Novel Catalytic Hydrosilane Mediated Reduction Reactions

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''Organosilicon chemistry will be involved at least in part in a new chapter of chemistry. The knowledge already achieved creates new fields of research oriented in terms of properties. In this area the only limitation for the chemist is mainly his own creativity.''

Robert Corriu

Abstract

This thesis starts with an *introduction* to the relevant organosilicon and reduction chemistry concepts that underpin the chemistry that is explored in later chapters. In particular, hyperconjugation, relevant organosilicon reagent classes and reduction of carbonyl-containing compounds are explored.

Chapter one describes a reductive amination reaction with carboxylic acids *in lieu* of lower oxidation state alternatives such as aldehydes or alkyl halides. A two-step reaction process is described, whereby the dual reactivity of phenylsilane is exploited in an initial amidation followed by a zinc acetate-catalysed amide reduction. The reaction is applicable to a wide range of substrates and several potential applications have been explored, as well as mechanistic studies.

Chapter two builds on the utility of the novel zinc acetate / phenylsilane reduction system for the reduction of carboxylic acids to the corresponding alcohols. However, this time employing the use of zinc acetate and *N*-methyl morpholine in a dual catalytic system. The protocol is applicable to a wide range of substrates and proceeds *via* activation using hydrosilanes. Mechanistic studies have also been undertaken to gain insights into the reaction mechanism.

Acknowledgements

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Abbreviations

2c-1e	Two-centre-one-electron
3c-4e	Three-centre-four-electron
acac	Acetylacetonate
API	Active Pharmaceutical Ingredient
ATR	Attenuated Total Reflection
BINAP	(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)
Boc	*tert*-Butyloxycarbonyl
BOP	Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BuLi	Butyllithium
Cbz	Carboxybenzyl
cod	1,5-cyclooctadiene
DAD	Diode Array Detector
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCC	Dicyclohexylcarbodiimide
DIBAL	Diisobutylaluminium Hydride
DMF	Dimethylformamide
DNA	Deoxyribonucleic Acid
dppe	1,2-Bis(diphenylphosphino)ethane
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
ESI	Electron Spray Ionisation
FLP	Frustrated Lewis Pairs
FTIR	Fourier Transform Infrared Spectrometry
HATU	1*H*-1,2,3-Triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate
HMDS	Hexamethyldisilazane
HRMS	High Resolution Mass Spectrometry
KHMDS	Potassium Hexamethyldisilazide
LAH	Lithium Aluminium Hydride

LiHMDS	Lithium Hexamethyldisilazide
MO	Molecular Orbital
mp	Melting Point
NHC	*N*-Heterocyclic Carbene
NMM	*N*-Methyl Morpholine
NMR	Nuclear Magnetic Resonance
PMHS	Polymethylhydrosiloxane
PyBOP	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
SET	Single Electron Transfer
TBAF	Tetrabutylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TES	Triethylsilyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TOF	Time of Flight
***t*PBO**	*trans*-4-Phenyl-but-3en-2-one
UV	Ultraviolet

Table of Contents

INTRODUCTION TO FUNDAMENTAL ORGANOSILICON AND REDUCTION CHEMISTRY

This introduction gives an insight into concepts of fundamental organosilicon and reduction chemistry which will be utilised in later chapters. More relevant and focussed literature will be given at the beginning of each chapter.

1 Organosilicon Reagents

1.1 Importance of Silicon

Silicon is a metalloid element and is the second most abundant element after oxygen, and constitutes 27.7% of the earth's crust by mass.[1] Since its discovery by Berzelius in 1823,[2] silicon has become an integral part of human life, and is now utilised to make alloys, as a semiconductor and also in the electronics, computing and automobile industries.[3] As it is a non-toxic element, it can also be used to make silicon-oxygen polymers known as silicones, which are utilised in the personal and healthcare industries as well as in construction.

In addition to these uses, organosilicon reagents have been widely used in organic synthesis to perform a variety of transformations.[4-7] The discovery of organosilicon chemistry was made by Charles Friedel and James Crafts in 1863, when they mixed tetrachlorosilane with diethylzinc to give tetraethylsilane – the first reported compound with a covalent Si-C bond.[8] The next breakthrough in organosilicon chemistry didn't come until 1907, when Kipping reacted tetrachlorosilane with ethylmagnesium iodide to give a mixture of ethylchlorosilanes.[9]

Subsequently, the scope of organosilicon use in organic chemistry as either reagents or intermediates has significantly expanded, for example silyl enol ethers can be utilised as enolate precursors or as carbon nucleophiles.[10-12] Additionally, organosilicon reagents can be used as protecting groups for alcohols;[13-14] as reagents in the synthesis of alkenes *via* the Peterson olefination;[15-16] and as hydride donors.[17-19] However, when compared with other organometallic reagents, they are much more moisture and air stable and typically readily prepared from a wide range of inexpensive starting materials.[1]

Organosilicon compounds are often considered as analogues to carbon compounds, with the difference in reactivity based on the electropositive character of silicon.[20] However, these

similarities only apply to organosilanes that possess four substituents. Unlike carbon, silicon is able to extend its coordination number to five or six as a result of hypercoordination, which gives unique structural and reactivity properties.[21] Silicon also makes much stronger bonds with oxygen and halides than the comparable carbon analogues, so the formation of strong Si-O and Si-F bonds is considered the driving force behind a significant proportion of organosilicon chemistry.[4]

1.2 Hypercoordination

As defined by Minkin, "hypervalent bonding implies a transfer of the electrons from the central (hypervalent) atom to the nonbonding molecular orbitals which it forms with (usually more electronegative) ligands".[22] First introduced by Musher in 1969, the term hypervalency was used to describe compounds and ions of main-block elements, whereby the use of traditional Lewis covalent bonds requires the additional assumption of "expansion of the octet" for the central atom (Figure 1A).[23-24] Initially, it was believed that this expansion was facilitated by the involvement of *d*-orbitals, however it has subsequently been demonstrated that, although *d*-functions are required for accurate computational calculations, the contribution provided by *d*-orbitals is negligible.[25]

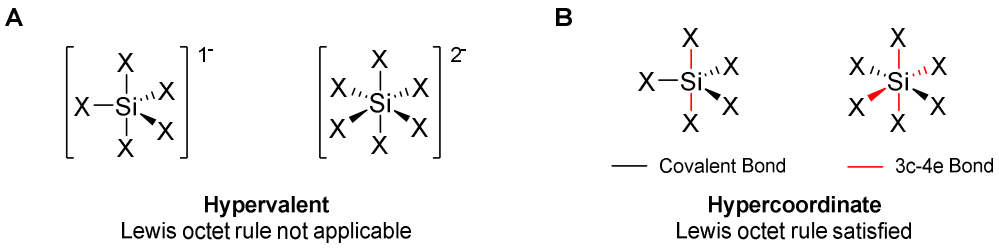


Figure 1 *Hypervalency vs Hypercoordination.* ***A*** *– Hypervalent molecules with expansion of octet at Si.* ***B*** *– Hypercoordination facilitated by the presence of three-centre-four-electron bonds*

A significant amount of criticism has been associated with the term hypervalent,[26-27] with some claiming the term redundant and unnecessary.[28-30] This has led to more people using the term hypercoordination as an alternative,[31] which refers to "atomic centres in an electron–deficient species with multicentre bonding, in which the bonding power of a pair of electrons is spread over more than two atoms".[22] Unlike hypervalency, hypercoordination

demands that the octet rule at the central atom remains satisfied and additional electrons must be stabilised by the ligands rather than the central atom. At least one pair of two-centre-one-electron (2c-1e) bonds are found in hypercoordinate molecules, which are commonly combined to give three-centre-four-electron (3c–4e) bonds (Figure 1B).

The concept of a 3c–4e bond was independently introduced by Rundle[32] and Pimentel[33] and is defined as an elongated, linear, electronically delocalized arrangement of two electronegative ligands around a central atom.[34-35] This interaction was described by Jensen as n-σ*, where n is a non-bonding pair of electrons on the donor and σ* are antibonding orbitals of an acceptor.[24] This is equivalent to a partial displacement of a ligand and in a 3c-4e bond the opposing ligand reciprocates, resulting in two bonds containing 1 electron (Figure 2). Qualitative molecular orbital (MO) analysis of pentacoordinate organosilicon compounds was carried out by Hoffmann and co-workers, which supported the proposal of a 3c-4e bond, and gave a series of three MOs – bonding (Ψ_1), non-bonding (Ψ_2) and antibonding (Ψ_3) with two electron pairs occupying Ψ_1 and Ψ_2.[36]

Figure 2 *Depictions of three-centre-four-electron bonds.* ***A*** *– Representation of charge distribution in a 3c-4e bond.* ***B*** *– MOs involved in 3c-4e bonding. The MOs are bonding (Ψ_1), non-bonding (Ψ_2) and antibonding (Ψ_3).*[36]

Silicon can expand its coordination number and form both stable and transient hypercoordinated molecules. This property has been exploited by chemists in organic synthesis, as reaction intermediates and in catalyst design.[37-39] It has been shown that compared to their tetravalent counterparts, hypercoordinate silicon complexes have higher Lewis acidity,[40] due to the presence of 3c-4e bonds.[41] The additional negative charge associated with the addition of more ligands is delocalised onto the electron withdrawing ligands, resulting in an increased effective positive charge at silicon.

This concept was demonstrated by Corriu *et al.* who showed that pentacoordinate silicon complexes showed increased reactivity toward a Grignard reagent, when compared to tetravalent species.[42] In addition to the increasing Lewis acidity of the pentavalent silicon species, the electronegative ligands also help to stabilise the intermediate resulting from the attack of the Grignard species, leading to faster reaction times.

1.3 Relevant Silicon Reagent Classes

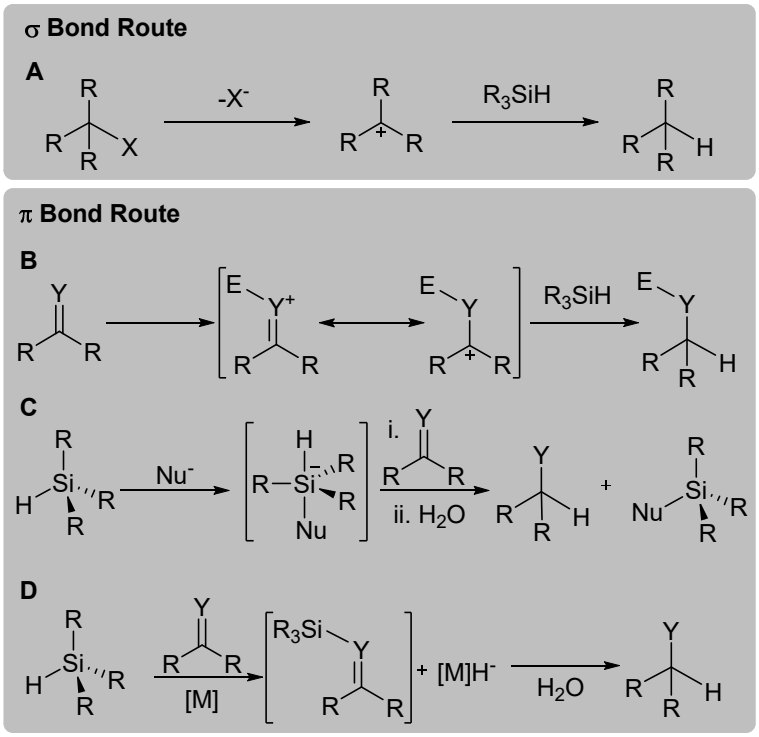
1.3.1 Hydrosilanes

Most reducing agents can be classified as either formal hydride donors, such as lithium aluminium hydride (LAH) or sodium borohydride, or formal H-radical donors, such as tri-butyltin hydride. However, organosilicon compounds with at least one Si-H bond, known as hydrosilanes, can act as either hydride or H-radical donors depending on the nature of the reaction. The low electronegativity of silicon (1.8) relative to hydrogen (2.1), combined with its metallic nature, leads to polarisation of the Si-H bond away from silicon, which imparts hydridic character.[43]

Hydrosilanes are produced on an industrial scale by reaction of chlorosilanes, such as trichlorosilane or methyldichlorosilane, with Grignard reagents. The remaining Si-Cl bonds can then be reduced using aluminium hydrides such as LAH[44] or diisobutylaluminium (DIBAL).[45] Additionally, some hydrosilanes are produced as side products of the Müller-Rochow process – a reaction between silicon and organic chlorides used to make chlorosilanes,[46] such as $MeHSiCl_2$ and Me_2HSiCl. There are a variety of commercially available silanes, which possess a wide range of different Si-H bond strengths,[47] demonstrating that the groups attached to silicon have a significant impact on the chemistry of the silane.

In general, hydrosilanes do not undergo spontaneous reactions, unless the substrate is a strong electrophile, or the silane has been first activated by the interaction of a nucleophilic species with the silicon centre, as tetravalent organosilicon hydrides are poor nucleophiles.

This gives the potential for selective reduction reactions to occur under mild reaction conditions.[48] Mechanistically, there are two main ways that a hydride can be transferred from a hydrosilane and effect an ionic reduction reaction (Scheme 1).



Scheme 1 *Mechanisms for hydrosilane reduction. σ-Bond route:* ***A*** *– generation of a carbocation to which hydride transfer can occur. π-Bond routes:* ***B*** *– activation of the π-bond with Brønsted or Lewis acids before hydride transfer.* ***C*** *– Activation of silane with a nucleophile, increasing the hydridic character.* ***D*** *– Insertion of a metal to the Si-H bond to give a metal hydride, which can effect the reduction.*

The first of these is *via* reaction with a strong electrophile, such as carbocation, to which hydride transfer can occur (Scheme 1A). This can also be referred to as the σ-route as it involves the stepwise cleavage of a σ-bond to give a carbocation intermediate that is reduced by the donation of hydride from a silane.[43]

The second of these routes is called a π-route as it involves the addition of the hydride across a π bond (Scheme 1B-D). However, compounds with weak electrophilic carbon centres such as ketones and aldehydes are normally unreactive in reactions with hydrosilanes. For these types of electrophiles, the electrophilicity of the carbon centre must be enhanced. A number of methods have been developed to achieve this, but one of the main ways is by activation of the π bond, such as a carbonyl, using Brønsted[49-50] or Lewis[51-52] acids (Scheme 1B).

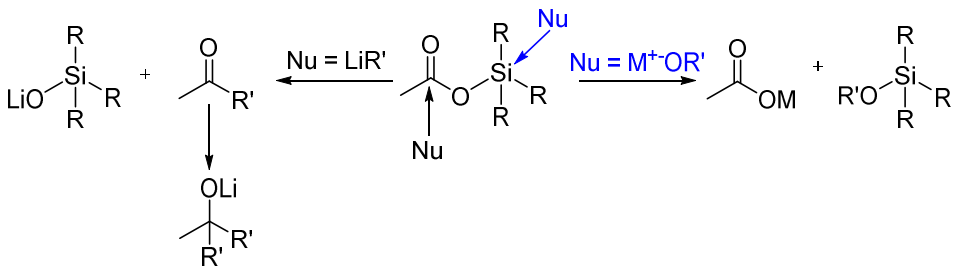
Alternatively, an additional nucleophilic species with a high affinity for silicon, such as a fluoride anion, can be added to the reaction mixture, leading to a pentacoordinate hydrosilanide ion (Scheme 1C).[53-55] This activation increases the hydridic nature of the Si-H bond compared to than their tetravalent precursors,[56] and so can perform a more facile reduction reaction.

Additionally, the insertion of a transition metal into the Si-H bond to give a metal hydride (MH^-) and a silylium ion (R_3Si^+) is frequently observed (Scheme 1D).[57] The resulting silylium cation can activate Lewis bases, increasing the potential for reaction with the metal hydride. A comprehensive review of the applications of ionic hydrosilane reduction reactions in organic synthesis has been compiled by Larson and Fry.[48]

It was also observed by Giller and Chatgilialogu that the Si-H bond energy of tris(trimethylsilyl)silane (351 kJ/mol) was similar to that of tributyltin hydride (322 kJ/mol) and could be a viable alternative which would eliminate the toxicity problems associated with the use of stannanes.[58] This hypothesis proved to be successful and there have been reports of silane mediated radical reductions on a range of functional groups including halides, esters and thioethers.[59-61]

1.3.2 Silyl Esters

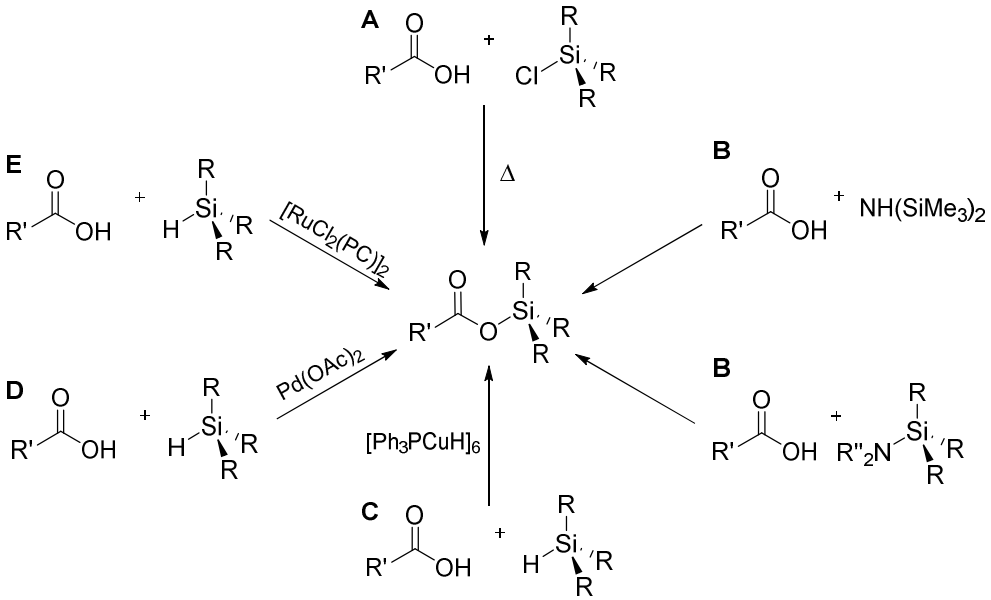
Acyloxysilanes, also known as silyl esters, are a class of compounds infrequently encountered within organic chemistry. Silyl esters possess two electrophilic centres – one at the carbonyl carbon and one at silicon, and the choice of nucleophile determines the position of attack. A report by Hudrlik and Feasley demonstrated that alkoxide nucleophiles preferentially react at silicon, whereas alkyllithium reagents show a preference for the carbonyl (Scheme 2).[62] Despite this, the presence of bulky substituents on the silyl ester, the solvent and nucleophile counterion can have a marked effect on the reaction and create a switch from the typical reactivity.



Scheme 2 *Reaction of silyl esters at the two electrophilic centres. Alkyllithium reagents react at the carbonyl centre, whereas alkoxides react at silicon.*[62]

Silyl esters containing Si-H bonds are reported even less frequently in the literature than other silyl esters, however they display interesting reactivity as they have been found to be stronger reducing agents than the parent silanes.[63]

Silyl esters can be synthesised in several ways (Scheme 3), however one of the simplest methods is to treat a chlorosilane with a carboxylic acid or a metal carboxylate (Scheme 3A). However, this method can lead to formation of silanol and siloxane side products, and also requires high temperatures to achieve reasonable yields.[64-65]



Scheme 3 *Methods for the synthesis of silyl esters.* ***A*** *– Treatment of chlorosilane with a carboxylic acid or metal carboxylate.* ***B*** *– Use of reactive silylating agents such as HMDS and aminosilanes.* ***C*** *– Catalytic copper mediated silyl ester synthesis.*[66] ***D*** *– Combination of carboxylic acid and silane with a palladium acetate catalyst.*[67] ***E*** *– Solvent-free Ru catalysed synthesis of silyl esters.*[68]

Another method for the silylation of carboxylic acids is based on reactive silylating reagents such as hexamethyldisilazane (HMDS) and aminosilanes. This method usually requires

continuous removal of ammonia and amines formed in the reaction (Scheme 3B).[69] Schubert and Lorenz reported a $[Ph_3PCuH]_6$ catalysed synthesis of silyl esters from mono-hydridic silanes, such as Ph_2MeSiH, Ph_3SiH and Et_3SiH, in conjunction with acetic acid (Scheme 3C).[66] More recent reports have been disclosed by Boudjouk and co-workers, who revealed that palladium(II) acetate could be used to catalyse the formation of silyl esters from carboxylic acids and hydrosilanes (Scheme 3D),[67] whereas Mizuno and co-workers disclosed a solvent-free $[RuCl_2(p\text{-cymene})]_2$ catalysed synthesis (Scheme 3E).[68]

One of the most familiar uses of silyl esters is as a protecting group for carboxylic acids,[70] however compared to their carbon analogues, their use is not as widespread. Silyl esters which are derived from smaller silyl groups, such as trimethylsilyl (TMS) (**1**), triethylsilyl (TES) (**2**) and *tert*-butyldimethylsilyl (TBS) (**4**) are less stable to harsh reaction conditions and so provide a transient protection.[71] In contrast, bulky silyl esters, such as *tert*-butyldiphenylsilyl (TBDPS)[72] (**5**) and triisopropylsilyl (TIPS)[73] (**3**) groups are able to withstand harsh non-aqueous reaction conditions, due to their increased kinetic stability.[74]

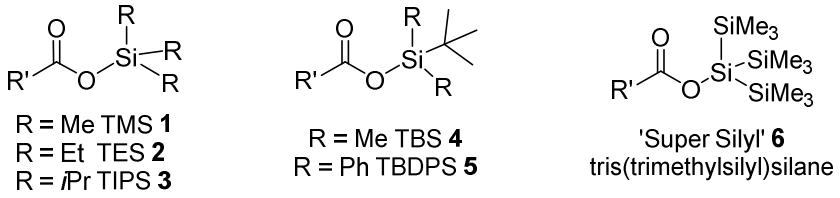
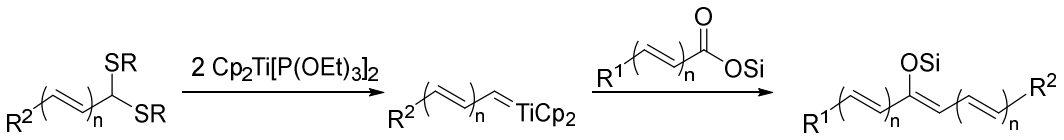


Figure 3 *Silicon protecting groups commonly utilised in organic synthesis*

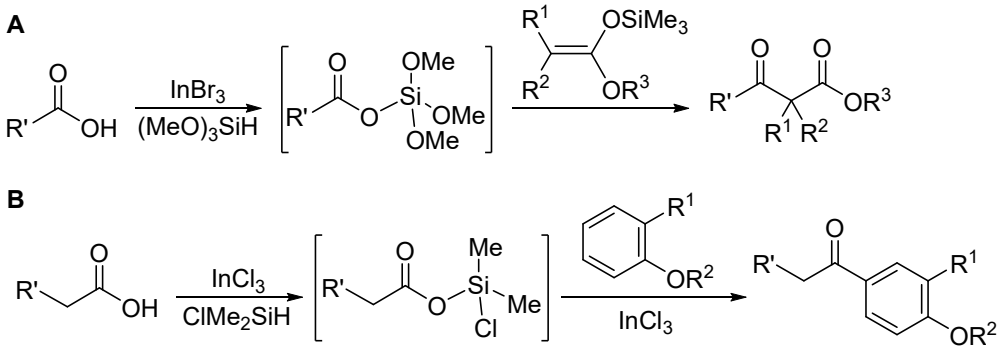
However, these protecting groups can be difficult to remove and typically require the use of excess fluoride,[72, 75] strong acids,[76] or bases[77] for their removal. The more recently reported super silyl ester (tris(trimethylsilyl)silane) (**6**) is tolerant of reaction conditions such as potassium and lithium hexamethyldisilazide (KHMDS and LiHMDS),[78] butyllithium (BuLi) and Grignard reagents,[79-80] but must be removed using UV irradiation or with excess fluoride.

Silyl esters can also be used as reactive functional groups in their own right. Takeda *et al.* reported that in a similar manner to traditional esters, silyl enol ethers have been synthesised from silyl esters using a titanium carbene transformation.[81]



Scheme 4 *Synthesis of silyl esters using an analogous method to traditional esters via a titanium carbene transformation.*[81]

Additionally, Baba and co-workers have reported an In-catalysed cross-Claisen condensation reaction,[82] between carboxylic acids and ketene silyl acetals. In the reaction the trimethoxysilane reacts with the carboxylic acid to give a silyl ester and reacts with the ketene silyl acetal to give *β*-ketoester products (Scheme 5A). Baba has also reported an In-catalysed Friedel-Crafts acylation directly from carboxylic acids (Scheme 5B).[83]



Scheme 5 *Silyl esters used as reactive functional groups.* ***A*** *– In-catalysed cross-Claisen reaction between carboxylic acids and ketene silyl acetals.*[82] ***B*** *– In-catalysed Friedel-Crafts acylation from carboxylic acids.*[83]

In both reactions, the key intermediates in the reaction are silyl esters, which behave as activated carboxylic acids. Exploiting this property of silyl esters, silane-mediated amidation reactions have been reported which proceed *via* silyl ester intermediates using a variety of different hydrosilanes and chlorosilanes.[84-88]

2 Reduction of Carbonyl-Containing Functional Groups

Reduction reactions are fundamental transformations which are used significantly in organic synthesis routes. There are several definitions of reduction and the traditionally accepted

definitions are the gain of electrons, loss of oxygen or gain of hydrogen. However, in organic chemistry the oxidation state of the carbon is rarely calculated, but instead oxidation levels are typically used.[89]

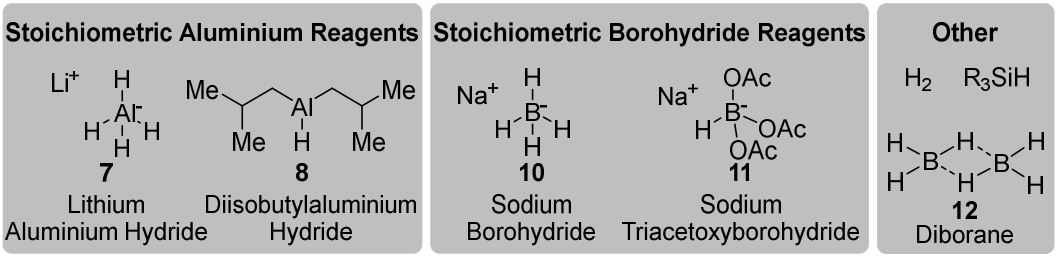


Figure 4 *Reducing agents which can be used to effect reductions of carbonyl-containing functional groups*

There are a variety of reducing agents that can be used to effect reduction reactions of a range of carbonyl-containing functional groups, which include stoichiometric aluminium reagents, stoichiometric borohydride reagents, borane, catalytic hydrogenation reactions and hydrosilane reductions (Figure 4).

2.1 Stoichiometric Reductions

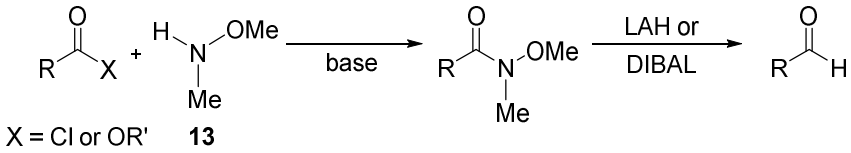
2.1.1 Aluminium Reagents

Schlesinger and co-workers reported the discovery of lithium aluminium hydride (**7**) in 1947, synthesised by reaction of lithium hydride with aluminium chloride.[90] LAH (**7**) has been shown to reduce aldehydes, ketones, esters, acid chlorides, acid anhydrides and carboxylic acids to the corresponding alcohols[91-92] and amides and imines to the corresponding amines.[93-94] However, the handling of this hazardous air and moisture sensitive reagent, in addition to instability and handling problems has led to the adoption of an alternative reagent, sodium bis(2-methoxyethoxy)aluminium hydride, also known as SMEAH and Red-Al. This alternative has similar reactivity to LAH but is easier to handle, safer and cheaper.[95-98]

Diisobutylaluminium hydride (**8**) is also an alternative reducing agent to LAH, and was originally investigated as a co-catalyst for alkene polymerisation.[99] DIBAL exists as a dimer or trimer with tetrahedral aluminium centres sharing bridging hydride ligands[100] and is prepared

by heating triisobutylaluminium which undergoes β-hydride elimination to give DIBAL.[101] In contrast to LAH (**7**) which is considered a nucleophilic reducing agent, DIBAL is considered an electrophilic reducing reagent as it reacts more quickly with electron-rich substrates.[102] DIBAL has been shown to be effective in the reduction of aldehydes, esters, acid halides and carboxylate salts to the corresponding alcohols and amides to the corresponding amines.[103]

The direct reduction of esters to aldehydes is also possible with DIBAL (**8**), however in practice the reaction is capricious as over-reduction to the alcohol is commonplace, leading to it rarely being used.[104] More recently, Webb and Jamison have reported a continuous flow system in which DIBAL (**8**) is used to reduce esters to aldehydes in less than 60 seconds at -78 °C, without observing any over-reduction products.[105] Alternatively, Weinreb amides can be synthesised from acid chlorides or esters and *N,O*-dimethylhydroxylamine (**13**) and these can be chemoselectively reduced to aldehydes (Scheme 6).[106]



Scheme 6 *Synthesis of aldehydes via reduction of Weinreb amides*[106]

Both LAH (**7**) and DIBAL (**8**) reactions are associated with difficult work-up procedures. In order to avoid the formation of inseparable aluminium salts, a modified work-up procedure known as a Fieser work-up is required,[107-108] whereby aqueous sodium hydroxide is added to the reaction mixture which allow the aluminium salts to be separated more easily. Alternatively, a saturated aqueous solution of Rochelle's salt (sodium potassium *L*(+)-tartrate tetrahydrate) can be used. Additionally, as many functional groups are readily reduced using LAH or DIBAL reactions, chemoselective late stage reductions are often not possible.

2.1.2 Borohydride Reagents

The success of aluminium hydrides prompted research into the properties of other hydride species, such as the borohydrides of aluminium,[109] gallium,[110] beryllium,[111] and lithium,[112] and

sodium.[113] Initial attempts to synthesise sodium borohydride from sodium hydride and diborane were unsuccessful, and so instead sodium hydride was reacted with trimethyl borate to give sodium trimethoxyborohydride ($NaBH(OCH_3)_3$).[114] This novel reagentx was shown to be an effective reducing agent for a range of functional groups including aldehydes, ketones, acid chlorides and acid anhydrides.[115]

Brown and co-workers subsequently discovered that borohydrides readily undergo displacement reactions,[116] and therefore trimethoxyborohydride could be displaced by diborane to give the first published synthesis of sodium borohydride ($NaBH_4$) (**9**).[117] Reductions of aldehydes, ketones and acid chlorides to the corresponding alcohols were demonstrated to be successful using sodium borohydride,[113] but reductions of more difficult substrates such as esters, carboxylic acids and nitriles were not initially possible. However, these reductions can be achieved when aluminium chloride is used as an additive in the reaction, generating aluminium borohydride *in situ*.[118] Additionally, in contrast to LAH (**7**) reduction reactions, which have to be performed in non-hydroxylic solvents, sodium borohydride-mediated reductions can be performed in methanol or water, meaning that there is no requirement for rigorous drying of glassware or solvents.[113]

Investigations have also focussed on the discovery of modified borohydride reagents. The first synthesis of a cyanoborohydride was reported in 1951 by Wittig, by reaction between of lithium borohydride with hydrogen cyanide under pressure.[119] Subsequently an improved synthesis of sodium cyanoborohydride was reported[120] and it was shown that unlike sodium borohydride, sodium cyanoborohydride is stable even in acidic solutions at pH 3.[121] This acid stability allows it to be used in applications such as trapping of carbocations generated using aqueous hydrogen chloride,[122] which would not be possible using sodium borohydride. Additionally, it was shown that sodium cyanoborohydride is a milder reducing agent than sodium borohydride. Therefore, it effects the reduction of iminium ions more rapidly than

the reduction of aldehydes or ketones, making it ideal for use in reductive amination reactions.[123]

More recently, Wartik and Pearson reported the synthesis of another novel borohydride reagent sodium triacetoxyborohydride (**10**), made by reaction of sodium borohydride and carbon dioxide.[124] Sodium triacetoxyborohydride has shown selective reduction of aldehydes even in presence of ketones.[125] Subsequently, synthesis of acyloxyborohydrides from reaction of carboxylic acids and sodium borohydride has been described.[126-127] Gribble *et al.* also reported that a combination of sodium borohydride and carboxylic acids can form acyloxyborohydrides *in situ*.[128] The reactivity of these species can be controlled by the structure and number of the acyloxy groups, allowing selective reductions of amides to amines in the presence of esters.[129]

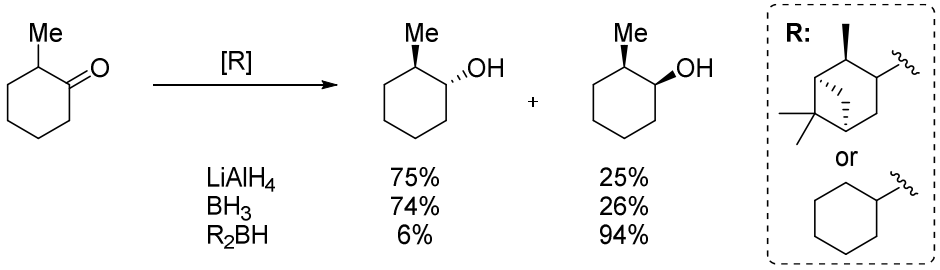
2.1.3 Borane Reagents

Diborane (B_2H_6) (**11**) was first isolated and characterised by Stock in 1912 by thermal decomposition of boron hydrides.[130] Interest in the use of diborane as a reductant was initially very low as its synthesis was very complex and yielded only small quantities of material.[131] However, Brown and co-workers reported a novel synthesis of diborane from lithium hydride[116] or sodium borohydride[132] and boron trifluoride-ethyl etherate, allowing it to be produced in reasonable quantities. Borane is a pyrophoric gas, but is commercially available in solution as a complex, most commonly with tetrahydrofuran (THF) or dimethylsulfide, although the borane dimethylsulfide complex is more stable.[133]

The increased availability of diborane led to the discovery of reductions of aldehydes, ketones, as well as esters albeit more slowly. Most surprisingly, carboxylic acids and nitriles are reduced more rapidly than ketones,[134] allowing selective reductions to be performed. Reductions facilitated by LAH (**7**) and sodium borohydride (**9**) occur by hydride transfer from an anion to an electron deficient centre, whereas borane (**11**) reductions occur by

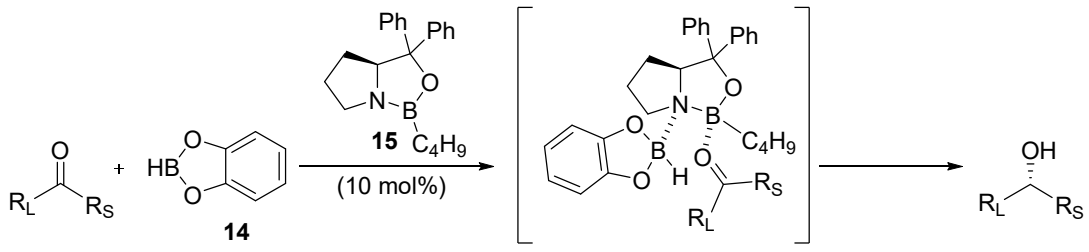
electrophilic attack.[135] Hydroboration of double and triple carbon-carbon bonds, producing predominantly *cis* anti-Markovnikov organoborane species, has also been reported.[136] Hydroboration has the potential to limit the utility of diborane for substrates containing alkenes or alkynes, as there is competition between hydroboration and the desired reduction reaction.

