Development of Metal-Free Reductive Processes Using Silanes and Brønsted Acid Activation

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“There is no magic to achievement. It is really about hard work, choices, and persistence”.

Michelle Obama

Abstract

Initial discussion centres on the importance of metal-free chemistry and organosilicon chemistry and its application to reductive processes. Silicon's uses, bonding and activation is also considered in more detail.

Chapter One discusses development of a reductive amination process using carboxylic acids as the electrophiles. Most reductive amination processes using carboxylic acids require transition metal activation, which causes selectivity and handling issues. However, Brønsted acids, specifically benzenesulfonic acid, with phenylsilane are shown to be effective, practical and chemoselective reducing agents. A range of amine substrates are synthesised, demonstrating potentially reducible functional groups, pharmaceuticals and large-scale synthesis. The reaction mechanism is also explored and shown to proceed *via* highly substituted silyl sulfonates upon the elimination of benzene from the silane. Computational calculations confirm increased reactivity over lower substituted sulfonates and the parent silane.

Chapter Two focusses on using the acid/silane reduction system for the methylation of amines using formic acid. Synthesis of tertiary amines, both through mono and di-methylation are demonstrated, along with complex compounds and pharmaceutical targets. The mechanism is shown to proceed *via* formaldehyde formed by the breakdown of the amide intermediate.

Chapter Three builds on the utility of this reductive system and investigates the reduction of phosphine oxides to phosphines, which are important for a range of processes. Reduction was shown to proceed at room temperature and a range of phosphine products are synthesised. Initial investigations are also made towards a catalytic Wittig reaction using this reduction system, and a proof of concept is demonstrated. Mechanistic studies are also undertaken, demonstrating that the reaction proceeds through formation of silyl sulfonates and subsequent interaction with the phosphine oxide.

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Abbreviations

Standard abbreviations and acronyms, as defined by the Journal of Organic Chemistry, are used throughout this thesis. All others are listed below:

$\Delta G^{\ddagger}$	**Gibbs free energy of the transition state**
2c-2e	Two-centre-two-electron
3c-4e	Three-centre-four-electron
9-BBN	9-borabicyclo[3.3.1] nonane
Ac	Acetyl
acac	Acetylacetone
Alk	Alkyl group
API	Active pharmaceutical ingredients
Ar	Aryl group
ATP	Adenosine triphosphate
B^-	Base
BINAP	(2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)
Boc	*tert*-Butyloxycarbonyl
CDI	1,1′-carbonyldiimidazole
CNS	Central nervous system
cod	Cyclooctadiene
Cy	Cyclohexane
d	Doublet
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N,N*-Diisopropylethylamine
DMAc	*N,N*-Dimethylacetamide

DMF	*N,N*-dimethylformamide
DNA	Deoxyribosenucleic acid
dppe	1,2-bis(diphenylphosphino)ethane
DPPF	1,1 ’-Bis (diphenylphosphino)ferrocene
E^+	Electrophile
EDCl	1-ethyl-3-(3’-dimethylaminopropyl)-carbodiimide hydrochloride
EWG	Electron withdrawing group
FA	Formic acid
FLP	Frustrated Lewis pair
GCIPR	Green Chemistry Institute Pharmaceutical Roundtable
HATU	Hexafluorophosphate azabenzotriazole tetramethyl uranium
HBTU	Hexafluorophosphate benzotriazole tetramethyl uranium
IR	Infrared
J	Coupling constant
LAH	Lithium aluminium hydride
LUMO	Lowest occupied molecular orbital
M	Metal
MO	Molecular orbital
NMP	1-Methyl-2-pyrrolidone
NMPi	*N*-methylpyrrolidine
NMR	Nuclear magnetic resonance
Nuc	Nucleophile
PhMe	Toluene
PMHS	Polymethylhydrosiloxane
PMP	*p*-methoxyphenyl

ppm	Parts per million
PTSA	*Para*-toluene sulfonic acid
REACH	Registration, Evaluation and Authorisation and Restriction of Chemicals'
red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
RLS	Rate limiting step
RNA	Ribose nucleic acid
S_NAr	Nucleophilic aromatic substitution
SSRI	Selective serotonin reuptake inhibitor
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBD	Triazabicyclodecene
TDMS	Tetramethyldisiloxane
Tf_2O	Triflic anhydride
TFA	Trifluoroactic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TPP	Triphenylphosphine
TPPO	Triphenylphosphine oxide
tzNHC	1,2,3-triazoly-5-ylidene *N*-heterocyclic carbene

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Introduction

Introduction to metal-free chemistry and organosilicon reagents, and how they are used in reduction chemistry. Further literature and insights will be given at the beginning of each chapter

Milly Stoneley

1 Metal-free Chemistry

Metals are of fundamental importance in chemical synthesis in the form of organometallic reagents and transition metal catalysts.[1–3] Reactions such as palladium cross-coupling reactions are extremely important, and Heck, Negishi and Suzuki were jointly honoured with the Nobel Prize in chemistry in 2010 for their successes in this area.[4–6] Other important transition metal catalysed reactions include the ruthenium-catalysed olefin cross-metathesis and the titanium-catalysed Sharpless epoxidation, both which also achieved their developers Nobel prize status.[7,8] Despite catalysis being one of 12 principles of green chemistry, investigations into the sustainability of the metal catalysts must also be considered.[9] Transition metals are often associated with significant toxicity, cost, and often have resource availability limitations and frequently require air and moisture free conditions.[10] The Federal Register of the United States classified 35 metals, including palladium, ruthenium and titanium as 'critical minerals' due to low availability.[11] In addition, there are strict boundaries implemented on the concentration of metallic impurities in the target compound, and as a result, purification of metal-mediated reactions are often rigorous and costly.[12] This has even more of an impact at manufacturing scale where these disadvantages are multiplied.[13] To try and circumvent this issue, there has been a drive towards more abundant, less expensive and lower toxicity metal catalysts such as copper, nickel and iron.[14,15] These metals are classed as 'relatively low toxicity', or 'low inherent toxicity' compared to palladium's 'route dependant toxicants' and have a much higher permitted concentration (European Medicines Agency 2022: Pd 11.1 μg/g and Cu 333 μg/g).[13] Despite the development of chemistry with these 'better' metals, the downsides of transition metal catalysis cannot be fully erased for example costly ligands which often cannot be fully recovered.

A 2010 review highlighted the similarities between heavier main block elements and transition metals for a range of critical reactions.[16] The ability of these main block elements to exist in multiple oxidation states and be easily tuneable through simple chemistry methodologies, allows for alternatives to transition metal reagents.[17] Further developments in metal-free chemistry have yielded

advancements for biochemistry[18,19] and organocatalysis,[20,21] culminating in the awarding of the Nobel Prize to Macmillan and List in 2021 for achievements in organocatalysis.[22] Despite the focus on organocatalysis, stoichiometric metal-free methods, represent some of the most popular and well used transformations.[1] These metal-free systems not only contain more stable, less toxic and more abundant reagents, but also are not constrained by impurity limits, often improving work up procedures. This, therefore, improves the attractiveness in a synthetic pathway. *Herein,* we discuss the metal-free silicon mediated reductive amination chemistry, with first a review of general silicon chemistry and methodology.

2 Organosilicon Chemistry

2.1 Importance of Silicon

Silicon was first isolated in 1823 by Berzelius (Figure 1A), and since this discovery, both inorganic and organic silicon compounds have become fundamental components for a diverse range of chemical uses. Inorganic compounds of silicon are vital in construction, automotive and technological industries. Silicon's affinity for oxygen has led to the development of silicones, which have found uses in lubricants, sealants and a range of medical supplies.[23]

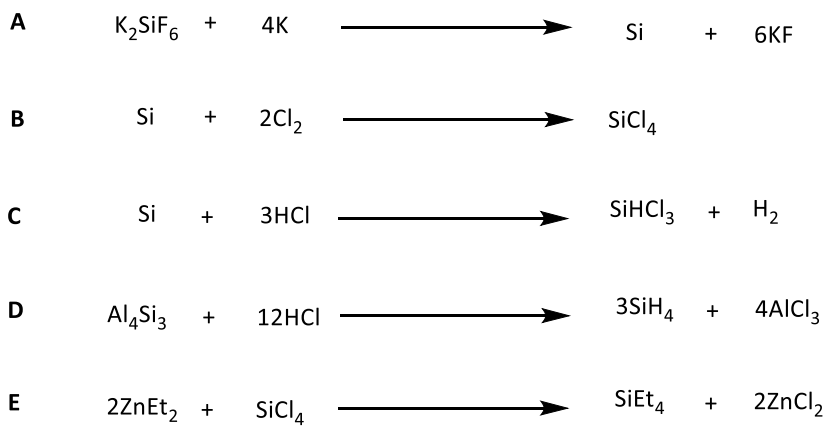


Figure 1: *Synthesis of early inorganic silicon compounds*

Initial silicon chemistry focused on the synthesis of simple inorganic silanes, with Berzelius reporting $SiCl_4$ (Figure 1B) in 1823, and Wöhler synthesising $SiHCl_3$ (Figure 1C) and SiH_4 later in 1858 (Figure 1D).[24] It wasn't until 1863 when the first organosilicon compound was synthesised by Friedel and Crafts. They reported the formation of tetraethylsilane, through the reaction of tetrachlorosilane and diethylzinc (Figure 1E).[25] Further development in this field did not come about until Kipping, between the years of 1899 and 1944, where he published 57 papers detailing a range of reactions involving the synthesis and characterisation of a wide range of organosilanes. [26–31]

Since these early developments, silicon chemistry has boomed in popularity, with its uses in organic synthesis growing rapidly.[32–35] Silyl ethers such as *tert*-butyldimethylsilyl ethers and *tert*-butyldiphenylsilyl ethers have found uses as alcohol protecting groups, and trimethylsilyl chloride has been used to synthesise silyl enol ethers for reactions such as Mukaiyama-Aldol (Figure 2A) and Mukaiyama-Michael additions (Figure 2B).[36–39] The ability of silicon to stabilise both α-carbanions and β-carbocations makes such reactions as the Peterson-olefination (Figure 2C) and the electrophilic substitution of vinyl silanes (Figure 2D) possible.[40–42]

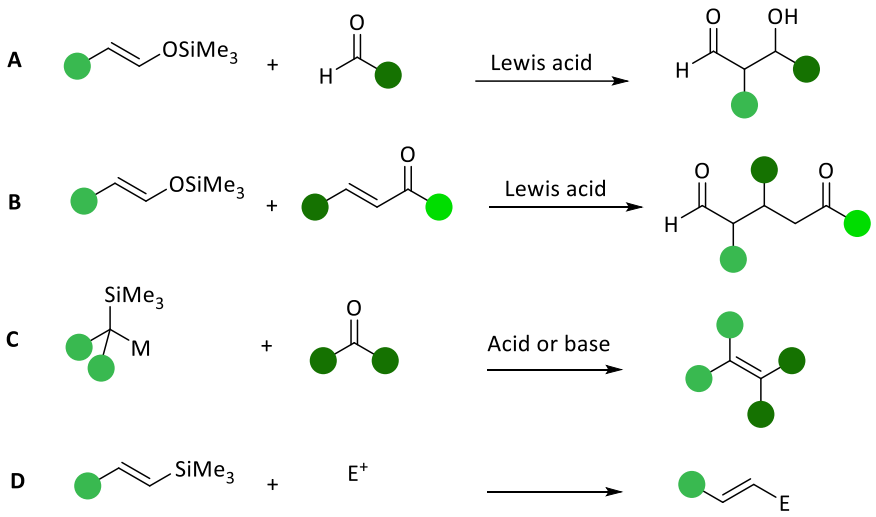


Figure 2: *The general reaction schemes for selected organosilicon reactions*

Its non-toxic nature, stability and diverse range of chemistry has made silicon compounds attractive synthetic intermediates.

2.2 Silicon Bonding and Hypervalancy

Being in the same group, organosilicon compounds are considered analogous to those of carbon. However, despite many similarities, they exhibit differing reactivity which is in part due to electronic effects.[43] The electronegativity of silicon is much lower than that of carbon, reversing the usual polarity associated with C-H bonds thereby creating hydridic hydrogens (Figure 3).

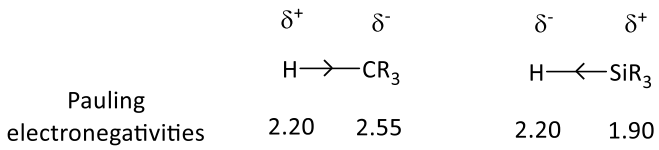


Figure 3: *Reversed polarity of Si-H bond due to Pauling electronegativities*

The parallels drawn between carbon and silicon are to four coordinate silanes only. However, organosilicon has a wide range of chemistry that carbon compounds cannot access, as they possess the ability to accommodate up to six bonds, in a hexavalent structure. There has been much debate over the origin of this ability, which is demonstrated not only by silicon, but also by a range of elements including, sulfur, phosphorus and iodine.[44] Initially, d-orbital hybridisation was suspected to be the cause of this phenomenon, although computational studies have since shown that the contribution of these orbitals is minimal.[45,46]

Lewis' explanation for these types of compounds was to champion his two-centre-two-electron (2c-2e) bonding theory, meaning that to accommodate the extra bonds, the central atom was forced to expand its octet.[47] In 1969 Musher officially designated these types of molecules as 'hypervalent', referring specifically to Lewis' 2c-2e bonding approach and the 'expanding the octet' theory.[44,48] However, contrasting concepts were put forward by Langmuir and Pauling who both argued the dominance of the octet rule and invoked full or partial ionic bonds to explain these types of compounds.[49,50] Computational studies have shown that for a wide range of hypervalent molecules, the bond order of the central atom was no more than four,[51–53] dismissing the 'expanding the octet' explanation and even calling into question the validity of the term hypervalent. [53–55]

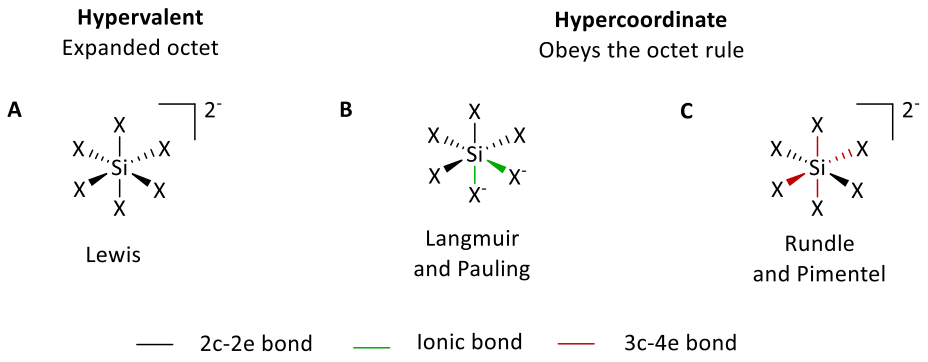


Figure 4: *Hexavalent and hexacoordinate silicon compounds - A. Hypervalent silicon compound using only 2c-2e bonds. B. Hypercoordinate silicon compound using partial ionic bonds. C. Hypercoordinate silicon compound using 3c-4e bonds*

Rundle and Pimentel independently introduced the concept of three-centre-four-electron (3c-4e) bonds as an alternative to other theories.[56,57] This approach utilised multicentre bonding where the bonding power of a pair of electrons is spread over three atoms in a linear arrangement. The central atom provides a single p-orbital, which forms two σ-bonds with the peripheral atoms. This combination creates three molecular orbitals (MO's): A bonding (MO ψ_1), non-bonding (MO ψ_2) and anti-bonding (MO ψ_3) orbitals. The resulting bond originates from the occupation of the bonding MO ψ_1, with electrons from the central atom, and electrons from the ligands occupying the non-bonding orbital (MO ψ_2). This results in electron density residing primarily on the peripheral atoms and away from the bonding system, leading to the formation two bonds from a single p-orbital (Figure 5).[58,59] Computational calculations have supported the formation of 3c-4e bonds,[60] and has been widely implemented in the explanation of bonding in hypervalent molecules.[59] With the discovery of 3c-4e bonding, the term 'hypervalent' is no longer favoured due to its specific definition, and as an alternative, 'hypercoordinate' is being used as the preferential definition.[61] Hypercoordination refers specifically to ensuring that the octet rule is satisfied through multicentre bonding.[61]

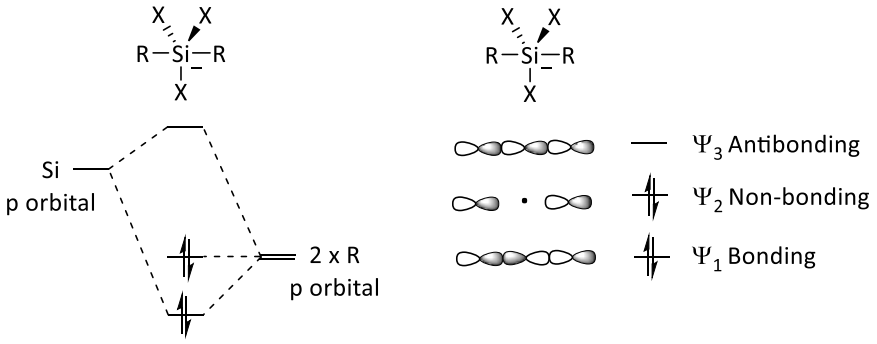


Figure 5: *Orbital description of 3c-4e bonding*

As the electron density from the non-bonding orbitals resides solely on the peripheral atoms, electronegative ligands stabilise hypercoordinate silicate compounds. As a result of the additional electron withdrawing nature of the groups, the central silicon atom experiences an increased effective positive charge.[62] Subsequently, the synthesis of hypercoordinate silicon compounds has become an important area,[63] and many of these compounds have been utilised as Lewis acids in a range of methodologies. [64,65]

2.3 Metal-free Activation of Silanes for Reduction

The hydrogens adjacent to a silicon atom are hydridic in nature, and as a result, silanes are extensively utilised as hydride donors in reduction chemistry.[66–68] Organosilanes represent a safer and more soluble alternative to traditional reducing agents such as, lithium aluminium hydride and sodium borohydride.[69] However, tetravalent Si-H bonds have poor nucleophilicity and often require activation to act as an effective reductant.

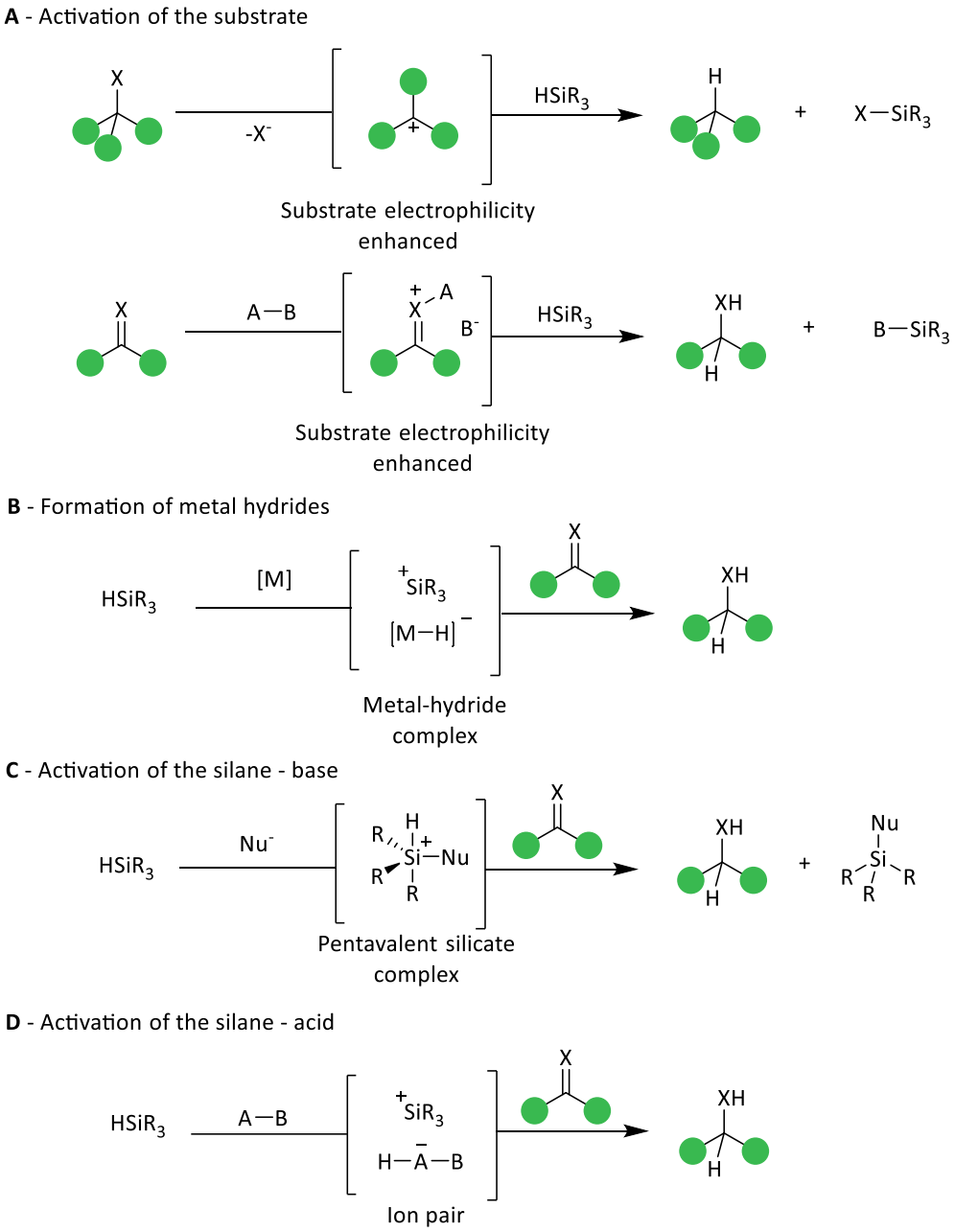


Figure 6: *General modes of action for silane reductions – A. Bronsted or Lewis activation of the substrate to increase electrophilicity. B. activation with a metal to form metal hydrides. C. Addition of basic nucleophiles to the silane improve hydride donation. D. Transfer of hydride and formation of ion pairs*

It is possible for four coordinate silanes to act as reductants in some cases. Additive-free reduction of phosphine oxides to phosphines has been realised using silanes alone.[70, 71] The use of tetravalent silanes for reduction chemistry is more common where the electrophilicity of the substrate has been enhanced (Figure 6A). Alcohols can be reduced to the corresponding alkanes, through formation of carbocation intermediates, using Brønsted[72] and Lewis acids[73] in conjunction with Et_3SiH. In the same

way, secondary and tertiary alkyl halides have also been reduced, but this process requires stronger Lewis acids such as $AlCl_3$.[74] In starting materials with carbon heteroatom double bonds, the dipole can be enhanced allowing for hydrosilylation with tetravalent silanes (Figure 6A). This has been demonstrated in the reduction of aldehydes and ketones to alcohols using BF_3 and $EtSiH_3$.[75] An I_2-hydrosilane system has also been employed in a reduction to symmetrical ethers,[76] and more recently has been used in the reduction of *N*-sulfonyl aldimines to *N*-alkylsulfonamides.[77]

Transition metal catalysts are often employed as silane activators, usually through oxidative addition into the Si-H bond, to form metal hydrides as the active reducing agents (Figure 6B).[67] Metals such as iridium, manganese and zinc have been used in conjunction with silanes to achieve reduction of esters, carboxylic acids and amides.[78–80] Ionic and basic compounds such as $^{t}BuOK$,[81] Cs_2CO_3[82] and tetrabutylammonium fluoride (TBAF),[83] have long been used as catalysts in silane mediated reductions (Figure 6C). However, the mode of activation hasn't been investigated in much detail, although hypercoordinate silicon species are often invoked. In 1997 Lawrence proposed a 'zipper mechanism' for his polymethylhydrosiloxane (PMHS) and TBAF reduction of esters, acids, ketones and aldehydes after identifying increased rate of reaction of polymeric silanes against their monomeric counterparts (Figure 7A). He proposed that due to the proximity of the silicon atoms on the polymeric backbone, the increased rate can be attributed to fast 1,3-fluoride transfer.[84] However, when the mechanism was probed in more detail recently, it was found that the base-catalysed the redistribution of the polymer to the reactive methylsilane. This species, upon activation with the base, is transformed into the active hypercoordinate silicate species (Figure 7B).[85,86] The mode of action for base and fluoride-catalysed reductions with phenylsilane was also investigated. The speciation was complex and readily interconverted at room temperature, but in all cases the reducing species were found to be hexavalent in nature with at least one Si-H bond.[85] The use of intramolecular interactions can also be utilised as a derivative of base activated hydrosilanes. A tetravalent silane with a substituent bearing a labile lone pair, usually nitrogen, can coordinate directly to the silicon centre, forming essentially a pentavalent structure, although the exact interaction is debated (Figure 7C).[87] A common and commercially

available example of this type of interaction is 1-hydrosilatrane. This compound has been used by the Adler group to reduce aryl aldehydes,[88] ketones[89] and in reductive amination reactions, although in some cases further base activation was required.[90] The rigidity of the silatrane motif activates the Si-H bond towards reduction by forcing axial positioning of the hydride, resulting in donation of the lone pair on the nitrogen into the Si-H σ* orbital. The increased lability of the hydride with the increased electropositivity at the silicon centre, allows for more facile hydrosilylation.

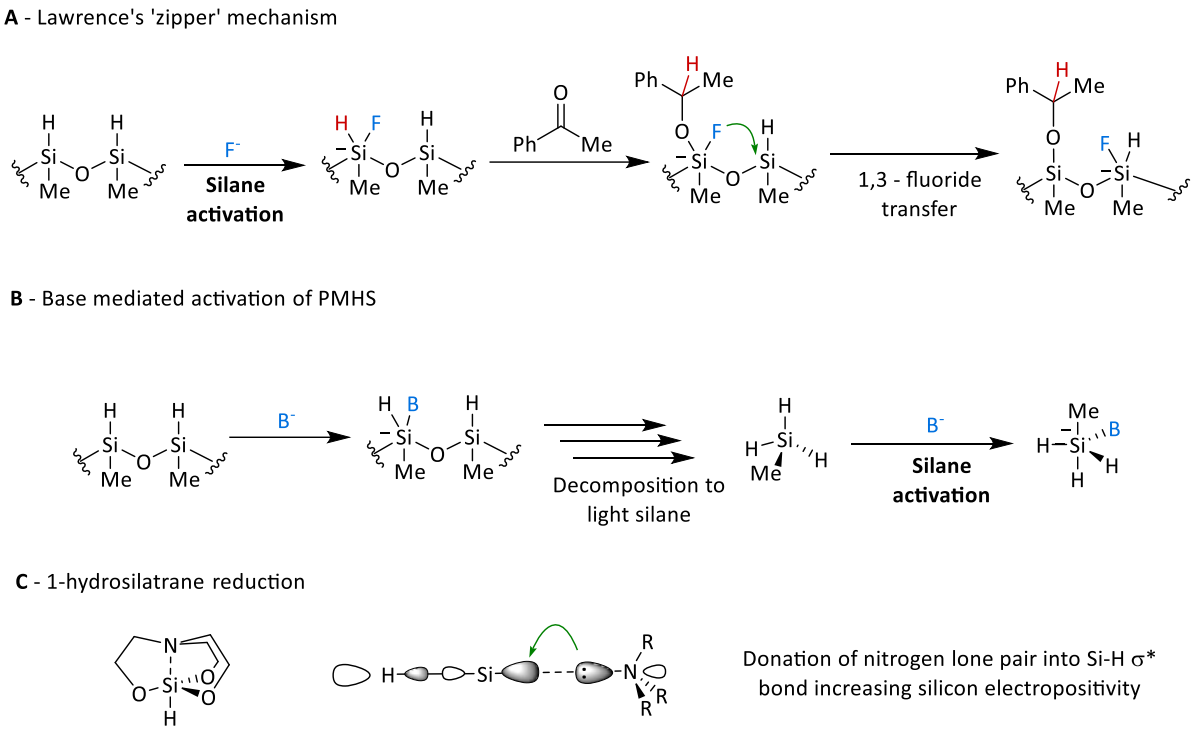


Figure 7: *Base activation of silanes*

In addition to base activation, Lewis acids are also commonly used as silane activators, employing catalysts such as boranes,[91] phosphonium cations[92] and trityl cations (Figure 6D).[93] A widely used additive is the borane compound, $B(C_6F_5)_3$. The initial mode of action was thought to be coordination of the borane to the substrate and subsequent reduction of the activated species with the tetravalent silane.[94] However, a study published by Piers, detailed extensive mechanistic investigations into hydrosilylation reactions using $B(C_6F_5)_3$ as the Lewis acid (Figure 8),[95] and found that the reducing active species was a silane-borane adduct, later termed a 'frustrated Lewis pair' (FLP) (**1**).[96,97] Computational studies confirmed an increase in positive charge on the silicon upon borane

coordination, allowing for attack of the carbonyl species at the silicon position. A computational model of the FLP LUMO, confirmed that the largest lobe was on the silicon atom, *trans* to the Si-H-B bond axis, and this orbital alignment facilitated the displacement of the borohydride (**2**). A large amount of computational and experimental data has supported the formation of silane-$B(C_6F_5)_3$ adducts, although the species has remained elusive to spectroscopic imaging.[98–100] It was claimed that the FLP was identified by ^{29}Si NMR spectroscopy however, it was later disproved due to ineffective drying procedures.[101] In further work, Piers isolated and imaged the adduct between 1,2,3-tris(pentafluorophenyl)-4,5,6,7-tetrafluoro-1-boraindene and triethylsilane, confirming the frustrated Lewis pair by X-ray crystallography.[102] This silane-$B(C_6F_5)_3$ adduct has been used to reduce aldehydes, ketones[99] and imines.[98] In addition, modified borane catalysts, bearing at least one B-C_6F_5 bond, have been applied to enantioselective hydrosilylations.[103] Reductions involving phosphonium cations have been shown to proceed *via* frustrated Lewis adducts.[92]

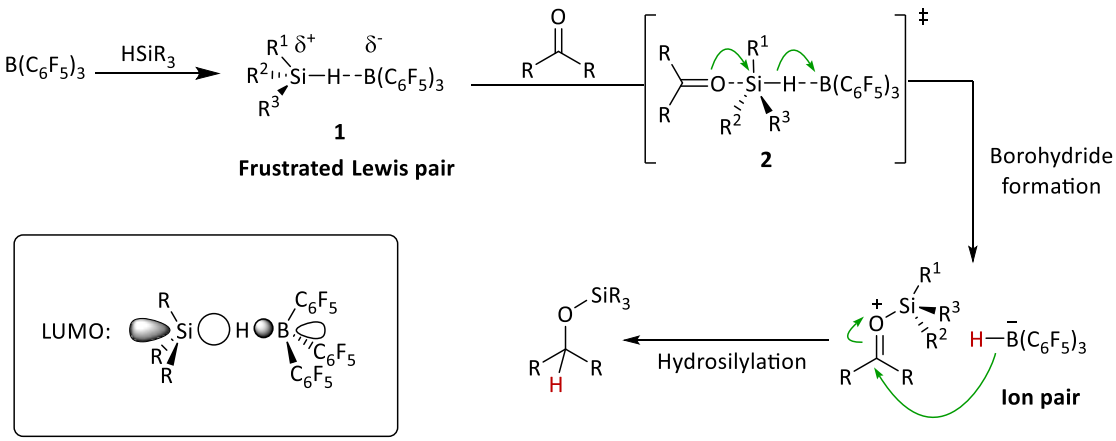


Figure 8: *$B(C_6F_5)_3$ catalysed silane reduction via a frustrated Lewis Pair*

3 References

1 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451–3476.
2 J. E. Zweig, D. E. Kim and T. R. Newhouse, *Chem. Rev.*, 2017, **117**, 11680–11752.
3 T. X. Gentner and R. E. Mulvey, *Angew. Chem. Int. Ed.*, 2021, **60**, 9247–9262.
4 C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem. Int. Ed.*, 2012, **51**, 5062–5085.
5 P. Devendar, R. Y. Qu, W. M. Kang, B. He and G. F. Yang, *J. Agric. Food Chem.*, 2018, **66**, 8914–8934.
6 K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem. Int. Ed.*, 2005, **44**, 4442–4489.
7 O. M. Ogba, N. C. Warner, D. J. O'Leary and R. H. Grubbs, *Chem. Soc. Rev.*, 2018, **47**, 4510–4544.
8 T. Katsuki and B. Sharpless, *J. Am. Chem. Soc.*, 1980, **102**, 5974–5976.
9 J. D. Hayler, D. K. Leahy and E. M. Simmons, *Organometallics*, 2019, **38**, 36–46.
10 K. S. Egorova and V. P. Ananikov, *Organometallics*, 2017, **36**, 4071–4090.
11 S. M. Fortier, N. T. Nassar, G. W. Lederer, J. Brainard, J. Gambogi and E. A. McCullough, *United states Geological Society*, 2018, 3–15.
12 M. Chatzopoulou, K. S. Madden, L. J. Bromhead, C. Greaves, T. J. Cogswell, S. Da Silva Pinto, S. R. G. Galan, I. Georgiou, M. S. Kennedy, A. Kennett, G. Apps, A. J. Russell and G. M. Wynne, *ACS Med. Chem. Lett.*, 2022, **13**, 262–270.
13 European Medicines Agency, 2022, 28–29.
14 H. Wu, B. Qu, T. Nguyen, J. C. Lorenz, F. Buono and N. Haddad, *Org. Process Res. Dev.*, 2022, **26**, 2281–2310.
15 R. A. Singer, S. Monfette, D. J. Bernhardson, S. Tcyrulnikov and E. C. Hansen, *Org. Process Res. Dev.*, 2020, **24**, 909–915.
16 P. P. Power, *Nature*, 2010, **463**, 171–177.
17 J. Lasso, D. J. Castillo-pazos and C. J. Li, *Chem. Soc. Rev.*, 2021, **50**, 10955–10982.
18 A. Kamal, M. A. Azhar, T. Krishnaji, M. S. Malik and S. Azeeza, *Coord. Chem. Rev.*, 2008, **252**, 569–592.
19 F. Hollmann, I. W. C. E. Arends, K. Buehler and B. Bruno, *Green Chem.*, 2011, **13**, 226–265.
20 D. W. C. Macmillan, *Nature*, 2008, **455**, 304–308.
21 B. Han, X.H. He, Y.Q. Lui, G. He, C. Peng and J.L. Li, *Chem. Soc. Rev.*, 2021, **50**, 1471–2214.
22 K. Geogheghan, *Nat. Chem.*, 2021, **13**, 41557.
23 N. N. Greenwood and A. Earnshaw, in *Chemistry of the Elements (Second edition)*, 1993, vol. 20, pp. 328–366.
24 S. Dietmar, *Organometallics*, 2001, **20**, 4978–4992.
25 J. Wisniak, *Educ. Química.*, 2009, **20**, 447–455.
26 N. R. Thomas, *Silicon*, 2011, **2**, 187–193.
27 B. Dunstan, W. Luff and F. S. Kipping, *J. Chem. Soc., Trans.*, 1908, **93**, 2090–2098.
28 R. Robinson and F. S. Kipping, *J. Chem. Soc., Trans.*, 1908, **93**, 439–456.
29 G. Martin and F. S. Kipping, *J. Chem. Soc., Trans.*, 1909, **95**, 302–314.
30 F. S. Kipping and H. Davies, *J. Chem. Soc., Trans.*, 1909, **95**, 69–80.
31 A. R. Steele and F. S. Kipping, *J. Chem. Soc.*, 1928, 1431–1439.
32 N. Lee, C. Tan and D. Leow, *Asian J. Org. Chem.*, 2019, **8**, 25–31.
33 F. Foubelo, C. Najera and M. Yus, *Chem. Rec.*, 2016, **16**, 2521–2533.
34 J. J. Davies, D. C. Braddock and P. D. Lickiss, *Organic and biomolecular chemistry*, 2021, **19**, 6746–6760.
35 K. Miura and A. Hosomi, in *Main Group Metals in Organic Synthesis*, 2004, pp. 409–592.
36 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190–6191.
37 M. Lalonde and T. H. Chan, *Synthesis*, 1985, **1985**, 817–845.
38 T. Mukaiyama, K. Narasaka and K. Banno, *Chem. Lett.*, 1973, **2**, 1011–1014.

39 K. Narasaka, K. Soai, Y. Aikawa and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 779–783.
40 E. W. Colvin, *Chem. Soc. Rev.*, 1978, **7**, 15–64.
41 J. Peterson, Donald, *J. Org. Chem.*, 1966, **33**, 780–784.
42 T. H. Chan and I. Flemming, *Synthesis*, 1979, **1979**, 761–786.
43 H. Gilman and G. E. Dunn, *J. Polym. Sci.*, 1952, **52**, 77–115.
44 W. B. Jensen, *J. Chem. Educ.*, 2006, **83**, 1751–1752.
45 E. Magnusson, *J. Am. Chem. Soc.*, 1990, **112**, 7940–7951.
46 A. E. Reed and F. Weinhold, *J. Am. Chem. Soc.*, 1986, **108**, 3586–3593.
47 G. N. Lewis, *J. Am. Chem. Soc.*, 1916, **38**, 762–785.
48 J. I. Musher, *Angew. Chem. Int. Ed.*, 1969, **8**, 54–68.
49 I. Langmuir, *Science*, 1921, **54**, 59–67.
50 L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Third edit., 1960.
51 B. A. Jackson, J. Harshman and E. Miliordos, *J. Chem. Educ.*, 2020, **97**, 3638–3646.
52 A. E. Reed and P. V. R. Schleyer, *J. Am. Chem. Soc.*, 1990, **112**, 1434–1445.
53 J. Cioslowski and S. T. Mixon, *Inorg. Chem.*, 1993, **32**, 3209–3216.
54 S. Noury, B. Silvi and R. J. Gillespie, *Inorg. Chem.*, 2002, **41**, 2164–2172.
55 R. Gillespie and E. Robinson, *Inorg. Chem.*, 1995, **34**, 978–979.
56 R. E. Rundle, *J. Phys. Chem.*, 1957, **61**, 45–50.
57 G. C. Pimentel, *J Chem Phys.*, 1951, **19**, 10–13.
58 Y. Cheung, C. Ng, S. Chiu and W. Li, *J. of Mol. Stuct.*, 2003, **623**, 1–10.
59 M. L. H. Green and G. Parkin, *Dalton Trans.*, 2016, **45**, 18784–18795.
60 G. A. Landrum, N. Goldberg and R. Hoffmann, *J. Chem. Soc., Dalton Trans.*, 1997, 3605–3613.
61 V. I. Minkin, *Pure Appl. Chem.*, 1999, **71**, 1919–1981.
62 H. Fleischer, *Eur. J. Inorg. Chem.*, 2001, **2001**, 393–404.
63 D. Kost and I. Kalikhman, *Hypervalent silicon compounds*, 1998, vol. 2.
64 S. Rendler and M. Oestreich, *Synthesis*, 2005, **2005**, 1727–1747.
65 G. Singh, G. Kaur and J. Singh, *Inorg. Chem. Commun.*, 2018, **88**, 11–20.
66 Y. Nagai, *Org. Prep. Proced. Int.*, 1989, **21**, 501–504.
67 G. L. Larson and R. J. Liberatore, *Org. Process Res. Dev.*, 2021, **25**, 1719–1787.
68 S. Rendler and M. Oestreich, in *Modern Reduction Methods*, 2008, pp. 183–207.
69 H. C. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567–607.
70 K. Marsi, *J. Org. Chem.*, 1974, **39**, 265–267.
71 J. A. Buonomo, C. G. Eiden and C. C. Aldrich, *Chem. Eur. J.*, 2017, **23**, 14434–14438.
72 M. Orfanopoulos and I. Smonou, *Synth. Commun.*, 1988, **18**, 833–839.
73 F. A. Carey and H. S. Tremper, *J. Am. Chem. Soc.*, 1968, **90**, 2578–2583.
74 M. P. Doyle, C. C. McOsker and C. T. West, *J. Org. Chem.*, 1976, **41**, 1393–1396.
75 J. L. Fry, M. Orfanopoulos, M. Adlington, W. Dittman Jr and S. Silverman, *J. Org. Chem.*, 1978, **43**, 374–375.
76 M. Sassaman, K. Kotian, G. Surya Prakash and G. Olah, *J. Org. Chem.*, 1987, **52**, 4314–4319.
77 J. Jiang and J. Jiang, *Synlett*, 2021, **32**, 291–294.
78 C. Cheng and M. Brookhart, *Angew. Chem. Int. Ed.*, 2012, **51**, 9422–9424.
79 E. Antico, P. Schlichter, C. Werl and W. Leitner, *J. Am. Chem. Soc. Au*, 2021, **1**, 742–749.
80 E. L. Stoll, T. Tongue, K. G. Andrews, D. Valette, D. J. Hirst and R. M. Denton, *Chem. Sci.*, 2020, **11**, 9494–9500.
81 D. Addis, S. Zhou, S. Das, K. Junge, H. Kosslick, J. Harloff, H. Lund, A. Schulz and M. Beller, *Chem. Asian J.*, 2010, **5**, 2341–2345.
82 G. Kumar, A. Muthukumar and G. Sekar, *Eur. J. Org. Chem.*, 2017, **2017**, 4883–4890.
83 S. Zhou, K. Junge, D. Addis, S. Das and M. Beller, *Org. Lett.*, 2009, **11**, 2461–2464.
84 M. Drew, N. Lawrence, D. Fontaine and S. Lakhdar, *Synlett*, 1997, **1997**, 989–991.
85 K. Revunova and G. I. Nikonov, *Chem. Eur. J.*, 2014, **20**, 839–845.
86 X. X. Zhao, P. Zhang and Z. X. Guo, *ChemistrySelect*, 2017, **2**, 7670–7677.

87 J. K. Puri, R. Singh and V. K. Chahala, *Chem. Soc. Rev.*, 2011, **40**, 1791–1840.
88 V. Skrypai, J. J. M. Hurley and M. J. Adler, *Eur. J. Org. Chem.*, 2016, **2016**, 2207–2211.
89 S. E. Varjosaari, V. Skrypai, P. Suating, J. J. M. Hurley, T. M. Gilbert and M. J. Adler, *Eur. J. Org. Chem.*, 2017, **2017**, 229–232.
90 S. E. Varjosaari, V. Skrypai, P. Suating, J. J. M. Hurley, A. M. D. Lio, T. M. Gilbert and M. J. Adler, *Adv. Synth. Catal.*, 2017, **359**, 1872–1878.
91 W. Yao, H. Fang, Q. He, D. Peng, G. Liu and Z. Huang, *J. Org. Chem.*, 2019, **84**, 6084–6093.
92 M. Pørez, Z. Qu, C. B. Caputo, V. Podgorny, L. J. Hounjet, A. Hansen, R. Dobrovetsky, S. Grimme and D. W. Stephan, *Chem. Eur. J.*, 2015, **21**, 6491–6500.
93 C. Laye, J. Lusseau, F. Robert and Y. Landais, *Adv. Synth. Catal.*, 2021, **363**, 3035–3043.
94 V. Gevorgyan, M. Rubin, S. Benson and J. Liu, *J. Org. Chem.*, 2000, **65**, 6179–6186.
95 D. J. Parks and W. E. Piers, *J. Am. Chem. Soc.*, 1996, **118**, 9440–9441.
96 J. S. J. Mccahill, G. C. Welch and D. W. Stephan, *Angew. Chem. Int. Ed.*, 2007, **46**, 4968–4971.
97 D. W. Stephan and G. Erker, *Angew. Chem. Int. Ed.*, 2010, **49**, 46–76.
98 J. M. Blackwell, E. R. Sonmor, T. Scoccitti and W. E. Piers, *Org. Lett.*, 2000, **2**, 3921–3923.
99 D. J. Parks, J. M. Blackwell and W. E. Piers, *J. Org. Chem.*, 2000, **65**, 3090–3098.
100 S. Rendler and M. Oestreich, *Angew. Chem. Int. Ed.*, 2008, **47**, 5997–6000.
101 Y. Jiang, B. Schirmer, O. Blacque, T. Fox, S. Grimme and H. Berke, *J. Am. Chem. Soc.*, 2013, **135**, 4088–4102.
102 A. H. Houghton, J. Hurmalainen, A. Mansikkmaki, W. Piers and Kh. Tuononen, *Nat. Chem.*, 2014, **6**, 983–988.
103 L. Susse, J. Hermeke and M. Oestreich, *J. Am. Chem. Soc.*, 2016, **138**, 6940–6943.

Chapter 1

Metal-free Reductive Amination from Carboxylic Acids

Amine formation is of paramount importance for a range of industries. However, current synthesis methods are plagued by hard-to-handle reagents and expensive metal catalysts and reducing agents. Here, we report a practical metal-free reductive amination using carboxylic acids through the use of phenylsilane and benzenesulfonic acid. This method is applied to a range of compounds displaying both functional group tolerance and the synthesis of complex motifs. Mechanistic investigations are carried out both experimentally and computationally and silyl sulfonates were implicated as the active reducing species.

Milly Stoneley

1 Introduction

1.1 Importance of Amines

Amines are fundamental functional groups and are present in a wide range of bioactive and commercially available molecules. Production capacity is in excess of over 100 000 tonnes per year.[1–3] Arguably, some of the most important nitrogen containing compounds are those necessary for the human body to function. Deoxyribonucleic acid (DNA) is formed from four amine containing base pairs which are stabilised in the double helix through amine mediated hydrogen bonds (Figure 9A).[4] In addition, amines are present in all amino acids, which are the constituent building blocks for proteins and enzymes (Figure 9B).[5]

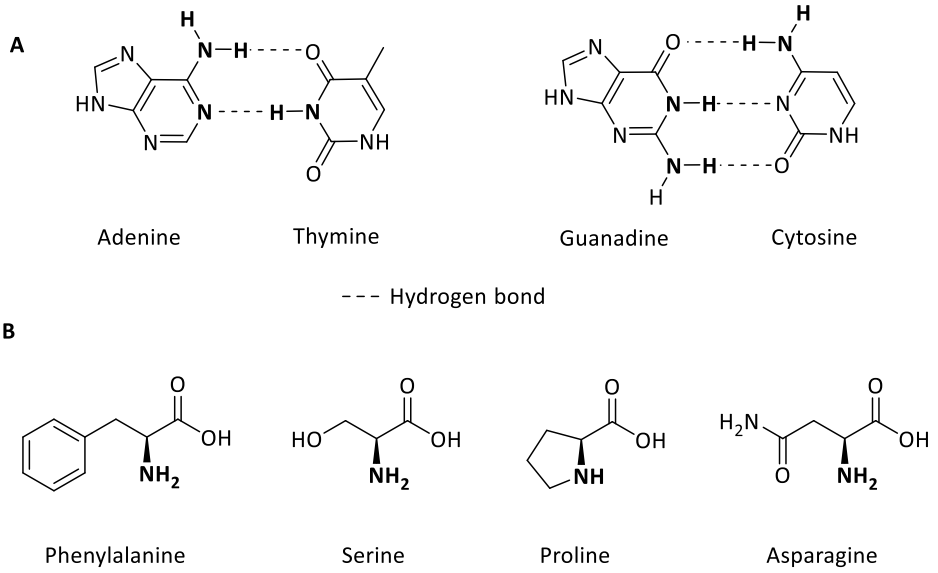


Figure 9: *Important biological uses for amines*

Nitrogen is present in many natural and synthetic compounds, and the nucleophilic and basic nature results in amines having a wide range of applications in organic synthesis. As a result, the amine market was estimated at $15.6 billion in 2021 with a projected increase to $23.8 billion in 2030.[6] The dominating and ever-increasing need for amines is for crop protection chemicals although amines are exceptionally prevalent in pharmaceuticals. Not only are they extremely versatile and easily tuneable, but are also able to ionise, improving aqueous solubility and cell membrane permeation.[7,8] As a result, amines are present in a huge number of compounds across a range of industries, and in a number of

natural products. A publication investigating the prevalence of amines found that they are present in over 40% of active pharmaceutical ingredients and over 20% of agrochemicals.[9]

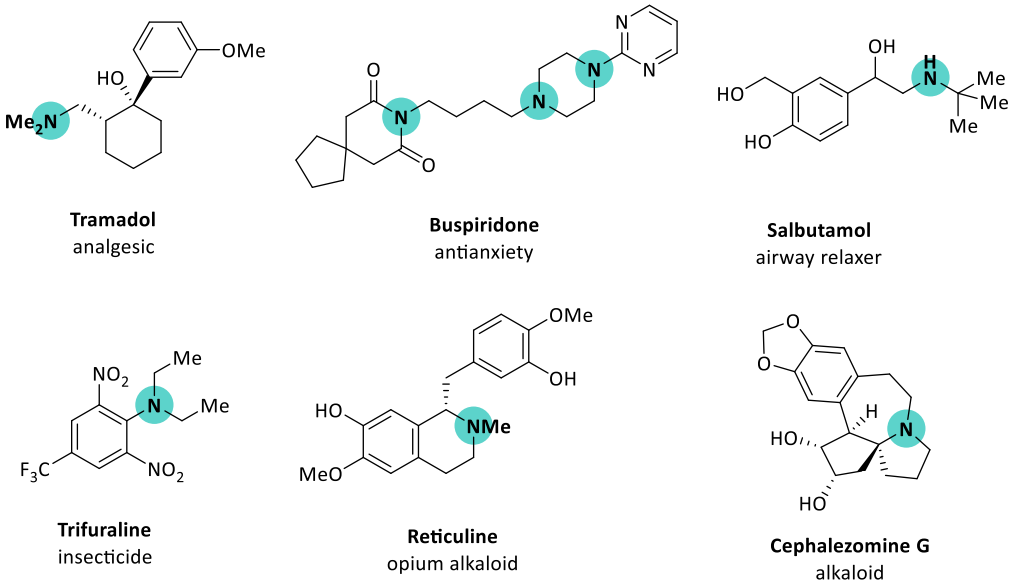


Figure 10: *Examples of amine containing pharmaceuticals, agrochemicals and natural products*

Further probing into the types of reactions used in drug candidates synthesis, found that C-N bond construction is the most common type of carbon-heteroatom synthesis and that 46% of all reactions carried out culminated in an amine or amide product.[10] In addition, of the top 10 reactions reported in 2008, over half involved amine products.[10] Looking into the breakdown of C-N bond forming reactions, *N*-acylation was by far the most common, accounting for 16% of all total reactions completed. For the synthesis of amines, protecting group manipulation is the most prevalent reaction, followed by *N*-aryl substitution, both S_NAr and Buchwald-Hartwig aminations. Reductive amination and *N*-alkyl substitution each account for 5% of total reactions published.[10]

Entry	Reaction Type	Percentage of Total Reactions (%)
	Amide	
1	*N*-acylation	16
	Amine	
2	N-H protection and deprotection	9.5
3	*N*-arylation with aryl halides	6.2
4	*N*-substitution with alkyl halides	5.3
5	Reductive amination	5.3
6	Nitro reduction	1.1
7	Amide reduction	0.7
8	Amide *N*-alkylation	0.7
9	Heteroaryl *N*-alkylation	0.6
10	Nitrile or imine reduction	0.2

Table 1: *Prevalence of C-N bond forming reactions in the pharmaceutical industry*[10]

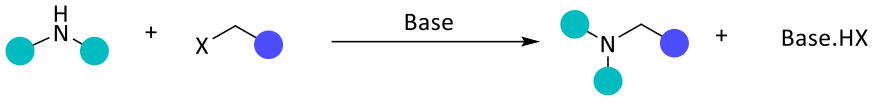
The prevalence of amines in a wide number of useful compounds across a range of industries, and the popularity of C-N bond forming reactions in the literature, has culminated in significant interest towards amine synthesis. However, many traditional methods rely on expensive metal catalysis and hazardous stoichiometric reducing agents, and often result in poor selectivity and require specialist set-ups.

1.2 Amine Synthesis

As outlined above, C-N bonds are of significant interest and as a result, there is a wide range of synthesis options for amine formation. In the following section, some of the more popular methods will be discussed, *N*-alkylation, S_NAr, amide reduction and later reductive amination in more detail.

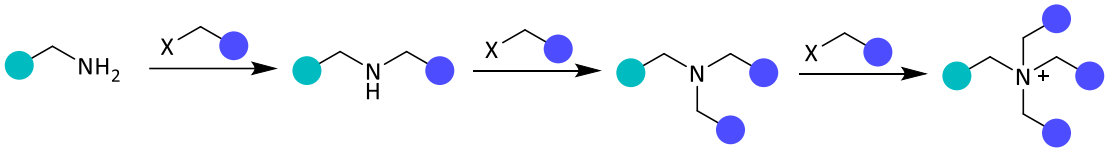
1.2.1 *N*-alkylation

One of the traditional and most simple methods for amine construction is the Hofmann alkylation, an *N*-alkylation of an amine with an alkyl halide, or equivalent, to form a higher substituted amine structure.[11]



Scheme 1: *N-alkylation using alkyl halides*

This methodology is usually employed for the construction of tertiary amines, and has been used in the synthesis of many pharmaceuticals on a discovery scale.[12–14] However, this method is not often used in a manufacturing route due to the drawbacks. This reaction often suffers with over-alkylation as the resulting product is more nucleophilic than the starting material and can react further, forming complex mixtures of the secondary, tertiary and quaternary products.[11]



Scheme 2: *Over alkylation of primary amines*

Due to this poor selectivity, reactions using this method often have low yields and difficult purifications. However, methods utilising microwave radiation,[15] ionic liquids[16,17] and biocatalysts,[18] have all been effective in preventing overalkylation, although many use high excesses of amine starting materials and expensive procedures. Other successful strategies have employed the formation of quaternary ammonium salts, deactivating the product to any further reaction at the nitrogen center. This was first accomplished by Jung, who used caesium hydroxide to form caesium-amine complexes to prevent overalkylation through steric effects and product acidity (Figure 11A).[19] However, due to the issues associated with CsOH, the process was reoptimised using the more handleable caesium carbonate.[20] An alternative procedure by Pathak, used the acid generated in the initial reaction, to form the quaternary ammonium salt.[21] As a result, further alkylation was suppressed through formation of a non-nucleophilic ammonium salt (Figure 11B).

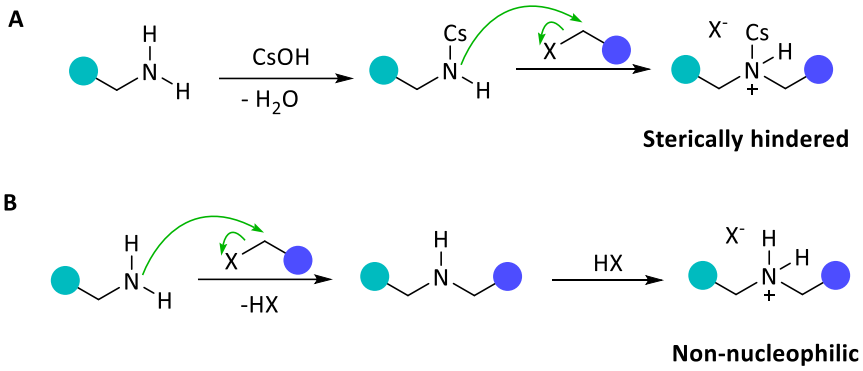
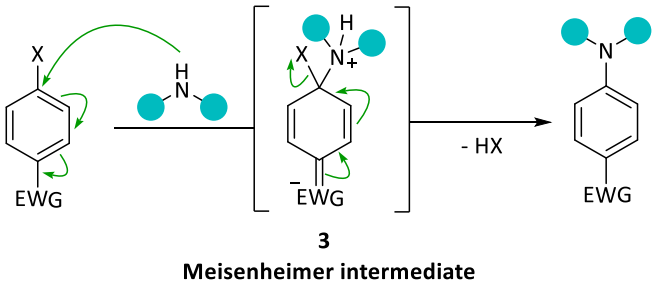


Figure 11: *Strategies towards mono-alkylation*

Despite the development of these methods, *N*-alkylation using alkyl halides is still not a widely used procedure. Alkylating agents are mutagenic, and as a result, are avoided when working on manufacturing scale.[22] In addition, more complex halide species have to be synthesised, usually from alcohols which employs harsh conditions and toxic halogenating agents.[23–25]

1.2.2 Nucleophilic Aromatic Substitution (S_NAr)

In the same way that amines can be derivatised with alkyl groups through using alkyl halides, this type of chemistry can also be applied to reactions using aryl halides.

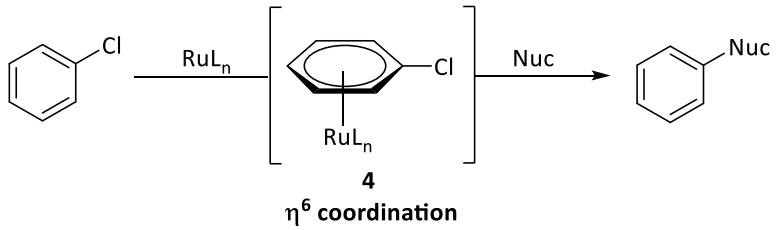


Scheme 3: *S_NAr reactions via addition-elimination*

S_NAr reactions involve addition of the nucleophile, forming a Meisenheimer complex (**3**) which readily eliminates the leaving group in the presence of a base, reforming the aromatic ring.[26,27] This process is higher in energy than its alkyl substitution counterpart, as the aromatic stability has to be overcome in order for the reaction to progress. The mechanism for the reaction is generally accepted to be the

two-step addition-elimination reaction as detailed above (Scheme 3),[27,28] although for some compounds a concerted mechanism has been proven.[29]

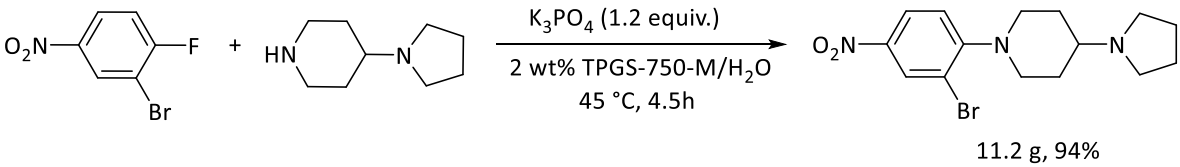
Aromatic substitution reactions are favoured on scale, due to high atom economy and metal-free conditions and have been utilised in the manufacture route for a range of nitrogen containing pharmaceuticals.[30] This process has been demonstrated for both alkyl and aryl amine nucleophiles in addition to a range of halide leaving groups. [31] However, one of the main drawbacks associated with S_NAr is the necessity of electron-withdrawing groups on *ortho* or *para* positions on the ring. These exist to increase electrophilicity, and act as an electron sink upon addition to the arene.[32] Although it is possible to complete reactions without electron-withdrawing groups present, the yields are diminished for less activated substrates.[33] Transition metals such as catalytic amounts of ruthenium[34,35] or stoichiometric chromium[36] can be utilised to activate arenes through η^6 complexation (**4**). However, one of the main benefits of this reaction is that it is metal-free, and the introduction of metal additives introduces concerns around purification, toxicity, and cost.



Scheme 4: *S_NAr with ruthenium catalysis via η^6 coordination*

In addition, polar aprotic solvents such as *N,N*-dimethylformamide (DMF), 1-Methyl-2-pyrrolidone (NMP) and *N,N*-dimethylacetamide (DMAc) are often required for this reaction.[37,38] These solvents have been linked to significant health issues and have been included on the Registration, Evaluation and Authorisation and Restriction of Chemicals' (REACH) 'substances of very high concern' due to reproduction toxicity.[39] The replacement of these solvents was announced by the ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) as a key area of research.[40] Greener solvents such as ionic liquids[41] and polyethylenegylol[42] have been demonstrated for this reaction, however one of the main advancements has been the use of commercial surfactants to allow for an aqueous

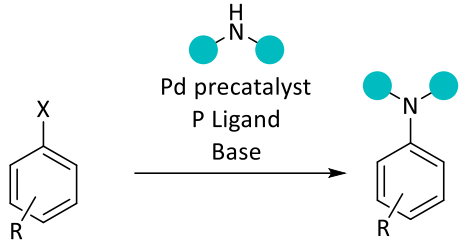
solvents. In 2015, Lipshutz showed that S_NAr reactions can be carried out using micellar catalysis and demonstrated a range of complex examples.[43] He later scaled up this protocol to demonstrate its utility on a larger scale.[44]



Scheme 5: *Scale up of aqueous S_NAr reaction by micellar catalysis*

1.2.3 Buchwald-Hartwig Coupling

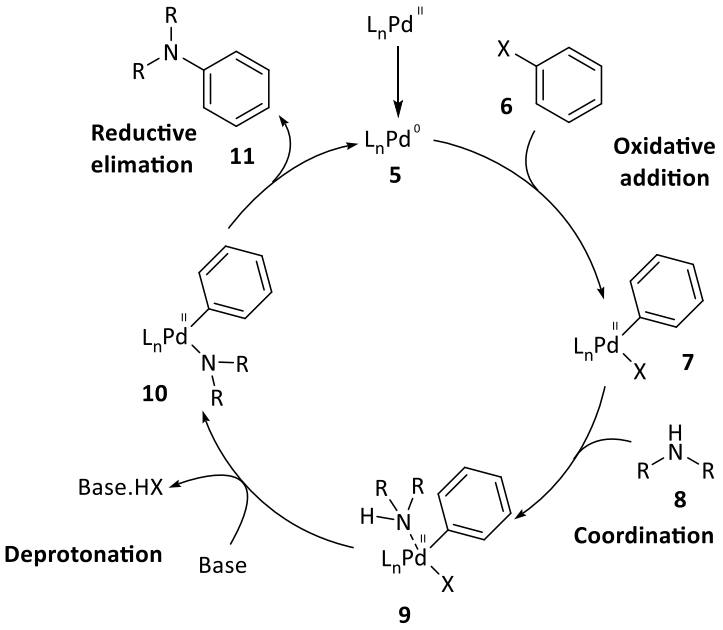
Palladium-catalysed couplings are an alternative method for the synthesis of secondary and tertiary aromatic amines without the substitution requirements of an S_NAr reaction. This process was initially developed by Migita, who used aminostannanes as the nucleophile.[45] Further development of this methodology was carried out independently by Buchwald[46] and Hartwig,[47] who expanded the scope of the reaction through generation of the unstable aminostannane *in situ,* and further developed the understanding of the mechanism. Buchwald and Hartwig later improved upon this protocol, using strong bases to allow for amines to be used directly as the coupling partners, negating the need for the toxic stannane.[48,49]



Scheme 6: *Buchwald-Hartwig reaction*

Reports detailing the mechanism for this reaction, in addition to kinetic studies, were published in 2000 and further reports have confirmed the original catalytic cycle.[50,51] The mechanism for the Buchwald-Hartwig reaction starts with reduction of the palladium (II) precatalyst to palladium (0) (**5**), following which, oxidative addition of the aryl bromide (**6**) can take place. The amine (**8**) coordinates to the palladium centre (**9**) and is deprotonated forming the amino-palladium complex (**10**). This

undergoes reductive elimination to form the product (**11**) and regenerate the Pd(0) species (**5**). An initial issue with the chemistry was that where β-hydrogens are present, β-hydride elimination could compete with reductive elimination to form the hydrodehalogenated product. Bulky or bidentate phosphine ligands have since been designed to overcome this problem.[52–54]



Scheme 7: *Buchwald-Hartwig catalytic cycle*

The development of Buchwald-Hartwig reactions has increased drastically since its conception. The use of electrophiles has extended to include aryl iodides,[55] triflates[56] and tosylates[57] in addition to alkyl bromides.[58] Additionally, the amine scope has expanded rapidly to not only include primary and secondary alkylamines,[53] but also anilines,[59] heteroanilines[60] and ammonia equivalents.[61] Interestingly, amides, which are less nucleophilic, can also be coupled with a range of electrophiles using this method.[62] Precatalysts have also been integral in the development of this process.[63–65] Commercial palladium sources bearing ligands that rapidly activate under the reaction conditions, have allowed for improved ease of reaction set up, milder conditions and lower catalyst loading. Although it is impossible *herein* to discuss the full scope of the Buchwald-Hartwig reaction, reviews by Buchwald, and Dorel and Haydl have provided extensive insights into the utilisation of this method.[66,67]

Despite the prevalence and utility of the Buchwald-Hartwig reaction, the use of palladium poses many issues. The problem with metal-based chemistry has been discussed in more detail in above sections

and as a result of these issues, there has been a drive to alternative metal-catalysed couplings. Examples of such metals include nickel, which can mediate aminations with a range of electrophiles, and copper in reactions such as the Chan-Lam coupling.[68,69]

1.2.4 Amide Reduction

1.2.4.1 Traditional Reducing Agents

Amides are extremely prevalent in both nature and in pharmaceuticals, and as a result, amine synthesis *via* amide reduction is common. However, amide reduction can be challenging due to lower reactivity and susceptibility to attack than other carbonyl compounds. This is a result of nitrogen delocalisation.[70] Before investigating more recent methods, the traditional stoichiometric reducing agents must be considered as they are widely used. These reducing methods can be classified by three main mechanisms: addition of a hydride from an anion (Figure 12A), attack onto the electrophilic reducing agent (Figure 12B) (intramolecular hydride transfer shown for simplicity) or hydrogenation (Figure 12C).[71,72]

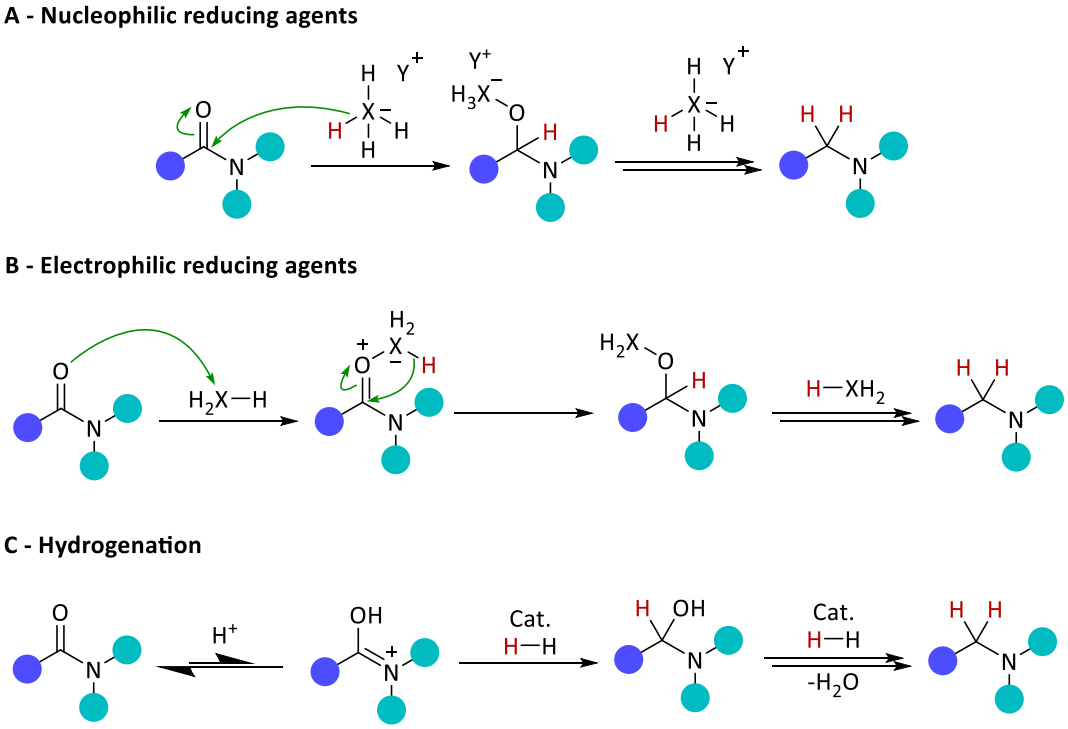
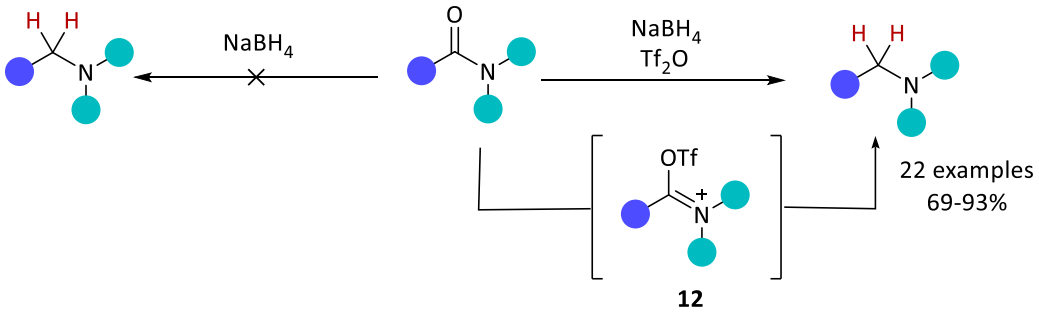


Figure 12: *Methods for amide reduction*

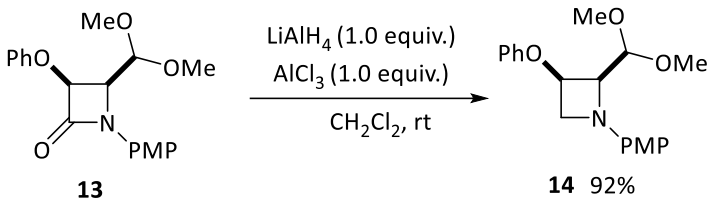
Looking at amide reduction using nucleophilic reagents, lithium aluminium hydride (LAH) is among the most commonly used. LAH was first synthesised in 1947,[73] and since then has been used extensively for the reduction of a wide range of carbonyl compounds.[74,75] For amides specifically, LAH has been used in the synthesis of pharmaceuticals,[76] natural products[77] and organocatalysts.[78,79] However, the issues with LAH are vast. The compound is not only extremely water and air sensitive, but the strong reductive potential results in low functional group tolerance. In addition, there are difficult workup procedures associated with LAH, due to the formation of insoluble aluminium salts, and potential ignition from liberated H_2, although different workups have been developed to circumvent this issue.[80] As an alternative, sodium bis(2-methoxyethoxy)aluminium hydride (red-Al) can be used. This reagent is comparable in reducing strength to LAH but is less hazardous, easier to handle and has increased solubility in organic solvents.[81,82] Sodium borohydride ($NaBH_4$) is commonly used in the reduction of carbonyl compounds, however as it is a milder reducing agent than LAH, it is unable to reduce amides. However, upon activation of the amide to the highly electrophilic alkoxyiminium species (**12**), reduction using $NaBH_4$ is possible (Scheme 8).[83,84]



Scheme 8: *Reduction of amides using $NaBH_4$ through activation by Tf_2O*

Electrophilic reducing agents have also been successful in the reduction of amides. Borane (BH_3) has been known since 1912,[85] however, its use as a reducing agent was not realised until 1939, where it was used to reduce some carbonyl compounds.[86] Since this initial discovery, the use of borane as a reducing agent has expanded to include amides, although resulting amino-borane product has to be cleaved in the workup to release the free amine.[87] This poses problems for secondary and primary amine products, where harsh conditions are required for this cleavage, although milder conditions

using iodine or metal catalysts have been developed.[88–90] As borane is a pyrophoric gas, borane THF or SMe_2 complexes in solution are used as an alternative, without any decrease in performance,[91,92] and have even been shown to reduce amides selectively in the presence of esters.[93] In addition, $NaBH_4$ can be converted to borane *in situ,* using additives such as iodine, $BF_3.OEt_2$ or H^+ and this method is generally preferred on-scale to using borane solutions.[94,95] Alkyl boranes such as 9-borabicyclo[3.3.1] nonane (9-BBN) has also been shown to reduce tertiary amides. However, as this method provides no advantage over borane, it is not widely used.[96] Another metal hydride, alane (AlH_3) has also been used in amide reductions, although it is not as prevalent as borane due to its lower selectivity and higher cost.[97] An alternative is monochloroalane (AlH_2Cl) formed *in situ* through the reaction of LAH and $AlCl_3$, and is more selective that AlH_3, allowing for the reduction of β-lactams (**13**) to azetidines (**14**) in the presence of acetals and ethers.[98]



13 **14** 92%

Scheme 9: *Selective reduction of β-lactams by AlH_2Cl*

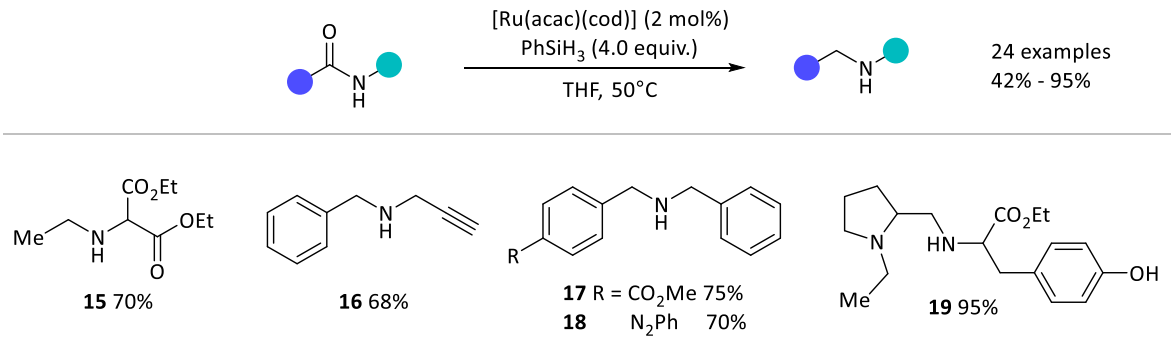
In addition to the stoichiometric reducing agents described above, catalytic methods can be employed. Use of hydrogen gas (H_2) for amide reduction is considered a highly sustainable process. However, the use of heterogeneous catalysts such as copper/chromium require high temperatures (250 ^oC) and pressures (200-300 bar) and result in low selectivity.[99] As an alternative, homogeneous catalysts have been developed that utilise hydrogen gas with more selective and mild conditions. These catalysts are most often ruthenium with the tridentate, triphos, ligand,[100–102] although protocols have been developed using manganese,[103] iridium[104] and cobalt.[105] Studies have shown that the bulky triphos ligand prevents deactivation of the catalyst and as a result, allows for reduction of more challenging amide substrates, although selectivity between higher order and lower order amine products is still relatively poor.[100] Reviews by Beller[72] and Whyman[3] cover further methods for catalytic dehydrogenation of amides. In addition to metal catalysed processes, there have been

reports of metal-free protocols, using tris(pentafluorophenyl)borane. However, the conditions still require high pressures of H_2 (80 bar) and triphosgene for the reduction of secondary amides.[106]

1.2.4.2 Transition-metal-Catalysed Silane Mediated Amide Reduction

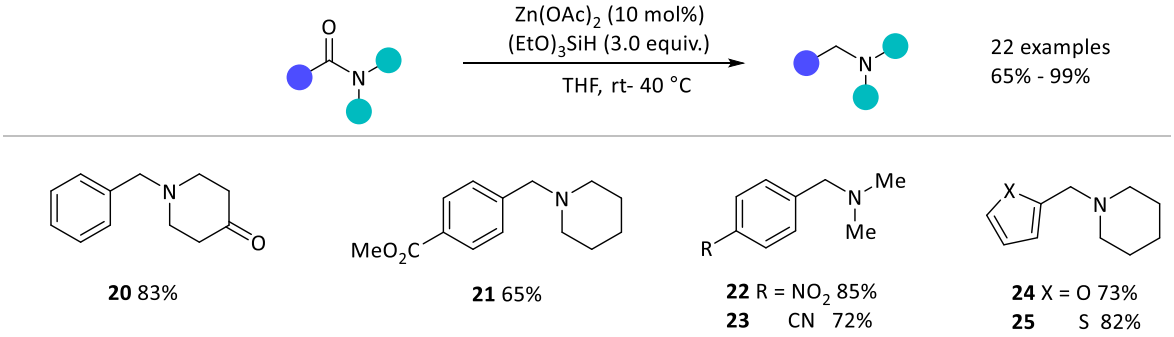
Despite the advancement of stoichiometric reducing agents to have both higher selectivity and milder conditions, there has been a drive towards the development of protocols that do not contain these reagents. This is a result of the ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) in 2018 announcing that a key research area would be amide reductions avoiding LAH and borane.[40] A popular alternative is hydrosilane mediated reductions due to increased handleability and stability.

Silanes used in conjunction with transition metal catalysts have shown to be effective reducing agents for amides. The first successful example was reported by Ito in 1998 who utilised a rhodium catalyst with diphenylsilane to reduce a range of tertiary amides to amines using mild conditions.[107] Another early publication on metal-catalysed hydrosilylation, demonstrated that groups 7-10 metals, (Mn, Re, Ru, Os, Rh, Ir, Pd and Pt) in conjunction with monosilanes, could be used for the reduction of amides to amines.[108] In particular, ruthenium catalysts were shown to be effective reducing agents and have since been used as the catalyst in a number of silane mediated reductions.[109,110] A particularly effective example used Ru(acac)(cod) in conjunction with phenylsilane to achieve the selective reduction of tertiary and secondary amides, *N*-acyl amino esters (**15**) and dipeptides (**19**) in good yields (Scheme 10).[111]



Scheme 10: *Beller's reduction of amides using [Ru(acac)(cod)]/$PhSiH_3$*

Despite many publications using catalysts such as iridium,[112] platinum,[113] and rhodium,[114] there has recently been an increase in methods using more available and less expensive metals. This area has been dominated by the Beller group, who have described the hydrosilylation of amides in the presence of non-precious metal catalysts such as copper,[115] iron[116] and zinc.[117] All of these protocols show increased selectivity over traditional hydride reductions, all tolerating esters and heterocycles, and the iron catalysed process further allowing alkenes and cyclopropanes. The zinc-catalysed reaction, shows an even more impressive functional group tolerance, demonstrating ketone (**20**), ester (**21**), nitro (**22**), nitrile (**23**) and heterocycles (**24** and **25**) functionality in excellent yields.[117] This method utilised both the inexpensive $Zn(OAc)_2$ and $(EtO)_3SiH$ and the reactive zinc hydride species was invoked as the main reducing agent (Scheme 11). This method was subsequently redeveloped using the safer $(EtO)_2SiMeH$, and was reoptimised towards secondary amides, however, the more reactive $Zn(OTf)_2$ was required as the catalyst.[118] Despite improved reaction conditions, and excellent functional group tolerance, ketone functionality was not tolerated like with the previous conditions.

