One Pot Silane Mediated Reductive Amination using Methyl Esters as Nominal Electrophiles

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Presented for the degree of Master of Research

On

September 2023

Abstract

Reductive aminations are a commonly employed method of C–N bond formation with a quarter of C–N bond formations in pharmaceutical synthesis performed *via* a reductive amination.[1] Conventional reductive amination reactions rely on aldehydes as electrophiles which can be difficult to handle as a result of aldol dimerisation and autooxidation.[1, 2] This poster describes a new class of reductive amination reaction in which readily available carboxylic acid esters are used as nominal electrophiles in place of aldehydes. The amination process involves organocatalytic amide formation followed by silane-mediated reduction of the derived amide. The thesis describes the optimisation, scope, and mechanism of this novel amination protocol.

Acknowledgements

Thank you to Professor Ross Denton for the opportunity to work on this interesting project and for all the guidance and support he has provided.

I would also like to thank members of the Denton group, past and present, for all of their support and encouragement alongside my studies. Special thanks go to Dr Tom Barber for answering all of my questions and helping me to develop my skills as a chemist. Thank you also to Milly Stoneley for her invaluable insight and help with my project. Finally, thank you to everyone in the CNL for making my time working in the lab so enjoyable, and providing support and advice.

Abbreviations

PMHS — Polymethylhydrosiloxane

TMDS — 1,1,3,3-Tetramethyldisiloxane

TMDH — 2,2,6,6-Tetramethyl-3,5-heptanedione

HARC — Halogen Abstraction Radical Capture

TBD — triazabicyclodecene

DBU — 1,8-Diazabicyclo[5.4.0]undec-7-ene

COE — cis-cyclooctene (C_8H_{14})

EWG — electron withdrawing group

acac — acetylacetonate

cod — 1,5-cyclooctadiene

dba — dibenzalacetone

Triphos — 1,1,1-Tris(diphenylphosphinomethyl)ethane

p-cymene — 1-Methyl-4-(propan-2-yl)benzene

NMR — Nuclear Magnetic Resonance

ppm — parts per million

CCR-5 — Chemokine receptor 5

HIV — Human Immunodeficiency Virus

WHO — World Health Organisation

ESI — Electrospray Ionisation

MS — Mass Spectrometry

DCM — Dichloromethane

TLC — Thin layer chomatography

s — singlet

d — doublet

t — triplet

dd — doublet of doublets

m — multiplet

app — apparent

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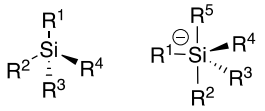
1 Silicon Chemistry

Silicon is abundant in the Earth in various forms, including organosilanes and silicon dioxides (silica), and has uses ranging from ceramics to semiconductors.[1] Within synthetic chemistry, silicon and its derivatives are employed for polymer synthesis, purification processes, protecting groups for alcohols and more recently for performing reduction reactions in the form of silanes.[2, 3] Silicon is most abundant as silicon dioxide or silicates, with pure silicon being formed from the carbothermal reduction of SiO_2. Tetrahedral SiR_4 compounds (1) are the most common, while higher order pentavalent silicon compounds (2) also known (Figure 1).[4, 5]



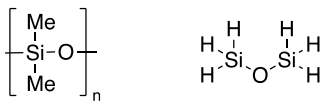
1 **2**

Figure 1. Silicon coordination; tetrahedral SiR_4, Pentavalent silicon anion.[4]

As a group 14 element, silicon shares some chemical properties with carbon, however silicon is more electropositive than carbon (Silicon 1.9, Carbon 2.6), with silicon–carbon bonds are also polarised towards carbon.[6] Silicon has a greater covalent radius, so silicon–carbon bonds (1.89 Å) are much longer than carbon–carbon bonds (1.54 Å). As a result of this, there is poorer orbital overlap and more diffuse orbitals in silicon–carbon, resulting in a weaker bond. Silicon forms stronger bonds with electronegative atoms such as oxygen and fluorine but weaker bonds to hydrogen than carbon; this difference in electronegativity provides silanes and organosilanes with their reactivity, as the Si–H bond has a hydridic character which renders hydrosilanes suitable for a range of reduction processes.[3]

1.1 Hydrosilanes

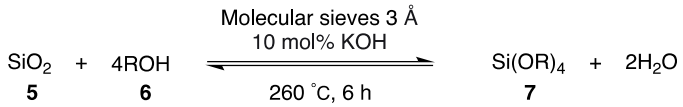
Hydrosilanes are tetravalent silicon compounds containing at least one silicon–hydrogen bond.[7] Where the silicon centre is bonded to an alkyl group or carbon, these hydrosilanes are known as organosilanes.[3, 5] Due to the weakly hydridic nature of the silicon–hydrogen bond, hydrosilane reactivity is centred around this reactive bond, however hydrosilane species can be selected for reactions based on their substituents, as different organosilanes offer different steric, electronic, and economic considerations, alongside the generation of different by-products.[3] Examples of these include phenylsilanes and alkylsilanes of varying substitution. Polymethylhydrosiloxane (PMHS) (3) and 1,1,3,3-Tetramethyldisiloxane (TMDS) (4) are both common inexpensive silane polymers (Figure 2) used mainly in hydrosilylations.[8-10]



PMHS (3) **TMDS (4)**

Figure 2. PMHS silane polymer (3) and TMDS (4). [8-10]

Hydrosilanes (7) are formed by reduction of either chloro- or alkoxysilane precursors, with the latter of increasing interest as feedstock-derived reactants from silica (SiO_2) (5) and alcohols (6) (Scheme 1).[7, 11]

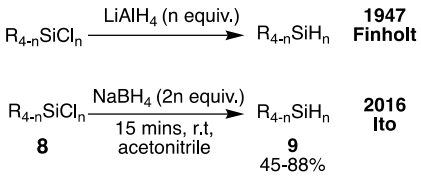


5 **6** **7**

Scheme 1. Formation of alkoxysilanes from feedstock derived silica and alcohols. [12]

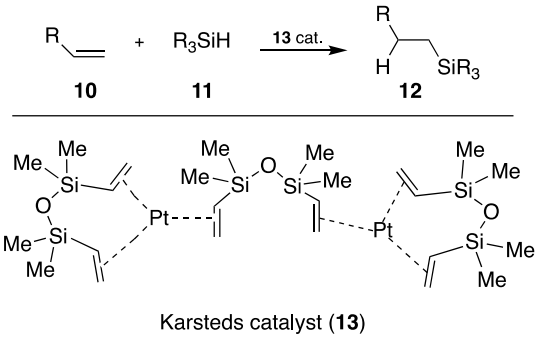
Reductions to form hydrosilanes have been performed using various reducing agents, with one of the first examples from 1947 using $LiAlH_4$ to reduce silicon halides, however an excess of reactive $LiAlH_4$ were required alongside laborious purification *via* an isopentane bath fractional condensation (Scheme 2).[13] Subsequent reagents have included sodium

borohydrides, tributyl tin reagents and molecular hydrogen.[7] More recent work by Ito used $NaBH_4$ for the reduction of chlorosilanes (8) to afford various organosilanes (9) in good yield; including phenyl- and alkylsilanes (Scheme 2).[14]



Scheme 2. Reduction of chlorosilanes to afford hydrosilanes, 1974 Finholt route employing $LiAlH_4$ and 2016 Ito route employing $NaBH_4$. [13, 14]

Hydrosilanes are known to form silicon–nitrogen, silicon–oxygen, silicon–silicon bonds, as a result they are useful for polymer synthesis. Hydrosilylations encompass an important class of reaction when considering hydrosilanes and they are used in the synthesis of silicon coupling agents, silicone polymers and organosilicon reagents.[8] Hydrosilylations involve addition of silicon hydrides (11) to olefins (10), with the first example being performed in 1947 by Sommer coupling trichlorosilane and 1-octene.[15]

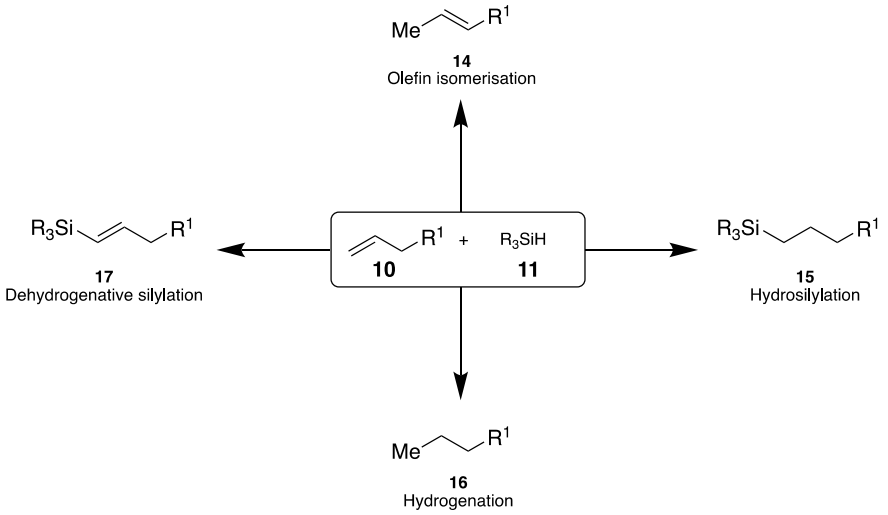


Scheme 3. General hydrosilylation for the synthesis of alkylsilanes (12) from alkenes (10), Karstedt's catalyst (13) frequently employed for these hydrosilylations. [8]

Most hydrosilylations require catalytic activation with a metal catalyst, with the most notable being Karstedt's catalyst (13) (Scheme 3) developed in 1973. [8] This paved the way for the development of other platinum catalysts.[8] Since this, many metal catalysts have been used in

hydrosilylations including Pt, Rh, Ir, Re, Mo, Ru, Fe, Ni, as well as aluminium hydrides and borane complexes.[8]

A major issue with hydrosilylations involves unwanted side reactions, including dehydrogenative silylation, olefin hydrogenation and olefin isomerisation (Scheme 4). These side reactions are commonly associated with the use of platinum catalysts, as a result alternative catalytic systems have been developed. [8]



Scheme 4. Side reactions associated with hydrosilylations and the by-products afforded, demonstrating olefin isomerisation, hydrosilylation, hydrogenation and dehydrogenative silylation reaction products (14-17). [8]

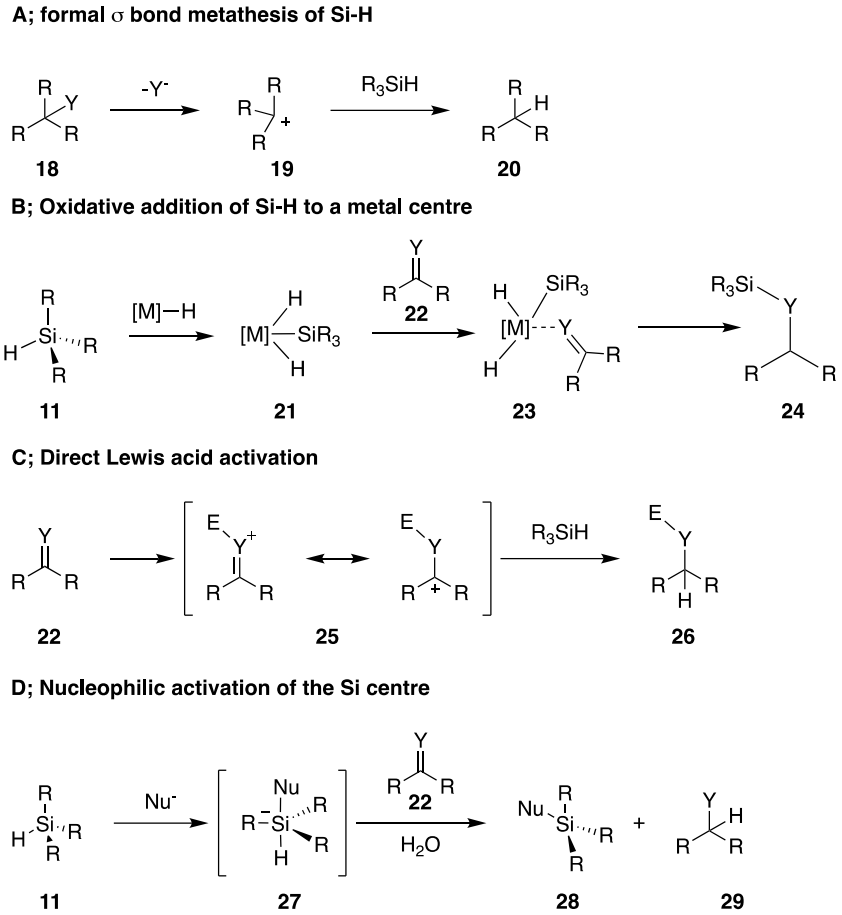
1.2 Hydrosilane mediated reduction reactions

As mentioned above, the weakly hydridic silicon-hydrogen bond can perform reductions if suitably activated and behave as a more kinetically competent reductant than molecular hydrogen alone due to the electronegativity difference between silicon and hydrogen.[6] For reductions, organosilanes provide stoichiometric hydrogen.[3] However they tend to be less reactive than classic reducing agents, such as aluminium hydrides or sodium borohydrides, allowing for more selective reductions than harsher alternatives and without their associated

hazards, most commercially available silanes can be handled without the need for special precautions.[3]

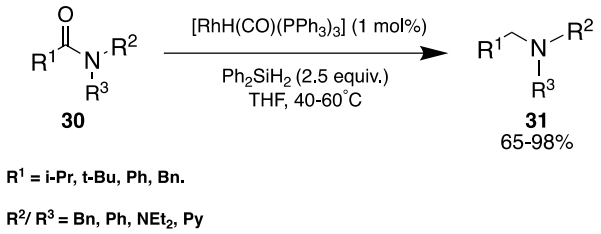
Hydrosilanes (11) are known to perform amide reductions, as well as asymmetric reductions of ketones, imines, esters, and nitriles.[3] This introduction will not encompass an exhaustive list of the reactivity of organosilanes and a more comprehensive summary can be found in a recent review of organosilanes in reductions by Larson.[3] Amide reductions encompass a large portion of hydrosilane reactions and a summary of alternative amide reduction routes can be found in a review of chemoslective amide reductions by Adolfsson,[16] additional detail of amide reductions can be found in *Section 2.1.6* of this thesis.

Activation, either catalytically or stoichiometrically, is required for these hydrosilyations and there are four general reaction pathways proposed, classified according to the nature of the activation process (Scheme 5). Firstly, **A** formal σ bond metathesis of Si–H, **B** Oxidative addition of Si–H to a low valent group transition metal centre to form a metal silane complex (21), **C** direct Lewis acid activation of the hydride or **D** nucleophilic activation of the Si centre and subsequent formation of a pentacoordinate silicon intermediate (27). [16, 17]



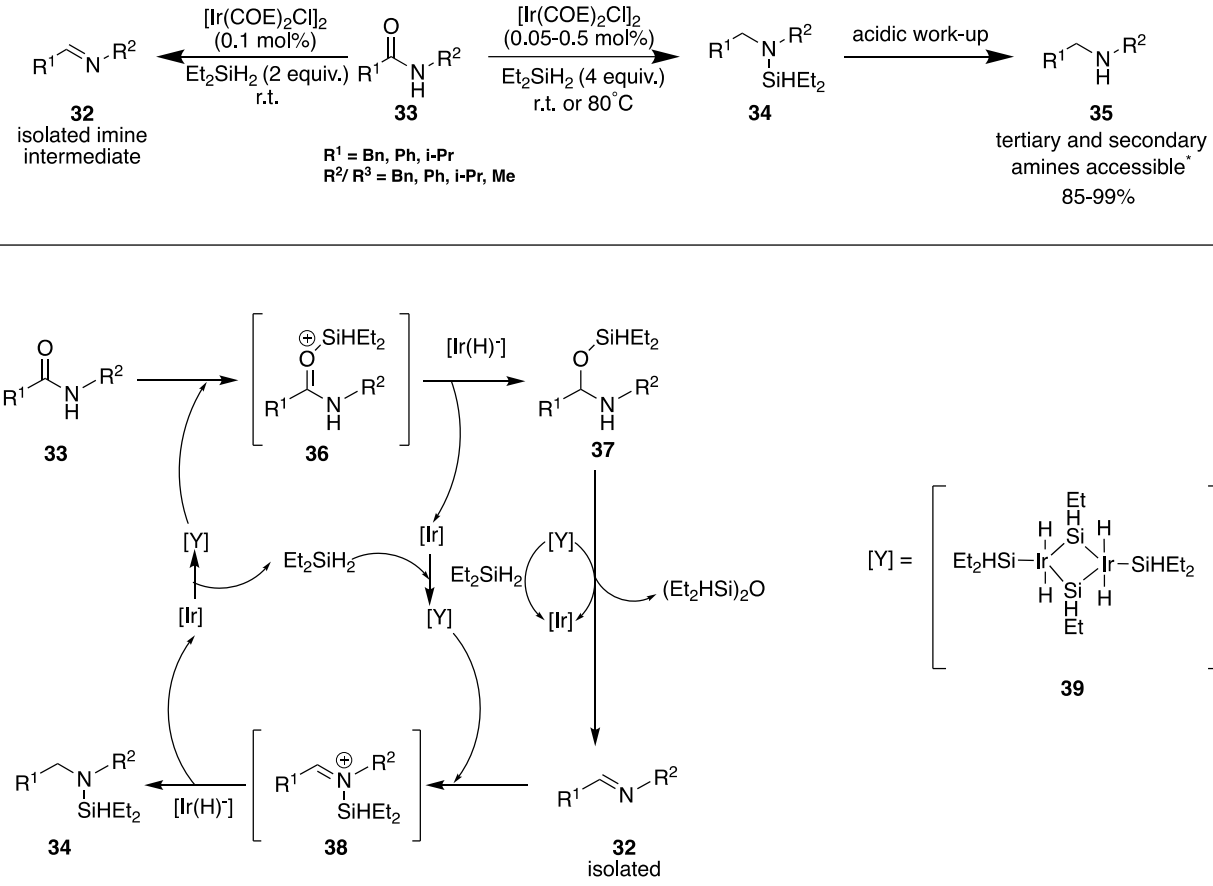
Scheme 5. Methods of activation of hydrosilanes for reduction reactions, where R = alkyl or aryl, Y = O or N, E = Lewis acid.[16]

Catalytic activation is preferable over the use of stoichiometric reagents due to the obvious economic and environmental benefits, as outlined in the 12 Principles of Green Chemistry catalytic methods generate less waste with reduced activation energy.[18] As such, many catalytic systems have been developed for activating silanes, comprising precious and non-precious metals, as well as some metal-free alternatives. Rhodium based catalysts have been commonly used, with one of the first examples from 1998 in work by Ito (Scheme 6).[19] This employed $RhH(CO)(PPh_3)_3$ and phenylsilane and was performed with good scope and only alkenes and alkynes were not tolerated, however this reduction was limited only to tertiary amines (31).[19] This was common for many of the subsequent catalytic systems and a system compatible with the reduction of secondary amides was an area of interest for the development of future systems.



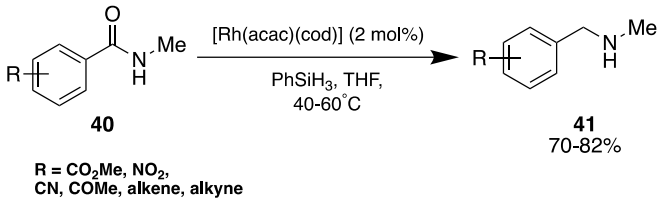
Scheme 6. Rhodium catalysed hydrosilane mediated reduction of tertiary amides (30). [19]

More recent examples include an $[Ir(COE)_2Cl_2]_2$ system, where COE is cis-cyclooctene (C_8H_{14}), with diethylsilane developed in 2012 by Brookhart (Scheme 7).[20] This reduction was performed neat in diethylsilane, and is one of the first examples of a catalytic silane-mediated reductive amination proceeding in good scope for both tertiary and secondary amines.[20] This work is of note as it demonstrated an isolatable imine intermediate (32), providing evidence that amide reduction was proceeding *via* an imine reduction pathway. Further detail into amide reduction pathways can be found in *Section 2.1.6* of this thesis.