Despite this limitation, borane reductions are still utilised frequently, and it has been demonstrated that asymmetric reductions using dialkylboranes are possible, to give the less stable epimer (Scheme 7).[137] High yields can be achieved with several boranes, including dicyclohexylborane and diisopinocampheylborane.



Scheme 7 *Asymmetric ketone reduction using dialkylboranes to give the less stable epimer.[137]*

Since this initial report, a number of asymmetric reductions of ketones have been disclosed, which are now regularly utilised. These include alkoxy-amine-borane complexes derived from α-amino acids,[138] boranes derived from pinene,[139-140] and lithium tri-*sec*-butylborohydride (*L*-Selectride®).[141-142] Additionally, Corey, Bakshi and Shibata reported a chiral oxazaborolidine (**15**) catalysed asymmetric ketone reduction which utilises borane or catecholborane (**14**) as the terminal reductant (Scheme 8).[143-144]



Scheme 8 *CBS Asymmetric ketone reduction using a chiral oxazaborolidine (**15**) and catechol (**14**) as the terminal reductant.[143-144]*

This reduction is known as the Corey-Bakshi-Shibata (CBS) Reduction and involves an initial coordination of the catecholborane (**14**) with the Lewis-basic amine of the CBS catalyst (**15**). This activates the catecholborane and increases the Lewis acidity of the endocyclic boron atom, which can coordinate to the ketone on the more sterically accessible side (R_S). This minimises any unfavourable steric interactions and aligns the carbonyl carbon atom and the coordinated catecholborane for a favourable, face-selective hydride transfer to give the desired chiral alcohol product.[145]

2.2 Catalytic Reduction Reactions

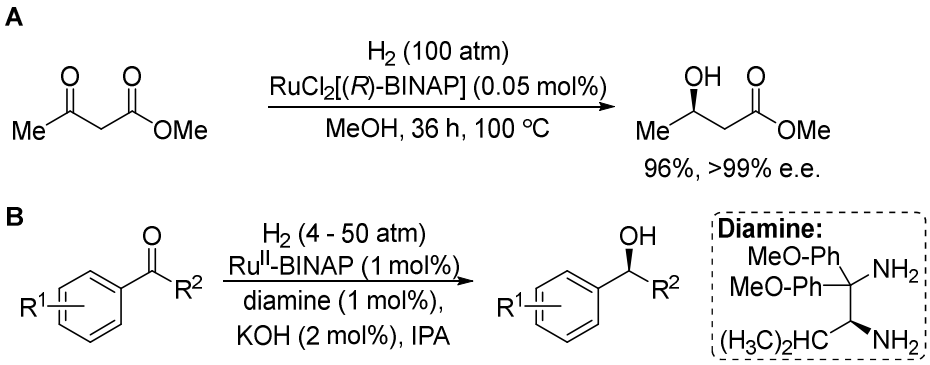
2.2.1 Hydrogenation Reactions

In addition to stoichiometric reduction methods, there are also a range of catalytic reduction methods. One of the most atom economical, green, and clean reduction methods is to use molecular hydrogen in combination with a transition metal catalyst. In addition, hydrogenation procedures are very cost effective, when compared to traditional metal hydride reductions, and have more straightforward work-up procedures and purifications.[146] Catalytic hydrogenations are commonly used for the reduction of many organic functional groups, such as alkenes, alkynes, nitriles, imines and nitro groups. However, historically hydrogenation reactions have not been typically associated with the reduction of carbonyl-containing functionalities, such as aldehydes, ketones, and carboxylic acid derivatives, as hydrogen is not nucleophilic enough to effect a facile reduction.[147]

Heterogeneous catalysts, such as Pd/C and Pt/C have been widely used in hydrogenation reactions. Despite simple removal of the catalyst by filtration on completion of the reactions, hydrogenations of carbonyl-containing groups typically require harsh conditions such as high temperatures and pressures.[146] Alternatively, homogeneous catalysts can be employed, which allow reactions to be performed under milder conditions and provide greater functional group tolerance and chemoselectivity.

Since the first reported homogenously catalysed hydrogenation of a carbonyl group reported by Coffey,[148] significant effort has been focussed on the discovery of catalysts that are highly active and selective for the reduction of carbonyl-containing compounds.[146] Presently there are a range of methods for the reductions of aldehydes,[149-150] ketones,[151] carboxylic acids,[152] esters,[152-153] and amides[154] and homogeneous hydrogenation reactions are now frequently utilised in a range of industrial processes.[155]

Additionally, asymmetric hydrogenation reactions of ketones can be performed to give chiral alcohol products. Noyori *et al.* reported an asymmetric hydrogenation of β-keto esters utilising a (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) (BINAP)-Ru^{II} catalyst (Scheme 9A),[156] which proceeds *via* a Ru-chelate intermediate.[157]



Scheme 9 *Asymmetric ketone hydrogenation reactions.* ***A*** *- Asymmetric reduction of β-keto esters reported by Noyori et al.*[156] ***B*** *- Reduction of simple ketones to chiral alcohols disclosed by Noyori and co-workers.*[158]

However, hydrogenation of simple ketones was not reported until 1995, when Noyori and co-workers disclosed that a $RuCl_2(diphosphane)_2(diamine)_2$ complex was able to catalyse the reduction (Scheme 9B).[158] Since these initial reports, a range of novel catalysts have been discovered for the asymmetric hydrogenation of ketones.[159-161]

2.2.2 Hydrosilane Reductions

In addition to catalytic hydrogenation reactions, hydrosilanes can be utilised, in combination with a catalyst, to effect a wide range of reduction reactions by donation of a hydride (Section 1.3.1).[43] Hydrosilanes are easy to handle, stable to air and moisture and are non-toxic, making

them desirable reducing agents.[162-164] Despite increased interest from academic research groups into the discovery of a wide variety of hydrosilane-mediated reductions, they are still utilised less frequently than metal hydride or hydrogenation reactions.[43]

A wide range of functional groups can be reduced using hydrosilanes, including aldehydes,[165] ketones,[166-169] esters[170] and carboxylic acids[171] to the corresponding alcohols. Additionally amides[172-173] and imines[174] can be reduced to give the corresponding amines. Amides can also undergo silane mediated dehydration reactions to give nitrile products.[175-176]

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CHAPTER 1 REDUCTIVE AMINATION REACTIONS USING CARBOXYLIC ACIDS

Carbon-Nitrogen bond formation is paramount to a wide range of chemical and biological compounds, however amine bond formation using carboxylic acid starting materials is still under-explored within the literature. In this chapter a two-step reaction process is described, whereby the dual reactivity of phenylsilane is exploited in an initial amidation followed by a zinc acetate-catalysed amide reduction. The reaction is applicable to a wide range of amines and carboxylic acids and several potential applications have been explored, such as di-substituted piperazines. Mechanistic studies demonstrate that residual 0.5 equivalents of carboxylic acid from the amidation step is responsible for the generation of augmented silane reductants, which allow secondary amides, previously unreactive in zinc/silane systems to be reduced.

1 Introduction

1.1 Importance of Amines

Nitrogen is a crucial element in many areas of both biology and chemistry, possessing both a lone pair of electrons and the possibility to act as both a hydrogen bond donor and acceptor.[1] These characteristics can be modified by substitution, making it a very versatile and desirable element. The importance of these properties can be found at a cellular level, more specifically between the base pairs in deoxyribonucleic acid (DNA), where hydrogen bonding provides the essential stabilisation of the double-helix structure (Figure 5).[2]

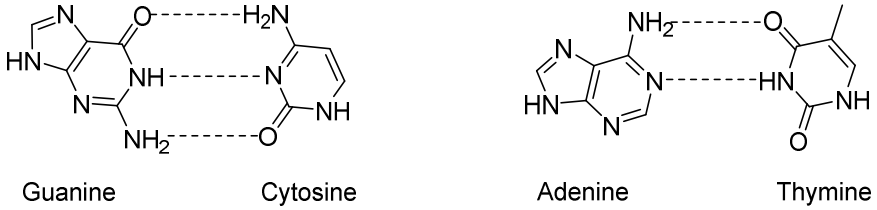


Figure 5 *Hydrogen bonding between the DNA Base Pairs*[2]

Amines are highly desirable functional groups, which present within a wide range of different chemical compounds, including important biological molecules such as amino acids, chlorophyll and haemoglobin; an array of different natural products, for example alkaloids, antibiotics and vitamins; pharmaceutically active compounds; agrochemicals; and polymers.[3] An assessment by Grand View Research, Inc. estimated the worth of the global amine market at $14.4 billion in 2016, which is expected to rise to $29.3 billion by 2025.[4]

According to analysis carried out by Roughley and Jordan on the types of reactions published by the medicinal chemistry departments of pharmaceutical companies,[5] 36% of reactions carried out in drug discovery produced either an amine or amide product (Table 1). As shown in Table 1, *N*-acylation to give amides (Entry 8) is the most popular class of C-N bond forming reactions. The most popular methods for amine synthesis are Buchwald-Hartwig reactions (Entry 3), *N*-substitution with alkyl halides (Entry 1) and reductive amination reactions (Entry 2).

Entry	Desired Product	Reaction Type	Percentage of Total Reactions / %
1	Amine	*N*-substitution with alkyl halides	5.3
2		Reductive amination	5.3
3		Buchwald-Hartwig	6.3
4		Amide *N*-Alkylation	0.7
5		Heteroaryl *N*-Alkylation	0.6
6		Nitro Reduction	1.1
7		Amide Reduction	0.7
8	Amide	*N*-Acylation to Amide	16.0

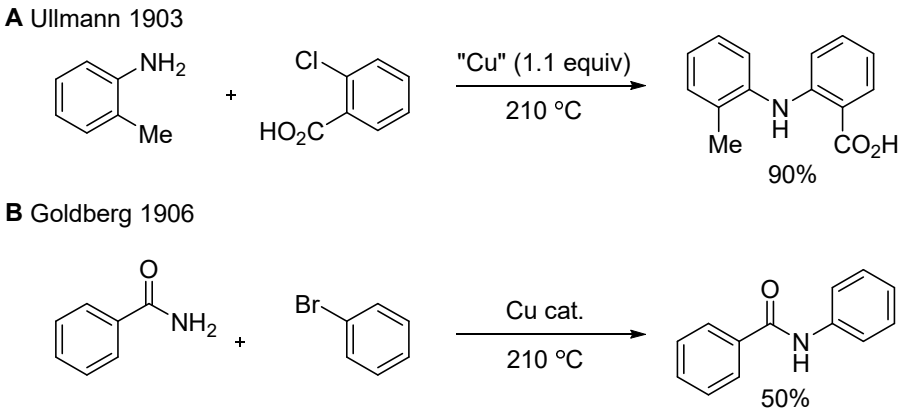
Table 1 *Prevalence of C-N bond forming reactions in the pharmaceutical industry*[5]

However, the construction of C-N bonds, has often proved to be challenging, especially in the synthesis of amines, where traditional methods can pose problems such as poor yields, low selectivity, and harsh reaction conditions.

1.2 Synthesis of Amines

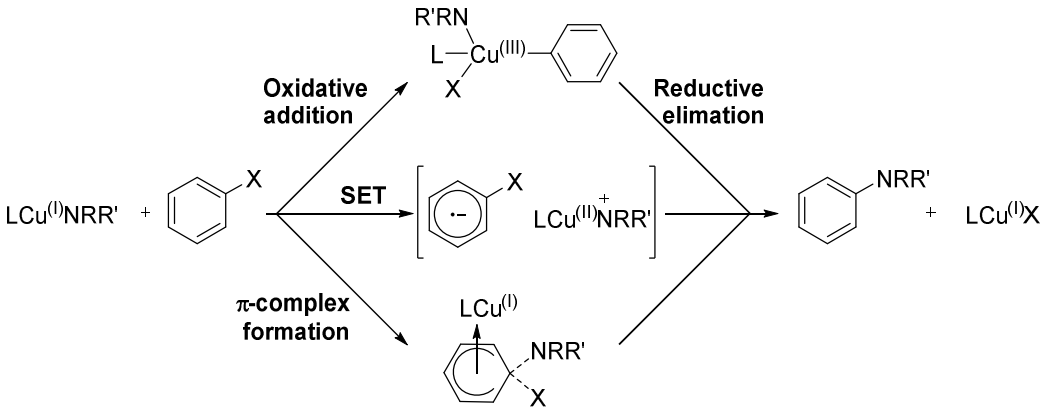
1.2.1 Ullmann Condensation Reaction

A common method for the synthesis of aryl amines is the use of the Ullmann condensation, a copper-mediated nucleophilic aromatic substitution reaction between amines and aryl halides which has been known for over a century (Scheme 10A).[6] Subsequently, a number of related reactions have been disclosed, such as the Goldberg reaction, whereby an amide is coupled with an aryl halide using copper catalysis (Scheme 10B).[7] However, both reactions require harsh conditions to effect the transformation, including temperatures greater than 200 °C, strong bases, stoichiometric amounts of copper or copper salts and long reaction times, resulting in only modest yields of the desired product. These issues have led to a narrow substrate scope and result in limitations in the use of this reaction, especially on a large scale.[8]



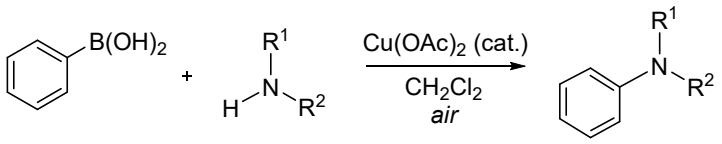
Scheme 10 *Synthesis of aryl amines.* ***A*** *– Ullmann reaction between aryl halides and amines.*[6] ***B*** *– Goldberg reaction between amides and aryl halides*[7]

A number of mechanistic hypotheses have been proposed for the Ullmann condensation reaction (Scheme 11). Various Cu(I) and Cu(II) salts and oxides have been shown to be effective in catalysing the reaction, and a report by Weston and Adkins suggested that virtually any copper compound could be used as a source of catalyst,[9] due to the formation of a common Cu(I) intermediate *in situ*.[10] Coordination of the copper catalyst to the amine nucleophile occurs during the reaction, however the reactivity of the aryl halides is the reverse of what is typically observed for a nucleophilic aromatic substitution, suggesting that the aryl halide must also be activated with the copper catalyst. The nature of this activation has remained unclear, with several suggestions such as oxidative addition-reductive elimination mechanisms, single electron transfer (SET) mechanisms or π-complex formation mechanisms (Scheme 11).[11-12]



Scheme 11 *Mechanistic proposals for the Ullmann reaction which include oxidative addition-reductive elimination, SET and π-complex formation*[11-12]

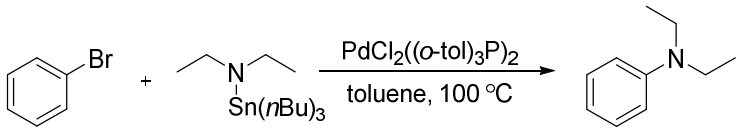
Since Ullman's initial report, there have been a number of improvements disclosed, which allow the reaction to be performed under milder conditions. These include the development of novel ligands,[13-16] as well as ligand free procedures.[17-18] Additionally, in 1998 Chan, Lam and Evans independently published a variation of the Ullmann condensation using boronic acids *in lieu* of aryl halides,[19-21] known as the Chan-Lam coupling reaction (Scheme 12).



Scheme 12 *Chan-Lam coupling reaction between aryl boronic acids and amines*[19-21]

1.2.2 Buchwald-Hartwig Coupling

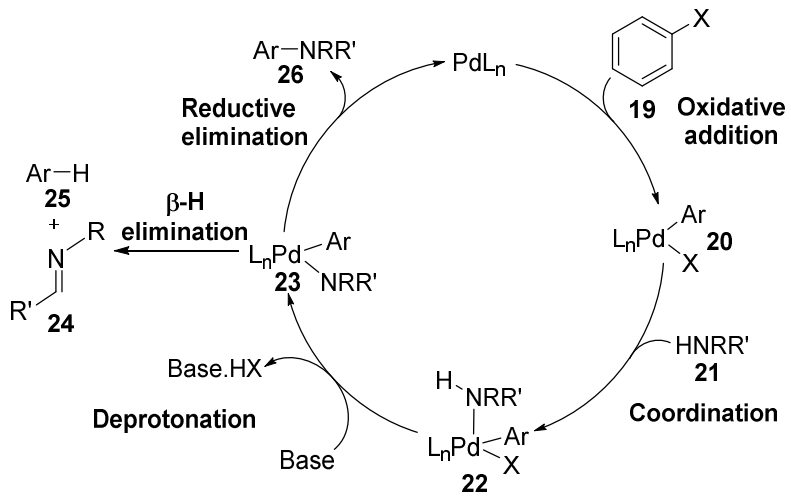
An alternative synthesis of secondary and tertiary aryl amines can be achieved using the Buchwald-Hartwig reaction, whereby an aryl halide and an amine are coupled, this time in the presence of a palladium catalyst. The first use of a palladium catalyst in the formation of C(sp^2)-N bonds was reported by Migita and co-workers in 1983,[22-23] where aminostannanes and aryl bromides were coupled using palladium catalysts containing P(*o*-tol)$_3$ ligands (**27**) (Scheme 13). Despite the novelty of the reaction, the substrate scope was narrow, limited to the use of *N*,*N*-diethylamino-tributyltin (**17**) as the aminostannane.



Scheme 13 *Formation of C(sp^2)-N bonds reported by Migita and co-workers*[22-23]

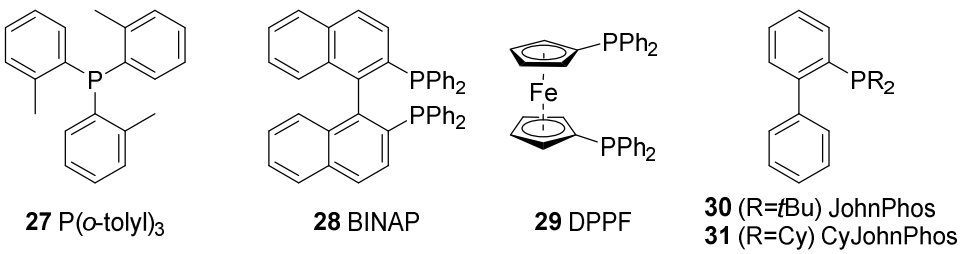
Buchwald and Hartwig independently reported improved protocols for the synthesis of aryl amines by coupling aryl bromides and aminostannanes.[24-25] These were then followed a year later by protocols which directly use amines as coupling partners, thereby avoiding the use of toxic aminostannane reagents, now known as Buchwald-Hartwig coupling.[26-27] The mechanism of the Buchwald-Hartwig coupling has been studied extensively and

investigations show that the steps are similar to those observed for palladium catalysed C-C bond forming reactions (Scheme 14).[28]



Scheme 14 *Proposed mechanistic cycle for the Buchwald-Hartwig coupling reaction*

Initial oxidative addition of the aryl halide (**19**) to the palladium complex gives an aryl palladium species (**20**). This is followed by coordination of the amine (**21**), deprotonation, and finally reductive elimination to give the desired product (**26**). Where the alkylamido group possesses β-hydrogen atoms, an unproductive β elimination can compete with the reductive elimination step, to give the reduced arene (**25**) and an imine (**24**) (Scheme 14). This β-hydride elimination was initially observed when P(*o*-tol)$_3$ ligands **27** were utilised in the reaction, therefore subsequently there has been a focus on developing a range of different ligands that decrease the amount of β-hydride elimination and also increase the generality of the reaction (Figure 6).[29-30]



27 P(*o*-tolyl)$_3$ **28** BINAP **29** DPPF **30** (R=*t*Bu) JohnPhos **31** (R=Cy) CyJohnPhos

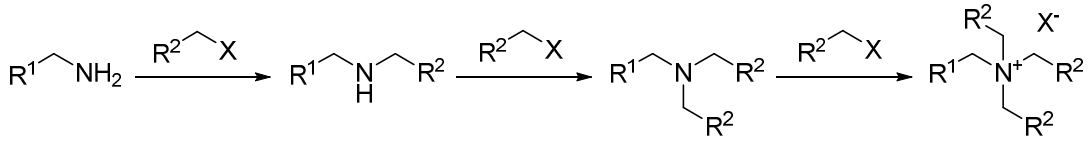
Figure 6 *Ligands developed for use in Buchwald-Hartwig coupling reactions.*

These include aromatic biphosphine ligands such as BINAP **28**[31-32] and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) **29**,[33] which promote reductive elimination of the product, due to the chelating effect of the phosphine ligands to the palladium centre. The

discovery of monophosphine ligands, such as JohnPhos **30** and CyJohnPhos **31**, resulted in a broader reaction scope and milder reaction conditions.[34-35] Additional ligand types have also been discovered which include Josiphos-based bidentate ligands,[36] which allow coupling with heterocyclic aryl halides, and *N*-heterocyclic carbene (NHC) ligands,[37-38] allowing expansion of the substrate scope to include aryl triflates and base sensitive substrates.

1.2.3 *N*-Substitution with Alkyl Halides

One of the most established methods for C-N bond formation is by the alkylation of primary amines using alkyl halides, or equivalents such dialkylsulfates or sulfonates, *via* an S_N2 reaction.[39] Sequential *N*-alkylation reactions can be performed, commonly known as the 'Hoffmann alkylation' (Scheme 15).[40]



Scheme 15 'Hoffmann alkylation' - sequential alkylation reactions with alkyl halides[40]

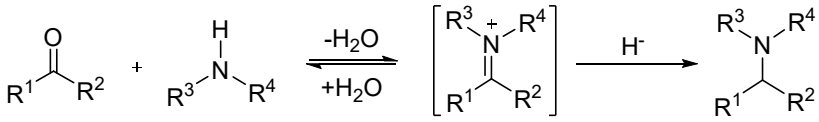
Despite these reactions appearing straightforward, over-alkylations are frequent, resulting in a mixture of primary, secondary, and tertiary amines as well as quaternary ammonium salts (Scheme 15). Therefore, the yield of the reaction is dependent on the starting amine. The yields for these reactions are variable, as well as providing poor atom economy and difficult purifications.[39] Additionally, alkylating agents are mutagenic,[41] which is undesired especially when working on a large scale and alternative, safer methods are preferable.

A common misconception is that over-alkylation in the synthesis of secondary amines can be prevented just by having a large excess of the primary amine present in the reaction mixture. However, the secondary amine generated is typically more nucleophilic than the primary amine[42] resulting in a complex mixture of products.[43] Therefore, adjustment of a range of reaction parameters such as temperature,[44] time[45] as well as stoichiometry[46] is required. An alternative solution was reported by Jung and co-workers, who disclosed a selective mono-

N-alkylation reaction using a cesium base additive.[47] In the presence of activated 4Å molecular sieves, the cesium base not only promotes mono-*N*-alkylations, but also suppresses overalkylations, favouring the formation of secondary amines.

1.2.4 Reductive Amination

One of the most widely used and traditional methods for the synthesis of amines is using reductive amination, due to the operational ease and wide variety of available protocols. The reaction occurs between either an aldehyde or ketone with a primary or secondary amine to give secondary and tertiary amine products (Scheme 16).



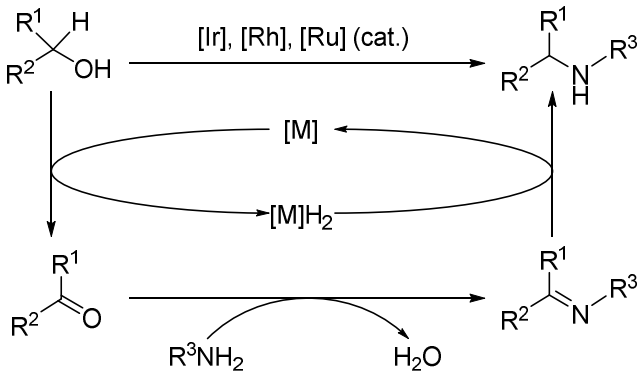
Scheme 16 *Reductive amination reaction between an aldehyde or ketone and an amine*

Nucleophilic attack of the aldehyde or ketone by the amine gives a hemiaminal, which is then dehydrated to give the corresponding imine. The imine is subsequently reduced to the desired amine, typically using a borohydride reducing agent (Section 2.1.2).[48] The choice of reducing agent is important to provide selective reduction of the imine, without unwanted reduction of the aldehyde or ketone. Milder reducing agents such as sodium cyanoborohydride[49] and sodium triacetoxyborohydride[50] provide a more selective reduction. Alternative reagents for reductive amination reactions include borane-pyridine;[51] borohydride exchange-resin; zinc and acetic acid;[52] zinc borohydride and zinc chloride;[53] sodium cyanoborohydride and titanium isopropoxide;[54] sodium borohydride and magnesium chlorate;[55] and sodium cyanoborohydride and zinc chloride.[56]

1.2.5 "Borrowing Hydrogen" Chemistry

Alcohols are commonly used as starting materials for reactions, due to their abundance and variety. However, they are quite unreactive and often require activation *via* protonation or functional group interconversion to halides or sulfonates before they can participate in a

reaction.[57] An alternative approach was independently reported by both Grigg and Watanabe in the 1980s,[58-59] whereby an Ir, Rh or Ru catalyst was used to 'borrow' hydrogen from the alcohol starting material, which is then returned to produce the desired product, termed 'borrowing hydrogen' (Scheme 17).



Scheme 17 *Borrowing hydrogen reaction for C-N bond formation*

The reaction mechanism consists of three steps, an initial oxidation of the alcohol to the carbonyl compound, typically using a transition metal catalyst. This is followed by reaction with the amine to form the corresponding imine, which is then reduced to the desired amine using the transition metal catalyst (Scheme 17). The reaction is redox neutral and is extremely atom efficient, with only water produced as a by-product.

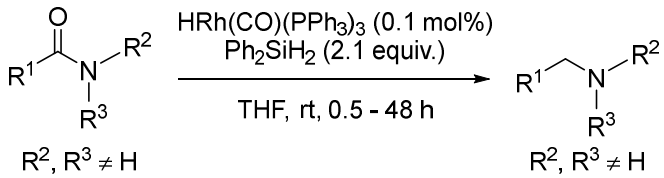
Despite the novelty of the initially reported methods, they were limited by the requirement for high temperatures, often combined with high catalyst loadings and low yields.[57, 60] Subsequent interest in this area has led to the development of more active catalysts.[61-62] Williams and co-workers have disclosed a ruthenium-catalysed reaction that can be performed under milder conditions[63] and Li and Andersson reported that use of a bidentate iridium NHC-phosphine complex allows solvent-free reactions to be performed at room temperature.[64] Additionally, Dong and co-workers have reported an enantioselective borrowing hydrogen method that utilises a Ru-pincer complex in combination with Ellman's sulfinamide chiral auxiliary.[65]

1.2.6 Reduction of Amides

The synthesis of amines *via* amide reduction is an attractive option due to the vast array of amide coupling reagents and methods for amide synthesis. However, delocalization of the nitrogen lone pair into the C-O π* renders the amide carbonyl less susceptible to nucleophilic attack than other carbonyl containing functionalities such as aldehydes, ketones, esters and carboxylic acids.[66] However, the Lewis basic character of amides, due to nitrogen lone pair resonance, allows them to be activated by Lewis acids, and a number of methods have been developed for their reduction.

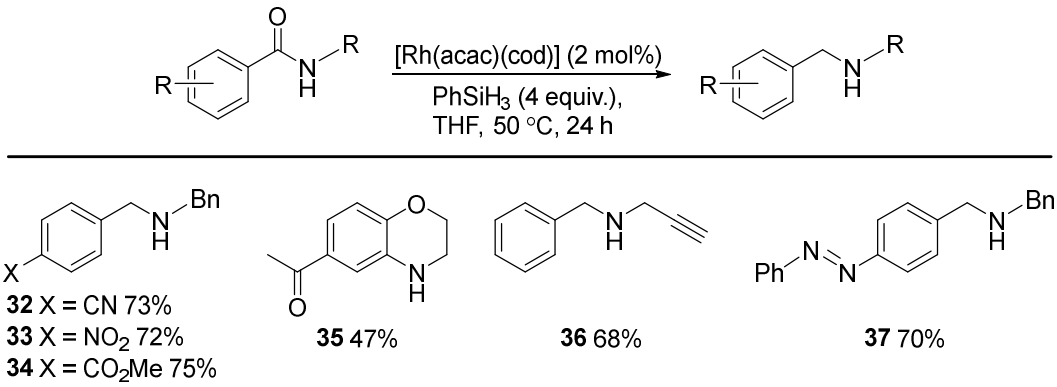
Traditionally, amide reduction has been achieved through the use of main group stoichiometric metal hydrides, such as LAH or DIBAL (Introduction Section 2.1.1). However, the ACS Green Chemistry Institute® Pharmaceutical Roundtable (GCIPR) identified "amide reductions avoiding $LiAlH_4$ and diborane" as a key green chemistry research area in 2018.[67] The use of hydrosilanes in combination with transition metal catalysts has been widely reported to be an effective method for the reduction of amides and has gained significant attention in recent years.

Corriu and co-workers reported the first hydrosilylation of amides in 1982 using Wilkinson's catalyst,[68] however the reaction was limited to only a single example. It was not until 1998 that Ito and co-workers reported the reduction of tertiary amides with low catalyst loadings of $HRh(CO)(PPh_3)_3$ in combination with diphenylsilane at room temperature.[69] The reaction is tolerant of functional groups such as esters and epoxides, which are traditionally incompatible with standard metal hydride alternative.



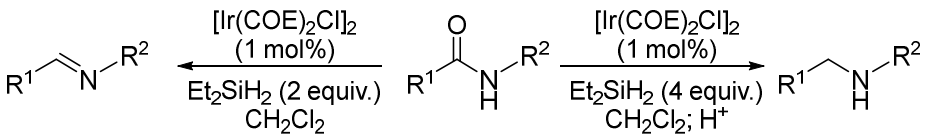
Scheme 18 *Reduction of tertiary amides using $HRh(CO)(PPh_3)_3$ in combination with diphenylsilane reported by Ito and co-workers[69]*

The scope of rhodium catalysed hydrosilylation reactions has subsequently been extended by Beller and co-workers, who report a chemoselective reduction of secondary and tertiary amides using [Rh(acac)(cod)] and phenylsilane (Scheme 19).[70] A range of potentially reducible functional groups are tolerated in this reaction, with amide substrates containing esters (**34**), ketones (**35**), alkynes (**36**), nitriles (**32**), nitro (**33**) and azo groups (**37**) chemoselectively reduced in good yield.



Scheme 19 *Chemoselective reduction of secondary and tertiary amides reported by Beller and co-workers[70]*

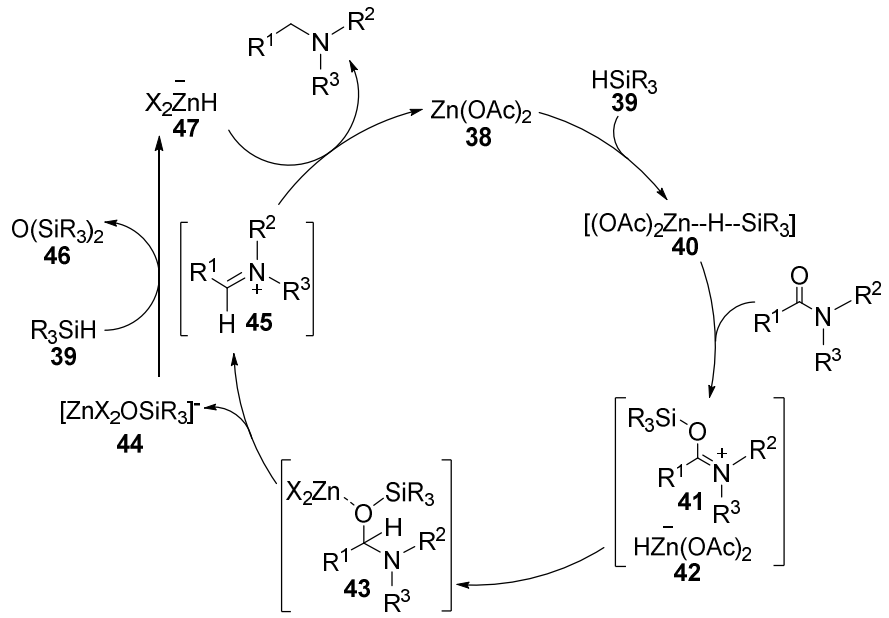
Iridium is another metal which has been commonly used as an efficient catalyst for the reduction of amides. In 2012 Brookhart and co-workers reported an iridium-catalysed reduction of secondary amides using $[Ir(COE)_2Cl_2]$ in combination with diethylsilane, tolerant of substrates bearing reducible groups such as alkenes, nitriles, azo and nitro groups.[71] Using this method, imines can be obtained by using two equivalents of diethylsilane, whereas if four equivalents are used then reduction to the corresponding secondary amine is achieved (Scheme 20).



Scheme 20 *Ir-catalysed reduction of secondary amides to give either imines or secondary amines depending on the amount of diethylsilane employed[71]*

It is proposed that the active catalyst species in the reaction is a silylene-bridged iridium dimer, formed from reaction of $[Ir(COE)_2Cl]_2$ with diethylsilane, which can perform selective hydrosilylations across carbonyl and imine bonds.

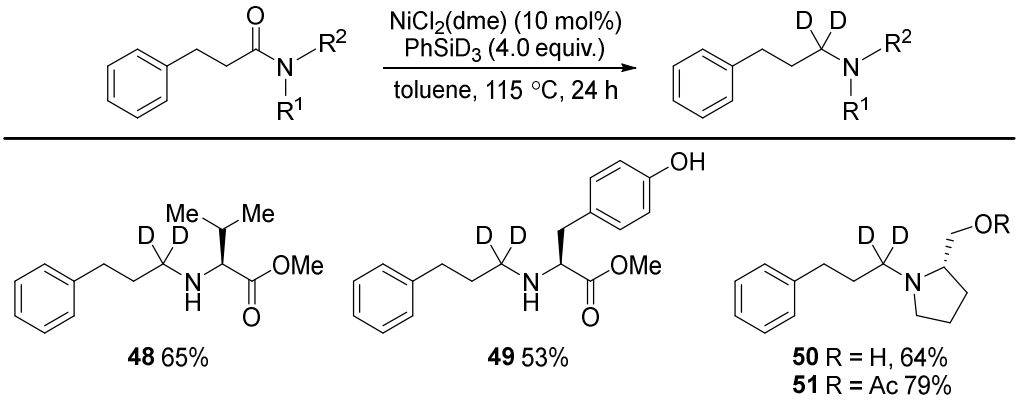
Although metals such as rhodium and iridium are commonly utilised in hydrosilylation reactions, many other non-precious metals are also active in these reactions. Beller and co-workers reported a chemoselective reduction of tertiary amides using a combination of zinc acetate and triethoxysilane.[72] Notably, amide reduction was shown to be effective even in the presence of a ketone group, which is known to be much more active, and preliminary mechanistic investigations have led to the proposal of a catalytic cycle (Scheme 21).



