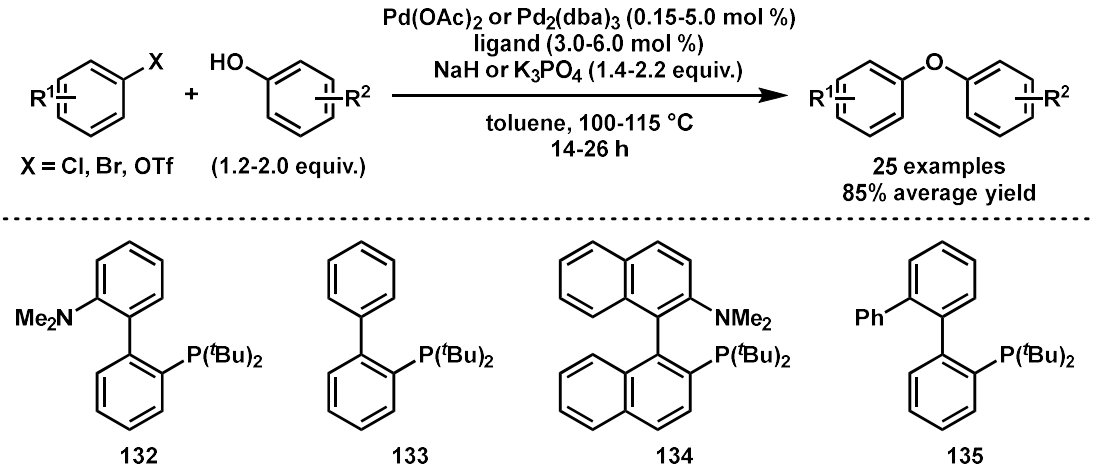
Scheme 3.4 - Copper-mediated biaryl ether formation

This transformation demonstrated high tolerance of a wide variety of functional groups. On the boronic acid, *para*-, *ortho*-, and *meta*-methyl and -methoxy groups were tolerated, demonstrating a lack of sensitivity towards electron-donating groups. Similarly, *ortho*-chloride and *meta*-nitro compounds are tolerated, demonstrating tolerance of electron-withdrawing groups and halides in this position. On the phenol component, *para*-alkyl, *ortho*-chloro, and *ortho*-methoxy substituents were tolerated. Furthermore, the authors demonstrated a formal synthesis of thyroxine through this method, arriving at intermediate **131** in 84% yield (scheme **3.5**). However, the use of stoichiometric metal salts here is less desirable, despite the mild reaction conditions.



Scheme 3.5 - Synthesis of intermediate 131, towards thyroxine

Other strategies involve the use of precious metal catalysis, such as the C-O bond forming reactions pioneered by the seminal works of Buchwald[10] and Hartwig.[11] A good example of these reactions in the synthesis of diaryl ethers is the work of Buchwald and co-workers[12] (scheme **3.6**).

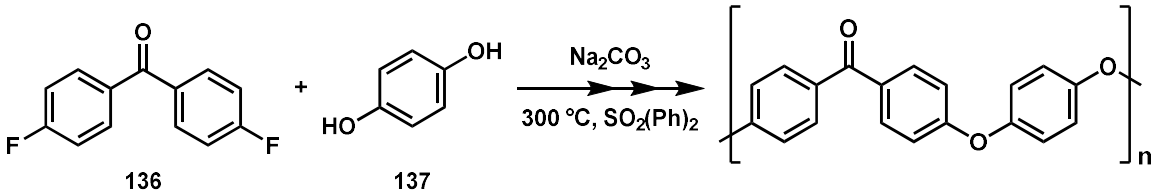


Scheme 3.6 - Palladium-catalysed biaryl ether formation

The authors reported a wide substrate scope, utilising a range of conditions to demonstrate 25 examples in 85% average yield. *Para*-ethers, -esters, -nitriles, -amides and -ketones were tolerated on the halide (or pseudohalide) partner, but only one example of electron-donating moieties was reported. The phenol scope demonstrated excellent tolerance of steric encumbrance, with *ortho*-alkyl substrates, and impressively 2,6-dimetyhlphenol. Furthermore, electron rich phenols were tolerated, as in the example of *para*-methoxyphenol. However, a variety of reactions exist without the use of metal catalysis at all, which provide alternative routes to such compounds.

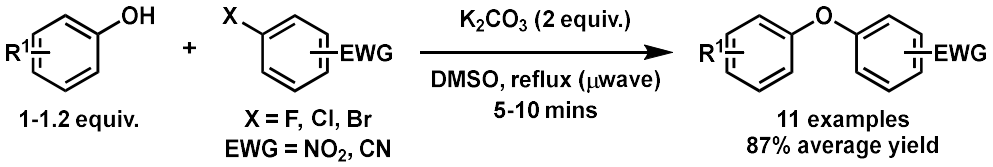
3.1.3. Synthesis of diaryl ethers without metal catalysis

A classical route for the synthesis of diaryl ethers without metal catalysts are S_NAr reactions, utilising phenols as nucleophiles. Such reactions are used to prepare the PEEK polymers discussed earlier[13] (scheme **3.7**).



Scheme 3.7 - PEEK synthesis *via* S_NAr reactions

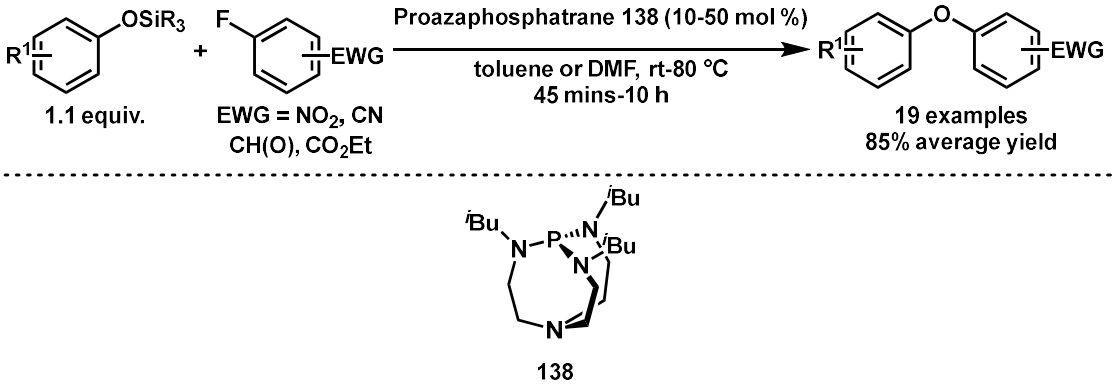
However, these polymerisation reactions typically require high temperatures, and are not representative of the conditions required for more general S_NAr reactions towards diaryl ethers, as such temperatures are typically destructive to the compounds of interest. Wang and co-workers demonstrated lower temperature S_NAr reactions to synthesise non-polymeric diaryl ethers.[14] Here microwave assisted heating was used to effect elevated temperatures with potassium carbonate as base, resulting in 11 examples with 87% average yield (scheme **3.8**).



Scheme 3.8 - Microwave assisted biaryl ether formation

Both *para*-, *ortho*-, and *meta*-electron-withdrawing groups were reported as the aryl halide partner. Despite their decreased efficacy in typical S_NAr processes,[15] two bromides were reported as starting materials. The phenol scope demonstrated *ortho*-methoxy and *para*-chloro substrates, as well as a range of electron poor phenols, such as *para*-nitro or -nitrile phenols, and *meta*-trifluoromethyl phenol. Despite the high reaction temperatures, the very low reaction times (of 5-10 minutes) required for this transformation were advantageous.

In an effort to lower the reaction temperature, a variety of methods to activate either phenol or aryl halide have been reported. Verkade and co-workers employed proazaphosphatrane **138** as Lewis basic activator for the desilylation of silyl-aryl-ethers, and the subsequent S_NAr reaction of the formed phenoxide[16] (scheme **3.9**).



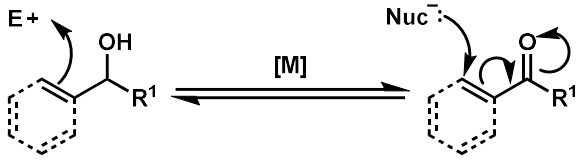
138

Scheme 3.9 - Proazaphosphatrane promoted biaryl ether formation

The reaction proceeds *via* Lewis base removal of the silyl protecting group, S_NAr reaction, and removal of the silyl group from the proazaphosphatrane by the generated fluoride. The authors noted that, while simply fluoride could be employed for the deprotection step of this reaction, the proazaphosphatrane afforded a wider range of unactivated substrates. This reaction reported 19 examples with 85% average yield. A range of conditions were reported, notably those with toluene as a solvent at low temperature - an unusual condition for such reactions that typically require heat and polar, aprotic solvents. The substrate scope tolerated a range of common electron-withdrawing groups on the aryl fluoride, specifically *para*-ester and *ortho*-aldehyde moieties. The silyl-aryl-ether tolerated *meta*-chloride and *para*-bromide moieties, and electron-withdrawing and -donating groups in the *para*-position, such as nitrile and methoxy functional groups. Impressively, this reaction also tolerated an *ortho-tert*-butyl moiety, demonstrating tolerance of high steric encumbrance. However, the starting materials here require the presence of an electron-withdrawing group.

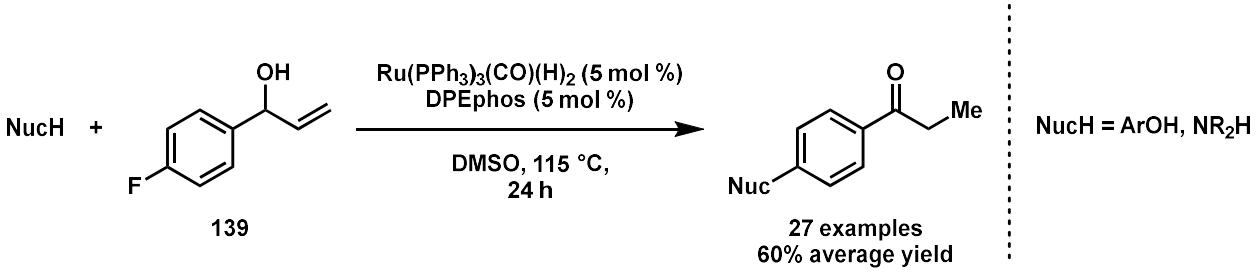
3.1.4. Electronic activation

Borrowing hydrogen chemistry provides access to a diverse range of carbonyl chemistry.[17] One example uses the principle of electronic activation.[18] Here, the change in oxidation state of the alcohol alters the reactivity of the conjugated alkene or arene (scheme **3.10**).



Sceme 3.10 - Electronic activation

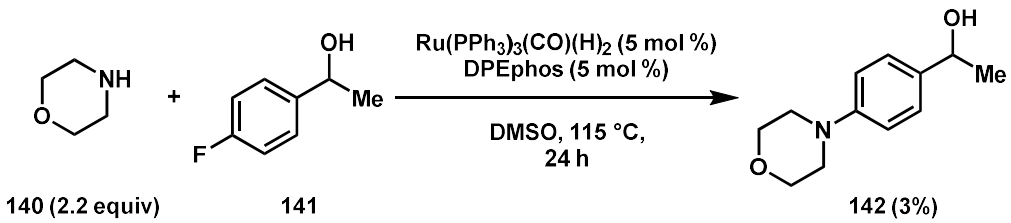
Pertinent examples in the literature include the work of Williams and co-workers[18c], who demonstrated the use of a ruthenium catalyst to perform borrowing hydrogen-induced electronic activation. This enabled a S_NAr reaction to occur, after transfer hydrogenation of the alcohol starting material (scheme **3.11**).



Scheme 3.11 - Electronic activation-S_NAr reaction

Here, the ruthenium catalyst oxidises a secondary allylic 1-arylalcohol, and then performs a selective 1,4-reduction on the resulting enone. This changes the electronics of the aryl ring, activating it towards S_NAr reactions. A selection of phenols as nucleophiles were reported. Examples included electron-donating groups, such as *para*-methoxy moieties, and extended aromatics such as 1-, and 2-naphthyl phenol. However, phenols with electron-withdrawing groups are not tolerated. The authors then went on to describe a range of secondary amines as nucleophiles, expanding the scope of this reaction, resulting in 27 total examples with 60% average yield.

However, this reaction had a substrate limitation, namely the ally alcohol (scheme **3.12**). Without this, complete transfer hydrogenation is not achievable, due to the lack of internal hydrogen acceptor.



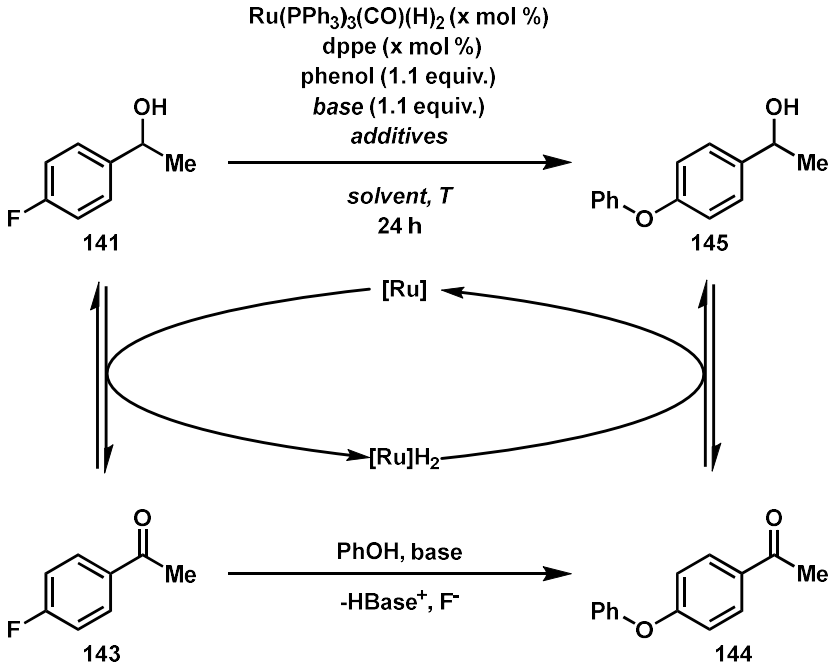
Scheme 3.12 - Substrate limitations of the remote electronic activation

A reaction without the internal hydrogen acceptor results in a 3% yield (as calculated by ^{1}H NMR) of the target material **142**. The authors attributed this to the action of the nucleophile as *para*-electron-donating group, precluding reduction of the formed ketone. Inspired by these limitations, the Morrill group sought to extend this work, by researching a procedure without the requirement for an internal hydrogen acceptor. This would allow alternative diaryl ethers (not based on propiophenone) to be synthesised.

3.2. Results and discussion

3.2.1. Results of the hydrogen transfer-S_NAr reaction

Drawing from the earlier described work of Williams and co-workers, the following optimisation was performed by Kurt Polidano, a PhD student in the group (table **3.1** yields of compounds determined by ^1H NMR of the crude reaction mixture, relative to 0.5 equivalents of mesitylene as internal standard, isolated yields in parentheses).

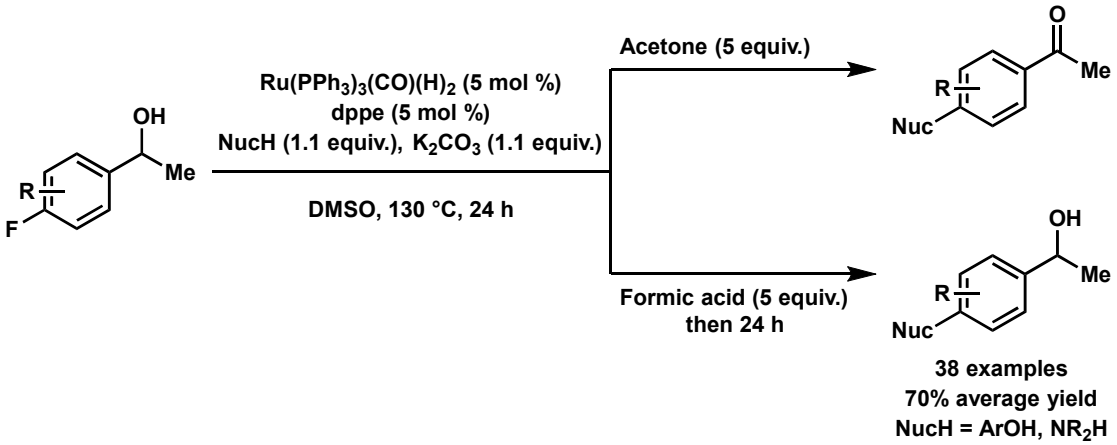


Entry	Catalyst and ligand (mol %)	Base	Additive (equiv.)	Solvent (mL)	*T* (°C)	141	143	144	145
1	5	K_2CO_3	Acetone (5)	DMSO (1)	130	0	0	**81 (79)**	**5**
2	5	K_2CO_3	HCO_2H (5)	DMSO (1)	130	0	0	**9**	**82 (80)**

Table 3.1 - Optimisation of hydrogen transfer-S_NAr reaction

After extensive optimisation, Kurt Polidano demonstrated that with 5 mol% of the eighteen-electron ruthenium catalyst, dppe as ligand, with 1.1 equivalents of potassium carbonate as base, in DMSO at 130 °C for 24 hours, optimal conversion

of starting material **141** to products could be observed by ^{1}H NMR. Further optimisation led to the use of superstoichiometric acetone and formic acid as hydrogen acceptors and donors. When acetone was employed as a hydrogen acceptor, this transformation produced ketone **144** in 79% isolated yield. Likewise, when employing formic acid as hydrogen source, alcohol **145** could be isolated in 80% yield. The use of additives erodes the atom economy of a reaction, however it still allowed the substrate limitation of previous work to be avoided, and could be utilised both to increase the yields of each possible product, and allow the selection of which product is returned from this transformation. With optimised conditions in hand, substrate scope of both the oxidative and redox neutral transformations was investigated by Kurt Polidano (scheme **3.13**).



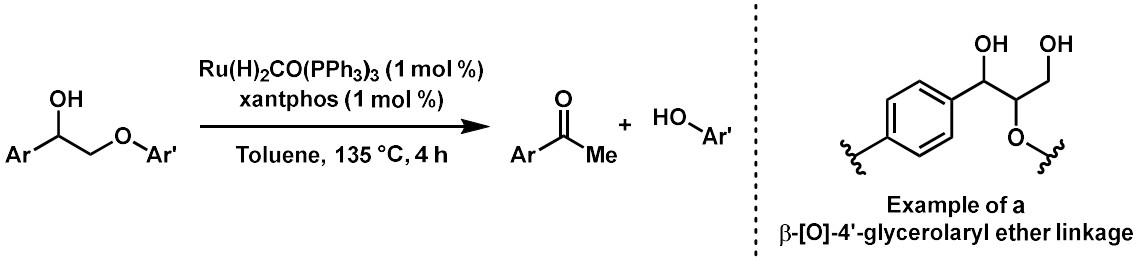
Scheme 3.13 - The substate scope of the hydrogen transfer-S_NAr reaction

Kurt Polidano reported 38 examples for this transformation in 70% average yield. A variety of functional groups were tolerated by the process, including electron-donating moieties and halogenation on the phenol nucleophile, and a small number of secondary amine nucleophiles.

3.2.2. A more atom economic process

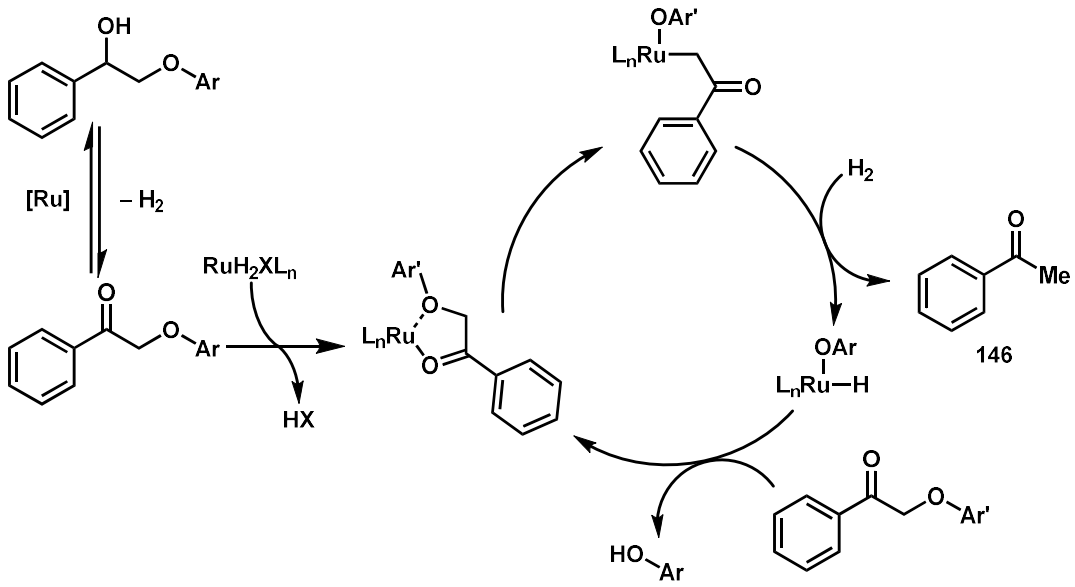
Mindful that reaction conditions with superstoichiometric additives were wasteful, an alternative process with higher atom economy was sought.[19] Inspiration was taken from the work of Ellman and co-workers[20]. Here, the same ruthenium catalyst as

used by Kurt Polidano was applied to 2-aryloxy-1-arylethanols, a motif designed to mimic the functionality of β-[O]-4'-glycerolaryl ethers, which are prevalent linkers in the structure of lignin (scheme **3.14**).[2a,d,f] This catalyst was able to effect C-O bond cleavage of the key C-O bonds, with the goal of breaking down lignin into useful chemicals.



Scheme 3.14 - C-O bond cleavage of 2-aryloxy-1-arylethanols

Ellman and co-workers proposed the following catalytic cycle, occurring through a 5-membered cyclic rhodium complex (scheme **3.15**).

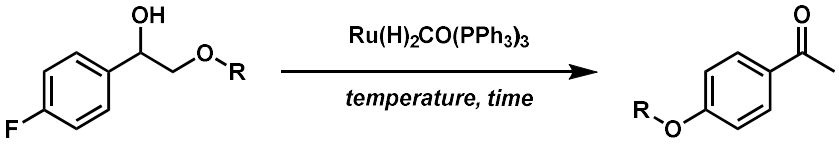


Scheme 3.15 - Postulated mechanism

However, this catalytic cycle is difficult to understand, does not suggest any oxidation states of the ruthenium, and does not provide any insights into how this reaction is taking place. An alternative catalytic cycle will be suggested later (scheme **3.32**). Ellman and co-workers then applied this work to lignin depolymerisation, to form phenols and acetophenone derivatives. However, an opportunity to use this work as the basis for a higher atom economy route towards

the oxidative part of the hydrogen transfer-S_NAr reaction was envisioned by our group.

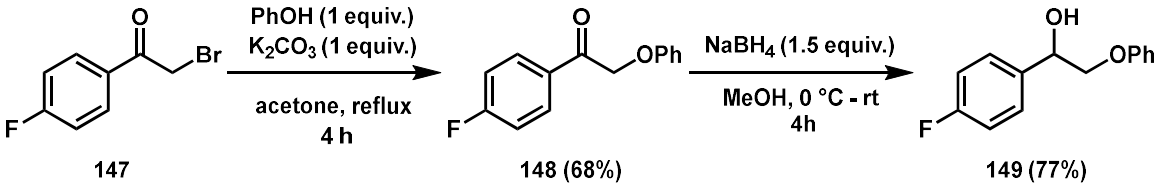
The hypothesis was as follows: by utilising *para*-fluorinated-2-aryloxy-1-arylethanols as substrates, a subsequent cleavage could be performed in tandem with the S_NAr reactions shown previously. This would result in significantly improved atom economy, with only the extrusion of hydrogen fluoride (which could be removed from the reaction mixture by a base) as sole by-product in the reaction. Compared to the super stoichiometric sacrificial hydrogen acceptors demonstrated previously, such a modification would be beneficial (scheme **3.16**).



Scheme 3.16 - Postulated reaction

This reaction design also has the potential for other C-heteroatom bond cleavages, unexplored by Ellman and co-workers due to the desired application of their work. This reaction was then investigated.

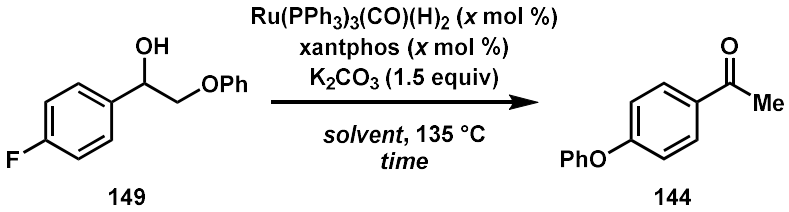
Kurt Polidano, Anaïs Basset (a summer student in the group) and myself worked on this optimisation. The parent substrate was synthesized via a S_N2 reaction with phenol, with acetophenone **147** as the starting material. The resulting aryloxyacetophenone **148** was recovered in 68% yield, and then reduced by sodium borohydride. Product **149**, the model substrate for this optimisation, was recovered in 77% yield (scheme **3.17**). Competitive S_NAr reaction of **147** with phenol was not observed.



Scheme 3.17 - Synthesis of the model substrate

Ellman's conditions were then investigated, and modifications made to make them more amenable to the desired work. First, polar aprotic solvents were utilised, and

reaction time increased to 24 hours. This is due to these solvents being optimal for S_NAr reactions (as they are able to stabilise the charged transition states of these reactions),[15] and to the previous works requiring lengthy times for the S_NAr reaction to proceed. A small range of polar aprotic solvents were screened, in a range conditions. The results of this optimisation, performed by Kurt Polidano, Anaïs Basset, and myself, are shown below (table **3.2**, ^1H NMR yields were determined by analysis of the crude NMR spectrum, relative to 1 mmol of mesitylene as internal standard).



149 144

Entry	[Ru] and ligand (mol %)	Time (h)	Solvent (Concentration)	NMR yield (Isolated)
1	5	24	DMF (0.4 M)	91%
2	5	24	DMSO (0.4 M)	76%
3	5	24	DMA (0.4 M)	>95%
4	2.5	24	DMA (0.4 M)	95%
5	1	24	DMA (0.4 M)	26%
6	2.5	24	DMA (1 M)	**>95% (79%)**
7	2.5	16	DMA (1 M)	**>95%**

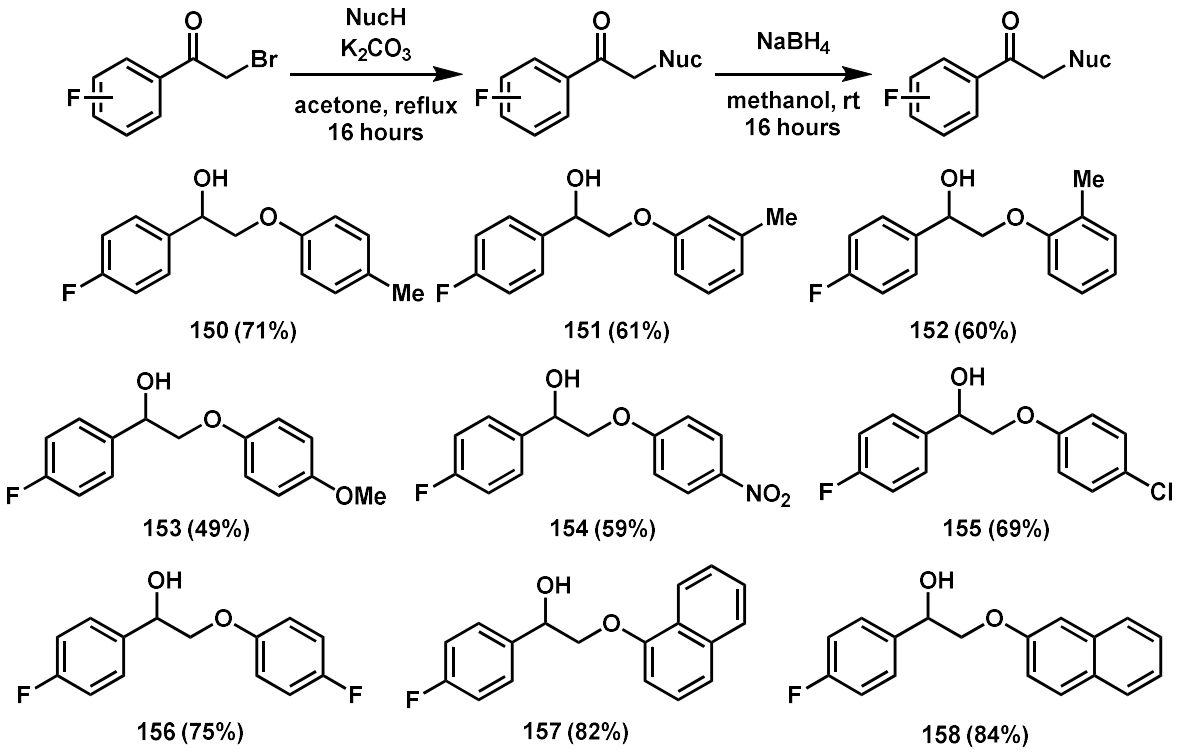
Table 3.2 - Optimisation of the hydrogen transfer-S_NAr procedure

Applying Ellman's temperature conditions of 135 °C, it was observed that polar aprotic solvents were highly compatible with both the initial ruthenium-catalysed oxidative cleavage, and subsequent S_NAr reaction. Entries **1**-**3** demonstrate the efficacy of a variety of available polar, aprotic solvents. DMF results in a 91% ^1H NMR spectroscopic yields, DMSO a 76% ^1H NMR yield, and DMA resulting in a quantitative NMR yield, all with 5 mol% of catalyst and xantphos ligand. Kurt Polidano isolated product **144** in 79% yield. Reductions in catalyst loading are shown in entries **4**-**5**. At 2.5 mol%, 95% ^1H NMR yield was observed. However, a reduction to 1 mol % resulted in a severe degradation in yield, down to 26% by ^1H NMR. This entry mimics the conditions of Ellman, for comparisons sake. Entries **6** and **7** demonstrate an increase in concentration which the catalyst and system

tolerated well, resulting in >95% ^{1}H NMR yield of desired product **144** after 24 hours. It was also observed that after 16 hours the starting material had undergone full conversion to the product (entry **7**). However, in order ensure that less reactive substrates would have a chance to react to their fullest, the conditions in entry **6** were retained as optimised conditions. With optimised conditions in hand, a substrate scope was investigated.

3.2.3. Substrate scope of the tandem oxidative cleavage-S_NAr reaction

The remaining work in this chapter is solely my own. A range of substrates were synthesised by an S_N2-reduction pathway (scheme **3.18**).

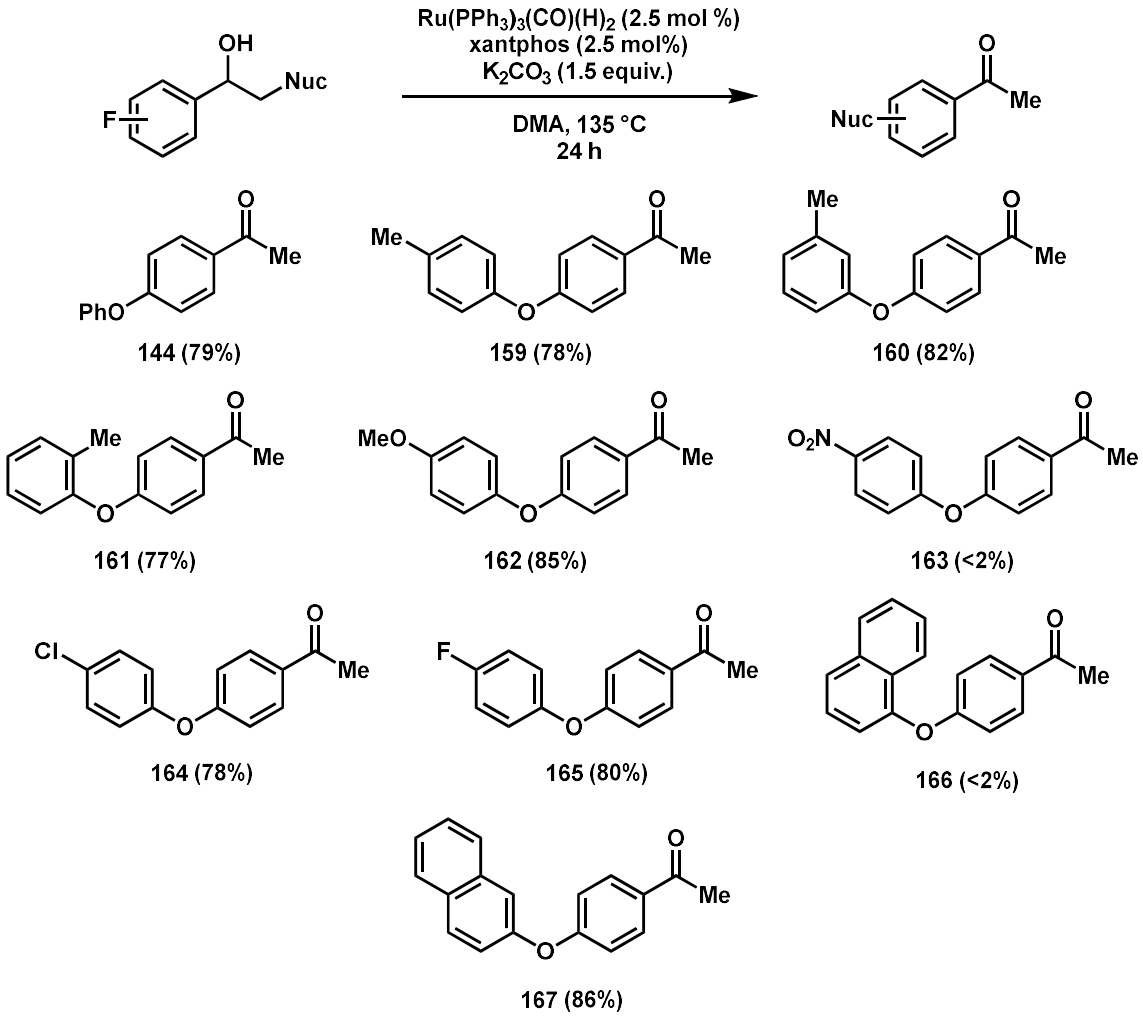


Scheme 3.18 - Synthesised substrates

A range of methylated phenols were prepared in good yields (**150**-**153**, 71%, 61% and 60% yield respectively. An electron-donating group at the phenol was utilised to prepare substrate **154**, in 49% yield, and an electron-withdrawing group at the phenol was used to prepare substrate **154**, in 59% yield. Halogenated substrates

were also synthesised, with chloride **155**, and fluoride **156** isolated in 69% and 75% isolated yield respectively. 1- and 2-naphtol were utilised, forming products **157** and **158** in 82% and 84% yield.

With these substrates in hand, they were employed under the optimised reaction conditions (figure **3.19**).

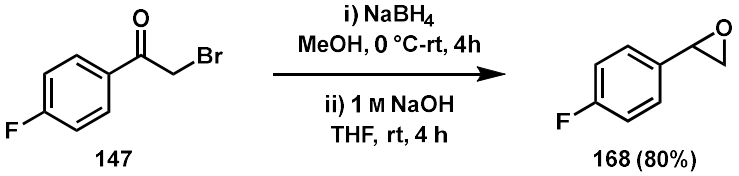


Scheme 3.19 - 1-Aryl-2-aryloxyethanol substrate scope

A wide range of functionalities were well tolerated by this procedure. Methylated substrates yielded products **159**, **160**, and **161** in 78%, 82% and 77% yield respectively. This also demonstrated the tolerance of mild steric encumbrance about the phenol, as product **160** was still isolated in high yield. Electron-donating groups at the phenol are well tolerated, as demonstrated by product **162**, isolated in 85% yield. However, electron-withdrawing groups were not tolerated, with no observable **163** present in the ^{1}H NMR spectrum of the crude reaction mixture. This can be

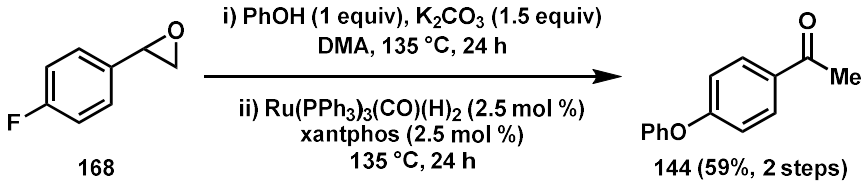
attributed to the electron-withdrawing group of the phenol leading to poor nucleophilicity – 4-fluoroacetophenone could be observed in the ^{1}H NMR spectrum of crude reaction mixture. Therefore, a plausible explanation is that the formed phenol was precluded from the S_NAr reaction due to electronics, as the oxidative-cleavage continued regardless. Halogenated examples **164** and **165** were recovered in 78% and 80% isolated yield, providing a functional handle for further elaboration.[8] By contrast to substrate **163** (where cleavage occurred but S_NAr is precluded), 1-naphtol substrate resulted in no observable **166**, returning only starting material, observed by ^{1}H NMR spectroscopy of the crude reaction mixture. There is also potential for this other reactions to occur with this starting material, such as *ortho*-metalation,[21] but this was not observed. This could be attributed to the sterically hindered substrate precluding the initial oxidative cleavage. However, 2-naphthol derivative **167** was isolated in 86% yield.

While this reaction provides a highly atom economic route for the formation of diaryl ethers, the synthesis of substrates requires 2 steps from commercially available materials. A proof of concept for a telescoped approach to these compounds was investigated. We envisioned the use of commercially available epoxide **168** as starting material (scheme **3.20**), which was prepared through reduction-ring closure in this case, due to its high cost.[22]



Scheme 3.20 - Synthesis of epoxide 168

This epoxide could be employed under the optimised reaction conditions, after initial regioselective epoxide ring opening under basic conditions, at 135 °C for 24 hours. Subsequent addition of the catalyst and heating for an additional 24 hours formed model diaryl ether **144** in a simple, one-pot fashion, in 59% yield over 2 steps (scheme **3.21**).

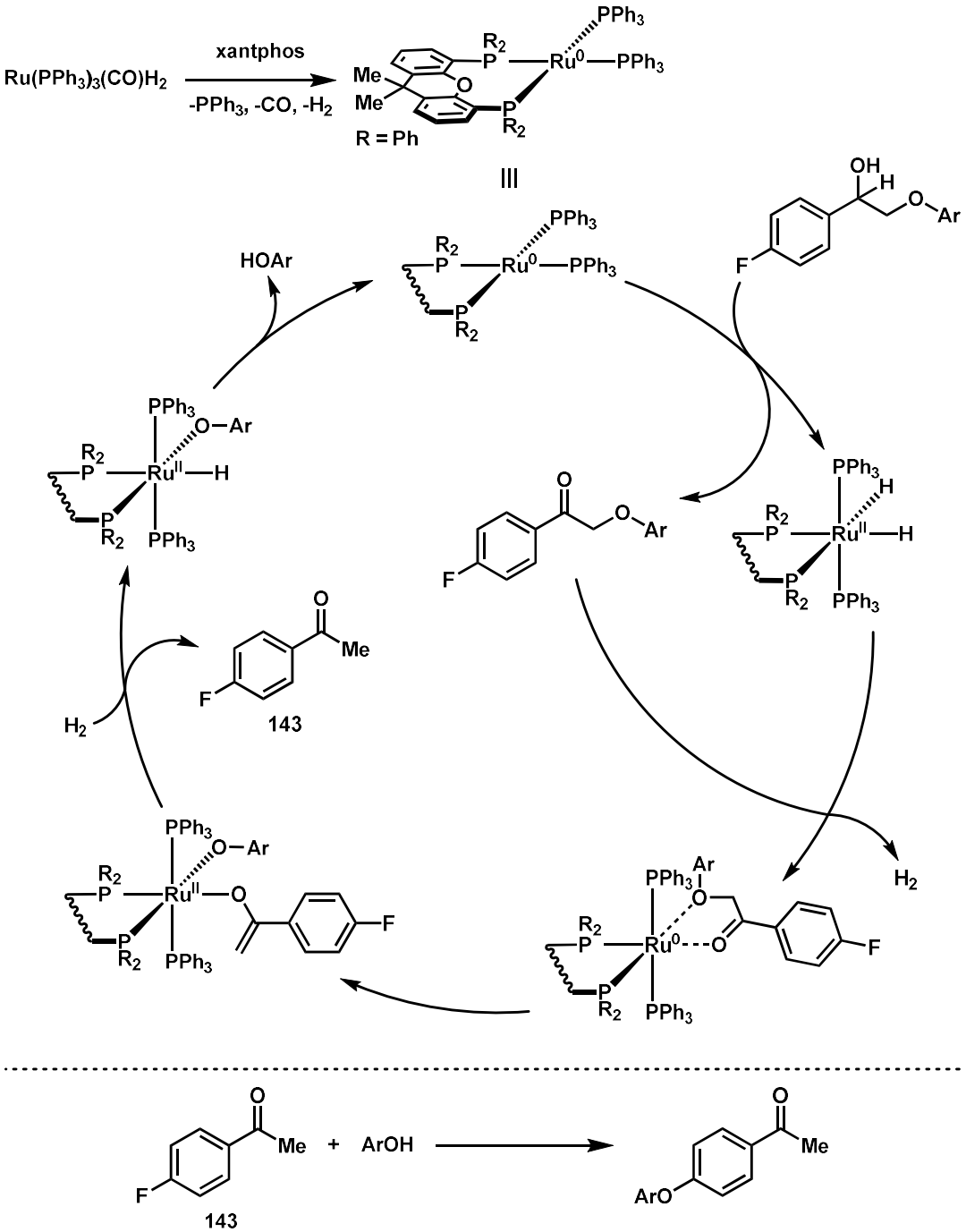


Scheme 3.21 - One pot diaryl ether synthesis

When compared to 41% over 3 steps for the original substrate (from 2-bromo acetophenone **147**), this modification both results in a higher overall yield, and an avoidance of multistep starting material synthesis when the commercial material would be employed.

3.2.4. Plausible mechanism

The proposed mechanism for this transformation is shown below (scheme **3.22**). The reaction begins with ligand exchange (which is relatively slow, due to this being a high spin d6 complex) of xantphos for a carbonyl, and a triphenyl phosphine ligand. Reductive elimination could then occur, resulting in a new sixteen electron ruthenium(0) species. This species can now effect the dehydrogenation of 2-aryloxy-1-arylethanol to generate intermediate 2-arlyoxy-acetophenone, and produce a ruthenium hydride species. This once again releases H_2 gas, and the catalyst coordinates to the ketone and ether of the aryloxy-acetophenone. The catalyst can now effect the cleavage of the aryl ether, yielding a ruthenium-enolate-alkoxide complex. Coordination of hydrogen and subsequent splitting yields a ruthenium-hydride-alkoxide, and a proton that is used to protonate the enolate, liberating intermediate acetophenone **143**. Reductive elimination regenerates eliminated phenol, and reforms the active catalyst, closing the catalytic cycle. The phenol and **143** can now undergo the S_NAr reaction, forming the final product.



Scheme 3.22 - Postulated mechanism

3.3. Future work

Future work in this field would be to investigate alternative ligand scaffolds or metal catalysts with the aim of effecting other C-heteroatom cleavage protocols. Likewise, a catalyst that would be more tolerant of sterically bulky phenols would be desirable.

Another valuable route to pursue would also be to attempt to transfer this chemistry to base metal catalysis, in order to provide greener transformations in metal-catalysed synthesis of diaryl ethers. Other such measures that could be taken in this area would include the use of greener solvent, or those from bio-renewable feedstocks.[23] An example of a solvent that would be appropriate for an S_NAr reaction is propylene carbonate, a polar aprotic solvent.

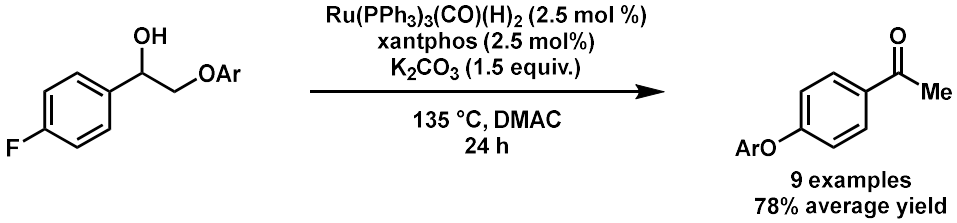
Other points for further research would be the synthesis of a biologically active diaryl ether utilising this transformation, or the late stage derivatisation of an extant 1-aryl-2-aryloxyethanol moiety, to effect the formation of a functionalised diaryl ether. However, significant effort to enhance the tolerance of this work (especially towards heterocyclic substrates), and reduce the high reaction temperature would need to be undertaken prior to attempting such molecules.

3.4. Summary

In summary, this work demonstrates an oxidation level selection approach to hydrogen-transfer chemistry in tandem with S_NAr reactions, demonstrating 30 examples in 70% average yield. This includes the oxidative cleavage and tandem S_NAr of 2-aryloxy-1-aryl alcohols, to generate diaryl ethers. Nine examples in 78% average yield were demonstrated.[24] This provides a higher atom economy route to the oxidative methodology. This work also included a telescoped synthesis in a 2-step, 1-pot method starting from an epoxide.

In the context of the aims and objectives of this thesis, this work was able to demonstrate a new synthetic route for diaryl ethers, from materials usually synthesised in two steps. This satisfies the aim to develop new borrowing hydrogen

reactions, although in this case it occurs *via* a non-classical mechanism (as proposed).



Scheme 3.23 - Oxidative cleavage-S_NAr reaction

3.5. References

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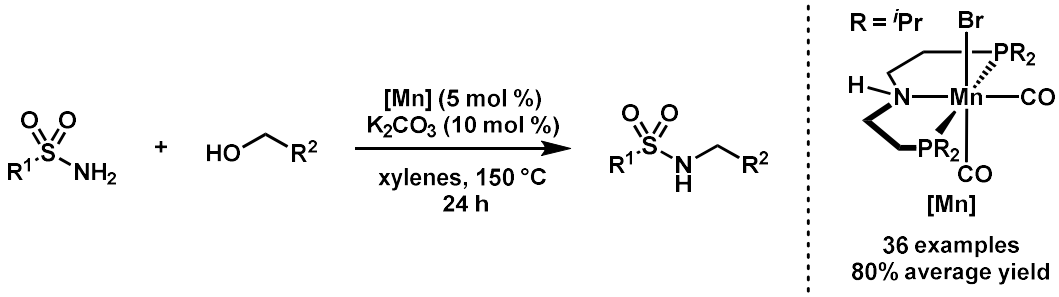
Chapter 4: Manganese-catalysed *N*-alkylation of sulfonamides using alcohols

Table of Contents

4. Preface

This chapter discusses the development of a general procedure for the *N*-alkylation of sulfonamides. The procedure employed a manganese *PNP*-pincer precatalyst, and reported a broad scope of primary benzylic and aliphatic alcohols as alkylating agents. These were reacted with a broad range of sulfonamide nucleophiles, undergoing mono-selective *N*-alkylation with excellent isolated yields (36 examples in 80% average yield). Mechanistic investigations provide evidence of a plausible reaction intermediate, reversible transfer hydrogenation, and a manganese hydride species.



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4.1. Introduction

4.1.1. The importance of sulfonamides

The sulfonamide functional group is prevalent in a huge array of biologically active compounds. This is largely due to the wide range of biological functions, from anti-bacterial and anti-cancer properties to a diuretic action on the kidneys.[1] The breadth of use of these moieties lies in their ease of administration and absorption orally, and their robust pharmacokinetics.[2] Many of the anti-microbial properties of sulfonamides arise from these molecules being isosteres for carboxylic acids, allowing them to act as competitive inhibitors for a variety of enzymes. A good example is sulfanilamide (**169**), which is a competitive inhibitor for the formation of folic acid (**170**) from *para*-amino benzoic acid (**171**, figure **4.1**).

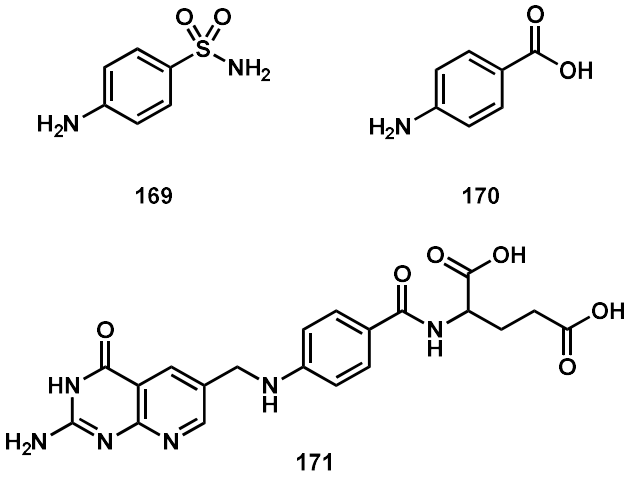


Figure 4.1 - Sulfonilamide as a competetive inhibitor to enzyme action on *para*-amino benzoic acid

Sulfonamides comprise approximately 25% of all FDA approved sulfur containing drug molecules.[3] Figure **4.2** shows pertinent literature examples. Marketed drug examples are sumantripan (**172**),[3a] an anti-retroviral used in the treatment of HIV and AIDS, udenafil (**173**),[3b] a phosphodiesterase-5 inhibitor used to treat erectile dysfunction, and lorapide (**174**),[3c] used for ulcer treatment. Further examples include multiple pharmaceutically active compounds, such as those being

investigated as potential treatments for antiarrhythmic effects (**175**),[4a] and neurological diseases (**176**)[4b] respectively.

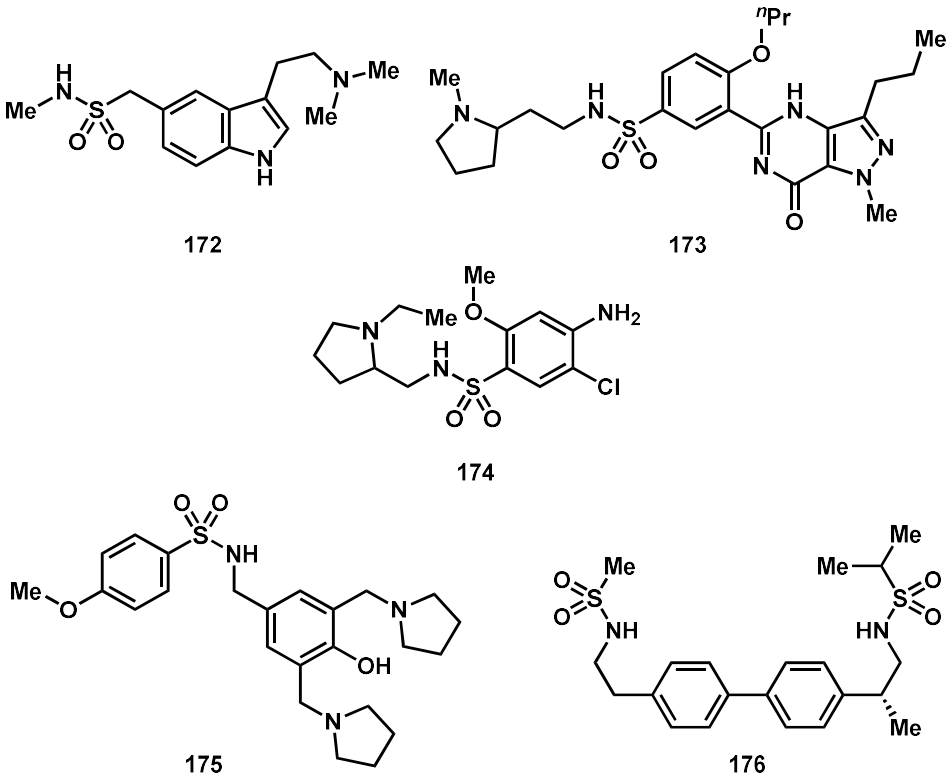
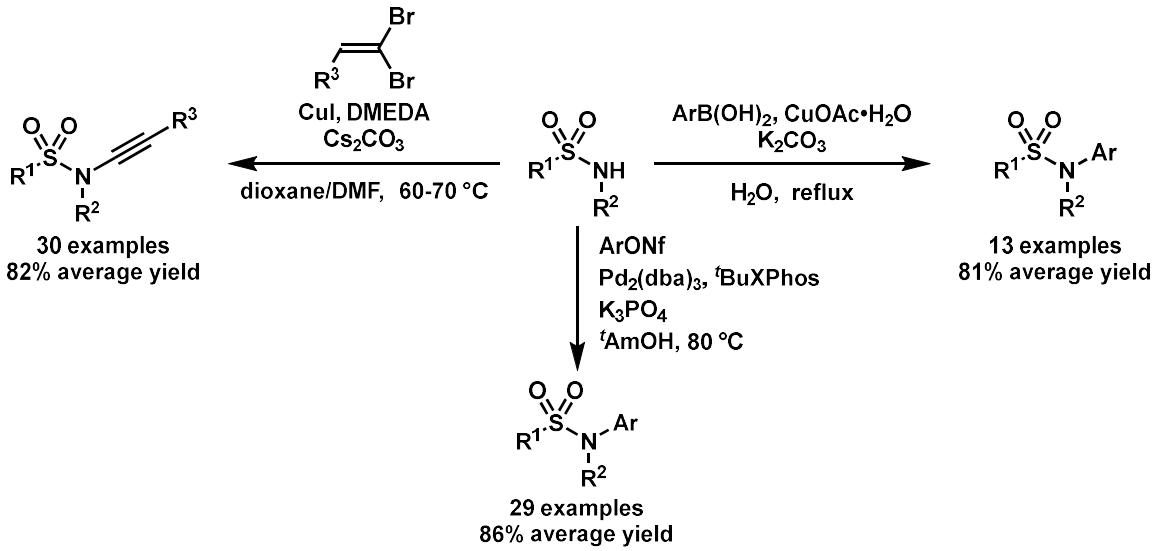


Figure 4.2 - Marketed drugs and phase II clinical trail reaching *N*-alkyl sulfonamides

4.1.2. Classical synthetic routes towards *N*-alkylsulfonamides

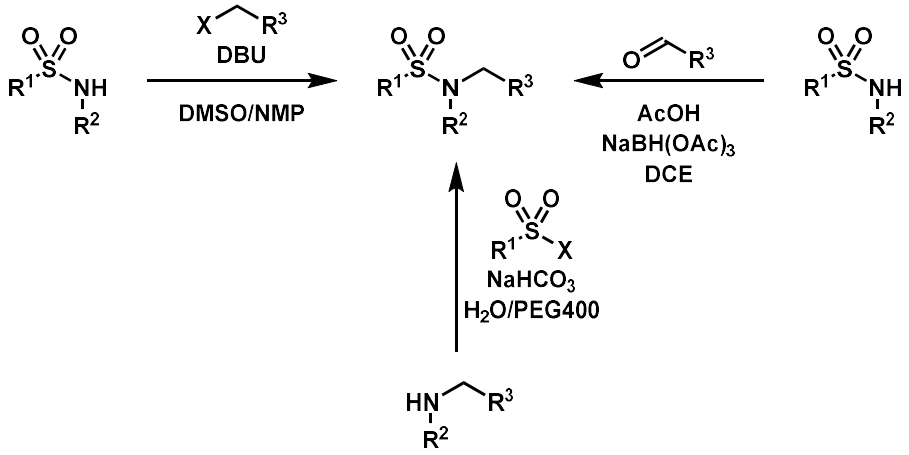
In the synthesis of such functionalised sulfonamides, it is important to consider the methods available. Classical synthetic routes for the formation of *N*-arylsulfonamides, and other unsaturated sulfonamides are highly diverse. Examples include routes such as the Chan-Lam coupling, and a wide variety of other metal-catalysed reactions, to yield *N*-aryl– or *N*-alkynylsulfonamides (scheme **4.3**).[5]



Scheme 4.3 - Example works of sulfonamide arylation and alkynylation

All the above selected examples give high-yielding examples of these processes, with broad substrate scopes. For instance, reaction of secondary sulfonamides with 1,1-dibromoalkanes, under copper catalysis, yields dehalogenation and subsequent formation of a range of tertiary alkynylsulfonamides, *via* carbene rearrangement.[5c] By contrast, palladium catalysis with aryl nonaflates and primary sulfonamides yields a range of secondary *N*-arylsulfonamides.[5d] Finally, in a classical Chan-Lam example, primary sulfonamides and boronic acids are subjected to copper catalysis, resulting in the generation of secondary *N*-alkylsulfonamides.[5f]

However, the classical ways by which one might perform *N*-alkylation of sulfonamides are much less varied, with three general strategies (scheme **4.4**).