*Scheme 7. Catalytic cycle of Brookharts iridium catalysed reduction of amides to afford tertiary and secondary amines, *secondary amines (35) depicted for clarity, highlighting the route for the reduction of amides and the formation of an isolatable imine intermediate (32)*.[20]

Work by Beller in 2016 demonstrated a [Rh(acac)(cod)]/$PhSiH_3$ system, where acac is acetylacetonate ($C_5H_7O_2$) and cod is 1,5-cyclooctadiene, for the reduction of secondary and tertiary amines (Scheme 8).[21] This system was capable of reducing secondary amides (40), which as a result of reduced nucleophilicity are often difficult to reduce. Additionally, reducible functional groups previously incompatible with this chemistry were tolerated in this system: nitro, nitrile, azo, alkene and alkyne containing amines were afforded in good yields.[21]



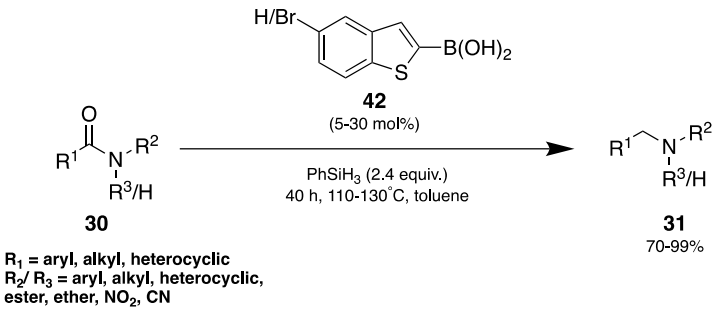
Scheme 8. Beller Rhodium catalysed silane mediated reduction of secondary substituted aromatic amides (40).[21]

Subsequently, various protocols to perform hydrosilyations with catalytic activation have emerged, examples including Rh, Ru, Ir, Co, Zn, Fe, Mo, Cu and Pt catalysts have been detailed. [20, 22-28] Many of these systems used commercially available PMHS or TMDS, with more reactive phenylsilane sometimes used instead despite the increased cost (Table 1).[29]

Silane	Cost (£ per mmol)
PMHS	0.01
TMDS	0.23
$PhSiH_3$	0.63
Et_3SiH	0.13

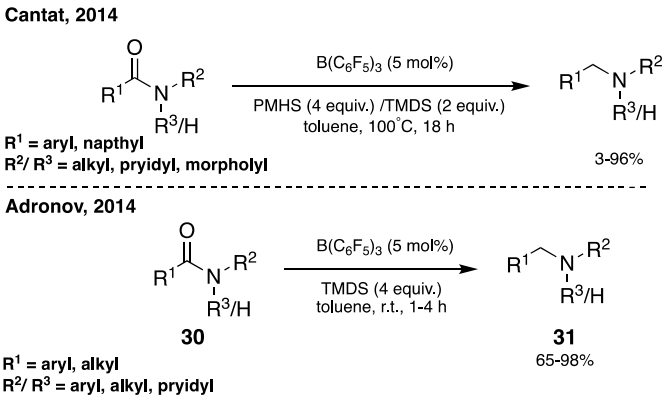
Table 1. Summary of cost per mmol for common silanes. [29]

In efforts to move away from transition metal catalysts, organoboron catalysts have been investigated for silane mediated reductions. The first of these was disclosed by Beller in 2013, using a 5-Br-benzothiophene derived boronic acid (42) and phenylsilane (Scheme 9). [30] These conditions tolerated reducible functional groups and able to reduce primary, secondary and tertiary amines.[30] The reaction conditions were limited by the required inert argon atmosphere, as well as long reaction times of up to 40 hours.



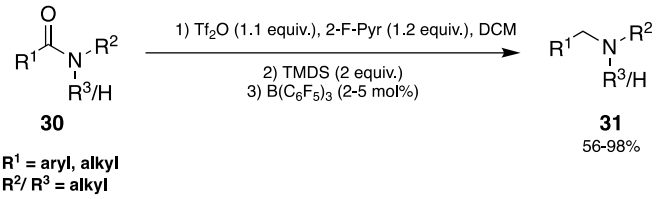
Scheme 9. Beller's reduction of amides using boronic acid and phenylsilane. [30]

Following this, work performed simultaneously in 2014 by Cantat and Adronav demonstrated an amide reduction using $B(C_6F_5)_3$ with PMHS or TMDS (Scheme 10). While this work proceeded in generally good scope, reducible functional groups were not well tolerated in either system, and Schlenk technique was required which limits reaction scalability.[31, 32]



Scheme 10. Boronic acid and silane mediated amide reductions by Cantat and Adronav. [31, 32]

Later developments by Wang in 2016 involved the use of Tf_2O to activate the amide, alongside 2-fluoropyridine as a base additive, in combination with $B(C_6F_5)_3$ and silane (Scheme 11). This route improved upon earlier work as it was able to tolerate many reducible functional groups with good chemoselectivity, however required the use of many expensive reagents across multiple steps.[33]

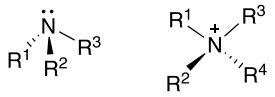


Scheme 11. Boron catalysed hydrosilane mediated reduction by Wang. [33]

Amide reductions are a useful route for the synthesis of amines, and silane mediated routes encompass a new generation of safer and greener reductive systems. Coupling these reductions with efficient amidation processes would expand the utility of this chemistry to N-alkylations and other amine functionalisations.

2 Amines

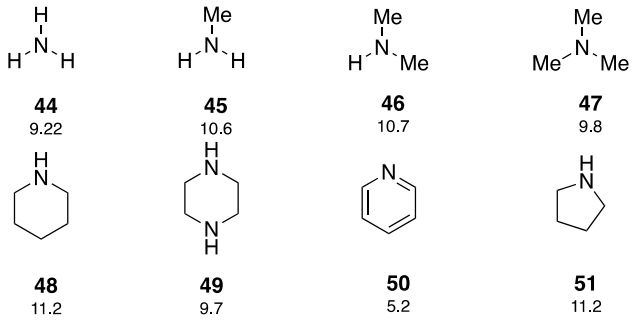
Amines are a valuable and prevalent functional group with a wide variety of applications including pharmaceuticals and dyes. Amines adopt a tetrahedral structure, with alkyl substitution possible to form primary, secondary, and tertiary amines, and further alkylation forming quaternary ammonium salts (Figure 3).[34]



42 **43**

Figure 3. General amine structure, trigonal pyramidal (42) and quaternary amine salt, tetrahedral (43) .[34]

The nucleophilic and basic properties of amines are essential when discussing their chemistry, as these properties are responsible for amine reactivity. The lone pair of electrons resides in an sp^3 hybrid orbital on the nitrogen atom and affords nucleophilic and basic character.[34] It is important to note that both nucleophilic and basic properties of amines can vary greatly depending on the substituents bonded to the nitrogen atom. Both electron withdrawing and electron donating groups can change the electron density around the nitrogen atom, subsequently altering its basic and nucleophilic properties (Figure 4).[35]



44 9.22 **45** 10.6 **46** 10.7 **47** 9.8

48 11.2 **49** 9.7 **50** 5.2 **51** 11.2

Figure 4. Representative amines and their $pK_{aH}(H_2O)$ values, demonstrating the variation with substitution and electronics for cyclic amines. [35]

Amines and their derivatives are ubiquitous in organic synthesis, with many compounds known to have anticancer, antimicrobial and antifungal properties that make them useful for pharmaceutical and agricultural applications.[36] In a recent review investigating the types of reactions and reagents most employed by medicinal chemists, 43% of the compounds investigated were found to contain an aliphatic amine making them one of the most prevalent functional groups aside from aromatic rings in pharmaceutical synthesis.[37] Direct functionalisation of an amine is advantageous for improved synthetic routes of compounds containing amine functionality; for example amine containing drugs, such as the antidepressant citalopram (55) and the dopamine D2 receptor agonist piribedil (56) (Figure 6), are commonplace.[37] Additionally, amines are a standard building block for polymer and material synthesis, notably amino acids as an essential building block of life (52-54) (Figure 5).[36]

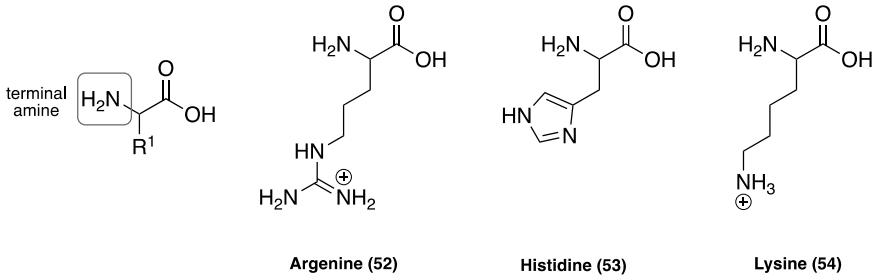


Figure 5, A general amino acid structure and common amine containing amino acids; Argenine (52), Histidine (53), Lysine (54). [38]

Cyclic amines such as pyrrolidine (51) and piperidine (48) are of interest as these functionalities are present in many pharmaceutically active compounds, including the antihistamine loratadine (57) and the anti-epilepsy medication levetiracetam (58) (Figure 6). [39, 40] They share similar reactivity to acyclic amines, with similar basic and nucleophilic properties. Alternatively, aromatic amines, such as piperidine (Figure 4), differ in reactivity. Resonance delocalisation into the conjugated ring system results in a near planar nitrogen meaning there is less electron density at the nitrogen, hence reduced nucleophilic character compared to their non-aromatic counterparts.[16]

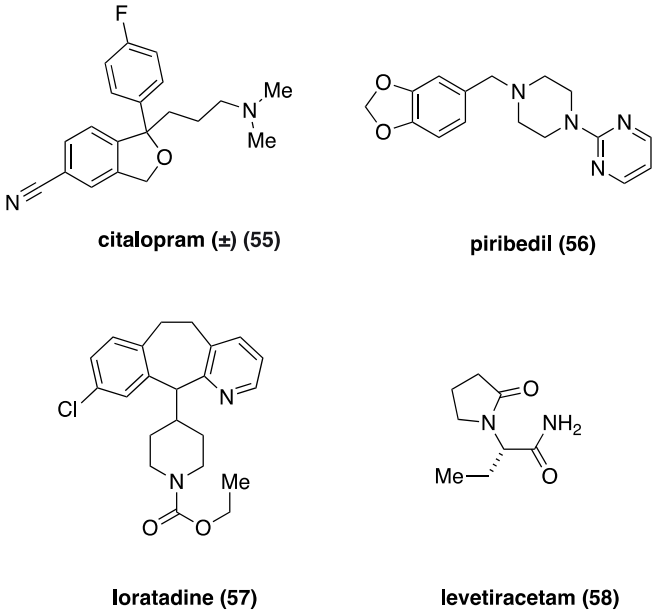
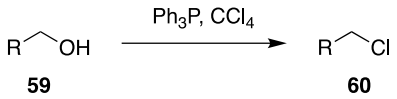


Figure 6. Representative bioactive amines; Citalopram (55), and Piribedil (56), [37] *Cyclic amine containing drugs, loratadine (57) and levetiracetam (58).*[39, 40]

2.1 Amine synthesis

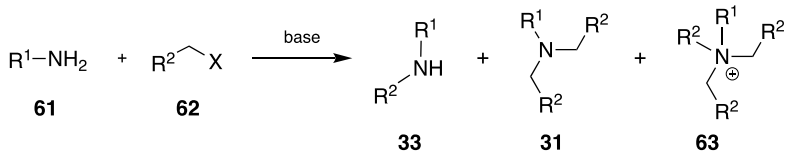
2.1.1 *N*-Alkylations

Alkylation of a nitrogen nucleophile with alkyl halides accounted for a quarter of amine formations in medicinal chemistry routes, and are still commonly used in industry, despite reported issues of uncontrolled over-alkylation and competing elimination pathways (Scheme 13).[37, 41] Additionally, alkylhalides are generally toxic, often genotoxic, and the synthesis of these reagents usually involves stoichiometric quantities of toxic reagents for deoxyhalogenation, commonly *via* an Appel reaction for the synthesis of alkylchlorides (60) (Scheme 12).[42] Despite being commonly used, this requires stoichiometric phosphorus activating agents and toxic chlorinating agents.



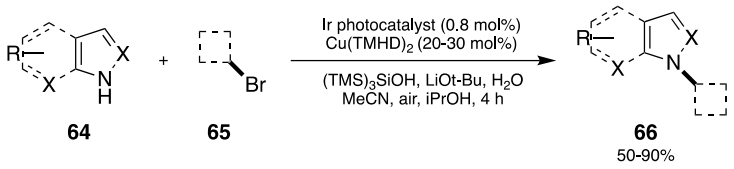
Scheme 12. The Appel reaction for the synthesis of alkylchlorides (60).[42]

The energy barrier for these reactions is dependent on steric factors, and often high temperatures or expensive metal catalysts are required to drive the reaction.[41, 43] . Basicity and nucleophilicity of amines increase with substitution, so more reactive secondary amines compete with primary for further alkylation. As a result, monoalkylation is often difficult to achieve for these *N*-alkylations, with uncontrolled further substitution affording a mixture of substituted amine products (31, 33, 63) (Scheme 13).



Scheme 13. General N-alkylations to afford a mixture of functionalised amines.[34]

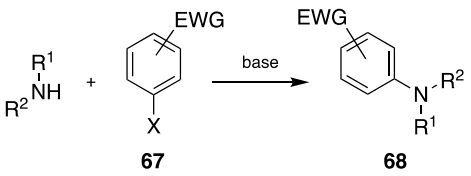
Advances in photochemistry have resulted in a range of new methods for *N*-alkylation. For example, MacMillan developed a halogen abstraction radical capture (HARC) strategy for N-alkylations under mild conditions, employing an iridium photocatalyst alongside $Cu(TMHD)_2$ where TMHD is the bidentate ligand 2,2,6,6-Tetramethyl-3,5-heptanedione.[41] This route demonstrated utility for late stage synthesis, however high loadings of copper reagent were required (Scheme 14).



Scheme 14. MacMillan HARC strategy for copper metallophotoredox alkylations of nitrogen nucleophiles. Reaction scope includes 1°, 2° and 3° alkylbromides, and indazoles, pyrazoles, azindoles, indoles, carbazoles and amides as the N-nucleophile. [41]

2.1.2 Nucleophilic Aromatic substitutions

Similarly, a nitrogen nucleophile can be used in nucleophilic aromatic substitution reactions to form new carbon–nitrogen bonds (Scheme 15). Many pharmaceutical compounds feature aromatic rings and systems, making manipulation such as these attractive for pharmaceutical synthesis.[37] This process requires a good halogen leaving group and activating groups on the aromatic ring. Alongside similar limitations to N-alklylations, the resulting generation of stoichiometric quantities of halogen waste and limited functional group tolerance make this route unattractive.



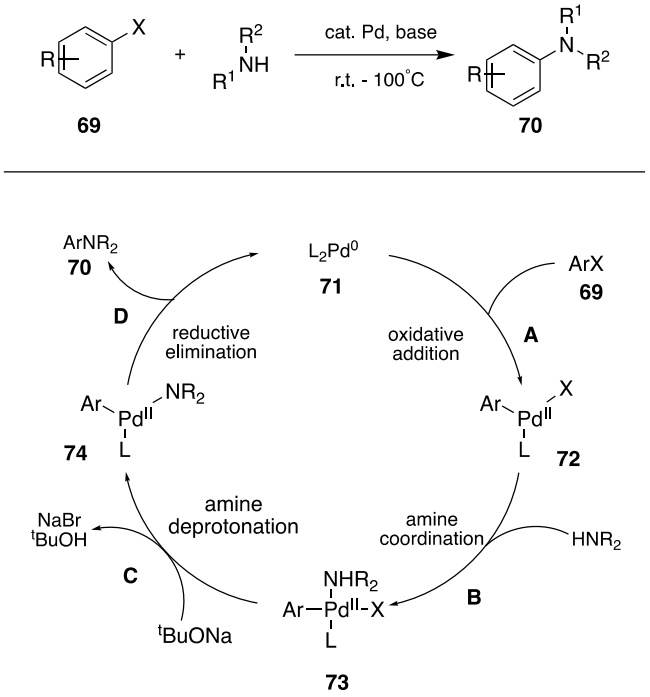
Scheme 15. General nucleophilic aromatic substitution to afford functionalised aromatic amines (68), X = F, Cl, Br, I, EWG = electron withdrawing group.[44]

2.1.3 Buchwald Hartwig amination

Transition metal catalysed cross-couplings for *N*-arylations are frequently employed in industrial synthesis.[37] While these cross couplings are of huge importance in chemical synthesis, they are not without limitations. The use of transition metals often employs specialised ligands, whilst the catalysts themselves often come at a high cost (Table 2).[45]

One such method, Buchwald-Hartwig amination (Scheme 16), involves a palladium catalysed cross-coupling of amines and aryl halides, and is significant in the synthesis of aromatic amines. An analysis of reactions carried out by medicinal chemists in 2014 has shown that 10% of the papers published employed this coupling at least once, with the reaction being compatible for large scale synthesis and of good functional group tolerance.[46-48] A variety of palladium complexes and sterically hindered bases are available for use in this coupling, with many different ligands for the palladium catalyst also developed.