Scheme 21 *Proposed catalytic cycle for zinc acetate and phenylsilane mediated amide reduction*[72]

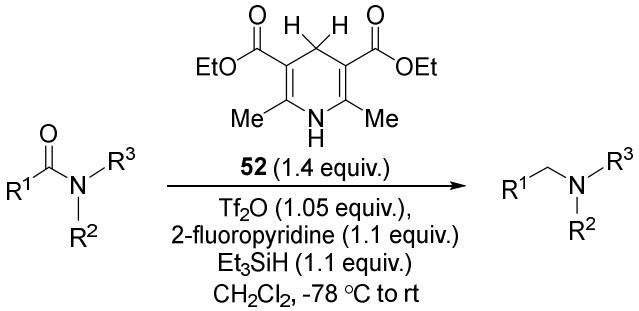
Similar to the mechanism proposed by Brookhart and co-workers, the proposed cycle shown in Scheme 21 commences with reaction of the silane (**39**) and zinc acetate (**38**), to give a zinc hydride species (**42**) and a silylium cation which activates the amide carbonyl. Reduction is then effected by the zinc hydride (**42**) to give a tetrahedral intermediate (**43**) which is then further reduced to the desired amine by another equivalent of zinc hydride.[72]

Garg and co-workers also reported a reduction of secondary and tertiary amides using $NiCl_2$(dme) and phenylsilane.[73] They also showed reduction of optically enriched amino acid derivatives using $PhSiD_3$ to give the corresponding α-deuteroamines, which have been shown to be more metabolically stable than their non-deuterated counterparts (Scheme 22).[74-75]



Scheme 22 *Reduction of optically enriched amino acid derivatives to give the corresponding α-deuteroamines*[73]

The reduction of tertiary amides has also been reported using Fe,[76] Pt,[77-78] Au,[79] Zn,[80] In,[81] Ti,[82] Os[83] and Ru[84] catalysts. Additionally, reduction of secondary and tertiary amides has also been shown using Ti,[85] Cu,[86] Ir,[71] Ni,[73] Mo,[87] Rh,[88] Ru[89-90] and Zn[91] catalysts. Metal-free reductions of amides have also been shown to be possible by employing the use of phosphonium cations[92] or boron organocatalysts[93] such as tris(pentafluorophenyl)borane ($B(C_6F_5)_3$),[94-96] boronic acids,[97-98] and triphenylborane.[99] Additionally, Charette and co-workers reported a reduction of secondary amides using triethylsilane and Hantzsch Ester Hydride (HEH) (**52**) in the presence of triflic anhydride and 2-flurorpyridine (Scheme 23).[100]

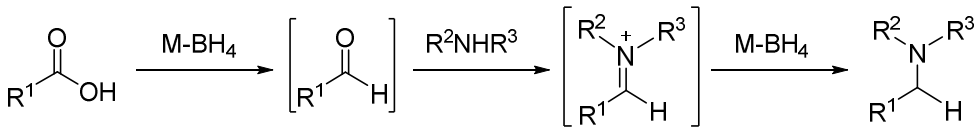


Scheme 23 *Reduction of amides using HEH **52** and triflic anhydride reported by Charette and co-workers*[100]

The reaction proceeds *via* the corresponding imine and has excellent functional group tolerance. However, the reaction requires the use of several stoichiometric reagents, making the atom economy very low.

1.2.7 Reductive Amination Reactions with Carboxylic Acids

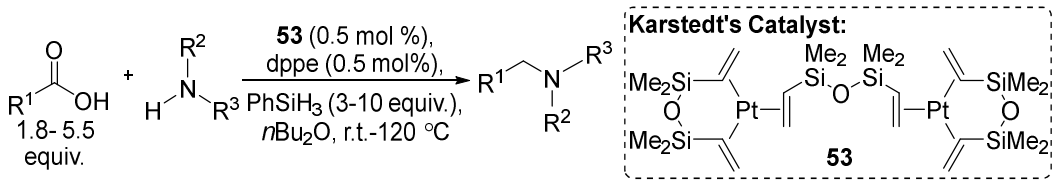
A much less explored, but powerful alternative to traditional amination reactions is to use carboxylic acids as nominal electrophiles. Despite carboxylic acids being less reactive than their lower oxidation state counterparts, they are easy to handle in the laboratory, more readily available and have no associated safety or stability issues.[101-103] The first reported use of carboxylic acids in reductive alkylation reactions was in the 1970s,[104-106] where aldehydes were generated *in situ* from carboxylic acids using stoichiometric metal borohydride reagents. The aldehyde then reacts with the amine starting material to form an imine, which is then reduced using the metal borohydride to the desired amine (Scheme 24).



Scheme 24 *Reductive alkylation reactions using carboxylic acids and stoichiometric quantities of sodium borohydride*[104-106]

Despite the novelty of these reactions, they show limited substrate scope and tolerance to a range of different functional groups and a liquid carboxylic acid must be used as the reaction solvent or require multiple equivalents of the carboxylic acid (up to 6 equiv.), in addition to the necessity for super-stoichiometric quantities of the metal borohydride.

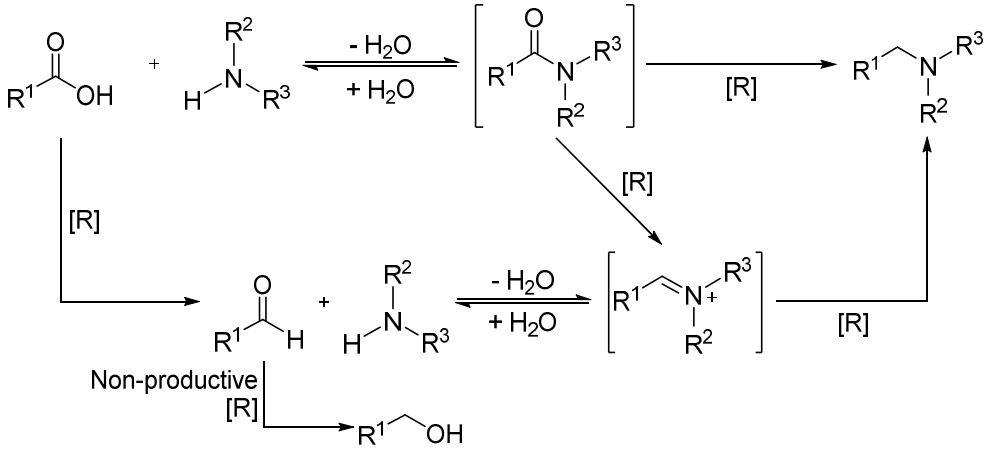
Beller and co-workers described the first preparative catalytic *N*-alkylation of both primary and secondary amines using a carboxylic acid starting material in 2014 (Scheme 25).[107] Inspiration was taken from the reported platinum-catalysed hydrosilylation reactions[108-109] and it was hypothesised that these catalysts could also be active in alkylations using carboxylic acid starting materials.



Scheme 25 *N-Alkylation from carboxylic acids using Karstedt's catalyst* ***53*** *in combination with phenylsilane, developed by Beller and co-workers*[107]

Beller and co-workers demonstrated that use of the commercially available Karstedt's catalyst **53**, in combination with phenylsilane could successfully produce the desired amine product. Additionally, if 1,2-bis(diphenylphosphino) ethane (dppe) was employed in the reaction to act as a ligand, the selectivity for the mono-alkylated product was significantly improved.[107]

Two complementary mechanisms have been proposed for this reaction (Scheme 26).[107] The first is that the carboxylic acid and amine react in the presence of phenylsilane to form an amide, which is then reduced using Karstedt's catalyst (**53**) to give either the corresponding imine or amine product. The imine could then be further reduced to give the desired amine.



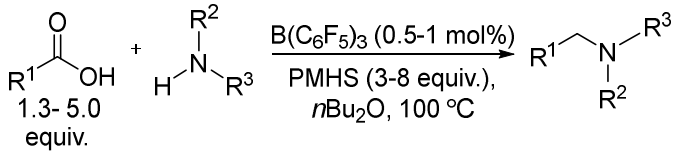
Scheme 26 *Proposed mechanism for the reductive alkylation using carboxylic acids, reported by Beller and co-workers*[107]

The second proposed mechanism is that an aldehyde is generated *in situ* from reduction of the carboxylic acid. The aldehyde can participate in a condensation reaction to give an imine which can be reduced to the amine product or can be further reduced to the corresponding alcohol in a non-productive reduction process. As both the corresponding amide and alcohol products have been observed as side products, both mechanistic pathways are likely to be operative.

Despite the reaction being the first catalytic example of a preparative alkylation utilising carboxylic acids as starting materials, the reaction requires high excesses of both phenylsilane (up to 10 equiv.) and the carboxylic acid starting material (up to 5.5 equiv.) to

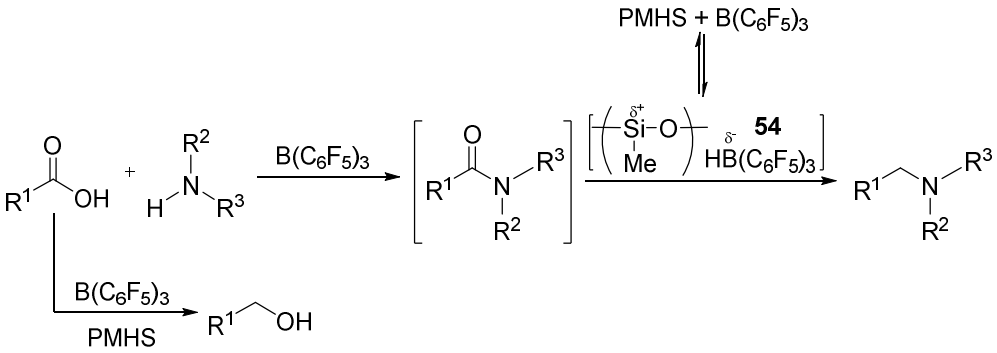
mitigate against the non-productive over-reduction of the carboxylic acid to the corresponding alcohol. The reactions were performed under an inert atmosphere using Schlenk apparatus, which is undesirable especially when performing on a large scale.

It has also been shown that boron catalysts are effective in mediating amidation reactions[110-112] as well as amide reduction reactions.[96, 98-99] Using this knowledge, Fu and co-workers have described a reductive alkylation of amines with a $B(C_6H_5)_3$ catalyst in combination with polymethylhydrosiloxane (PMHS) as the terminal reductant (Scheme 27).[113]



Scheme 27 *Metal-free N-alkylation of carboxylic acids reported by Fu and co-workers[113]*

The proposed mechanism for the reaction proceeds *via* the corresponding amide intermediate. The catalyst can form frustrated Lewis pairs (FLP) (**54**) with the silane which are able to reduce amide carbonyl bonds in preference to the reduction of the carboxylic acid starting material. However this selectivity is poor, as high excesses of both the carboxylic acid (up to 5 equiv.) and PMHS (up to 8 equiv.) are required for the reaction, indicating that a large amount is consumed by the reduction of the carboxylic acid starting material.[113]

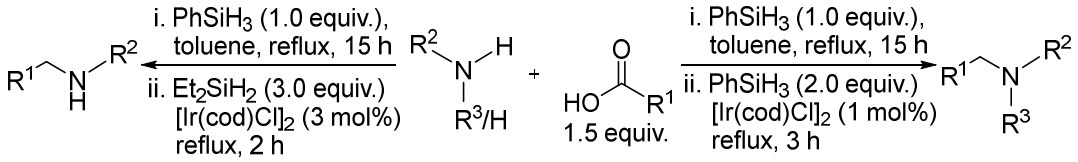


Scheme 28 *Mechanism of metal-free N-alkylation of carboxylic acids via FLP catalysis[113]*

Similar reactions have also been disclosed by Kobayashi and co-workers, who reported a reductive alkylation of anilines and carboxylic acids using a rhodium-NHC catalyst and phenylsilane.[114] Minakawa *et al.* also reported a reaction between anilines or secondary alkyl amines and carboxylic acids using a $[RuCl_2(p\text{-cymene})]_2$ catalyst in combination with a

tris(pentafluorophenyl)-phosphine ligand and methyldiphenylsilane as the terminal reductant.[115] Additionally, methylation reactions have also been disclosed which utilise formic acid as a C_1 source, which can be readily prepared from carbon dioxide by catalytic hydrogenation.[116-117] Zhu and co-workers disclosed a methylation of anilines using a Pt/C catalyst and phenylsilane[118] and He and co-workers reported a methylation of amines using a copper acetate catalyst in combination with phenylsilane.[119]

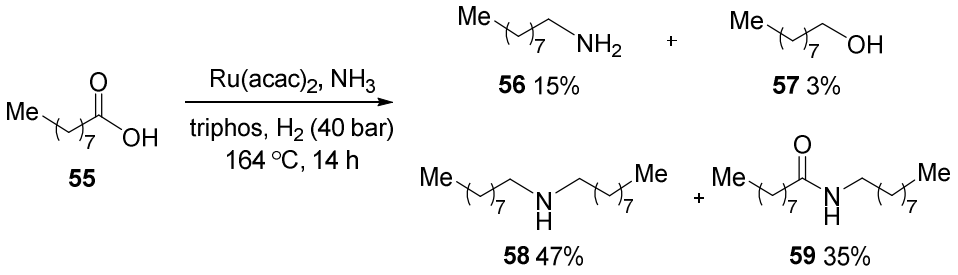
Previous work in the Denton group disclosed a reductive amination reaction using carboxylic acids via an amide intermediate. The reaction employs an $[Ir(cod)Cl]_2$ catalyst in combination with phenylsilane for synthesis of tertiary amines, and both phenylsilane and diethylsilane in the synthesis of secondary amines (Scheme 29).[120]



Scheme 29 *Reductive amination from carboxylic acids reported by Denton and co-workers for the synthesis of secondary and tertiary amines*[120]

The reaction is a one-pot, two-step process, comprising an initial phenylsilane-mediated amidation reaction (Section 1.3), followed by a reduction of the resultant amide intermediate. This is mechanistically different to other reported reductive alkylation reactions using carboxylic acids, as it eliminates the potential for unwanted reduction of the carboxylic acid starting material, resulting in the need for less carboxylic acid and silane in the reaction mixture.

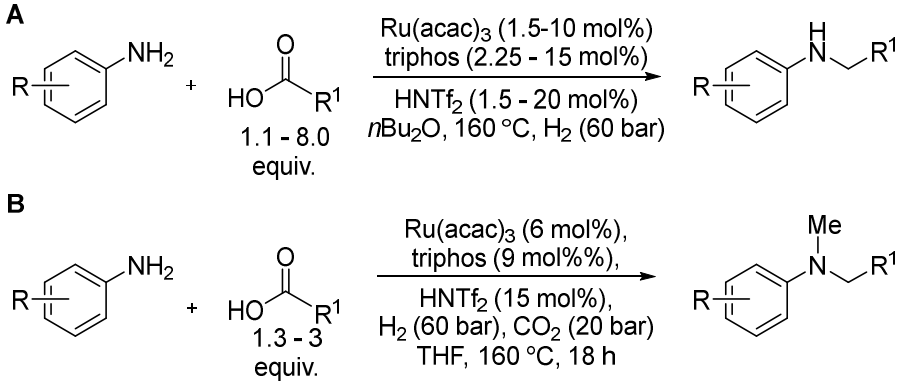
There have also been several examples of amination reactions using carboxylic acids and molecular hydrogen as the terminal reductant. From a green chemistry perspective, molecular hydrogen is a desirable reducing agent to use when compared to expensive silanes. Cole-Hamilton and co-workers reported a hydrogenation reaction of nonanoic acid (**55**) with a ruthenium catalyst under an atmosphere of ammonia, however it had both low yield and selectivity for the desired product.[121]



Scheme 30 *Hydrogenation reaction of nonanoic acid reported by Cole-Hamilton and co-workers*[121]

The reaction with liquid ammonia produces multiple products including the primary amine (**56**) (15%), secondary amine (**58**) (47%), alcohol (**57**) (3%) and secondary amide (**59**) (35%). To increase the selectivity for the primary amine (**56**), aqueous ammonia can also be used in the reaction which leads to an increase in yield to 41%.[121] However, the reaction must be performed in an autoclave at high temperature and pressure, making it highly impractical for most synthetic chemists.

More recently, Beller and co-workers described a Ru-catalysed *N*-alkylation of anilines and carboxylic acids that utilise molecular hydrogen as a reducing agent (Scheme 31A).[122] It was found that the use of ruthenium acetylacetonate (acac) in combination with a triphos ligand forms a ruthenium/triphos based catalyst *in situ*. A variety of both Lewis and Brønsted acids were also tested as co-catalysts, and it was shown that aluminium triflate and lithium triflimide produced the largest increase in selectivity for the mono-alkylated amine.



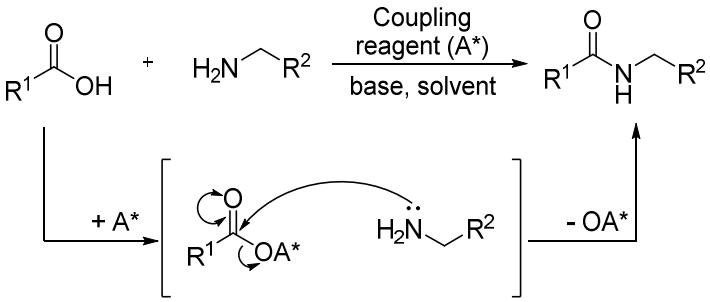
Scheme 31 *N-alkylation using molecular hydrogen as a reductant reported by Beller and co-workers* ***A*** *– Two component coupling between an aniline and a carboxylic acid.*[122] ***B*** *– Three component coupling between an aniline, a carboxylic acid and carbon dioxide*[122]

Beller and co-workers built on this initial report to develop a three-component coupling reaction between an aniline, a carboxylic acid and carbon dioxide (Scheme 31B). [122] The one-pot reaction makes use of carbon dioxide as renewable C_1 building block, to produce unsymmetrical amines. Previous methods required the use of protecting groups, making this reaction even more desirable from a green chemistry perspective.

Despite the use of molecular hydrogen in both of these reactions, high excesses of carboxylic acid (up to 8 equiv.) and high catalyst loadings (between 1.5 – 20 mol%) are required for the reaction. Attempts were made to lower the reaction temperature from 160 °C and also decrease the pressures of hydrogen and carbon dioxide, however these attempts resulted in a marked decrease in the yield of the desired product.

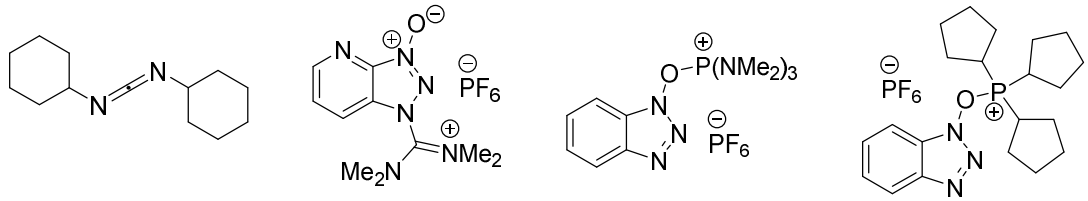
1.3 Silane Mediated Amide Couplings

Amides are one of the most popular and widely used groups in organic synthesis, since they possess many desirable properties such as high stability, polarity, and conformational diversity.[1] Direct reactions between amines and carboxylic acids are very atom efficient, producing only water as a by-product. However, these reactions must be performed at high temperatures of over 200 °C to overcome the thermodynamic barrier of carboxylate-ammonium salt formation.[123] Therefore, a range of stochiometric reagents and coupling agents have been developed, which are able to activate the carboxylic acid and allow the reaction to occur under milder conditions (Scheme 32).[123]



Scheme 32 *Amide bond formation utilising coupling agents to activate the carboxylic acid*[123]

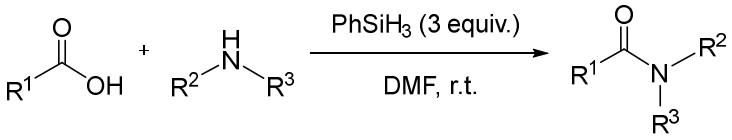
This activation is normally achieved by substituting the -OH group of the carboxylic acid to produce a more reactive species, for example acid chlorides, anhydrides or activated esters, which then react with the amine to produce the desired amide. Commonly utilised coupling agents include carbodiimides such as dicyclohexylcarbodiimide (DCC) (**60**); aminium salts such as salt 1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) (**61**); and phosphonium salts such as (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (**62**) and (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) (**63**) (Figure 7).



60 DCC **61** HATU **62** BOP **63** PyBOP

Figure 7 *A range of commonly used, commercially available amide coupling reagents*

There has been a rise in the development of silicon-based reagents as an alternative to traditional coupling reagents. Chan and Wong disclosed the use of silicon tetrachloride as an amide coupling reagent in 1969,[124-125] however there have only been two reports which utilise hydrosilanes as amide coupling reagents.[126-127] In 2006, Ruan and co-workers described the use of phenylsilane for the synthesis of amides (Scheme 33).[126]

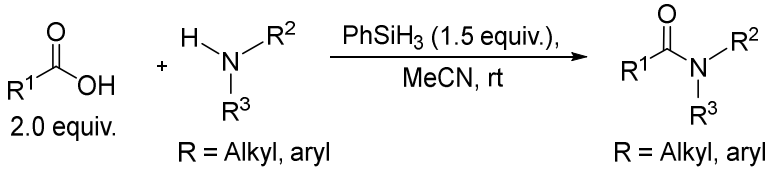


Scheme 33 *Phenylsilane mediated amidation reaction reported by Ruan and co-workers[126]*

A range of amides were successfully obtained using these conditions, however no product was observed when using sterically hindered substrates or anilines. Additionally, the reaction requires the use of three equivalents of phenylsilane, as well as being performed in dimethylformamide (DMF). Solid phase peptide synthesis was also attempted, however the

reaction conditions used 10 equivalents of the amine substrate and 20 equivalents of phenylsilane.[126]

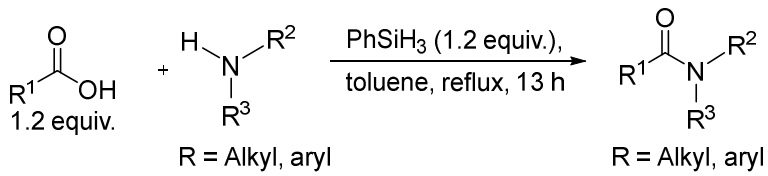
The utility of this work was extended by Blanchet and co-workers, who reported a phenylsilane-mediated amidation in either acetonitrile or dichloromethane at ambient temperature (Scheme 34).[128] The amount of phenylsilane utilised in the reaction was decreased to 1.5 equivalents, however two equivalents of carboxylic acid were required.



Scheme 34 *Phenylsilane-mediated amidation reported by Blanchet and co-workers*[128]

The scope of the reaction was also expanded to include anilines and dipeptides. In addition, Weinreb amide formation is possible when one equivalent of triethylamine and magnesium sulfate are added to the reaction mixture.

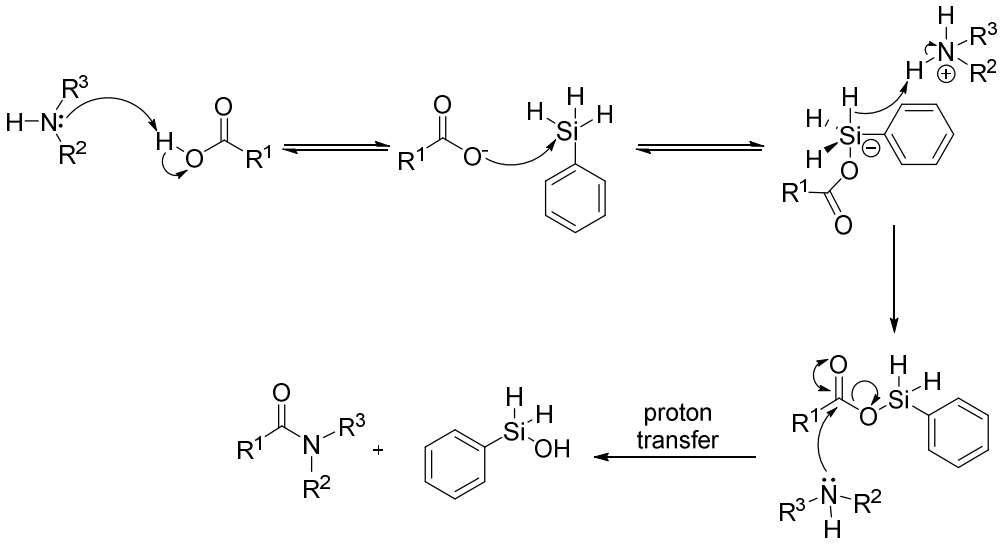
Unpublished work performed by Andrews and Denton also focussed on adaptation and optimisation of the phenylsilane-mediated amidation published by Ruan (Scheme 35),[129] so it could be performed in toluene and therefore utilised in reductive amination procedures (Section 1.2.7).[120] The amount of phenylsilane required in the reaction was able to be decreased to 1.2 equivalents, with 1.2 equivalents of carboxylic acid required.



Scheme 35 *Optimised phenylsilane-mediated amidation for reductive amination reactions*[129]

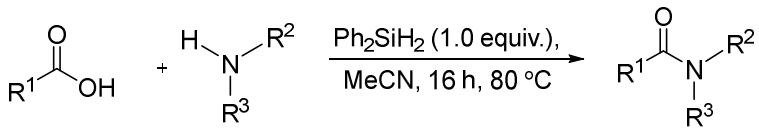
Andrews and Denton also performed qualitative and quantitative mechanistic studies and proposed a reaction mechanism (Scheme 36), as one had not been suggested previously.[129] It is hypothesised that the carboxylic acid is initially deprotonated by the amine to give a carboxylate which can then undergo a dehydrogenative coupling with phenylsilane, to form

a silyl ester. Silyl esters act as both activated carboxylic acids and as enhanced reductants when compared to the parent silane (Introduction Section 1.3.2). Therefore, the amine can then attack the silyl ester to produce an amide and a silanol by-product (Scheme 36). For the sake of simplicity, it has been assumed that phenylsilane only reacts once, however the speciation is more complex, due to the tri-hydridic nature of phenylsilane.



Scheme 36 *Proposed mechanism for the phenylsilane mediated amidation reaction*

Another reported use of hydrosilanes as amide coupling reagents was disclosed by Sayes and Charette, who discovered that diphenylsilane was able to mediate amide coupling of a range of commercially available carboxylic acids and amines (Scheme 37).[127]



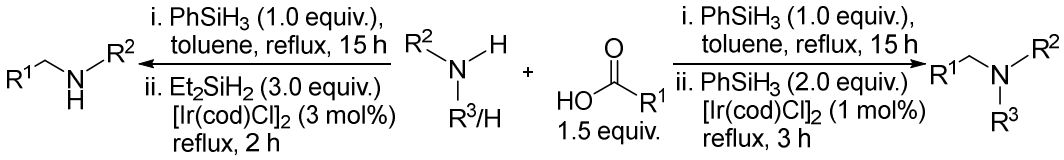
Scheme 37 *Diphenylsilane-mediated amidation reported by Sayes and Charette*[127]

Additionally, a range of dipeptides was synthesised by diphenylsilane-mediated couplings, however considerable epimerisation was observed in some cases. It was also found that whilst Boc and Cbz protecting groups were tolerated, the Fmoc protecting group, traditionally utilised in solid-phase peptide synthesis, was cleaved under the reaction conditions.[127]

2 Results and Discussion

2.1 Project Aims

The aim of this project was to develop a more practical and general reductive amination reaction of carboxylic acids, in order to improve upon a method previously published by the Denton group.[120] Separation of the amidation phase of the reaction from the resultant reduction of the amide intermediate has been shown to prevent undesired reduction of the carboxylic acid starting material.



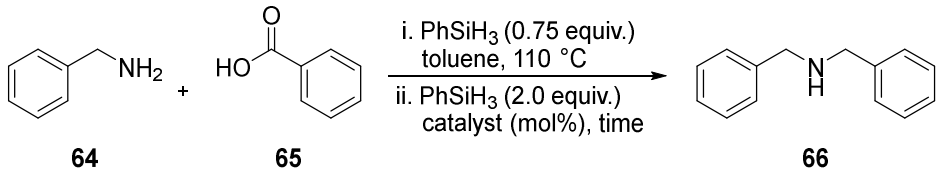
Scheme 38 *Reductive amination from carboxylic acids reported by Denton and co-workers for the synthesis of secondary and tertiary amines.*[120]

However, iridium is one of the rarest elements in the periodic table, produced on only a three-tonne scale annually,[130] and the use of an alternative catalyst which is more environmentally and economically sustainable than $[Ir(COD)Cl]_2$ is highly desirable. Additionally, the development of a set of general conditions for both secondary and tertiary amide reductions using only one silane is highly desirable, as the previously published method required the use of two different silanes for the synthesis of secondary amines, as well as an increased loading of $[Ir(COD)Cl]_2$.[120]

2.2 Reaction Optimisation

After a review of the literature, a number of silane-mediated amide reductions were identified that would be suitable for incorporation into a reductive amination procedure.[69, 72, 76, 87] An initial exploration of the catalysts used in these reactions was performed by Dr Tom Tongue to ascertain the reactivity of these catalysts, in combination with phenylsilane as the terminal reductant, in a reductive amination reaction with carboxylic acids (Table 2). Benzylamine (**64**) and benzoic acid (**65**) were selected as model substrates for the reaction,

producing *N*-benzylbenzamide as an intermediate. This was then reduced *in situ* and gave the desired product dibenzylamine (**66**).



64 **65** **66**

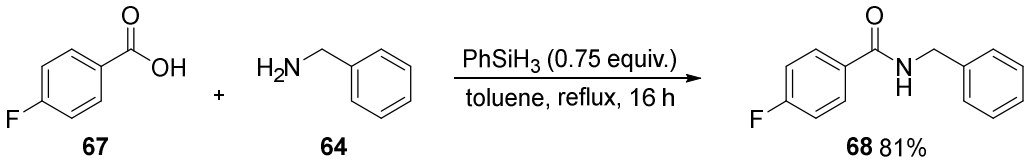
Table 2 *Identification of an alternative catalyst for the reductive amination reaction. a – ^{1}H NMR yield measured using 1,1,2,2-tetrachloroethane as an internal standard.*

Entry	Catalyst	Loading /mol%	Time / h	Yield / %	Cost / mmol[131]
1	$[Ir(COD)Cl]_2$	1	4	67	£88.52
2	$[Ir(COD)Cl]_2$	0.5	16	30	£88.52
3	$Rh(PPh_3)_3Cl$	5	4	60	£61.88
4	MoO_2Cl_2	10	16	18	£7.07
5	$Fe_3(CO)_{12}$	10	16	23	£4.42
6	$Zn(OAc)_2$	10	16	33	£0.55
7	$Zn(OAc)_2$	10	46	94[a]	£0.55

A reaction using $[Ir(COD)Cl]_2$ was initially performed as a control reaction so that any new catalysts could be compared to the previously published method.[120] When 1 mol% loading of $[Ir(COD)Cl]_2$ (Table 2, entry 1) was used, efficient conversion to the desired amine was observed, as previously published. However, when the catalyst loading was lowered to 0.5 mol% (Table 2, entry 2), this resulted in limited conversion to the desired amine (**66**) even after extended reaction time. Wilkinson's catalyst (Table 2, entry 3) was successful affording the amine in good yield,[69] however whilst this catalyst is cheaper per mmol than $[Ir(cod)Cl]_2$, a higher loading is required to effect the reduction. Molybdenum[87] and iron[76] catalysts (Table 2, entries 4 and 5) proved largely ineffective, however pleasingly zinc acetate[72] (Table 2, entry 6) was shown to be active in the reduction. A final reaction using the zinc acetate catalyst was performed where the reaction time was extended to 46 hours (Table 2, entry 7), resulting in a significantly improved yield of the desired product **66** of 94% by ^{1}H NMR analysis. Despite

a longer reaction time, zinc acetate is significantly cheaper than the other active catalysts that were trialled,[131] and so was selected for further reaction optimisation.

The optimisation initially focussed on the reduction step of the proposed reductive amination reaction in isolation, commencing with the more difficult reduction of secondary amides (Table 3). *N*-benzyl-4-fluorobenzamide (**68**) was selected as a model secondary amide for the optimisation reactions and synthesised in good yield using a phenylsilane mediated amidation between 4-fluorobenzoic acid **67** and benzylamine **64**.



Scheme 39 *Synthesis of N-benzyl-4-fluorobenzamide **68** from 4-fluorobenzoic acid **67** and benzylamine **64***

An initial experiment with 1 equivalent of phenylsilane and 10 mol% of zinc acetate (Table 3, entry 1) gave a very poor conversion of 1% which was increased to a maximum of 22% as the amount of phenylsilane was increased (Table 3, entries 2-3). The remainder of the mass balance in these reactions was the unreacted amide starting material, and so the reaction time was increased to 24 hours in an attempt to increase the conversion (Table 3, entry 4).

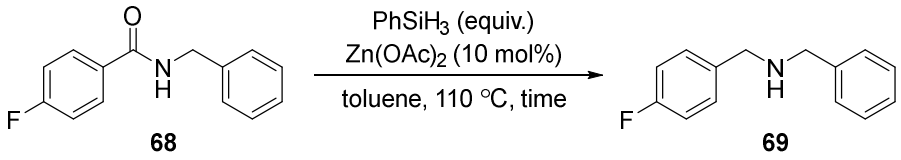


Table 3 *Optimisation of a zinc acetate-catalysed amide reduction reaction. a – Yields measured by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard*

Entry	$PhSiH_3$ / equiv.	$Zn(OAc)_2$ / mol%	Time / h	Yield[a] / %
1	1	10	6	1
2	2	10	6	20
3	3	10	6	22
4	2	10	24	27
5	3	0	6	0

However, this resulted in only a very modest improvement in the yield and gave 27% of the amine product (**69**). Additionally, a control reaction without any zinc acetate was performed (Table 3, entry 5), which showed that the catalyst is essential for the reduction to occur. These initial results were in agreement with the observations of Beller and co-workers, who reported that the combination of zinc acetate and triethoxysilane was poor for the reduction of secondary amides.[72] Additionally, Beller had also shown that zinc triflate in combination with phenylsilane gave similar results.[91]

It had previously been observed that Brønsted acids react rapidly with phenylsilane to generate modified silanes with enhanced reducing properties.[132] It was hypothesised that the addition of a carboxylic acid to the amide reduction reaction could result in the generation of silyl esters. When compared to phenylsilane, silyl esters are stronger reductants and could potentially reduce secondary amides more effectively and therefore increase the yield of the desired product.

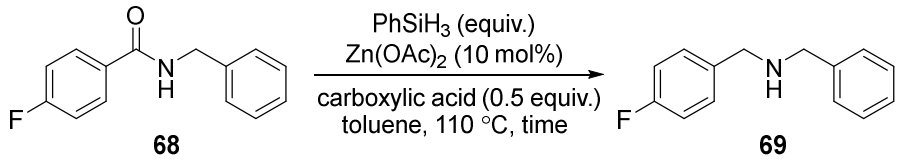


Table 4 *Carboxylic acid-enhanced zinc acetate-catalysed reduction of secondary amides to secondary amines. a – Yields measured by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard*

Entry	$PhSiH_3$ / equiv.	$Zn(OAc)_2$ / mol%	Carboxylic Acid	Time / h	Yield[a] / %
1	3	10	-	6	22
2	3	10	$C_6H_5CO_2H$ (**65**)	6	65
3	3	10	*p*-F-$C_6H_4CO_2H$ (**67**)	6	60

Gratifyingly, the addition of 0.5 equivalents of benzoic acid (**65**) to the amide reduction reaction (Table 4, entry 2) resulted in a substantial improvement in the yield from 22% to 65% of the desired product (**69**). Perhaps more significantly, it was also shown that the carboxylic acid could be changed to match that from which the secondary amide was derived (Table 4, entry 3), in this case employing 4-fluorobenzoic acid (**67**). This result implies that a

0.5 equivalent excess of carboxylic acid at the beginning of the reductive amination procedure could result in the catalytic reductive amination of primary amines that was sought.

This hypothesis was then tested in a one-pot two stage-process, for synthesis of the same secondary amine (**69**) (Table 5). The use of only one equivalent of 4-fluorobenzoic acid (**67**) at the beginning of the reaction (Table 5, entry 1) gave a poor yield of 24% of the desired product (**69**). Whereas, the same reaction employing 1.5 equivalents of 4-fluorobenzoic acid (**67**) at the beginning of the reaction (Table 5, entry 2) gave a significantly improved yield of 75%. Additionally, attempts were made to try and decrease the amount of phenylsilane required in the reduction step from 3 equivalents to 2 equivalents (Table 5, entry 2), however this resulted in a significant reduction in the yield to 36%.