Scheme 4.4 - Classical routes towards *N*-alkylsulfonamides

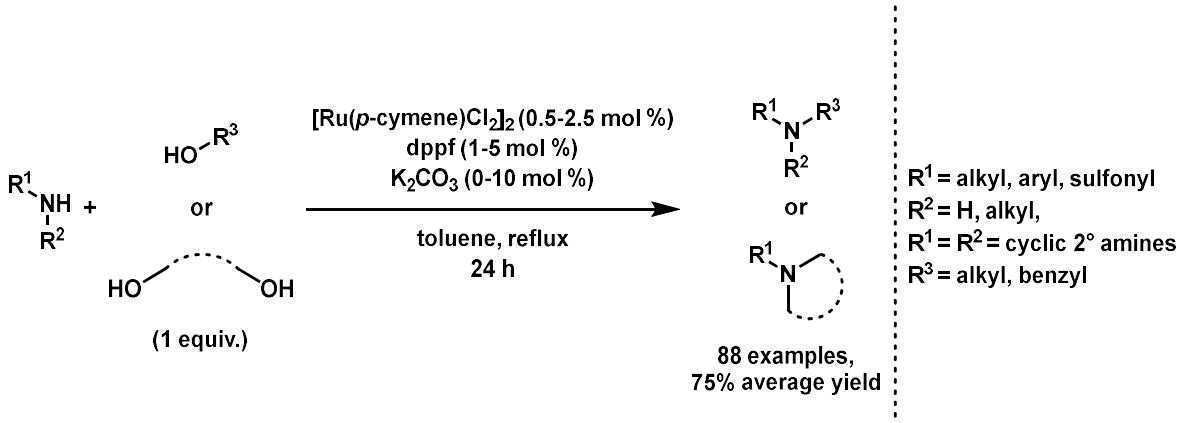
One route is the action of sulfonamides with base and an alkyl halide, or other active alkylating agents.[6a] The example shown above takes polymer-supported secondary sulfonamides, and uses alkylating reagents, such as alkyl iodides or alcohols under Mitsunobu conditions,[6b] with DMAP as base, to perform this alkylation and yield tertiary sulfonamides. A complimentary route is the use of sulfonyl chlorides, with primary and secondary amine nucleophiles and sodium hydrogencarbonate as base to effect the formation of secondary and tertiary *N*-alkylsulfonamides.[7] A final example is reductive amination, in this case performed with sodium triacetoxyborohydride. This occurs *via* condensation of a sulfonamide and aldehyde to generate an aldimine, and subsequent reduction to yield the alkylsulfonamides.[8]

However, each of these classical routes has drawbacks. The first route involves the use of toxic alkyl halides, or stoichiometric activation steps for alcohols, which generate stoichiometric, undesirable waste. This approach also has the further risk of over-alkylation of the reactive intermediates. Alternatively, the use of sulfonyl halides (or other activated sulfonyl compounds) with amines may be employed, but this often involves making the sulfonyl halides from sulfonic acids due to their wider commercial availability. Likewise, sulfonyl halides are often corrosive, harmful, and allergenic compounds.[9] Perhaps the most widely used method to effect selective mono-alkylation of sulfonamides is reductive amination, however, this process involves a stoichiometric reductant. Furthermore, if the aldehyde is not commercially available, it must be made by oxidation of an alcoholic starting material, or reduction of either an acid or ester. Both of these steps generate stoichiometric waste.

4.1.3. Borrowing hydrogen approaches for sulfonamide *N*-alkylation

An alternative, less explored avenue for this chemistry is the borrowing hydrogen principle. Here, we are able to take inexpensive, relatively non-toxic, and widely commercially–available alcohols as starting materials, and directly utilise them as alkylating agents. This provides an alternative route that overcomes many of the discussed limitations of the classical approaches to sulfonamide *N*-alkylation.

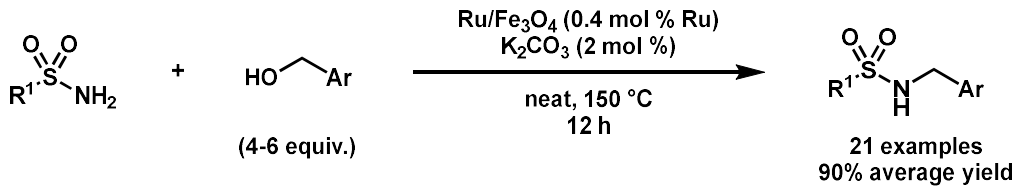
There is much past work for this chemistry performed with rare earth metals. An early example is the work of Williams and co-workers.[10] Here, the authors demonstrated the use of a ruthenium catalyst to perform *N*-alkylation on a wide range of primary and secondary amines, and sulfonamide starting materials (scheme **4.5**), with 88 total examples in 75% average yield.



Scheme 4.5 - Primary and secondary amine alkylation with alcohols

This procedure reported 13 examples of sulfonamide alkylation in 80% average yield. The scope showed tolerance for electron-donating and -withdrawing groups, reducible functionalities, and halide moieties. Alkyl sulfonamide nucleophiles were tolerated, however, no heteroaromatic sulfonamides, such as pyridyl or furanyl sulfonamides were reported. The use of precious metals, combined with relatively high catalyst loading (1-5 mol % ruthenium) was also undesirable.

An example of a complementary strategy to this work is that of Beller and co-workers,[11] who reported the use of a heterogeneous ruthenium catalyst to effect sulfonamides alkylation, using alcohols as alkylating reagent (scheme **4.6**). Here the authors demonstrated 21 examples of sulfonamide alkylation in 90% average yield.

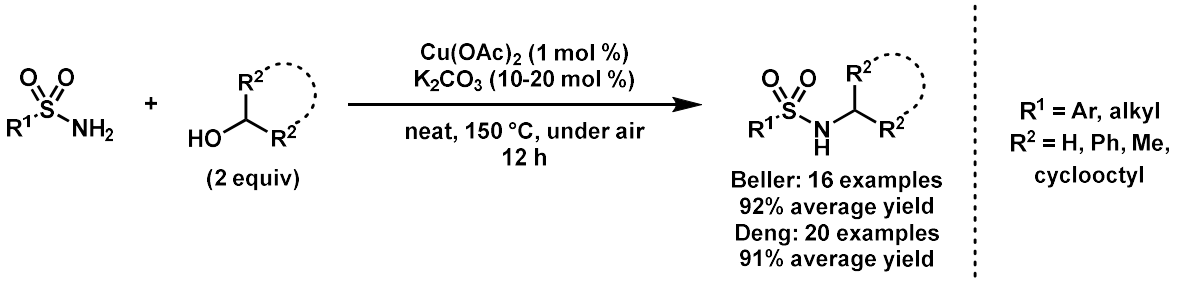


Scheme 4.6 - Hetereogenous alkylation of sulfonamides with alcohols

The substrate scope demonstrated tolerance of arylsulfonamides bearing electron-donating and -withdrawing moieties. Heteroaryl sulfonamides and alcohols were

also tolerated, as were benzylic alcohols bearing halides. However, despite the impressive yields, only benzylic alcohols as alkylating reagents were tolerated. In addition, no reducible functionalities, such as nitro, carbonyl, or nitrile moieties were reported by the authors. Once again, the use of precious metal catalysts was less desirable.

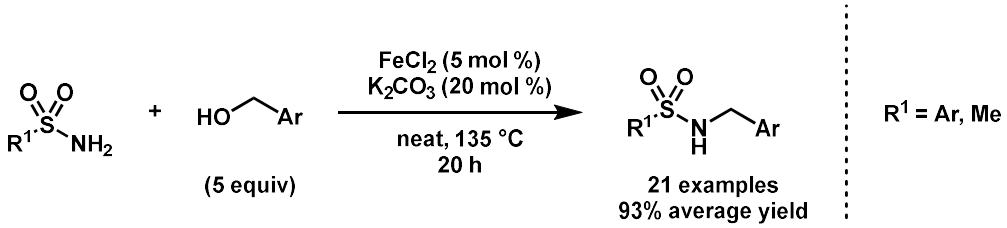
Further work in this area has since been undertaken to convert this chemistry to earth-abundant transition metal catalysis. The earliest examples of these works are those of Deng and Beller,[12] who in the same year collaboratively reported the same transformation of copper(II) acetate-catalysed alkylation of sulfonamides with alcohols (scheme **4.7**). Here, a range of primary, and a few selected examples of secondary alcohols were utilised as alkylating agents, obtaining 16 and 20 examples of *N*-alkylsulfonamides in 92 and 91% average yield respectively.



Scheme 4.7 - Homogeneous copper-catalysed alkylation of sulfonamides with alcohols

The reported range of examples in these works include small variation of the sulfonamide, with incorporation electron-donating moieties about both alcohol and sulfonamide. Benzylic alcohols bearing halogens, electron-withdrawing groups, and heteroaromatic alcohols were tolerated. Examples of secondary alcohols were reported in good yields, however, a narrow range of substituents or functional groups on the sulfonamides were reported. Reducible functionalities, such as alkenes, carbonyl compounds, or nitro moieties were not reported. Both works contained mechanistic studies with deuteration experiments, and the Deng work[12b] acquired and discussed kinetic data. Despite the high reaction temperatures required, and the similarity of this work to that discussed in scheme **4.6**,[11] the use of an earth-abundant transition metal catalyst was advantageous.

Deng and co-workers reported similar work with iron catalysis,[13] where it was found that simple iron(II) chloride was capable of performing this alkylation reaction (scheme **4.8**).

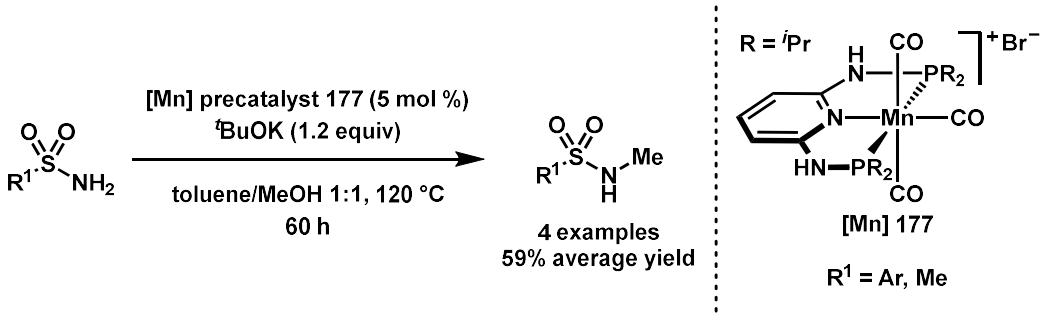


Scheme 4.8 - Homogenous iron-catalysed alkylation of sulfonamides with alcohols

The authors reported 21 examples in 93% average yield. Examples of heteroaryl sulfonamides, and sulfonamides bearing halide moieties were reported. A wide range of benzyl alcohols, for example those containing electron-withdrawing and -donating moieties were tolerated, as were thioether functionalities present in the alcohol scope. The authors also performed some deuteration experiments, observing the desired deuterated products by LCMS, to support a mechanistic hypothesis.

In both the above base-earth metal examples (schemes **4.7** and **4.8**), we see the use of simple, widely commercially available metal salts as catalysts. This can be viewed as beneficial for several reasons, but somewhat limits the mechanistic understanding of these reactions, as the presence of an active metal species is less easily validated by analytical methods.

A final example is from the work of Sortais and co-workers.[14] This work demonstrated the methylation of amines with methanol and a manganese *PNP*-pincer precatalyst (**177**). In addition to the range of reported amines in this work, the authors were also able to perform sulfonamide methylation. However only 4 examples of this kind were reported, requiring lengthy reaction times, to give 59% average yield (scheme **4.9**).



Scheme 4.9 - Sulfonamide methylation with a managanese pincer complex

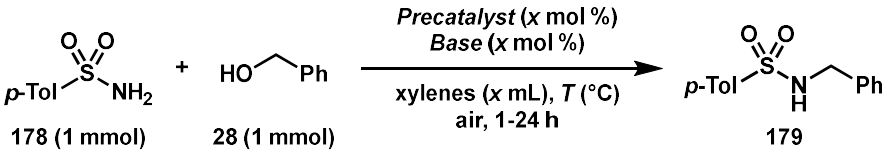
Substrate scope demonstrated halide tolerance, but due to the few examples a broader scope was lacking. A sole example of an alkylsulfonamide as a nucleophile was demonstrated, however in only 44% isolated yield.

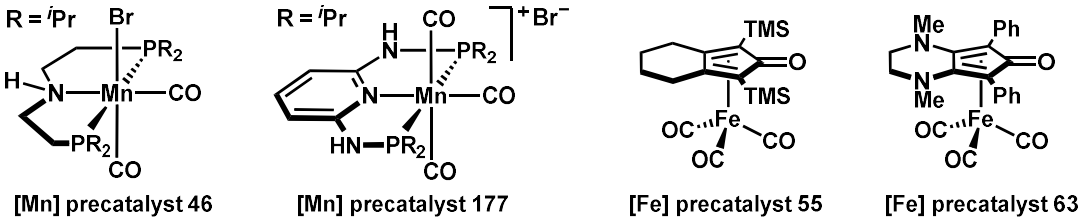
Due to the prolonged reaction time, and small scope of this reaction, it was desirable to develop a general, efficient transformation using other base metal precatalysts. Routes were sought for an earth-abundant transition metal-catalysed, general alkylation of sulfonamides with a well-defined metal catalyst or precatalyst.

4.2. Results and discussion

4.2.1. Optimisation of the *N*-alkylation of sulfonamides

A model reaction was the starting point of these investigations; *para*-toluene sulfonamide and benzyl alcohol were employed as model starting materials. The results of the optimisation are shown below (table **4.1**, NMR yields determined by ^{1}H NMR spectroscopy of the crude reaction mixture, relative to 0.5 equivalents of mesitylene as internal standard).





Entry	Precatalyst (mol %)	Base (mol %)	T (°C)	Solvent (mL)	Reaction time (h)	NMR Yield (%)
1	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	24	**98 (86)**
2	**177** (5)	K_2CO_3 (10)	150	Xylenes (1)	24	<2
3	**55** (5)[a]	K_2CO_3 (10)	150	Xylenes (1)	24	<2
4	**63** (5)[a]	K_2CO_3 (10)	150	Xylenes (1)	24	<2
5	**46** (5)	-	150	Xylenes (1)	24	5
6	**46** (5)	K_2CO_3 (100)	150	Xylenes (1)	24	91
7	-	K_2CO_3 (10)	150	Xylenes (1)	24	<2
8	**46** (4)	K_2CO_3 (10)	150	Xylenes (1)	24	94
9	**46** (3)	K_2CO_3 (10)	150	Xylenes (1)	24	42
10	**46** (2)	K_2CO_3 (10)	150	Xylenes (1)	24	7
11	**46** (5)	K_2CO_3 (10)	110	Xylenes (1)	24	18
12	**46** (5)	KO^{t}Bu (10)	150	Xylenes (1)	24	41
13	**46** (5)	KOH (10)	150	Xylenes (1)	24	5
14	**46** (5)	Cs_2CO_3 (10)	150	Xylenes (1)	24	94
15	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	8	100
16	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	6	82
17	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	4	70
18	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	1	20
19	**46**(5)	K_2CO_3 (10)	150	Xylenes (0.5)	24	92
20	**46** (5)	K_2CO_3 (10)	150	Xylenes (2)	24	92

a: reactions run with 10 mol % $Me_3NO{\cdot}2H_2O$ as activator

Table 4.1 - Optimisation of earth-abundant metal-catalysed *N*-alkylation of sulfonamides

Entry **1** demonstrated that, with 5 mol % of catalyst **46** (first used by Beller and co-workers),[15] 10 mol % of K_2CO_3 as base and activator, in xylenes at 150 °C after 24

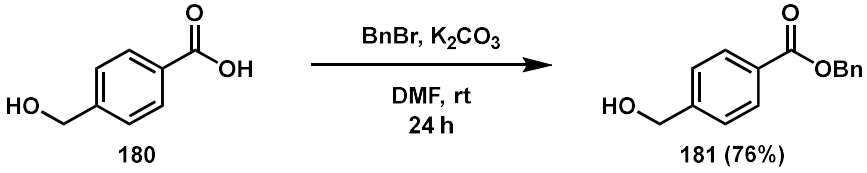
hours, product **179** could be recovered in a 98% ^{1}H NMR yield, and a 86% isolated yield. This procedure required only 1 equivalent of alcohol, and occurred under aerobic conditions without exclusion of moisture. It was noted that other available catalysts attempted in this work returned only starting materials, with no formation of the product observed by ^{1}H NMR spectroscopy of the crude reaction mixtures (entries **2**-**4**). Base loading is crucial for efficient reaction; without base this reaction proceeded to only 5% formation of the product – an observation that will be discussed in the catalytic cycle (entry **5**). By contrast, with a full equivalent of base, a slight drop in yield of **179** was observed, to 91% yield by ^{1}H NMR spectroscopy. This was tentatively attributed to poorer mixing of the reaction (entry **6**). In the absence of precatalyst **46**, <2% of desired product **179** was observed by ^{1}H NMR spectroscopy, demonstrating that this was not simply a base mediated process (entry **7**).[16] A large reduction in yield was observed when reducing catalyst loading below 5 mol % (entries **8**-**10**) with 4, 3 and 2 mol % producing 92%, 42%, and 7% of target material **179** by ^{1}H NMR spectroscopy respectively. When reducing reaction temperature, an 18% ^{1}H NMR yield of product **179** was observed (entry **11**). This implied that more elevated thermal conditions were required for this reaction to work, which was attributed to the poor nucleophilicity of the sulfonamide, as small quantities of aldehyde (5%) were observed regardless of the low temperature. A short screen of bases demonstrated potassium carbonate to be optimal for this transformation (entries **12**-**14**). The use of KO^{t}Bu resulted in only 41% of product **179** by ^{1}H NMR spectroscopy, whereas KOH resulted in only 4% of product **179**. Caesium carbonate, however, gave comparable yields, with 94% of **179** by ^{1}H NMR spectroscopy. Reducing reaction time to 8 hours resulted in a 100% ^{1}H NMR spectroscopic yield of product **179** (entry **15**). However, as these model conditions were with electron neutral species, the optimised time remained 24 hours, in order to allow more poorly reactive substrates to reach higher conversion. Reaction times lower than 8 hours resulted in incomplete conversion to the desired product, with 6, 4, and 1-hour reactions resulting in 82%, 70% and 20% yield by ^{1}H NMR spectroscopy respectively (entry **16**-**18**). Finally, small fluctuations in yield at double- and half-reaction concentrations were observed, both resulting in a 92% yield by ^{1}H NMR spectroscopy. This indicates that 1 mL of xylenes is optimal for this procedure (entries **19**-**20**).

Throughout this optimisation it was observed that this procedure is selective for monoalkylation of the sulfonamide, with no dialkylated products being observed. This can be tentatively attributed to greater steric encumbrance of the nitrogen nucleophile, due to the alkylation yielding a secondary amine. This in turn leads to lower reactivity, and hence no further alkylation.

4.2.2. Electrophile substrate scope

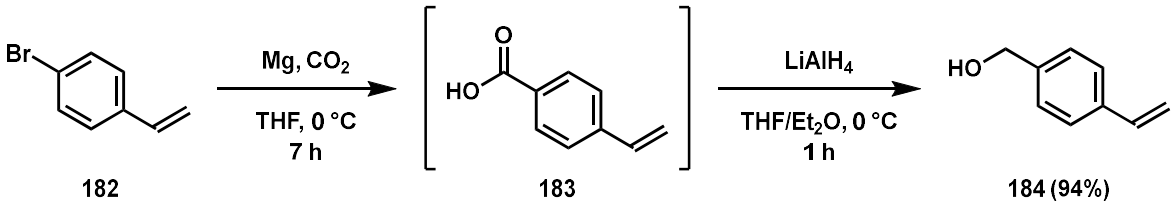
With optimised conditions in hand, a wider substrate scope was investigated. Due to the expense or lack of commercial availability of certain sulfonamides and alcohols, some substrates were synthesized through a variety of means.

When first examining the electrophile (alcohol) substrate scope, a small selection of non-commercially available alcohols were synthesised. In order to investigate reducible functionalities in this transformation, substrates **181** and **184** were prepared, as both of these compounds have moieties that could be potential hydrogen acceptors under transfer hydrogenation .[17] First, substrate **180** was synthesised from 4-(hydroxymethyl) benzoic acid (**180**) with benzyl bromide and potassium carbonate in 76% yield (scheme **4.10**).



Scheme 4.10 - Synthesis of substrate 180

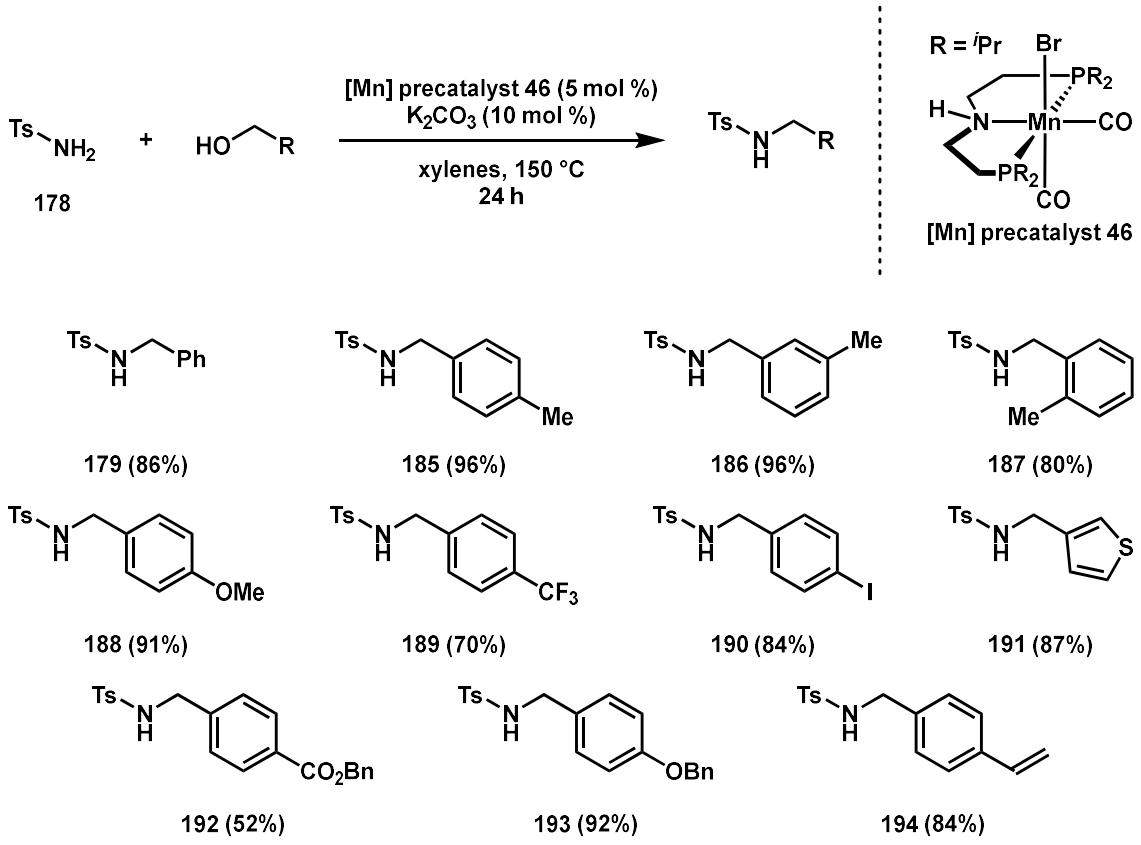
Substrate **184** was then synthesised in a 2-step procedure from 4-bromostyrene **182**. First, a Grignard reagent was formed *in situ*, then CO_2 bubbling yielded intermediate 4-vinylbenzoic acid (**183**), which was used without isolation. Reduction with lithium aluminium hydride yielded the desired (4-vinylphenyl)methanol **184** in 94% overall yield (scheme **4.11**)



Scheme 4.11 - Synthesis of substrate 184

With these materials in hand, electrophile substrate scope began.

Scheme **4.12** shows the successful results of the scope of benzylic alcohols and other aryl methanol derivatives. Substrate **187** demonstrated that this procedure tolerated moderate steric encumbrance, and is isolated in 80% yield. Electron-donating and -withdrawing groups in the *para*-position were tolerated, resulting in products **188** and **189**, which were isolated in 91% and 70% yield respectively. Halogenated substrates were tolerated, as with product **190**, which was isolated in 74% yield. This provided a site for further elaboration.[18] The production of thiophene **191** demonstrates the tolerance of a heteroaromatic alcohol, in 87% isolated yield. This transformation has high tolerance of a range of reducible functional groups, or those that could be targets for transfer hydrogenations – ester **192**, benzyl ether **193**, and styrene derivative **194** are isolated in 52%, 92% and 84% yields respectively.



Scheme 4.12 - Successful aryl methanol results

However, not all compounds were so well tolerated. Figure **4.1** shows the unsuccessful aryl methanol results.

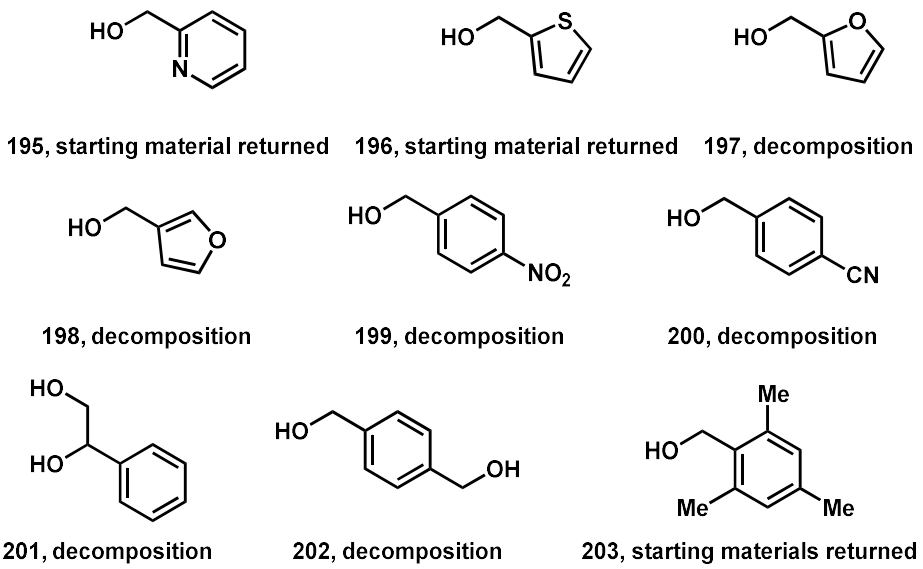
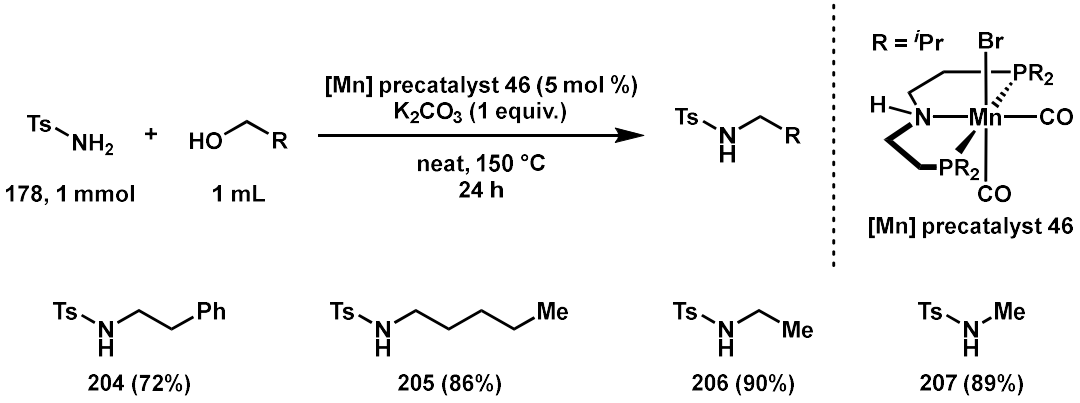


Figure 4.1 - Unsuccessful aryl methanol substrates

Substrates **195**-**198** demonstrated the incompatibility of other heteroaromatic alcohols (besides product **191**) in this procedure. Substrates **195** and **196** resulted in starting materials being returned under reaction conditions. In the absence of any catalyst poisoning studies, this could be tentatively be attributed to the result of irreversible coordination of these substrates to the catalyst. This coordination could occur in a bidentate fashion between heteroatom, and alcohol, and result in a loss of reactivity. Furthermore, substrates **197** and **198** demonstrate that furyl compounds were incompatible with this catalytic system, as complex mixtures were observed by ^{1}H NMR spectroscopy of the crude reaction mixture. This could be due to decomposition, or the chelation to the metal, leading to undesired reactivity. In the case of strong electron-withdrawing groups, such as the nitro moiety present in substrate **199**, the formation of a complex mixture was again observed *via* ^{1}H NMR spectroscopy of the crude reaction mixture, with loss of starting material. Substrate **200** also produced a complex mixture, observed via ^{1}H NMR spectroscopy. As both of these functional groups could be reduced by hydrogenating conditions, it is plausible that side reactions of this kind led to the formation of these mixtures. No starting material was recovered in either case by ^{1}H NMR spectroscopy. Substrates **201** and **202** showed the incompatibility of diols in this system, as both resulted in the production of a complex mixture, as observed by ^{1}H NMR spectroscopy. This could be attributed to decomposition pathways, or a series of transfer hydrogenations. In addition, substrate **203** was not tolerated, as while moderate steric encumbrance was well tolerated by the system (as with substrate **187**), highly sterically demanding substrates such as mesitylmethanol **203** are not compatible with these reaction conditions. This could be attributed to steric encumbrance precluding either the initial dehydrogenation step, or the subsequent condensation or hydrogenation steps.

Further electrophiles were then investigated, with a range of aliphatic, allylic, and propargylic alcohols employed. Scheme **4.13** shows the successful substrates.



Scheme 4.13 - Other successful alcohol results

These reactions required altered reaction conditions. This is partly due to lower boiling point, in some cases, but also due to the difficulties in the oxidation of such alcohols.[19] As such, solvent alcohol and a greater amount of base were required to produce the products in high yields. Product **204** was isolated in 72% yield, demonstrating homobenzyl alcohol compatibility. Product **207** demonstrated a long chain alcohol as alkylating agent, with isolation in 86% yield. Additionally, both ethanol and methanol were tolerated in this transformation, resulting in products **206** and **207**, in 90% and 89% isolated yield respectively. *N*-Methylated sulfonamide **207** represents an improvement on the current state of the art manganese methylation work.[14] Furthermore, under these conditions with excess of alkylating agent, no di-alkylation was observed, with mono-alkylation selectivity retained. This can again be attributed to the low nucleophilicity of sulfonamides, and initial alkylation providing a further steric barrier to di-alkylation.

However, not all aliphatic and lower molecular weight substrates were well tolerated by this procedure. Figure **4.2** shows the unsuccessful results.

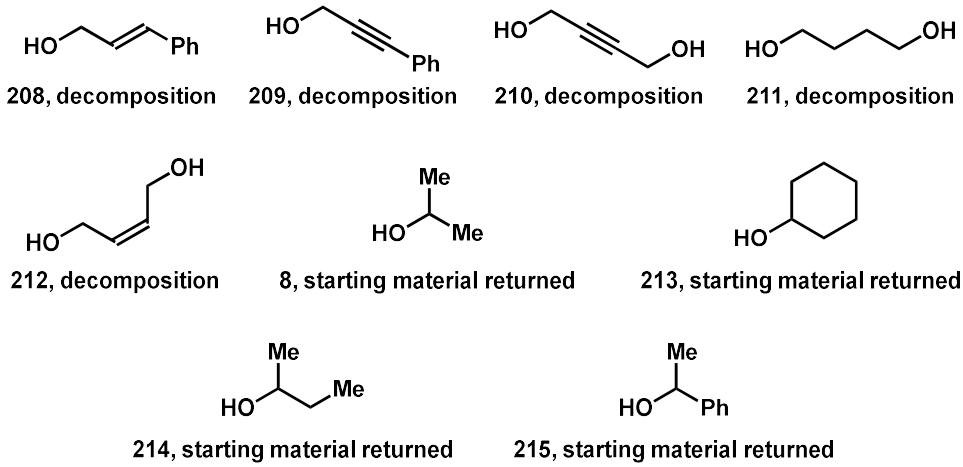
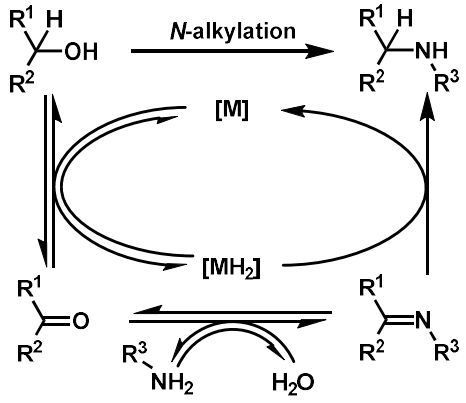


Figure 4.2 - Other unsuccessful alcohol results

Substrates **208** and **209** underwent decomposition under the reaction conditions, forming a complex mixture that was observed by ^{1}H NMR spectroscopy of the crude reaction mixture. Diols **210**, **211**, and **212** were also observed to form complex mixtures of unidentified products by ^{1}H NMR spectroscopy. This was presumably due to multiple transfer hydrogenations leading to competing side reactions. Furthermore, secondary alcohols **8**, **213**, **214**, and **215** were not tolerated under these reaction conditions. In each case, returned starting material was observed with no generation of product observed by ^{1}H NMR spectroscopy.

To understand why this is, the generalised borrowing hydrogen catalytic cycle must be referred to (scheme **4.14**).



Scheme 4.14 - A generalised borrowing hydrogen catalytic cycle

Primary alcohols are less electron-rich than secondary alcohols, and thus less easily oxidized. However, the formed intermediate aldehyde is highly reactive, and aldehydes are known to condense with amines with relative ease. Furthermore, the

corresponding imine can be hydrogenated readily by the metal hydride species. This final reduction of the aldimine is irreversible under all known conditions. Therefore, if even small quantities of product can be formed, over time the reaction will progress to completion. The work of Sabater and co-workers[20] showed that the rate-determining step of a heterogeneous borrowing hydrogen reaction is the condensation of nucleophile and aldehyde. A tentative proposal – in the absence of kinetic data for this reaction – is that in this case too, the condensation of sulfonamide with alcohol is the rate limiting step.

With this assumption, if alkylated sulfonamides are unable to be observed in the reactions with secondary alcohols, it is indicative of the process being interrupted.

When changing from primary to secondary alcohols, the sterics of the *α*-alcohol hydrogen atoms are altered significantly. Instead of a secondary centre, oxidation of a tertiary centre is now occurring. However, a more electron-rich carbon centre now favours oxidation. Under the assumption that the catalyst is able to perform this oxidation, additional steps of this catalytic cycle must be inspected.

While the condensation of amines with aldehydes is simple, ketone condensations often require the use of Lewis acid, water-sequestering reagents, and harsher reaction conditions. Therefore, it can be presumed that this reaction is accordingly slower than with aldehydic starting materials. This does not preclude the formation of the corresponding ketimine however, and production of small amounts of this ketimine would still lead to product formation, as before.

However, the terminal reduction may also face additional problems. Firstly, the ketimine is more bulky than the corresponding aldimine, thus harder to reduce. Secondly, the ketimine is more electron rich than the aldimine, once again disfavouring reduction. These two things combined could lead to the ketimine being a more persistent species in the reaction mixture, which in turn could lead to it being hydrolysed by water before any reaction can take place, resulting in no production of the desired product, and no further conditions were able to furnish the desired products.

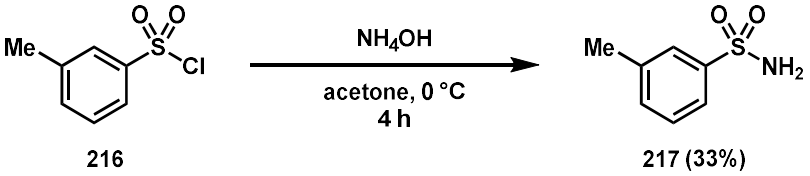
While it is difficult to prove any of these theories, or to say definitively what part of the catalytic cycle is responsible for the lack of reaction of secondary alcohols, these

are all plausible explanations for this problem. Due to the lack of observed ketimine or ketone in the ^{1}H NMR spectra of the crude reaction mixtures, it is believed that initial oxidation was the barrier to successful reaction of these secondary alcohol substrates. Unfortunately, these issues were never overcome in this work.

With electrophile scope completed, nucleophile substrate scope was investigated; testing the range of sulfonamides tolerated by the reaction conditions.

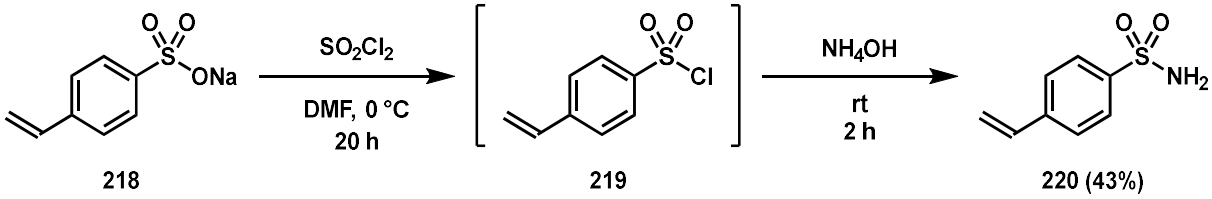
4.2.3. Nucleophile substrate scope

A range of sulfonamides that were not commercially available were synthesised for investigation in the substrate scope. First, 3-methylbenzenesulfonamide (**217**), was synthesised from the corresponding commercially available sulfonyl halide (**216**), and ammonium hydroxide in a 33% yield (scheme **4.15**).



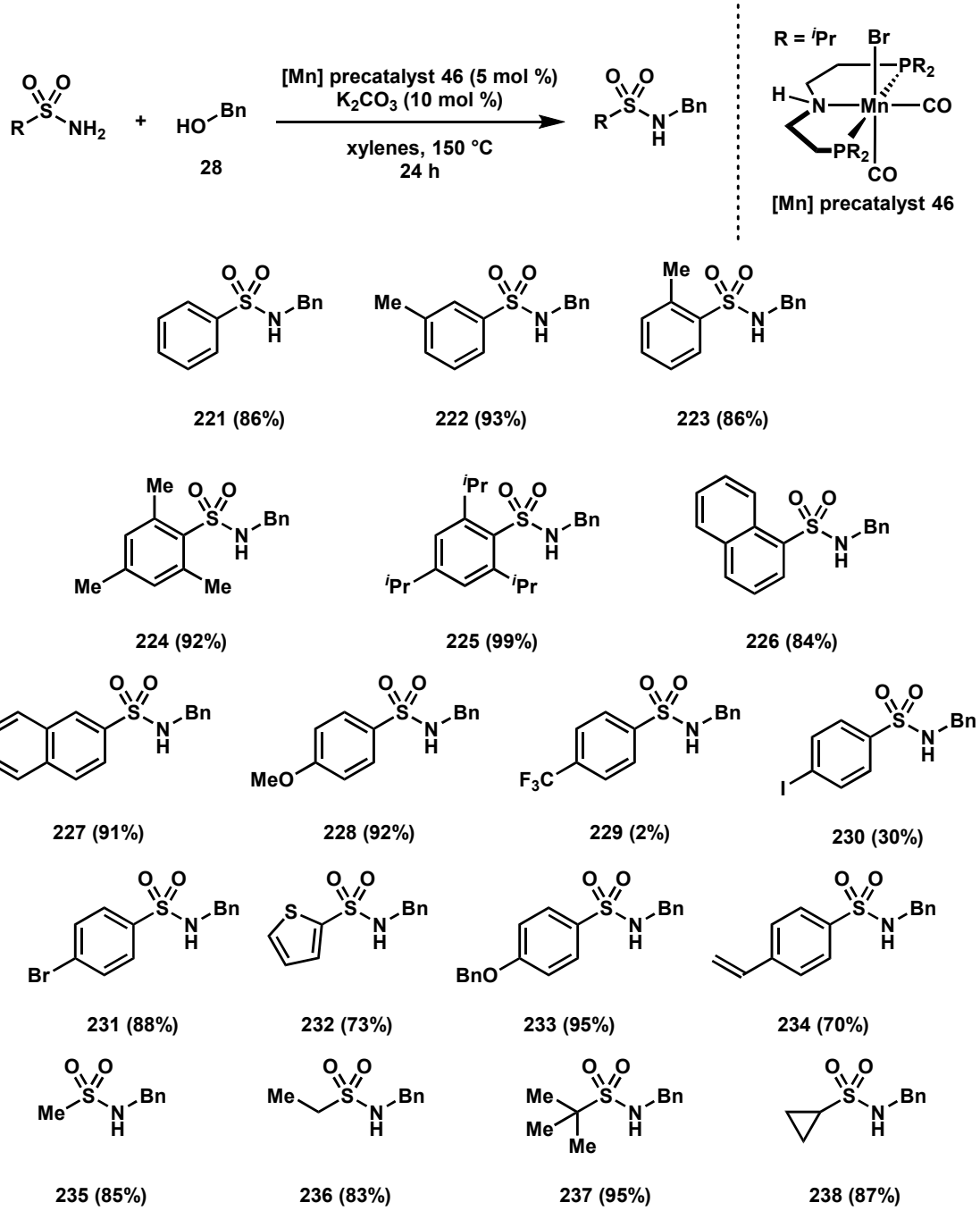
Scheme 4.15 - Synthesis of substrate 217

An alternative route for the preparation of vinyl substrate **220** was undertaken, starting with the commercially available sodium sulfonate **218**. Here, sulfuryl chloride was used to transform sulfonate **219** into sulfonyl chloride **220**, which was used without isolation. Subsequent addition of ammonium hydroxide yielded sulfonamide **220** in 43% overall yield (scheme **4.16**).



Scheme 4.14 - Synthesis of substrate 220

With target sulfonamides in hand, nucleophilic substrate scope was then investigated, under standard reaction conditions. Scheme **4.17** shows the range of successfully tolerated sulfonamides, and isolated yields for each.

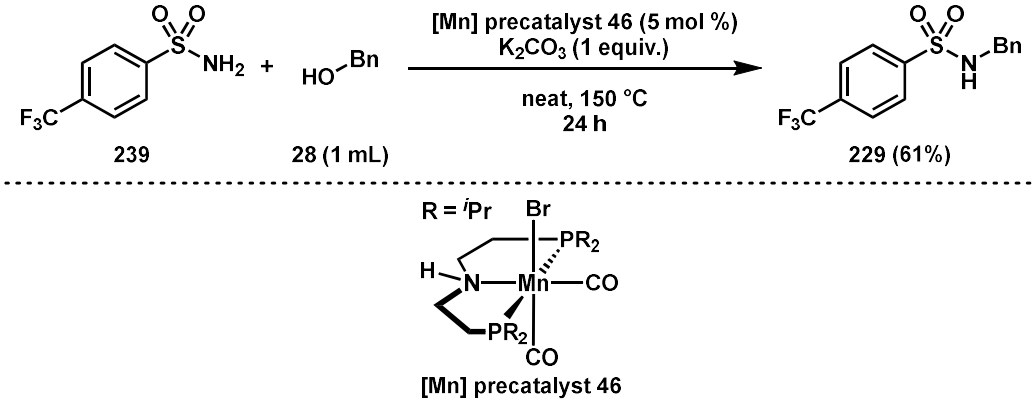


Scheme 4.17 - Successful sulfonamide results

This scope demonstrated the high steric tolerance of the sulfonamide nucleophiles, with mesityl product **224** and 2,4,6-TRIPP derivative **225** being isolated in 92% and 99% yield respectively. Extended aromatic systems were also well tolerated, as

demonstrated by naphthyl products **226** and **227**, isolated in 84% and 91% yield respectively. Electron-donating substituents were tolerated, as with product **228**, in 92% isolated yield. However, an example with an electron-withdrawing group, **229**, was only recovered in a 2% isolated yield under standard conditions. Halogen-containing sulfonamides were also well tolerated, albeit low-yielding with iodide **230**, which was recovered in 30% yield. This can be tentatively attributed to Mn-insertion into the C-I bond. However, bromide **231** was isolated in 88% yield. **232** showed that 2-thiophenyl moieties were well tolerated (in contrast to the alcohol scope) resulting in a 73% isolated yield. Reducible functionalities were tolerated, with no reduced products observed. Benzyl ether **233** and styryl derivative **234** demonstrated this in 95% and 70% isolated yield respectively. Finally, 4 alkylsulfonamide examples were also reported as nucleophiles, including a cyclopropyl sulfonamide, which furnished product **238** in 87% yield.

Observing the low yield of **229**, the more forcing conditions from the alcohol scope (scheme **4.13**) were utilised, which involved the use of stoichiometric base and solvent alcohol (scheme **4.18**).



Scheme 4.18 - Condition modification for a sulfonamide with an electron-withdrawing moiety

These conditions resulted in a greatly increased yield of product **229**, which was isolated in 61% yield. However, attempts to employ other sulfonamides as nucleophiles were less successful. Figure **4.3** shows the unsuccessful results.

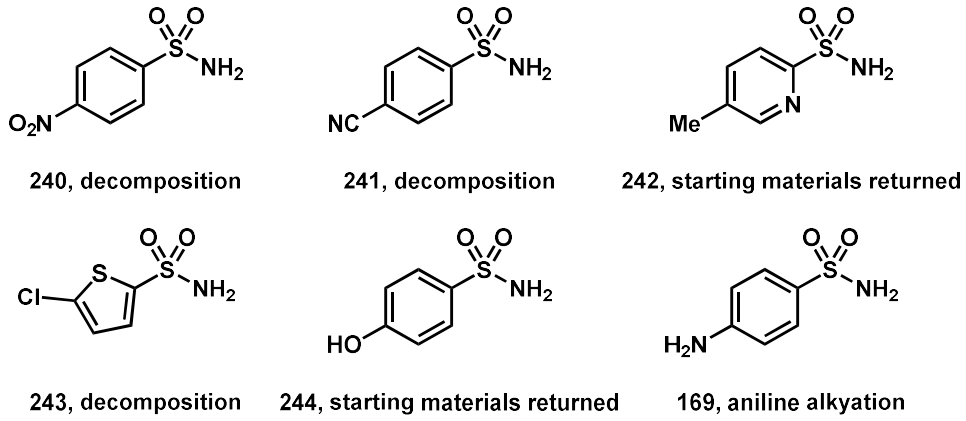
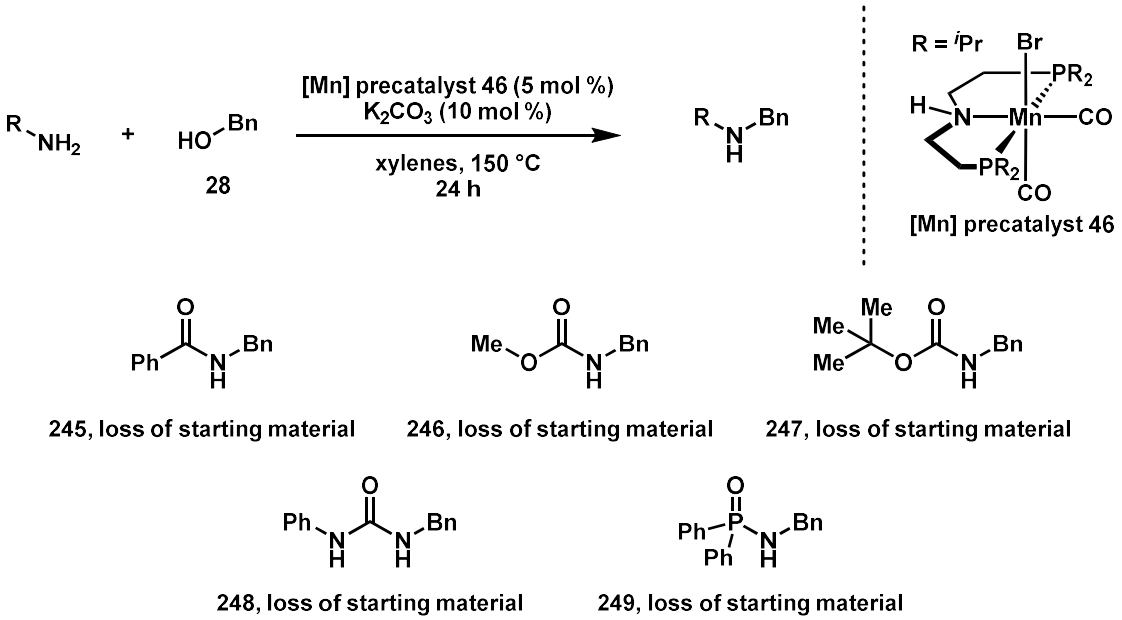


Figure 4.3 - Unsuccessful sulfonamide substrates

In the case of other electro-deficient sulfonamides, *para*-nitro substrate **240** underwent side reactions, resulting in the formation of a complex mixture observed by ^{1}H NMR spectroscopy of the crude reaction mixture. Complete loss of starting material was also observed. Substrate **241** demonstrated that nitrile-containing substrates are unsuitable; under these reaction conditions, this compound gave a complex mixture in the ^{1}H NMR spectrum of the crude reaction mixture. Substrate **242** shows that pyridyl substrates are once again not tolerated, and only starting material was recovered from this reaction. This could be tentatively attributed to the ability of the heteroatom to coordinate strongly to the catalyst, perhaps forming a chelated complex with the sulfonamide also, and preclude further reactivity. By contrast to the earlier result of product **232**, substrate **243** was also incompatible under the reaction conditions. This could be due to the ability of the manganese catalyst to insert into the C-Cl bond, with subsequent poisoning of the catalyst, as starting material only is returned from the reaction mixture. Substrate **244** also returned only starting material. This could be attributed to coordination of the phenol moiety to the catalyst, due to its electron rich nature, which thus prevented the desired reactivity. Finally, substrate **169** returns competitive alkylation products (observed in the ^{1}H NMR spectrum of the crude reaction mixture), due to competing aniline alkylation, demonstrating poor selectivity for sulfonamide nucleophiles.

In an attempt to expand the scope of this reaction, several other selected electron poor amine nucleophiles were screened.[21] The results of this screening are shown below (scheme **4.19**).



Scheme 4.19 - Other electron poor nucleophile results

Here, it was observed that amides, carbamates, ureas, and phosphinamides were not tolerated by the reaction conditions. In all these cases, the ^{1}H NMR spectra of these compounds showed no generation of product, and all resulting a complete loss of starting material. The amide and urea results can be tentatively explained by pK_a values:[22] the pK_a of benzenesulfonamide is 16.1 in DMSO, whereas the pK_a of the corresponding benzamide is 23.3, and of urea is 26.9. The pK_a of diphenylphosphinamide is not reported. It is possible that the disparity in pK_a could preclude the formation of a sufficiently nucleophilic species *via* deprotonation, especially with a carbonate base. This could in turn lead to a slower rate of condensation, which as mentioned before (*cf.* scheme **4.12**), could be sufficient to prevent the formation of the product. This could then lead to further side reactions, leading to loss of the starting material. While there is some literature to indicate the thermal decomposition of carbamates at elevated temperatures,[23] as recovery of benzyl alcohol in these instances is poor, it is possible that either substrate or formed product are decomposed under these harsh reaction conditions. Regardless, all substrates tested proved to be incompatible with the reaction in hand, even when the more forcing, neat reaction conditions were employed (*cf*. scheme **4.18**).

4.2.4. Mechanistic investigations

With the substrate scope completed, a plausible mechanistic hypothesis was investigated. Reaction intermediates were envisioned for this transformation, under the assumption that it proceeds through a typical borrowing hydrogen mechanism (figure **4.4**).