The catalytic cycle (Scheme 16) takes advantage of the variable oxidation state of palladium complexes, with initial oxidative addition of the Pd(0) (71) species into the aryl halide (69) (**A**) forming a Pd(II) complex (72). Coordination of the amine (**B**) increases the acidity of the palladium complex (73), allowing for deprotonation by hindered bases to form a palladium amide (74) (**C**). The final reductive elimination (**D**) affords the arylated amine product (70) and regenerates the Pd(0) catalyst (71).[49]



*Scheme 16. Catalytic cycle of Buchwald Hartwig coupling for amine synthesis, with (**A**) oxidative addition of Pd(0) (71) into aryl halide (69), (**B**) amine coordination to Pd (II) complex (72), (**C**) amine deprotonation, and (**D**) reductive elimination to afford the arylated amine product (70). X = F, Cl, Br, I. L = Ligand* [49]

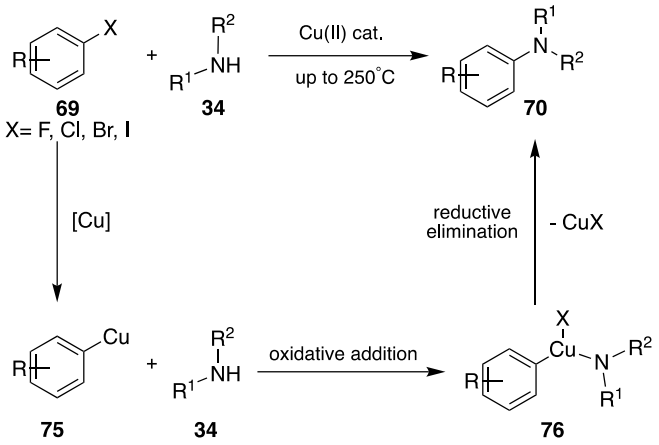
2.1.4 Copper catalysed couplings

Copper catalysed couplings were developed as an alternative to palladium catalysis, with copper being less expensive, less toxic, and more commercially available (Table 2).[50]

Catalyst	Cost (£ per mmol)
$Pd(OAc)_2$	59.00
$Pd_2(dba)_3$	59.16
Karstedt's catalyst [Pd]	24.30
$Cu(OAc)_2$	0.33
$Cu(OTf)_2$	6.34
CuI	0.10
CuCl	0.06

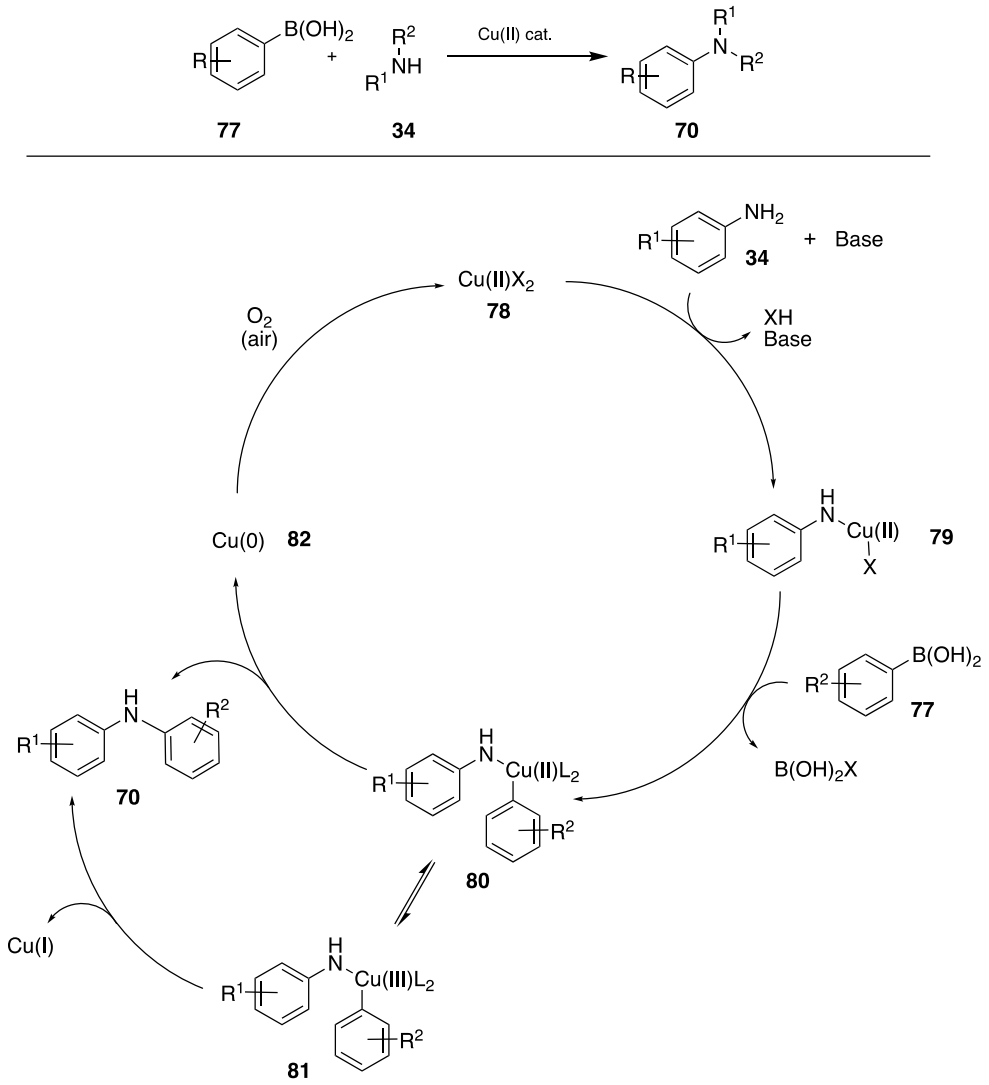
Table 2. Common palladium and copper catalysts with relative cost per mmol, values obtained from Sigma-Aldrich June 2023.

One example is the copper-mediated Ullmann-type coupling of amines and aryl halides.[49] The Ullmann coupling was first published in 1903, and is widely utilised for large scale industrial synthesis despite the high temperatures required for the reaction resulting in greatly limited scope (Scheme 17).[51]



Scheme 17. Ullmann coupling of aryl halides and amines for functionalised amine synthesis.[52]

An additional copper catalysed cross-coupling of note is the Chan-Evans-Lam coupling, involving the oxidative coupling of amines with aryl boronic acids (77), mediated by copper salts (79-82) (Scheme 18).[50] This route has the advantage of requiring milder conditions than the Ullmann coupling and is more compatible with sensitive substrates. However, the success of this coupling is known to be very substrate specific, with conditions reported to vary between amines, anilines, tetrazoles, aminopyridines, and aminophenols. As a result, a general protocol has been difficult to define.[53]

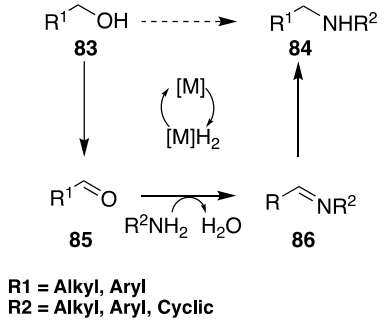


Scheme 18. Chan-Evans-Lam coupling of aryl boronic acids and amines for functionalised amine synthesis with proposed mechanism for the copper catalytic cycle.[50]

2.1.5 "Borrowing Hydrogen" alkylations

The Borrowing hydrogen strategy involves the use of alcohols (83) as electrophile precursors and an amine as a nucleophile, alongside catalytic activation to form Carbon–Carbon and Carbon–Nitrogen bonds (Scheme 19). This route is advantageous due to the non-toxic reagents and water being the only by-product. The use of alcohols as opposed to alkyl halides required for many other routes is desirable, with alcohols being generally safer and more commercially available. The reaction is selective to avoid over-alkylation often associated with

amine alkylations, and is tolerable of a wide range of functional groups; for the amine and the alcohol.[54]

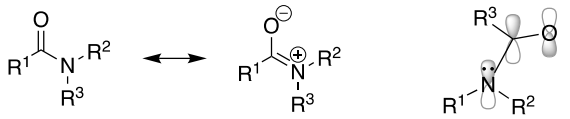


Scheme 19. Borrowing Hydrogen Strategy for amine synthesis from alcohols. [54]

Generally, this route requires high temperatures and long reaction times, as well as metal catalysts including ruthenium and iridium. This route has been performed in solvent free microwave conditions by Williams, with reduced reaction times (1.5 -2 h rather than 24 h). This was demonstrated in good scope for a variety of amines and alcohols, and was employed in the synthesis of primary amines.[54]

2.1.6 Amide Reductions

An important route for the synthesis of amines involves the reduction of amides. A discussion of silane mediated amide reductions can be found in *Section 1.2* of this thesis. Amides are a derivative of carboxylic acids and are the least reactive of the carbonyl compounds: esters, aldehydes, ketones and carboxylic acids.[55] They are ubiquitous in many areas of chemistry and are vital for peptide synthesis and in the synthesis of artificial polymers such as the polyamide Nylon.[56] Resonance delocalisation of the nitrogen lone pair of electrons provides partial double bond character and reduces electron density around the nitrogen atom compared to amines. The amide bond is planar, which allows orbital overlap between the nitrogen lone pair and the C=O π antibonding orbital resulting in reduced electrophilicity and reactivity (Scheme 20). By distorting the planarity of the amide with sterically hindered N-substituents, it is possible to increase the reactivity of the amide carbonyl group.[16]



Scheme 20. Amide conjugation, resonance delocalisation and orbital overlap to explain the stability of amides.[16]

As a result of the resonance interaction depicted above, amides exhibit low reactivity and can be challenging to reduce, particularly in a chemoselective sense. A general reduction pathway involves 2 steps: formation of the hemiaminal and subsequent reduction of the iminium to form the amine. [16] This reductive pathway is centred around C–O bond cleavage, whereas alternative pathways may involve C–N bond cleavage, which results in a mixture of alcohol and amine products (Scheme 21).[16]

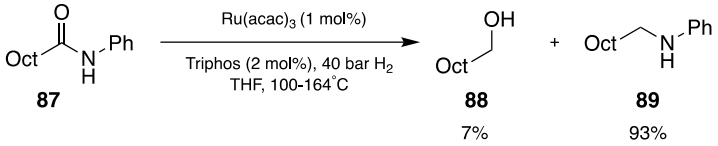
Scheme 21. General amide reduction pathway via iminium ion pathway. [16]

The main strategies for the reduction of amides involve nucleophilic metal hydride reagents, with common strong reducing agents such as $LiAlH_4$ and $NaBH_4$. Strong reducing agents such as these are required for the reduction of generally highly stable amides, but come with low chemoselectivity and functional group tolerance, poor control of further reductions and generation of stoichiometric amounts of waste by-products.[57, 58] Despite this, these harsh reductants are still some of the most commonly employed reagents for amide reductions.[59]

Alternatively, direct hydrogenation with molecular hydrogen is an attractive alternative, with the main by-product being the generation of water. Despite the route being less harmful to the environment in theory, high temperatures and high pressure of H_2 are required, alongside high loadings of metal catalyst which limits functional group tolerance.[60] The concept of a direct catalytic hydrogenation of amides using molecular hydrogen is attractive as an atom economical approach where the main by-product is water. Generally, this route has been

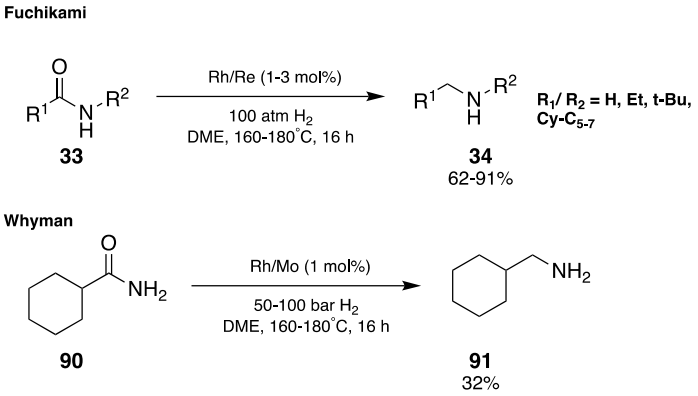
difficult to achieve for many carboxylic acid derivatives, with amides regarded as the most challenging.[61]

In 2007 Cole-Hamilton reported an *in-situ* generated ruthenium catalytic system with molecular hydrogen for the reduction of *N*-phenylnonamide (87) (Scheme 22). Unwanted alcohol by-products (88) were observed in this system, and there was no detailed investigation into reaction scope, however the desired amine (89) was afforded as the major product. The system also required high temperatures and pressures, something which is universal with other hydrogenation systems developed.[62]



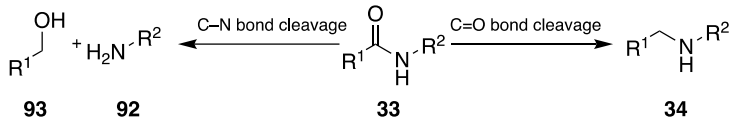
Scheme 22. Cole-Hamilton Ruthenium catalysed reduction of N-phenylnonamide (87).[62]

Platinum group metal catalysts are also required for reductions with molecular hydrogen, with some examples of bimetallic systems reported, including Rh/Re by Fuchikami and Rh/Mo by Whyman.[63, 64] The latter of these examples was demonstrated only for the reduction of cyclohexanecarboxamide (90) to cyclohexanemethylamine (91), being incompatible with acyclic aliphatic and aromatic amides. These routes are limited by high reaction temperatures and high pressures, alongside the use of expensive bimetallic catalysts.



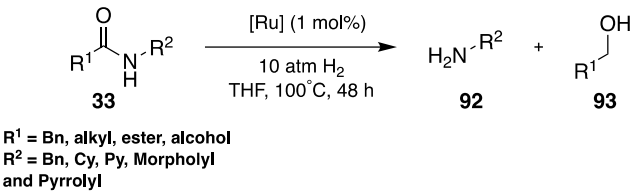
Scheme 23. Molecular hydrogen reduction of amides by Fuchikami and Whyman, employing bi- metallic catalyst systems.[63, 64]

The above routes are designed around C=O bond cleavage, which is the general route for amide reductions, although some direct hydrogenation systems have been designed around C–N bond cleavage as an alternative, generating alcohols (93) and amines (92) (Scheme 24).[61]



Scheme 24. C=O bond cleavage vs C–N bond cleavage to afford.[61]

While this approach is of interest, it is not universally applicable as a reduction of amides where the original amide structure is maintained in the amine product.[61] This C–N bond cleavage pathway was observed and noted as a by-product in the Cole-Hamilton reduction (Scheme 22).[62] There are some examples of this route having been exploited in a useful way, notably the C–N bond cleavage route was performed by Milstein using a ruthenium catalyst and molecular hydrogen (Scheme 25). While this route is of interest, it is limited by the loss of the original amide structure, as well as long reaction times and high pressures.[61]

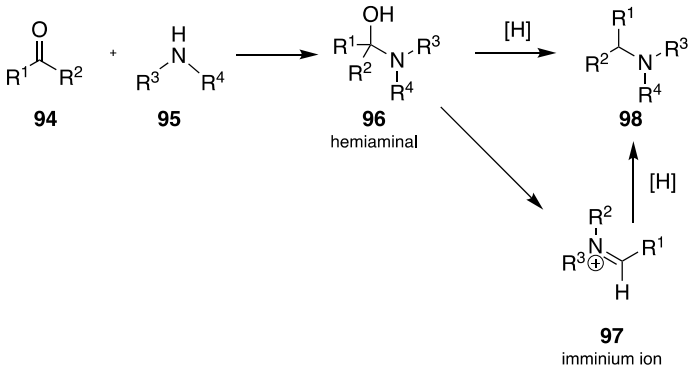


Scheme 25. Milstein ruthenium amide reduction to afford amine (92) and alcohol (93) products via C–N bond cleavage pathway.[61]

Silane mediated reductions of amides have expanded in popularity in recent years, demonstrating superior chemoselectivity, functional group tolerance and reaction conditions, as described in detail in *Section 1.2* of this thesis.

3.1 Reductive Aminations

Reductive aminations make up about one quarter of C-N bond formations in pharmaceutical synthesis, owing to a good general functional group tolerance, a proclivity for one-pot synthesis and a variety of reagents and conditions available to perform the reaction.[37] A general reductive amination pathway (Scheme 26) involves nucleophilic attack of the amine (95) into the carbonyl (94), forming a hemiaminal (96). Subsequent reduction of this hemiaminal follows two potential pathways: formation of an iminium cation (97) which is then reduced or direct reduction of the hemiaminal to yield the amine product (98).[65, 66]



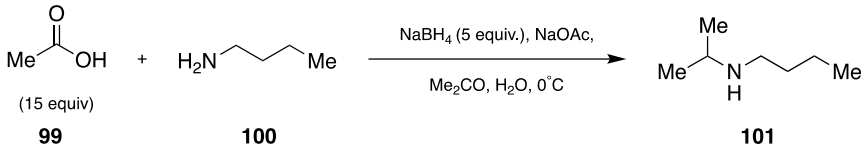
Scheme 26. General reductive amination pathway via hemiaminal formation and subsequent iminium ion reduction. [65, 66]

This is done in a single reaction vessel without isolation of any intermediates. The hemiaminal reduction step which can be considered the key step within a reductive amination and as such many developments to reductive aminations focus on this step. A summary of common reagents in the synthesis of pharmaceuticals by Chusov details the variety of reagents and methods for which they are employed in large scale pharmaceutical synthesis.[65]

Stoichiometric quantities of sodium borohydrides are commonly employed for reductive aminations. These reagents are generally safe and non-toxic, with the exception of $NaBH_3CN$ which releases HCN upon reaction with acid, and tolerant of a variety of functional groups. However, on larger scales the formation of boric acid derivatives can be difficult to dispose of.[67] While $NaBH_4$ is commonly used, modified complexes such as $NaBH(OAc)_3$ and $NaBH_3CN$

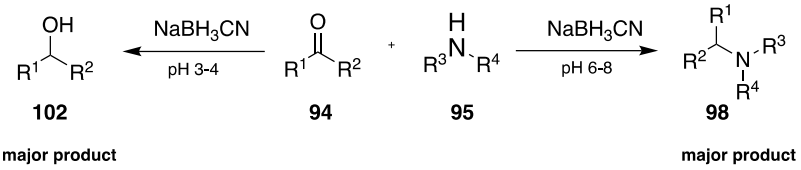
are preferred as the electron withdrawing groups stabilise the boron-hydrogen bond providing milder reducing properties, enhancing functional group tolerance. [66, 68, 69]

The first example of a direct reductive amination using $NaBH_4$ was performed in 1963 by Schellenberg for the synthesis of *N*-isopropylbutylamine (101) from formic acid (99) and butylamine (100) (Scheme 27).[70] This initial route is of interest as a carboxylic acid behaved as a nominal electrophile, contrasting with later routes which mainly employed aldehydes as the electrophile. Since then, this reagent has been used in large scale reactions; of note are the synthesis of drugs such as propranolol, codeine, and sertraline.[65] While this reagent is cheap and non-toxic, selectivity issues are often encountered regarding reduction of starting materials rather than the hemiaminal intermediate (Scheme 29).



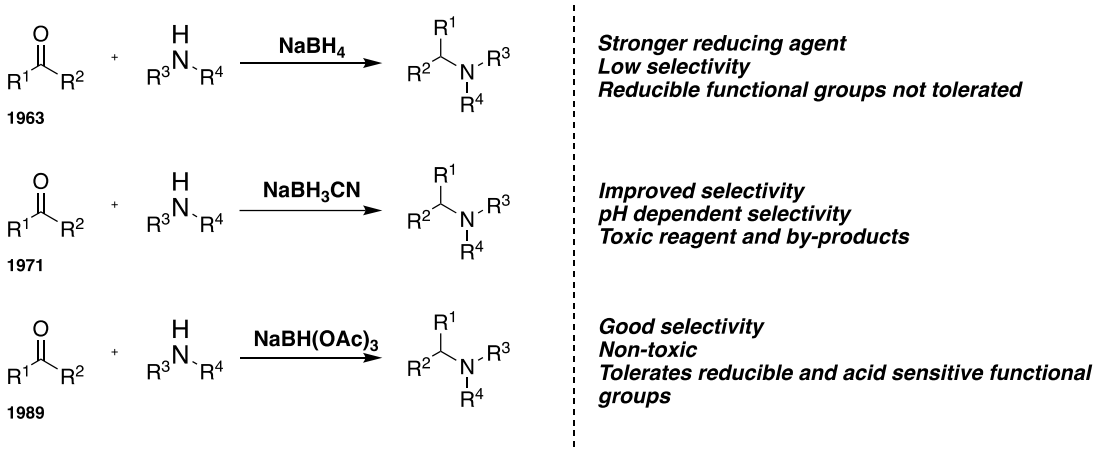
Scheme 27, 1963 Schellenberg direct reductive amination using $NaBH_4$ in the synthesis of N-isopropylbutylamine (101). [70]

Following this, a reductive amination protocol involving $NaBH_3CN$ was developed by Borch.[69] Owing to the pH dependent variable selectivity of $NaBH_3CN$, this modified borohydride provided enhanced selectivity; at pH 3-4 aldehydes and ketones are reduced selectively, at pH 4-6 more basic imines are protonated & reduced faster. This route offered good selectivity for the reduction of imines over carbonyls when performed at pH 6 (Scheme 28).[66, 68, 69] While the development of this modified borohydride provided improved selectivity, the generation of toxic cyanide by-products poses a major limitation (Scheme 29). Additionally, production of these by-products is generally increased in the acidic conditions required to achieve good selectivity.