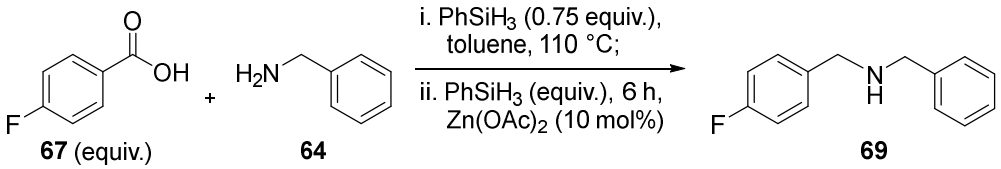
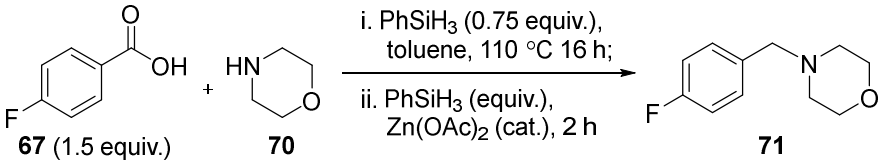


Table 5 *One pot synthesis of secondary amines via a carboxylic acid-enhanced amide redution. a – Yields measured by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard*

Entry	Carboxylic Acid / equiv.	$PhSiH_3$ / equiv.	Yield[a] / %
1	1.0	3	24
2	1.5	3	75
3	1.5	2	36

Following this optimisation of the reaction for the synthesis of tertiary amines was undertaken. This was performed using 4-fluorobenzoic acid (**67**), this time in combination with morpholine (**70**) (Table 6). As it had been already demonstrated for the synthesis of secondary amines that 1.5 equivalents of carboxylic acid was necessary in order for successful reduction of the resultant secondary amide intermediate, 1.5 equivalents of 4-fluorobenzoic acid was also used in the tertiary amide reduction. An initial experiment with 1 equivalent of phenylsilane and 10 mol% of zinc acetate (Table 6, entry 1) gave a moderate 54% yield of the

desired tertiary amine (**71**). Increasing the amount of phenylsilane to two equivalents (Table 6, entry 2) gave an increase in yield to 65%, however the addition of an extra equivalent of phenylsilane (Table 6, entry 3) did not increase the yield substantially, as amine **71** was obtained in 67% yield.



67 (1.5 equiv.) **70** **71**

Table 6 *Optimisation of a zinc acetate-catalysed synthesis of tertiary amines. a – Yields measured by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard*

Entry	$PhSiH_3$ / equiv.	$Zn(OAc)_2$ / mol%	Yield[a] / %
1	1	10	54
2	2	10	63
3	3	10	67
4	2	5	25
5	2	20	65

Following this, the amount of zinc acetate used in the reaction was examined. A reduction to only 5 mol% of zinc acetate (Table 6, entry 4) resulted in a decrease in yield from 63% to 25%. However, doubling the amount of catalyst to 20 mol% (Table 6, entry 5) did not result in significant improvement in yield, and gave 65% of the desired product.

2.3 Substrate Scope

Following the optimisation of both secondary and tertiary amine synthesis procedures, reaction conditions had been found which only differ by the number of equivalents of phenylsilane required to effect the reduction, with three equivalents needed for the synthesis of secondary amines and two equivalents required for tertiary amine synthesis.

With this information in hand, the scope of the reaction was explored, to ascertain its functional group tolerance and general applicability.

Beginning with the secondary amines (Figure 8), it can be seen that the scope of the reaction includes electron rich aromatic carboxylic acids (**73**, **75** and **77**), electron deficient aromatic carboxylic acids (**74** and **78**) as well as aliphatic carboxylic acids (**80** and **81**). A range of potentially reducible functional groups are tolerated in both the acid and amine component, including aryl halides (**72**, **76** and **79**), alkenes (**75** and **80**) and nitro groups (**74**).

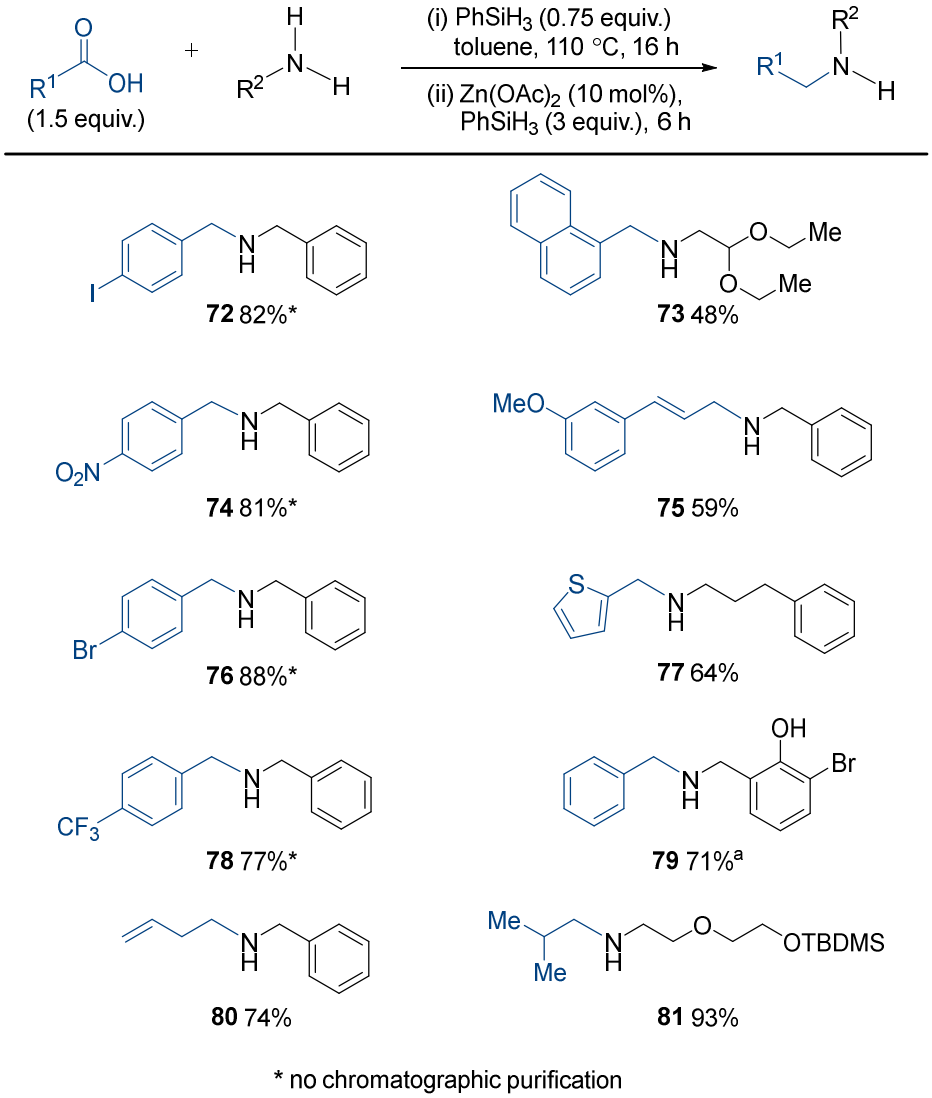


Figure 8 *Scope of the zinc acetate-catalysed reductive amination reaction with carboxylic acids to synthesise secondary amines. a – Conditions: $PhSiH_3$ (1.75 equiv.), toluene, 110 °C, 16 h; $Zn(OAc)_2$ (10 mol%), $PhSiH_3$ (3 equiv.), 6 h*

Acetals (**73**) are also compatible with the reaction conditions, however 1-naphthalenemethanol was also isolated as a major side product. It is hypothesised that amidation was sluggish and therefore the additional excess residual carboxylic acid was also reduced *in situ*. Free hydroxyl groups are also tolerated (**79**) but the addition of an extra equivalent of phenylsilane at the beginning of the reaction is required, as the hydroxyl group is silylated *in situ*, therefore consuming an equivalent of phenylsilane. However the silyl group was removed during the work up and gave the desired product as a free alcohol (**79**). Alternatively, standard silyl ether protected substrates (**81**) can be used without the need for addition of extra phenylsilane.

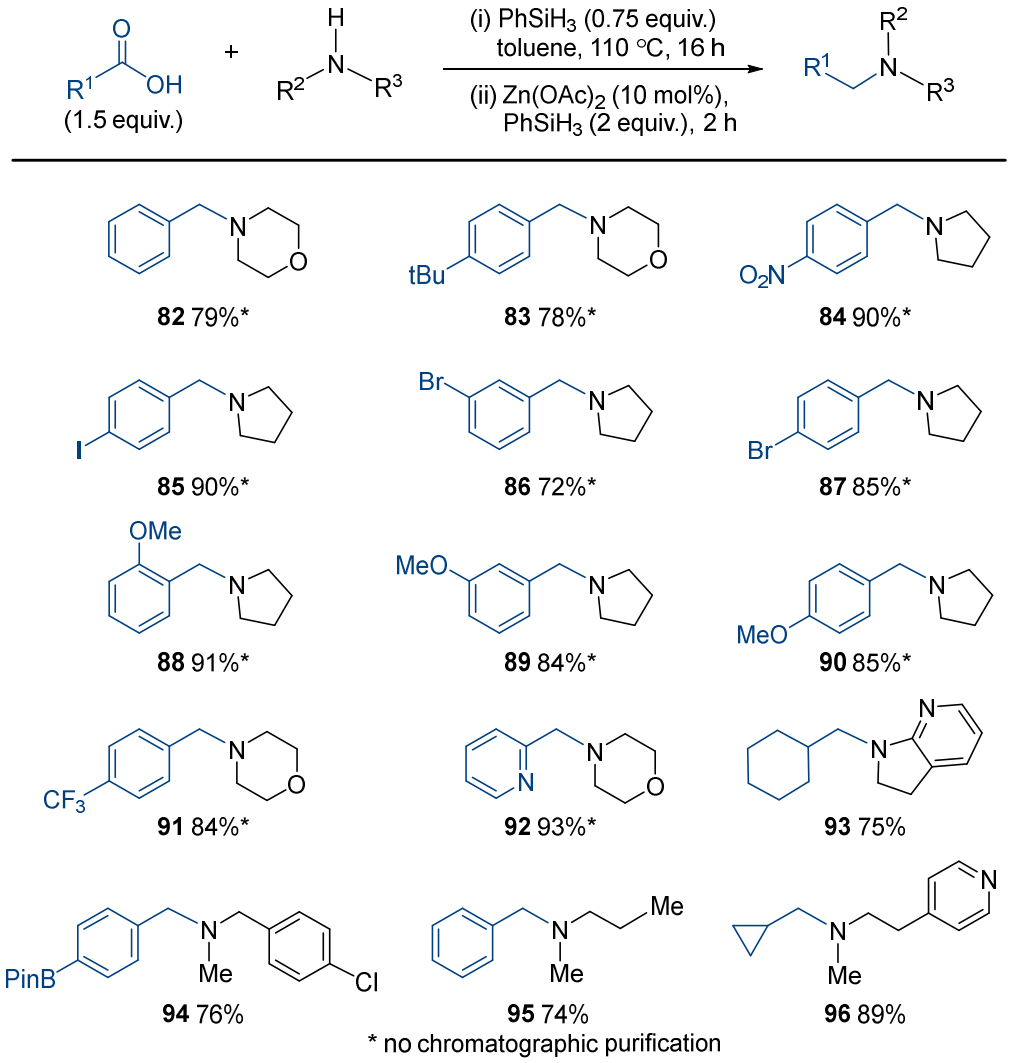


Figure 9 *Scope of the zinc acetate-catalysed reductive amination reaction with carboxylic acids to synthesise tertiary amines*

Following on from the secondary amine synthesis, the scope of tertiary amine synthesis was then explored (Figure 9). With respect to tertiary amine synthesis it was noted that the reduction of the resultant amide intermediate in this case was faster and complete within 2 hours compared to 6 hours for secondary amide intermediates. Additionally, in all but 4 cases, the tertiary amine products were obtained by acid-base work-up without any requirement for purification by column chromatography.

Amination was efficient for a wide range of substituted benzoic acids containing electron donating groups (**83**, **88**, **89** and **90**), electron withdrawing groups (**84** and **91**), halides (**85**, **86** and **87**) and a boronic acid ester (**94**). The latter example provides a good illustration of how the reductive amination can be deployed for the construction of a tertiary amine building block with two versatile functional groups for further derivatization. Pyridines are tolerated in both the acid and amine component (**92**, **93** and **96**) and aliphatic carboxylic acids also undergo efficient coupling with both cyclic and acyclic amines (**93**, **95** and **96**). Additionally, strained ring systems such as cyclopropanes (**96**), not typically compatible with traditional metal hydride reductions are well tolerated under the reaction conditions. Anilines were also trialled in the reaction, however disappointingly amidation with these substrates was poor due to their lower nucleophilicity, leading to long reaction times and low yields.

A range of carboxylic acids containing potentially reducible functional groups were reacted with morpholine (**70**) selected to ascertain the level of chemoselectivity of the zinc acetate-catalysed reductive amination reaction (Figure 10). Ester-containing substrates (**97** and **100**) showed reduction of both the amide and ester functional groups, with the size of the ester substituent making little difference to the amount of the ester reduction. Despite having demonstrated alkenes (**75** and **80**) are compatible with the reaction conditions, alkynes are partially reduced (**101**). Additionally, substrates containing nitriles (**98**), azides (**99**) and nitro

(**84**) groups were tested under the standard reaction conditions. As had been observed previously, nitro groups (**84**) were compatible with the reaction conditions, however this was not the case for nitriles (**98**) and azides (**99**). In both instances, the same product was observed by HRMS, corresponding with a reduction of both groups to the primary amine.

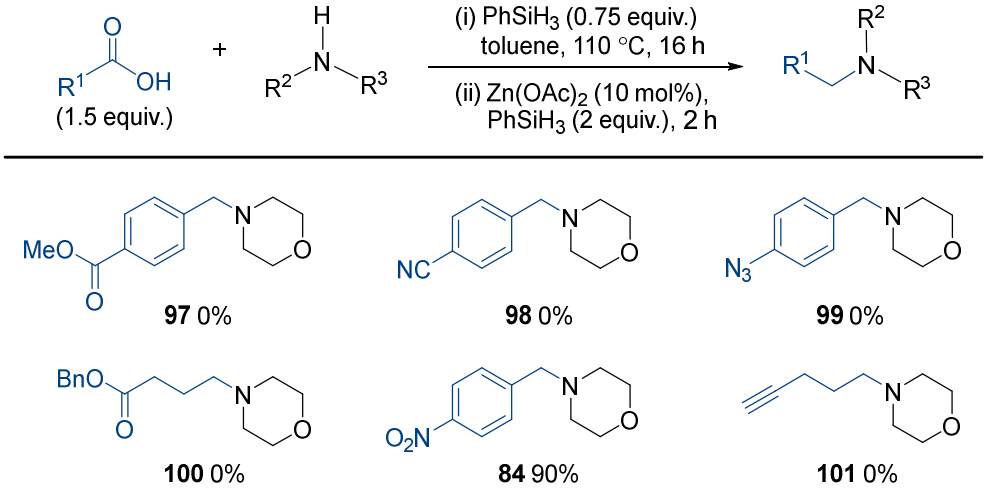
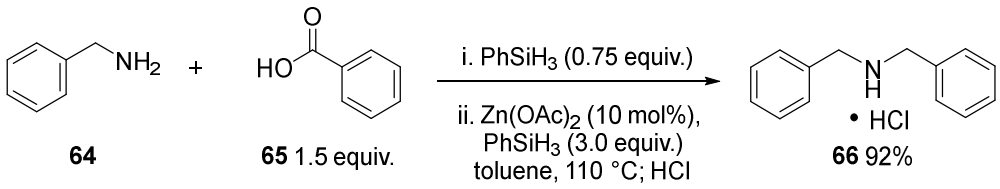


Figure 10 *Assessing the chemoselectivity of the zinc acetate-catalysed reductive amination reaction*

Following exploration of the substrate scope, further studies were performed to demonstrate the utility and practicality of the zinc acetate-catalysed reductive amination reaction. Firstly, a large-scale reaction was performed by Dr Tom Tongue, between benzylamine (**64** 305 mmol) and benzoic acid (**65**) (Scheme 40).



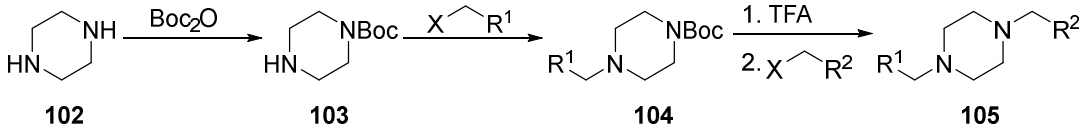
Scheme 40 *305 mmol scale reductive amination reaction between benzylamine (**64**) and benzoic acid (**65**)*

The reaction was carried out in a one litre controllable lab reactor equipped with overhead stirring and a heating jacket and given that hydrogen gas is generated during the amidation-phase of the process, the silane was added by syringe pump at a rate of 2 mL/min (Figure 11A). Following completion of the reductive amination reaction, the crude reaction mixture was filtered through Celite to remove zinc precipitate, and gave 70.9 g of dibenzylamine (**66**), which was obtained in an isolated yield of 92% (with an HPLC purity of 93%) (Figure 11C and

D). The product (**66**) was isolated as the hydrochloride monohydrate after treatment of the filtrate with concentrated hydrochloric acid, without any requirement for further column chromatography.

Figure 11 *Large Scale reductive amination reaction.* ***A*** *– Phenylsilane addition during amidation phase of reaction.* ***B*** *– After addition of zinc acetate and phenylsilane for reduction phase of reaction.* ***C*** *– Filtration of HCl salt precipitate.* ***D*** *– Amine product* ***66*** *after filtration and drying.*

In a second study, the construction of differentially *N*,*N*-disubstituted piperazines (**105**) was examined. These are a privileged class of compounds with biological activities including antifungals, antidepressants, antivirals, and serotonin receptor (5-HT) antagonists/agonists.[133] The conventional four step approach for the synthesis of unsymmetrical piperazines involves a mono-Boc protection of piperazine (**102**) followed by reductive amination or alkylation, carbamate cleavage and a second reductive amination or alkylation (Scheme 41), to give the desired unsymmetrical piperazine (**105**).



Scheme 41 *Conventional approach for the synthesis of unsymmetrical N,N-disubstituted piperazines (**105**)*

A more efficient orthogonal approach was proposed, using 2-oxopiperazine (**106**) as a building block in *lieu* of *N*-Boc piperazine (**103**). It was proposed that a reductive amination of 2-oxopiperazine (**106**) could afford the corresponding amine **108**, resulting from a combination of both *N*-alkylation and lactam reduction (Table 7). This method allows

selective mono-alkylation, as the lactam can act initially as a protecting group before it is then reduced.

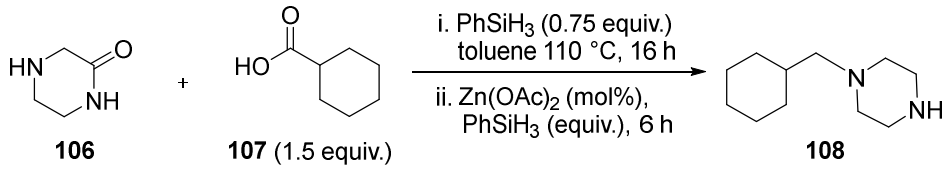
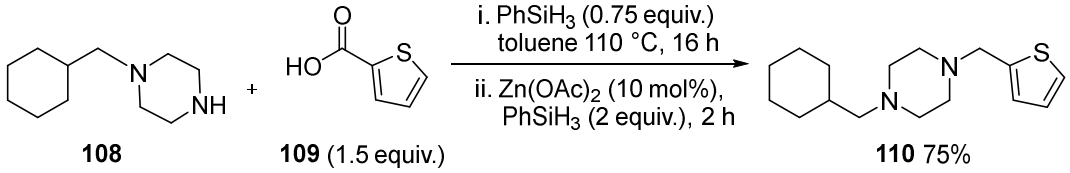


Table 7 *Synthesis of* ***108*** *from 2-oxopiperazine (****106****) via a reductive amination and lactam reduction*

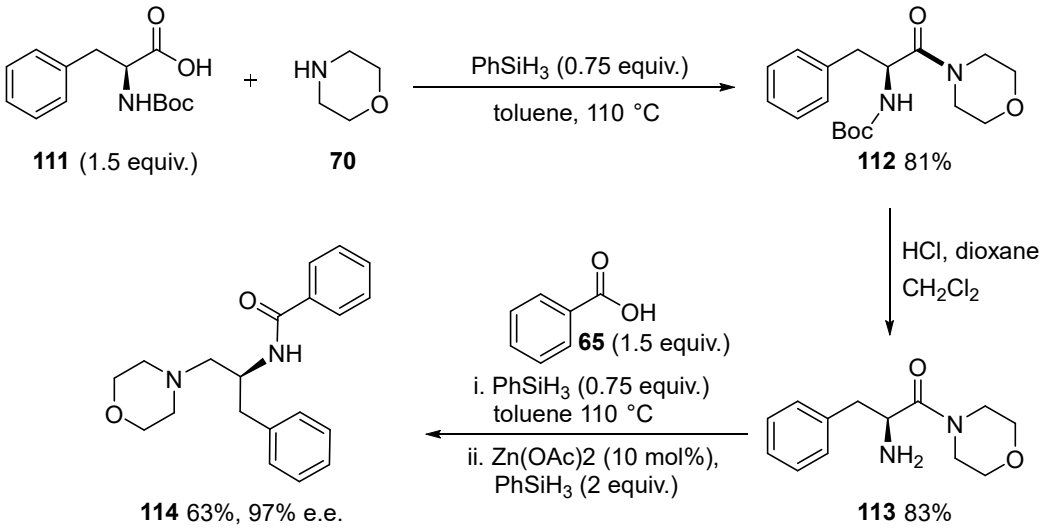
Entry	$Zn(OAc)_2$ / mol%	$PhSiH_3$ / equiv.	Yield[a] / %
1	10	2	27
2	25	3	54

Initial reaction using the standard reaction conditions (Table 7, entry 1) gave the desired product **108** in only 27% yield. However, increasing the loading of zinc acetate to 25 mol% and the addition of an extra equivalent of phenylsilane (Table 7, entry 2) gave the desired product (**108**) in 54% yield. A subsequent reductive amination reaction using **108** and with 2-thiophenecarboxylic acid (**109**) afforded the differentially substituted product **110** in good yield (Scheme 42).



Scheme 42 *Synthesis of unsymmetrical piperazines using 2-oxopiperazine*

During the optimization studies, it was established that catalytic reduction of secondary amides is significantly slower than tertiary substrates, therefore a study was performed to ascertain whether selective reductive aminations were possible. It was proposed that it would be possible to synthesise tertiary amines in the presence of secondary amides or amide intermediates (Scheme 43).



Scheme 43 *Selective reduction of tertiary amide in the presence of a secondary amide*

Phenylsilane-mediated direct amidation of morpholine (**70**) with *N*-Boc-phenylalanine (**111**) gave amide **112** in 81% yield. This was then deprotected using HCl in dioxane and gave the primary amine **113**, which upon treatment with benzoic acid (**65**) formed a secondary amide intermediate. Subsequent addition of further zinc acetate and phenylsilane resulted in selective reduction of only the tertiary amide, without any reduction of the secondary amide observed, to afford tertiary amine **114** in good yield and excellent stereochemical integrity (63%, 97% e.e.).

2.4 Mechanistic Investigations

Having explored the scope and utility of the zinc acetate-catalysed reductive amination reaction, experiments were then carried out to probe the role played by residual carboxylic acid in the amide reduction step. Beller and co-workers had previously reported that the combination of zinc triflate and phenylsilane was poor for the reduction of secondary amides[91] and our own experiments demonstrated that the combination of zinc acetate and phenylsilane gave similar results. However, the addition of a carboxylic acid resulted in a significantly improved reduction process. It was reasoned that the carboxylic acid was modifying the silane *in situ* generating a more reactive species, which, in combination with zinc acetate, was able to reduce secondary amides at enhanced rates. In order to investigate

this possibility, a ^{19}F NMR study using 4-fluorobenzoic acid (**67**) and benzylamine (**64**) was performed (Figure 12).

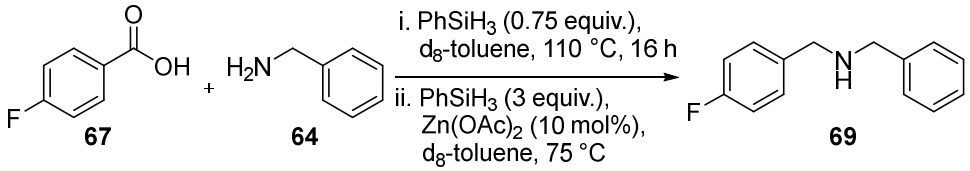
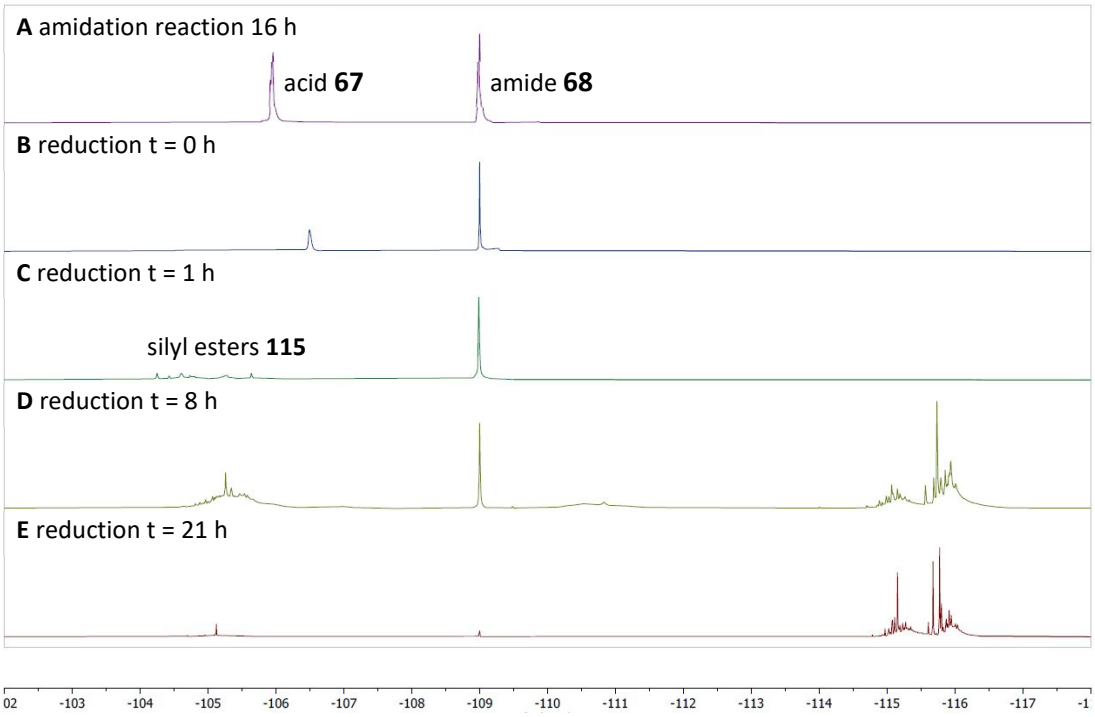


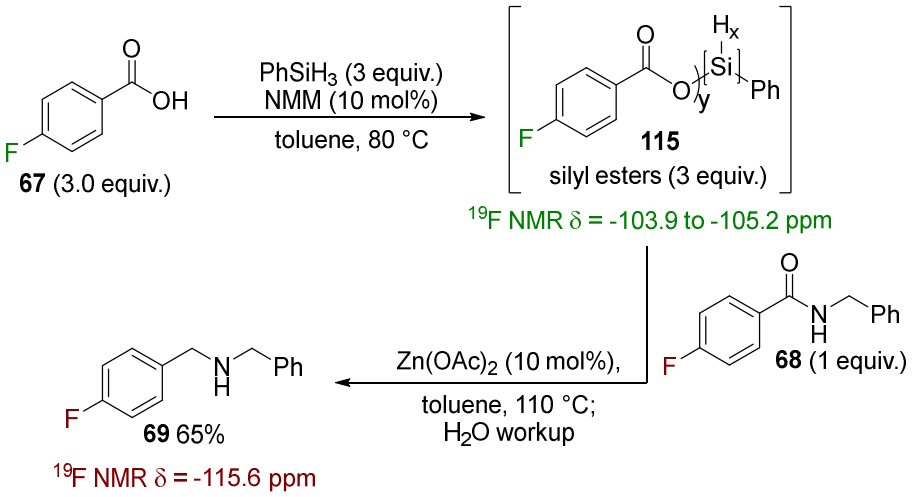
Figure 12 *^{19}F NMR spectra of the reductive amination of acid **67** and amide **64**. **A** – After amidation step. **B** - **E** – Reduction steps.*



On examination of the ^{19}F NMR spectrum of the reaction mixture at the end of the amidation phase of the reaction (Figure 12A), amide **68** was visible (^{19}F δ = –107.9) along with the remaining 0.5 equivalents of excess carboxylic acid **67** (^{19}F δ = –105.6). Subsequent addition of zinc acetate and additional phenylsilane resulted in the generation of hydrogen gas and a broad range of new ^{19}F environments downfield of the carboxylic acid (^{19}F δ = –103.3 to –105.2) (Figure 12C and Figure 12D). These signals are attributed to multiple silyl esters (**115**) that are generated by a dehydrogenative silylation process, which could be catalysed by residual amine from the amidation step (**64**) or, as the reaction progresses, by the amine product (**69**).[132] Over the course of the reaction, a decrease in the amount of silyl esters (**115**)

is observed and an emergence of a range of new signals can be seen (^{19}F δ = –114.8 to –116.3) believed to be silanamines,[134] which are cleaved to give the desired product on work up.

Having observed species that are believed to be silyl ester intermediates in the reduction phase of the reaction, a further experiment was carried out in which 4-fluorobenzoic acid (**67**) was treated with phenylsilane and catalytic *N*-methylmorpholine (NMM), to generate a mixture of silyl esters (**115**). A similar ^{19}F NMR profile was observed (^{19}F δ=–103.9 to –105.2) along with some residual carboxylic acid (**67**). Subsequent addition of 3 equivalents of this mixture of silyl esters (**115**) to the secondary amide **68** and zinc acetate, effected the amide reduction and gave the desired amine product (**69**) in 65% yield (Scheme 44).



Scheme 44 *Synthesis of silyl esters which are able to effect the reduction of amide* ***68***

This yield is comparable to what had been previously observed during the optimisation of the reaction (Table 4, entry 3), providing further evidence that silyl esters participate in the reduction phase of the reaction.

The reactivity of phenylsilane was then compared with an independently prepared silyl ester, representative of silyl esters present in the reduction phase of the reaction. Refluxing phenylsilane with one equivalent of zinc acetate for one hour resulted in no observable reaction as judged by ^{1}H NMR spectroscopy (Figure 13).

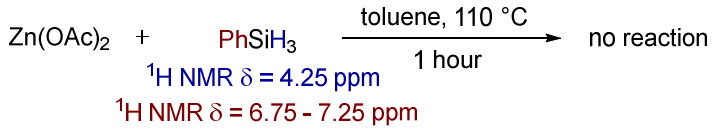
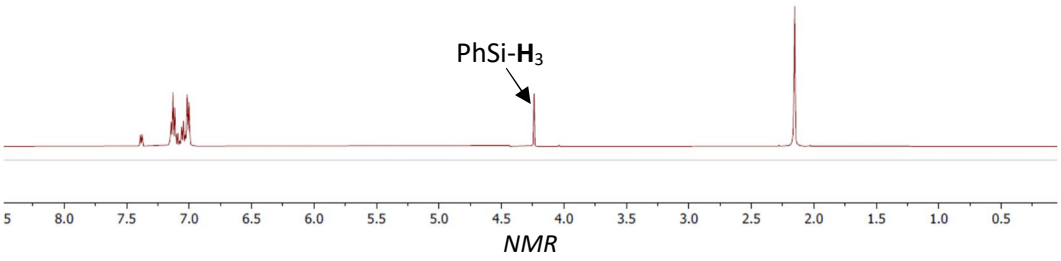


Figure 13 *Reaction mixture of zinc acetate and phenylsilane after 1 h, showing no reaction by ^1H*



Phenylsilyl acetate (**117**) was then synthesised from reaction between chlorophenylsilane (**116**) and sodium acetate (Figure 14). ^1H NMR showed a new Si-H peak (^1H δ = 5.19) consistent with that of silyl esters, as well as the presence of residual phenylsilane (Figure 14A).

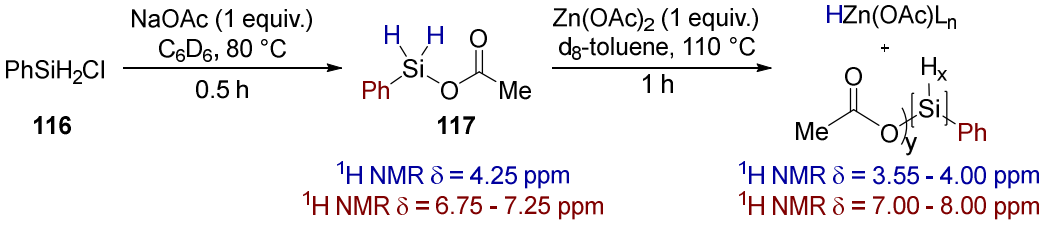
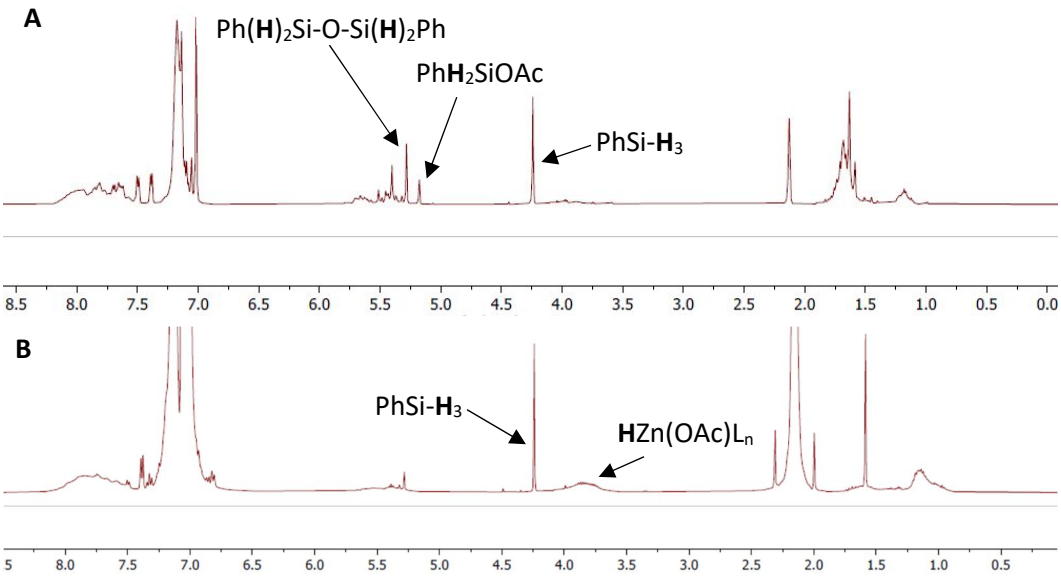
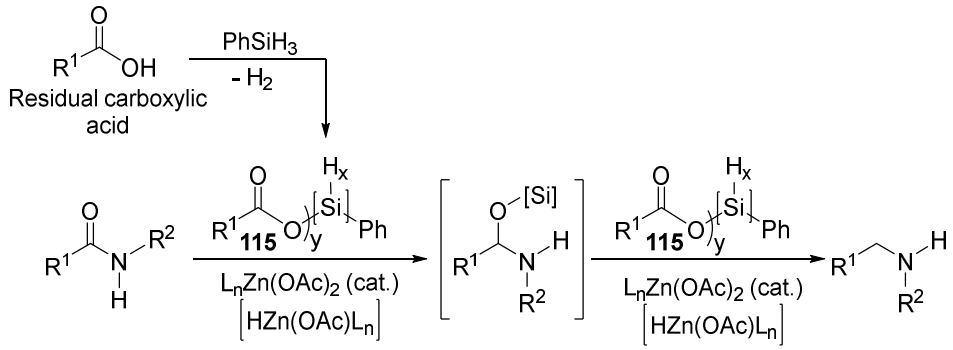


Figure 14 *Reaction between silyl ester **117** and zinc acetate. **A** – ^1H NMR spectrum of silyl ester **117** formation. **B** – ^1H NMR spectrum of reaction of **117** with zinc acetate, leading to the formation of a new species proposed to be a zinc hydride*



The crude phenylsilyl acetate (**117**) was reacted with zinc acetate for one hour and, in contrast to the experiment using phenylsilane, reaction was observed (Figure 14B). Further analysis of the reaction mixture by ^{1}H NMR spectroscopy revealed a range of new aromatic environments (^{1}H δ = 8.15 to 7.45) were visible. Additionally, the silyl ester (**117**) had been consumed and new broad hydride environments (^{1}H δ = 4.15 to 3.55) upfield of phenylsilane were observed, which are consistent with silane modification, and possibly the formation of a zinc hydride species.[135]

On the basis of these observations, a plausible pathway for the catalytic amide reduction can be derived. It is proposed that the residual carboxylic acid from the amidation step of the reaction undergoes dehydrogenative silylation to afford a mixture of silyl esters (**115**). Once formed this mixture reacts with zinc acetate more rapidly than the parent silane and this combination is responsible for activation and reduction of the amide (Scheme 45).