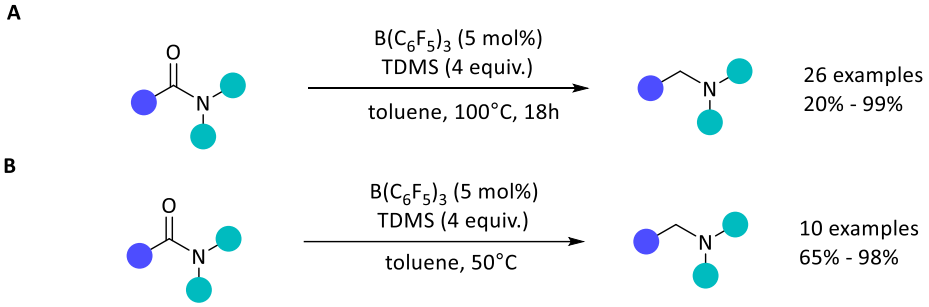


***Scheme 11**: Beller's reduction of amides using $Zn(OAc)_2/(EtO)_3SiH$*

1.2.4.2 Metal-free Silane Mediated Amide Reduction

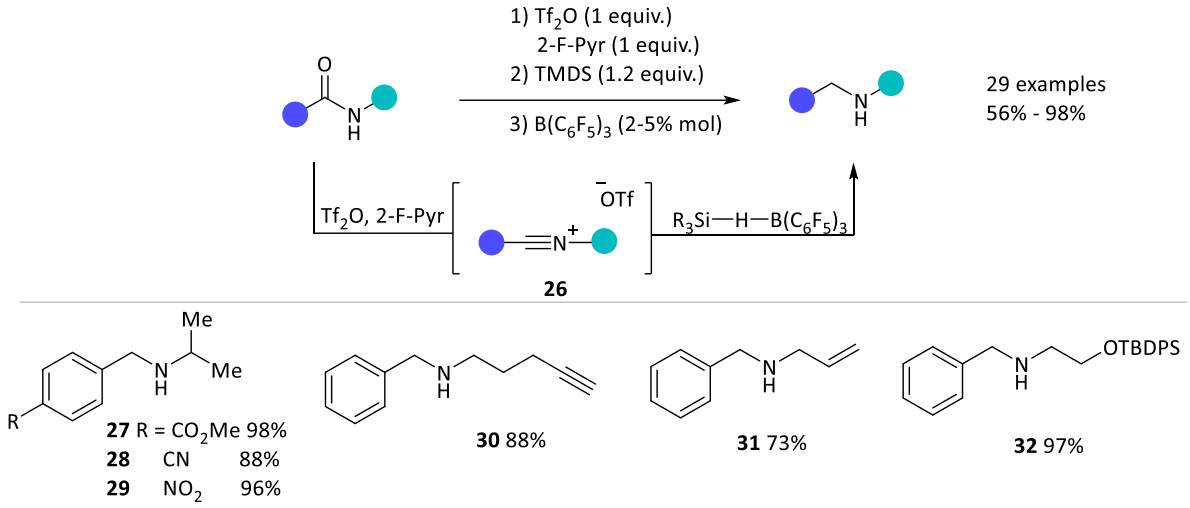
In addition to the advancements in metal-catalysed reactions, there has also been developments in metal-free silane mediated amide reductions, utilising either base or acid activation. In 2013, Cui published a Cs_2CO_3-catalysed reduction with $PhSiH_3$,[119] and a TBAF-catalysed reduction of α-keto amines was also reported.[120]

Acid-catalysed processes are a lot more common, and reduction of amides have been demonstrated using a range of activators such as electrophilic phosphonium cations[121] and Hantzsch esters.[122] This chemistry, however, is dominated by boron catalysis. The borane $B(C_6F_5)_3$ was first used in conjunction with a silane for amide reduction by Zhang in 2009 to reduce three amides with good yields, although the compounds contained no extra functionality.[123] This work was expanded by Cantat[124] and Adronov[125] independently, who used $B(C_6F_5)_3$ along with either poly(methylhydrosiloxane) (PMHS) or tetramethyldisiloxane (TDMS) to achieve reduction of a range of tertiary and secondary amines (Scheme 12). Although both protocols tolerated nitro and halide functionality, any other functional groups prevented reactivity, potentially due to coordination of the strong Lewis acid. Cantat found that in the case of conjugated amides, the double bond would reduce preferentially over the amide and that where ester substituents were present, breakdown of the ester to the aldehyde and toluene derivatives were significant side products.



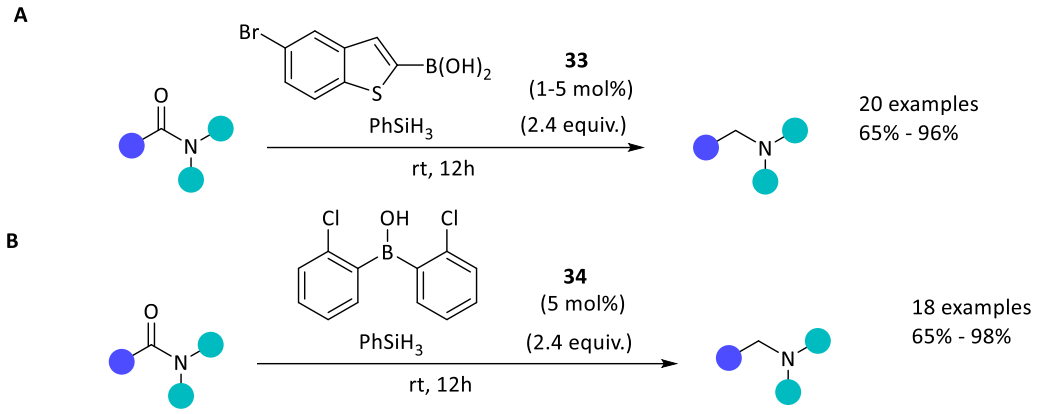
Scheme 12: *Cantat and Adronov's reduction of amides using $B(C_6F_5)_3$/tetramethyldisiloxane (TDMS)*

This problem was circumvented in a method published by Wang, who used triflic anhydride and 2-fluropyridine to initially form the nitrilium ion (**26**), increasing the electrophilicity and allowing for chemoselective hydride transfer from the Piers intermediate (Scheme 13).[126] As a result, this method demonstrated a much broader functional group tolerance, with esters (**27**), nitriles (**28**), nitros (**29**), alkynes (**30**) and alkenes (**31**) all tolerated. However, as formation of the nitrilium ion (**26**) is a requirement for the mechanism, this method is restricted to the synthesis of secondary amines only.



***Scheme 13**: Wang's reduction of amides using Tf_2O, 2-F-Pyr, $B(C_6F_5)_3$/TMDS*

One of the difficulties associated with $B(C_6F_5)_3$ is the strong electrophilic nature affecting the functional group tolerance. Methods using other less reactive boranes have been reported, although this is not as common. A protocol using triphenylborane and phenylmethylsilane has been reported, with good functional group tolerance.[127] A further method using triethyl borane in conjunction with $PhSiH_3$ has also been published, although a base was required to facilitate borohydride formation.128 Another way this has been resolved is through the use of boric acids. This work was pioneered by Beller who used the commercial boronic acid **33** and $PhSiH_3$ to achieve reduction of tertiary and secondary amides. This transformation tolerated a range of functional groups such as, nitro, ester, nitrile and ether functionality (Scheme 14A).[129] This methodology was also applied to the reduction of primary amides although the yields were modest when compared to other reduction methods. This work was expanded by Blanchet, who developed a borinic acid catalyst (**34**), and with $PhSiH_3$ was able to complete the reduction in a room temperature process (Scheme 14B).[130] Although this protocol only investigated tertiary amides, it boasts an impressive scope with excellent functional group tolerance, including ketones and carbamates. The authors invoke the formation of an initial siloxyboron species with the elimination of hydrogen, which with further reaction with phenyl silane, forms the borane which is postulated to be the active reducing species.



Scheme 14: *Beller and Blanchet's reduction of amides using boric acids/$PhSiH_3$*

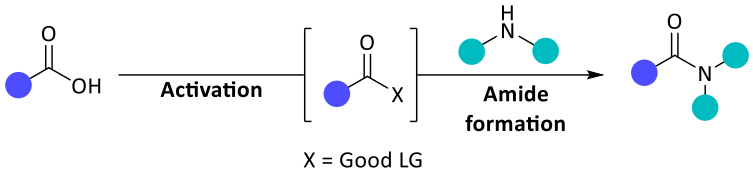
Despite all the development towards mild and metal-free amide reductions, there is one common disadvantage: the amide has to be constructed in a separate step, usually through stoichiometric amide coupling methods, which requires further isolation and purification procedures.

1.3 Amide synthesis

As the reduction of amides has been discussed, it is pertinent to investigate methods for amide synthesis. Amide bond formation is the most performed reaction in medicinal chemistry and as such there are many published synthesis methods.[10]

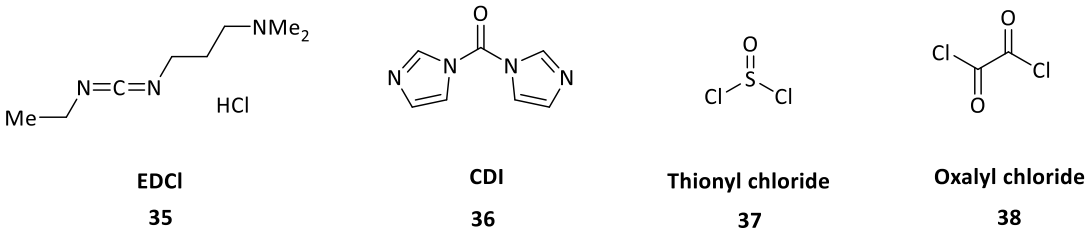
1.3.1 Traditional methods

The most efficient way for amide synthesis is the direct reaction of amines and carboxylic acids, with water as the only by-product. However, these processes require extremely harsh conditions (180 ^{o}C) to overcome formation of the ammonium carboxylate species, and as a result, the yields and scope are often low.[131] Most traditional methods utilise stoichiometric activation of the carboxylic acid starting material to improve the leaving group capacity of the hydroxyl substituent, allowing for reactions to occur with a weaker nucleophile (Scheme 15).[132] Other novel catalytic reaction pathways have been developed,[133] such as oxidative amination of aldehydes,[134] aminocarbonylation of aryl halides[135] and transamidation of primary amides,[136,137] although these methods are not frequently used.



Scheme 15: *General method for amide formation*

According to a review published by Magano,[138] the reactions that are most commonly utilised on a manufacturing scale can be categorised into five principal areas: Activation through acid chloride formation, mixed anhydride formation (carboxylic acids, carbonic acids, sulfonates, phosphorus and boron based), imidazolium formation, *via* ester formation (O-acylisourea, benzotriazole, *N*-oxide and triazene) and through silyl esters. The most commonly used coupling agents on a manufacturing scale were found to be 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride (EDCl) (**35**), 1,1'-carbonyldiimidazole (CDI) (**36**), thionyl chloride (**37**) and oxalyl chloride (**38**) (Figure 13).[138]



EDCl **CDI** **Thionyl chloride** **Oxalyl chloride**

35 **36** **37** **38**

Figure 13: *The most common coupling reagents*

Despite these protocols being the most popular on a large scale, there are many drawbacks. This includes harsh conditions, limited scope and hazardous and stoichiometric by-products, in addition to high cost and extensive purification procedures. Amide formation *via* acid chlorides appears to be the most simple and convenient, however, by-products of the chlorination step are toxic gases such as carbon monoxide and sulfur dioxide. Additionally, the amidation step forms hydrochloric acid (HCl), which not only requires further scrubbing procedures, but also limits the scope to non-acid sensitive functionalities. Amide synthesis using guanidine *N*-oxide salts, hexafluorophosphate benzotriazole tetramethyl uronium (HBTU) and hexafluorophosphate azabenzotriazole tetramethyl uronium (HATU), forms tetramethylurea as a by-product, which is highly cytotoxic. Therefore, although these reagents provide fast couplings with low racemisation, the by-product along with the high reagent

cost, limits the use on a larger scale. Drawbacks to the other methods concern the use of repotoxic and mutagenic coupling agents along with to the need for column chromatography purification.[138]

1.3.2 Silane Mediated Amide Coupling

Due to the issues associated with the coupling agents described above, there has been a drive to discover improved protocols. A review highlighting the large-scale synthesis of amides, concluded that "the ideal reagent is inexpensive, widely available, non-toxic, safe, simple to handle, easy to purge from reaction mixtures, and contributes only minimally to waste streams"[139] and as a result, silanes have become a popular choice for amide formation. Silanes are not only easy to handle, and non-toxic, but simple work-up procedures allow for the efficient removal of by products, which are in most cases water-soluble and benign. *Herein*, the focus will be on hydrosilane mediated couplings, although there have been protocols published using tetrasubstitued silanes such as tetrachlorosilane (**39**),[140] alkyl (**40**) and aryl (**41**) chlorosilanes,[141,142] imidazolesilanes (**42**),[143] tetramethyl orthosilicate (**43**),[144] methyltrimethoxysilane (**44**)[145] and silicon tetraacetate (**45**) (Figure 14).[146] A comprehensive review by Braddock and Lickiss provide further insights into more silanes capable of amide formation.[147]

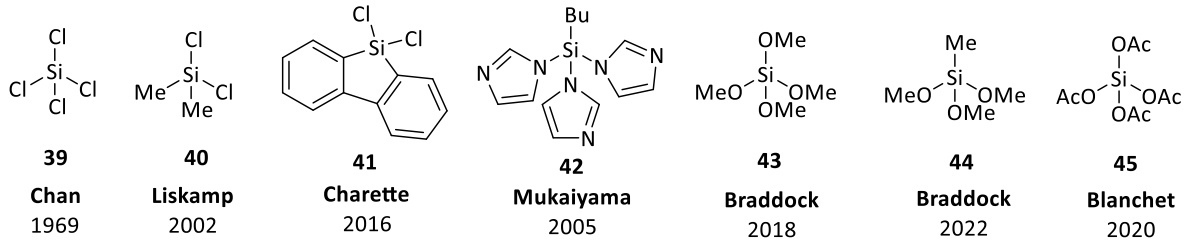
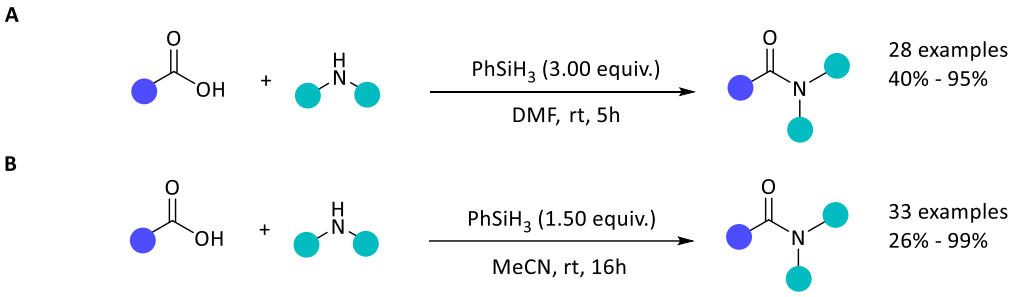


Figure 14: *tetrasubstituted silane reagents for amide formation*

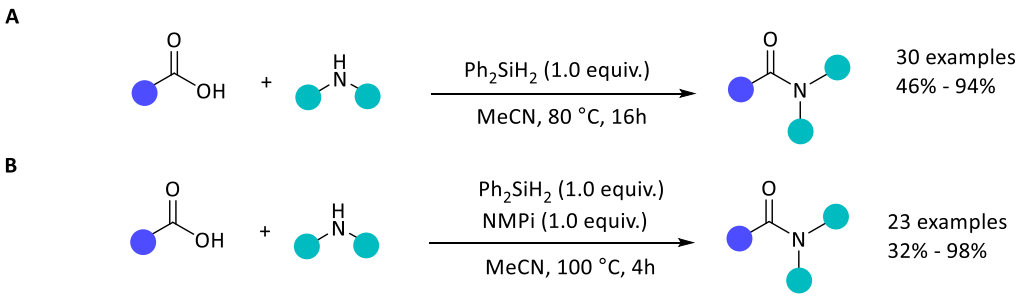
The first example of hydrosilane mediated amidation was published by Ruan in 2016. [148] This process used $PhSiH_3$ in the coupling of a small number of amines and carboxylic acids (Scheme 16A). However, this reaction did not provide any product when anilines or sterically hindered amines were subjected to the reaction conditions. In addition, three equivalents of $PhSiH_3$ were required and the reaction was carried out using DMF as the solvent. The authors attempted to apply these conditions to solid-phase synthesis, although high equivalents of both amine (10.0 equiv.) and silane (20.0 equiv.) were

required to obtain suitable yields. This work was further expanded by Blanchet, who reoptimised the reaction, using only one and a half equivalents of silane and used acetonitrile (MeCN) as the solvent (Scheme 16B).[146] These conditions were able to achieve a wider scope, including protected amino acids and Weinreb amides, although anilines and sterically hindered substrates were still not possible.



Scheme 16: *Ruan and Blanchet's $PhSiH_3$ mediated amidations*

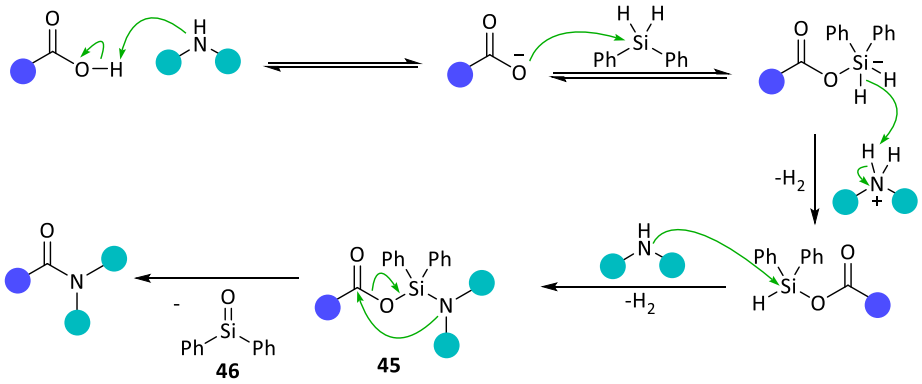
Diphenylsilane (SiH_2Ph_2) has also been utilised for this reaction, and under specific conditions was shown to be a superior coupling reagent to other tri- and di- hydridic silanes (Scheme 17A).[149] This method was also able to obtain a range of secondary and tertiary amides, including dipeptides and lactams, although no anilines were demonstrated. A benefit of this reaction is the 1:1:1 ratio of amine: acid: silane, and that the only by-products were hydrogen gas and a soluble siloxane. More recently this work was expanded by Adler, who demonstrated increased reactivity of the system upon addition of the base, *N*-methylpyrrolidine (NMPi) (Scheme 17B).[150] The base was able to rapidly break the initial carboxylate salt formation. Continuing to use an equimolar equivalent of all reactants, including the base, Adler was able to obtain a range of tertiary and secondary amides, including dipeptides. Adler also demonstrated an extensive robustness study, showing a range of functional group tolerance, with only aldehydes, ketones and alcohols affecting the reaction yield.



Scheme 17: *Charette and Adler's Ph_2SiH_2 mediated amidations*

Less common examples include the use of tris[(1,1,1,3,3,3-hexafluoropropan-2-yl)oxy]silane and ($HSi(OCH(CF_3)_2)_3$) for the synthesis of dipeptides,[151] and PMHS in a organocatalysed amide formation.[152]

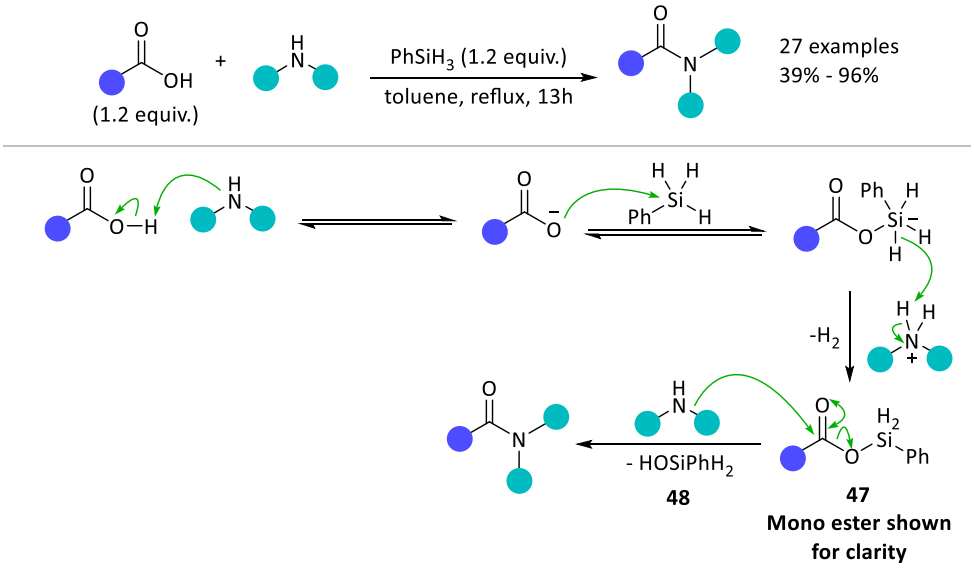
There has been some debate over the mechanism for hydrosilane mediated amide formation with two pathways postulated.[153] The first is the reaction of both carboxylic acid and amine with the silane (**45**) and the product is extruded in a reductive elimination like process (Scheme 18). This method was first proposed by Charette in his work involving chlorosilanes, but again invoked this mechanism for his work using Ph_2SiH_2.[143,149] Despite not being able to identify the silicon intermediate, a series of control experiments showed reaction of both components with the silane, seemly supporting this mechanistic pathway. However, computation studies have shown that the formation of the silanone by-product (**46**) is too unstable and the energy barrier for formation is too high.[154]



Scheme 18: *Chemical ligation mechanism*

The alternative mechanism is *via* silyl ester formation (Scheme 19). This pathway involves activation of the carboxylic acid by the silane. The resulting silyl esters (**47**) are increasingly electrophilic, which allows for the amine to attack, with the elimination of silanol (**48**) as the by-product. Silyl esters, have been shown to react with nucleophiles,[155,156] and as a result, silyl ester intermediates have been proposed for a range of processes.[157–159] A study completed by Blanchet showed that the amine acylation can occur using $Si(OAc)_4$, essentially confirming this pathway.[146] He also demonstrated increased reactivity of this tetra- acyl compound, compared to di- and tri- acyl silanes, concluding that a higher order silyl esters are likely the active intermediate. This was corroborated in a study

completed by Denton, whereby an excess of carboxylic acid improved reaction kinetics.[157] This pathway has been confirmed in unpublished work by Denton and Andrews, who conducted an in-depth study investigating the phenylsilane-mediated amidation pathway.[153] They first optimised Ruan's conditions, altering both the silane and carboxylic acid loadings, and demonstrating an amide scope, including peptides and anilines, and were able to use HCl amine salts as the starting material. Further investigation involved both qualitative and quantitative mechanistic analysis, demonstrating complex speciation from reaction of the acid and silane, and identifying higher order silyl esters in a range of solvents. It was found that although the higher order esters are more reactive, they take longer to form, and as a result, the less substituted silyl esters may be the main species responsible for amidation.



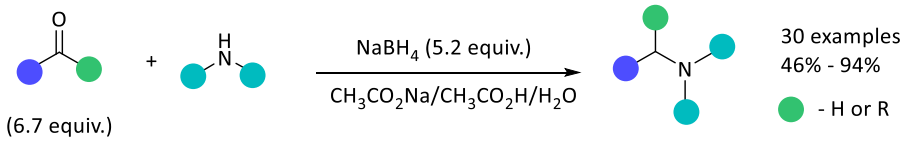
Scheme 19: *Denton's optimised amidation conditions and silyl ester mechanism*

1.4 Reductive Amination

1.4.1 Traditional Methods

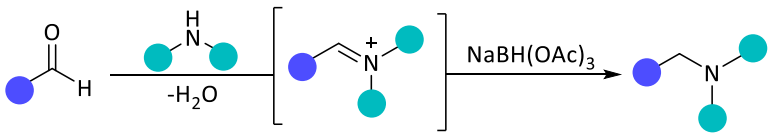
Another common method for the synthesis of amines, and the main focus of this chapter is reductive amination. Not only does reductive amination avoid genotoxic alkyl halides and expensive palladium catalysts, but it also provides a direct method from a lower order to higher order amine without any need to isolate any intermediates. This method utilises aldehydes or ketones with primary or

secondary amines with commercially available stoichiometric reducing agents, to afford a wide range of higher order amine products. This was first reported by Schellenburg in 1963 who used $NaBH_4$ to form some examples of secondary and tertiary amines (Scheme 20).[160] A review by Chusov details the extensive applications of reductive amination in the synthesis of pharmaceuticals; it is clear that this process is highly important on manufacturing scale.[2]



Scheme 20: *Schellenburg's reductive amination using $NaBH_4$*

The mechanism for this reaction starts with nucleophilic attack of the amine onto the electrophile, forming an imine or iminium intermediate (Scheme 21). This is subsequently reduced using a metal reducing agent.[2] Although this method can be completed using more traditional reducing agents such as LAH or $NaBH_4$, there is often significant reduction of the carbonyl starting materials, resulting in low conversion. As a result, milder reducing agents such as sodium triacetoxyborohydride ($NaBH(OAc)_3$) and sodium cyanoborohydride ($NaBH_3CN$) are often utilised as an alternative.[161,162] These compounds reduce the iminium ion faster than the starting material carbonyl, due to the electron-withdrawing groups deactivating the hydride. Although $NaBH_3CN$ can be used on a large scale, the release of hydrogen cyanide (HCN) as a by-product makes this process unattractive, and instead $NaBH(OAc)_3$ is more commonly used for scale-up processes. Other reducing methods such as hydrogenation with metal catalysts,[163,164] zinc and acetic acid,[165] bis(triphenylphosphine) copper(I) tetrahydroborate[166] and $NaBH_4$ and magnesium chlorate[167] have also been demonstrated, although these methods are not as widely used.

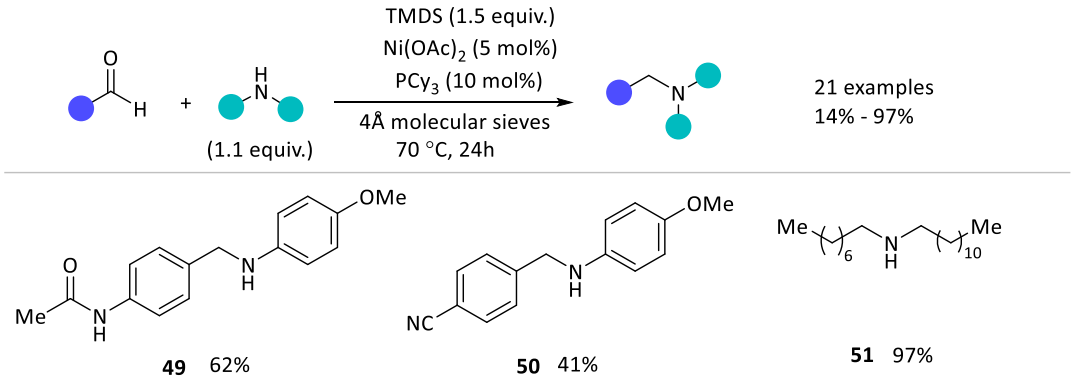


Scheme 21: *General mechanism for reductive amination*

1.4.2 Metal-mediated Silane Reductive Amination

In an effort to move away from superstoichiometric reducing agents, methods using silanes and metal catalysts have been developed, although these methods are not without disadvantages. Many of the metals used are toxic or scarce such as tin,[168,169] indium[170] and iridium[171,172] and other processes are limited to specific substrates, such as amines bearing electron withdrawing groups[173,174] and aromatic aldehydes.[175] Despite this, there have been metal-catalysed silane-mediated methods that use non-toxic metals, such as nickel and iron that are not bound by these limitations.[176,177]

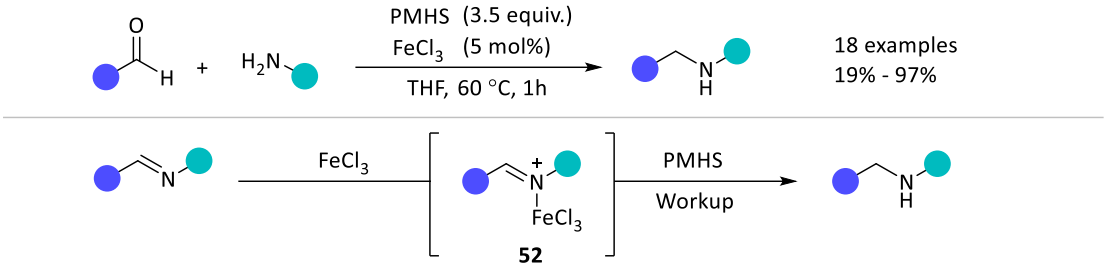
The commercially available nickel acetate ($Ni(OAc)_2$) has been used in a reductive amination reaction in conjunction with TMDS and a phosphine ligand (Scheme 22).[177] This protocol was used for the synthesis of a range of tertiary and secondary amines, demonstrating chemoselectively potentially reduceable functionalities for example esters (**49**), although nitro and nitrile groups (**50**) significantly impacted the yield. However, it was found that for non-activated or deactivated amines, iminium ion formation was significantly slower and required increased reaction time.



Scheme 22: *Darcel and Sortais' hydrosilane mediated reductive amination using $Ni(OAc)_2$*

A further process utilising iron(III) chloride ($FeCl_3$) in conjunction with PMHS was published by Enthaler in 2010 (Scheme 23).[176] Despite the use of inexpensive and commercially available reagents, the poor scope reduces the attractiveness of this process for complex amine synthesis. Firstly, only aromatic amines were demonstrated, and the authors state that ketones are not compatible with these reaction conditions. Investigations into the mechanism showed that this reaction does not proceed

through metal hydride formation, but instead the iron acts as a Lewis acid, allowing for improved hydrosilylation of the iminium ion (**52**).



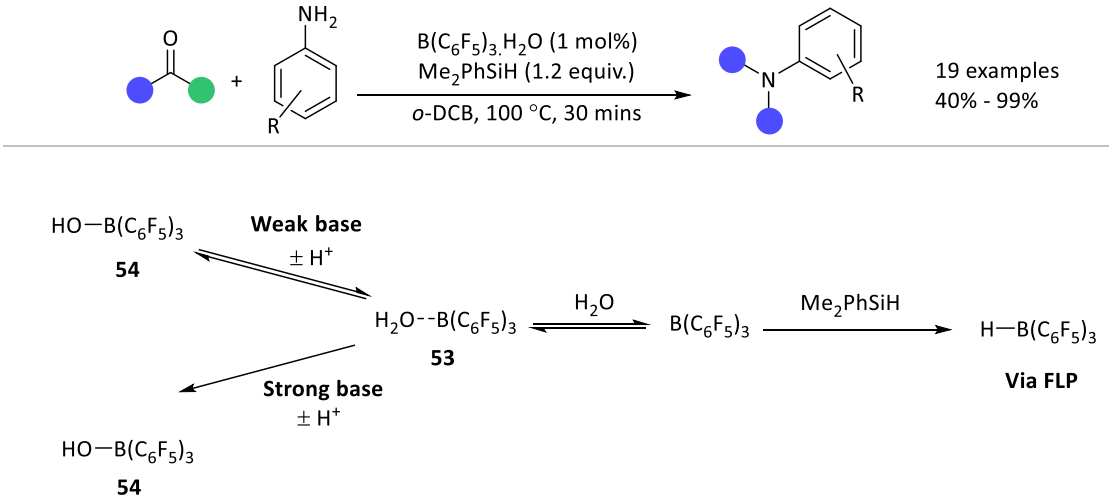
Scheme 23: *Enthaler's reductive amination using PMHS/$FeCl_3$*

1.4.3 Metal-free Silane Reductive Amination

In addition to amide reduction chemistry, metal-free methods have also been introduced for reductive amination processes. Lewis acid catalysed hydrosilylations of imines have been known in the literature, so the development of a reductive amination is an obvious extension to this process.[178] However, until recently this had not been widely reported. It was thought that, due to the oxophilic nature of the borane catalyst, water produced during imine formation would result in water-borane adducts (**53**). These adducts have significantly increased Brønsted acidity[179] and in the presence of the amine would irreversibly form a hydroxyborate (**54**), poisoning the catalyst to further reduction. As a result, imine hydrosilylation had only been conducted as a separate step and not as part of the reductive amination process.

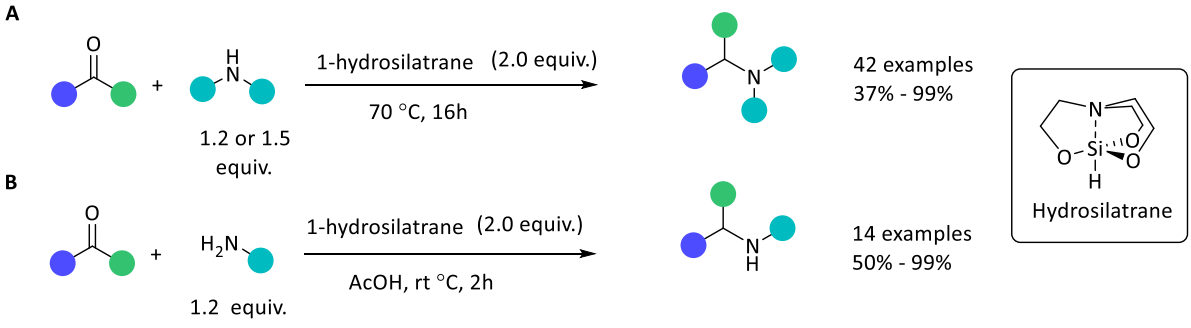
However, in 2016 Ingelson reported the first practical reductive amination using dimethylphenylsilane (Me_2PhSiH) and $B(C_6F_5)_3$ (Scheme 24).[180] He demonstrated that for aniline substrates, hydroxyborate (**54**) formation is reversible, however, with the use of more basic alkylamines, **54** is formed irreversibly, and no reaction was observed. Using this method, he demonstrated both aldehydes and ketones as starting materials, and showed that a range of functional groups were tolerated under the reaction conditions. The nature of the reaction mechanism allows for the use of non-dried glassware and solvent in addition to non-purified $B(C_6F_5)_3$ which is a huge benefit to this transformation. This group

later modified these conditions to allow for more basic amines through the use of a less Lewis acidic borane, which is more tolerant of strong base.[181]



Scheme 24: *Ingleson's reductive amination using $Me_2PhSiH/B(C_6F_5)_3$*

A further example of metal-free reduction amination was demonstrated by Adler who utilised hydrosilatrane for reductive amination.[182] A base-mediated reduction of aldehydes and ketones using hydrosilatrane had already been demonstrated, and due to the increased electrophilicity of iminium ions, the silane alone was able to affect this reduction. [183,184] However, where an imine is formed as the intermediate, reduction to the amine was not possible with hydrosilatrane alone and required the use of acetic acid to form the iminium ion *in situ* (Scheme 25). This process demonstrated excellent chemoselectivity, with a range of potentially reducible functional groups being tolerated under the reaction conditions. This group later extended this work to encompass enantioselective asymmetric reductive amination using a bulky chiral phosphoric acid to selectively direct hydride addition to a specific face. [185]



Scheme 25: *Adler's reductive amination using 1-hydrosilatrane*

1.4.4 Reductive Amination Using Carboxylic Acids

Despite the developments towards a greener and more efficient reductive amination process, the use of aldehydes as the electrophiles presents a disadvantage due to availability, handling and decomposition issues. Aliphatic aldehydes react *via* an aldol dimerisation process to the β-hydroxy aldehyde and aromatic aldehydes undergo auto-oxidation to the carboxylic acid (Figure 15).

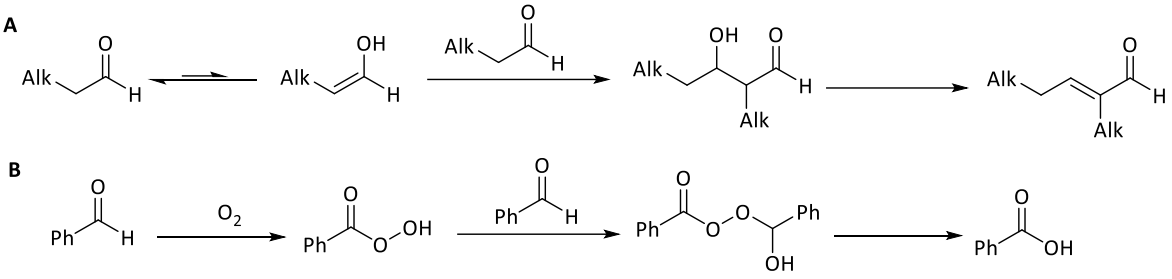
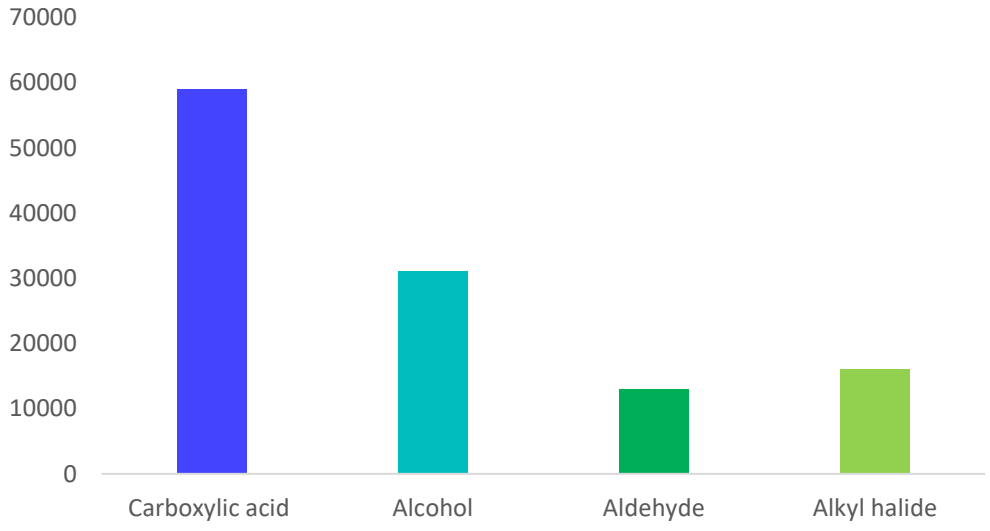


Figure 15: *Decomposition of aldehydes by A: aldol dimerization; B: autoxidation*

A report in 2022 investigated the spread of monofunctionalised building blocks used in medicinal chemistry and found that behind amines, carboxylic acids were the most prevalent. When compared to other electrophiles, carboxylic acids are significantly more abundant (Graph 1).[186] For traditional reductive amination, more complex aldehydes must be synthesised, often in reduction then partial oxidation from the carboxylic acid *via* the alcohol. These oxidation methods often use stoichiometric amounts of undesirable oxidants, making this process unpopular on-scale.[187–189]



Graph 1: *Number of monofunctional building blocks*

As a result, there has been a drive towards reductive amination processes using more abundant electrophiles, such as alcohols and carboxylic acids. Alcohols have been used as the electrophiles in a reductive amination, through a metal catalysed 'borrowing hydrogen' process (Figure 16).[190] Metal catalysts are used to oxidise the alcohol *in situ* to the aldehyde and subsequently catalyse the imine reduction. Although this chemistry presents a step towards the removal of aldehydes from reductive amination, the use of precious metals diminishes the attractiveness on scale.

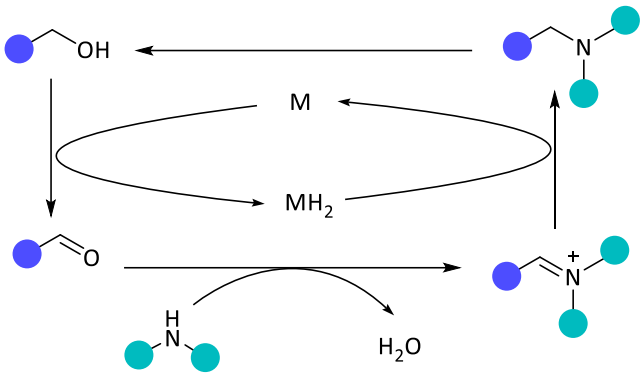


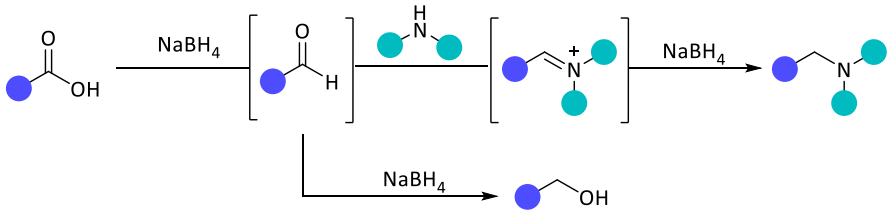
Figure 16: *General catalytic cycle of hydrogen borrowing*

The use of the highly available carboxylic acids as electrophiles in reductive amination would present a powerful process, however they are not often utilised. This is due to resonance stability, resulting in increased thermodynamic and kinetic inertness of the carboxyl group relative to other carbonyl compounds. This causes diminished electrophilicity.[191] In addition, control of the deoxygenation of carboxylic acids is challenging, as many pathways proceed *via* the reactive aldehyde intermediate. As a result, the alcohol derivative is often a major by-product, even with an efficient reduction pathway. A review published by Li in 2022 describes in detail the advancement of reductive amination chemistry using carboxylic acids as the electrophiles.[192]

1.4.5 Metal-Catalysed Reductive Amination Using Silanes

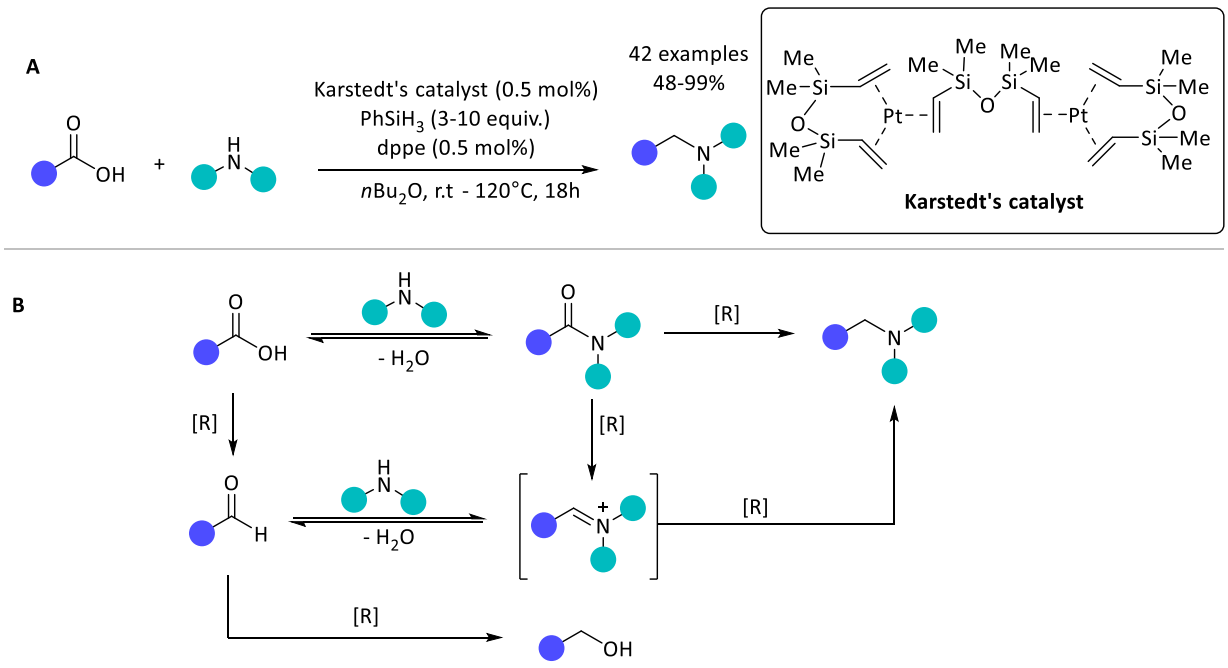
Despite the current prevalence of silane activation, the first reported use of carboxylic acids electrophiles for reductive amination processes utilised borohydride reagents. These protocols, first published in the 1970s, used $NaBH_4$ to reduce the carboxylic acid *in situ* to the aldehyde, which then

proceeded through a traditional reductive amination process (Scheme 26). Despite the novelty of this transformation, the scope was limited to liquid carboxylic acids to act as the solvent and required superstoichiometric amounts of borohydride.[193–195] A more recent reductive amination publication has used $NaBH_4$ in a more selective process in conjunction with a nickel catalyst,[196] and many processes utilising hydrogen gas as the terminal reductant have also been realised.[197–200]



Scheme 26: *General mechanism for reductive amination from carboxylic acids using $NaBH_4$*

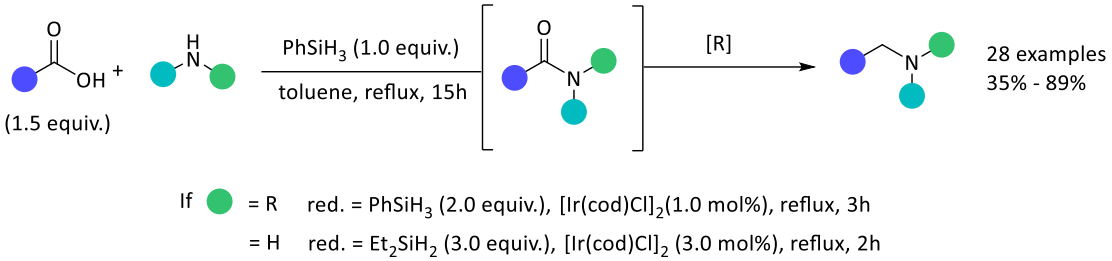
Looking towards silane mediated protocols, seminal work was published by Beller in 2014, who demonstrated *N*-alkylation to tertiary and secondary amines from carboxylic acid starting materials.[201] This transformation utilised the commercially available platinum Karstedt's catalyst in combination with phenylsilane (Scheme 27A). Initially, overalkylation of secondary amine products was observed. However, upon addition of 1,2-bis(diphenylphosphino)ethane (dppe) as a ligand, selectivity towards mono-alkylation was increased. The authors propose two complimentary mechanisms for this process (Scheme 27B): the first being reduction of the carboxylic acid to the aldehyde and then following a traditional reductive amination process, and the second being initial formation of an amide, which is subsequently reduced. The identification of both alcohol and amide as side-products confirm that both pathways are in operation. Despite being the first process of this kind, this transformation required high excesses of the carboxylic acid and silane, and rigorous exclusion of air and moisture through the use of Schlenk equipment.



Scheme 27: *Beller's reductive amination using $PhSiH_3$/Karstedt's catalyst*

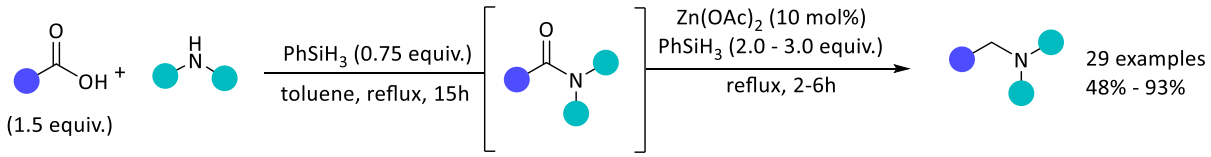
Since this publication, there have been further metal-catalysed silane mediated protocols, and in most cases, the authors have proposed similar reaction pathways.[202–207] However, routes *via* the aldehyde present challenges. This is because over reduced alcohol or di-alkylated amine are often seen as a side-products. As a result, large excesses of the carboxylic acid or silane are often required to prevent this. This issue was circumvented in a publication by Denton in 2016 who demonstrated a one-pot two-step process, *via* an amide intermediate (Scheme 28).[208] This process utilised phenylsilane as an amidation agent and the addition of further silane and an iridium pre-catalyst, $[Ir(cod)Cl]_2$, to affect reduction of the amide intermediate to the amine product. As this method forces an amidation pathway, over-reduction of the starting material is eliminated, improving yield, and negating the need for large excesses of carboxylic acids. In addition, optimisation of Ruan's amidation process, allowed for decreased loading of silane and a change in solvent to the less hazardous toluene.[148] The use of standard glassware is also a huge benefit to this reaction, with only a 6% decrease in yield when non-dry glassware and Winchester grade solvent was used.[208] However, despite the reduction of tertiary amides proceeding with $PhSiH_3$, the less reactive secondary amides required the more reactive and more volatile diethylsilane (Et_2SiH_2), which presents a potential hazard. In addition, nitro, ester and

nitrile functional groups were either not tolerated or poorly tolerated due to competing reduction pathways.



Scheme 28: *Denton's Reductive amination using silanes/[Ir(COD)Cl]$_2$*

Denton further developed this chemistry in an effort to exchange the iridium catalyst for a lower cost and more available metal. Drawing inspiration from the reduction of amides using zinc compounds and phenylsilane,[117,118] Denton published a general reductive amination using carboxylic acids in the presence of phenylsilane and zinc acetate ($Zn(OAc)_2$) (Scheme 29).[158] Like the iridium-catalysed process, this protocol followed an initial phenylsilane mediated amidation, and subsequent reduction using further silane and a zinc catalyst. Using these conditions, a range of secondary and tertiary amines, were synthesised, with these milder conditions tolerating nitro and boronate esters, although nitriles and esters were not tolerated. In addition, scale-up processes and the synthesis of a pharmaceutical target was also described, along with the use of acid-base workup procedures over column chromatography. This protocol represents a major advancement for reductive amination using carboxylic acids as the nominal electrophile.



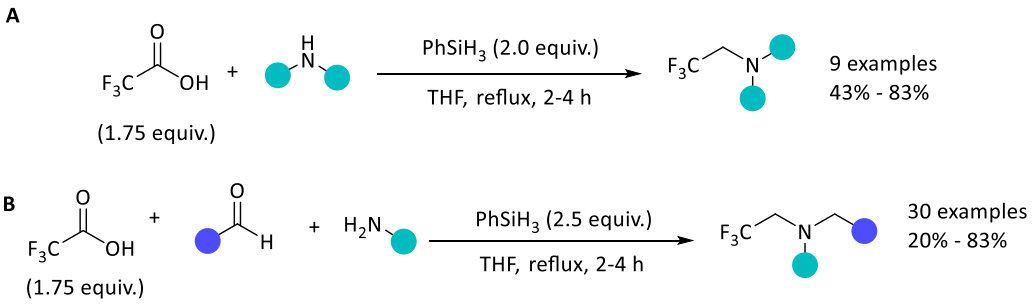
Scheme 29: *Denton's reductive amination using PhSiH$_3$/Zn(OAc)$_2$*

1.4.6 Metal-free Reductive Amination Using Silane

As discussed previously, a metal-free process would represent an extremely powerful transformation, especially with the added benefit of carboxylic acid electrophiles. Despite having already been

realised, these processes are often limited in scope, require superstoichiometric reagent loadings, or use air and moisture sensitive compounds leading to the requirement of specialist equipment. Similar to the metal-catalysed systems, most of the published protocols utilise silanes as the terminal reductant, although borazane in conjunction with methanesulfonic acid has also been demonstrated as an efficient method.[209]

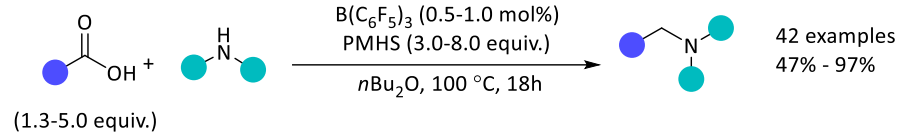
In 2017, Denton published a trifluroethytlation amination, exploiting the natural acidity of trifluoracetic acid (TFA) in a catalyst-free system in conjunction with phenylsilane (Scheme 30A).[210] Using these conditions, a wide range of amines were synthesised, demonstrating a remarkable functional group tolerance, even showing selectivity in the presence of lactams and esters. In addition, a three-component process using aldehydes and carboxylic acids to form tertiary amines from primary amine starting materials in a single-step process was also demonstrated (Scheme 30B). Mechanistic investigations ruled out reduction through an amide intermediate, although varying the stoichiometry of the TFA allowed for access to amide products. It was found that the reaction likely proceeds through silyl acetals derived from trifluoroacetaldehyde, itself formed through the silane mediated reduction of TFA. As other carboxylic acids cannot be reduced by phenylsilane alone, this process is limited to trifluoroethylation reactions only. This work was expanded to include further carboxylic acids by Lin in 2020, however it required the addition of potassium phosphate as an additive.[211]



Scheme 30: *Denton's trifluoroethylation using $PhSiH_3$*

In 2015, Fu and Shang reported a general metal-free reductive amination protocol (Scheme 31).[212] This process utilised the boron catalyst, $B(C_6F_5)_3$ in conjunction with the inexpensive PMHS as the

terminal reductant. Initial work utilised formic acid in *N*-methylation chemistry (discussed in more detail in Chapter 2) and was expanded to encompass a range of alkyl and aryl acids with excellent functional group tolerance. As with previous uses of this catalyst with silanes,[123–125] the reaction proceeded through a frustrated Lewis-Pair, which reacts preferentially in an amide reduction process over reduction of the carboxylic acid starting material.[212] Despite constituting a metal-free reductive amination, this process has many downsides. The first is the high equivalents of both silane and carboxylic acid required for this reaction, (up to eight equivalents) due to reduction of the carboxylic acid in a completing side reaction. The second is that this reaction must be conducted in Schlenk equipment with rigorous exclusion of air and moisture. These two downsides make this process unsuitable for scale-up processes.



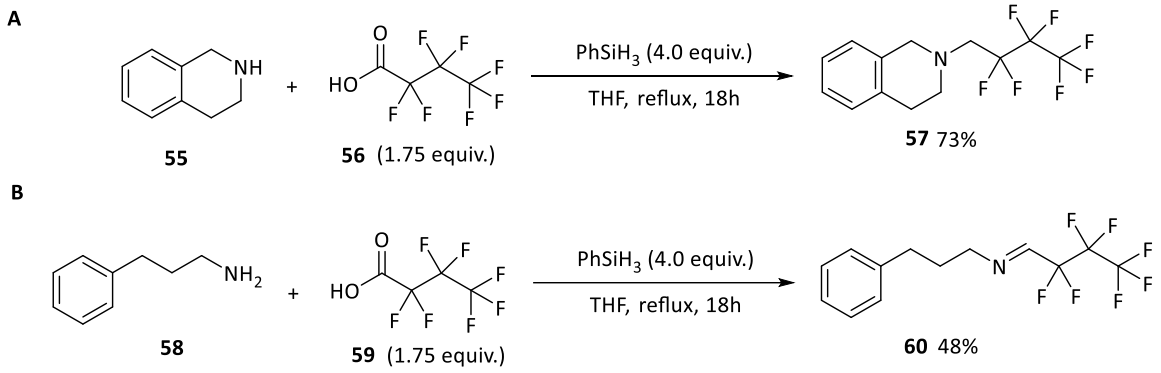
Scheme 31: *Fu and Shang's reductive amination using PMHS/B(C_6F_5)$_3$*

1.5 Previous Work in the Denton Group

Three reductive amination protocols using carboxylic acids have been developed in the Denton group. The trifluoroethylation reaction represented the first metal-free process, however, is not applicable to other substrates (Scheme 30).[210] The Denton group has also published two metal-catalysed reductive aminations, using an iridium (Scheme 28) and a zinc catalyst (Scheme 29).[158,208] As these processes involve separate C-N bond forming and reduction steps, reduction of the carboxylic acid does not directly affect amine yield. Despite the success of these protocols, the use of metals is problematic and as a result of the strong reducing power of the metal hydride formed *in situ*, many functional groups cannot be tolerated.

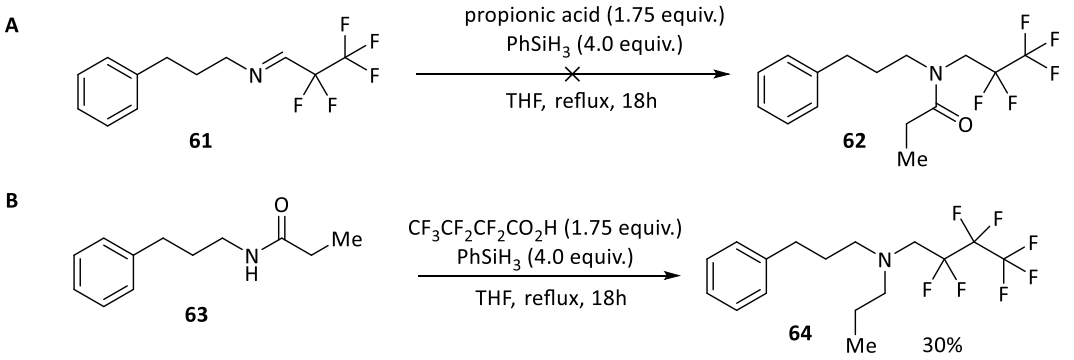
The challenge surrounding metal-free reductive amination using carboxylic acids was addressed in the group by Alex Scollan through investigations into the synthesis of perfluorinated amines.[213] This work

centred on expanding the trifluoroethylation reductive amination using longer chain perfluorinated acids (**56** and **59**). It was found that for secondary amine starting materials (**55**), the perfluorinated tertiary product could be made in the same way (**57**); although when primary amines were used as starting materials (**58**), the imine was the only product and $NaBH_4$ was required in a separate step to achieve the reduced secondary amine product (Scheme 32).



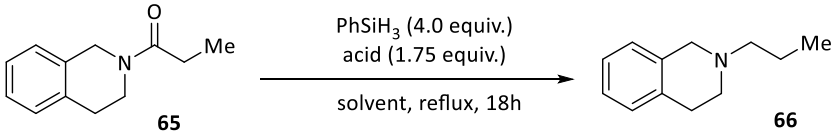
Scheme 32: *Reductive amination using perfluorinated carboxylic acids*

To expand this work, double alkylation of primary amines to form tertiary products was investigated. Firstly, dialkylation using two different perfluorinated carboxylic acids was demonstrated, and following this success, attempts were made to expand this to prepare partially fluorinated tertiary amines from a primary starting material. Initially, a dialkylation procedure from the fluorinated imine and a non-fluorinated carboxylic acid in the presence of phenylsilane (Scheme 33A) was attempted. Unsurprisingly, this process did not yield any product, as the amidation mechanism requires attack of a nucleophilic amine. A different approach was then explored through addition of the fluorinated acid onto a preformed amide in an attempt to synthesise the tertiary amide and surprisingly the tertiary amine was detected in a 30% yield (Scheme 33B).



Scheme 33: *Attempts towards dialkylated tertiary amines*

Looking towards reduction of a non-fluorinated tertiary amide, it was found that using perfluorinated carboxylic acids as an additive with phenylsilane could achieve reduction in moderate yields. However, the highly acidic sulfonic acids at higher temperatures were more successful (Table 2). In addition, sulfonic acids were shown not to react into the compound, whereas the fluorinated acids would form perfluorinated amines where a suitable N-H bond was present.

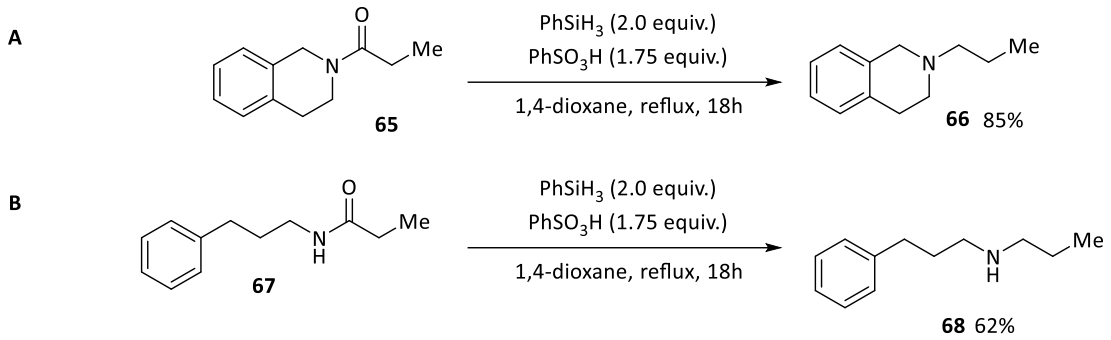


Entry	Acid	PKa (H_2O)	Solvent (Temp ^oC)	Yield (%)
1	perfluoropropionic	0.18	THF (70 ^oC)	34
			1,4-dioxane (105 ^oC)	37
2	benzenesulfonic	-2.8	THF (70 ^oC)	53
			1,4-dioxane (105 ^oC)	77
			PhMe (110 ^oC)	63
3	triflic	-14.7	PhMe (110 ^oC)	91

Table 2: *Investigations into Bronsted acid and reaction temperature*

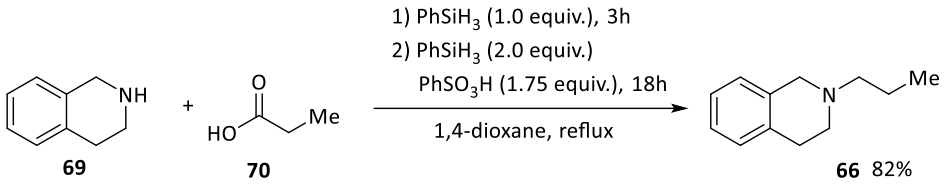
A range of silanes were also trialled, and it was discovered that trihydridic silanes were necessary for any reactivity to occur. The ratio of silane to acid was investigated, discovering that 2.00 equivalents of phenylsilane and 1.75 equivalents of sulfonic acid were able to achieve reduction in high yields

(Scheme 34A). In addition, investigations into the reduction of secondary amides using these conditions were carried out and moderate yields were obtained (Scheme 34B).



Scheme 34: *Optimised conditions of the metal-free amide reduction*

The use of $PhSiH_3$ allowed for the possibility of a two-step one-pot process from the carboxylic acids using a $PhSiH_3$ mediated coupling method.[208] This was demonstrated with the synthesis of *N*-propyl-1,2,3,4-tetrahydroisoquinoline in good yields. It should be noted however, that these were NMR spectroscopy yields, and no products were isolated.[213]



Scheme 35: *One-pot metal-free reductive amination from carboxylic acids*

1.6 Project Aims

The aim of this project was to develop a practical and general metal-free reductive amination reaction of primary and secondary amines and develop its utility in target synthesis. This will be achieved through building on the previous work in the group, that demonstrated that reduction of amides could be achieved through the combination of phenylsilane and benzenesulfonic acid.

A figure of all previous reductive aminations from carboxylic acids are shown below (Figure 17). This demonstrates the development of this process from unsustainable and expensive metals towards metal-free and more easily handleable reagents.

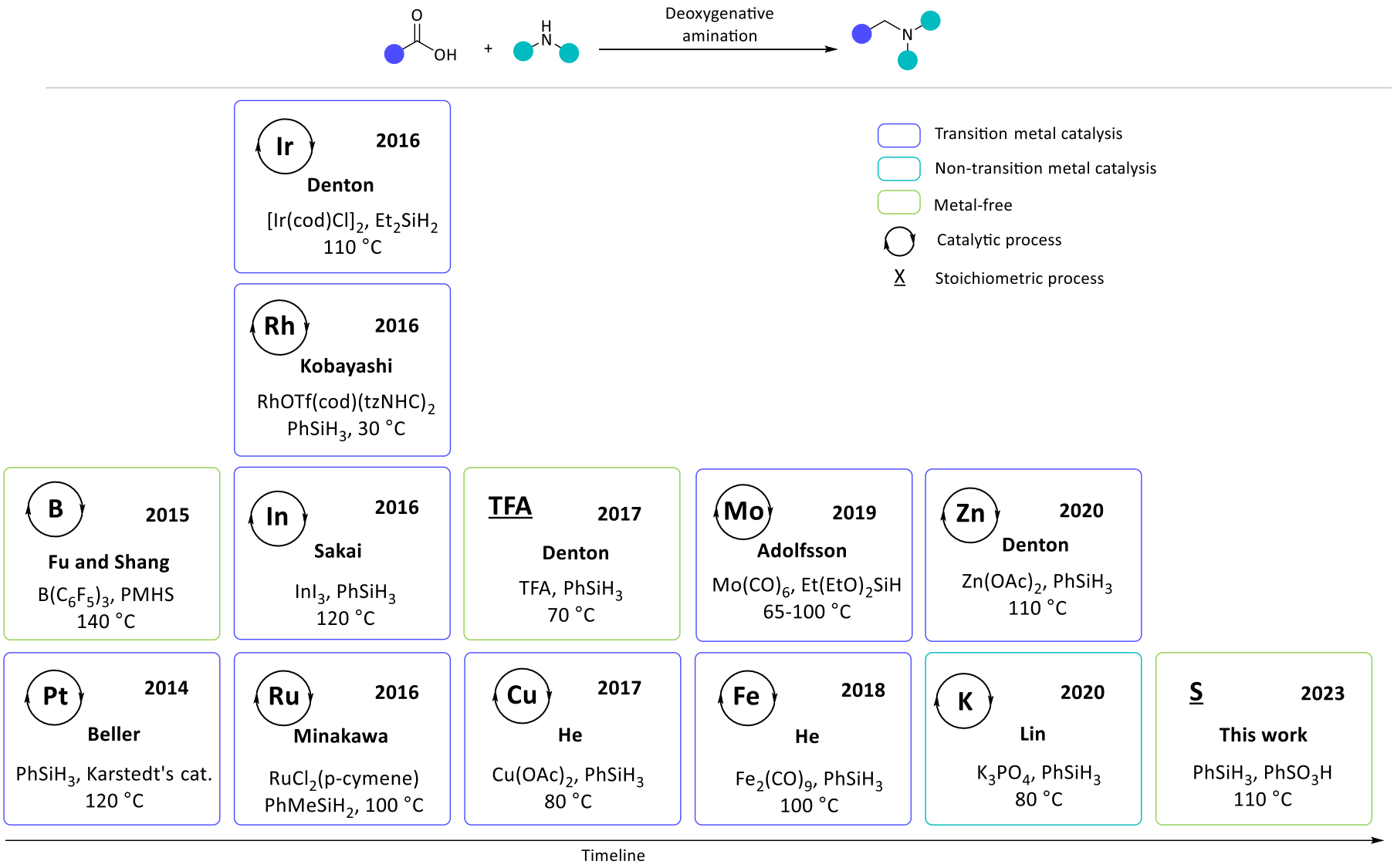


Figure 17: *Silane mediated reductive aminations from carboxylic acids*

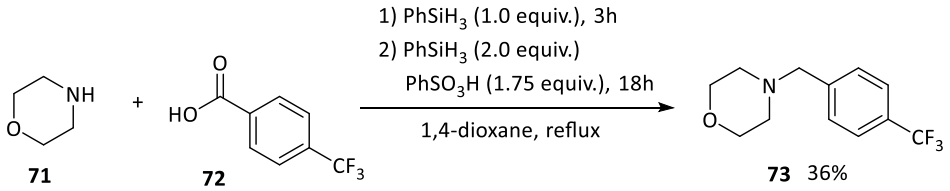
2 Results and Discussion

2.1 Optimisation

2.1.1 Tertiary Amines

2.1.1.1 Amidation Optimisation

We began by re-examining previous conditions developed in the group.[213] Morpholine and 4-(trifluoromethyl)benzoic acid were selected as model substrates for this reaction, which allowed for easy identification of the product and any intermediates or side reactions by ^{19}F NMR spectroscopy. It was decided that further optimisation would take place with benzenesulfonic acid ($PhSO_3H$) as the Brønsted acid, despite triflic acid (CF_3SO_3H) being demonstrated as producing higher yields (Table 2). This is due to ease of handling and likely substrate incompatibility.

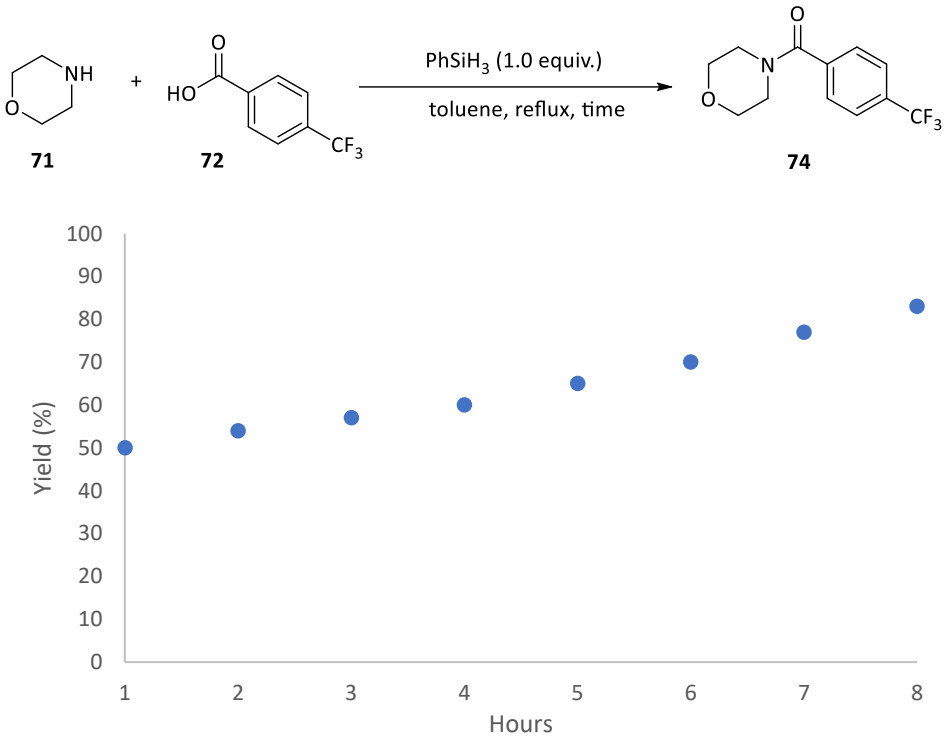


71 **72** **73** 36%

Scheme 36: *Optimised conditions from previous work done in the group*

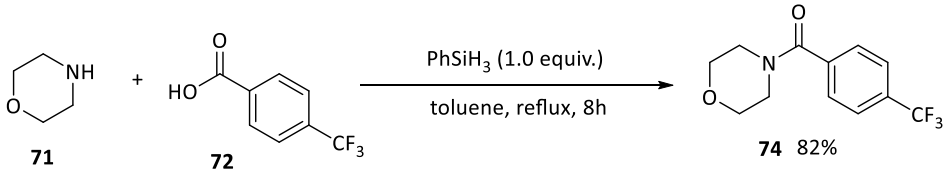
Using these conditions, a moderate isolated yield of 36% of the amine product was achieved. An acid-base workup was utilised for the isolation and purification of this compound. Pleasingly, no further purification was required. The remaining mass balance comprised of the parent amine and carboxylic acid as a result of incomplete amidation. Comparison of related silane-mediated amidations identified a disparity in reaction time, with other protocols requiring significantly longer than 3h.[146,149,158,208]

As a result, we obtained a time profile of the reaction over eight hours (Graph 2), replacing 1,4-dioxane with toluene. The solvent switch was made on the basis of precedent for this solvent in amidation reactions, in addition to improved environmental impact and increased reaction temperature.[39,158,208] It was assumed that any negative impact that the change in solvent imparted on the reduction, could be corrected through optimisation procedures.



Graph 2: *Time profile of the amidation reaction. Yield determined by 19F NMR using fluorobenzene as an internal standard*

From this investigation it was found that a three-hour amidation resulted in only a 57% conversion, which confirmed that the low yield seen in the initial reaction, was due to poor amide formation. However, after eight hours the reaction was near complete and a conversion of 87% was obtained.

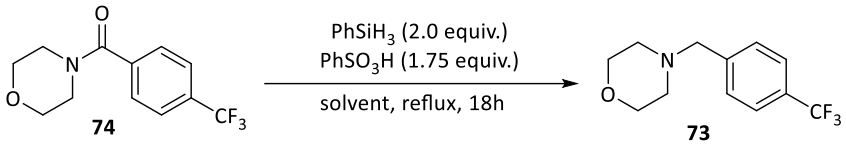


Scheme 37: *Optimised amidation conditions*

With these optimised amidation conditions in hand, amide **74** was obtained in an excellent 82% yield after workup and purification.

2.1.1.2 Reduction Optimisation

Prior to development of a one-pot reductive amination (as discussed below 2.1.1.3), toluene and 1,4-dioxane were compared in the reduction step.

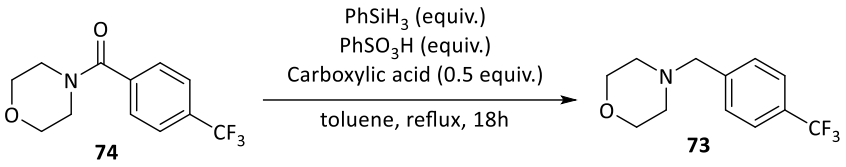


Entry	Solvent (temp °C)	Yield (%)[a]
1	1,4-dioxane (105 °C)	67
2	toluene (110 °C)	70

[a] Isolated yields

Table 3: *Optimisation of solvent for amide reduction*

The use of toluene not only provided a marginally higher yield but also a cleaner reaction profile, likely due to the increase in reaction temperature. As a result, all further optimisation was carried out using toluene. Next the effect of $PhSiH_3$ and $PhSO_3H$ stoichiometry were examined.



Entry	$PhSiH_3$ equiv.	$PhSO_3H$ equiv.	Carboxylic acid	Yield[a] (%)
1	**2.00**	**1.75**	**-**	**70**
2	0.00	1.75	-	0[b]
3	2.00	0.00	-	0[b]
4	2.00	0.50	-	8
5	2.00	1.00	-	46
6	2.00	2.00	-	76
7	2.00	3.00	-	82
8	2.00	4.00	-	88
9	2.00	2.00	$CF_3C_6H_4CO_2H$	76

[a] Isolated yield; [b] Yield determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard

Table 4: *Optimisation of the reduction step*

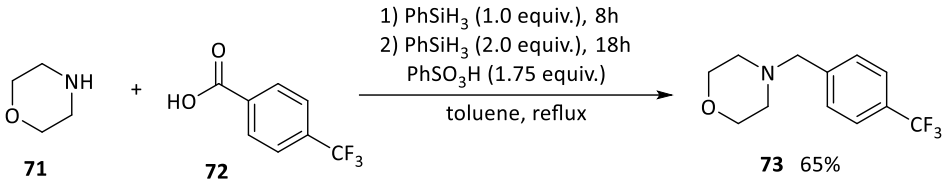
Control reactions (Table 4, entry 2 and 3) showed that both silane and acid are necessary for the reduction to occur. A positive correlation between the sulfonic acid loading and conversion was observed. (Table 4, entries 4-8). This is possibly indicative of the formation of higher order modified

silanes, which are more reactive than the less substituted counterparts.[153] Interestingly, increased carboxylic acid did not show any improvement in yield, likely due to the presence of an excess amount of a much stronger and more reactive acid (Table 4, entry 9).

An 18% yield increase was demonstrated from the optimised loading of 1.75 equivalents (Table 4, entry 1) to 4.00 equivalents (Table 4, entry 8). However, the increased waste made this unattractive despite the increase in yield. For more complex and less reactive substrates, it was beneficial to be aware of the effect that increased sulfonic acid had.

2.1.1.3 One-pot Reductive Amination

Having optimised both amidation and reduction, these conditions were telescoped in a one-pot reductive amination.



71 **72** **73** 65%

Scheme 38: *Optimised one-pot reductive amination conditions*

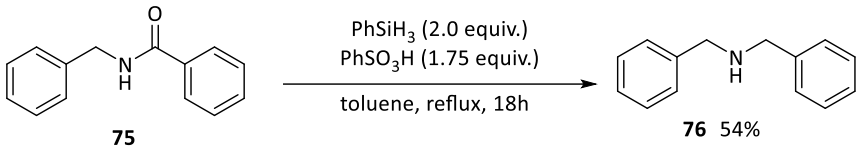
Pleasingly, the combination of the two steps to the one-pot process resulted in a yield of 65%. Initially, the H_2 evolution upon addition of the sulfonic acid caused some concerns, but this was controlled through portionwise addition of $PhSO_3H$.

2.1.2 Secondary Amines

Secondary amines are less reactive than their tertiary counterparts, due to decreased hyperconjugation towards the nitrogen atom. In the same way, secondary amides are less reactive and more resistant to reduction. As a result, it was envisioned that further optimisation would be required to achieve suitable yields.

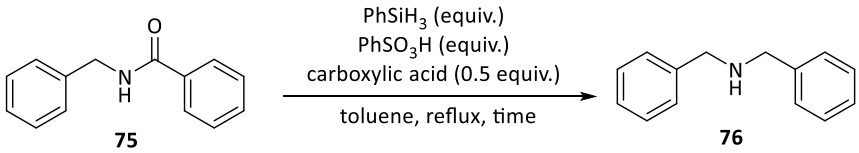
2.1.2.1 Amide Reduction

The reduction was investigated as a stand-alone transformation with *N*-benzylbenzamide as the model substrate.



Scheme 39: *Initial reaction conditions for reduction of N-benzylbenzamide*

Unsurprisingly, the conditions optimised for the reduction of tertiary amides was not as successful for secondary amides and resulted in a yield of only 54%. The remaining mass balance was attributed to unreacted amide starting material. As this reaction demonstrated modest conversion, initial optimisation focused on the ratio of silane and acid. It was thought that using a more acidic sulfonic acid or using a higher boiling solvent would have the desired effect. However, this would lead to non-generalised conditions across tertiary and secondary products.



Entry	$PhSiH_3$ (equiv.)	$PhSO_3H$ (equiv.)	Carboxylic acid	Reaction time (h)	Yield (%)[a]
1	2.00	1.75	-	18	54
2	3.00	1.75	-	18	51
3	2.00	1.75	-	24	64
4	2.00	2.00	-	18	64
5	2.00	2.50	-	18	70
6	2.00	2.50	-	24	75
7	**2.00**	**3.00**	**-**	**18**	**73**
8	2.00	3.00	$C_6H_5CO_2H$	18	75

[a] *Isolated yields*

Table 5: *Optimisation of secondary amide reduction*

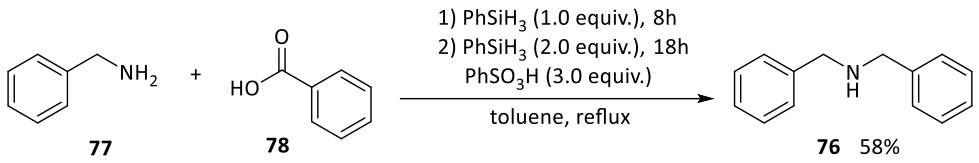
It was identified that an increase in silane had almost no effect on the yield (Table 5, entry 2) and resulted in a messier reaction profile, even after the workup procedure. After this, attention was focussed on the ratio of sulfonic acid and the potential effect of increased carboxylic acid.

Unsurprisingly, both an increase in the sulfonic acid and reaction time resulted in an improved yield as shown in the optimisation of tertiary amine reduction (Table 4). An increase from two equivalents to three (Table 5, entries 4, 5 and 7) again demonstrated the positive effect that the sulfonic acid had on the reduction process. Alternatively, an increase in reaction time (Table 5, entries 3 and 6) was shown to have the same effect. Despite this, the increase in sulfonic acid was deemed to be preferable over a longer reaction length, improving the ease and efficiency of the reaction and the low cost of benzenesulfonic acid allows for this increase with minimal financial impact.