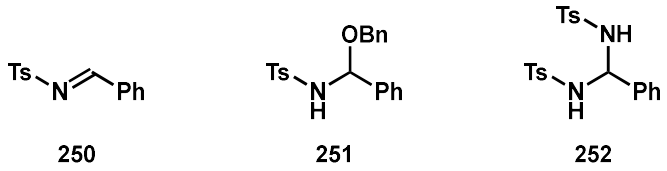
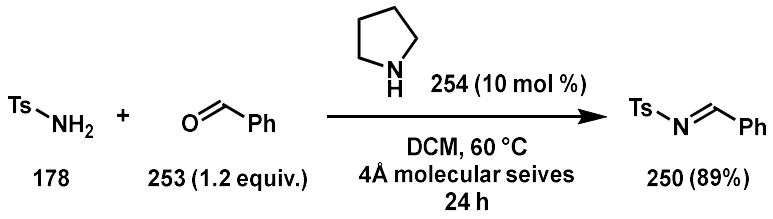


Figure 4.4 - Targeted plausible intermediates

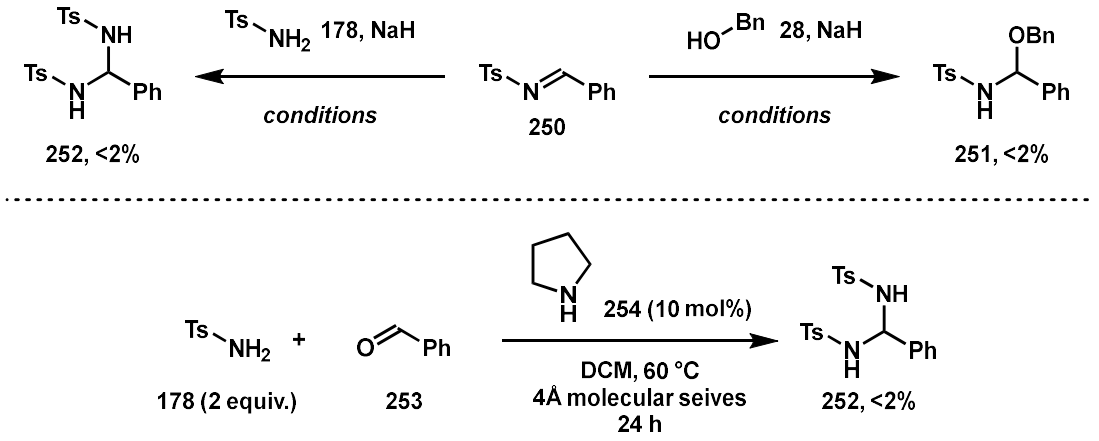
By subjecting these intermediates to the standard reaction conditions, an existing mechanistic hypothesis can be supported or disproven. Imine **250** was key here, as it could be used to generate the other two intermediates. Both intermediates **251** and **252** could result from *in situ* addition to the formed imine of benzyl alcohol, and *para*-toluenesulfonamide respectively.

Imine **250** was readily prepared through condensation of *para*-toluenesulfonamide with benzaldehyde, in an 89% isolated yield (scheme **4.20**).



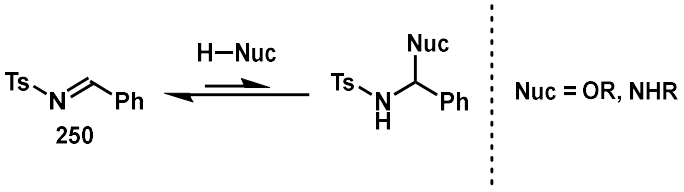
Scheme 4.20 - Synthesis of imine 250

Secondary amine catalysis yields the target material.[24] From here, multiple routes towards the other target compounds were attempted, summarised below (scheme **4.21**).



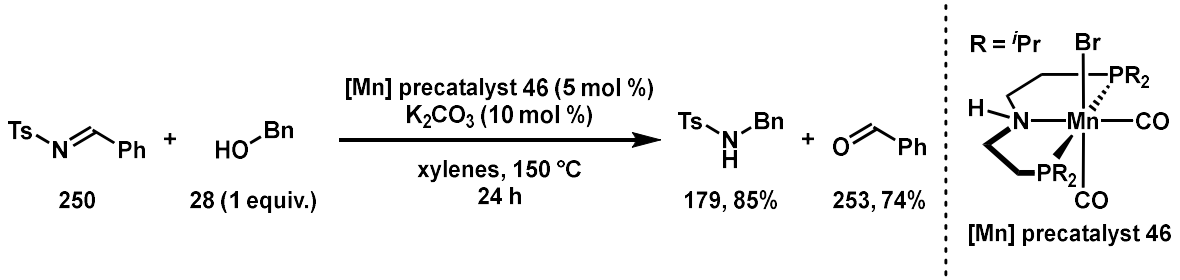
Scheme 4.21 - Attempts towards other plausaible intermediates

Other routes in the synthesis of the targeted substrates were unsuccessful. In every case, only imine **250** was observed in the ^{1}H NMR spectrum of the crude reaction mixtures. In the case of the second line of scheme **4.19**, only imine **253** and *para*-toluenesulfonamide **178** were isolated from this reaction. However, this was a good indication that these intermediates were not plausible. It can be tentatively inferred here that imine **250** was reactive enough to be attacked by the *in-situ* generated nucleophiles, but that compounds **251** and **252** are transient species that immediately fragment to the corresponding imine (scheme **4.22**). This hypothesis was further corroborated by the fact that, when stored under air (i.e. under wet conditions), imine **250** decomposed return **178** and **253**.



Scheme 4.22 - Presumed reactivity of 250 towards attempted nucleophiles

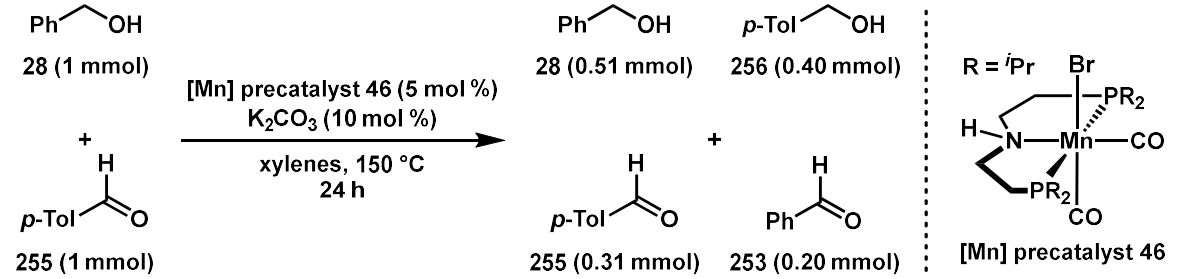
Imine **250** was the only intermediate isolated, and was subjected to standard reaction conditions, with 1 equivalent of benzyl alcohol **28**, in order to demonstrate its validity it as a plausible intermediate (scheme **4.23**).



Scheme 4.23 - Validation of a plausible intermediate

Imine **250** underwent transfer hydrogenation with benzyl alcohol **28**, resulting in an 85% ^{1}H NMR yield of target material **179**, with concomitant generation of benzaldehyde in 74% ^{1}H NMR yield. The loss of mass balance could be attributed to the decomposition of benzaldehyde under the reaction conditions. This reaction demonstrates that, if imine **250** is formed under reaction conditions, it will be transformed into the product, thus indicating that it is a plausible intermediate for a classical borrowing hydrogen mechanism.

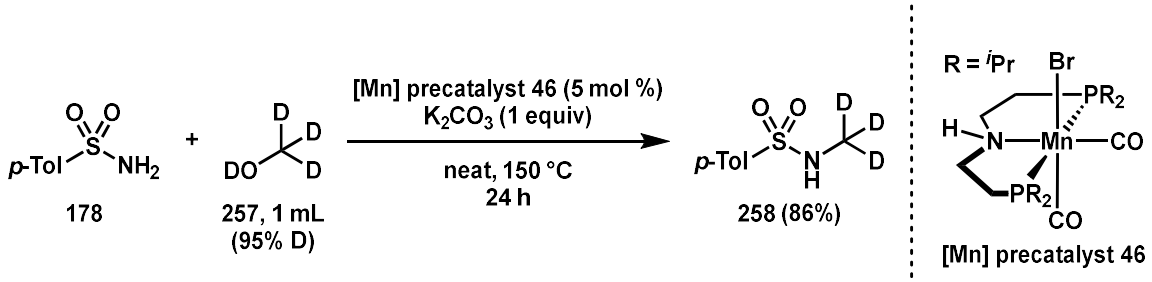
The next mechanistic reaction undertaken was to support the hypothesis of reversible transfer hydrogenation. By taking a mixture of benzyl alcohol **28** and *para*-tolualdehyde **255**, and observing the resulting products, reversible transfer hydrogenation could be demonstrated or disproved (scheme **4.24**).



Scheme 4.24 - Reversible transfer hydrogenation experiment

This experiment returns a variety of products in the ratio shown above, determined by ^{1}H NMR spectroscopy of the crude reaction mixture (relative to 0.5 mmol of mesitylene as internal standard). This supports the hypothesis that reversible transfer hydrogenation was occurring, as all 4 possible products were observed. While mass balance was lost in this reaction (returning 1.42 mmol; 71% total recovery), this could be a result of stoichiometric aldehyde under these reaction conditions decomposing to unobserved products, under the harsh reaction conditions. Indeed, no compounds other than **28**, **255**, **253** and **256** were observed.

Final mechanistic work was to perform deuteration to demonstrate that the alcohol was indeed the active alkylating reagent, and that the mechanism proceeds *via* a metal-hydride intermediate. A readily available alcohol was found in place of deuterated benzyl alcohols, due to their expense and poor commercial availability; methanol-D_4 (**257**). This was applied to alkylation conditions discussed above (*cf.* scheme **4.13**) in the place of methanol as alkylating agent (scheme **4.25**).



Scheme 4.25 - Deuteration experiments with CD_3OD

HRMS confirmed the presence of the CD_3 moiety, and NMR analysis shows 95% deuterium incorporation at the desired carbon (equation **4.1**). This provided evidence to support methanol as the methyl source, and hence that all other alcohols are the alkyl source in the rest of this work. It also supports that a manganese deuteride is being formed *in situ*, as high deuterium incorporation is observed. This in turn supports the formation of a manganese hydride intermediate in non-deuterated reactions. However, there were a large number of very small peaks present at the appropriate chemical shift to correspond to the *α*-amino-protons, which are indicative of a mixture of compounds with varying degrees of deuteration (Figure **4.5**). Kinetic isotope studies were not undertaken, however.

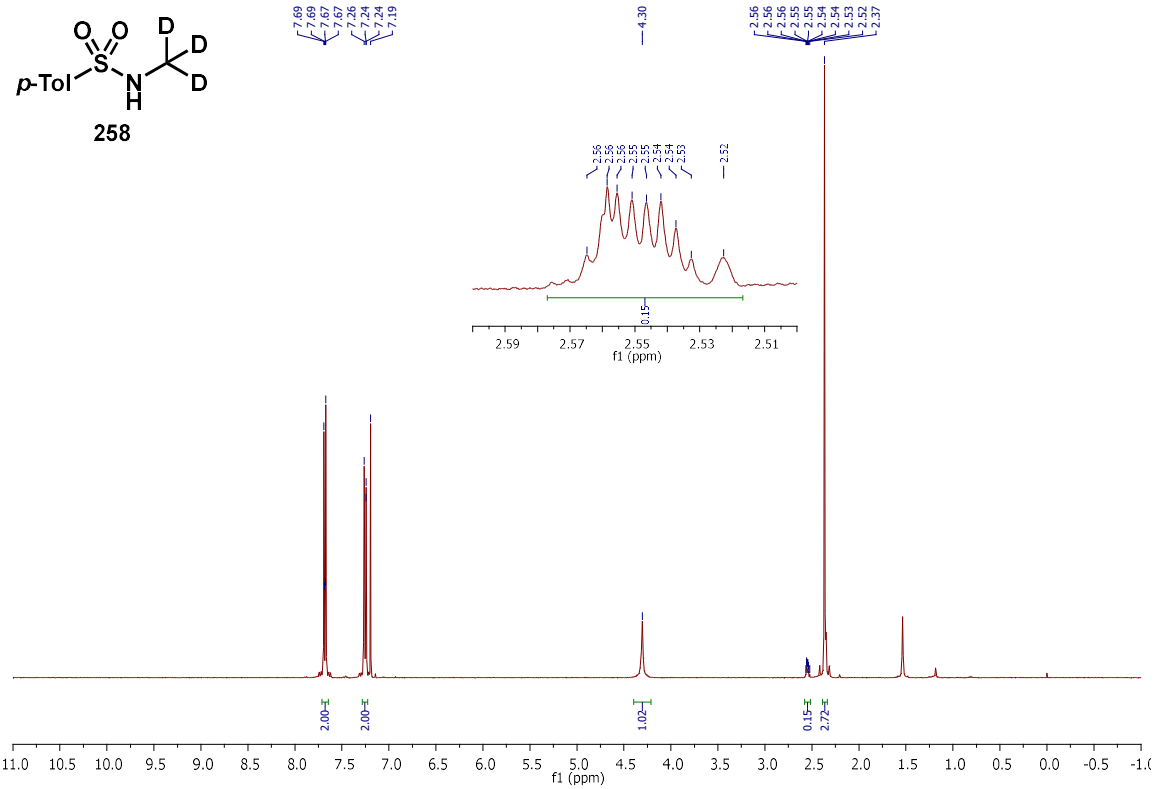


Figure 4.5 - NMR spectrum of 258

$$\textit{Percent deuterium incorporation} = \frac{\textit{Number of protons without deuteration} - \textit{Integral of residual proton peak}}{\textit{Number of protons without deuteration}} \times 100$$

$$\therefore \frac{3 - 0.15}{3} \times 100 = 95\%$$

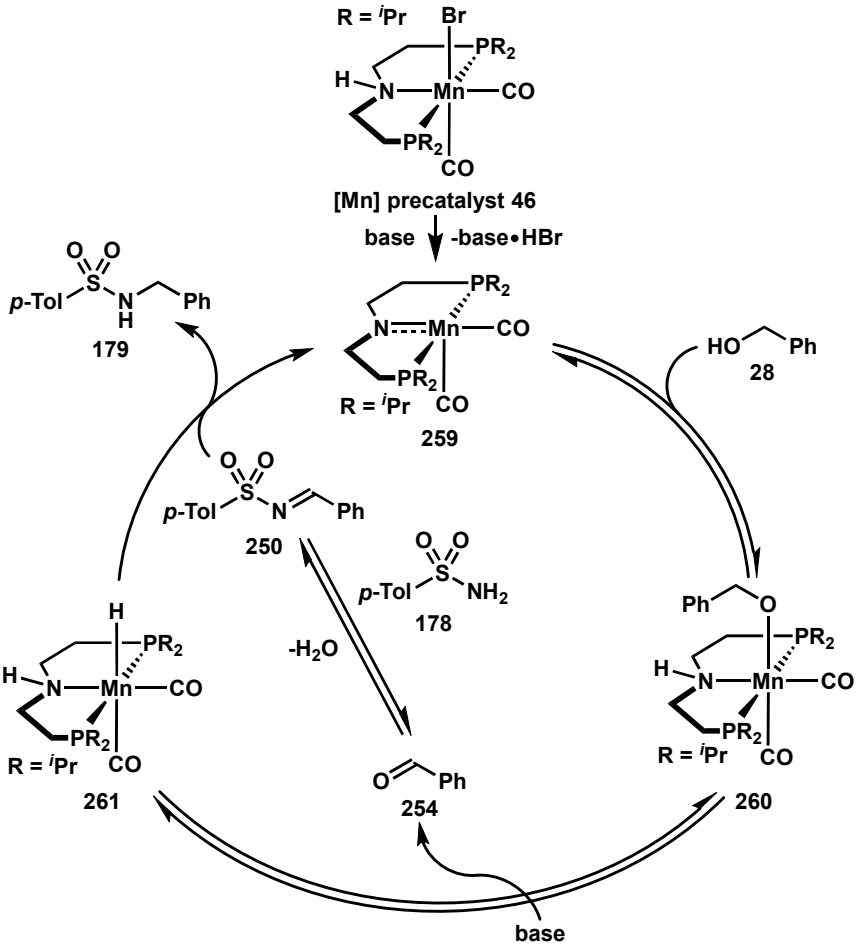
Equation 4.1 - Calculation of deuterium incorporation

This suggested that there was an off cycle mechanism for forming a manganese hydride species under these conditions, instead of a manganese deuteride. However, this alternative pathway only resulted in 5% hydrogen incorporation, so was a minor pathway, and not responsible for the major product.

In summary, imine **250** has been demonstrated as a plausible reaction intermediate, and transfer hydrogenation has been supported as parts of the catalytic cycle. Likewise, it was demonstrated that alcohols are the active alkylating reagent, and support for the formation of a manganese hydride complex has been provided. These pieces of information, combined with the earlier assessment that base is

critical to the reaction (table **4.1**), and results from the work of Beller and co-workers,[15] led to the following mechanistic hypothesis (scheme **4.26**).

The proposed mechanism initiates with base-induced deprotonation, to extrude HBr, and form a manganese centre with a vacant coordination site (**259**). Coordination of benzyl alcohol forms a manganese alkoxide complex (**260**). Here, the action of base facilitates a *β*-hydride elimination, yielding benzaldehyde (**254**), and a manganese hydride complex (**261**). Benzaldehyde **254** can now condense with *para*-toluenesulfonamide (**178**) with the aid of base to yield the corresponding imine (**250**). Imine **250** is a validated reaction intermediate.



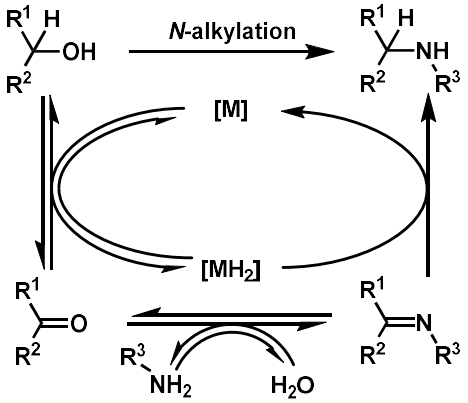
Scheme 4.26 - Postulated mechanism for *N*-alkylation of sulfonamides using alcohols

Hydrogenation of imine **250** by the formed manganese hydride **261** both liberates the target *N*-alkylsulfonamide (**179**), and regenerates the active catalyst (**259**), closing the cycle.

4.2.5. Limitations and future work

Aside from the substrate limitations discussed, one of the greatest limitations of this work is the elevated temperature; the harsh reaction conditions involved. This can be tentatively attributed to low reactivity of sulfonamide, due to the electron-deficient nature of the nitrogen nucleophile. Once again scheme **4.14** can be referred to, seeking some explanation for why these conditions are necessary.

As mentioned before, one of the key requirements for an efficient borrowing hydrogen reaction is ensuring the secondary reaction (in this case is condensation) occurs readily.

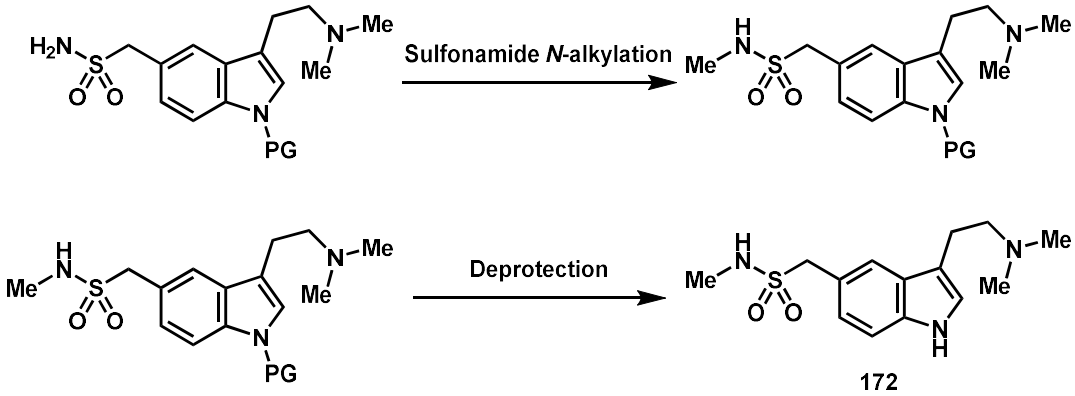


Scheme 4.14 - A generalised borrowing hydrogen catalytic cycle

It is likewise clear from the optimisation, and previous literature,[25] that this catalyst works well even at lower temperatures, as benzaldehyde was observed in the ^{1}H NMRs of crude reaction mixtures at reduced temperature. This indicates that, at low temperatures, the limiting factor is the ability of the nucleophilic to react. Potential modifications could be to reduce reaction temperature, and through the utilisation of Lewis acids, or other methods, activate the formed aldehydes towards condensation reactions. This overcomes the lower reactivity of sulfonamides in an alternative way. Such carbonyl activation methods have some precedent in the literature,[26] and could lead to less forcing reaction conditions. Another option could be to prepare the corresponding sulfonamide anion by deprotonation and isolation of the formed salt. This salt could then be used in the place of sulfonamide starting materials, and

could lead to more reactive, easily-condensing substrates, thus allowing reaction temperature to be decreased.

If it is possible to reduce reaction temperature, then an obvious application of this work would be to extend it towards the synthesis of drugs, or pharmaceutically active compounds. A primary concern was that, under harsh reaction conditions more sensitive compounds (such as biologically active precursors) might decompose in a fashion similar to some substrates. As such, such work was not attempted. A simple target would be compound **172**, sumantripan.[3a] Under the assumption that the indole nitrogen could be protected to ensure compatibility with the manganese catalyst, this procedure cloud be employed to affect methylation with methanol, as demonstrated earlier (scheme **4.11**). This would lead to protected precursor, which would then only require deprotection to form the active pharmaceutical (scheme **4.27**).



Scheme 4.27 - Hypothetical synthesis of sumantripan

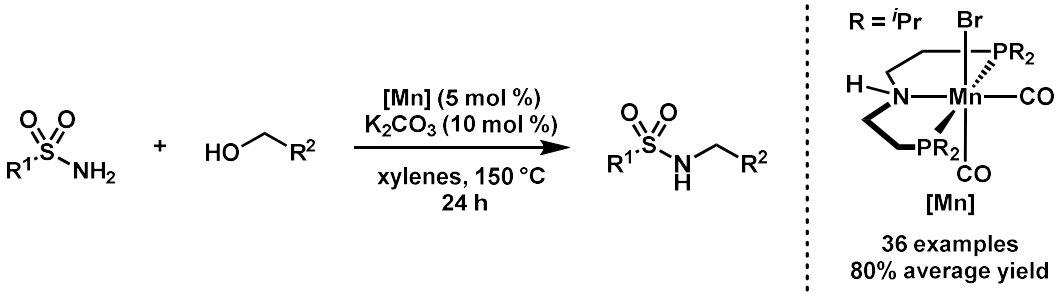
Another limitation that this reduction in temperature could solve would be the intolerance of the substrate scope towards allylic and propargylic systems. These particular alcohols, if successful in this chemistry, could broaden the synthetic applications of this reaction towards much more diverse compounds with functional handles for wider elaboration.

A particular limitation that might limit this chemistry in wider use is the intolerance of heterocycles, with the exception of thiophenyl moieties. As heteroaromatics are widely incorporated into a large array of materials and compounds, a wider range of compatible substrates is highly desirable. This could possibly be achieved with an

alternative catalyst scaffold, or perhaps an alternative metal catalyst that would be less sensitive to such compounds.

4.3. Summary

In summary, an earth-abundant transition metal-catalysed, general alkylation procedure of a range of aryl- and alkylsulfonamides was reported. This procedure demonstrated 36 examples in 80% average yield. A broad scope of substrates was reported in high average yields, and mechanistic studies undertaken to support a postulated mechanism. This procedure is operationally simple, with no efforts to exclude air or moisture from the reaction vessel required. In addition, this work is selective for mono-alkylation, without risk of over alkylation. This work was recently highlighted on organic-chemistry.org.[28] In the context of the aims and objectives, this reaction well demonstrated the transference of an extant precious metal-catalysed process to an earth-abundant metal-catalysed process, thus satisfying the aims and objectives. While not the first earth-abundant catalysed sulfonamide alkylation (nor the first example with manganese) this reaction presented a reduction in reaction time compared to previous manganese-catalysed reactions, and an example of a well-defined metal precatalyst in such reactions.



Scheme 4.28 - Manganese-catalysed *N*-alkylation of sulfonamides

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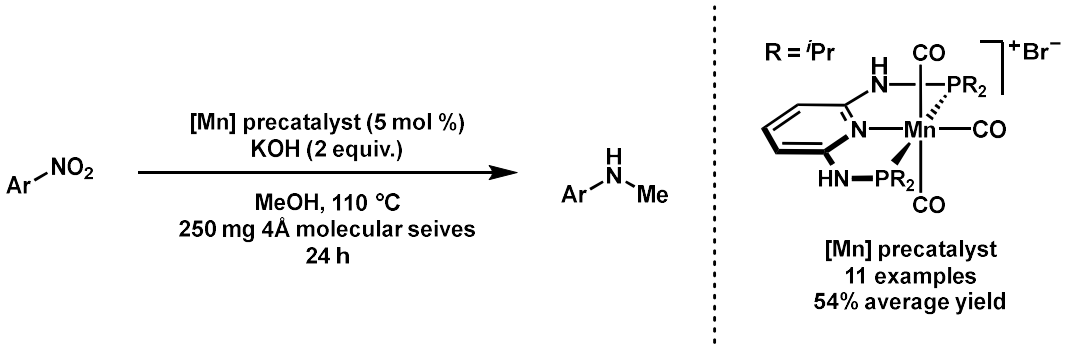
Chapter 5: Manganese-catalysed one-pot conversion of nitroarenes to *N*-methylarylamines using methanol

Table of contents

5. Preface

This chapter discusses the development of the first earth-abundant transition metal-catalysed procedure for the conversion of nitroarenes to *N*-methylarylamines. Eleven examples are demonstrated in 54% average yield, with complete selectivity for mono-methylation. Further work shows the results with other substrates that undergo unforeseen reactivity. Mechanistic investigations and time course experiments give evidence towards a plausible mechanistic hypothesis.



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Benjamin G. Reed-Berendt – Responsible for the optimisation, substrate scope, parts of the time course experiments and plausible intermediate experiments, catalyst stability studies, and reaction headspace analysis.

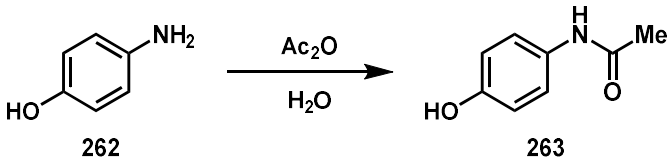
Nicolas Mast – Responsible for the remainder of work in the time course and plausible intermediate experiments.

Louis C. Morrill – Supervisor, Cardiff University

5.1. Introduction

5.1.1. The importance of aromatic and *N*-methyl aromatic amines

Aromatic amines are important in the synthesis of a wide range of compounds and materials, from applications in the synthesis of urethane polymers, to uses in herbicides, pharmaceuticals, dyes and pigments.[1] An example is the production of the commonly used analgesic, paracetamol (**263**) from *para*-aminophenol (**262**, scheme **5.1**).[2]



262 263

Scheme 5.1 - Production of paracetamol

Specifically *N*-methyl aromatic amines are widely found in a range of pharmaceuticals and biologically active compounds (figure **5.1**).

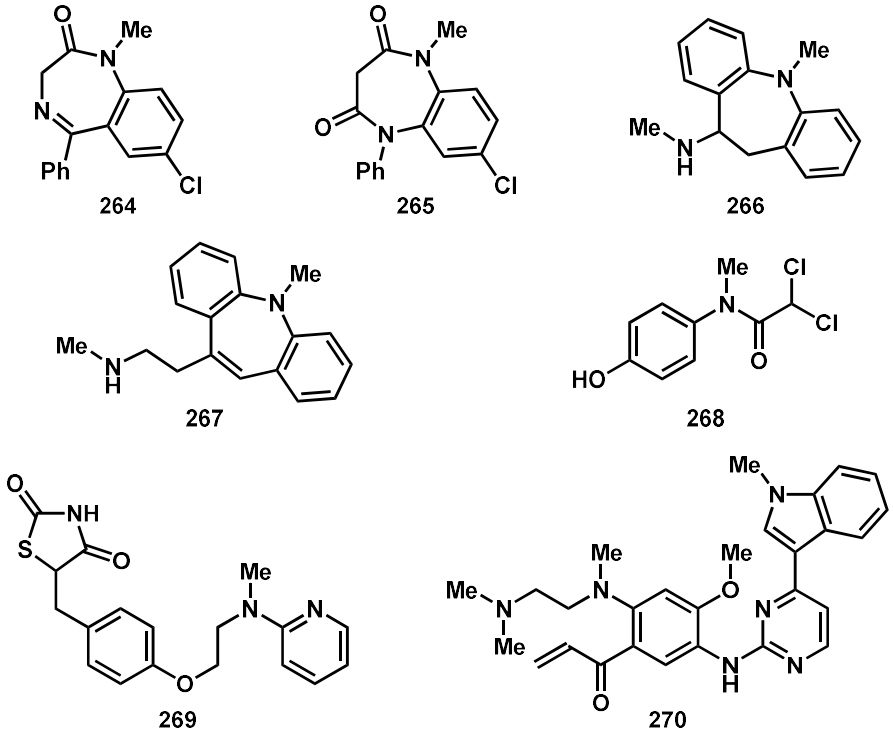
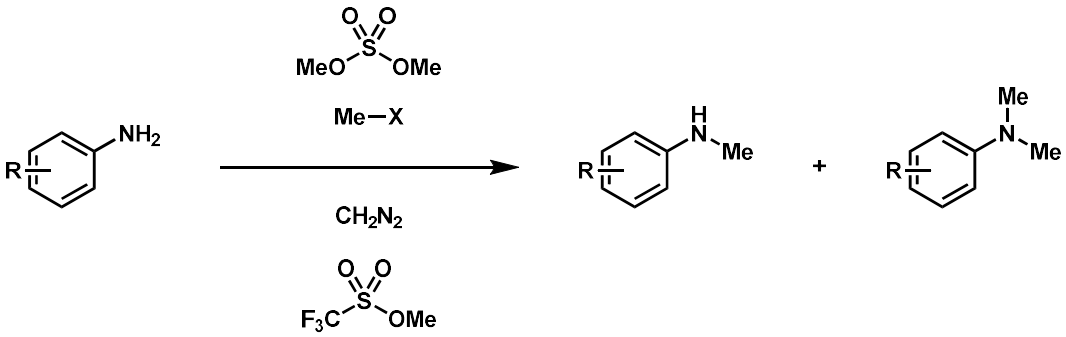


Figure 5.1 - Marketed drug compounds containing *N*-methylated arylamines

Examples include the drug molecules diazepam (**264**), clobazam (**265**), metapramine (**266**), amezepine (**267**), diloxanide (**268**), rosiglitazone (**269**), and osimertinib (**270**) which find a range of applications from antidepressants to epilepsy treatments.[3]

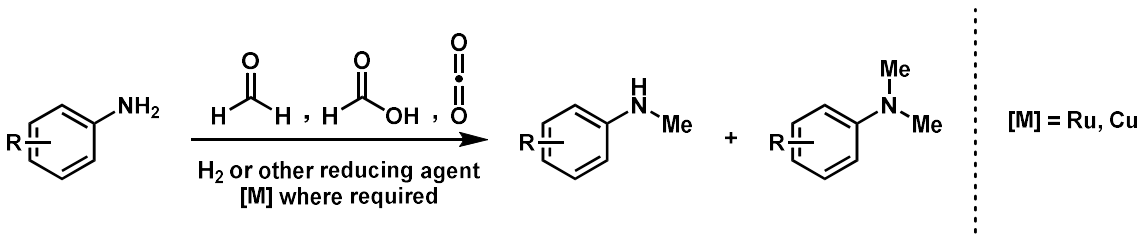
5.1.2. Methods for the *N*-methylation of arylamines

Traditional techniques for arylamine methylation include the use of methyl halides, or other activated methyl sources, such as dimethyl sulfate, diazomethane or other active methylating reagents (scheme **5.2**).[4] These in turn often yield a mixture of mono– and dimethylated products, and generate stoichiometric waste.



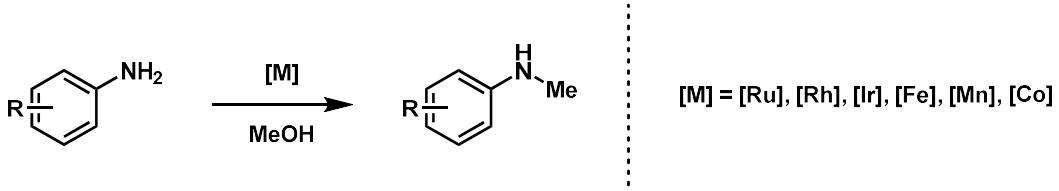
Scheme 5.2 - Classical methods for *N*-methylation of arylamines

Other methods demonstrate more selectivity for monomethylation. A key examples is reductive methylation, using formaldehyde, formic acid, or carbon dioxide as methylating reagents.[5] However, in this case reduction is required, often in the form of molecular hydrogen as reductant. Furthermore, these procedures are not always exclusively selective for monomethylation, as reaction conditions are largely responsible for the selectivity (scheme **5.3**).



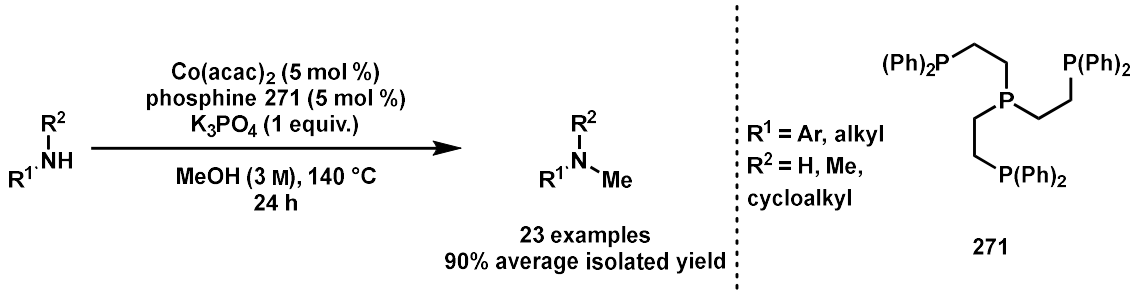
Scheme 5.3 - Reductive methods for *N*-methylation of arylamines

In order to move away from stoichiometric reducing agents, alternative routes can be employed, such as borrowing hydrogen catalysis for *N*-methylation. These reactions are common in the literature,[6] and allows the use of an abundant, inexpensive and widely available solvent for methylation – methanol. This transformation utilises formally redox-neutral conditions to yield highly selective mono-alkylation with a wide range of catalysts and conditions (scheme **5.4**).



Scheme 5.4 - Borrowing hydrogen routes for *N*-methylation of arylamines

A representative example of this work is that of Liu and co-workers.[6g] Here, the authors demonstrate the use of cobalt(II) acetylacetonate and a phosphine ligand for the alkylation of a wide range of primary and secondary aryl- and alkylamines. This work demonstrated a moderate substrate scope of 23 examples, with high average isolated yields (scheme **5.5**).



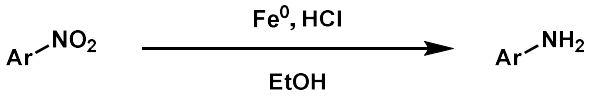
Scheme 5.5 - Cobalt-catalysed methylation work

Reducible functionalities, such as nitrile moieties, are well tolerated by this system, as are *para*-electron-withdrawing groups, and a small range of *ortho*-substituted anilines demonstrating good tolerance of this catalytic system towards moderate steric bulk. However, a limitation of this work comes from the alkylation of primary benzylic amines. Here, exclusive dimethylation was observed, with only tertiary amines formed in this transformation. This reaction is therefore much less useful for mono-methylation of more reactive amines, however no di-methylation of the arylamines was reported.

When investigating these generalised methylations, it is important also to consider the source of the corresponding nucleophile. In this case, it is the arylamine, which can be classically prepared by the reduction of nitroarenes.

5.1.3. Methods for the reduction of nitroarenes

The reduction of nitroarenes[7] can be utilised to generate the corresponding arylamines. This process was initially discovered with the Béchamp reduction (scheme **5.6**).[8]

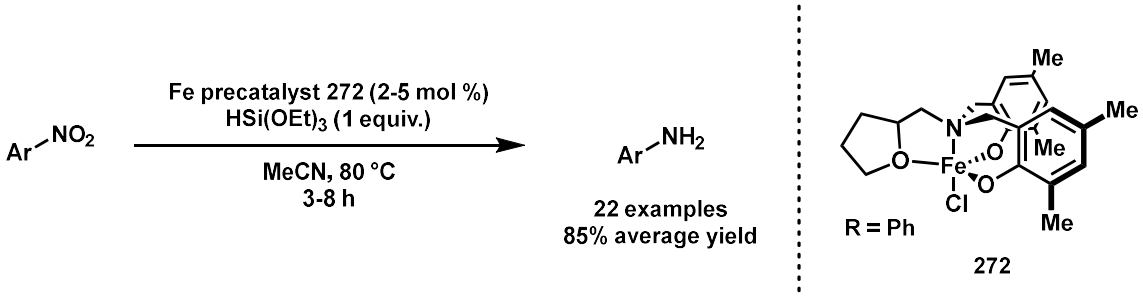


Scheme 5.6 - The Béchamp reduction

Here, the action of iron metal and concentrated acid results in the reduction of nitroarenes in a widely applicable manner. However, this dated reaction results in the generation of superstoichiometric metal waste.

Alternative routes can be employed to prevent such waste being produced. A popular strategy is the use of a metal catalyst in tandem with a reducing agent. Here a huge range of reductants can be utilised, but these can be broadly broken up into several key areas by reductant - hydrogen gas (or other surrogates that yield H_2 *in situ*), hydrazines, inorganic hydrides (e.g. borohydrides or silyl hydrides), and transfer hydrogenation based processes.

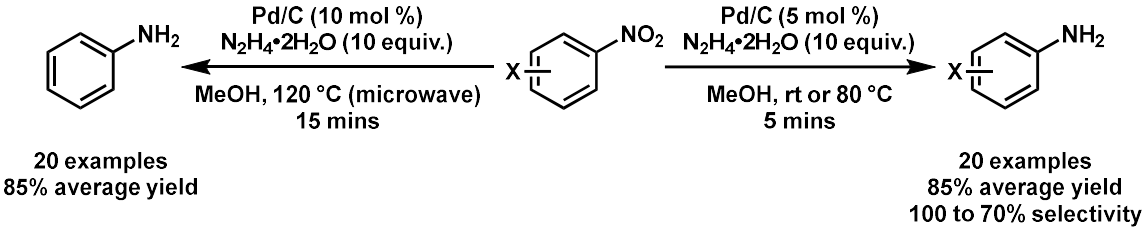
An example can be found in the work of Thomas and co-workers.[9] This work reported the use of a fifteen-electron iron(III) precatalyst with a tetradentate ligand, to effect the selective reduction of nitroarenes with silanes (scheme **5.7**).



Scheme 5.7 - Iron-catalysed nitroarene reduction

The well-defined iron catalyst was used to effect this reduction at very short timescales, and with isolated yields. In addition, a range of products show the tolerance and compatibility of this reaction. High steric encumbrance was tolerated, demonstrated with a product 2,6-dimethylaniline. Likewise, reducible functionalities, including *para*-esters, ketones and nitriles are tolerated well by this catalytic system. Heteroaromatic systems are also tolerated, and the authors reported the synthesis of a pincer ligand intermediate, and a drug precursor. This work was then extended towards hydroamination of alkenes with the *in situ* formed anilines.

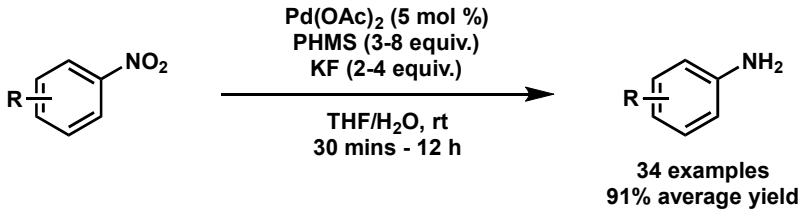
Another example can be taken from the work of Li and co-workers.[10] This work utilised palladium on charcoal to effect the reduction of nitroarenes with hydrazines (scheme **5.8**).



Scheme 5.8 - Palladium-catalysed nitroarene reduction

Here, the authors report two different sets of conditions to yield different sets of products. Using the ability of the palladium catalyst to insert into carbon-halogen bonds, it was shown that slight variance in conditions resulted in either the sole reduction of the nitroarene, or concomitant dehalogenation with the aforementioned reduction. This reaction proceeds with many examples, in high yields and good selectivity in the case of the right hand reactions. However, the substrate scope reported few functional groups beyond methyl groups and further nitro or amine groups, leaving this reaction somewhat limited in broader applications.

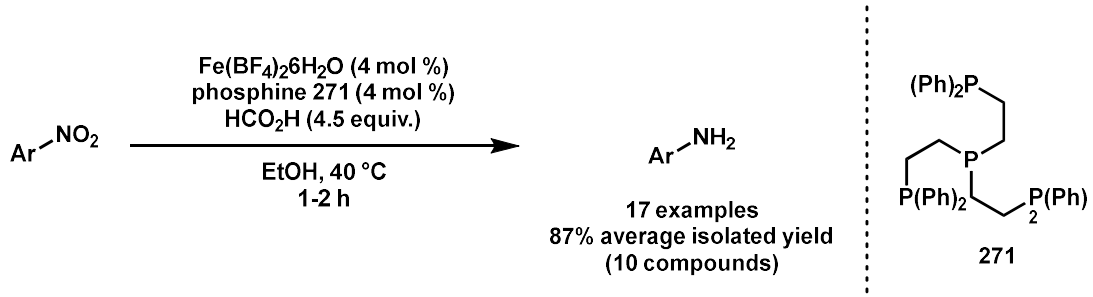
Further examples can be found in the work of Maleczka and co-workers.[11] Here, polymethylhydrosiloxane (PMHS) was used as a reductant for nitroarene reduction by palladium catalysis (scheme **5.9**).



Scheme 5.9 - Palladium-catalysed reduction of nitroarenes with silanes

The reaction proceeded with a broad substrate scope, with tolerance for a wide variety of functional groups. Examples showed high steric tolerance, as demonstrated by 2,6-dimethylated products. Multiple examples of heteroaromatic and carbonyl compounds can also be observed. However, the authors did not report any aryl halides, besides aryl fluorides. This limits the applications of this work, especially regarding elaborations *via* palladium catalysis.

A final example in nitroarene reduction protocols is one using transfer hydrogenation. Once again the work of Beller and co-workers[12] provides a good example. Here, formic acid is used to generate an iron hydride *in-situ* that can perform the reduction (scheme **5.10**).



Scheme 5.10 - Iron-catalysed nitroarene reduction with formic acid

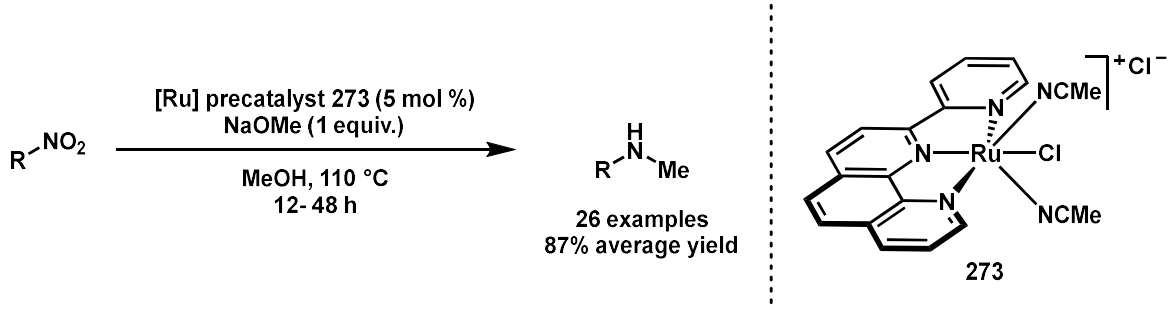
The authors reported a range of substrates; a selection of *para*-halogenated compounds were shown to be successful substrates. In addition, this procedure was tolerant of reducible functional groups – a *meta*-alkene is tolerated, yielding the target aniline without comments on observed reduction. Similarly, *para*-carbonyl moieties were tolerated.

However, these steps therefore represent stoichiometric waste generation in the synthesis of *N*-methylarylamines. Furthermore, the reducing agents described above (especially H_2 and hydrazine) are highly hazardous compounds, with significant risks associated in their use. While a simple route could be to perform a stoichiometric reduction, followed by one of the methylation procedures described previously, this will generate waste over 2 steps. As such, it is desirable to investigate and develop procedures for an operationally simple, one-pot process for nitroarene reduction and subsequent *N*-methylation. This could provide an alternative route to *N*-methylarylamines, while potentially providing higher atom economy in such reactions.

5.1.4. Methods for tandem reduction-*N*-methylation of nitroarenes

There are many extant methods to perform this transformation, such as reductive methods using formaldehyde,[13] formic acid[14] or carbon dioxide,[15] utilising a range of reducing agents. However, one of the most elegant ways to effect this one-pot process is the fusion of reduction by transfer hydrogenation, and borrowing hydrogen methylation. This would allow the use of simple, inexpensive methanol as both hydrogen source for the reduction, and an active methylation reagent; a highly attractive route that avoids the risks of using harmful or dangerous reagents, such as hydrogen gas. While there are examples of this transformation being performed *via* heterogeneous catalysis, these methods are often lacking in mono-selectivity for the alkylation.[16] There are few examples of this route being performed homogenously, all of which are recent literature.

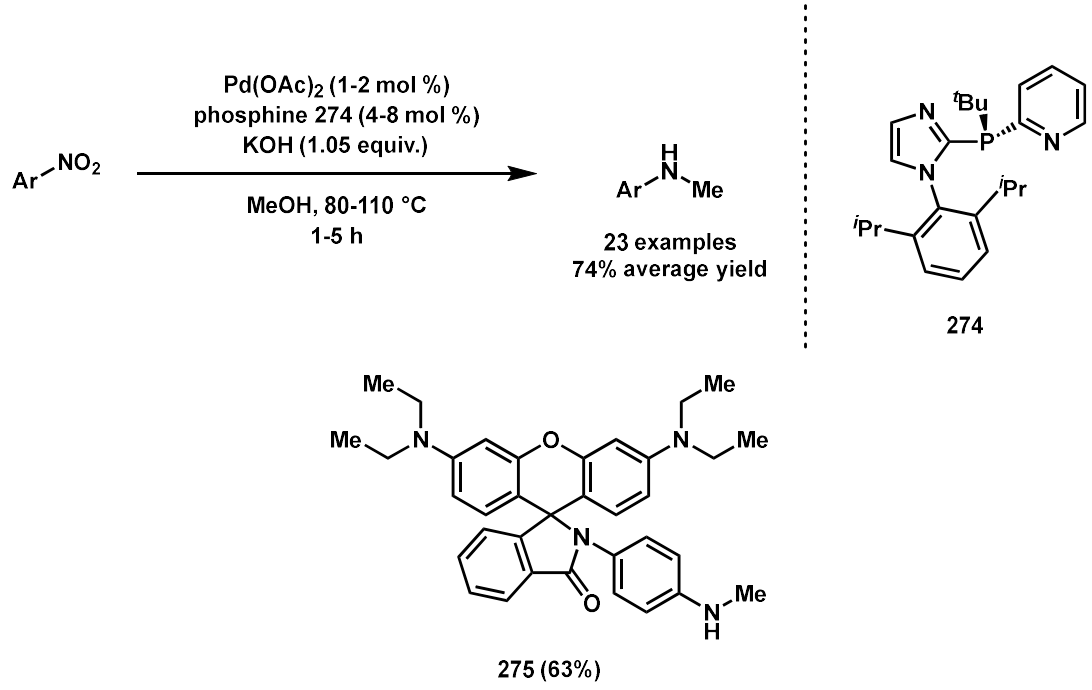
The first example, reported by Kundu and co-workers, showed the use of a homogeneous eighteen-electron ruthenium(II) precatalyst to effect this one-pot reductive methylation.[17] Here, the authors reported an efficient procedure, with multiple examples for this reduction-methylation reaction (scheme **5.11**).



Scheme 5.11 - Ruthenium-catalysed reduction-methylation

A small range of *meta*- and *para*-halogenated compounds were reported, as were heteroaromatics. Reducible functionalities, such as *meta*-alkene moieties and *β*-nitrostyrene as starting material were tolerated. No comment was made on the observation of alkene reduction. A range of nitroalkanes were also reported, but with exclusive di-methylation. The authors also demonstrated tolerance of the catalytic system to a range of impurities in the reaction. This was done by reacting the parent nitrobenzene with stoichiometric “impurities”; other substances added that could have an impact on the reaction. Here, it was demonstrated that other alcohols, ketones, ethers, and alkyl halides did not prevent this reaction from occurring.

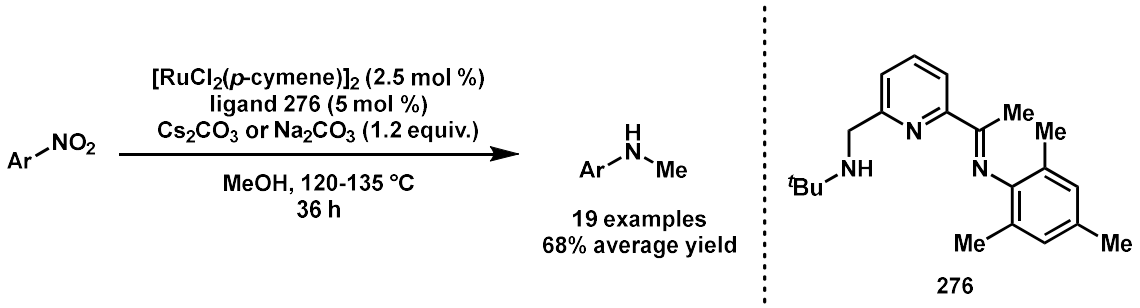
The second example can be found in the work of Beller and co-workers.[18] Here, palladium acetate was used to perform nitroarene reduction-methylation, with an enantioenriched phosphine ligand (scheme **5.12**).



Scheme 5.12 - Palladium-catalysed reduction-methylation

The authors here reported a substrate scope with many examples in high yields. Multiple *ortho*-functionalised compounds are reported, demonstrating steric tolerance. Reducible functionalities in the *para*-position were also reported, as were indole and pyrrole derivatives. Furthermore, the authors report the functionalisation of a rhodamine derivative (**275**), which was recovered in 63% isolated yield. This shows the broad applicability of this procedure. In addition, this particular borrowing hydrogen reaction boasted very short reaction times up to 5 hours or less. However, there are no electron-withdrawing substituents or halogenated products reported, limiting the further synthetic applications of this work.

The third example is from the work of Yang and co-workers,[19] where once again ruthenium catalysis is used to effect nitroarene reduction-*N*-methylation (scheme **5.13**). This reaction proceeded with multiple examples, in moderate to high yields. A range of *meta*- and *para*-halogenated products were reported, as were *para*-electron-withdrawing and -donating groups, in the form of nitrile and methoxy moieties, respectively. The inclusion of nitrile moieties also demonstrated the tolerance of this procedure towards reducible functional groups, as was corroborated by the success of *para*-ester containing substrates. Likewise, a range of heteroaromatic and heterocyclic products were reported.



Scheme 5.13 - Ruthenium catalysed nitroarene reduction-methylation

The authors also reported a small range of other alcohols, which were compatible in this procedure in the place of methanol.

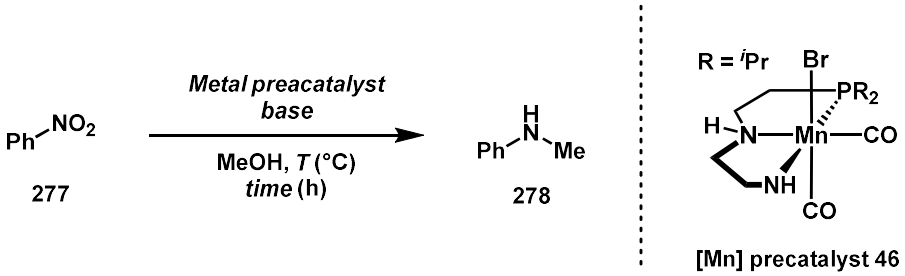
This concludes the review of borrowing hydrogen routes towards tandem nitroarene reduction-*N*-methylation procedures. All of these transformations were performed with rare earth catalysts; while providing an attractive route for the use of methanol as reducing agent and alkylating agent, there was no base metal catalytic route for

this procedure. As such, a base metal-catalysed nitroarene reduction-*N*-methylation is an attractive research target.

5.2. Results and discussion

5.2.1. Optimisation

Optimisation began by screening standard base metal catalysts in a parent reaction. Drawing from the works of Kundu,[17] Beller,[18] and Yang,[19] optimisation began with model substrate nitrobenzene (**277**). Anticipating high temperatures necessary to initiate reaction, initial work utilised pressure tubes, to reach elevated temperatures while using methanol as solvent. Inspiration for initial reaction conditions was taken from previous work[20] (table **5.1**, yields shown were determined by ^{1}H NMR spectroscopy, relative to 0.5 equivalents of mesitylene as internal standard).

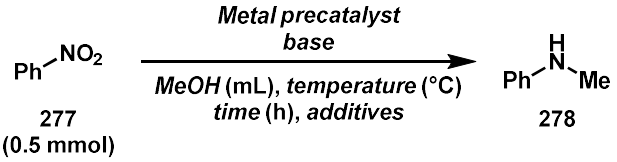


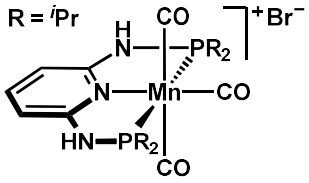
Entry	Precatalyst (mol %)	Base (equiv.)	Methanol (mL)	T (°C)	Time (h)	277 (%)	278 (%)
1	**46** (5)	NaOMe (1)	1	150	24	60	**27**
2	**46** (5)	NaOMe (5)	1	150	24	42	**35**
3	**46** (5)	NaOMe (5)	1	150	24	81	0

Table 5.1 - Early optimisation results

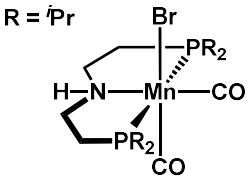
Desired *N*-methylaniline (**278**) was observed in 27% yield by ^{1}H NMR spectroscopy of the crude reaction mixture, when using manganese *PNP*-pincer precatalyst **46**[21] (entry **1**). However, significant loss of mass balance was also observed, attributed to decomposition of the starting material. Raising the base loading resulted in inconsistent results and poor reproducibility (entries **2** and **3**, 35% and 0% ^{1}H NMR

yield respectively), once again attributed to decomposition occurring. Thus, a lower temperature system was investigated, where use of simple microwave vials would be sufficient to prevent complete evaporation of methanol. Table **5.2** shows the results of further optimisation (yields shown were determined by ^{1}H NMR spectroscopy, relative to 0.5 equivalents of mesitylene as internal standard).