Scheme 28, pH dependency of $NaBH_3CN$ for reductions and the products afforded at different pH [66, 68, 69]

In 1989, $NaBH(OAc)_3$ was developed to bypass the cyanide contamination issues associated with $NaBH_3CN$. [68] This reagent offered good selectivity and tolerance of reducible functional groups, while remaining a safe, non-toxic reducing agent (Scheme 29). $NaBH(OAc)_3$ is now one of the most popular reagents for reductive aminations,[65] however it is still required in super-stoichiometric quantities and generates large amounts of boron containing waste.[66]

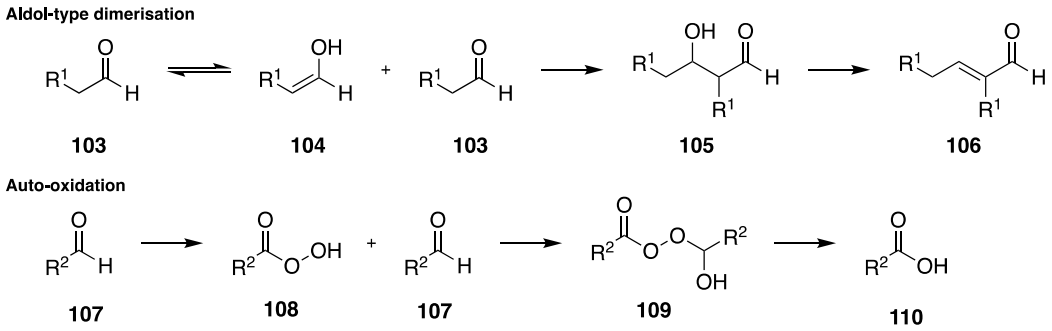


Scheme 29, Comparison of borohydride reducing agents, with standard sodium borohydrides followed by modified borohydrides with enhanced reducing properties [66, 68, 69]

An alternative method for reduction involves hydrogenation with molecular hydrogen activated with metal catalysts; examples include Pt, Pd, Ru, Rh, Co, Ir and Ni.[65] Reduction with molecular hydrogen is attractive owing to a generally low cost and low waste system. However, the conditions required for the activation of molecular hydrogen raise selectivity issues, with high temperatures and high pressures of hydrogen required. [65] As a result, reduced functional group tolerance is observed, with reducible functional groups, such as nitro and cyano groups

not tolerated. Toxic and expensive metal catalysts are required, which may result in contamination of products with residual metal. Additionally, the procedures often require the use of specialised equipment which increases costs and limits scalability when compared to alternative routes.[65] Less common systems involve the use of formic acid derivatives, however. These reagents do not tolerate acid sensitive functional groups, and their generally corrosive nature makes them undesirable for scaled up synthesis.[65]

While these routes commonly employ aldehydes or ketones as the electrophile, these reactants can pose some limitations. Aliphatic aldehydes (103) are reactive species and are often not bench stable, often decomposing readily through an aldol dimerization process at room temperature (Scheme 30).[71] Aromatic aldehydes (107) are also known to decompose *via* an auto-oxidation process to afford the carboxylic acid (110) (Scheme 30).[72] Due to this they are generally less commercially available than more stable carbonyls, such as carboxylic acids.[73] This is especially true for more complicated aldehydes which synthesis prior to their use as reagents. As a result, alternative electrophiles for reductive aminations are an attractive area of research.

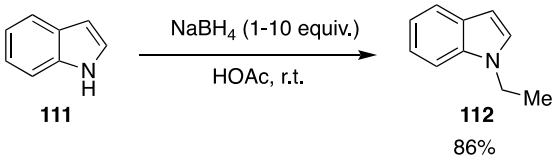


Scheme 30, Aldol-type decomposition of aldehydes, Auto-oxidation of aldehydes to afford carboxylic acid [71, 72]

3.2 Reductive Aminations Using Carboxylic Acids In Lieu Of Aldehydes and Ketones.

Carboxylic acids have been proposed as an alternative electrophile for reductive aminations, owing to their stability and good commercial availability. Recently there have been many advances in the development of these direct reductive aminations from carboxylic acids.[68] Direct reductive aminations involve direct mixing of the carbonyl compound with the reducing agent without forming the imine first, this intermediate is instead formed *in situ*. In a recent review of commercially available medicinal chemistry building blocks, 13,000 aldehydes were identified, compared to 59,000 carboxylic acids.[73]

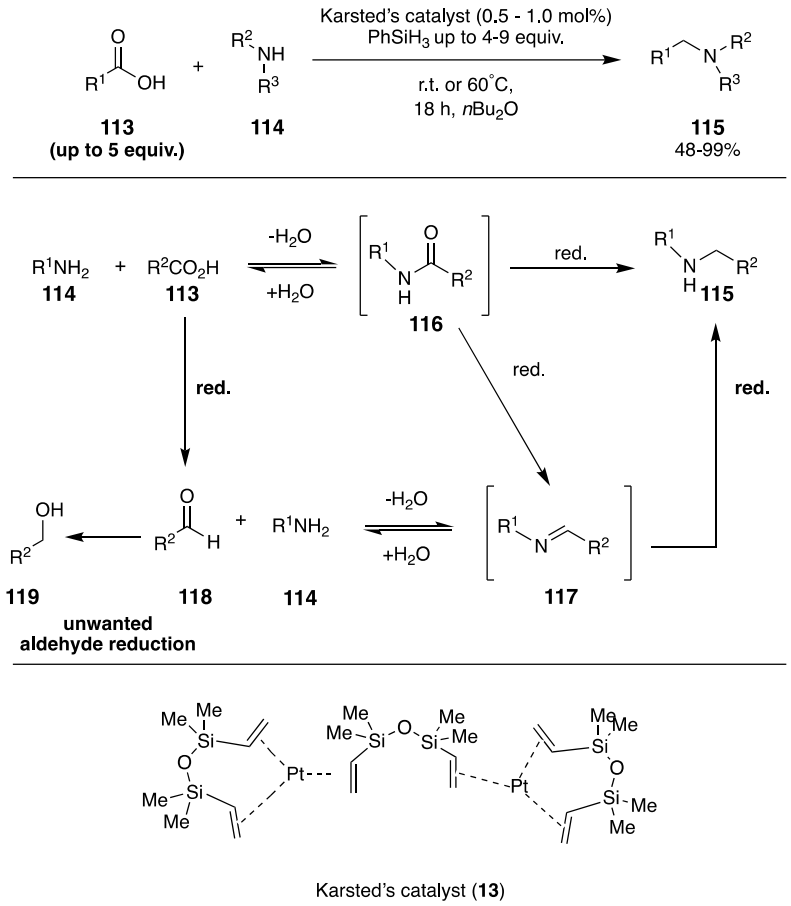
As described above, one of the first examples of a reductive amination was described by Schellenberg in 1963 and employed formic acid as the coupling electrophile (Scheme 27).[70] Following this a reductive amination with carboxylic acids was described by Gribble in 1974, using sodium borohydride and acetic acid as the reaction solvent with indole (111) being used as the starting amine (Scheme 31). While good yields of N-ethylindole (112) were afforded, superstoichiometric quantities of $NaBH_4$ were used and many examples did not show full reduction to the amine with amide being the main side product.[74]



Scheme 31, Gribble $NaBH_4$ reductive amination from carboxylic acids. [74]

A breakthrough was described by Beller in 2014, using phenyl silane and Karstedt's catalyst (13) to promote reductive amination reactions of amines (114) and carboxylic acids (113) (Scheme 32). Within this work it was found that without catalytic activation of the silane, reduction would not occur. This remained true regardless of excesses of silane; as a result, the development of catalytically activating systems for silane mediated reductions has been an area of interest.[75] This method was limited by the need for inert conditions, alongside the high loadings of phenylsilane and carboxylic acid required. These large excesses of carboxylic acid

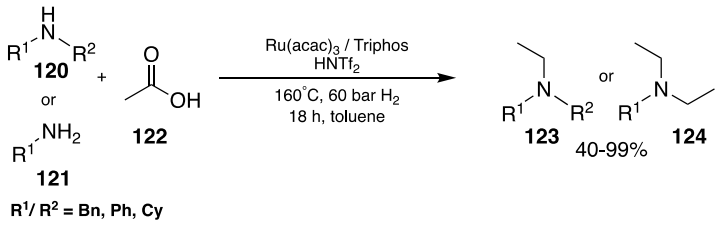
and silane were generally required for less reactive amines and carboxylic acids, or to afford a diarylated product. The reduction of carboxylic acid starting material alongside amide was a commonly encountered problem, alongside unwanted reduction of the more reactive aldehyde intermediate (118) (Scheme 32), often resulting in reduced yields or excesses of starting material to account for the loss of starting material.[75] Unwanted reduction of the more reactive aldehyde to afford an alcohol product (119) is also observed.



Karsted's catalyst (**13**)

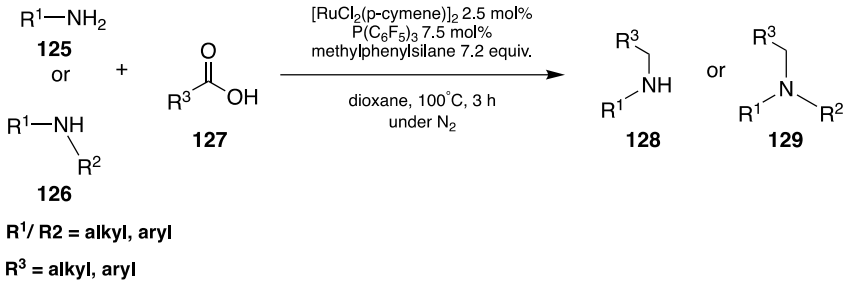
Scheme 32. Beller silane mediated reduction with Karstedt's catalyst where R^1 = aliphatic, aromatic, heterocyclic, amino, olefinic, amino, hydroxy substituents and R^2/ R^3 = aliphatic, aromatic substituents. [75]

Beller also demonstrated a reductive amination from acetic acid (122) using molecular hydrogen for the reduction, with a ruthenium catalyst (Scheme 33).[76] This work avoided the use of stoichiometric reagents, however high temperatures and pressure were required, alongside high loadings of expensive metal catalyst.



Scheme 33. Beller molecular hydrogen route for the reductive amination of acetic acid, where Triphos = 1,1,1-Tris(diphenylphosphinomethyl)ethane ligand. [76]

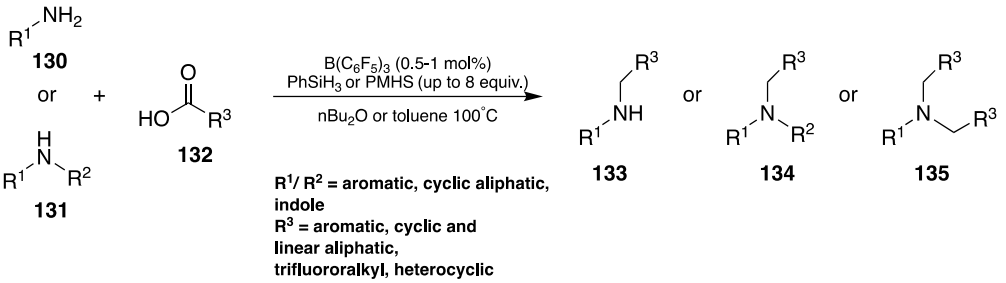
This was followed by various metal catalysed silane mediated reductive aminations; where different metal complexes were used to activate silane to enhance reduction. Of note was work by Minakawa in 2016, where $[RuCl_2(p\text{-cymene})]_2$ (p-cymene is 1-Methyl-4-(propan-2-yl)benzene) and tris(pentafluorophenyl)-phosphine ligand were used with methylphenyl silane to form secondary and tertiary amines from carboxylic acids (Scheme 34).[77] This work was performed in good scope, however required a nitrogen atmosphere, alongside an additional phosphorus agent in high loadings to aid silane reactivity.



Scheme 34. Minakawa Ru catalysed, silane mediated reductive amination of carboxylic acids.[77]

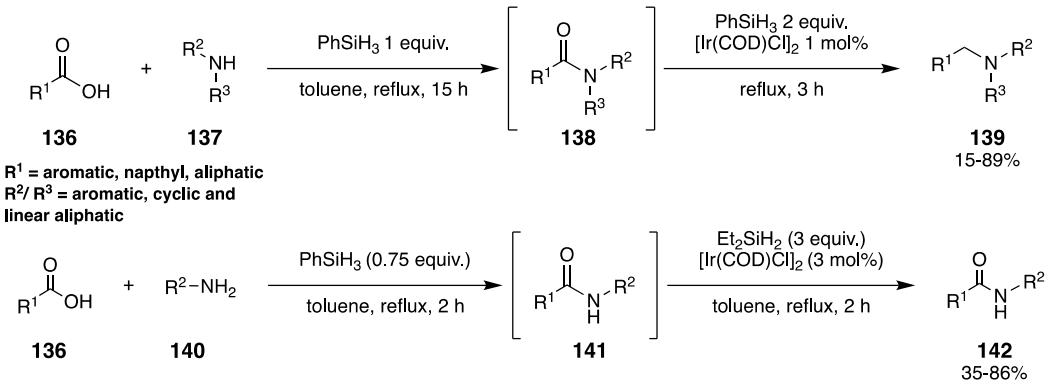
A metal-free system was described by Fu in 2015, using a perfluorinated triphenyl borane catalyst, $(B(C_6F_5)_3$, and phenylsilane (Scheme 35).[78] This was proposed as a "greener" alternative to Karstedt's catalyst, avoiding the toxicity associated with metal catalysts, and tolerating reducible functional groups such including nitro and cyano groups. While this route is attractive, boron catalysts such as these are expensive, and cheaper alternatives would be

preferred. The catalyst is very strongly Lewis acidic which limits functional group tolerance, with required Schlenk conditions further limiting the usefulness of this reaction.



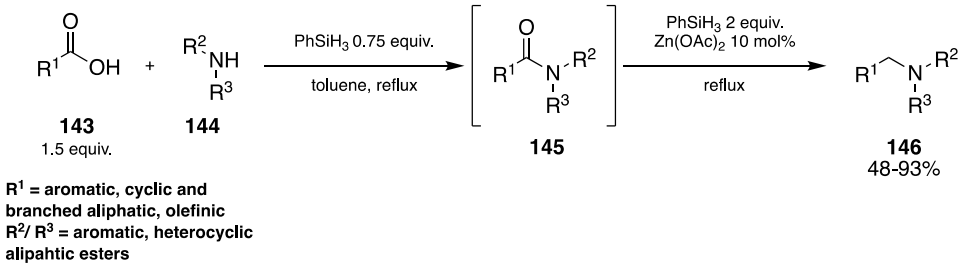
Scheme 35. Fu borane catalysed reductive amination for the syntheisis of secondary and tertiary amines.[78]

In 2016, Denton developed a one pot reductive amination employing silane and $[Ir(COD)Cl]_2$.[79] This work was especially interesting as it proposed the reductive amination as a two-step, one-pot system where C–N bond formation was performed before the reduction to eliminate the risk of unwanted reduction of the carboxylic acid and derived aldehyde, something which had not been considered in previous routes (Scheme 36). The two steps can be described as an initial amidation step, followed by the reduction step. The dual reactivity of phenylsilane was exploited for both steps; mediating the amide formation and subsequent reduction when activated by the iridium catalyst. While this work showed promise, it came with a limited scope as these conditions would not tolerate reducible functional groups or sterically hindered amines. Furthermore, for the synthesis of secondary amines, two different silanes were required for the amidation and reduction steps. The reduction step in the synthesis of secondary amines was instead performed using conditions determined by Brookhart using diethylsilane, with an increased silane loading.[20] These conditions were required to reduce secondary amides which are more weakly Lewis acidic than tertiary amides, and form a less reactive intermediate and more challenging reduction.[79]



Scheme 36. Denton Ir two phase catalysed reductive amination of carboxylic acids; highlighting the importance of separating the carbon – nitrogen bond formation from reduction to avoid unwanted reduction of starting materials[79]

Subsequent work in the Denton group developed a similar system with $[Zn(OAc)_2]$ and phenyl silane (Scheme 37).[80] Keeping amide formation and reduction as two separate steps, this route offered an improved scope and lower loadings of an inexpensive zinc catalyst ($[Ir(COD)Cl]_2$ £80/mmol), $[Zn(OAc)_2]$ £0.55/mmol, values obtained from Sigma-Aldrich June 2023). [80]

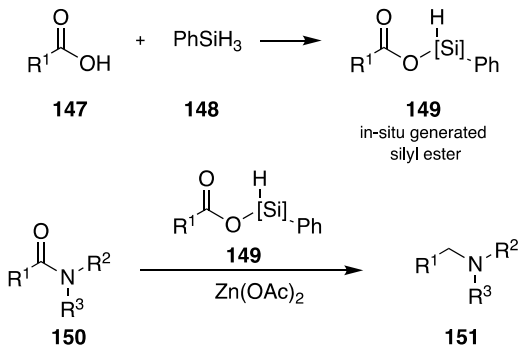


Scheme 37. Denton two phase silane mediated reductive amination form carboxylic acids, again, viewing the system as a two-step one-pot process. [80]

Previous investigations of catalytic Staudinger reactions by Denton observed the ability of Brønsted acids to react with phenylsilane and generate modified silanes which demonstrated enhanced reducing properties.[81] In this reductive amination it was found that initial additional equivalents of carboxylic acid greatly improved yields. It was proposed that the excess carboxylic acid from the amidation step was modifying silane *in situ* to generate a more reactive species. This was confirmed by ^{19}F NMR mechanistic investigations conducted using

^{19}F NMR spectroscopy, where the excess carboxylic acid reacted upon addition of $Zn(OAc)_2$ and phenylsilane to generate observable hydrogen gas formation, and additional peaks in ^{19}F NMR spectrum attributed to silyl ester formation.[81]

This led to a general proposed mechanism where the residual carboxylic acid (147) undergoes dehydrogenative silylation to generate silyl esters (149). These more reactive species (149) react more rapidly with $Zn(OAc)_2$ to activate and reduce the amide. This work presented dual reactivity of silanes and their potential to form more reactive silicon species with enhanced reducing properties through reactions with Brønsted acids (Scheme 38). [80] [81]

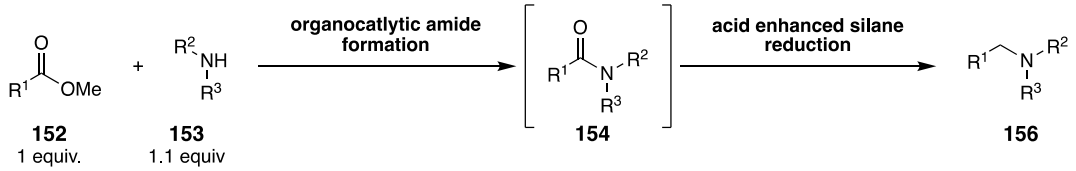


Scheme 38. Formation of the silyl etser species (149) from residual carboxylic acid for the enhanced reduction of amides in Denton's Zn catalysed reductive amination.[80]

There have been many routes developed for simple reductive aminations from carboxylic acids. These are attractive alternatives to the use of aldehydes and ketones, with carboxylic acids known to be more bench-stable and commercially available reagents. Silane mediated reductive aminations are especially attractive, avoiding the use of harsh reagents or conditions employed by other routes. While carboxylic acids offer improved commercial availability over other carbonyls, their tendency for thermal decarboxylation limits their use in reactions employing high temperatures.[82]

4 Aims

For the synthesis of tertiary amines, we propose a one-pot reductive amination employing methyl esters (152) as nominal electrophiles, without the use of inert atmospheres or metal catalysts. This reaction can be considered a two-phase one-pot reaction system, with organocatalysed formation of an amide intermediate (154), followed by a metal free silane mediated reduction (Scheme 39).[83, 84] For clarity, the two phases of this reaction are discussed separately as the *organocatalytic amide formation* and the *silane mediated reduction*.



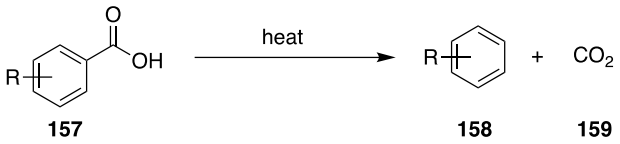
Scheme 39. Proposed reductive amination with C–N bond formation prior to a silane mediated reduction.