Scheme 45 *Proposed mechanistic pathway for the zinc acetate-catalysed reduction of amides*

The nature of the activation and reduction process is obscured by the complex speciation of the silyl esters. However, the formation of a zinc hydride species is feasible[135] and have been invoked by Mlynarksi and co-workers in zinc acetate catalysed reduction of imines[136] and, more recently, by Beller and co-workers[72] in zinc acetate silane reductions of tertiary amides. The initial reduction would lead to a silylated tetrahedral intermediate which is then likely to be further activated and then reduced to the amine product. Although zinc has been depicted with acetate ligands, exchange with the residual carboxylic acid is possible but has not been depicted for the sake of clarity.

2.5 Conclusions

A practical zinc acetate-catalysed *N*-alkylation reaction of amines that allows carboxylic acids to be used directly in *lieu* of aldehydes and alkyl halides has been demonstrated. The reactions are conducted in conventional laboratory glassware, are tolerant of other potentially reducible functional groups and have been shown to be effective even on large scale (305 mmol with respect to the amine component). Finally, the elucidation of the role played by the residual carboxylic acid provides mechanistic insight that can potentially be transferred to the design of new reduction reactions in which silane reactivity is augmented *in situ* using Brønsted acids.

3 Experimental

3.1 General Experimental

Reagents were purchased from commercial suppliers and used directly without further purification. Solvents were dried according to published methods[137] and distilled before use; except for toluene which was pre-dried over sodium wire and obtained from a solvent tower, where degassed solvent was passed through two columns of activated alumina and 7-micron filter under a 4-bar pressure. Petrol refers to the fraction of petroleum ether boiling between 40–60 °C. All water was deionised before use, and unless specified, all experiments were carried out in oven dried glassware with an argon balloon atmosphere.

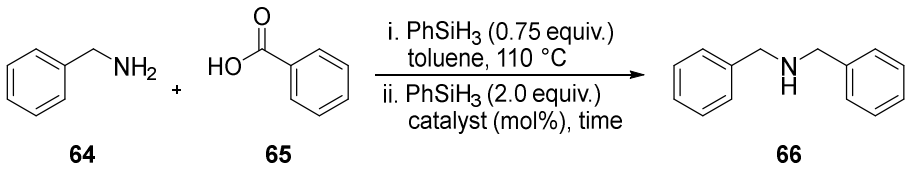
Analytical Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed silica-gel plates 60 F_{254} plates and visualized by ultraviolet (UV) irradiation (254 nm) or by staining with a solution of potassium permanganate or ninhydrin. Column chromatography was carried out using Fluorochem silica gel 60 Å (40-63 mesh). Melting points were calculated using a Stuart SMP3 and Fourier Transform Infrared Spectrometry (IR) was carried out using a Bruker Tensor 27 using an Attenuated Total Reflection (ATR) attachment and peaks are reported in terms of frequency of absorption (cm^{-1}). High Resolution Mass Spectrometry (HRMS) were measured on a Bruker microTOF II with Electron Spray Ionisation (ESI). Specific rotations ([α]D) were measured using an Anton Paar MCP 100 Modular Circular Polarimeter.

^{1}H NMR spectra were recorded on either a Bruker AV 400, AV(III) 400HD or AV(III) 500HD in $CDCl_3$ or d_6-DMSO. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz), with residual protic solvent as the internal reference ($CDCl_3$ δ = 7.26 ppm, d_6-DMSO δ = 2.50 ppm). The proton spectra are reported as follows: δ (multiplicity, coupling constant *J*, number of protons). ^{13}C NMR were recorded on a 400 MHz spectrometer, chemical shifts (δ) were reported in ppm relative to the ^{13}C signals in the solvent (central peak of $CDCl_3$ δ = 77.16 ppm, d_6-DMSO δ = 39.52) and coupling

constants (*J*) are given in Hertz (Hz). All ^{13}C NMR are reported as proton decoupled spectra. ^{19}F NMR were recorded on a 376 MHz spectrometer, chemical shifts (δ) were reported in ppm relative to $CFCl_3$ at 0.00 ppm and are reported as proton decoupled spectra.

3.2 Reaction Optimisation

Catalyst Screen



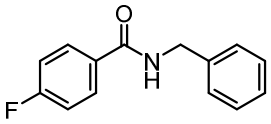
64 **65** **66**

Entry	Catalyst	Loading /mol%	Time / h	Yield / %	Cost / mmol[131]
1	$[Ir(COD)Cl]_2$	1	4	67	£88.52
2	$[Ir(COD)Cl]_2$	0.5	16	30	£88.52
3	$Rh(PPh_3)_3Cl$	5	4	60	£61.88
4	MoO_2Cl_2	10	16	18	£7.07
5	$Fe_3(CO)_{12}$	10	16	23	£4.42
6	$Zn(OAc)_2$	10	16	33	£0.55
7	$Zn(OAc)_2$	10	46	94[a]	£0.55

a – ^1H NMR yield measured using 1,1,2,2-tetrachloroethane as an internal standard.

To a refluxing solution of benzoic acid (**65**) (61 mg, 0.50 mmol) in toluene (0.6 mL) was added phenylsilane (47 µL, 0.38 mmol), followed by benzylamine (**64**) (55.0 µL, 0.50 mmol) dropwise. The reaction mixture was then heated for 2 h after which time catalyst (as table) and further phenylsilane (123 µL, 1.0 mmol) were added. The reaction mixture was heated at reflux for a further 6 h before being cooled to room temperature and quenched with acetic acid (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the product extracted with acetic acid (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL).

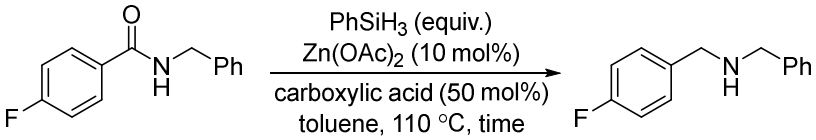
N-benzyl-4-fluorobenzamide (68)



To a refluxing solution of 4-fluorobenzoic acid (**67**) (3.15 g, 22.5 mmol) in toluene (18.0 mL) was added phenylsilane (1.40 mL, 11.3 mmol), followed by benzylamine (**64**) (1.64 mL, 15.0 mmol) dropwise. The reaction mixture was then heated for 16 h after which time the reaction mixture was cooled and diluted with EtOAc (10 mL) and washed with HCl (15 mL of a 3 M aqueous solution). The aqueous phase was then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (EtOAc / petrol 1:4, to EtOAc / petrol 1:1) to give the product as a colourless solid (2.77 g, 12.1 mmol, 81%), m.p. 138-140 °C.

IR (ATR) νmax/cm^{-1} 3319, 3067, 3031, 1680, 1639, 1592, 1548, 1450, 1420; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.75 (m, 2H), 7.39 – 7.27 (m, 5H), 7.14 – 7.05 (m, 2H), 6.42 (s, 1H), 4.63 (d, *J* = 5.6 Hz, 2H); **^{13}C NMR**[^{19}F] (101 MHz, $CDCl_3$) δ 166.3, 166.0, 138.0, 130.5, 129.4, 128.9, 128.0, 127.7, 115.8, 44.2; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -108.09; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{13}FNO$ 230.0976, found 230.0977.

Secondary Amide Reduction Optimisation

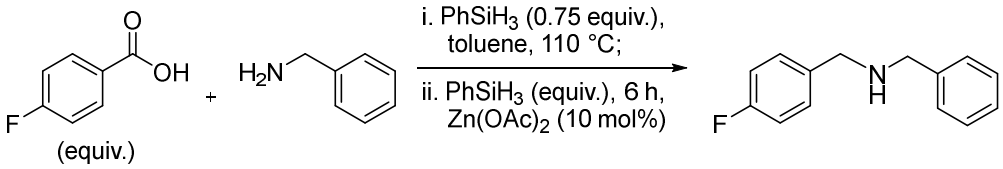


Entry	$PhSiH_3$ / equiv.	$Zn(OAc)_2$ / mol%	Time / h	Yield[a] / %
1	1	10	6	1
2	2	10	6	20
3	3	10	6	22
4	2	10	24	27
5	3	0	6	0

a – ^{1}H NMR yield measured using α,α,α-trifluorotoluene as an internal standard.

To a refluxing solution of *N*-benzyl-4-fluorobenzamide (**68**) (229 mg, 1.00 mmol) and carboxylic acid (as table) in toluene (1.20 mL) was added zinc acetate (mol% as table), followed by phenylsilane (equiv. as table). The reaction mixture was then heated for the specified length of time (as table), after which the heating was removed and acetic acid (1 mL of a 3 M aqueous solution) was added dropwise. The reaction mixture was cooled and diluted with EtOAc (10 mL), before the product was extracted with acetic acid (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. α,α,α-Trifluorotoluene (146 mg, 1.00 mmol) was added to the crude product and the yield was determined by ^{19}F NMR spectroscopy.

Secondary Amine Synthesis Optimisation



a – ^1H NMR yield measured using α,α,α-trifluorotoluene as an internal standard.

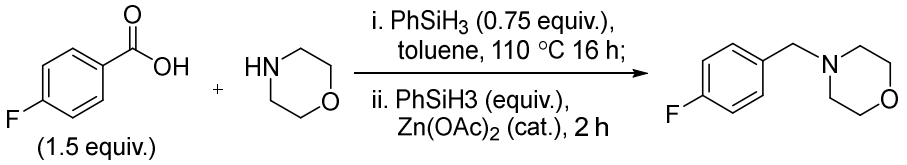
Entry	Carboxylic Acid / equiv.	$PhSiH_3$ / equiv.	Yield[a] / %
1	1.0	3	24
2	1.5	3	75
3	1.5	2	36

a – ^1H NMR yield measured using α,α,α-trifluorotoluene as an internal standard.

To a refluxing solution 4-fluorobenzoic acid (**67**) (equiv. as table) in toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol), followed by benzylamine (**64**) (109 µL, 1.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time (amidation now complete) zinc acetate (mol% as table) and further phenylsilane (equiv. as table) were added. The reaction mixture was heated at reflux for a further 6 h before being cooled to room temperature and quenched with acetic acid (1 mL of a 3 M aqueous solution) added

dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the product extracted with acetic acid (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. α,α,α-Trifluorotoluene (146 mg, 1.00 mmol) was added to the crude product and the yield was determined by ^{19}F NMR spectroscopy.

Tertiary Amine Synthesis Optimisation



a – ^1H NMR yield measured using α,α,α-trifluorotoluene as an internal standard.

Entry	$PhSiH_3$ / equiv.	$Zn(OAc)_2$ / mol%	Yield[a] / %
1	1	10	54
2	2	10	63
3	3	10	67
4	2	5	25
5	2	20	65

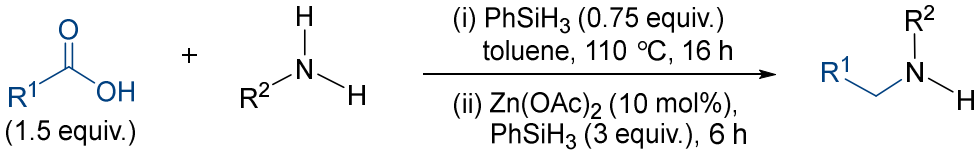
a – ^1H NMR yield measured using α,α,α-trifluorotoluene as an internal standard.

To a refluxing solution of 4-fluorobenzoic acid (**67**) (210 mg, 1.50 mmol) in toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol), followed by morpholine (**70**) (87.5 µL, 1.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time zinc acetate (mol% as table) and phenylsilane (equiv. as table) were added. The reaction mixture was heated at reflux for a further 2 h before being cooled to room temperature and quenched with HCl (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the amine product extracted with HCl (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. α,α,α-

Trifluorotoluene (146 mg, 1.00 mmol) was added to the crude product and the yield was determined by ^{19}F NMR spectroscopy.

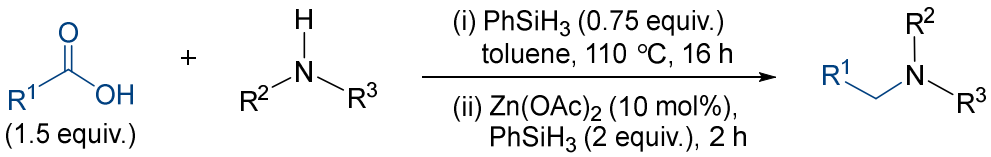
3.3 Substrate Scope

General Procedure 1 – Secondary Amine Synthesis



To a refluxing solution of carboxylic acid (1.50 mmol) in anhydrous toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol), followed by amine (1.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time (amidation now complete) zinc acetate (18.3 mg, 10 mol%) and further phenylsilane (370 µL, 3.00 mmol) were added. The reaction mixture was heated at reflux for a further 4 h before being cooled to room temperature and quenched with acetic acid (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the amine product extracted with acetic acid (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. If necessary, the products were purified by column chromatography.

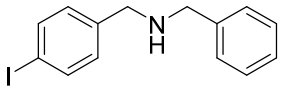
General Procedure 2 – Tertiary Amine Synthesis



To a refluxing solution of carboxylic acid (1.50 mmol) in anhydrous toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol), followed by amine (1.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time (amidation now complete) zinc

acetate (18.3 mg, 10 mol%) and further phenylsilane (247 µL, 2.00 mmol) were added. The reaction mixture was heated at reflux for a further 2 h before being cooled to room temperature and quenched with HCl (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the amine product extracted with HCl (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. If necessary, the products were purified by column chromatography.

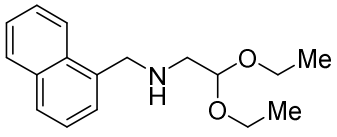
N-Benzyl-1-(4-iodophenyl)methanamine (**72**)



Prepared according to general procedure 1, using 4-iodobenzoic acid (372 mg, 1.50 mmol) and benzylamine (**64**) (109 µL, 1.00 mmol) to afford the title compound as colourless oil (264 mg, 0.820 mmol, 82%).

IR (ATR) νmax/cm^{-1} 3061, 2822, 1482, 1452, 1006; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 2H), 7.44 – 7.24 (m, 5H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.87 (s, 1H), 3.81 (s, 2H), 3.77 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.7, 138.6, 137.5, 130.4, 128.5, 128.4, 127.4, 92.7, 52.4, 51.8; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{14}H_{15}IN$ 324.0244, found 324.0251. The data matches that found in the literature.[138]

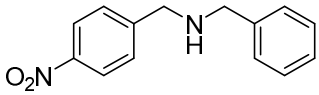
2,2-Diethoxy-*N*-(naphthalen-1-ylmethyl)ethan-1-amine (**73**)



Prepared according to general procedure 1, using 1-napthoic acid (258 mg, 1.50 mmol) and amino acetaldehyde diethyl acetal (145 µL, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 3:7) to afford the title compound as a colourless oil (131 mg, 0.480 mmol, 48%).

IR (ATR) νmax/cm^{-1} 3043, 2872, 1443, 1372, 1121, 1057; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 1H), 7.93 – 7.83 (m, 1H), 7.81 – 7.74 (m, 1H), 7.57 – 7.38 (m, 4H), 4.65 (t, *J* = 5.6 Hz, 1H), 4.27 (s, 2H), 3.68 (dq, *J* = 9.4, 7.0 Hz, 2H), 3.52 (dq, *J* = 9.4, 7.0 Hz, 2H), 2.88 (d, *J* = 5.6 Hz, 2H), 1.20 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.7, 133.8, 131.7, 128.6, 127.7, 126.0, 126.0, 125.6, 125.3, 123.6, 102.1, 62.3, 51.9, 51.4, 15.3; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{17}H_{23}NO_2$ 274.1802, found 274.1802. The data matches that found in the literature.[120]

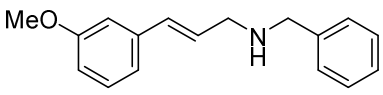
N-Benzyl-1-(4-nitrophenyl)methanamine (**74**)



Prepared according to general procedure 1, using 4-nitrobenzoic acid (251 mg, 1.50 mmol) and benzylamine (**64**) (109 µL, 1.00 mmol) to afford the title compound as yellow oil (197 mg, 0.810 mmol, 81%).

IR (ATR) νmax/cm^{-1} 3027, 2837, 1514, 1383.; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.7 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.29 – 7.17 (m, 5H), 3.83 (s, 2H), 3.74 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.2, 147.1, 139.8, 128.8, 128.6, 128.2, 127.3, 123.7, 53.3, 52.4. **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{14}H_{15}N_2O_2$ 243.1128, found 243.1128. The data matches that found in the literature.[139]

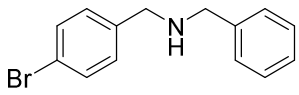
(*E*)-*N*-Benzyl-3-(3-methoxyphenyl)prop-2-en-1-amine (**75**)



Prepared according to general procedure 1, using 3-(3-methoxyphenyl)acrylic acid (267 mg, 1.50 mmol) and benzylamine (**64**) (109 µL, 1.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 9:1) to afford the title compound as a colourless oil (151 mg, 0.590 mmol, 59%).

IR (ATR) νmax/cm^{-1} 3315, 2920, 2833, 1598, 1489, 1453, 1261, 1154, 907; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 5H), 7.25 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.99 (ddd, *J* = 7.7, 1.2, 1.2 Hz, 1H), 6.94 (dd, *J* = 2.6, 1.2 Hz, 1H), 6.81 (ddd, *J* = 7.7, 2.6, 1.2 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.35 (dt, *J* = 15.8, 6.2 Hz, 1H), 3.89 (s, 2H), 3.83 (s, 3H), 3.48 (d, *J* = 6.2 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 139.9, 138.5, 131.6, 129.5, 128.5, 128.4, 128.3, 127.1, 119.0, 113.1, 111.5, 55.2, 53.2, 51.0; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{17}H_{20}NO$ 254.1539, found 254.1531.

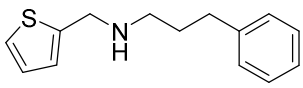
N-Benzyl-1-(4-bromophenyl)methanamine (76)



Prepared according to general procedure 1, using 4-bromobenzoic acid (302 mg, 1.50 mmol) and benzylamine (**64**) (109 µL, 1.00 mmol) to afford the title compound as colourless oil (243 mg, 0.880 mmol, 88%).

IR (ATR) νmax/cm^{-1} 3025, 2923, 2349, 1485, 1452; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.43 – 7.35 (m, 4H), 7.35 – 7.29 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.81 (s, 2H), 3.77 (s, 2H), 2.97 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.6, 138.9, 131.4, 129.9, 128.4, 128.2, 127.1, 120.7, 52.8, 52.1; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{14}H_{15}BrN$ 276.0382, found 276.0392. The data matches that found in the literature.[140]

3-Phenyl-*N*-(thiophen-2-ylmethyl)propan-1-amine (77)

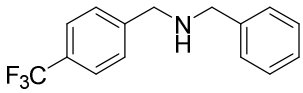


Prepared according to general procedure 1, using 2-thiophenecarboxylic acid (192 mg, 1.50 mmol) and 3-phenylpropylamine (142 µL, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 2:3, R_f = 0.12) to afford the title compound as a colourless oil (149 mg, 0.640 mmol, 64%).

IR (ATR) νmax/cm^{-1} 3025, 2926, 2855, 2814, 1602, 1452, 1329, 1109, 1031.; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.30 – 7.23 (m, 4H), 7.02 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.99 (d,

J = 3.4 Hz, 1H), 4.04 (s, 2H), 2.77 (t, *J* = 7.1 Hz, 2H), 2.74 (t, *J* = 8.1 Hz, 2H), 2.00 – 1.83 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.1, 142.0, 128.3, 128.3, 126.6, 125.7, 124.8, 124.2, 48.5, 48.3, 33.5, 31.5; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{18}NS$ 232.1154, found 232.1164.

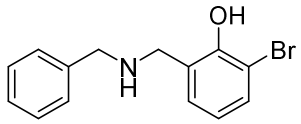
N-Benzyl-1-(4-(trifluoromethyl)phenyl)methanamine (78)



Prepared according to general procedure 1, using 4-(trifluoromethyl)benzoic acid (285 mg, 1.50 mmol) and benzylamine (**64**) (109 µL, 1.00 mmol) to afford the title compound as a colourless oil (205 mg, 0.770 mmol, 77%).

IR (ATR) νmax/cm^{-1} 3028, 2836, 1618, 1494, 1362, 1159; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.36 (m, 4H), 7.32 – 7.27 (m, 1H), 3.88 (s, 2H), 3.82 (s, 2H), 1.78 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 140.1, 129.4 (q, *J* = 32.3 Hz), 128.6, 128.4, 128.3, 127.2, 125.4 (q, *J* = 4.0 Hz), 125.2 (q, *J* = 271.7 Hz), 53.3, 52.7; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{15}H_{15}F_3N$ 266.1151, found 266.1161. The data matches that found in the literature.[86]

2-((Benzylamino)methyl)-6-bromophenol (79)

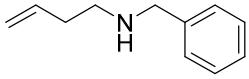


Prepared according to general procedure 1, using 3-bromo-2-hydroxybenzoic acid (326 mg, 1.50 mmol) and benzylamine (**64**) (109 µL, 1.00 mmol). The product was purified by column chromatography (EtOAc / petrol 2:3, R_f = 0.36) to give the product as a colourless oil (192 mg, 0.710 mmol, 71%).

IR (ATR) νmax/cm^{-1} 3293, 2846, 2359, 1452, 1405, 1260; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.39 – 7.27 (m, 5H), 6.96 – 6.89 (m, 1H), 6.66 (dd, *J* = 7.7, 7.7 Hz, 1H), 3.97 (s, 2H), 3.79 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.0, 137.8, 132.1, 128.8, 128.5, 127.8,

127.6, 123.5, 120.0, 110.5, 52.5, 51.7; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{15}BrNO$ 292.0332, found 292.0333.

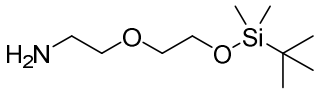
N-Benzylbut-3-en-1-amine (80)



Prepared according to general procedure 1, using 3-butenoic acid (127 µL, 1.50 mmol) and benzylamine (**64**) (109 µL, 1.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 9:1) to afford the title compound as a pale yellow oil (119 mg, 0.740 mmol, 74%).

IR (ATR) νmax/cm^{-1} 2917, 2813, 1639, 1453, 1116; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.21 (m, 5H), 5.82 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.15 – 5.08 (m, 1H), 5.08 – 5.03 (m, 1H), 3.83 (s, 2H), 2.74 (t, *J* = 6.8 Hz, 2H), 2.37 – 2.26 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.2, 136.3, 128.3, 128.0, 126.8, 116.3, 53.8, 48.2, 34.2; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{16}N$ 162.1277, found 162.1279. The data matches that found in the literature.[141]

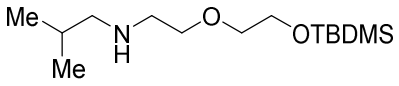
2-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)ethan-1-amine (SI-1)



To 2-(2-aminoethoxy)ethanol (502 µL, 5.00 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added imidazole (1.02 g, 15.0 mmol), DMAP (61.1 mg, 0.500 mmol) and *tert*-butyldimethylsilyl chloride (829 mg, 5.50 mmol). The reaction mixture was stirred at room temperature for 5 h. The reaction mixture was washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a colourless oil (790 mg, 3.60 mmol, 72%).

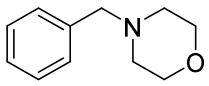
IR (ATR) νmax/cm^{-1} 3335, 2928, 2856, 1561, 1098; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.77 (t, *J* = 5.3 Hz, 2H), 3.56 – 3.49 (m, 4H), 2.85 (t, *J* = 5.3 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 73.5, 72.6, 62.9, 42.1, 26.1, 18.5, -5.10; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{10}H_{25}NO_2Si$ 220.1727, found 220.1742. The data matches that found in the literature.[142]

N-(2-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)ethyl)-2-methylpropan-1-amine (81)



Prepared according to general procedure 1, using isobutyric acid (139 µL, 1.50 mmol) and 2-(2-((*tert*-Butyldimethylsilyl)oxy)ethoxy)ethan-1-amine (**SI-1**) (219 mg, 1.00 mmol), omitting the acidic and basic washes. The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 9:1) to afford the title compound as a yellow oil (256 mg, 0.930 mmol, 93%). **IR** (ATR) νmax/cm^{-1} 2954, 2857, 1463, 1253, 1131; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.72 (t, *J* = 5.2 Hz, 2H), 3.52 (t, *J* = 5.2 Hz, 2H), 3.46 (t, *J* = 5.2 Hz, 2H), 2.69 (t, *J* = 5.2 Hz, 2H), 2.35 (d, *J* = 6.9 Hz, 2H), 1.81 – 1.69 (m, 1H), 0.88 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 6H), 0.05 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 72.3, 70.1, 62.5, 57.6, 49.2, 27.9, 25.8, 20.5, 18.2, -5.4; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{34}NO_2Si$ 276.2353, found 276.2348. The data matches that found in the literature.[120]

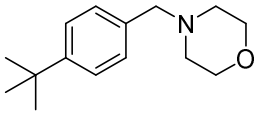
4-Benzylmorpholine (82)



Prepared according to general procedure 2, using benzoic acid (183 mg, 1.50 mmol) and morpholine (**70**) (87.5 µL, 1.00 mmol) to afford the title compound as a pale yellow oil (140 mg, 0.790 mmol, 79%).

IR (ATR) νmax/cm^{-1} 2804, 2763, 1453, 1350, 1115, 1070, 1007, 913; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 5H), 3.71 (t, *J* = 4.6 Hz, 4H), 3.50 (s, 2H), 2.45 (t, *J* = 4.6 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.7, 129.2, 128.2, 127.1, 67.0, 63.4, 53.6; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{16}ON^+$ 178.1232, found 178.1229. The data matches that found in the literature.[143]

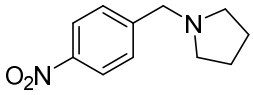
4-(4-(*tert*-butyl)benzyl)morpholine (**83**)



Prepared according to general procedure 2, using 4-*tert*-butylbenzoic acid (267 mg, 1.50 mmol) and morpholine (**70**) (87.5 µL, 1.00 mmol) to afford the title compound as a colourless oil (182 mg, 0.780 mmol, 78%).

IR (ATR) νmax/cm^{-1} 2958, 2854, 2805, 1513, 1393, 1315, 1265, 1115, 1006; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 3.71 (t, *J* = 4.7 Hz, 4H), 3.47 (s, 2H), 2.44 (t, *J* = 4.7 Hz, 4H), 1.32 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.1, 134.6, 129.0, 125.2, 67.1, 63.2, 53.7, 34.5, 31.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{15}H_{24}NO$ 234.1852, found 234.1862.

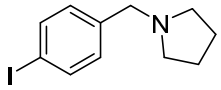
1-(4-Nitrobenzyl)pyrrolidine (**84**)



Prepared according to general procedure 2, using 4-nitrobenzoic acid (251 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a yellow oil (187 mg, 0.900 mmol, 90%).

IR (ATR) νmax/cm^{-1} 2961, 2786, 1515, 1342; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 2H), 3.67 (s, 2H), 2.52 – 2.45 (m, 4H), 1.83 – 1.70 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.5, 147.0, 129.3, 123.5, 59.9, 54.3, 23.6; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{11}H_{15}N_2O_2^+$ 207.1128, found 207.1144. The data matches that found in the literature.[144]

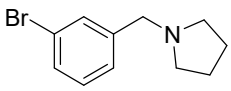
1-(4-Iodobenzyl)pyrrolidine (85)



Prepared according to general procedure 2, using 4-iodobenzoic acid (372 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a pale yellow oil (250 mg, 0.900 mmol, 90%).

IR (ATR) νmax/cm^{-1} 2960, 2784, 1491, 1371, 1240; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 3.52 (s, 2H), 2.62 – 2.25 (m, 4H), 1.87 – 1.61 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.3, 137.2, 130.8, 92.3, 59.9, 54.0, 23.4; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{11}H_{15}IN$+ 288.0244, found 288.0251. The data matches that found in the literature.[98]

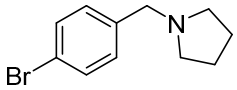
1-(3-Bromobenzyl)pyrrolidine (86)



Prepared according to general procedure 2, using 3-bromobenzoic acid (302 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a yellow oil (172 mg, 0.720 mmol, 72%).

IR (ATR) νmax/cm^{-1} 2960, 2780, 1568; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.14 (dd, J = 7.8, 7.8 Hz, 1H), 3.55 (s, 2H), 2.59 – 2.40 (m, 4H), 1.83 – 1.68 (m, 4H);**^{13}C** NMR (101 MHz, $CDCl_3$) δ 141.8, 131.7, 123.0, 129.8, 127.4, 122.4, 60.0, 54.1, 23.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{11}H_{15}BrN^+$ 240.0382, found 240.0388. The data matches that found in the literature.[145]

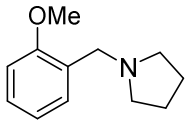
1-(4-Bromobenzyl)pyrrolidine (87)



Prepared according to general procedure 2, using 4-bromobenzoic acid (302 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a colourless oil (203 mg,

0.850 mmol, 85%). **IR** (ATR) νmax/cm^{-1} 2960, 2783, 1487; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 3.62 (s, 2H), 2.71 – 2.46 (m, 4H), 1.88 – 1.68 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.5, 131.3, 130.6, 120.9, 59.6, 53.9, 23.3; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{15}BrN^+$ 240.0382, found 240.0387. The data matches that found in the literature.[146]

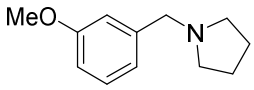
1-(2-Methoxybenzyl)pyrrolidine (88)



Prepared according to general procedure 2, using 2-methoxybenzoic acid (228 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a pale yellow oil (174 mg, 0.910 mmol, 91%).

IR (ATR) νmax/cm^{-1} 2953, 2780, 1654, 1510, 1247; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.23 (ddd, *J* = 8.0, 8.0, 1.3 Hz, 1H), 6.94 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H), 6.86 (dd, *J* = 8.0, 0.9 Hz, 1H), 3.81 (s, 3H), 3.70 (s, 2H), 2.67 – 2.48 (m, 4H), 1.91 – 1.70 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 130.4, 127.9, 127.2, 120.2, 110.3, 55.3, 54.1, 53.7, 23.5; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{12}H_{18}NO^+$ 192.1383, found 192.1390.

1-(3-Methoxybenzyl)pyrrolidine (89)

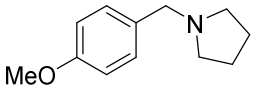


Prepared according to general procedure 2, using 3-methoxybenzoic acid (228 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a colourless oil (160 mg, 0.840 mmol, 84%).

IR (ATR) νmax/cm^{-1} 2957, 2781, 1597, 1262; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.95 – 6.89 (m, 2H), 6.79 (dd, *J* = 8.0, 2.2 Hz, 1H), 3.79 (s, 3H), 3.59 (s, 2H), 2.55 – 2.42 (m, 4H), 1.82 – 1.71 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 139.1, 129.4, 121.5, 114.6,

113.3, 60.3, 55.4, 53.9, 23.5; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{12}H_{18}NO^+$ 192.1383, found 192.1404. The data matches that found in the literature.[147]

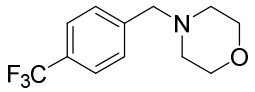
1-(4-Methoxybenzyl)pyrrolidine (90)



Prepared according to general procedure 2, using 4-methoxybenzoic acid (228 mg, 1.50 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title compound as a yellow oil (162 mg, 0.850 mmol, 85%).

IR (ATR) νmax/cm^{-1} 2955, 2778, 1654, 1511, 1242; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H), 3.54 (s, 2H), 2.58 – 2.40 (m, 4H), 1.82 – 1.61 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.6, 131.3, 130.1, 113.6, 60.0, 55.2, 54.0, 23.4; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{12}H_{18}NO^+$ 192.1383, found 192.1387. The data matches that found in the literature.[148]

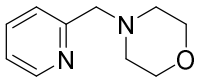
4-(4-(Trifluoromethyl)benzyl)morpholine (91)



Prepared according to general procedure 2, using 4-(trifluoromethyl)benzoic acid (285 mg, 1.50 mmol) and morpholine (**70**) (87.5 µL, 1.00 mmol) to afford the title compound as a yellow oil (205 mg, 0.840 mmol, 84%).

IR (ATR) νmax/cm^{-1} 2918, 2856, 2809, 1418; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 3.73 – 3.65 (m, 4H), 3.52 (s, 2H), 2.46 – 2.36 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.3, 129.5 (q, *J* = 31.6 Hz), 125.2 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 267 Hz), 67.0, 62.8, 53.7; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{12}H_{15}F_3NO^+$ 246.1100, found 246.1102. The data matches that found in the literature.[149]

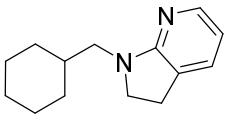
4-(Pyridin-2-ylmethyl)morpholine (92)



Prepared according to general procedure 2, using 2-picolinic acid (185 mg, 1.50 mmol) and morpholine (**70**) (87.5 µL, 1.00 mmol) to afford the title compound as an orange oil (166 mg, 0.930 mmol, 93%).

IR (ATR) νmax/cm^{-1} 3384, 2959, 2815, 1650, 1593, 1069; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 4.6 Hz, 1H), 7.49 (ddd, *J* = 7.7, 7.7, 1.6 Hz, 1H), 7.25 (d, *J* = 7.7 Hz, 1H), 7.00 (ddd, *J* = 7.7, 4.6, 1.2 Hz, 1H), 3.56 (t, *J* = 4.6 Hz, 4H), 3.49 (s, 2H), 2.34 (t, *J* = 4.6 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.1, 149.3, 136.4, 123.3, 122.1, 66.9, 65.0, 53.8; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{10}H_{15}ON_2^+$ 179.1184, found 179.1185. The data matches that found in the literature.[150]

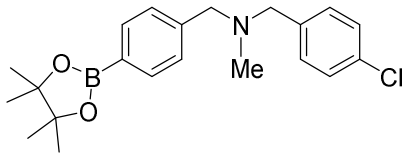
1-(Cyclohexylmethyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (93)



Prepared according to general procedure 2, using cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and 2,3-dihydro-1H-pyrrolo[2,3-b]pyridine (120 mg, 1.00 mmol) to afford the title compound as a colourless oil (163 mg, 0.750 mmol, 75%).