Thankfully, even with increased carboxylic acid, only secondary amine formation was observed with no tertiary amine formation. The unreacted carboxylic acid was identified, confirming that reduction to the aldehyde and traditional reductive amination processes does not take place.

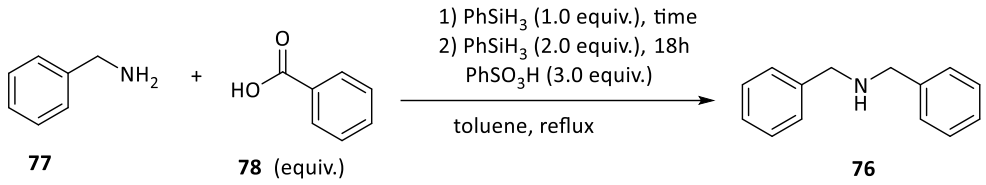
2.1.2.2 One-pot Reductive Amination

After the development of optimised conditions for secondary amide reduction, application to a full reductive amination procedure was then investigated.



Scheme 40: *Initial one-pot reductive amination*

This achieved a conversion of only 58%. This lower yield was attributed to an incomplete amidation step following identification of a significant amount of amine starting material after the completion of isolation procedures. From previous investigations, both an increased reaction time and carboxylic acid equivalents are known to improve amide conversion.



77 + **78** (equiv.) → **76**

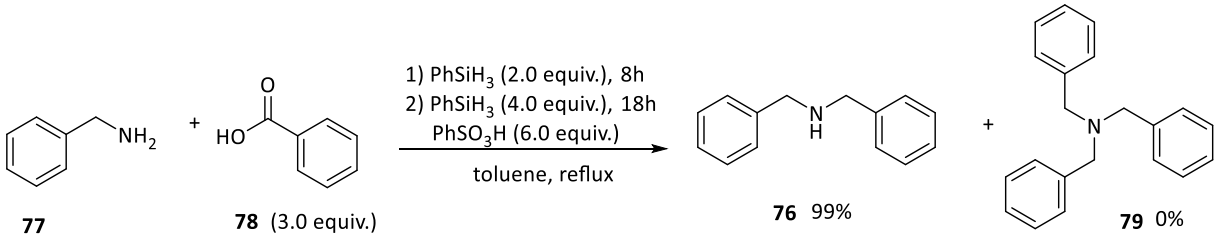
Entry	$PhCO_2H$ (equiv.)	Reaction time (h)	Yield (%)[a]
1	1	8	54
2	1	20	75
3	**1.5**	**8**	**79**

[a] *Isolated yield*

Table 6: *One-pot reductive amination optimisation*

Pleasingly, both an increase in reaction time (Table 6, entry 2) and carboxylic acid (Table 6, entry 3) had a positive effect on the yield. A shorter reaction time provides increased efficiency and as such was selected preferentially over lower equivalents of carboxylic acid. Despite this, in cases where the acid is increasingly precious or expensive, a longer reaction time would be preferential to minimise waste and cost.

It was demonstrated above (Table 5 entry 8) that excess carboxylic acid did not affect the yield of the reaction and was not incorporated into the product. To fully ensure this, a process using increased amidation and reducing agents was attempted.



77 + **78** (3.0 equiv.) → **76** 99% + **79** 0%

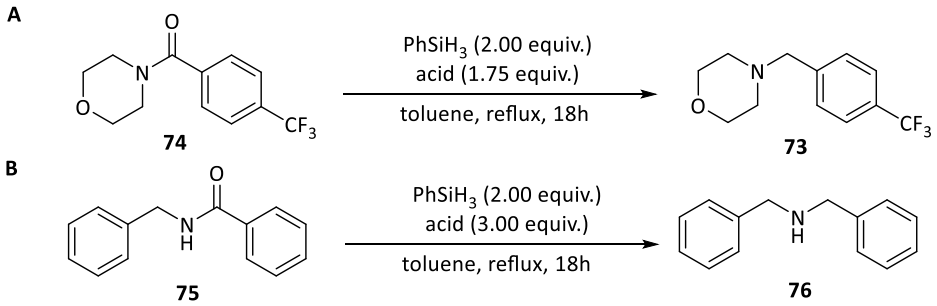
Scheme 41: *Attempt towards tertiary amine synthesis*

Even with increased reducing agents, tertiary amine (**79**) formation did not occur, and only the secondary amine product (**76**) was isolated in high yields. This again highlighted the stability of the secondary amide towards further alkylation.

2.1.3 The Use of *p*-toluenesulfonic Acid

One of the aims of this project was to achieve a generalised and more efficient process, and a constituent of that is the use of common and cheap laboratory chemicals.

Para-toluene sulfonic acid (PTSA) is inexpensive and frequently used in common transformations, and as a result is a chemical staple in most laboratories.[214] However, it was initially ruled out by Alex as the sacrificial Brønsted acid, due to diminished yield compared to $PhSO_3H$. However, it was not specified if PTSA used was dry or the commercial monohydrate. As a result, both the hydrated and dried forms of PTSA were trialled in the reduction of secondary and tertiary amides.



Entry	Transformation	Acid	Cost (£/100g)	Yield (%)[a]
1	A	$PhSO_3H$	£74.2	70
2	A	PTSA	£27.6	89
3	A	$PTSA.H_2O$	£27.6	57
4	B	$PhSO_3H$	£74.2	73
5	B	PTSA	£27.6	61

[a] *Isolated yields*

Table 7: *Effect of PTSA on amide reduction*

It was demonstrated that although PTSA is effective for this reduction, it must be dried to achieve comparative yields to $PhSO_3H$ and as such provided no additional benefit.

2.2 Scope

After reaction optimisation for tertiary and secondary amines, which had been found to only differ by carboxylic acid and sulfonic acid equivalents, the functional group tolerance and general application

was then explored. Compared to metal-catalysed processes, this transformation boasts mild conditions and as a result, was expected to chemoselectively reduce the amide over other functional groups.

2.2.1 Tertiary Amines

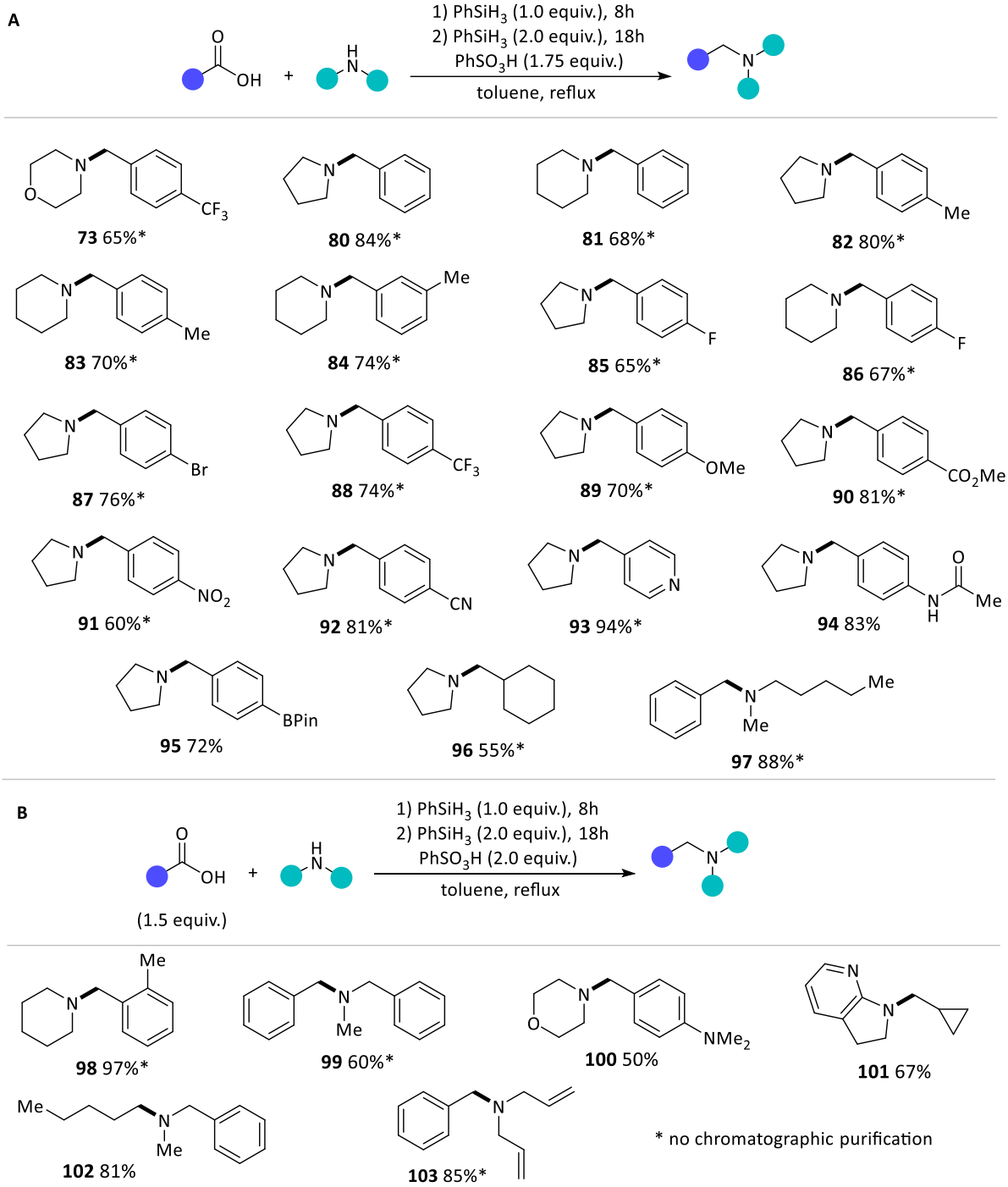


Figure 18: *Tertiary amine scope*

Beginning with tertiary amines (Figure 18A), it can be seen that the scope of this reaction covers a wide range of functional groups and both aliphatic and aromatic amines and acids. In addition, only four compounds had to be purified by column chromatography over the standard acid-base workup. It was found that both sterically and electronically hindered compounds could be tolerated although the amidation was sluggish. As a result, they required an increase in carboxylic acid to improve conversion (Figure 18B).

Benzoic acids bearing electron-withdrawing groups (**88**, **90**, **91** and **92**), electron-donating groups (**89** and **94**) and heterocycles (**93** and **101**) were well tolerated. It was also important to demonstrate functional group tolerance to groups that allow for further derivatisation like esters (**90**), amides (**94**) and boronic ester (**95**) compounds. A small amount of pinacol was identified after the formation of **95**, as the acidic conditions affected the deprotection of the ester. Investigations into how substitution patterns would affect the yield, concluded with compounds bearing *para* (**83**) and *meta* (**84**) substituents achieving high yields. However, the *ortho* (**98**) substituted compound required a 0.5 equivalent increase in carboxylic acid to achieve comparative conversion. A comparison of aliphatic and aromatic starting materials towards the same product was also conducted (**97** and **102**), allowing for identification of the optimal dissociation of a more complex compound. Although in both cases, product was achieved, an aliphatic amine in conjunction with an aromatic acid was the best combination (**97**), as this did not require excess acid to force the reaction to completion. This is unsurprising given the increased nucleophilicity of the aliphatic amine over the aromatic one. Cyclopropanes (**101**) were also well tolerated, which was pleasing given their incompatibility towards traditional metal hydride reducing agents.

Carboxylic acids bearing potentially reduceable functional groups were also trialled in this reaction to ascertain the chemoselectivity. Functional groups such as nitros (**91**) and alkenes (**103**) are often compatible with many reductive processes and thankfully this was shown to be the case here. Pleasingly, both ester (**90**) and nitrile (**92**) functionality were tolerated with no evidence of any

reduction occurring. Tolerance to these moieties is seldom demonstrated, due to reduction of the functional groups along with the amide or imine. Extending this, the reduction of **85** was carried out using MeCN as the solvent and achieved a 79% yield, allowing for a possible alternative to toluene where solubility is an issue for more polar starting materials. Finally, the difference in reactivity of tertiary and secondary amides was demonstrated, where the tertiary amide was reduced preferentially (**94**) with only a small amount of diamine observed.

Like with other transformations, anilines were not tolerated due to poor amidation as a result of lower nucleophilicity. As the Brønsted acid is a major part of the reaction and required in excess, any acid labile functional groups were not tolerated. Alkyl acetals, Boc groups and silyl and phenyl ethers were all trialled in the reaction but unfortunately resulted in degradation or reduction.

2.2.2 Secondary Amines

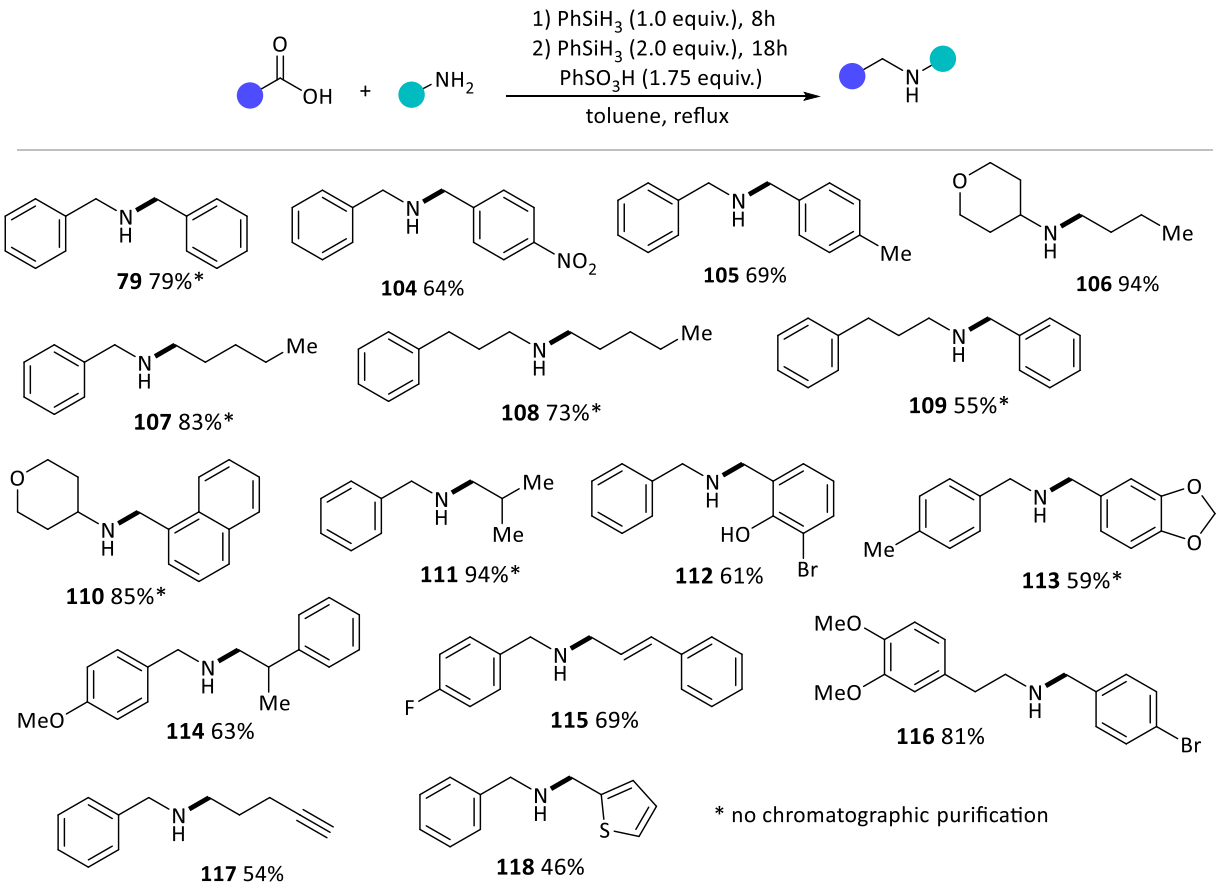


Figure 19: *Secondary amine scope*

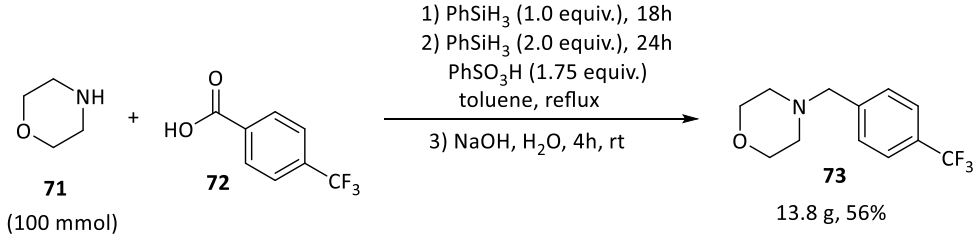
Having already demonstrated impressive functional group tolerance for the synthesis of tertiary amines (Figure 18), the secondary amine scope was then investigated, not only to confirm applicability to secondary amines, but also to demonstrate further functionality. In addition, acid base workups were again employed for isolation and purification with column chromatography not often required.

As with tertiary amines, a range of functional groups were tolerated including compounds bearing electron-rich (**112**, **113** and **114**) and electron-poor functional groups (**104**), in addition to halides (**112**, **115** and **116**) and heterocycles (**118**). Pleasingly, the acid sensitive thiophene was demonstrated (**118**), *albeit* in a diminished yield due to decomposition under the reaction conditions. α-Branched and *ortho*-substituted carboxylic acids were also shown to have no effect on the yield despite increased sterics. Free hydroxyl groups were tolerated (**112**), although an extra equivalent of silane was required due to alcohol silylation, which can be removed *in situ* during the work up. Both double (**115**) and triple (**117**) bonds were shown to be tolerant and chemoselective in the reaction conditions, which is an additional benefit, as alkynes are often reduced using metal catalysed methods. The use of an alkyne also presents a handle for further reactions and derivatisation.

2.2.3 Large Scale Synthesis

Following investigations into the reaction scope, it was pertinent to investigate the potential application of this reaction on an increased scale. Initial concerns centred on controlling the evolution of H_2 and the isolation and purification procedure. It was reasoned that gas evolution could be controlled through slow reactant addition at a decreased temperature. The use of a jacketed vessel allowed for ease of temperature control and closely resembles industrial manufacturing vessels. The usual workup for this reaction involves consecutive washes with acid, basification of the aqueous layer and subsequent washes with DCM. On a large scale, this amount of solvent is not attractive, so alternatives were investigated. It was hoped that addition of ethereal HCl to the reaction mixture would cause the precipitation of the HCl salt. However, upon completion of this process, analysis of the solid showed the benzene sulfonic acid salt of the amine product not the hydrochloride. As a

result, the salting process was refined to the addition of Et_2O after the reaction was complete, precipitating the sulfonic acid ammonium salt, which could be free-based in NaOH to release the free amine.



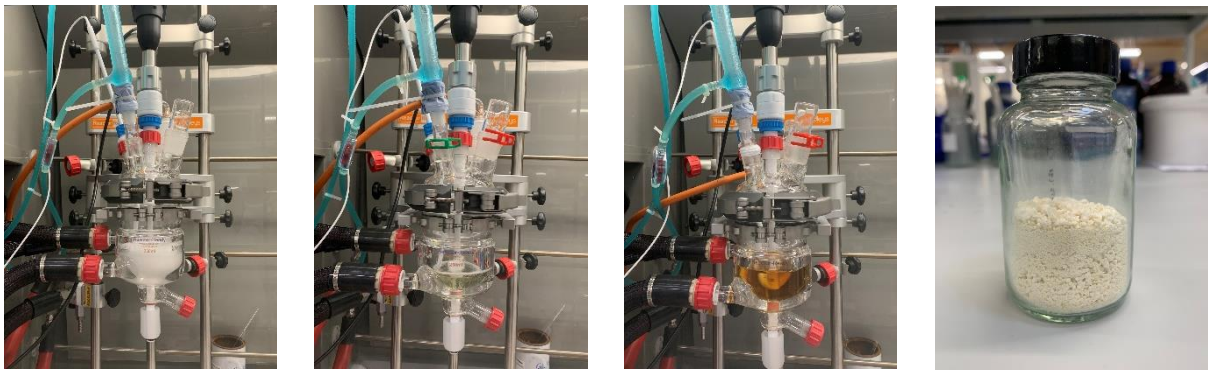


Figure 20: *Large scale reductive amination – A. Reaction set up using jacketed vessel. Before addition of silane and amine. B. Reaction mixture after amidation phase complete. C. Reaction mixture after reduction phase complete. D. Benzene sulfonic acid salt of the product*

Pleasingly, the large-scale reaction was a success with only an 9% drop in yield from the small-scale transformation. The isolation of the product by obtaining the salt and subsequently free basing, allowed for the amine to be obtained without the need for any further purification.

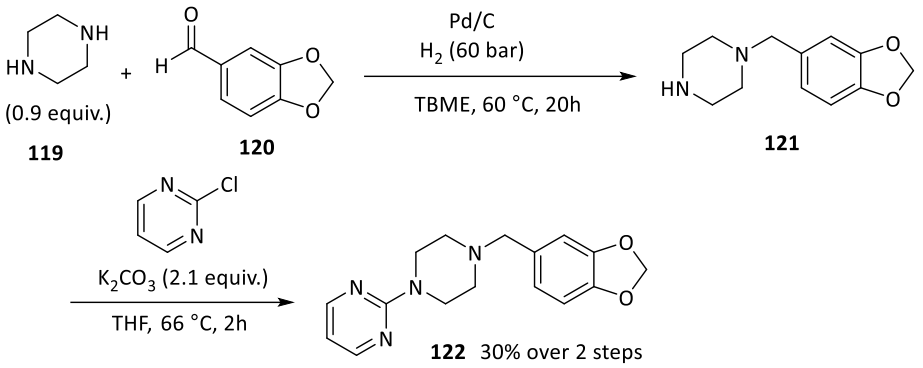
2.3 API Synthesis

Following the synthesis of more basic compounds, the applicability of this process to more complex active pharmaceutical ingredients (API) needed to be evaluated.

2.3.1 Piribedil

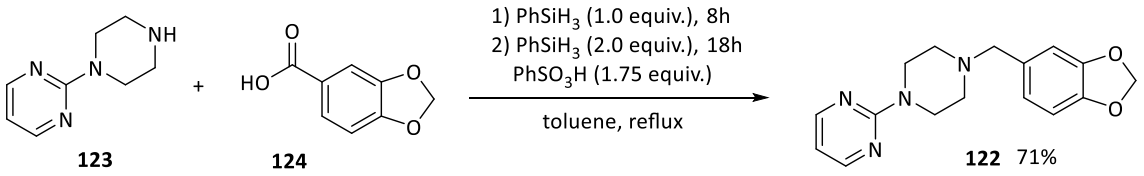
Piribedil is used as a treatment for Parkinson's disease and has been shown to be an effective therapy against other neurological conditions. This drug acts as an agonist towards the dopamine D2 and D3 receptors and is an antagonist towards α_2 adrenergic receptors, explaining why Piribedil seems to

cause less drowsiness than other dopamine agonists. In addition, there is a lack of affinity towards the serotonin receptor 5-HT_{2B} which theoretically results in no risk of heart valve impairment.[215,216]



Scheme 42: *Patent synthesis of Piribedil*

The patent concerning the synthesis of piribedil, utilises a H_2 and palladium-catalysed reductive amination between piperonyl aldehyde (**120**) and piperazine (**119**), and a subsequent S_NAr process to assemble the final structure (**122**) (Scheme 42).[217]



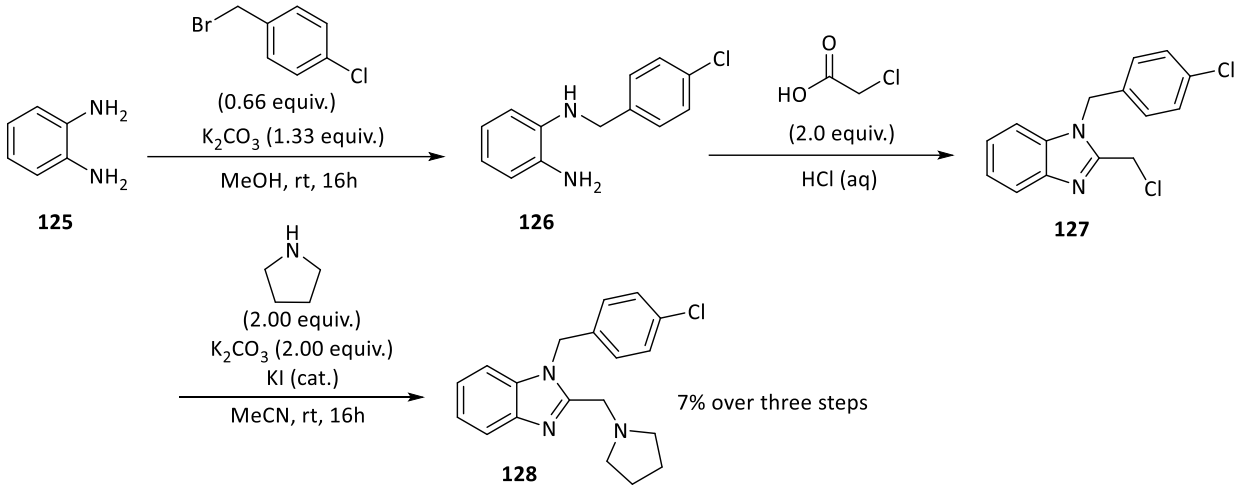
Scheme 43: *Synthesis of Piribedil*

We demonstrated that the reductive amination could be carried out using the metal-free protocol from the carboxylic acid (**124**) in an 71% yield (Scheme 43). Pleasingly, the acid-base workup was sufficient to both isolate and purify the product and column chromatography was not required. Even more impressively, this transformation was repeated using Winchester grade solvent and non-dried glassware and achieved a yield of 66%. This demonstrated that rigorous exclusion of air and water are not necessary, further simplifying this procedure.

2.3.2 Clemizole

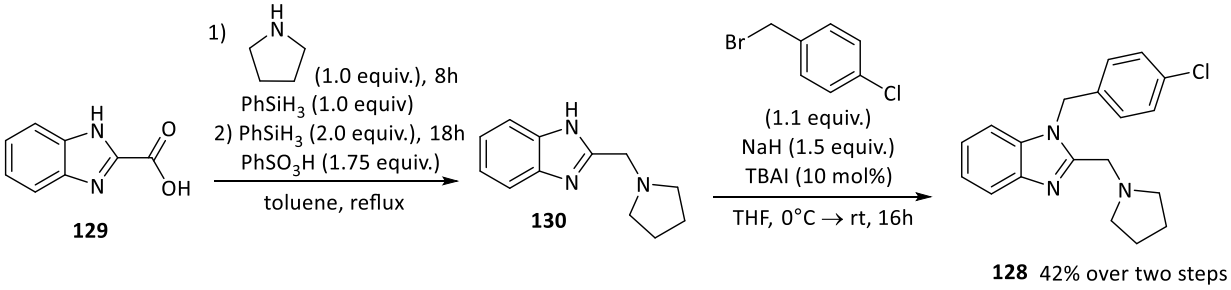
Clemizole is a H_1 antagonist and blocks the action of histamine at the H_1 receptor and initially, was used for the treatment of allergic disease. [218] It has also been found to possess a high affinity for

serotonin (5-HT) receptors and as a result has been shown to demonstrate anti-epileptic properties. In addition, Clemizole has been found to inhibit one of the membrane channel proteins (TRPC5) and is currently in clinical trials for the treatment of hepatitis C.[219]



Scheme 44: *Patent synthesis of Clemizole*

A patent involving the synthesis of Clemizole and its derivatives, formed the compound through the synthesis of the imidazole ring from *ortho*-phenylenediamine (**125**). Subsequent reaction of the resulting aryl chloride (**127**) with piperidine, gave the product in three steps.[220] Since this publication, other higher yielding transformations to this pharmaceutical have been reported.[221,222]



Scheme 45: *Synthesis of Clemizole*

Our synthesis commenced from the commercially available 1H-benzimidazole-2-carboxylic acid (**129**) and piperidine in the metal-free reductive amination, achieving the intermediate (**130**) in 64% yield. The active compound (**128**) was then achieved through a further alkylation process. Using the acid (**129**) as a starting material, not only circumvented the use of the halide **127**, but also shortened the synthesis as the imidazole ring did not have to formed in a separate step.

2.4 Complex Compound Synthesis

Having demonstrated not only excellent functional group tolerance for simple molecules and applied this to more complex pharmaceutical targets, it was hoped that this method could be applied for more complex transformations towards the synthesis of highly derivatised compounds.

2.4.1 Unsymmetrical Diamines

N,N-disubstituted piperazines are privileged motifs and are third most common aliphatic amines found in pharmaceutical compounds.[10,223] Structures containing this motif have been used in the treatment of neurological disorders, respiratory conditions and as anticancer agents, among others.[158]

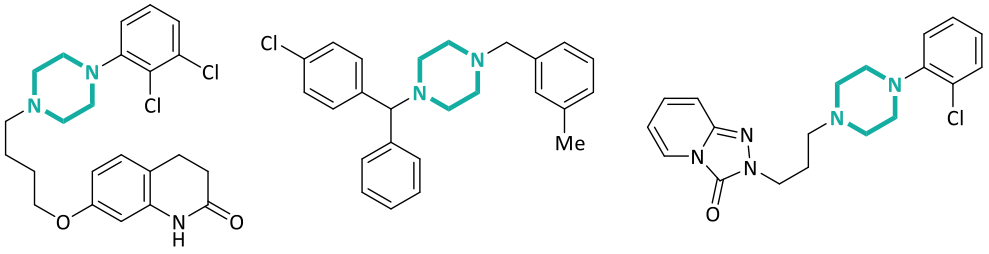
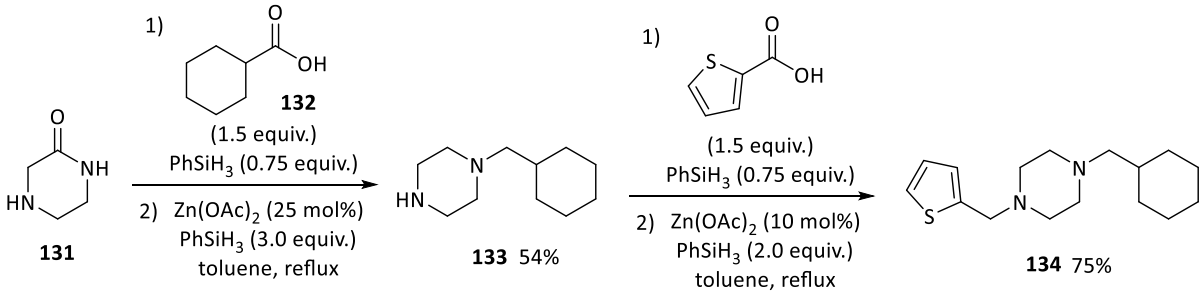


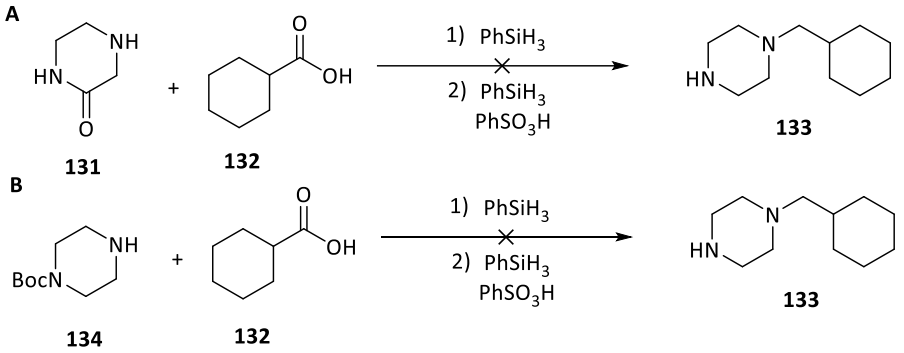
Figure 21: Pharmaceuticals containing *N,N*-disubstituted piperazines

Traditional methods for the synthesis of *N,N*-disubstituted piperazines involves a protecting group strategy. However, an elegant two step protocol was proposed by Denton, which used piperazinone (**131**) as the starting material (Scheme 46).[158] This process not only formed a higher order amine, but also reduced the lactam simultaneously to reveal the second reaction site (**133**).



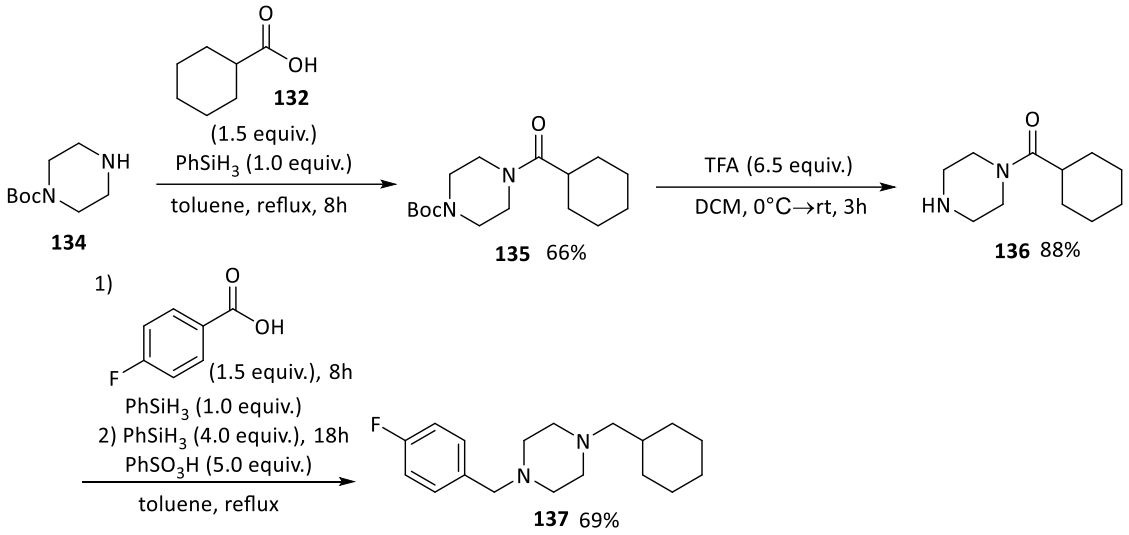
Scheme 46: *Denton's synthesis of N,N-disubstituted piperazines*

This protocol reducing both the formed amide and the lactam was attempted using the metal-free process and although further optimisation was carried out, only trace product was obtained. Attempts were also made with *N*-Boc-piperazine as the starting material, to exploit the susceptibility of Boc towards benzenesulfonic acid. Again, this did not yield any product.



Scheme 47: *Attempts towards N,N-disubstituted piperazines*

The synthesis of *N,N*-disubstituted piperazines was completed through utilising Boc group protection along with the demonstration of diamide reduction.

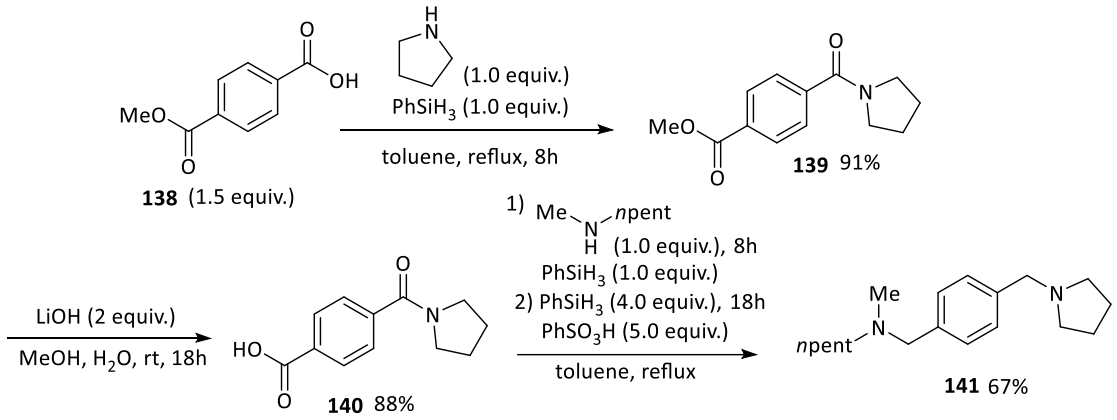


Scheme 48: *Synthesis of an N,N-disubstituted piperazine*

Boc groups were shown not to be compatible with the reduction procedure, although have been demonstrated in the amidation protocol. As a result, the Boc protected amide was isolated (**135**), followed by deprotection to reveal a further reaction site (**136**). Subsequent reductive amination,

using excess silane and acid was then carried out to functionalise the open site and reduce the amide to form the diamine product (**137**).

In the same way that a diamine (**134**) was shown to be a successful starting material, it was pertinent to demonstrate that a diacid could be used. It was demonstrated above that methyl esters were tolerated under the reaction conditions (**90**). Cleavage of the protecting group would reveal a further reaction site, however, due to isolation issues this route was not possible. Attempts were made towards utilising direct amidation from the ester starting material although this was also unsuccessful.



Scheme 49: *Synthesis of an unsymmetrical p-xylylenediamine*

Synthesis was carried out the same as above, the protected amide was synthesised (**139**), followed by ester deprotection using hydroxide (**140**), and further reaction at the newly revealed acid, along with reduction of the amide (**141**).

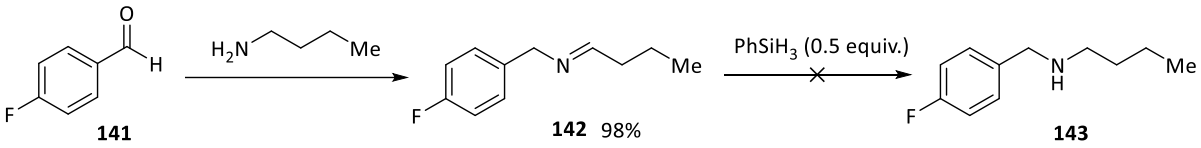
2.4.2 Sequential Reductive Aminations

Finally, the one-pot synthesis of tertiary amines from primary amines were investigated, through two sequential reductive amination protocols. This allows for the formation of highly functionalised bespoke compounds without the need for workup and purification waste.

A similar process was introduced by Denton in the synthesis of complex β-fluorinated compounds, although this process was only investigated using TFA. Initial studies set to emulate this

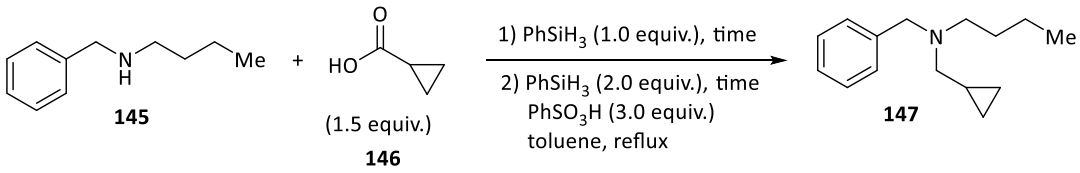
transformation, using an aldehyde in combination with $PhSiH_3$, to rapidly form the secondary amine and subsequent addition of a carboxylic acid in the reductive amination procedure.

It was found that $PhSiH_3$ alone cannot reduce the resulting imine, and **142** was the only compound isolated from the reaction mixture.



Scheme 50: *Attempted synthesis of a secondary amine from benzaldehyde with $PhSiH_3$*

As an alternative, we looked towards the removal of aldehydes from the process, and focussed on the use of carboxylic acids, despite the increase in reaction time. Initial investigations looked at the synthesis of a tertiary compound, using butyric acid and benzylamine for the formation of the secondary amine (**145**). Addition of cyclopropanecarboxylic acid (**146**) would then achieve the tertiary amine (**147**) in a subsequent step. From the secondary amine scope, it is known that benzylamines with short chain alkyl acids provide products in high yields (**107**). However, the synthesis of tertiary amines from starting materials with increased sterics are known to be more challenging.



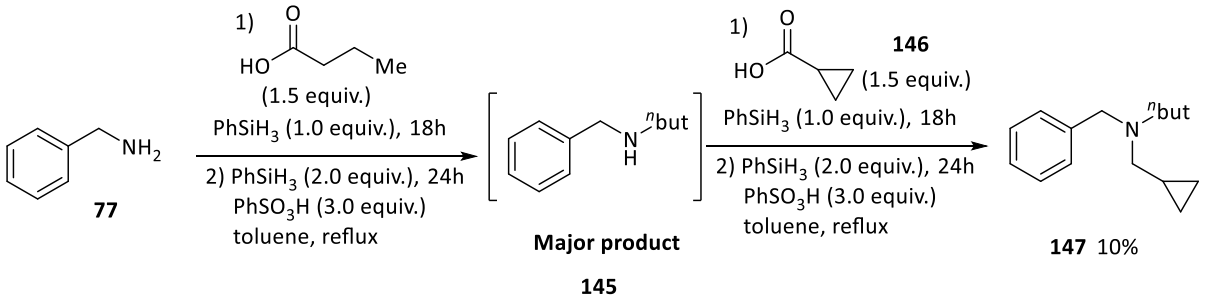
Entry	Amidation time (h)	Reduction time (h)	Yield (%)[a]
1	8	18	38
2	18	24	85

[a]Isolated yield

Table 8: *Optimisation of tertiary amine formation*

Using the general conditions for the *N*-alkylation of secondary amines, resulted only in a 38% yield. This is likely due to slowed reactivity as a result of increased sterics around the central nitrogen. It had been demonstrated previously that an increase in carboxylic acid equivalents would increase the speed of the amidation and an increase in sulfonic acid would increase the speed of the reduction.

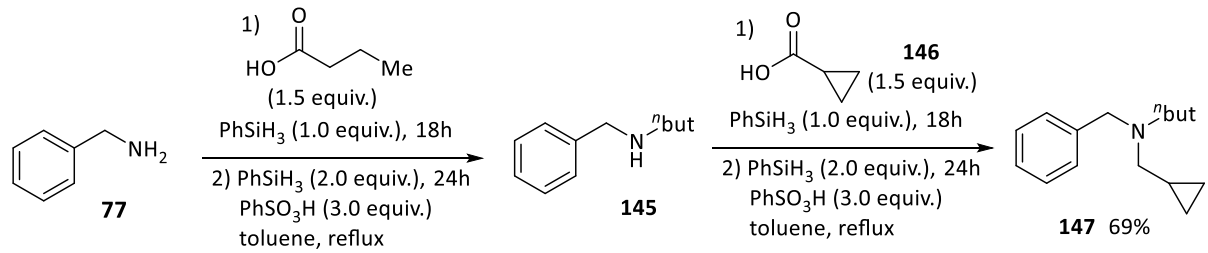
However, in this case, keeping the original timings would be incompatible with one-pot reaction progression. Pleasingly, an increase in reaction time of both the amidation and reduction steps, yielded sufficiently high conversion to allow for telescoping into the full transformation.



Scheme 51: *Initial synthesis of tertiary amines from primary amines in one-pot process*

However, upon attempting the full process, only a 10% yield was obtained, with the major product after workup being the secondary amine intermediate. This suggested that there was an issue with the initiation of the second process. From the large-scale synthesis (2.2.3), precipitation of the sulfonic acid salt, suggested that the reaction product before workup was not the free amine. As a result, the non-nucleophilic amine salt could not initiate the amidation process and conversion was low.

The addition of a base after the formation of the secondary amine was considered, however it was rationalised that this would affect the acid mediated reduction process. Instead, an intermediate workup was proposed, using the minimum amount of solvent to minimise waste, before being concentrated and returned to the flask for a further *N*-alkylation process. This workup involved the addition of a 2M sodium hydroxide (NaOH) aqueous solution, which would free-base the amine, remove any excess acid and quench any remaining silane.



Scheme 52: *Synthesis of tertiary amines from primary amines*

Pleasingly, this was successful, with the formation of the desired product in a much elevated yield. Following the success of this synthesis, it was pertinent to demonstrate this process for further examples, to introduce not only functionality but also to investigate the order of connectivity.

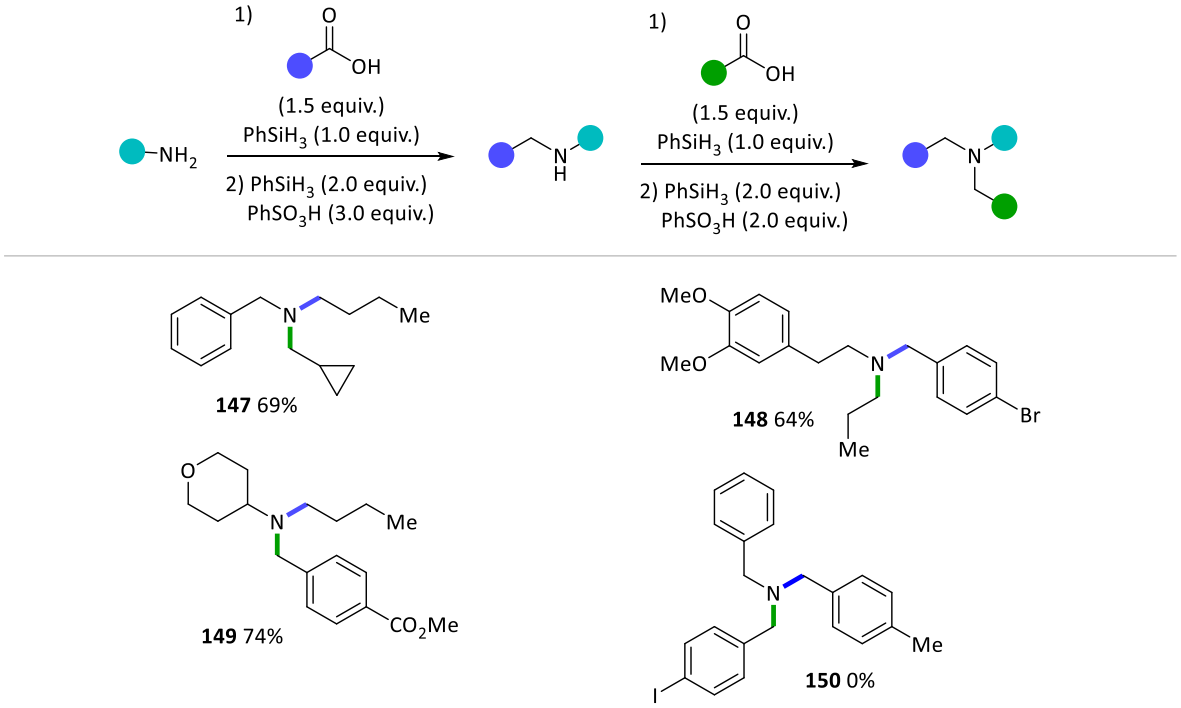


Figure 22: *Synthesis of tertiary amines from primary amine starting materials*

Using this method, we demonstrated three examples, building novel compounds from readily available components. Although functional group tolerance had already been investigated, it was gratifying to display this in the synthesis of more complex compounds, allowing for further derivatisation if required. Pleasingly, minimal reaction between the amine starting material and second carboxylic acid was observed, and the only major by-product seen, was unreacted secondary amine formed from the first reductive amination process. Unsurprisingly, initial formation of the less hindered alkyl amine and subsequent reaction with an aromatic acid (**149**) was found to result in the highest yield. Formation of a triaryl species (**150**) was attempted, although this was not successful and only the secondary amine was isolated cleanly without need for further purification. This was likely due to increased sterics surrounding the diaryl intermediate preventing the formation of a dibenzylbenzamide.

2.5 Mechanistic Studies

After investigation of the scope and utility of the metal-free reductive amination, studies were conducted to elucidate the mechanism of the reaction. The mechanism for the amidation is well-known and has already been discussed *herein* (Scheme 19). As such, further mechanistic discussion will centre on the reduction alone.

From the control experiments, it is known that both the acid and the silane are required for reduction to occur (Table 4, entry 2 and 3), and it was initially assumed that silyl esters were the active species. Silyl esters have been implicated in a range of reductive processes and have shown increased reducing ability compared to the parent silane alone.[153,158,208,210]

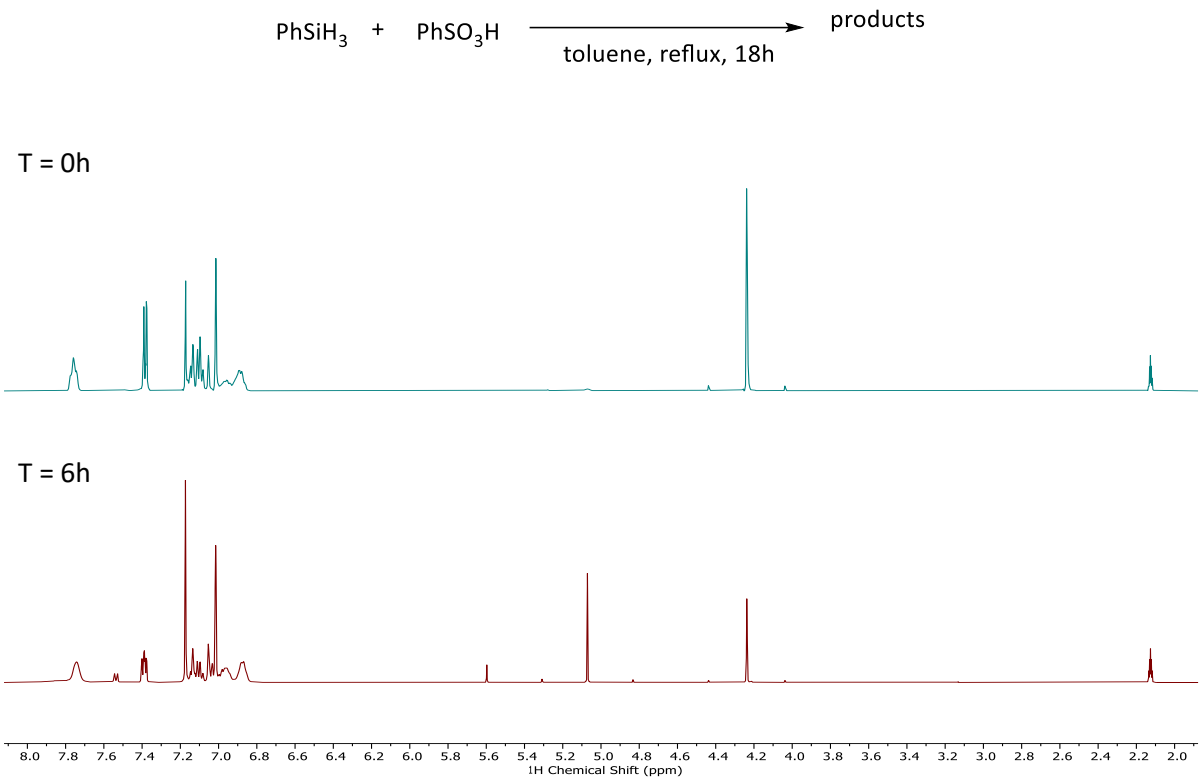


Figure 23: *^{1}H NMR of the reaction mixture of $PhSiH_3$ and $PhSO_3H$ after 0h and 18h*

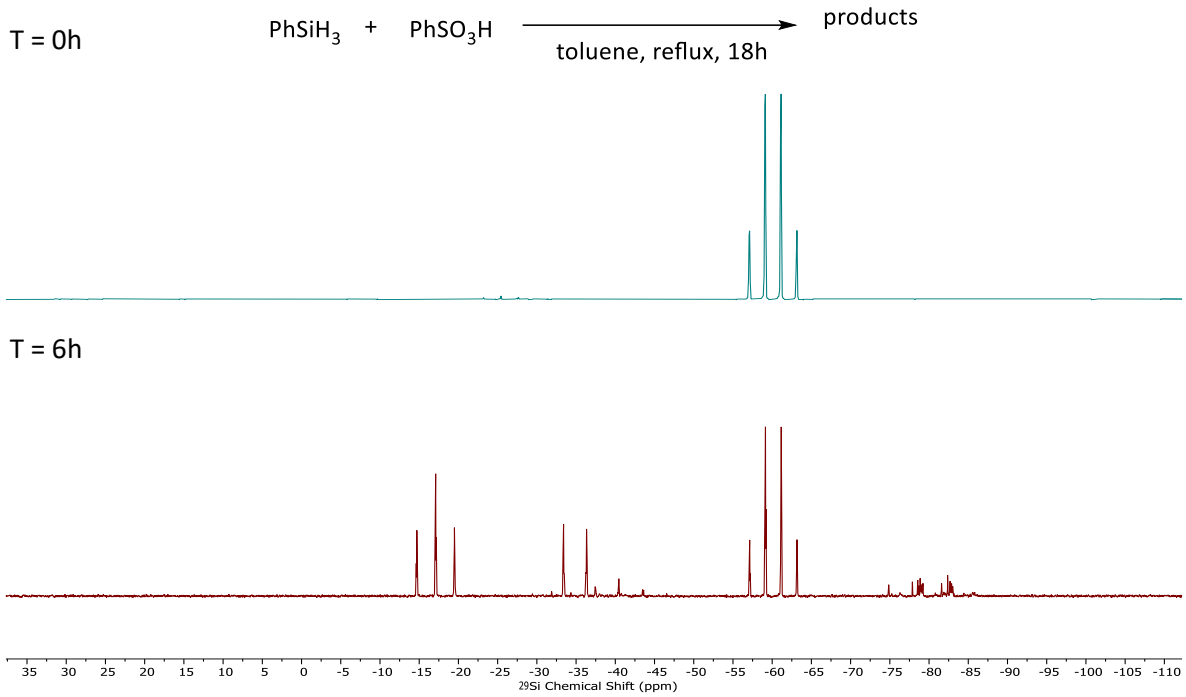
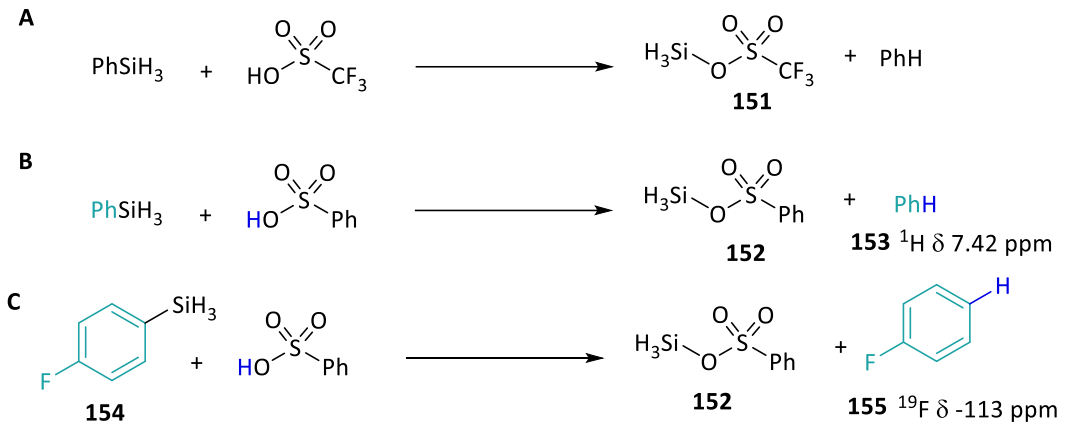


Figure 24: *^{29}Si NMR of the reaction mixture of $PhSiH_3$ and $PhSO_3H$ after 0h and 6h*

However, both ^{1}H and ^{29}Si NMR (Figure 23 and 24) spectroscopic investigations of the reaction between the silane and acid did not show the characteristic peaks associated with silyl ester formation; instead, the formation of two discreet species were observed. Pleasingly, the formation of the highly flammable monosilane (^{1}H δ = 3.10 ppm, ^{29}Si δ = -96.1 ppm) was not identified.

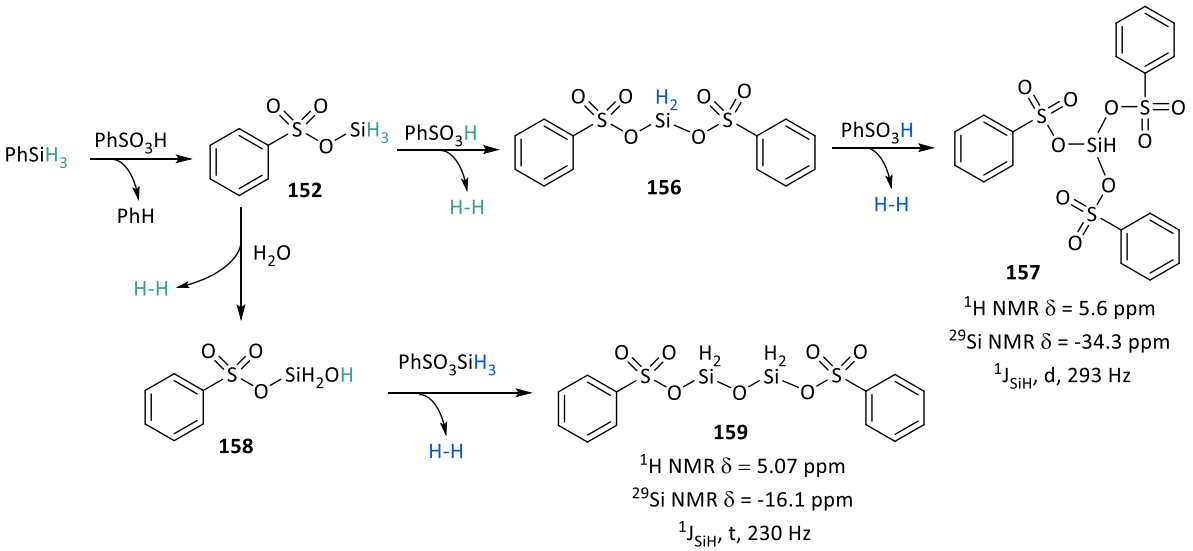
Reactions of silanes and triflic acid, was investigated by Bassindale in 1964, who demonstrated the formation of silyl triflates (Scheme 53A).[224] This reaction was shown to proceed through elimination of one of the substituents attached to the silicon core and investigations with $PhSiH_3$, demonstrated that benzene was removed to allow for silyl triflate formation.



Scheme 53: *Formation of silyl sulfonates: A. Bassindale's synthesis of silyl triflates. B. Proposed active reducing agent. C. Identification of the fluorobenzene*

This ideology was applied to the reduction using $PhSO_3H$, and pleasingly benzene, (^1H δ = 7.42) was identified in the ^1H NMR spectrum, following reaction with $PhSiH_3$ (Scheme 53B). Further validation came from the synthesis of 4-fluorophenylsilane and identification of fluorobenzene in the in the ^{19}F NMR spectrum (^{19}F δ = -113). This confirmed the synthesis of silyl sulfonate specifies (Scheme 53C).

Despite verifying that the reaction proceeds through this type of elimination, the multiplicities observed in the ^{29}Si NMR spectrum do not correlate to the proposed structure, **152**, and do not account for H_2 evolved from the reaction mixture.

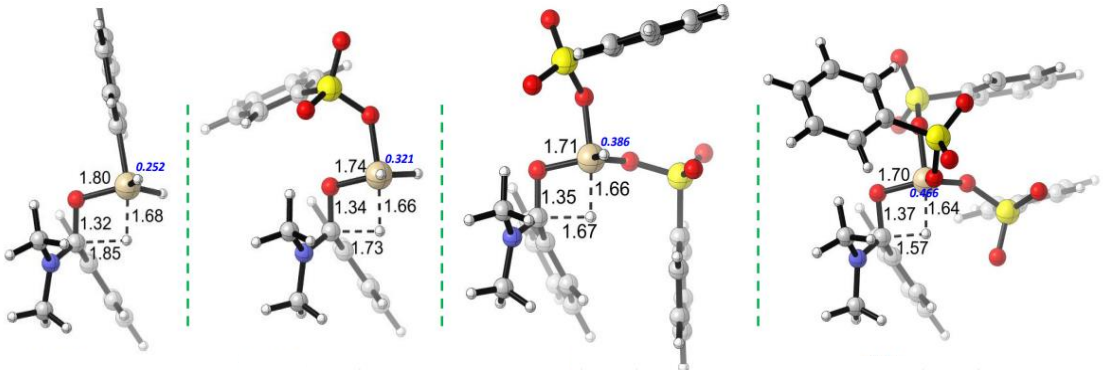


Scheme 54: *Proposed active reducing species*

From optimisation procedures, it was known that an increase in sulfonic acid had a positive effect on the yield (Table 4, entries 4-8), and as a result, we proposed the formation of higher order silyl sulfonate species. NMR spectroscopy shifts lead to the speculation of a disulfonate disiloxane (**159**) species over a doubly substituted silyl compound (**156**). However, despite speculation, the species shown in NMR spectroscopy have been demonstrated to be the active reducing agents, as upon addition of an amide to the silane/sulfonic acid mixture, reduction in a high yield was observed.

Computational calculations to compare the hydride transfer reduction barrier of increasingly sulfonated silanes were carried out by the Houk group.

A



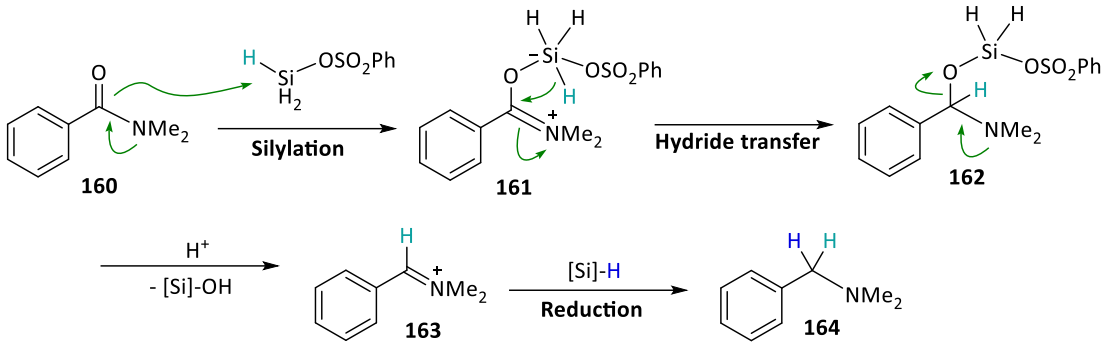
B

	$PhSiH_3$	$PhSO_3SiH_3$	$(PhSO_3)_2SiH_2$	$(PhSO_3)_3SiH$
$\Delta G^{\ddagger}$	42.6	28.9	27.0	25.0
Charge	0.252	0.321	0.386	0.466

Table 9: *Computational calculations of increasingly substituted silyl sulfonates ωb97xd/6 31g(d,p)//SMD(solvent = toluene)//ωb97xd/6-311+g(d,p)//SMD(solvent = toluene): A: Transition state structure. B. $\Delta G^{\ddagger}$ and charge on silicon for each species*

Unsurprisingly, the higher substituted sulfonate species demonstrated a decreased barrier to hydride transfer. This is due to increased electron withdrawal from the sulfonate groups, resulting in more electropositivity and increased Lewis acidity at the silicon centre. These computational results also reflected our experimental data where $PhSiH_3$ alone could not affect reduction of an amide and increased sulfonic acid resulted in increased yields (Table 4, entries 4-8).

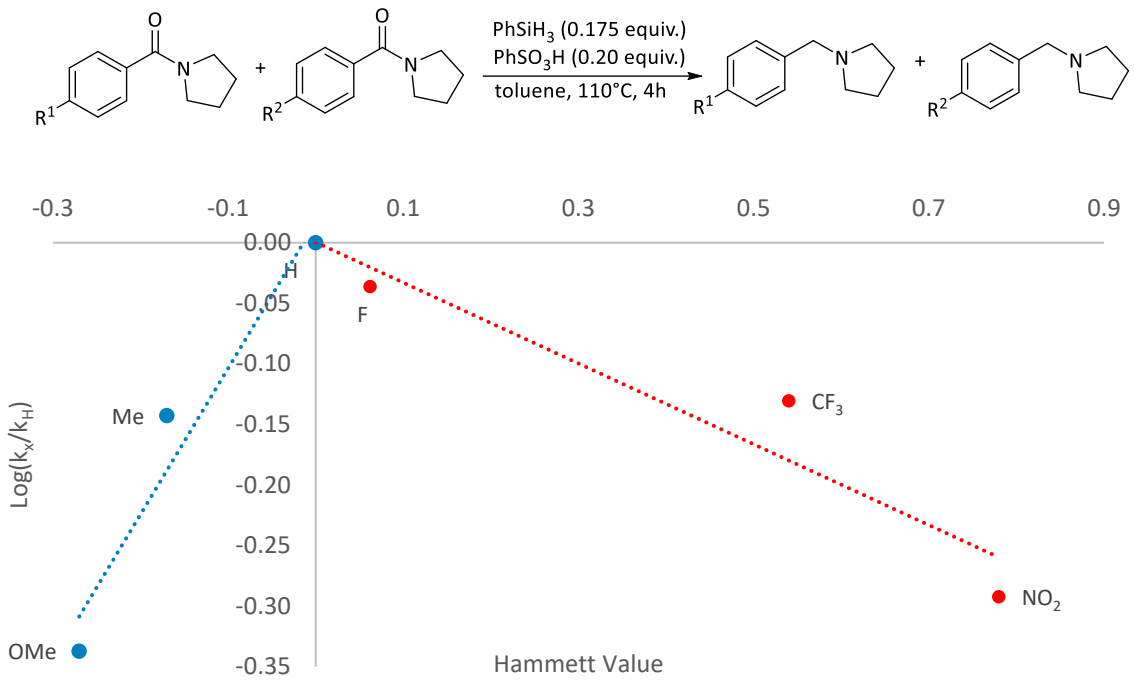
Following identification of the active reducing species, we turned towards elucidation of the reduction mechanism itself, and the following was proposed:



Scheme 55: *Proposed mechanism. mono substituted silyl sulfonate shown for clarity*

The mechanism involves initial addition of the silyl sulfonate to the amide forming 'ate' complex **161**, which subsequently undergoes hydride transfer to form tetrahedral intermediate **162**. Following this, elimination of the siloxide, which under the acidic conditions rapidly forms a silanol, results in the formation of an iminium ion (**163**). This can then be reduced to the amine (**164**) through hydrosilylation with a further hydride species.

Following this proposal, further investigations into the mechanism was carried out. NMR spectroscopy studies confirmed that any intermediates were short lived and as a result, silylation of the amide was theorised to be the rate-limiting step (RLS). To confirm this, a Hammett competition study was carried out and amides bearing a range of *para* substituted electron donating and withdrawing substituents were subjected to the reduction conditions.



Graph 3: *Hammett study*

Interestingly, the Hammett plot demonstrated a change in the gradient which is indicative of a change in the RLS. However, this can be explained by the proposed mechanism. For more electron donating substituents, silylation would become increasingly slow due to decreased electrophilicity of the amide, however the siloxide would be rapidly eliminated due to mesomeric contributions. For electron withdrawing substituents the converse is true; silylation would occur readily for electron deficient amides and the elimination of the siloxide would become RLS. An alternative theory is an asynchronous concerted transition state, although the gradient change may be too drastic for this conclusion to be valid.

2.6 Conclusions

To conclude, a novel metal-free reductive amination from carboxylic acid starting materials has been developed. This process not only replaces aldehydes with more commercially available and less expensive carboxylic acids, but also exchanges hazardous metal reducing agents for stable silanes and can be carried out in conventional laboratory glassware. Optimisation for the synthesis of tertiary amines was brief, investigating the length of the amidation time only. However, secondary amine

formation proved to be more challenging, with an increase in both carboxylic acid and sulfonic acid to form the product in high yields. With these conditions, a range of both secondary and tertiary amines were synthesised (41 examples), demonstrating a wide range of functional groups including potentially reduceable substituents and those that provide a handle for further derivatisation. In addition, this method was shown to be successful on a large scale (100 mmol), in the synthesis of pharmaceuticals and in the formation of more complex amines. Finally, using both computational and experimental investigations, the active reductive compounds were shown to be silyl sulfonates, formed through the elimination of benzene and subsequent reaction with the sulfonic acid. A Hammett study demonstrated that the RDS changed depending on the electronics of the substituent, cementing the potential mechanism *via* an initial silylation and hydride transfer.

3 Experimental

3.1 General Experimental

Reagents were purchased from commercial suppliers and used directly without further purification. Solvents were dried unless specified 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 and stored under inert atmosphere using 4Å molecular sieves. 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). High Pressure Liquid Chromatography (HPLC) was carried out on a Thermo Ultimate reverse phase column using 1% formic acid solution and acetonitrile. Computational calculations were carried out by the Houk group using ωb97xd/6-31g(d,p)//SMD(solvent = toluene)//ωb97xd/6-311+g(d,p)//SMD(solvent = toluene) and the energies quoted are electronic energies in kcal/mol.

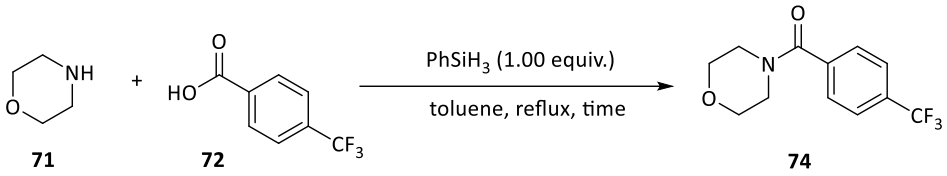
NMR spectra were recorded on either a Bruker AV 400, AV(III) 400HD or AV(III) 500HD in $CDCl_3$, DMSO or PhMe-d8. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz), with residual protic solvent as the internal reference: ^{1}H NMR ($CDCl_3$ δ = 7.26 ppm, DMSO δ = 2.50 ppm, PhMe δ = 2.08 ppm), ^{13}C NMR (central peak of $CDCl_3$ δ = 77.16 ppm, DMSO δ = 39.52, PhMe δ = 20.43 ppm). NMR spectra are reported as follows: δ (multiplicity, coupling constant (if appropriate), number of protons). Abbreviations used include s – singlet, d – doublet, t – triplet, q – quartet, sept – septet, m – multiplet, pent - pentet, br – broad, app. – apparent. and coupling constants (J) are given in Hertz (Hz). All NMR are reported as proton decoupled spectra. NMR yields were determined by the following formula, where P and IS refer to the product and internal standard respectively, n refers to the moles and N is the number of nuclei represented in the chosen peak:

$$n_P = n_{IS}\left(\frac{I_P/N_P}{I_{IS}/N_{IS}}\right)$$

3.2 Optimisation

3.2.1 Tertiary Amines

General Amidation Optimisation

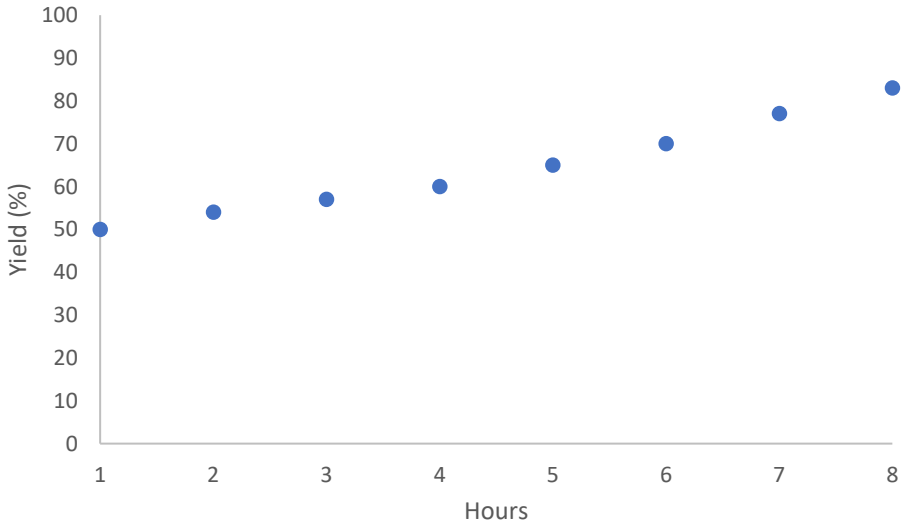


71 72 74

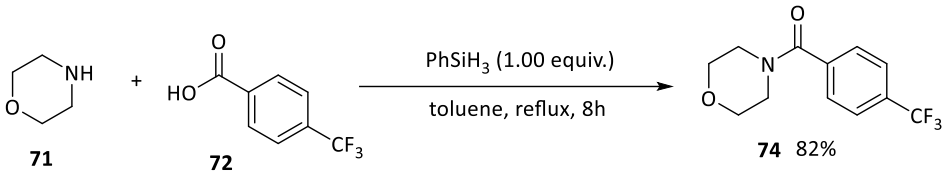
Entry	Time (h)	Yield (%)[a]
1	1	50
2	2	54
3	3	57
4	4	60
5	5	65
6	6	70
7	7	77
8	8	83

[a] Yield determined by ^{19}F NMR using fluorobenzene as an internal standard.

To a refluxing solution of 4-(trifluoromethyl)benzoic acid (190 mg, 1.00 mmol) in dry toluene (1.20 mL) was added phenylsilane (123 µL, 1.00 mmol) followed by morpholine (87.2 µL, 1.00 mmol) added dropwise. The reaction mixture was heated for the allotted time (as Table), before quenching with EtOH (2 mL) and cooling to room temperature. The reaction was concentrated and fluorobenzene (93.8 µL, 1.00 mmol) was added to the crude product and the yield was determined by ^{19}F NMR spectroscopy.

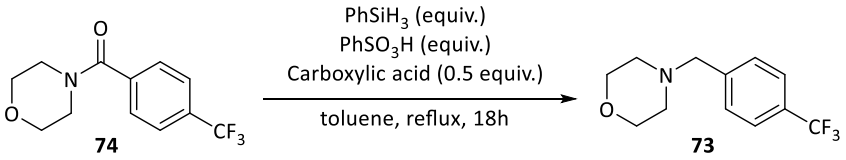


Morpholino(4-(trifluoromethyl)phenyl)methanone – **74**



To a refluxing solution of 4-(trifluoromethyl)benzoic acid (190 mg, 1.00 mmol) in dry toluene (1.20 mL) was added phenylsilane (123 µL, 1.00 mmol) followed by morpholine (87.0 µL, 1.00 mmol) dropwise. The reaction mixture was heated for 8 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc (10 mL) and washed with HCl (10 mL of a 1M aqueous solution) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography (1:1, pentane: EtOAc) to afford to the title product as colourless crystals (228.6 mg, 82%); **M.P:** 52-54 °C (lit: 53-54 °C)[225]; **R.f.**: 0.56 (1:1 pentane: EtOAc); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.70 (d, J= 7.7 Hz, 2H, Ar-**H**), 7.54 (d, J= 7.7, 2H, Ar-**H**), 3.79 (br s, 4H, O-C**H$_2$**-CH_2), 3.64 (br s, 2H, N-C**H$_2$**-CH_2), 3.41 (br s, 2H, N-C**H$_2$**-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 168.9 (C), 138.9 (C), 131.7 (q, J= 32.2 Hz, C), 127.5 (CH), 125.6 (q, J = 3.7 Hz, CH), 123.6 (q, J= 271 Hz, C), 66.8 (CH_2), 48.1 (CH_2), 42.6 (CH_2); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) -62.95 (CF_3); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{12}F_3NO_2$ [M^+H] 260.0893 found 260.0893. The data matches that found in the literature.[225]

Amide Reduction



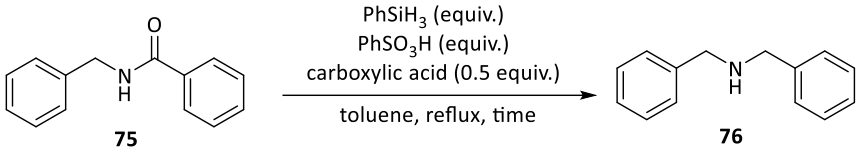
Entry	$PhSiH_3$ equiv.	$PhSO_3H$ equiv.	Carboxylic acid	Solvent	Yield[a] (%)
1	2.00	1.75	-	1,4-dioxane	67
2	2.00	1.75	-	toluene	70
3	0.00	1.75	-	toluene	0[b]
4	2.00	0.00	-	toluene	0[b]
5	2.00	0.50	-	toluene	8
6	2.00	1.00	-	toluene	46
7	2.00	2.00	-	toluene	76
8	2.00	3.00	-	toluene	82
9	2.00	4.00	-	toluene	88
10	2.00	1.75	$CF_3C_6H_4CO_2H$	toluene	76

[a] Isolated yield; [b] Yield determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard

To a refluxing solution of pyrrolidin-1-yl(4-(trifluoromethyl)phenyl)methanone (259 mg, 1.00 mmol) and carboxylic acid (as Table) in dry toluene (as Table), was added benzene sulfonic acid (277 mg, 1.75 mmol) and phenylsilane (123 µL, 1.00 mmol) dropwise. The reaction mixture was heated for 18 hours before being cooled to room temperature and quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title product

3.2.2 Secondary Amines

Amide Reduction

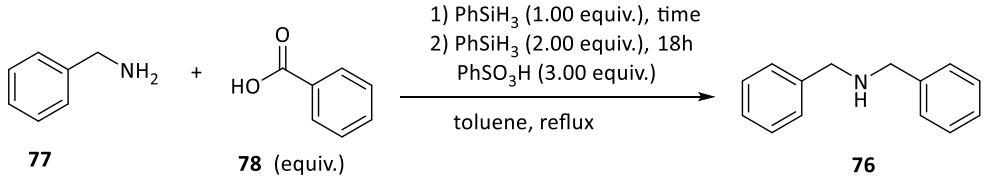


Entry	$PhSiH_3$ (equiv.)	$PhSO_3H$ (equiv.)	Carboxylic acid	Reaction time (h)	Yield (%)[a]
1	2.00	1.75	-	18	54
2	3.00	1.75	-	18	51
3	2.00	1.75	-	24	64
4	2.00	2.00	-	18	64
5	2.00	2.50	-	18	70
6	2.00	2.50	-	24	75
7	2.00	3.00	-	18	73
8	2.00	3.00	$C_6H_5CO_2H$	18	75

[a] Isolated yield

To a refluxing solution of *N*-benzylbenzamide (259 mg, 1.00 mmol) and carboxylic acid (as Table) in dry solvent (as Table), was added benzenesulfonic acid (279 mg, 1.75 mmol) and phenylsilane (123 µL, 1.00 mmol) dropwise. The reaction mixture was heated for 18 hours before being cooled to room temperature and quenched with acetic acid (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with acetic acid (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title product.

One-pot Reductive Amination



Entry	Amidation time (h)	Benzoic acid (equiv.)	Yield (%)[a]
1	8	1.00	54
2	20	1.00	74
3	8	1.50	79

[a] Isolated yield

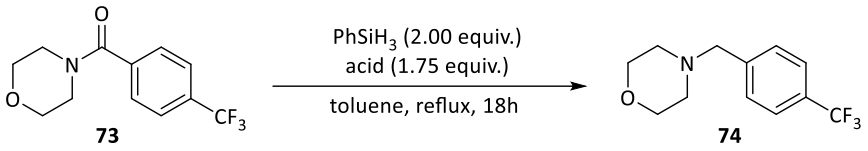
To a refluxing solution of benzoic acid (as Table) in toluene (1.20 mL) was added phenylsilane (123 µL, 1.00 mmol) followed by benzylamine (1.00 mmol) dropwise. The reaction mixture was heated (as table), after which time benzenesulfonic acid (475 mg, 3.00 mmol) and phenylsilane (247 µL, 2.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with acetic acid (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with acetic acid (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product.