4.1 Reductive Amination from Methyl Esters

The use of methyl esters for direct reductive aminations is underexplored, despite being an attractive starting material as a cheap, readily available and bench stable reagent. Existing examples of this transformation employ expensive metal catalysts and high pressures of molecular hydrogen to drive the reaction forward, often employing metal catalysts including nickel.[85, 86]. To date a simple and mild route for the reductive amination of methyl esters has not been described.[87]

The use of carboxylic acids as the coupling electrophile was developed to bypass the instability and relative scarcity associated with the use of aldehydes and ketones, yet these cannot be considered a panacea. A general issue with some aromatic carboxylic acids is a tendency to decarboxylate, rendering the starting material useless (Scheme 40). Methyl esters are a more stable carbonyl, so it was proposed they would pose less risk of decarboxylation in these conditions. This provides an opportunity to expand the functional group tolerance of this

reaction to include examples previously unattainable, some aromatic carboxylic acids (157) are known to be especially prone to decarboxylation at high temperatures and had not previously been tolerated in these conditions.



Scheme 40. Decarboxylation of aromatic carboxylic acids. [88]

Methyl esters are commonly employed as protecting groups for carboxylic acids in synthesis. Our proposed chemistry allows exploitation of the presence of methyl esters in late stage synthesis to directly functionalise these protecting groups as opposed to deprotection for further reaction, reducing the number of required steps.[37] The use of methyl esters expands upon the available starting materials, therefore increasing the versatility of reaction.

4.2 Organocatalytic Amide formation

Due to methyl esters possessing inherently lower reactivity than carboxylic acids, activation of either the carbonyl or amine is required to mediate the nucleophilic attack by the amine into the carbonyl for amide formation. Even with activation, weakly nucleophilic amines are not generally compatible with methyl esters as the coupling electrophile or require especially forcing conditions to afford good yields.[85]

Generally, activation involves the use of metal catalysts, such as nickel, the use of which is increasingly unattractive and problematic.[86] Organocatalysts have expanded in popularity in recent years as a greener alternative to metal catalysts, with nucleophilic catalysts such as TBD (triazabicyclodecene) (160) and DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene) (161) (Figure 7) being employed to mediate many different reactions, including the activation of methyl esters for amide formation.[83, 89] A majority of organocatalysts are bicyclic guanidines, which behave as nucleophilic organocatalysts.[83] They possess both basic and nucleophilc properties and are

known to activate methyl esters to allow for amine attack into the carbonyl for amide formation.

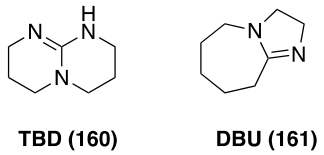
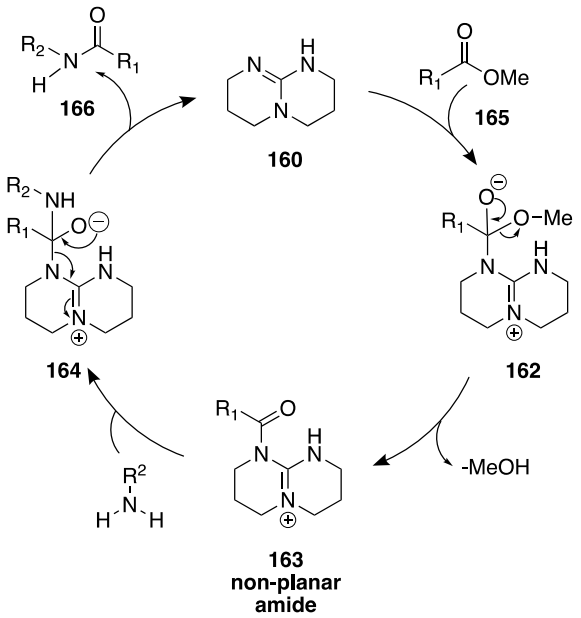


Figure 7. Chemical structures of triazabicyclodecene (TBD) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU). [83]

One such example is the cyclic guanidine TBD (160) (Scheme 41). Despite lower basicity and nucleophilicty, TBD has been shown to outperform other structurally similar organocatalysts, specifically in the activation of methyl esters for the formation of amides. Computational studies performed by Waymouth and coworkers demonstrated that the catalytic activity of TBD lies in its structure, whereby the sterically bulky bicyclic ring structure forms a non-planar amide intermediate (163), disrupting the resonance delocalisation resulting in a carboxyl intermediate which is less stable and more susceptible to nucleophile attack.[83]



Scheme 41. TBD Organocatalytic cycle for the formation of amides from methyl esters and amines. [89]

This route is a generally reliable route for amide formation from methyl esters, however scope is somewhat limited as sterically hindered or weakly nucleophilic substrates are not well tolerated. Additionally, substrates which possess a strong hydrogen bonding ability are not compatible in the system and result in catalyst deactivation.[90]

DBU (161) is an alternative amidine based organocatalyst which has been used successfully to catalyse a ring opening polymerisation of cyclic esters and lactones.[91] DBU is less expensive than TBD, and there are some examples in the literature of its ability to catalyse amide formation from esters, however these reactions display limited scope and require very high catalytic loadings.[92]

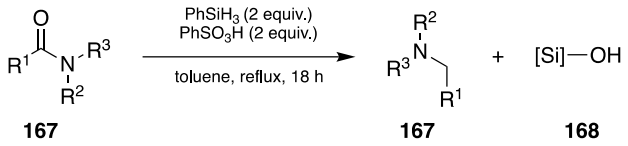
With activation necessary for the amidation step of our reductive amination, TBD is an obvious choice as a relatively cheap and safe organocatalyst, which poses a good alternative to existing transition metal catalysed systems.

4.3 Metal-Free Silane mediated reduction

The second phase of the reaction is the acid enhanced silane mediated reduction. A reductive system using benzene sulfonic acid and phenyl silane has been developed by Denton and Stoneley; work which is currently unpublished.[84] This was developed to by-pass the functional group limitations associated with the use of strong reducing agents, including harsh metal hydrides, and to provide an effective metal free reductive system to avoid problematic metal catalysts.

Previous work had demonstrated the use of strongly acidic sulfonic acids alongside phenylsilane to mediate reductions (Scheme 42).[84] This proof of concept paved the way for the use of benzene sulfonic acid in this reduction to activate phenylsilane to form a species with enhanced reducing properties. It is noteworthy that other sulfonic acids were compatible

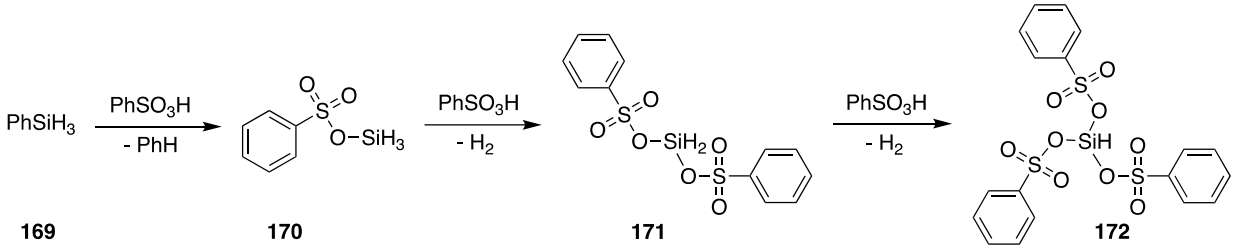
with this system including *para*-toluenesulfonic acid, however this acid demonstrated poor yields unless dry conditions were used.[84]



167 **167** **168**

Scheme 42. Benzene sulfonic acid activated phenylsilane reduction of amides (167), with formation of a silyl alcohol side product (168), as detailed in Scheme 44.[84]

Phenylsilane does not act alone for the reduction and requires this activation, something which is well documented for other silane mediated reductions. Mechanistic studies have demonstrated the formation of silylsulfonates as the active species upon reaction of phenylsilane (169) and benzene sulfonic acid (Scheme 43). [84] Higher order silylsulfonates (170-172) were proposed to explain the observable formation of hydrogen gas in the reaction system, these species were confirmed by ^{29}Si NMR spectroscopy. It was proposed that the electron withdrawing effects of the sulfonate groups resulted in a more electropositive and Lewis acidic silicon centre, with greater reducing capabilities. By consequence, more substituted silyl sulfonates were more strongly lewis acidic at the silicon centre and demonstrated a decreased barrier to hydride transfer.[84]

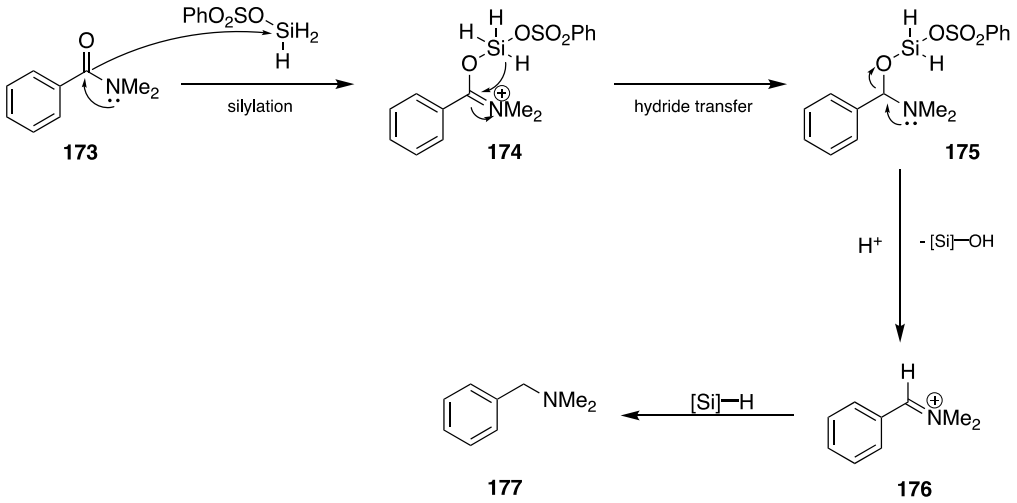


169 **170** **171** **172**

Scheme 43. Formation of the active silyl sulfonate species, with further substitution affording more enhanced reducing properties.[84]

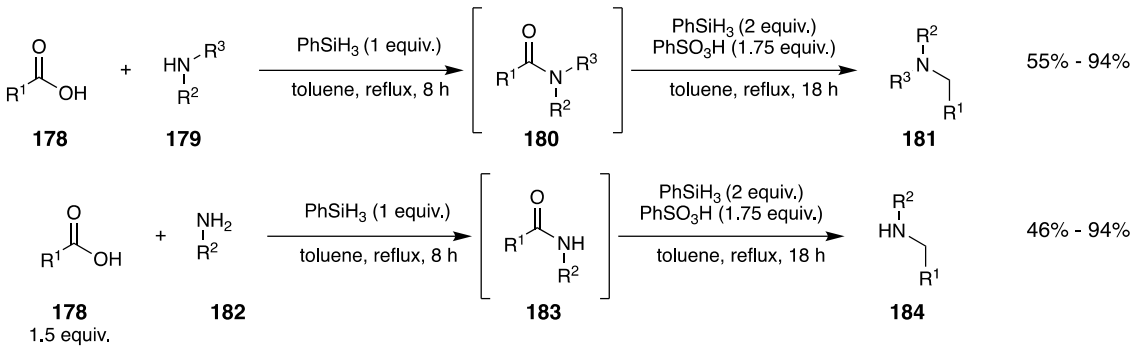
A proposed mechanism for the reduction of *N,N*-dimethylbenzamide (173) (Scheme 44) begins with an initial silylation to form an enamine-silylsulfonate intermediate (174), followed

by hydride transfer to afford silyl ester (175)**.** Elimination of silanol affords enamine (176) which is subsequently reduced to the amine product (177) by a silyl hydride species.[84]



Scheme 44. Proposed mechanism for the formation of a more active silylsulfonate species in the reduction of amides. N,N-dimethylbenzamide (173) undergoes a silylation to afford an enamine-silylsulfonate intermediate (174), hydride transfer affords silyl ester (175) followed by silanol elimination to afford enamine (176) which is reduced to amine product (177) [84]

The reductive system was employed in a reductive amination, where carboxylic acids behaved as the nominal electrophile (178) to afford *N*-alkylated products (Scheme 45). This work was generally performed in good scope, tolerating aromatic, aliphatic, sterically hindered and electronically hindered amines and carboxylic acids.[84] Reducible functional groups including nitro, nitrile, ester, and alkene functionalities were also well tolerated. However, aromatic heterocycles were not tolerated, with these methyl esters being incompatible with the silane mediated amidation step. Yields for sterically and electronically hindered substrates were generally poor, this was attributed to a sluggish amide formation and was mediated through increasing the equivalents of the starting carboxylic acid to aid conversion. Additionally, it was demonstrated that an additional 0.25 equivalents of the benzene sulfonic acid would aid reduction for some poorer performing substrates.[84]



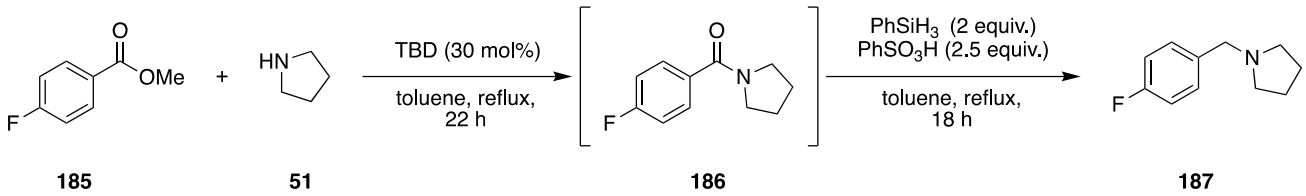
Scheme 45. Denton silane mediated reductive amination of carboxylic acids.[84]

Methyl esters pose a reduced risk of decarboxylation, so the application of this reduction to amides initially formed from methyl esters in a two-phase, one-pot reductive amination presents a simple reductive amination process with methyl esters as the nominal electrophile.

5 Results and discussion

5.1 Initial Investigation

Based upon previous work,[93] a test reductive amination was performed with the two steps telescoped in a one-pot system (Scheme 46). The reaction combines a known method for the formation of amides from methyl esters and a silane mediated reduction developed in our laboratory.[84, 94]



185 **51** **186** **187**

Scheme 46. Model reaction for the optimisation of the reductive amination using pyrrolidine (51) and methyl-4-flurorobenzoate (185).

Initial conditions were selected from literature precedent and previous work. The loading of TBD (160) was set at 30 mol% according to the literature and 2 equivalents of phenylsilane and 2.5 equivalents of benzene sulfonic acid were used for the reduction.[84] An increase of 0.5 equivalents of benzene sulfonic acid were used initially in an attempt to account for the strongly basic catalyst (TBD, 30 mol%) presumed to remain *in situ*. Standard reaction times, temperature and solvent had been predetermined for the reduction step.[84] It was important to maintain the same solvent and general conditions for both steps to facilitate a one-pot process when the two steps were telescoped, so the conditions for the amidation step had been designed around compatibility with the subsequent reduction step.

Methyl-4-fluorobenzoate (185) was selected as the model methyl ester to provide a fluorine handle that allows for a simpler analysis through ^{19}F NMR spectroscopy, and pyrrolidine (51) was selected for the simple secondary amine nucleophile. Literature values for the ^{19}F NMR chemical shifts of the desired amine product, alongside potential side products, of this model reaction have been collated (Figure 8) for straightforward identification.

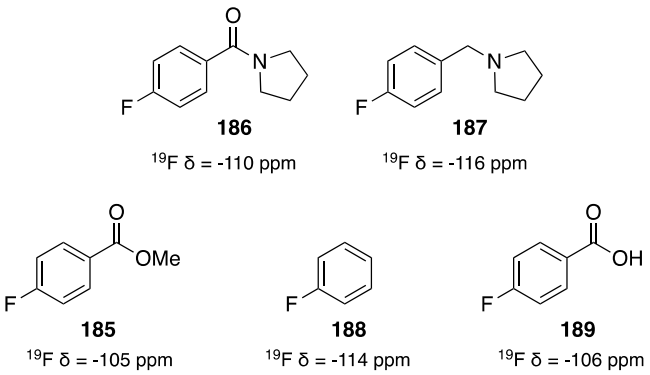
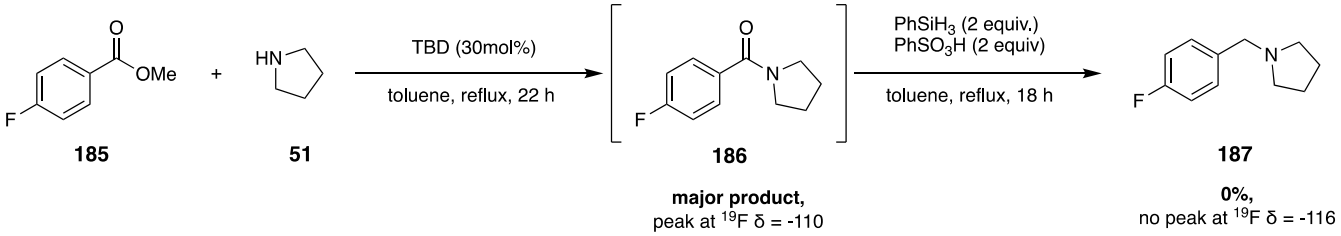


Figure 8. Summary of fluorobenzene derived potential side products from the model reaction and their ^{19}F NMR spectroscopy chemical shifts.[95-99]

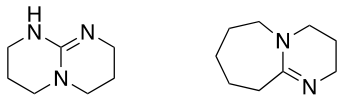
The initial reaction did not form amine (Scheme 47), with amide identified qualitatively as the major product through ^{19}F NMR spectroscopic analysis, suggesting the amide reduction was not proceeding. For this reason, further optimisation was performed independently on the two steps, with the aim to telescope these into the desired one-pot system.



Scheme 47. Reductive amination, with unsuccessful amide reduction to the desired amine.

5.2 Organocatalytic Amidation Optimisation

Methyl esters require forcing conditions to behave as an electrophile for the formation of amides *via* nucleophilic attack by an amine.[85] Organocatalysts are cheap and known to be an effective method for this , with TBD (20) and DBU (21) being two nucleophilic catalysts commonly used for this transformation in the literature (Figure 9).

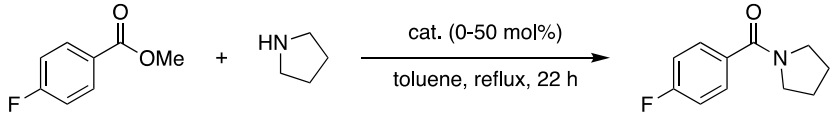


TBD (160)
$pK_aH(H_2O)$ = 15.0
£1.39 per mmol

DBU (161)
$pK_aH(H_2O)$ = 13.5
£0.17 per mmol

Figure 9, TBD (160) and DBU (161),[83, 90] costs obtained from sigma Aldrich June 2023.

Investigations into the organocatalytic amide formation were performed using the same general amine (30) and methyl ester (29) (Table 3). Solvent and reaction temperature had been predetermined according to conditions known to be compatible with the reduction,[93] to ensure the desired telescoped process could subsequently be realised.