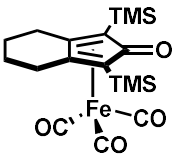




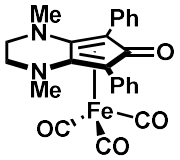
[Mn] precatalyst 177



[Mn] precatalyst 46



[Fe] precatalyst 55



[Fe] precatalyst 63

Entry	Precatalyst (mol %)	Base (equiv.)	MeOH (mL)	temp (°C)	time (h)	277 (%)	278 (%)	Additives
1	**177** (5)	KOH (2)	1	110	16	**3**	**94**	250 mg 4Å molecular sieves (dust)
2	N/A	KOH (2)	1	110	16	89	<2	250 mg 4Å molecular sieves (dust)
3	**177** (5)	N/A	1	110	16	97	<2	250 mg 4Å molecular sieves (dust)
4	**177** (5)	KOH (2)	1	110	16	79	<2	N/A
5	**177** (5)	KOH (2)	1	110	16	<2	79	500 mg 4Å molecular sieves (dust)
6	**177** (5)	KOH (2)	1	110	16	<2	36	250 mg 4Å molecular sieves (balls)
7	**177** (5)	KOH (1)	1	110	16	15	49	250 mg 4Å molecular sieves (dust)

8	**177** (5)	NaOMe (2)	1	110	16	80	4	250 mg 4Å molecular sieves (dust)
9	**177** (5)	KO^{t}Bu (2)	1	110	16	<2	61	250 mg 4Å molecular sieves (dust)
10	**177** (5)	K_2CO_3 (2)	1	110	16	<2	83	250 mg 4Å molecular sieves (dust)
11	**177** (5)	NaOH (2)	1	110	16	9	83	250 mg 4Å molecular sieves (dust)
12	**46** (5)	KOH (2)	1	110	16	13	14	250 mg 4Å molecular sieves (dust)
13	**55** (5)	KOH (2)	1	110	16	60	4	250 mg 4Å molecular sieves (dust), 10 mol % $Me_3NO{\cdot}2H_2O$
14	**63** (5)	KOH (2)	1	110	16	55	2	250 mg 4Å molecular sieves (dust), 10 mol % $Me_3NO{\cdot}2H_2O$
15	**177** (5)	KOH (2)	0.5	110	16	24	33	250 mg 4Å molecular sieves (dust)
16	**177** (2.5)	KOH (2)	1	110	16	<2	74	250 mg 4Å molecular sieves (dust)
17	**177** (5)	KOH (2)	1	80	16	100	0	250 mg 4Å molecular sieves (dust)

Table 5.2 - Optimisation of the one-pot conversation of nitroarenes to *N*-methylarylamines

Upon reduction of reaction temperature, altering the catalyst to **177**[22] and adding ground 4 Å molecular sieves to the reaction medium, *N*-methylaniline **278** was observed in a 94% ^{1}H NMR yield, with trace recovery of starting material **277** (entry **1**). First, control reactions were performed without catalyst, base, or molecular sieves. These control reactions rule that this could be a background, base mediated

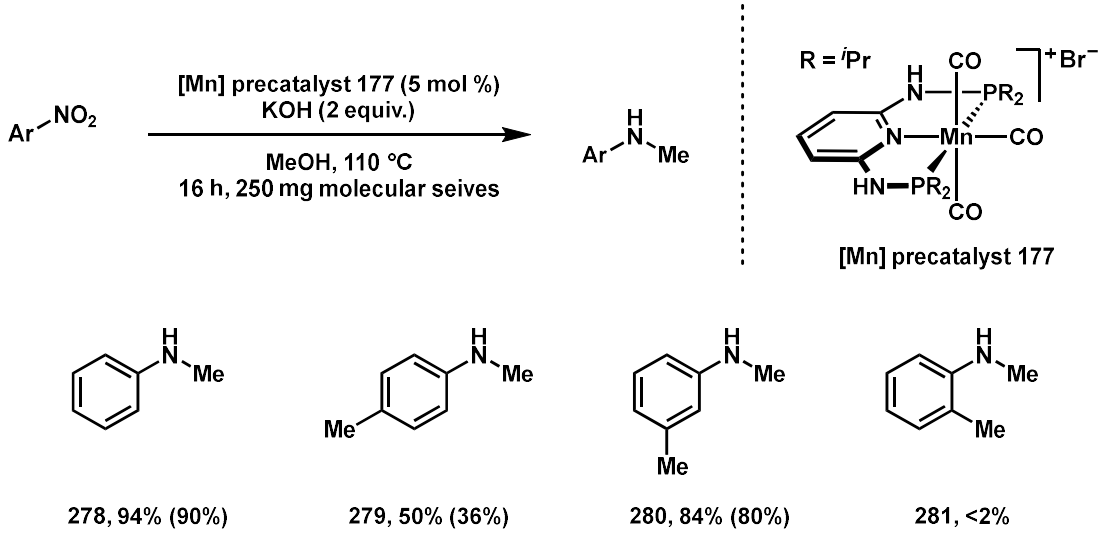
process,[23] as reaction without the addition of precatalyst **177** shows <2% of product **278** by ^{1}H NMR spectroscopy (entry **2**). These results also highlight the necessity of KOH as base, as reaction without base also results in <2% of **278** observed ^{1}H NMR spectroscopy (entry **3**). This can be attributed to the base being required for catalyst activation, and aiding in condensation processes during the methylation part of this tandem reaction. As for the molecular sieves, it was observed that in their absence, product **278** was once again observed in <2% yield by ^{1}H NMR spectroscopy. It is plausible that the acidic properties[24] of these compounds could promote either the reductive or alkylative parts of the process, but equally the ability of these compounds to sequester water could be beneficial throughout the reaction. Entries **5**-**6** show the effect of altering molecular sieve amounts. First, the quantity of molecular sieves was doubled. This results in a decrease in ^{1}H NMR yield of **278** to 79%, which can be tentatively attributed to poor mixing due to the large amount of insoluble material now present. When changing the molecular sieves away from dust to balls, it was observed that only 36% of **278** formed by ^{1}H NMR. This demonstrates that high surface area of the dust molecular sieves was crucial for efficient reactivity. Entry **7** shows the effect of halving base loading - a decrease in ^{1}H NMR yield of **278** to 49%, showing the necessity for 2 equivalents of base in this reaction. In a brief base screen (entries **8**-**11**), it was observed that potassium hydroxide was the optimal base for the reaction - sodium methoxide, potassium *tert*-butoxide, potassium carbonate, and sodium hydroxide bases were unable to obtain comparable yields to potassium hydroxide (4, 61, 83, and 83% ^{1}H NMR yield respectively). Entries **12**-**14** show a catalyst screen of the other common base metal catalysts utilised in borrowing hydrogen literature.[25] Under these altered conditions, catalyst **46** shows greatly decreased efficacy, resulting in only 14% ^{1}H NMR yield (*cf.* table **5.1**), but with extensive loss of the starting material **277**. Similarly, both iron catalysts screened (**55** and **63**) showed only trace amounts of product formation (4 and 2%), with extensive decomposition of the starting material, observed by ^{1}H NMR spectroscopy. In addition, in entry **15**, halving the volume of added methanol resulted in poor recovery of **277**, and moderate production of **278**; 24 and 33% by ^{1}H NMR spectroscopy. This can be attributed to loss of solvent methanol under these high temperatures leading to poor mixing, insufficient methanol for further methylation, and decomposition of the reactants and intermediates under highly concentrated conditions. Entry **16** shows the result of halving catalyst loading, which

resulted in a 74% ^{1}H NMR yield of **278**. Finally, a reduction in reaction temperature to 80 degrees resulted in <2% observation of product **278** by ^{1}H NMR spectroscopy, indicating that elevated temperatures were necessary to perform this reaction (entry **17**).

Throughout the course of this optimisation, no dimethylation was observed by ^{1}H NMR spectroscopy, demonstrating the selectivity of this procedure towards monomethylation, despite the excess of methanol present in the reaction mixture.

5.2.2. Substrate scope

With optimised conditions in hand, the scope of this reaction was investigated. Initial experiments simply utilised the variation of nitrotoluenes, to assess how mild steric encumbrance and mild electron-donating groups affected the reaction (scheme **5.14**, ^{1}H NMR yields determined by ^{1}H NMR spectroscopy of the crude reaction mixture, relative to 0.5 equivalents of mesitylene as internal standard, isolated yields shown in parentheses).

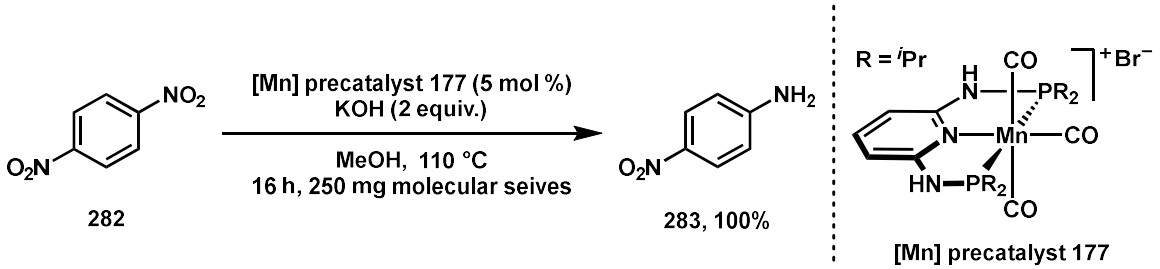


Scheme 5.14 - Nitrotoluene scope under standard conditions

As can be seen from the array of products, compared to model product **278**, *para*-methylated product **279** gave only 50% conversion (observed by ^{1}H NMR spectroscopy). This change in yield was attributed to electronics. That even this

small alteration resulted in such a change in yield indicated that this reaction was highly sensitive to electronic changes about the nitro-moiety. A *meta*-methyl substituent however had only a small impact on the yield of the reaction, with the product **280** isolated in 80% yield. Finally, an *ortho*-methyl substituent resulted in complete preclusion of hydrogenation, with only starting material being returned (no visible product **281** by ^{1}H NMR spectroscopy). This can be attributed to steric shielding of the nitro-group, resulting in no observable reduction of the starting material.

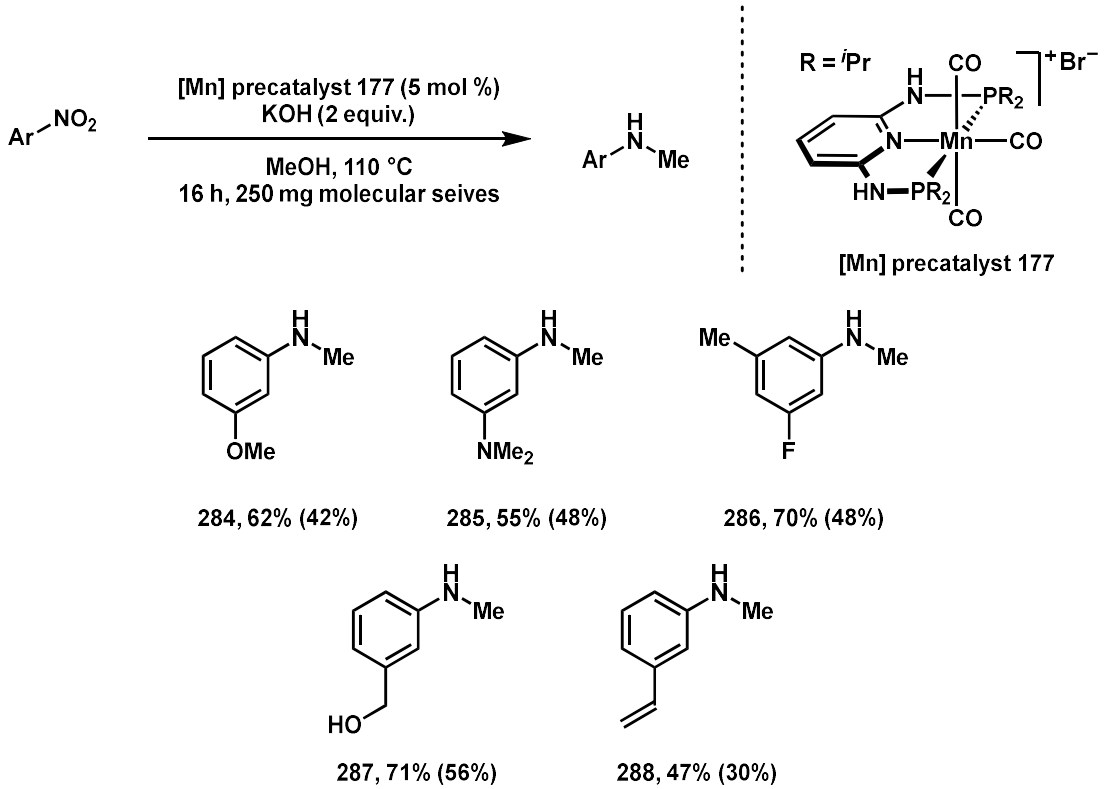
While the reaction was clearly sensitive to electron-donating substituents in this position, it was suggested that electron-withdrawing substituents in the *para*-position might be tolerated. Dinitrobenzene **282** was employed to test this hypothesis (scheme **5.15**).



Scheme 5.15 - Reduction of substrate 282

This demonstrated another facet of the electronic sensitivity of this process: substrates with electron-donating groups in the *para*-position inhibit reduction of the nitro-group. However, electron-withdrawing groups in the *para*-position rendered the nitro-group capable of reduction, but the subsequently formed aniline was electron poor, reducing its reactivity towards further methylation. Product nitroaniline **283** demonstrated both of these facets - an electron-donating group precluded further reduction of the second nitro-moiety, while an electron-withdrawing group precluded alkylation of the formed amine.

This in turn led to a scope of primarily *meta*-substituted nitroarenes giving positive results, as here the electronic effects at the nitro-group may be minimised by such substrates.

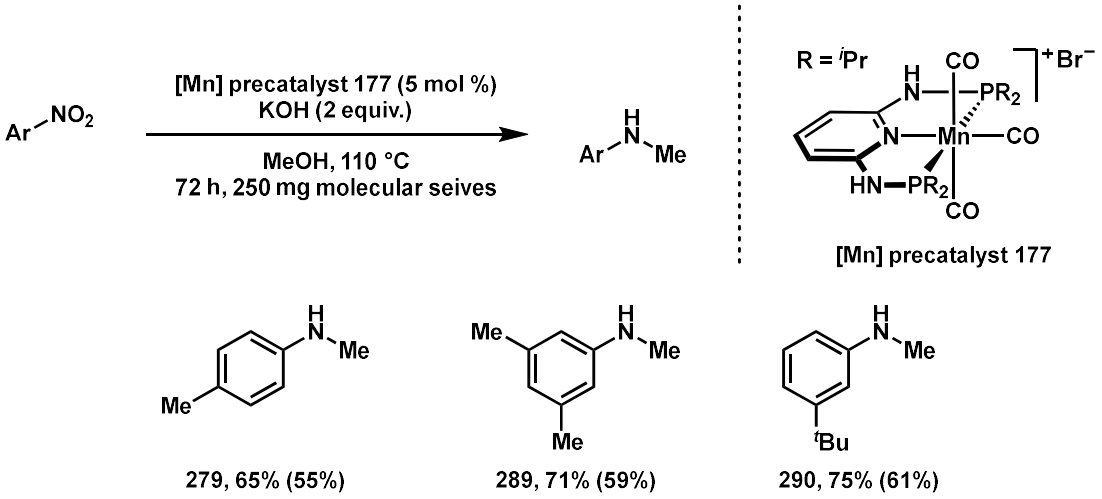


Scheme 5.16 - Further products obtained under standard conditions

Scheme **5.16** shows further products of this reaction under standard reaction conditions (crude yields determined by ^{1}H NMR spectroscopy of the crude reaction mixture, relative to 0.5 equivalents of mesitylene as internal standard, isolated yields in parentheses). Products 3-methoxy-*N*-methylaniline **284** and *N*^{1},*N*^{1},*N*^{3}-trimethylbenzene-1,3-diamine **285** demonstrated that electron-donating substituents were tolerated much better in the *meta*-position than the *para*-position, with moderate isolated yields (42% for **284**, and 48% for **285** respectively). These results demonstrated that lessening electron density at the nitro-group was key to allowing electron-donating group tolerance. Mass balance, however, was lost in these cases, with only product being returned, and no remaining starting material observable by ^{1}H NMR spectroscopy. Product 3-fluoro-*N*,5-dimethylaniline (**286**) demonstrated a sole example of halide tolerance (as a functional group for further elaboration[26]) in 70% yield by ^{1}H NMR spectroscopy, but was isolated in moderate yield (48%). Once again ^{1}H NMR spectroscopy of the crude reaction mixture shows a loss of mass balance, indicating decomposition of the starting material. Alcoholic product (3-(methylamino)phenyl)methanol **287** was isolated in moderate yield (56%), despite the possibility for oxidation under the reaction conditions, or potential for this alcohol to act as an alkylating agent in its own right. Loss of mass balance

was again observed in this case. Furthermore, product 3-vinyl-*N*-methylaniline **288** was recovered in a 30% isolated yield. While this was a poor yield, it was observed in the ^{1}H NMR spectrum of the crude reaction that (despite the styryl moiety) no reduction of this alkene occurs in the reaction. This demonstrates a tolerance of reducible functional groups. Loss of mass balance in this case can be attributed to decomposition of starting material or product, and complex mixtures were observed in the ^{1}H NMR spectrum of the crude reactions.

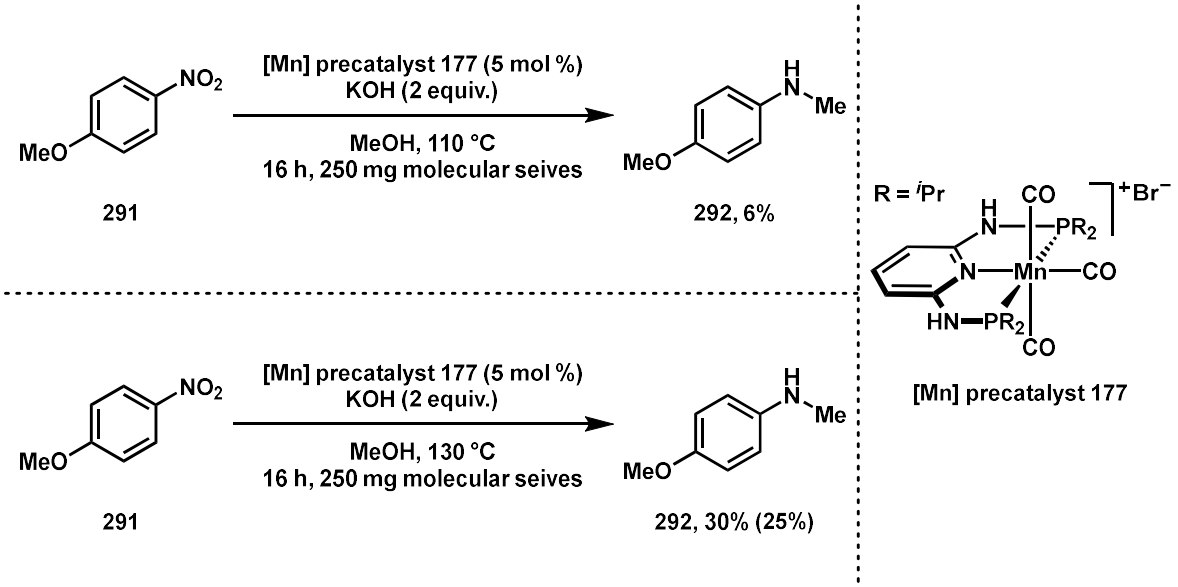
Alternative conditions were then investigated, in order to allow more difficult substrates to react fully. The following products were all ones that showed intermediate results under standard conditions, but gave mass balance with remaining starting material (for example, the substrate of **279**, 4-nitrotoluene). Therefore by increasing reaction time, the yield of these products could be increased (scheme **5.17**, crude yields determined by ^{1}H NMR spectroscopy of the crude reaction mixture, relative to 0.5 equivalents of mesitylene as internal standard, isolated yield in parentheses).



Scheme 5.17 - Modified conditions with increased time

By increasing reaction time to 72 hours, good ^{1}H NMR yields were observed across a small range of methylated and butylated nitroarenes, yielding products **279**, **289**, and **290** in 55%, 59%, and 61% isolated yields. In these cases, after elongated reaction time, residual starting material or mass balance was no longer observed by ^{1}H NMR spectroscopy of the crude reaction mixture. Nevertheless, these results yielded an improvement on previous yields at lower reaction times, especially for product **279** (*cf*. scheme **5.14**).

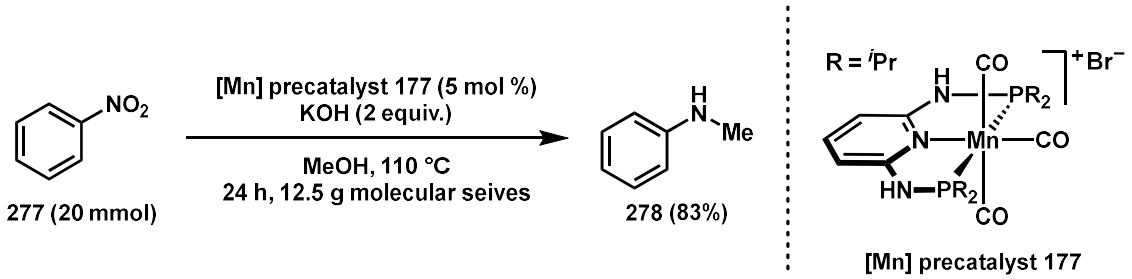
A method for utilising yet more unreactive substrates was then sought, to expand the scope of the reaction. Taking *para*-nitroanisole **291** as a target substrate, standard reaction conditions, and conditions at elevated temperature were utilised (scheme **5.18**, crude yields determined by ^{1}H NMR spectroscopy of the crude reaction mixture, relative to 0.5 equivalents of mesitylene as internal standard, isolated yield in parentheses).



Scheme 5.18 - Forcing conditions for substrate 291

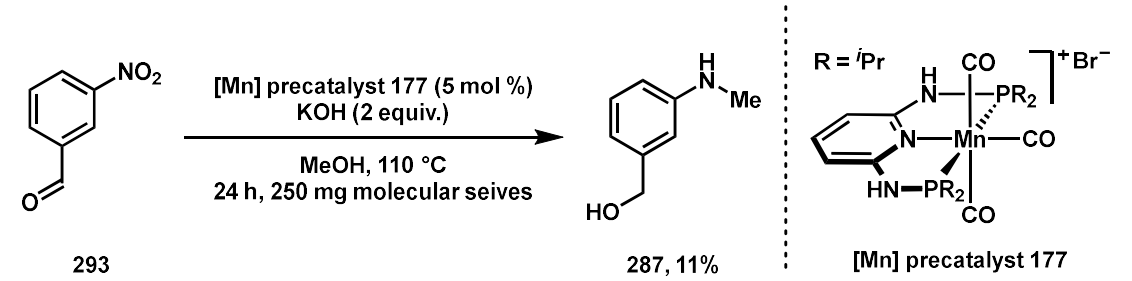
An increase from 6% of desired 4-methoxy-*N*-methylaniline **292** (under the standard conditions) to 30% (under the modified conditions) was observed by ^{1}H NMR spectroscopy of the crude reaction mixture. Despite this poor yield, this demonstrated tolerance of a problematic, *para*-electron-donating group with this procedure, having previously demonstrated sensitivity to this substrate. Product **292** was isolated in 25% yield.

Finally, a reaction was performed at elevated scale in order to demonstrate the utility of this procedure (scheme **5.19**). Product **278** was isolated in 83% yield at 20 mmol scale, although the pressure of gases in the used reactor tube had to be alleviated during the reaction for efficient conversion. This was achieved by cooling the reaction to room temperature after 8 hours, and opening the reaction vessel to release gas pressure. The reaction was then stirred at 110 °C for a further 16 hours. While this resulted in a loss of atom economy, it was necessary to drive the reaction forward.



Scheme 5.19 - Twenty mmol scale reaction

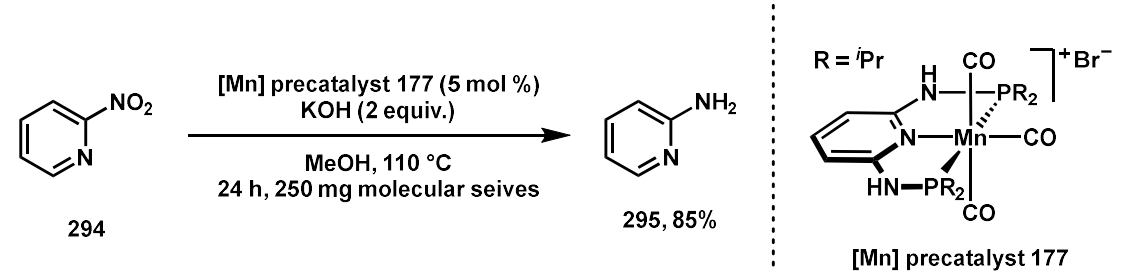
When other substrates were exposed to standard reaction conditions, interesting and unanticipated results were observed. For example, when aldehyde **291** was employed as substrate, both aldehyde reduction, and reduction-*N*-methylation were observed, resulting in the sole observation of product **287** again, in 11% ^{1}H NMR yield (scheme **5.20**, ^{1}H NMR yield calculated by ^{1}H NMR spectroscopy of the crude reaction mixture, relative to 0.5 equivalents of mesitylene as internal standard).



Scheme 5.20 - Global reduction–*N*-methylation of substrate 293

In addition to this, complete loss of starting material was observed by ^{1}H NMR spectroscopy, indicating the poor compatibility of aldehydes in this procedure.

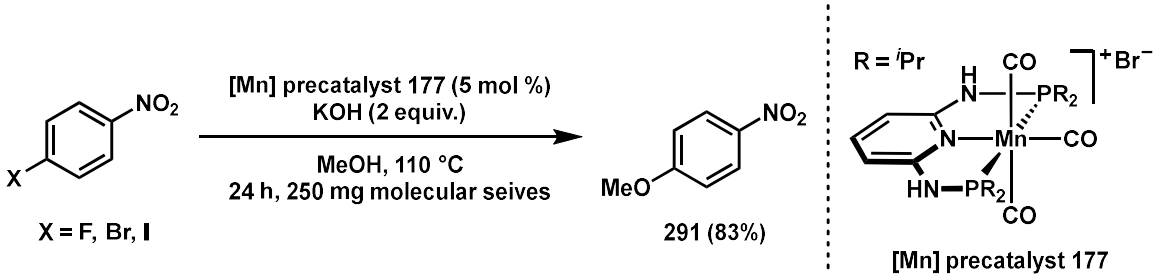
Other compound yielded exclusive reduction in their products, such as was show before with 1,4-dinitrobenzene (**282**, scheme **5.15**). When employed in this transformation, pyridine **294** underwent reduction only (scheme **5.21**).



Scheme 5.21 - Exclusive reduction of nitropyridine 294

The reduced product, 2-aminopyridine **295** was isolated in 85% yield. Despite this substrate being precluded from alkylation (due to the electron poor nature of the amine), this example demonstrates that heteroaromatic substrates were tolerated by this procedure, and did not result in a loss of reactivity.

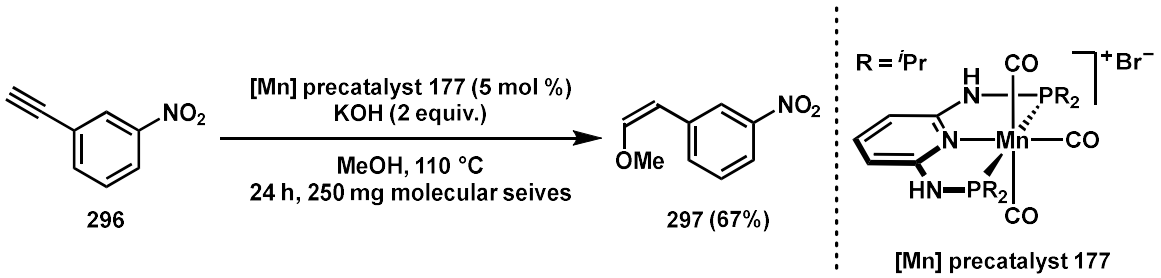
With a range of *para*-halogenated compounds screened, S_NAr-type processes were observed, recovering only nitroanisole **291** (scheme **5.22**).



Scheme 5.22 - The reactivity of *para*-halogenated compounds

Product **291** was isolated in 83% from the S_NAr reaction of *para*-fluoronitrobenzene with methanol, under basic conditions. In this instance it can be surmised that any occurring S_NAr reaction was significantly faster than the reduction, due to the sole isolation of product **291** (>95% by ^1H NMR spectroscopy of the crude reaction mixture), with no reduction-*N*-methylation observed. However, there is precedent in the literature to suggest manganese insertion into carbon-halogen bonds.[27] This could provide a plausible alternative route to **289** from bromo- and iodonitrobenzene substrates, as opposed to S_NAr reactions.

Substrate **296** (1-ethynyl-3-nitrobenzene) underwent hydroetherification under the reaction conditions[28] (scheme **5.23**).

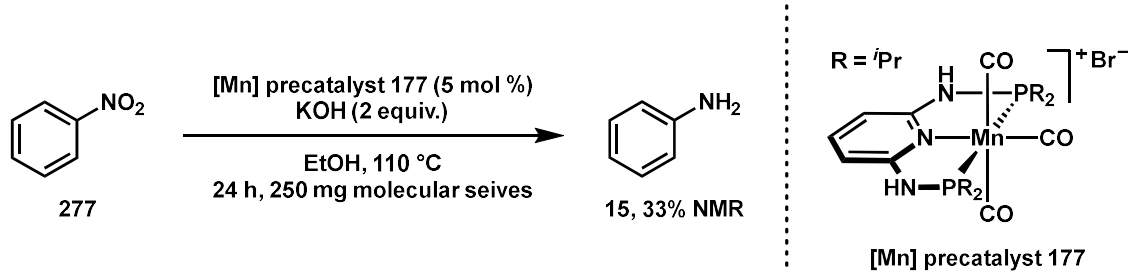


Scheme 5.23 - Hydroetherification of substrate 296

Enol ether **295** was isolated in a 67% yield from the reaction mixture. It was observed by ^1H NMR that this reaction yields exclusively the (*Z*)-enol ether, showing

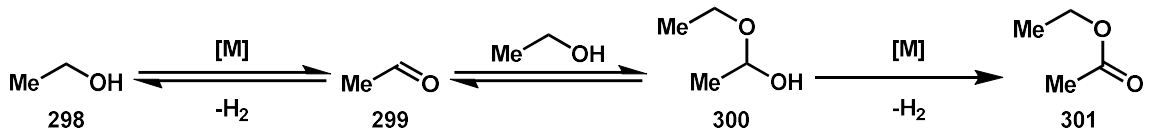
selective anti–Markovnikov functionalisation. However, in the absence of the catalyst, enol ether **297** was observed in 73% ^{1}H NMR yield, demonstrating that only KOH and methanol were required for this background transformation.

Finally, when using ethanol in the place of methanol under standard reaction conditions, only transfer hydrogenation of **277** was observed (scheme **5.24**), with no observed ethylaniline formation by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. However, aniline **15** was observed in 33% NMR yield (^{1}H NMR yield determined by spectroscopy of the crude reaction mixture, relative to 0.5 equivalents of mesitylene).



Scheme 5.24 - The use of ethanol in place of methanol

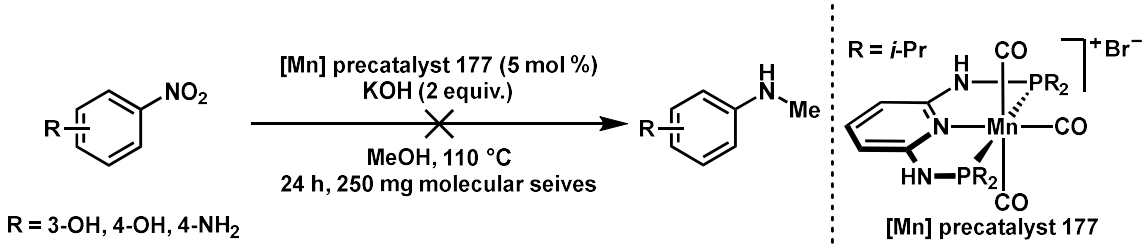
This unusual result indicates that further reaction of aniline with formed acetaldehyde was either precluded in some fashion, or that other side reactions sequester the acetaldehyde *in situ*. There are examples of the utility of ethanol as a reducing agent alone,[29] with selected literature reporting the formation of ethyl acetate from ethanol under similar transfer hydrogenation conditions[29d] (scheme **5.25**).



Scheme 5.25 - Generation of ethyl acetate from ethanol, under dehydrogenative conditions

This provides a plausible route for the removal of acetaldehyde from the reaction mixture, which in turn would lead to selective reduction of **277**, without sequential alkylation. However, ethyl acetate production was not observed *via* ^{1}H NMR spectroscopy of the crude reaction mixture, so this rationale remains tentative.

Many substrates were incompatible with this procedure. Examples include screened nitrophenols, and nitroaniline (scheme **5.26**).



Scheme 5.26 - Reactions with aniline and phenol substrates

Here, returned starting material was fully recovered, indicating neither decomposition pathways, nor desired reactivity of these substrates. This was tentatively attributed to either large electron-donating ability precluding reduction, or potential coordination of the heteroatom to the catalyst, resulting in a loss of reactivity.

Furthermore, a range of *meta*-substituted substrates were employed to investigate the tolerance of this reaction towards electron-withdrawing, halogenated, or other reducible functional groups (figure **5.2**).

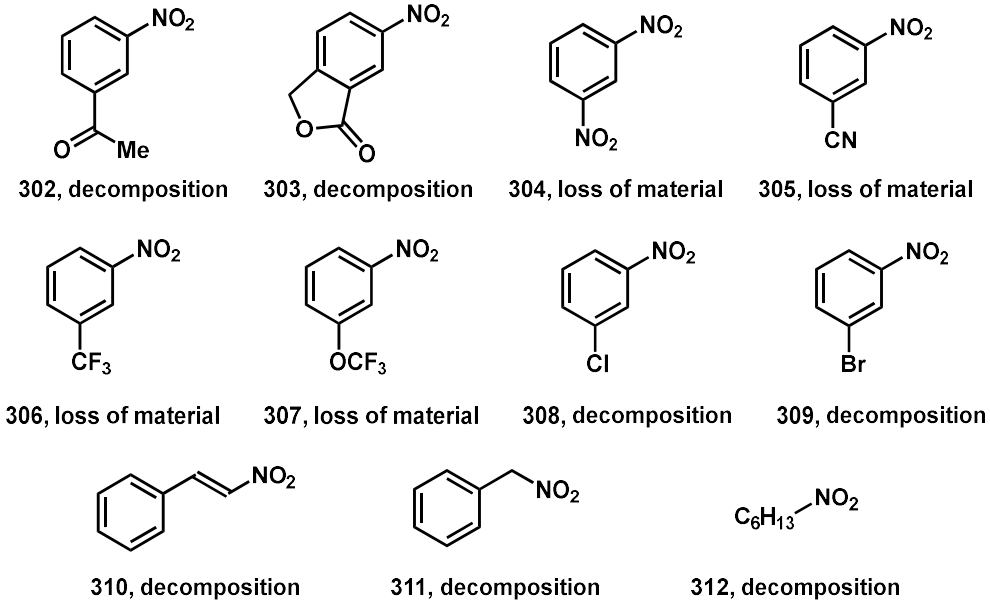


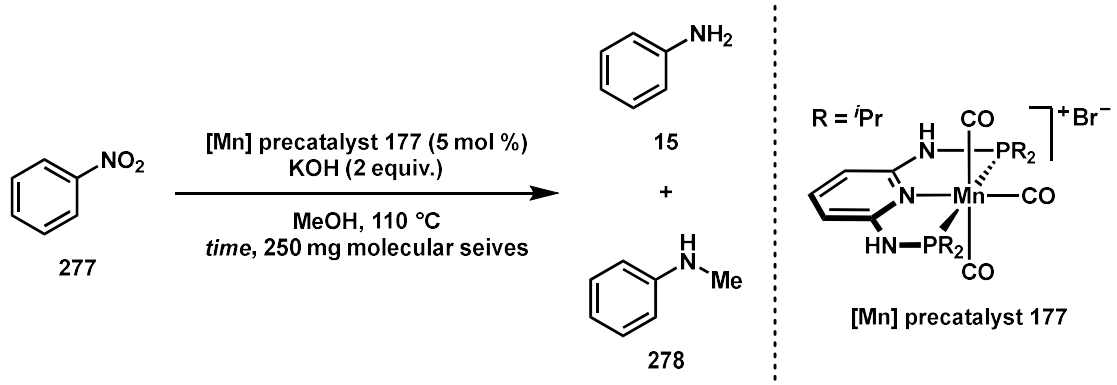
Figure 5.2 - Unproductive substrates

A range of electron-withdrawing substituents were employed in this reaction. Substrates **302** and **303** demonstrated the poor tolerance of this reaction towards carbonyl compounds beyond the previously discussed product **293** (scheme **5.20**), as both of these compounds resulted in the formation of a complex mixture, observed by ^{1}H NMR spectroscopy of the crude reaction mixtures. This can be tentatively attributed to decomposition pathways, or polymeric reactivity with the

formed anilines. By contrast, substrates **304-307** resulted in the loss of all observable material by ^{1}H NMR spectroscopy of the crude reaction mixture, which could be tentatively attributed to competing side reactions. Next, a range of other *meta*-halogenated nitroarenes were employed. Despite the success of product **286** (scheme **5.16**), these other compounds (substrates **308** and **309**) result in formation of complex mixtures, as observed by ^{1}H NMR spectroscopy of the crude reaction mixtures. As before, this could be tentatively attributed to manganese insertion into carbon-halogen bonds,[27] and further undesired reactivity. Similar results were observed during the screening of other nitrated compounds besides nitroarenes. *β*-nitrostyrene **310** and nitroalkanes **311** and **312** gave similar complex mixtures, observed by ^{1}H NMR spectroscopy of the crude reaction mixture.

5.2.3. Mechanistic studies

With substrate scope completed, mechanistic studies were performed to ascertain how this reaction occurred. First, time course experiments were investigated. Here, the intent was to observe the *in situ* generation of intermediates in this reaction, thus providing evidence towards a plausible mechanistic hypothesis. These data were gathered by myself and Nicolas Mast, a visiting student. Table **5.3**, and graph **5.1** show the details (^{1}H NMR yields determined by spectroscopy of the crude reaction mixture, relative to 0.5 equivalents of mesitylene as internal standard).

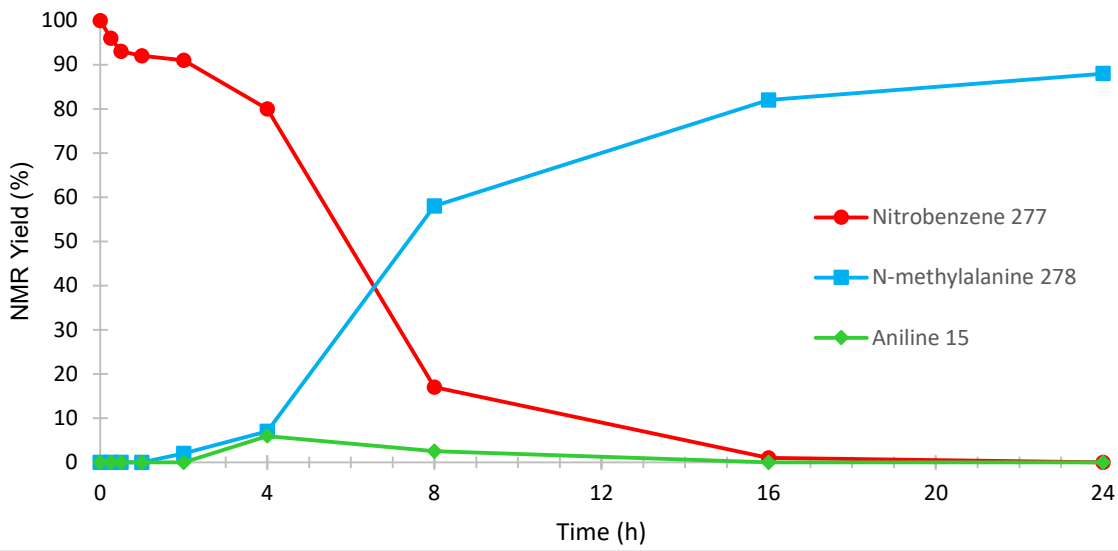


Entry	Time (h)	277 (% NMR yield)	15 (% NMR yield)	278 (% NMR yield)
1	0	100	0	0

2	0.25	96	0	0
3	0.5	93	0	0
4	1	92	0	0
5	2	91	0	2
6	4	80	6	7
7	8	17	2.5	58
8	16	1	0	82
9	24	0	0	88

Table 5.3 - Time course experiment results

Graph 5.1 - Time course experiment



Intermediate aniline **15** was observed by ^{1}H NMR spectroscopy after 4 and 8 hours. However, a long induction period can be observed, with clear consumption of starting material **277**. This consumption can be attributed to potential decomposition of nitrobenzene **277**, or to some activation sequence that involves consumption of such material. However, once the active catalyst was obtained (*ca* 2 hours), clean conversion of **277** into product **278** can be observed. Due to this long induction time, the stability of the catalyst under the reaction conditions was subsequently investigated, as the formation of a heterogeneous species was in question.[30]

In order to assess the stability of the catalyst, IR spectroscopy was employed. It was suggested that if the catalyst was decomposing into a heterogeneous manganese species, the IR stretching frequencies corresponding to the carbonyl ligands bound to the metal centre would be lost throughout the reaction. The precatalyst was analysed by IR spectroscopy, and aliquots from the reaction mixture taken at t = 0

h and t = 6 h to assess its stability during the reaction. Figures **5.3**-**5.5** show the corresponding spectra.

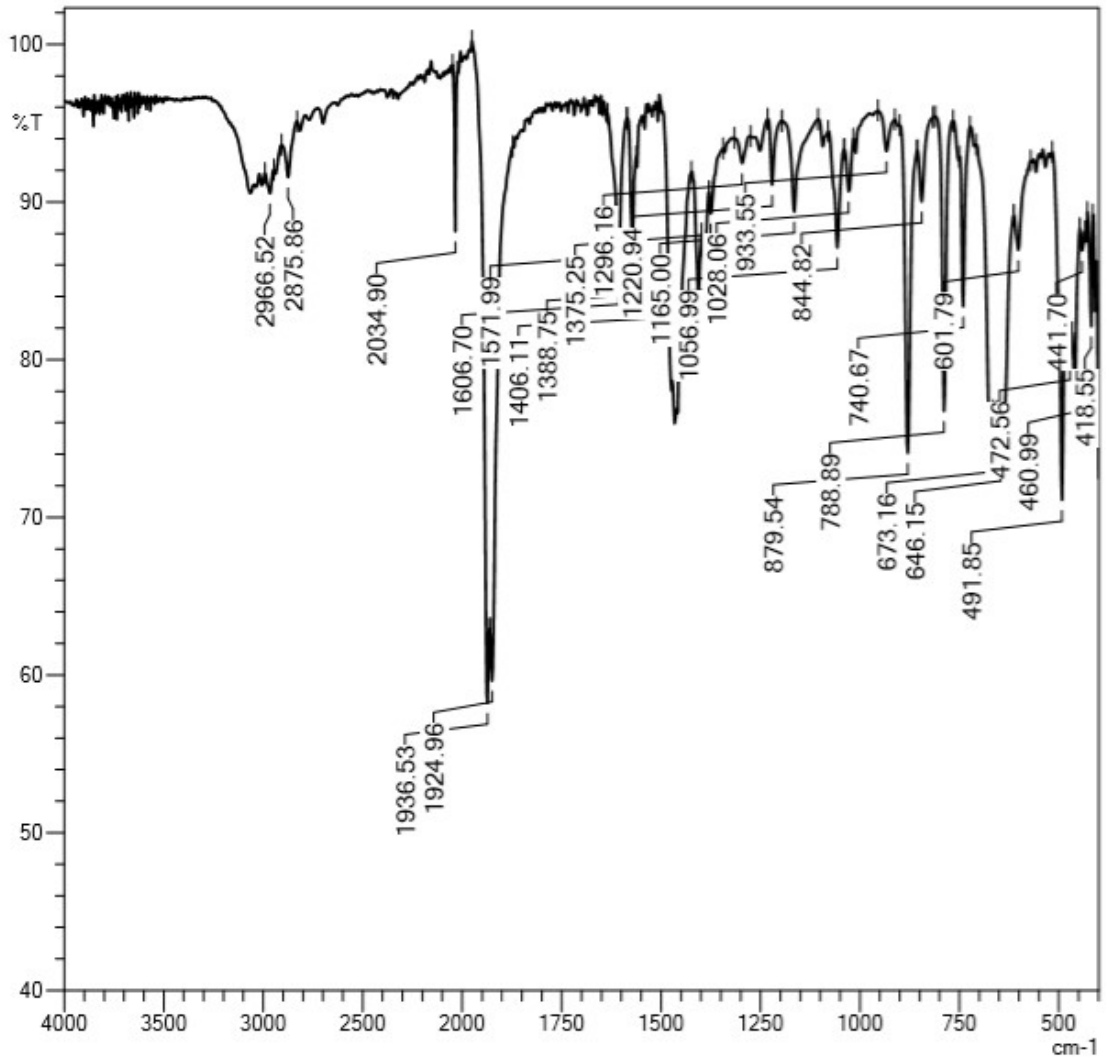


Figure 5.3 - IR spectrum of precatalyst 177

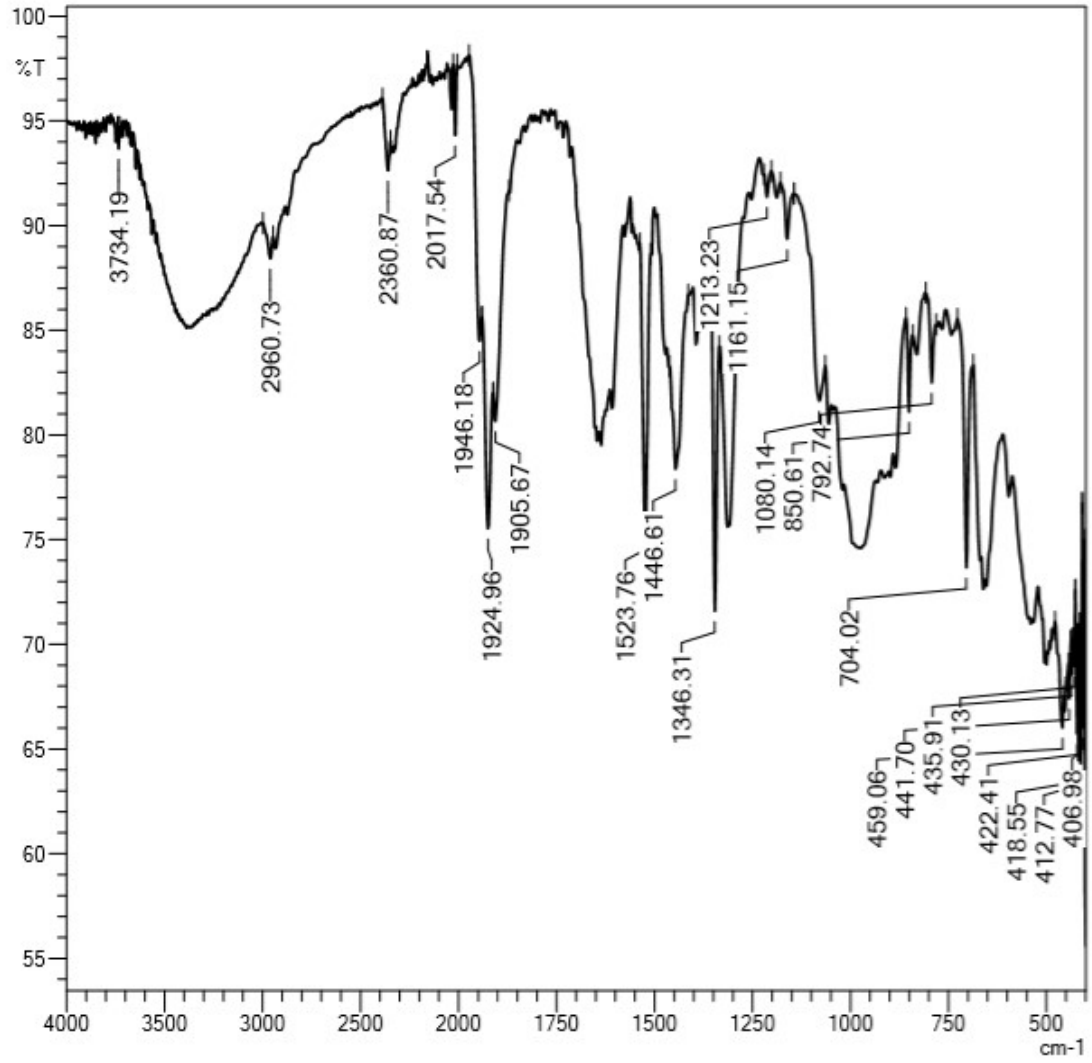


Figure 5.4 - IR spectrum of the reaction mixture at t = 0 h

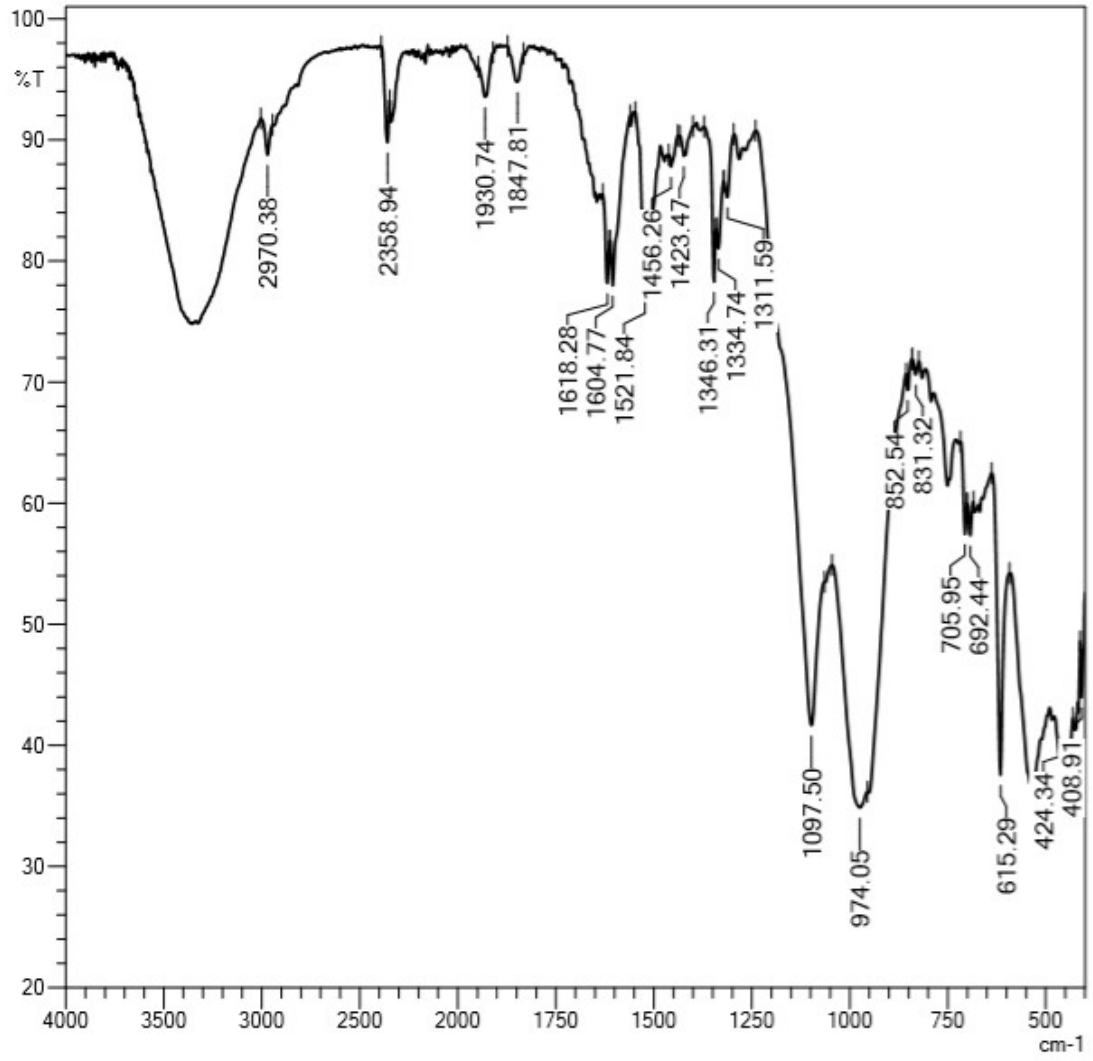
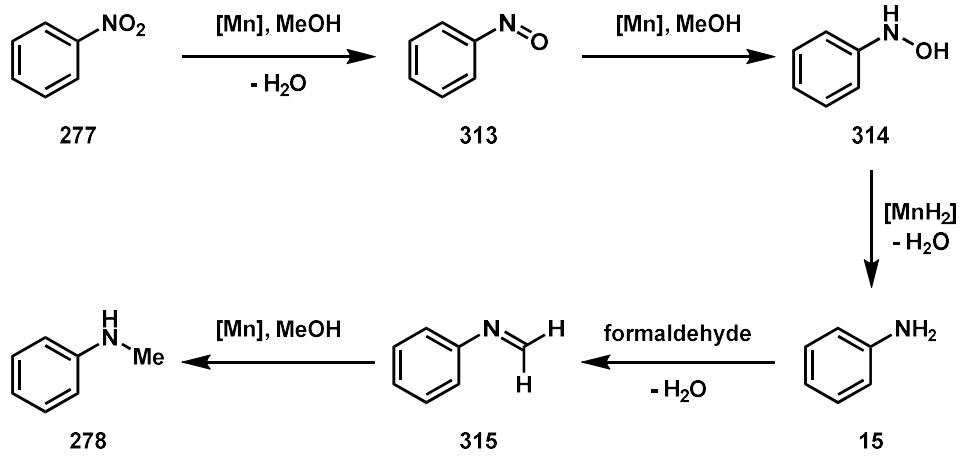


Figure 5.5 - IR spectrum of the reaction mixture at t = 6 h

The indicative peaks of the catalyst are the carbonyl peaks, observed 1937 and 1925 cm^{-1}. It was observed that, at t = 0 h, corresponding carbonyl peaks at 1925 cm^{-1} were still present, as well as others, presumably from coordination of methanol or other reactants to the catalyst. However, at t = 6 h, a smaller peak at 1931 cm^{-1} was observed.