3.2.3 PTSA Investigations

Drying Procedure for PTSA.H_2O

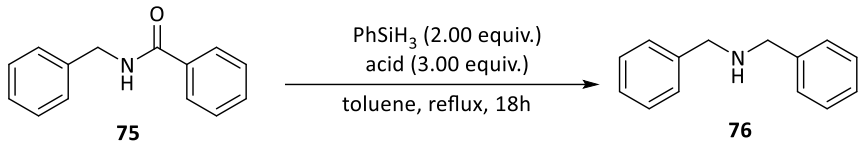
A solution of PTSA.H_2O (2.00 g, 10.5 mmol) in toluene (6.00 mL) was refluxed vigorously using Dean-Stark apparatus until water (0.189 mL, 10.5 mmol) had been collected. The reaction mixture was concentrated in vacuo to form dry PTSA as a yellow solid (1.81 g, >99%, 10.5 mmol)

Comparison of $PhSO_3H$, PTSA and PTSA.H_2O



Entry	Acid	Yield (%)[a]
1	$PhSO_3H$	70
2	PTSA	89
3	PTSA.H_2O	57

[a] *Isolated yields*



Entry	Acid	Yield (%)[a]
1	$PhSO_3H$	73
2	PTSA	61

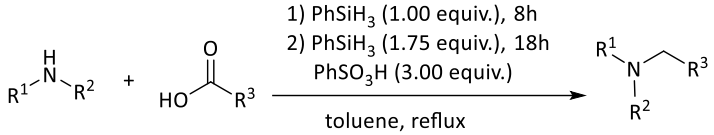
[a] *Isolated yields*

To a refluxing solution of amide (1.00 mmol) in dry toluene (1.2 mL), was added sulfonic acid (1.75 – 3.00 mmol) and phenylsilane (123 µL, 1.00 mmol) dropwise. The reaction mixture was heated for 18 hours before being cooled to room temperature and quenched with the appropriate acid (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with the appropriate acid (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product.

3.3 General Procedures and Experimental Data

General Procedures

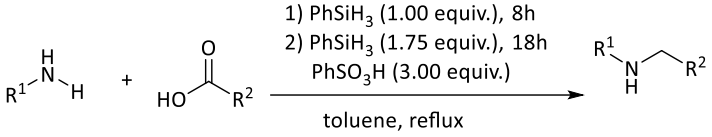
3.3.1 Tertiary Amine Synthesis



To a refluxing solution of carboxylic acid (1.00 mmol or 1.50 mmol) in dry toluene (1.20 mL) was added phenylsilane (123 µL, 1.00 mmol) followed by amine (1.00 mmol) dropwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (277 mg, 1.75 mmol or 314 mg, 2.00 mmol)

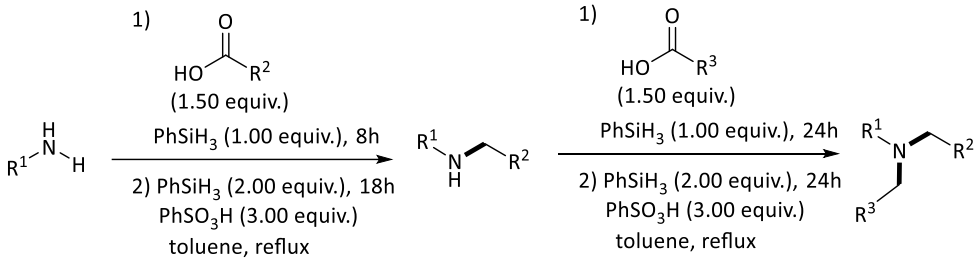
and phenylsilane (247 µL, 2.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product. If necessary, the products were purified by column chromatography.

3.3.2 Secondary Amine Synthesis



To a refluxing solution of carboxylic acid (1.50 mmol) in dry toluene (1.20 mL) was added phenylsilane (123 µL, 1.00 mmol) followed by amine (1.00 mmol) dropwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (474 mg, 3.00 mmol) and phenylsilane (247 µL, 2.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with acetic acid (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with acetic acid (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product. If necessary, the products were purified by column chromatography.

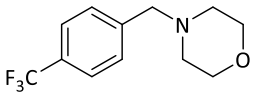
3.3.3 Tertiary Amine Synthesis from Primary Amines



To a refluxing solution of carboxylic acid (1.50 mmol) in dry toluene (1.20 mL) was added phenylsilane (123 µL, 1.00 mmol) followed by amine (1.00 mmol) dropwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (474 mg, 3.00 mmol) and phenylsilane (247 µL, 2.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with NaOH (3.00 mL of a 2 M aqueous solution). The reaction mixture was stirred vigouously for 30 minutes, washed with EtOAc (3 x 5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude intermediate was returned to the reaction flask with carboxylic acid (1.50 mmol) and dry toluene (1.20 mL) before being heated to reflux and phenylsilane (123 µL, 1.00 mmol) was added dropwise. The reaction was heated for 24 hours, after which time benzenesulfonic acid (314 mg, 2.00 mmol) and phenylsilane (247 µL, 2.00 mmol) were added dropwise and heated for a further 24 hours before being cooled to room temperature and quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product and purified by column chromatography.

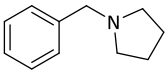
Experimental Data

4-(4'-trifluoromethyl-benzyl)morpholine – **73**



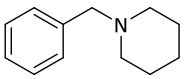
Followed general procedure 3.3.1 using 4-(trifluoromethyl)benzoic acid (190 mg, 1.00 mmol) and morpholine (95.0 µL, 1.00 mmol) to afford the title product as an orange oil (161 mg, 66%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.59 (d, J= 8.2 Hz, 2H, Ar-**H**), 7.48 (d, J= 8.2 Hz, 2H, Ar-**H**), 3.76-3.70 (m, 4H, O-C**H$_2$**-CH_2), 3.56 (s, 2H, N-C**H$_2$**), 2.50-2.39 (m, 4H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 142.2 (C), 129.4 (q, J= 31.9 Hz, C), 129.2 (CH), 125.5 (q, J=3.35 Hz, CH), 124.2 (q, J= 271.7 Hz, C), 66.9 (CH_2), 62.7 (CH_2), 53.6 (CH_2); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) -62.44 (CF_3); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{15}F_3NO$ [M^+H]: 246.1100 found 246.1099. The data matches that found in the literature.[158]

1-Benzylpyrrolidine - **80**



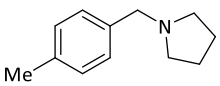
Followed general procedure 3.3.1 using benzoic acid (122 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as an orange oil (136 mg, 84%);**^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.41-7.23 (m, 5H, Ar-**H**), 3.64 (s, 2H, N-C**H$_2$**), 2.57-2.49 (m, 4H, N-C**H$_2$**-CH_2), 1.81 (tt, J= 3.8, 3.8 Hz, 4H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 139.5 (C), 129.0 (CH), 128.1 (CH), 126.9 (CH), 60.80 (CH_2), 54.21 (CH_2), 23.49 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{15}N$ [M^+H]: 162.1277 found 162.1281. The data matches that found in the literature.[226]

1-Benzylpiperidine - **81**



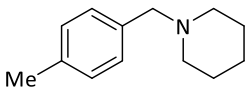
Followed general procedure 3.3.1 using benzoic acid (122 mg, 1.00 mmol) and piperidine (98.8 µL, 1.00 mmol) to afford the title product as an orange oil (119 mg, 68%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.40-7.21 (m, 5H, Ar-**H**), 3.49 (s, 2H, N-C**H$_2$**), 2.39 (br s, 4H, N-C**H$_2$**-CH_2), 1.59 (tt, J= 5.8, 5.8 Hz, 4H, N-CH_2-C**H$_2$**), 1.49-1.41 (m, 2H, CH_2-**H$_2$**C-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 138.6 (C), 129.3 (CH), 128.1 (CH), 126.9 (CH), 63.9 (CH_2), 54.5 (CH_2), 26.0 (CH_2), 24.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{17}N$ [M^+H]: 176.1434 found 176.1436. The data matches that found in the literature.[227]

1-(4-methylbenzyl)pyrrolidine – **82**



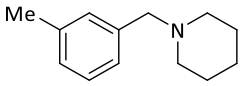
Followed general procedure 3.3.1 using benzoic acid (136 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as an orange oil (140 mg, 80%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.24 (d, J= 7.8 Hz, 2H, Ar-**H**), 7.14 (d, J= 7.8 Hz, 2H, Ar-**H**), 3.61 (s, 2H, N-C**H$_2$**), 2.58-2.49 (m, 4H, N-C**H$_2$**-CH_2), 2.36 (s, 3H, Ar-C**H$_3$**), 1.81 (tt, J= 3.5, 3.5 Hz, 4H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 136.4 (C), 136.4 (C), 128.9 (CH), 128.9 (CH), 60.5 (CH_2), 54.1 (CH_2), 23.5 (CH_2), 21.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{17}N$ [M^+H]: 176.1434 found 176.1434. The data matches that found in the literature.[227]

1-(4-methylbenzyl)piperidine - **83**



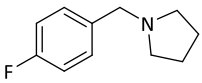
Followed general procedure 3.3.1 using 4-methyl benzoic acid (136 mg, 1.00 mmol) and piperidine (98.8 µL, 1.00 mmol) to afford the title product as an orange oil (119 mg, 68%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.25 (d, J= 7.2 Hz, 2H, Ar-**H**), 7.16 (d, J= 7.2 Hz, 2H, Ar-**H**), 3.48 (s, 2H, N-C**H$_2$**), 2.41 (br s, 4H N-C**H$_2$**-CH_2), 2.38 (s, 3H, Ar-C**H$_3$**), 1.59 (tt. J= 5.5, 5.5 Hz, 4H, N-CH_2-C**H$_2$**), 1.48-1.40 (m, 2H, H_2C-C**H$_2$**-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 136.4 (C), 135.5 (C), 128.3 (CH), 128.8 (CH), 63.6 (CH_2), 54.5 (CH_2), 26.0 (CH_2), 24.5 (CH_2), 21.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{20}N$ [M^+H]: 190.1590 found 190.1589. The data matches that found in the literature.[182]

1-(3-methylbenzyl)piperidine - **84**



Followed general procedure 3.3.1 using 3-methyl benzoic acid (136 mg, 1.00 mmol) and piperidine (98.8 µL, 1.00 mmol) to afford the title product as an orange oil (141 mg, 74%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.24-7.20 (m, 1H, Ar-**H**), 7.17 (s, 1H, Ar-**H**), 7.14 (d, J= 7.6 Hz, 1H, Ar-**H**), 7.09 (d, J= 7.1 Hz, 1H, Ar-**H**), 3.49 (s, 2H, N-C**H$_2$**), 2.42 (br s, 4H, N-C**H$_2$**-CH_2), 2.37 (s, 3H, Ar-C**H$_3$**), 1.62 (tt, J= 5.6, 5.6 Hz, 4H, N-CH_2-C**H$_2$**), 1.49-1.42 (m, 2H, H_2C-C**H$_2$**-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 138.2 (C), 137.7 (C), 130.1 (CH), 128.0 (CH), 127.7 (CH), 126.5 (CH), 63.9 (CH_2), 54.5 (CH_2), 25.9 (CH_2), 24.4 (CH_2), 21.4 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{20}N$ [M^+H]: 190.1590 found 190.1581. The data matches that found in the literature.[227]

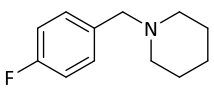
1-(4-fluorobenzyl)pyrrolidine - **85**



Followed general procedure 3.3.1 using 4-fluorobenzoic acid (140 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as an orange oil (116 mg, 65%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.35-7.27 (m, 2H, Ar-**H**), 7.04-6.97 (m, 2H, Ar-**H**), 3.59 (s, 2H, N-C**H$_2$**), 2.51 (br s, 4H, N-C**H$_2$**-CH_2), 1.80 (tt, J= 3.6, 3.6 Hz, 4H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 161.9 (d, J= 244.9 Hz, C), 135.1 (d, J= 2.97 Hz, C), 130.3 (d, J= 7.29 Hz, CH), 114.9 (d, J= 21.4 Hz, CH), 59.87 (CH_2), 54.06 (CH_2), 23.43 (CH_2); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) -116.3 (CF); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{15}NF$ [M^+H]: 180.1183 found 180.1186. The data matches that found in the literature.[228]

N.B Reaction carried out MeCN afforded the product in 79% yield

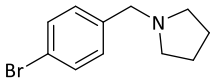
1-(4-fluorobenzyl)piperidine - **86**



Followed general procedure 3.3.1 using 4-fluorobenzoic acid (140 mg, 1.00 mmol) and piperidine (98.8 µL, 1.00 mmol) to afford the title product as an orange oil (130 mg, 67%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.35-7.26 (m, 2H, Ar-**H**), 7.01 (t, J= 8.4 Hz, 2H, Ar-**H**), 3.45 (s, 2H, N-C**H$_2$**), 2.38 (br s, 4H, N-C**H$_2$**-CH_2),

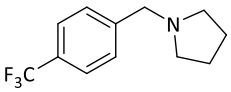
1.58 (tt, J= 5.9, 5.9 Hz, 4H, N-CH_2-C**H_2**), 1.50-1.41 (m, 2H, CH_2-**H_2**C-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 161.9 (d, 243.9 Hz, C), 134.4 (C), 130.6 (d, J= 7.7 Hz, CH), 114.9 (d, J= 21.4 H, CH), 63.04 (CH_2), 54.42 (CH_2), 25.98 (CH_2), 24.39 (CH_2);**^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) δF -116.3 (CF); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{16}NF$ [M^+H]: 194.1340 found 194.1339. The data matches that found in the literature. The data matches that found in the literature.[229]

1-(4-bromobenzyl)pyrrolidine - **87**



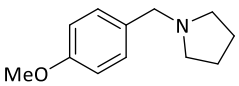
Followed general procedure 3.3.1 using 4-bromobenzoic acid (201 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as a dark orange oil (183 mg, 76%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.45 (d, J= 8.3 Hz, 2H, Ar-**H**), 7.24 (d, J= 8.3 Hz, 2H, Ar-**H**), 3.59 (s, 2H, N-C**H_2**), 2.52 (br s, 4H, N-C**H_2**-CH_2), 1.81 (tt, J= 3.5, 3.5 Hz, 4H, N-CH_2-C**H_2**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 138.5 (C), 131.3 (CH), 130.5 (CH), 120.7 (C), 59.9 (CH_2), 54.1 (CH_2), 23.5 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{15}NBr$ [M^+H]: 240.0382 found 240.0376. The data matches that found in the literature.[158]

1-(4-(trifluoromethyl)benzyl)pyrrolidine - **88**



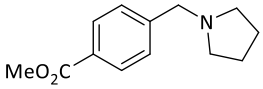
Followed general procedure 3.3.1 using (4-trifluoromethyl)benzoic acid (190 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as a yellow oil (170 mg, 74%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.59 (d, J= 8.1 Hz, 2H, Ar-**H**), 7.48 (d, J= 8.1 Hz, 2H, Ar-**H**), 3.69 (s, 2H, N-C**H_2**), 2.53 (br s, 4H, N-C**H_2**-CH_2), 1.82 (br s, 4H, N-CH_2-C**H_2**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 143.6 (C), 129.8 (q, J= 31.7 Hz, C), 128.9 (CH), 125.1 (q, J= 4.08 Hz, CH), 124.3 (q, J= 271.0 Hz, C), 60.2 (CH_2), 54.2 (CH_2), 23.5 (CH_2); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) δF -62.37 (CF_3); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{14}NF_3$ [M^+H]: 230.1151 found 230.1152. The data matches that found in the literature.[230]

1-(4-methoxybenzyl)pyrrolidine - **89**



Followed general procedure 3.3.1 using 4-methoxybenzoic acid (152 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as an orange oil (134 mg, 70%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.27 (d, J= 8.3 Hz, 2H, Ar-**H**), 6.87 (d, J= 8.3 Hz, 2H, Ar-**H**), 3.82 (s, 3H, OC**H_3**), 3.59 (s, 2H, N-C**H_2**), 2.53 (br s, 4H, N-C**H_2**-CH_2), 1.81 (tt, J= 3.3, 3.3 Hz, 4H, N-CH_2-C**H_2**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 158.6 (C), 131.4 (C), 130.1 (CH), 113.6 (CH), 60.0 (CH_2), 55.2 (CH_3), 54.0 (CH_2), 23.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{18}NO$ [M^+H]: 192.1383 found 192.1388. The data matches that found in the literature.[158]

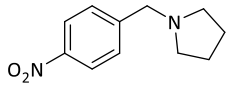
Methyl 4-(pyrrolidin-1-ylmethyl)benzoate - **90**



Followed general procedure 3.3.1 using 4-(methoxycarbonyl)benzoic acid (180 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as an orange oil (177 mg, 81%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 8.00 (d, J= 8.0 Hz, 2H, Ar-**H**), 7.43 (d, J= 8.0 Hz, 2H, Ar-**H**), 3.93 (s, 3H, OC**H_3**), 3.69

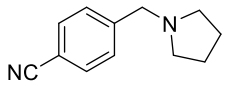
(s, 2H, N-C**H₂**), 2.57-2.49 (m, 2H, N-C**H₂**-CH_2), 1.85-1.78 (m, 2H, N-CH_2-C**H₂**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 166.9 (C), 144.9 (C), 129.6 (CH), 128.7 (C), 128.6 (CH), 60.3 (CH_2), 54.2 (CH_2), 51.9 (CH_3), 23.5 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{17}NO_2$ [M^+H]: 220.1332 found 220.1330. The data matches that found in the literature.[231]

1-(4-nitrobenzyl)pyrrolidine - **91**



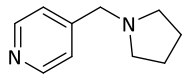
Followed general procedure 3.3.1 using 4-nitrobenzoic acid (167 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as an orange oil (123 mg, 60%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 8.20 (d, J= 8.8 Hz, 2H, Ar-**H**), 7.55 (d, J= 8.8 Hz, 2H, Ar-**H**), 3.75 (s, 2H, N-**CH₂**), 2.56 (br s, 4H, N-C**H₂**-CH_2), 1.90-1.78 (m, 4H, N-CH_2-C**H₂**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 147.4 (C), 146.9 (C), 129.3 (CH), 123.5 (CH), 59.9 (CH_2), 54.2 (CH_2), 23.6 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{14}N_2O_2$ [M^+H]: 207.1128 found 207.1121. The data matches that found in the literature.[158]

4-(pyrrolidin-1-ylmethyl)benzonitrile - **92**



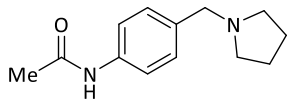
Followed general procedure 3.3.1 using 4-cyanobenzoic acid (147. mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as an orange oil (151 mg, 81%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.63 (d, J= 8.2 Hz, 2H, Ar-**H**),7.48 (d, J= 8.2 Hz, 2H, Ar-**H**), 3.69 (s, 2H, N-**CH₂**), 2.53 (br s, 4H, N-C**H₂**-CH_2), 1.83 (tt, J= 3.3, 3.3 Hz, 4H, N-CH_2-C**H₂**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 145.2 (C), 132.1 (CH), 129.3 (CH), 119.0 (C), 110.7 (C), 60.2 (CH_2), 54.2 (CH2), 23.5 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{14}N_2$ [M^+H]: 187.1230 found 187.1235. The data matches that found in the literature.[232]

4-(pyrrolidine-1-ylmethyl)piperidine - **93**



Followed general procedure 3.3.1 using pyridine-4-carboxylic acid (123 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as a red oil (153 mg, 94%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 8.54 (d, J= 4.9 Hz, 2H, Ar-**H**), 7.27 (d, J= 4.9 Hz, 2H, Ar-**H**), 3.62 (s, 2H, N-C**H₂**), 2.52 (br s, 4H, N-C**H₂**-CH_2), 1.85-1.79 (m, 4H, N-CH_2-C**H₂**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 149.7 (CH), 148.6 (C), 123.6 (CH), 59.4 (CH_2), 54.2 (CH_2), 23.5 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{10}H_{14}N_2$ [M^+H]: 163.1230 found 163.1235. The data matches that found in the literature.[233]

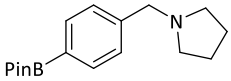
[4-(pyrrolidin-1-ylmethyl)phenyl]acetamide - **94**



Followed general procedure 3.3.1 using 4-acetamidobenzoic acid (179 mg, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) and purified by column chromatography (90:9:1 EtOAc: MeOH: NH_4OH) to afford the title product as a yellow oil as a 4:1 inseparable mixture of diamide (180.9 mg, 83%); R.f.: 0.13

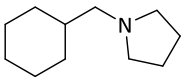
(90:1:9 EtOAc: MeOH: NH_4OH) **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.46 (d, J= 8.2 Hz, 2H, Ar-**H**), 7.30 (d, J= 8.2 Hz, 2H, Ar-**H**), 3.59 (s, 2H, N-C**H$_2$**), 2.51 (t, J= 6.9 Hz, 4H, N-C**H$_2$**-CH_2), 2.18 (s, 3H, C**H$_3$**-C=O), 1.86-1.75 (m, 4H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 168.3 (C), 130.2 (C), 129.5 (CH), 119.8 (CH), 115.0 (C), 60.2 (CH_2), 54.9 (CH_2), 24.6 (CH_3), 23.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{18}N_2O_1$ [M^+H]: 219.1492 found 219.1484; **IR** vmax/cm^{-1} (ATR): 3305, 2964, 2874, 2971, 1597, 1537, 1514, 1410, 1371, 1345, 1318, 1264, 1176, 11234, 1070, 1018.

1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)benzyl)pyrrolidine - **95**



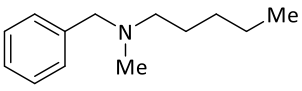
Followed general procedure 3.3.1 using 4-carboxylic phenylboronic acid pinacol ester (248 µL, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) and purified by column chromatography (98:1.8:0.2 DCM: MeOH: NH_4OH) to afford the title product as an orange oil as a 3:1 inseparable mixture with pinacol (206 mg, 72%); **R.f.:** 0.10 (98:1.8:0.2 DCM: MeOH: NH_4OH); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.79 (d, J= 7.8 Hz, 2H, Ar-**H**), 7.36 (d, J= 7.8 Hz, 2H, Ar-**H**), 3.65 (s, 2H, N-C**H$_2$**), 2.52 (br s, 4H, N-C**H$_2$**-CH_2), 1.78 (tt, J= 4.0, 4.0 Hz, 4H, N-CH_2-C**H$_2$**), 1.36 (s, 12H, C-C**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 142.3 (C), 134.8 (CH), 128.3 (CH), 127.5 (C), 83.7 (C), 60.7 (CH_2), 54.0 (CH_2), 24.9 (CH_3), 23.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{17}H_{27}N_1B_1O_2$ [M^+H]: 288.2129 found 288.2133. The data matches that found in the literature.[234]

1-(cyclohexylmethyl)pyrrolidine - **96**



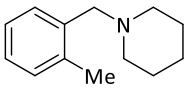
Followed general procedure 3.3.1 using cyclohexane carboxylic acid (119 µL, 1.00 mmol) and pyrrolidine (83.5 µL, 1.00 mmol) to afford the title product as a yellow oil (92.1 mg, 55%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 2.48 (br s, 4H, H_2C-C**H$_2$**), 2.27 (d, J= 7.2 Hz, 2H, N-C**H$_2$**), 1.86-1.63 (m, 9H, H_2C-C**H$_2$**, CH_2-C**H$_2$**-C**H$_2$**), 1.54-1.42 (m, 1H, C**H**), 1.32-1.11 (m, 3H, N-CH_2-C**H$_2$**), 0.97-0.84 (m, 2H, CH-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 64.0 (CH_2), 54.6 (CH_2), 37.1 (CH), 32.0 (CH_2), 26.8 (CH_2), 26.2 (CH_2), 24.6 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{21}N_1$ [M^+H]: 168.1747 found 168.1736. The data matches that found in the literature.[235]

N-pentyl-*N*-methylbenzenemethanamine – **97**



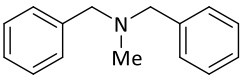
Followed general procedure 3.3.1 using benzoic acid (122 mg, 1.00 mmol) and *N*-methyl pentylamine (137 µL, 1.00 mmol) to afford the title product as a pale yellow oil (168 mg, 88%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.37-7.32 (m, 4H, Ar-**H**), 7.30-7.25 (m, 1H, Ar-**H**), 3.52 (s, 2H, N-C**H$_2$**), 2.40 (t, J= 7.8 Hz, 2H, N-C**H$_2$**-CH_2), 2.22 (s, 3H, N-C**H$_3$**), 1.56 (pent, J= 6.8 Hz, 2H, **H$_2$**C-CH_2), 1.40-1.28 (m, 4H, H_2C-C**H$_2$**), 0.93 (t, J= 6.3 Hz, 3H, H_2C-C**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 139.3 (C), 129.1 (CH), 128.2 (CH), 126.9 (CH), 62.4 (CH_2), 57.6 (CH_2), 42.3 (CH_3), 29.7 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{22}N_1$ [M^+H]: 192.1747 found 192.1748; **IR** vmax/cm^{-1} (ATR): 3028, 2930, 2859, 2785, 1494, 1453, 1365, 1292, 1252, 1162, 1131, 1074, 1018.

1-(2-methylbenzyl)piperidine - **98**



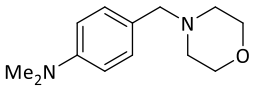
Followed general procedure 3.3.1 using 2-methyl benzoic acid (204 mg, 1.50 mmol) and piperidine (98.8 µL, 1.00 mmol) to afford the title product as an orange oil (184 mg, 97%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.33-7.29 (m, 1H, Ar-**H**), 7.19- 7.13 (m, 3H, Ar-**H**), 3.45 (s, 2H, N-C**H_2**), 2.42 (br s, 4H, N-C**H_2**-CH_2), 2.38 (s, 3H, Ar-C**H_3**), 1.59 (tt, J= 5.8, 5.8 Hz, 4H, N-CH_2-C**H_2**), 1.49- 1.43 (m, 2H, H_2C-C**H_2**-CH_2) ; **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 137.4 (C), 137.1 (C), 130.2 (CH), 129.7 (CH), 126.8 (CH), 125.4 (CH), 61.5 (CH_2), 54.7 (CH_2), 26.2 (CH_2), 24.6 (CH_2), 19.3 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{20}N$ [M^+H]: 190.1590 found 190.1581. The data matches that found in the literature.[227]

N-benzyl-*N*-methyl-1-phenylmethanamine - **99**



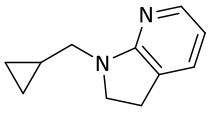
Method 1: Followed general procedure 3.3.1 using benzoic acid (183 mg, 1.50 mmol) and *N*-benzyl methylamine (129 µL, 1.00 mmol) to afford the title product as a pale yellow oil (209 mg, 99%);
Method 2: Followed general procedure 3.1.3 using formic acid (55.5 µL, 1.50 mmol) and dibenzylamine (192 µL, 1 mmol) to afford the title product as a pale yellow oil (210 mg, 99%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.47-7.25 (m, 10H, Ar-**H**), 3.56 (s, 4H, N-C**H_2**), 2.22 (s, 3H, N-C**H_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 139.5 (C), 129.0 (CH), 128.3 (CH), 127.0 (CH), 62.0 (CH_2), 42.4 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{15}H_{18}N$ [M^+H]: 212.1434 found 212.1435. The data matches that found in the literature.[236]

N,N-dimethyl-4-(morpholinomethyl)aniline - **100**



Followed general procedure 3.3.1 using 4-(dimethylamino)benzoic acid (248 mg, 1.50 mmol) and morpholine (87.3 µL, 1.00 mmol) and purified by column chromatography (98:2 DCM: MeOH) to afford the title compound as a pale yellow oil (109 mg, 50%); **R.f.**: 0.33 (98:2 DCM: MeOH); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.20 (d, J= 8.7 Hz, 2H, Ar-**H**; 6.72 (d, J= 8.7 Hz, 2H, Ar-**H**), 3.72 (t, J= 5.5 Hz, 4H, O-C**H_2**-CH_2), 3.44 (s, 2H, N-C**H_2**), 2.96 (s, 6H, N-(C**H_3**)$_2$), 2.45 (br s, 4H, N-C**H_2**-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 149.9 (C), 130.3 (CH), 125.3 (C), 112.4 (CH), 67.1 (CH_2), 60.3 (CH_2), 53.5 (CH_2), 40.7 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{20}N_2O_1$ [M^+H]: 221.1648 found 221.1651; **IR** vmax/cm^{-1} (ATR): 2954, 2890, 2799, 1614, 1567, 1520, 1479, 1453, 1394, 1345, 1284, 1264, 1221, 1186, 1162, 1114, 1069, 1034, 1004.

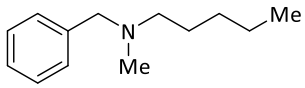
1-(cyclopropylmethyl)-2,3-dihydro-1H-pyrrolo[2,3-b]pyridine – **101**



Following general procedure 3.3.1 using cyclopropane carboxylic acid (119 µL, 1.50 mmol) and 7-azaindoline (120 mg, 1.00 mmol) and purified by flash column chromatography (9:1 pentane: EtOAc) to afford the title product as a yellow oil (117 mg, 67%); **R.f.:** 0.5 (9:1 pentane: EtOAc); **^{1}H NMR:** (400

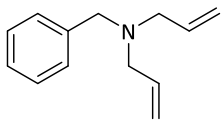
MHz, $CDCl_3$) δH 7.83 (d, J= 5.4 Hz, 1H, Ar-**H**), 7.14 (dd, J= 6.9, 1.4 Hz, 1H, Ar-**H**), 6.38 (dd, J= 6.9, 5.4 Hz, 1H, Ar-**H**), 3.58 (t, J= 8.44 Hz, 2H, N-C**H₂**-CH_2), 3.23 (d, J= 6.83 Hz, 2H, N-C**H₂**), 2.95 (t, J= 6.83 Hz, 2H, N-CH_2-C**H₂**), 1.06-0.99 (m, 1H, N-CH_2-C**H**), 0.56-0.48 (m, 2H, C**H₂**-CH_2), 0.26-0.21 (m, 2H, CH_2-C**H₂**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 163.3 (C), 145.7 (CH), 130.6 (CH), 123.0 (C), 111.9 (CH_2), 50.2 (CH_2), 49.7 (CH_2), 29.7 (CH), 26.0 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{14}N_2$ [M^+H]: 175.1230 found; 175.1229; **IR** vmax/cm^{-1} (ATR): 3075, 2999, 2905, 2845, 1610, 1576, 1496, 1463, 1444, 1382, 1326, 1286, 1267, 1243, 1190, 1169, 1143, 1104, 1086, 1047, 1016.

N-pentyl-*N*-methylbenzenemethanamine – **102**



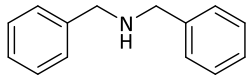
Followed general procedure 3.3.1 using valeric acid (163 µL, 1.50 mmol) and *N*-methyl benzylamine (130 µL, 1.00 mmol) and purified by flash column chromatography (19:1 pentane: EtOAc) to afford the title product as a pale-yellow oil; (155 mg, 81%); **R.f.:** 0.22 (19:1 pentane: EtOAc); data matches that shown above for this compound.

diallylbenzylamine - **103**



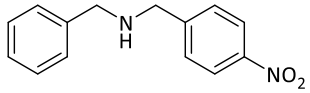
Followed general procedure 3.3.1 using benzoic acid using benzoic acid (183 mg, 1.50 mmol) and diallylamine (123 µL, 1.00 mmol) to afford the title product as an orange oil (159 mg, 85%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.38-7.22 (m, 5H, Ar-**H**), 5.97-5.83 (m, 2H, N-CH_2-C**H**=CH_2), 5.26- 5.14 (m, 4H, N-CH_2-CH=C**H₂**), 3.60 (s, 2H, Ar-C**H₂**-N), 3.10 (dt, J= 6.4, 1.4 Hz, 4H, N-C**H₂**-CH=CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 139.5 (C), 135.9 (CH), 128.9 (CH), 128.2 (CH), 126.8 (CH), 117.4 (CH_2), 57.5 (CH_2), 56.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{18}N$ [M^+H]: 188.1434 found 188.1434. The data matches that found in the literature.[237]

dibenzylamine – **79**



Followed general procedure 3.3.2 using benzoic acid (183 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) to afford the title product as a pale yellow oil (157 mg, 79%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.40-7.33 (m, 8H, Ar-**H**), 7.31-7.25 (m, 2H, Ar-**H**), 3.85 (s, 4H, **H₂**C-N-C**H₂**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 140.4 (C), 128.5 (CH), 128.2 (CH), 127.0 (CH), 53.3 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{14}H_{15}N$ [M^+H]: 198.1279 found 198.1277; The data matches that found in the literature. [208]

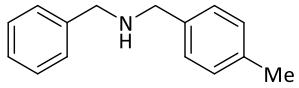
benzyl(4-nitrobenzyl)amine - **104**



Followed general procedure 3.3.2 using 4-nitrobenzoic acid (251 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) and purified by flash column chromatography to afford the title product (2:1 pentane: EtOAc) as a pale yellow oil (155 mg, 64%); **R.f.:** 0.27 (2:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 8.21 (d, J= 8.8 Hz, 2H, Ar-**H**), 7.56 (d, J= 8.7 Hz, 2H, Ar-**H**), 7.38- 7.36 (m, 4H, Ar-**H**),

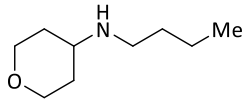
7.32- 7.28 (m, 1H, Ar-**H**), 3.94 (s, 2H, Ar-C**H₂**-N), 3.84 (s, 2H, Ar-C**H₂**-N), 1.71 (s, 1H, N**H**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 148.2 (C), 147.1 (C), 139.8 (C), 128.7 (CH), 128.5 (CH), 128.1 (CH), 127.2 (CH), 123.6 (CH), 53.3 (C**H₂**), 52.3 (C**H₂**); **HRMS** (ESI-TOF) m/z calc'd $C_{14}H_{15}N_2O_2$ [M^+H]: 243.1128 found 243.1131; The data matches that found in the literature.[158]

benzyl(4-methylbenzyl)amine – **105**



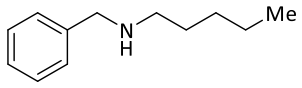
Followed general procedure 3.3.2 using 4-methylbenzoic acid (204.2 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) to afford the title product as a pale yellow oil (145 mg, 69%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.40- 7.33 (m, 5H, Ar-**H**), 7.31- 7.23 (m, 4H, Ar-**H**), 7.19- 7.12 (m, 2H, Ar-**H**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 140.5 (C), 137.3 (C), 136.5 (C), 129.1 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 126.9 (C_H), 53.2 (CH_2), 52.9 (CH2), 21.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{15}H_{18}N$ [M^+H]: 212.1434 found 212.1439; The data matches that found in the literature.[182]

N-butyl-*N*-(tetrahydro-2H-pyran-4-yl)-amine – **106**



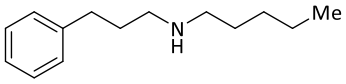
Followed general procedure 3.3.2 using butanoic acid (137 µL, 1.50 mmol) and 4-aminotetrahydropyran (104 µL, 1.00 mmol) and purified by flash column chromatography (95:4.5:0.5 DCM: MeOH: NH_4OH) to afford the title product as a pale yellow oil (150 mg, 94%); **R.f.:** 0.25 (95:4.5:0.5 DCM: MeOH: NH_4OH); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 3.99 (dt, J= 11.2, 3.2 Hz, 2H, O-C**H₂**-CH_2), 3.42 (td, J= 11.7, 2.1 Hz, 2H, O-C**H₂**-CH_2), 2.74- 2.60 (m, 3H, NH-C**H**, N-C**H₂**-CH_2-CH_2-CH_3), 1.91-1.79 (m, 2H, O-CH_2-C**H₂**), 1.57- 1.27 (m, 6H, O-C**H₂**-CH_2, N-CH_2-C**H₂**-C**H₂**-CH_3), 0.94 (t, J= 7.3 Hz, 3H, N-CH_2-CH_2-CH_2-C**H₃**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 66.7 (CH_2), 54.1 (CH), 46.3 (CH_2), 33.9 (CH_2), 32.6 (CH_2), 20.6 (CH_2), 14.0 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_9H_{20}NO$ [M^+H]: 158.1539 found 158.1542; **IR** vmax/cm^{-1} (ATR): 2955, 2929, 2841, 1466, 1364, 1299, 1236, 1171, 1145, 1118, 1087, 1011

N-benzyl-*N*-pentylamine – **107**



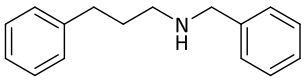
Followed general procedure 3.3.2 using valeric acid (163 µL, 1.50 mmol) and benzylamine (109 µL, 1 mmol) to afford the title product as a pale yellow oil (147 mg, 83%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.37-7.23 (m, 5H, Ar-H), 3.81 (s, 2H, Ar-C**H₂**-N); 2.65 (t, J= 7.3 Hz, 2H, N-C**H₂**-CH_2), 1.54 (tt, J= 7.3, 7.3 Hz, 2H, N-CH_2-C**H₂**), 1.39-1.26 (m, 4H, C**H₂**-C**H₂**), 0.92 (t, J= 7.01 Hz, 3H, CH_2-C**H₃**);**^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 140.7 (C), 128.4 (CH), 128.1 (CH), 126.9 (CH), 54.2 (CH_2), 49.6 (CH_2), 29.9 (CH_2), 29.6 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{20}N$ [M^+H]: 178.1590 found 178.1590. The data matches that found in the literature.[238]

N-pentyl-3-phenylpropylamine - **108**



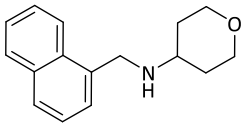
Followed general procedure 3.3.2 using valeric acid (163 µL, 1.50 mmol) and 3-phenyl-1-propylamine (142 µL, 1.00 mmol) to afford the title product as an orange oil (151 mg, 73%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.33-7.27 (m, 2H, Ar-**H**), 7.23-7.17 (m, 3H, Ar-**H**), 2.71-2.57 (m, 6H, C**H$_2$**-CH_2), 1.84 (tt, J= 7.5 7.5 Hz, 2H, C**H$_2$**-CH_2), 1.50 (tt J= 6.8, 6.8 Hz, 2H, CH_2-C**H$_2$**), 1.39-1.25 (m, 4H, C**H$_2$**-CH_3), 0.92 (t, J= 6.8, CH_2-C**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 142.2 (C), 128.4 (CH), 128.3 (CH), 125.8 (CH), 50.1 (CH_2), 49.6 (CH_2), 33.8 (CH_2), 31.8 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.63 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{14}H_{23}N$ [M^+H]: 206.1903 found 206.1903. The data matches that found in the literature. [239]

benzyl-(3-phenyl-propyl)-amine - **109**



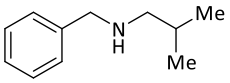
Followed general procedure 3.3.2 using benzoic acid (183 µL, 1.50 mmol) and 3-phenyl-1-propylamine (142 µL, 1.00 mmol) to afford the title product as a pale yellow oil (123 mg, 55%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.44-7.20 (m, 10H, Ar-**H**), 3.48 (s, 2H, N-C**H$_2$**), 2.77-2.68 (m, 4H, Ar-C**H$_2$**, N-C**H$_2$**-CH_2), 1.90 (tt, J= 8.0, 8.0 Hz, 2H, CH_2-C**H$_2$**), 1.33 (br s, 1H, N**H**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 142 (C), 141 (C), 128.5 (CH), 128.4 (CH), 128.4 (CH), 128.2 (CH), 54.1 (CH_2), 49.0 (CH_2), 33.7 (CH_2), 31.8 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{16}H_{20}N$ [M^+H]: 226.1590 found 226.1587. The data matches that found in the literature.[240]

N-(naphthalen-1-ylmethyl)oxan-4-amine – **110**



Followed general procedure 3.3.2 using napthoic acid (258 mg, 1.50 mmol) and 4-aminotetrahydropyran (104 µL, 1.00 mmol) to afford the title compound as a yellow oil (205 mg, 85%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 8.16 (d, J= 8.9 Hz, 1H, Ar-H), 7.90 (d, J= 7.6 Hz, Ar-H), 7.80 (d, J= 7.6 Hz, Ar-**H**), 7.59-7.43 (m, 4H, Ar-**H**), 4.29 (s, 2H, Ar-C**H$_2$**-N), 4.03 (td, J= 11.7, 3.6 Hz, 2H, O-C**H$_2$**-CH_2), 3.46 (td, J= 11.7, 2.2 Hz, 2H, O-C**H$_2$**-CH_2), 2.92-2.80 (m, 1H, N-C**H**), 1.99-1.89 (m, 2H, CH-C**H$_2$**-CH_2), 1.61-1.48 (m, 2H, CH-C**H$_2$**-CH_2), 1.35 (br s, 1H, N**H**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 136.1 (C), 134.0 (C), 131.6 (C), 128.8 (CH), 127.8 (CH), 126.2 (CH), 126.1 (CH), 125.7 (CH), 125.5 (CH), 123.7 (CH), 66.9 (CH_2), 54.0 (CH), 48.4 (CH_2), 33.8 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{16}H_{20}NO$ [M^+H]: 242.1531 found 242.1539; **IR** νmax/cm^{-1} (ATR): 3306, 3045, 2934, 2841, 1653, 1597, 1510, 1465, 1384, 1362, 1314, 1300, 1235, 1167, 1138, 1089, 1011.

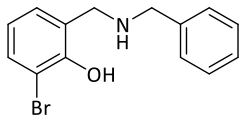
benzyl(2-methylpropyl)amine – **111**



Followed general procedure 3.3.2 using isobutyric acid (125 µL, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) to afford the title product as a pale yellow oil (153 mg, 94%); **^{1}H NMR:** (400 MHz, $CDCl_3$)

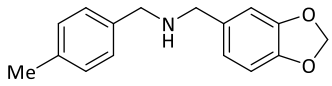
δH 7.38-7.22 (m, 5H, Ar-**H**), 3.81 (s, 2H, Ar-C**H₂**-N), 2.47 (d, J= 6.7 Hz, 2H, N-C**H₂**-CH), 1.87-1.73(m, 1H, C**H**-(CH_3)$_2$), 0.94 (d, J= 6.6 Hz, 6H, C**H₃**-CH); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 140.7 (C), 128.4 (CH), 128.1 (CH), 126.8 (C), 57.5 (CH_2), 54.1 (CH_2), 28.4 (CH), 20.7 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{18}N$ [M^+H]: 164.1434 found 164.1438. The data matches that found in the literature.[241]

2-((benzylamino)methyl)-6-bromophenol - **112**



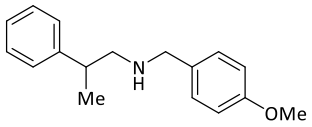
Followed a modified general procedure 3.3.2 using 3-bromo-2-hydroxybenzoic acid (326 mg, 1.50 mmol), benzylamine (109 µL, 1.00 mmol) and phenylsilane (247 µL, 2.00 mmol) for the amidation step and purified by flash column chromatography (9:1 pentane: EtOAc) to afford the title compound as a pale yellow oil (179 mg, 61%); **R.f.:** 0.17 (9:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.52-7.25 (m, 6H, Ar-**H**), 6.95 (d, J= 8.4 Hz, 1H, Ar-**H**), 6.69 (dd, J= 8.6, 8.6 Hz, 1H, Ar-**H**), 4.01 (s, 2H, Ar-C**H₂**-N), 3.83 (s, 2H, N-C**H₂**-Ar); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) 155.0 (C), 137.8 (C), 132.2 (CH), 128.9 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 123.5 (C), 119.9 (), 110.5 (C), 52.6 (CH_2), 51.7 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{14}H_{15}NOBr$ [M^+H]: 292.0323 found 292.0332; The data matches that found in the literature.[158]

1-(benzo[d][1,3]dioxol-5-yl)-*N*-(4-methylbenzyl)methanamine - **113**



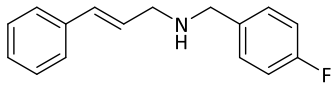
Followed general procedure 3.3.2 using *p*-toluic acid (204 mg, 1.50 mmol) and piperonylamine (124 µL, 1.00 mmol) to afford the title compound as an orange oil (150 mg, 59%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.25 (d, J= 7.8 Hz, 2H, Ar-**H**), 7.17 (d, J= 7.8 Hz, 2H, Ar-**H**), 6.89 (s, 1H, Ar-**H**), 6.82-6.77 (m, 2H, Ar-**H**), 5.96 (s, 2H, O-C**H₂**-O), 3.78 (s, 2H, Ar-C**H₂**-N), 3.74 (s, 2H, N-C**H₂**-Ar), 2.38 (s, 3H, C**H₃**-Ar); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) 147.7 (C), 146.5 (C), 137.3 (C), 136.5 (C), 134.4 (C), 129.1 (CH), 128.1 (CH), 121.2 (CH), 108.7 (CH), 108.1 (CH), 100.1 (CH_2), 52.9 (CH_2), 52.7 (CH_2), 21.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{16}H_{18}NO_2$ [M^+H]: 256.1332 found 256.1334; The data matches that found in the literature.[242]

N-(4-methoxybenzyl)-2-phenylpropan-1-amine – **114**



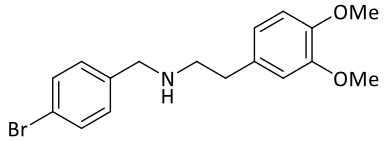
Followed general procedure 3.3.2 using 2-phenylpropanoic acid (205 µL, 1.50 mmol) and 4-methoxybenzylamine (131 µL, 1.00 mmol) and purified by flash column chromatography (19:1 DCM:MeOH) to afford the title compound as a yellow oil (161 mg, 63%); **R.f.:** 0.29 (19:1 DCM:MeOH); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.37-7.13 (m, 7H, Ar-**H**), 6.88-6.83 (m, 2H, Ar-**H**), 3.81 (s, 3H, OC**H₃**), 3.72 (app. q, J= 12.9 Hz, 2H, N-C**H₂**-Ar), 2.99 (app. h, J= 7.2 Hz, 1H, C**H**-CH_2), 2.80 (d, J= 7.3 Hz, 2H, CH-C**H₂**), 1.28 (d, J= 7.9 Hz, 3H, C**H₃**-CH); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) 158.6 (C), 145.3 (C), 132.3 (C), 129.2 (CH), 128.6 (CH), 127.2 (CH), 126.4 (CH), 113.7 (CH), 56.2 (CH_2), 55.3 (CH_3), 53.2 (CH_2), 40.0 (CH), 20.2 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{17}H_{22}NO$ [M^+H]: 256.1696 found 256.1699; The data matches that found in the literature.[243]

N-[(4-fluorophenyl)methyl]-3-phenylprop-2-en-1-amine – **115**



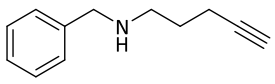
Followed general procedure 3.3.2 using trans-cinnamic acid (222 mg, 1.50 mmol), 4-fluorobenzoic acid (114 µL, 1 mmol) and purified by flash column chromatography (1:1 pentane: EtOAc) to afford the title compound as a pale yellow oil (163 mg, 67%); **R.f.:** 0.22 (1:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.42-7.39 (m, 2H, Ar-**H**), 7.37-7.33 (m, 4H, Ar-**H**), 7.29-7.25 (m, 1H, Ar-**H**), 7.05 (t, J= 8.96 Hz, Ar-**H**), 6.58 (d, J= 15.8 Hz, 1H, Ar-**H**C=CH), 6.35 (dt, J= 15.5, 6.3 Hz, 1H, Ar-HC=C**H**), 3.84 (s, 2H, N-C**H$_2$**-Ar), 3.46 (dd, J= 6.3, 1.4 Hz, 2H, N-C**H$_2$**-CH); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) 161.9 (d, J= 244.5 Hz, C), 137.1 (C), 136.0 (d, J= 2.90 Hz, C), 131.6 (CH), 129.7 (d, J= 8.4 Hz, CH), 128.6 (CH), 128.3 (CH), 126.3 (CH), 115.2 (d, J= 21.9 Hz, CH), 52.6 (CH_2), 51.2 (CH_2); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) δF -116.3 (F); **HRMS** (ESI-TOF) m/z calc'd $C_{16}H_{17}NF$ [M^+H]: 242.1340 found 242.1340; **IR** vmax/cm^{-1} (ATR): 3027, 2819, 1890, 1736, 1601, 1448, 1416, 1359, 1294, 1155, 1117, 1092, 1046, 1029, 1015

N-(4-bromobenzyl)-2-(3,4-dimethoxyphenyl)ethan-1-amine - **116**



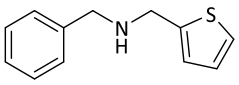
Followed general procedure 3.3.2 using 4-bromobenzoic acid (302 mg, 1.50 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine (169 µL, 1.00 mmol) to afford the title product as a yellow oil (284 mg, 81%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.43 (d, J= 8.4 Hz, 2H, Ar-**H**), 7.17 (d, J= 8.4 Hz, 2H, 2H, Ar-**H**), 6.83-6.70 (m, 3H, Ar-**H**), 3.87 (s, 6H, O-C**H$_3$**), 3.75 (s, 2H, Ar-C**H$_2$**-N), 2.86 (t, J= 6.4 Hz, 2H, C**H$_2$**-CH_2), 2.77 (t, J= 6.4 Hz, 2H, CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) 148.9 (C), 147.5 (C), 139.4 (C), 132.5 (C), 131.8 (CH), 129.7 (CH), 120.63 (C), 120.61 (CH), 111.9 (CH), 111.3 (CH), 55.9 (CH_3), 55.8 (CH_3), 53.2 (CH_2), 50.5 (CH_2), 35.9 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{17}H_{21}NO_2Br$ [M^+H]: 350.0750 found 350.0743; **IR** vmax/cm^{-1} (ATR): 3318, 3000, 2933, 2832, 2253. 2110, 1607, 1590, 1514, 1486, 1462, 1416, 1331, 1259, 1234, 1191, 1155, 1139, 1069, 1027, 1010

N-benzylpent-4-yn-1-amine - **117**



Followed general procedure 3.3.2 using 4-pentynoic acid (147 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) and purified by flash column chromatography (1:1 pentane: EtOAc) to afford the title compound as a yellow oil (97.8 mg, 56%); **R.f.:** 0.17 (1:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.37- 7.32 (m, 4H, Ar-**H**), 7.30- 7.24 (m, 1H, Ar-**H**), 3.82 (s, 2H, Ar-C**H$_2$**-N), 2.77 (t, J= 6.9 Hz, 2H, HN-C**H$_2$**-CH_2-CH_2-C≡CH), 2.30 (td, J= 7.1, 2.7 Hz, 2H, HN-CH_2-CH_2-C**H$_2$**-C≡CH), 1.97 (t, J= 2.7 Hz, 1H, HN-CH_2-CH_2-CH_2-C≡C**H**), 1.76 (tt, J= 7.1, 7.1 Hz, 2H, HN-CH_2-C**H$_2$**-CH_2-C≡CH); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) 140.5 (C), 128.4 (CH), 128.1 (CH), 126.9 (CH), 84.2 (C), 68.5 (CH), 54.0 (CH_2), 48.2 (CH_2), 28.8 (CH_2), 16.3 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{18}H_{28}NO_3$ [M^+H]: 306.2064 found 306.2057; The data matches that found in the literature.[241]

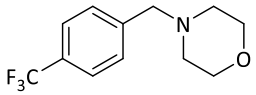
N-benzyl-1-(thiophen-2-yl)methanamine – **118**



Followed general procedure 3.3.2 using thiophene-2-carboxylic acid (192 mg, 1.50 mmol) and benzylamine (109 µL, 1.00 mmol) and purified by flash column chromatography (4:1 pentane: EtOAc) to afford the title compound as a colourless oil (93.8 mg, 46%); **R.f.:** 0.29 (4:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.41-7.35 (m, 4H, Ar-**H**), 7.33-7.27 (m, 1H, Ar-**H**), 7.27-7.23 (m, 1H, Ar-**H**), 7.01-6.95 (m, 2H, Ar-**H**), 4.04 (s, 2H, Ar-C**H$_2$**-N), 3.88 (s, 2H, N-C**H$_2$**-Ar); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) 144.2 (C), 140.0 (C), 128.5 (CH), 128.2 (CH), 127.1 (CH), 126.7 (CH), 124.9 (CH), 124.4 (CH), 52.8 (CH_2), 47.6 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{14}NS$ [M^+H]: 204.0841 found 204.0843; The data matches that found in the literature.[244]

3.3.4 Large-scale Synthesis

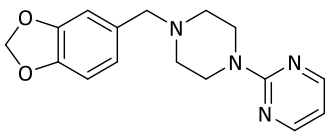
4-(4'-trifluoromethyl-benzyl)morpholine – **73**



To a solution of 4-(Trifluoromethyl)benzoic acid (19.0 g, 100 mmol) in toluene (120 mL) at 90 ^{o}C, was added phenylsilane (12.3 mL, 100 mmol) followed by morpholine (8.70 mL, 100 mmol) by syringe pump (~1.75 mL/min) and maintained at 90 ^{o}C for 18 hours. $PhSO_3H$ (27.5 g, 175 mmol) was added portionwise followed by $PhSiH_3$ (24.7 mL, 200 mmol) by syringe pump (~2.00 mL/min) and maintained at 90 ^{o}C for a further 24 hours. The reaction mixture was cooled to room temperature and decanted from the reaction vessel and the reactor was washed with toluene (50 mL) and was added to the reaction solution. Et_2O (250 mL) was added to the reaction mixture stirred for 1 hour the precipitate was collected by filtration. The remaining solution was concentrated *in vacuo* and added to Et_2O (250 mL), stirred for 1 hour and the precipitate was collected by filtration and combined with the first crop of solid to achieve the benzene sulfonic acid salt. The salt was taken up in DCM (200 mL) and NaOH (200 mL of a 6M aqueous solution) was added and stirred at room temperature for 4 hours and the aqueous layer was washed with DCM (3 x 100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo to afford the title product as an orange oil (13.8 g, 56%); data matches that shown above for this compound.

3.4 Pharmaceutical Synthesis

3.4.1 Piribedil - 122



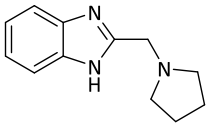
Followed general procedure 3.3.1 using 1-(2-pyrimidyl piperazine (164 mg, 1.00 mmol) and piperonylic acid (166 mg, 1.00 mmol) to achieve the title product as an off-white powder (231.2 mg, 71%); **M.P:** 164-166 °C (lit: 162-163.5 °C[244]); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 8.31 (t, d= 4.7 Hz, 2H, Ar-**H**), 6.91 (s, 1H, Ar-**H**), 6.78 (s, 2H, Ar-H), 6.48 (t, J= 4.7 Hz, 1H, Ar-**H**), 5.97 (s, 2H, O-C**H$_2$**-O), 3.84 (t, J= 4.2 Hz, 4H, N-C**H$_2$**-CH_2-N), 3.47 (s, 2H, N-C**H$_2$**), 2.50 (t, J= 4.9 Hz, 4H, N-CH_2-C**H$_2$**-N); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 161.7 (C), 157.7 (CH), 147.7, (C), 146.7 (C), 131.9 (C), 122.2 (CH), 109.8 (CH), 109.5 (CH), 107.9 (CH), 100.9 (CH_2), 62.9 (CH_2), 52.9 (CH_2), 43.7 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{15}H_{11}F_3NO$ [M^-H] 278.0798

found 278.0802. The data matches that found in the literature.[244]

N.B – This reaction carried out on a 1.00 mmol scale using non dry glassware and Winchester grade solvent afforded the title product at 66% yield

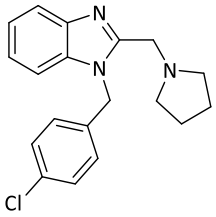
3.4.2 Clemizole

2-(pyrrolidin-1-ylmethyl)-1H-benzimidazole – **130**



Followed general procedure 3.3.1 using pyrrolidine (83.5 µL, 1.00 mmol) and (1H-Benzimidazole-2-carboxylic acid (243 mg, 1.00 mmol) and was purified by flash column chromatography (97:3 DCM: MeOH) to afford the title product as an off white powder (129 mg, 64%); **M.P:** 141-142 °C (lit: 140-142 °C)[245]; **R.f.**: 0.19 (19:1 DCM: MeOH); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.32-7.21 (m, 4H, Ar-H), 4.00 (s, 2H, Ar-CH_2-N), 2.73-2.65 (m, 4H, N-C**H_2**-CH_2), 1.92-1.83 (m, 4H, N-CH_2-C**H_2**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 152.7 (CH), 140.5 (C), 122.8 (C), 122.4 (CH), 54.5 (CH_2), 53.9 (CH_2), 23.8 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{15}N_3$ [M^+H] 202.1339 found 202.1335. The data matches that found in the literature.[245]

Clemizole – **128**



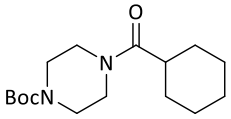
To a solution of **130** (101 mg, 0.500 mmol) in THF (1.50 mL) at 0 °C, was added NaH (30.0 mg of a 60% wt dispersion in mineral oil, 0.750 mmol) and warmed to r.t and stirred for 5 minutes. 4-chlorobenzylbromide (18.0 mg, 0.550 mmol) and tetrabutylammonium iodide (18.0 mg, 0.0500 mmol) was added and stirred at r.t for 16 hours. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by flash column chromatography (100% EtOAc) to afford the title product as a white solid (106 mg, 65%, 0.324 mmol); **M.P:** 102-103 °C (lit: 101-102°C)[245]; **R.f.**: 0.24 (100% EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.79 (d, J= 7.6 Hz, 1H, Ar-**H**), 7.32-7.21 (m, 6H, Ar-**H**), 7.06 (d, J= 8.5 Hz, 2H, Ar-**H**), 5.57 (s, 2H, Ar-C**H_2**-Ar), 3.88 (s, 2H, Ar-C**H_2**-N), 2.63-2.50 (m, 4H, N-C**H_2**-C**H_2**), 1.83-1.70 (m, N-C**H_2**-C**H_2**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 152.4 (C), 142.4 (C), 135.8 (C), 135.3 (C), 133.5 (C), 128.9 (CH), 127.9 (CH), 127.3 (CH), 122.8 (CH), 122.1 (CH), 119.9 (CH), 109.6 (CH), 54.2 (CH_2), 53.2 (CH_2), 46.7 (CH_2), 23.7 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{19}H_{20}N_3Cl$ [M^+H] 326.1419 found 326.1419. The data matches that found in the literature.[245]

3.5 Complex Compound Synthesis

3.5.1 Unsymmetrical Diamines

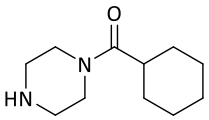
1-(cyclohexylmethyl)-4-(4-fluorobenzyl)piperazine Synthesis

tert-butyl 4-(cyclohexanecarbonyl)piperazine-1-carboxylate – **135**



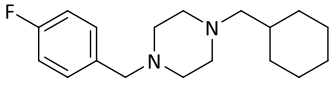
Followed phenylsilane amidation (**74**) using cyclohexanecarboxylic acid (192 mg, 1.50 mmol) and 1-Boc-piperazine (186 mg, 1.00 mmol) and purified by flash column chromatography (3:2 pentane: EtOAc) to afford the title compound as colourless crystals (196 mg, 66%); **M.P:** 144-145 °C; **R.f.**: 0.10 (3:2 pentane: EtOAc); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 3.64-3.35 (m, 8H, N-C**H_2**-C**H_2**-N), 2.47 (tt, J= 11.9, 3.31 Hz, 1H, CO-C**H**), 1.88-1.78 (m, 2H, CH_2-C**H_2**), 1.76-1.67 (m, 3H, CH-C**H_2**), 1.61-1.52 (m, 2H, CH_2-C**H_2**), 1.49 (s, 9H, C-(C**H_3**)$_3$), 1.36-1.19 (m, 3H, CH_2-C**H_2**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 175.0 (C), 155.0 (C), 80.3 (C), 45.2 (CH_2), 41.4 (CH_2), 40.5 (CH), 29.4 (CH_2), 28.4 (CH_3), 25.8 (CH_2), 25.8 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{16}H_{29}N_2O_3$ [M^+H] 297.2173 found 297.2172; **IR** vmax/cm^{-1} (ATR): 2944, 2843, 1909, 1591, 1502, 1465, 1391, 1304, 1225, 1191, 1163, 1122, 1070, 1017

cyclohexyl(piperazin-1-yl)methanone - **136**



To a solution of **135** (298 mg, 1.00 mmol) in DCM (2.50 mL) at 0 ^{o}C, was added trifluoracetic acid (0.500 mL, 6.50 mmol) dropwise. The reaction mixture was warmed to room temperature and stirred for 3h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in DCM (20 mL) and washed with NaHCO3 (20 mL). The aqueous layer was washed with DCM (2x20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to form an off-white solid (173 mg, 88%); **M.P:** 79-80 °C; **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 3.68 (br s, 2H, N-C**H_2**-CH_2-N), 3.75 (br s, 2H, N-C**H_2**-CH_2-N), 2.94 (br s, 4H, N-CH_2-C**H_2**-N), 2.46 (tt, J= 11.6, 3.5 Hz, 1H, CO-C**H**), 1.88-1.78 (m, 2H, C**H_2**-CH_2), 1.77-1.65 (m, 3H, C**H_2**-CH_2), 1.61-1.47 (m, 2H, CH_2-C**H_2**), 1.37-1.17 (m, 3H, CH_2-C**H_2**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) 174.6 (C), 45.9 (CH_2), 45.4 (CH_2), 41.6 (CH_2), 40.3 (CH), 29.4 (CH_2), 25.8 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{21}N_2O$ [M^+H] 197.1658 found 197.1644; **IR** vmax/cm^{-1} (ATR): 3319, 3012, 2932, 2852, 2811, 2792, 2739, 1622, 1477, 1437, 1364, 1336, 1318, 1298, 1281, 1261, 1247, 1217, 1198

1-(cyclohexylmethyl)-4-(4-fluorobenzyl)piperazine synthesis – **137**

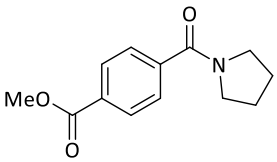


To a solution of 4-fluorobenzoic acid (105, 0.750 mmol) in dry toluene (0.600 mL) at reflux, was added phenylsilane (61.5 µL, 0.500 mmol) followed by amine **136** (148 mg, 0.500 mmol) portionwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (394 mg, 2.50 mmol) and phenylsilane (245 µL, 2.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with HCl (0.500 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (5 mL) and extracted with HCl (3 x 5 mL of a 3 M aqueous

solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and the crude product was purified by flash column chromatography (1:1 pentane: EtOAc) to afford the title product as a pale yellow oil (134 mg, 69%, 0.461 mmol); **R.f.**: 0.41 (1:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.33-7.26 (m, 2H, Ar-**H**), 7.01 (dd, J= 8.6, 8.6 Hz, 2H, Ar-**H**), 3.50 (s, 2H, N-C**H$_2$**-Ar), 2.68-2.13 (m, 9H, C**H$_2$**-CH_2), 1.83-1.64 (m, 5H, C**H$_2$**-CH_2), 1.51 (br s, 1H, N-CH_2-C**H**), 1.38-1.10 (m, 4H, C**H$_2$**-CH_2), 0.98-0.79 (m, 2H, C**H$_2$**-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 163.2 (C), 160.8 (C), 130.7 (d, J= 8.6 Hz, CH), 115.0 (d, J= 21.9 Hz, CH), 65.5 (CH_2), 62.2 (CH_2), 53.5 (CH_2), 52.7 (CH_2), 34.9 (CH), 32.0 (CH_2), 26.7 (CH_2), 26.1 (CH_2); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) δF -116.0 (F); **HRMS** (ESI-TOF) m/z calc'd $C_{18}H_{28}N_2F$ [M^+H]: 291.2231 found 291.2227; **IR** νmax/cm^{-1} (ATR): 2939, 2917, 2847, 2764, 2668, 1892, 1600, 1506, 1450, 1416, 1380, 1360, 1345, 1333, 1312, 1291, 1273, 1220, 1189, 1153, 1128, 1089, 1009

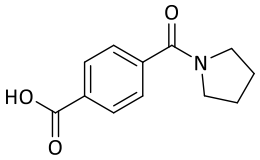
***N*-methyl-*N*-(4-(pyrrolidin-1-ylmethyl)benzyl)pentan-1-amine**

methyl 4-(pyrrolidine-1-carbonyl)benzoate - **139**



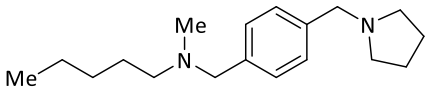
Followed phenylsilane amidation (**74**) using, mono-methyl terephthalate 180 mg, 1.00 mmol) and pyrrolidine (83.4 µL, 1.00 mmol) and purified by flash column chromatography (4:1 EtOAc: pentane) to afford the title compound as colourless crystals (213 mg, 91%); **M.P:** 97-98 °C (Lit: 96-98 °C[246]); **R.f.**: 0.32 (4:1 EtOAc: pentane); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 8.10 (d, J= 7.8 Hz, 2H, Ar-H), 7.59 (d, J= 7.9 Hz, 2h, Ar-H), 3.96 (s, 3H, OMe), 3.68 (t, J = 7.0 Hz, 2H, N-C**H$_2$**-CH_2), 3.40 (t, J = 6.6 Hz, 2H, N-C**H$_2$**-CH_2), 1.99 (tt, J= 6.9 Hz, 2H, N-CH_2-C**H$_2$**), 1.91 (tt, J = 6.9 Hz, 2H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 168.7 (C), 166.4 (C), 141.5 (C), 131.2 (C), 129.7 (CH), 127.0 (CH), 52.3 (CH_3),5 (CH_2), 46.2 (CH_2), 26.4 (CH_2), 24.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{16}NO_3$ [M^+H] 234.1125 found 234.1125. The data matches that found in the literature. [247]

4-(pyrrolidine-1-carbonyl)benzoic acid – **140**



To a solution of amide **139** (252 mg, 1.00 mmol) in methanol (3.00 mL) was added lithium hydroxide (2.00 mL of a 1M aqueous solution) and stirred at room temperature for 18h. The reaction mixture was concentrated *in vacuo*, diluted with water (2 mL), acidified to pH12 with HCl (6 M aqueous solution) and filtered. The filter cake was washed with ice cold water (2 x 2 mL) to afford the title compound as colourless crystals (209 mg, 88%); **M.P:** 239-240 °C (Lit: 240-241 °C[247]); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 8.17 (d, J= 8.6 Hz, 2H, Ar-H), 7.64 (d, J= 8.6 Hz, 2H, Ar-H), 3.71 (t, J = 7.0 Hz, 2H, N-C**H$_2$**-CH_2), 3.42 (t, J = 6.6 Hz, 2H, N-C**H$_2$**-CH_2), 2.01 (tt, J =6.7 Hz, 2H, N-CH_2-C**H$_2$**), 1.93 (tt, J =6.7 Hz, 2H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 170.2 (C), 168.8 (C), 141.9 (C), 130.5 (C), 130.3 (CH), 127.2 (CH), 49.5 (CH_2), 46.3 (CH_2), 26.4 (CH_2), 24.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{14}NO_3$ [M^+H] 220.0968 found 220.0971. The data matches that found in the literature.[247]

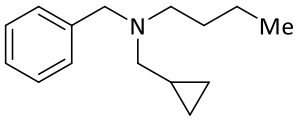
N-methyl-*N*-(4-(pyrrolidin-1-ylmethyl)benzyl)pentan-1-amine – **141**



To a solution of acid **140** (178 mg, 0.750 mmol) in dry toluene (0.600 mL) at reflux, was added phenylsilane (61.5 µL, 0.500 mmol) followed by *N*-benzylmethylamine (68.5 µL, 0.500 mmol) dropwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (394 mg, 2.50 mmol) and phenylsilane (247 µL, 2.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with HCl (0.500 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (5 mL) and extracted with HCl (3 x 5 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* and the crude product was purified by flash column chromatography (99:1 EtOAc: 7M NH_3 in MeOH) to afford the title product as a pale yellow oil (98.3 mg, 67%, 0.358 mmol); **R.f.**: 0.16 (1:1 99:1 EtOAc: 7M NH_3 in MeOH); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.35-7.23 (m, 4H, Ar-**H**), 3.62 (s, 2H, Ar-C**H_2**-N), 3.48 (s, 2H, Ar-C**H_2**-N), 2.57-2.49 (m, 4H, N-C**H_2**-CH_2), 2.37 (t, J= 7.9 Hz, N-C**H_2**-CH_2), 2.37 (s, 3H, N-C**H_3**), 1.84-1.76 (m, 4H, N-CH_2-C**H_2**), 1.53 (tt, J= 9.0 9.0 Hz, CH_2-C**H_2**-CH_2), 1.37-1.25 (m, 4H, CH_3-C**H_2**-C**H_2**), 0.91 (t, J= 5.4 Hz, C**H_3**-CH_2);**^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 137.9 (C), 137.9 (C), 128.9 (CH), 128.8 (CH), 62.1 (CH_2), 60.5 (CH_2), 57.6 (CH_2), 54.2 (CH_2), 42.3 (CH_3), 29.7 (CH_2), 27.1 (CH_2), 23.4 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{18}H_{31}N_2$ [M^+H]: 275.2482 found 275.2481; **IR** vmax/cm^{-1} (ATR): 2955, 2929, 2872, 2779, 1512, 1459, 1416, 1374, 1347, 1325, 1290, 1250, 1200, 1127, 1099, 1051, 1019

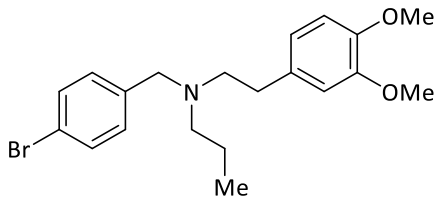
3.5.2 Sequential Reductive Amination

N-benzyl-*N*-(cyclopropylmethyl)butan-1-amine - **147**



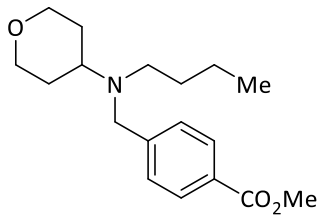
Followed general procedure 3.3.3 using butyric acid (137 µL, 1.50 mmol), benzylamine (109 µL, 1.00 mmol) and cyclopropanecarboxylic acid (119 µL, 1.50 mmol) and purified by flash column chromatography (19:1 pentane: EtOAc) to afford the title product as a colourless oil (150 mg, 69%); **R.f.**: 0.16 (19:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.46- 7.20 (m, 5H, Ar-**H**), 3.67 (s, 2H, Ar-C**H_2**-N), 2.55 (t, J= 7.5 Hz, 2H, N-C**H_2**-CH_2-CH_2-CH_3), 2.35 (d, J= 6.4 Hz, 2H, N-C**H_2**- CH-CH_2), 1.55-1.44 (m, 2H, N-CH_2-C**H_2**-CH_2-CH_3), 1.40- 1.28 (m, 2H, N-CH_2-C**H_2**-CH_2-CH_3), 0.97- 0.86 (m, 4H, N-CH_2-CH_2-CH_2-C**H_3**, N-CH_2-C**H**-CH_2), 0.53- 0.45 (m, 2H, N-CH_2-CH-C**H_2**), 0.11- 0.048 (m, 2H, N-CH_2-CH-C**H_2**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 140.4 (C), 128.8 (CH), 128.1 (CH), 126.6 (CH), 58.6 (CH_2), 58.3 (CH_2), 53.6 (CH_2), 29.1 (CH_2), 20.7 (CH_2), 14.09 (CH), 8.59 (CH_3), 3.92 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{15}H_{24}N$ [M^+H]: 218.1903 found 218.1908; **IR** vmax/cm^{-1} (ATR): 3076, 3002, 2955, 2930, 2861, 2796, 1602, 1494, 1453, 1367, 1253, 1160

N-(4-bromobenzyl)-N-(3,4-dimethoxyphenethyl)propan-1-amine - **148**



Followed general procedure 3.3.3 using 4-bromocarboxylic acid (302 mg, 1.50 mmol), 2-(3,4-dimethoxyphenyl)ethylamine (169 µL, 1.00 mmol) and propanoic acid (112 µL, 1.50 mmol) and purified by flash column chromatography (4:1 pentane: EtOAc) to afford the title product as a colourless oil (251 mg, 64%); **R.f.**: 0.29 (4:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.41 (d, J= 8.2 Hz, 2H, Ar-**H**), 7.19 (d, J= 8.2 Hz, 2H, Ar-**H**), 6.82- 6.77 (m, 1H, Ar-**H**), 6.71- 6.64 (m, 2H, Ar-**H**), 3.88 (s, 3H, Ar-OC**H$_3$**), 3.86 (s, 3H, Ar-OC**H$_3$**), 3.58 (s, 2H, N-C**H$_2$**-Ar), 2.77- 2.63 (m, 4H, N-C**H$_2$**-C**H$_2$**-Ar), 2.46 (t, J= 7.4 Hz, 2H, N-C**H$_2$**-CH_2-CH_3), 1.55- 1.46 (m, 2H, N-CH_2-C**H$_2$**-CH_3), 0.88 (t, J= 7.4 Hz, 3H, N-CH_2-CH_2-C**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 148.7 (C), 147.2 (C), 139.3 (C), 133.4 (C), 131.2 (CH), 130.4 (CH), 120.6 (CH), 120.3 (C), 112.6 (CH), 111.1 (CH), 58.0 (CH_2), 56.0 (CH_2), 55.9 (CH_2), 55.8 (CH_3), 55.7 (CH_3), 33.3 (CH_2), 20.4 (CH_2), 11.9 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{20}H_{27}NO_2Br$ [M^+H]: 392.1220 found 392.1216; **IR** vmax/cm^{-1} (ATR): 2956, 2932, 2871, 2831, 1590, 1514, 1485, 1463, 1417, 1363, 1260, 1235, 1191, 1155, 1140

methyl 4-((butyl(tetrahydro-2H-pyran-4-yl)amino)methyl)benzoate - **149**



Followed general procedure 3.3.3 using butyric acid (137 µL, 1.50 mmol), 4-aminotetrahydropyran (104 µL, 1.00 mmol) and 4-(methoxycarbonyl)benzoic acid (180 mg, 1.00 mmol) and purified by flash column chromatography (9:1 pentane: EtOAc) to afford the title product as a pale yellow oil (226 mg, 74%); **R.f.**: 0.28 (9:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.99 (d, J= 7.2 Hz, 2H, Ar-H), 7.44 (d, J= 7.2 Hz, 2H, Ar-**H**), 4.07- 3.98 (m, 2H, O-C**H$_2$**-CH_2), 3.93 (s, 3H, CO_2C**H$_3$**), 3.70 (s, 2H, Ar-C**H$_2$**-N), 3.33 (td, J= 11.4, 3.0 Hz, 2H, O-C**H$_2$**-CH_2), 2.78- 2.67 (m, 1H, N-C**H**-CH_2-CH_2-O), 2.51 (t, J= 7.1 Hz, 2H, N-C**H$_2$**-CH_2-CH_2-CH_3), 1.74- 1.58 (m, 4H, N-CH-C**H$_2$**-CH_2-O), 1.48- 1.23 (m, 4H, N-CH_2-C**H$_2$**-C**H$_2$**-CH_3), 0.87 (t, J= 7.2 Hz, 3H, N-CH_2-CH_2-CH_2-C**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 167.2 (C), 147.3 (C), 129.5 (CH), 128.6 (C), 128.1 (CH), 67.9 (CH_2), 56.8 (CH), 54.2 (CH_2), 52.0 (CH_3), 50.0 (CH_2), 30.7 (CH_2), 29.2 (CH_2), 20.4 (CH_2), 14.0 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{18}H_{28}NO_3$ [M^+H]: 306.2064 found 306.2057; **IR** vmax/cm^{-1} (ATR): 2952, 2841, 2367, 2074, 1994, 1923, 1720, 1610, 1576, 1507, 1434, 1414, 1382, 1274, 1233, 1171

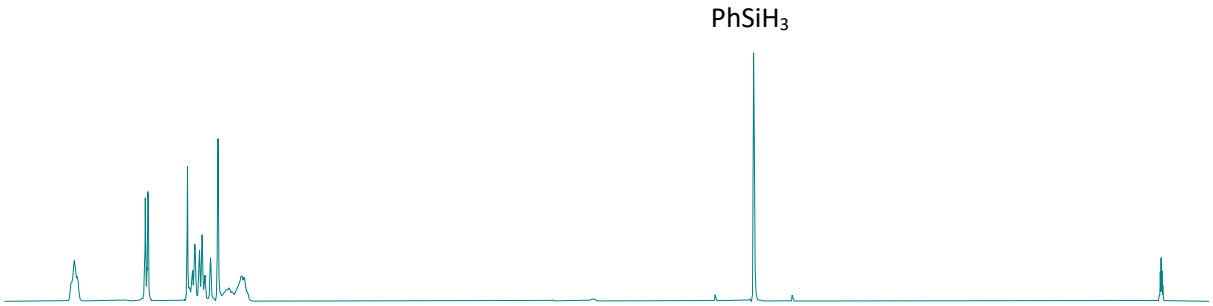
3.6 Mechanistic Studies

3.6.1 Reaction of Phenylsilane and Benzenesulfonic Acid

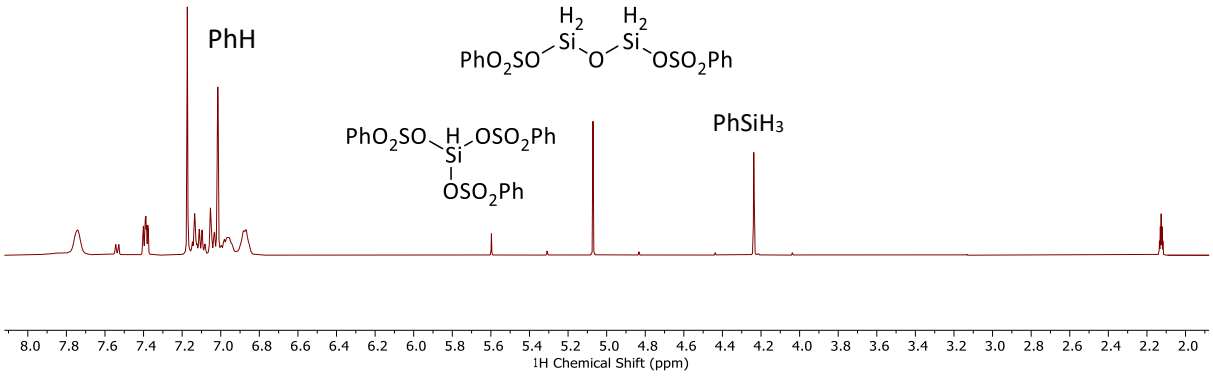
To a refluxing solution of benzenesulfonic acid (276 mg, 1.75 mmol) in d^8-toluene (1.2 mL) was added phenylsilane (247 µL, 2.00 mmol) dropwise and heated for 8 hours. A sample was removed initially, and the reaction was run for 8 hours where a final sample was taken and ^{1}H and ^{29}Si NMR spectroscopy was carried out on both samples. Traces are depicted below which show the formation of silyl sulfonate. In the ^{1}H NMR spectra, after eight hours, phenyl silane (4.24 ppm) remained along with new