185 **51** **186**

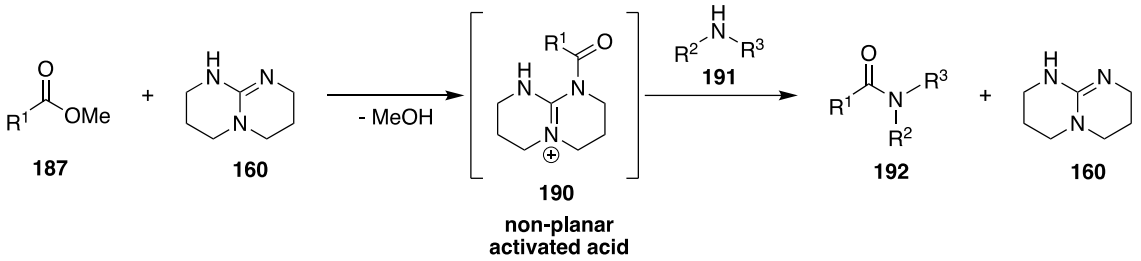
Entry	Catalyst	Catalyst loading (mol%)	Amide (%)[a]
1	None	0	0
2	TBD	30	75
3	TBD	40	78
4	TBD	50	69
5	DBU	30	0

Table 3. effect of TBD loading in amidation, [a]Yields determined by quantitative ^{19}F NMR spectroscopy with trifluortoluene ($C_6H_5CF_3$)internal standard.

As expected, no amide was formed in absence of TBD (*entry 1*), confirming the need for activation of the methyl ester to elicit reaction. An increase in catalyst loading beyond 30 mol% (*entry 3 & 4*) did not provide any considerable increase in yield, so 30 mol% (*entry 2*) was selected as the optimal catalyst loading. Much larger increases in strongly basic organocatalyst

would negatively impact the reaction yields in the telescoped process, and increased equivalents of benzene sulfonic acid would be required to mediate any addition, so unnecessary increases were avoided.

Organocatalytic amide formation is mediated by the structure of TBD (20) and the non-planar amide intermediate (23) (Scheme 48), formed upon reaction with the methyl ester, being sterically held in a non-planar structure, disrupting carbonyl conjugation, and enhancing electrophilicity of the carbonyl for amine nucleophile attack (*Section 4.2*). [83]



Scheme 48. Non-planar amide intermediate (23) formed from methyl ester reaction with TBD in the synthesis of amides.[83]

DBU (21) catalysed amide formations from methyl esters have been demonstrated in the literature, however these often require much higher catalytic loadings than necessary for TBD (20).[92, 100] DBU (21) is structurally similar to TBD (20) with comparable basicity, and is less expensive, however at 30 mol% did not yield any amide (entry 5). While this is a cheaper organocatalyst, much higher loadings would be required for amide formation.[100] The resulting increase in strongly basic organocatalyst in situ may result in depreciated yields for the reduction step in the telescoped process, so further increases in the loading of DBU (21) were not investigated.

With catalytic loading optimised, investigations into the reaction time were undertaken (Figure 10). This was based on the same model reaction, with the conversion monitored by ^{19}F NMR yields every 2 hours over 24 hours, with trifluorotoluene as the reaction internal standard. To gather the most complete set of data, two separate runs of the reaction were performed with Reaction 1 monitored from 0-10 hours and Reaction 2 monitored for 14-24

hours. Reaction 2 was repeated to investigate the apparent inconsistencies in the two runs, however similar trends were observed.

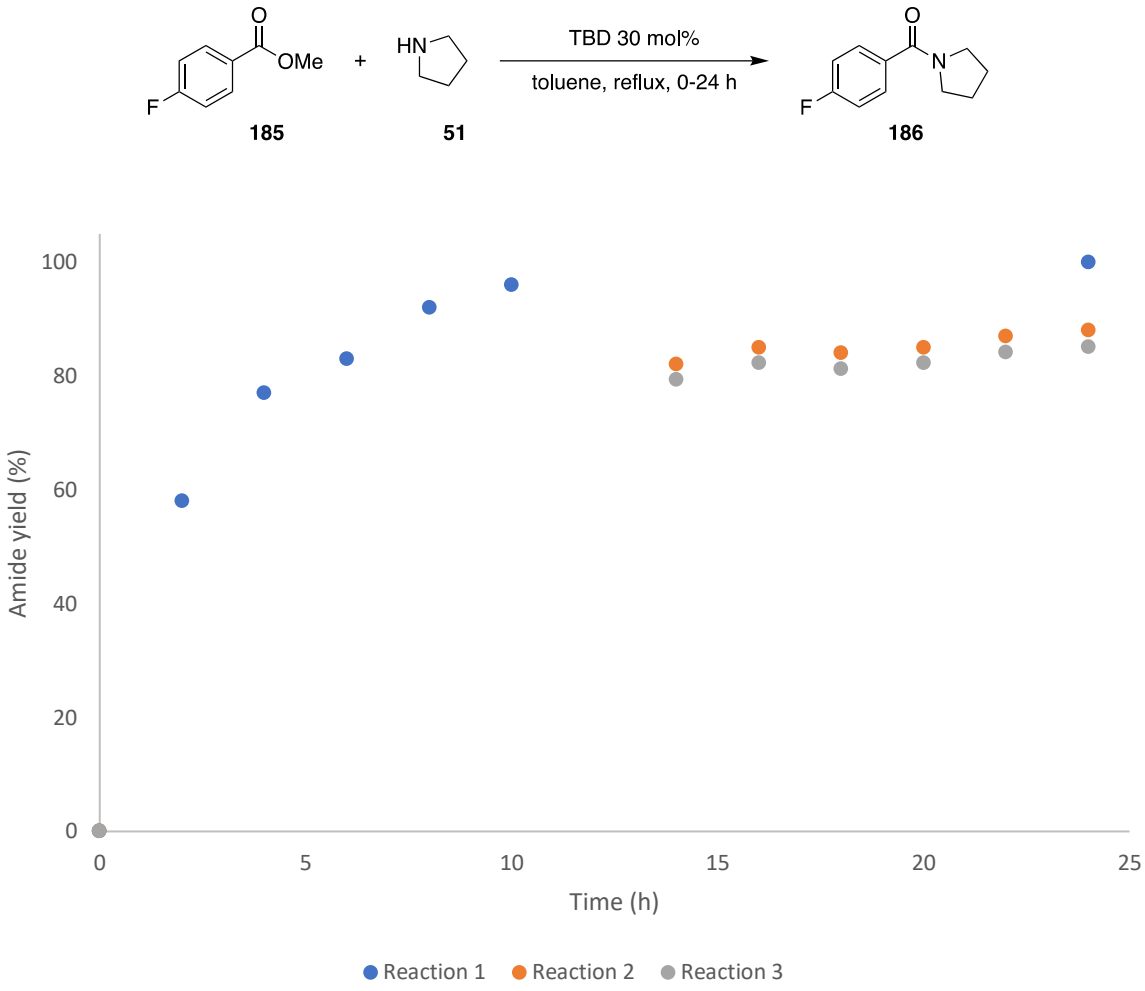


Figure 10. Plot of amide (31) yield against time, [a]yields determined by quantitative ^{19}F NMR spectroscopy, using trifluorotoluene internal standard.

Amide (31) formation began to plateau around 14 hours, however these studies employed pyrrolidine (30), a strongly nucleophilic cyclic amine, which was likely to work well in this system and may not be representative of less reactive amines or methyl esters. Apparent discrepancies between the two runs were investigated through a repeat of Reaction 2, however similar trends and yields were observed. While initially we considered potential decomposition of the final product to explain the decrease in yield between 10 and 14 hours, Reaction 1 observed full conversion to the amide product without a decrease in yield after 24

hours, suggesting the difference was likely the result of a weighing error of the internal standard.

While amide (31) conversion appeared to plateau around 14 hours, it is reasonable to assume that a longer reaction time would not depreciate yields, suggesting that a longer reaction duration may be beneficial for poorer performing substrates. As such 22 hours was kept as the optimised reaction time to ensure full conversion for all potential substrates.

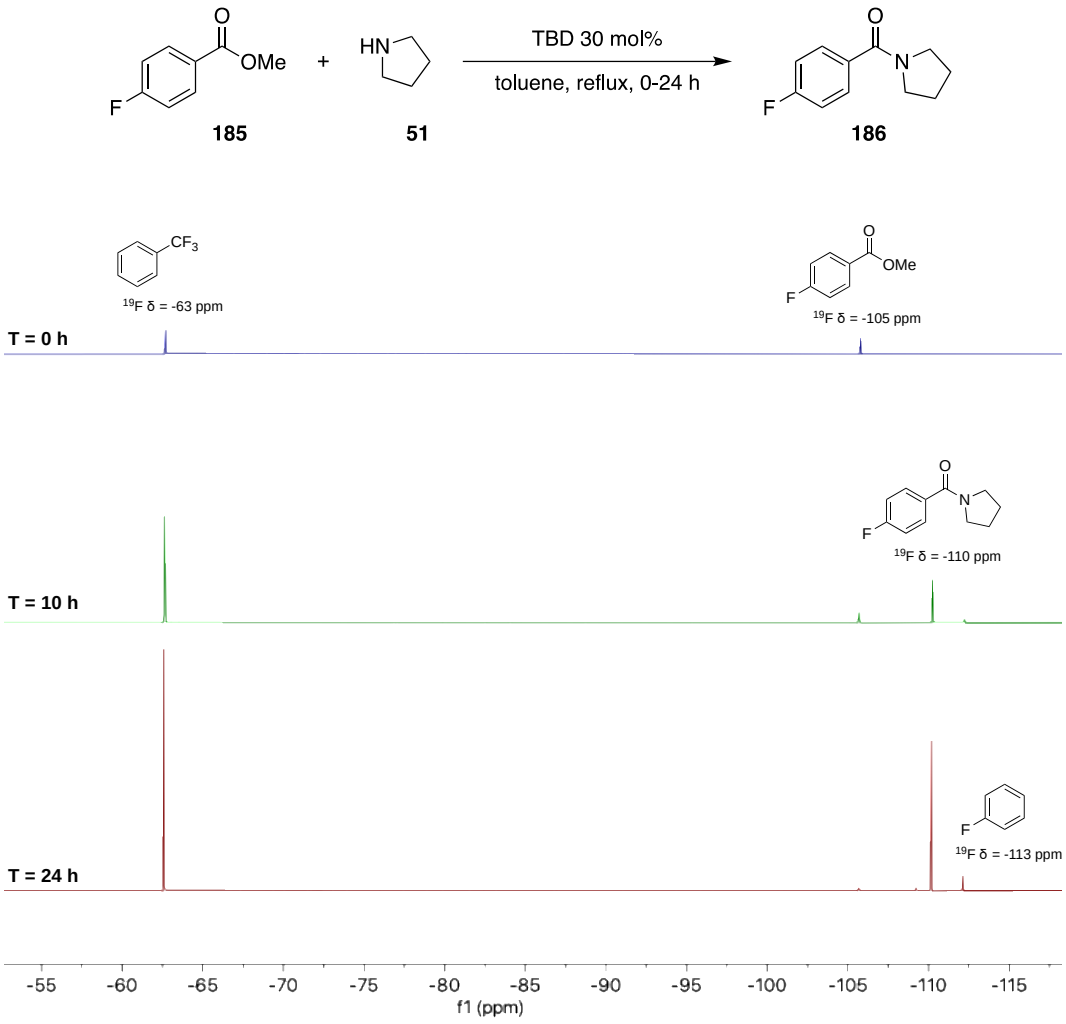
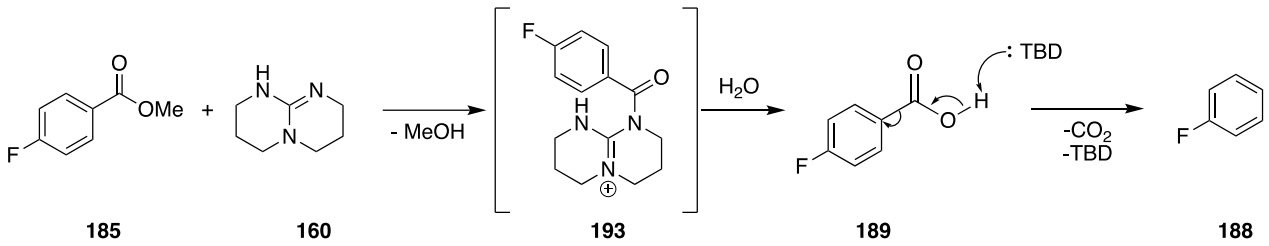


Figure 11. ^{19}F NMR analysis of reaction for monitoring amide (31) formation, with trifluorotoluene internal standard.

This method of amide formation is attractive with the main by-product being a low molecular weight alcohol, methanol, which could easily be distilled out of the reaction system, however the desired one-pot system would not leave opportunity for this and methanol would remain in the reaction system.[90]

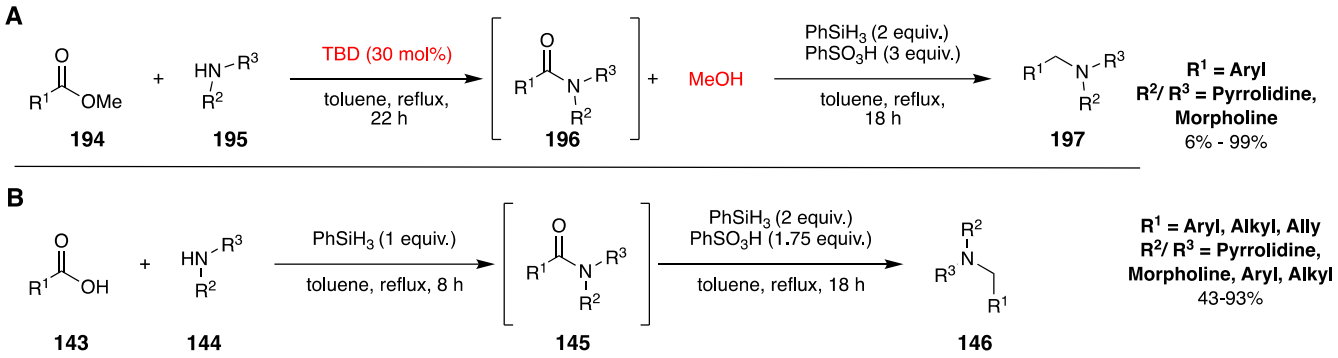
Through these ^{19}F NMR spectroscopy investigations, the generation of fluorobenzene was observed as a third peak in the ^{19}F NMR spectra (Figure 11), indicative of decarboxylation having occurred (Scheme 49). This was likely a side reaction mediated by the presence of water in situ and TBD, as thermal decarboxylation of more stable methyl esters is not as commonly observed. While this is not a desirable outcome, fluorobenzene was not a major product and could be easily removed in the acid-base work-up at the end of the full reaction.



Scheme 49. Decarboxylation of methyl-4-fluorobenzoate, mediated by the presence of TBD and water, to afford fluorobenzene.

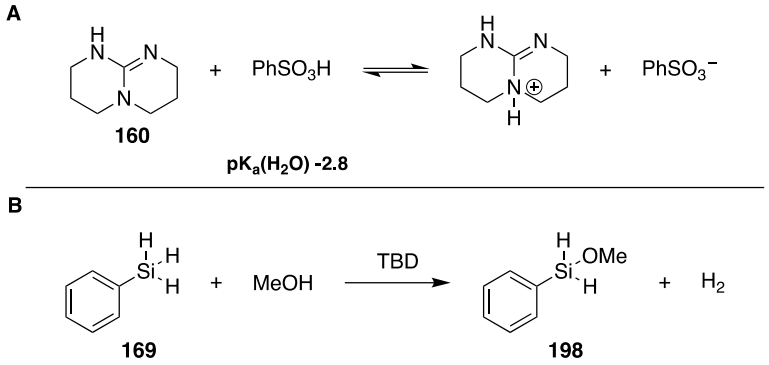
5.3 Development of A Telescoped Process

Having established optimised conditions for the amidation step, the full reductive amination was revisited (Scheme 50). Again, this reaction failed to afford the desired amine product, with amide identified as the major product by ^{19}F NMR spectroscopy. The reduction conditions had previously been employed as the second step of a reductive amination from carboxylic acids, however this route utilised a phenylsilane mediated amide formation, and generated water as a by-product (Scheme 50). We reasoned the reduction process was inhibited by the presence of either methanol or strongly basic TBD which remained *in situ* from the amidation step.



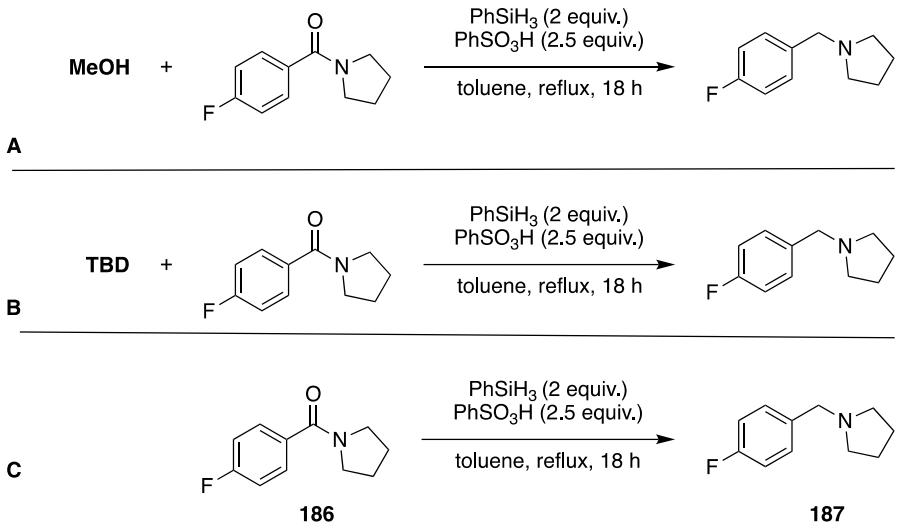
Scheme 50. This chemistry, with methanol and TBD highlighted as potential inhibitors of the reduction step (A), previous route with carboxylic acid starting material (B).

These conditions posed two potential problems. Firstly, the strongly basic TBD could interact with the benzene sulfonic acid used to generate the reactive silane species (Scheme 51.**A**). Secondly, the methanol may interact with the phenyl silane to afford a silyl ester species, with possible formation of a trisubstitued silyl ester species without the necessary hydride groups required for the reduction to occur (Scheme 51.**B**). Both routes would hinder the formation of the activated silyl sulfonate species and could prevent reduction from occurring.



Scheme 51. ***A*** *Proposed TBD interaction with benzene sulfonic acid to afford a sulfonate salt;* ***B*** *Proposed methanol interaction with phenylsilane to afford a silyl ester.* [101]

Consequently, we investigated the model reduction step, qualitatively, in the presence of TBD and MeOH (Scheme 52). Standard reduction conditions were used, with amide ((4-fluorophenyl)(pyrrolidin-1-yl)methanone) isolated before reduction (Scheme 52).



Scheme 52. Model amide reductions with additions of methanol and TBD.