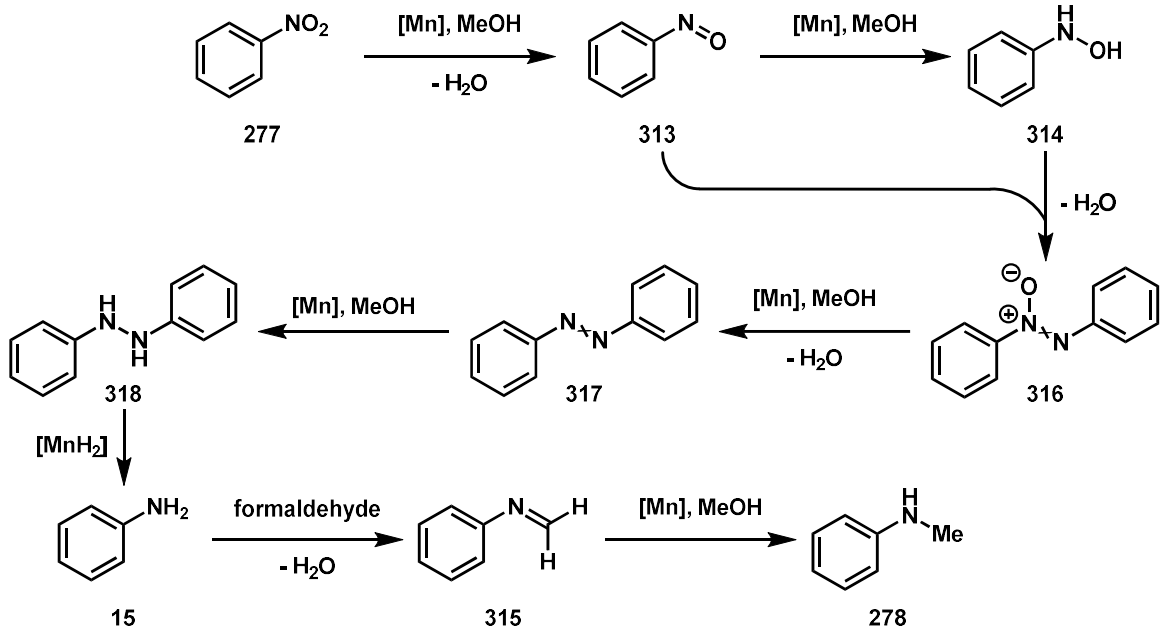
This ambiguous result neither precluded the formation of an active heterogeneous species, nor proved the formation of one. Likewise, that a carbonyl peak can be observed was evidence towards the existence of a homogeneous species. Therefore, the plausible mechanism suggested for this reaction will be one for the homogeneous species that can be observed. Regardless, the formation of an active heterogeneous species was a possibility that could not be excluded.

Next, validation of plausible intermediates was performed. An initially posited mechanism, involving sequential transfer hydrogenations to the nitro-group, involved four plausible intermediates (scheme **5.27**).



Scheme 5.27 - Inital mechanistic hypothesis

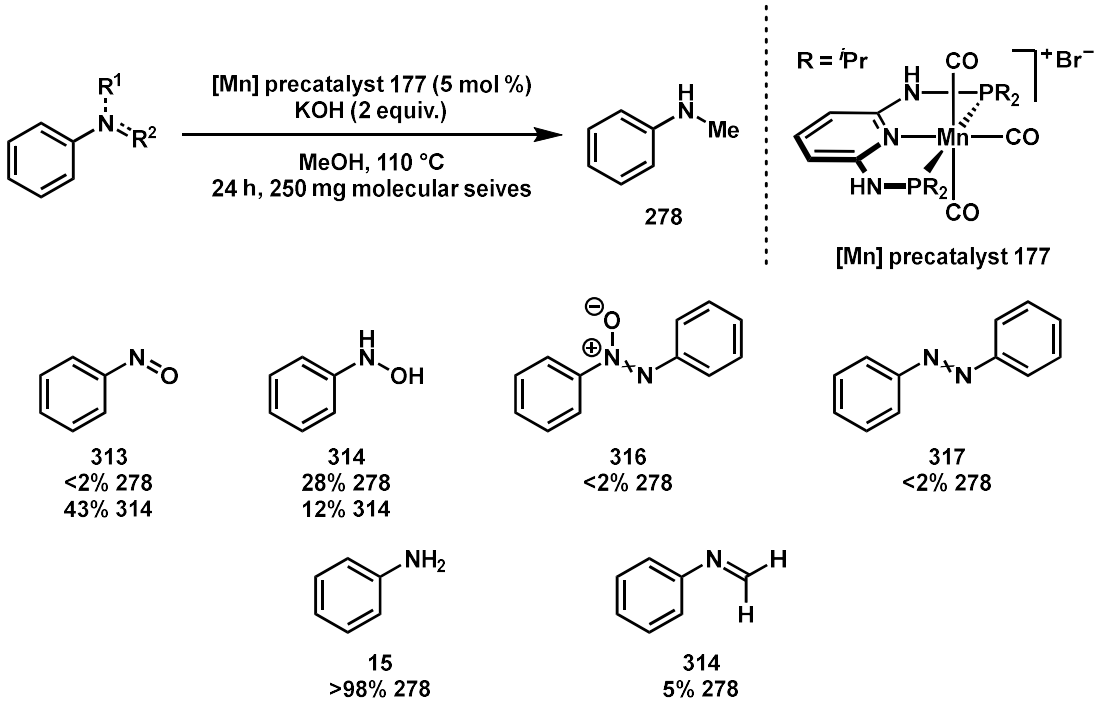
Nitrosobenzene **313**, *N*-phenylhydroxylamine **314**, aniline **15**, and imine **315** are plausible intermediates for such a reaction. However, an alternative mechanistic hypothesis exists, one that is discussed in several key literature precedents,[9,17,18] involving an alternative route for reduction, *via* other intermediates (scheme **5.28**).



Scheme 5.28 - Secondary mechanistic hypothesis

Here, three other plausible intermediates can be postulated, in the form of azoxybenzene **316**, diazene **317**, and hydrazine **318**.

A range of these compounds were employed under standard reaction conditions to give evidence of which pathway was occurring in this manganese-catalysed procedure (scheme **5.29**, ^{1}H NMR yields calculated by spectroscopy of the crude reaction mixture, relative to 0.5 equivalents of mesitylene as internal standard).

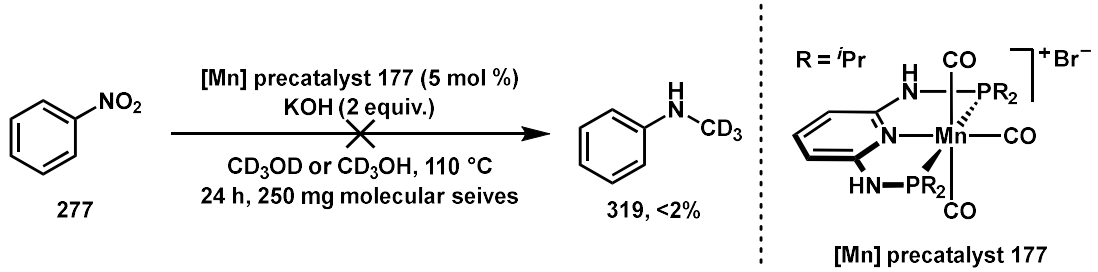


Scheme 5.29 - Validation of plausible intermediates

These compounds and their reactivity under these conditions were all studied using crude ^{1}H NMR yields. Nitrosobenzene **313** undergoes no observable conversion to *N*-methylaniline **278** under the reaction conditions, instead generating azoxybenzene **316**, observable by ^{1}H NMR spectroscopy in 43% yield. By contrast, hydroxylamine **314** forms product **278** in 28% NMR yield, with 12% NMR yield of resulting azoxybenzene **316**. When **316** and diazene **317** are employed, neither results in observable production of *N*-methylaniline **278** by ^{1}H NMR spectroscopy. Aniline **15** itself was methylated readily and efficiently, resulting in quantitative transformation to product **278**. Finally, there was minor observable transfer hydrogenation from imine **315** (synthesised by Nicolas Mast) to *N*-methylaniline **278**, yielding 5% of the target compound by ^{1}H NMR. It is noteworthy that all these reactions (with the exception of aniline **15**) occurred with extensive loss of starting material under the reaction conditions.

While these reactions do not conclusively answer which pathway this reaction is occurring by, the results of plausible intermediates **316** and **317** suggest that the mechanistic hypothesis discussed in scheme **5.28** is less plausible, as these two compounds do not yield product **278** under reaction conditions. This, combined with the results of intermediates **313** and **314** may suggest that the formation of these compounds under reaction conditions is a non-productive pathway. However, none of these compounds are observed in the time course experiment besides aniline **15** (graph **5.1**). Therefore, the lack of desired reactivity of many of these plausible intermediates can be tentatively attributed to these compounds being highly reactive under these reaction conditions. This in turn leads to their rapid consumption, and transience in the standard reaction, where they are only generated in small amounts, not observable by ^{1}H NMR spectroscopy. Their subsequent reaction could then lead to product formation. By contrast, in these mechanistic probes, these compounds are present in high concentrations. As such, side reactions could occur, leading to degradation, or the formation of non-productive side products.

Finally, deuteration experiments were conducted. Methanol-d_4, and methanol-d_3 (common deuterating agents in the literature [18]) were employed under the standard reaction conditions (scheme **5.30**).

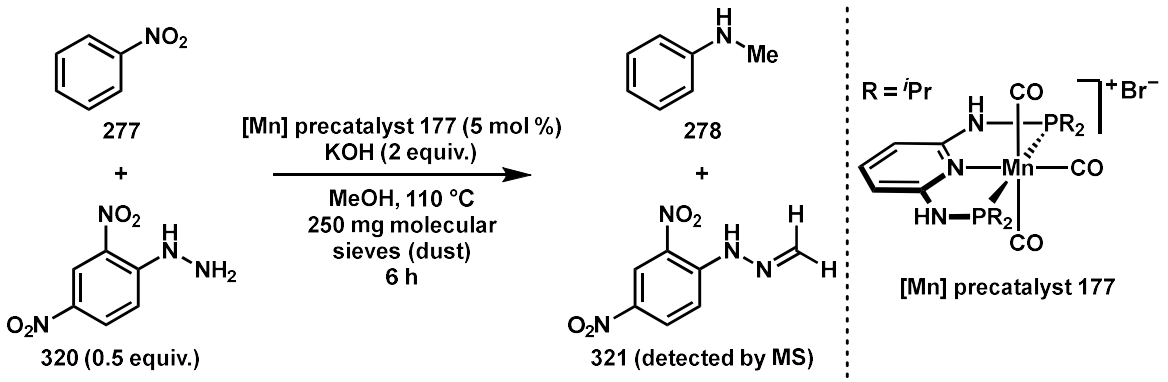


Scheme 5.30 - Deuteration experiment

No production of product **317**, or *in situ* generation of aniline **15** was observed by ^{1}H NMR spectroscopy of the crude reaction mixture under these conditions. This was attributed to initial reduction of the nitroarene being sufficiently retarded by the kinetic isotope effect such as to preclude any reactivity, resulting in only returned starting material in this case.

Next, investigations were undertaken to test the reaction vial for the presence of reactive gases. This was in order to observe the production of formaldehyde, and to test for production of hydrogen gas. Formaldehyde was detected *via* addition of an

acidic solution 2,4-dinitrophenylhydrazine to the crude reaction mixture, and subsequent GCMS of the resulting mixture (scheme **5.31**).

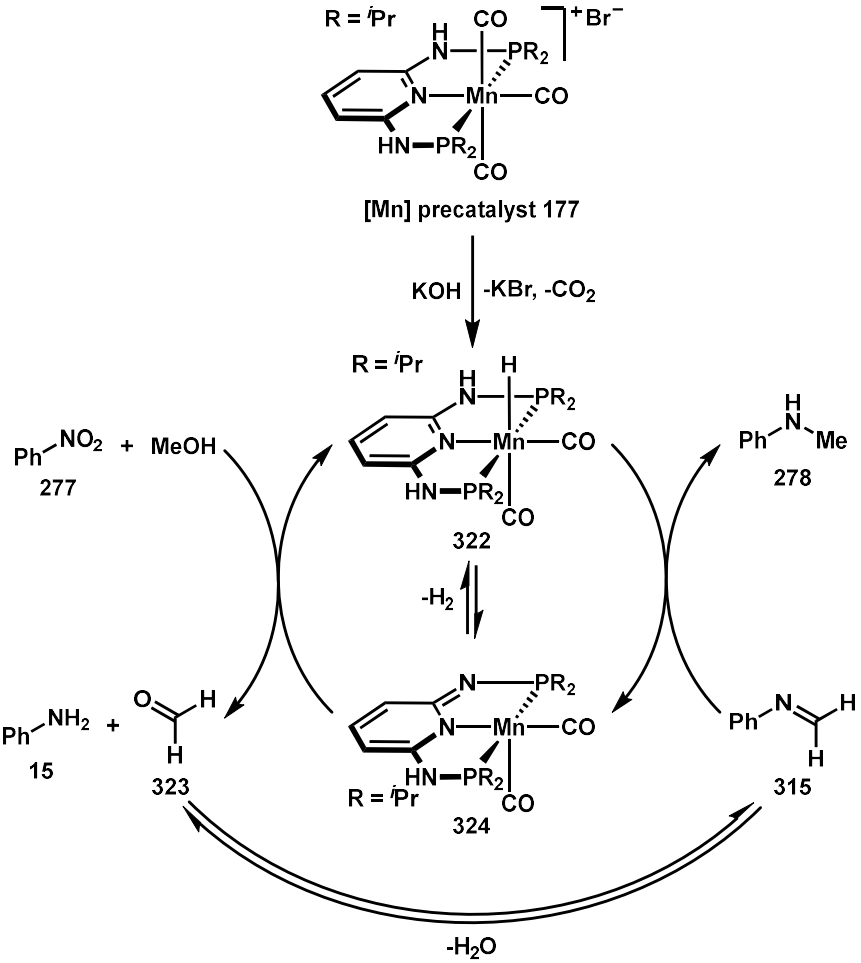


Scheme 5.31 - Detection of formaldehyde

The product hydrazone, 1-(2,4-dinitrophenyl)-2-methylenehydrazine **321**, was detected by low resolution mass spectroscopy, demonstrating the production of formaldehyde *in situ*.

In order to observe the production of hydrogen gas, the headspace of a reaction was sampled *via* a gas syringe after 6 h. This gas sample was then subjected to gas chromatography, against a hydrogen standard. Both samples demonstrated similar retention times, providing evidence for the generation of hydrogen gas by the catalyst *in situ*.

With these results in hand, and previously performed work in the literature,[20,21,22] the following mechanistic hypothesis can be suggested (scheme **5.32**). This mechanism begins with Heiber-type activation of the complex,[32] resulting in the formation of catalytically active manganese hydride species **322**, as well as the extrusion of potassium bromide, and carbon dioxide. Here, loss of hydrogen can generate manganese complex **324**, which has a vacant coordination site. Transfer hydrogenation processes can now reduce nitrobenzene **277** to aniline **15**, with concurrent generation of formaldehyde **323** from methanol, and a corresponding manganese hydride species **322.** Formaldehyde **323** and aniline **15** can now condense to form imine **315**. The formed manganese hydride complex **322** can now hydrogenate the formed imine, yielding target *N*-methylaniline **278**, and regenerating manganese complex **322**.



Scheme 5.32 - Plausible mechanistic hypothesis

As imine **315** was neither observed during the time course experiments, nor productive under the reaction conditions, it is plausible that this intermediate was consumed rapidly under the reaction conditions. Likewise, as the specifics of how the nitroarene reduction occurs, and what intermediates this transformation proceeds by are not known at this time, this scheme is left generic.

5.2.4. Future work

While this reaction is the first example of an earth-abundant transition metal catalysis for this one-pot process, the transformation suffers from poor yields, high electronic sensitivity, and an substrate scope that demonstrates incompatibility towards a wide range on functional groups. This significantly limits the broader synthetic utility of this reaction. Thus, clear future work would be to investigate

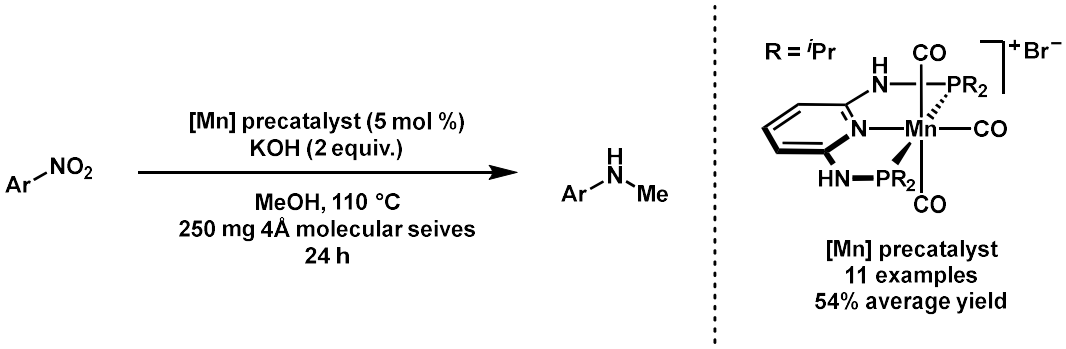
alternative precatalysts that could lead to a more functional group tolerant, broader substrate scope. However, as many of the commonly used earth-abundant metal precatalysts were screened in this work, this could also involve the design of specific (pre)catalysts for such a process. Once such a process is found with greater functional group tolerance, applications towards the synthesis of pharmaceutically active intermediates could be explored. However, given the small range of compatible substrates in this reaction, no attempts at functionalising pharmaceutically relevant molecules were undertaken.

Additionally, the unanswered questions about the identity of the catalytically activate species; *i.e.* whether this a homogeneously or heterogeneously-catalysed transformation are good points for further investigation. While there are many available techniques to probe the phase of a catalyst in a catalytic reaction,[31] powerful and general techniques include mercury poisoning experiments, quantitative or partial ligand poisoning experiments, or hot filtration tests. In this case, both mercury poisoning and hot filtration test may prove inadequate; this reaction requires molecular sieves to occur, hence removing them from the reaction media by filtration may well disrupt the reaction and yield a false positive. Likewise, mercury metal, while being known to form amalgams with metal particles, can often give rise to side reactions, increasing the chances of a false positive. Furthermore, ligand poisoning experiments often display a thermal component, with dissociation possible at elevated temperatures. This would again yield false positives. Other routes would need to be investigated in order to assess the phase of the active catalyst.

5.3. Summary

In summary, the first earth-abundant transition metal-catalysed process for the one-pot conversion of nitroarenes to *N*-methylarylamines was demonstrated, using methanol as both alkylating agent and hydrogen source. This operationally simple procedure demonstrated 11 examples in 54% average isolated yield, including a 20 mmol scale reaction (scheme **5.33**). In addition, this work was completely selective towards monomethylation. Additional experiments showed that other tolerated

compounds undergo alternative reactivity to yield a range of other products. Mechanistic work was undertaken towards a plausible mechanistic pathway. In terms of the aims and objectives, this work was able to transfer extant precious metal-catalysed reactions to the first earth-abundant metal-catalysed reaction of time type. As such, it satisfies the aims and objectives of this PhD. However, this reaction worked poorly in many cases, and not at all in others, resulting in low average yields. Further work is required to bring this transformation, using earth-abundant metal catalysts, to a stage where higher yields, and better general reactivity are possible.



Scheme 5.33 - Manganese-catalysed reduction-*N*-methylation of nitroarenes

5.4. References

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Experimental – General information

Unless stated otherwise, all reactions were performed using oven-dried glassware, and were stirred with Teflon-coated magnetic stirrer bars. Anhydrous tetrahydrofuran (THF), toluene, hexanes, dichloromethane and diethyl ether 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. Organocatalysts **117** and **325** were synthesised by James Ayres, a PhD student in the group, according to literature procedures,[1] and were assessed as pure by NMR spectroscopy.

Room temperature (rt) refers to 20-25 °C. Ice/water baths were used to obtain temperatures of 0 °C. All reactions involving heating were carried out using DrySyn blocks and a contact thermometer, unless otherwise stated. *In vacuo* refers to reduced pressure through the use of a rotary evaporator.

Analytical thin layer chromatography was carried out using aluminium plates coated with silica (Kieselgel 60 F254 silica) and visualization was achieved using ultraviolet light (254 nm), followed by staining with a 1% aqueous $KMnO_4$ solution. Flash chromatography used Kieselgel 60 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 IRAffinity-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, and ^{31}P NMR spectra were obtained on either a Bruker Avance 300 (300 MHz ^{1}H), Bruker Avance 400 (400 MHz ^{1}H, 101 MHz ^{13}C, 376 MHz ^{19}F) or Bruker Avance 500 (500 MHz ^{1}H, 126 MHz ^{13}C, 471 MHz ^{19}F, 203 MHz ^{31}P) spectrometer at rt in the solvent stated. Chemical shifts are reported in parts per million (ppm) relative to the residual solvent signal in ^{1}H and ^{13}C NMR spectra. All

coupling constants, *J*, are quoted in Hz. Multiplicities are reported with the following symbols: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and multiples thereof. The abbreviation Ph is used to denote phenyl, br to denote broad.

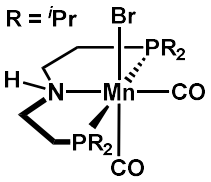
Gas chromatography (GC) was acquired at Cardiff University on a Clarus 480 Perkin Elmer gas spectrograph, at 100 °C.

Liquid chromatography - mass spectroscopy (LCMS) was acquired at Cardiff University on a Agilent 1290 Infinity UHPLC system, coupled to an Agilent 6530 quadrupole time-of-flight mass spectrometer. Chromatographic separation was achieved with a C_{18} Poroshell column (2.1 × 100 m, 2.7 µm particle size) with a gradient of water and acetonitrile, amended with 0.1% formic acid.

High resolution mass spectrometry (HRMS, m/z) data was acquired at Cardiff University on a Micromass LCT spectrometer, or at the ESPRC UK National Mass Spectroscopy Facility as Swansea University.

Metal precatalysts were synthesized according to the following literature procedures, with Kurt Polidano synthesising [Fe] precatalyst **55**, and myself synthesising the remainder.

Manganese precatalyst **46**:[2]



[Mn] precatalyst 46

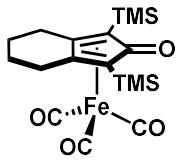
A flame dried 3-necked round bottomed flask was charged with a magnetic stirrer, manganese(I)pentacarbonyl bromide (412 mg, 1.5 mmol), under inert atmosphere. Rigorously degassed toluene (15 mL) was then added, and the reaction stirred vigorously. Bis(2-(diisoproylphoasphanyl)ethyl)amine (500 mg, 10% w/w in THF) was the added dropwise, and the reaction stirred for 10 minutes at room temperature, before heating at 100 ˚C for 24 hours, during which time the reaction colour changed from deep orange to yellow. The reaction was then cooled to room temperature, and the solvent removed under reduced pressure to yield a crude yellow gum. The crude mixture was then triturated thoroughly in *n*-heptane, utilising

sonication to break up sizable aggregates. After filtration, the product was then dried under vacuum to yield **46** (702 mg, 95%) as a yellow solid; ^{1}H NMR (400 MHz, C_6D_6) δ_H: 1.06 (6H, dd, *J* 6.7, 10.7), 1.22 (6H, dd, *J* 6.9, 12.9), 1.32 (6H, dd, *J* 7.0, 13.5), 1.52 (6H, dd, *J* 7.0, 14.5), 1.62-1.67 (2H, m), 1.90-1.99 (2H, m), 2.12-2.26 (2H, m), 2.39-2.49 (2H, m), 2.78-2.84 (1H, m), 3.28 (2H, dd, *J* 6.4, 12.0); ^{13}C NMR (101 MHz, C_6D_6) δ_C: 18.7, 19.2, 20.5, 20.7, 24.7, 26.7, 27.5, 53.0, 215.3, 220.6; ^{31}P NMR (162 MHz, C_6D_6) δ_P: 81.2.

Spectroscopic data were in accordance with the literature, and were used as a basis for purity of the material.

The metal source (manganese(I)pentacarbonyl bromide, 98%) was purchased from Alfa Aesar. Lot Z13E064 was used, and was assayed at ≥98.5% by argentometric titration. However, no trace metal anaylsis was provided for this lot. Additionally, no further analysis of this compound was performed.

Iron precatalyst **55**:[3]



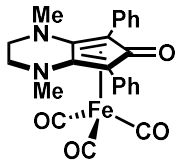
[Fe] precatalyst 55

An ACE pressure tube was charged with a magnetic stirrer, 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). The tube was then sealed, and heated in an oil bath at 140 °C for 24 h. The reaction was then cooled and concentrated in vacuo. The remaining solid residue was dissolved in boiling hexane (20 mL) and filtered hot. The filtrate was then cooled and the resulting mixture filtered, yielding **55** (2.2 g, 66% yield) as a yellow crystalline solid (needles); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.27 (18H, s), 2.47-2.65 (4H, m,), 1.73-1.92 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: -0.1, 22.6, 24.9, 71.9, 111.2, 181.4, 229.2.

Spectroscopic data were in accordance with the literature, and were used as a basis for purity of the material.

The metal source (iron pentacarbonyl) was purchased from Acros Organics. Lot A0381797 was used, and was assayed at ≥95.5. However, no trace metal anaylsis was provided for this lot. Additionally, no further analysis of this compound was performed.

Iron precatalyst **63**:[4]



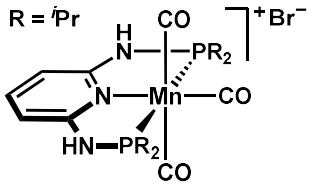
[Fe] precatalyst 63

A flame dried Schlenk flask was charged with a magnetic follower, 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 roundbottomed flask and washed several times with toluene (3 x 10 mL). The mixture was concentrated in vacuo. Purification by flash alumina chromatography (eluent = 0-1% MeOH in CH2Cl2, 50 x 200 mm alumina) gave a crude oil. Precipitation of the crude oil with diethyl ether and pentane yielded **63** (800 mg, 69%) as an orange-yellow crystalline solid (needles); 1H NMR (500 MHz, $CDCl_3$) δ_H: 2.38 (6H, s), 2.87-2.97 (2H, m), 3.39-3.50 (2H, m), 7.29-7.35 (2H, m,), 7.36-7.42 (4H, m), 7.51-7.58 (4H, m); ^{13}C NMR (126 MHz, CDCl3) δ_C: 41.6, 50.2, 71.1, 114.6, 128.0, 128.4, 131.9, 132.4, 165.8, 210.3.

Spectroscopic data were in accordance with the literature, and were used as a basis for purity of the material.

The metal source (diiron nonacarbonyl) was purchased from Sigma Aldrich. Lot A0381797 was used, and was assayed at 98% *via* IPC analysis. However, no trace metal anaylsis was provided for this lot. Additionally, no further analysis of this compound was performed.

Mangenese precatalyst **177**:[5]



[Mn] precatalyst 177

A flame dried 250 mL flask was charged with pyridine-2,6-diamine (546 mg, 5.00 mmol) and dissolved in 65 mL dry and degassed THF under mild stirring. Freshly distilled triethylamine (1.53 mL, 11.0 mmol) was then added, and the solution was cooled to 0 °C. Then chlorodiisopropylphosphine (6.7 mL, 10.5 mmol) was added dropwise *via* syringe. The solution was allowed to warm to room temperature and stirred over night at 50 °C. The suspension was filtered over a glass filter via cannulation, and the filter washed with 50 mL of dry and degassed THF. The filtrate was concentrated in vacuo, and the resultant crude oil used directly in the next step.

To the flask containing the crude oil and a stirrer bar was added dry and degassed toluene (50 mL), and the mixture stirred until the oil was dissolved. To the resulting solution was then added bromopentacarbonyl manganese, (1.24 g, 4.5 mmol), and the reaction heated at 110 ˚C overnight. The reaction mixture was then cooled, and filtered through a glass filter, resulting in a grey-brown solid on the glass frit. This solid was then washed with dry THF (4 × 20 mL) and dried n-pentane (5 × 10 mL). The solid product was then collected, and dried under vacuum to yield the **177** (1.96 g, 70%) as a brown solid; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ_H: 1.29 (12 H, dd, *J* 6.9, 17.0), 1.39 (12 H, dd, *J* 7.1, 16.8), 2.65-2.86 (4H, m), 6.37-6.38 (2H, m) 7.48-7.50 (m, 1H), 9.00 (2H, s); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ_C: 17.5 (d, *J* 16), 30.0-30.7 (m), 98.9, 140.5, 160.1 (t, *J* 7.2), 214.9, 220.7; ^{31}P NMR (162 MHz, DMSO-d$_6$) δ_P: 132.56.

Spectroscopic data were in accordance with the literature, and were used as a basis for purity of the material.

The metal source (manganese(I)pentacarbonyl bromide, 98%) was purchased from Alfa Aesar. Lot Z13E064 was used, and was assayed at ≥98.5% by argentometric titration. However, no trace metal anaylsis was provided for this lot. Additionally, no further analysis of these compound were performed.

The experimental data from Chapters 6 and 7 contains only ^{1}H NMR for identification purposes of known compounds. In later projects, ^{1}H and ^{13}C were acquired for all compounds as standard.

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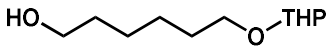
Chapter 6: Experimental – Investigations into Stereoselective Borrowing Hydrogen

Table of Contents

6.1. Synthesis of enamine substrates

6-[(Tetrahydro-2*H*-pyran-2-yl)oxy]hexan-1-ol



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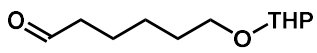
Following a literature procedure,[1] hexane-1,6-diol (2.50 g, 21.3 mmol) was dissolved in 3,4-dihydro-*2H*-pyran (1.70 mL, 17.8 mmol) and dichloromethane (2.00 mL). *p*-Toluene sulphonic acid (33 mg, 0.178 mmol) was added, and the reaction stirred at room temperature for 2 hours. The reaction was then washed with saturated aqueous potassium carbonate solution (10 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. This yields the title compound (3.75 g, quant.) as a colourless oil; R_F: 0.32 (20% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.38-1.42 (4H, m, C(3)H_2+C(4)H_2) 1.50-1.64 (10H, m, pyranyl C(3)H_2+C(4)H_2+C(5)H_2 and C(2)H_2+C(5)H_2), 3.36-3.41 (1H, m, pyranyl C(5)H_AH_B), 3.46-3.52 (1H, m, pyranyl C(5)H_AH_B), 3.61-3.67 (2H, m, C(2)H_2), 3.71-3.76 (1H, m C(5)H_AH_B), 3.84-3.89 (1H, m, C(5)H_AH_B), 4.57 (1H, t, *J* 3.6, pyranyl C(2)*H*).

Spectroscopic data were in accordance with the literature.[2]

6-((Tetrahydro-2*H*-pyran-2-yl)oxy)hexanal

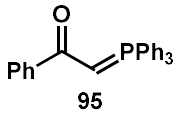


94

To a solution of pyridinium chlorochromate (4.0 g, 18.5 mmol) in DCM (12.5 mL) was added 6-((tetrahydro-2*H*-pyran-2-yl)oxy)hexan-1-ol (2.5 g, 12.4 mmol) dropwise. The reaction was then stirred at room temperature for 1 hour, or until reaction completion observed by TLC. The reaction was then filtered through silica, flushing with DCM (50 mL). The combined organic phases were then concentrated *in vacuo*, yielding the title compound (2.36 g, 95%) as a colourless oil; R_F: 0.70 (20% ethyl acetate/hexanes); ^{1}H NMR: (300 MHz, $CDCl_3$), 1.36-1.86 (12H, m), 2.45 (2H, td, *J* 7.3, 1.8), 3.38 (1H, dt, *J* 9.6, 6.7), 3.46-3.53 (1H, m), 3.74 (1H, dt, *J* 9.6, 6.7), 3.82-3.89 (1H, m), 4.56 (1H, t, *J* 3.6), 9.77 (1H, t, *J* 1.8).

Spectroscopic data were in accordance with the literature.[2]

1-Phenyl-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one

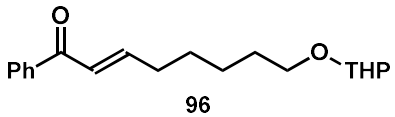


95

Triphenylphosphine (1.05 g, 4.00 mmol) and 2-bromo-1-phenylethan-1-one (796 mg, 4.00 mmol) were refluxed in toluene (40.0 mL) for 4 hours. After this time, the reaction was cooled, diluted in diethyl ether, and then the crude solid filtered, and washed with diethyl ether (3 × 10 mL). The resulting intermediate salt was added to a dichloromethane/ water mixture (4.71 mL:7.14 mL), and sodium hydroxide solution added (2 mL, 4.00 mmol, 2 M).The reaction was then stirred at room temperature overnight, diluted in DCM (100 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the title compound (1.51 g, 99%) as a colourless amophous solid; Mp: 176-178 °C (Lit.[2] 178-180 °C); R_F: 0.62 (50% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.43 (1H, d, *J* 22.5), 7.35-7.36 (3H, m), 7.47 (6H, m), 7.56 (3H, m), 7.70-7.74 (6H, m), 7.97 (2H, m); ^{31}P NMR (203 MHz, $CDCl_3$) δ_P: 16.6.

Spectroscopic data were in accordance with the literature.[3]

(*E*)-1-Phenyl-8-[(tetrahydro-2*H*-pyran-2-yl)oxy]oct-2-en-1-one

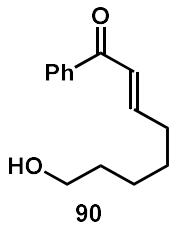


96

6-[(tetrahydro-2*H*-pyran-2-yl)oxy]hexanal (200 mg, 1.00 mmol) and 1-phenyl-2-(triphenyl-λ^5-phosphanylidene)ethan-1-one (570 mg, 1.50 mmol) were dissolved in chloroform (2 mL, 0.5 M) and refluxed for 48 hours. The reaction was then cooled, and concentrated under reduced pressure, before purification by column chromatography (100 × 25 mm silica, 30% Ethyl Acetate/ Hexanes) to yield the title compound (238mg, 80%) as a colourless oil; R_f: 0.74 (30% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.40-1.85 (10H, m), 1.82 (1H, dt, *J* 5.9, 10.2), 2.31-2.37 (1H, m), 3.40 (1H, dt, *J* 9.6, 6.5), 3.47-3.53 (1H, m), 3.75 (1H, dt, *J* 9.6, 6.7), 3.84-3.89 (1H, m), 4.56-4.58 (1H, m), 6.88 (1H, dt, *J* 15.4, 1.4), 7.00-7.10 (1H, m), 7.47 (2H, tt, *J* 8.1, 1.1), 7.53-7.58 (1H, m), 7.91-7.93 (2H, m).

Spectroscopic data were in accordance with the literature.[2]

(*E*)-8-Hydroxy-1-phenyloct-2-en-1-one

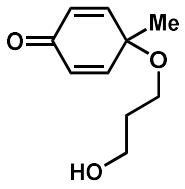


90

Following a modified literature procedure,[2] (*E*)-1-phenyl-8-((tetrahydro-2*H*-pyran-2-yl)oxy)oct-2-en-1-one (506 mg, 1.67 mmol) was dissolved in methanol (33.4 mL). Para-toluene sulphonic acid monohydrate (317 mg, 1.67 mmol) was then added, and the reaction stirred at room temperature for 1 hour. The reaction was then quenched in saturated aqueous sodium hydrogen carbonate solution (10 mL), partitioned with water (20 mL), and extracted in ethyl acetate (3 × 15 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was then purified by column chromatography (100 × 25 mm silica, 40% Ethyl Acetate/ Hexanes) to yield the title compound (337 mg, 93%) as a colourless oil; R_F: 0.49 (40% ethyl acetate/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.21-1.66 (7H, m), 2.35 (2H, q, *J* 7.0), 3.66 (2H, t, *J* 6.4), 6.89 (1H, dd, *J* 15.4, 1.0), 7.02-7.12 (1H, m), 7.46 (2H, dd, *J* 11.0, 4.5), 7.56 (1H, dd, *J* 10.7, 3.8), 7.91-7.94 (2H, m).

Spectroscopic data were in accordance with the literature.[2]

4-(3-Hydroxypropoxy)-4-methylcyclohexa-2,5-dien-1-one

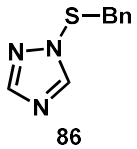


91

Following a literature procedure,[4] *p*-cresol (1.08 g, 10.0 mmol), was dissolved in DCM (2 mL, 5.00 M), and propane-1,3-diol (21.5 mL, 300 mmol) added. Then, a solution of Iodosobenzene diacetate (4.83 g, 15.0 mmol) in DCM (40 mL, 0.375 mmol) was added dropwise at room temperature, over the course of 2 hours. The reaction was then stirred for half an hour at room temperature, then concentrated under reduced pressure. The crude oil was then purified by column chromatography (150 × 45 mm silica, 60% ethyl acetate/hexanes) to yield the title compound (670 mg, 48%) as a yellow oil; R_F: 0.61 (60% ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H:1.44 (1H, s, 4-Me C*H*$_3$), 1.77-1.83 (2H, m, hydroxypropoxy C(2)*H*$_2$, 1.98 (1H, s, br, O*H*), 3.50 (2H, t, *J* 5.9, hydroxypropoxy C(1)*H*$_2$), 3.76 (2H, *J* 5.6, hydroxypropoxy C(3)*H*$_2$), 6.28-6.32 (2H, m, C(2)*H*+C(6)*H*), 6.77-6.81 (2H, m, C(3)*H*+C(5)*H*).

Spectroscopic data were in accordance with the literature.[4]

1-(Benzylthio)-1*H*-1,2,4-triazole



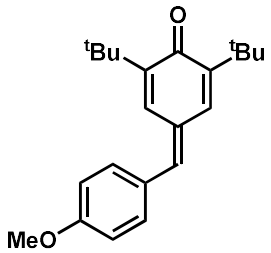
86

Following a literature procedure,[5] to a solution of dibenzyl disulfide (4.94 g, 20.0 mmol) in dichloromethane (20 mL, 1.00 M) was added sulfuryl chloride (1.62 mL, 20.0 mmol) dropwise, and the reaction stirred for 15 minutes at room temperature. This solution was then added to a solution of 1,2,4-triazole (3.45 g, 50.0 mmol) and triethylamine (6.14 mL, 44.0 mmol) in dichloromethane (20 mL) that had been pre-stirred for 20 minutes. The reaction was then stirred at room temperature for an additional 25 minutes, until reaction completion (determined by TLC). The solvent

was then removed *in vacuo*, and the crude product extracted in hexane (2 × 100 mL) and 30% dichloromethane/hexane (2 × 100 mL). The combined organic extracts were concentrated *in vacuo*, and the residue purified by column chromatography (100 × 50.0 mm silica, gradient 50% Et_2O/hexanes - neat Et_2O) to yield the title compound (2.66 g, 70% yield) as sticky colourless crystals (plates), which decompose rapidly in air, R_F: 0.17 (eluent = 50% Et_2O/hexanes);^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.22 (1H, s, CH_2), 7.01-7.03 (2H, m, ArC(2,6)*H*), 7.27-7.29 (3H, m, ArC(2,4,6)*H*), 7.64 (1H, s, C(3)*H*), 8.04 (1H, s, C(5)*H*).

Spectroscopic data were in accordance with the literature.[5]

2,6-Di-*tert*-butyl-4-(4-methoxybenzylidene)cyclohexa-2,5-dien-1-one



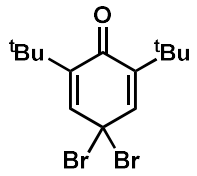
87

Following a literature procedure,[6] a flame dried, 3-necked flask was fitted with a Dean-Stark trap, and charged with 2,6-di-*tert*-butyl phenol (5.16 g, 25.0 mmol), *para*-anisaldehyde (3.04 mL, 25.0 mmol) and toluene (100 mL). The reaction mixture was then heated to reflux, and piperidine (4.94 mL, 50.0 mmol) added dropwise over 1 hour, after which the reaction was maintained at reflux for an additional 3 hours. The reaction was then cooled to room temperature, acetic anhydride (2.36 mL, 50.0 mmol) was added, and the resulting mixture was stirred for an additional 15 minutes at that temperature. The mixture was then poured over ice-water (500 mL), and extracted in dichloromethane (3 × 200 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. The resulting crude mixture was then purified by column chromatography (45 × 150 mm silica, 10% ethyl acetate/hexanes) and recrystallization from hexanes to give the title compound (2.91 g, 36%) as deep yellow crystals (prisms); Mp 124-126 °C (Lit[6] 125-126 °C); R_F: 0.66 (20% ethyl acetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.32 (18H, d, *J* 6.3, ^{t}BuH_9), 3.88 (3H, s, OMeH_3), 6.97-7.01 (3H, m, ArC(2,6)*H* +

C(5)*H*), 7.14 (1H, s, C(3)*H*), 7.44 (2H, d, *J* 8.6, ArC(3,5)*H*), 7.56 (1H, d, *J* 2.2, C(7)*H*Ar).

Spectroscopic data were in accordance with the literature.[6]

4,4-Dibromo-2,6-di-tert-butylcyclohexa-2,5-dien-1-one



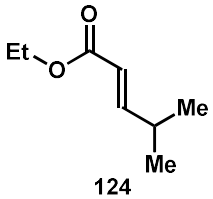
84

Following a literature procedure,[5] to a solution of 2,6-ditertbutylphenol (2.06 g, 10.0 mmol) in methanol (30.0 mL) was added a solution of bromine (1.03 ml, 20.0 mmol) in methanol (5.00 mL) over 10 minutes. The mixture was then stirred at room temperature for 90 minutes, and then water (5.00 mL) was added. The resulting precipitate was then filtered, and the crude material recrystallized from petroleum ether to yield the title compound (2.54 g, 70%) as a brown crystalline solid (needles); Mp 130-132 °C (Lit[7] 129-131 °C (petroleum ether)); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.36 (18H, s, ^{t}BuH_{18}), 7.70 (2H, s, C(3,5)*H*).

Spectroscopic data were in accordance with the literature.[7]

6.2. Synthesis of dienamine substrates

Ethyl (*E*)-4-methylpent-2-enoate



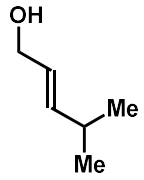
124

Following a literature procedure,[8] isobutyraldehyde (456 µL, 5.00 mmol) was dissolved in THF (35 ml), then sodium hydride (60% in Paraffin, 259 mg, 6.50 mmol) was added. The reaction was then cooled to 0 °C, and stirred at this temperature

for 20 minutes. Triethylphosphonoacetate (1.29 mL, 6.50 mmol) was then added dropwise, over 20 minutes. The reaction was then allowed to warm to room temperature, and stirred at this temperature for an hour, and is then quenched with saturated aqueous ammonium chloride solution (15.0 mL), and extracted with ethyl acetate (3 × 60 mL). The combined organic extracts were then washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (100 × 45 mm silica, 20% ethyl acetate/ petroleum ether), yields the title compound (699mg, 98%) as a colourless oil; R_F: 0.78 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.06 (6H, d, *J* 6.8, 2 × Me C*H*$_3$), 1.29 (3H, t, *J* 7.1, OEt C*H*$_3$), 2.39-2.51 (1H, m, C(4)*H*), 4.18 (2H, q, *J* 7.1, OEt C*H*$_2$), 5.76 (1H, dd, 15.7, 1.5, C(2)*H*), 6.94 (1H, dd, 15.73, 6.6, C(3)*H*).

Spectroscopic data were in accordance with the literature.[8]

(*E*)-4-Methylpent-2-en-1-ol

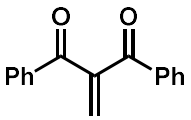


119

Following a literature procedure,[8] ethyl (*E*)-4-methylpent-2-enoate (711 mg, 5 mmol) was dissolved in anhydrous DCM (11.9 mL) and stirred vigorously. The solution was then cooled to −78 °C, and a solution of DIBAL-H (15 mL, 15 mmol, 1 M in hexanes) was added. The reaction was then slowly warmed to room temperature, and stirred at this temperature for 1.5 hours. The solution was then cooled back to −78 °C, and 1 M HCl added until the formed solid is dissolved. The resulting mixture is then extracted in DCM (3 × 10 mL), and the combined organic extracts dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was then purified by flash column chromatography (100 × 30 mm silica, 20% ethyl acetate/petroleum ether 40-60) to yield the title compound (206 mg, 41%) as a colourless oil; R_F: 0.46 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.00 (2H, d, *J* 6.7, 2 × C*H*$_3$), 1.58 (1H, s, br, O*H*), 2.26-2.35 (1H, m, C(4)*H*), 4.09 (2H, d, *J* 5.6, C(1)*H*$_2$), 5.55-5.70 (2H, m, alkene C*H*$_A$C*H*$_B$).

Spectroscopic data were in accordance with the literature.[8]

2-Methylene-1,3-diphenylpropane-1,3-dione

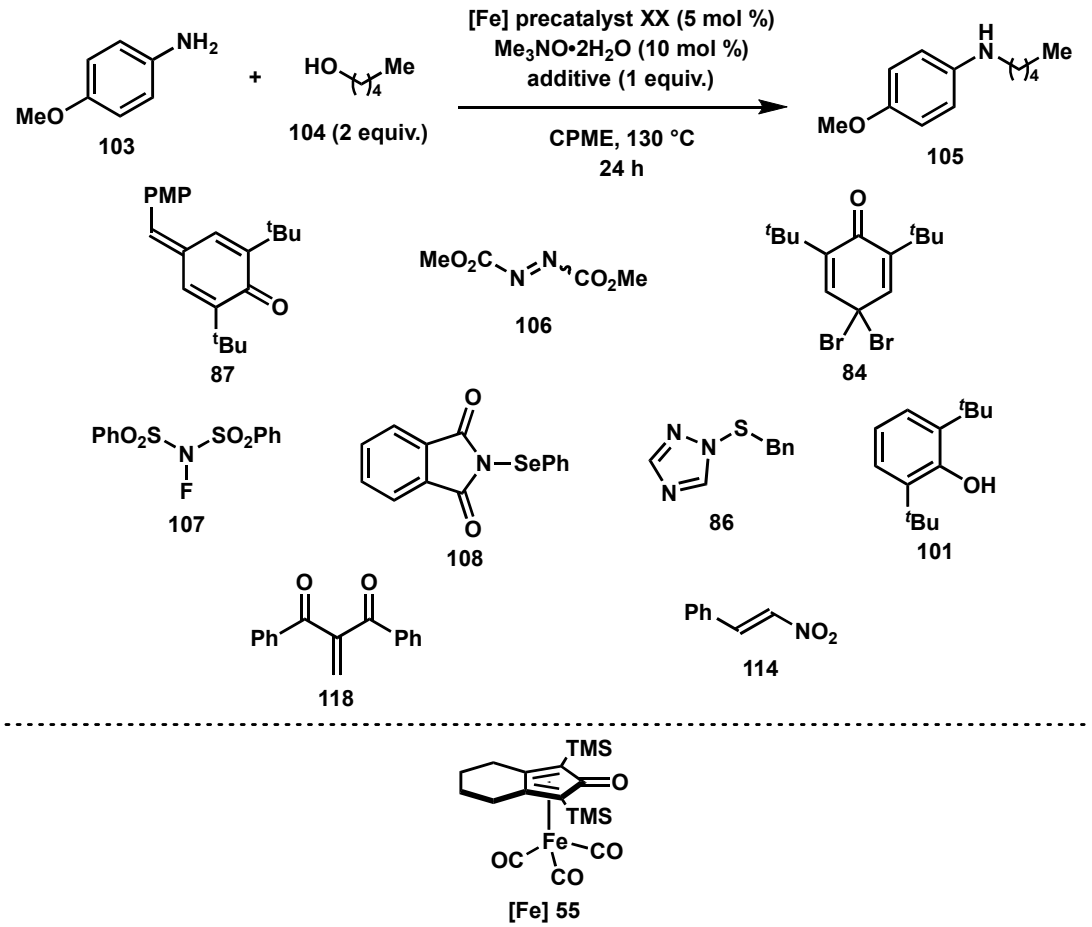


118

Following a literature procedure,[9] dibenzoylmethane (1.12 g, 5.00 mmol) was dissolved in *N,N*-Dimethylacetamide (20 ml, 0.25 M), then iron trichloride hexahydrate (135 mg, 0.500 mmol) and potassium persulphate (2.70 g, 10.0 mmol) were added, under air. The reaction was then heated to 110 °C for 4 hours, cooled, and diluted in ether (150 ml). The mixture was then washed with brine (3 × 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography (100 × 25 mm silica, 60% ethyl acetate/ petroleum ether 40-60), and recrystallisation from diethyl ether/hexanes yields the title compound (587 mg, 50%) as a colourless amorphous solid; Mp: 175-178 (Et_2O/Hexanes) (Lit: 178-179)[10] ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.75 (1H, t, *J* 7.0, C(4)H_AH_B), 5.74 (1H, t, *J* 7.0, C(4)H_AH_B), 7.47-7.51 (4H, m, ArC(3,5)*H*), 7.57-7.61 (2H, m, ArC(4)*H*), 8.14 (4H, m, ArC(2,6)*H*), R_F: 0.51 in 20% ethyl acetate/Hexanes.

Spectroscopic data were in accordance with the literature.[9]

6.3. General procedure 1 – Compatibility screening

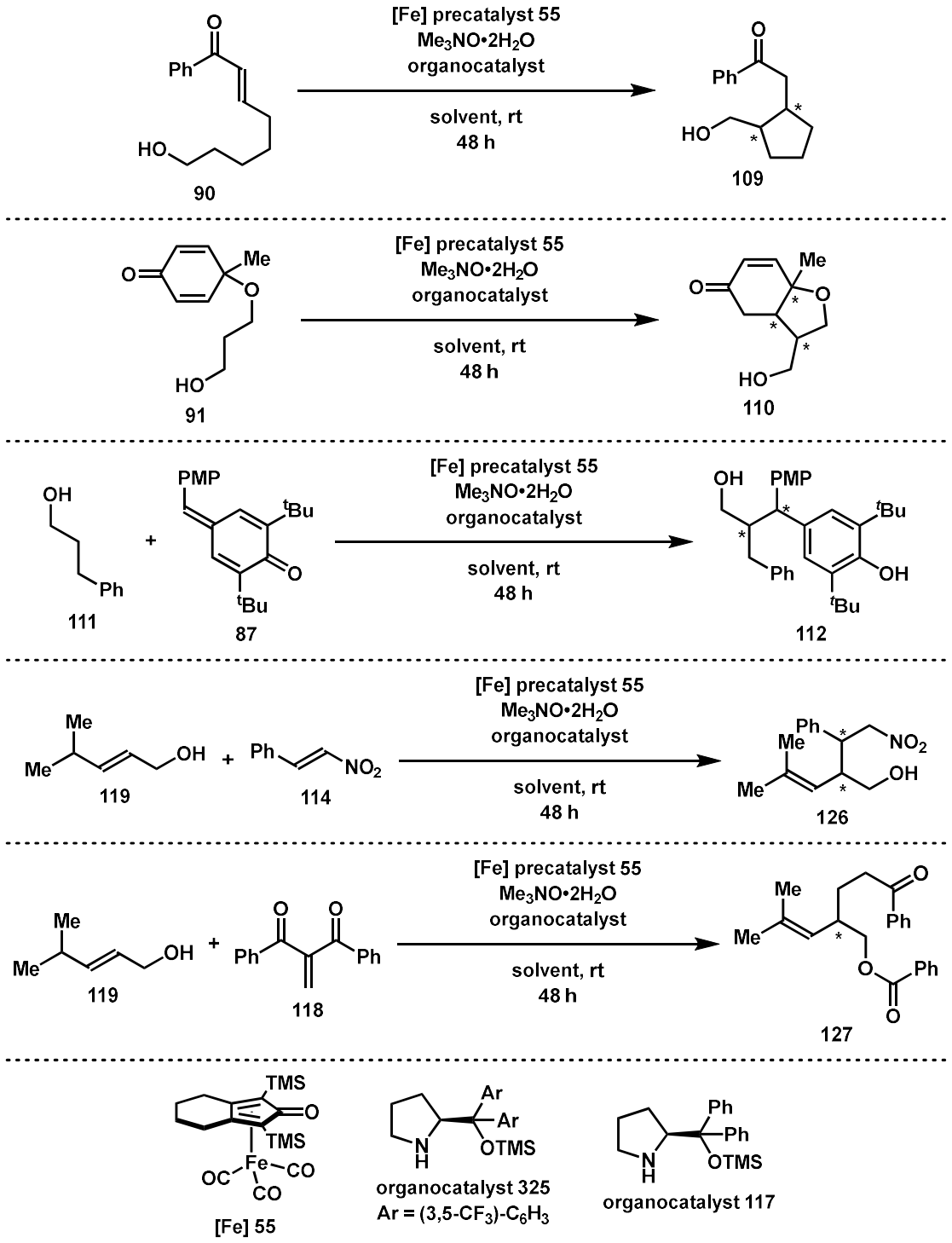


To a flame dried 10 mL microwave vial was added *para*-anisidine (61.6 mg, 0.50 mmol), iron precatalyst **55** (10.8 mg, 5 mol %), trimethylamine *N*-oxide dihydrate (5.6 mg, 10 mol %)**,** an additive (0.50 mmol, varied masses) and a magnetic stirrer bar. The vial was then sealed with a suba seal, and subjected to three rounds of vacuum-nitrogen exchange. Through the suba seal was added 1-pentanol (108 µL, 1.00 mmol) and cyclopentyl methyl ether (2 mL). The suba seal was then removed from the vial, and replaced with a crimp cap, fitted with a PTFE septum. The cap was crimped shut, and the reaction mixture stirred vigorously at 130 °C for 24 hours. After the allotted reaction time, the reaction was cooled to room temperature, and the cap removed with a decrimper. Mesitylene (69.6 µL, 0.5 mmol) was then added as internal, and the reaction stirred at room temperature for an additional 5 minutes. The reaction was then sampled, and the sample subjected the ^{1}H NMR spectroscopy to yield the results below (table **6.1**). All NMR yields are reported relative to mesitylene as internal standard.