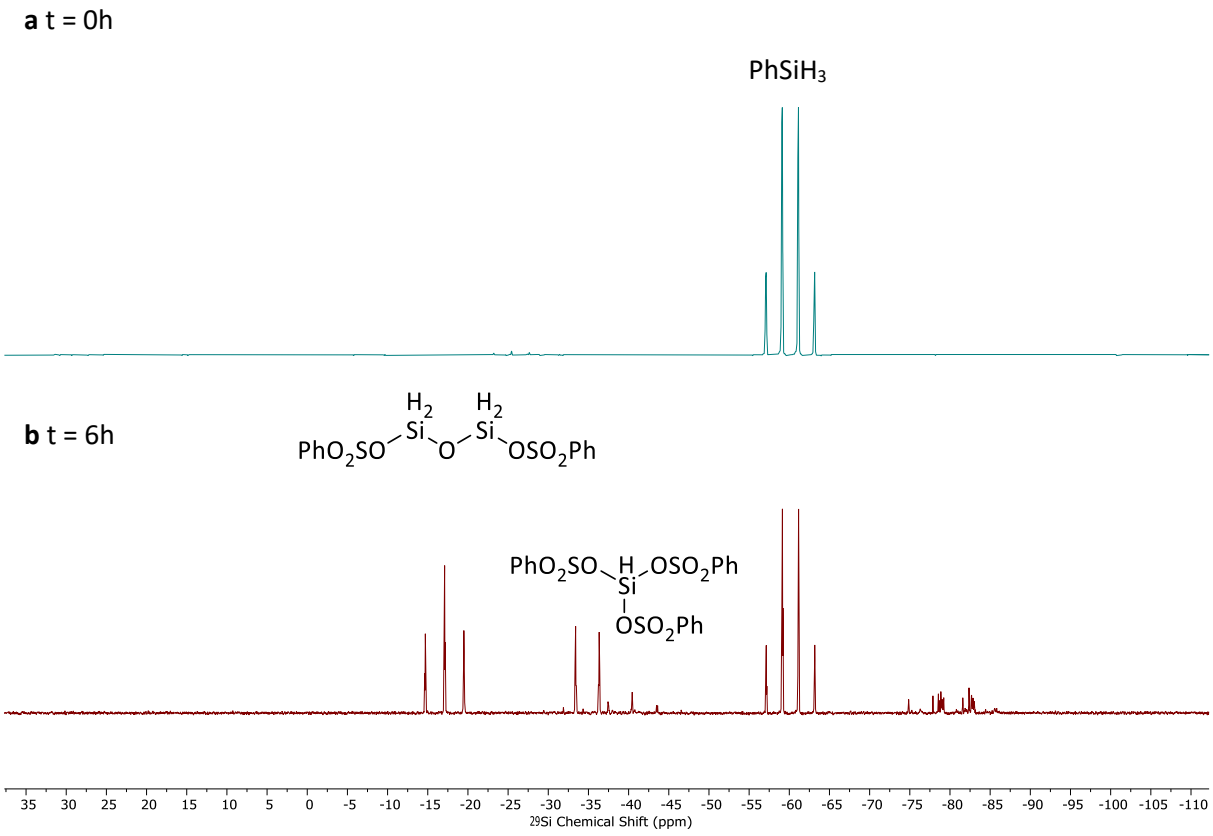
peaks at 5.07 and 5.60 ppm. This is assumed to be the Si-H shift of the Si-H shift of silylsulfonate species and identification of benzene (7.17 ppm) in the NMR confirms formation for a species of this type. ^{29}Si NMR depicts a similar view, as after 8 hours, phenylsilane remained (-58.9 ppm) and two new species (-17.1 and -34.9 ppm) were formed. The shifts and multiplicities of these peaks, the formation of benzene and the H_2 effervescence suggests that the peak at 5.60 ppm in Figure S4b and -34.9 ppm in Figure S5b is the tris-substituted silybenzene sulfonate species. The peak at 5.07 ppm in Figure S4b and -17.1 ppm in Figure S5b is likely to be a disiloxane dibenzenesulfonate. The correlation between these NMR was observed through ^{1}H-^{29}Si HSQC experiments.

a t = 0h



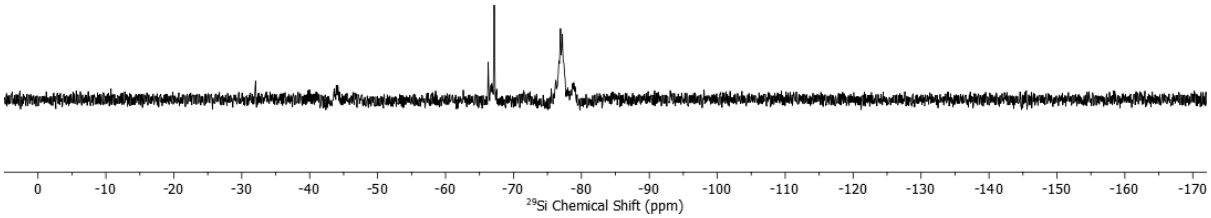
b t = 8h





3.6.2 Reaction of Silylbenzene Sulfonates with (4-fluorophenyl)(pyrrolidin-1-yl)methanone

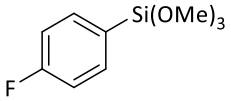
To a refluxing solution of benzenesulfonic acid (276 mg, 1.75 mmol) in d^8-toluene (1.2 mL) was added phenylsilane (247 µL, 2.00 mmol) dropwise and heated for 8 hours, after which **SI-4** (193 mg, 1 mmol) was added and heated for a further 18 hours and cooled to room temperature. At this time a sample was submitted for ^{29}Si NMR and the remaining reaction mixture was quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the amine as a yellow oil (132 mg, 74%, 0.736 mmol). NMR details were consistent with those above. The success of this reaction confirms that the active reducing species is formed from phenylsilane and benzenesulfonic acid only. The ^{29}Si NMR after the reaction compared to before (Figure S4 trace b), demonstrates the consumption of all active reducing species, leaving different silicon compounds at -32.04, -66.28, -67.16 and -76.69 ppm



3.6.3 Reaction of (4-fluorophenyl)silane and Benzenesulfonic Acid

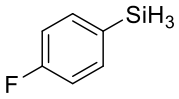
Synthesis of (4-fluorophenyl)silane

(4-fluorophenyl)trimethoxysilane - **165**



To a solution of tetramethyl siloxane (6.69 mL, 45.0 mmol) in Et_2O (17.0 mL) at -5 ^oC, was added 4-fluorophenylmagnesium bromide (2.00 M in Et_2O, 7.50 mL) dropwise over 5 minutes, warmed to r.t and stirred for 24h. Water (20 mL) was added dropwise, and the aqueous layer was extracted with pentane (3 x 20 mL), the organic layers were combined, washed with brine (20 mL), dried over MgSO4 and concentrated *in vacuo*. The crude product was purified by distillation to afford the title compound as a clear colourless oil (2.24 g, 69%, 6.92 mmol); **B.P:** 94 °C, 10 mbar (Lit.: 150 °C, 110 mbar[248]); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.66 (dd, J= 6.8, 6.1 Hz, 2H, Ar-**H**), 7.11 (t, J= 8.7 Hz, 2H, Ar-**H**), 3.64 (s, 9H, OC**H_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 164.6 (d, J= 250 Hz, C), 136.9 (d, J= 8.2 Hz, CH), 125.2 (d, J= 4.6 Hz, C), 115.2 (d, J= 19.9 Hz, CH), 50.8 (CH_3); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) -109.2 (F); **IR** vmax/cm^{-1} (ATR): 2944, 2843, 1909, 1502, 1465, 1391, 1304, 1225, 1191, 1163, 1122, 1070, 1017. The data matched that found in the literature. [248]

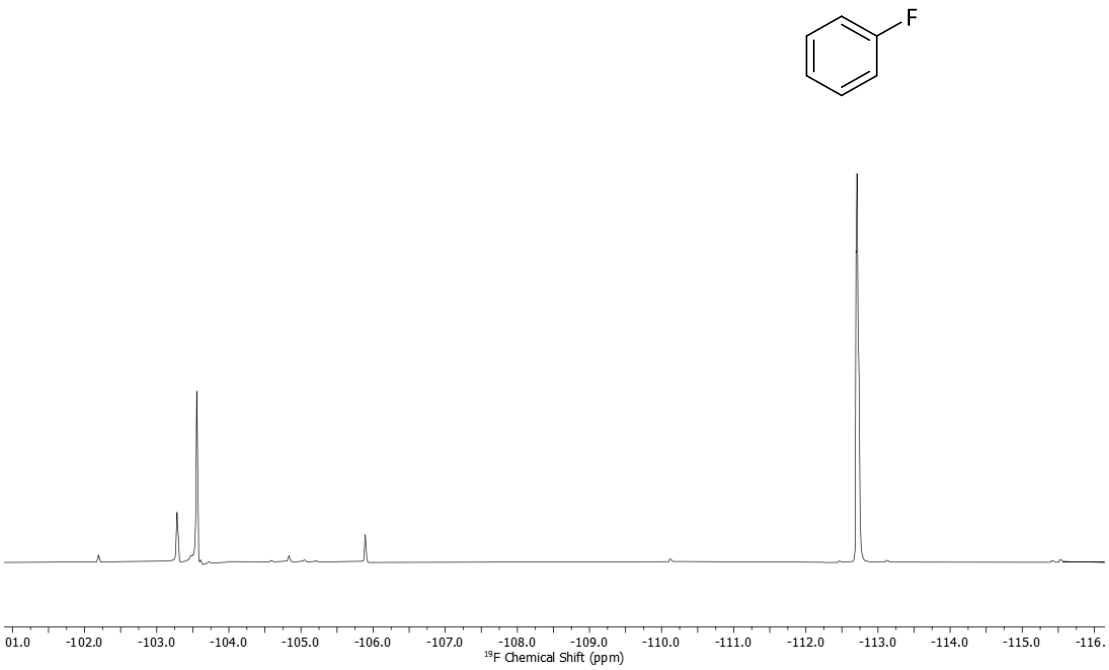
(4-fluorophenyl)silane – **154**



To a suspension of $LiAlH_4$ (789 mg, 20.8 mmol) in Et_2O (50.0 mL) at 0^{o}C, was added **165** (2.24g, 10.4 mmol) in Et2O (10.0 mL) dropwise, warmed to room temperature and stirred for 24h. The reaction mixture was diluted with pentane (150 mL), filtered through celite and concentrated *in vacuo.* The resulting residue was diluted with pentane (150 mL), filtered through celite and concentrated *in vacuo* to afford the title compound as a clear colourless oil (1.46 g). The product is very volatile so was concentrated to a 60% solution in pentane and used in the next step as a solution; **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.59 (dd, J= 8.7, 6.1 Hz, 2H, Ar-**H**), 7.09 (t, J= 8.7 Hz, 2H, Ar-**H**), 4.22 (s, 2H, Si-**H_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 164.6 (d, J= 260 Hz, C), 137.8 (d, J= 6.96 Hz, CH), 123.6 (d, J= 3.99 Hz, C), 114.4 (d, J= 20.2 Hz, CH), 34.2 (SiH_3); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) -110.5 (F); **IR** vmax/cm^{-1} (ATR): 2958, 2154, 1590, 1499, 1387, 1304, 1231, 11645, 1108 The data matched that found in the literature. [248]

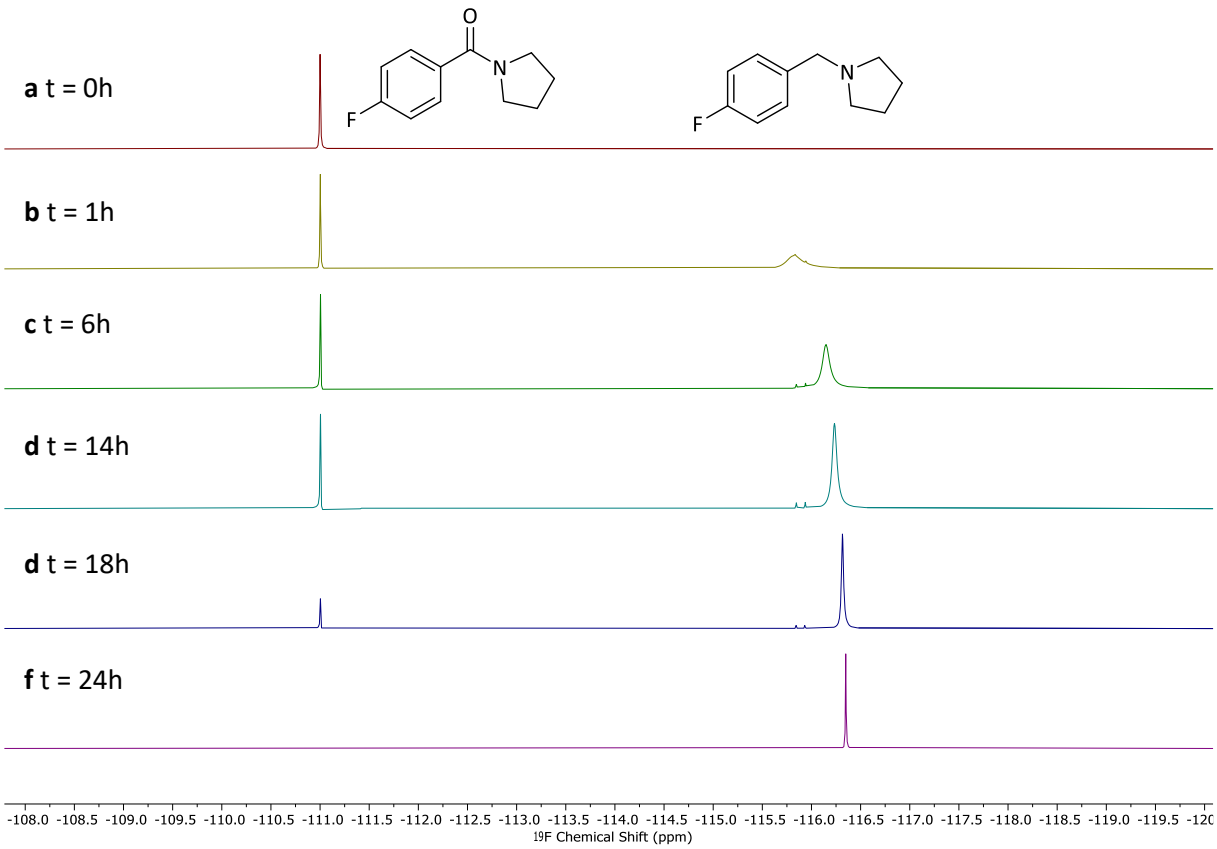
Reaction of (4-fluorophenyl)silane and Benzenesulfonic Acid

To a refluxing solution of benzenesulfonic acid (314 mg, 2.00 mmol) in toluene (1.00 mL) was added (4-fluorophenyl)silane (419 µL, 2.00 mmol of a 60% solution in pentane) in toluene (0.200 mL) dropwise and heated for 8 hours. An ^{19}F NMR spectrum was measured in $CDCl_3$ and a peak at -113 ppm confirmed the presence of 4-fluorobenzene.



3.6.4 Reaction Monitoring

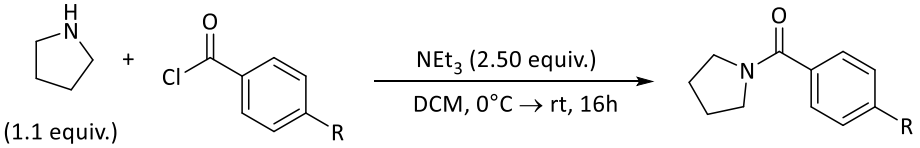
To a refluxing solution of (4-fluorophenyl)(pyrrolidin-1-yl)methanone (synthesis described below) (96.6 mg, 0.500 mmol) in toluene-d^8 (0.600 mL), was added benzenesulfonic acid (138.4 mg, 0.875 mmol) and phenyl silane (123 µL, 1.00 mmol) dropwise. The reaction mixture was heated to 75 °C in an NMR machine for 24 hours and ^{19}F NMR was performed every hour. Six representative traces are depicted (Figure S3 (a), (b), (c), (d), (e) and (f) from varying times in the 24-hour reaction run. As can be observed, the amide (-111.0 ppm) is reacted directly to the amine (-116.4 ppm) with no major visible intermediates.



3.6.5 Competition Experiments

Amide Synthesis

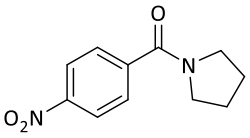
General Procedure



To a solution of amine (1.10 equiv.) and triethylamine (2.50 equivs.) in dry DCM (0.500 M) at 0 °C was added the appropriate acid chloride (1.00 equiv.) dropwise over 5 minutes. The reaction mixture was warmed to r.t and stirred for 16 h. The reaction mixture was diluted with DCM (10 mL) and washed with HCl (25mL of a 1M aqueous solution) and extracted with DCM (3 x 10 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford to the amide product.

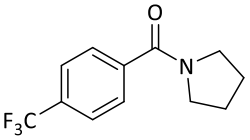
Experimental Data

(4-nitrophenyl)(pyrrolidine-1-yl)menthanone – **166**



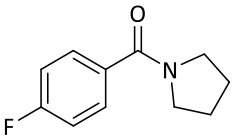
Followed general procedure 4.2 using pyrrolidine (459 µL, 5.50 mmol), 4- nitro benzoyl chloride (928 mg, 5.00 mmol) and triethylamine (871 µL, 6.25 mmol) in dry DCM (10.0 mL). The crude material was purified using flash column chromatography (3:7, pentane: EtOAc) to afford the title compound as pale yellow crystals (870 mg, 79%, 3.95 mmol); **M.P:** 79-80 °C (Lit.: 78-80 °C[249]); **R.f.**: 0.25 (3:7 pentane: EtOAc); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 8.29 (d, J= 6.9 Hz, 2H, Ar-**H**), 7.70 (d, J= 8.5 Hz, 2H, Ar-**H**), 3.69 (t, J= 6.0 Hz, 2H, N-C**H$_2$**-CH_2), 3.40 (t, J= 6.7 Hz, 2H, N-C**H$_2$**-CH_2), 2.01 (tt, J= 6.8, 6.8 Hz, 2H, N-CH_2-C**H$_2$**), 1.95 (tt, J= 6.8, 6.8 Hz, 2H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 167.4 (C), 148.4 (C), 143.2 (C), 128.2 (CH), 123.7 (CH), 49.5 (CH_2), 46.4 (CH_2), 26.4 (CH_2), 24.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{12}N_2O_3$ [M^+H] 221.0921 found 221.0920. The data matched that found in the literature. [249]

(Pyrrolidin-1-yl)(4-(trifluoromethyl)phenyl)methanone – **167**



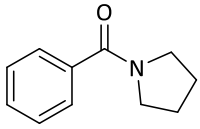
Followed general procedure 4.2 using pyrrolidine (459 µL, 5.50 mmol), 4-trifluoromethyl benzoyl chloride (743 µL, 5.00 mmol) and triethylamine (871 µL, 6.25 mmol) in dry DCM (10.0 mL). The crude material was purified using flash column chromatography (1:1, pentane: EtOAc) to afford the title compound as colourless crystals (1.14 g, 94%, 4.69 mmol); **M.P:** 78-79 °C (Lit.: 79-80 °C[249]); **R.f.:** 0.24 (1:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.69 (d, J= 8.3 Hz, 2H, Ar-**H**), 7.64 (d, J= 8.3 Hz, 2H, Ar-**H**), 3.68 (t, d= 6.92 Hz, 2H, N-C**H$_2$**-CH_2), 3.41 (t, J= 6.57 Hz, 2H, N-C**H$_2$**-CH_2), 2.00 (tt, J= 7.0, 7.0 Hz, 2H, N-CH_2-C**H$_2$**), 1.92 (tt, J= 7.0, 7.0 Hz, 2H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 168.2 (C), 140.6 (C), 131.7 (q, J= 34.7 Hz, C)127.5 (CH), 125.4 (q, J= 3.4 Hz, CH), 123.5 (q, J= 272.2 Hz, C), 49.5 (CH_2), 46.3 (CH_2), 26.4 , (CH_2), 24.4 (CH_2); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) -62.88 (CF_3); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{13}NOF_3$ [M^+H] 244.0944 found 244.0947. The data matched that found in the literature.

(4-fluorophenyl)(pyrrolidin-1-yl)methanone – **168**



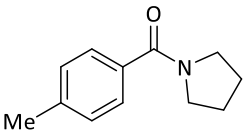
Followed general procedure 4.2 using pyrrolidine (459 µL, 5.50 mmol), 4-flurorobenzoyl chloride (591 µL, 5.00 mmol) and triethylamine (871 µL, 6.25 mmol) in dry DCM (10.0 mL). The crude material was purified using flash column chromatography (1:1, pentane: EtOAc) to afford the title compound as colourless crystals (919 mg, 95%, 4.76 mmol); **M.P**: 90-91 °C (Lit.: 87-90 °C[250]); **R.f.:** 0.25 (1:1 pentane: EtOAc); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.57-7.53 (m, 2H, Ar-**H**), 7.09 (t, J= 8.7 Hz, 2H, Ar-**H**), 3.64 (br s, 2H, N-C**H$_2$**-CH_2), 3.46 (br s, 2H, N-C**H$_2$**-CH_2), 1.94 (br s, 4H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 168.7 (C), 163.4 (d, J= 249.0 Hz, C), 133.3 (d, J= 3.3 Hz, C), 129.4 (d, J= 9.0 Hz, CH), 115.3 (d, J= 21.9 Hz, CH), 49.6 (CH_2), 46.4 (CH_2), 26.2 (CH_2), 24.7 (CH_2); **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) -110.4 (CF); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{12}NOF$ [M^+H] 194.0981 found 194.0976 The data matched that found in the literature. [250]

N-benzoylpyrrolidine – **169**



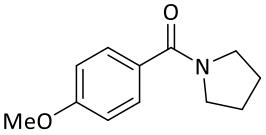
Followed general procedure 4.2 using pyrrolidine (459 µL, 5.50 mmol), benzoyl chloride (581 µL, 5.00 mmol) and triethylamine (871 µL, 6.25 mmol) in dry DCM (10.0 mL). The crude material was purified using flash column chromatography (1:1, pentane: EtOAc) to afford the title compound as a pale yellow oil (832.2 mg, 95%, 4.64 mmol); **R.f.**: 0.29 (1:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.59-7.49 (m, 2H, Ar-**H**), 7.45-7.37 (m, 3H, Ar-**H**), 3.64 (t, J= 6.5 Hz, 2H, N-C**H$_2$**-CH_2), 3.44 (t, J= 6.7 Hz, 2H, N-C**H$_2$**-CH_2), 1.98 (tt, J= 6.3, 6.3 Hz, 2H, N-CH_2-C**H$_2$**), 1.88 (tt, J= 6.3, 6.3 Hz, 2H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 169.7 (C), 137.3 (C), 129.7 (CH), 128.2 (CH), 127.1 (CH), 49.6 (CH_2), 46.1 (CH_2), 26.4 (CH_2), 24.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{13}NO$ [M^+H] 176.1070 found 176.070. The data matched that found in the literature. [249]

Pyrrolidin-1-yl(p-tolyl)methanone – **170**



Followed general procedure 4.2 using pyrrolidine (459 µL, 5.50 mmol), p-toluyl chloride (661 µL, 5.00 mmol) and triethylamine (871 µL, 6.25 mmol) in dry DCM (10.0 mL). The crude material was purified using flash column chromatography (1:1, pentane: EtOAc) to afford the title compound as colourless crystals (845 mg, 89%, 4.47 mmol); **M.P**: 76-78 °C (Lit.: 75-76 °C[249]); **R.f:** 0.15 (1:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.44 (d, J= 8.1 Hz, 2H, Ar-**H**), 7.21 (d, J= 8.1 Hz, 2H, Ar-**H**), 3.63 (br s, 2H, N-C**H$_2$**-CH_2), 3.48 (br s, 2H, N-C**H$_2$**-CH_2), 2.39 (s, 3H, Ar-C**H$_3$**), 1.93 (br s, 4H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 169.8 (C), 139.9 (C), 134.3 (C), 128.8 (CH), 127.2 (CH), 49.6 (CH_2), 46.3 (CH_2), 26.2 (CH_2), 24.0 (CH_2), 21.4 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{15}NO$ [M^+H] 190.1226 found 190.1226. The data matched that found in the literature. [249]

1-(4-methoxybenzoyl)pyrrolidine – **171**



Followed general procedure 4.2 using pyrrolidine (459 µL, 5.50 mmol), 4-methoxy benzoyl chloride (677 µL, 5.00 mmol) and triethylamine (871 µL, 6.25 mmol) in dry DCM (10.0 mL). The crude material was purified using flash column chromatography (1:1, pentane: EtOAc) to afford the title compound as colourless crystals (949 mg, 93%, 4.63 mmol); **M.P**: 76-77 °C (Lit.: 76-71 °C[249]); **R.f:** 0.23 (1:1 pentane: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.53 (d, J= 8.8 Hz, 2H, Ar-**H**), 6.91 (d, J= 8.7 Hz, 2H, Ar-**H**), 3.84 (s, 3H, OC**H$_3$**), 3.63 (br s, 4H, N-C**H$_2$**-CH_2), 1.92 (br s, 4H, N-CH_2-C**H$_2$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 169.4 (C), 160.8 (C), 129.5 (C), 129.2 (CH), 113.4 (CH), 55.3 (CH_3), 49.8 (CH_2), 46.4 (CH_2), 26.4 (CH_2), 24.1 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{16}NO_2$ [M^+H] 206.1176 found 206.1172. The data matched that found in the literature. [249]

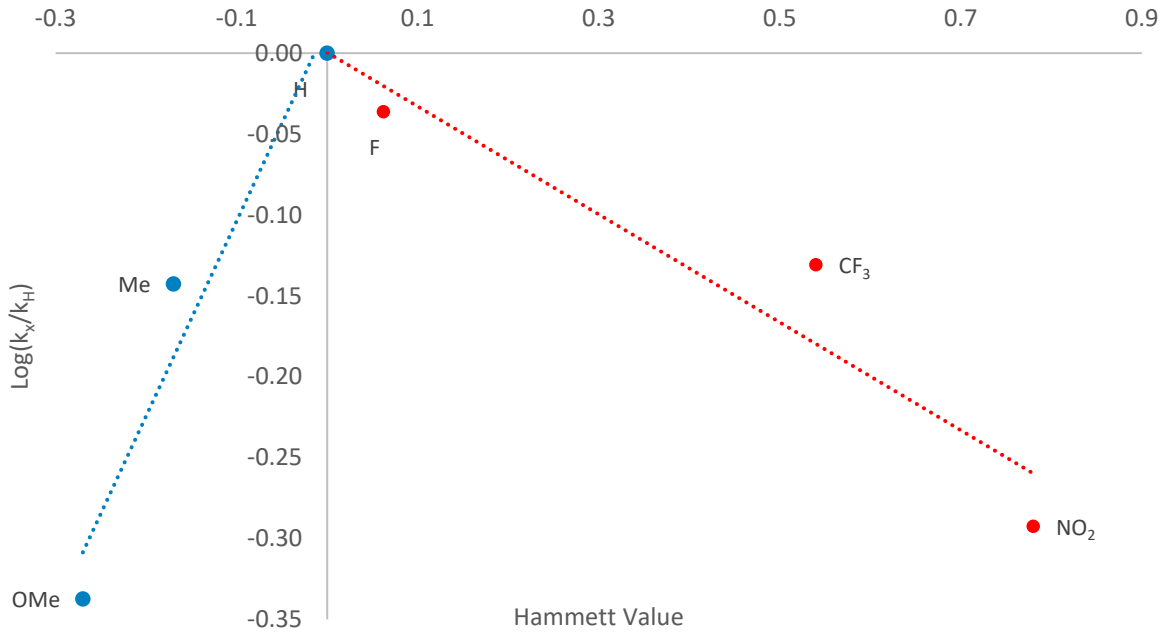
Competition Experiments

To a refluxing solution of amide 1 (0.500 mmol) and amide 2 (0.500 mmol) in dry toluene (1.20 mL), was added benzenesulfonic acid (10.8 µL, 0.100 mmol) and phenylsilane (13.8 mg, 0.0875 mmol) and heated for 4 hours. The reaction mixture was quickly cooled to room temperature, quenched with ethanol (2.00 mL) and concentrated *in vacuo*. The ratios of amine products were determined through starting material identification by reverse phase HPLC analysis (80:20, 0.1% formic acid: acetonitrile).

Amide pair	Ratio of amides[a]	Calculated ratio of amines[b]
***p*-NO_2: *p*-CF_3**	0.65:1	1.54:1
***p*-CF_3: *p*-H**	0.72:1	1.39:1
***p*-F: *p*-H**	0.93:1	1.08:1
***p*-H: *p*-Me**	1.35:1	0.74:1
***p*-Me: *p*-OMe**	1.43:1	0.69:1

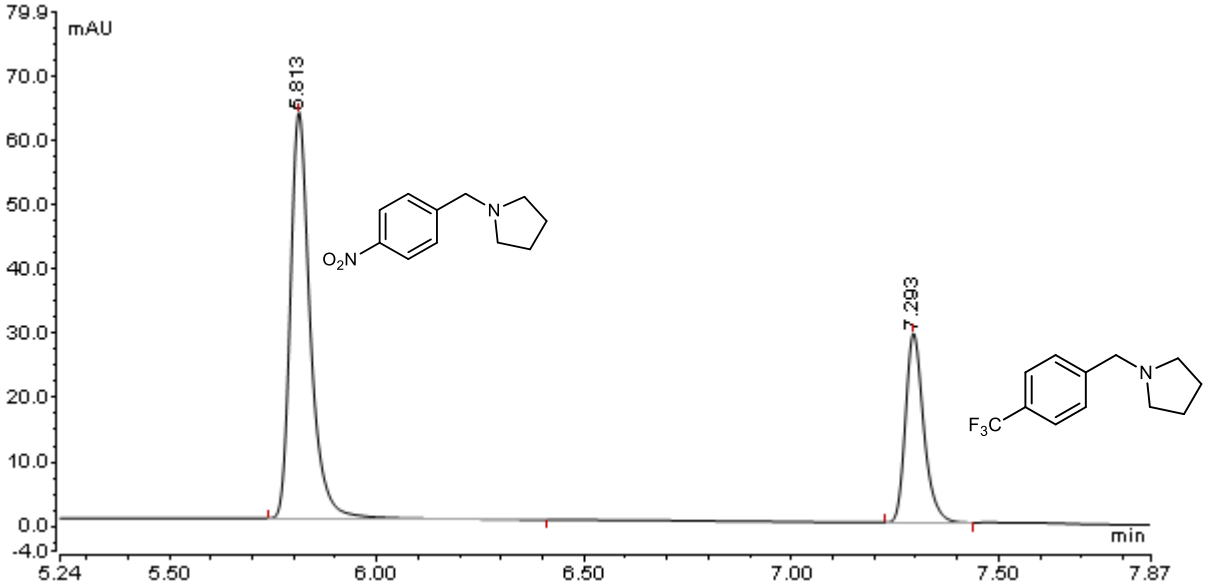
a Calibrated ratio; b Assumed direct conversion to amine

Amine	K_X/K_H	$Log(K_X/K_H)$	Hammett Value[251]
***p*-NO_2**	0.51	-0.29	0.78
***p*-CF_3**	0.74	-0.13	0.54
***p*-F**	0.92	-0.04	0.062
***p*-H**	1	0.00	0.00
***p*-Me**	0.72	-0.14	-0.17
***p*-OMe**	0.46	-0.34	-0.27



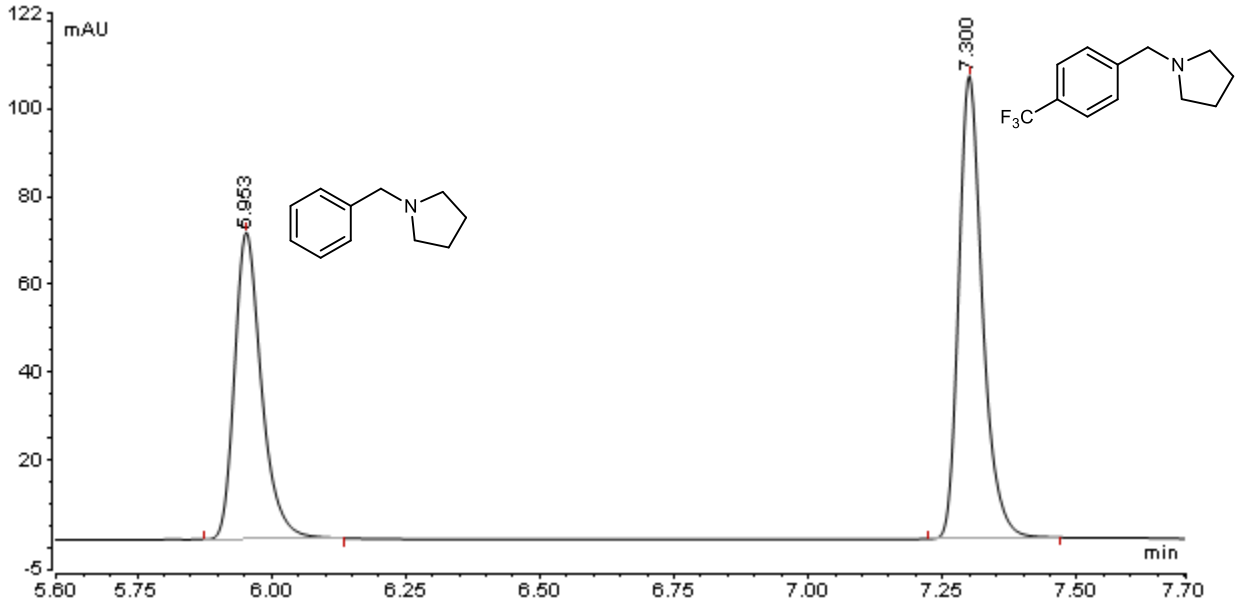
HPLC Traces

166:167



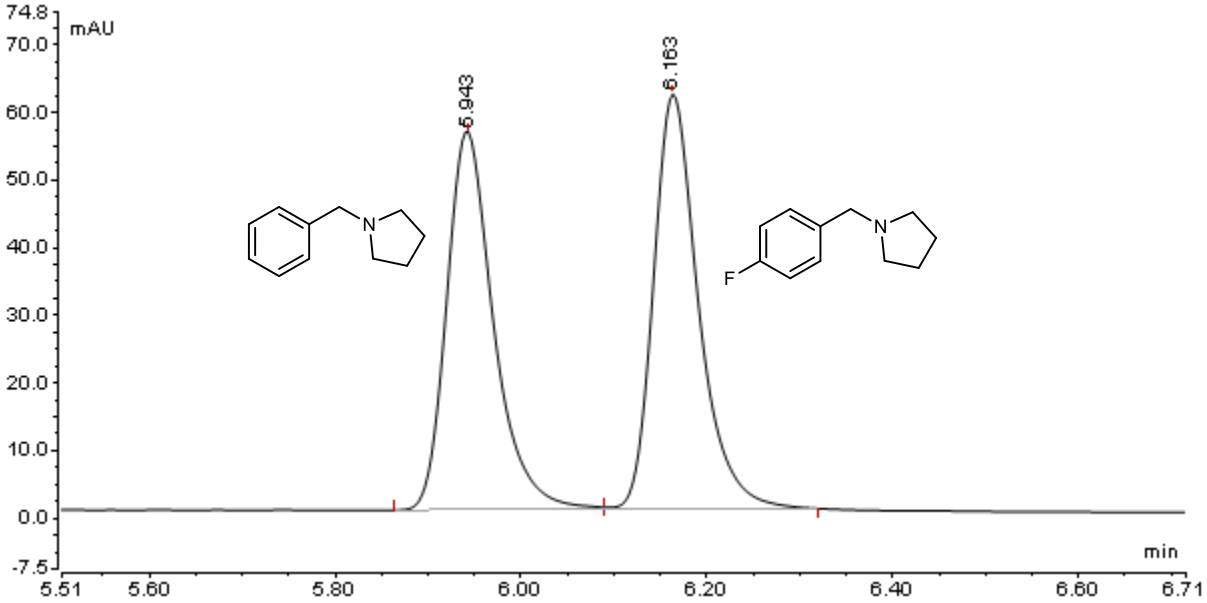
Ret. Time (min)	Relative area (%)	Height	Width (50% min)
5.813	70.07	63.09	0.048
7.293	29.93	29.40	0.046

167:168



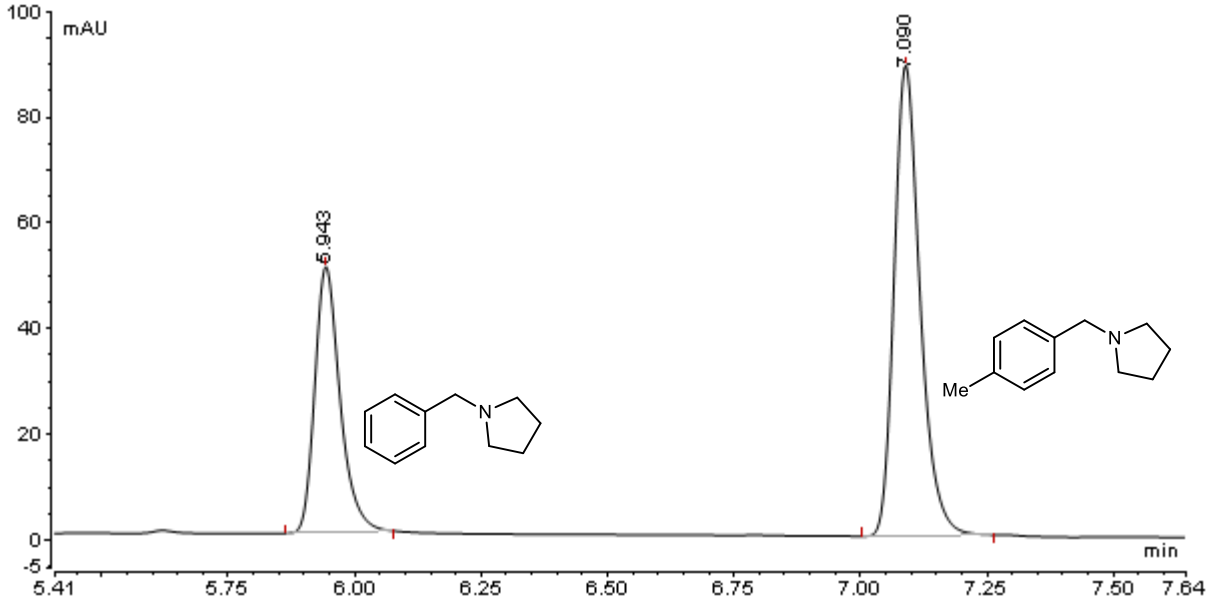
Ret. Time (min)	Relative area (%)	Height	Width (50% min)
5.953	42.92	69.99	0.052
7.399	57.08	105.58	0.046

168:169



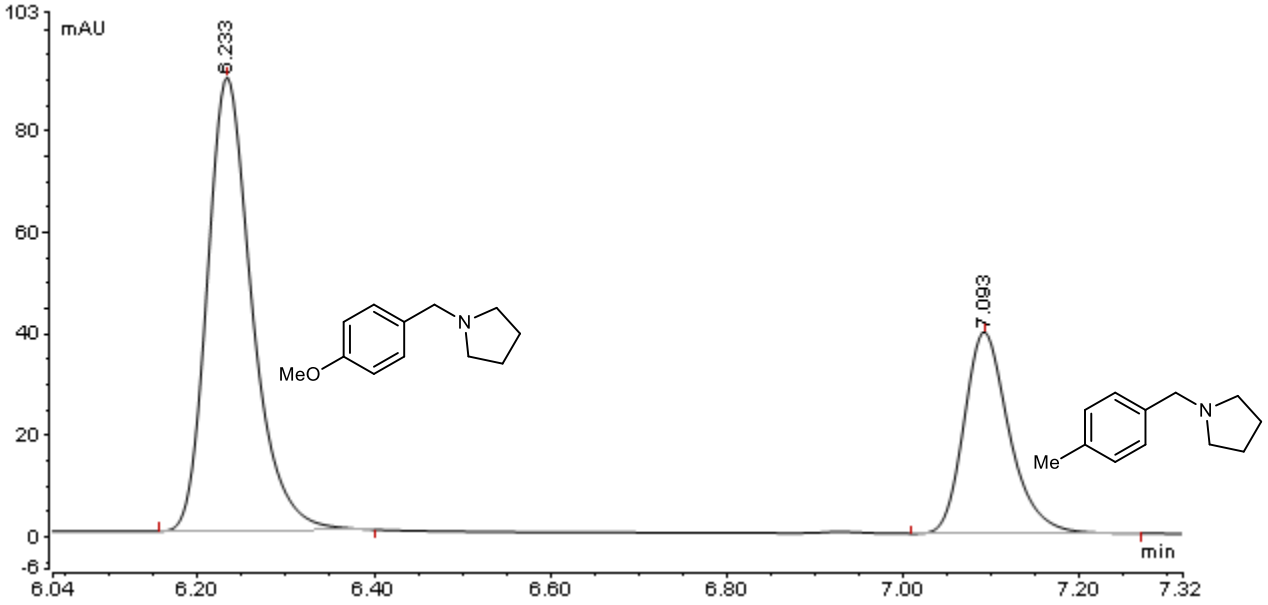
Ret. Time (min)	Relative area (%)	Height	Width (50% min)
5.953	48.74	55.87	0.052
6.163	51.26	61.38	0.050

169:170



Ret. Time (min)	Relative area (%)	Height	Width (50% min)
5.953	35.51	50.32	0.052
7.090	64.49	64.49	0.053

170:171



Ret. Time (min)	Relative area (%)	Height	Width (50% min)
6.233	68.97	89.36	0.052
7.090	31.03	39.64	0.053

4 References

1 R. Hili and A. K. Yudin, *Nat Chem Biol*, 2006, **2**, 284–287.
2 O. I. Afanasyev, E. Kuchuk, D. L. Usanov and D. Chusov, *Chem Rev*, 2019, **119**, 11857–11911.
3 A. M. Smith and R. Whyman, *Chem Rev*, 2014, 114, 5477–5510.
4 J. Watson and F. Crick, *Nature*, 1953, **171**, 737–738.
5 A. H. Gordon, A. J. P. Martin and R. L. M. Synge, *Biochemical Journal*, 1943, **37**, 79–86.
6 Grand View Research, 2022, 1–113.
7 S. Kim, N. G. Yoon, B. Jana, B. H. Kang and J. H. Ryu, *Bull Korean Chem Soc*, 2022, **43**, 391–395.
8 Z. Yue, C. Li, G. A. Voth and J. M. J. Swanson, *J Am Chem Soc*, 2019, **141**, 13421–13433.
9 J. Yang, A. Buekenhoudt, M. van Dael, P. Luis, Y. Satyawali, R. Malina and S. Lizin, *Org Process Res Dev*, 2022, **26**, 2052–2066.
10 S. D. Roughley and A. M. Jordan, *J Med Chem*, 2011, **54**, 3451–3476.
11 R. N. Salvatore, H. Yoon and K. Woon, *Tetrahedron*, 2001, **57**, 7785–7811.
12 V. Aranapakam, G. T. Grosu, J. M. Davis, B. Hu, J. Ellingboe, J. L. Baker, J. S. Skotnicki, A. Zask, J. F. DiJoseph, A. Sung, M. A. Sharr, L. M. Killar, T. Walter, G. Jin and R. Cowling, *J Med Chem*, 2003, **46**, 2361–2375.
13 N. Tibrewal and G. I. Elliott, *ChemMedChem*, 2020, **15**, 2269–2272.
14 C. Yao, X. Jiang, R. Zhao, Z. Zhong, J. Ge, J. Zhu, X. Y. Ye, Y. Xie, Z. Liu, T. Xie and R. Bai, *Bioorg Chem*, 2022, **122**, 105724.
15 G. Marzaro, A. Guiotto and A. Chilin, *Green Chemistry*, 2009, **11**, 774–776.
16 C. Chiappe, P. Piccioli and D. Pieraccini, *Green Chemistry*, 2006, **8**, 277–281.
17 A. Monopoli, P. Cotugno, M. Cortese, D. Calvano, F. Ciminale and A. Nacci, *European J Org Chem*, 2012, **2012**, 3031–3176.
18 B. Singh, H. Lobo and G. Shankarling, *Catal Letters*, 2011, **141**, 178–182.
19 R. N. Salvatore, A. S. Nagle, S. E. Schmidt and K. W. Jung, *Org Lett*, 1999, **1**, 1893–1896.
20 J. Castillo, J. Orrego-hernández and J. Portilla, *European J Org Chem*, 2016, **2016**, 3824–3835.
21 S. Bhattacharyya, U. Pathak, S. Mathur, S. Vishnoi and R. Jain, *RSC Adv*, 2014, **4**, 18229–18233.
22 E. Bautz and E. Freese, *Proceedings of the National Acadamy of the Sciences*, 1960, **46**, 1585–1594.
23 R. Appel, *Angewandte Chemie - International Edition*, 1975, **14**, 801–811.
24 J. Norris and H. Taylor, *J Am Chem Soc*, 1924, **46**, 753–757.
25 R. J. Ouellette and J. D. Rawn, in *Organic Chemistry*, 2018, pp. 463–505.
26 S. W. Goldstein, A. Bill, J. Dhuguru and O. Ghoneim, *J Chem Educ*, 2017, **94**, 1388–1390.
27 J. F. Bunnett and R. E. Zahler, *Chem Rev*, 1951, **49**, 273–412.
28 G. Artamkina, M. Egerov and I. Beletskaya, *Chem Rev*, 1982, **82**, 427–459.
29 S. Rohrbach, A. J. Smith, J. H. Pang, D. L. Poole, T. Tuttle, S. Chiba and J. A. Murphy, *Angewandte Chemie - International Edition*, 2019, **58**, 16368–16388.
30 T. Hirose, S. Mishio, J. ichi Matsumoto, S. Minami and S. Minami, *Chem Pharm Bull (Tokyo)*, 1982, **30**, 2399–2409.
31 D. L. Hughes, *Org Process Res Dev*, 2016, **20**, 1855–1869.
32 N. A. Senger, B. Bo, Q. Cheng, J. R. Kee, S. Gronert and W. Wu, *J Org Chem*, 2012, **77**, 9535–9540.
33 D. Dehe, I. Munstein, A. Reis, R. Thiel and F. Chemie, *Journal of Organic Chemistry*, 2011, **76**, 1151–1154.
34 M. Otsuka, K. Endo and T. Shibata, *Chemical Communications*, 2010, **46**, 336–338.
35 J. W. Walton and J. M. J. Williams, *Chemical Communications*, 2015, **51**, 2786–2789.
36 S. Maiorana, C. Baldoli, P. del Buttero, M. di Ciolo and A. Papagni, *Synthesis (Stuttg)*, 1998, **1998**, 735–738.
37 B. J. Miller and A. J. Parker, *J Am Chem Soc*, 1961, **83**, 117–123.
38 C. P. Ashcroft, P. J. Dunn, J. D. Hayler and A. S. Wells, *Org Process Res Dev*, 2015, **19**, 740–747.
39 F. P. Byrne, S. Jin, G. Paggiola, T. H. M. Petchey, J. H. Clark, T. J. Farmer, A. J. Hunt, C. R. Mcelroy and J. Sherwood, *Sustainable Chemical Processes*, 2016, **4**, 7.

40 M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven and F. J. Weiberth, *Green Chemistry*, 2018, **20**, 5082–5103.
41 X. Zhang, G. Lu and C. Cai, *Green Chemistry*, 2016, **18**, 5580–5585.
42 J. Campos, M. Loubidi, M.-C. Scherrmann and S. Berteina-Raboin, *Molecules*, 2018, **23**, 684–699.
43 N. A. Isley, R. T. H. Linstadt, S. M. Kelly, F. Gallou and B. H. Lipshutz, *Org Lett*, 2015, **17**, 4734–4737.
44 N. R. Lee, F. Gallou and B. H. Lipshutz, *Org Process Res Dev*, 2017, **21**, 218–221.
45 M. Kosugi, M. Kameyama and T. Migita, *Chem Lett*, 1983, **12**, 927–928.
46 A. Guram and S. L. Buchwald, *J Am Chem Soc*, 1994, **116**, 7901–7902.
47 F. Paul, J. Patt and J. F. Hartwig, *J Am Chem Soc*, 1994, **116**, 5969–5970.
48 J. Louie and J. F. Hartwig, *Tetrahedron Lett*, 1995, **36**, 3609–3612.
49 A. Guram, R. Rennels and S. L. Buchwald, *Angewandte Chemie - International Edition*, 1995, **34**, 1261–1372.
50 L. M. Alcazar-roman, J. F. Hartwig, A. L. Rheingold, L. M. Liable-sands, I. A. Guzei, Y. U. V and P. O. Box, *J Am Chem Soc*, 2000, **122**, 4618–4630.
51 U. K. Singh, E. R. Strieter, D. G. Blackmond and S. L. Buchwald, *J Am Chem Soc*, 2002, **124**, 14104–14114.
52 J. F. Hartwig, S. Richards, D. Baranano and F. Paul, *J Am Chem Soc*, 1996, **118**, 3626–3633.
53 M. S. Driver and J. F. Hartwig, *J Am Chem Soc*, 1996, **118**, 7217–7218.
54 J. P. Wolfe and S. L. Buchwald, *Journal of Organic Chemistry*, 2000, **65**, 1144–1157.
55 B. P. Fors, N. R. Davis and S. L. Buchwald, *J Am Chem Soc*, 2009, **131**, 5766–5768.
56 J. Louie, M. S. Driver, B. C. Hamann and J. F. Hartwig, *J Org Chem*, 1997, **62**, 1268–1273.
57 T. Ogata and J. F. Hartwig, *J Am Chem Soc*, 2008, **130**, 13848–13849.
58 D. M. Peacock, C. B. Roos and J. F. Hartwig, *ACS Cent Sci*, 2016, **2**, 647–652.
59 J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy and L. M. Alcazar-roman, *J Org Chem*, 1999, **64**, 5575–5580.
60 J. Yin, M. M. Zhao, M. A. Huffman and J. M. Mcnamara, *Org Lett*, 2002, **4**, 3481–3484.
61 D. Lee and J. F. Hartwig, *Org Lett*, 2005, **7**, 1169–1172.
62 J. Yin and S. L. Buchwald, *Org Lett*, 2000, **2**, 1101–1104.
63 M. R. Biscoe, B. P. Fors and S. L. Buchwald, *J Am Chem Soc*, 2008, **130**, 6686–6687.
64 A. Schnyder, A. F. Indolese, M. Studer and H. Blaser, *Angewandte Chemie - International Edition*, 2002, **41**, 3509–3722.
65 D. Zim and S. L. Buchwald, *Org Lett*, 2003, **5**, 2413–2415.
66 P. Ruiz-Castillo and S. L. Buchwald, *Chem Rev*, 2016, **116**, 12564–12649.
67 R. Dorel, C. P. Grugel and A. M. Haydl, *Angewandte Chemie - International Edition*, 2019, **58**, 17083–17479.
68 M. Marin, R. Rama and M. Carmen Nicasio, *The Chemical record*, 2016, **16**, 1741–2183.
69 J. Chen, J. Li and Z. Dong, *Adv Synth Catal*, 2020, **362**, 3257–3446.
70 A. Volkov, F. Tinnis, T. Slagbrand, P. Trillo and H. Adolfsson, *Chem Soc Rev*, 2016, **45**, 6685–6697.
71 H. Brown and S. Krishnamurthy, *Tetrahedron*, 1979, **35**, 567–607.
72 J. R. Cabrero-Antonino, R. Adam, V. Papa and M. Beller, *Nat Commun*, 2020, **11**, Article 3893.
73 A. E. Finholt, A. C. Bond and H. Schlesinger, *J Am Chem Soc*, 1947, **69**, 1199–1203.
74 V. M. Miúović and M. L. Mihailović, *J Org Chem*, 1953, **18**, 1190–1200.
75 R. Nystrom and W. Brown, *J Am Chem Soc*, 1947, **69**, 1197–1199.
76 T. J. Watson, T. A. Ayers, N. Shah, D. Wenstrup, M. Webster, D. Freund, S. Horgan and J. P. Carey, *Org Process Res Dev*, 2003, **7**, 521–532.
77 C. Botuha, C. Galley and T. Gallagher, *Org Biomol Chem*, 2004, **2**, 1825–1826.
78 S. Hu, L. Zhang, J. Li, S. Luo and J. P. Cheng, *European J Org Chem*, 2011, **2011**, 3347–3352.
79 P. Li, Z. Chai, S.-L. Zhao, Y.-Q. Yang, H.-F. Wang, C.-W. Zheng, Y.-P. Cai, G. Zhao and S.-Z. Zhu, *Chemical Communications*, 2009, **2009**, 7369–7371.
80 A. Tsolakidou, *Research and reviews: Journal of Chemistry* , 2021, **10**, 1–1.

81 M. Cerny, J. Malek, M. Capka and V. Chvalovsky, *Collect Czechoslov Chem Commun*, 1969, **34**, 1033–1041.
82 V. Bazant, M. Capka, M. Cerny, V. Chvalovsky, K. Kochleof, M. Kraus and J. Malek, *Tetrahedron Letters* , 1968, **9**, 3303–3306.
83 M. Kuehne and P. Shannon, *J Org Chem*, 1977, **42**, 2082–2087.
84 S. H. Xiang, J. Xu, H. Q. Yuan and P. Q. Huang, *Synlett*, 2010, **2010**, 1829–1832.
85 W. N. Lipscomb, *Advances in Organic Chemistry and Radiochemistry*, 1959, **1**, 117–156.
86 H. Brown, H. Schlesinger and A. Burg, *J Am Chem Soc*, 1939, **61**, 673–680.
87 H. Brown and P. Heim, *J Am Chem Soc*, 1964, **86**, 3566–3567.
88 H. Brown, Y. M. Choi and S. Narasimhan, *J Org Chem*, 1982, **47**, 3153–3163.
89 D. G. Hall, C. Laplante, S. Manku and J. Nagendran, *Journal of Organic Chemistry*, 1999, **64**, 698–699.
90 M. Couturier, J. L. Tucker, B. M. Andresen, P. Dubé and J. T. Negri, *Org Lett*, 2001, **3**, 465–467.
91 R. O. Hutchins and F. Cistone, *Org Prep Proced Int*, 1981, **13**, 225–240.
92 M. Potyen, K. V. B. Josyula, M. Schuck, S. Lu, P. Gao and C. Hewitt, *Org Process Res Dev*, 2007, **11**, 210–214.
93 P. C. Tang, Y. D. Su, J. Feng, J. H. Fu, J. L. Yang, L. Xiao, J. H. Peng, Y. L. Li, L. Zhang, B. Hu, Y. Zhou, F. Q. Li, B. B. Fu, L. G. Lou, A. S. Gong, G. H. She, W. H. Sun and X. T. Mong, *J Med Chem*, 2010, **53**, 8140–8149.
94 A. S. B. Prasad, J. V. B. Kanth and M. Periasamy, *Tetrahedron*, 1992, **48**, 4623–4628.
95 J. V. B. Kanth and H. C. Brown, *Inorg Chem*, 2000, **39**, 1795–1802.
96 G. Godjoian and B. Singaram, *Tetrahedron Lett*, 1997, **38**, 1717–1720.
97 T. A. Smith, X. Yang, H. Wu, B. Pouw, R. R. Matsumoto and A. Coop, *J Med Chem*, 2008, **51**, 3322–3325.
98 B. Alcaide, P. Almendros, C. Aragoncillo and N. R. Salgado, *Journal of Organic Chemistry*, 1999, **64**, 9596–9604.
99 B. Wojcik and H. Adkins, *J Am Chem Soc*, 1934, **56**, 2419–2424.
100 M. Meuresch, S. Westhues, W. Leitner and J. Klankermayer, *Angewandte Chemie International Edition*, 2016, **55**, 1215–1564.
101 J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinski, W. Leitner, A. M. Z. Slawin and D. J. Cole-Hamilton, *Chemistry - A European Journal*, 2013, **19**, 10765–11095.
102 J. R. Cabrero-Antonino, E. Alberico, K. Junge, H. Junge and M. Beller, *Chem Sci*, 2016, **7**, 3432–3442.
103 Y. Q. Zou, S. Chakraborty, A. Nerush, D. Oren, Y. Diskin-Posner, Y. Ben-David and D. Milstein, *ACS Catal*, 2018, **8**, 8014–8019.
104 M. L. Yuan, J. H. Xie, S. F. Zhu and Q. L. Zhou, *ACS Catal*, 2016, **6**, 3665–3669.
105 V. Papa, J. R. Cabrero-Antonino, A. Spannenberg, K. Junge and M. Beller, *Catal Sci Technol*, 2020, **10**, 6116–6128.
106 L. Köring, N. A. Sitte and J. Paradies, *Synthesis (Germany)*, 2022, **54**, 1287–1300.
107 R. Kuwano, M. Takahashi and Y. Ito, *Tetrahedron Lett*, 1998, **39**, 1017–1020.
108 M. Igarashi and T. Fuchikami, *Tetrahedron Lett*, 2001, **42**, 1945–1947.
109 Y. Motoyama, K. Mitsui, T. Ishida and H. Nagashima, *J Am Chem Soc*, 2005, **127**, 13150–13151.
110 H. Sasakuma, Y. Motoyama and H. Nagashima, *Chemical Communications*, 2007, 4916–4918.
111 S. Das, Y. Li, L. Q. Lu, K. Junge and M. Beller, *Chemistry - A European Journal*, 2016, **22**, 7050–7053.
112 C. Cheng and M. Brookhart, *J Am Chem Soc*, 2012, **134**, 11304–11307.
113 S. Hanada, E. Tsutsumi, Y. Motoyama and H. Nagashima, *J Am Chem Soc*, 2009, **131**, 15032–15040.
114 T. V. Q. Nguyen, W. J. Yoo and S. Kobayashi, *Adv Synth Catal*, 2016, **358**, 452–458.
115 S. Das, B. Join, K. Junge and M. Beller, *Chemical Communications*, 2012, **48**, 2683–2685.
116 S. Zhou, K. Junge, D. Addis, S. Das and M. Beller, *Angewandte Chemie - International Edition*, 2009, **48**, 9507–9510.
117 S. Das, D. Addis, S. Zhou, K. Junge and M. Beller, *J Am Chem Soc*, 2010, **132**, 1770–1771.
118 S. Das, D. Addis, K. Junge and M. Beller, *Chemistry - A European Journal*, 2011, **17**, 12186–12192.
119 W. Xie, M. Zhao and C. Cui, *Organometallics*, 2013, **32**, 7440–7444.

120 N. C. Mamillapalli and G. Sekar, *RSC Adv*, 2014, **4**, 61077–61085.
121 A. Augurusa, M. Mehta, M. Perez, J. Zhu and D. W. Stephan, *Chemical Communications*, 2016, **52**, 12195–12198.
122 G. Pelletier, W. S. Bechara and A. B. Charette, *J Am Chem Soc*, 2010, **132**, 12817–12819.
123 M. X. Tan and Y. Zhang, *Tetrahedron Lett*, 2009, **50**, 4912–4915.
124 E. Blondiaux and T. Cantat, *Chemical Communications*, 2014, **50**, 9349–9352.
125 R. C. Chadwick, V. Kardelis, P. Lim and A. Adronov, *Journal of Organic Chemistry*, 2014, **79**, 7728–7733.
126 P. Q. Huang, Q. W. Lang and Y.-R. Wang, *Journal of Organic Chemistry*, 2016, **81**, 4235–4243.
127 W. Yao, H. Fang, Q. He, D. Peng, G. Liu and Z. Huang, *Journal of Organic Chemistry*, 2019, **84**, 6084–6093.
128 D. Mukherjee, S. Shirase, K. Mashima and J. Okuda, *Angewandte Chemie International Edition*, 2016, **55**, 13321–13329.
129 Y. Li, J. A. Molina De La Torre, K. Grabow, U. Bentrup, K. Junge, S. Zhou, A. Brückner and M. Beller, *Angewandte Chemie - International Edition*, 2013, **52**, 11577–11580.
130 A. Chardon, T. Mohy El Dine, R. Legay, M. de Paolis, J. Rouden and J. Blanchet, *Chemistry - A European Journal*, 2017, **23**, 2005–2009.
131 B. S. Jursic and Z. Zdravkovski, *Synth Commun*, 1993, **23**, 2761–2770.
132 E. Valeur and M. Bradley, *Chem Soc Rev*, 2009, **38**, 606–631.
133 V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471–479.
134 S. C. Ghosh, J. S. Y. Ngiam, A. M. Seayad, D. T. Tuan, C. L. L. Chai and A. Chen, *Journal of Organic Chemistry*, 2012, **77**, 8007–8015.
135 J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday and S. L. Buchwald, *Angewandte Chemie - International Edition*, 2007, **46**, 8460–8463.
136 M. Zhang, S. Imm, S. Bähn, L. Neubert, H. Neumann and M. Beller, *Angewandte Chemie - International Edition*, 2012, **51**, 3905–3909.
137 C. Liana Allen, B. N. Atkinson and J. M. J. Williams, *Angewandte Chemie - International Edition*, 2012, **51**, 1383–1386.
138 J. Magano, *Org Process Res Dev*, 2022, **26**, 1562–1689.
139 J. R. Dunetz, J. Magano and G. A. Weisenburger, *Org Process Res Dev*, 2016, **20**, 140–177.
140 T.-H. Chan and L. T. L. Wong, *J Org Chem*, 1969, **34**, 2766–2767.
141 S. H. van Leeuwen, P. J. L. M. Quaedflieg, Q. B. Broxterman and R. M. J. Liskamp, *Tetrahedron Lett*, 2002, **43**, 9203–9207.
142 T. Tozawa, Y. Yamane and T. Mukaiyama, *Chem Lett*, 2005, **34**, 734–735.
143 S. J. Aspin, S. Taillemaud, P. Cyr and A. B. Charette, *Angewandte Chemie International edition*, 2016, **55**, 13833–13837.
144 D. C. Braddock, P. D. Lickiss, B. C. Rowley, D. Pugh, T. Purnomo, G. Santhakumar and S. J. Fussell, *Org Lett*, 2018, **20**, 8–11.
145 D. C. Braddock, J. J. Davies and P. D. Lickiss, *Org Lett*, 2022, **24**, 1175–1179.
146 E. Morisset, A. Chardon, J. Rouden and J. Blanchet, *European J Org Chem*, 2020, **2020**, 388–392.
147 J. J. Davies, D. Christopher Braddock and P. D. Lickiss, *Org Biomol Chem*, 2021, **19**, 6746–6760.
148 Z. Ruan, R. M. Lawrence and C. B. Cooper, *Tetrahedron Lett*, 2006, **47**, 7649–7651.
149 M. Sayes and A. B. Charette, *Green Chemistry*, 2017, **19**, 5060–5064.
150 M. C. D'Amaral, N. Jamkhou and M. J. Adler, *Green Chemistry*, 2021, **23**, 288–295.
151 W. Muramatsu, C. Manthena, E. Nakashima and H. Yamamoto, *ACS Catal*, 2020, **10**, 9594–9603.
152 D. F. J. Hamstra, D. C. Lenstra, T. J. Koenders, F. P. J. T. Rutjes and J. Mecinović, *Org Biomol Chem*, 2017, **15**, 6426–6432.
153 M. C. D'Amaral, K. G. Andrews, R. M. Denton and M. J. Adler, *Synthesis (Stuttg)*, , DOI:10.1039/x0xx00000x.
154 B. Hu, Y. Y. Jiang, P. Liu, R. X. Zhang, Q. Zhang, T. T. Liu and S. Bi, *Org Biomol Chem*, 2019, **17**, 9232–9242.

155 P. F. Hudrlik and R. Feasley, *Tetrahedron Lett*, 1972, **13**, 1781–1784.
156 T.-H. Chan and L. Wong, *J. Org. Chem*, 1971, **36**, 850–853.
157 K. G. Andrews and R. M. Denton, *Chemical Communications*, 2017, **53**, 7982–7985.
158 E. L. Stoll, T. Tongue, K. G. Andrews, D. Valette, D. J. Hirst and R. M. Denton, *Chem Sci*, 2020, **11**, 9494–9500.
159 E. L. Stoll, T. Barber, D. J. Hirst and R. M. Denton, *Chemical Communications*, 2022, **58**, 3509–3512.
160 K. Schellenberg, *J Org Chem*, 1963, **28**, 3259–3261.
161 A. F. Abdel-Magid and S. J. Mehrman, *Org Process Res Dev*, 2006, **10**, 971–1031.
162 R. Borch, M. Bernstein and H. Dupont Durst, *Journal of the American Chemical Society* , 1971, **93**, 2897–2904.
163 K. Murugesan, T. Senthamarai, V. G. Chandrashekhar, K. Natte, P. C. J. Kamer, M. Beller and R. v. Jagadeesh, *Chem Soc Rev*, 2020, **49**, 6273–6328.
164 T. Irrgang and R. Kempe, *Chem Rev*, 2020, **120**, 9583–9674.
165 I. Micovic, M. Ivanovic, D. Piatak and V. Bojic, *Synthesis (Stuttg)*, 1991, **1991**, 1043–1045.
166 M. J. Bhanushali, N. S. Nandurkar, M. D. Bhor and B. M. Bhanage, *Tetrahedron Lett*, 2007, **48**, 1273–1276.
167 J. Brussee, R. A. T. M. van Benthem, A. Kruse' and C. van Der, *Tetrahedron Asymmetry*, 1990, **1**, 163–166.
168 H. Kato, I. Shibata, Y. Yasaka, S. Tsunoi, M. Yasuda and A. Baba, *Chemical Communications*, 2006, **2006**, 4189–4191.
169 R. Apodaca and W. Xiao, *Org Lett*, 2001, **3**, 1745–1748.
170 O.-Y. Lee, K.-L. Law, C.-Y. Ho and D. Yang, *Journal of Organic Chemistry*, 2008, **73**, 8829–8837.
171 R.-Y. Lai, C.-I. Lee and S.-T. Liu, *Tetrahedron*, 2008, **64**, 1213–1217.
172 T. Mizuta, S. Sakaguchi and Y. Ishii, *Journal of Organic Chemistry*, 2005, **70**, 2195–2199.
173 B. G. Das and P. Ghorai, *Chemical Communications*, 2012, **48**, 8276–8278.
174 B. G. Das and P. Ghorai, *Org Biomol Chem*, 2013, **11**, 4379–4382.
175 K. Miura, K. Ootsuka, S. Suda, H. Nishikori and A. Hosomi, *Synlett*, 2001, **2001**, 1617–1619.
176 S. Enthaler, *ChemCatChem*, 2010, **2**, 1411–1415.
177 J. Zheng, T. Roisnel, C. Darcel and J. B. Sortais, *ChemCatChem*, 2013, **5**, 2861–2864.
178 J. M. Blackwell, E. R. Sonmor, T. Scoccitti and W. E. Piers, *Org Lett*, 2000, **2**, 3921–3923.
179 C. Bergquist, B. M. Bridgewater, C. J. Harlan, J. R. Norton, R. A. Friesner and G. Parkin, *J Am Chem Soc*, 2000, **122**, 10581–10590.
180 V. Fasano, J. E. Radcliffe and M. J. Ingleson, *ACS Catal*, 2016, **6**, 1793–1798.
181 V. Fasano and M. J. Ingleson, *Chemistry - A European Journal*, 2017, **23**, 2217–2224.
182 S. E. Varjosaari, V. Skrypai, P. Suating, J. J. M. Hurley, A. M. D. Lio, T. M. Gilbert and M. J. Adler, *Adv Synth Catal*, 2017, **359**, 1872–1878.
183 S. E. Varjosaari, V. Skrypai, P. Suating, J. J. M. Hurley, T. M. Gilbert and M. J. Adler, *European J Org Chem*, 2017, **2017**, 229–232.
184 V. Skrypai, J. J. M. Hurley and M. J. Adler, *European J Org Chem*, 2016, **2016**, 2207–2211.
185 V. Skrypai, S. E. Varjosaari, F. Azam, T. M. Gilbert and M. J. Adler, *Journal of Organic Chemistry*, 2019, **84**, 5021–5026.
186 Y. Zabolotna, D. M. Volochnyuk, S. V Ryabukhin, D. Horvath, K. S. Gavrilenko, G. Marcou, Y. S. Moroz, O. Oksiuta and A. Varnek, *J Chem Inf Model*, 2022, **62**, 2171–2185.
187 J. E. Steves and S. S. Stahl, *J Am Chem Soc*, 2013, **135**, 15742–15745.
188 J. R. Parikh and W. v Doering, *Journal of the American Chemical Society* , 1967, **89**, 5505–5507.
189 A. J. Mancuso, S.-L. Huang and D. Swern, *J Org Chem*, 1978, **43**, 2480–2482.
190 B. G. Reed-Berendt, D. E. Latham, M. B. Dambatta and L. C. Morrill, *ACS Cent Sci*, 2021, **7**, 570–585.
191 P. A. Dub and T. Ikariya, *ACS Catal*, 2012, **2**, 1718–1741.
192 J. Li, C. Y. Huang and C. J. Li, *Angewandte Chemie - International Edition*, 2022, **61**, e202112770.
193 P. Marchini, G. Liso, A. Reho, F. Liberatore and F. Micheletti Moracci, *J Org Chem*, 1975, **40**, 3453–3456.

194 G. Gribble, P. Lord, J. Skotnicki, S. Dietz, J. Eaton and J. Johnson, *J Am Chem Soc*, 1974, **96**, 7812–7814.
195 G. Gribble, J. Jasinski, J. Pellicone and J. Panetta, *Synthesis (Stuttg)*, 1978, **1978**, 766–768.
196 S. A. I. Quadri, T. C. Das, S. Jadhav and M. Farooqui, *Synth Commun*, 2018, **48**, 267–277.
197 B. Emayavaramban, P. Chakraborty and B. Sundararaju, *ChemSusChem*, 2019, **12**, 3089–3093.
198 W. Liu, B. Sahoo, A. Spannenberg, K. Junge and M. Beller, *Angewandte Chemie International Edition*, 2018, **130**, 11673–11677.
199 I. Sorribes, J. R. Cabrero-Antonino, C. Vicent, K. Junge and M. Beller, *J Am Chem Soc*, 2015, **137**, 13580–13587.
200 Y. Shi, P. C. J. Kamer and D. J. Cole-Hamilton, *Green Chemistry*, 2017, **19**, 5460–5466.
201 I. Sorribes, K. Junge and M. Beller, *J Am Chem Soc*, 2014, **136**, 14314–14319.
202 M. Minakawa, M. Okubo and M. Kawatsura, *Tetrahedron Lett*, 2016, **57**, 4187–4190.
203 C. Qiao, X. Y. Yao, X. F. Liu, H. R. Li and L. N. He, *Asian J Org Chem*, 2018, **7**, 1815–1818.
204 Y. Ogiwara, T. Uchiyama and N. Sakai, *Angewandte Chemie International edition*, 2016, **55**, 1864–1867.
205 T. V. Q. Nguyen, W. J. Yoo and S. Kobayashi, *Adv Synth Catal*, 2016, **358**, 452–458.
206 P. Trillo and H. Adolfsson, *ACS Catal*, 2019, **9**, 7588–7595.
207 C. Qiao, X. F. Liu, X. Liu and L. N. He, *Org Lett*, 2017, **19**, 1490–1493.
208 K. G. Andrews, D. M. Summers, L. J. Donnelly and R. M. Denton, *Chemical Communications*, 2016, **52**, 1855–1858.
209 Y. Wei, Q. Xuan, Y. Zhou and Q. Song, *Organic Chemistry Frontiers*, 2018, **5**, 3510–3514.
210 K. G. Andrews, R. Faizova and R. M. Denton, *Nat Commun*, 2017, **8**, 1–6.
211 C. Lu, Z. Qiu, M. Xuan, Y. Huang, Y. Lou, Y. Zhu, H. Shen and B. Lin, *Synthesis and Catalysis*, 2020, **362**, 4151–4158.
212 M. Fu, R. Shang, W. Cheng and Y. Fu, *Angewandte Chemie - International Edition*, 2015, **54**, 9042–9046.
213 A. Scollan, University of Nottingham, 2020.
214 B. Baghernejad, *Curr Org Chem*, 2011, **15**, 3091–3097.
215 A. Newman-Tancredi, D. Cussac, V. Audinot, J. P. Nicolas, F. de Ceuninck, J. A. Boutin and M. J. Millan, *Journal of Pharmacology and Experimental Therapeutics*, 2002, **303**, 805–814.
216 M. J. Millan, D. Cussac, G. Milligan, C. Carr, V. A. L. Erie, A. Gobert, J. Rivet, M. Brocco, D. Duqueyroix, J. Nicolas, J. A. Boutin and A. Newman-tancredi, *Journal of Pharmacology and Experiental Thrapeutics*, 2001, **297**, 876–887.
217 CN1884280A, 2017, 1–7.
218 A. Griffin, K. R. Hamling, K. Knupp, S. G. Hong, L. P. Lee and S. C. Baraban, *Brain*, 2017, **140**, 669–683.
219 J. M. Richter, M. Schaefer and K. Hill, *Mol Pharmacol*, 2014, **86**, 514–521.
220 World Intellectual Property Organization, WO2010118286A2, 2010.
221 X. Zhang, R. Huang, J. Marrot, V. Coeffard and Y. Xiong, *Tetrahedron*, 2015, **71**, 700–708.
222 J. Z. Vlahakis, D. Vukomanovic, K. Nakatsu and W. A. Szarek, *Bioorg Med Chem*, 2013, **21**, 6788–6795.
223 K. M. Korch, C. Eidamshaus, D. C. Behenna, S. Nam, D. Horne and B. M. Stoltz, *Angewandte Chemie - International Edition*, 2015, **54**, 179–183.
224 A. R. Bassindale and T. Stout, *J Organomet Chem*, 1984, **271**, 1–3.
225 M. B. Johansen and A. T. Lindhardt, *Org Biomol Chem*, 2020, **18**, 1417–1425.
226 S. Nishimoto, H. Nakahashi and M. Toyota, *Tetrahedron Lett*, 2020, **61**, 152599.
227 O. O. Kovalenko, A. Volkov and H. Adolfsson, *Org Lett*, 2015, **17**, 446–449.
228 D. Wei, C. Netkaew, V. Carré and C. Darcel, *ChemSusChem*, 2019, **12**, 3008–3012.
229 N. J. Taylor, E. Emer, S. Preshlock, M. Schedler, M. Tredwell, S. Verhoog, J. Mercier, C. Genicot and V. Gouverneur, *J Am Chem Soc*, 2017, **139**, 8267–8276.
230 R. A. Snelling, G. Amberchan, A. Resendez, C. L. Murphy, L. Porter and B. Singaram, *Tetrahedron Lett*, 2017, **58**, 4073–4077.
231 R. Alam and G. A. Molander, *Org Lett*, 2018, **20**, 2680–2684.

232 O. I. Afanasyev, D. L. Usanov and D. Chusov, *Org Biomol Chem*, 2017, **15**, 10164–10166.
233 R. M. B. Dyer, P. L. Hahn and M. K. Hilinski, *Org Lett*, 2018, **20**, 2011–2014.
234 W. M. J. Ma, T. D. James and J. M. J. Williams, *Org Lett*, 2013, **15**, 4850–4853.
235 X. Guo and O. S. Wenger, *Angewandte Chemie - International Edition*, 2018, **57**, 2469–2473.
236 Q. Zou, G. Long, T. Zhao and X. Hu, *Green Chemistry*, 2020, **22**, 1134–1138.
237 Y. Kon, T. Nakashima, T. Fujitani, T. Murayama and W. Ueda, *Synlett*, 2019, **30**, 287–292.
238 Z. Shao, S. Fu, M. Wei, S. Zhou and Q. Liu, *Angewandte Chemie - International Edition*, 2016, **55**, 14653–14657.
239 R. W. Bowman, P. T. Stephenson, N. K. Terrett and Young Adrain R., *Tetrahedron*, 1995, **51**, 7959–7980.
240 S. L. Montgomery, J. Mangas-sanchez, M. P. Thompson, G. A. Aleku, B. Dominguez and N. J. Turner, *Angewandte Chemie - International Edition*, 2017, **56**, 10491–10494.
241 P. Q. Huang, Q. W. Lang and Y. R. Wang, *Journal of Organic Chemistry*, 2016, **81**, 4235–4243.
242 T. D. Nixon, M. K. Whittlesey and J. M. J. Williams, *Tetrahedron Lett*, 2011, **52**, 6652–6654.
243 Q. M. Kainz, M. Zeltner, M. Rossier, W. J. Stark and O. Reiser, *Chemistry - A European Journal*, 2013, **19**, 10038–10045.
244 P. Ye, Y. Shao, X. Ye, F. Zhang, R. Li, J. Sun, B. Xu and J. Chen, *Org Lett*, 2020, **22**, 1306–1310.
245 X. Zhang, R. Huang, J. Marrot, V. Coeffard and Y. Xiong, *Tetrahedron*, 2015, **71**, 700–708.
246 X. Wang, S. Yu, C. Wang, D. Xue and J. Xiao, *Org Biomol Chem*, 2016, **14**, 7028–7037.
247 P. Wang, S. M. Batt, B. Wang, L. Fu, R. Qin, Y. Lu, G. Li and G. S. Besra, *J Med Chem*, 2021, **64**, 6241–6261.
248 M. D. Visco, J. M. Wieting and A. E. Mattson, *Org Lett*, 2016, **18**, 2883–2885.
249 D. Leow, *Org Lett*, 2014, **16**, 5812–5815.
250 T. W. Bousfield, K. P. R. Pearce, S. B. Nyamini, A. Angelis-Dimakis and J. E. Camp, *Green Chemistry*, 2019, **20**, 3675–3681.
251 C. Hansch, A. Leo and R. W. Taft, *Chem Rev*, 1991, **91**, 165–195.

Chapter 2

Metal-free Reductive Methylation of Amines

The methylation of amines often requires toxic reagents and can result in complex mixtures of products. Here, we report an extension of the process described in Chapter One to achieve reductive methylation using formic acid. This method is successful for the mono-methylation of secondary amines and the di-methylation of primary amines. Mono-methylation of primary amines is investigated and found not to be possible at this time. Several mono- and di-methylations are carried out, demonstrating not only non-racemic chiral amines but also the synthesis of a range of pharmaceuticals and derivatives. Mechanistically, the reaction is shown to proceed *via* a formamide intermediate, however reduction of this compound is proposed *via* a complex multi pathway process.