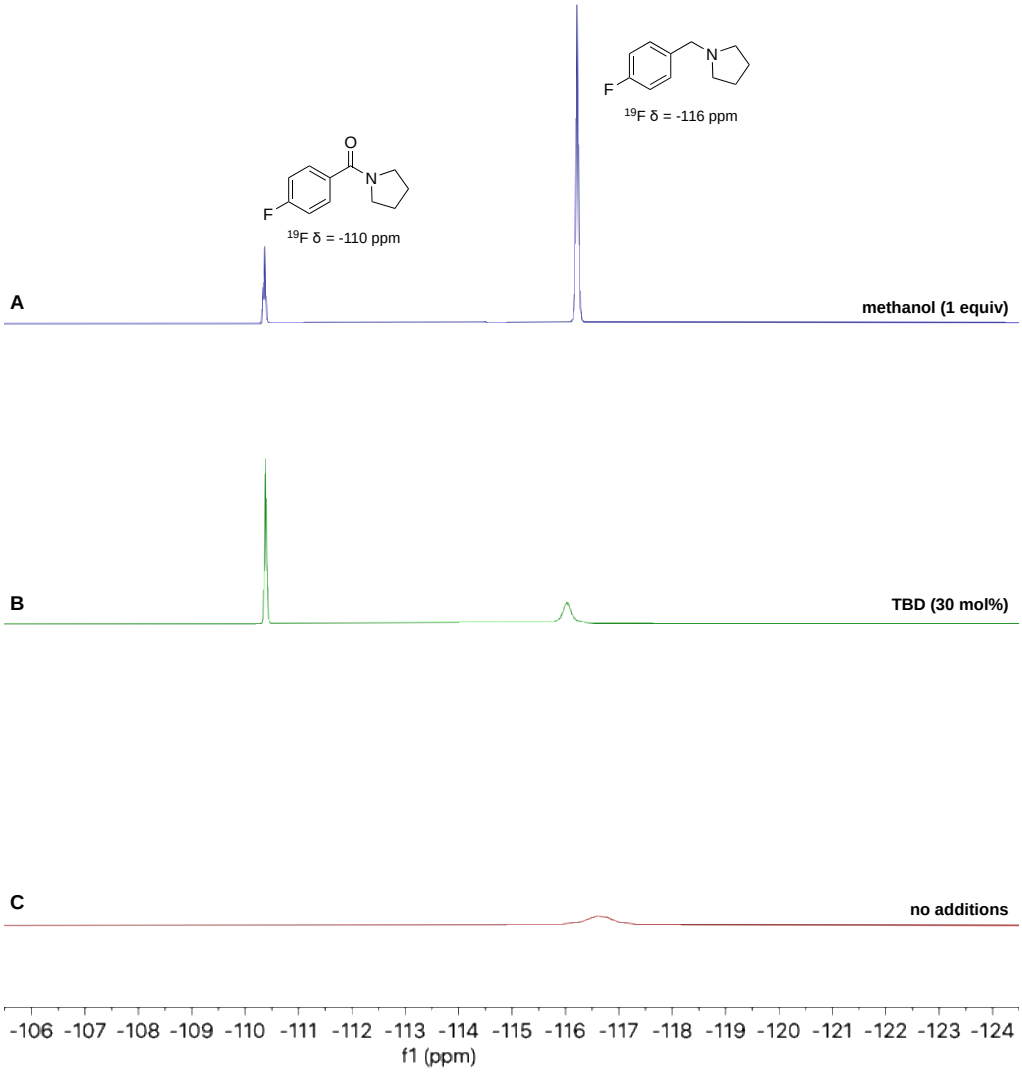


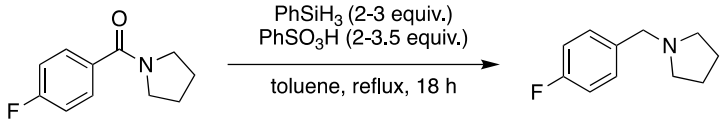
*Figure 12. **A** ^{19}F NMR spectra for reduction of amide (31) with additional TBD (20), **B** with additional methanol, **C** with no additions.*

From examination of the relevant crude ^{19}F NMR spectra (Figure 12), it was immediately apparent that the presence of methanol (**A**) and TBD (**B**) negatively impacted the amide reduction. In the absence of TBD and methanol the reduction proceeded unhindered to afford the desired amine as the sole product (**C**), whereas unreacted amide was observed in the presence of methanol and TBD. Qualitatively, the presence of TBD hindered reduction more than methanol, suggesting TBD was the main problem.

This qualitative study demonstrated the negative effects of TBD and methanol on the reduction, while presenting a potential area of improvement for the reaction if the effects of these could be effectively mediated.

5.4 Silane Mediated Reduction Optimisation

We next performed a quantitative analysis of the reduction in the presence and absence of TBD and methanol (Table 4). The equivalents of benzenesulfonic acid and phenyl silane were altered in an attempt to mediate the effects of TBD and methanol and provide potential conditions for the reduction in the telescoped reaction.



186 **187**

Entry	$PhSiH_3$ (eq.)	$PhSO_3H$ (eq.)	MeOH (eq.)	TBD (eq.)	Amine (%)
1	2.0	2.5	1	0.3	15[a]
2	2.0	3.0	1.0	0.3	52
3	3.0	3.0	1.0	0.3	54
4	2.0	3.5	1.0	0.3	86

Table 4. Reduction with varied phenylsilane and benzenesulfonic acid equivalents, additional methanol and TBD to mimic in situ condition, isolated yields obtained following column chromatography, [a]yield obtained via quantitative ^{19}F NMR spectroscopy with trifluorotoluene internal standard.

Consistent with the initial test reductive amination additions of methanol and TBD were detrimental to the reduction and yield of amine (Entry 1). Increasing the amount of benzene sulfonic acid to 3 equivalents improved the reduction yield in the presence of methanol and TBD (Entry 2). An increase in the amount of phenylsilane alongside the increase in

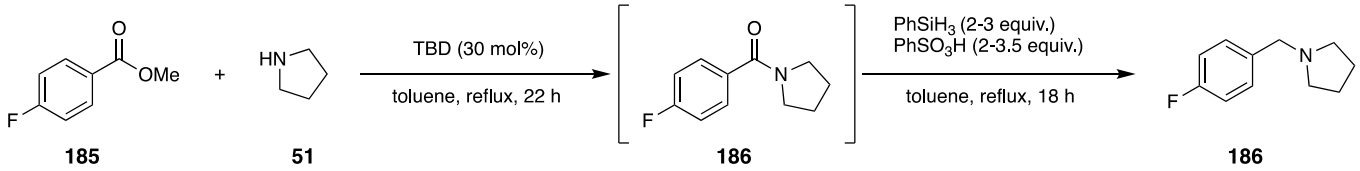
benzenesulfonic acid also afforded improved yields (Entry 3), however an increase in silane used in the reaction is not preferable as it resulted in an observable increase in the generation of silane polymer by-product. This could potentially limit the reactions scalability, making large increases in equivalents of phenylsilane undesirable. Increasing the amount of benzenesulfonic acid to 3.5 equivalents further improved the reduction yield, suggesting this could be beneficial in the telescoped process (Entry 4).

Altering the stoichiometry of the phenylsilane and benzene sulfonic acid was identified as a reliable method for compensating for the effects of methanol by-product and residual TBD in the reaction system. At this stage we were now ready to investigate the telescoped one-pot reductive amination reaction we had sought.

The reduction is known to be compatible with other sulfonic acids, and was trialled with *para*-nitrobenzene sulfonic acid, however this resulted in incomplete reaction and the formation of side products resulting in poorer yields. Benzene sulfonic acid is known to be a costly sulfonic acid, and it is noteworthy that while this was the acid used in our investigation, the reduction has been shown to be compatible with cheaper sulfonic acid alternatives, including *para*-toluene sulfonic acid. More electron withdrawing sulfonic acids are known to work well in the system as they are able to form a silyl sulfonate with a more Lewis acidic silicon centre with greater reducing properties.[84]

5.5 Reductive Amination Optimisation

With optimised conditions established for both steps of the reaction, a full telescoped reductive amination was investigated (Table 5).



Entry	TBD (equiv.)	$PhSiH_3$ (equiv.)	$PhSO_3H$ (equiv.)	Amine (%)
1	**0.3**	**2.0**	**3.0**	**81**
2	0.3	3.0	3.0	62
3	0.3	2.0	3.5	58

Table 5. optimisation of reductive amination with varied equivalents of phenylsilane and benzenesulfonic acid, isolated yields obtained with column chromatographic purification.

Gratifyingly, the conditions developed in Table 5 were applicable to the full telescoped process (Table 5), with an increase in benzene sulfonic acid affording the desired amine in good yields (Entry 1). Increasing the amount of silane alongside the increase in acid resulted in depreciated yields of the final product (Entry 2), so the original silane stoichiometry was maintained. Contrasting with results in Table 5, 3.5 equivalents of benzene sulfonic acid did not improve the reaction yield (Entry 3). As a result of these investigations, optimised conditions for the full telescoped reductive amination were achieved, and investigations into scope were undertaken.

5.6 Reaction Scope

With optimised reaction conditions ascertained, the reaction scope was investigated (Table 6). Methyl esters whose parent carboxylic acids are known to be especially prone to thermal decarboxylation were of particular interest, as these had been previously incompatible with the reductive amination from carboxylic acids.[84]

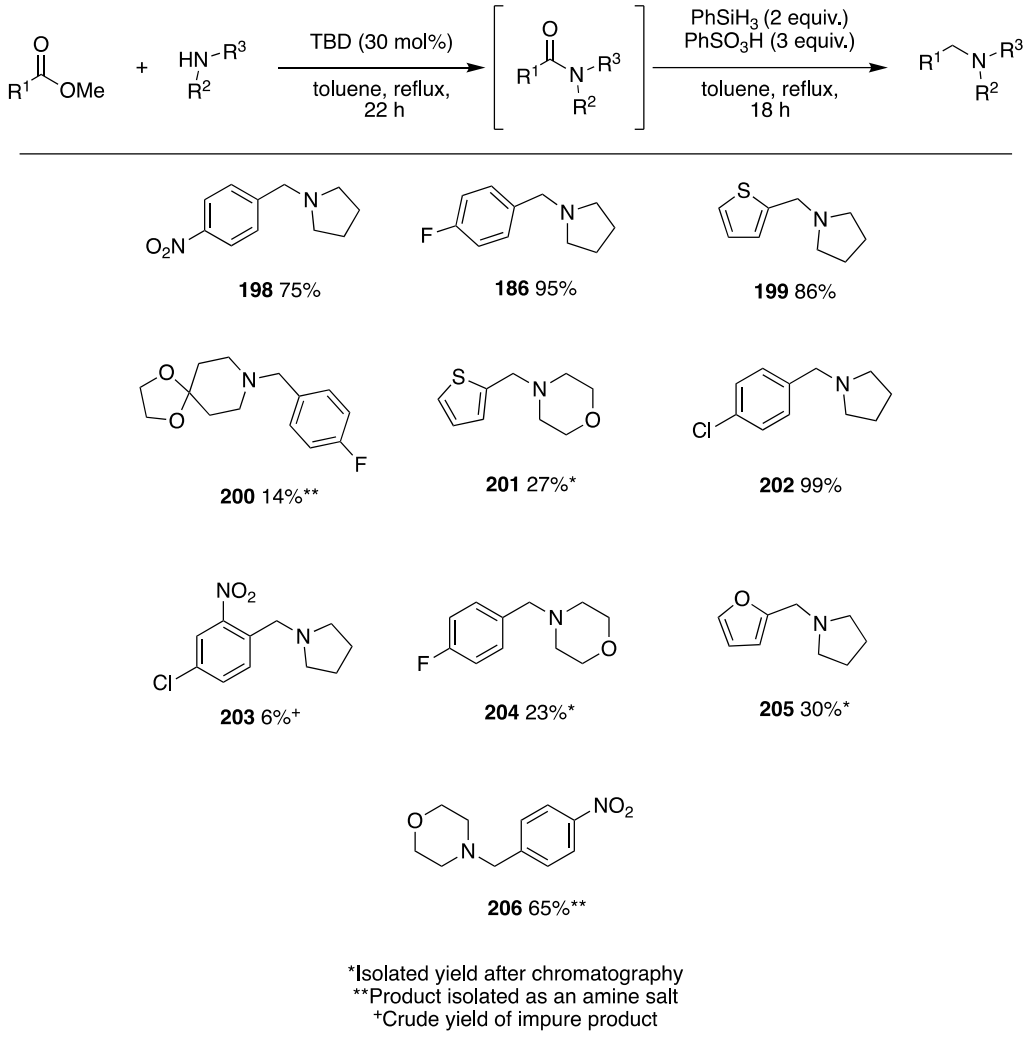


Table 6. Reaction scope of optimised reductive amination with variation of the methyl ester (R^1) and tertiary amine (R^2, R^3).

A range of functional groups were tolerated for the methyl ester, with *para* substituted aromatic methyl esters with electron withdrawing groups (**198, 186, 202**) affording generally

superior yields. Simple cyclic amines were well tolerated, with pyrrolidine generally better tolerated than morpholine. This is likely due to morpholine having weaker nucleophilic character than pyrrolidine, resulting in poorer yields from the initial amide formation. This is supported by investigations in previous work where it was observed that more weakly nucleophilic amines, such as anilines, were not as well tolerated in the reaction and afforded generally poorer yields.[84]

Compounds **106** and **202** featured a benzylic methyl ester with a halogen in the *para* position, with the fluoro- and chloro- substituted methyl esters afforded the desired amine in very good yields. However, a bromo- substituted example trialled failed to yield any amine product. This is likely the result of electronegativity trends of the halogens, with the more electronegative fluoro- and chloro- substituted examples affording the superior yields, and bromo being less compatible. This trend in reaction yields agrees with the observed trend whereby more electron withdrawing para-substituted aromatic methyl esters afford superior yields.

Gratifyingly, aromatic heterocyclic methyl esters were well tolerated, affording good yields for thiophene and furan derivatives (**199, 205**). The thiophene was exceptionally well tolerated, while the furan demonstrated lower yields. This was especially pleasing as it demonstrates a resistance to decarboxylation which was not previously observed for carboxylic acids as the coupling electrophile, consequently expanding the general reaction scope as desired.

Acetals were tolerated in the reaction system (**200**), albeit in low yields. The general acid-base work-up was not compatible with this compound, with aqueous acidic conditions known to hydrolyse the acetal. Instead, the amine was afforded through isolation of the amine salt formed, with addition of base to deprotonate and afford the desired amine product. This method of purification could be applied to other examples (**206**) where the amine was isolated as the salt from the reaction mixture rather than a full acid base work up, however not all compounds precipitate as a solid salt so this method cannot be applied consistently.

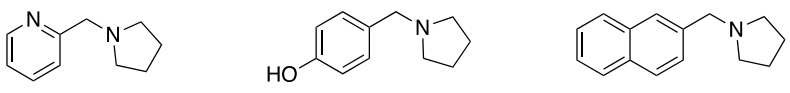
Some examples (**198, 186, 199, 200, 202, 206**) were isolated from the acid-base (or alternative) work-up without the need for further purification. Where this was not the case, column chromatography was required for purification. Impurities were predominantly

residual amide which had not been reduced, however for some examples small amounts of decarboxylated methyl ester starting material were also observed, notably fluorobenzene was observed in the amide formation of compound **198**.

Difficulties with column chromatographic purification methods were encountered, with the amine products often precipitating as a salt within the acidic conditions of a silica column, resulting in depreciated yields due to loss of the product on the column. As a result, basic solvent systems were employed for column chromatography where the general acid-base work-up was not successful.

With a 2-step process such as this, substrates need to be well tolerated through both steps. The organocatalytic amide formation may be a limiting factor, with sterically hindered, weakly nucleophilic and strong hydrogen bonding substrates known to be poorly tolerated in TBD catalysed amide formations, with the latter resulting in catalyst deactivation.[83, 94] The reduction is known to be poorly tolerable of sterically and electronically hindered compounds, however previous work has demonstrated that increasing the equivalents of benzene sulfonic acid could aid in the reduction of these examples.[84]

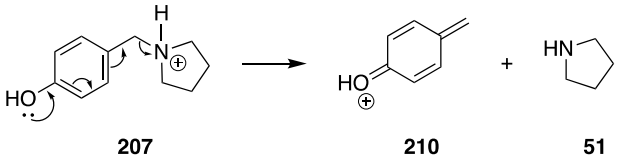
Compound **203** was afforded in low yields, with side products and impurities that could not be identified observed in the final product *via* NMR spectroscopy, likely due to combined electron withdrawing effects of the two electron withdrawing groups in the *ortho* and *para* positions potentially interfering with both the amide formation and silane mediated reduction steps. Steric considerations for the nitro group in the ortho position may also result in poorer yields, as ortho substituents had not been well tolerated by the reduction in previous work.[84]



207 **208** **209**

Figure 13. Amines which were not successfully formed under these reaction conditions.

3 examples (Figure 13) were trialled unsuccessfully, with no amine formed. Compound **207** demonstrated no amine formation, likely due to the strongly nucleophilic piperidine substituent interfering with the TBD catalysed amide formation step. The naphthalene derived example **209** also did not yield amine, most likely due to electron delocalisation into the extended aromatic system increasing the likelihood of methyl ester decarboxylation. Compound **208** featured a phenol, which was not tolerated well by the reaction or purification processes. Both compounds **208** and **209** were likely prone to acid promoted decomposition of the amine product (Scheme 53), due to the potential for electron delocalisation, which may be responsible for the failed reaction in these cases.



207 **210** **51**

Scheme 53. Potential acid promoted decomposition of phenolic amine compound.

6 Conclusions

Herein, we have demonstrated a one-pot silane mediated reductive amination where methyl esters are employed as a nominal electrophile. This work was performed in moderate to good yields for a variety of methyl esters and amines; strongly nucleophilic amines and with para substituted aromatic methyl esters with electron withdrawing groups afforded generally superior yields. Reducible functional groups were tolerated in the reduction, alongside aromatic heterocyclic compounds previously inaccessible due to decarboxylation of the parent carboxylic acids employed previously.

The reaction was somewhat limited by in-situ reagents from the amide formation step, methanol generated from the condensation reaction and residual TBD catalyst, resulting in poorer yields than previously observed unless additional equivalents of the benzenesulfonic acid were used to account for these conditions.

Overall, this two-step one-pot process highlights an important approach to reductive aminations, where reduction of the starting material is limited by separating C–N bond formation from the reduction and decarboxylation of starting materials is limited by the use of bench stable methyl esters as opposed to carboxylic acids previously employed, or unstable aldehydes used in classic reductive aminations.

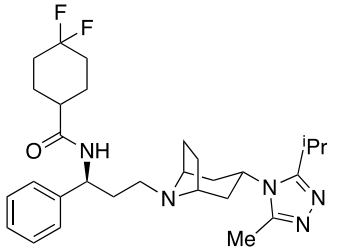
7 Future work

Further development of this route is of interest. Identifying a general method for improving the yield of poorer performing substrates would be attractive, likely through further investigation into the phenylsilane and benzene sulfonic acid stoichiometry. Mechanistic investigations into the reduction step have been previously undertaken, however a greater understanding of the mechanism of the full reaction system, including the interaction of side products from the first step with the reduction in the second step, would be beneficial for enhanced understanding and ability to further optimise the reaction.

With this chemistry having been previously demonstrated in the synthesis of secondary amines using carboxylic acids, the development of a system for the synthesis of these secondary amines using methyl esters would be of interest. Less nucleophilic secondary amines are generally not as well tolerated in the initial TBD catalysed amide formation or subsequent reduction step so further optimisation of both steps is likely required.

Demonstration of this chemistry within the synthesis of an amine containing API would also be of interest to investigate if the reaction conditions are compatible within extended synthesis routes. A scale-up of this reaction would also be of interest to investigate and demonstrate the potential usefulness of this reaction on industrial scales.

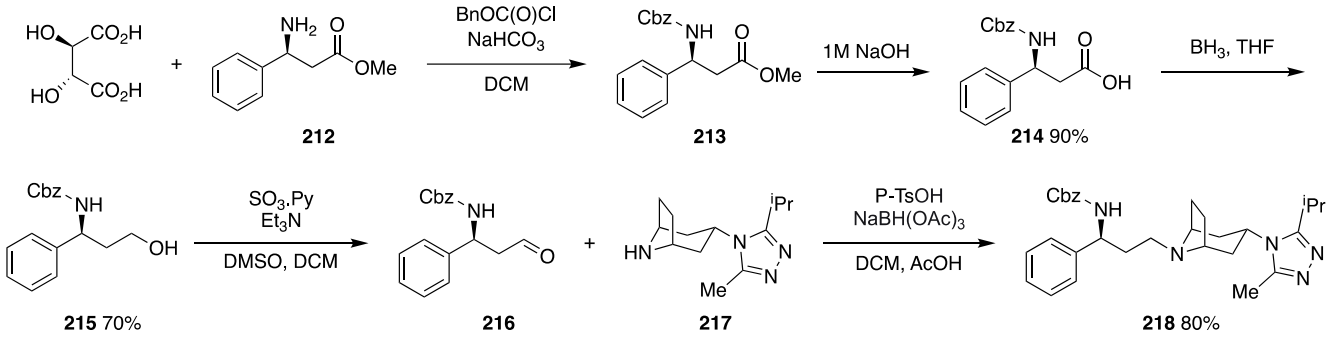
Maraviroc is a chemokine receptor 5 (CCR-5) receptor antagonist, used for the treatment of HIV (Figure 14). It was approved for use in 2007 and remains the only CCR-5 receptor antagonist used for treatment of HIV infection.[102, 103]



maraviroc (211)

Figure 14. Maraviroc (211), chemokine receptor 5 (CCR-5) receptor antagonist.