Entry	Additive	105 (^{1}H NMR yield)	Comments/observations
1	**87**	84%	**87** returned
2	**106**	<2%	Gas evolution observed, **106** not returned
3	**84**	<2%	Starting materials returned, **84** not returned
4	**107**	<2%	Starting materials and **107** not returned
5	**108**	<2%	Starting materials and **108** not returned
6	**86**	<2%	Starting materials and **86** not returned
7	**101**	>98%	**101** returned
8	**118**	70%	**118** returned
9	**114**	50%	**114** not returned

Table 6.1 - Compatibility screening results

6.4. General procedure 2 – Low temperature reaction conditions



To a flame dried 10 mL microwave vial was added substrates (where solid, 0.50 mmol), iron precatalyst **55** (varied masses and loadings), trimethylamine *N*-oxide dihydrate (2 equivalents relative to **55**), an organocatalyst (0.50 mmol, varied masses) and a magnetic stirrer bar. The vial was then sealed with a suba seal, and

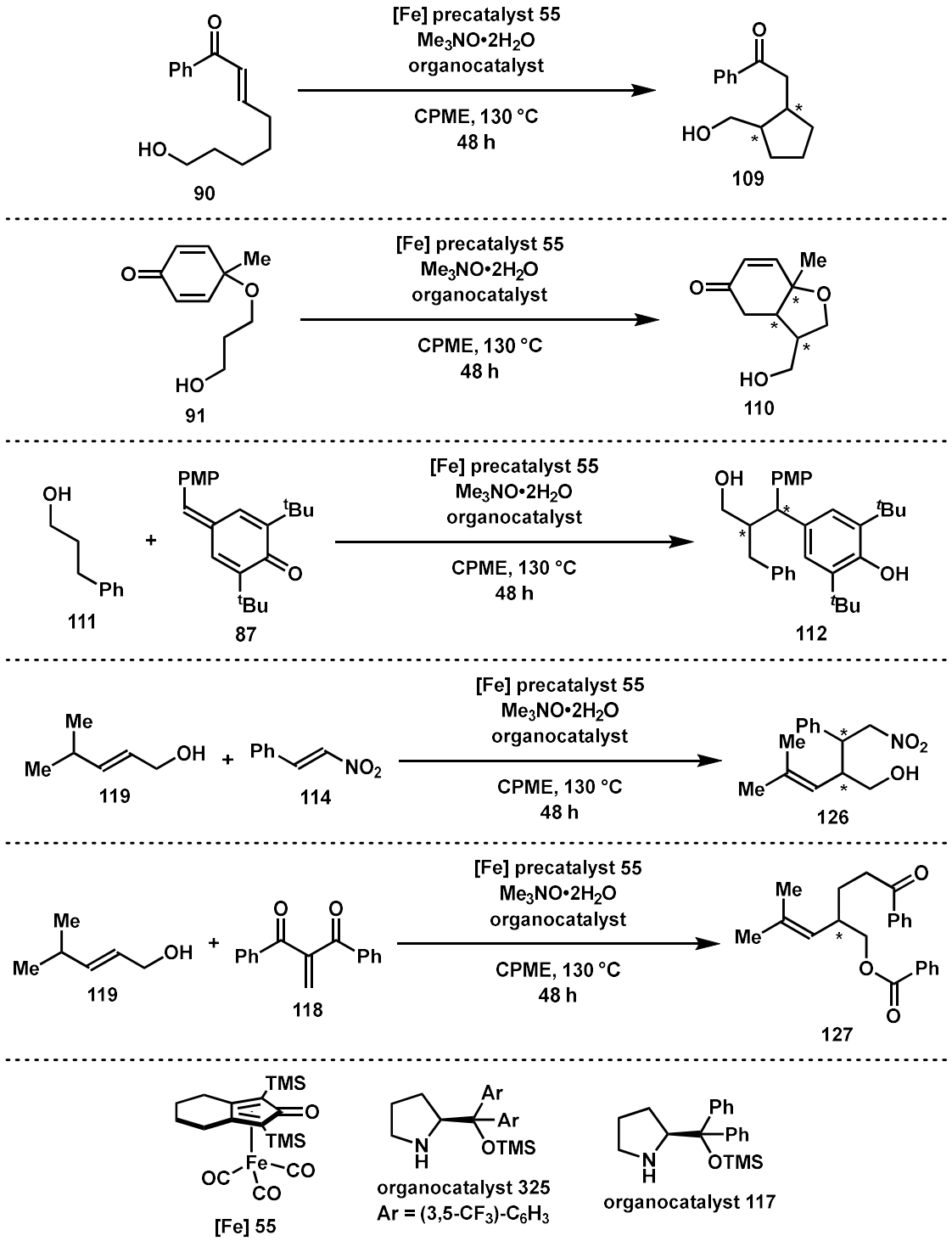
subjected to three rounds of vacuum-nitrogen exchange. Through the suba seal was added solvent (2 mL) and substrates (where liquid, 0.50 mmol). The suba seal was then removed from the vial, and replaced with a crimp cap, fitted with a PTFE septum. The cap was crimped shut, and the reaction mixture stirred vigorously at rt for 48 hours. After the allotted reaction time, the cap removed with a decrimper. Mesitylene (69.6 µL, 0.50 mmol) was then added as internal, and the reaction stirred at room temperature for an additional 5 minutes. The reaction was then sampled, and the sample subjected the ^{1}H NMR spectroscopy to yield the results below (table **6.2**). All NMR yields are reported relative to mesitylene as internal standard.

Entry	Substrate(s)	[Fe] 55 (mol %)	Organocatalyst	Organocatalyst loading (mol %)	Solvent	Product (%)
1	**90**	5	**117**	10	CPME	<2
2	**90**	5	**117**	10	toluene	<2
3	**90**	10	**117**	20	CPME	<2
4	**90**	10	**117**	20	toluene	<2
5	**90**	5	**325**	10	CPME	<2
6	**90**	5	**325**	10	toluene	<2
7	**90**	10	**325**	20	CMPE	<2
8	**90**	10	**325**	20	toluene	<2
9	**91**	5	**117**	10	CPME	<2
10	**91**	5	**117**	10	toluene	<2
11	**91**	10	**117**	20	CPME	<2
12	**91**	10	**117**	20	toluene	<2
13	**91**	5	**325**	10	CPME	<2
14	**91**	5	**325**	10	toluene	<2
15	**91**	10	**325**	20	CMPE	<2
16	**91**	10	**325**	20	toluene	<2
17	**111 + 87**	5	**117**	10	CPME	<2
18	**111 + 87**	5	**117**	10	toluene	<2
19	**111 + 87**	10	**117**	20	CPME	<2
20	**111 + 87**	10	**117**	20	toluene	<2
21	**111 + 87**	5	**325**	10	CPME	<2
22	**111 + 87**	5	**325**	10	toluene	<2
23	**111 + 87**	10	**325**	20	CMPE	<2
24	**111 + 87**	10	**325**	20	toluene	<2
25	**119 + 114**	10	**117**	20	CPME	<2

26	**119 + 114**	10	**117**	20	toluene	<2
27	**119 + 114**	10	**325**	20	CPME	<2
28	**119 + 114**	10	**325**	20	toluene	<2
29	**119 + 118**	10	**117**	20	CPME	<2
30	**119 + 118**	10	**117**	20	toluene	<2
31	**119 + 118**	10	**325**	20	CMPE	<2
32	**119 + 118**	10	**325**	20	toluene	<2

Table 6.2 - Results of low temperature reaction screening

6.5. General procedure 3 – High temperature reaction conditions



To a flame dried 10 mL microwave vial was added substrates (where solid, 0.50 mmol), iron precatalyst **55** (varied masses and loadings), trimethylamine *N*-oxide dihydrate (2 equivalents relative to **55**), an organocatalyst (0.50 mmol, varied masses) and a magnetic stirrer bar. The vial was then sealed with a suba seal, and

subjected to three rounds of vacuum-nitrogen exchange. Through the suba seal was added CPME (2 mL) and substrates (where liquid, 0.50 mmol). The suba seal was then removed from the vial, and replaced with a crimp cap, fitted with a PTFE septum. The cap was crimped shut, and the reaction mixture stirred vigorously at 130 °C for 24 hours. After the allotted reaction time, the cap removed with a decrimper. Mesitylene (69.6 µL, 0.50 mmol) was then added as internal, and the reaction stirred at room temperature for an additional 5 minutes. The reaction was then sampled, and the sample subjected the ^{1}H NMR spectroscopy to yield the results below (table **6.3**). All NMR yields are reported relative to mesitylene as internal standard.

Entry	Substrate(s)	[Fe] 55 (mol %)	Organocatalyst	Organocatalyst loading (mol %)	Product (% by ^{1}H NMR)
1	**90**	5	**117**	10	<2
2	**90**	5	**325**	10	<2
3	**90**	10	**117**	20	<2
4	**90**	10	**325**	20	<2
5	**91**	5	**117**	10	<2
6	**91**	5	**325**	10	<2
7	**91**	10	**117**	20	<2
8	**91**	10	**325**	20	<2
9	**111 + 87**	5	**117**	10	<2
10	**111 + 87**	5	**325**	10	<2
11	**111 + 87**	10	**117**	20	<2
12	**111 + 87**	10	**325**	20	<2
13	**119 + 114**	10	**117**	20	<2
14	**119 + 114**	10	**325**	20	<2
15	**119 + 118**	10	**117**	20	<2
16	**119 + 118**	10	**325**	20	<2

Table 6.3 - High temperature reaction screening

6.6. References

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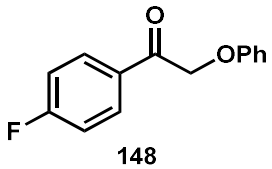
Chapter 7: Experimental – Exploring Tandem Ruthenium-Catalysed Hydrogen Transfer and S_NAr Chemistry

Table of Contents

7.1. Synthesis of substrates

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



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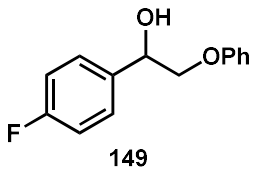
A 500 mL round bottomed flask containing a magnetic stirrer bar was charged with K_2CO_3 (9.54 g, 69.0 mmol), Phenol (4.30 g, 46.0 mmol) and acetone (200 mL) To this mixture was added dropwise a solution of 2-bromo-4'-fluoroacetophenone (10.0 g, 46.0 mmol) in acetone (50 mL) over 30 min at rt. The resulting suspension was heated under reflux for 4 h, cooled to room temperature, filtered and concentrated *in vacuo*. Purification by recrystallization (in petroleum ether 40-60) yielded the title compound (7.21 g, 68 %) as a colourless amorphous solid; Mp: 77-80 °C (petroleum ether 40-60); R_F = 0.53 (20% ethyl acetate/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(2)H_2), 6.94 (2H, d, *J* 8.0, OPh ArC(2,6)*H*), 6.99 (1H, t, *J* 7.6, OPh ArC(4)*H*), 7.17 (2H, m, OPh, ArC(3,5)*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*(2)H_2), 114.9 (OPh Ar*C*(2,6)H), 116.2 (d, *J* 22.1, Ar*C*(3,5)H), 121.9 (OPh Ar*C*(4)H), 129.8 (OPh Ar*C*(2,6)H), 131.1 (Ar*C*(1)C(O)), 131.2 (d, *J* 9.5, Ar*C*(2,6)H), 158.0 (OPh Ar*C*(1)(O)), 166.3 (d, *J* 256.5, Ar*C*(4)F), 193.5 (*C*(1)O); HRMS (NSI$^+$) $C_{14}H_{12}O_2F$ $[M+H]^+$ found 231.0816, requires 231.0816 (+0.2 ppm).

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

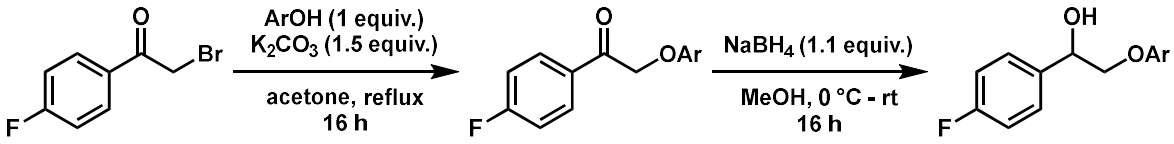


149

A 500 mL round bottomed flask was charged with 1-(4-fluorophenyl)-2-phenoxyethan-1-one (6.50 g, 28.2 mmol) and methanol (300 mL). Sodium

borohydride (1.17 g, 30.9 mmol) was then added portion wise at 0 °C. The mixture was left to react at RT for 4 h. Sat. aq. NH_4Cl (200 mL) was then added to the mixture. The reaction mixture was transferred to a separatory funnel and the vial washed with ethyl acetate (100 mL) and H_2O (100 mL). The organic phase was collected and the aqueous phase washed with ethyl acetate (2 x 100 mL). The organics were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by recrystallization (in *n*-hexane) yielded the title compound (5.05 g, 77%) as a colourless crystalline solid (needles); Mp: 42-45 °C (*n*-hexane); R_F = 0.35 (20% ethyl acetate/hexanes); ν_{max} / cm^{-1} (film) 3237, 3067, 2938, 2878, 1599, 1585, 1510, 1497, 1456, 1225, 1152, 1078, 1042, 870, 752, 691, 592; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 3.98 (1H, dd, 9.5, 9.0 C(2)H_AH_B), 4.09 (1H, dd, *J* 10.0, 3.0 C(2)H_AH_B), 5.11 (1H, dd, *J* 9.0, 3.0, C(1)*H*OH), 6.89-6.95 (2H, m, ArC(3,5)*H*), 6.95-7.02 (1H, m, OPh ArC(4)*H*), 7.04-7.10 (2H, m, OPh 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*(2)H_2, 73.3 (*C*(1)H), 114.7 (OPh Ar*C*(2,6)H), 115.6 (d, *J* 21.5, ArC(3,5)H), 121.6 (OPh Ar*C*(4)H), 128.1 (d, *J* 8.2, Ar*C*(2,6)H), 129.7 (OPh (Ar*C*(3,5)H, 135.5 (Ar*C*(1)C(O)), 158.4 (OPh Ar*C*(1)O), 162.7 (d, *J* 247.0 Ar*C*(4)F); HRMS (EI^+) $C_{14}H_{13}FO_2$ $[M]^+$ found 232.0900, requires 232.0901 (+0.4 ppm).

7.1.1. General Procedure 1 – Synthesis of substrates

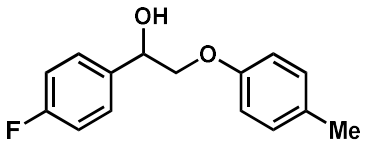


A 250 mL flask was charged with a magnetic stirrer bar, 2-bromo-4'-fluoroacetophenone (2.17 g, 10.0 mmol), a substituted phenol (10.0 mmol), and potassium carbonate (2.07 g, 15 mmol). This mixture of powders was then dissolved in acetone (100 mL, 0.100 M). The reaction was then stirred and heated to reflux, and these conditions held for up to 16 hours. The reaction was then filtered, and the filtrate concentrated under reduced pressure to dryness. The crude 2-

aryloxyacetophenone was then subjected to crude ^{1}H NMR to assess reaction completion, and used without purification, unless otherwise specified.

The crude 2-aryloxyacetophenone was dissolved in methanol (80.0 mL, 0.138 M), and a magnetic stirrer was added. The reaction was then cooled to 0 °C, and sodium borohydride (416 mg, 11.0 mmol) added portionwise under vigorous stirring. The reaction was then warmed back up to room temperature, and stirred at this temperature for up to 16 hours. The reaction was then quenched in saturated aqueous ammonium chloride (20 mL), partitioned with water (20 mL) and extracted in ethyl acetate (3 × 30 mL). The combined organic phases were then washed with brine (40 mL), dried over $MgSO_4$, filtered and the solvent removed under removed pressure. The resulting crude 2-aryloxy ethanols were then purified by column chromatography to yield the products shown below.

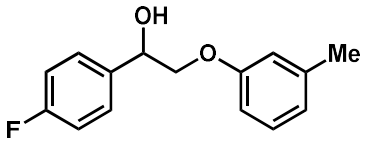
1-(4-Fluorophenyl)-2-(*p*-tolyloxy)ethan-1-ol



150

The title compound was prepared according to general procedure 1 using *p*-cresol (1.08 g, 10.0 mmol). Purification by flash silica chromatography (60 x 150 mm Silica, gradient 5-10% ethyl acetate/hexanes) gives the title compound (1.75 g, 71%) as an off-white amorphous solid. Mp 54-57 °C; R_F: 0.33 (20% ethyl acetate/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), 3.90-3.98 (1H, m), 4.06 (1H, dd, *J* 9.5, 3.5), 5.09 (1H, dd, *J* 9.0, 3.0), 6.78-6.85 (2H, m), 7.03-7.12 (4H, m), 7.39-7.46 (2H, m); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -114.2; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 20.6, 72.1, 73.5 (d, *J* 1.0), 114.6, 115.6 (d, *J* 21.4), 128.1 (d, *J* 8.2), 130.2, 130.8, 135.5 (d, *J* 3.2), 156.3, 162.7 (d, *J* 247.0); HRMS (EI^+) $C_{15}H_{15}FO_2$ $[M]^+$ found 246.1068, requires 246.1056 (+4.9 ppm).

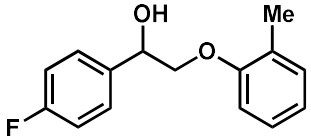
1-(4-Fluorophenyl)-2-(*m*-tolyloxy)ethan-1-ol



151

The title compound was prepared according to general procedure 1 using *m*-cresol (1.05 mL, 1.08 g, 10.0 mmol). Purification by flash silica chromatography (50 x 170 mm Silica, 5% ethyl acetate/hexanes,) gives the title compound (1.51 g, 61%) as a colourless amorphous solid; Mp 72-75 °C, R_F: 0.33 (20% ethyl acetate/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), 3.92-4.00 (1H, m), 4.07 (1H, dd, *J* 9.5, 3.5), 5.10 (1H, dd, *J* 9.0, 3.5), 6.69-6.77 (2H, m), 6.78-6.83 (1H, m), 7.03-7.12 (2H, m), 7.17 (1H, t, *J* 7.8), 7.39-7.47 (2H, m); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -114.1; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.6, 72.1, 73.3, 111.7, 115.6, 115.6 (d, *J* 21.5), 122.4, 128.1 (d, *J* 8.2), 129.5, 135.6 (d, *J* 3.2), 139.9, 158.4, 162.7 (d, *J* 247.0); HRMS (EI^+) calculated for $C_{15}H_{15}FO_2$ $[M]^+$: found 246.1051, requires 246.1056 (-2.0 ppm).

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

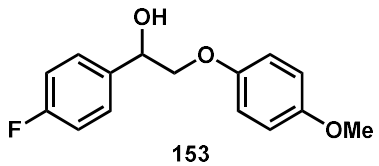


152

The title compound was prepared according to general procedure 1 using *o*-cresol (1.03 mL, 1.08 g, 10.0 mmol). Purification by flash silica chromatography (50 x 170 mm Silica, 5-7% ethyl acetate/hexanes) gives the title compounds (1.47 g, 60%) as a pale yellow oil; R_F: 0.33 (20% ethyl acetate/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), 2.77 (1H, br), 4.00 (1H, t, *J* 8.5), 4.10 (1H, dd, *J* 9.5, 3.5), 5.14 (1H, dd, *J* 8.5, 3.5), 6.79 (1H, d, *J* 8.0), 6.90 (1H, t, *J* 7.5), 7.08 (2H, t, *J* 9.0), 7.11-7.18 (2H, m), 7.43-7.46 (2H, m); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -114.2; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 16.4, 72.2, 73.4, 111.4, 115.6 (d, *J* 21.4), 121.3, 126.9, 127.0, 128.2 (d, *J* 8.2), 131.0, 135.7 (d, *J*

3.2), 156.5, 162.7 (d, *J* 246.7); HRMS (EI$^+$) $C_{15}H_{15}FO_2$ [M]$^+$ found 246.1057, requires 246.1056 (+0.4 ppm).

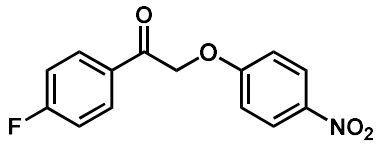
1-(4-Fluorophenyl)-2-(4-methoxyphenoxy)ethan-1-ol



153

The title compound was prepared according to general procedure 1 using 4-methoxyphenol (1.24 g, 10.0 mmol). Purification by flash silica chromatography (60 x 200 mm Silica, 2% MeOH/CH_2Cl_2) gives the title compound (1.28 g, 49%) as a pale yellow oil. R_F: 0.17 (20% ethyl acetate/hexanes); ν_{max} / cm^{-1} (film) 3422, 2922, 2832, 1603, 1504, 1456, 2127, 1155, 1105, 1036, 1012, 870, 822, 729; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.77 (3H, s), 3.88-3.95 (1H, m), 4.03 (1H, dd, *J* 9.5, 3.0), 5.08 (1H, dd, 9.0, 3.0), 6.79-6.89 (4H, m), 7.02-7.12 (2H, m), 7.37-7.46 (2H, m); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -114.1; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 55.8, 72.1, 74.1, 114.8, 115.5 (d, *J* 21.4), 115.8, 128.1 (d, *J* 8.2), 135.6 (d, *J* 3.0), 152.5, 154.4, 162.7 (d, *J* 247.0); HRMS (EI$^+$) $C_{15}H_{15}FO_3$ [M]$^+$ found 262.1010, requires 262.1005 (+1.9 ppm).

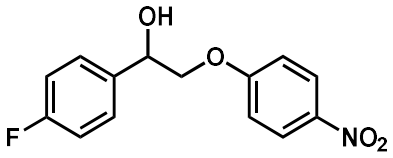
1-(4-Fluorophenyl)-2-(4-nitrophenoxy)ethan-1-one



A 250 mL round-bottomed flask containing a magnetic stirrer bar was charged with K_2CO_3 (2.07 g, 15 mmol), 4-nitrophenol (1.39 g, 10.0 mmol) and acetone (50.0 mL). To this mixture was added dropwise a solution of 2-bromo-4'-fluoroacetophenone (2.17 g, 10.0 mmol) in acetone (50.0 mL) over 30 min at rt. The suspension was heated under reflux for 4 h and left to react at room temperature for 20 h. The mixture was the filtered, washed with brine extracted in CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The organic phases were combined, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by recrystallization (from ethyl acetate) gives the title compound (1.69 g, 61%) as a

yellow solid (prisms); Mp 150-154 °C (ethyl acetate); R_F: 0.28 (eluent: 20 % ethyl acetate in Hexanes); ν_{max} / cm^{-1} (film) 3128, 3082, 2968, 2903, 1701, 1593, 1503, 1327, 1265, 1221, 1159, 1009, 982, 841, 324, 750, 691, 642, 590; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 5.37 (s, 2H), 6.96-7.01 (m, 2H), 7.18-7.23 (m, 2H), 8.01-8.06 (m, 2H), 8.18-8.23 (m, 2H); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -102.2; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 70.8, 114.9, 116.5 (d, *J* 22.2), 126.1, 130.6 (d, *J* 3.0), 131.0 (d, *J* 9.5), 142.4, 162.9, 166.5 (d, *J* 257.8), 191.6. HRMS (EI^+) $C_{14}H_{10}NO_4F$ $[M]^+$ found 275.0592, requires 275.0594 (-0.4 ppm).

1-(4-Fluorophenyl)-2-(4-nitrophenoxy)ethan-1-ol

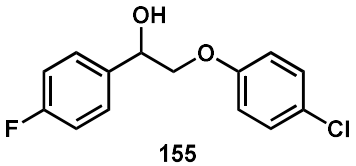


154

A 500 mL round bottomed flask was charged with 1-(4-fluorophenyl)-2-(4-nitrophenoxy)ethan-1-one (1.38 g, 5.00 mmol) and methanol (40.0 mL). Sodium borohydride (208 mg, 5.5 mmol) was then added portion wise at 0 °C. The mixture was left to react at rt for 16 h. Sat. aq. NH_4Cl (20 mL) was then added to the mixture. The reaction mixture was transferred to a separatory funnel and the vial washed with ethyl acetate (30 mL) and H_2O (20 mL). The organic phase was collected and the aqueous phase washed with ethyl acetate (2 x 30 mL). The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash silica chromatography (40 x 75 mm silica, 40% ethyl acetate in hexanes,) gives the title compound (1.33 g, 96%) as a colourless amorphous solid; Mp 102-104 °C; R_F: 0.46 (40% ethyl acetate/hexanes); ν_{max} / cm^{-1} (film) 3244, 2916, 2862, 1605, 1586, 1503, 1454, 1339, 1331, 1298, 1252, 1221, 1194, 1173, 1084, 1076, 1026, 908, 874, 849, 829, 750, 691, 648, 575, 545, 530, 500; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 2.67 (1H, d, *J* 2.8), 4.13 (2H, m), 5.16 (1H, dt, 8.0, 3.1), 6.96-7.00 (2H, m), 7.07-7.13 (2H, m), 7.41-7.46 (2H, m), 8.18-8.22 (2H, m); ^{19}F NMR (376 MHz, $CDCl_3$) δ_F: -113.35; ^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 71.9, 73.8 (d, *J* 1.1), 114.7, 115.8 (d, *J* 21.6), 126.1, 128.1 (d, *J* 8.2), 135.0 (d, *J* 3.2),

142.1, 162.9, (d, *J* 248.0), 164.1; HRMS (ASAP$^+$) $C_{14}H_{13}FNO_4$ $[M+H]^+$ found 278.0832, requires 278.0829 (+1.1 ppm).

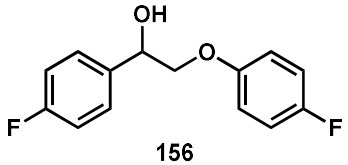
2-(4-Chlorophenoxy)-1-(4-fluorophenyl)ethan-1-ol



155

The title compound was prepared according to general procedure 1 using 4-chlorophenol (1.29 g, 10.0 mmol). Purification by flash silica chromatography (45× 95 mm Silica, 5% ethyl acetate/hexanes) gives the title compound (1.85 g, 69%) as an off-white amorphous solid; Mp 52-54 °C; R_F: 0.35 (20% ethyl acetate/hexanes); ν_{max} / cm^{-1} (film) 3537, 2928, 2868, 1603, 1578, 1510, 1487, 1454, 1281, 1217, 1157, 1094, 1080, 1018, 1005, 924, 910, 870, 826, 808, 658, 571, 550, 507; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.71 (1H, br), 3.94-3.98 (1H, m), 4.04 (1H, dd, *J* 9.5, 3.0), 5.10 (1H, dd, *J* 8.7, 3.2), 6.81-6.88 (2H, m), 7.04-7.12 (2H, m), 7.21-7.27 (2H, m), 7.38-7.49 (2H, m); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -113.8; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 72.1, 73.7, 115.7 (d, *J* 21.5), 116.1, 126.5, 128.1 (d, *J* 8.2), 129.6, 135.4 (d, *J* 3.0), 157.1, 162.8 (d, *J* 247.0). HRMS (NSI$^+$) $C_{14}H_{11}{}^{35}ClFO_2$ $[M-H]^+$ found 265.0437, requires 265.4037 (-0.0 ppm).

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

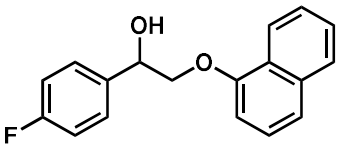


156

The title compound was prepared according to general procedure 1 using 4-fluorophenol (1.12 g, 10.0 mmol). Purification by flash silica chromatography (45 × 75 mm Silica, 40% ethyl acetate/hexanes,) gives the title compound (1.42 g, 95%) as a pale orange amorphous solid (; Mp 47-50 °C; R_F: 0.35 (20% ethyl acetate/hexanes); ν_{max} / cm^{-1} (film) 3289, 2938, 2872, 1601, 1504, 1458, 1296, 1253, 1219, 1192, 1155, 1105, 912, 876, 827, 800, 727, 577, 561, 513, 490; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.85 (1H, s), 3.92-3.96 (1H, m), 4.03 (1H, dd, *J* 9.5, 3.3), 5.09 (1H, dd, *J* 8.6, 3.0), 6.82-6.88 (2H, m), 6.95-7.01 (2H, m), 7.05-7.11 (2H, m),

7.39-7.44 (2H, m); ^{19}F NMR (377 MHz, $CDCl_3$) δ_F: -113.9, -123.0; ^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 72.1, 74.0 (d, *J* 1.1), 115.6 (d, *J* 23.7), 115.8 (d, *J* 10.3), 116.1 (d, *J* 23.3), 128.1 (d, *J* 8.2), 135.4 (d, *J* 3.1), 154.5 (d, *J* 3.1), 157.7 (d, *J* 240.0), 162.7 (d, *J* 247.3); HRMS (NSI$^+$) $C_{14}H_{11}F_2O_2$ $[M-H]^+$ found 249.0733, requires 249.0733 (+0.2 ppm).

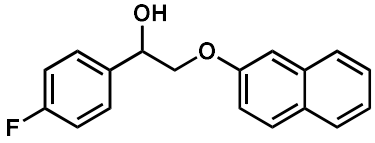
1-(4-Fluorophenyl)-2-(naphthalen-1-yloxy)ethan-1-ol



157

The title compound was prepared according to general procedure 1 using 1-naphthol (1.44 g, 10.0 mmol). Purification by flash silica chromatography (55 x 160 mm Silica, gradient 10-20% ethyl acetate/hexanes) gives the title compound (2.32 g, 82%) as an off-white amorphous solid; Mp 92-96 °C; R_F: 0.27 (20% ethyl acetate/hexanes); ν_{max} / cm^{-1} (film) 3291, 3053, 2922, 2862, 1607, 1593, 1578, 1506, 1456, 1389, 1267, 1221, 1163, 1109, 1086, 1024, 1013, 918, 883, 835, 787, 768, 723. 611, 581, 567, 534, 515; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.21 (1H, dd, *J* 8.4, 9.5), 4.27 (1H, dd, *J* 3.6, 9.6), 5.29 (1H, dd, *J* 3.7, 8.4), 6.81 (1H, dd, *J* 0.6, 7.6), 7.07-7.16 (2H, m), 7.33-7.39 (1H, m), 7.43-7.57 (5H, m), 7.77-7.86 (1H, m), 8.21-8.27 (1H, m); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -114.0. ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 72.3, 73.6 (d, *J* 1.0), 105.3, 115.7 (d, *J* 22.0), 121.2 121.8, 125.6, 125.6, 125.9, 126.7, 127.8, 128.2 (d, *J* 8.2), 134.7, 135.7 (d, *J* 3.2), 154.1, 162.8 (d, *J* 246.8). HRMS (ASAP$^+$) $C_{18}H_{15}FO_2$ $[M]^+$ found 282.0157, requires 282.0156 (+0.4 ppm).

1-(4-Fluorophenyl)-2-(naphthalen-2-yloxy)ethan-1-ol



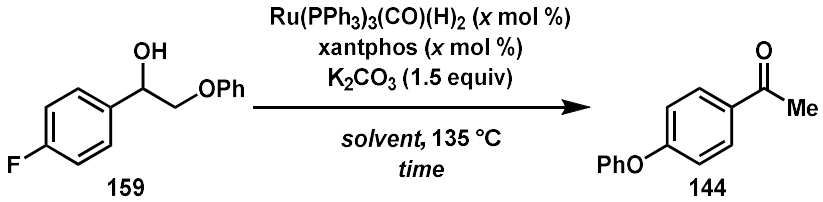
158

The title compound was prepared according to general procedure 1 using 2-naphthol (1.44 g, 10.0 mmol). Purification by flash silica chromatography (40 x 100 mm Silica, neat CH_2Cl_2,) gives the title compound (2.38 g, 84%) as an off-white

amorphous solid; Mp 70-73 °C; R_F: 0.23 (eluent = 20% ethyl acetate in hexanes); ν_{max} / cm^{-1} (film) 3246, 3057, 2928, 2872, 1628, 1595, 1506, 1454, 346, 1269, 1223, 1173, 1125, 1080, 1039, 1013, 957, 912, 895, 851, 831, 802, 743, 563, 476; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.83 (1H, d, *J* 2.5), 4.09-4.14 (1H, m), 4.21 (1H, dd, *J* 9.5, 3.2), 5.19 (1H, dt, *J* 8.7, 2.6), 7.06-7.16 (3H, m), 7.19 (1H, dd, *J* 8.9, 2.5), 7.36 (1H, m), 7.41-7.51 (3H, m), 7.70 (1H, d, *J* 8.2), 7.77 (2H, dd, *J* 8.5, 5.2); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -114.0 ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 72.1, 73.4 (d, *J* 1.0), 107.2, 115.7 (d, *J* 21.5), 118.7, 124.1, 126.7, 126.9, 127.8, 128.2 (d, *J* 8.2), 129.4, 129.8, 134.6, 135.6 (d, *J* 3.1), 156.4, 162.9 (d, *J* 246.3). HRMS (ASAP) $C_{18}H_{15}FO_2$ $[M]^+$ found 282.1055, requires 282.1056 (-0.4 ppm).

7.2. Optimisation of S_NAR/isomerisation protocol

7.2.1. General procedure 2 – Optimisation conditions



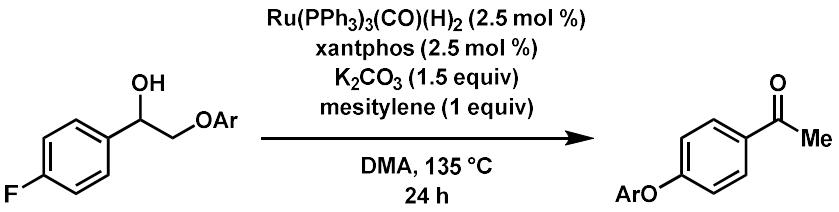
A 10 mL microwave vial was charged with dihydridocarbonyltris(triphenylphosphine)ruthenium (23.0 mg, 2.50 mol %), xantphos (14.5 mg, 2.50 mol %), 1-(4-fluorophenyl)-2-phenoxyethan-1-ol (232 mg, 1.00 mmol), a polar aprotic solvent (varied amounts), potassium carbonate (207 mg, 1.50 mmol), a magnetic stirrer, and mesitylene (139 µL, 1.00 mmol) as internal standard. The reaction vial was then crimped shut, and heated to 135 °C for varied times. After the allotted time, the reaction was cooled to rt, sampled and analysed using ^{1}H NMR spectroscopy of the crude reaction mixture, yielding the results below (table **7.1**). All NMR yields are reported relative to mesitylene as internal standard. Entry **6** was taken as optimal conditions.

Entry	[Ru] and ligand (mol %)	Time (h)	Solvent (concentration)	NMR yield (Isolated)
1	5	24	DMF (0.4 M)	91%

2	5	24	DMSO (0.4 M)	76%
3	5	24	DMA (0.4 M)	100%
4	2.5	24	DMA (0.4 M)	95%
5	1	24	DMA (0.4 M)	26%
6	2.5	24	DMA (1 M)	100% (79%)
7	2.5	16	DMA (1 M)	100%

Table 7.1 - Optimisation of S_NAR/isomerisation protocol

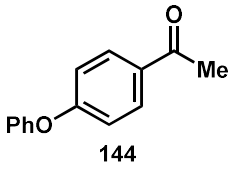
7.3. General procedure 3 – Isomerisation/S_NAr protocol



A 10 mL microwave vial was charged with $Ru(PPh_3)_3(CO)(H)_2$ (23.0 mg, 2.50 mol %), xantphos (14.5 mg, 2.50 mol %), a 1-(4-fluorophenyl)-phenoxyethanol (1.00 mmol), dimethylacetamide (1.00 mL), potassium carbonate (207 mg, 1.50 mmol) and a magnetic stirrer. The reaction vial was then crimped shut, and heated to 135 °C for 24 hours. The reaction was cooled to rt, and the contents of the vial poured over H_2O (50 mL). The phases were separated, and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and dried under reduced pressure. The resulting crude diaryl ether was then purified by flash silica column chromatography to yield the products shown below (extra purification steps are listed as necessary).

7.4. Substrate scope

1-(4-Phenoxyphenyl)ethan-1-one

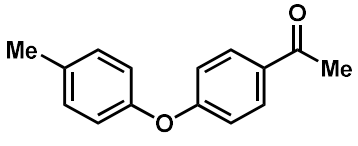


144

The title compound was prepared according to general procedure 2, using 1-(4-fluorophenyl)-2-phenoxy-ethan-1-ol (232 mg, 1.00 mmol). Purification by flash silica column chromatography (150 x 30 mm Silica, 5% ethyl acetate/hexanes) gives the title compound (168 mg, 79%) as a colourless crystalline solid (needles); Mp 43-44 °C (Lit.[2] 45-47 °C); R_F: 0.43 (20% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.57 (3H, s, C(2)*H*$_3$), 6.99-7.02 (2H, m, OPh ArC(2,6)*H*), 7.06-7.08 (2H, m, ArC(3,5)*H*), 7.19-7.22 (1H, m, OPh ArC(4)*H*), 7.38-7.42 (2H, m, OPh ArC(3,5)*H*), 7.93-7.96 (2H, m, ArC(2,6)*H*).

Spectroscopic data were in accordance with the literature.[1]

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

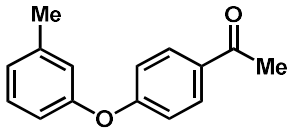


159

The title compound was prepared according to general procedure 2, using 1-(4-fluorophenyl)-2-(*p*-tolyloxy)-ethan-1-ol (246 mg, 1.00 mmol). Purification by flash silica column chromatography (150 x 30 mm silica, 5% ethyl acetate/hexanes) gives the title compound (177mg, 78%) as a colourless amorphous solid; Mp 40-43 °C (Lit.[2] 46-47 °C); R_F: 0.48 (20% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.38 (3H, s), 2.57 (3H, s), 6.95-699 (4H, m), 7.19-7.20 (2H, m), 7.91-7.94 (2H, m).

Spectroscopic data were in accordance with the literature.[3]

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

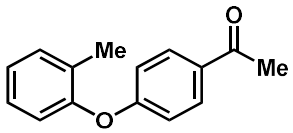


160

The title compound was prepared according to general procedure 2, using 1-(4-fluorophenyl)-2-(*m*-tolyloxy)-ethan-1-ol (246 mg, 1.00 mmol). Purification by flash silica column chromatography (130 x 30 mm Silica, neat CH_2Cl_2) gives the title compound (186 mg, 82 %) as a colourless amorphous solid; Mp 40-42 °C (Lit.[3] 39-40 °C); R_F: 0.50 (20% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.36 (3H, s), 2.57 (3H, s), 6.86-6.89 (2H, m), 6.98-7.02 (3H, m), 7.27 (1H, t, *J* 7.7), 7.92-7.95 (2H, m).

Spectroscopic data were in accordance with the literature.[3]

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

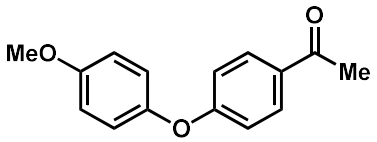


161

The title compound was prepared according to general procedure 2, using 1-(4-fluorophenyl)-2-(*o*-tolyloxy)-ethan-1-ol (246 mg, 1.00 mmol). Purification by flash silica column chromatography (30 x 140 mm Silica, neat CH_2Cl_2) gives the title compound (174 mg, 77%) as a colourless oil; R_F: 0.33 (10% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.19 (3H, s), 2.56 (3H, s), 6.88-6.91 (2H, m), 6.99 (1H, dd, *J* 8.0, 1.0), 7.15 (1H, td, 7.4, 1.2), *J* 7.21-7.25 (1H, m), 7.29 (1H, dd, *J* 7.5, 1.0), 7.91-7.93 (2H, m).

Spectroscopic data were in accordance with the literature.[3]

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

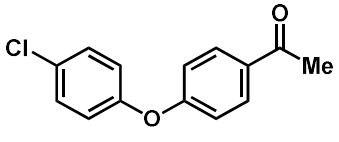


162

The title compound was prepared according to general procedure 2 using 1-(4-fluorophenyl)-2-(4-methoxyphenoxy)ethan-1-ol (262 mg, 1.00 mmol). Purification by flash silica column chromatography (150 x 30 mm Silica, 10% ethyl acetate/hexanes) gives the title compound (206 mg, 85%) as a colourless amorphous solid; Mp 49-51 °C (Lit.[3] 48-51 °C); R_F: 0.35 (20% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.56 (3H, s), 3.83 (3H, s), 6.94 (4H, ddd, *J* 9.1, 6.1. 2.5), 7.00-7.03 (2H, m), 7.90-7.92 (2H, m).

Spectroscopic data were in accordance with the literature.[3]

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

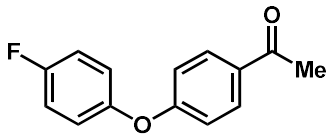


164

The title compound was prepared according to general procedure 2, using 2-(4-chlorophenoxy)-1-(4-fluorophenyl)ethan-1-ol (267 mg, 1.00 mmol). Purification by flash silica column chromatography (130 x 30mm Silica, 10% ethyl acetate/hexanes) to give the title compound (193 mg, 78%) as a colourless amorphous solid; Mp 58-61 °C (Lit.[2] 63-64 °C), R_F: 0.45 (20% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.58 (3H, s), 6.98-7.02 (4H, m), 7.34-7.37 (2H, m), 7.93-7.96 (2H, m).

Spectroscopic data were in accordance with the literature.[3]

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

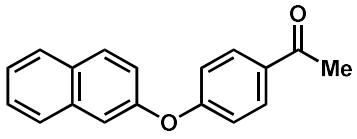


165

The title compound was prepared according to general procedure 2, using 2-(4-fluorophenoxy)-1-(4-fluorophenyl)ethan-1-ol (250 mg, 1.00 mmol). Purification by flash silica column chromatography (145 x 30 mm Silica, 10% ethyl acetate/hexanes) gives the title compound (184 mg, 80%) as a colourless amorphous solid; Mp 56-59 °C (Lit.[3] 56-59 °C); R_F: 0.43 (20% ethyl acetate in hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.57 (3H, s), 6.95-6.98 (2H, m), 7.03-7.12 (4H, m), 7.93-7.95 (2H, m); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -122.0.

Spectroscopic data were in accordance with the literature.[3]

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



167

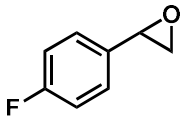
The title compound was prepared according to general procedure 2, using 1-(4-fluorophenyl)-2-(naphthalen-2-yloxy)ethan-1-ol (282 mg, 1.00 mmol). Purification by flash silica column chromatography (100 x 45 mm Silica, neat CH_2Cl_2) gives the title compound (226 mg, 86%) as a colourless amorphous solid; Mp 62-63 °C (Lit.[3] 62-65 °C); R_F: 0.45 (20% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.59 (3H, s), 7.05-7.08 (2H, m), 7.26 (1H, dd, *J* 8.8, 2.4), 7.48 (3H, m), 7.76 (1H, d, *J*, 8.0), 7.88 (2H, dd, *J* 12.9, 8.4), 7.95-7.98 (2H, m).

Spectroscopic data were in accordance with the literature.[3]

7.5. Telescoped diaryl ether synthesis

7.5.1. Synthesis of epoxide 168

2-(4-Fluorophenyl)oxirane



168

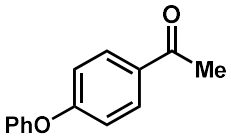
Following a modified literature procedure,[5] a 100 mL round bottomed flask was charged with 2-bromo-1-(4-fluorophenyl)-ethan-1-one (2.17 g, 10.0 mmol) and methanol (20 mL). The reaction was then cooled to 0 °C, and $NaBH_4$ (267 mg, 15.0 mmol) added portionwise. The reaction was then warmed to room temperature, and stirred until reaction completion (ca. 4 hours, confirmed by TLC), then concentrated *in vacuo*, and partitioned with water (20 mL). The phases were separated, and the aqueous phase extracted in Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

The resulting crude material was dissolved in THF (30 mL). The reaction was stirred at room temperature, and aq. NaOH (1 N, 20 mL, 40.0 mmol) was added. The reaction was then stirred at this temperature until completion (*ca.* 4 hours, confirmed by TLC), at which point water (50 ml) was added. The reaction was then separated, and the aqueous phase extracted in Et_2O (3 x 40 mL). The combined organic extracts were washed in brine, dried over $MgSO_4$, filtered, and dried carefully in vacuo. Purification by flash chromatography (30 x 40 mm Silica, 10% ethyl acetate/hexanes,) gave the title compound (980 mg, 80%) as a colourless oil. R_F: 0.36 (10% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.77 (1H, dd, *J* 2.6, 5.4 (C(1)H_AH_B), 3.14 (1H, dd, *J* 4.0, 5.4), 3.85 (1H, dd, *J* 2.6, 4.0, C(2)*H*), 7.00-7.07 (2H, m, ArC(2,6)*H*), 7.21-7.28 (2H, m, ArC(3,5)*H*).

Spectroscopic data were in accordance with the literature.[4]

7.5.2. Telescoped one pot diaryl ether synthesis

1-(4-Phenoxyphenyl)-ethan-1-one



144

A 10 mL microwave vial was charged with 2-(4-fluorophenyl)oxirane (138 mg, 1.00 mmol), phenol (94.1 mg, 1.00 mmol), potassium carbonate (207 mg, 1.50 mmol), dimethylacetamide (1.00 mL) and a magnetic follower. The reaction vessel was crimped shut, and the reaction heated to 135 °C, and stirred at this temperature for 24 hours. The reaction vessel was then cooled to room temperature, and opened. $Ru(PPh_3)(CO)(H)_2$ (23.0 mg, 2.50 mol%) and xantphos (14.5 mg, 2.50 mol%) were then added, the reaction vessel crimped shut once more, and heated to 135 °C. The reaction was stirred at this temperature for 24 hours, cooled to room temperature, and the contents of the vial poured over H_2O (50 mL). The phases were separated, and the aqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered, and dried under reduced pressure. The resulting crude diaryl ether was purified by flash silica column chromatography (30 x 150 mm Silica, 5% ethyl acetate/hexanes) to give the title compound (124 mg, 59%) as a colourless amorphous solid; Mp 40-43 (Lit.[1] 45-47); R_F: 0.43 (20% ethyl acetate/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.57 (3H, s), 6.99-7.02 (2H, m), 7.06-7.09 (2H, m), 7.19-7.22 (1H, m), 7.38-7.42 (2H, m), 7.93-7.96 (2H, m).

Spectroscopic data were in accordance with that in the literature.[3]

7.6. References

[1]: Y. Zhai, X. Chen, W. Zhou, M. Fan, Y. Lai and D. Ma, *J. Org. Chem.*, 2017, **82**, 4964–4969.

[2]: J. Chen, X. Wang, X. Zheng, J. Ding, M. Liu and H. Wu, *Tetrahedron*, 2012, **68**, 8905–8907.

[3]: 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.

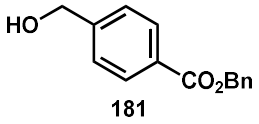
[4]: K. T. Man, M. Klawonn, S. Bhor, C. Döbler, G. Anilkumar, H. Hugl, W. Mägerlein and M. Beller, *Org. Lett.*, 2005, **7**, 987–990.

Chapter 8: Experimental – Manganese-catalysed *N*-alkylation of sulfonamides using alcohols

Table of Contents

8.1. Synthesis of substrates

Benzyl 4-(hydroxymethyl)benzoate



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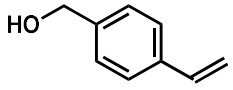
A 100 mL round-bottomed flask equipped with a magnetic stirrer bar was charged with 4-(hydroxymethyl)benzyl alcohol (3.04 g, 20 mmol), K_2CO_3 (3.04 g, 22 mmol), DMF (23 mL) and benzyl bromide (2.40 mL, 3.42 g, 20 mmol), and the reaction heated at 30 °C for 24 h. The resulting mixture was then cooled, and H_2O added (30 mL). The mixture was then transferred to a separatory funnel filled with ethyl acetate (50 mL). The organic phase was collected, and aqueous phase was washed with ethyl acetate (2 × 50 mL). The organic phases were then combined, washed with brine (7 × 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by recrystallisation (Et_2O/hexanes) gave the title compound (3.7g, 76%) as a colourless crystalline solid (prisms); Mp 56-58 °C (Et_2O/hexanes); R_F: 0.16 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 1719, 1611, 1454, 1416, 1366, 1263, 1171, 1115, 1098, 1080, 1040, 1015, 934, 914, 845, 822, 785, 746, 700, 598, 523, 465, 438, 415, 403; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 1.83 (1H, t, *J* 6.0), 4.77 (2H, d, *J* 6.0), 5.37 (2H, s), 7.30-7.50 (7H, m), 8.07 (2H, d, *J* 8.0); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 64.9, 66.9, 126.6, 128.3, 128.4, 128.7, 129.4, 130.1, 136.2, 146.2, 166.4; HRMS (ES^+) $C_{15}H_{15}O_3$ $[M+H]^+$ found 243.1002, requires 243.1021 (+0.4 ppm).

(4-Vinylphenyl)methanol



184

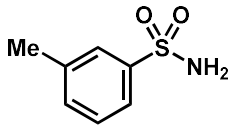
Following modified literature procedure,[1] a flame dried round bottomed flask was charged with a magnetic stirrer bar, magnesium turnings (262 mg, 11.5 mmol), a crystal of iodine, and dry THF (20 mL), under inert atmosphere. The resulting suspension was cooled to 0 °C under vigorous stirring. To the reaction mixture was

added 4-bromostyrene dropwise (1.00 mL, 7.64 mmol) over 30 minutes, and the reaction was warmed to room temperature. After stirring at this temperature for 4 hours, a multi-necked flame dried round bottomed flask was fitted with a drying column of anhydrous calcium sulfate, fitted with a suba seal. Through the side arm of the flask was added small quantities of CO_2(s), and the side arm sealed with a suba seal. The resultant CO_2(g) was passed through the drying column, and bubbled into the reaction solution at rt, by use of a cannula. This process was continued with a low flow rate for 3 hours, after which time the reaction mixture was quenched with 2 M H_2SO_4 (10 mL), and extracted in Et_2O (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. The crude solid was recrystallized from boiling petroleum ether 40-60 to remove major impurities, yielding crude 4-vinylbenzoic acid that was used directly in the next step.

Following a literature procedure,[2] a flame dried round bottomed flask was charged with a magnetic stirrer bar, lithium aluminium hydride (758 mg, 20.0 mmol) and THF (80 mL) under inert atmosphere. The resulting slurry was cooled to 0 °C under rapid stirring, and a solution of 4-vinylbenzoic acid (500 mg, 3.37 mmol) in Et_2O (25 mL) was added dropwise. The resulting reaction mixture was then warmed to room temperature and stirred for one hour at this temperature, then quenched with dropwise H_2O (256 µL), 10% w/w NaOH/H_2O (512 µL), then H_2O (768 µL). The mixture was stirred vigorously, until a white slurry was formed, and then filtered. The filtrate was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting crude material was then purified by flash column chromatography (30 × 110 mm Silica, 10-20% ethyl acetate/petroleum ether 40-60) to give the title compound (423 mg, 94%) as a colourless oil; R_F: 0.20 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.62 (1H, t, *J* 6.0, O*H*), 4.68 (2H, d, *J* 5.9, CH_2OH), 5.25 (1H, dd, *J* 10.9, 0.8, alkene CH_AH$_B$), 5.75 (1H, dd, *J* 17.6, 0.8, alkene CH$_A$$H_B$), 6.72 (1H, dd, *J* 17.6, 10.9, alkene C*H*), 7.33 (2H, d, *J* 8.2 ArC(3,5)*H*), 7.40-7.42 (2H, m, ArC(2,6)*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 65.3 (*C*H_2OH), 114.1 (alkene *C*H$_A$H$_B$), 126.5 (Ar*C*(3,5)H), 127.3 (Ar*C*(2,6)H), 136.6 (alkene *C*H), 137.2 (Ar*C*(4)CHCH$_2$), 140.5 (Ar*C*(1)CH$_2$OH).

Spectroscopic data were in accordance with the literature.[3]

3-Methylbenzenesulfonamide

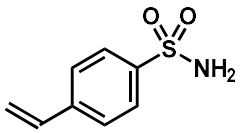


217

Following a modified literature procedure,[4] a round bottomed flask was charged with a magnetic follower, 3-methylbezene sulfonyl chloride (290 µL, 2.00 mmol), and acetone (3 mL). The resulting solution was stirred, and cooled to 0 °C. Concentrated ammonium hydroxide solution (28-30% w/w, 8 mL, 118 mmol) was then added, and the resulting solution allowed to warm to room temperature, before stirring at this temperature for 4 hours. The reaction was then concentrated *in vacuo*, until a precipitate was observed. The resulting slurry was then filtered, and washed with water, to yield the title compound (112 mg, 33%) as a colourless amorphous solid, Mp 107-108 °C (Lit. 109-111 °C (MeOH/hexanes))[6]; R_F: 0.20 (30% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.43 (3H, s, ArC*H*$_3$), 4.81 (2H, s, br, N*H*$_2$), 7.38-7.43 (2H, m, ArC(3,4)*H*), 7.72-7.75 (2H, m, ArC(2,6)*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ_C: 21.5 (Ar*C*H$_3$), 123.7 (Ar*C*(5)H), 127.0 (Ar*C*(4)H), 129.2 (Ar*C*(2)H), 133.7 (Ar*C*(6)H), 139.6 (Ar*C*(3)CH$_3$), 141.9 (Ar*C*(1)SO$_2$NH$_2$).

Spectroscopic data were in accordance with the literature.[5]

4-Vinylbenzenesulfonamide



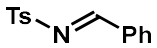
220

Following a literature procedure,[6] a round bottomed flask was charged with a magnetic follower, sodium 4-vinylbenzenesulfonate (1.03 g, 5.00 mmol) and dimethyl formamide (8.3 mL). The reaction mixture was stirred, and cooled in ice, Thionyl chloride (4.14 mL, 41.0 mmol) was then added dropwise, over the course of half an hour. The reaction mixture was then stirred at 0 °C for 6 hours, before stirring was stopped, and the reaction vessel was sealed and left in the fridge overnight. The solution was then poured slowly over ice water (15 mL), and extracted in diethyl ether (3 × 7 mL), dried over $MgSO_4$, filtered, and concentrated under reduced

pressure. To the resulting crude mixture was then added a magnetic follower, and concentrated ammonium hydroxide solution (28-30% w/w, 18 mL) was added slowly. This reaction mixture was then stirred for two hours, before dilution in water (5 mL), and subsequent extraction in diethyl ether (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to yield the title compound (400 mg, 43%) as a colourless amorphous solid; Mp 138-140 °C (Lit.[7] 141 °C (diethyl ether)); R_F: 0.21 (30% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.81 (2H, s, br), 5.44 (1H, d, *J* 10.9), 5.88 (1H, d, *J* 17.6), 6.75 (1H, dd, *J* 10.9, 17.6), 7.53 (2H, d, *J* 8.1), 7.88 (2H, d, *J* 8.1); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 117.8, 127.0, 127.1, 135.5, 140.9, 142.3.