Milly Stoneley

1 Introduction

1.1 Importance of *N*-methylated Amines

The fundamental importance of amines has already been demonstrated. This chapter will focus specifically on mono- and di- *N*-methylated amines. This functional group is especially prevalent in pharmaceutical compounds and accounts for 17% of all amines reported in the literature. It is also present in over 13% of the top selling small molecule pharmaceuticals in 2018.[1,2]

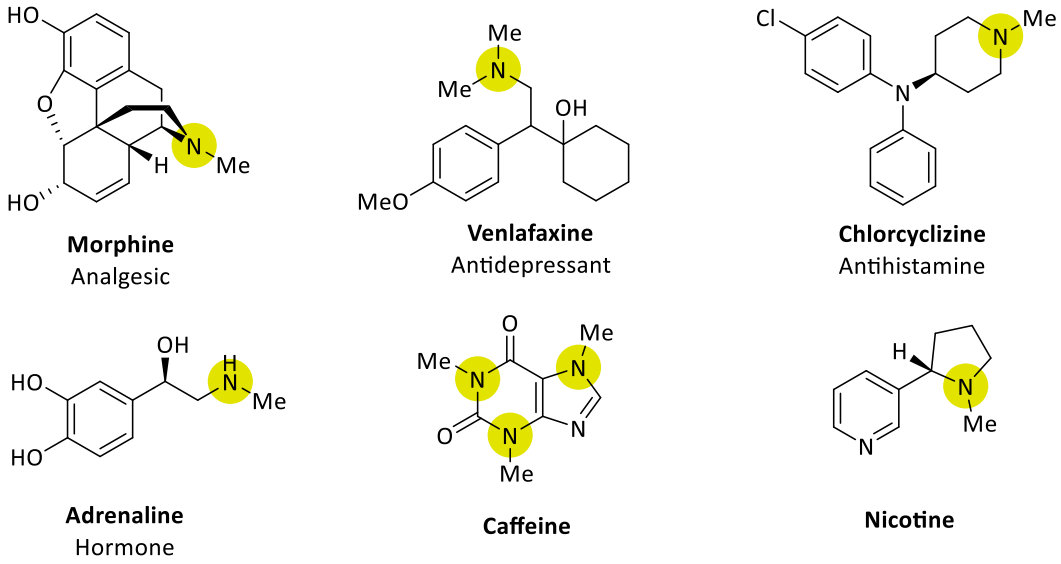


Figure 25: *Examples of N-methylated amines*

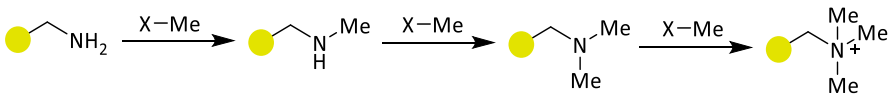
The importance of methylated amines stems from the 'magic methyl' effect which is usually demonstrated for C-H bonds, but has been shown to be present for N-H to N-Me transformations. This effect is attributed to physical phenomena such as solvation effects, metabolic stability, hydrophobic interactions and conformational changes.[3] Together these effects can cause an increase in potency of two to three orders of magnitude. This is especially evident in a comparison of normorphine with morphine, where a six-fold reduction in the analgesic properties was demonstrated and was attributed to passage through the blood-brain barrier being more difficult as a result of the increased polarity of the secondary amine. In the same way, the tri- methylated caffeine leads to increased central nervous system (CNS) stimulation, due to increased lipophilicity compared to the di methylated theobromine.[4]

1.2 Synthesis of *N*-methylated Amines

As *N*-methylated amines are of such importance, there are many methods for this synthesis. However, synthesis methods for the construction of *N*-methyl amines are often complicated by the formation of dimethylated products as well as quaternary ammonium salts. A summary of the most common approaches follows.

1.2.1 Amine Methylation Using Traditional Electrophiles

One of the most common methods for methylation is based upon simple electrophilic reagents. For example, methyl iodide (MeI),[5,6] diazomethane[7] and dimethyl sulfate[8] are commonly used for this process, although others are known.[9–11] This reaction proceeds through an S_N2 mechanism and, due to increased nucleophilicity of the resulting product, complex mixtures are often formed. As such, this process is usually reserved for the synthesis of tertiary amine products; although mono-methylation reactions of primary amines are known, however they usually require large excesses of the amine.[7,12]



Scheme 56: *Over methylation of primary amines*

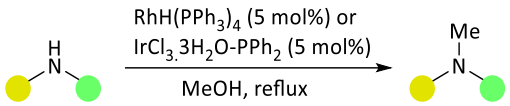
The main issues associated with electrophilic methylating reagents are their handling. These compounds are not only carcinogenic, but also acutely toxic, and as such are unattractive, particularly on a process or manufacturing scale.[13] Diazomethane presents additional problems since it is extremely explosive, its precursors are no longer commercially available, and it requires specialised glassware for use.

1.2.1 Amine Methylation Using Methanol – "hydrogen borrowing"

A popular alternative to the classical method described above involves the use of methanol in so called "hydrogen borrowing" methodology.[14] The use of MeOH as the source of the methyl group is significant in terms of cost and availability. It also has much reduced toxicity compared to other

conventional electrophilic reagents. Furthermore, it can be employed as the reaction solvent in addition to functioning as the C1 donor.[13] The availability of methanol is also significant, with approximately 100 million tons per year being produced *via* a plethora of methods, making it a sustainable source.[15] The general mechanism has been described in Chapter 1 (Scheme 16) and here specific applications with respect to methylation are described.

The use of alcohols for *N*-alkylation had previously been disclosed,[16,17] but was only applied specifically to methylation by Grigg in 1981.[18] He used both rhodium and iridium catalysts to investigate a range of simple amines, demonstrating both mono and dimethylation.

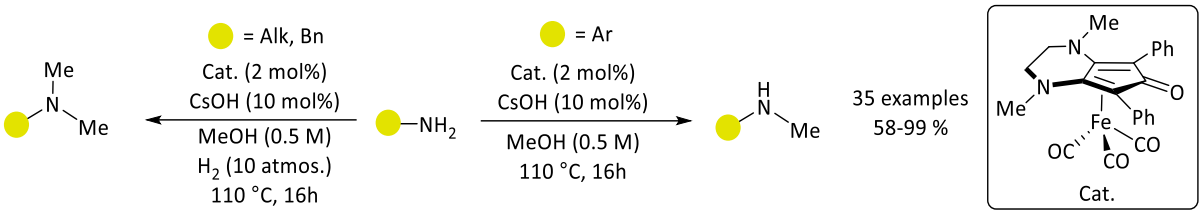


Scheme 57: Grigg's N-methylation using Rh or Ir catalysis

However, the activation of methanol is challenging due to its high dehydrogenation energy. As a result, it was not until 2010 that this was investigated further, when Huang demonstrated *N*-methylation in the presence of a palladium catalyst.[15,19] Since then, a range of precious metals such as iridium,[20,21] palladium,[22,23] ruthenium[24–26] and platinum[27] have been shown to catalyse *N*-methylation reactions. However, the cost and availability of these metals make these processes undesirable. As a result, less expensive and more environmentally benign metals such as iron,[28] copper[29] and nickel[30] have also been demonstrated.

In 2018, Renaud published an iron-catalysed *N*-methylation process detailing the synthesis of aromatic and aliphatic mono- and di- methylamines (Scheme 58).[28] For aniline type structures, the product was exclusively found to be the mono-methylated compounds, however aliphatic and benzylic amines gave tertiary amine products. The functional group tolerance was also shown to be good, with free alcohols, ketones, alkenes and nitriles being demonstrated in the reaction scope, in addition to chiral amines

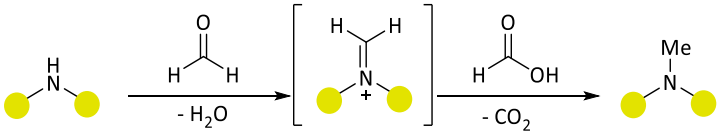
and the chemoselective methylation of tryptamine. In some cases, H_2 was required to promote dehydration over dehydrogenation.



Scheme 58: Renaud's synthesis of mono- and di- methylated amines

1.2.2 Amine Methylation Using Formaldehyde – Reductive Amination

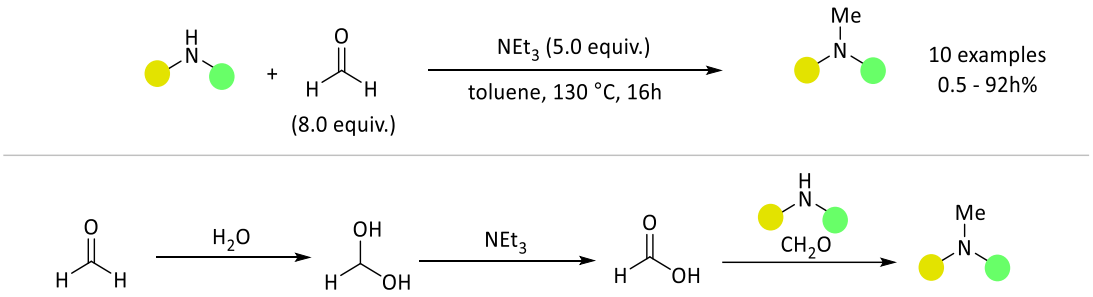
The use of reductive amination chemistry is also commonly employed for *N*-methylation. Formaldehyde is used as the C1 source in the formation of the iminium ion, which is then reduced to the methylamine product. Traditional reductants such as $NaBH(OAc)_3$[31,32] and $NaBH_3CN$[33,34] have been demonstrated for this process, although formic acid is commonly used as the hydride donor in an Eschweiler-Clarke reaction.[35,36]



Scheme 59: *General mechanism for Eschweiler-Clarke pathway*

Classic Eschweiler-Clarke reactions require an excess of both formic acid and formaldehyde, elevated temperatures and long reaction times and as a result, improved methods utilising formaldehyde have been published. Metal catalysts such as ruthenium,[37,38] cobalt[39] and gold[40] in addition to the less expensive and more easily handleable nickel[41,42] and zinc,[43] have all been demonstrated in the synthesis of methylamines. Despite this, synthesis of mono-methylated secondary amines was not possible for these examples and the *N,N*-dimethyl product was formed preferentially. Formation of *N*-methyl secondary amines is possible using metal-catalysis through control of formaldehyde stoichiometry and reaction time, although selective adsorption onto a metal surface, has also been demonstrated.[44–47]

Looking towards metal-free reductive methylations, only a single example exists in the literature. [48] Here, formaldehyde acts as both the methyl source and the reductant through base mediated conversion to formic acid *in situ* through the Cannizzaro reaction (Scheme 60). This allows methylation *via* an Eschweiler-Clarke pathway. However, due to the general inefficiency of this reaction, large excesses of both formaldehyde and base were required. In addition, Mannich reactions were shown to be a competitive side reaction and the scope was limited to electron rich amines.



Scheme 60: Wu's methylation using formaldehyde and NEt_3

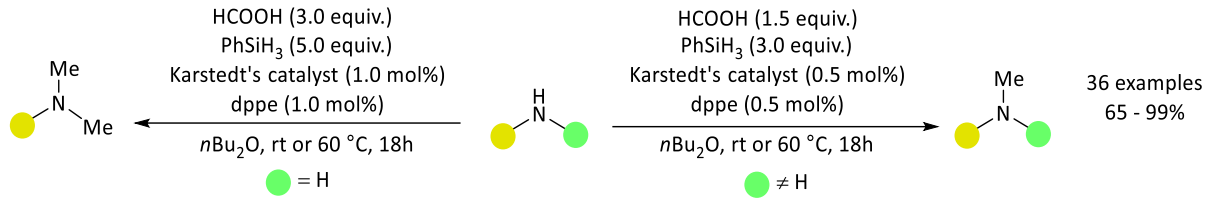
1.2.3 **Amine Methylation Using Formic Acid – Reductive Amination**

The use of metals is disadvantageous from a sustainability perspective and the use of toxic formaldehyde is also undesirable at a manufacturing scale. This has stimulated the investigation of less toxic and easier to handle C1 sources, and CO_2,[49,50] dimethyl carbonate[51,52] and formic acid have emerged as practical alternatives. The use of formic acid (FA) will be discussed in more detail below, and reviews by Jagadeesh and Chen summarise these alternative C1 sources.[53,54]

FA is a non-toxic and abundant by-product of biomass processing and CO_2 hydrogenation, making it a highly attractive and a sustainable alternative to other C1 sources.[55] Although FA has been used as a nominal electrophile for reductive methylation in combination with a range of silanes, this process is not well-represented in the literature. The known processes are discussed below.

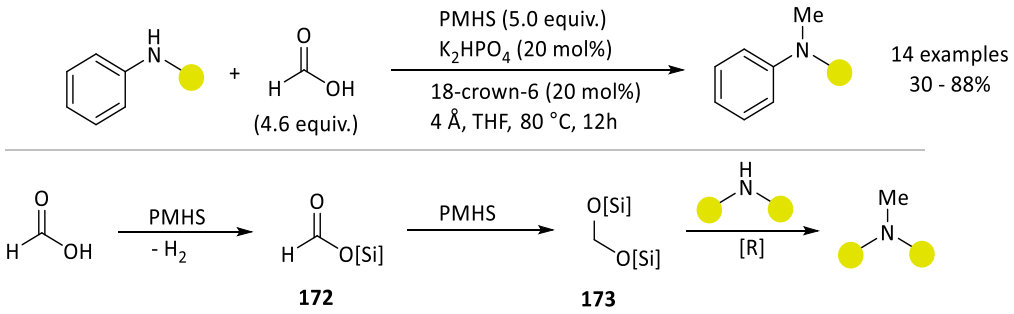
This transformation was first investigated by Beller in 2014, who as a precursor to his novel use of Karstedt's catalyst for general reductive amination from carboxylic acids, developed a methylation process using the same conditions (Scheme 61)[56] Compounds containing a range of functional groups

were mono- or di-methylated in good yields, however the formation of monomethylated secondary amine products was not possible. This was rationalised through the proposed mechanism whereby both formamide and urea intermediates were implicated in a complex multi-path process.



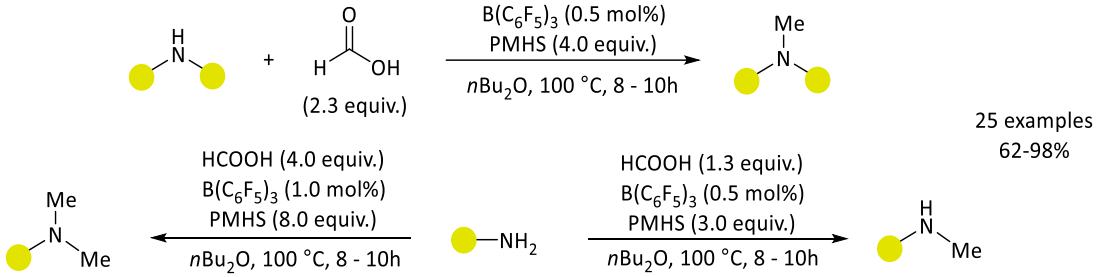
Scheme 61: *Beller's mono- and di-methylation using $PhSiH_3$/Karstedt's catalyst*

Iridium[57] and a further example of platinum catalysis[58] have also been demonstrated for this transformation, however the financial and environmental impact make these methods unattractive. As an alternative, processes using more benign copper[59] and iron[60] catalysts have also been published. In 2019, Deng and Lin published an air stable PMHS mediated process catalysed by a simple inorganic base (Scheme 62).[61] The scope was limited, investigating only the methylation of secondary anilines with some functionality. However, the presence of strong electron-donating groups lead to formation of the formamide over methylation. In addition, high equivalents of acid and silane were needed to achieve a single methylation. Interestingly, the mechanism was demonstrated to not proceed *via* a formamide intermediate, as with the other processes, but rather through a silyl formate (**172**) and subsequent reduction to a silylated acetal (**173**) which acts as the active C1 source.



Scheme 62: *Deng and Lin's methylation using PMHS/K_2HPO_4*

The only metal-free methylation was published by Fu and Shang in 2014 as discussed in Chapter One (Scheme 63).[62] This process utilised an electrophilic boron catalyst, in conjunction with PMHS, to achieve methylated tertiary amines. In addition, one example of mono-methylation was demonstrated through control of the formic acid and PMHS stoichiometry. Functional group tolerance was shown to be broad with a range of varying compounds demonstrated including sensitive moieties. However, for a single methylation, 2.3 equivalents of acid were required, and this number increases to up to eight for a dimethylation process. Despite being a metal-free transformation, the use of high equivalents of both the acid and the silane and the need for Schlenk apparatus make this process unattractive particularly on a large scale.



Scheme 63: *Fu and Shang's mono- and di-methylation using $B(C_6F_5)_3$/PMHS*

1.3 Project Aims

The aim of this project was to expand upon the reductive amination developed in Chapter One to encompass the use of formic acid as a C1 source for the methylation of primary and secondary amines.

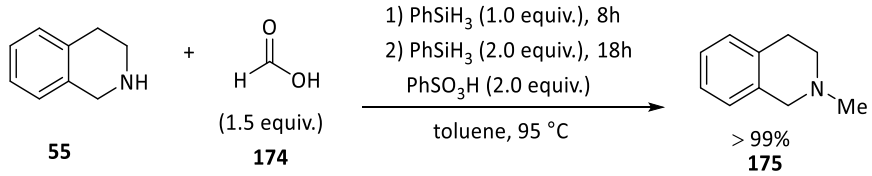
2 Results and Discussion

2.1 Optimisation

2.1.1 Mono-methylation of Secondary Amines

It was hoped that a protocol for the methylation of secondary amines could be developed directly from the general method described in Chapter One, with only minor adaptations. For example, the boiling point of formic acid is below the proposed reaction temperature, so to prevent evaporation, the

reaction was conducted at 95 °C. It is known that the reaction proceeds at lower temperatures but is more sluggish, and as a result, we decided to use the conditions with slightly elevated stoichiometries of carboxylic and sulfonic acids. 1,2,3,4-tetrahydroisoquinoline was chosen as the model substrate.

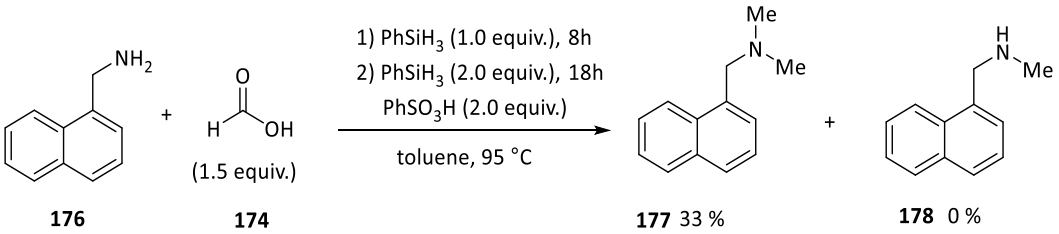


Scheme 64: *Optimised methylation conditions*

Pleasingly, with these minor modifications, the methylated product was obtained in quantitative yield and required no further purification beyond the standard acid-base workup used for the purification of the amine products in Chapter one.

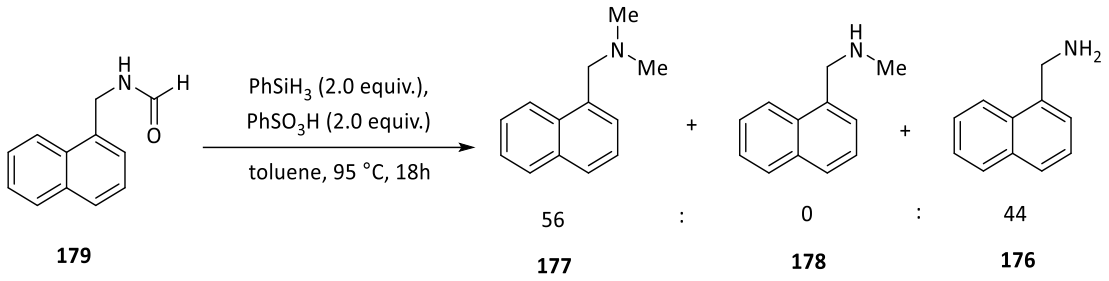
2.1.2 Attempts Towards Mono-methylation of Primary Amines

Achieving selective mono-methylation is known to be difficult. However, we hoped that the separate C-N bond forming step and proposed mechanism would prevent any di-methylation. In addition, di-alkylation was not observed in the synthesis of previous secondary amines, even under forcing conditions (Scheme 41). For the next optimisation, 1-napthylmethylamine was chosen as the model substrate.



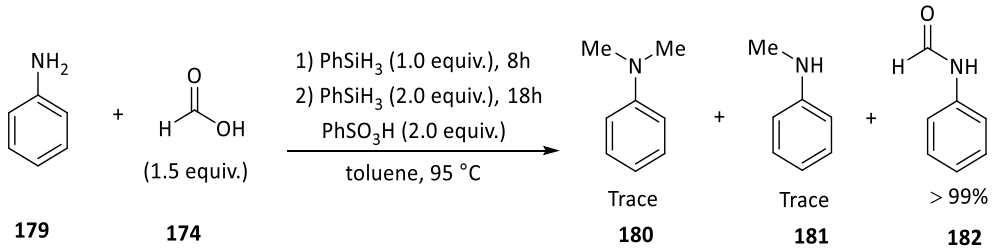
Scheme 65: *Attempts towards mono-methylation*

Unfortunately, the mono-methylated amine was not formed; although the di-methylated product was isolated in a 33% yield, and the starting material and the derived formamide accounted for the remainder of the mass balance. In an attempt to synthesise the mono-methylamine, the formamide intermediate was synthesised and subjected to the reduction conditions (Scheme 66).



Scheme 66: *Reduction of formamide*

However, this also resulted in the di-methylated product, suggesting cleavage of the formamide *in situ* to the constituent amine and formaldehyde. This allowed for di-methylation to occur through conventional reductive amination. In a final attempt aniline was employed. It was hoped that the decrease in reactivity would slow down the reduction, allowing for mono-methylation to take place.

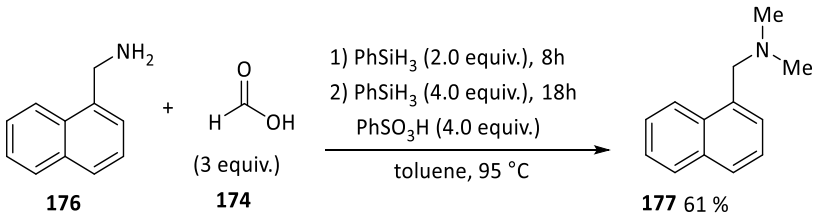


Scheme 67: Aniline reduction

Although both mono- and di-methylated products were identified, the formamide intermediate was observed as the main product. Unfortunately, the decrease in reactivity was too great to allow for the reduction to take place. More forcing conditions could be applied, however, dimethylation would likely occur preferentially.

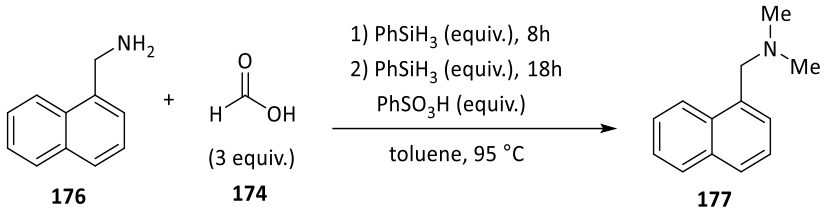
2.1.3 Di-methylation of Primary Amines

Following difficulties in developing a mono-methylation reaction, we decided to optimise this process for dimethylation, which is also an important transformation. Initially, the loading of benzenesulfonic acid and phenylsilane were doubled from the general conditions, again using 1-napthylmethylamine as the model substrate.



Scheme 68: *Initial di-methylation conditions*

This transformation was successful giving a good yield of 61% and provided a platform for further optimisation (Table 10).



Entry	Step 1 $PhSiH_3$ (equiv.)	Step 2 $PhSiH_3$ (equiv.)	$PhSO_3H$ (equiv.)	Yield (%)[a]
1	2	4	4	61
2	2	4	5	77
3	1	5	4	72
4	**1**	**5**	**5**	**89**
5	0	5	5	69

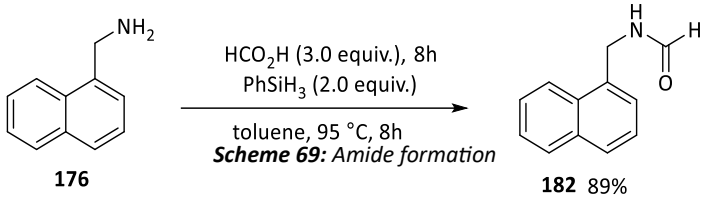
[a] *Isolated yields*

Table 10: Di-methylation optimisation

It was known from previous investigations, that an increase in sulfonic acid lead to the formation of more reactive higher order silyl sulfonates. As a result, optimisation began with increasing the equivalents of $PhSO_3H$ (Table 10, entry 2). Although this resulted in an increased yield, we wanted to, if possible, avoid the use of unnecessarily high equivalents of sulfonic acid.

Following an investigation of the amidation step (Scheme 69), it was observed that the formamide was formed exclusively, despite increased acid and silane loadings. As a result, only one equivalent of silane would be necessary in the first step. Pleasingly, alteration of the silane equivalents resulted in a good yield of 72%, a 10% increase from the original conditions, even with identical equivalents of sulfonic acid (Table 10, entry 3). In a final attempt to improve the yield, the loading of sulfonic acid was

increased (Table 10, entry 4), which resulted in a much-improved yield of 89%. Although 5 equivalents are high, $PhSO_3H$ is inexpensive and compares favorably with other metal-free methylations.[61,62]



Scheme 69: *Amide formation*

In addition, a control experiment was carried out as formic acid is known to react with amines with no silane present (Table 10, entry 5).[63] This reaction achieved a yield of 69% which is a 20% decrease from the optimised conditions. This confirmed that silane activation of the carboxylic acid is required for the high yield obtained in entry 4.

2.2 Scope

Following optimisation of the reaction conditions, the scope of the methylation reaction was investigated. As this process was designed to accompany the *N*-alkylation described in Chapter 1, this survey was more limited, although more complex pharmaceuticals and API's were investigated.

2.2.1 Mono-methylation

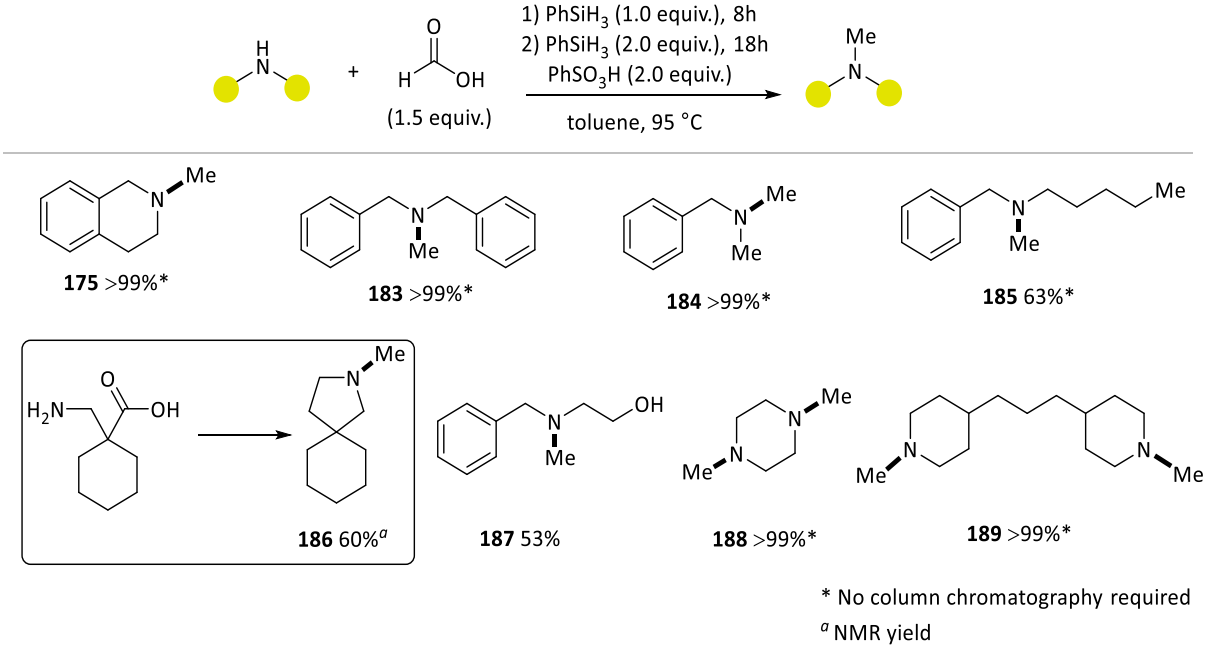


Figure 26: *Mono-methylation scope*

Pleasingly, methylation occurred in quantitative yields in most cases, and column chromatography was only required in one case. Gabapentin, a primary amine, was subjected to the reaction conditions in the hope that dimethylation would occur and the amine would react with FA preferentially over the tethered acid. However, the dimethylated product was not observed and the main product was shown to be the methylated spirocylclic compound (**186**). In addition, *N*-benzylethanolamine was also methylated (**187**) in a moderate yield, with the remaining mass balance shown to be the starting materials. This example was important, not only to demonstrate a further tolerance to hydroxyl groups, but also due to the frequent occurrence of ethanolamines in pharmaceutical targets. We were also able to demonstrate two methylations at different sites (**188** and **189**) in a one-pot process through simple scale-up of the reaction conditions.

2.2.2 Di-methylation

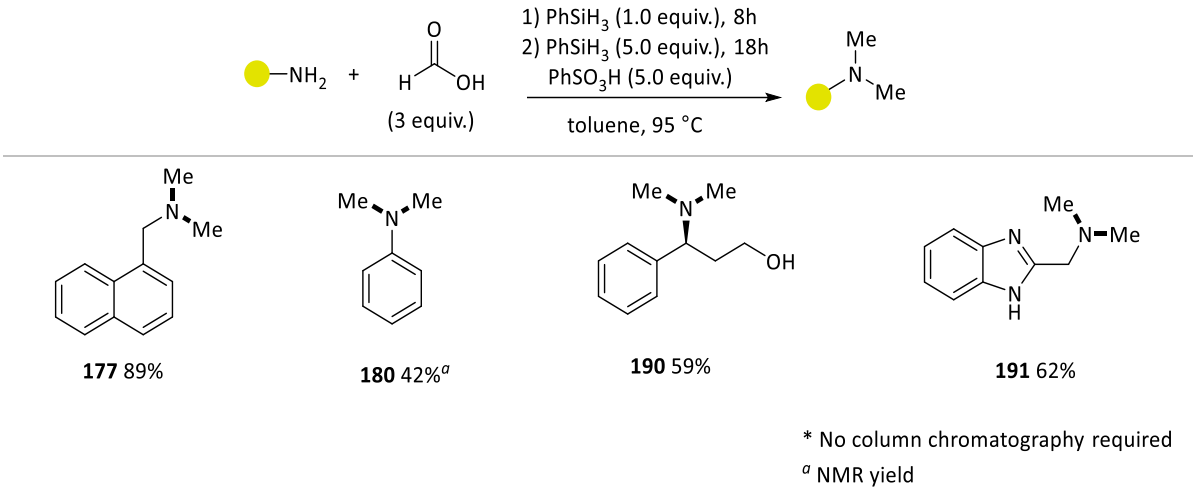


Figure 27: *Di-methylation scope*

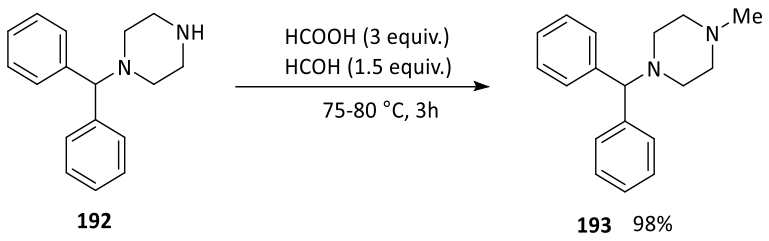
Following the synthesis of mono-methylated amines, efforts then turned to the development of di-methylated compounds. Pleasingly, aniline, which usually cannot be used for this chemistry due to its inactivity towards the amidation process, was able to be di-methylated (**180**) in a moderate yield. This is likely due to increased reactivity of FA compared to other carboxylic acids and with more forcing conditions, a higher yield could be achievable. We also demonstrated compounds with handles for further reaction (**190** and **191**) also confirming the functional group tolerance for this process.

2.3 Pharmaceutical and Complex Compound Synthesis

In order to exemplify the utility of this process, we next examined the synthesis of API's and bioisosteres to access more complex amine products.

2.3.1 Cyclizine

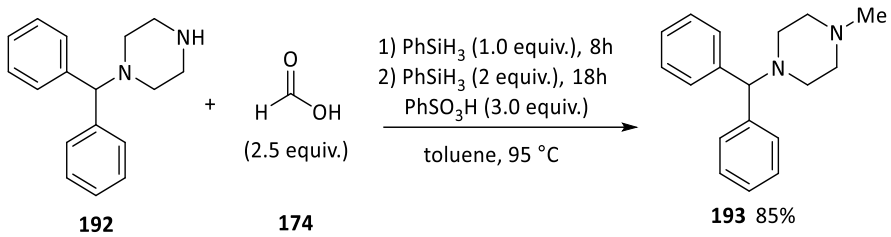
Cyclizine is an H1 receptor antagonist and acts as an antihistamine and antiemetic to treat nausea, vomiting, and dizziness associated with motion sickness, and vertigo. It is also known to display activity as a muscarinic receptor antagonist, however, the exact mode of action is unknown.[64]



192 **193** 98%

Scheme 70: *Patent synthesis of cyclizine*

In the patent literature, the methylation process used to sythesise this compound is a traditional Eschweiler-Clarke reductive methylation with formaldehyde and FA.[65]



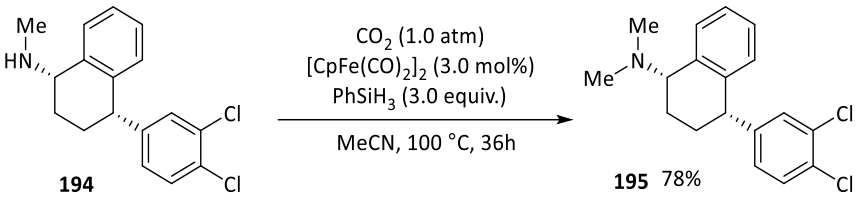
192 **174** **193** 85%

Scheme 71: *Synthesis of cyclizine*

Initial application of the metal-free process resulted in a poor yield of 20%, with the remaining mass balance attributed to the starting material. This suggested that the amidation phase of the reductive amination was slow. Therefore, the equivalents of FA were increased from 1.5 to 2.5, and pleasingly a much-improved yield was obtained, and column chromatography was not required.

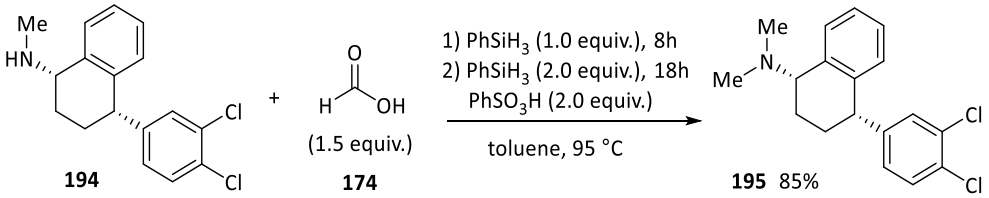
2.3.2 *N*-methylsertraline

We next sought to assess the late-stage functionalization of biologically active pharmaceuticals. Sertraline itself is a selective serotonin reuptake inhibitor (SSRI) and used to treat a range of metal health disorders like major depressive disorder, post-traumatic stress disorder and social anxiety disorder.[66] This process occurs through binding of the pharmaceutical to the serotonin receptor (5-HT) preventing absorption of serotonin but having little effect on norephinephrine and dopamine uptake, improving mood.



Scheme 72: *Literature synthesis of N-methylsertraline*

While there are several published methods for this methylation, which use CO_2 as the C1 source along with a silane and a metal catalyst, their practicality is limited by the requirement for Schlenk apparatus.[67,68]

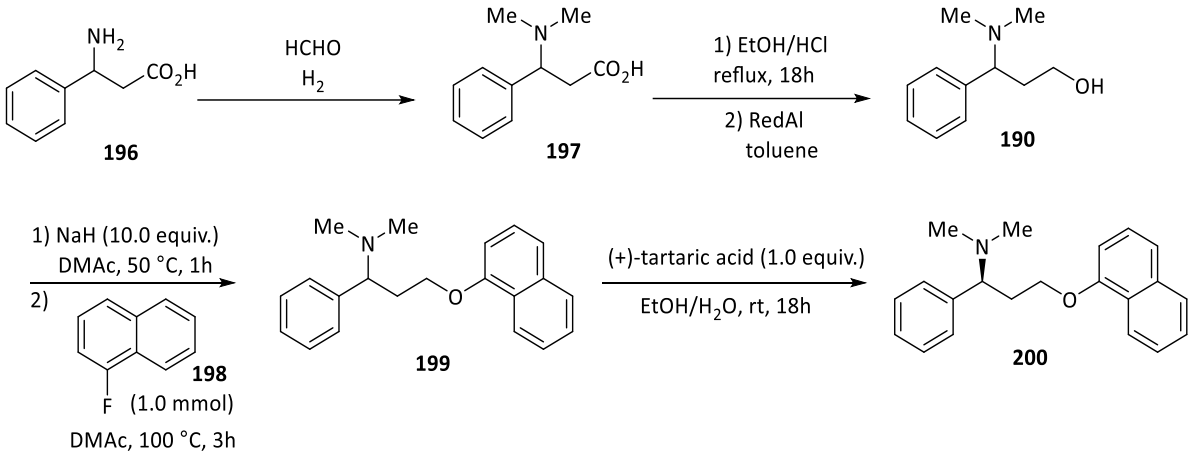


Scheme 73: *Synthesis of N-methylsertraline*

The use of this metal-free process not only provides a simple and effective methylation, but the use of basic laboratory equipment is a huge benefit for this transformation. In addition, this is an example of where a non-racemic chiral amine was the starting material, and pleasingly, no epimerisation was observed as demonstrated by no change in the specific rotation (Scheme 73).

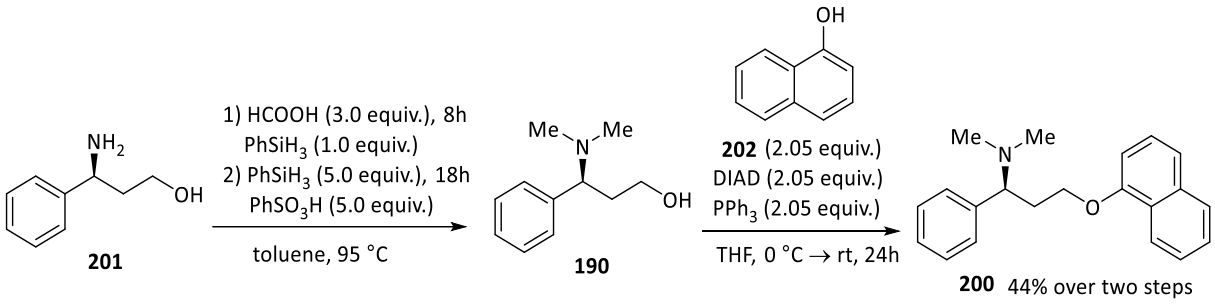
2.3.3 Dapoxetine

Dapoxetine is also an SSRI and was originally designed as an anti-depressant. However, it was found to be rapidly absorbed and eliminated from the body, and as such not suitable for this use. As an alternative, it was found to be effective in the treatment of premature ejaculation although the exact mechanism by which this pharmaceutical is effective is unclear.[69]



Scheme 74: *Patent synthesis of Dapoxetine*

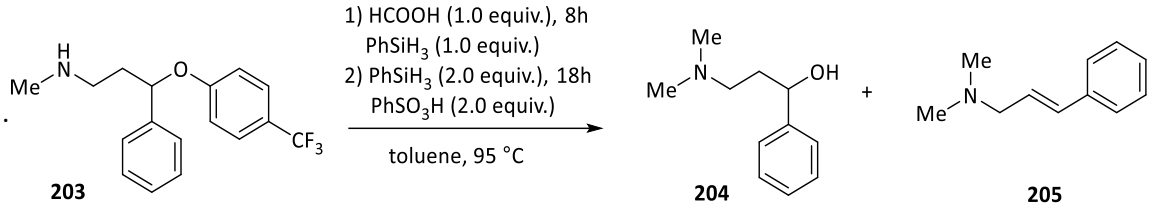
In the patent literature, very few processes utilise methylation on a single enantiomer of the primary amine, instead preferring to sythesise the racemic compound and carry out chiral resolution for the final step.[70] The methylation processes however, both in patent and paper literature, involve simple methylations using formic acid and formaldehyde in a reductive process.[71–73]



Scheme 75: *Synthesis of Dapoxetine*

We were able to achieve di-methylation of the chiral non-racemic amine in a 59% yield (**190**) and followed this with a Mitsunobu process to achieve the active pharmaceutical (**200**) (Scheme 75). From

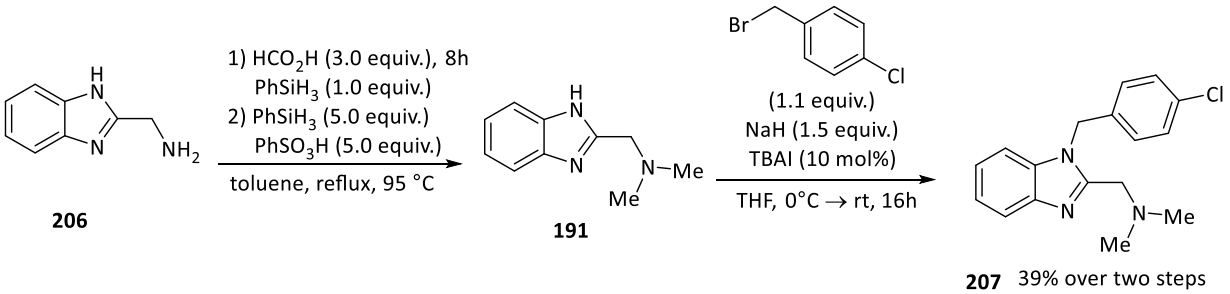
our previous investigations, the presence of a free-hydroxyl group is known to decrease yield. Despite this, the methylation was carried out as the first step, as decomposition of aryl ethers was discovered upon attempts towards the methylation of Fluoxetine (Scheme 76). In this example, the free alcohol (**204**) and olefin (**205**) were isolated as the only products. The protonation of the oxygen under the acidic conditions lead to elimination of the aryl group as a phenol.



Scheme 76: *Decomposition of N-methylfluoxetine*

2.3.4 *N,N*-dimethyl Bioisostere of Clemizole

Having already demonstrated the synthesis of Clemizole (Chapter One 2.3.2), we then demonstrated the *N,N*-di-methylated bioisostere of this compound which is a common alteration.[74] Bioisosteres are chemical substituents or groups that produce the same biological properties as the original compound, *albeit* with slightly altered physical or chemical effects.



Scheme 77: *Sythesis of [1-(4-chloro-benzyl)-1H-benzimidazol-2-ylmethyl]-dimethyl-amine*

Pleasingly, we were able to form the dimethylated compound in a comparative yield to the original synthesis.

2.4 Mechanism

It was initially assumed that the process for methylations would take place following the same mechanism as that shown in Chapter One (Scheme 55). However, this was shown to not be the case

when the dimethylated amine was identified as the major product over the mono. The possible mechanisms were then considered as multiple products were possible, following the amidation process.

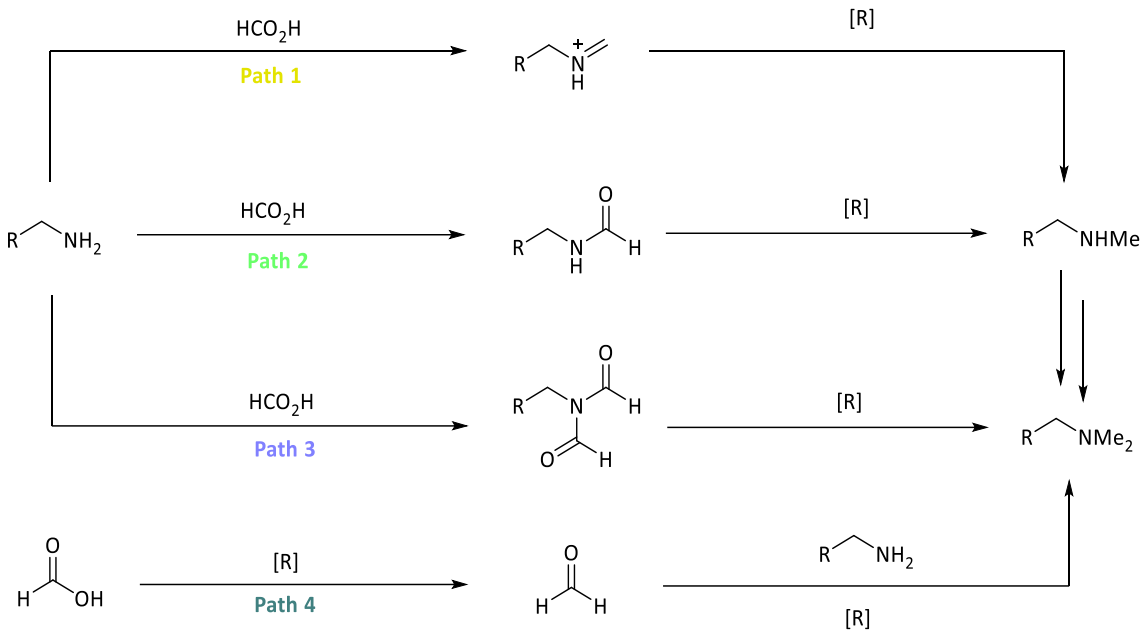
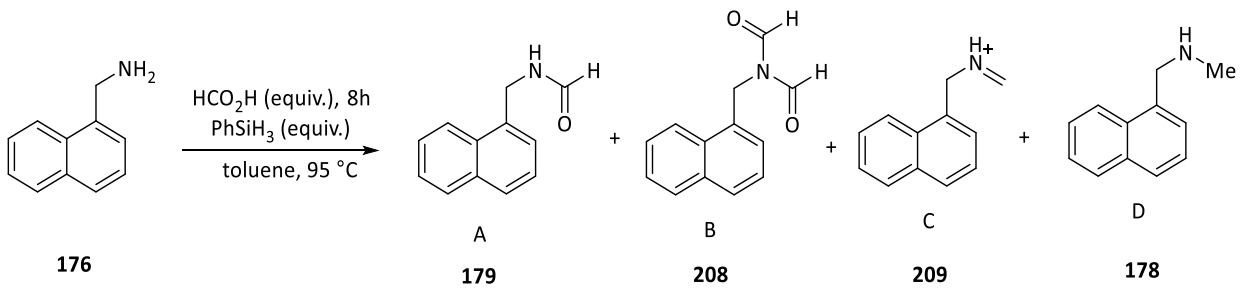


Figure 28: *Potential reaction pathways*

Iminium ion (Figure 28, Path 1), formamide (Figure 28, Path 2) or imide (Figure 28, Path 3) could all result after the initial step, which could then be reduced by the silyl sulfonates. It could also be possible for the iminium ion to be reduced by FA in an Eschweiler-Clarke process. Alternatively, reduction of FA to formaldehyde could take place (Figure 28, Path 4) and methylation could occur *via* a traditional reductive amination process. As a result, investigation into the amidation step was conducted, as this would provide the most insight into the mechanistic process.

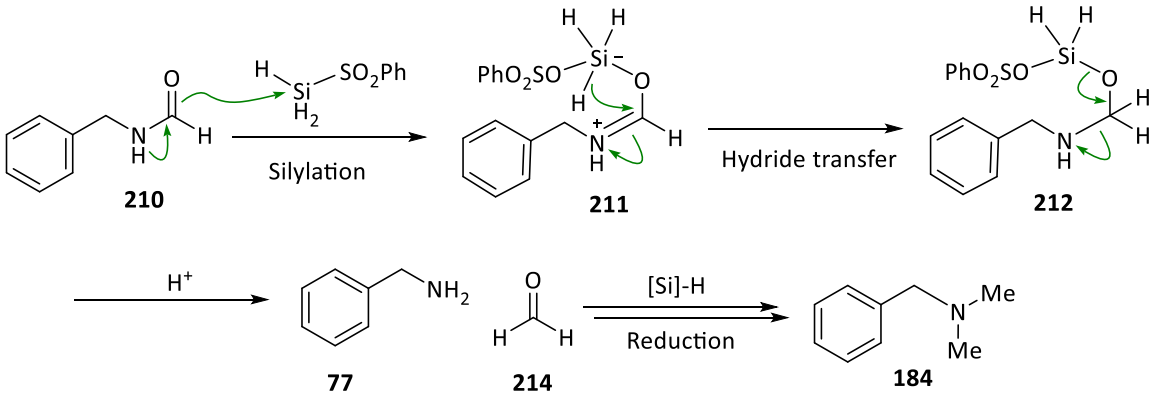


Entry	HCO_2H (equiv.)	$PhSiH_3$ (equiv.)	Yield A (%)[a]	Yield B (%)	Yield C (%)	Yield D (%)
1	1.5	1	85	0	0	0
2	3	2	89	0	0	0

[a] *Isolated yield*

Table 11: *Reaction of napthylmethylamine with FA*

Following this investigation, the only product identified after the amidation step was formamide, irrespective of the amount of FA and silane present. This confirmed the dominance of Path 2. From previous experimentation, it is known that this system reduces formamides to the corresponding dimethylamines (Scheme 66) with the parent amine as the only other compound observed. As a result, we postulated that the reduction conditions caused decomposition of the 'ate' complex (**212**) to form the aldehyde and starting material amine instead of a hydride transfer to form the tetrahedral intermediate. The formation of the aldehyde then allows for a traditional reductive amine *via* the iminium ion intermediate and explaining the formation of dimethylated compounds.



Scheme 78: *Proposed formation of formaldehyde*

Despite proposing a single pathway for methylation, the real mechanism is likely a much more complex multipath process. In addition to the pathway depicted in Scheme 78, the pathway proposed for the Chapter One process (Scheme 55) is likely occurring as well; in both cases rapidly reacting with either excess FA or formaldehyde following formation of the mono-methylated amine (**216**). This process must happen extremely rapidly as there is no secondary methylated amine visible in the NMR spectrum. In addition, the occurrence of formaldehyde and FA at the same time could also suggest contributions from an Eschweiler-Clarke process, although this would only occur when running a full reductive amination process where excess FA would be available. In Beller's publications concerning amine methylation, he invokes a urea intermediate which could also play a part for this process although was not investigated in this study.[56]

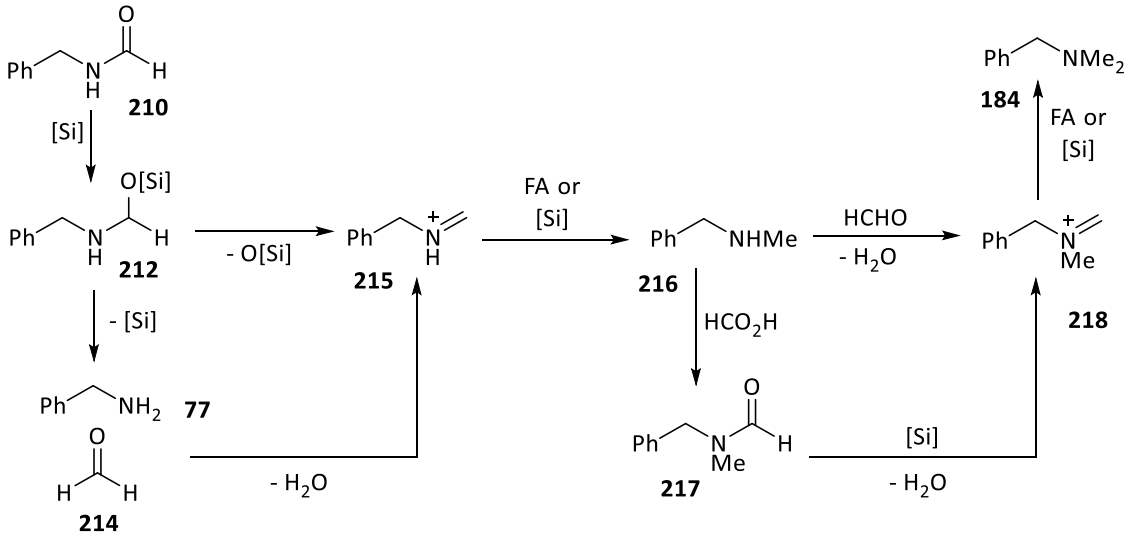


Figure 29: *Proposed mechanism for the formation of dimethylated amines*

2.5 Conclusions

Overall, this process has achieved the first convenient and metal-free reductive methylation using FA, both removing the need for toxic methylating agents and also circumventing issues associated with using gaseous CO_2. The processes for mono-methylation of secondary amines and di-methylation of primary amines were optimised and a small scope was carried out. Within this scope, we demonstrated the methylation of non-racemic chiral amines without any epimerisation, in addition to functionalisation of pharmaceuticals and synthesis of methylated bioisosteres. The synthesis of two

further active pharmaceuticals was carried out, demonstrating both mono- and di- methylation. The mechanism was also investigated, as it was shown to be different to that shown in Chapter One. The formamide was shown to be the only product after the first step, so we proposed the formation of formaldehyde, in addition to other processes to account for the dimethylation.

2.6 Future Work

The main work that needs to be carried out, is the investigation into mono-methylation, in addition to further elucidation of the mechanism. Mono-methylation could be applied through deactivation of the silylsulfonate using a less acidic sulfonic acid or through use of a temporary protecting group, like a trimethylsilyl (TMS). Despite the ease of installation, TMS groups are removed in the presence of aqueous acid and although the acid in the reduction is not in an aqueous medium, it is likely that this group would be cleaved *in situ*. As a result, further investigations to allow for mono-methylation would significantly improve the utility of this process. In addition, the mechanism could be confirmed through NMR and IR spectroscopy monitoring to try and observe some of the intermediates, along with computational calculations on the stability of the proposed structures. Formaldehyde could also be applied to the reaction to confirm formation of a dimethylated product *via* this route, and investigation of a urea under the reaction conditions would provide further insight to possible reaction pathways.

3 Experimental

3.1 General Experimental

Reagents were purchased from commercial suppliers and used directly without further purification. Solvents were dried unless specified 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 and stored under inert atmosphere using 4Å molecular sieves. 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.

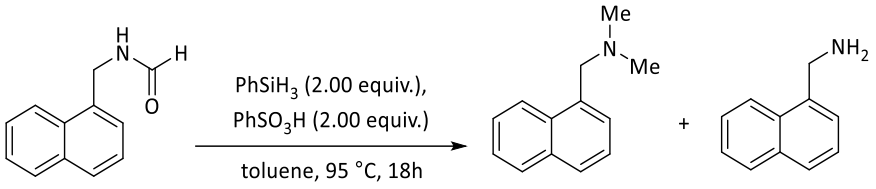
Analytical Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed silica-gel plates 60 F_{254} plates and visualized by ultraviolet (UV) irradiation (254 nm) or by staining with a solution of potassium permanganate or ninhydrin. Column chromatography was carried out using Fluorochem 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). High Pressure Liquid Chromatography (HPLC) was carried out on a Thermo Ultimate reverse phase column using 1% formic acid solution and acetonitrile. Computational calculations were carried out by the Houk group using ωb97xd/6-31g(d,p)//SMD(solvent = toluene)//ωb97xd/6-311+g(d,p)//SMD(solvent = toluene) and the energies quoted are electronic energies in kcal/mol.

NMR spectra were recorded on either a Bruker AV 400, AV(III) 400HD or AV(III) 500HD in $CDCl_3$, DMSO or PhMe-d8. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz), with residual protic solvent as the internal reference: ^{1}H NMR ($CDCl_3$ δ = 7.26 ppm, DMSO δ = 2.50 ppm, PhMe δ = 2.08 ppm), ^{13}C NMR (central peak of $CDCl_3$ δ = 77.16 ppm, DMSO δ = 39.52, PhMe δ = 20.43 ppm). NMR spectra are reported as follows: δ (multiplicity, coupling constant (if appropriate), number of protons). Abbreviations used include s – singlet, d – doublet, t – triplet, q – quartet, sept – septet, m – multiplet, pent - pentet, br – broad, app. – apparent. and coupling constants (J) are given in Hertz (Hz). All NMR are reported as proton decoupled spectra. NMR yields were determined by the following formula, where P and IS refer to the product and internal standard respectively, n refers to the moles and N is the number of nuclei represented in the chosen peak:

$$n_P = n_{IS}\left(\frac{I_P/N_P}{I_{IS}/N_{IS}}\right)$$

3.2 Optimisation

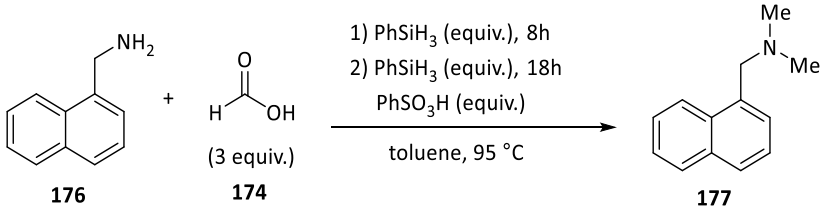
3.2.1 Formamide Reduction



179 **177** **176**

To a solution of *N*-(naphthalen-1-ylmethyl)formamide (185.2 mg, 1.00 mmol) in toluene (1.20 mL), was added benzenesulfonic acid (314.4 mg, 2.00 mmol) and phenylsilane (247 µL, 2.00 mmol) were added dropwise and heated for 18 hours before being cooled to room temperature and quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product and the ratio of the *N,N*-dimethyl(naphthalen-1-yl)methanamine and 1-napthylmethylamine (56:44) was found by ^1H NMR ($CDCl_3$).

3.2.2 Di-methylation Optimisation



176 **174** **177**

Entry	Step 1 $PhSiH_3$ (equiv.)	Step 2 $PhSiH_3$ (equiv.)	$PhSO_3H$ (equiv.)	Yield (%)[a]
1	2	4	4	66
2	2	4	5	77
3	1	5	4	72
4	1	5	5	89
5	0	5	5	69
6	0.5	5	5	66

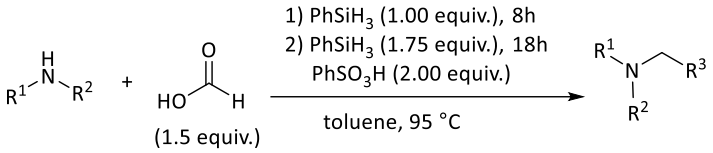
[a]Isolated yield

To a solution of formic acid (56.5 µL, 1.50 mmol) in dry toluene (1.20 mL) at 95 °C, was added phenylsilane (see Table) followed by (naphth-1-yl)methylamine (147 µL, 1.00 mmol) dropwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (see Table) and phenylsilane (see Table) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product.

3.3 General Procedures and Experimental Data

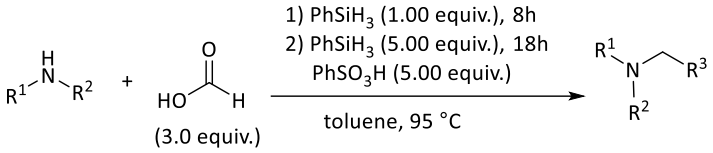
General Procedures

3.3.1 Methylation of Secondary Amines



To a solution of formic acid (56.5 µL, 1.50 mmol) in dry toluene (1.20 mL) at 95 °C, was added phenylsilane (123 µL, 1.00 mmol) followed by amine (1.00 mmol) dropwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (314.4 mg, 2.00 mmol) and phenylsilane (247 µL, 2.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product. If necessary, the products were purified by column chromatography.

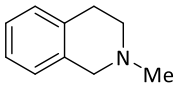
3.3.2 Di-methylation of Primary Amines



To a solution of formic acid (113 µL, 3.00 mmol) in dry toluene (1.20 mL) at 95 °C, was added phenylsilane (123 µL, 1.00 mmol) followed by amine (1.00 mmol) dropwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (786 mg, 5.00 mmol) and phenylsilane (615 µL, 5.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product. If necessary, the products were purified by column chromatography.

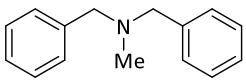
Experimental Data

2-methyl-1,2,3,4-tetrahydroisoquinoline – **175**



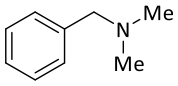
Followed general procedure 3.3.1 using formic acid (55.5 µL, 1.50 mmol) and 1,2,3,4-tetrahydroisoquinoline (125 µL, 1 mmol) to afford the title product as orange oil (146 mg, 99%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.18-7.10 (m, 3H, Ar-**H**), 7.07-7.01 (m, 1H, Ar-**H**), 3.61 (s, 2H, N-C**H_2**), 2.95 (t, J= 6.0 Hz, 2H, N-C**H_2**-CH_2), 2.71 (t, J= 6.0 Hz, 2H, N-CH_2-C**H_2**), 2.48 (s, 3H, N-C**H_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 134.8 (C), 133.9 (C), 129.4 (CH), 126.4 (CH), 126.1 (CH), 125.6 (CH), 58.1 (CH_2), 53.0 (CH_2), 46.2 (CH_3), 29.3 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{10}H_{14}N$ [M^+H]: 148.1121 found 148.1114. The data matches that found in the literature.[75]

N-benzyl-*N*-methyl-1-phenylmethanamine - **183**



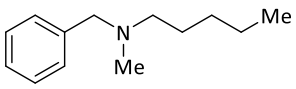
Followed general procedure 3.3.1 using formic acid (55.5 µL, 1.50 mmol) and dibenzylamine (192 µL, 1 mmol) to afford the title product as a pale yellow oil (210 mg, 99%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.47-7.25 (m, 10H, Ar-**H**), 3.56 (s, 4H, N-C**H_2**), 2.22 (s, 3H, N-C**H_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 139.5 (C), 129.0 (CH), 128.3 (CH), 127.0 (CH), 62.0 (CH_2), 42.4 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{15}H_{18}N$ [M^+H]: 212.1434 found 212.1435. The data matches that found in the literature.[50]

N,N-dimethyl-1-benzylamine - **184**



Followed general procedure 3.3.1 using formic acid (55.5 µL, 1.50 mmol) and N-methylbenzylamine (130 µL, 1.00 mmol) to afford the title product as pale yellow oil (135 mg, quant.); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.44-7.22 (m, 5H, Ar-**H**), 3.45 (s, 2H, N-C**H_2**-Ar), 2.27 (s, 6H, N-(C**H_3**)$_2$); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 138.9 (C), 129.1 (CH), 128.2 (CH), 127.0 (C), 64.4 (CH_2), 45.4 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_9H_{14}N$ [M^+H]: 136.1121 found 136.1126. The data matches that found in the literature. [76]

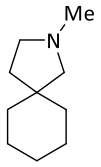
N-pentyl-*N*-methylbenzenemethanamine – **185**



Followed general procedure 3.3.1 using formic acid (55.5 µL, 1.50 mmol) and amine **27** (177 mg, 1 mmol) to afford the title product as a pale yellow oil (121 mg, 63%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.37-7.32 (m, 4H, Ar-**H**), 7.30-7.25 (m, 1H, Ar-**H**), 3.52 (s, 2H, N-C**H_2**), 2.40 (t, J= 7.8 Hz, 2H, N-C**H_2**-CH_2), 2.22 (s, 3H, N-C**H_3**), 1.56 (pent, J= 6.8 Hz, 2H, **H_2**C-CH_2), 1.40-1.28 (m, 4H, H_2C-C**H_2**), 0.93 (t, J= 6.3 Hz, 3H, H_2C-C**H_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 139.3 (C), 129.1 (CH), 128.2 (CH), 126.9 (CH), 62.4

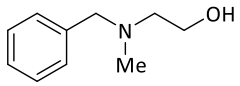
(CH_2), 57.6 (CH_2), 42.3 (CH_3), 29.7 (CH_2), 27.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{22}N_1$ [M^+H]: 192.1747 found 192.1748; **IR** vmax/cm^{-1} (ATR): 3028, 2930, 2859, 2785, 1494, 1453, 1365, 1292, 1252, 1162, 1131, 1074, 1018.

2-Methyl-2-azaspiro<4.5>decan - **186**



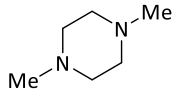
Followed general procedure 3.3.2 using gabapentin (153 mg, 1.00 mmol) to afford the title product in a 62% yield (determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 2.37 (s, 3H, N-C**H_3**).

2-(*N*-benzyl-*N*-methyl)amino-1-ethanol -**187**



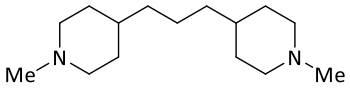
Followed general procedure 3.3.1 using formic acid (55.5 µL, 1.50 mmol) and *N*-benzylethanolamine (142 µL, 1.00 mmol) and purified by flash column chromatography (9:1 DCM: MeOH) to afford the title product as pale yellow oil; **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.38-7.25 (m, 5H, Ar-**H**), 3.65 (t, J= 5.3 Hz, 2H, HO-C**H_2**-CH_2-N), 3.60 (s, 3H, Ar-C**H_2**-N), 2.63 (t, J= 5.3 Hz, 2H, HO-CH_2-C**H_2**-N), 2.26 (s, 3H, N-C**H_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 138.4 (C), 129.0 (CH), 128.4 (CH), 127.2 (CH), 62.3 (CH_2), 85.4 (CH_2), 85.3 (CH_2), 41.5 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{10}H_{16}NO$ [M^+H]: 166.1226 found 166.1213. The data matches that found in the literature.[77]

1,4-dimethylpiperazine – **188**



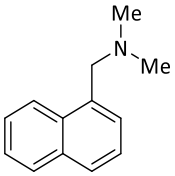
To a solution of formic acid (113 µL, 3.00 mmol) in dry toluene (1.20 mL) at 95 ^{o}C, was added phenylsilane (247 µL, 2.00 mmol) followed by piperazine (86.1 µL, 1.00 mmol) dropwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (786 mg, 5.00 mmol) and phenylsilane (492 µL, 4.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title product as a brown oil (114 mg, >99%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 2.66- 2.34 (br s, 8H, N-C**H_2**-C**H_2**-N), 2.29 (s, 6H, N-C**H_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 55.1 (CH_2), 46.1 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_6H_{15}N_2$ [M^+H]: 115.1230 found 115.1219. The data matches that found in the literature.[78]

1-methyl-4-(3-(1-methylpiperidin-4-yl)propyl)piperidine – **189**



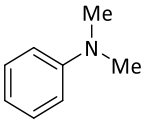
To a solution of formic acid (113 µL, 3.00 mmol) in dry toluene (1.20 mL) at 95 ^{o}C, was added phenylsilane (247 µL, 2.00 mmol) followed by 1,3-di(piperidin-4-yl)propane (210 mg, 1.00 mmol)dropwise. The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (786 mg, 5.00 mmol) and phenylsilane (492 µL, 4.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with HCl (1.00 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (10 mL) and extracted with HCl (3 x 10 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title product as a brown oil (114 mg, >99%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 2.87-2.79 (m, 4H, C**H$_{2A}$**-N-C**H$_{2A}$**), 2.26 (s, 6H, N-C**H$_3$**), 1.93-1.84 (m, 4H, C**H$_{2B}$**-N-C**H$_{2B}$**), 1.70-1.61 (m, 4H, N-CH_2-C**H$_{2A}$**), 1.37-1.15 (m, 12H, N-CH_2-C**H$_{2B}$**, CH_2-C**H**-CH_2, C**H$_2$**-CH_2-CH_2, CH_2-C**H$_2$**-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 56.1 (CH_2), 46.4 (CH_3), 36.8 (CH_2), 35.2 (CH), 32.6 (CH_2), 23.9 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{15}H_{31}N_2$ [M^+H]: 239.2482 found 239.2468. The data matches that found in the literature.[78]

N,N-dimethyl(naphthalen-1-yl)methanamine – **177**



Followed general procedure 3.3.2 using (naphth-1-yl)methylamine (147 µL, 1.00 mmol) to afford the title product as an orange oil (166 mg, 89%); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 8.29 (d, J= 8.4, 1H, Ar-**H**), 7.87 (d, J= 8.2 Hz, 1H, Ar-**H**), 7.83-7.78 (m, 1H, Ar-**H**), 7.58-7.48 (m, 2H, Ar-**H**), 7.44-7.40 (m, 2H, Ar-**H**), 3.85 (s, 2H, N-C**H$_2$**-Ar), 2.33 (s, 6H, N(C**H$_3$**)$_2$); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 134.9 (C), 133.9 (C), 132.5 (C), 128.4 (CH), 128.0 (CH), 127.4 (CH), 126.0 (CH), 125.6 (CH), 125.0 (CH), 124.5 (CH), 62.6 (CH_2), 46.7 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{13}H_{16}N$ [M^+H]: 186.1277 found 186.1275. The data matches that found in the literature. [79]

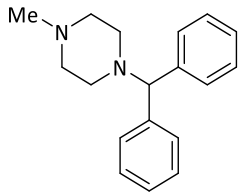
N,N-dimethyl-aniline – **180**



Followed general procedure 3.3.2 using aniline (91 µL, 1.00 mmol) to afford the title product in a 42% yield (determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard); **^{1}H NMR:** (400 MHz, toluene-d^{8}) δH 2.98 (s, 6H, N(C**H$_3$**)$_2$). The data matches that found in the literature.[61]

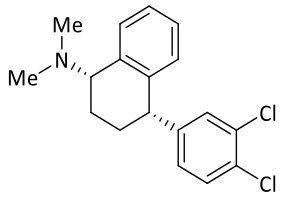
3.4 Pharmaceutical Synthesis and Complex Compounds

3.4.1 Cyclizine - 193



Followed a modified general procedure 3.3.1 To a solution of formic acid (94.0 mg, 2.50 mmol) in dry toluene (1.20 mL) at 95 ^{o}C, was added phenylsilane (123 µL, 1.00 mmol) followed by 1-(Diphenylmethyl)piperazine (252 µL, 1.00 mmol). The reaction mixture was heated for 8 hours, after which time benzenesulfonic acid (474 mg, 3.00 mmol) and phenylsilane (247 µL, 2.00 mmol) were added dropwise and heated for a further 18 hours before being cooled to room temperature and quenched with HCl (0.500 mL of a 3 M aqueous solution). The rection mixture was diluted with EtOAc (5 mL) and extracted with HCl (3 x 5 mL of a 3 M aqueous solution). The aqueous layers were combined and adjusted to pH 12 with NaOH (6 M aqueous solution) and extracted using DCM (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title product as a brown solid (225 mg, 85%); **M.P:** 106-107 °C (lit: 107 °C)[64]; **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.45-7.41 (m, 4H, Ar-**H**), 7.29 (dd, J= 7.3, 7.3 Hz, 4H, Ar-**H**), 7.20 (dd, J= 7.2, 7.2 Hz, 2H, Ar-**H**), 4.24 (s, 1H, Ar-C**H$_2$**-Ar), 2.63-2.34 (m, 8H, N-C**H$_2$**-C**H$_2$**-N), 2.31 (s, 3H, N-C**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 142.8 (C), 128.5 (CH), 127.9 (CH), 126.9 (CH), 76.3 (CH), 55.4 (CH_2), 51.9 (CH_2), 45.9 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{18}H_{23}N_2$ [M^+H] 267.1856 found 267.1855. The data matches that found in the literature.[80]

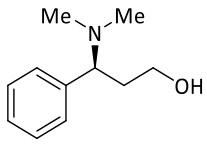
3.4.2 *N*-methylsertraline - 195



Followed general procedure 3.3.1 using sertraline (306 mg, 1.00 mmol) and purified by column chromatography (3:1 pentane: EtOAc) to achieve the title product as a yellow oil (272 mg, 85%); **R.f:** 0.17 (3:1 pentane: EtOAc); **[α]$_D$** = +109° (c = 0.257, $CHCl_3$); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.72 (d, J= 7.8 Hz, 1H, Ar-**H**), 7.34 (d, J= 8.3 Hz, 1H, Ar-**H**), 7.28-7.24 (m, 1H, Ar-**H**), 7.19-7.13 (m, 2H, Ar-**H**), 6.92-6.84 (m, 2H, Ar-**H**), 4.14 (t, J= 5.17 Hz, 1H, C**H**-N(CH_3)$_2$), 3.80 (t, J= 8.3 Hz, 1H, Ar-C**H**), 2.33 (s, 6H, N(C**H$_3$**)$_2$), 2.21-1.99 (m, 2H, C**H$_2$**-CH-N(CH_3)$_2$), 1.79-1.66 (m, 2H, C**H$_2$**-CH-Ar); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 147.7 (C), 139.2 (C), 138.2 (C), 132.1 (C), 130.8 (CH), 130.2 (CH), 130.0 (CH), 129.8 (C), 128.9 (CH), 128.2 (CH), 126.9 (CH), 126.7 (CH), 62.6 (CH), 43.9 (CH), 40.9 (CH_3), 29.7 (CH_2), 15.9 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{18}H_{20}Cl_2N$ [M^+H]: 320.0967 found 320.0960. The data matches that found in the literature.