IR (ATR) νmax/cm^{-1} 2923, 2850, 2795, 1612, 1505, 1447, 1287; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 5.3, 1.2 Hz, 1H), 7.12 (ddd, *J* = 6.9, 2.9, 1.4 Hz, 1H), 6.36 (dd, *J* = 6.9, 5.3 Hz, 1H), 3.48 (t, *J* = 8.4 Hz, 2H), 3.16 (d, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 8.4 Hz, 2H), 1.82-1.61 (m, 6H), 1.30-1.12 (m, 3H), 1.05-0.93 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.7, 145.8, 130.6, 122.9, 111.6, 52.3, 50.3, 36.7, 31.2, 26.7, 26.1, 26.0; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{14}H_{21}N_2^+$ 217.1705, found 217.1702.

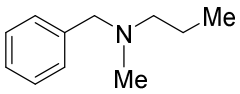
N-(4-chlorobenzyl)-*N*-methyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (94)



Prepared according to general procedure 2, using 4-carboxylphenylboronic acid pinacol ester (372 mg, 1.50 mmol) and 1-(4-chlorophenyl)-*N*-methanamine (145 µL, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 1:9, R_f = 0.32) to afford the title compound as a colourless oil (284 mg, 0.760 mmol, 76%).

IR (ATR) νmax/cm^{-1} 2977, 2788, 1670, 1513, 1356, 1142, 1086, 981; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.27 (m, 4H), 3.55 (s, 2H), 3.47 (s, 2H), 2.18 (s, 3H), 1.36 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.2, 137.6, 134.9, 132.7, 130.5, 130.4, 128.5, 128.5, 83.9, 61.9, 61.0, 42.2, 25.0; **HRMS** [ESI (M + Na^+)] m/z calculated for $C_{21}H_{27}BClNNaO_2$ 394.1716, found 394.1711.

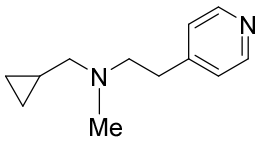
N-benzyl-*N*-methylpropan-1-amine (95)



Prepared according to general procedure 2, using propionic acid (112 µL, 1.50 mmol) and *N*-benzylmethylamine (129 µL, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 1:9 to EtOAc / petrol 2:3, R_f = 0.14) to afford the title compound as a colourless oil (121 mg, 0.740 mmol, 74%).

IR (ATR) νmax/cm^{-1} 2957, 2787, 1494, 1452, 1364, 1132, 1108, 1043; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.22 (m, 5H), 3.50 (s, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.20 (s, 3H), 1.61 – 1.51 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.4, 129.2, 128.3, 127.0, 62.5, 59.7, 42.4, 20.7, 12.0; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{18}N$ 164.1434, found 164.1439.

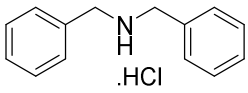
N-(cyclopropylmethyl)-*N*-methyl-2-(pyridin-3-yl)ethan-1-amine (96)



Prepared according to general procedure 2, using cyclopropane carboxylic acid (119 µL, 1.50 mmol) and *N*-methyl-*N*-(2-pyridin-4-ylethyl)amine (136 mg, 1.00 mmol). The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 19:1, R_f = 0.12) to afford the title compound as a yellow oil (170 mg, 0.890 mmol, 89%).

IR (ATR) νmax/cm^{-1} 2929, 1632, 1603, 1453, 1416, 1224, 1069, 908; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 – 8.38 (m, 2H), 7.14 – 7.03 (m, 2H), 2.80 – 2.71 (m, 2H), 2.71 – 2.62 (m, 2H), 2.35 (s, 3H), 2.29 (d, *J* = 6.5 Hz, 2H), 0.94 – 0.74 (m, 1H), 0.55 – 0.41 (m, 2H), 0.18 – 0.00 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7, 149.4, 124.2, 62.4, 57.9, 42.1, 32.9, 8.6, 4.0; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{12}H_{19}N_2$ 191.1543, found 191.1545.

Dibenzylamine hydrochloride (66)

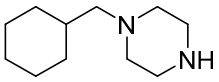


Benzoic acid (55.8 g, 457 mmol) and benzylamine (33.3 mL, 305 mmol) were added to toluene (360 mL) under nitrogen and heated to reflux. Phenylsilane (28.2 mL, 228 mmol) was added slowly (~2 mL/min) by syringe pump, the reaction was maintained at 110 °C for 24 h then cooled at 0.5 °C/min to 50 °C and maintained until the reduction. The reaction jacket was heated to 110 °C and zinc acetate (5.59 g, 30.5 mmol) was added, followed by the slow addition of phenylsilane (75.0 mL, 609 mmol) and the reaction was stirred for 20 h then cooled to 25 °C. The reaction solution was decanted from controllable lab reactor and the vessel was washed with toluene (50 mL) which was added to the reaction solution. The zinc precipitate was removed by filtration through Celite and the pad was washed with ethyl acetate (75 mL). The solution remained grey and cloudy so activated charcoal was added and the solution was filtered through Celite and washed with ethyl acetate (75 mL) to afford ~700

mL yellow clear solution. HCl (457 mmol, 1.5 equiv. of a 12 M aqueous solution) was added slowly and the precipitate was collected by filtration, the wet cake was stirred in ethyl acetate for 0.5 minutes and filtered, followed by washing with methyl tert-butyl ether. The solid was dried to afford the product HCl salt (70.9 g, 92%) as a colourless solid. HPLC purity = 93%, KF titration showed the product is a monohydrate.

IR (ATR) νmax/cm^{-1} 3025, 2920, 2850, 1494, 1452, 1115, 1027; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.16 (m, 10H), 3.82 (s, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.2, 128.7, 128.6, 127.5, 52.3; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{16}N^+$ 198.1283, found 198.1291. The data matches that found in the literature.[120]

1-(Cyclohexylmethyl)piperazine (108)

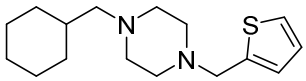


To a refluxing solution of cyclohexanoic acid (192 mg, 1.50 mmol) and 2-oxopiperazine (100 mg, 1.00 mmol) in toluene (1.20 mL) was added phenylsilane (92.5 µL, 0.750 mmol) dropwise. The reaction mixture was then heated for 16 h after which time (amidation now complete) zinc acetate (45.9 mg, 0.25 mmol) and further phenylsilane (370 µL, 3.00 mmol) were added. The reaction mixture was heated at reflux for a further 6 h before being cooled to room temperature and quenched with HCl (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the amine product extracted with HCl (3 × 10 mL of a 3 M aqueous solution). The combined aqueous phases were then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo.* The crude product was purified by column chromatography (CH_2Cl_2 / MeOH 9:1) to afford the title compound as a pale yellow oil (99 mg, 0.540 mmol, 54%).

IR (ATR) νmax/cm^{-1} 2919, 2848, 2804, 1658, 1448, 1123, 1004; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.86 (t, J = 4.9 Hz, 4H), 2.46 – 2.22 (m, 4H), 2.07 (d, J = 7.1 Hz, 2H), 2.03 (s, 1H), 1.82 – 1.57

(m, 4H), 1.47 (ttt, J = 10.8, 7.1, 3.5 Hz, 1H), 1.30 – 1.04 (m, 4H), 0.93 – 0.75 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 66.5, 55.2, 46.2, 34.9, 32.1, 26.9, 26.3; **HRMS** [ESI ($M + H^+$)] m/z calculated for $C_{11}H_{23}N_2$ 183.1856, found 183.1853.

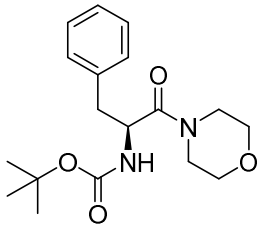
1-(Cyclohexylmethyl)-4-(thiophen-2-ylmethyl)piperazine (110)



Prepared according to general procedure 1, using 2-thiophene carboxylic acid (**109**) (192 mg, 1.50 mmol) and 1-(cyclohexylmethyl)piperazine (**108**) (182 mg, 1.00 mmol). The crude product was purified by column chromatography (EtOAc / petrol 1:4, R_f = 0.27) to afford the title compound as a colourless oil (209 mg, 0.750 mmol, 75%).

IR (ATR) νmax/cm^{-1} 2919, 2848, 2805, 2768, 1447, 1360, 1269, 1009; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.94 (dd, *J* = 5.0, 3.4 Hz, 1H), 6.90 (dd, *J* = 3.4, 1.2 Hz, 1H), 3.72 (s, 2H), 2.51 (m, 4H), 2.42 (m, 4H), 2.12 (d, *J* = 7.1 Hz, 2H), 1.80 – 1.60 (m, 4H), 1.52 – 1.41 (m, 1H), 1.30 – 1.11 (m, 4H), 0.97 – 0.78 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.7, 126.5, 126.2, 125.0, 65.8, 57.3, 53.8, 53.0, 35.2, 32.1, 27.0, 26.3; **HRMS** [ESI ($M + Na^+$)] m/z calculated for $C_{16}H_{26}N_2NaS$ 301.1709, found 301.1718.

tert-Butyl (*S*)-(1-morpholino-1-oxo-3-phenylpropan-2-yl)carbamate (112)

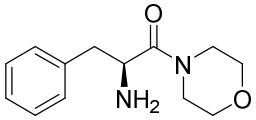


To a refluxing solution of *N*-Boc-L-Phenylalanine (**111**) (1.19 g, 4.50 mmol) in toluene (3.6 mL) was added phenylsilane (278 µL, 2.25 mmol), followed by morpholine (**70**) (262 µL, 3.00 mmol) dropwise. The reaction mixture was then heated for 16 h after which time the reaction mixture was quenched with HCl (1 mL of a 3 M aqueous solution) added dropwise. The reaction mixture was diluted with EtOAc (10 mL) and the amine product washed with HCl (10 mL of a 3 M aqueous solution). The aqueous phase was then adjusted to pH 12 with NaOH (6

M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (EtOAc / petrol 1:1 R_f = 0.23) to give a pale yellow solid (812 mg, 2.43 mmol, 81%).

[α]$_D$ 76.0° (c = 1.0, CH_2Cl_2) Lit - [α]$_D$ 75.7° (c = 1.0, CH_2Cl_2); **IR** (ATR) νmax/cm^{-1} 3305, 2973, 2923, 2855, 1701, 1634; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H), 5.42 (d, *J* = 8.9 Hz, 1H), 4.85 – 4.73 (m, 1H), 3.65 – 3.39 (m, 5H), 3.35 – 3.25 (m, 1H), 3.11 – 2.84 (m, 4H), 1.45 (s, 9H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.4, 155.2, 136.5, 129.7, 128.7, 127.2, 80.0, 66.6, 66.2, 50.9, 46.1, 42.4, 40.6, 28.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{18}H_{27}N_2O_4$ 335.1965, found 335.1957. The data matches that found in the literature.[151]

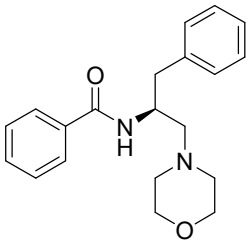
(*S*)-2-Amino-1-morpholino-3-phenylpropan-1-one (113)



To a solution of *tert*-Butyl-(*S*)-(1-morpholino-1-oxo-3-phenylpropan-2-yl)carbamate (**112**) (800 mg, 2.40 mmol) in CH_2Cl_2 (8 mL) at 0 °C was added HCl (3.60 mL of a 4 M solution in dioxane) dropwise. The reaction mixture was warmed to room temperature and stirred for 16 h, after which it was diluted with CH_2Cl_2 and extracted with HCl (3 × 10 mL of a 3 M aqueous solution). The aqueous phase was then adjusted to pH 12 with NaOH (6 M aqueous solution) and the product was re-extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo* to give a colourless oil (466 mg, 1.99 mmol, 83%).

IR (ATR) νmax/cm^{-1} 3356, 2921, 2857, 1700, 1446, 1068; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.15 (m, 5H), 3.91 (t, *J* = 7.3 Hz, 1H), 3.69 – 3.57 (m, 2H), 3.52 – 3.41 (m, 3H), 3.35 – 3.24 (m, 1H), 3.06 – 2.91 (m, 2H), 2.90 – 2.79 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ173.5, 137.5, 129.5, 128.8, 127.1, 66.7, 66.2, 52.4, 45.8, 43.3, 42.4; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{13}H_{19}N_2O_2$ 235.1441, found 235.1440. The data matches that found in the literature.[152]

(*S*)-*N*-(1-Morpholino-3-phenylpropan-2-yl)benzamide (**114**)



Prepared according to general procedure 2, using benzoic acid (**65**) (183 mg, 1.50 mmol) and (S)-2-amino-1-morpholino-3-phenylpropan-1-one (**113**) (234 mg, 1.00 mmol) with the critical exception that the reduction phase of the reaction (tertiary amide reduction) was 1 h at reflux. The crude product was purified by column chromatography (EtOAc / petrol 3:2, R_f = 0.17) to give the desired product as a yellow oil (204 mg, 0.630 mmol, 63%).

[α]$_D$ +8.00° (c = 1.0, chloroform); **IR** (ATR) νmax/cm^{-1} 3322, 2922, 2860, 2816, 1631, 1530, 1110; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.54 – 7.47 (m, 1H), 7.46 – 7.39 (m, 2H), 7.35 – 7.27 (m, 2H), 7.26 – 7.20 (m, 3H), 6.36 (d, *J* = 6.7 Hz, 1H), 4.46 (app. dqd, *J* = 8.7, 6.5, 4.8 Hz, 1H), 3.66 (t, *J* = 4.8 Hz, 4H), 3.14 – 2.96 (m, 2H), 2.57 – 2.34 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.5, 137.6, 134.9, 131.6, 129.9, 128.7, 128.5, 126.9, 126.7, 67.1, 60.5, 53.7, 47.5, 38.5; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{20}H_{25}N_2O_2$ 325.1911, found 325.1900. Enantiomeric excess was determined by chiral HPLC with a Chiral Pak AS-H column (*iso*-hexane / EtOH 90:10), 1.0 mL/min, 254 nm, 25 °C, t_r (minor) = 7.62 min, t_r (major) = 8.58 min, 97% *e.e*.

3.4 Mechanistic Studies

Reaction Monitoring

To a refluxing solution of 4-fluorobenzoic acid (105 mg, 0.750 mmol) in d_8-toluene (0.6 mL) was added phenylsilane (46.0 µL, 0.375 mmol), followed by benzylamine (55.0 µL, 0.500 mmol) dropwise. The reaction mixture was then heated for 16 h after which time ^{19}F NMR analysis was performed (Figure 12A), which showed the presence of amide **68** along with residual carboxylic acid **67**. Zinc acetate (9.20 mg, 0.050 mmol) and further phenylsilane (185

µL, 1.50 mmol) were added to the reaction mixture, the reaction was heated to 75 °C in the NMR spectrometer and ^{19}F NMR analysis was performed every 15 mins. Four representative traces are depicted (Figure 12B-E), which show the formation and decay of silyl ester species. The broad peaks observed at circa -115 ppm in traces D and E are likely to be silanamines derived from the dehydro coupling of silanes with the secondary amine product. The reaction mixture was then subjected to the standard acid/base workup protocol after which a single species, amine **69**, was present.

Reaction of Phenylsilane and Zinc Acetate

Zinc acetate (91.7 mg, 0.500 mmol) and phenylsilane (61.7 µL, 0.500 mmol) were suspended in d_8-toluene (0.5 mL) and heated to reflux. The cooled reaction mixture was analysed by ^{1}H NMR spectroscopy (Figure S5), which showed phenylsilane was unchanged.

Preparation of Phenylsilylacetate (117)

Chloro(phenyl)silane (21.3 µL, 0.160 mmol) was added to a refluxing suspension/solution of sodium acetate (13.1 mg, 0.160 mmol) in C_6D_6 (0.5 mL) and heated with stirring for 30 min. ^{1}H NMR (400 MHz, C_6D_6) δ 7.69 - 7.64 (m, 2H), 7.20 - 7.10 (m, 3H), 5.19 (SiH_2, s, 2H), 1.61 (s, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 171.7, 135.8, 131.3, 130.8, 128.4, 21.5; ^{29}Si NMR (79 MHz, C_6D_6) δ −21.2.

Preparation of 1,3-Diphenyldisiloxane

Chloro(phenyl)silane (0.160 mmol, 21.3 µL) was added to C_6D_6 (0.4 mL) and stirred overnight at room temperature in the presence of 2 drops (an excess) of water. The resulting solution was filtered by gravity through magnesium sulfate to remove water/HCl. ^{1}H NMR spectroscopy showed the disiloxane to be the major species (91% of the Si-H ^{1}HNMR signals present are the disiloxane). ^{1}H NMR (400 MHz, C_6D_6) δ 7.53 - 7.47 (m, 4H), 7.15 - 7.08 (m, 6H), 5.28 (s, 4H); ^{13}C NMR (101 MHz, C_6D_6) δ 134.4, 134.0, 130.8, 128.4; ^{29}Si NMR (79 MHz, C_6D_6) δ −25.3.

Reaction of Phenylsilyl acetate 117 with Zinc Acetate

Chlorophenylsilane (67.0 µL, 0.500 mmol) and sodium acetate (41.0 mg, 0.500 mmol) were suspended in d_8-toluene (0.5 mL) and heated for 1 h at reflux. Analysis of the cooled crude reaction mixture by ^{1}H NMR spectroscopy (Figure S6) confirmed that the desired mono silyl ester species **39** was present (Figure S6) along with diphenyldisiloxane and further silyl ester species. After analysis zinc acetate (91.7 mg, 0.50 mmol) was added and the reaction mixture heated for a further 1 h at reflux. Further analysis of the reaction mixture by ^{1}H NMR spectroscopy revealed that the silyl ester had been consumed and a new broad signal ^{1}H δ 3.55-4.30 ppm was now present. This is in the region expected for a zinc hydride species of general structure $HZn(OAc)L_n$ and it is tentatively proposed to be zinc hydride species.

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CHAPTER 2 A DUAL CATALYTIC SYSTEM FOR THE REDUCTION OF CARBOXYLIC ACIDS TO ALCOHOLS

A dual catalytic system for the reduction of carboxylic acids to alcohols using zinc acetate and N-methyl morpholine, in combination with phenylsilane as the nominal terminal reductant is described. This reduction protocol is applicable to a wide range of substrates and proceeds via activation with hydrosilanes, limiting the amount of stoichiometric waste produced in the reaction. The catalysts utilised in the reaction are widely, cheaply and routinely available in most laboratories and the method is tolerant of both air and moisture. Elucidation of the key role played by silyl esters has allowed mechanistic insights to be gained, which could be applied to the design of future reduction protocols.

1 Introduction

1.1 Importance of Alcohols

Alcohols are a common functional group in organic chemistry and are among the most abundant industrially produced chemicals. They are found widely in nature and natural products such as in sugars, terpenes, retinol, and cholesterol (Figure 15).

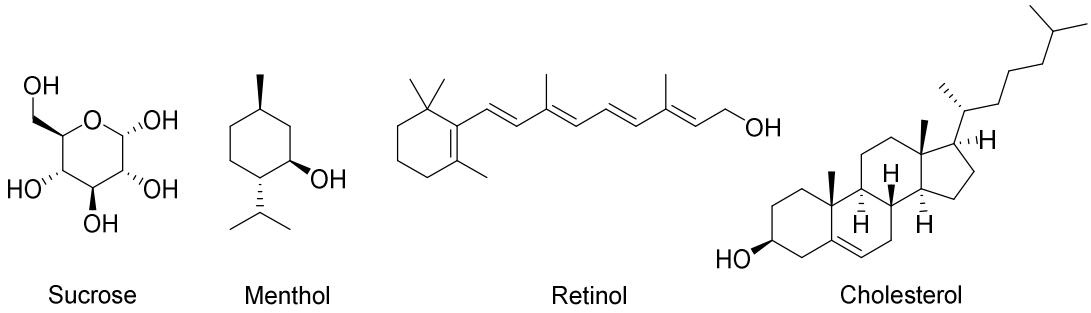


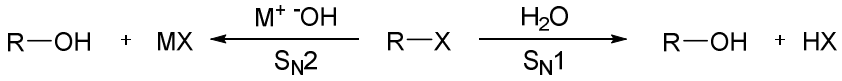
Figure 15 *Natural products containing alcohol functional groups*

Alcohols are used as sweeteners, in making perfumes, as fuels, solvents and are also valuable intermediates in the synthesis of other compounds, as they can be synthesised from and converted to a range of functional groups.[1]

1.2 Synthesis of Alcohols

1.2.1 Substitution with Alkyl Halides

A simple method for the synthesis of alcohols is by displacement of an alkyl halide with water via an S_N1 mechanism or a hydroxide anion *via* an S_N2 mechanism (Scheme 46).[2]



Scheme 46 *Synthesis of alcohols by displacement of an alkyl halide with a hydroxide anion or water*

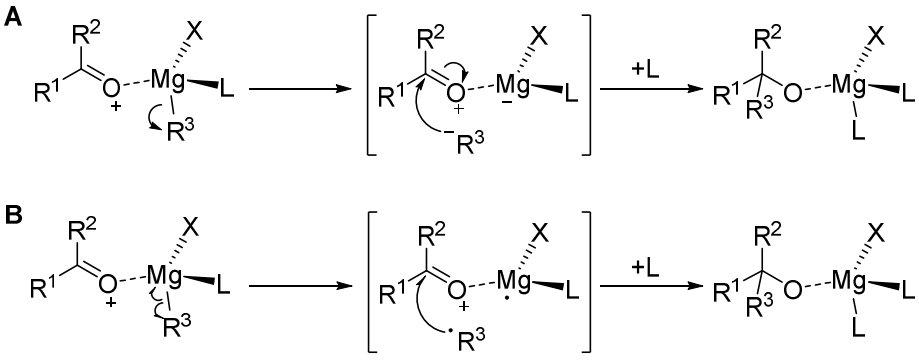
However, this method is not used frequently to synthesise alcohols, as it is more common for the reverse reaction to be carried out, to produce alkyl halides from alcohol starting materials.

1.2.2 Addition of Organometallic Reagents

A common way to synthesise alcohols is by addition of a Grignard reagent (**118**) to a carbonyl-containing compound (A) or at the least-substituted side of an epoxide (B). Grignard reagents **118** are made *via* the oxidative addition of magnesium to an alkyl halide,[3] and in the absence of water and oxygen are stable in ethereal solution.[4]

Scheme 47 *Alcohol synthesis using Grignard reactions.* ***A*** *– Reaction between carbonyl-containing compound and Grignard reagent* ***118****.* ***B*** *– Reaction between epoxide and Grignard reagent* ***118***

Grignard reactions are widely used due to ease of preparation and broad applications,[4] however despite the fact that the Grignard reaction was discovered over 100 years ago,[5] the mechanism is still not established.[6] This is partly due to the fact that Grignard reagents exist as multiple different species which are all in equilibrium, making the process of ascertaining the mechanism more complex. There are two main hypotheses for the mechanism of the Grignard reaction, which include a polar mechanism (Scheme 48A) and a radical SET mechanism (Scheme 48B).[6]

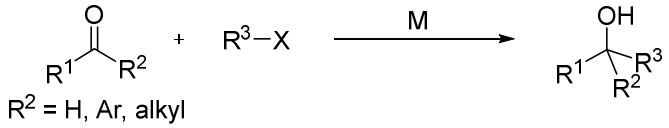


Scheme 48 *Two proposed mechanisms for the Grignard reaction.* ***A*** *– Polar mechanism which occurs via nucleophilic substitution.* ***B*** *– Radical SET mechanism.*[6]

The reaction has generally been recognised in the literature to proceed *via* a polar mechanism, whereby initial heterolytic cleavage of the Mg-C bond, forms a nucleophilic

carbon which can undergo attack at the carbonyl carbon (Scheme 48A). However, no experimental evidence has supported this hypothesis. Instead, experimental evidence has supported the existence of an alternative radical mechanism, as intermediates have been observed that could only have been produced by combination of radical ions.[7] This mechanism is proposed to commence by initial homolytic cleavage of the Mg-C bond to give two radical ions, followed by recombination of these species to give the desired product (Scheme 48B).[6]

Alternatively, the Barbier reaction can be employed, whereby an organometallic reagent is prepared *in situ*, from an alkyl halide and a metal, and reacted with an aldehyde or ketone to give primary, secondary or tertiary alcohols (Scheme 49).[8]

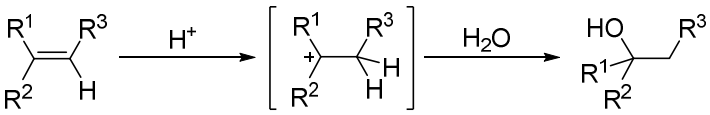


Scheme 49 *Barbier reaction between an alkyl halide and an aldehyde or ketone to give an alcohol*[8]

The reaction was originally published by Barbier in 1899 using magnesium,[8] however since the first report it has been found that range of metals or metal salts can be used to effect the reaction, including zinc,[9-10] aluminium,[11] indium,[11-12] tin,[13-14] and samarium.[15] The organometallic reagents produced in the Barbier reaction are typically more stable than Grignard reagents (**118**), and so Barbier reactions can be performed in water.[16]

1.2.3 Alcohol Synthesis from Alkenes

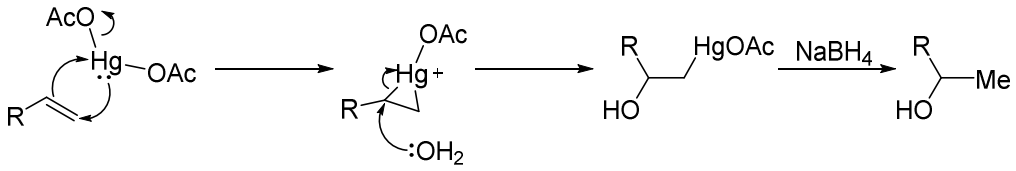
The simplest method for the synthesis of alcohols from alkenes is by hydration of alkenes with water in the presence of an acid catalyst (Scheme 50). The mechanism of the reaction involves initial protonation of the alkene by the acid catalyst, forming a carbocation.[17]



Scheme 50 *Hydration of alkenes using water in the presence of an acid catalyst*[17]

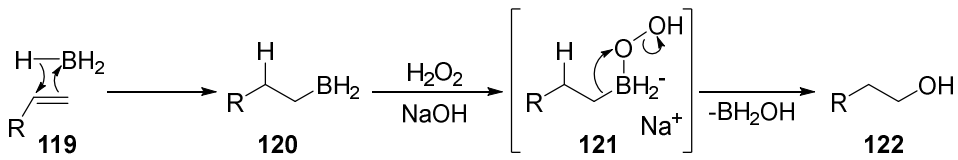
In case of unsymmetrical alkenes, the carbocation is formed at the most stable position and this is followed by addition of the hydroxyl group. This occurs at the most substituted carbon and leads to the formation of Markovnikov products.

An alternative way to access these products is to perform an oxymercuration-reduction reaction (Scheme 51). The alkene reacts in a concerted manner with aqueous mercury (II) acetate to form a mercurium ion, which is able to stabilise the positive charge and prevent cation rearrangement. Water then reacts at the most substituted carbon, giving an anti-addition product and finally demercuration occurs *via* reduction with a metal hydride such as sodium borohydride.[18-20]



Scheme 51 *Mechanism for the oxymercuration-reduction of alkenes to synthesise alcohols at the most substituted carbon*

To access the opposite anti-Markovnikov regioisomer, hydroboration-oxidation can be employed (Scheme 52).[21] This two-step process consists of an initial hydroboration step, whereby concerted *syn* addition of borane to the alkene occurs, to give an organoborane compound with anti-Markovnikov regiochemistry (**120**). This regiochemistry arises due to the higher electronegativity of hydrogen (2.2) when compared to boron (2.0), and so the partial positive charge is more stabilised at the most substituted alkene carbon.[22]



Scheme 52 *Hydroboration-oxidation of alkenes to give the opposite anti-Markovnikov regioisomer*

This is then followed by oxidation of the organoborane compound (**120**) using hydrogen peroxide, which proceeds with retention of stereochemistry. Deprotonation of the hydrogen peroxide using sodium hydroxide gives the more nucleophilic conjugate base. This can then

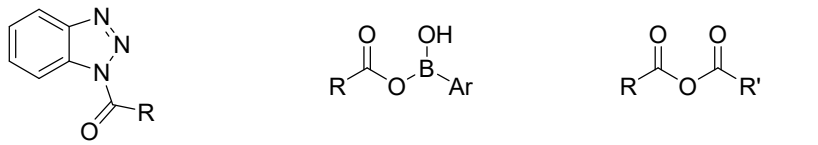
add to the empty orbital of boron to form a negatively charged boron species (**121**). Following this, migration of the C-B bond onto oxygen occurs, proceeded by hydrolysis to eliminate borinic acid and give the desired alcohol product (**122**).[2]

1.2.4 Reduction of Carbonyl Compounds

Carbonyl compounds such as aldehydes, ketones, carboxylic acids and esters are commonly reduced with stoichiometric borohydride (Introduction Section 2.1.2) or aluminium hydride reagents (Introduction Section 2.1.1), however these reagents can exhibit poor chemoselectivity and are air and moisture sensitive. To combat these problems, borane reagents (Introduction Section 2.1.3) or catalytic hydrogenation (Introduction Section 2.2.1) are utilised as alternatives.

1.2.5 Reduction of Carboxylic Acids

Carboxylic acids are frequently used as starting materials for organic reactions due to their stability, wide availability and low cost.[23-26] An orthogonal strategy to using traditional stoichiometric metal hydride reductions is to convert carboxylic acids to activated derivatives, which include benzotriazoles (**123**),[27-30] boronic acid esters (**124**)[31-32] and mixed anhydrides (**125**) (Figure 16).[33-36] These derivatives can be reduced to alcohols under much milder conditions, allowing greater functional group tolerance. Despite these advantages, the stoichiometric conversion of carboxylic acids into activated derivatives requires the use of additional stoichiometric reagents, which is not atom efficient.[37]

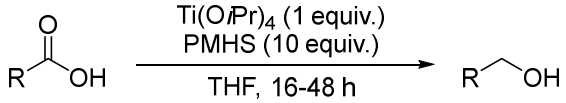


123 *N*-acylbenzotriazoles **124** Boronic Acid Esters **125** Mixed Anhydrides

Figure 16 *Activated derivatives utilised in the reduction of carboxylic acids*

There have been a variety of catalytic reductions of carboxylic acids disclosed in the literature, which employ the use of pinacol borane or hydrosilanes as the terminal reductant.[32, 38] In particular, the combination of hydrosilanes with a metal catalyst presents

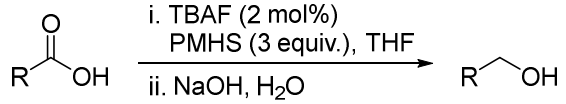
an attractive alternative to the traditional metal hydride reduction methods, as hydrosilanes are easy to handle, stable to air and moisture, and are non-toxic. However, when compared to other carbonyl containing groups, such as amides or esters, there have been limited reports of carboxylic acid hydrosilylations. The first hydrosilane-mediated reduction of carboxylic acids was reported by Breeden and Lawrence in 1994, using a combination of titanium(IV) isopropoxide and PMHS (Scheme 53).[39]



Scheme 53 *Hydrosilane and titanium isopropoxide-mediated reduction of carboxylic acids to alcohols reported by Breeden and Lawrence[39]*

It is proposed that the reaction proceeds *via* a silyl ester intermediate (Introduction Section 1.3.2), which is supported by observation of vigorous hydrogen evolution on addition of the titanium(IV) isopropoxide to the reaction mixture. However, the reaction is not catalytic, requiring stoichiometric quantities of both titanium(IV) isopropoxide and ten equivalents of PMHS in the reaction. Additionally, only ethers and nitro groups have been reported to be compatible under the reaction conditions.

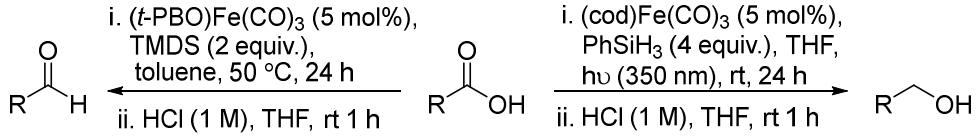
Subsequently, the first catalytic hydrosilylation of carboxylic acids to give alcohol products was disclosed by Lawrence and co-workers which utilised PMHS as the terminal reductant, in combination with catalytic quantities of TBAF (Scheme 54).[40]



Scheme 54 *First catalytic hydrosilylation of carboxylic acids to give alcohols using TBAF and PMHS[40]*

It is also proposed that the reaction, which is also effective in the reduction of esters to alcohols, initially gives a silyl ether product, which can then be cleaved to the alcohol upon addition of sodium hydroxide to the reaction mixture. Again, the functional group tolerance of the reaction is quite limited as only halide- or ether-substituted benzoic acids have been reported.[40]

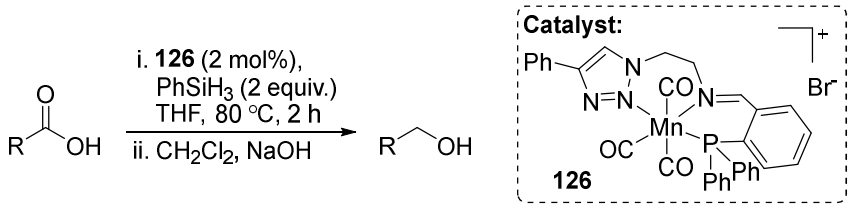
In 2012 Darcel and co-workers reported an iron-catalysed hydrosilylation reduction of carboxylic acids that is switchable, and can produce either aldehyde or alcohol products (Scheme 55).[41]



Scheme 55 *Switchable catalytic hydrosilylation of carboxylic acids to give either aldehyde or alcohol products*[41]

Iron-carbonyl complexes containing labile bidentate ligands ($Fe(CO)_3L$) were selected as catalysts for the reduction reactions. When the *trans*-4-phenyl-but-3en-2-one (t-PBO) ligand is utilised in combination with TMDS, an aldehyde product is obtained, whereas if 1,5-cyclooctadiene (COD) is employed in combination with phenylsilane and UV irradiation, the alcohol product is achieved.[41]

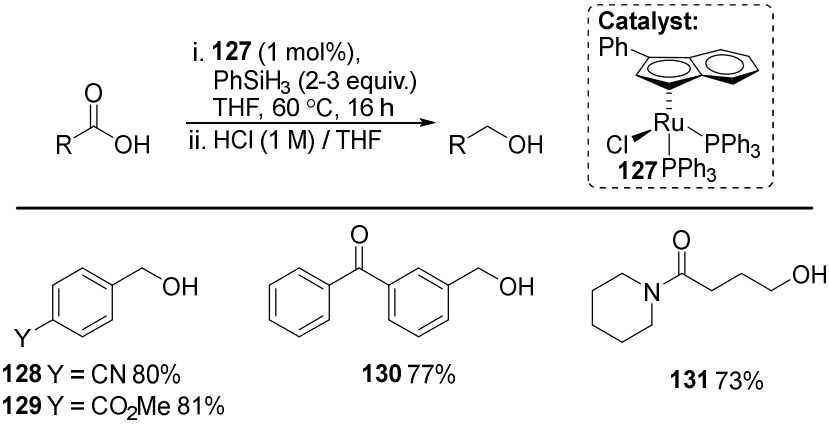
Other metals are also active in the hydrosilane-mediated reduction of carboxylic acids. Sakai *et al.* reported that catalytic indium bromide and TMDS were effective for the reduction of aliphatic carboxylic acids[42] and Lemaire and co-workers disclosed a copper triflate and TMDS system which is successful in the reduction of both aromatic and aliphatic carboxylic acids.[43] Additionally, Leitner and co-workers reported a manganese-catalysed reduction in combination with phenylsilane (Scheme 56).[44]



Scheme 56 *Manganese-catalysed reduction of carboxylic acids to alcohols reported by Leitner and co-workers*[44]

The reaction utilises a novel manganese(I) catalyst **126** and is able to reduce both aromatic and aliphatic carboxylic acids in good yield. In addition, the same catalyst (**126**) can also be utilised to reduce ketones and esters to the corresponding alcohols.