The current Pfizer synthesis route for maraviroc fragment **20** requires multiple redox steps from the methyl ester starting material **14** to an aldehyde **18** before performing a reductive amination to couple fragments **18** and **19**.[102] Our Chemistry would allow the key reductive amination step to be performed directly from the methyl ester **14**, without the use of harsh reducing agents or multiple redox steps (Scheme 54). Protection of the primary amine would likely also not be required, however further investigation into scope for our system into reaction selectivity would be required to confirm this. Provisionally, this provides a route for the synthesis of a WHO essential medicine with greatly improved atom and step economy, in conditions which do not require harsh reducing agents or multiple redox steps.



Pfizer synthesis of maraviroc

Proposed synthesis of maraviroc using this chemistry

*Scheme 54. Pfizer synthesis of maraviroc fragment **218** (5 steps),* [102] *our proposed synthesis of maraviroc fragment **218** employing silane mediated reductive amination from methyl ester **212** (1 step).*

Experimental Section

General Experimental

Unless stated otherwise, all reactions were carried out in standard glassware. All reagents were purchased from reputable suppliers and used without any further purification. All water used was deionised before use.

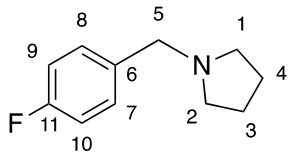
TLC (Thin layer chromatography) was performed on Merck aluminium backed silica gel 60 F254 plates that were visualised under ultraviolet radiation (254 nm) and stained using $KMnO_4$ solution when necessary. Flash column chromatography was performed using Fluorochem silica gel 60 Å (40-63 microns). Mass spectroscopy was done using the high-resolution ESI (electron spray ionisation) mass spectrometer Bruker micrOTOF II. Melting point was determined using the Stuart SMP3.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on either Bruker AV(III)400HD or Bruker AV(III)500HD in the deuterated solvent $CDCl_3$ and their chemical shifts (δ) given in parts per million (ppm) and are internally referenced to residual solvent signals ($CDCl_3$ is referenced at δ 7.26 and 77.16 for ^{1}H and ^{13}C NMR respectively. For ^{1}H and ^{13}C NMR spectra tetramethylsilane ($Si(CH_3)_4$) is used as an external standard and attributed a chemical shift of 0 ppm. For ^{19}F NMR spectra trichlorofluoromethane ($CFCl_3$) is used as an external standard and attributed a chemical shift of 0 ppm. All coupling constants (J) are given in Hz. ^{1}H NMR multiplicities are designated using the abbreviations: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, p = pentet, m = multiplet. The ^{1}H NMR spectra are reported as follows: δ (multiplicity, coupling constant J, number of protons). The ^{13}C NMR coupling constants (J) are quoted to the nearest 0.1 Hz.

General procedure 1- Full reductive amination

To a solution of methyl ester (1.00 mmol, 1.0 equiv.) and secondary amine (1.10 mmol, 1.1 equiv.) in toluene (5.0 mL) was added TBD (0.3 mmol, 30 mol%), and the reaction mixture was heated at 110 °C for 22 hours. After this, benzene sulfonic acid (3.00 mmol, 3.0 equiv.) was added, followed by phenyl silane (2.00 mmol, 2.0 equiv.) dropwise. The reaction mixture was kept at 110 °C for a further 18 hours before being diluted with EtOAc (20.0 mL). The mixture was then extracted with HCl (3 × 10.0 mL of 3 M of aqueous solution), and the pH of the aqueous extract was adjusted to 14 using NaOH (30.0 mL of a 6 M aqueous solution). The mixture was then extracted using CH_2Cl_2 (3 × 10.0 mL) and dried over anhydrous $MgSO_4$, the solvent was then removed under reduced pressure pressure to afford the product which was either justified pure by ^1H NMR spectroscopy or purified by flash chromatoraphy where necessary. (Solvent mixtures specified below)

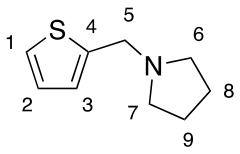
1-(4-Fluorbenzyl)-pyrrolidine (186)



Following general procedure 1, using methyl 4-fluorobenzoate (0.129 mL, 1.00 mmol) and pyrrolidine (0.090 mL, 1.10 mmol). 1-(4-Fluorbenzyl)-pyrrolidine was isolated as a pale-yellow oil (0.146 g, 0.950 mmol, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 2H, C^7-H, C^8-H), 7.04-6.97 (m, 2H, C^9-H, C^{10}-H), 3.57 (s, 2H, C^5-2H), 2.57-2.44 (m, 4H, C^3-2H, C^4-2H), 1.84-1.74 (m, 4H, C^1-2H, C^2-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.9 (d, J = 244.3 Hz, C^{11}), 135.2 (d, J = 3.3 Hz, C^6), 130.4 (d, J = 7.7 Hz, C^7, C^8), 115.0 (d, J = 21.2, C^9, C^{10}), 59.9 (C^5), 54.2 (C^1, C^2), 23.5 (C^3, C^4) **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.29 **MS** (ESI) $[M + H]^+$ m/z calculated for $C_{11}H_{14}FN$ 180.1183, found at 180.1177. The data matches that found in the literature.[95]

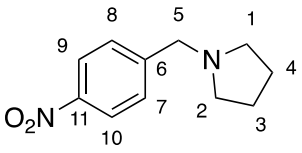
1-(Thiophen-2-ylmethyl)pyrrolidine (199)



Following general procedure 1, using methyl thiophene-2-carboxylate (0.117 mL, 1.00 mmol) and pyrrolidine (0.090 mL, 1.10 mmol). 1-(Thiophen-2-ylmethyl)pyrrolidine was isolated as a yellow oil (0.122 g, 0.860 mmol, 86%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.21 (m, 1H, C^1-H) 6.97-6.91 (m, 2H, C^3-H, C^4-H), 3.83 (s, 2H, C^5-2H), 2.58-2.53 (t, J = 5.5 Hz, 4H, C^6-2H, C^7-2H), 1.83-1.76 (app q, J = 3.4 Hz, 4H, C^8-2H, C^9-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.8 (C^4), 126.4 (C^3), 125.4 (C^2), 124.6 (C^1), 54.6 (C^6, C^7), 53.9 (C^5), 23.5 (C^8, C^9) **MS** (ESI) $[M + H]^+$ m/z calculated for $C_9H_{13}NS$ 168.0841, found at 168.0836. Compound is known, however analytical data is not present. [104]

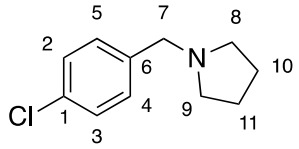
1-(4-Nitro-benzyl)-pyrrolidine (198)



Following general procedure 1, using methyl 4-nitrobenzoate (0.139 mL, 1.00 mmol) and pyrrolidine (0.090 mL, 1.10 mmol). 1-(4-Nitro-benzyl)-pyrrolidine was isolated as a brown oil (0.135 g, 0.750 mmol, 75%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.6 Hz, 2H, C^9-H, C^{10}-H), 7.55 (d, J = 8.4 Hz, 2H, C^7-H, C^8-H), 3.73 (s, 2H, C^5-2H), 2.56-2.52 (m, 4H, C^1-2H, C^2-2H), 1.87-1.80 (m, 4H, C^3-2H, C^4-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 129.3 (C^7, C^8), 123.5 (C^9, C^{10}), 59.9 (C^5), 54.3 (C^1, C^2), 23.6 (C^3, C^4) **MS** (ESI) $[M + H]^+$ m/z calculated for $C_{11}H_{14}N_2O_2$ 207.1128, found at 207.1127. The data matches that found in the literature.[80]

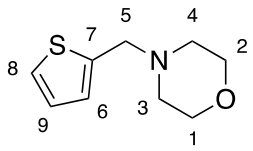
1-(4-Chlorobenzyl)-pyrrolidine (202)



Following general procedure 1, using methyl 4-chlorobenzoate (0.173 g, 1.00 mmol) and pyrrolidine, (0.090 mL, 1.10 mmol). 1-(4-Chlorobenzyl)-pyrrolidine was isolated as a brown oil (0.194 g, 0.990 mmol, 99%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.22 (m, 4H, C^2-C^5-4H), 3.60 (s, 2H, C^7-2H), 2.55-2.43 (m, 4H, C^8-2H, C^9-2H), 1.84-1.74 (m, 4H, C^{10}-2H, C^{11}-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0 (C^6), 130.2 (C^5, C^4), 128.4 (C^2, C^3), 59.9 (C^7), 54.1 (C^9, C^8), 23.5 (C^{10}, C^{11}) **MS** (ESI) $[M + H]^+$ m/z calculated for $C_{11}H_{14}ClN$ 196.0888, found at 196.0889. The data matches that found in the literature. [105]

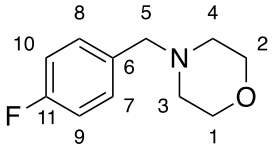
4-(Thiophen-2-ylmethyl)morpholine (201)



Following general procedure 1, using methyl thiophene-2-carboxylate (0.117 mL, 1.00 mmol) and morpholine (0.950 mL, 1.10 mmol). Product purified by column chromatography (EtOAc/pentane 3:7) to give 4-(Thiophen-2-ylmethyl)morpholine as a colourless oil (0.050 g, 0.270 mmol, 27%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 1H, C^8-H), 6.33 (dd, J = 3.2 Hz, 1H, C^6-H), 6.23 (d, J = 3.2 Hz, 1H, C^9-H), 3.78-3.67 (m, 4H, C^1-2H, C^2-2H), 3.54 (s, 2H, C^5-2H), 2.54-2.40 (m, 4H, C^3-2H, C^4-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.2 (C^7), 142.3 (C^6), 110.1 (C^9), 109.0 (C^8), 66.9 (C^1, C^2), 55.3 (C^5), 53.3 (C^3, C^4) **MS** (ESI) $[M + H]^+$ m/z calculated for $C_9H_{13}NOS$ 184.0791, found at 184.0793. Compound is known in the literature, however conflicting spectroscopic analysis has been reported. [106, 107]

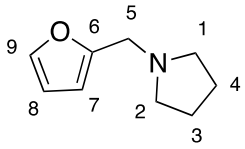
4-(4-Fluorobenzyl)morpholine (204)



Following general procedure 1, using methyl 4-fluorobenzoate (0.129 mL, 1.00 mmol) and morpholine (0.095 mL, 1.10 mmol). Product purified by column chromatography (EtOAc/pentane 3:7) to give 4-(4-Fluorobenzyl)morpholine as a colourless oil (0.045 g, 0.230 mmol, 23%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.25 (m, 2H, C^8-H, C^7-H), 7.05-6.97 (m, 2H, C^9-H, C^{10}-H), 3.77-3.63 (m, 4H, C^1-2H, C^2-2H), 3.48 (s, 2H, C^5-2H), 2.49-2.36 (m, 4H, C^3-2H, C^4-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.7 (C^{11}), 130.6 (C^6), 115.2 (C^7, C^8), 114.9 (C^9, C^{10}), 67.0 (C^1, C^2), 62.6 (C^5), 53.6 (C^3, C^4) **^{19}F NMR** (376 MHz, $CDCl_3$) δ -115.70 **MS** (ESI) $[M + H]^+$ m/z calculated for $C_{11}H_{14}FNO$ 196.1132, found at 196.1128. The data matches that found in the literature. [108]

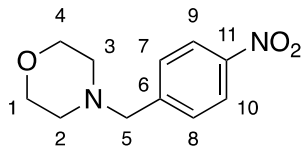
2-(N-pyrrolidinylmethyl)furan (205)



Following general procedure 1, using methyl-2-fuorate (0.107 μL, 1.00 mmol) and pyrrolidine (0.090 μL, 1.10 mmol). Product purified by column chromatography (1:9 ammonium hydroxide:methanol/DCM 5:95) to give 2-(N-pyrrolidinylmethyl)furan as a yellow oil (0.0467 g, 0.30 mmol, 30%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (app s, 1H, C^9-H), 6.34-6.30 (m, 1H, C^8-H), 6.21 (d, J = 3.3 Hz, 1H, C^7-H), 3.66 (s, 2H, C^5-2H), 2.60-2.50 (m, 4H, C^1-2H, C^2-2H), 1.85-1.75 (m, 4H, C^3-2H, C^4-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ141.9 (C^9), 110.0 (C^7), 107.6 (C^8), 53.9 (C^1, C^2), 52.1 (C^5), 23.5 (C^3, C^4) **MS** (ESI) $[M + H]^+$ m/z calculated for $C_9H_{13}NO$ at 152.1070, found at 152.1060. The data matches that found in the literature.[95, 109]

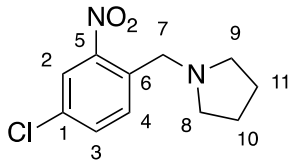
4-(4-Nitrobenzyl)morpholine (206)



Following general procedure 1, using methyl 4-nitrobenzoate (0.181 g, 1.00 mmol) and morpholine (0.095 mL, 1.10 mmol). Product isolated as an impure amine salt upon addition of Et_2O to afford a pale-yellow solid (0.299 g). Amine extracted from its impure salt (0.299 g), taken to pH 12 with NaOH (30 mL, 2M) and extracted with DCM. Organic dried with $MgSO_4$ and excess solvent removed *en vacuo* to afford 4-(4-Nitrobenzyl)morpholine as a yellow solid (0.145 g, 0.650 mmol, 65%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 8.7 Hz, 2H, C^9-H, C^{10}-H), 7.55 (d, 8.7 Hz, 2H, C^7-H, C^8-H), 3.76-3.69 (m, 4H, C^1-2H, C^4-2H), 3.61 (s, 2H, C^5-2H), 2.51-2.41 (m, 4H, C^2-2H, C^3-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.9 (C^{11}), 129.5 (C^6), 123.6 (C^7, C^8), 66.9 (C^9, C^{10}), 62.5 (C^1, C^4), 53.7 (C^5), 42.7 (C^2, C^3) (**MS** (ESI) $[M + H]^+$ m/z calculated for 223.1077, found at 223.1077. The data matches that found in the literature. [110]

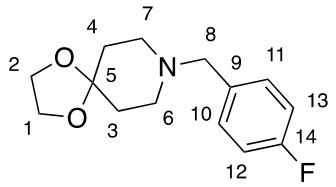
1-(2-Chloro-4-Nitro-benzyl)-pyrrolidine 7 (203)



Following general procedure 1, using methyl 4-chloro-2-nitrobenzoate (0.215 g, 1.00 mmol) and pyrrolidine (0.090 mL, 1.10 mmol). Product purified by column chromatography (1% ammonia methanol in DCM) to give 1-(2-Chloro-4-Nitro-benzyl)-pyrrolidine as an impure brown oil (0.0154 g, 0.06 mmol, 6%). 1-(2-Chloro-4-Nitro-benzyl)-pyrrolidine has been characterised however isolated yield of pure compound was not obtained due to time constraints.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H, C^2-H), 7.69 (d, J = 8.5 Hz, 1H, C^3-H), 7.55 (d, J = 8.4 Hz, 1H, C^4-H), 3.91 (s, 2H, C^7-2H), 2.55-2.47 (m, 4H, C^8-2H, C^9-2H), 1.81-1.74 (m, 4H, C^{10}-2H, C^{11}-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.8 (C^3), 132.0 (C^4), 124.4 (C^6), 56.0 (C^8, C^9), 54.2 (C^7), 23.7 (C^{10}, C^{11}) **MS** (ESI) $[M + H]^+$ m/z calculated for 241.0739, found at 241.0742

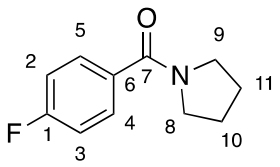
8-(4-Fluorobenzyl)-1,4-dioxa-8-azaspiro[4.5]decane (200)



Following general procedure 1, using 4,4-ethylenedioxy-piperidine (0.138 mL, 1.10 mmol), methyl-4-fluorobenzoate (0.129 mL, 1.00 mmol). Product was isolated as an impure solid upon addition of EtOAc, to afford a pale yellow solid (0.1395 g). Amine was isolated through addition of NaOH to the amine salt and extracted with DCM. Afforded a colourless oil (0.0352 g). 8-(4-Fluorobenzyl)-1,4-dioxa-8-azaspiro[4.5]decane has been characterised however isolated yield of pure compound is not quoted. Due to time constraints, separation from 4,4-ethylenedioxy-piperidine (observed by ^{1}H and ^{13}C NMR spectroscopy) was not performed.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, J = 4.2 Hz, 2H, C^{10}-H, C^{11}-H), 7.01 (t, J = 8.6 Hz, 2H, C^{12}-H, C^{13}-H), 3.94 (s, 4H, C^{1}-2H, C^{2}-2H), 3.48 (s, 2H, C^{8}-2H), 2.53-2.45 (m, 4H, C^{7}-2H, C^{6}-2H), 1.75-1.70 (m, 4H, C^{4}-2H, C^{3}-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.9 (d, J = 244.0 Hz, C^{14}), 134.4 (d, J = 2.9 Hz, C^{9}), 130.5 (d, J = 7.9 Hz, C^{10}, C^{11}), 115.1 (d, J = 21.2, C^{12}, C^{13}), 61.8 (C^{8}), 51.2 (C^{1}, C^{2}), 36.3 (C^{7}, C^{6}), 34.8 (C^{3}, C^{4}) (**^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.15 **MS** (ESI) $[M + H]^+$ m/z calculated for $C_{14}H_{18}FNO_2$ 252.1394, found at 252.1400. Compound is known, however analytical data is not present.[111]

Methyl-4-Fluorobenzoate (186)



4 -fluorobenzoyl chloride (1.18 mL, 10.00 mmol) was added dropwise to pyrrolidine (0.92 mL 11.03 mmol) and triethylamine (1.74 mL) in dry DCM (20 mL). The solution was stirred for 16 hours, after which it was diluted with DCM, washed with HCl and the organics were extracted with DCM. The organics were dried with $MgSO_4$ and purified by column chromatography (1:1 pentane/EtOAc) to afford Methyl-4-Fluorobenzoate as a white solid (1.2831 g, 6.65 mmol, 65%)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 8.2 Hz, 2H, C^4-H, C^5-H), 7.13-7.03 (m, 2H, C^2-H, C^3-H), 3.75-3.56 (m, 2H, C^9-2H), 3.55-3.38 (m, 2H, C^8-2H), 2.06-1.82 (m, 4H, C^{10}-2H, C^{11}-2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.7 (C^7), 163.5 (d, J = 249.4 Hz) (C^1), 133.3 (d, J = 3.2 Hz, C^6), 129.4 (d, J = 8.7 Hz, C^4, C^5), 115.3 (d, J = 21.7 Hz, C^2, C^3), 49.7 (C^8), 46.3 (C^9), 26.5 (C^{10}), 24.5 (C^{11}) **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.38 **MS** (ESI) $[M + H]^+$ m/z calculated for $C_{11}H_{13}FNO$ at 194.0976, found at 194.0973. MP 91-93 °C (lit. 80-90 °C)[112]**.** The data is consistent with that found in the literature. [96]

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