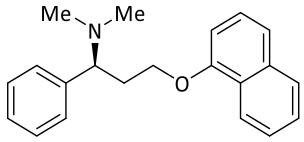
3.4.4 Dapoxetine - 200

(S)-3-(dimethylamino)-3-phenylpropan-1-ol – **190**



Followed general procedure 3.3.2 using (S)-3-amino-phenylpropan-1-ol (151 mg, 1.00 mmol) and purified by column chromatography (90:9:1 DCM: MeOH: NH_4OH) to afford the title product as pale yellow oil (105 mg, 59%);**R.f:** 0.39 (90:9:1 DCM: MeOH: NH_4OH); **$[\alpha]_D$** = +40.7° (c = 0.371, $CHCl_3$); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.40-7.30 (m, 3H, Ar-**H**), 7.23-7.17 (m, 2H, Ar-**H**), 3.91-3.83 (m, 2H, CH-CH_2-C**H₂**), 3.78 (dd, J= 10.6, 3.7 Hz, C**H**-CH_2-CH_2), 2.49-2.36 (m, 1H, CH-C**H₂**-CH_2), 2.20 (s, 6H, N(C**H₃**)$_2$), 1.69 (dq, J= 14.5. 3.5 Hz, 1H, CH-C**H₂**-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 136.1 (C), 128.9 (CH), 127.9 (CH), 127.5 (CH), 70.2 (CH_2), 63.6 (CH_2), 41.1 (CH_3), 32.1 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{18}NO$ [M^+H]: 180.1383 found 180.1386. The data matches that found in the literature.[71]

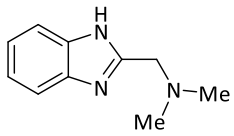
Dapoxetine - **200**



To a solution of **190** (89.6 mg, 0.500 mmol) and 1-napthol (148 mg, 1.025 mmol), in THF (7.30 mL) at 0 °C, was added triphenylphosphine (269 mg, 1.025 mmol) and diisopropyl azodicarboxylate (202 µL, 1.025 mmol). The reaction mixture was warmed to r.t and stirred for 24h, concentrated in vacuo and purified by column chromatography (19:1 EtOAc:MeOH) to afford the title product as a pale yellow oil (114 mg, 74%); **R.f:** 0.27 (19:1 EtOAc:MeOH); **$[\alpha]_D$** = +64.7° (c = 0.636, $CHCl_3$); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 8.26-8.23 (m, 1H, Ar-**H**), 7.84-7.77 (m, 1H, Ar-**H**), 7.54-7.46 (m, 2H, Ar-**H**), 7.43-7.26 (m, 7H, napth-**H**), 6.68 (d, J= 7.6 Hz, 1H, napth-**H**), 4.14-4.06 (m, 1H, N-CH-CH_2-C**H₂**), 3.99 (m, 1H, N-CH-CH_2-C**H₂**), 3.63 (dd, J= 9.1, 5.3 Hz, N-C**H**-CH_2-CH_2), 2.72-2.61 (m, N-CH-C**H₂**-CH_2), 7.09-2.24 (m, N(C**H₃**)$_2$, N-CH-C**H₂**-CH_2); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 154.6 (C), 139.6 (C), 134.5 (C), 128.6 (CH), 128.2 (CH), 127.4 (CH), 127.3 (CH), 126.3 (CH), 125.9 (CH), 125.9 (CH), 125.7 (C), 125.1, 122.0 (CH), 120.1 (CH), 104.6 (CH), 67.7 (CH), 65.7 (CH_2), 42.8 (CH_3), 33.0 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{21}H_{24}NO$ [M^+H]: 306.1854 found 306.1852. The data matches that found in the literature.[71]

3.4.5 *N,N*-dimethyl Bioisostere of Clemizole - 207

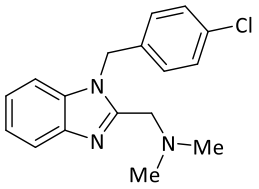
2-(*N,N*-Dimethylaminomethyl)-benzimidazol - **191**



Followed general procedure 3.3.2 using 2-aminomethylbenzimidazole (147 mg, 1.00 mmol) and purified by column chromatography (9:1 DCM: MeOH) to afford the title compound as a pale yellow solid (109 mg, 62%); **M.P:** 136-137 °C (lit: 136-137 °C)[81]; **R.f:** 0.27 (9:1 DCM: MeOH); **^{1}H NMR:** (400 MHz, DMSO-d^6) δH 12.3 (br s, 1H, N**H**), 7.61-7.37 (m, 2H, Ar-**H**), 7.21-7.05 (m, 2H, Ar-**H**), 3.65 (s, 2H,

Ar-C**H₂**-N), 2.24 (s, 6H, N-(C**H₃**)₂); **^{13}C NMR {^{1}H}:** (101 MHz, DMSO-d^{6}) δC 152.7 (C), 142.4 (C), 139.0 (C), 122.2 (CH), 121.2 (CH), 118.9 (CH), 111.6 (CH), 57.5 (CH_2), 45.7 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{10}H_{14}N_3$ [M^+H]: 176.1182 found 176.1183. The data matches that found in the literature.[82]

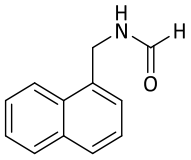
[1-(4-chloro-benzyl)-1H-benzimidazol-2-ylmethyl]-dimethyl-amine – **207**



To a solution of **191** (87.6 mg, 0.500 mmol) in THF (1.50 mL) at 0 °C, was added NaH (30.0 mg of a 60% wt dispersion in mineral oil, 0.750 mmol) and warmed to r.t and stirred for 5 minutes. 4-chlorobenzylbromide (18.0 mg, 0.550 mmol) and tetrabutylammonium iodide (18.0 mg, 0.0500 mmol) was added and stirred at r.t for 16 hours. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* The crude product was purified by column chromatography (99:1 EtOAc: NEt_3) to afford the title product as an off-white solid (93.8 mg, 63%, 0.313 mmol); **M.P:** 113-114 ^{o}C; **R.f:** 0.26 (99:1 EtOAc: NEt_3); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH 7.79 (d, J= 7.3 Hz, 1H, Ar-**H**), 7.32-7.22 (m, 5H, Ar-**H**), 7.06-7.02 (m, 2H, Ar-**H**), 5.58 (s, 2H, Ar-C**H₂**-Ar), 3.68 (s, 2H, Ar-C**H₂**-N), 2.29 (s, 6H, N(C**H₃**)₂); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 151.8 (C), 142.4 (C), 135.9 (C), 136.1 (C), 133.5 (C), 129.0 (CH), 127.9 (CH), 122.9 (CH), 122.2 (CH), 120.0 (CH), 109.7 (CH), 57.2 (CH_2), 46.6 (CH_2), 45.6 (CH_3); **HRMS** (ESI-TOF) m/z calc'd $C_{17}H_{19}N_3Cl$ [M^+H]: 300.1262 found 300.1258. **IR** vmax/cm^{-1} (ATR): 3084, 3059, 2982, 2953, 2859, 2815, 2769, 1913, 1610, 1595, 1515, 1488, 1461, 1442, 1405, 1349, 1330, 1302, 1286, 1267, 1250, 1202, 1168, 1146, 1088, 1015

3.5 Mechanistic Investigations

N-(naphthalen-1-ylmethyl)formamide - **182**



To a solution of formic acid (113 µL, 3.00 mmol) in dry toluene (1.20 mL) at 95 ^{o}C, was added phenylsilane (247 µL, 2.00 mmol) followed by (naphth-1-yl)methylamine (147 µL, 1.00 mmol) dropwise and heated for 8 hours. The reaction mixture was cooled to r.t and purified by column chromatography (4:1 DCM: EtOAc) to afford the title product as an off-white solid (165 mg, 89%);**M.P:** 121 ^{o}C (lit: 122 ^{o}C[83]); **R.f:** 0.26 (4:1 DCM: EtOAc); **^{1}H NMR:** (400 MHz, $CDCl_3$) δH (mixture of rotamers) 8.29 (s, 1H, NH-C**H**O), 8.04 (d, J= 8.0 Hz, 1H, Ar-**H**), 7.92 (d, J= 7.7 Hz, 2H, Ar-**H**), 7.86 (d, J= 7.2 Hz, 2H, Ar-**H**), 7.61-7.52 (m, 2H, Ar-**H**), 7.50-7.43 (m, 2H, Ar-**H**), 5.76 (br s, 1H, N**H**), 4.98 (d, J= 5.5 Hz, 2H, Ar-C**H₂**-NH major), 4.93 (d, J= 6.3 Hz, 2H, 0.22H, C**H₂**-NH minor); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 160.7 (C), 133.9 (C), 132.8 (C), 131.7 (C), 128.9 (CH), 128.8 (CH), 126.9 (CH), 126.8 (CH), 126.2 (CH), 125.4 (CH), 123.4 (CH), 40.4 (CH_2); **HRMS** (ESI-TOF) m/z calc'd $C_{12}H_{11}NO$ [M^+H]: 186.0913 found 186.0912. The data matches that found in the literature.[83]

4 References

1 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451–3476.
2 N. A. Mcgrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.*, 2010, **87**, 1348–1349.
3 D. Aynetdinova, M. C. Callens, H. B. Hicks, C. Y. X. Poh, B. D. A. Shennan, A. M. Boyd, Z. H. Lim, J. A. Leitch and D. J. Dixon, *Chem. Soc. Rev.*, 2021, **50**, 5517–5563.
4 E. J. Barreiro, A. E. Kümmerle and C. A. M. Fraga, *Chem. Rev.*, 2011, 111, 5215–5246.
5 A. V. Malkov, K. Vranková, M. Černý and P. Kočovský, *J. Org. Chem.*, 2009, **74**, 8425–8427.
6 H. K. R. Santhapuram, A. Datta, O. E. Hutt and G. I. Georg, *J. Org. Chem.*, 2008, **73**, 4705–4708.
7 A. Le Pera, A. Leggio and A. Liguori, *Tetrahedron*, 2006, **62**, 6100–6106.
8 M. Prashad, D. Har, B. Hu, H. Y. Kim, O. Repic and T. J. Blacklock, *Org. Lett.*, 2003, **5**, 125–128.
9 S. Miller and T. Scanlan, *J. Am. Chem. Soc.*, 1997, **119**, 2301–2302.
10 E. Abdelraheem, B. Thair, R. F. Varela, E. Jockmann, D. Popadić, H. C. Hailes, J. M. Ward, A. M. Iribarren, E. S. Lewkowicz, J. N. Andexer, P. L. Hagedoorn and U. Hanefeld, *ChemBioChem*, 2022, 23.
11 A. Leggio, A. Liguori, F. Perri, C. Siciliano and M. C. Viscomi, *Chemical Biology & Drug Design*, 2009, **73**, 287–291.
12 T. Lebleu, X. Ma, J. Maddaluno and J. Legros, *Chem. Commun.*, 2014, **50**, 1836–1838.
13 M. Selva and A. Perosa, *Green Chem.*, 2008, **10**, 457–464.
14 Sheetal, P. Mehara and P. Das, *Coord. Chem. Rev.*, 2023, 475, 1–37.
15 L. M. Kabadwal, S. Bera and D. Banerjee, *Org. Chem. Front.*, 2021, 8, 7077–7096.
16 C. F. Winans and H. Adkins, *J. Am. Chem. Soc.*, 1932, **54**, 306–312.
17 M. Klyuev and M. Khidekel, *Russian Chem. Rev.*, 1980, **49**, 542–597.
18 R. Grigg, T. R. Mitchell, S. Sutthivaiyakit and N. Tongpenyai, *J. Chem. Soc. Chem. Comm.*, 1981, 611–612.
19 C. P. Xu, Z. H. Xiao, B.-Q. Zhuo, Y.-H. Wang and P.-Q. Huang, *Chem. Commun.*, 2010, **46**, 7834–7836.
20 C. Meng, P. Liu, N. T. Tung, X. Han and F. Li, *J. Org. Chem.*, 2020, **85**, 5815–5824.
21 A. Fu, Q. Liu, M. Jiang and G. Xu, *Asian J. Org. Chem.*, 2019, **8**, 487–491.
22 L. Jiang, F. Guo, Y. Wang, J. Jiang, Y. Duan and Z. Hou, *Asian J. Org. Chem.*, 2019, **8**, 2046–2049.
23 L. Zhang, Y. Zhang, Y. Deng and F. Shi, *RSC Adv.*, 2015, **5**, 14514–14521.
24 S. N. R. Donthireddy, P. Mathoor Illam and A. Rit, *Inorg Chem*, 2020, **59**, 1835–1847.
25 G. Choi and S. H. Hong, *ACS Sustainable Chem. Eng.*, 2019, **7**, 716–723.
26 O. Ogata, H. Nara, M. Fujiwhara, K. Matsumura and Y. Kayaki, *Org. Lett.*, 2018, **20**, 3866–3870.
27 M. A. R. Jamil, A. S. Touchy, M. N. Rashed, K. W. Ting, S. M. A. H. Siddiki, T. Toyao, Z. Maeno and K. ichi Shimizu, *J. Catal.*, 2019, **371**, 47–56.
28 A. Lator, S. Gaillard, A. Poater and J. L. Renaud, *Org. Lett.*, 2018, **20**, 5985–5990.
29 K. M. Li, Q. Zhang, Z. M. Xu, R. Chen, T. T. Liu, J. Y. Luo, Y. W. Wu, Y. B. Huang and Q. Lu, *Green Chem.*, 2022, **24**, 5965–5977.
30 L. Xu, X. Li, Y. Zhu and Y. Xiang, *New J. Chem.*, 2009, **33**, 2051–2054.
31 B. M. O'Keefe, D. M. Mans, D. E. Kaelin and S. F. Martin, *J. Am. Chem. Soc.*, 2010, **132**, 15528–15530.
32 S. D. Banister, M. Manoli, M. L. Barron, E. L. Werry and M. Kassiou, *Bioorg. Med. Chem.*, 2013, **21**, 6038–6052.
33 M. Kannan and T. Punniyamurthy, *Tetrahedron Asymmetry*, 2014, **25**, 1331–1339.
34 Z. X. Hu, N. Ma, J. H. Zhang, W. P. Hu and H. X. Wang, *Polyhedron*, 2014, **83**, 30–35.
35 B. T. Clarke, B. Gillespie and S. Z. Weisshaus, *J. Am. Chem. Soc.*, 1933, **55**, 4571–4587.
36 F. Orlandi, M. Coronnello, C. Bellucci, S. Dei, L. Guandalini, D. Manetti, C. Martelli, M. N. Romanelli, S. Scapecchi, M. Salerno, H. Menif, I. Bello, E. Mini and E. Teodori, *Bioorg. Med. Chem.*, 2013, **21**, 456–465.

37 D. van der Waals, L. E. Heim, C. Gedig, F. Herbrik, S. Vallazza and M. H. G. Prechtl, *ChemSusChem*, 2016, **9**, 2343–2347.
38 J. Liu, Y. Song, X. Wu and L. Ma, *ACS Omega*, 2021, **6**, 22504–22513.
39 R. V Jagadeesh, K. Murugesan, A. S. Alshammari, H. Neumann, M.-M. Pohl, J. Radnik and M. Beller, *Science (1979)*, 2017, **358**, 326–332.
40 Z. Ke, X. Cui and F. Shi, *ACS Sustainable Chem. Eng.*, 2016, **4**, 3921–3926.
41 X. Ge, C. Luo, C. Qian, Z. Yu and X. Chen, *RSC Adv.*, 2014, **4**, 43195–43203.
42 J. Liu, Y. Song, X. Zhuang, M. Zhang and L. Ma, *Green Chem.*, 2021, **23**, 4604–4617.
43 H. Alinezhad, M. Tajbakhsh, F. Salehian and K. Fazli, *Synth. Commun.*, 2010, **40**, 2415–2420.
44 H. Wang, H. Yuan, B. Yang, X. Dai, S. Xu and F. Shi, *ACS Catal.*, 2018, **8**, 3943–3949.
45 C. Guyon, M. C. Duclos, E. Métay and M. Lemaire, *Tetrahedron Lett.*, 2016, **57**, 3002–3005.
46 K. Natte, H. Neumann, R. V. Jagadeesh and M. Beller, *Nat. Commun.*, 2017, **8**, 1344.
47 H. Wang, Y. Huang, X. Dai and F. Shi, *Chem. Commun.*, 2017, **53**, 5542–5545.
48 N. Y. T. Man, W. Li, S. G. Stewart and X. F. Wu, *Chimia*, 2015, **69**, 345–347.
49 Y. Li, X. Cui, K. Dong, K. Junge and M. Beller, *ACS Catal.*, 2017, 7, 1077–1086.
50 Q. Zou, G. Long, T. Zhao and X. Hu, *Green Chem.*, 2020, **22**, 1134–1138.
51 J. R. Cabrero-Antonino, R. Adam, K. Junge and M. Beller, *Catal. Sci. Technol.*, 2016, **6**, 7956–7966.
52 J. Zheng, C. Darcel and J. B. Sortais, *Chem. Commun.*, 2014, **50**, 14229–14232.
53 V. Goyal, G. Naik, A. Narani, K. Natte and R. V. Jagadeesh, *Tetrahedron*, 2021, **98**, 132414.
54 Y. Chen, *Chem. Eur. J.*, 2019, **25**, 3405–3439.
55 X. Liu, S. Li, Y. Liu and Y. Cao, *Chinese J. Catal.*, 2015, 36, 1461–1475.
56 I. Sorribes, K. Junge and M. Beller, *Chem. Eur. J.*, 2014, **20**, 7878–7883.
57 L. Ouyang, R. Miao, Z. Yang and R. Luo, *J. Catal.*, 2023, **418**, 283–289.
58 W. Li, F. Yan, S. Cai, L. Ding, B. Li, B. Zhang, Y. Zhang and L. Zhu, *J. Saudi Chem. Soc.*, 2022, **26**, 101421.
59 C. Qiao, X. Liu, X. Liu and L. He, *Org. Lett.*, 2017, **19**, 1490–1493.
60 C. Qiao, X. Y. Yao, X. F. Liu, H. R. Li and L. N. He, *Asian J. Org. Chem.*, 2018, **7**, 1815–1818.
61 Y. Huang, W. Deng and B. L. Lin, *Chin. Chem. Lett.*, 2020, **31**, 111–114.
62 M. Fu, R. Shang, W. Cheng and Y. Fu, *Angew. Chem. Int. Ed.*, 2015, **54**, 9042–9046.
63 M. Rahman, D. Kundu, A. Hajra and A. Majee, *Tetrahedron Lett.*, 2010, **51**, 2896–2899.
64 L. M. Monene, C. Goosen, J. C. Breytenbach and J. Hadgraft, *Eur. J. Pharm. Sci.*, 2005, **24**, 239–244.
65 WO Pat., 2018002696A1, 2018.
66 G. MacQueen, L. Born and M. Steiner, *CNS Drug Reviews*, 2001, **7**, 1–24.
67 S. Das, F. D. Bobbink, G. Laurenczy and P. J. Dyson, *Angew. Chem. Int. Ed.*, 2014, **53**, 12876–12879.
68 W. D. Li, D. Y. Zhu, G. Li, J. Chen and J. B. Xia, *Adv. Synth. Catal.*, 2019, **361**, 5098–5104.
69 M. J. Dresser, D. Desai, S. Gidwani, A. D. Seftel and N. B. Modi, *Int. J. Impot. Res.*, 2006, **18**, 104–110.
70 US Pat., 5135947A, 1992.
71 F. Hessler, A. Korotvička, D. Nečas, I. Valterová and M. Kotora, *Eur. J. Org. Chem.*, 2014, **2014**, 2543–2548.
72 P. You, J. Qiu, E. Su and D. Wei, *Eur. J. Org. Chem.*, 2013, **2013**, 557–565.
73 S. A. Siddiqui and K. V. Srinivasan, *Tetrahedron Asymmetry*, 2007, **18**, 2099–2103.
74 M. Wirth, V. Zoete, O. Michielin and W. H. B. Sauer, *Nucleic Acids Res.*, 2013, 41, D1137-D1143.
75 P. Liu, J. Yang, Y. Ai, S. Hao, X. Chen and F. Li, *J. Catal.*, 2021, **396**, 281–290.
76 W. Yao, H. Fang, Q. He, D. Peng, G. Liu and Z. Huang, *J. Org. Chem.*, 2019, **84**, 6084–6093.
77 J. J. Klein and S. Hecht, *Org. Lett.*, 2012, **14**, 330–333.
78 X. Cui, X. Dai, Y. Zhang, Y. Deng and F. Shi, *Chem. Sci.*, 2014, **5**, 649–655.
79 M. A. Hussein, A. H. Dinh, V. T. Huynh and T. V. Nguyen, *Chem. Commun.*, 2020, **56**, 8691–8694.

80 A. M. Borys, J. M. Gil-negrete and E. Hevia, *Chem. Commun.*, 2021, **57**, 8905–8908.
81 E. A. Steck, G. W. Ewing and F. C. Nachod, *J. Am. Chem. Soc.*, 1948, **70**, 3410–3416.
82 D. Zaher, A. K. Tomov, V. C. Gibson and A. J. P. White, *J. Organomet. Chem.*, 2008, **693**, 3889–3896.
83 T. Lebleu, H. Kotsuki, J. Maddaluno and J. Legros, *Tetrahedron Lett.*, 2014, **55**, 362–364.

Chapter 3

Metal-free Reduction of Phosphine Oxides

Phosphine oxide reduction is an important transformation in both the synthesis of complex phosphine ligands, but also for organophosphorus catalysed systems. Here, we report a practical and mild reduction of phosphine oxides using phenylsilane and benzenesulfonic acid. This method is applied to a range of starting materials and the chemoselectivity of this process is confirmed. This reduction is also applied to the catalytic Wittig reaction and a proof of concept is demonstrated. The mechanism is also investigated and is shown to proceed through formation of silyl sulfonates and subsequent interaction with the phosphine oxide, rather than initial activation of the P=O bond with the acid and reduction of the resulting species.

Milly Stoneley

1 Introduction

1.1 Importance of Phosphorus and Uses in Organic Chemistry

1.1.1 Importance of Phosphorus

Phosphorus was first discovered in 1669 by Henning Brandt in the form white phosphorus (P_4) and since this discovery, the uses for this compound have expanded rapidly.[1] Phosphorus containing compounds are used for munitions, incendiary devices and chemicals weapons, but conversely are also necessary for life and have other important uses.[2]

A wide range of phosphorus compounds are known, and arguably the most important class is phosphates (PO_4^{3-}), which are required for all known forms of life.[3] Phosphates play a major role in the structural framework of DNA and RNA, in addition to being present in adenosine triphosphate (ATP), which is critical to cellular function through energy provision. Phospholipids are the main components of cellular membranes and calcium phosphate salts comprise up about 85-90% of bones and teeth. Both inorganic and organic phosphorus compounds are also used in flame retardants,[4,5] fertilisers and pesticides, although concerns about the environmental impact have been raised.[6,7] In addition, organophosphorus compounds are commonly used as pharmaceutical targets and play an important role in organic chemistry.[8]

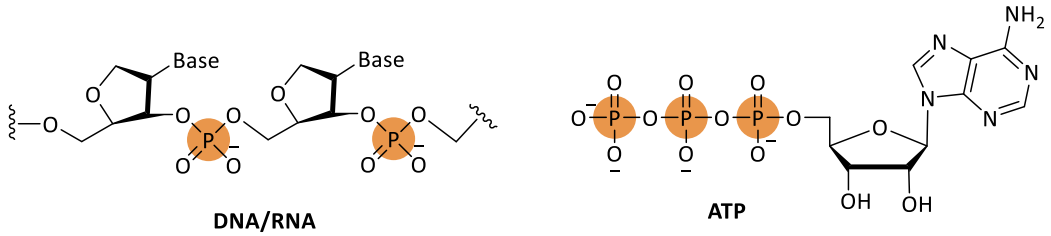


Figure 30: *Biological phosphorus containing compounds*

1.1.2 Organophosphines in Organic Synthesis

Despite phosphates being the most prevalent in nature, organophosphines and their reactivity will be discussed *herein,* as they are ubiquitous in the chemical sciences and catalysis. The first tertiary phosphine to be synthesised was trimethylphosphine in 1847 by Thénard, through reaction of methyl

chloride and calcium phosphide at a high temperature (Figure 31A).[9] Despite this, phosphine chemistry did not advance until 1857, where a safer process was developed by Hofmann and Cahours through reaction of methyl zinc and phosphorus trichloride (Figure 31B).[9]

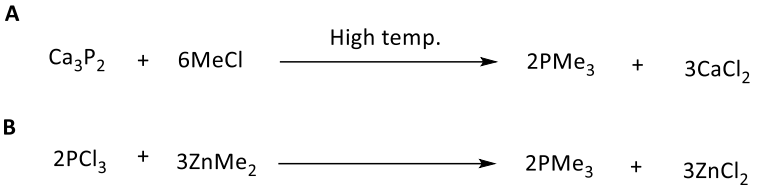


Figure 31: *Original synthesis of organophosphines*

Since this discovery, the uses of organophosphines have expanded rapidly. Phosphines are one of the most common ligands used for transition metal catalysis. This is due to strong metal binding and ease of preparation, which has led to a range of sterically and electronically varied ligands.[10,11] These ligands control not only the orientation of metal-substrate binding, leading to chemoselective or enantioselective reactivity, but can also influence the electronics of the metal center.[12,13] The introduction of bulky or bidentate phosphine ligands to palladium-catalysed cross-coupling reactions, prevent unwanted β-hydride elimination and promote reductive elimination through blocking open coordination sites.[10,11,14–16]

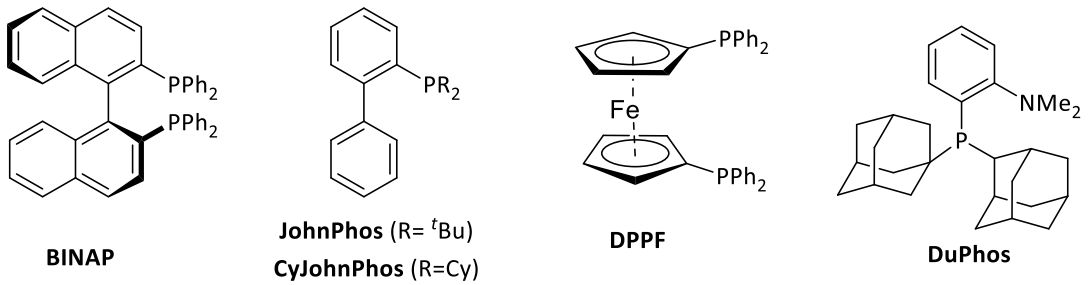


Figure 32: *Examples of phosphine ligands*

Phosphines themselves are nucleophilic, and can add either across double bonds, or to alkyl halides, which is important for a range of processes.[9,17,18] The formation of phosphine oxides from phosphines has been exploited as the driving force for a range of reactions, through formation of strong P-O double bonds (Figure 33).[19] The Mitsunobu,[20] Staudinger[21] and Wittig[20] reactions all rely on formation of phosphine activation through P(V) intermediates. These reactions are some of the most used in organic synthesis.

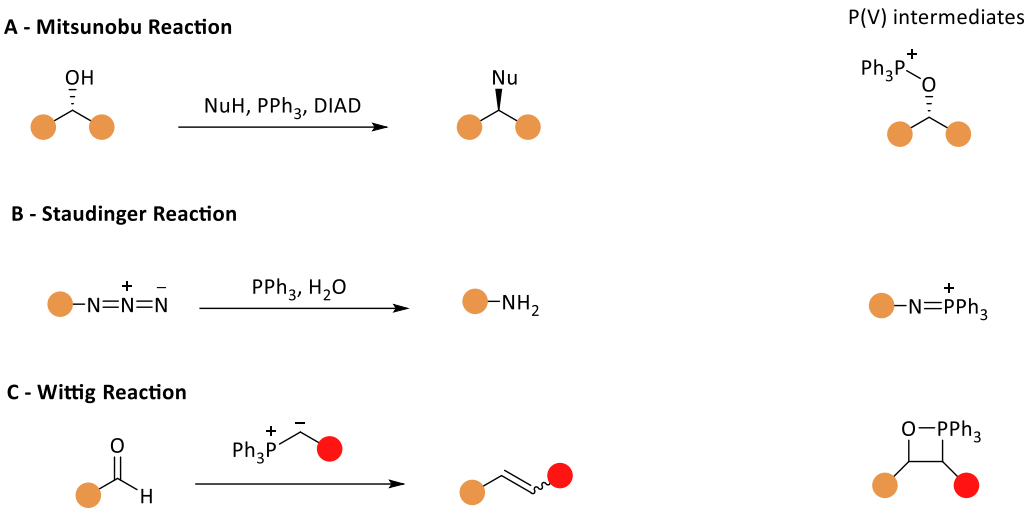


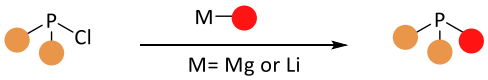
Figure 33: *Examples of phosphine mediated reactions*

1.2 Synthesis of Phosphines

There are many methods used for the synthesis of tertiary phosphines, and although the most common methods will be discussed *herein*, reviews by Balueva,[22] Chusov[23] and Hérault[24] cover other methods in more detail.

1.2.1 Treatment of Chlorophosphines with Organometallics

One of the most common synthesis methods for the formation of phosphines is the reaction of organometallic reagents with chlorophosphines (Scheme 79).



Scheme 79: *General transformation of chlorophosphines with organometallic reagents*

For the synthesis of phosphines, where all the substituents are the same, phosphorus trichloride (PCl_3) can be used in the presence of three equivalents of the organometallic reagent to displace three chlorines in a single reaction.[25,26] The number of substitutions can also be controlled to allow for synthesis of more complex phosphines from PCl_3; although high equivalents of chlorophosphine or bulky ligands are required to prevent over substitution.[27,28] Alternatively, the chlorophosphine can be synthesised through treatment of secondary phosphine oxides with chlorinating agents and can be

used in the presence of a differing organometallic reagents to allow for varied substituents.[29,30] As a more common alternative, many mono- and di- chlorophosphines are commercially available.[10,25,31,32] The modular nature of this pathway makes the synthesis of a wide range of structurally diverse phosphines very simple and has been used extensively without change to the reaction conditions.

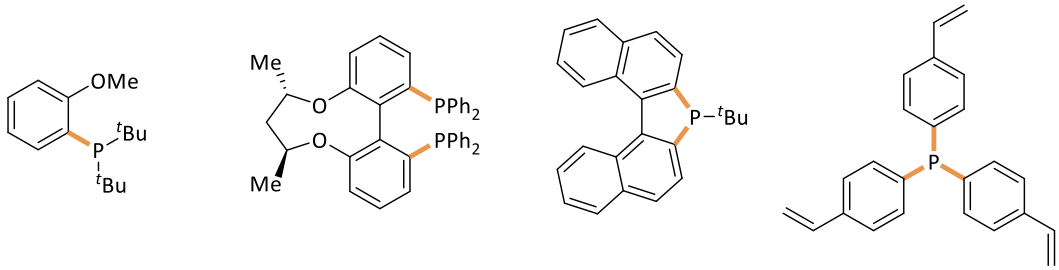
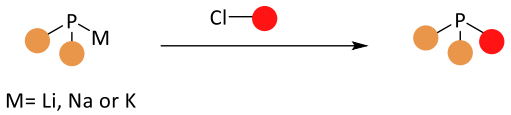


Figure 34: *Examples of phosphines made through reaction of chlorophosphines and organometallic reagents*

Despite its widespread use, this method possesses significant disadvantages. The generation of the highly reactive organometallic reagent *in situ*, requires low temperatures and as a result, is not attractive on scale. In addition, chlorophosphines themselves are highly reactive, corrosive and have a foul odour, and are often avoided in process routes.

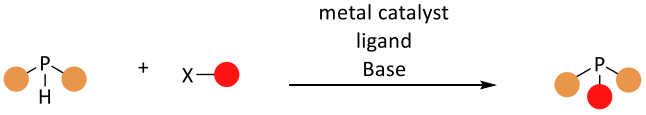
Conversely, metalated phosphines can also be employed in conjunction with alkyl halides, although this method is less commonly employed due to stability issues of the metal phosphide (Scheme 80).[22]



Scheme 80: *General transformation of metalated phosphines with chloroalkanes*

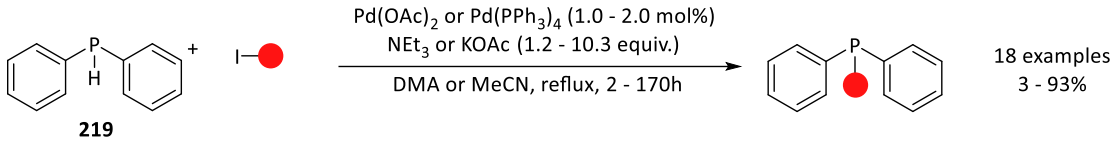
1.2.2 Metal-Catalysed P-C(sp2) Cross-coupling

Another synthesis pathway is through a metal-catalysed cross-coupling of a secondary phosphine and an aryl halide.



Scheme 81: *General transformation for metal-catalysed cross-coupling of secondary phosphines*

P-C(sp2) coupling from the secondary phosphine and aryl iodide was first introduced by Stelzer in 1996. This type of coupling had already been disclosed in earlier publications, however, the phosphine starting material was required to be the stannyl, silyl[33] or borane derivative.[34] Stelzer used diphenylphosphine (**219**) directly, in conjunction with aryl iodides in the presence of a palladium catalyst to achieve C-P bond formation.[35]



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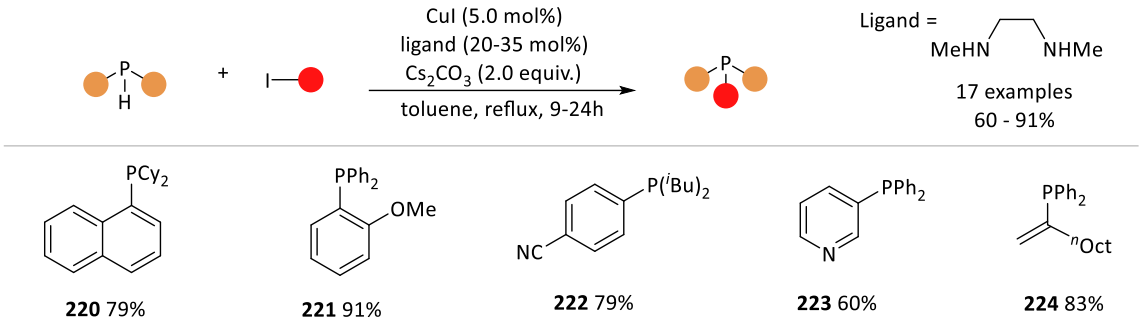
Scheme 82: *Stelzer's palladium catalysed cross coupling of diphenylphosphine and aryl iodides*

Since Stelzer's publication, the palladium-catalysed transformation has been further developed to include electrophiles such as bromides, triflates[36] and aryldiazonium tetrafluoroborates.[37] This coupling has also been demonstrated in ionic liquids,[38] with microwave irradiation[36] and in the synthesis of chiral compounds, both *via* chiral starting materials,[39] and through kinetic resolution of a racemic phosphine.[40,41]

Palladium-catalysed couplings have been demonstrated in the synthesis of a range of phosphines, although other metals have also been shown to be effective.[11,42–44] A review by Włodarczyk discloses these processes, stating that nickel and copper are widely used for this transformation, and discussing other select metals.[45] Despite the use of more benign catalysts, many of these processes are primarily demonstrated for the synthesis of phosphine oxides or phosphites, with a few phosphine products included as part of the scope.[46–48]

In 2002, Buchwald published a copper-mediated cross coupling between secondary phosphines and aryl and vinyl iodides.[49] This method utilised both commercially available copper(I) iodide as the catalyst and *N,N'*-dimethylethylenediamine as the ligand (Scheme 83). Initial investigations were conducted without the ligand present and despite the coupled product being formed, reduction of the aryl iodide was seen as a side-product, and excess phosphine to circumvent this issue caused workup

complications. Using these conditions, a range of phosphines were synthesised bearing varied functional groups.



Scheme 83: *Buchwald's P-C(sp2) coupling using CuI/ N,N'-dimethylethylenediamine*

P-C(sp3) coupling is also possible using transition metal catalysts although this is usually restricted to benzylic and allylic coupling partners.[50–52]

1.3 Reduction of Tertiary Phosphine Oxides

Reduction of phosphine oxides is a common method for phosphine synthesis. This is not only due to operational simplicity, but also due to stability of phosphine oxides. Chlorophosphines are highly reactive, and electron rich phosphines readily oxidise in solution or upon exposure to air. However, phosphine oxides are bench stable and generally easy to handle in the laboratory. However, P=O bonds are exceptionally strong (547 kJ/mol), due to their small bond length and high polarity and as a result can be difficult to reduce. The exact nature of the P=O bond is highly contested with π-backbonding, Ω-banana bonding and negative hyperconjugation all being proposed.[53] The currently accepted explanation is that negative hyperconjugation between oxygen P-orbitals and C-P σ* orbitals allow for the formation of the "double bond".[54]

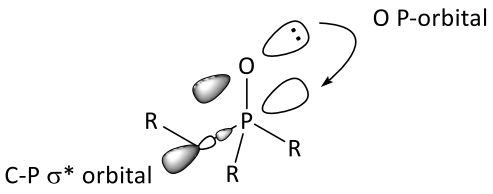
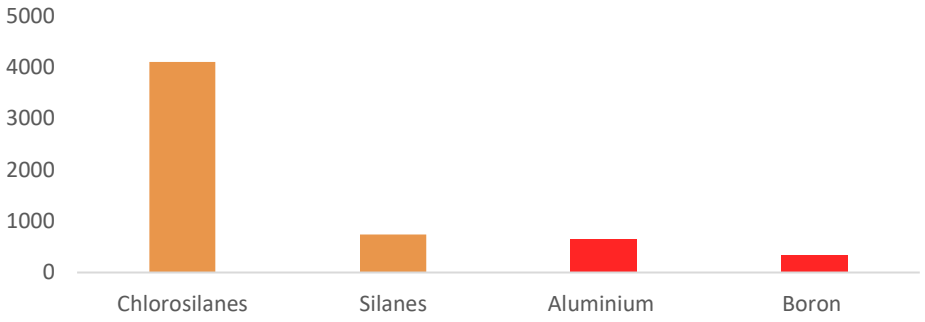


Figure 35: *Negative hyperconjgation description of phosphine oxides*

1.3.1 Traditional Reducing Reagents

Common reducing agents such as $LiAlH_4$,[55,56] AlH_3,[57,58] DIBAL-H[59] and boranes[60,61] have all been demonstrated for the reduction of phosphine oxides and have been applied to external publications.[62–64] However, these reducing agents are relatively scarce, with many publications opting for silane reducing agents. This is likely due to undesirable reaction conditions when using these reagents.



1.3.2 Silane Reducing Agents

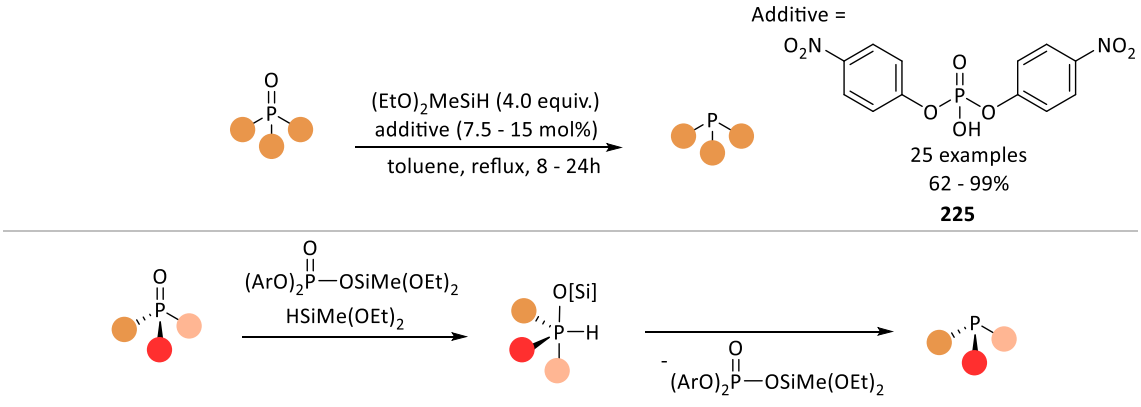
The first reduction of phosphine oxide with silanes was carried out by Fritzsche in 1964.[65] A range of silanes including PMHS, $PhSiH_3$, Ph_2SiH_2, and Ph_3SiH were shown to be successful in the reduction of a range of alkyl and aryl phosphine oxides. However, high temperatures and long reaction times, coupled with high silane equivalents and hazardous solvents, lead to the same group publishing a new method using trichlorosilane just one year later.[66] This process not only used toluene as a solvent, but also required two equivalents of silane or one equivalent if triethylamine was present to suppress silane deactivation. As can be seen in Graph 4, chlorosilanes are extremely popular for phosphine oxide reductions.[67–69] However, their low boiling points and high reactivity make them difficult to handle and severely impact functional group tolerance. As a result, efforts have turned towards more easily handleable silanes, although, their lower comparative reactivity means that activation is required to allow for mild conditions and functional group tolerance.

Although transition metals are well known for the activation of silanes, there are surprisingly few transition-metal catalysed reductions of phosphine oxides with silanes. Only titanium,[70] copper[71] and

indium[72] have been demonstrated for this process, displaying a range of functional group tolereance, and invoking a metal hydride as the active reducing species.

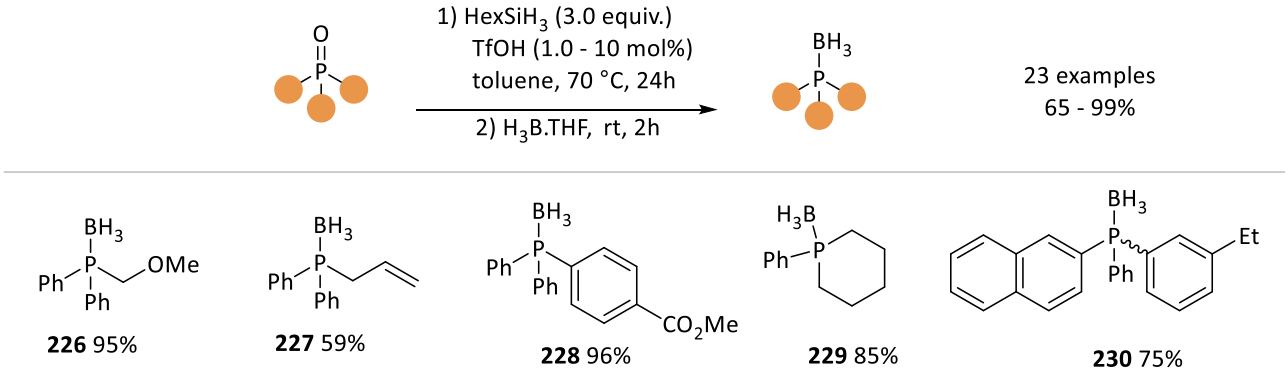
Silane mediated reductions with metal-free initiators are well-represented in the literature. This is likely because metal-free processes prevent problematic complexation of metals to phosphine oxide starting materials and phosphine products. A range of initiators, including phosphoric acids,[73] sulfonic acids,[74,75] $B(C_6F_5)_3$ compounds[76,77] and hydrazides,[78] have all been shown to reduce phosphine oxides in combination with silanes in high yields.

Beller published the first silane-mediated phosphine oxide reduction using metal-free initiators in 2012.[73] A range of Brønsted acids and silanes were trialed and phosphoric acids, bearing electron-withdrawing groups to increase acidity (**225**), alongside methyldiethoxysilane were shown to be the most effective reductants. Using this process, a range of phosphines were synthesised, both aromatic and aliphatic compounds, bearing a range of potentially reducible functional groups, including olefins, carbonyl groups and nitriles. The observation that the reduction occurred with retention of stereochemistry was rationalized through a mechanism involving concerted hydrosilylation and deoxygenation (Scheme 84). However, the need for the synthesis of the phosphoric acid (**225**), despite being relatively simple, decreases the utility of this reaction for further processes.



Scheme 84: *Beller's phosphine oxide reduction using $(EtO)_2MeSiH$ and a phosphoric acid*

As a result, processes using commercially available reagents are of significant importance. In 2016 Werner published a process using catalytic triflic acid and hexylsilane to affect the reduction of phosphine oxides.[75] This process demonstrated a range of sterically and electronically altered aromatic phosphines, however, racemisation was observed for chiral non-racemic substrates. An explanation is not provided for this, although loss of stereocontrol at the pentacoordinate phosphorane intermediate could be to blame, and racemisation of triaryl phosphines is known to occur more rapidly at elevated temperatures.[79] As a result, the process itself may proceed with retention of stereochemistry as is expected, and racemisation may happen following reaction completion. This highlights the necessity for mild conditions for this transformation.

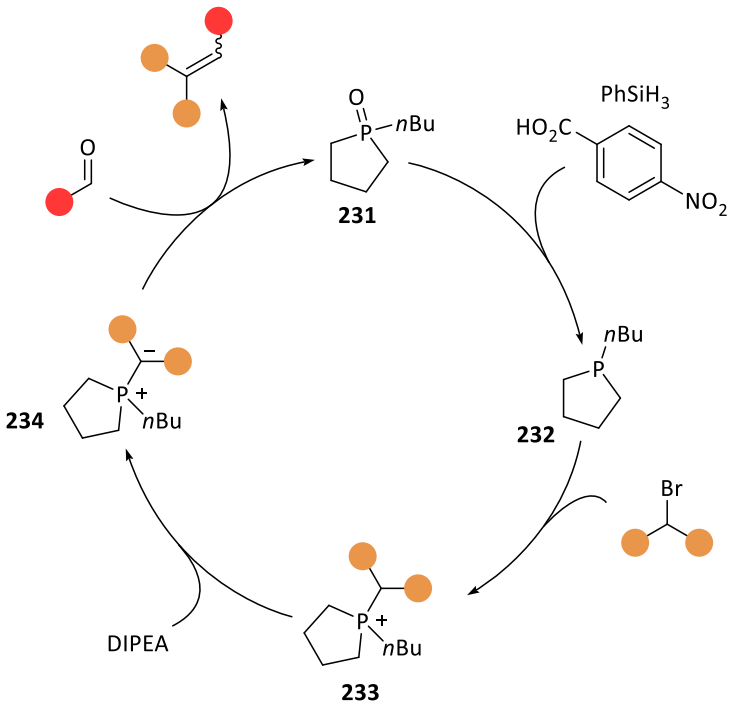


Scheme 85: *Werner's phosphine oxide reduction using hexylsilane and triflic acid*

1.3.3 Application of Phosphine Oxide Reductions in Organophosphorus Catalysis

The main problem associated with processes as described in Figure 33, is the low atom economy and increased purification procedures resulting from stoichiometric phosphine oxide waste. As a result, efforts towards the implementation of phosphine recycling in these processes are highly desirable. Phosphine recycling has been applied to many reactions such as the Mitsunobu reaction,[80] the Wittig reaction[81–83] and the Staudinger reaction.[84] The development of a Wittig reaction containing a phosphine redox manifold, however, is exceptionally important due to its high use across a range of industries. A key challenge for this transformation is that the redox cycle must be chemoselective and remain inert to both the starting material aldehyde and the alkene product.

This was first demonstrated by O'Brien in 2009, through the use of a phospholane oxide and Ph_2SiH_2.[81] Later in 2013, O'Brien published an improved protocol, allowing for the reaction to be conducted at room temperature, through the addition of 4-nitrobenzoic acid; this acted to increase the reducing power of the silane.[85] The specific choice of this acid allowed for the reduction of the phosphine oxide to be improved without protonation of the base or the phosphonium ylide. Work conducted in the Denton group has begun to probe the mechanism and kinetics of this reaction, although this is ongoing.[86]



Scheme 86: *O'Brien's general Wittig reaction catalytic cycle*

1.4 Project Aims

The aim of this project was to develop the benzenesulfonic acid and phenylsilane reduction system towards the reduction of phosphine oxides. It was also hoped that this process could be applied to the catalytic Wittig transformation.

2 Results and Discussion

2.1 Optimisation

Firstly, we wanted to compare the reactivity of this system with phenylsilane alone. With the increased acidity imparted on the silane from the sulfonic acid, it was expected that this system would be more reactive, and thus show improved conversion. Triphenylphosphine oxide (TPPO) was chosen as the model substrate due to the commercial availability, and known ^{31}P NMR spectrum shifts of the product, and potential intermediates. In addition, triphenyl phosphine (TPP) is relatively stable to re-oxidation.

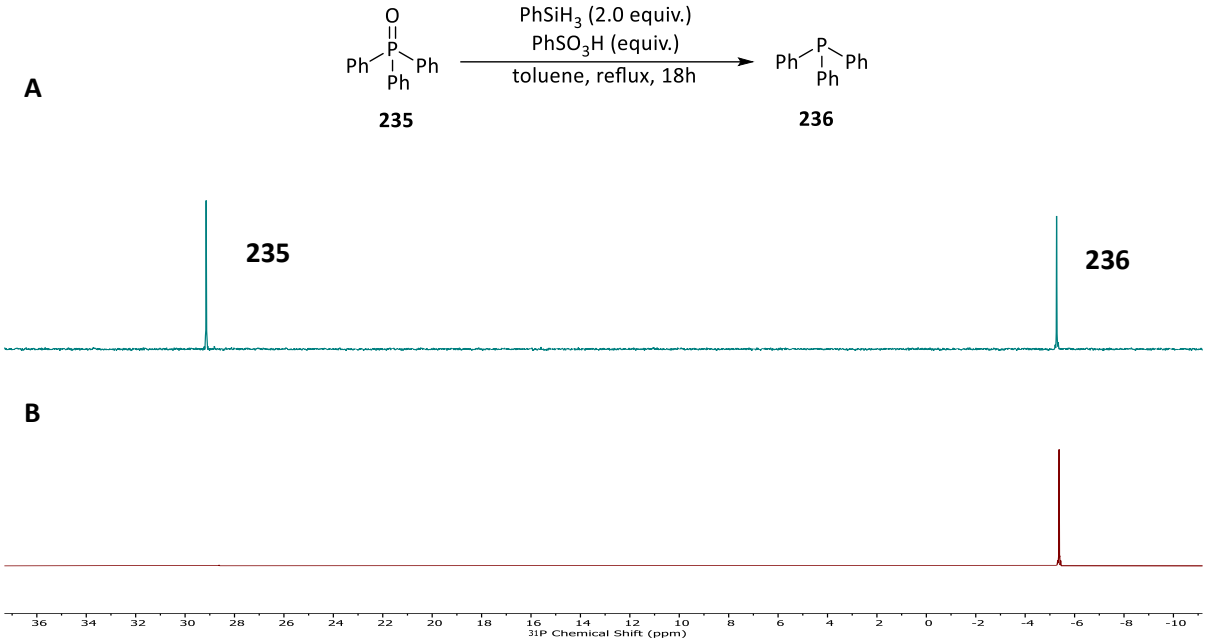


Figure 36: *^{31}P NMR spectrum of the reaction mixture following phosphine oxide reduction with A. $PhSiH_3$ alone. B. $PhSiH_3$ and $PhSO_3H$*

Pleasingly, this was shown to be the case, with phenylsilane alone demonstrating both starting material and product in a 56:44 ratio after 18h at 110 ^{o}C (Figure 36A). However, the addition of 2.00 equivalents of benzenesulfonic acid allowed for complete conversion to the phosphine in this time (Figure 36B). Interestingly, Beller attempted to use benzene sulfonic acid in a catalytic capacity and achieved a low yield, demonstrating the need for stoichiometric loading and confirming alteration of the acid under the reaction conditions.[73]

Following this result, we investigated the possibility of altering the conditions to allow for a milder transformation. This would allow for not only an increased tolerance to functional groups, but would also provide improved utility over other methods.

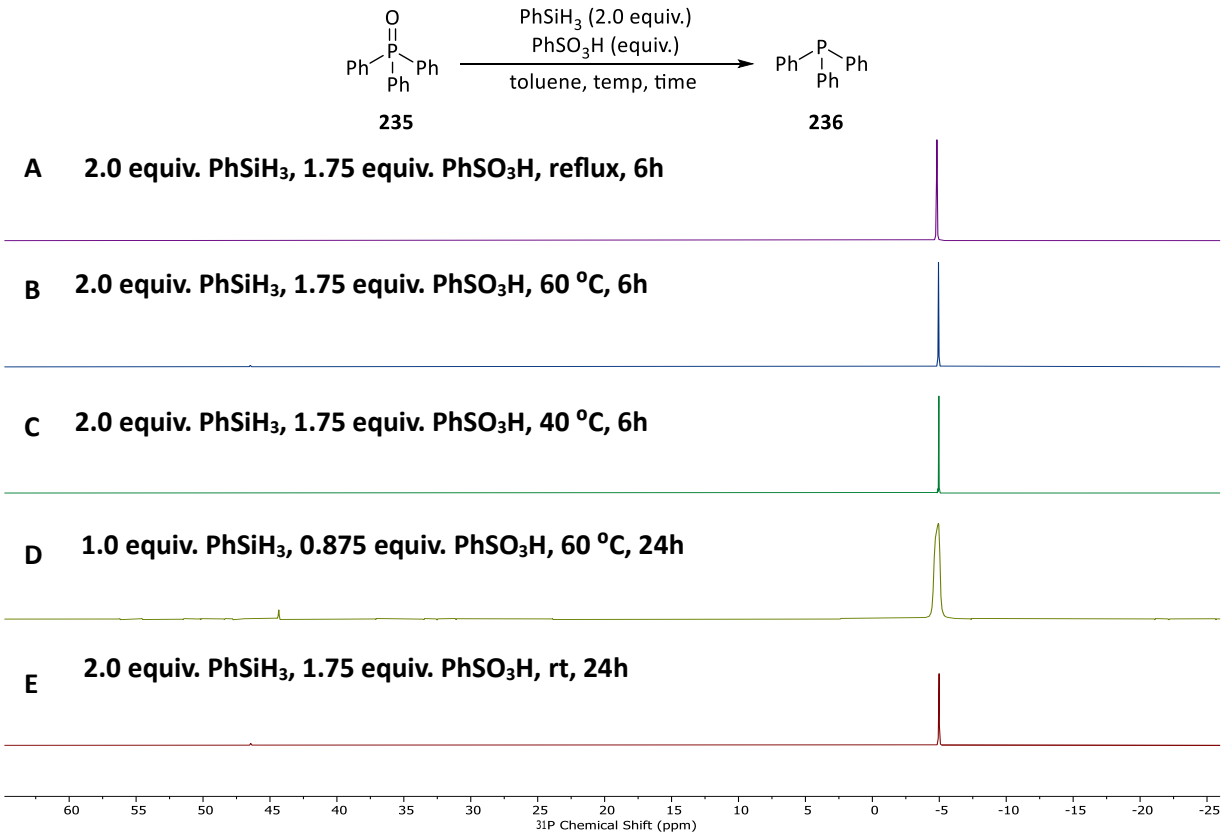
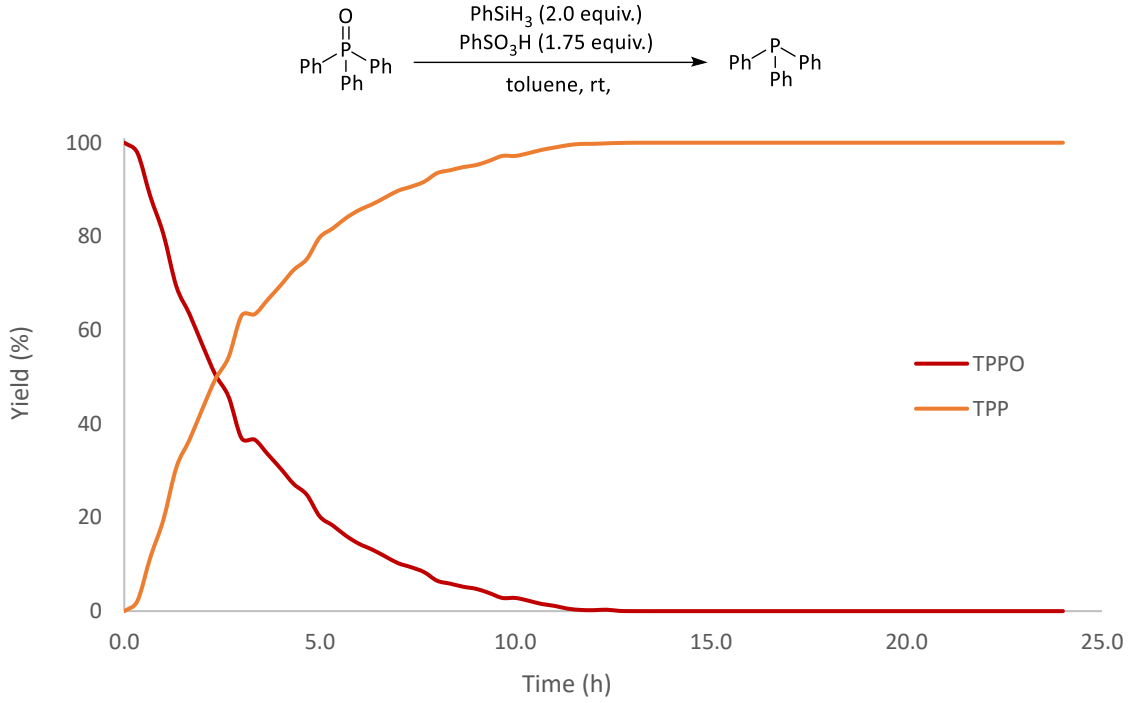


Figure 37: *^{31}P NMR spectrum of the reaction mixture following reduction with: A 2.0 equiv. $PhSiH_3$, 1.75 equiv. $PhSO_3H$, reflux, 6h. B. 2.0 equiv. $PhSiH_3$, 1.75 equiv. $PhSO_3H$, 60 °C, 6h. C. 2.0 equiv. $PhSiH_3$, 1.75 equiv. $PhSO_3H$, 40 °C, 6h. D. 1.0 equiv. $PhSiH_3$, 0.875 equiv. $PhSO_3H$, 60 °C, 24h. E. 2.0 equiv. $PhSiH_3$, 1.75 equiv. $PhSO_3H$, rt °C, 24h*

Initial investigations began with shortening the reaction time, and pleasingly a 100% conversion was obtained with a six-hour process (Figure 37A). Following this, it was hoped that a decrease in temperature would also provide a high conversion and pleasingly, after six hours at both 60 °C and 40 °C, only product was identified by ^{31}P NMR spectroscopy (Figure 37B and C). For the reduction of amides, two equivalents of reducing agents are required, however for the deoxygenation of phosphine oxides, theoretically only one is needed. Pleasingly, halving the silane and acid equivalents resulted in reduction of the phosphine oxide, although an impurity at δ= 44.9 ppm was observed (Figure 37D). This was attributed to association of the silyl sulfonate with the phosphine oxide and essentially

represents unreacted starting material. It is likely that this reduction could be pushed to completion with an increased reaction time or temperature, however further addition to an already 24-hour 60 °C reaction decreases the benefits of this transformation.

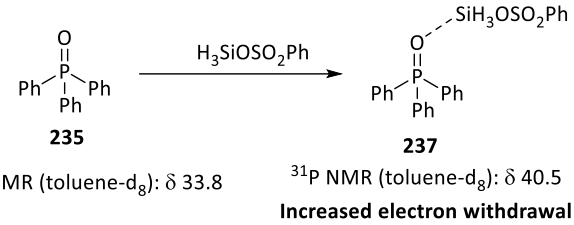
Pleasingly, this reaction was able to proceed at room temperature with two equivalents of silane and 1.75 equivalents of sulfonic acid (Figure 37E). Initial investigations into the room temperature process, allowed the reaction to run for 24 hours, however it is possible that it was complete sooner. It is important to identify a correct reaction length due to reoxidation of the phosphine in the reaction medium following consumption of the reducing agents. To identify the reaction length, a reaction monitoring study using ^{31}P NMR spectroscopy was carried out with spectra recorded every 20 minutes.



Graph 5: *Reduction of TPPO over 24 hours*

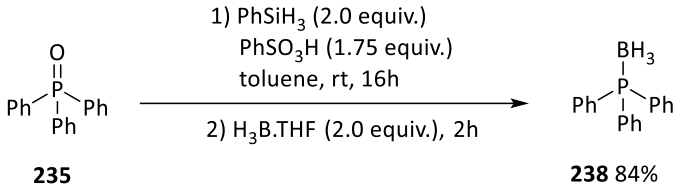
It was discovered that the reaction actually required 14 hours. Interestingly an intermediate was identified at the start of the reaction, although was rapidly consumed before regular monitoring began, and as such has not been included in Graph 5. The intermediate formed had a ^{31}P NMR spectrum shift of 40.5 ppm and was attributed to partial association of the silyl sulfonate with the phosphine oxide. Full protonation would result in a hydroxyphosphonium salt with a ^{31}P NMR chemical shift of *circa* 60

ppm. Association of this species with the phosphine oxide would explain the initial construction and rapid breakdown due to commencement of the reductive process.



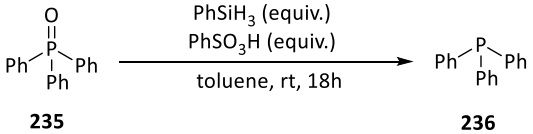
Scheme 87: Proposed identity and formation of the intermediate

Following this successful reduction, isolation was attempted by column chromatography. However, during this process re-oxidation took place and only 15% of phosphine was isolated, despite 100% conversion shown in the crude ^{31}P NMR spectrum. It is known that formation of the borane complex following reduction, prevents re-oxidation and improves isolation and purification procedures. Pleasingly, introduction of $H_3B.THF$ following the reduction, allowed for an isolatable product in a high yield.



Scheme 88: Optimised conditions for the reduction of TPPO

Finally, control reactions were carried out to ascertain the effectiveness of both silane and acid towards reduction.



Entry	$PhSiH_3$ (equiv.)	$PhSO_3H$ (equiv.)	Yield (%)[a]
1	2.00	0.00	1
2	0.00	1.75	0

[a] Yield determined by ^{31}P NMR spectroscopy using triphenylphosphate as an internal standard

Table 12: *Control reactions*

Silanes alone are known to reduce phosphine oxides; although due to the high temperatures usually required for this transformation, it is unsurprising that only a trace amount of phosphine was formed.

There was no reaction observed in the presence of the sulfonic acid alone. It is unsurprising that reduction did not take place, although strong acids are known to protonate phosphine oxides, however the quantitative recovery of starting material suggests that protonation is not happening in this system.[74]

2.2 Scope

2.2.1 Tertiary Phosphines

Following development of optimised conditions, which pleasingly had been shown to be effective at room temperature, a range of phosphines were synthesised. Compared to other methods,[73–75] this transformation boasts mild conditions and as a result should be selective towards the P=O double bond.

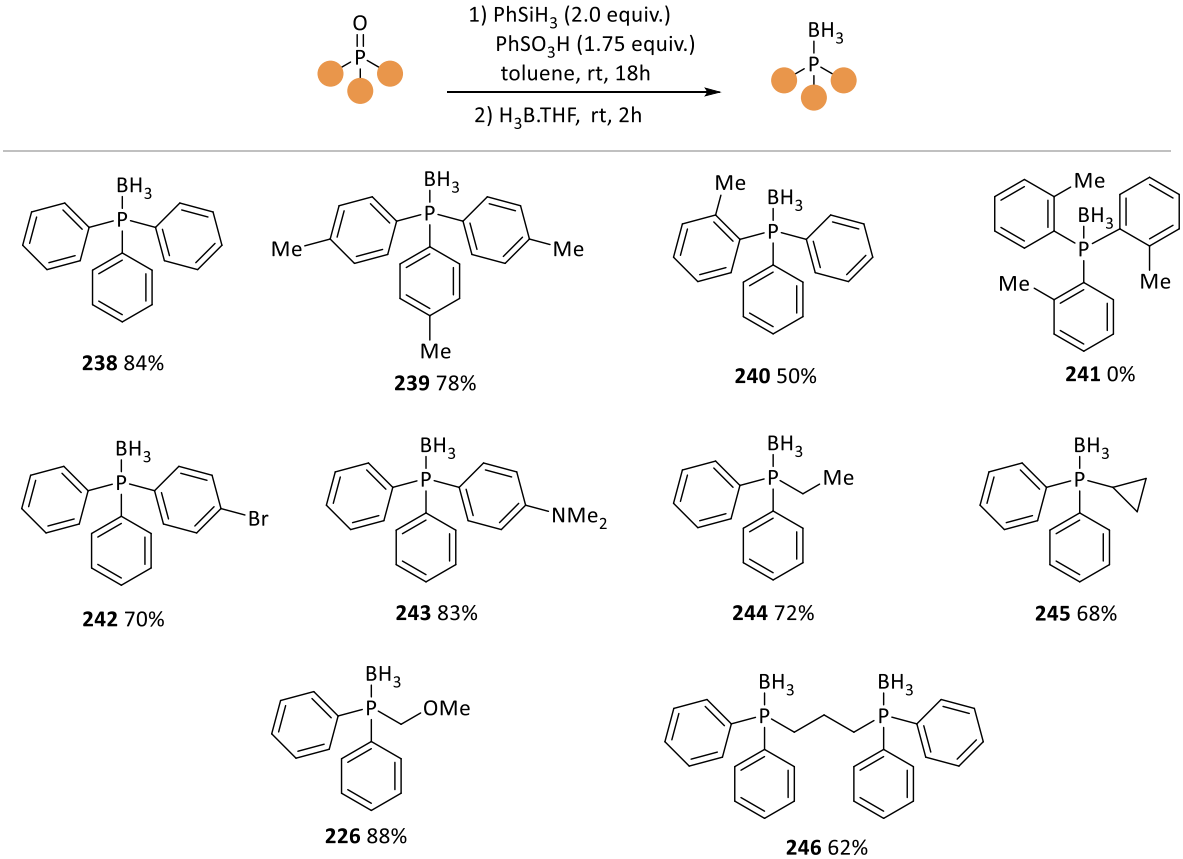


Figure 38: *Phosphine-borane scope*

Pleasingly, in this scope we were able to achieve a range of phosphines with varying functional groups, influencing both electronics and sterics. The addition of *para*-methyl groups (**239**) had almost no effect

on the yield. However, the introduction of one *ortho*-methyl group (**240**) significantly lowered the yield and three-*ortho* (**241**) groups completely prevented reactivity. This is unsurprising given the increased crowding surrounding the P=O bond. It is likely however, with a higher reaction temperature this yield could be increased although this was never attempted.

In addition, the tolerance of this system to halogen substitution (**242**) presents a handle for further reactivity, and the presence of an amine (**243**) demonstrates electron-donating substituents. Investigation of alkyl substituents was also carried out (**244**, **245** and **226**) and it was found that they could be tolerated without any impact to the yield despite being more electron-rich. Finally, a bisphosphine (**246**) was synthesised from the diphosphine oxide starting material, and the stable borane adduct was achieved in a high yield. This process is exceptionally valuable due to the prevalence of bisphosphines as ligands for a variety of processes.[16,87]

However, the combination of sulfonic acid and borane lead to the reduction of some functional groups.[88] In addition, electron-rich phosphines are prone to re-oxidation, and for strongly electron-poor phosphines formation of the borane adduct is more challenging. As a result, for these more sensitive substrates, yields were collected using ^{31}P NMR spectroscopy using triphenylphosphate as an internal standard.

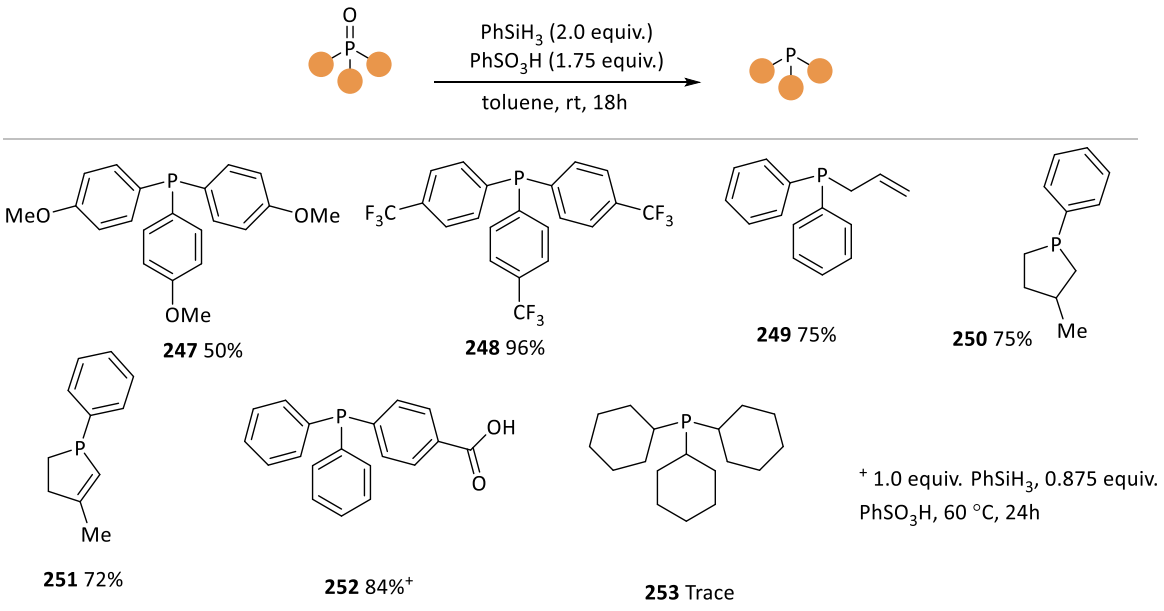
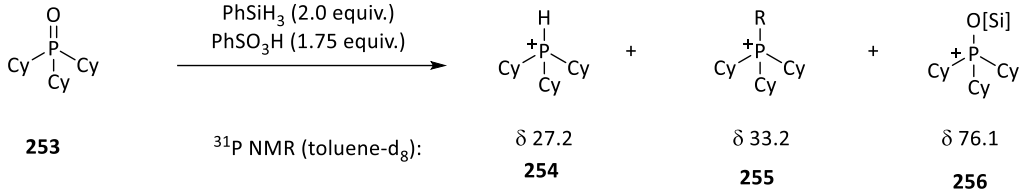


Figure 39: *Additional phosphine scope calculated using ^{31}P NMR spectroscopy. 252 u*

We were able to demonstrate that olefins (**249**) were not only untouched under the reaction conditions and could achieve chemoselective reduction of the phosphine oxide, but also the reduction of strongly electron-rich (**247**) and deficient (**248**) aromatic phosphine oxides. It is likely that the diminished yield for **247** is a result of partial reoxidation following the consummation of the reducing materials. We were also able to demonstrate the reduction of cyclic phosphine oxides **250** and **251** in high yields. As these compounds are used as catalysts for Wittig and aza-Wittig transformations,[81,89] the ability of this system to reduce these compounds in high yields is extremely important. Interestingly, reduction of the carboxylic acid containing phosphine (**252**) using the standard conditions, resulted in reduction of the phosphine and partial reduction of the carboxylic acid to the aldehyde. This reduction occurred due to the super stoichiometric loadings of both the silane and the acid. During our initial optimisation, it was found that increased reductants were required to achieve milder reaction conditions. However, for this example the increased loading prevented chemoselectivity towards the phosphine oxide. As a result, the conditions were altered to only use one equivalent of silane and upon heating at 60 ^{o}C for 24 hours, the phosphine oxide was reduced chemoselectively. Pleasingly, this example demonstrates that for substrates with reduceable groups, the phosphine oxide can be reduced selectively with only a minor alteration to the conditions.

Interestingly, reduction of tricyclohexylphosphine oxide (**253**) was not successful, and only trace product was visible by ^{31}P NMR spectroscopy. This compound is electron-rich and suffers from rapid re-oxidation. The crude ^{31}P NMR spectrum showed that this was not the case as from first investigations, it appeared that all of the starting material had been consumed. There was a trace amount of product identified, along with a further three compounds seen at δ = 76.1, 33.2 and 27.2 ppm (Scheme 89). We have tentatively assumed the peak at 76.1 to be the siloxyphosphonium species due to its high shift, and the peak at 27.2 ppm to be the protonated phosphonium product, due to the doublet seen in the ^{31}P NMR spectrum. Although we are unsure of the exact identity of the remaining peak, the multiplicity and chemical shift suggest a phosphonium species. It is likely that the salt formation of the product prevented formation of reactive silylsulfonates leading to accumulation of

the intermediates. Therefore, with increased sulfonic acid, it is assumed that this reaction could proceed to the H-phosphonium product (**254**) and could be liberated using a basic workup.

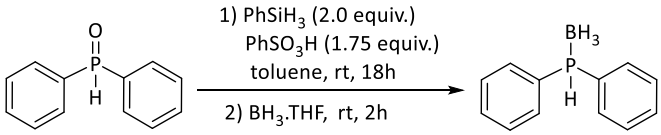


253 **254** **255** **256**

Scheme 89: Postulated products in the reduction of tricyclohexylphosphine

2.2.2 Attempts Towards Secondary Phosphines

Following our tertiary phosphine scope, we next wanted to demonstrate the reduction for secondary phosphines.



257 **258** 10%

Scheme 90: *Attempted reduction of diphenylphosphine oxide*

However, applying our optimised reaction conditions for tertiary amines, we were only able to achieve the crude borane adduct in a 10% yield, with the remaining mass balance attributed to the starting material phosphine oxide. Due to the decreased reactivity of secondary phosphines, this low yield is not surprising, and further optimisation would have to be carried out to achieve reduction of these compounds.

2.3 Towards the Catalytic Wittig Reaction

Despite demonstrating the reduction of a range of phosphine oxides, our main aim for this chemistry is the application to phosphorus (III)/(V) redox system. Given the Denton groups recent interest in the catalytic Wittig reaction, we decided to apply the reduction system to this transformation.

Kinetic experiments completed by Fillipo Ficarra, found that phosphine oxide reduction is rate-limiting in O'Brien's room-temperature Wittig reaction.[85,86] Therefore, improved methods for phosphine oxide

reduction, such as the one described above, could be used to develop more efficient catalytic Wittig reactions.

Whilst O'Brien has already demonstrated a that room temperature catalytic Wittig olefination is possible with an alkyl phospholane (**232**), the synthesis required to make this catalyst is lengthy, uses hazardous chemicals and requires a high-pressure system for the transformation of **259** to **260** (Figure 40A). Even with an improved method, developed in our group by Fillipo Ficarra (Figure 40B), which circumvents most of the hazards associated with O'Brien's method, the yield is significantly diminished. As a result, the utility of the room temperature catalytic Wittig reaction in manufacturing processes is reduced, due to the impracticability of the catalyst synthesis. As an alternative, we proposed the use of 3-methyl-1-phenylphospholane-1-oxide (**264**) which was used as the catalyst in O'Brien's initial publication on the catalytic Wittig olefination.[90] This catalyst can be synthesised in a single step from a commercially available starting material in quantitative yields (Figure 40C).[90] Under O'Brien's conditions, heat is required to affect the reduction of the phosphine oxide, which as a result affected the *E/Z* ratio of the products. However, we believe that utilising an activated silane for a phosphine oxide reduction, as demonstrated *herein*, would allow this transformation to occur at room temperature. This would represent a significant improvement upon current state-of-the-art catalytic Wittig olefinations.

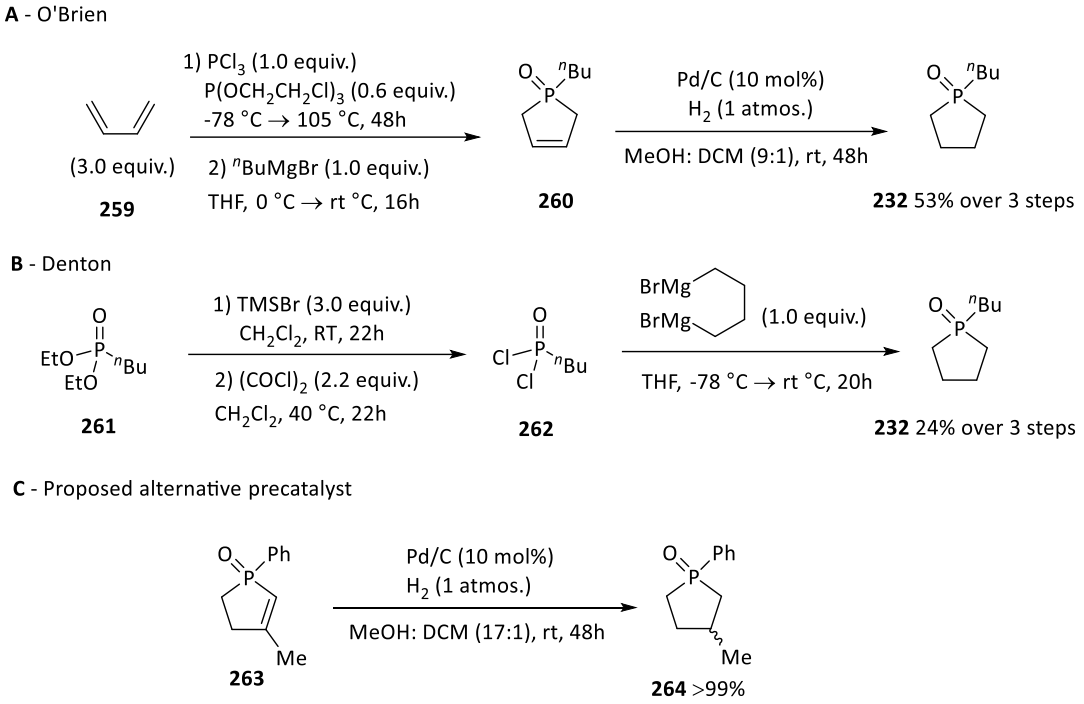
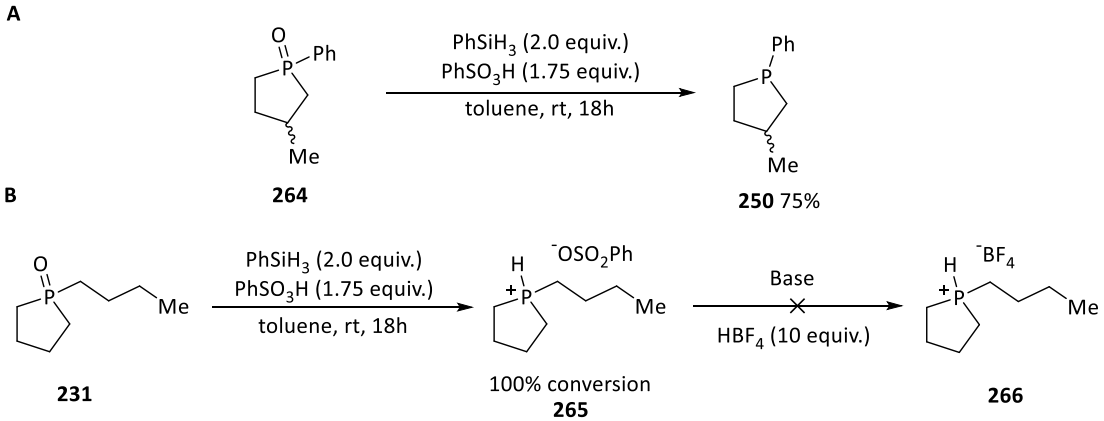


Figure 40: *Routes towards Wittig precatalysts*

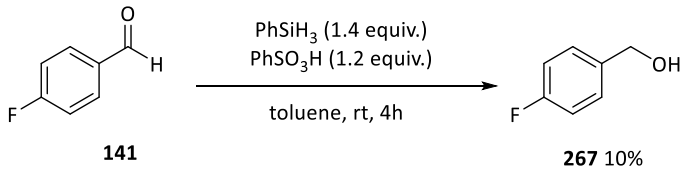
Investigations began by ensuring that the phosphine oxides (**264** and **232**) would be reduced under the phenylsilane/benzenesulfonic acid conditions. As demonstrated in our reaction scope (Scheme 91A), **264** was reduced to the corresponding phosphine in good yield. However, attempts towards the reduction of **231** by Laura Blair, resulted in quantitative formation of the sulfonic acid phosphonium salt (**265**), which was shown to be unreactive in the catalytic Wittig reaction and attempts to obtain the free phosphine were unsuccessful (Scheme 91B).



Scheme 91: *Reduction of the phospholane oxides **264** and **266***

For this reason, **264** was selected for this study. However, before undertaking this reaction, we first needed to confirm that the silane/acid conditions would not immediately reduce the aldehyde. During

the reaction scope of both amines and phosphines, tolerance towards both olefins and esters was demonstrated (Figure 18) and so potential reduction of these functional groups were not considered.

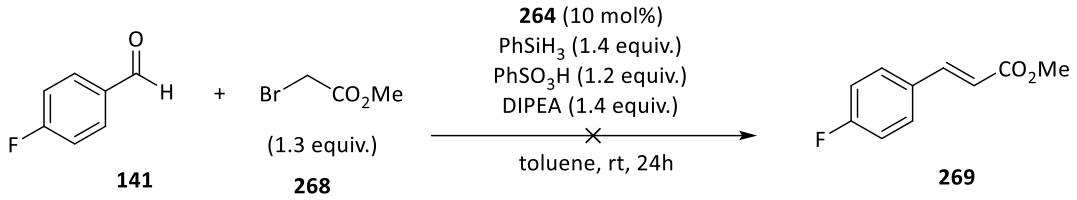


141 **267** 10%

Scheme 93: *Attempted reduction of 4-fluorobenzaldehyde*

Pleasingly, only a small amount of the alcohol was detected by ^{19}F NMR spectroscopy after 4 hours, and so we were confident that reduction of the starting material would not be a competitive pathway.

Initial catalytic Wittig reaction conditions mirrored those used by O'Brien, although using the appropriate silane to acid ratio as required by our transformation.[85]



141 **268** **269**

Scheme 93: *First attempt at the room temperature catalytic Wittig*

Unfortunately, the reaction was not successful with full recovery of the aldehyde and halide starting materials along with the catalyst in its oxide form. After 24 hours, formation of two distinct layers were identified (Figure 41). Following investigation by NMR spectroscopy, these were shown to comprise of a toluene layer, containing the aldehyde, bromo compound, catalyst and silane and a salt layer containing the ammonium salt of benzenesulfonic acid and DIPEA.

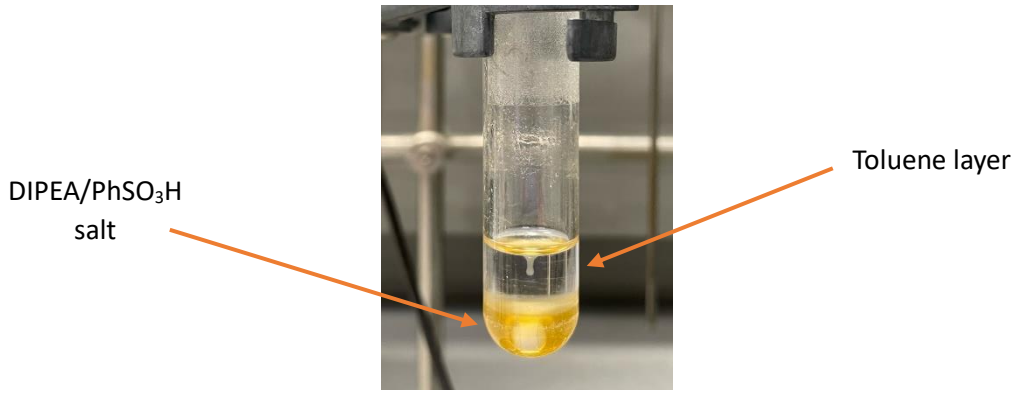
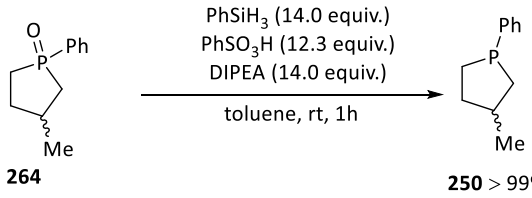


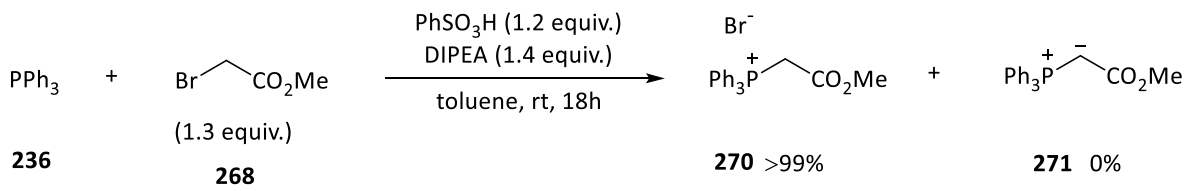
Figure 41: *Reaction mixture after 24 hours*

Investigation of the pKa's in MeCN (benzenesulfonic acid pKa = 8.2,[91] DIPEA pKa_H = 18.2[92]) does suggest that salt formation will occur. However, it was hoped that in the non-polar toluene, proton transfer would be significantly slowed, and this process could be minimised. Unfortunately, this was shown not to be the case and as a result, salt formation prevented the reaction from occurring. Salt formation would impact both phosphine oxide reduction and ylide formation, and as such these steps were investigated independently.