Spectroscopic data were in accordance with the literature.[7]

***N*-Benzylidene-4-methylbenzenesulfonamide**



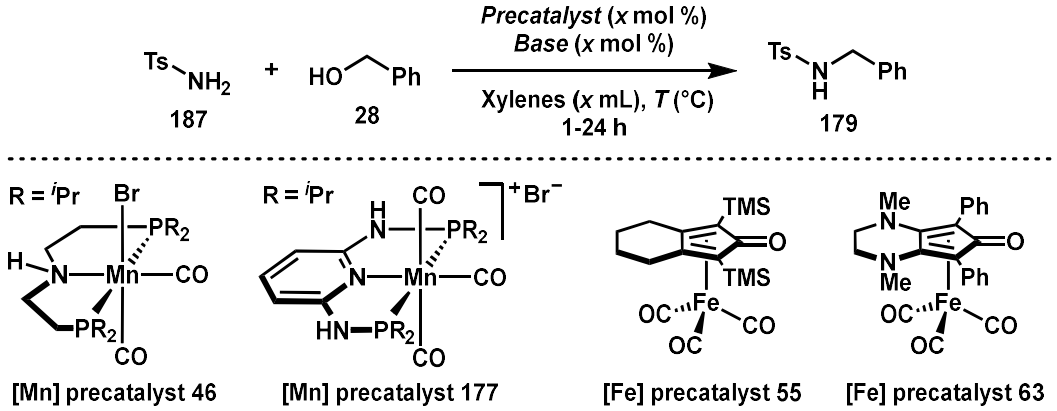
250

Following a literature procedure,[8] an oven dried pressure tube was charged with a magnetic stirrer, *p*-toluenesulfonamide (1.03 g, 6.0 mmol), and DCM (18.8 mL). The solution was stirred vigorously, and benzaldehyde (704 µL, 7.2 mmol), molecular sieves (6.0 g, 1 g/mmol) and pyrollidine (49.3 µL, 0.6 mmol) were added. The reaction vessel was then sealed, and heated to 60 °C in an oil bath for 24 hours. The reaction vessel was cooled to room temperature, and filtered through a pad of celite. The solvent was removed *in vacuo* to yield a crude oil. The residual benzaldehyde was removed under high vacuum with gentle heating (40 °C), to yield the title compound (1.38 g, 89%) as a yellow solid (hexagonal), Mp 104-106 (Lit.[9] 105 °C (DCM)); R_F: 0.30 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.44 (3H, s (tolyl C*H*$_3$), 7.35 (2H, d, *J* 8.1, tolyl ArC(3,5)), 7.49 (2H, t, *J* 7.7, phenyl ArC(3,5)*H*), 7.62 (1H, t, *J* 7.4, phenyl ArC(4)*H*) 7.89 (2H, d, *J* 8.2, phenyl ArC(2,6)*H*), 7.93 (2H, d, *J* 7.3, tolyl ArC(2,6)*H*), 9.04 (1H, s, C*H*(N)Ts); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.8 (tolyl *C*H$_3$), 128.3 (tolyl Ar*C*(3,5)H), 129.3 (phenyl Ar*C*(3,5)H), 130.0 (tolyl Ar*C*(2,6)H), 131.5 (phenyl Ar*C*(4)H), 132.6 (tolyl Ar*C*(4)CH$_3$), 135.1 (phenyl Ar*C*(2,6)H), 135.3 (phenyl (Ar*C*(1)), 144.8 (tolyl Ar*C*(1)), 170.3 (*C*(N)Ts).

Spectroscopic data were in accordance with the literature.[9]

8.2. Optimisation of the Mn-catalysed *N*-benzylation

8.2.1. General procedure 1 – Optimisation conditions



A 10 mL microwave vial was charged with a magnetic stirrer bar, *p*-toluenesulfonamide (171 mg, 1.0 mmol), a base (varied masses and loadings), a base metal precatalyst (varied masses and loadings), benzyl alcohol (104 µL, 1.0 mmol) and xylenes (varied volumes). The vial was then crimped shut, and stirred vigorously at the indicated temperature for the required amount of time. The reaction vessel was then cooled, decrimped, and to the reaction mixture was added mesitylene (69.6 µL, 0.5 mmol), water (1 mL) and ethyl acetate (1 mL). The reaction mixture was then stirred for an additional 5 minutes, and then allowed to separate for a further 5 minutes. The top phase of the crude reaction mixture was then sampled directly, and analysed by ^{1}H NMR spectroscopy to give the NMR yields shown table **8.1**), relative to mesitylene. Where required, the crude reaction mixture was then concentrated under reduced pressure, loaded directly onto silica, and purified by flash column chromatography.

Entry	Catalyst (mol %)	Base (mol %)	T (°C)	Solvent (mL)	Reaction time (h)	Yield (%)
1	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	24	**98 (86)**
2	**117** (5)	K_2CO_3 (10)	150	Xylenes (1)	24	<2

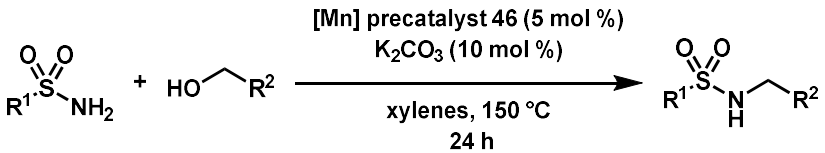
3	**55**[a] (5)	K_2CO_3 (10)	150	Xylenes (1)	24	<2
4	**66**[a] (5)	K_2CO_3 (10)	150	Xylenes (1)	24	<2
5	**46** (5)	K_2CO_3 (100)	150	Xylenes (1)	24	91
6	-	K_2CO_3 (10)	150	Xylenes (1)	24	<2
7	**46** (5)	-	150	Xylenes (1)	24	5
8	**46** (4)	K_2CO_3 (10)	150	Xylenes (1)	24	94
9	**46** (3)	K_2CO_3 (10)	150	Xylenes (1)	24	42
10	**46** (2)	K_2CO_3 (10)	150	Xylenes (1)	24	7
11	**46** (1)	K_2CO_3 (10)	110	Xylenes (1)	24	18
12	**46** (5)	KO*t*Bu (10)	150	Xylenes (1)	24	41
13	**46** (5)	KOH (10)	150	Xylenes (1)	24	5
14	**46** (5)	Cs_2CO_3 (10)	150	Xylenes (1)	24	94
15	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	8	100
16	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	6	82
17	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	4	70
18	**46** (5)	K_2CO_3 (10)	150	Xylenes (1)	1	20
19	**46** (5)	K_2CO_3 (10)	150	Xylenes (0.5)	24	92
20	**46** (5)	K_2CO_3 (10)	150	Xylenes (2)	24	92

a: Reactions run with 10 mol% $Me_3NO{\cdot}2H_2O$ as activator

Table 8.1 - Optimisation of the Mn-catalysed *N*-benzylation

8.3. General procedures

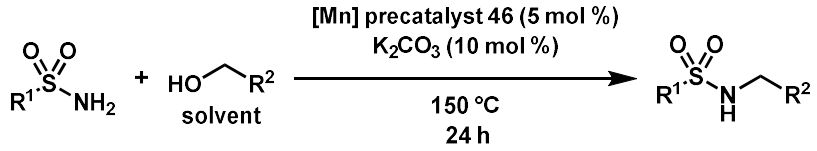
8.3.1. General procedure 2 – Synthesis of *N*-alkylated sulfonamides



A 10 mL microwave vial was charged with a magnetic stirrer bar, an amide (1.00 mmol), potassium carbonate (13.8 mg, 10 mol %), [Mn] precatalyst **46** (24.8 mg, 0.05 mol %), an alcohol (1.00 mmol) and xylenes (1 mL). The vial was then crimped shut, and stirred vigorously at 150 °C for 24 hours. The reaction vessel was then cooled, decrimped, and to the reaction mixture was added mesitylene (69.6 µL, 0.5 mmol), water (1 mL), and ethyl acetate (1 mL). The reaction mixture was then stirred

for an additional 5 minutes, then sampled directly, and analysed by ^{1}H NMR spectroscopy. The crude reaction mixture was then separated, washing the aqueous phase with ethyl acetate (3 × 5 mL). The organic phases were then combined, dried over $MgSO_4$, and filtered. The resulting solution was then concentrated under reduced pressure, loaded directly onto silica, and purified by flash column chromatography. Extra purification steps are listed as applicable.

8.3.2. General procedure 3 – Synthesis of *N*-alkylated sulfonamides with solvent alcohol

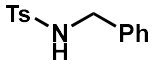


A 10 mL microwave vial was charged with a magnetic stirrer bar, an amide (1.00 mmol), potassium carbonate (138 mg, 1.00 mmol), [Mn] precatalyst **46** (24.8 mg, 5 mol %), and an alcohol (1 mL). The vial was then crimped shut, and stirred vigorously at 150 °C for 24 hours. The reaction vessel was then cooled, decrimped, and to the reaction mixture was added mesitylene (69.6 µL, 0.5 mmol), water (1 ml) and ethyl acetate (1 mL). The reaction mixture was then stirred for an additional 5 minutes, then sampled directly, and analysed by proton NMR. The crude reaction mixture was then separated, washing the aqueous phase with ethyl acetate (3 × 5 mL). The organic phases were then combined, dried over $MgSO_4$, and filtered. The resulting solution was then concentrated under reduced pressure, loaded directly onto silica, and purified by flash column chromatography. Extra purification steps are listed as applicable.

8.4. Substrate scope

8.4.1. Alcohol scope

N-Benzyl-4-methylbenzenesulfonamide

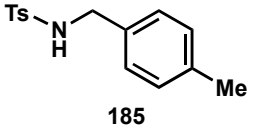


179

The title compound was prepared according to general procedure 1, using K_2CO_3 (13.8 mg, 10 mol %), [Mn] precatalyst 46 (24.8 mg, 5 mol %), and xylenes (1 mL). The reaction was stirred at 150 °C for 24 hours, and purified by flash column chromatography (30 × 150 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (225 mg, 86%) as a colourless crystalline powder (needles); Mp 163-165°C (Lit.[11] 166-168 °C (cyclohexane/ethyl acetate)); R_F: 0.20 (20% ethyl acetate/petroleum ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.44 (3H, s, tolyl C*H*$_3$), 4.13 (2H, d, *J* 6.2, benzyl C*H*$_2$), 4.61 (1H, t, *J* 5.8, N*H*), 7.19-7.21 (2H, m, benzyl ArC(2,6)*H*), 7.24-7.33 (5H, m, benzyl ArC(3,4,5)*H* + tolyl ArC(3,5)*H*) 7.75-7.78 (2H, m, tolyl ArC(2,6)*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7 (tolyl *C*H_3), 47.5 (benzyl *C*H_2), 127.4 (tolyl Ar*C*(3,5)H), 128.0 (phenyl Ar*C*(2,6)H), 128.1 (phenyl Ar*C*(4)H), 128.9 (phenyl Ar*C*(3,5)H), 129.9 (tolyl Ar*C*(2,6)H), 136.4 (tolyl Ar*C*(4)CH_3), 137.0 (phenyl Ar*C*(1)CH_2), 143.7 (tolyl Ar*C*(1)SO_2NH).

Spectroscopic data were in accordance with the literature.[10]

4-Methyl-*N*-(2-methylbenzyl)benzenesulfonamide



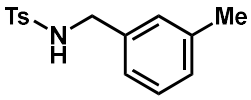
185

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and 4-methylbenzyl alcohol (122 mg, 1.00 mmol), and was purified by flash column chromatography (30 × 100 mm silica, 20% ethyl acetate/petroleum ether 40-60) to yield the title compound (263 mg, 96%) as

a pale yellow amorphous solid, Mp 93-94 °C (Lit.[11] 95 °C (ethyl acetate/cyclohexane)); R_F: 0.25 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.31 (3H, s), 2.44 (3H, s), 4.07 (2H, d, *J* 6.1), 4.56 (1H, t, *J* 5.9), 7.06-7.10 (4H, m), 7.30-7.32 (2H, d, *J* 8.0), 7.76 (2H, d, *J* 8.2); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.2, 21.7, 47.2, 127.4, 128.0, 129.5, 129.9, 133.3, 137.0, 137.9, 143.6.

Spectroscopic data were in accordance with the literature.[11]

3-Methyl-*N*-(2-methylbenzyl)benzenesulfonamide

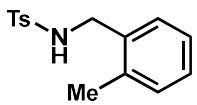


186

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and 3-methylbenzyl alcohol (122 mg, 1.00 mmol), and was purified by flash column chromatography (30 × 110 mm silica, 20% ethyl acetate/petroleum ether 40-60) to yield the title compound (264 mg, 96%), as an off-white amorphous solid; Mp 65-66 °C (Lit.[12] 64-66 °C (ethyl acetate/hexanes); R_F: 0.29 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.28 (3H, s), 2.44 (3H, s), 4.09 (2H, d, *J* 6.2), 4.68 (1H, t, *J* 5.9), 6.97-6.98 (2H, m), 7.05-7.08 (1H, m), 7.14-7.17 (1H, m), 7.31 (2H, d, *J* 7.9), 7.74-7.77 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.4, 21.7, 47.4, 125.0, 127.4, 128.7, 128.8, 128.8, 129.9, 136.3, 137.1, 138.6, 143.7.

Spectroscopic data were in accordance with the literature.[12]

2-Methyl-*N*-(2-methylbenzyl)benzenesulfonamide



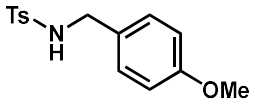
187

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and 2-methylbenzyl alcohol (122 mg, 1.00 mmol), and was purified by flash column chromatography (30 × 100 mm silica, 20%

ethyl acetate/petroleum ether 40-60) to yield the title compound (219 mg, 80%) as a pale yellow amorphous solid; Mp 115-117°C (Lit.[12] 113-117 °C (ethyl acetate/hexanes)); R_F: 0.24 (20% ethyl acetate/petroleum ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.25 (3H, s), 2.45 (3H, s), 4.09 (2H, d, *J* 6.0), 4.44 (1H, t, br, *J* 5.7), 7.10-7.13 (3H, m), 7.16-7.20 (1H, m), 7.32 (2H, d, *J* 8.0), 7.76-7.78 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 18.9, 21.7, 45.6, 126.4, 127.4, 128.4, 129.0, 129.9, 130.8, 134.0, 136.8, 136.9, 143.7.

Spectroscopic data were in accordance with the literature.[12]

_N_-(4-Methoxybenzyl)-4-methylbenzenesulfonamide

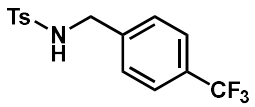


188

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and 4-methoxybenzyl alcohol (138 mg, 1.00 mmol),and was purified by flash column chromatography (30 × 100 mm silica, 20% ethyl acetate/petroleum ether 40-60) to yield the title compound (269 mg, 91%) as an off-white amorphous solid; Mp 120-123 °C (Lit.[12] 119-121 °C (ethyl acetate/hexanes)); R_F: 0.13 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.44 (3H, s), 3.78 (3H, s), 4.06 (2H, d, *J* 6.1), 4.51 (1H, t, *J* 5.7), 6.80 (2H, d, *J* 8.7), 7.11 (2H, d, *J* 8.6), 7.31 (2H, d, 8.0), 7.76 (2H, d, *J* 2.8); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 47.0, 55.4, 114.2, 127.4, 128.4, 129.4, 129.9, 137.0, 143.4, 159.5.

Spectroscopic data were in accordance with the literature.[12]

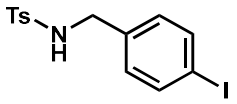
4-Methyl-_N_-(4-(trifluoromethyl)benzyl)benzenesulfonamide



189

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and (4-(trifluoromethyl)phenyl)methanol (126 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 110 mm silica, 20% ethyl acetate/petroleum ether 40-60) and trituration in petroleum ether 40-60 to give the title compound (235 mg, 70%) as an off-white crystalline solid (needles), Mp 134-137 °C; R_F: 0.29 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3263, 2980, 1618, 1446, 1317, 1308, 1288, 1155, 1111, 1092, 1067, 1018, 878, 822, 812, 731, 706, 662, 631, 594, 561, 544, 490, 419; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.43 (3H, s), 4.20 (2H, d, *J* 6.4), 4.91 (1H, t, br, *J* 6.3), 7.28 (2H, d, *J* 8.0), 7.30 (2H, d, *J* 8.0), 7.51 (2H, d, *J* 8.1), 7.72 (2H, d, *J* 8.3); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -62.65; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 46.8, 124.1 (q, *J* 272.5), 125.8 (q, *J* 3.8), 127.2, 128.2, 130.0, 130.1 (q, *J* 32.5), 136.8, 140.5, 143.9; HRMS (ES^+) $C_{15}H_{15}NO_2SF_3$ $[M+H]^+$ found 330.0774, requires 330.0776 (-0.6 ppm).

_N_-(4-Iodobenzyl)-4-methylbenzenesulfonamide

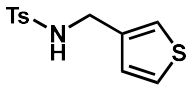


190

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and (4-iodophenyl)methanol (234 mg, 1.00 mmol), and was purified by flash column chromatography (30 × 100 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the product (326 mg, 84%) as an off-white amorphous solid, Mp 135-137 °C (Lit.[13] 135-137 °C (ethyl acetate)); R_F: 0.22 (20% ethyl acetate/petroleum ether 40-60), ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.45 (3H, s), 4.08 (2H, d, *J* 6.3), 4.62 (1H, t, br, *J* 6.0), 6.95 (2H, d, *J* 8.4), 7.30 (2H, d, *J* 8.0), 7.60 (2H, d, *J* 8.3), 7.73 (2H, d, *J* 8.3); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 46.9, 93.6, 127.3, 129.9, 129.9, 136.1, 137.0, 137.9, 143.9.

Spectroscopic data were in accordance with the literature.[13]

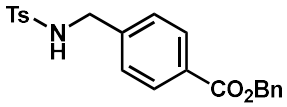
4-Methyl-*N*-(thiophen-3-ylmethyl)benzenesulfonamide



191

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and thiophen-3-ylmethanol (94.3 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 150 mm silica, 20% ethyl acetate/petroleum ether) to give the title compound (234 mg, 87%) as a dark yellow amorphous solid, Mp 108-110 °C; R_F: 0.18 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3264, 1599, 1456, 1422, 1335, 1319, 1308, 1163, 1094, 1065, 874, 856, 812, 772, 706, 696, 656, 590, 552, 540, 509, 476; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.44 (3H, s), 4.16 (2H, d, *J* 6.1), 4.56 (1H, t, br, *J* 5.7), 6.89 (1H, dd, *J* 5.0, 1.1), 7.03-7.07 (1H, m), 7.24 (1H, dd, *J* 5.0, 3.0), 7.31 (2H, d, *J* 8.1), 7.75 (2H, d, *J* 8.3); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 42.6, 123.1, 126.8, 127.2, 127.3, 129.9, 137.0, 137.2, 143.7; HRMS (ES$^+$) $C_{12}H_{14}NO_2S_2$ $[M+H]^+$ found 268.0470, requires 268.0466 (+1.5 ppm).

Benzyl 4-[((4-methylphenyl)sulfonamido)methyl]benzoate

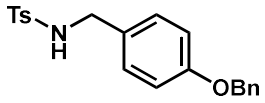


192

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and benzyl 4-(hydroxymethyl)benzoate (242 mg, 1.00 mmol), and was purified by flash column chromatography (30 × 120 mm silica, 20% ethyl acetate/petroleum ether 40-60), followed by trituration in petroleum ether 40-60, to give the title compound (205 mg, 52%) as a colourless amorphous solid, Mp 120-123 °C; R_F: 0.11 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3250, 1701, 1609, 1499, 1433, 1420, 1383, 1360, 1333, 1315, 1279, 1244, 1179, 1159, 1123, 1113, 1094, 1059, 1032, 1018, 982, 907, 883, 853, 814, 787, 762, 733, 719,708, 694, 656, 648, 583, 561, 546, 530, 519, 492,459, 419; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.42 (3H, s), 4.18 (2H, d, *J* 6.3), 4.79 (1H, t, br, *J* 6.0), 5.35 (2H, s), 7.28-7.44 (9H, m), 7.74 (2H, d, *J* 7.9), 7.97 (2H, d, *J* 8.0); ^{13}C

NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 47.0, 66.9, 127.3, 127.8, 128.3, 128.5, 129.8, 130.0, 130.2, 136.1, 136.9, 141.7, 143.9, 166.1; HRMS (AP^+) $C_{22}H_{22}NO_4S$ $[M+H]^+$ found 396.1274, requires 396.1270 (+1.0 ppm).

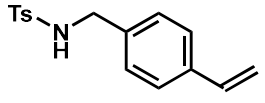
_N_-(4-(benzyloxy)benzyl)-4-methylbenzenesulfonamide



193

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and (4-(benzyloxy)phenyl)methanol (214 mg, 1.00 mmol), and was purified by flash column chromatography (30 × 125 mm silica, 20% ethyl acetate/petroleum ether) to yield the title compound (342 mg, 92%) as a colourless solid, Mp 123-126 °C; R_F: 0.19 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3291, 3269, 1616, 1597, 1585, 1495, 1452, 141412, 1383, 1323, 1256, 1153, 1090, 1028, 862, 841, 812, 743, 723, 689, 565, 546, 532, 513, 492, 461; ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.44 (3H, s), 4.06 (2H, d, *J* 6.1), 4.46 (1H, t, br, *J* 6.0), 5.04 (2H, s), 6.87-6.89 (2H, m), 7.09-7.12 (2H, m), 7.31-7.34 (3H, m), 7.36-7.42 (4H, m), 7.75-7.77 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 47.0, 70.2, 115.2, 127.4, 127.6, 128.2, 128.7, 128.8, 129.4, 129.9, 136.9, 137.1, 143.7, 158.7; HRMS (EI^+) $C_{21}H_{21}NO_3S$ $[M]^+$ found 367.1237, requires 367.1242 (-1.4 ppm).

4-Methyl-_N_-(4-vinylbenzyl)benzenesulfonamide



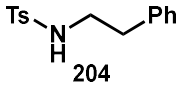
194

The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and (4-vinylphenyl)methanol (134 mg, 1.00 mmol), and was purified by flash column chromatography (30 × 95 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (240 mg, 84%) as a pale yellow amorphous solid, Mp 108-110 °C, (Lit.[14] 111-113 °C (ethyl acetate/hexanes)); R_F: 0.27 (20% ethyl acetate/petroleum ether 40-60); ^1H NMR

(500 MHz, $CDCl_3$) δ_H: 2.44 (3H, s), 4.11 (2H, d, *J* 6.2), 4.57 (1H, t, br, *J* 6.0), 5.24 (1H, dd, *J* 10.9, 0.5), 5.72 (1H, dd, *J* 17.6, 0.5), 6.67 (1H, dd, *J* 17.6, 10.9), 7.15 (2H, d, *J* 8.1), 7.30-7.33 (4H, m), 7.52-7.53 (2H, m), 7.76 (2H, d, *J* 8.3); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 47.2, 114.4, 126.6, 127.3, 128.2, 129.9 135.8, 136.3, 137.0, 137.5, 143.8.

Spectroscopic data were in accordance with the literature.[14]

4-Methyl-*N*-phenethylbenzenesulfonamide

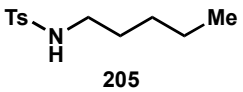


204

The title compound was prepared according to general procedure 3, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and 2-phenylethanol (1 mL), and was purified by flash column chromatography (45 × 115 mm silica, 5-20% ethyl acetate/petroleum ether 40-60), followed by trituration in petroleum ether 40-60 to give the title compound (198 mg, 72%) as a colourless amorphous solid, Mp 59-60 °C (Lit.[15] 62-64 °C (ethyl acetate/petroleum ether 40-60)); R_F: 0.27 (20% ethyl acetate/petroleum ether 40-60); ^1H NMR (500 MHz, $CDCl_3$) δ_H: 2.43 (3H, s), 2.76 (2H, t, *J* 6.9), 3.22 (2H, q, *J* 6.8), 4.36 (1H, t, br, *J* 5.9), 7.08 (2H, d, *J* 6.9), 7.20-7.23 (1H, m), 7.26-7.30 (4H, m), 7.39 (2H, d, *J* 8.3); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 35.9, 44.3, 127.0, 127.2, 128.9, 128.9, 129.9, 137.1, 137.8, 143.6.

Spectroscopic data were in accordance with the literature.[16]

4-Methyl-*N*-pentylbenzenesulfonamide



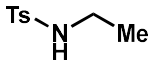
205

The title compound was prepared according to general procedure 3, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and *n*-pentanol (1 mL), and was purified by flash column chromatography (30 × 80 mm silica, 20% ethyl acetate/petroleum ether 40-60) to yield the title compound (208 mg, 86%) as a yellow oil; R_F: 0.31 (20% ethyl acetate/petroleum ether 40-60). ^1H NMR (500 MHz, $CDCl_3$) δ_H: 0.83-0.85 (3H,

m), 1.20-1.27 (4H, m), 1.42-1.48 (2H, m), 2.43 (3H, s), 2.93 (2H, q, *J* 7.1), 4.35 (1H, t, br, *J* 6.0), 7.31 (2H, d, *J* 8.0), 7.73-7.76 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 14.0, 21.7, 22.3, 28.8, 29.4, 43.4, 127.2, 129.8, 137.1, 143.5.

Spectroscopic data were in accordance with the literature.[17]

_N_-Ethyl-4-methylbenzenesulfonamide

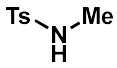


206

The title compound was prepared according to general procedure 3, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and ethanol (1 mL), and was purified by flash column chromatography (30 × 150 mm silica, 20% ethyl acetate/petroleum ether 40-60) to yield the title compound 179 mg (90%) as a yellow oil; R_F: 0.30 (20% ethyl acetate/petroleum ether 40-60). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.10 (3H, t, *J* 7.2), 2.43 (3H, s), 3.00 (2H, qd *J* 7.2, 6.2), 4.39 (1H, t, br, *J* 5.3), 7.31 (2H, d, *J* 7.9), 7.74-7.76 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 15.2, 21.7, 38.4, 127.3, 129.8, 137.1, 143.5.

Spectroscopic data were in accordance with the literature.[18]

_N_-Methyl-4-methylbenzenesulfonamide



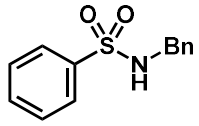
207

The title compound was prepared according to general procedure 3, using *p*-toluenesulfonamide (171 mg, 1.00 mmol) and methanol (1 mL), and was purified by flash column chromatography (30 × 150 mm silica, 20% ethyl acetate/petroleum ether 40-60) to yield the title compound (165 mg, 89%) as a colourless amorphous solid, Mp 72-73 °C (Lit.[19] 70-71 °C (hexanes)); R_F: 0.28 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.43 (3H, s), 2.65 (3H, d, *J* 5.4), 4.37 (1H, d, br, *J* 3.8) 7.32 (2H, d, *J* 2.1), 7.75 (2H, d, *J* 2.1); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 22.8, 29.5, 127.4, 129.9, 136.0, 143.7.

Spectroscopic data were in accordance with the literature.[19]

8.4.2. Sulfonamide scope

N-Benzylbenzenesulfonamide

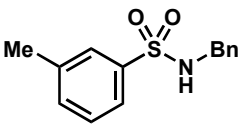


221

The title compound was prepared according to general procedure 2, using benzene sulfonamide (157 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 100 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (232 mg, 93%) as a yellow amorphous solid; Mp 77-79°C (Lit.[20] 78-80 °C (ethyl acetate/petroleum ether 40-60)); R_F: 0.27 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.15 (2H, d, *J* 6.2, benzyl C*H*$_2$), 4.75 (1H, t, br, N*H*), 7.18-7.20 (2H, m, phenyl ArC(2,6)*H*), 7.24-7.30 (3H, m, phenyl ArC(3,4,5)*H*), 7.50-7.54 (2H, m, tolyl ArC(3,5)*H*), 7.58-7.61 (1H, m, tolyl ArC(4)*H*), 7.87-7.89 (2H, m, ArC(2,6)*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 47.5 (benzyl *C*H$_2$), 127.3 (phenyl Ar*C*(2,6)H), 128.0 (phenyl Ar*C*(4)H), 128.1 (phenyl Ar*C*(2,6)), 128.9 (tolyl Ar*C*(3,5)H), 129.3 (tolyl Ar*C*(4)H), 132.9 (tolyl Ar*C*(2,6)H), 136.3 (phenyl Ar*C*(1)CH$_2$), 140.0 (tolyl Ar*C*(1)SO$_2$N).

Spectroscopic data were in accordance with the literature.[20]

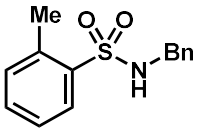
N-Benzyl-3-methylbenzenesulfonamide



222

The title compound was prepared according to general procedure 2, using 3-methylbenzenesulfonamide (171 mg, 1.00 mmol) and benzyl alcohol (109 μL, 1.00 mmol), and was purified by flash column chromatography (30 × 100 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (242 mg, 93%) as a colourless amorphous solid, Mp 46-48 °C; R_F: 0.20 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3265, 1599, 1454, 1427, 1360, 1319, 1256, 1209, 1150, 1099, 1055, 916, 889, 866, 810, 783, 746, 694, 658, 584,559, 527, 511, 484, 434, 407; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.42 (3H, s), 4.15 (2H, d, *J* 6.2), 4.61 (1H, t, br, *J* 5.4), 7.19-7.21 (2H, m), 7.24-7.30 (3H, m), 7.38-7.42 (2H, m), 7.67-7.69 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.5, 47.4, 124.4, 127.6, 128.0, 128.1, 128.8, 129.1, 133.6, 136.3, 139.5, 139.8; HRMS (ES^+) $C_{14}H_{16}NO_2S$ $[M+H]^+$ found 262.0901, requires 262.0902 (-0.4 ppm).

_N_-Benzyl-2-methylbenzenesulfonamide

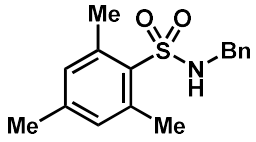


223

The title compound was prepared according to general procedure 2, using 2-methylbenzenesulfonamide (171 mg, 1.00 mmol) and benzyl alcohol (109 μL, 1.00 mmol), and was purified by flash column chromatography (30 × 100 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (231 mg, 86%) as an off-white amorphous solid, Mp 98-100 °C (Lit.[21] 101.2-102.5 °C (ethyl acetate)); R_F: 0.27 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.62 (3H, s), 4.12 (2H, d, *J* 6.1), 4.67 (1H, t, br, *J* 4.9), 7.16-717 (2H, m), 7.24-7.34 (m, 5H), 7.47 (1H, td, *J* 7.5, 1.0), 8.00 (1H, d, *J* 7.9); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 20.4, 47.3, 126.4, 128.1, 128.2, 128.9, 129.8, 132.7, 133.0, 136.4, 137.2, 137.9.

Spectroscopic data were in accordance with the literature.[21]

_N_-Benzyl-2,4,6-trimethylbenzenesulfonamide

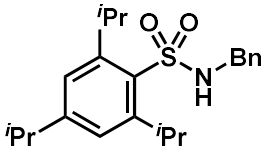


224

The title compound was prepared according to general procedure 2, using 2,4,6-trimethylbenzenesulfonamide (199 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 120 mm silica, 20% ethyl acetate/petroleum ether 40-60) to yield the title compound (266 mg, 92%) as a colourless crystalline solid (needles), Mp 94-97 °C (Lit.[22] 96-98 °C (ethyl acetate/hexanes)); R_F: 0.41 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.31 (3H, s), 2.64 (6H, s), 4.08 (2H, d, *J* 6.2), 4.64 (1H, t, br, *J* 5.8), 6.96 (2H, s), 7.23-7.25 (1H, m), 7.27-7.29 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.1, 23.1, 46.9, 128.0, 128.0, 128.8, 132.1, 133.5, 136.4, 139.3, 142.5.

Spectroscopic data were in accordance with the literature.[22]

_N_-Benzyl-2,4,6-triisopropylbenzenesulfonamide

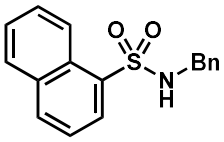


225

The title compound was prepared according to general procedure 2, using 2,4,6-triisopropylbenzenesulfonamide (283 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 100 mm silica, 20% ethyl acetate/petroleum ether 40-60) to yield the title compound (368 mg, 99%) as a colourless amorphous powder, Mp 83-85 °C; R_F: 0.60 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3316, 2959, 2866, 1763, 1599, 1454, 1425, 1383, 1362, 1319, 1298, 1256, 1196, 1152, 1105, 1057, 968, 941, 916, 889, 862, 810, 746, 694, 658, 627, 594, 559, 546, 529, 509, 436, 419; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.27 (18 H, t, *J* 6.9), 2.92 (1H, dt, *J* 13.9, 6.9), 4.15-4.21 (4H, m), 4.51 (1H, t, br, *J* 6.1), 7.18 (2H, s), 7.19-7.21 (2H, m), 7.27-7.30 (3H, m); ^{13}C NMR

(126 MHz, $CDCl_3$) δ_C: 23.8, 25.0, 29.9, 34.3, 47.2, 124.0, 128.1, 128.2, 128.9, 132.4, 136.6, 150.5, 153.0; HRMS (ES^+) $C_{22}H_{32}NO_2S$ $[M+H]^+$ found 374.2153, requires 374.2154 (-0.3).

_N_-Benzylnaphthalene-1-sulfonamide

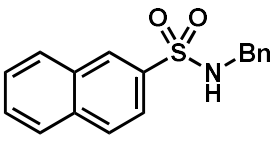


226

The title compound was prepared according to general procedure 2, using naphthalene-1-sulfonamide (207 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 110 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (251 mg, 84%) as a colourless amorphous solid, Mp 165-166 °C (Lit.[10] 166-168 °C (ethyl acetate/hexanes)); R_F: 0.30 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.08 (2H, d, *J* 6.1), 4.82 (1H, t, br, *J* 5.9), 7.05-7.07 (2H, m), 7.16-7.19 (3H, m), 7.53 (1H, dd, *J* 8.1, 7.5), 7.60-7.63 (1H, m), 7.65-7.69 (1H,m), 7.96 (1H, d, *J* 8.1), 8.07 (1H, d, *J* 8.2), 8.28 (1H, dd, *J* 7.3, 1.2), 8.65 (1H, d, *J* 8.6); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 47.5, 124.3, 124.4, 127.0, 127.9, 128.0, 128.3, 128.6, 128.7, 129.3, 130.1, 134.4, 134.5, 134.5, 136.2.

Spectroscopic data were in accordance with the literature.[10]

_N_-Benzylnaphthalene-2-sulfonamide



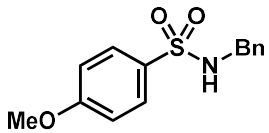
227

The title compound was prepared according to general procedure 2, using naphthalene-2-sulfonamide (207 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 105 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (270 mg, 91%) as

an off-white amorphous solid, Mp 121-122 °C (Lit.[23] 126.5 °C (acetone)); R_F: 0.28 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.18 (2H, d, *J* 6.2), 4.77 (1H, t, br, 5.9), 7.18-7.25 (5H, m), 7.61-7.68 (2H, m), 7.84 (1H, dd, *J* 8.7, 1.9), 7.92 (1H, d, *J* 8.1), 7.96-7.98 (2H, m), 8.45 (2H, d, *J* 1.2); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 47.6, 122.4, 127.8, 128.0, 128.1, 128.2, 128.8, 128.9, 129.0, 129.4, 129.8, 132.3, 135.0, 136.2, 136.8.

Spectroscopic data were in accordance with the literature.[23]

_N_-Benzyl-4-methoxybenzenesulfonamide

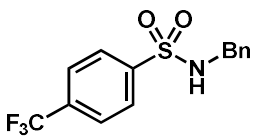


228

The title compound was prepared according to general procedure 2, using *p*-methoxybenzene sulfonamide (187 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 100 mm silica, gradient 20 - 40% ethyl acetate/petroleum ether 40-60) to give the title compound (255 mg, 92%) as an off-white amorphous solid; Mp 109-111°C (Lit.[24] 112-113 °C (ethyl acetate)); R_F: 0.35 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.88 (3H, s), 4.12 (2H, d, *J* 6.2), 4.63 (1H, t, br, *J* 6.0), 6.96-6.99 (2H, m), 7.18-7.21 (2H, m), 7.24-7.30 (3H, m), 7.80-7.83 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 47.4, 55.8, 114.4, 128.0, 128.1, 128.9, 129.5, 131.6, 136.4, 163.1.

Spectroscopic data were in accordance with the literature.[24]

_N_-Benzyl-4-(trifluoromethyl)benzenesulfonamide

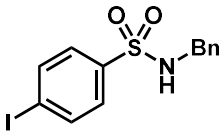


229

The title compound was prepared according to general procedure 3, using 4-(trifluoromethyl)benzenesulfonamide (225 mg, 1.00 mmol) and benzyl alcohol (109

µL, 1.00 mmol), and purified by flash column chromatography (45 × 150 mm silica, 10% ethyl acetate/petroleum ether 40-60), then triturated in petroleum ether 40-60 to yield the product (193 mg, 61%) as an off-white crystalline solid (needles), Mp 119-121 °C; R_F: 0.21 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3271, 1404, 1323, 1157, 1130, 1111, 1094, 1061, 1028, 1013, 907,876, 841, 733, 712, 696, 613, 598, 532, 488, 453, 430; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.21 (2H, d, *J* 8.1), 4.76 (1H, t, br, *J* 5.8), 7.16-7.18 (2H, m), 7.27-7.30 (3H, m), 7.75 (2H, d, *J* 8.2), 7.96 (2H, d, *J* 8.2); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -63.16; ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 475, 123.4 (q, *J* 273), 126.4 (q, *J* 3.7), 127.7, 128.0, 128.2, 128.9, 134.5 (q, *J* 33.1), 1235.8, 143.8; HRMS (ES^+) $C_{14}H_{13}NO_2SF_3$ $[M+H]^+$ found 316.0623, requires 316.0619 (+1.3 ppm).

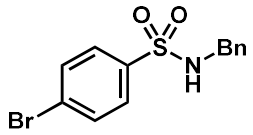
_N_-Benzyl-4-iodobenzenesulfonamide



230

The title compound was prepared according to General Procedure D using 4-iodobenzenesulfonamide (283 mg), and was purified by flash column chromatography (30 × 150 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (113 mg, 30%) as an off-white amorphous solid; Mp 117-118°C; R_F: 0.28 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3265, 3061, 3032, 1568, 1493, 1466, 1437, 1383, 1321, 1296, 1159, 1107, 1088, 1047, 1030, 1007, 989, 910, 867, 814, 750, 733, 586, 523, 471, 447, 419; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.16 (2H, d, *J* 6.1), 4.67 (1H, t, br, *J* 5.9), 7.17-7.19 (2H, m), 7.27-7.31 (3H, m), 7.55-7.58 (2H, m), 7.85-7.87 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 47.5, 100.2, 128.0, 128.3, 128.7, 129.0, 136.0, 138.5, 139.9; HRMS (ES^+) $C_{13}H_{13}NO_2S^{127}I$ $[M+H]^+$ found 373.9712, requires 373.9712 (+0.0 ppm).

_N_-Benzyl-4-bromobenzenesulfonamide

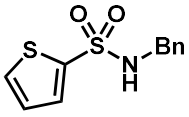


231

The title compound was prepared according to general procedure 2, using 4-bromobenzenesulfonamide (236 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 150 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (288 mg, 88%) as a colourless amorphous solid; Mp 117-118 °C (Lit.[21] 119-120 °C (ethyl acetate)); R_F: 0.32 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.13 (2H, d, *J* 6.1), 5.11 (1H, t, br, *J* 5.3), 7.16-7.17 (2H, m), 7.25-7.26 (3H, m), 7.60 (2H, d, *J* 8.2), 7.68 (2H, d, *J* 8.2); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 47.4, 127.7. 128.0, 128.1, 128.8, 128.8, 132.5, 132.5, 136.0, 139.1.

Spectroscopic data were in accordance with the literature.[21]

_N_-Benzylthiophene-2-sulfonamide

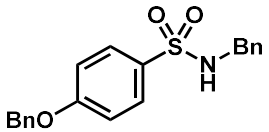


232

The title compound prepared according to general procedure 2, using 2-thiophenesulfonamide (163 mg, 1.00 mmol) and benzyl alcohol (104 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 100 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (186 mg, 73%) as a yellow crystalline solid (prisms), Mp 69-71 °C (Lit.[25] 70-72 °C (ethyl acetate)); R_F: 0.20 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.22 (2H, d, *J* 5.8), 4.94 (1H, s, br), 7.08 (1H, s), 7.22-7.30 (5 H, m) 7.59-7.61 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 47.7, 127.6, 128.1, 128.3, 129.0, 132.2, 132.6, 136.0, 141.0.

All spectroscopic data were in accordance with the literature.[25]

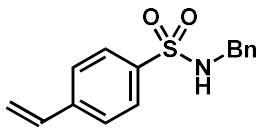
_N_-Benzyl-4-(benzyloxy)benzenesulfonamide



233

The title compound was prepared according to general procedure 2, using 4-(benzyloxy)benzene sulfonamide (263 mg) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 95 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (315 mg, 99%) as an off-white amorphous solid, Mp 131-132 °C; R_F: 0.22 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3265, 1593, 1576, 1497, 1452, 1425, 1321, 1250, 1152, 1094, 1047, 993, 862, 840, 829, 810, 752, 656, 608, 590, 511, 455, 407; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.13 (2H, d, *J* 6.2), 4.60 (1H, t, br, *J* 6.1), 5.14 (2H, s), 7.05 (2H, d, *J* 8.7), 7.19-7.20 (2H, m), 7.19 (2H, d, *J* 6.6), 7.24-7.28 (2H, m), 7.35-7.43 (5H, m) 7.81 (2H, d, *J* 8.7); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 47.4, 70.4, 115.2, 127.6, 128.0, 128.0, 128.5, 128.8, 128.9, 129.4, 131.7, 135.9. 136.4, 162.1; HRMS (EI$^+$) $C_{20}H_{20}NO_3S$ $[M+H]^+$ found 354.1159, requires 354.1164 (-1.4 ppm).

_N_-Benzyl-4-vinylbenzenesulfonamide

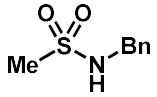


234

The title compound was prepared according to general procedure 2, using 4-vinylbenzene sulfonamide (183 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and purified by flash column chromatography (30 × 95 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (191 mg, 72%) as a colourless solid, Mp 85-87 °C; R_F: 0.30 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3267, 1597, 1495, 1456, 1437, 1395, 1319, 1310, 1153, 1055, 1028, 986, 914, 868, 841, 731, 696, 654, 594, 563, 529, 484, 449, 411; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.14 (2H, d, *J* 6.2), 4.71 (1H, t, br, *J* 5.9), 5.44 (1H, d, *J* 10.9), 5.89 (1H, d, *J* 17.6), 6.76 (1H, dd, *J* 17.6, 10.9), 7.20 (2H, d, *J* 7.32), 7.19-7.30 (3H, m), 7.52 (2H, d, *J* 8.2), 7.82 (2H, d, *J* 8.3); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 47.5, 177.6, 126.9,

127.6, 128.0, 128.1, 128.9, 135.5, 136.3, 138.8, 142.1; HRMS (ES$^+$) $C_{15}H_{16}NO_2S$ $[M+H]^+$ found 274.0903, requires 274.0902 (+0.4ppm).

N-Benzylmethanesulfonamide

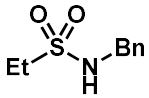


235

The title compound was prepared according to general procedure 2, using methane sulfonamide (95.1 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 105 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (158 mg, 85%) as an off-white amorphous solid, Mp 58-61 °C (Lit.[26] 57-60 °C (acetonitrile)); R_F: 0.29 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.88 (3H, s), 4.34 (2H, d, *J* 6.1), 4.58 (1H, s, br), 7.31-7.40 (5H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 41.3, 47.4, 128.1, 128.3, 129.1, 136.8.

Spectroscopic data were in accordance with the literature.[26]

N-Benzylethanesulfonamide

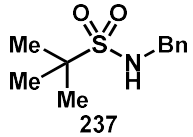


236

The title compound was prepared according to general procedure 2, using ethane sulfonamide (109 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 105 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (165 mg, 83%) as a colourless amorphous solid, Mp 58-59 °C; R_F: 0.31 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3287, 1456, 1429, 1314, 1283, 1227, 1130, 1055, 993, 854, 779, 758, 718, 704, 640, 584, 538, 517, 496, 444; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.33 (3H, t, *J* 7.4), 2.97 (2H, q, *J* 7.4), 4.31 (2H, d, *J* 6.1), 4.46 (1H, s, br), 7.30-7.39 (5H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 8.4, 47.4, 47.8, 128.0, 128.3,

129.0, 137.1; HRMS (ES$^+$) $C_9H_{14}NO_2S$ $[M+H]^+$ found 200.0740, requires 200.0745 (-2.5 ppm).

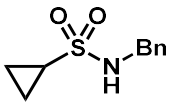
_N_-Benzyl-2-methylpropane-2-sulfonamide



237

The title compound was prepared according to general procedure 2, using *tert*-butyl sulfonamide (137 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 110 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (215 mg, 95%) as a colourless amorphous solid, Mp 125-126 °C; R_F: 0.32 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3283, 1497, 1474, 1447, 1296, 1202, 1119, 1092, 1070, 1026, 1007, 903, 868, 731, 693, 662, 615, 592, 521, 509, 459; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.44 (9H, s), 4.08 (1H, t, br, *J* 5.0), 4.37 (2H, d, *J* 6.0) 7.29-7.33 (1H, m), 7.34-7.38 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 24.5, 48.8, 63.2, 127.9, 128.1, 129.0, 137.8; HRMS (ES$^+$) $C_{11}H_{18}NO_2S$ $[M+H]^+$ found 228.1063, requires 228.1058 (+0.5 ppm).

_N_-Benzylcyclopropanesulfonamide



238

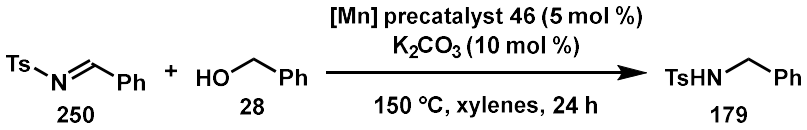
The title compound was prepared according to general procedure 2, using cyclopropane sulfonamide (121 mg, 1.00 mmol) and benzyl alcohol (109 µL, 1.00 mmol), and was purified by flash column chromatography (30 × 105 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (184 mg, 87%) as a colourless amorphous solid, Mp 62-64 °C (Lit.[23] 62.3 °C (acetone)); R_F: 0.30 (20% ethyl acetate/petroleum ether 40-60); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 0.88-0.92 (2H, m), 1.10-1.14 (2H, m), 2.32 (1H, tt, *J* 8.0, 4.9), 4.32 (2H d, *J* 6.2), 4.89 (1H, t, br, *J*

5.6), 7.28-7.36 (5H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 5.6, 30.7, 47.5, 127.9, 128.2, 129.0, 137.2.

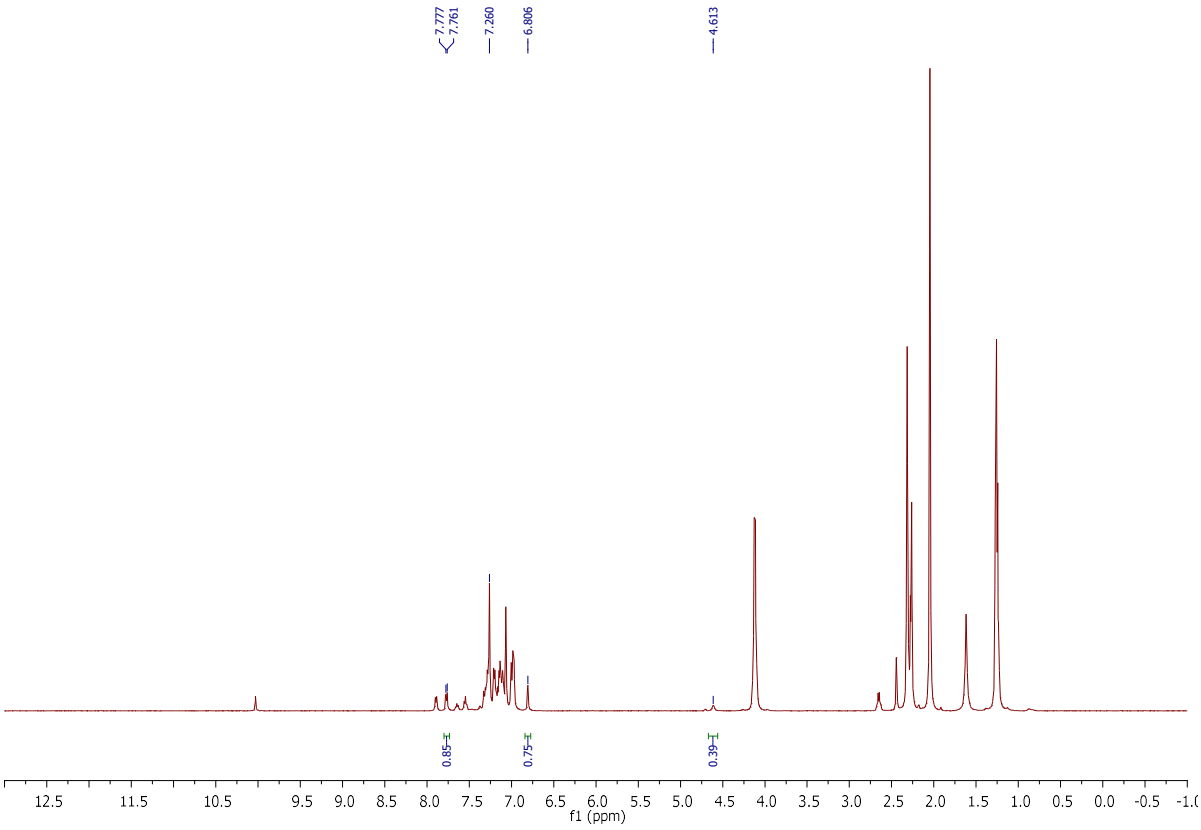
Spectroscopic data were in accordance with the literature.[23]

8.5. Mechanistic experiments

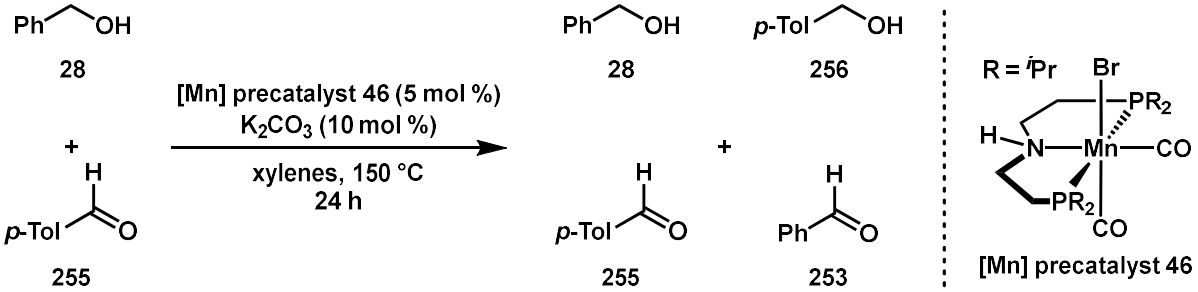
8.5.1. Transfer hydrogenation reactions



A 10 mL microwave vial was charged with a magnetic stirrer bar, compound **39** (259 mg, 1.00 mmol), potassium carbonate (13.8 mg, 10 mol %), [Mn] precatalyst **3** (24.8 mg, 5 mol %), benzyl alcohol (104 µL, 1.0 mmol) and xylenes (1 mL). The vial was then crimped shut, and stirred vigorously at 150 °C for 24 hours. The reaction vessel was then cooled, decrimped, and to the reaction mixture was added mesitylene (69.6 µL, 0.5 mmol), water (1 mL), and ethyl acetate (1 mL). The reaction mixture was then stirred for an additional 5 minutes, then sampled directly, and analysed by ^{1}H NMR, to give the NMR yield of the product, as shown overleaf, as 85% (An integral of 0.85, relative to mesitylene's 3 × CH protons, set to 0.75).

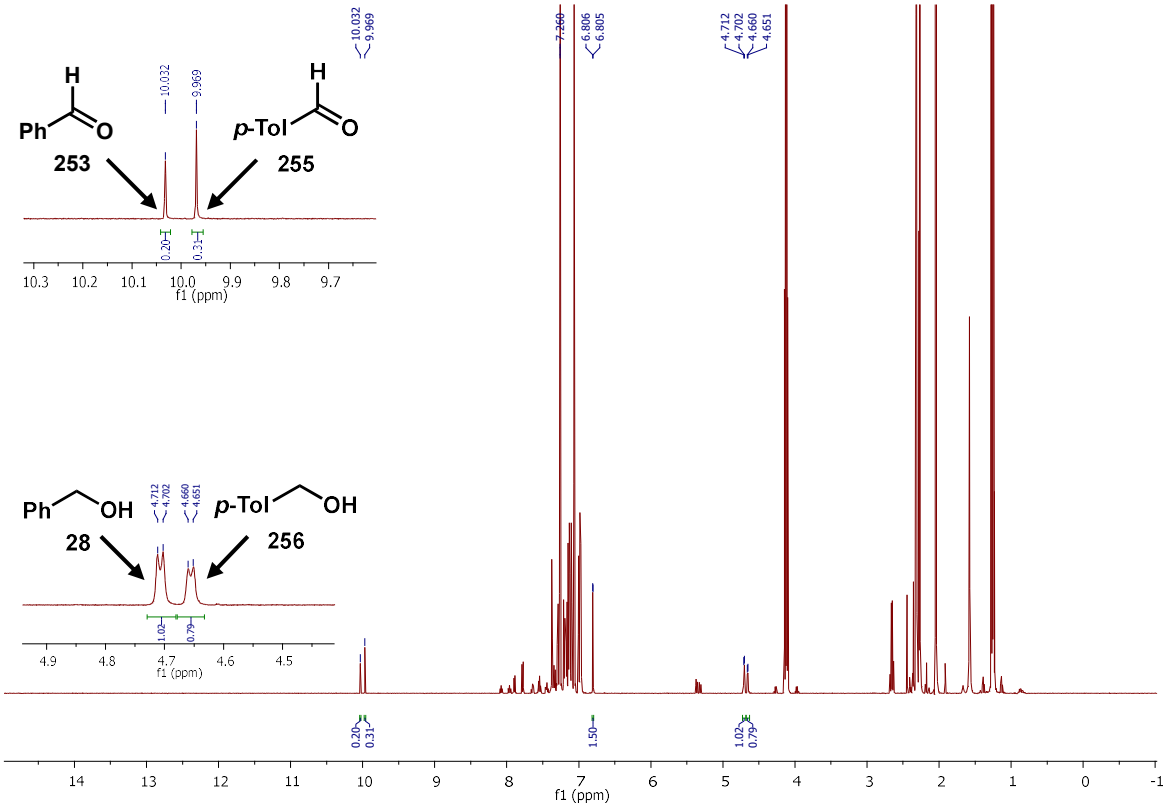


8.5.2. Crossover experiment



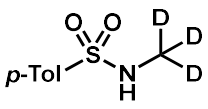
A 10 mL microwave vial was charged with a magnetic stirrer bar, *para*-tolualdehyde (108 µL, 1.0 mmol), potassium carbonate (13.8 mg, 10 mol %), [Mn] precatalyst **46** (24.8 mg, 5 mol %), benzyl alcohol (104 µL, 1.0 mmol) and xylenes (1 mL). The vial was then crimped shut, and stirred vigorously at 150 °C for 24 hours. The reaction vessel was then cooled, decrimped, and to the reaction mixture was added mesitylene (69.6 µL, 0.5 mmol) as internal standard, water (1 mL), and ethyl acetate (1 mL). The reaction mixture was then stirred for an additional 5 minutes, then sampled directly, and analysed by ^{1}H NMR, to give the NMR yield of compounds

28, **253**, **255**, and **256**, as 20%, 31%, 51%, and 40% respectively. (Integrals of 0.20, 0.31, 1.02 and 0.79 relative to mesitylene's aromatic CH's, set to 1.5).