Nagashima and co-workers demonstrated the use of a tri-ruthenium carbonyl catalyst in combination with phenylsilane.[45] More recently, Nolan and co-workers reported an alternative ruthenium-catalysed reduction of carboxylic acids using phenylsilane and a $RuCl(PPh_3)_2$(3-phenylindenyl) catalyst **127** (Scheme 57).[46]

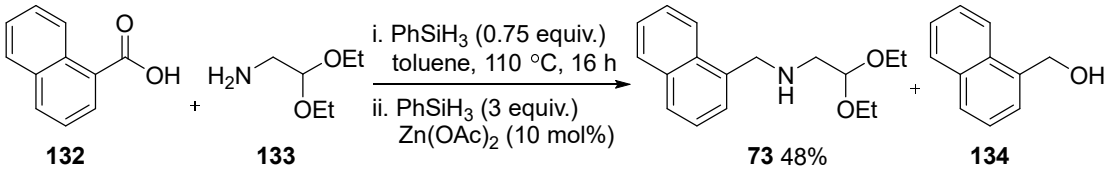


Scheme 57 *Chemoselective reduction of carboxylic acids to alcohols using a Ru catalyst reported by Nolan and co-workers[46]*

The reaction is much more chemoselective than previously reported methods, allowing reduction of carboxylic acids in the presence of other potentially reducible functional groups, such as esters, nitriles, amides and most notably, ketones in good yield (Scheme 57). It is proposed that the selectivity results from the formation of silyl esters *in situ* which are able to be selectively reduced, using the ruthenium catalyst **127**. Despite the high chemoselectivity of the reaction, the catalyst is not commercially available, and reactions must be performed using Schlenk techniques.[46]

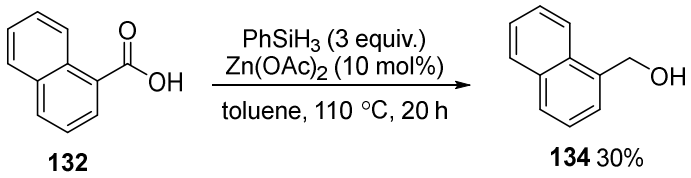
2 Results and Discussion

Given that zinc acetate has been described as a catalyst for the hydrosilylation of tertiary amides,[47] it was reasoned that a zinc acetate/silane system could potentially also be applied to the reduction of carboxylic acids. During the reductive amination of 1-napthoic acid (**132**) and 2,2-diethoxyethan-1-amine (**133**), the corresponding alcohol (**134**) was observed as a side product (Scheme 58). It is hypothesised that amidation was sluggish and therefore the excess residual carboxylic acid (**132**) was also reduced *in situ*.



Scheme 58 *Alcohol (**134**) observed as a side product in reductive amination reaction of 1-napthoic acid (**132**) and 2,2-diethoxyethan-1-amine (**133**)*

Direct reduction of 1-napthoic acid (**132**) to the corresponding alcohol (**134**) was attempted using the standard reduction conditions used in the reductive amination reaction with an extended reaction time (Scheme 59).

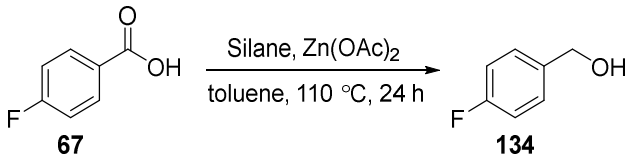


Scheme 59 *Reduction of 1-napthoic acid **132** to the corresponding alcohol to provide a proof of concept that zinc acetate-catalysed reductions are possible*

Pleasingly, the reaction was successful and gave 30% of 1-napthlenemethanol product (**134**), providing a proof of concept that reduction of carboxylic acids is possible using this system, and with further optimisation could be a useful tool in organic synthesis.

2.1 Reaction Optimisation

4-Fluorobenzoic acid (**67**) was selected as a test substrate for reaction optimisation, as yields could be obtained using ^{19}F NMR spectroscopy. Initially a range of hydrosilanes were trialled in the reaction to ascertain which were effective reductants (Table 8).



67 **134**

Table 8 *Optimisation of carboxylic acid reduction using a range of different silanes*
a – Yields measured by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard

Entry	Hydrosilane	Silane equiv.	$Zn(OAc)_2$ mol%	Yield[a] / %
1	Diethylsilane	5	10	1
2	Diphenylsilane	5	10	6
3	Phenylsilane	5	10	95
4	Triethylsilane	5	10	0
5	Triethoxysilane	5	10	22
6	Triphenylsilane	5	10	0
7	PMHS	5	10	0
8	PMHS	10	10	0

A number of hydrosilanes proved to be mostly ineffective in the reduction of the carboxylic acid (**67**), including diethylsilane (Table 8, entry 1), diphenylsilane (Table 8, entry 2), triethylsilane (Table 8, entry 4), triphenylsilane (Table 8, entry 6), and PMHS (Table 8, entries 7 and 8). The use of triethoxysilane (Table 8, entry 5) gave 22% of the desired alcohol product (**134**), however when phenylsilane was employed (Table 8, entry 3) this resulted in a significant increase in the yield to 95%.

With the ideal hydrosilane for the zinc acetate-catalysed reduction identified, work was then focused on optimisation of the reaction parameters. Initially, the amount of phenylsilane required for the reaction was investigated, with a minimal decrease in yield observed when the amount of phenylsilane was reduced from 5 equivalents (Table 9, entry 1) to 2 equivalents (Table 9, entry 3). However, when the amount of phenylsilane was reduced further to 1 equivalent (Table 9, entry 4), a significant decrease in the yield of the desired product (**134**) to only 10% was observed.

Attempts at reducing the temperature of the reaction in toluene were unsuccessful due to poor substrate solubility at lower temperatures. However, changing the solvent to 2-Me THF (Table 9, entry 5), derived from natural sources such as sugars in biomass,[48] allowed the temperature of the reaction to be lowered to 80 °C without a reduction in the yield of the desired product (**134**).

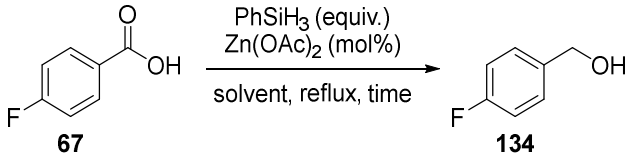
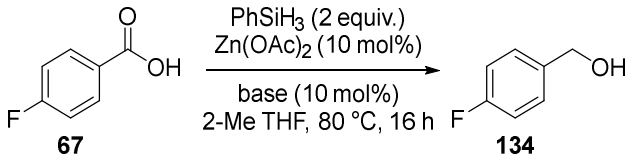


Table 9 *Optimisation of zinc acetate-catalysed reduction of carboxylic acids. a – Yields measured by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. b – Isolated yield.*

Entry	$PhSiH_3$ / equiv.	$Zn(OAc)_2$ / mol%	Solvent	Time / h	Yield[a] / %
1	5	10	Toluene	24	95
2	3	10	Toluene	24	82[b]
3	2	10	Toluene	24	90
4	1	10	Toluene	24	10
5	2	10	2-Me THF	24	91
6	2	10	Toluene	16	51

Following this, a reduction in the reaction time was attempted from 24 hours (Table 9, entry 3) to 16 hours (Table 9, entry 6), however this resulted in a decrease in yield from 90% to only 51% of the desired product (**134**). The remainder of the mass balance in this reaction was the carboxylic acid starting material, suggesting the cause of the low yield was due to incomplete reaction. If a method to increase the rate of the reaction could be identified, this could provide a way to obtain good yields in a shorter reaction time.

It had been previously shown that amines catalyse reactions between hydrosilanes and carboxylic acids to generate silyl esters, which act as both activated carboxylic acids and more crucially enhanced reductants when compared to the parent silane.[49] It was reasoned that the addition of a tertiary amine to the reaction mixture could catalyse the formation of silyl esters and help to increase the rate of reaction (Table 10).



67 **134**

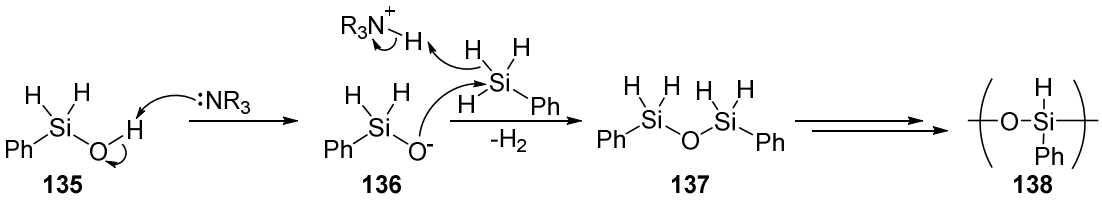
Table 10 *Reduction of 4-fluorobenzoic acid (**67**) with the addition of catalytic base. a – Yields measured by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard*

Entry	Base	pKaH[50]	Yield[a] / %
1	-	-	53
2	NMM	7.38	87
3	Triethylamine	10.60	70
4	DBU	12.50	53

Gratifyingly, the addition of 10 mol% NMM (Table 10, entry 2) to the reaction mixture resulted in an increase in the yield of the desired alcohol from 53% to 87%. Different bases with range of pKaH (water) values were trialled in the reaction to ascertain their effect on the yield. As the pKaH value increased from 7.38 using NMM (Table 10, entry 2) to 12.50 using 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) (Table 10, entry 4), the yield decreased from 87% to 53%, comparable to the rate of reaction without the use of any base. The use of a milder base allows deprotonation of the carboxylic acid substrate without promotion of unproductive side reactions.

It is hypothesised that silanols, which are proposed to be by-products of carboxylic acid reduction, can be deprotonated using stronger bases to give siloxides (**136**). These siloxides (**136**) can participate in a competing reaction with phenylsilane, leading to the formation of siloxanes (**137**) and potentially polysiloxanes (**138**). However, this process consumes some of the phenylsilane in the reaction mixture, reducing the amount which is available to effect the reduction reaction, resulting in lower yields of the desired product (**134**) (

Scheme 60).



Scheme 60 *Proposed formation of siloxanes (**137**) and polysiloxanes (**138**) via deprotonation of silanol by-products.*

Finally, the amounts of zinc acetate and NMM catalysts in the reaction were investigated. A control reaction without any zinc acetate or NMM (Table 11, entry 1) did not show any reduction of 4-fluorobenzoic acid. This was also observed when 20 mol% of NMM was used without any zinc acetate catalyst in the reaction (Table 11, entry 2), showing that zinc acetate is essential for the reduction to occur. When the amount of NMM was increased from 5% to 20% (Table 11, entries 4-6), the yield was also increased, with 99% of the desired product (**134**) obtained after 16 h on addition of 20 mol% NMM (Table 11, entry 6).

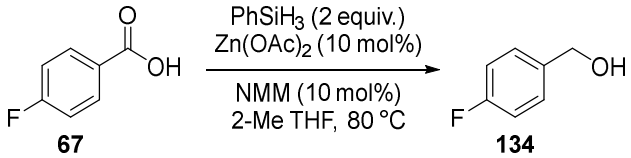


Table 11 *Optimisation of zinc acetate- and NMM-catalysed reduction of carboxylic acids.*
a - Yield determined by ^{19}F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard.

Entry	$Zn(OAc)_2$ / mol%	NMM / mol%	Time / h	Yield[a] / %
1	0	0	24	0
2	0	20	24	0
3	10	0	16	53
4	10	5	16	83
5	10	10	16	87
6	10	20	16	99
7	5	10	16	49
8	10	20	6	72

A reduction of the zinc acetate loading was also attempted (Table 11, entry 7), however use of 5 mol% zinc acetate lead to a decreased yield of alcohol of 49%. Additionally, attempts were made to further decrease the reaction time (Table 11, entry 8), however a reduction in yield was also observed. A balance between the quantity of reagents required and the reaction yield was found using 10 mol% of both zinc acetate and NMM (Table 11, entry 5) and these conditions were selected for exploring the scope of the reaction.

2.2 Substrate Scope

A range of commercially available carboxylic acids were subjected to the reaction conditions (Figure 17), giving good to very good results. Various substituted electron withdrawing (**143**, **142** and **147**) and electron donating (**144**) aromatic carboxylic acids were examined, as well as aryl halides (**139**, **140**, **141** and **143**) and a boron pinacol ester (**146**).

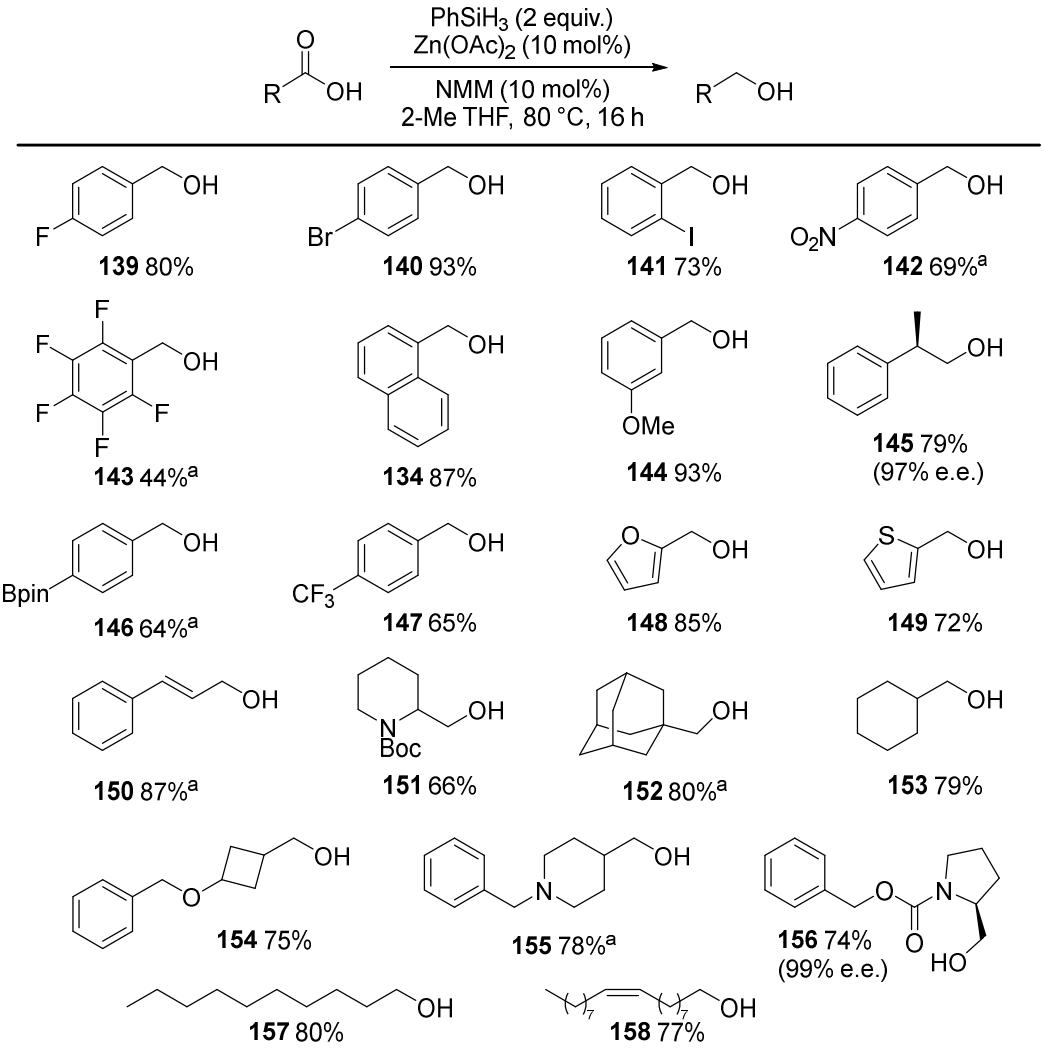
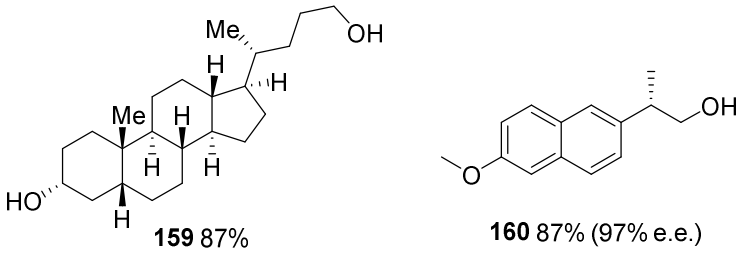


Figure 17 *Scope of the zinc acetate- and NMM-catalysed reduction of carboxylic acids to the corresponding alcohol. a – Conditions: $PhSiH_3$ (2 equiv.), $ZnOAc_2$ (10 mol%), NMM (10 mol%), toluene, 110 °C, 16 h*

Other aromatic carboxylic, acids such as naphthoic acid (**134**), 2-furancarboxylic acid (**148**) and 2-thiophenecarboxylic acid (**149**), were also reduced in good yields. Aliphatic carboxylic acids were also reduced in good to very good yields with both cyclic (**151**, **152**, **153**, **154**, **155** and **156**) and linear (**157** and **158**) substrates well tolerated. Hindered substrates such as adamantane carboxylic acid (**152**) and substrates containing strained rings, such as 3-(benzyloxy)cyclobutyl methanol (**154**) were also successfully reduced in good yield. Difficulties were observed with more acidic carboxylic acids, such as pentafluorobenzoic acid (**143**) with a pK_a (water) of 1.60, which only gave 44% yield of the desired product.

A variety of protecting groups were also compatible under the reaction conditions, such as Boc groups (**151**), benzyl groups (**154** and **155**) and Cbz groups (**156**). It was also found that enantiopure carboxylic acids could also be reduced without any significant racemisation of the stereocentre (**130** and **156**) with very good e.e. observed in both cases. Of particular interest is that enantiopure amino acids such as Cbz-L-proline (**156**) can be reduced in very good yield and e.e.. Additionally, APIs such as lithocholic acid (**159**) and naproxen (**160**) were successfully reduced in good yield and e.e. (Figure 18).



159 87% **160** 87% (97% e.e.)

Figure 18 *Reductions of carboxylic acids in Active Pharmaceutical Ingredients*

Initially, several substrates (**142**, **143**, **146**, **150**, **152** and **155**) gave low reaction yields, as they were poorly soluble in 2-Me THF at reflux. However, changing the solvent to toluene at reflux improved the solubility of the substrates and allowed the reduction to proceed in good to very good yields.

Subsequently, attempts were made to ascertain the chemoselectivity of the zinc acetate and NMM-catalysed carboxylic acid reduction reaction. A range of carboxylic acids containing potentially reducible functional groups were selected and were subjected to the reaction conditions (Figure 19).

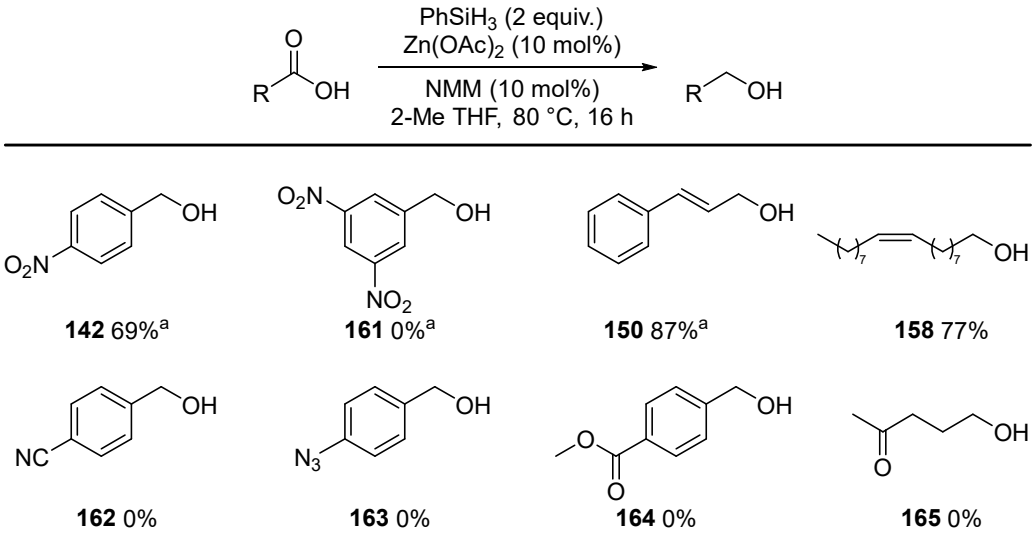
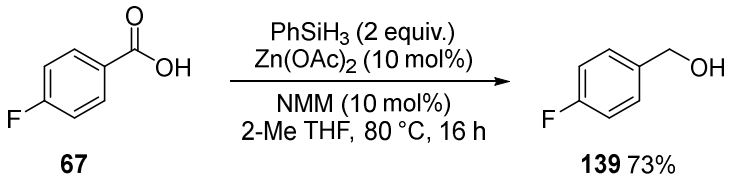


Figure 19 *Attempts at chemoselective reductions of carboxylic acids in the presence of potentially reducible functional groups. a – Reactions performed in toluene at reflux.*

Substrates containing nitro groups (**142**), α,β-unsaturated carboxylic acids (**150**) and fatty acids (**158**) were able to be successfully reduced chemoselectively in good yields. However, unlike had been observed with 4-nitrobenzoic acid, 3,5-dinitrobenzoic acid showed poor solubility even in toluene at reflux, resulting in a lack of desired product obtained (**161**). Additionally, substrates containing ester (**164**), nitrile (**162**), azide (**163**) and ketone (**165**) functional groups were unsuccessful in providing a chemoselective reduction, as a mixture of products was produced.

The standard protocol involves carrying out reactions in round bottom flasks fitted with a reflux condenser under a nitrogen or argon atmosphere in anhydrous solvent, but it was investigated whether rigorous anhydrous conditions were essential. A 7 mmol reduction was performed using 4-fluorobenzoic acid in Winchester grade 2-Me THF and open to air in glassware that had not been dried (Scheme 61).



67 **139** 73%

Scheme 61 *1 g scale carboxylic acid reduction of 4-fluorobenzoic acid (**67**) in Winchester grade 2-Me THF with the reaction vessel open to the air*

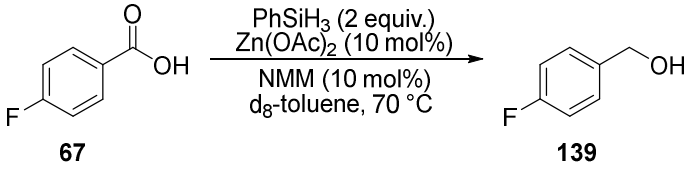
Not only did this reaction only show a minor decrease in the reaction yield from 80% to 73%, it also demonstrated that it was possible to perform this reaction on a larger scale than the 1 mmol reactions which had been utilised for investigating the substrate scope.

2.3 Mechanistic Investigations

Having explored the scope and chemoselectivity of the zinc acetate and NMM-catalysed reduction of carboxylic acids, experiments were then carried out to probe the role played by NMM in the reaction and ascertain an insight into the mechanism of the reaction. It is clear from optimisation of the reaction that the reduction is successful without the addition of NMM. However, when present in the reaction mixture NMM acts to increase the rate of the reaction and, in combination with zinc acetate, facilitates a more rapid reduction of carboxylic acids to the corresponding alcohols.

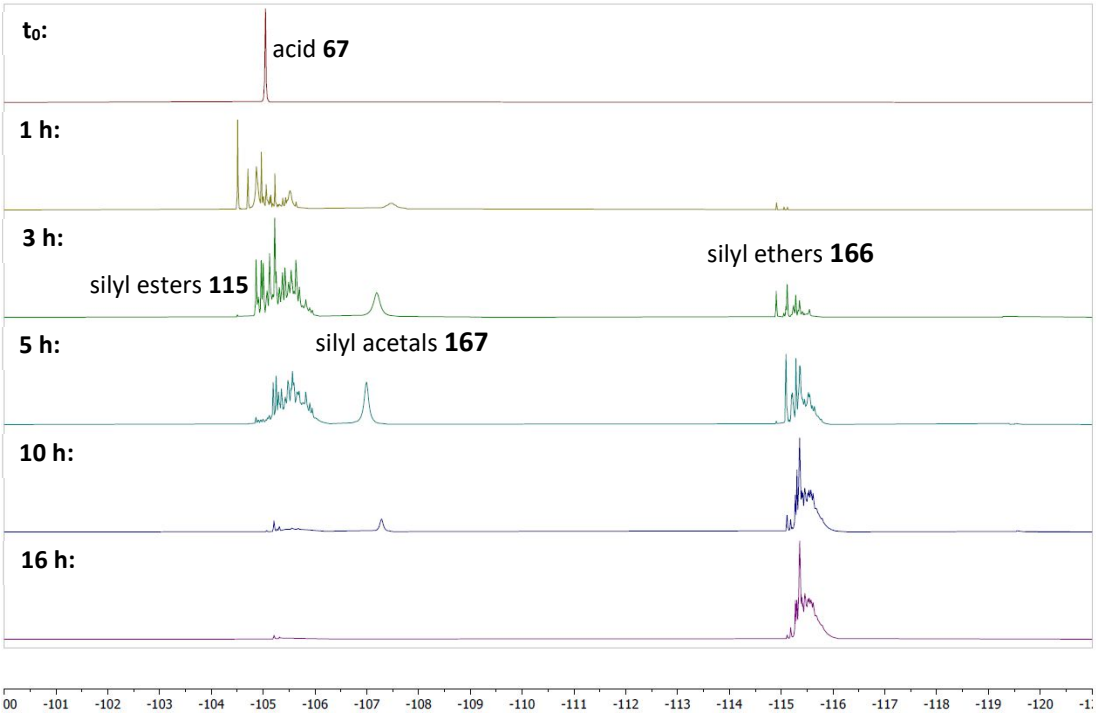
An initial reaction to investigate the mechanism of the reaction was performed, whereby ^{19}F NMR was used to monitor the reduction of 4-fluorobenzoic acid **67** (^{19}F δ = -105.76 ppm) to the corresponding benzyl alcohol **139** (Figure 20). As shown in Figure 20, rapid formation of silyl esters (**115**) (^{19}F δ = -104.5 to -106.2 ppm) from reaction between the carboxylic acid (**67**) (δ = - 105.1 ppm) and phenylsilane was initially observed. Over the course of the reaction, a reduction in the amount of silyl esters (**115**) present and an increase in the amount of silyl ethers (**166**) (^{19}F δ = -114.9 to -116.0 ppm) is observed. A third species (^{19}F δ = -107.0 to -107.5 ppm) is also observed, which is proposed to correspond with silyl acetals **167**. After 16

hours of reaction time only silyl ethers (**166**) are observed, which are cleaved to give the desired product on work up.



67 **139**

Figure 20 *^{19}F NMR spectra of the reduction of 4-fluorobenzoic acid (**67**) using a zinc acetate and NMM dual catalytic system*



Subsequently, ^{19}F NMR analysis was performed on the same reduction but without the addition of NMM, in an attempt to ascertain the role of NMM in the reaction (Figure 21). After 1 hour of reaction time it was observed that the formation of silyl esters (**115**) was significantly slower in the absence of NMM, with mainly 4-fluorobenzoic acid (**67**) starting material present. Over the course of the reaction the generation of silyl esters (**115**) was observed at a significantly slower rate, hypothesised to be due to lack of deprotonation of the carboxylic acid (**67**). Reduction of silyl esters (**115**) to silyl ethers (**166**) was also consequently diminished. After 16 hours reaction time without NMM present, silyl esters (**115**) are mainly observed with a limited amount of silyl ethers (**166**), whereas there is complete conversion to silyl ethers (**166**) in the presence of NMM.

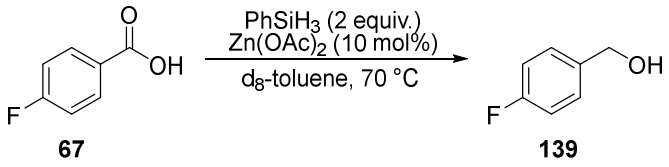
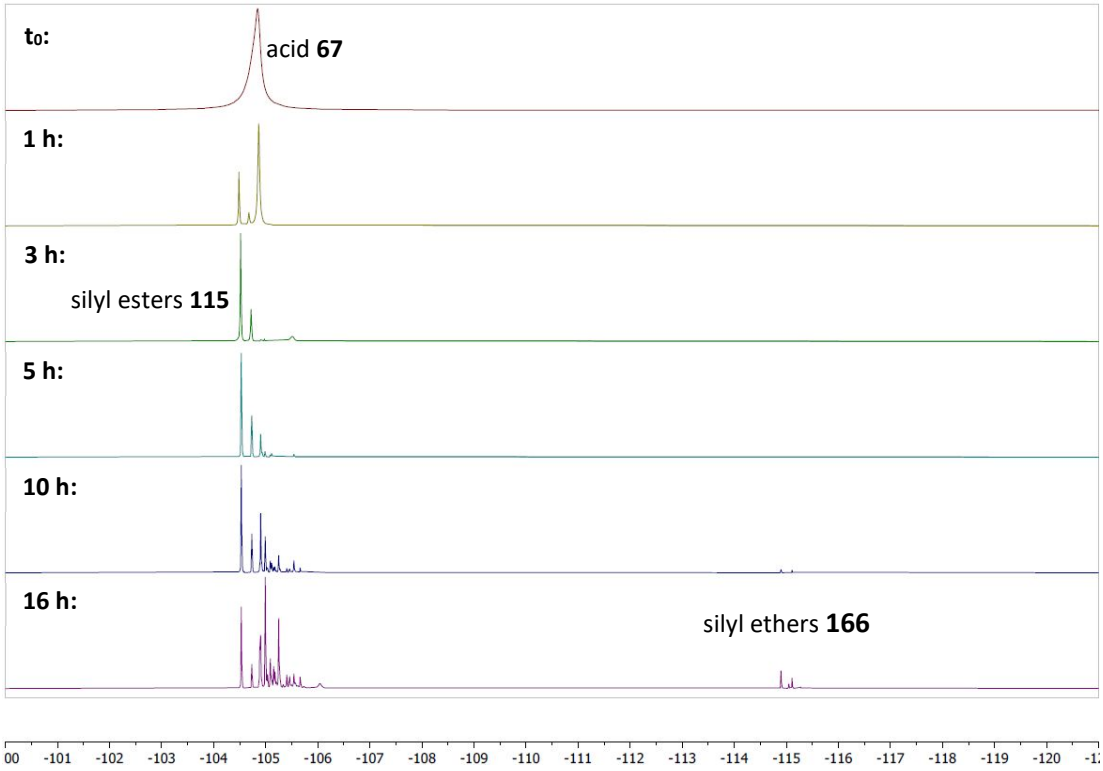
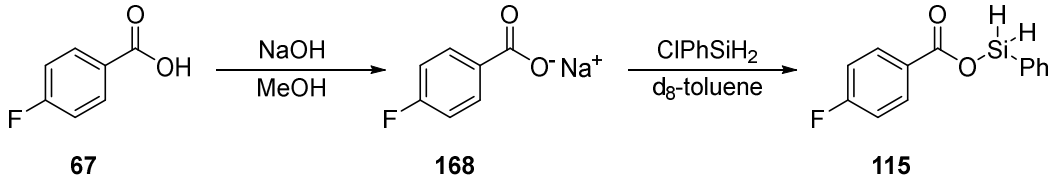


Figure 21 *^{19}F NMR spectra of the reduction of 4-fluorobenzoic acid (**67**) in the absence of NMM*

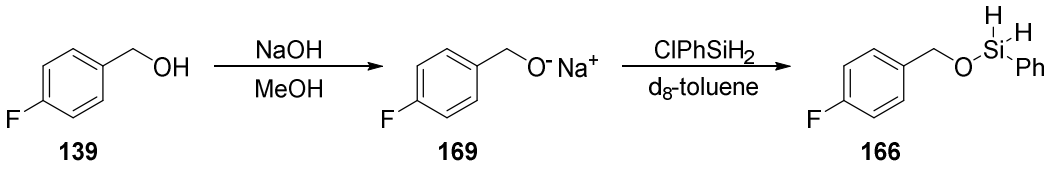


Having observed species that are believed to be silyl ester (**115**) and silyl ether (**166**) intermediates in the reaction, independent syntheses of both of these species were performed. Commencing with silyl esters (**115**), sodium 4-fluorobenzoate (**168**) was synthesised by reaction of 4-fluorobenzoic acid (**67**) and sodium hydroxide, and directly used in a reaction with chlorophenylsilane (Scheme 62).



Scheme 62 *Independent synthesis of silyl esters (**115**) from sodium 4-fluorobenzoate (**168**) and chlorophenylsilane*

Following this, independent synthesis of silyl ethers was then performed, using 4-fluorobenzyl alcohol (**139**) and chlorophenylsilane, *via* formation of sodium (4-fluorophenyl)methanolate (**169**) (Scheme 63).



139 **169** **166**

Scheme 63 *Independent synthesis of silyl ethers (**166**) from sodium (4-fluorophenyl)methanolate (**169**) and chlorophenylsilane*

The ^{19}F NMR spectra of the independently synthesised proposed intermediates were compared with the ^{19}F NMR spectrum of the reduction reaction (Figure 22). As shown in Figure 22, both of the independently synthesised silyl esters (^{19}F δ = -104.8 to -106.9) (**115**) (Figure 22A) and silyl ethers (^{19}F δ = -115.3 to -116.4) (**166**) (Figure 22C) corresponded with the ^{19}F NMR shifts of the intermediates observed in the reduction reaction (Figure 22B), providing further evidence to support the proposed hypothesis.

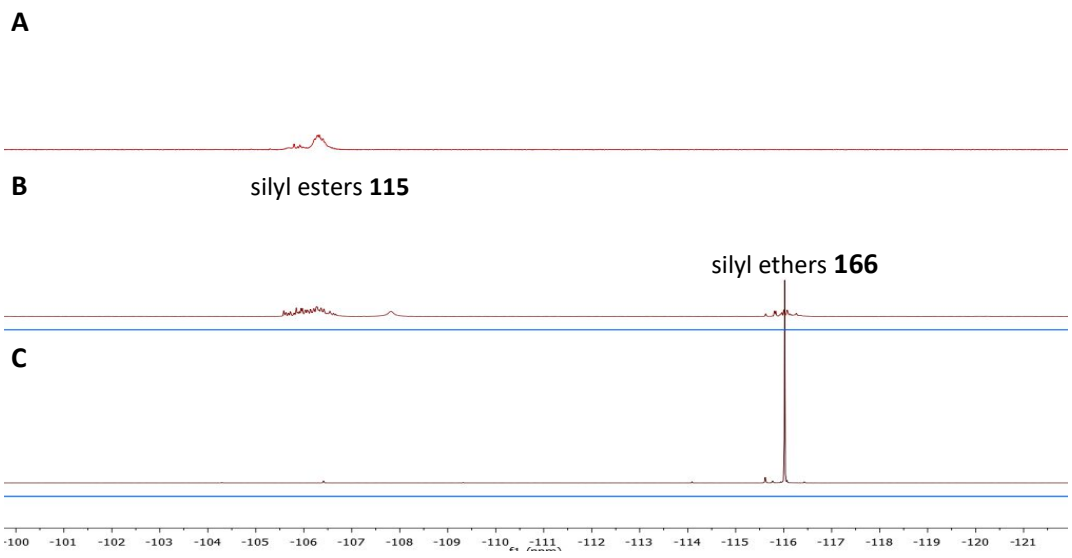
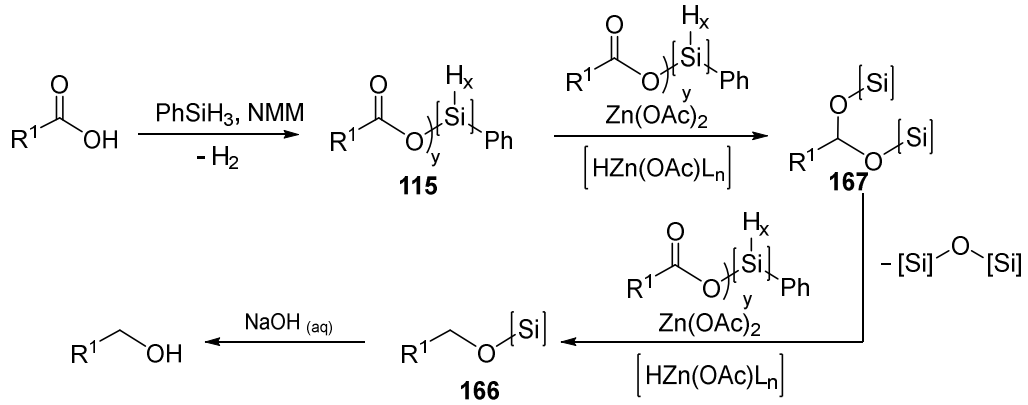


Figure 22 *^{19}F NMR spectra of the proposed reduction reaction intermediates. **A** – ^{19}F NMR of independently synthesised silyl ester. **B** – ^{19}F NMR of carboxylic acid reduction reaction. **C** – ^{19}F NMR of independently synthesised silyl ether.*

Based on the observations from the ^{19}F NMR reaction monitoring and independent synthesis of reaction intermediates, the reaction pathway shown in Scheme 64 is proposed. The initial step of the proposed mechanism is the formation of a silyl ester (**115**), generated by initial

deprotonation of the carboxylic acid by NMM, followed by a dehydrogenative coupling between the carboxylate and phenylsilane.