8.5.3. Deuteration experiment

4-methyl-*N*-(methyl-d_3)benzenesulfonamide



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The title compound was prepared according to general procedure 2, using *p*-toluenesulfonamide (171mg, 1.00 mmol) and methanol-d_4 (1 mL), and was purified by flash column chromatography (30 × 150 mm silica, 20% ethyl acetate/petroleum ether 40-60) to give the title compound (150 mg, 86%) as a colourless crystalline solid (prisms), Mp 72-75 °C; R_F: 0.24 (20% ethyl acetate/petroleum ether 40-60); ν_{max} / cm^{-1} (film) 3266, 1595, 1315, 1306, 1290, 1153, 1088, 1057, 820, 660, 492,

548, 492, 471, 401, 378, 355, 340, 328, 316; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.43 (3H, s), 4.37 (1H, s, br), 7.31-7.33 (2H, m), 7.73-7.76 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7, 21.8, 127.4, 129.9, 135.8, 143.6; HRMS (ES^-) $C_8H_7D_3NO_2S$ $[M-H]^-$ found 187.0618, requires 187.0621 (-1.6 ppm).

8.6. References

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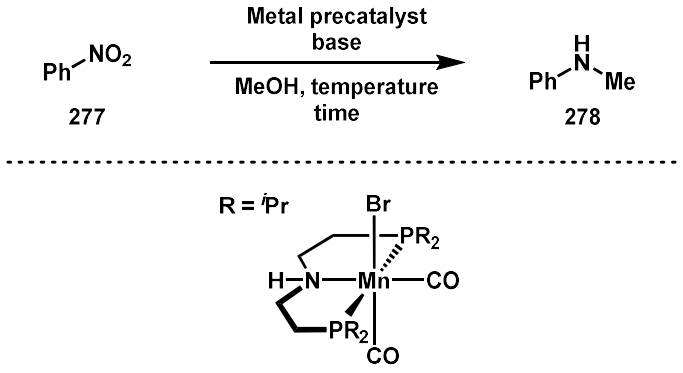
Chapter 9: Manganese-catalysed one-pot conversion of nitroarenes to *N*-methylarylamines using methanol

Table of Contents

9.1. Optimisation of the one pot nitroarene reduction-methylation

9.1.1. General procedure 1 – Pressure tube reactions



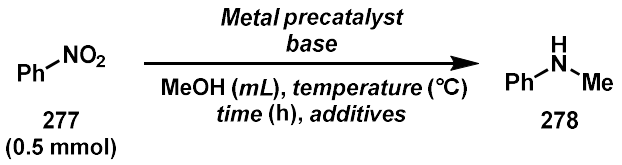
[Mn] precatalyst 46

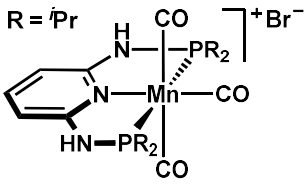
A 4 mL screw cap Ace Pressure Tube was charged with a magnetic stirrer bar sealed with a suba seal, placed under vacuum, and vigorously flame dried. To the flame dried tube was added [Mn] precatalyst **46** (varied masses and loadings), an additive when appropriate (varied masses and loadings) and a base (varied masses and loadings). The tube was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the tube was then added nitrobenzene (51.3 µL, 0.5 mmol) and methanol (varied amounts) through the suba seal. The reaction vessel was then sealed with a front seal #15 Ace thread screw cap, and stirred vigorously at the desired for the allotted time. The vessel was then cooled to room temperature and unsealed, and to the tube was added mesitylene (34.8 µL, 0.25 mmol, 0.5 equiv.), ethyl acetate (1 mL) and sat. aq. NH_4Cl (1 mL). The reaction was stirred for 5 minutes, and allowed to settle for an additional 5 minutes. The top phase was then sampled, and analysed directly by ^1H NMR spectroscopy to give the yields shown below, relative to mesitylene as internal standard.

Entry	Precatalyst (mol %)	Base (equiv.)	MeOH (mL)	temp (°C)	time (h)	277 (%)	288 (%)
1	5	NaOMe (1)	1	150	24	60	27
2	5	NaOMe (5)	1	150	24	42	35
3	5	NaOMe (5)	1	150	24	81	0

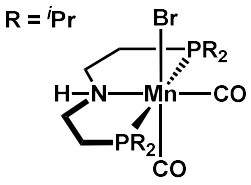
Table 9.1 - Pressure tube reactions

9.1.2. General procedure 2 – Optimisation conditions

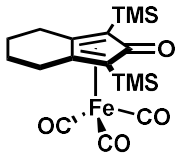




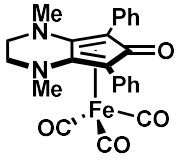
[Mn] precatalyst 177



[Mn] precatalyst 46



[Fe] precatalyst 55



[Fe] precatalyst 63

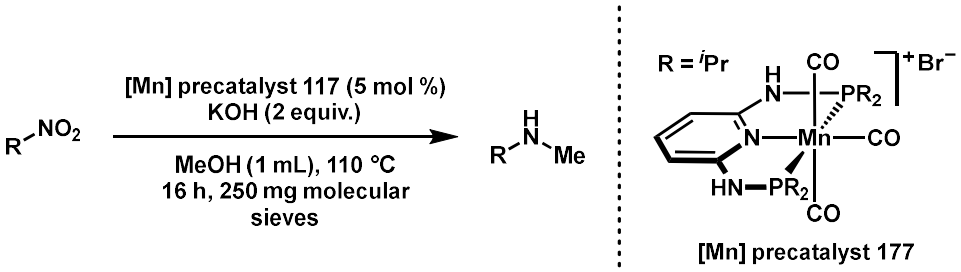
A 10 mL microwave vial was charged with a magnetic stirrer bar, and 250 mg of dust 4Å molecular sieves. The vial was then sealed with a suba seal, placed under vacuum, and vigorously flame dried to activate the molecular sieves. To the flame dried vial was added a metal precatalyst (varied masses and loadings), an additive when appropriate (varied masses and loadings) and a base (varied masses and loadings). The vial was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the vial was then added nitrobenzene (51.3 µL, 0.5 mmol) and methanol (varied amounts) through the suba seal. The reaction was then sealed with a crimpable lid and crimper, and stirred vigorously at the desired temperature for 16 hours. The vial was then cooled to room temperature and decrimped, and to the vial was added mesitylene (34.8 µL, 0.25 mmol, 0.5 equiv.), ethyl acetate (1 mL) and sat. aq. NH_4Cl (1 mL). The reaction was stirred for 5 minutes, and allowed to settle for an additional 5 minutes. The top phase was then sampled, and analysed directly by ^1H NMR spectroscopy to give the yields shown below, relative to mesitylene as internal standard.

Catalyst	mol %	Base (equiv.)	MeOH (mL)	temp. (°C)	time (h)	277 (%)	278 (%)	Mol. Sieves
177	5	K_2CO_3 (5)	1	110	16	95	4	none
177	5	K_2CO_3 (5)	1	110	16	<2	94	250 mg (dust)
177	5	K_2CO_3 (5)	1	110	16	2	36	250 mg (balls)
177	5	K_2CO_3 (5)	1	110	16	<2	79	500 mg (dust)
177	5	K_2CO_3 (2)	1	110	16	<2	83	250 mg (dust)
177	5	K_2CO_3 (1)	1	110	16	29	44	250 mg (dust)
177	5	K_2CO_3 (0.5)	1	110	16	94	<2	250 mg (dust)
177	5	K_2CO_3 (0.5)	1	110	16	94	<2	250 mg (dust)
177	2	KO^{t}Bu (2)	1	110	16	1	61	250 mg (dust)
None	0	KO^{t}Bu (2)	1	110	16	>98	<2	250 mg (dust)
177	5	KOH (2)	1	110	16	<2	<98	250 mg (dust)
177	5	KOH (2)	1	110	16	3	94	250 mg (dust)
None	0	KOH (2)	1	110	16	89	<2	250 mg (dust)
177	5	NaOH (2)	1	110	16	9	83	250 mg (dust)
177	5	KOH (2)	1	110	16	15	49	250 mg (dust)
177	5	KOH (2)	1	110	16	49	37	250 mg (dust)
177	5	KOH (2)	1	110	16	98	< 2	250 mg (dust)
177	5	KOH (2)	1	110	16	3	94	250 mg (dust)
None	0	KOH	1	110	16	89	<2	250 mg (dust)

		(2)						
177	5	None (N/A)	1	110	16	97	<2	250 mg (dust)
177	5	KOH (2)	1	110	16	79	<2	None
177	5	KOH (2)	1	110	16	15	49	250 mg (dust)
46	5	KOH (2)	1	110	16	13	14	250 mg (dust)
55	5	KOH (2)	1	110	16	60	4	250 mg molecular sieves (dust), 10 mol % $Me_3NO{\cdot}2H_2O$
63	5	KOH (2)	1	110	16	55	2	250 mg molecular sieves (dust), 10 mol % $Me_3NO{\cdot}2H_2O$
177	5	KOH (2)	1	110	16	24	33	250 mg (dust)
177	2.5	KOH (2)	1	110	16	<2	74	250 mg (dust)
177	5	KOH (2)	1	80	16	>98	<2	250 mg (dust)

Table 9.2 - Optimisation of the one pot nitroarene reduction-methylation

9.2. General procedures



9.2.1. General procedure 3 – Reaction with liquid substrates

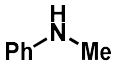
A 10 mL microwave vial was charged with a magnetic stirrer bar, and 250 mg of dust 4Å molecular sieves. The vial was then sealed with a suba seal, placed under vacuum, and vigorously flame dried to activate the molecular sieves. To the flame dried vial was added [Mn] precatalyst **177** (14.0 mg, 0.025 mmol, 5 mol %) and freshly ground KOH (56.1 mg, 1.0 mmol, 2 equiv.). The vial was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the vial was then added liquid nitro-compound (0.5 mmol) and methanol (1 mL) through the suba seal. The reaction was then sealed with a crimpable lid and crimper, and stirred vigorously at 110 °C for 16 hours. The vial was then cooled to room temperature and decrimped, and to the vial was added mesitylene (34.8 µL, 0.25 mmol, 0.5 equiv.), ethyl acetate (1 mL) and sat. aq. NH_4Cl (1 mL). The reaction was stirred for 5 minutes, and allowed to settle for an additional 5 minutes. The top phase was then sampled, and analysed directly by ^1H NMR spectroscopy, to give the NMR yields reported, relative to mesitylene as internal standard. The crude reaction mixture was then diluted with water (5 mL), and extracted in ethyl acetate (3 × 5 mL). The combined organic phases were then combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was then loaded directly onto silica, and purified by flash column chromatography.

9.2.2. General procedure 4 – Reaction with solid substrates

A 10 mL microwave vial was charged with a magnetic stirrer bar, and 250 mg of dust 4Å molecular sieves. The vial was then sealed with a suba seal, placed under vacuum, and vigorously flame dried to activate the molecular sieves. To the flame dried vial was added [Mn] precatalyst **177** (14.0 mg, 0.025 mmol, 5 mol %), solid nitro-compound (0.5 mmol) and freshly ground KOH (56.1 mg, 1.0 mmol, 2 equiv.). The vial was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the vial was then added methanol (1 mL) through the suba seal. The reaction was then sealed with a crimpable lid and crimper, and stirred vigorously at 110 °C for 16 hours. The vial was then cooled to room temperature and decrimped, and to the vial was added mesitylene (34.8 µL, 0.25 mmol, 0.5 equiv.), ethyl acetate (1 mL) and sat. aq. NH_4Cl (1 mL). The reaction was stirred for 5 minutes, and allowed to settle for an additional 5 minutes. The top phase was then sampled, and analysed directly by ^1H NMR to give the NMR yields reported, relative to mesitylene as internal standard. The crude reaction mixture was then diluted with water (5 mL), and extracted in ethyl acetate (3 × 5 mL). The combined organic phases were then combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was then loaded directly onto silica, and purified by flash column chromatography.

9.3. Substrate scope

N-Methyl aniline



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The title compound was prepared according to general procedure 3, using [Mn] precatalyst **177** (14.0 mg, 0.025 mmol, 5.0 mol %), KOH (56.1 mg, 1.0 mmol), and methanol (1 mL). The crude reaction mixture was then diluted with water (5 mL), and extracted in ethyl acetate (3 × 5 mL). The combined organic phases were then combined, washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and

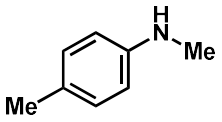
concentrated *in vacuo*. The crude reaction mixture was then loaded directly onto silica, and purified by flash column chromatography (130 × 35mm Silica, neat CH_2Cl_2) to give the title compound (48.2 mg, 90% yield) as a yellow oil; R_F: 0.68 (50% CH_2Cl_2/cyclohexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.86 (3H, s, NC*H*$_3$) 3.70 (1H, s, br, N*H*), 6.63-6.66 (2H, m, ArC(2,6)*H*), 6.74 (1H, tt, *J* 7.3, 1.1, ArC(4)*H*), 7.20-7.24 (2H, m, ArC(3,5)*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 30.8 (N*C*H$_3$), 112.5 (Ar*C*(2,6)H), 117.4 (Ar*C*(4)H), 129.3 (Ar*C*(3,5)H), 149.5 (Ar*C*(1)N).

The title compound was also prepared according to the following procedure:

A 185 mL screw cap Ace Pressure Tube was charged with a magnetic stirrer bar, and 5 g of dust 4Å molecular sieves. The vial was then sealed with a suba seal, placed under vacuum, and vigorously flame dried to activate the molecular sieves. To the flame dried vial was added [Mn] precatalyst **177** (280.0 mg, 0.50 mmol, 5 mol %), and freshly ground KOH (1.12 g, 20 mmol, 2 equiv.). The vial was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the vial was then added nitrobenzene (1.03 mL, 10 mmol), and methanol (20 mL) through the suba seal. The reaction vessel was then sealed with a front seal #15 Ace thread screw cap, and stirred vigorously at 110 °C in a silicon oil bath for 8 hours. The reaction was then cooled, and the contents of the reaction vented to relieve pressure. The reaction was then reheated at 110 °C for a further 16 hours. The vessel was then cooled to room temperature and unscrewed, and to the vial was added mesitylene (696 µL, 5.0 mmol, 0.5 equiv.), ethyl acetate (20 mL) and saturated aqueous ammonium chloride solution (20 mL). The reaction was stirred for 5 minutes, and allowed to settle for an additional 5 minutes. The top phase was then sampled, and analysed directly by ^{1}H NMR. The crude reaction mixture was then diluted with water (100 mL), and extracted in ethyl acetate (3 × 10 mL). The combined organic phases were then combined, washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was then loaded directly onto silica, and purified by flash column chromatography (210 × 45mm Silica, 50% CH_2Cl_2/pentane) to give the title compound (889 mg, 83% yield) as a yellow oil, with data identical as described above.

Spectroscopic data were in accordance with the literature.[1]

_N_,4-Dimethylaniline



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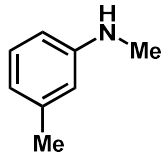
The title compound was prepared according to general procedure 4, using 4-nitrotoluene (68.6 mg, 0.5 mmol), and stirred at 110 °C for 72 h. The compound was then purified by flash column chromatography (130 × 35mm Silica, 50% CH_2Cl_2/pentane) to give the title compound (33.2 mg, 55% yield) as a yellow oil; R_F: 0.38 (50% CH_2Cl_2/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.25 (3H, s), 2.82 (3H, s), 6.54-6.57 (2H, m), 6.99-7.02 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 20.5, 31.3, 112.8, 126.6, 129.8, 147.3.

Spectroscopic data were in accordance with the literature.[1]

_N_,3-Dimethylaniline

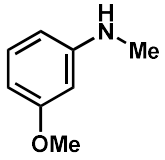


280

The title compound was prepared according to general procedure 3, using 3-nitrotoluene (59.3 µL, 0.5 mmol), and purified by flash column chromatography (130 × 35mm Silica, 50% CH_2Cl_2/pentane) to give the title compound (48.5 mg, 80% yield) as a yellow oil; R_F: 0.29 (50% CH_2Cl_2/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.29-2.29 (3H, m), 2.83 (3H, s), 6.42-6.44 (2H, m), 6.53-6.55 (1H, m), 7.06-7.10 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.8, 30.9, 109.8, 113.3, 118.4, 129.2, 139.1, 149.5.

Spectroscopic data were in accordance with the literature.[2]

3-Methoxy-*N*-methylaniline

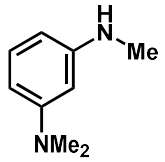


284

The title compound was prepared according to general procedure 4, using 3-nitroanisole (69.0 mg, 0.5 mmol), and purified by flash column chromatography (120 × 35mm Silica, 50% CH_2Cl_2/pentane) to give the title compound (28.8 mg, 42% yield) as a colourless oil; R_F: 0.33 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.83 (3H, s), 3.78 (3H, s), 6.17 (1H, t, *J* 2.3), 6.23-6.25 (1H, m), 6.27-6.29 (1H, m), 7.09 (1H, t, *J* 8.1); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 30.9, 55.2, 28.5, 102.5, 105.8, 130.1, 150.9, 161.0.

Spectroscopic data were in accordance with the literature.[3]

***N*^{1},*N*^{1},*N*^{3}-Trimethylbenzene-1,3-diamine**

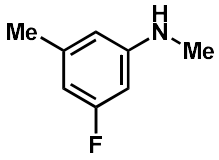


285

The title compound was prepared according to general procedure 3, using *N,N*-dimethyl-3-nitroaniline (83.1 mg, 0.5 mmol), and purified by flash column chromatography (165 × 35mm Silica, CH_2Cl_2) to give the title compound (36.1 mg, 48% yield) as a yellow oil; R_F: 0.24 (1% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.84 (3H, s), 2.93 (6H, s), 6.00 (1H, t, *J* 2.2), 6.05-6.08 (1H, m), 6.17-6.19 (1H, m), 7.06-7.09 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 31.0, 40.9, 97.2, 102.0, 103.0, 129.9, 150.5, 152.0.

Spectroscopic data were in accordance with the literature.[4]

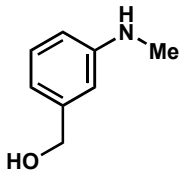
3-Fluoro-*N*,5-dimethylaniline



286

The title compound was prepared according to general procedure 4, using 3-fluoro-5-nitrotoluene (77.6 mg, 0.5 mmol), and purified by flash column chromatography (160 × 35mm Silica, 50% CH_2Cl_2/pentane) to give the title compound (33 mg, 48% yield) as a yellow oil; R_F: 0.48 (50% CH_2Cl_2/pentane); ν_{max} / cm^{-1} (film) 3422, 2980, 2916, 2814, 1618, 1586, 1514, 1449, 1427, 1410, 1308, 1250, 1182, 1153, 1130, 1086, 1036, 1011, 991, 966, 937, 822, 679, 610, 542, 507, 492, 446, 428, 420, 415, 401; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.26 (3H, d, *J* 0.6), 2.81 (3H, s), 6.11 (1H, dt, *J* 11.4, 2.1), 6.18-6.19 (1H, m), 6.21-6.24 (1H, m); ^{19}F NMR (471 MHz, $CDCl_3$) δ_F: -114.26 (t, *J* 9.4); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.7 (d, *J* 2.2), 30.8, 96.4 (d, *J* 25.4), 104.7 (d, *J* 21.5), 109.1 (d, *J* 1.9), 140.8 (d, *J* 10.0), 151.0 (d, *J* 11.5), 124.3 (d, *J* 241.7); HRMS (EI$^+$) $C_{15}H_{15}O_3$ $[M+H]^+$ found 243.1002, requires 243.1021 (+0.4 ppm).

(3-(Methylamino)phenyl)methanol

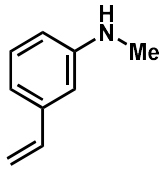


287

The title compound was prepared according to general procedure 3, using 4-nitrotoluene (81.5 µL, 0.5 mmol), and purified by flash column chromatography (125 × 35mm Silica, 50% CH_2Cl_2/pentane - 5% MeOH/CH_2Cl_2) to give the title compound (38.7 mg, 56% yield) as a yellow oil; R_F: 0.35 (1% MeOH/CH_2Cl_2); ν_{max} / cm^{-1} (film): 3412, 2961, 2901, 2866, 2810, 1605, 1587, 1512, 1487, 1468, 1429, 1408, 1393, 1362, 1321, 1302, 1275, 1204, 1175, 1155, 1115, 1067, 1022, 991, 907, 891, 853, 775, 700, 538, 492, 465, 434, 417; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.83 (3H, s), 4.60 (2H, s), 6.54 (1H, dd, *J* 8.1, 1.8), 6.61 (1H, s), 6.69 (1H, d, *J* 7.5),

7.17 (1H, d, *J* 7.8); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 30.9, 65.7, 111.0, 111.9, 115.9, 129.5, 142.2, 149.7; HRMS (EI$^+$) $C_8H_{11}NO$ [M]$^+$ found 137.0843, requires 137.0841 (+1.5 ppm).

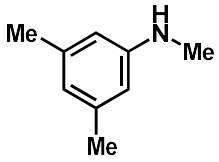
_N_-Methyl-3-vinylaniline



288

The title compound was prepared according to general procedure 3, using 3-Nitrostyrene (69.7 µL, 0.5 mmol), and purified by flash column chromatography (165 × 35mm Silica, 50% CH_2Cl_2/pentane) to give the title compound (48.2 mg, 30% yield) as a yellow oil; R_F: 0.28 (50% CH_2Cl_2/pentane); ν_{max} / cm^{-1} (film) 3414, 3084, 3005, 2980, 2901, 2808, 1601, 1582, 1508, 1487, 1470, 1449, 1429, 1414,1395, 1321, 1296, 1273, 1256, 1180, 1167, 1125, 1092, 1069, 1042, 1026, 988, 905, 851, 779, 714, 669, 476, 432, 415, 403; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.86 (3H, m), 5.21 (1H, dd, *J* 10.9, 1.1), 5.71 (1H, dd, *J* 17.6, 1.0), 6.52-6.55 (1H, m), 6.64-6.69 (2H, m), 6.78-6.80 (1H, m), 7.14-7.17 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 30.9, 110.2, 112.4, 113.6, 115.7, 129.5, 137.5, 138.7, 149.6; HRMS (EI$^+$) $C_9H_{11}N$ [M]$^+$ found 133.0891, requires 133.0891 (+0.0 ppm).

_N_,3,5-Trimethylaniline



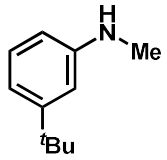
289

The title compound was prepared according to general procedure 4, using 1,3-dimethyl-5-nitrobenzene (75.6 mg, 0.5 mmol), and stirred at 110 °C for 72h. The compound was then purified by flash column chromatography (150 × 35mm Silica, 50% CH_2Cl_2/pentane) to give the title compound (39.7 mg, 59% yield) as a yellow

oil; R_F: 0.45 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.25 (6H, d, *J* 0.6), 2.82 (3H, s), 6.26 (2H, s), 6.38 (1H, s); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 21.6, 31.0, 110.6, 119.5, 139.0, 149.6.

Spectroscopic data were in accordance with the literature.[5]

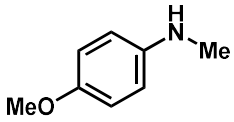
3-(*Tert*-butyl)-*N*-methylaniline



290

The title compound was prepared according to general procedure 4, using 4-nitrotoluene (81.5 µL, 0.5 mmol), and stirred at 110 °C for 72 h. The compound was then purified by flash column chromatography (210 × 35mm Silica, gradient 50% CH_2Cl_2/pentane-neat CH_2Cl_2) to give the title compound (50.1 mg, 61% yield) as a yellow oil; R_F: 0.48 (50% CH_2Cl_2/pentane); ν_{max} / cm^{-1} (film): 2916, 2849, 2812, 1607, 1589, 1508, 1489, 1472, 1418, 1323, 1271, 1165, 1125, 1088, 1011, 989, 860, 777, 694. 457, 443, 420, 413; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 1.30 (9H, s), 2.85 (3H, s), 6.45-6.47 (1H, m), 6.65 (1H, t, *J* 2.1), 6.77-6.78 (1H, m), 7.15 (1H, t, *J* 7.9); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 31.0, 31.5, 34.8, 109.5, 110.3, 114.9, 129.0, 149.3, 152.4; HRMS (EI$^+$) $C_{11}H_{17}N$ [M]$^+$ found 163.1361, requires 163.1361 (+0.0 ppm).

4-Methoxy-*N*-methylaniline



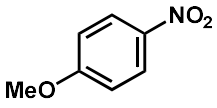
292

The title compound was prepared according to general procedure 4, using 4-nitroanisole (76.6 mg, 0.5 mmol), and stirred at 130 °C. The resulting compound was purified by flash column chromatography (160 × 35mm Silica, CH_2Cl_2 to 5% MeOH/ CH_2Cl_2) to give the title compound (17.1 mg, 25% yield) as a pale yellow oil; R_F: 0.24 (CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 2.81 (3H, s), 3.75 (3H, s), 6.58-

6.61 (2H, m), 6.79-6.82 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 31.8, 56.0, 113.8, 115.1, 143.8, 152.2.

Spectroscopic data were in accordance with the literature.[4]

1-Methoxy-4-nitrobenzene

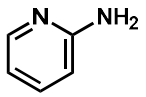


291

The title compound was prepared according to general procedure 3, using 1-fluoro-4-nitrobenzene (57.2 µL, 0.5 mmol), and purified by flash column chromatography (110 × 40mm Silica, 50% CH_2Cl_2/pentane) to give the title compound (60.9 mg, 80% yield) as a colourless oil; R_F: 0.35 (5% MeOH/ CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.90 (3H, s), 6.93-6.96 (2H, m), 8.17-8.20 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 56.1, 114.1, 126.0, 141.7, 164.7.

Spectroscopic data were in accordance with the literature.[6]

Pyridin-2-amine

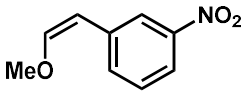


295

The title compound was prepared according to general procedure 4, using 2-nitropyridine (62.1 mg, 0.5 mmol), and purified by flash column chromatography (150 × 35mm Silica, 1% MeOH/ CH_2Cl_2 to 5% MeOH/ CH_2Cl_2) to give the title compound (40.0 mg, 85% yield) as a colourless solid, Mp 53-56 °C (Lit:[7] 56-57 °C (commercial sample)); R_F: 0.35 (5% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 4.47 (2H, br s), 6.48 (1H, dt, *J* 8.3, 0.9), 6.61-6.63 (1H, m), 7.39-7.42 (1H, m), 8.05-8.06 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 108.7, 114.2, 137.8, 148.3, 158.5.

Spectroscopic data were in accordance with the literature.[7]

(*Z*)-3-(2-Methoxyvinyl)-*N*-methylaniline

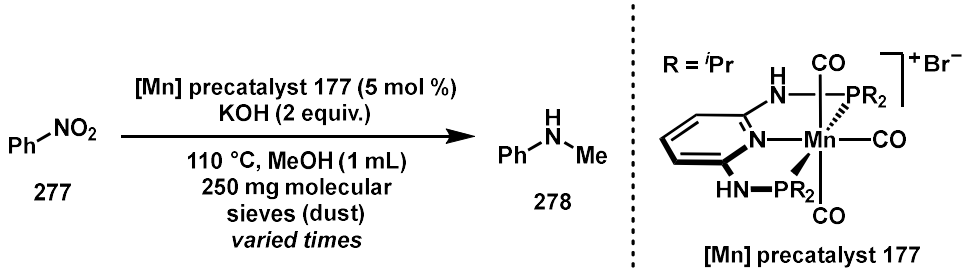


297

The title compound was prepared according to general procedure 4, using 3-nitrostyrene (69.7 mg, 0.5 mmol), and purified by flash column chromatography (165 × 35mm Silica, 5% ethyl acetate/hexane) to give the title compound (60.2 mg, 67% yield) as a yellow oil; R_F: 0.36 (5% ethyl acetate/hexane); ν_{max} / cm^{-1} (film) 1713, 1570, 1647, 1479, 1520, 1479, 1456, 1402, 1348, 1314, 1290, 1271, 1207, 1188, 1098, 1074, 999, 903, 804, 758,731, 677, 530; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 3.86 (3H, s), 5.28 (1H, d, *J* 7.0), 6.28 (1H, d, *J* 7.0), 7.41 (1H, t, *J* 8.0), 7.81-7.83, (1H, m), 7.96-7.98 (1H, m), 8.45 (1H, t, *J*, 1.9); ^{13}C NMR (126 MHz, $CDCl_3$) δ_C: 61.3, 103.8, 120.4, 122.8, 129.0, 134.0, 137.7, 148.5, 150.4; HRMS (EI$^+$) $C_9H_9NO_3$ $[M]^+$ found 179.0591, requires 179.0582 (+5.0 ppm).

9.4. Mechanistic studies

9.4.1. Time course experiment



A set of nine 10 mL microwave vials were charged with a magnetic stirrer bar, and 250 mg of dust 4Å molecular sieves. The vials was then sealed with a suba seal, placed under vacuum, and vigorously flame dried to activate the molecular sieves. To each flame dried vial was added [Mn] precatalyst **177** (14.0 mg, 0.025 mmol, 5 mol %), and ground KOH (56.1 mg, 1 mmol, 2 equiv.). The vial was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the vial was then added nitrobenzene (51.3 µL, 0.5 mmol) and methanol (1 mL) through the suba seal. Each

reaction was then sealed with a crimpable lid and crimper, and stirred vigorously at 110 °C for a variety of times, as shown in the table below. The vials were then cooled to room temperature and decrimped, and to each vial was added mesitylene (34.8 µL, 0.25 mmol, 0.5 equiv.), ethyl acetate (1 mL) and saturated aqueous ammonium chloride solution (1 mL). The reactions were stirred for 5 minutes, and allowed to settle for an additional 5 minutes. The top phase was then sampled, and analysed directly by ^{1}H NMR spectroscopy, to give the proportions of reactants at a given times relative to mesitylene as internal standard, as shown below. This data was then used to construct the following chart.

Time	277 (%)	278 (%)	15 (%)
0	100	0	0
0.25	96	0	0
0.5	93	0	0
1	92	0	0
2	91	2	0
4	80	7	6
8	17	58	2.5
16	1	82	0
24	0	88	0

Table 9.3 - Time course experiment results

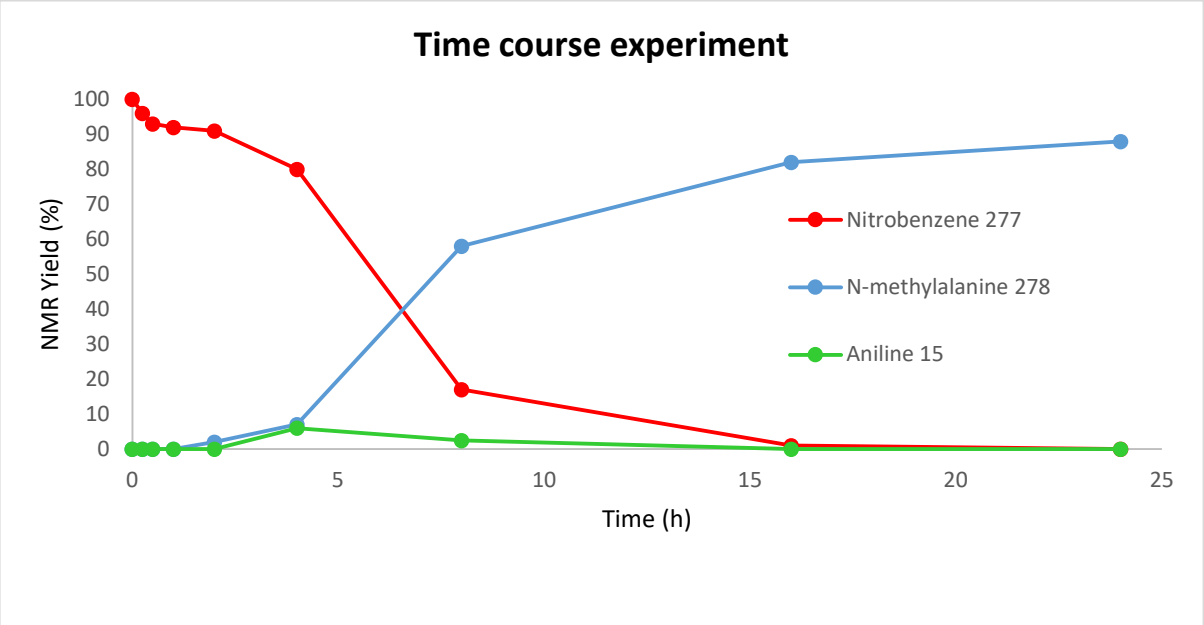
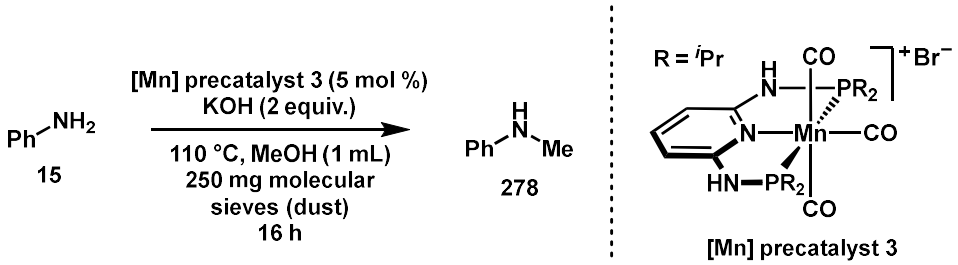


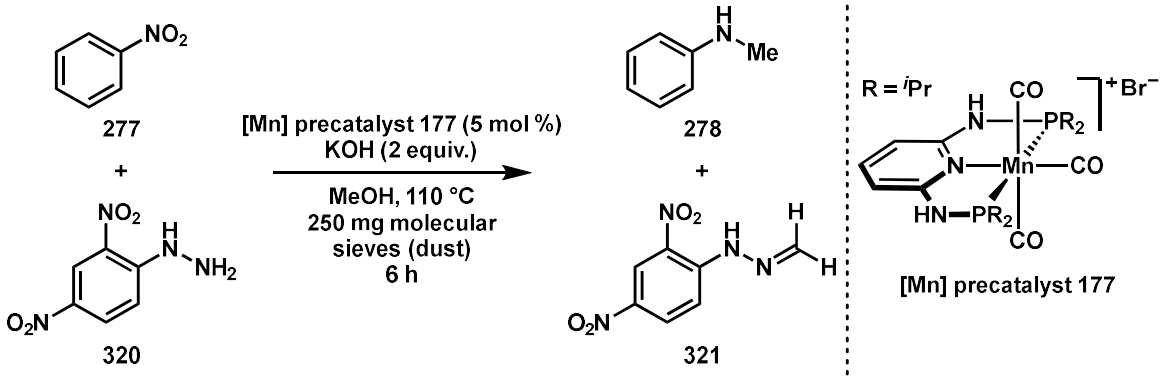
Chart 9.1 - Time course experiment results

9.4.2. Reaction with aniline

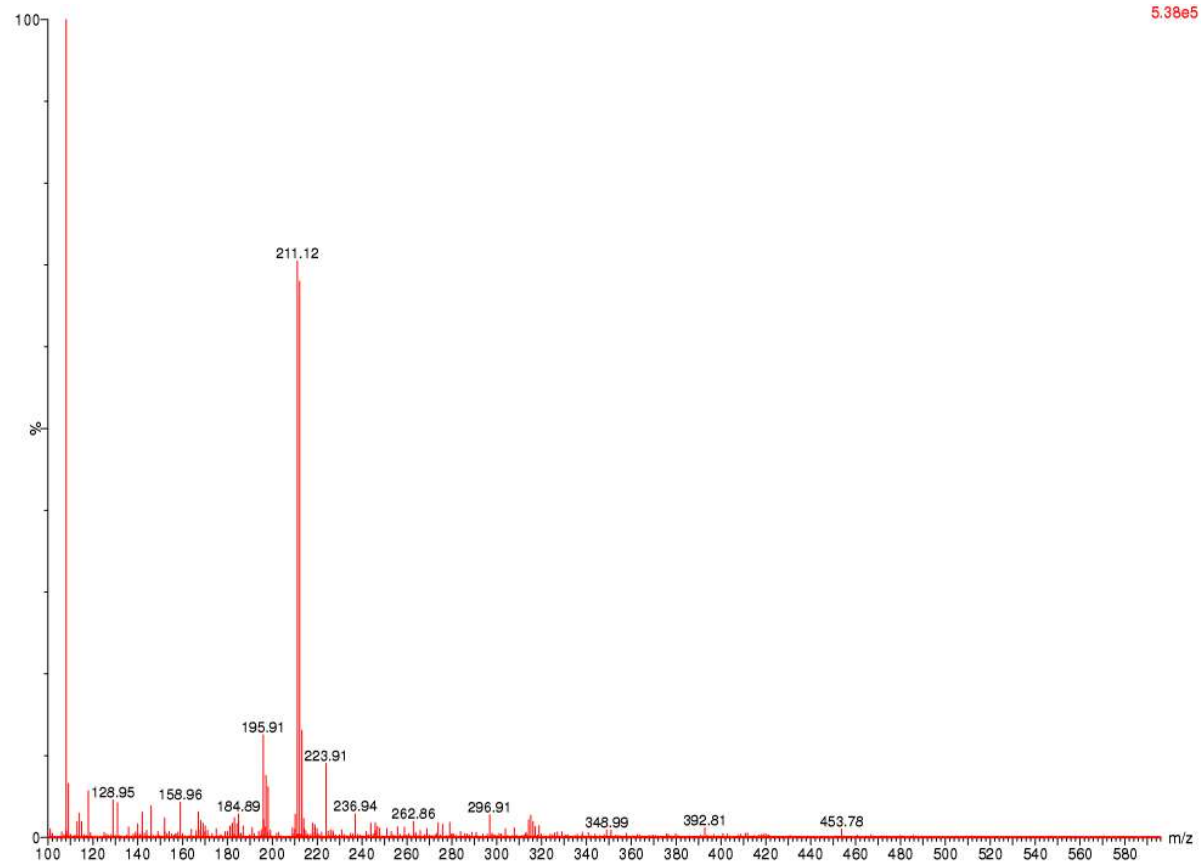


A 10 mL microwave vial was charged with a magnetic stirrer bar, and 250 mg of dust 4Å molecular sieves. The vial was then sealed with a suba seal, placed under vacuum, and vigorously flame dried to activate the molecular sieves. To the flame dried vial was added [Mn] precatalyst **3** (14.0 mg, 0.025 mmol, 5 mol %) and freshly ground KOH (56.1 mg, 1.0 mmol, 2 equiv.). The vial was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the vial was then added aniline (45.6 µL, 0.5 mmol) and methanol (1 mL) through the suba seal. The reaction was then sealed with a crimpable lid and crimper, and stirred vigorously at 110 °C for 16 hours. The vial was then cooled to room temperature and decrimped, and to the vial was added mesitylene (34.8 µL, 0.25 mmol, 0.5 equiv.), ethyl acetate (1 mL) and saturated aqueous ammonium chloride solution (1 mL). The reaction was stirred for 5 minutes, and allowed to settle for an additional 5 minutes. The top phase was then sampled, and analysed directly by ^{1}H NMR for the presence of product. In this case, it was found that there was 98% product, with no remaining aniline, relative to the mesitylene internal standard.

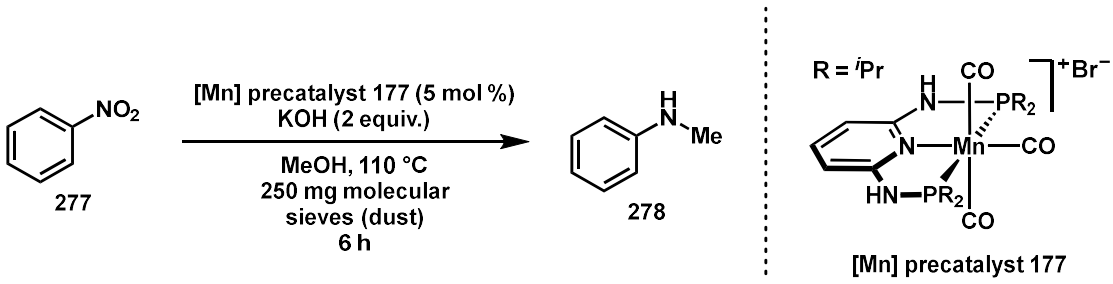
9.4.3. Detection of formaldehyde



A 10 mL microwave vial was charged with a magnetic stirrer bar, and 250 mg of dust 4Å molecular sieves. The vial was then sealed with a suba seal, placed under vacuum, and vigorously flame dried to activate the molecular sieves. To the flame dried vial was added [Mn] precatalyst **177** (14.0 mg, 0.025 mmol, 5 mol %) and freshly ground KOH (56.1 mg, 1.0 mmol, 2 equiv.). The vial was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the vial was then added nitrobenzene (51.3 µL, 0.5 mmol) and methanol (1 mL) through the suba seal. The reaction was then sealed with a crimpable lid and crimper, and stirred vigorously at 110 °C for 6 hours. The vial was then cooled to room temperature and through the crimped cap was added a pre-stirred solution of 2,4-dinitrophenylhydrazine (50% w/w with water, 99.0 mg, 0.25 mmol, 0.5 equiv.) in methanol (1.5 mL) with a drop of concentrated sulfuric acid. The vial was then shaken vigorously, and stirred at 40 °C for 5 minutes. From the resulting solution was taken 10 µL, which was added to 990 µL of water. This sample was then subjected to LCMS, and through mass analysis the formation of 1-(2,4-dinitrophenyl)-2-methylenehydrazine was observed, the mass spectrum of which is shown below. LRMS (EI$^+$) $C_7H_7N_4O_4$ $[M+H]^+$ found 211.12.



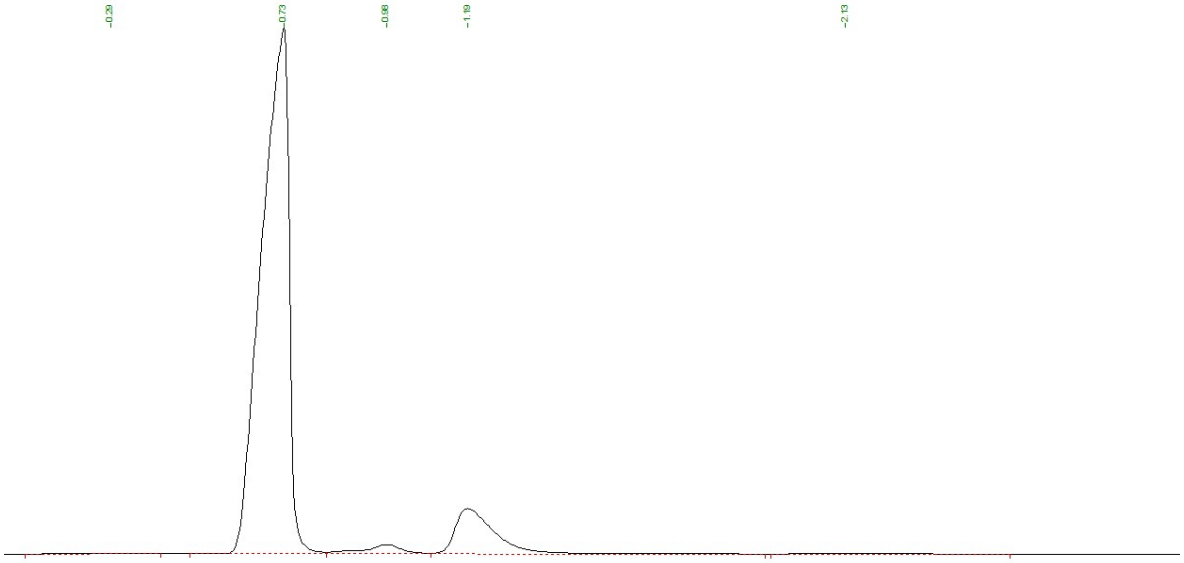
9.4.4. Detection of hydrogen



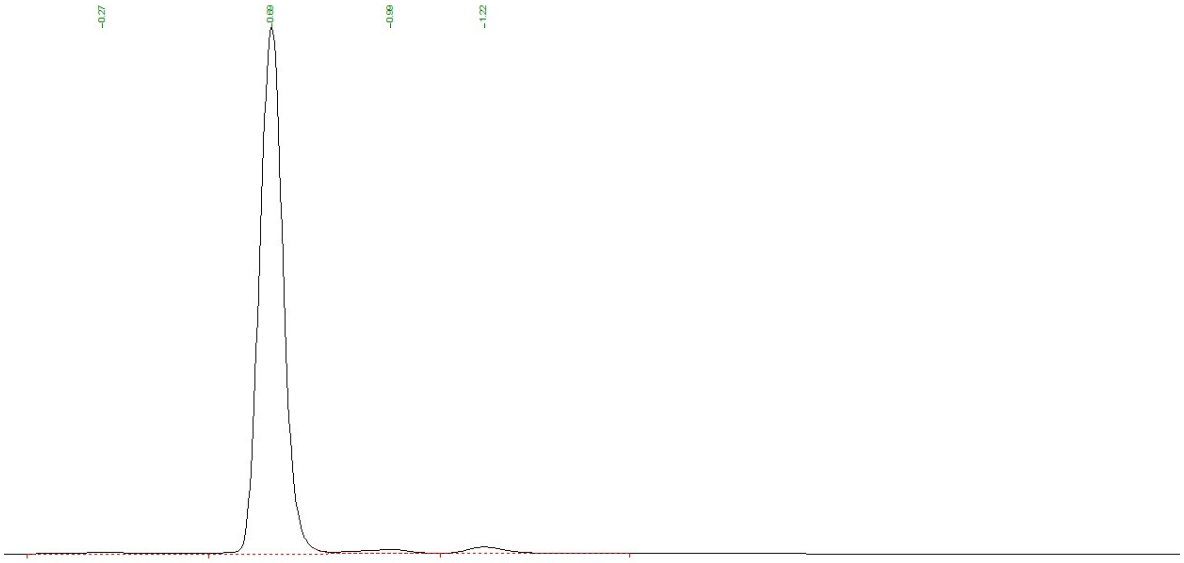
A 10 mL microwave vial was charged with a magnetic stirrer bar, and 250 mg of dust 4Å molecular sieves. The vial was then sealed with a suba seal, placed under vacuum, and vigorously flame dried to activate the molecular sieves. To the flame dried vial was added [Mn] precatalyst **177** (14.0 mg, 0.025 mmol, 5 mol %) and freshly ground KOH (56.1 mg, 1.0 mmol, 2 equiv.). The vial was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the vial was then added nitrobenzene (51.3 µL, 0.5 mmol) and methanol (1 mL) through the suba seal. The

reaction was then sealed with a crimpable lid and crimper, and stirred vigorously at 110 °C for 6 hours. The headspace of the reaction was then sampled with a 1 mL gas syringe, and the sample subjected to GC, showing the presence of hydrogen in the headspace of the reaction by comparison to 10% H_2 in argon as a standard, as shown below.

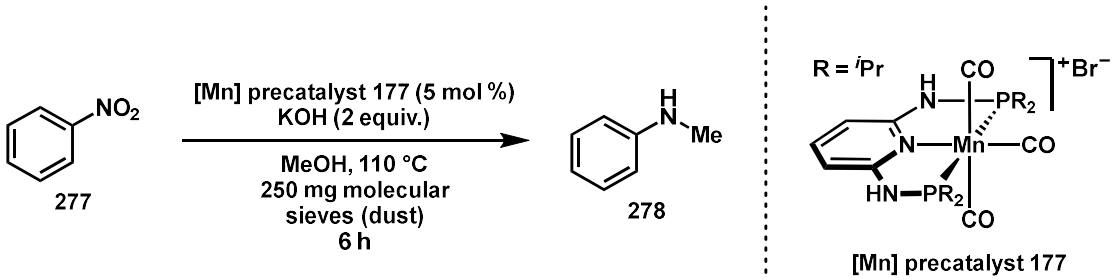
GC spectrum of the headspace sample:



GC spectrum of 10% H_2 in argon:

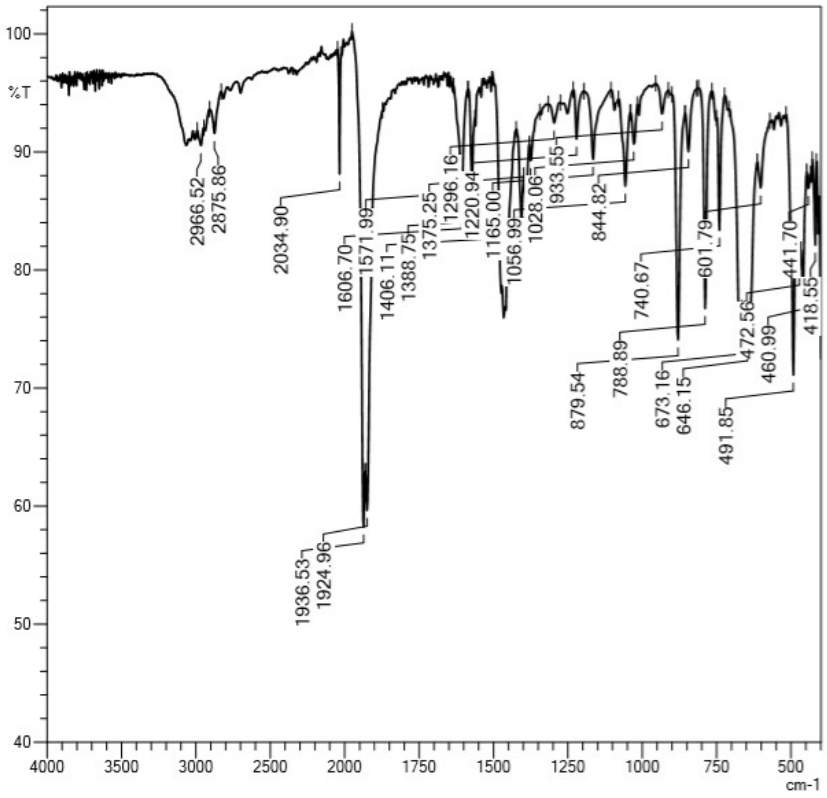


9.4.5. Catalyst stability studies

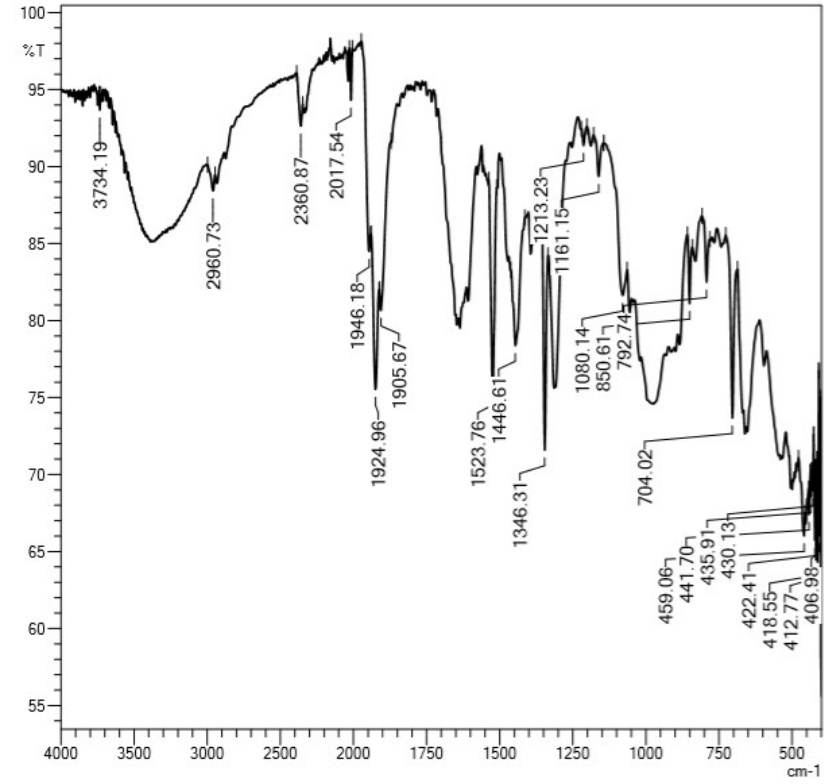


A 10 mL microwave vial was charged with a magnetic stirrer bar, and 250 mg of dust 4Å molecular sieves. The vial was then sealed with a suba seal, placed under vacuum, and vigorously flame dried to activate the molecular sieves. To the flame dried vial was added [Mn] precatalyst **3** (14.0 mg, 0.025 mmol, 5 mol %) and freshly ground KOH (56.1 mg, 1.0 mmol, 2 equiv.). The vial was sealed with a suba seal, and subjected to vacuum-nitrogen exchange. To the vial was then added nitrobenzene (51.3 µL, 0.5 mmol) and methanol (1 mL) through the suba seal. The reaction was then sampled, and analysed by IR spectroscopy to show the presence of the carbonyl ligands. The reaction was then sealed with a crimpable lid and crimper, and stirred vigorously at 110 °C for 6 hours. The reaction was then cooled to room temperature, diluted in methanol (2 mL), sampled and analysed by IR spectroscopy.

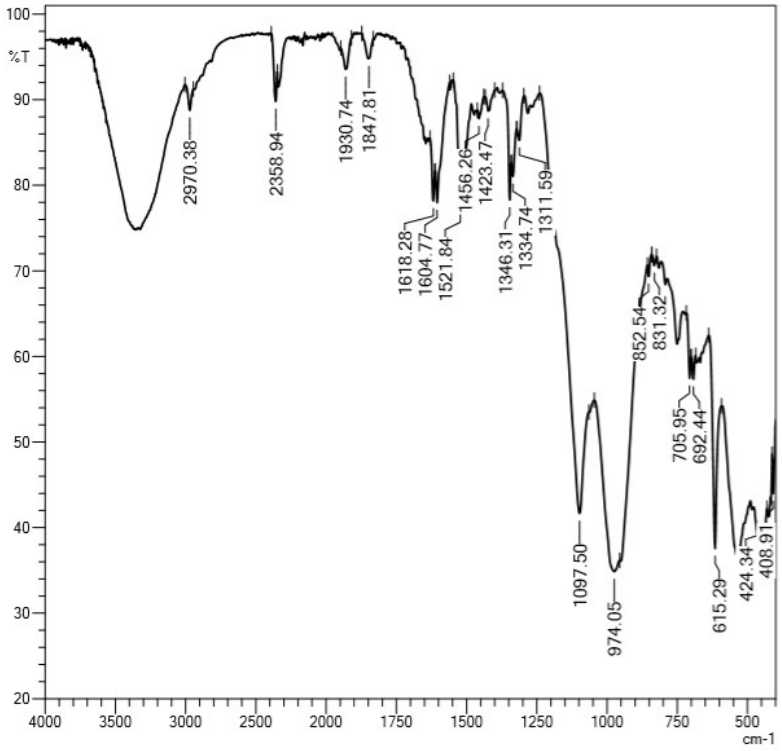
IR spectrum of the precatalyst:



IR spectrum of the reaction mixture at t = 0 h:



IR spectrum of the reaction mixture at t = 6 h:



9.5. References

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