Scheme 64 *Proposed mechanism for the dual-catalyst system for the reduction of carboxylic acids*

Zinc acetate reacts rapidly with an additional silyl ester (**115**), generating a zinc hydride species, which reduces the silyl ester (**115**) to a silyl acetal (**167**). This intermediate can be further silylated and undergo elimination of a disiloxane (not shown) resulting in an oxocarbenium ion that can be further reduced by another zinc hydride species or a silane to give silyl ethers (**166**) and regenerating the zinc acetate catalyst. Finally, during work-up hydrolysis of silyl ethers (**166**) occurs to give the desired alcohol product. It is possible that the carboxylic acid can exchange with the acetate ligands on zinc, but for simplicity this has not been shown.

2.4 Conclusions

In conclusion, a robust dual catalytic reduction protocol has been developed which is applicable to a wide range of substrates. The reaction proceeds *via* activation using hydrosilanes, limiting the amount of stoichiometric waste produced in the reaction. The catalysts utilised in the reaction are widely, cheaply and routinely available in most laboratories and the method is both air and moisture stable making it amenable to a typical flask/condenser set-up. Finally, elucidation of the key role played by silyl esters has allowed mechanistic insights to be gained, which could be applied to the design of future reduction protocols.

3 Experimental

3.1 General Experimental

Reagents were purchased from commercial suppliers and used directly without further purification. Solvents were dried according to published methods[51] and distilled before use; except for toluene which was pre-dried over sodium wire and obtained from a solvent tower, where degassed solvent was passed through two columns of activated alumina and 7-micron filter under a 4-bar pressure. Petrol refers to the fraction of petroleum ether boiling between 40–60 °C. All water was deionised before use, and unless specified, all experiments were carried out in oven dried glassware with an argon balloon atmosphere.

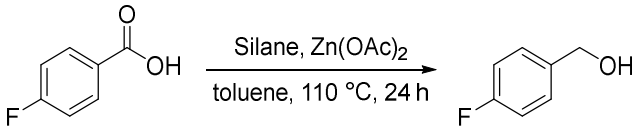
Analytical Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed silica-gel plates 60 F_{254} plates and visualized by ultraviolet (UV) irradiation (254 nm) or by staining with a solution of potassium permanganate or ninhydrin. Column chromatography was carried out using Fluorochem silica gel 60 Å (40-63 mesh). Melting points were calculated using a Stuart SMP3 and Fourier Transform Infrared Spectrometry (IR) was carried out using a Bruker Tensor 27 using an Attenuated Total Reflection (ATR) attachment and peaks are reported in terms of frequency of absorption (cm^{-1}). High Resolution Mass Spectrometry (HRMS) were measured on a Bruker microTOF II with Electron Spray Ionisation (ESI). Specific rotations ([α]D) were measured using an Anton Paar MCP 100 Modular Circular Polarimeter.

^{1}H NMR spectra were recorded on either a Bruker AV 400, AV(III) 400HD or AV(III) 500HD in $CDCl_3$ or d_6-DMSO. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) are given in Hertz (Hz), with residual protic solvent as the internal reference ($CDCl_3$ δ = 7.26 ppm, d_6-DMSO δ = 2.50 ppm). The proton spectra are reported as follows: δ (multiplicity, coupling constant *J*, number of protons). ^{13}C NMR were recorded on a 400 MHz spectrometer, chemical shifts (δ) were reported in ppm relative to the ^{13}C signals in the solvent (central peak of $CDCl_3$ δ = 77.16 ppm, d_6-DMSO δ = 39.52) and coupling

constants (*J*) are given in Hertz (Hz). All ^{13}C NMR are reported as proton decoupled spectra. ^{19}F NMR were recorded on a 376 MHz spectrometer, chemical shifts (δ) were reported in ppm relative to $CFCl_3$ at 0.00 ppm and are reported as proton decoupled spectra.

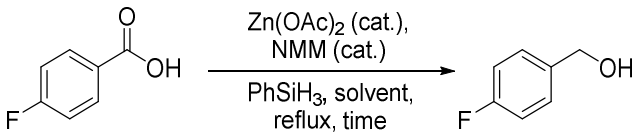
3.2 Reaction Optimisation

Silane Screening



To a solution of 4-fluorobenzoic acid (140 mg, 1.00 mmol) and zinc acetate (18.4 mg, 0.1 mmol) in toluene (1.2 mL) at reflux was added silane (see table) dropwise. The reaction mixture was stirred at reflux for 24 hours before NaOH (2 mL of a 2 M aqueous solution) was added to the reaction mixture dropwise and it was stirred for a further 30 mins. The pH was adjusted to pH 5 using HCl (1 M aqueous solution), and the product was extracted using EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. α,α,α-Trifluorotoluene (146 mg, 1.00 mmol) was added to the crude product and the yield was calculated using ^{19}F NMR.

Optimisation of Reaction Conditions



To a solution of 4-fluorobenzoic acid (140 mg, 1.00 mmol) and zinc acetate (mol% as table) in solvent (see table, 1.2 mL) at reflux was added phenylsilane (equiv. as table) and *N*-methyl morpholine (mol% as table) dropwise. The reaction mixture was stirred at reflux for time (see table) before NaOH (2 mL of a 2 M aqueous solution) was added to the reaction mixture dropwise and it was stirred for a further 30 mins. The pH was adjusted to pH 5 using HCl (1 M aqueous solution), and the product was extracted using EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. α,α,α-

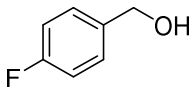
Trifluorotoluene (146 mg, 1.00 mmol) was added to the crude product and the yield was calculated using ^{19}F NMR.

3.3 Substrate Scope

General Procedure 1 – Reduction of Carboxylic Acids

To a solution of carboxylic acid (1.00 mmol) and zinc acetate (18.3 mg, 0.1 mmol) in 2-Me THF (1.2 mL) at reflux was added phenylsilane (247 µL, 2.00 mmol) dropwise, followed by *N*-Me morpholine (11.0 µL, 0.1 mmol). The reaction mixture was stirred at reflux for 16 h, after which it was allowed to cool. NaOH (2 mL of a 2 M aqueous solution) was added to the reaction mixture dropwise and it was stirred for a further 30 mins. The pH was adjusted to pH 5 using HCl (1 M aqueous solution), and the product was extracted using EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography to give the desired product.

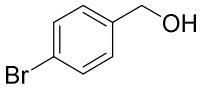
(4-Fluorophenyl)methanol (139)



Prepared according to general procedure 1, using 4-fluorobenzoic acid (140 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 2:3, R_f = 0.24) to afford the desired product as a colourless oil (114 mg, 0.900 mmol, 90%).

IR (ATR) ν_{max}/cm^{-1} 3311, 1604, 1509, 1429, 1221, 1131; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.07 – 7.00 (m, 2H), 4.63 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4 (d, *J* = 245.6 Hz), 136.7 (d, *J* = 3.5 Hz), 128.9 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 21.6 Hz), 64.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.91; GCMS [EI ($M + H^+$)] m/z calculated for C_7H_7OF 126.0475, found 126.0474. The data matches those found in the literature.[52]

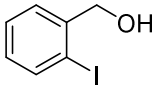
(4-Bromophenyl)methanol (140)



Prepared according to general procedure 1, using 4-bromobenzoic acid (201 mg, 1.00 mmol), and the crude product was purified by column chromatography (pure petrol to EtOAc / petrol 1:1 (EtOAc / petrol 2:3 R_f = 0.23)) to afford the desired product as a colourless solid (173 mg, 0.930 mmol, 93%), mp 76-77 °C.

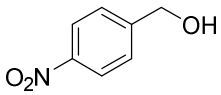
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.57 (s, 2H) 2.40 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.7, 131.5, 128.5, 121.3, 64.3. The data matches those found in the literature[53]

(2-Iodophenyl)methanol (141)



Prepared according to general procedure 1, using 2-iodobenzoic acid (248 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 1:4, R_f = 0.14) to afford the desired product as a colourless solid (172 mg, 0.730 mmol, 73%), mp 90 - 91 °C. **IR** (ATR) ν_{max}/cm^{-1} 3229, 2395, 1445, 1433, 1362, 1196, 1051, 1034, 1010; **^{1}H NMR** (400 MHz, MeOD) δ 7.81 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.38 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.99 (dd, *J* = 7.5, 7.5 Hz, 1H), 4.59 (s, 2H); **^{13}C NMR** (101 MHz, MeOD) δ 144.3, 140.1, 129.8, 129.3, 128.8, 97.5, 69.3; **HRMS** [ESI (M + Na^+)] m/z calculated for C_7H_7INaO 256.9434, found 256.9429. The data matches those found in the literature.[54]

(4-Nitrophenyl)methanol (142)

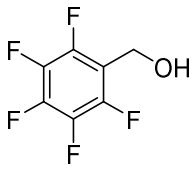


Prepared according to general procedure 1, using 4-nitrobenzoic acid (167 mg, 1.00 mmol) in toluene, and the crude product was purified by column chromatography (EtOAc / petrol

2:3, R_f = 0.17) to afford the desired product as a pale yellow solid (105 mg, 0.690 mmol, 69%), mp 91-93 °C.

IR (ATR) ν_{max}/cm^{-1} 3507, 1600, 1504, 1457, 1333, 1196, 1055; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.29 – 8.15 (m, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 4.83 (s, 1H), 1.98 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.2, 147.4, 127.1, 123.9, 64.2; **HRMS** [ESI (M + H^+)] m/z calculated for $C_7H_8NO_3$ 154.0499, found 154.0501 (σ = 0.0174). The data matches those found in the literature.[55]

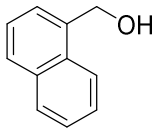
(Perfluorophenyl)methanol (**143**)



Prepared according to general procedure 1, using pentafluorobenzoic acid (212 mg, 1.00 mmol) in toluene, and the crude product was purified by column chromatography (EtOAc / petrol 1:4) to afford the desired product as a colourless oil (88.0 mg, 0.440 mmol, 44%).

IR (ATR) ν_{max}/cm^{-1} 3317, 1522, 1505, 1430, 1306, 1121, 1062, 1022; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.74 (s, 2H), 3.12 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 146.7, 144.2, 134.2, 128.0, 52.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -144.73 (ddd, *J* = 22.5, 9.0, 1.9 Hz), -154.42 (app. t, *J* = 20.5 Hz), -161.75 – -162.49 (m); **GCMS** [EI] m/z calculated for $C_7H_3OF_5$ 198.0099, found 198.0102. The data matches those found in the literature.[56]

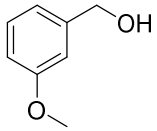
Naphthalen-1-ylmethanol (**134**)



Prepared according to general procedure 1, using 2-naphthoic acid (172 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 1:9, R_f = 0.25) to afford the desired product as a colourless solid (137 mg, 0.870 mmol, 87%), mp 61-63 °C.

IR (ATR) ν_{max}/cm^{-1} 3315, 3047, 2876, 1510, 1392, 1329, 1141, 1067; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (m, 1H), 7.94 – 7.86 (m, 1H), 7.82 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.47 – 7.40 (m, 2H), 5.01 (s, 2H), 2.91 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.3, 133.7, 131.2, 128.6, 128.4, 126.2, 125.8, 125.4, 125.2, 123.6, 63.2; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_{11}H_{10}O$ 158.0726, found 158.0732. The data matches those found in the literature.[52]

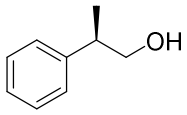
(3-Methoxyphenyl)methanol (**144**)



Prepared according to general procedure 1, using 3-methoxybenzoic acid (152 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 1:9, R_f = 0.23) to afford the desired product as a colourless oil (129 mg, 0.930 mmol, 93%).

IR (ATR) ν_{max}/cm^{-1} 3317, 2937, 2836, 1596, 1488, 1454, 1434, 1284, 1151, 1036; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 – 7.23 (m, 1H), 6.94 – 6.89 (m, 2H), 6.84 – 6.80 (m, 1H), 4.62 (s, 2H), 3.79 (s, 3H), 2.23 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.9, 142.7, 129.7, 119.2, 113.3, 112.3, 65.2, 55.3; **HRMS** [ESI (M + H$^+$)] m/z calculated for $C_8H_{10}NaO_2$ 161.0573, found 161.0565 (σ = 0.0176). The data matches those found in the literature.[57]

(*R*)-2-Phenylpropan-1-ol (**145**)

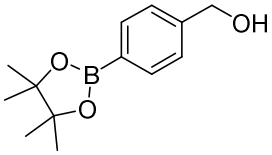


Prepared according to general procedure 1, using (*R*)-(-)-2-phenylpropionic acid (150 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 1:4, R_f = 0.17) to afford the desired product as a colourless oil (108 mg, 0.790 mmol, 79%).

IR (ATR) ν_{max}/cm^{-1} 3342, 2961, 2927, 2874, 1493, 1383, 1130; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 2H), 7.28 – 7.23 (m, 3H), 3.69 (d, *J* = 6.9 Hz, 2H), 2.95 (t, *J* = 6.9 Hz, 1H), 1.82 – 1.76 (m, 1H), 1.30 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.9, 128.7, 127.6, 126.7,

68.7, 42.5, 17.7. Enantiomeric excess was determined by chiral HPLC with a AMY-C column (CO_2 / MeOH 85:15), 4.0 mL/min, 210-400 nm, 125 BarG, 40 °C, t_r (minor) = 1.72 min, t_r (major) = 1.96 min, 97% *e.e.*. The data matches those found in the literature.[58]

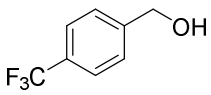
(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanol (146)



Prepared according to general procedure 1, using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (248 mg, 1.00 mmol) in toluene, and the crude product was purified by column chromatography (EtOAc / petrol 1:4) to afford the desired product as a colourless oil (208 mg, 0.640 mmol, 64%).

IR (ATR) ν_{max}/cm^{-1}3389, 2977, 2927, 1613, 1517, 1398, 1356, 1141, 1085, 1017; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.80 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 4.69 (s, 2H), 1.35 (s, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ144.1, 135.2, 126.2, 83.9, 65.3, 25.0; **^{11}B NMR** (128 MHz, $CDCl_3$) δ 30.88; **HRMS** [ESI (M + Na^+)] m/z calculated for $C_{13}H_{19}BNaO_3$ 252.1766, found 252.1762. The data matches those found in the literature.[59]

(4-(Trifluoromethyl)phenyl)methanol (147)

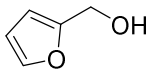


Prepared according to general procedure 1, using 4-(trifluoromethyl)benzoic acid (190 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 3:7, R_f = 0.12) to afford the desired product as a colourless oil (115 mg, 0.650 mmol, 65%).

IR (ATR) ν_{max}/cm^{-1} 3298, 1324, 1108, 1064, 1015; **^{1}H NMR** (400 MHz, $CDCl_3$) δ δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 2H), 4.65 (s, 2H), 2.86 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.7, 129.8 (q, *J* = 32.3 Hz), 126.9, 125.5 (q, *J* = 3.8 Hz), 124.3 (q, *J* = 271.9 Hz), 64.3; **^{19}F NMR**

(376 MHz, $CDCl_3$) δ -62.46; **GCMS** [EI ($M + H^+$)] m/z calculated for $C_8H_7OF_3$ 176.0444, found 176.0449. The data matches those found in the literature.[60]

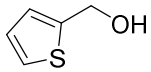
Furan-2-ylmethanol (148)



Prepared according to general procedure 1, using furan-2-carboxylic acid (112 mg, 1.00 mmol) in toluene, and the crude product was purified by column chromatography (pure petrol to EtOAc / petrol 2:3, R_f = 0.29) to afford the desired product as a colourless oil (83.0 mg, 0.850 mmol, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 1H), 6.35 – 6.29 (m, 1H), 6.29 – 6.24 (m, 1H), 4.56 (s, 2H), 2.52 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 154.0, 142.4, 110.3, 107.6, 57.2. The data matches those found in the literature.[61]

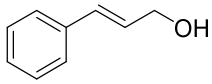
Thiophen-2-ylmethanol (149)



Prepared according to general procedure 1, using 2-thiophene carboxylic acid (128 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 1:4, R_f = 0.19) to afford the desired product as a colourless oil (82.0 mg, 0.720 mmol, 72%).

IR (ATR) ν_{max}/cm^{-1} 3288, 2870, 1432, 1374, 1210, 1153, 1133, 1077, 1002; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.04 – 6.96 (m, 2H), 4.78 (s, 2H), 2.60 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.0, 126.9, 125.6, 125.5, 59.9; GCMS [EI] m/z calculated for $C_7H_{14}O$ 114.1039, found 114.1041. The data matches those found in the literature.[53]

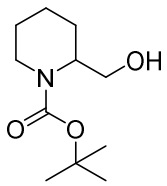
(*E*)-3-Phenylprop-2-en-1-ol (**150**)



Prepared according to general procedure 1, using *E*-cinnamic acid (148 mg, 1.00 mmol) in toluene, and the crude product was purified by column chromatography (EtOAc / petrol 1:4, R_f = 0.15) to afford the desired product as a colourless oil (117 mg, 0.870 mmol, 87%).

IR (ATR) ν_{max}/cm^{-1} 3319, 2916, 2849, 1493, 1449, 1265, 1131, 1090, 1069; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 – 7.25 (m, 5H), 6.65 (dt, *J* = 15.7, 1.6 Hz, 1H), 6.39 (dt, *J* = 15.9, 5.6 Hz, 1H), 4.34 (dd, *J* = 5.6, 1.6 Hz, 2H), 3.11 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.7, 130.8, 128.6, 128.5, 127.6, 126.5, 63.4; GCMS [EI] m/z calculated for $C_9H_{10}O$ 134.0726, found 134.0729. The data matches those found in the literature.[62]

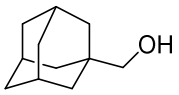
tert-Butyl 2-(hydroxymethyl)piperidine-1-carboxylate (**151**)



Prepared according to general procedure 1, using *N*-boc-2-piperidine carboxylic acid (229 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 3:17) to afford the desired product as a colourless solid (142 mg, 0.660 mmol, 66%).

IR (ATR) ν_{max}/cm^{-1} 2932, 1661, 1447, 1312, 1247; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.20 (m, 1H), 3.87 (d, *J* = 13.6 Hz, 1H), 3.69 (at, *J* = 9.8 Hz, 1H), 3.59 – 3.48 (m, 1H), 3.00 – 2.70 (m, 2H), 1.73 – 1.62 (m, 1H), 1.59 – 1.47 (m, 3H), 1.39 (s, 9H), 1.35 – 1.29 (m, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 156.1, 79.7, 61.0, 52.4, 40.0, 28.4, 25.3, 25.1, 19.5; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{22}NO_3$ 216.1594, found 216.1583. The data matches those found in the literature.[63]

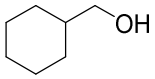
1-Adamantanemethanol (152)



Prepared according to general procedure 1, using 1-adamantane carboxylic acid (180 mg, 1.00 mmol) in toluene, and the crude product was purified by column chromatography (EtOAc / petrol 1:4, R_f = 0.17) to afford the desired product as a colourless solid (133 mg, 0.800 mmol, 80%), mp 113-115 °C.

IR (ATR) ν_{max}/cm^{-1} 2895, 2844, 2404, 1430, 1132, 1040; **^{1}H NMR** (400 MHz, MeOD) δ 3.10 (s, 2H), 1.97 (p, *J* = 2.9 Hz, 3H), 1.82 – 1.64 (m, 6H), 1.53 (d, *J* = 3.1 Hz, 6H); **^{13}C NMR** (101 MHz, MeOD) δ 73.9, 40.2, 38.3, 35.5, 29.7; **HRMS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{18}O$ 166.1352, found 166.1360. The data matches those found in the literature.[64]

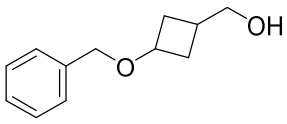
Cyclohexylmethanol (153)



Prepared according to general procedure 1, using cyclohexane carboxylic acid (128 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 1:4, R_f = 0.23) to afford the desired product as a colourless oil (90.0 mg, 0.790 mmol, 79%).

IR (ATR) ν_{max}/cm^{-1} 3313, 2919, 2850, 1448, 1133, 1090, 1023; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.42 (d, *J* = 6.3 Hz, 2H), 1.82 – 1.61 (m, 4H), 1.53 – 1.40 (m, 1H), 1.27 – 1.18 (m, 2H), 1.18 – 1.12 (m, 1H), 0.98 – 0.86 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 68.9, 40.6, 29.7, 26.7, 26.0. The data matches those found in the literature.[53]

(3-(Benzyloxy)cyclobutyl)methanol (154)

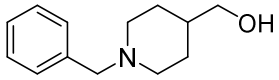


Prepared according to general procedure 1, using 3-(benzyloxy)cyclobutane-1-carboxylic acid as a mixture of diastereoisomers (206 mg, 1.00 mmol) and the crude product was purified by

column chromatography (pure petrol to EtOAc / petrol 1:1, R_f = 0.31) to afford the desired product as a colourless oil (144 mg, 0.750 mmol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 - 7.32 (m, 5 H), 4.38 (d, *J* = 5.38 Hz, 2 H), 3.86 - 4.11 (m, 1 H) 3.51 (d, *J* = 6.85 Hz, 2 H) 2.60 (s, 1 H) 2.26 - 2.37 (m, 1 H) 1.94 - 2.16 (m, 3 H) 1.65 - 1.73 (m, 1 H); **^{13}C NMR** (101 MHz, $CDCl_3$) mixture of diastereomers: δ 138.1 (major), 138.0 (minor), 128.2, 127.7 (minor), 127.7 (major), 127.4 (minor), 127.4 (major), 71.7, 69.8 (major), 69.3 (minor), 66.7 (minor), 66.2 (major), 32.8 (minor), 31.5 (major), 29.5 (major), 28.0 (minor). The data matches those found in the literature.[65]

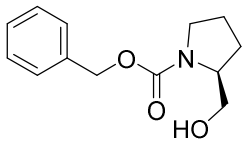
(1-Benzylpiperidin-4-yl)methanol (155)



Prepared according to general procedure 1, using 1-benzylpiperidine-4-carboxylic acid (219 mg, 1.0 mmol) in toluene, and the crude product was purified by column chromatography (KPNH column) (pure petrol to EtOAc / petrol 3:2 (EtOAc / petrol 1:1, R_f = 0.16)) to give the desired product as a colourless oil (161 mg, 0.784 mmol, 78 % yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.34 (m, 4 H), 7.24 - 7.26 (m, 1 H), 3.51 (s, 2 H), 3.46 (d, *J* = 6.36 Hz, 2H), 2.89 - 2.94 (m, 2 H), 2.49 - 2.58 (m, 1 H), 1.97 (ddd, *J* = 11.7, 11.7, 2.5 Hz, 2 H), 1.68 - 1.74 (m, 2 H), 1.44 - 1.52 (m, 1 H), 1.28 (qd, *J* = 11.5, 3.9 Hz, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.1, 129.2, 128.1, 126.9, 67.6, 63.4, 53.3, 38.4, 28.7; **HRMS** [ESI ($M + H^+$)] m/z calculated for $C_{13}H_{19}NO$ 206.1539, found 206.1539. The data matches those found in the literature.[66]

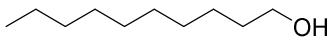
Benzyl (*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (156)



Prepared according to general procedure 1, using ((benzyloxy)carbonyl)-L-proline (249 mg, 1.00 mmol) and the crude product was purified by column chromatography (pure petrol to EtOAc / petrol 2:3, R_f = 0.21) to afford the desired product as a colourless oil (173 mg, 0.740 mmol, 74 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 - 7.36 (m, 5 H), 5.12 (s, 2 H), 4.43 (s, 1 H), 3.91 - 3.99 (m, 1 H), 3.62 (s, 2 H), 3.49 (m, 1 H), 3.34 - 3.41 (m, 1 H), 1.72 - 2.01 (m, 4 H); **^{13}C NMR** (101 MHz, $CDCl_3$) mixture of rotamers δ156.7 (major), 155.0 (minor), 136.5, 128.4, 127.9, 127.7, 67.0 (major), 66.8 (minor), 66.0 (major), 63.7 (minor), 60.4 (major), 58.6 (minor), 47.1, 28.3 (major), 26.8 (minor), 23.9 (major), 23.0 (minor). Enantiomeric excess was determined by chiral HPLC with a Chiralpak IG5 column (MeOH), 1.0 mL/min, 215 nm, 25 °C, t_r (minor) = 4.75 min, t_r (major) = 5.32 min, >99% *e.e.*. The data matches those found in the literature.[67]

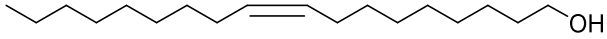
Decan-1-ol (157)



Prepared according to general procedure 1, using decanoic acid (172 mg, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 1:4, R_f = 0.21) to afford the desired product as a colourless oil (126 mg, 0.800 mmol, 80%).

IR (ATR) ν_{max}/cm^{-1} 2922, 2853, 1464, 1430, 1130, 1055; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.60 (t, *J* = 6.7 Hz, 2H), 2.00 (s, 1H), 1.59 – 1.47 (m, 2H), 1.34 – 1.19 (m, 14H), 0.92 – 0.81 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 63.0, 32.9, 32.0, 29.7, 29.7, 29.6, 29.4, 25.9, 22.8, 14.2. The data matches those found in the literature.[64]

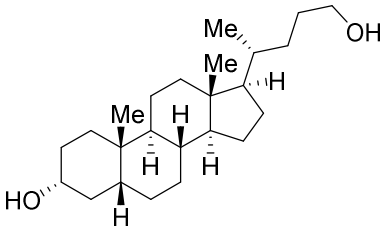
(*Z*)-Octadec-9-en-1-ol (158)



Prepared according to general procedure 1, using oleic acid (317 µL, 1.00 mmol), and the crude product was purified by column chromatography (EtOAc / petrol 1:9) to afford the desired product as a colourless oil (206 mg, 0.770 mmol, 77%).

IR (ATR) ν_{max}/cm^{-1} 3319, 2922, 2853, 1462, 1133, 1056; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.35 – 5.31 (m, 2H), 3.60 (t, *J* = 6.7 Hz, 2H), 1.99 (m, 4H), 1.54 (p, *J* = 6.8 Hz, 2H), 1.37 – 1.19 (m, 22H), 0.90 – 0.83 (m, 3H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 130.0, 129.9, 63.0, 32.9, 32.0, 29.9, 29.8, 29.7, 29.6, 29.6, 29.5, 29.4, 29.4, 27.3, 27.3, 25.9, 22.8, 14.2. The data matches those found in the literature.[42]

(3*R*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-17-((*R*)-5-hydroxypentan-2-yl)-10,13-dimethylhexadeca-hydro-1H-cyclopenta[a]phenanthren-3-ol (159)

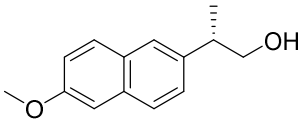


(4*R*)-4-((3*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-3-hydroxy-10,13-dimethylhexadecahydro-1H-cyclopenta[a]-phenanthren-17-yl)pentanoic acid (337 mg, 1.00 mmol) and zinc acetate (18.3 mg, 0.1 mmol) were dissolved in 2-Me THF (1.2 mL) and heated to reflux. Phenylsilane (370 µL, 3.00 mmol) was added to the reaction mixture dropwise, followed by *N*-Me morpholine (11.0 µL, 0.1 mmol). The reaction mixture was stirred at reflux for 16 h, after which it was allowed to cool. Aqueous 2 M NaOH (2 mL) was added to the reaction mixture dropwise and it was stirred for a further 30 mins. Aqueous 1 M HCl was then added to the reaction mixture until pH 5 was reached, and the product was extracted using EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude

product was purified by column chromatography (pure petrol to EtOAc / petrol 3:2) to afford the desired product as a colourless solid (317 mg, 0.87 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 - 3.58 (m, 3 H), 1.91 - 1.72 (m, 4 H), 1.69 - 1.51 (m, 6 H), 1.46 - 1.36 (m, 8 H), 1.29 - 1.21 (m, 4 H), 1.55 - 0.99 (m, 7 H), 0.94 - 0.91 (m, 6 H), 0.65 (s, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 71.9, 63.6, 56.5, 56.2, 42.7, 42.1, 40.5, 40.2, 36.5, 35.9, 35.6, 35.4, 34.6, 31.8, 30.6, 29.5, 28.3, 27.2, 26.4, 24.2, 23.4, 20.9, 18.6, 12.1. The data matches those found in the literature.[68]

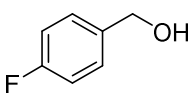
(*S*)-2-(6-Methoxynaphthalen-2-yl)propan-1-ol (160)



Prepared according to general procedure 1, using (*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid (230 mg, 1.00 mmol), and the crude product was purified by column chromatography (pure petrol to EtOAc / petrol 2:3, R_f = 0.22) to afford the desired product as a colourless solid (188 mg, 0.870 mmol, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ7.73 (dd, *J* = 8.56, 2.69 Hz, 2 H), 7.62 - 7.64 (m, 1 H), 7.36 (dd, *J* = 8.56, 1.71 Hz, 1 H), 7.15 - 7.22 (m, 2 H), 3.93 (s, 3 H), 3.71 - 3.80 (m, 2 H), 3.03 - 3.12 (m, 1 H), 1.38 (d, *J* = 6.85 Hz, 3 H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.4, 138.7, 133.5, 129.1, 129.1, 127.2, 126.3, 125.9, 118.9, 105.6, 68.6, 55.3, 42.4, 17.6. Enantiomeric excess was determined by chiral HPLC with an (*R*, *R*) Whelk-O1 column (Heptane / EtOH 60:40), 1.0 mL/min, 230 nm, 25 °C, t_r (minor) = 8.01 min, t_r (major) = 7.15 min, 97% *e.e.*. The data matches those found in the literature.[61]

Large Scale Synthesis of (4-Fluorophenyl)methanol (139)

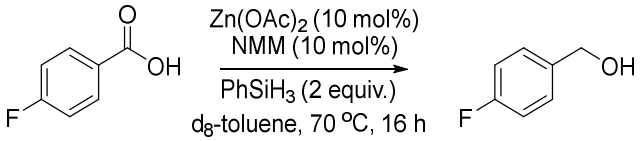


4-Fluorobenzoic acid (1.00 g, 7.14 mmol) and zinc acetate (131 mg, 0.71 mmol) were dissolved in 2-Me THF (8.5 mL) and heated to reflux. Phenylsilane (1.76 mL, 14.28 mmol) was

added to the reaction mixture dropwise, followed by *N*-Me morpholine (78.8 µL, 0.71 mmol). The reaction mixture was stirred at reflux for 18 h, before it was allowed to cool. 2M NaOH (5 mL) was added dropwise to the reaction mixture and it was stirred at room temperature for a further 1 h. 1M HCl was added to the reaction mixture until pH 7 was reached, and the product was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed *in vacuo*. The crude product was purified by column chromatography (EtOAc / petrol 1:4) to give the product as a colourless oil (657 mg, 5.21 mmol, 73%).

IR (ATR) ν_{max}/cm^{-1} 3311, 1604, 1509, 1429, 1221, 1131; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 2H), 7.07 – 7.00 (m, 2H), 4.63 (s, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.4 (d, *J* = 245.6 Hz), 136.7 (d, *J* = 3.5 Hz), 128.9 (d, *J* = 8.0 Hz), 115.5 (d, *J* = 21.6 Hz), 64.7; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.91; GCMS [EI (M + H^+)] m/z calculated for C_7H_7OF 126.0475, found 126.0474. The data matches those found in the literature.[52]

3.4 Mechanistic Studies



^{19}F NMR study (with the addition of NMM):

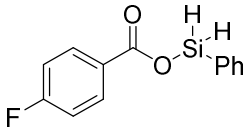
4-Fluorobenzoic acid (70.0 mg, 0.50 mmol) and zinc acetate (9.17 mg, 0.05 mmol) were added to an NMR tube, with trifluorotoluene (61.4 µL, 0.50 mmol) and d_8-toluene (0.5 mL). A ^{19}F NMR spectrum acquired at 70 °C (t_0 below). Phenylsilane (123 µL, 1.00 mmol) and *N*-Me morpholine (5.50 µL, 0.05 mmol) were then added to the NMR tube and ^{19}F NMR spectra were acquired at 70 °C at 15 min intervals for 16 h.

^{19}F NMR study (without the addition of NMM):

4-Fluorobenzoic acid (70.0 mg, 0.50 mmol) and zinc acetate (9.17 mg, 0.05 mmol) were added to an NMR tube, with trifluorotoluene (61.4 µL, 0.50 mmol) and d_8-toluene (0.5 mL).

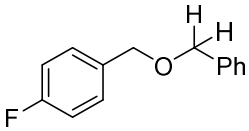
A ^{19}F NMR spectrum was acquired at 70 ˚C (t_0 below). Phenylsilane (123 µL, 1.00 mmol) was then added to the NMR tube and ^{19}F NMR spectra were acquired at 70 °C at 15 min intervals for 16 h.

Phenylsilyl 4-fluorobenzoate (115)



4-Fluorobenzoic acid (701 mg, 5.00 mmol) was dissolved in methanol (5 mL) and sodium hydroxide (202 mg, 5.05 mmol) was added. The reaction mixture was stirred at room temperature for 18 h before the solvent was removed *in vacuo* to give the product as a colourless solid. The crude product was directly used in the next reaction. Sodium 4-fluorobenzoate (81.1 mg, 0.50 mmol) was dissolved in d_8-toluene (0.5 mL) and heated to reflux. Chlorophenylsilane (66.7 µL, 0.50 mmol) was added to the reaction mixture, which was stirred for 1 h at reflux. ^{19}F NMR analysis was performed at 70 °C. **^{19}F NMR** (376 MHz, Tol) δ -104.8 to -106.9.

1-((Benzyloxy)methyl)-4-fluorobenzene (166)



4-Fluorobenzyl alcohol (630 mg, 5.00 mmol) was dissolved in methanol (5 mL) and sodium hydroxide (202 mg, 5.05 mmol) was added. The reaction mixture was stirred at room temperature for 16 h before the solvent was removed *in vacuo* to give the product as a colourless solid. The crude product was directly used in the next reaction. Sodium (4-fluorophenyl)methanolate (74.1 mg, 0.50 mmol) was dissolved in d_8-toluene (0.5 mL) and heated to reflux. Chlorophenylsilane (66.7 µL, 0.50 mmol) was added to the reaction mixture, which was stirred for 1 h at reflux. ^{19}F NMR analysis was performed at 70 °C. **^{19}F NMR** (376 MHz, Tol) δ -115.61.

4 References

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