Scheme 94: Phosphine oxide reduction in the presence of DIPEA

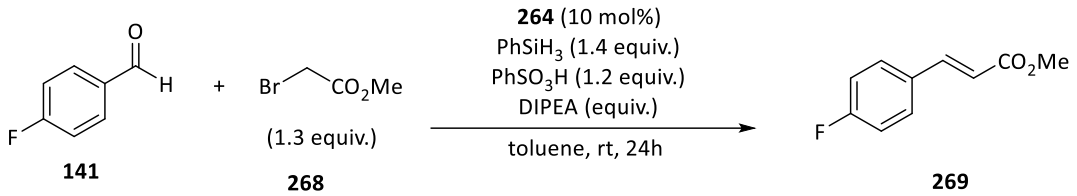
Increased stoichiometries were utilised for the phosphine oxide reduction to mimic a 10% catalyst loading (Scheme 94). Pleasingly, reduction of the phosphine oxide (**264**) to the free phosphine (**250**) was able to take place rapidly in the presence of DIPEA. However, the DIPEA-sulfonic acid salt was also identified as a major side product, even after a short reaction time, leading to concerns about catalyst turnover.



Scheme 95: *Attempted ylide formation in the presence of $PhSO_3H$*

The rapid interaction of DIPEA and $PhSO_3H$ was shown to prevent ylide formation (Scheme 95), as the only phosphorus containing product identified was the phosphonium salt (**270**). This result explained why no reaction was seen initially.

Due to this, optimisation procedures centered on preventing the base/sulfonic acid salt formation. Initial attempts utilised inorganic bases as an alternative, although this resulted in the precipitation of an insoluble solid which prevented reaction stirring, even upon the addition of a large amount of solvent. As DIPEA has been shown to be effective for ylide formation, further optimisation was carried out using this base, and alternations were introduced to manage the interaction with the sulfonic acid.



Entry	Preformation of silyl sulfonates	DIPEA (equiv.)	Concentration (M)	Yield (%)[a]
1	No	1.4	2	0
2	Yes	1.4	2	Trace
3	No	3	2	5
4	No	1.4	0.33	Trace
5	Yes	3	2	Trace
6	Yes	1.4	0.33	Trace
7	No	3	0.33	15

[a] Yield determined by 19F NMR using trifluorotoluene as the NMR standard

Table 13: *Optimisation of the catalytic Wittig reaction*

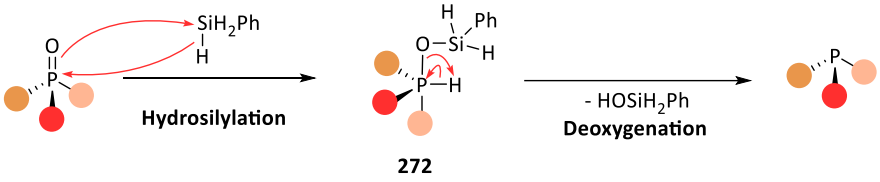
It was hoped that preforming the reactive silyl sulfonates, would sequester the acid and prevent interaction with the base (Table 13, entries 2, 5 and 6). However, in these examples, 4-fluorobenzylalcohol was shown to have formed in an unusually high ratio, with only a trace amount of olefin formed. It is likely that pre-forming the silyl sulfonates allowed the higher order, more reactive species to form and these were able to reduce the aldehyde. Further solutions included increased

dilution (Table 13, entries 4,6 and 7) to suppress DIPEA/$PhSO_3H$ interactions and using higher equivalents of DIPEA (Table 13, entries 3, 5 and 7) which should favour ylide formation.

Pleasingly, it was found that a combination of increased dilution and DIPEA was able to suppress salt formation long enough to achieve a 15% yield, demonstrating catalyst turnover within the system. The remainder of the mass was attributed to starting materials as salt formation had prevented further reactivity. Despite achieving proof of concept, the yield was disappointingly low and presents an area for improvement.

2.4 Mechanistic Studies

The mechanism for the phenylsilane mediated reduction of phosphine oxides is well known and has been studied both experimentally and computationally.[93,94]



Scheme 96: *Reduction mechanism for the reduction of phosphine oxides with $PhSiH_3$*

This process proceeds through a four-membered concerted transition-state structure to form the phosphorane intermediate (**272**). Elimination of the siloxide and subsequent deprotonation of the H-phosphonium releases the phosphine product. In some computational studies, the elimination and deprotonation is shown as a concerted process although the exact nature of this step is unknown.[93]

This general process is not being disputed *herein,* although in similar works employing Brønsted acids in addition to silanes, there is debate on the exact nature of the role of the acid. In both O'Brien's[85] and Slootweg's[74] methods, they propose initial activation of the phosphine oxide using the acid, and in Beller's[73] method, reaction of the acid and silane forms silyl esters which are the active reducing agents. Although it was assumed that this reduction occurs though formation of silyl sulfonates, (as demonstrated by the other processes reported *herein*) it is possible that activation of the phosphine oxide and subsequent reduction pathway, accounts for some of the product formed.

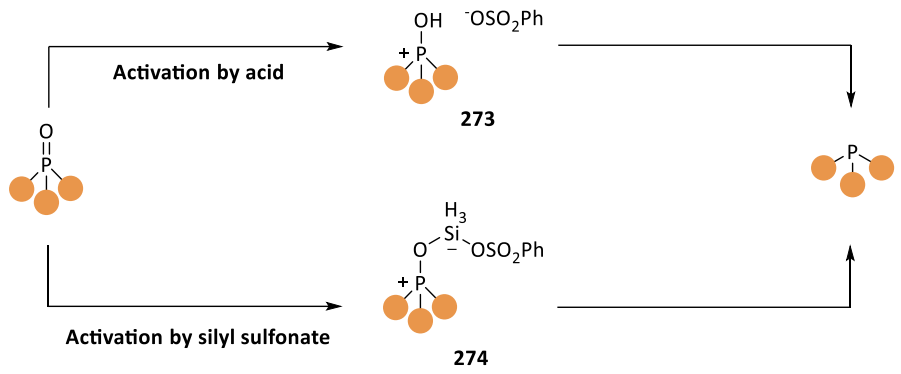
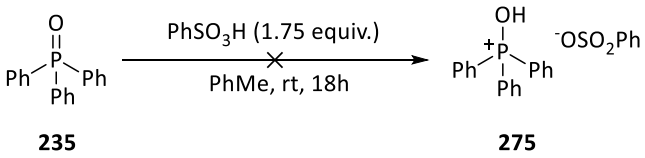


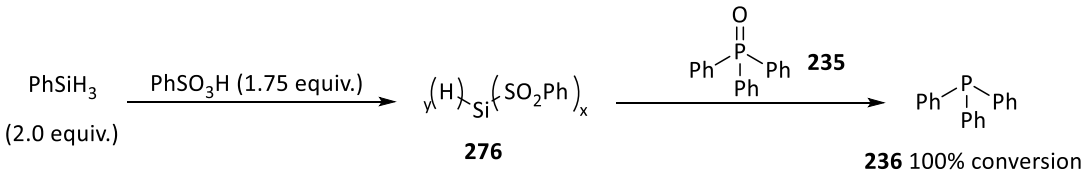
Figure 42: *Potential reaction pathways. Mono substituted silyl sulfonate shown for clarity*

However, quantitative starting material was recovered upon the reaction of a phosphine oxide and $PhSO_3H$, showing that the protonation pathway does not occur for this process. Although protonation of phosphine oxides is known using strong acids,[74] these results suggest that benzene sulfonic acid is not strong enough to affect this process.



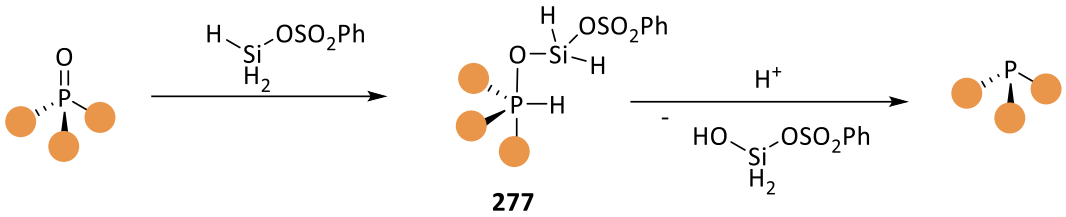
Scheme 97: *Attempted protonation of PPh_3 using $PhSO_3H$*

As a result, it is likely that the role of the sulfonic acid is to activate the silane through formation of silyl sulfonates, which has been demonstrated *herein*. To confirm this, $PhSiH_3$ and $PhSO_3H$ were allowed to react to form the reducing species, and introduction of the phosphine oxide resulted in complete reduction to the phosphine product.



Scheme 98: *Reduction of TPPO using a pre-formed silylsulfonate*

As a result, the mechanism proposed is identical to the reduction by $PhSiH_3$ alone (Scheme 96), however with silyl sulfonates as the active reducing species.



Scheme 99: *Proposed pathway for reduction of phosphine oxides. Mono substituted silyl sulfonate shown for clarity*

Despite proposing a concerted process for the formation of the phosphorane (**277**) and release of the phosphine product, it is likely that the silyl sulfonate can also activate the P=O bond initially, followed by subsequent hydride transfer in a stepwise process.

2.5 Conclusions

Overall, a mild and efficient reduction of phosphine oxides has been developed. The reaction temperature was able to be reduced from 110 ^{o}C to room temperature providing a clear benefit over other reductive processes. Further to this, the reaction can be conducted without the need for rigorous exclusion of air and water. A range of phosphine products were obtained using this method, demonstrating the range of functional groups that this process can tolerate. This method was also applied to the catalytic Wittig reaction, and despite issues associated with the presence of a strong acid, proof of concept was achieved, and an olefin product was identified. In addition, the mechanism was investigated. It was concluded that the reaction proceeds through activation of the silane with the sulfonic acid, and subsequent interaction with the phosphine oxide commences the reductive process.

2.6 Future Work

This project has a lot of room for further development. Not only can the scope be expanded to include more functional groups with varying sterics and electronics, which may require further optimisation, but the reduction of a chiral phosphine oxide would be an excellent inclusion into the reaction scope. It is expected that this would proceed with retention of stereochemistry, and the outcome could provide further confirmation of the mechanism. In addition, this process could be further optimised to include secondary phosphines and a subsequent investigation of this reaction scope. Finally, further optimisation of the catalytic Wittig reaction could be investigated to improve upon the preliminary

investigations carried out *herein*. Investigations into a range of organic bases, in addition to sulfonic acids with varying pKa's and solid supported acid could potentially slow salt formation enough for the reaction to occur. In addition, this process could be developed for use in other systems that are catalytic in phosphine. The mild conditions of this reduction make it perfect for these transformations.

3 Experimental

3.1 General Experimental

Reagents were purchased from commercial suppliers and used directly without further purification. Solvents were dried unless specified 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 and stored under inert atmosphere using 4Å molecular sieves. 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.

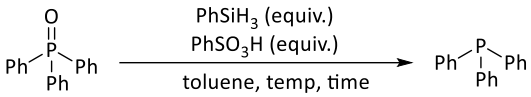
Analytical Thin Layer Chromatography (TLC) was performed on Merck aluminium-backed silica-gel plates 60 F_{254} plates and visualized by ultraviolet (UV) irradiation (254 nm) or by staining with a solution of potassium permanganate or ninhydrin. Column chromatography was carried out using Fluorochem 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). High Pressure Liquid Chromatography (HPLC) was carried out on a Thermo Ultimate reverse phase column using 1% formic acid solution and acetonitrile. Computational calculations were carried out by the Houk group using ωb97xd/6-31g(d,p)//SMD(solvent = toluene)//ωb97xd/6-311+g(d,p)//SMD(solvent = toluene) and the energies quoted are electronic energies in kcal/mol.

NMR spectra were recorded on either a Bruker AV 400, AV(III) 400HD or AV(III) 500HD in $CDCl_3$, DMSO or PhMe-d8. Chemical shifts (δ) were reported in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz), with residual protic solvent as the internal reference: ^{1}H NMR ($CDCl_3$ δ = 7.26 ppm, DMSO δ = 2.50 ppm, PhMe δ = 2.08 ppm), ^{13}C NMR (central peak of $CDCl_3$ δ = 77.16 ppm, DMSO δ = 39.52, PhMe δ = 20.43 ppm). NMR spectra are reported as follows: δ (multiplicity, coupling constant (if appropriate), number of protons). Abbreviations used include s – singlet, d – doublet, t – triplet, q – quartet, sept – septet, m – multiplet, pent - pentet, br – broad, app. – apparent. and coupling constants (J) are given in Hertz (Hz). All NMR are reported as proton decoupled spectra. NMR yields were determined by the following formula, where P and IS refer to the product and internal standard respectively, n refers to the moles and N is the number of nuclei represented in the chosen peak:

$$n_P = n_{IS}\left(\frac{I_P/N_P}{I_{IS}/N_{IS}}\right)$$

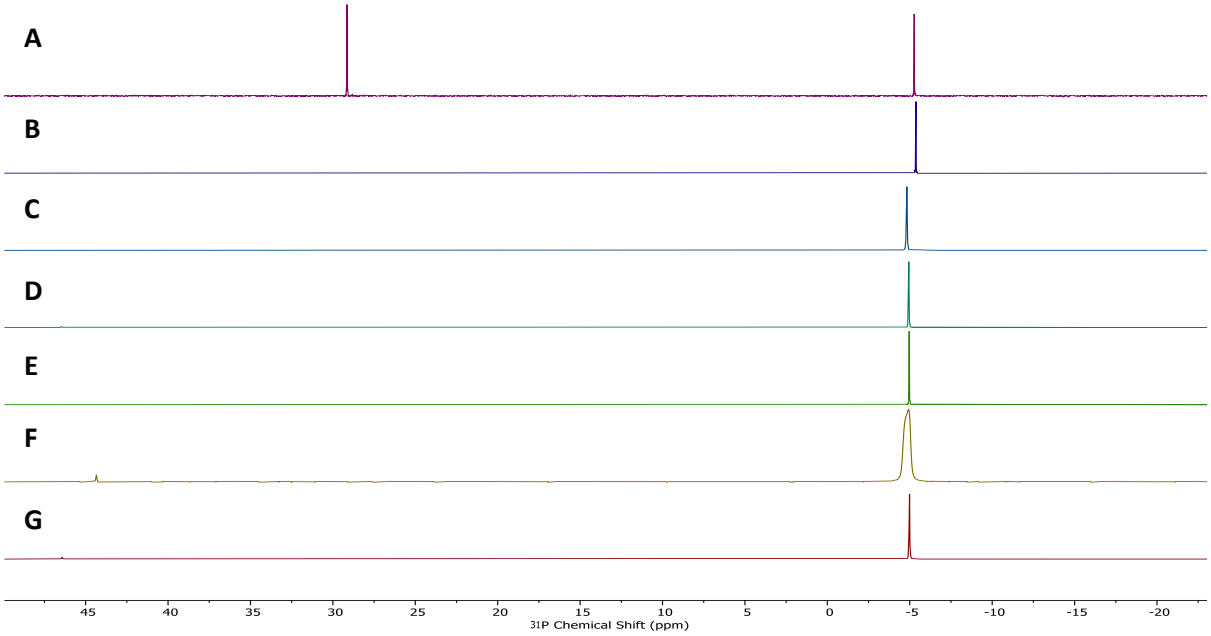
3.2 Optimisation

3.2.1 Reduction Optimisation



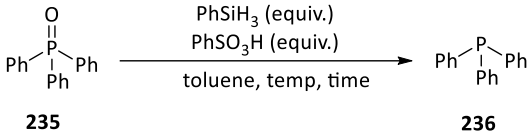
235 **236**

NMR trace	$PhSiH_3$ (equiv.)	$PhSO_3H$ (equiv.)	Reaction temperature (°C)	Reaction time (h)
A	2.00	0.00	110	18
B	2.00	1.75	110	18
C	2.00	1.75	110	6
D	2.00	1.75	60	6
E	2.00	1.75	40	6
F	1.00	0.875	60	24
G	2.00	1.57	rt	24

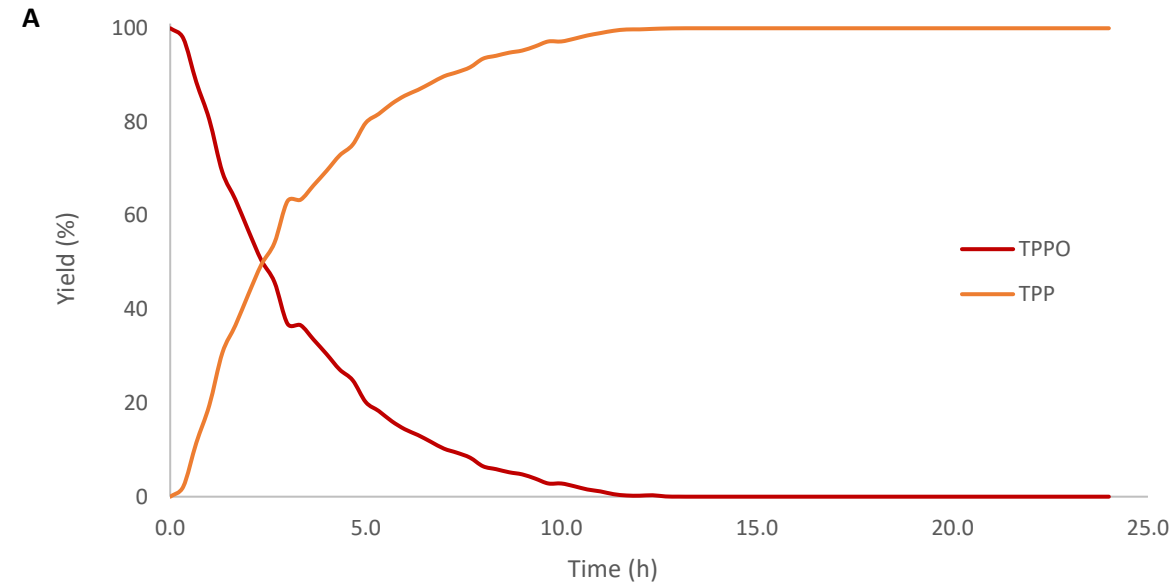


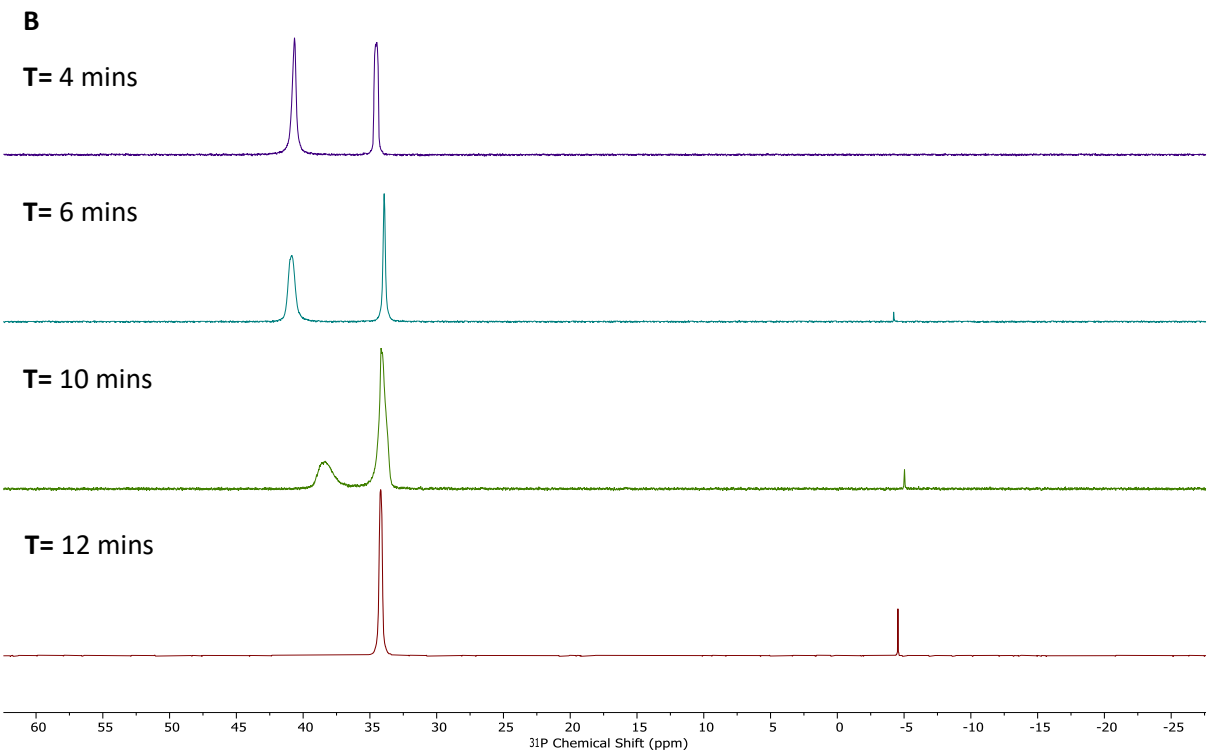
To a solution of triphenylphosphine oxide (278 mg, 1.00 mmol) in toluene-d^8 (1.2 mL), at the allotted temperature (see table), was added $PhSiH_3$ (see table) and $PhSO_3H$ (see table) and stirred for the allotted time (see table). The reaction mixture was cooled to room temperature and the conversion was determined by ^{31}P NMR spectrum.

3.2.2 Reaction Monitoring



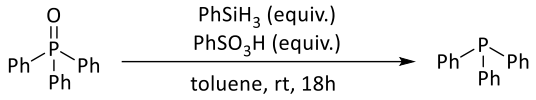
235 **236**





To a solution of triphenylphosphine oxide (139 mg, 0.500 mmol) in toluene-d^8 (0.600 mL), was added benzenesulfonic acid (138.4 mg, 0.875 mmol) and phenyl silane (123 µL, 1.00 mmol) dropwise. The reaction mixture was transferred to an NMR tube and monitored by ^{31}P NMR every 20 minutes. The ratio of the starting material and product were plotted as a function of time. Select ^{31}P NMR traces depicted showing initial association of the sulfonic acid with the phosphine oxide (δ = 40.5 ppm) and rapid consumption by 12 minutes.

3.2.3 Control Reactions



235 **236**

Entry	$PhSiH_3$ (equiv.)	$PhSO_3H$ (equiv.)	Yield (%)[a]
1	2.00	0.00	1
2	0.00	1.75	0

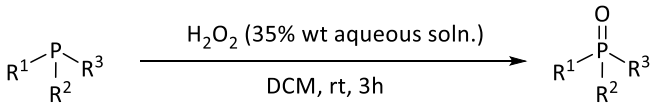
[a] Yield determined by ^{31}P NMR spectroscopy using triphenylphosphate as an internal standard

To a solution of triphenylphosphine oxide (139 mg, 0.500 mmol) in toluene-d^8 (0.600 mL), was added $PhSiH_3$ (see table) and $PhSO_3H$ (see table) and stirred for 18h. Triphenylphosphate (362 mg, 1.00 mmol) was added to the reaction mixture and the yield was determined by ^{31}P NMR.

3.3 General Procedures and Experimental Data

Staring Material Synthesis

General Procedures



3.3.1 Phosphine Oxidation

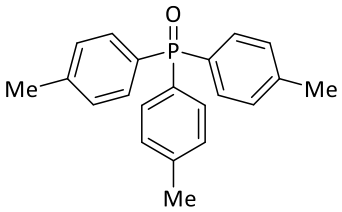
To a solution of phosphine (1.00 equiv), in DCM (20.0 mL) was added H_2O_2 (3.00 equiv of a 35% wt aqueous solution) dropwise and the reaction mixture was stirred vigorously at room temperature for 3 hours. The reaction mixture was quenched with $Na_2S_2O_5$ (8.5 mL of a saturated aqueous solution) and HCl (16.5 mL of a 1.00 M aqueous solution). The aqueous layer was washed with DCM (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product.

3.3.2 Phosphine Oxidation

To a solution of phosphine (1.00 equiv), in DCM (28.0 mL) was added H_2O_2 (70.0 equiv of a 35% wt aqueous solution) dropwise and the reaction mixture was stirred vigorously at room temperature for 3 hours. The reaction mixture was cooled to 0^oC and quenched with $Na_2S_2O_3$ (30 mL of a saturated aqueous solution). The aqueous layer was washed with DCM (3 x 20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the desired product.

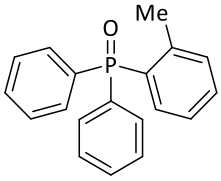
Experimental Data

Tri(4-methylphenyl)phosphine oxide - **278**



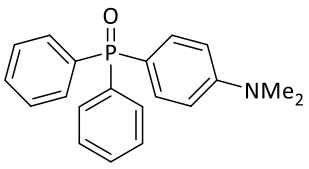
Followed general procedure 3.3.1 using tri(4-methylphenyl)phosphine (1.00g, 3.28 mmol) and H_2O_2 (861 µL of a 35% wt aqueous solution) to afford the title product as a pale yellow solid (1.05 g, >99%, 3.28 mmol); **M.P:** 138-139 °C (Lit: 135-137 °C[95]); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.55 (dd, J= 12.0, 8.0 Hz, 6H, Ar-**H**), 7.27 (dd, J= 8.0, 3.1 Hz, 6H, Ar-**H**), 2.41 (s, 9H, Ar-**CH_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 142.2 (d, J= 2.8 Hz, C), 132.1 (d, J= 10.2 Hz, CH), 130.3 (C), 129.2 (d, J= 12.4 Hz, CH), 21.6 (CH_3);**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 29.3; **HRMS** (ESI-TOF) m/z calc'd $C_{21}H_{22}OP$ $[M^+H]$ 321.1403 found 321.1396. The data matches that found in the literature.[95]

Diphenyl(o-tolyl)phosphine oxide – **279**



Followed general procedure 3.3.1 using diphenyl(o-tolyl)phosphine (1.00g, 3.62 mmol) and H_2O_2 (953 µL of a 35% wt aqueous solution) to afford the title product as a colourless solid (1.07 g, >99%, 3.62 mmol); **M.P:** 122-123 °C (Lit: 122-123 °C[96]); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.72-7.63 (m, 4H, Ar-**H**), 7.61-7.54 (m, 2H, Ar-**H**), 7.52-7.40 (m, 5H, Ar-**H**), 7.32-7.28 (m, 1H, Ar-**H**), 7.18-7.12 (m, 1H, Ar-**H**), 7.09-7.00 (m, 1H Ar-**H**), 2.48 (s, 3H, Ar-**CH_3**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 143.3 (d, J= 8.0 Hz, C), 133.5 (d, J= 12.9 Hz, CH), 132.8 (d, J= 103.4 Hz, C), 132.1 (d, J= 2.6 Hz, CH), 131.9 (d, J= 9.3 Hz, CH), 131.8 (d, J= 4.9 Hz, CH), 130.8 (d, J= 103.1 Hz, C), 128 (d, J= 12.1 Hz, CH), 125.2 (d, J= 12.8 Hz, CH), 21.7 (d, J= 4.7 Hz, CH_3);**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 31.6; **HRMS** (ESI-TOF) m/z calc'd $C_{19}H_{18}OP$ $[M^+H]$ 293.1090 found 293.1092. The data matches that found in the literature.[96]

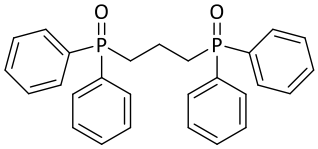
(4-(dimethylamino)phenyl)diphenylphosphine oxide – **280**



Followed general procedure 3.3.1 using (4-(dimethylamino)phenyl)diphenylphosphine (1.00g, 3.27 mmol) and H_2O_2 (859 µL of a 35% wt aqueous solution) to afford the title product as a colourless solid (1.07 g, >99%, 3.62 mmol); **M.P:** 189-190 °C (Lit: 190-192 °C[77]); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.74-7.66 (m, 4H, Ar-H), 7.56-7.41 (m, 8H, Ar-H), 6.72 (dd, J= 8.9, 2.4 Hz, 2H, Ar-H), 3.03 (s, 6H, Ar-N(CH_3)$_2$); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 152.5 (d, J= 2.4 Hz, C), 133.7 (d, J= 103.9 Hz, C, 133.5 (d, J= 11.3 Hz, CH), 132.1 (d, J= 9.8 Hz, CH), 131.5 (d, J= 2.71 Hz, CH), 128.3 (d, J= 11.7 Hz, CH), 116.9 (d, J= 115.2 Hz,

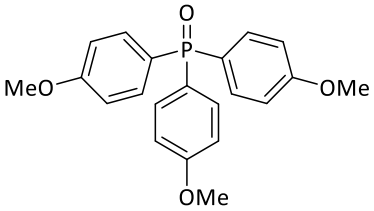
C), 111.3 (d, J= 12.9 Hz, CH), 39.9 (s, CH_3); **^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 29.4; **HRMS** (ESI-TOF) m/z calc'd $C_{20}H_{20}OPN$ [M^+H] 322.1355 found 322.1357. The data matches that found in the literature.[77]

1,3-bis(diphenylphosphinoyl)propane – **281**



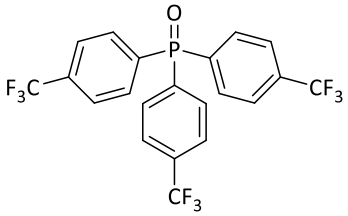
Followed general procedure 3.3.2 using 1,3-bis-(diphenylphosphino)propane (1.00 g, 2.42 mmol) and H_2O_2 (15.0 mL of a 35% wt aqueous solution) to afford the title product as a white solid (1.08 g, >99%, 2.42 mmol); **M.P:** 141-142 °C (Lit: 140-141 °C[97]); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.82-7.65 (m, 8H, Ar-H), 7.57-7.37 (m, 12H, Ar-H), 2.59-2.41 (m, 4H, P-C**H$_2$**-CH_2-C**H$_2$**-P), 2.11-1.93 (m, 2H, P-CH_2-C**H$_2$**-CH_2-P); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 132.7 (d, J= 98.6 Hz, C), 131.8 (d, J= 2.9 Hz, CH), 130.7 (d, J= 9.4 Hz, CH), 128.7 (d, J= 11.5 Hz, CH), 30.5 (d, J= 10.9 Hz, CH_2), 29.8 (d, J= 10.7 Hz, CH_2), 15.0 (t, J= 3.6 Hz, CH_2); **^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 32.2; **HRMS** (ESI-TOF) m/z calc'd $C_{27}H_{27}O_2P_2$ [M^+H] 445.1481 found 445.1477. The data matches that found in the literature.[97]

Tris(4-methoxyphenyl)phosphine oxide – **282**



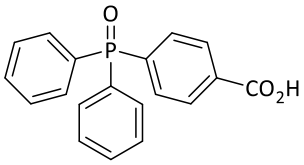
Followed general procedure 3.3.2 using tris(4-methoxyphenyl)phosphine (1.00g, 2.80 mmol) and H_2O_2 (19.0 mL of a 35% wt aqueous solution) to afford the title product as a colourless solid (1.03 g, >99%, 2.80 mmol); **M.P:** 148 °C (Lit: 147-149 °C[77]); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.62-7.54 (m, 6H, Ar-**H**), 6.99-6.94 (m, 6H, Ar-**H**), 3.86 (s, 9H, Ar-O**CH$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 162.3 (d, J= 2.8Hz, C), 133.9 (d, J= 11.3 Hz, CH), 124.5 (d, J= 111 Hz, C), 114.0 (d, J= 13.1 Hz, CH), 55.3 (CH_3);**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 28.8; **HRMS** (ESI-TOF) m/z calc'd $C_{21}H_{22}O_4P$ [M^+H] 369.1250 found 369.1252. The data matches that found in the literature.[77]

Tris(p-trifluoromethylphenyl)phosphine oxide - **283**



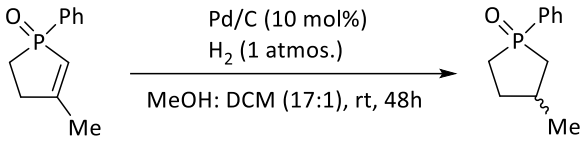
Followed general procedure 3.3.2 using tris(p-trifluoromethylphenyl)phosphine (1.00g, 2.14 mmol) and H_2O_2 (13.0 mL of a 35% wt aqueous solution) to afford the title product as a colourless solid (1.03 g, >99%, 2.14 mmol); **M.P:** 190 °C (Lit: 189-191 °C[77]); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.88-7.77 (m, 12H, Ar-**H**);**^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 135.4 (d, J= 103.2 Hz, C), 134.6 (dd, J= 33.0, 3.0 Hz, C), 132.5 (d, J= 10.3 Hz, CH), 125.8 (dq, J= 12.6, 3.8 Hz, CH), 123.3 (d, J= 273 Hz, C); **^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 25.6; **^{19}F NMR {^{1}H}:** (376 MHz, $CDCl_3$) δF -63.3 (CF_3); **HRMS** (ESI-TOF) m/z calc'd $C_{21}H_{13}O_4F_9P$ [M^+H] 483.0555 found 483.0546. The data matches that found in the literature.[77]

4-(diphenylphosphoryl)benzoic acid – **284**



Followed a modified general procedure 3.3.1 using 4-diphenylphosphanobenzoic acid (1.00 g, 3.26 mmol) and H_2O_2 (856 µL of a 35% wt aqueous solution), stirred at room temperature for 3 hours and filtered to afford the title product as a pale yellow solid (864 mg, 82%, 2.68 mmol); **M.P:** 269-270 °C (Lit: 270-271 °C[98]); **^{1}H NMR**: (400 MHz, DMSO-d_6) δH 13.2 (br s, 1H, Ar-CO_2**H**), 8.08 (dd, J= 8.0, 2.5 Hz, 2H, Ar-**H**), 7.76 (dd, J= 11.4, 8.0 Hz, 2H, Ar-**H**), 7.68-7.52 (m, 10H), Ar-**H**); **^{13}C NMR {^{1}H}:** (101 MHz, DMSO-d_6) δC 167.1 (C), 137.9 (d, J= 99 Hz, C), 134.4 (CH), 132.7 (d, J= 2.7 Hz, C),132.6 (d, J= 102 Hz, C), 132.3 (d, J= 10.1 Hz, CH), 132.0 (d, J= 9.8 Hz, CH), 129.8 (d, J= 11.9 Hz, CH), 129.4 (d, J= 11.8 Hz, CH); **^{31}P NMR {^{1}H}:** (162 MHz, DMSO-d_6) δP 25.2; **HRMS** (ESI-TOF) m/z calc'd $C_{19}H_{16}O_3P$ [M^+H] 323.0833 found 323.0832. The data matches that found in the literature.[98]

3.3.3 Synthesis of 3-methyl-1-phenylphospholane-1-oxide – 264

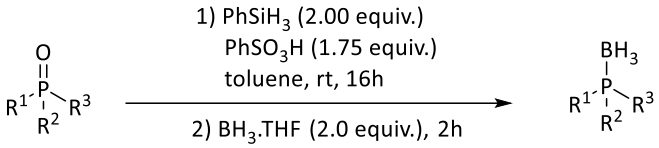


To a solution of Pd/C (550 mg, 0.0500 mmol of a 10% w/w,) in DCM (1.00 mL), was added 3-methyl-1-phenyl-2-phospholene-1-oxide (1.00 g, 5.20 mmol) in MeOH (17.0 mL) and the reaction mixture was purged with H_2 using a balloon and the reaction mixture was stirred under a H_2 environment at room temperature for 48h. The crude mixture was filtered through a plug of celite and concentrated *in vacuo* to afford the title compound as a pale yellow oil (1.01 g, >99%, 5.20 mmol); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH (mixture of diastereomers) 7.81-7.69 (m, 2H, Ar-**H**), 7.59-7.46 (m, 3H, Ar-**H**), 2.59-2.45 (m, 1H, CH_3-C**H**-CH_2), 2.40-2.04 (m, 4H, P-C**H$_2$**-C**H$_2$**-CH), 1.59-1.31 (m, 2H, P-C**H$_2$**-CH), 1.24 (d, J= 5.8 (d, J= 1.2 Hz, 0.4H, C**H$_3$***(minor)*), 1.21 (d, J= 5.9 Hz, 2.5H, C**H$_3$***(major)*); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 134.5 (d, J= 89.8 Hz, C), 131.6 (d, 3.9 Hz, CH), 129.9 (d, J= 9.8 Hz, CH), 128.7 (d, J= 11.6 Hz, CH), 37.7 (d, J= 65.8 Hz, CH_2), 34.2 (d, J= 6.4 Hz, CH_2), 33.8 (d, J= 8.6 Hz, CH), 31.1 (d, J= 65.7 Hz, CH_2), 21.1 (d, J= 14.0 Hz, CH_3); **^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 60.0; **HRMS** (ESI-TOF) m/z calc'd $C_{11}H_{16}OP$ [M^+H] 195.0933 found 195.0929. The data matches that found in the literature.[99]

Reduction of Phosphine Oxides

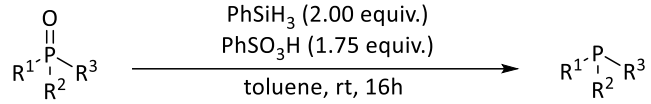
General Procedures

3.3.4 Phosphine-borane Product



To a solution of phosphine oxide (1.00 mmol) in toluene (1.20 mL), was added benzenesulfonic acid (277 mg, 1.75 mmol) and phenylsilane (247 µL, 2.00 mmol) dropwise. The reaction mixture was stirred at room temperature for 18 hours after which time BH_3.THF (2.00 mL, of a 1.00 M solution in THF) was added dropwise and the reaction mixture stirred at room temperature for a further 2 hours. The solvent was removed in vacuo and the crude mixture was purified by column chromatography (pentane: Et_2O)

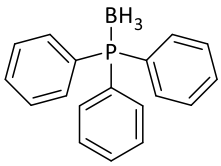
3.3.5 ^{31}P NMR Yields



To a solution of phosphine oxide (1.00 mmol) in toluene (1.20 mL), was added benzenesulfonic acid (277 mg, 1.75 mmol) and phenylsilane (247 µL, 2.00 mmol) dropwise and the reaction mixture was stirred at room temperature for 18 hours. Triphenylphosphate (362 mg, 1.00 mmol) was added to the reaction mixture and the yield was determined by ^{31}P NMR.

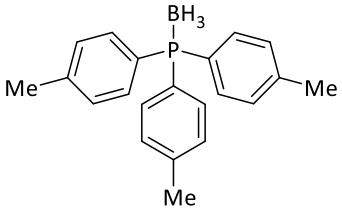
Experimental Data

Triphenylphosphine borane – **238**



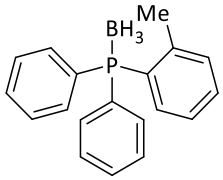
Followed general procedure 3.3.4 using triphenylphosphine oxide (278 mg, 1.00 mmol) and purified by column chromatography (19:1 pentane: Et_2O) to afford the title product as a colourless crystalline solid (231 mg, 84%); **M.P**: 182 °C (Lit.: 182-183 °C[100]); **R.f.:** 0.31 (19:1 pentane: Et_2O); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.64-7.57 (m, 6H, Ar-**H**), 7.56-7.50 (m, 3H, Ar-**H**), 7.49-7.42 (m, 6H, Ar-**H**), 1.73-0.84 (br m, 3H, B**H₃**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 133.2 (d, J= 9.6 Hz, CH), 131.3 (d, J= 2.5 Hz, CH), 129.2 (d, J= 57.9 Hz, C), 128.8 (d, J= 10.2 Hz);**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 21.4-19.7 (m); **^{11}B NMR {^{1}H}:** (128 MHz, $CDCl_3$) δB -37.9 (d, J= 56.4 Hz); **HRMS** (ESI-TOF) m/z calc'd $C_{18}H_{18}BNaP$ [M^+Na] 299.1131 found 299.1137. The data matches that found in the literature.[100]

Tri(4-methylphenyl)phosphine borane - **239**



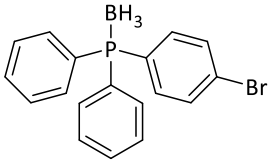
Followed general procedure 3.3.4 using tri(4-methylphenyl)phosphine oxide (320 mg, 1.00 mmol) and purified by column chromatography (5:1 pentane: Et_2O) to afford the title product as a colourless crystalline solid (250 mg, 78%); **M.P**: 216-217 °C (Lit.: 217-218 °C[100]); **R.f.:** 0.29 (5:1 pentane: Et_2O); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.52-7.43 (m, 6H, Ar-**H**), 7.27-7.22 (m, 6H, Ar-**H**), 2.41 (s, 9H, Ar-C**H$_3$**), 1.65-0.82 (br m, 3H, B**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 141.5 (d, J= 2.4 Hz, C), 133.1 (d, J= 10 Hz, CH), 129.5 (d, J= 10 Hz, CH), 126.2 (d, J= 60Hz, C), 21.5 (s, CH_3);**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 19.1-17.6 (m); **^{11}B NMR {^{1}H}:** (128 MHz, $CDCl_3$) δB -34.5- -40.4 (m); **HRMS** (ESI-TOF) m/z calc'd $C_{21}H_{24}BNaP$ [M^+Na] 341.1601 found 341.1604. The data matches that found in the literature.[100]

Diphenyl(o-tolyl)phosphine borane – **240**



Followed general procedure 3.3.4 using diphenyl(o-tolyl)phosphine oxide (292 mg, 1.00 mmol) and purified by column chromatography (19:1 pentane: Et_2O) to afford the title product as a colourless crystalline solid (145 mg, 50%); **M.P**: 135-136 °C (Lit.: 135-136 °C[101]); **R.f.:** 0.28 (19:1 pentane: Et_2O); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.70-7.60 (m, 4H, Ar-**H**), 7.58-7.39 (m, 7H, Ar-**H**), 7.28-7.25 (m, 1H, Ar-**H**), 7.17 (dd, J= 7.6, 7.6 Hz, 1H, Ar-**H**), 7.04 (dd, J= 12, 7.7 Hz, Ar-**H**), 2.29 (s, 3H, Ar-C**H$_3$**), 1.87-0.81 (br m, 3H, B**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 142.9 (d, J= 11 Hz, C), 134.2 (d, J= 8.6 Hz, CH), 133.3 (d, J= 9.0 Hz, CH), 131.9 (d, J= 9.0 Hz, CH), 131.4 (d, J= 3.0 Hz, CH), 131.2 (d, J= 2.0 Hz, CH), 129.2 (d, J= 46 Hz, C), 128.9 (d, J= 10 Hz, CH), 127.6 (d, J= 55.4 Hz, C), 125.9 (d, J= 10 Hz, CH), 22.5 (d, J= 5Hz, CH_3);**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 21.0-19.2 (m); **^{11}B NMR {^{1}H}:** (128 MHz, $CDCl_3$) δB -36.7 (d, J= 56 Hz); **HRMS** (ESI-TOF) m/z calc'd $C_{19}H_{20}BNaP$ [M^+Na] 313.1288 found 313.1289. The data matches that found in the literature.[101]

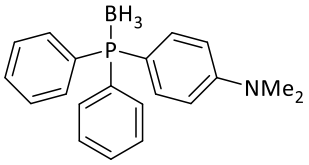
(4-bromophenyl)diphenylphosphine borane – **241**



Followed general procedure 3.3.4 using (4-bromophenyl)diphenylphosphine (357 mg, 1.00 mmol) and purified by column chromatography (pentane: Et_2O 98:2) to afford to title product as a colourless crystalline solid (246 mg, 70%); **M.P**: 134-135 °C; **R.f.:** 0.19 (98:2 pentane: Et_2O); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.65-7.44 (m, 14H, Ar-**H**), 1.86-0.56 (br m, B**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 134.7 (d, J= 10.3 Hz, CH), 133.2 (d, J= 9.8 Hz, CH), 132.1 (d, J= 10.4 Hz, CH), 131.6 (d, J= 2.5 Hz, CH), 129.0 (d, J=

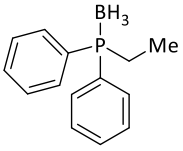
10.3 Hz, CH), 128.9 (d, J= 2.3 Hz, C), 128.3 (d, J= 1.9 Hz, C), 126.5 (d, J= 2.9 Hz, C) ;**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 20.7 (d, J= 58.8 Hz); **^{11}B NMR {^{1}H}:** (128 MHz, $CDCl_3$) δB -38.0 (d, J= 57.2 Hz); **HRMS** (ESI-TOF) m/z calc'd $C_{18}H_{17}BBrNaP$ [M^+Na] 377.0237 found 377.0237; **IR** vmax/cm^{-1} (ATR): 3059, 2921, 2382, 2343, 2263, 2107, 1912, 1824, 1652, 1576, 1557, 1480, 1435, 1384

(4-(dimethylamino)phenyl)diphenylphosphine borane – **242**



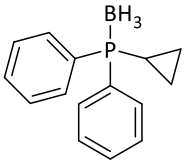
Followed general procedure 3.3.4 using (4-(dimethylamino)phenyl)diphenylphosphine oxide (323 mg, 1.00 mmol) and purified by column chromatography (19:1 pentane: Et_2O) to afford the title product as a colourless crystalline solid (265 mg, 83%); **M.P**: 180-181 °C; **R.f.:** 0.28 (19:1 pentane: Et_2O); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.64-7.55 (m, 4H, Ar-**H**), 7.52-7.39 (m, 4H, Ar-**H**), 6.81-6.68 (m, 2H, Ar-**H**), 3.04 (s, 6H, Ar-N(C**H$_3$**)$_2$); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 152.1 (d, J= 2.1 Hz, C), 134.6 (d, J= 10.9 Hz, CH), 133.0 (d, J= 10 Hz, CH), 130.8 (d, J= 2.4 Hz, CH), 130.7 (d, J= 59.2 Hz, C), 128.6 (d, J= 10.1 Hz, CH), 112.2 (d, J= 66.8 Hz, C), 111.8 (d, J= 11.0 Hz, CH), 40.0 (s, CH_3);**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 19.3-17.3 (m); **^{11}B NMR {^{1}H}:** (128 MHz, $CDCl_3$) δB -37.8 (d, J= 60 Hz); **HRMS** (ESI-TOF) m/z calc'd $C_{20}H_{23}BNNaP$ [M^+Na] 342.1553 found 342.1557; **IR** vmax/cm^{-1} (ATR): 3216, 3061, 2900, 2823, 2372, 2342, 2192, 2105, 2016, 1987, 1898, 1814, 1774, 1639, 1594, 1542, 1515, 1479, 1446, 1433, 1365, 1365, 1309, 1295

Ethyldiphenylphosphine borane – **244**



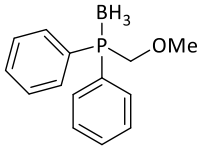
Followed general procedure 3.3.4 using ethyldiphenylphosphine oxide (230 mg, 1.00 mmol) and purified by column chromatography (19:1 pentane: Et_2O) to afford the title product as a clear colourless oil (164 mg, 72%); **R.f.:** 0.30 (19:1 pentane: Et_2O); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.74-7.65 (m, 4H, Ar-**H**), 7.54 (m, 6H, Ar-**H**), 2.27 (dq, 11.0, 7.5 Hz, 2H, P-C**H$_2$**-CH_3), 1.46-0.44 (m, including 1.17 (dt, J= 17.5, 7.5 Hz), 6H, BH_3, P-CH_2-C**H$_3$**); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 132.2 (d, J= 9.0 Hz, CH), 131.1 (d, J= 2.5 Hz, CH), 129.4 (d, J= 54.8 Hz, C), 128.8 (d, J= 9.8 Hz, CH), 18.9 (d, J= 38.4 Hz, CH_2), 7.25 (CH_3);**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 19.3-17.5 (m); **^{11}B NMR {1H}:** (128 MHz, $CDCl_3$) δB -40.1 (d, J= 58.7 Hz); **HRMS** (ESI-TOF) m/z calc'd $C_{14}H_{18}BNaP$ [M^+Na] 251.1131 found 251.1137; **IR** vmax/cm^{-1} (ATR): 3056, 2974, 2937, 2879, 2374, 2339, 1961, 1894, 1816, 1590, 1484, 1456, 1435, 1413, 1381, 1333

Cyclopropyl(diphenyl)phosphine oxide - **245**



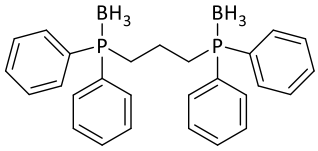
Followed general procedure 3.3.4 using cyclopropyl(diphenyl)phosphine (242 mg, 1.00 mmol) and purified by column chromatography (pentane: Et_2O 19:1) to afford the title product as a clear colourless oil (163 mg, 68%); **R.f.:** 0.30 (19:1 pentane: Et_2O); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.80-7.63 (m, 4H, Ar-**H**), 7.58-7.40 (m, 6H, Ar-**H**), 1.36 (app quint, J= 6.2 Hz, P-C**H**-$(CH_2)_2$), 1.13-0.98 (m, 4H, P-CH-$(C\mathbf{H_2})_2$), 0.98-0.18 (br m, 3H, B$\mathbf{H_3}$); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 132.2 (d, J= 8.9 Hz, CH), 131.0 (d, J= 2.5 Hz, CH), 130.8 (d, J= 58.2 Hz, C), 128.7 (d, J= 9.9 Hz, CH), 4.46 (d, J= 60.9 Hz, CH), 3.93 (CH_2) ;**^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 25.5-23.2 (m); **^{11}B NMR {1H}:** (128 MHz, $CDCl_3$) δB -41.8 (d, J= 59.9 Hz); **HRMS** (ESI-TOF) m/z calc'd $C_{15}H_{18}BNaP$ [M^+Na] 263.1131 found 263.1131; **IR** vmax/cm^{-1} (ATR): 3077, 3056, 3007, 2924, 2377, 2343, 2260, 2118, 1972, 1891, 1815, 1776, 1616, 1589, 1573, 1484, 1436, 1384, 1360

methoxymethyl(diphenyl)phosphine borane - **226**



Followed general procedure 3.3.4 using methoxymethyl(diphenyl)phosphine (246 mg, 1.00 mmol) and purified by column chromatography (9:1 pentane: Et_2O) to afford the title product as a colourless oil (216 mg, 88%); **R.f.:** 0.30 (9:1 pentane: Et_2O); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.83-7.75 (m, 4H, Ar-H), 7.57-7.44 (m, 6H, Ar-H), 4.29 (d, J= 1.57 Hz, 2H, P-C$\mathbf{H_2}$-OCH_3), 3.44 (s, 3H, P-CH_2-OC$\mathbf{H_3}$), 1.71-0.41 (br m, 3H, B$\mathbf{H_3}$); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 133.0 (d, J= 9.1 Hz, CH), 131.5 (d, J= 2.3 Hz, CH), 127.7 (d, J= 10.1 Hz, CH), 127.5 (d, J= 56.5 Hz, C), 70.2 (d, J= 44.4 Hz, CH_2), 61.8 (d, J= 8.3 Hz, CH_3); **^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 16.3-14.4 (m); **^{11}B NMR {1H}:** (128 MHz, $CDCl_3$) δB -40.1 (d, J= 54.3 Hz); **HRMS** (ESI-TOF) m/z calc'd $C_{14}H_{18}BNaOP$ [M^+Na] 267.1081 found 267.1085. The data matches that found in the literature.[75]

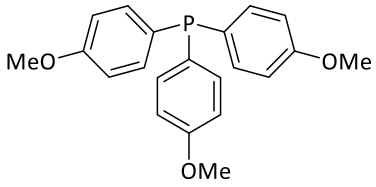
1,3-bis(diphenylphosphanyl)propane diborane - **246**



Followed general procedure 3.3.4 using 1,3-bis(diphenylphosphinoyl)propane (444 mg, 1.00 mmol) and purified by column chromatography (1:1 pentane: Et_2O) to afford the title product as a colourless crystalline solid (273 mg, 62%); **M.P**: 154-155 °C (Lit.: 155 °C[100]); **R.f.:** 0.27 (1:1 pentane: Et_2O); **^{1}H NMR**: (400 MHz, $CDCl_3$) δH 7.68 (m, 8H, Ar-**H**), 7.54-7.38 (m, 12H, Ar-**H**), 2.41-2.31 (m, 4H, P-C$\mathbf{H_2}$-CH_2-C$\mathbf{H_2}$-P), 1.93-1.78 (m, 2H, P-CH_2-C$\mathbf{H_2}$-CH_2-P), 1.43-0.500 (br m, 3H, B$\mathbf{H_3}$); **^{13}C NMR {^{1}H}:** (101 MHz, $CDCl_3$) δC 132.1 (d, J= 9.1 Hz, CH), 131.3 (d, J= 2.4 Hz, CH), 128.9 (d, J= 55.8 Hz, C), 128.9 (d, J= 9.9 Hz, CH), 26.7 (dd, J= 36.4, 11.2 Hz, CH_2), 17.4 (CH_2); **^{31}P NMR {^{1}H}:** (162 MHz, $CDCl_3$) δP 16.6-14.7 (m); **^{11}B NMR**

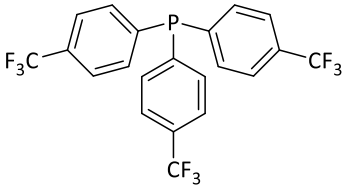
{1H}: (128 MHz, $CDCl_3$) δB -39.6 (d, J= 53.9 Hz); **HRMS** (ESI-TOF) m/z calc'd $C_{27}H_{32}B_2NaP_2$ [M^+Na] 463.2058 found 463.2066. The data matches that found in the literature.[100]

Tris(4-methoxyphenyl)phosphine – **247**



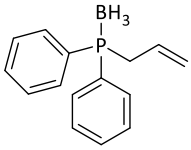
Followed general procedure 3.3.5 using tris(4-methoxyphenyl)phosphine oxide (368 mg, 1.00 mmol) and obtained the title product in a 50% yield (determined by ^{31}P NMR from the reaction mixture); **^{31}P NMR {^1H}:** (162 MHz, toluene-d_8) δP -10.28. The data matches that found in the literature.[102]

Tris(p-trifluoromethylphenyl)phosphine - **248**



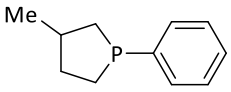
Followed general procedure 3.3.5 using tris(p-trifluoromethylphenyl)phosphine oxide and obtained the title product in a 95% yield (determined by ^{31}P NMR from the reaction mixture); **^{31}P NMR {^1H}:** (162 MHz, toluene-d_8) δP -6.1. The data matches that found in the literature.[102]

Allyldiphenylphosphane – **249**



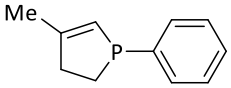
Followed a general procedure 3.3.5 using 4-(diphenylphosphoryl)benzoic acid (324 g, 1.00 mmol) and obtained the title product in a 75% yield (determined by ^{31}P NMR from the reaction mixture); **^{31}P NMR {^1H}:** (162 MHz, toluene-d_8) δP -16.8. The data matches that found in the literature. [73]

3-Methyl-1-phenylphospholan - **250**



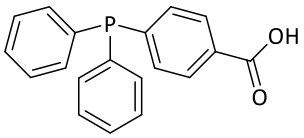
Followed a general procedure 3.3.5 using 3-Methyl-1-phenyl-2-phospholane 1-oxide (194 mg, 1.00 mmol) and obtained the title product in a 75% yield (determined by ^{31}P NMR from the reaction mixture); **^{31}P NMR {^1H}:** (162 MHz, toluene-d_8) δP -10.1. The data matches that found in the literature.[90]

3-methyl-1-phenyl-2-phospholene - **251**



Followed a general procedure 3.3.5 using 3-Methyl-1-phenyl-2-phospholene 1-oxide (192 mg, 1.00 mmol) and obtained the title product in a 72% yield (determined by ^{31}P NMR from the reaction mixture); **^{31}P NMR {^{1}H}:** (162 MHz, toluene-d_8) δP 3.17. The data matches that found in the literature.[75]

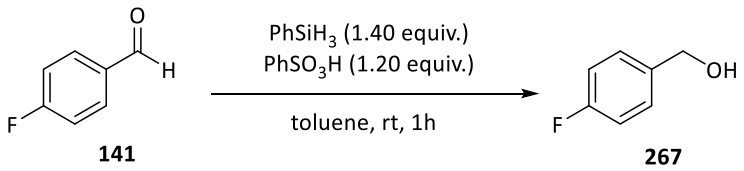
4-diphenylphosphanobenzoic acid – **252**



Followed a modified general procedure 3.3.5, to a solution of 4-(diphenylphosphoryl)benzoic acid (162 g, 0.500 mmol in toluene (0.600 mL), was added benzenesulfonic acid (69 mg, 0.44 mmol) and phenylsilane (62 µL, 0.500 mmol) and heated to 60 °C for 24. The reaction mixture was cooled to room temperature and the title product was obtained in a 84% yield (determined by ^{31}P NMR from the reaction mixture). **^{31}P NMR {^{1}H}:** (162 MHz, toluene-d_8) δP -4.7. The data matches that found in the literature.[103]

3.4 Catalytic Wittig Investigations

3.4.1 Reduction of 4-fluorobenzaldehyde

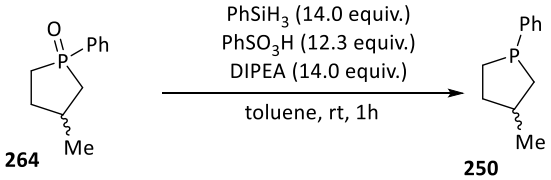


141 **267**

To a solution of $PhSO_3H$ (188 mg, 1.20 mmol) in toluene (0.500 mL), was added $PhSiH_3$ (172 µL, 1.40 mmol) and 4-fluorobenzaldehyde (107 µL, 1.00 mmol) and stirred at room temperature for 1h. Benzotrifluoride was added as an NMR standard and the yield was determined to be 10% by ^{19}F NMR. **^{19}F NMR {^{1}H}:** (376 MHz, toluene-d_8) δF -115.6. The data matches that found in the literature.[104]

3.4.2 Effect of DIPEA/$PhSO_3H$ salt on Wittig Reaction Steps

Reduction of the Phosphine Oxide

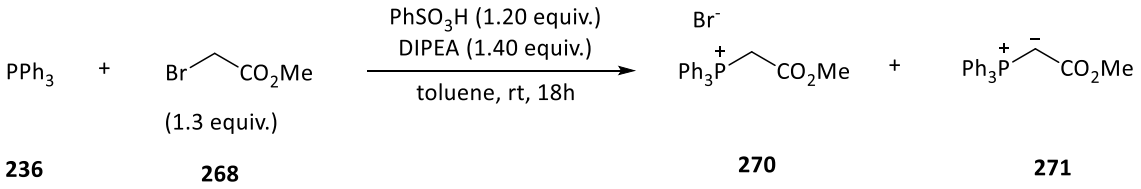


264 **250**

To a solution of $PhSO_3H$ (967 mg, 6.15 mmol) in toluene (2.50 mL), was added $PhSiH_3$ (861 µL, 7.00 mmol), **264** (97.1 mg, 0.500 mmol) and DIPEA (1.20 mL, 7.00 mmol) and stirred at room temperature

for 1h. The reaction mixture was transferred into an NMR tube and conversion was determined to be quantitative by ^{31}P NMR. Data matches that shown above for this compound.

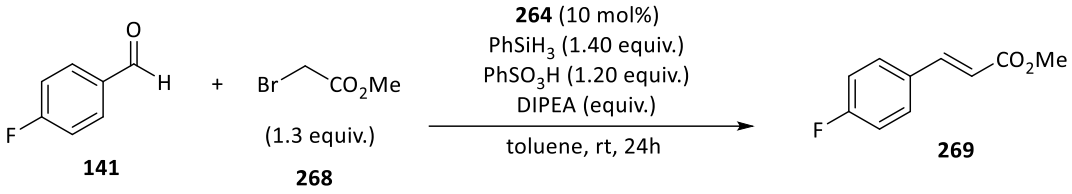
Attempted Ylide Formation



236 **268** **270** **271**

To a solution of TPP (262 mg, 1.00 mmol) and $PhSO_3H$ (189 mg, 1.20 mmol) in toluene (0.500 mL), was added methyl bromoacetate (123 µL, 1.30 mmol) and DIPEA (244 µL, 1.40 mmol) and stirred at room temperature for 18h. The reaction mixture was transferred into an NMR tube and the main product was shown to be the phosphonium salt **270** and conversion was determined by ^{31}P NMR. **^{31}P NMR {^{1}H}:** (162 MHz, toluene-d_8) δP 20.8. The data matches that found in the literature.[105]

3.4.4 Catalytic Wittig Optimisation



141 **268** **269**

Entry	Preformation of silyl sulfonates	DIPEA (equiv.)	Concentration (M)	Yield (%)a
1	No	1.40	2.00	0
2	Yes	1.40	2.00	Trace
3	No	3.00	2.00	5
4	No	1.40	0.33	Trace
5	Yes	3.00	2.00	Trace
6	Yes	1.40	0.33	Trace
7	No	3.00	0.33	15

[a] Yield determined by 19F NMR using trifluorotoluene as the NMR standard

Entries 1, 3, 4 and 7

To a solution of $PhSO_3H$ (189 mg, 1.20 mmol) in toluene (see table), was added $PhSiH_3$ (172 µL, 1.40 mmol), **264** (19.4 mg, 0.100 mmol), 4-fluorobenzaldehyde (107 µL, 1.00 mmol), methyl bromoacetate (123 µL, 1.30 mmol) and DIPEA (see table). The reaction mixture was stirred at room temperature for 24 hours, trifluorotoluene was added as an NMR standard and the yield was determined by ^{19}F NMR.

Entries 2, 5 and 6

To a refluxing solution of $PhSO_3H$ (189 mg, 1.20 mmol) in toluene (see table), was added $PhSiH_3$ (172 µL, 1.40 mmol) and stirred for 2 hours. The reaction was cooled to room temperature and **264** (19.4 mg, 0.100 mmol), 4-fluorobenzaldehyde (107 µL, 1.00 mmol), methyl bromoacetate (123 µL, 1.30 mmol) and DIPEA (see table) was added and stirred for a further 24 hours. The reaction mixture was stirred at room temperature for 24 hours, trifluorotoluene was added as an NMR standard and the yield was determined by ^{19}F NMR.

3.5 Mechanistic Studies

3.5.1 Reaction of Silylsulofnates with Triphenylphosphine Oxide

To a solution of $PhSO_3H$ (157 mg, 1.00 mmol) in toluene (0.600 mL), was added $PhSiH_3$ (123 µL, 1.00 mmol) and stirred at room temperature for 24h. Triphenylphosphine oxide (139 mg, 0.500 mmol) was added and stirred at room temperature for a further 18h. Triphenylphosphate (362 mg, 1.00 mmol) was added, and the yield was determined by ^{31}P NMR (quant.).

4 References

1 H. P. Jarvie, A. N. Sharpley, D. Flaten and P. J. A. Kleinman, *J Environ Qual*, 2019, **48**, 1127–1132.
2 A. Sharpley, H. Jarvie, D. Flaten and P. Kleinman, *J Environ Qual*, 2018, **47**, 774–777.
3 A. R. Jupp, S. Beijer, G. C. Narain, W. Schipper and J. C. Slootweg, *Chem Soc Rev*, 2021, 50, 87–101.
4 A. Granzow, *Acc Chem Res*, 1978, **11**, 177–183.
5 J. Green, *J Fire Sci*, 1992, **10**, 470–487.
6 M. P. Hébert, V. Fugère and A. Gonzalez, *Front Ecol Environ*, 2019, **17**, 48–56.
7 A. Witczak, A. Pohoryło, H. Abdel-Gawad and J. Cybulski, *Phosphorus Sulfur Silicon Relat Elem*, 2018, **193**, 711–720.
8 J. B. Rodriguez and C. Gallo-Rodriguez, *ChemMedChem*, 2019, **14**, 190–216.
9 S. Khong, T. Venkatesh and O. Kwon, *Asian J Org Chem*, 2021, 10, 2699–2708.
10 R. Martin and S. L. Buchwald, *Acc Chem Res*, 2008, **41**, 1461–1473.
11 Á. Sinai, D. C. Simkó, F. Szabó, A. Paczal, T. Gáti, A. Bényei, Z. Novák and A. Kotschy, *European J Org Chem*, 2020, **2020**, 1122–1128.
12 D. S. Surry and S. L. Buchwald, *Chem Sci*, 2011, **2**, 27–50.
13 B. T. Ingoglia, C. C. Wagen and S. L. Buchwald, *Tetrahedron*, 2019, **75**, 4199–4211.
14 J. P. Wolfe and S. L. Buchwald, *Journal of Organic Chemistry*, 2000, **65**, 1144–1157.
15 M. S. Driver and J. F. Hartwig, *J Am Chem Soc*, 1996, **118**, 7217–7218.
16 J. P. Wolfe, S. Wagaw and S. L. Buchwald, *J Am Chem Soc*, 1996, **118**, 7215–7216.
17 Y. C. Fan and O. Kwon, *Chemical Communications*, 2013, **49**, 11588–11619.
18 C. Xie, A. J. Smaligo, X. R. Song and O. Kwon, *ACS Cent Sci*, 2021, **7**, 536–558.
19 S. Marsden, *Nat Chem*, 2009, **1**, 685–687.
20 P. A. Byrne and D. G. Gilheany, *Chem Soc Rev*, 2013, **42**, 6670–6696.
21 Y. G. Gololobov and L. F. Kasukhin, *Tetrahedron*, 1992, **48**, 1353–1406.
22 E. I. Musina, A. V. Shamsieva, A. S. Balueva and A. A. Karasik, in *Organophosphorus Chemistry*, Royal Society of Chemistry, 2020, vol. 49, pp. 1–63.
23 E. Podyacheva, E. Kuchuk and D. Chusov, *Tetrahedron Lett*, 2019, 60, 575–582.
24 D. Herault, D. H. Nguyen, D. Nuel and G. Buono, *Chem Soc Rev*, 2015, **44**, 2508–2528.
25 Y. B. Zhou, C. Y. Li, M. Lin, Y. J. Ding and Z. P. Zhan, *Adv Synth Catal*, 2015, **357**, 2503–2508.
26 C. B. Caputo, D. Winkelhaus, R. Dobrovetsky, L. J. Hounjet and D. W. Stephan, *Dalton Transactions*, 2015, **44**, 12256–12264.
27 A. Tsurusaki, T. Sasamori, A. Wakamiya, S. Yamaguchi, K. Nagura, S. Irle and N. Tokitoh, *Angewandte Chemie - International Edition*, 2011, **50**, 10940–10943.
28 K. Esfandiarfard, S. Ott and A. Orthaber, *Phosphorus Sulfur Silicon Relat Elem*, 2015, **190**, 816–820.
29 J. Q. Zhang, S. Yang and L. B. Han, *Tetrahedron Lett*, , DOI:10.1016/j.tetlet.2019.151556.
30 R. E. Montgomery and L. D. Quin, *The Journal of Organic Chemistry* , 1965, **30**, 2393–2395.
31 L. Pang, Q. Sun, Z. Huang, G. Li, J. Liu, J. Guo, C. Yao, J. Yu and Q. Li, *Angewandte Chemie - International Edition*, , DOI:10.1002/anie.202211710.
32 X. Tan, S. Gao, W. Zeng, S. Xin, Q. Yin and X. Zhang, *J Am Chem Soc*, 2018, **140**, 2024–2027.
33 S. E. Tunney and J. K. Stille, *J Org Chem*, 1987, **52**, 748–753.
34 T. Oshiki and T. Imamoto, *J Am Chem Soc*, 1992, **114**, 3975–3977.
35 O. Herd, A. Hebler, M. Hingst, M. Tepper and O. Stelzer, *J Organomet Chem*, 1996, **522**, 69–76.
36 A. Stadler and C. O. Kappe, *Org Lett*, 2002, **4**, 3541–3543.
37 R. Berrino, S. Cacchi, G. Fabrizi, A. Goggiamani and P. Stabile, *Org Biomol Chem*, 2010, **8**, 4518–4520.
38 H. Vallette, S. Pican, C. Boudou, J. Levillain, J. C. Plaquevent and A. C. Gaumont, *Tetrahedron Lett*, 2006, **47**, 5191–5193.

39 H.-B. Kraatz and A. Pletsch, *Tetrahedron Asymmetry*, 2000, **11**, 1617–1621.
40 C. Korff and G. Helmchen, *Chemical Communications*, 2004, **4**, 530–531.
41 J. R. Moncarz, N. F. Laritcheva and D. S. Glueck, *J Am Chem Soc*, 2002, **124**, 13356–13357.
42 J. Wen, B. Dong, J. Zhu, Y. Zhao and Z. Shi, *Angewandte Chemie - International Edition*, 2020, **59**, 10909–10912.
43 B. S. Aweke, C. H. Yu, M. Zhi, W. C. Chen, G. P. A. Yap, L. Zhao and T. G. Ong, *Angewandte Chemie - International Edition*, , DOI:10.1002/anie.202201884.
44 H. Qi, Z. Huang, M. Wang, P. Yang, C. X. Du, S. W. Chen and Y. Li, *J Catal*, 2018, **363**, 63–68.
45 A. Włodarczyk, *Tetrahedron*, , DOI:10.1016/j.tet.2021.132550.
46 J. S. Zhang, T. Chen, J. Yang and L. B. Han, *Chemical Communications*, 2015, **51**, 7540–7542.
47 J. Yang, T. Chen and L. B. Han, *J Am Chem Soc*, 2015, **137**, 1782–1785.
48 J. Yang, J. Xiao, T. Chen and L. B. Han, *J Organomet Chem*, 2016, 820, 120–124.
49 D. Gelman, L. Jiang and S. L. Buchwald, *Org Lett*, 2003, **5**, 2315–2318.
50 P. Butti, R. Rochat, A. D. Sadow and A. Togni, *Angewandte Chemie - International Edition*, 2008, **47**, 4878–4881.
51 C. Scriban and D. S. Glueck, *J Am Chem Soc*, 2006, **128**, 2788–2789.
52 V. S. Chan, I. C. Stewart, R. G. Bergman and F. Dean Toste, *J Am Chem Soc*, 2006, **128**, 2786–2787.
53 D. G. Gilheany, *Chem Rev*, 1994, **94**, 1339–1374.
54 D. B. Chesnut and A. Savin, *J Am Chem Soc*, 1999, **121**, 2335–2336.
55 T. Imamoto, T. Takeyama and T. Kusumoto, *Chem Lett*, 1985, **14**, 1491–1492.
56 W. K. Wong, H. Liang, M. Y. Yung, J. P. Guo, K. F. Yung, W. T. Wong and P. G. Edwards, *Inorg Chem Commun*, 2004, **7**, 737–740.
57 S. Griffin, L. Heath and P. Wyatt, *Tetrahedron Lett*, 1998, **39**, 4405–4406.
58 S. Yang, X. Han, M. Luo, J. Gao, W. Chu and Y. Ding, *Russ J Gen Chem*, 2015, **85**, 1156–1160.
59 C. A. Busacca, R. Raju, N. Grinberg, N. Haddad, P. James-Jones, H. Lee, J. C. Lorenz, A. Saha and C. H. Senanayake, *Journal of Organic Chemistry*, 2008, **73**, 1524–1531.
60 G. Keglevich, M. Fekete, T. Chuluunbaatar, A. Dobó, V. Harmat and L. Toke, *J Chem Soc Perkin 1*, 2000, 4451–4455.
61 S. Sowa and K. M. Pietrusiewicz, *Tetrahedron*, , DOI:10.1016/j.tet.2021.132057.
62 A. J. Kendall, C. A. Salazar, P. F. Martino and D. R. Tyler, *Organometallics*, 2014, **33**, 6171–6178.
63 L. Zhang, Z. Han, X. Zhao, Z. Wang and K. Ding, *Angewandte Chemie International edition*, 2015, **127**, 6186–6189.
64 A. K. Ghosh, D. R. Nicponski and J. Kass, *Tetrahedron Lett*, 2012, **53**, 3699–3702.
65 H. Fritzsche, U. Hasserodt and F. Korte, *Chem Ber*, 1964, **97**, 1988–1993.
66 H. Fritzsche, U. Hasserodt and F. Korte, *Chem Ber*, 1965, **98**, 171–174.
67 K. Naumann, G. Zon and K. Mislow, *J Am Chem Soc*, 1969, **91**, 7012–7023.
68 S. Cremer and R. J. Chorvat, *J Org Chem*, 1962, **32**, 4066–4070.
69 S. Duprat De Paule, S. Jeulin, V. Ratovelomanana-Vidal, J.-P. Genêt, N. Champion and P. Dellis, *Tetrahedron Lett*, 2003, **44**, 823–826.
70 T. Coumhe, N. J. Lawpence and F. Muhammad, *Tetrahedron Lett*, 1994, **35**, 625–628.
71 Y. Li, S. Das, S. Zhou, K. Junge and M. Beller, *J Am Chem Soc*, 2012, **134**, 9727–9732.
72 L. Pehlivan, E. Métay, D. Delbrayelle, G. Mignani and M. Lemaire, *Tetrahedron*, 2012, **68**, 3151–3155.
73 Y. Li, L. Lu, S. Das, S. Pisiewicz, K. Junge and M. Beller, *J Am Chem Soc*, 2012, **134**, 18325–18329.
74 T. Krachko, V. Lyaskovskyy, M. Lutz, K. Lammertsma and C. J. Slootweg, *Z Anorg Allg Chem*, 2017, **643**, 916–921.
75 M. Schirmer, S. Jopp, J. Holz, A. Spannenberg and T. Werner, *Adv Synth Catal*, 2016, **358**, 26–29.

76 M. Mehta, I. Garcia De La Arada, M. Perez, D. Porwal, M. Oestreich and D. W. Stephan, *Organometallics*, 2016, **35**, 1030–1035.
77 C. Laye, J. Lusseau, F. Robert and Y. Landais, *Adv Synth Catal*, 2021, **363**, 3035–3043.
78 S. Janardan, A. S. V. Anand, P. Suman, M. Y. Lone, P. C. Jha, C. V. S. B. Rao and A. Sivaramakrishna, *Silicon*, 2021, **13**, 2881–2893.
79 J. Holz, H. Jiao, M. Gandelman and A. Börner, *European J Org Chem*, 2018, **2018**, 2984–2994.
80 R. H. Beddoe, H. F. Sneddon and R. M. Denton, *Org Biomol Chem*, 2018, 16, 7774–7781.
81 C. J. O'Brien, J. L. Tellez, Z. S. Nixon, L. J. Kang, A. L. Carter, S. R. Kunkel, K. C. Przeworski and G. A. Chass, *Angewandte Chemie - International Edition*, 2009, **48**, 6836–6839.
82 T. Werner, M. Hoffmann and S. Deshmukh, *European J Org Chem*, 2015, **2015**, 3286–3295.
83 E. E. Coyle, B. J. Doonan, A. J. Holohan, K. A. Walsh, F. Lavigne, E. H. Krenske and C. J. O'Brien, *Angewandte Chemie - International Edition*, 2014, **53**, 12907–12911.
84 K. G. Andrews and R. M. Denton, *Chemical Communications*, 2017, **53**, 7982–7985.
85 C. J. O'Brien, F. Lavigne, E. E. Coyle, A. J. Holohan and B. J. Doonan, *Chemistry - A European Journal*, 2013, **19**, 5854–5858.
86 F. Ficarra, 2022.
87 T. Werner, M. Hoffmann and S. Deshmukh, *European J Org Chem*, 2014, **2014**, 6630–6633.
88 H. C. Brown and K. J. Murray, *Tetrahedron*, 1986, **42**, 5497–5504.
89 S. P. Marsden, A. E. McGonagle and B. McKeever-Abbas, *Org Lett*, 2008, **10**, 2589–2591.
90 C. J. O'Brien, Z. S. Nixon, A. J. Holohan, S. R. Kunkel, J. L. Tellez, B. J. Doonan, E. E. Coyle, F. Lavigne, L. J. Kang and K. C. Przeworski, *Chemistry - A European Journal*, 2013, **19**, 15281–15289.
91 A. Kütt, S. Tshepelevitsh, J. Saame, M. Lõkov, I. Kaljurand, S. Selberg and I. Leito, *European J Org Chem*, 2021, **2021**, 1407–1419.
92 Z. B. G. Fickenscher, P. Lönnecke, A. K. Müller, O. Hollóczki, B. Kirchner and E. Hey-Hawkins, *Molecules*, 2023, **28**, 2574.
93 A. M. Kirk, C. J. O'Brien and E. H. Krenske, *Chemical Communications*, 2020, **56**, 1227–1230.
94 K. Marsi, *Journal of Organic Chemistry*, 1974, **39**, 265–267.
95 H. McErlain, L. M. Riley and A. Sutherland, *Journal of Organic Chemistry*, 2021, **86**, 17036–17049.
96 P. Woźnicki and M. Stankevič, *European J Org Chem*, 2021, **2021**, 3484–3491.
97 C. J. A. Warner, S. S. Berry and S. Jones, *Tetrahedron*, 2019, **75**, 130733.
98 W. S. Tay, Y. Li, X. Y. Yang, S. A. Pullarkat and P. H. Leung, *J Organomet Chem*, , DOI:10.1016/j.jorganchem.2020.121216.
99 G. Keglevich, M. Fekete, T. Chuluunbaatar, A. Dobó, Z. Böcskei and L. Töke, *Synth Commun*, 2000, **30**, 4221–4231.
100 M. Van Overschelde, E. Vervecken, S. G. Modha, S. Cogen, E. Van der Eycken and J. Van der Eycken, *Tetrahedron*, 2009, **65**, 6410–6415.
101 D. B. G. Williams, P. D. R. Kotze, A. C. Ferreira and C. W. Holzapfel, *Journal of the Iranian Chemical society*, 2011, **8**, 240–246.
102 A. J. Stepen, M. Bursch, S. Grimme, D. Stephan and J. Paradies, *Angewandte Chemie*, 2018, **57**, 15253–15256.
103 J. A. Buonomo, C. G. Eiden and C. C. Aldrich, *Chemistry - A European Journal*, 2017, **23**, 14434–14438.
104 P. Tang, W. Wang and T. Ritter, *J Am Chem Soc*, 2011, **133**, 11482–11484.
105 R. A. Aitken, V. Bjørnstad, T. Massil and J. Skramstad, *Phosphorus, Sulfur and Silicon and Related Elements*, 1999, **144**, 577–580.

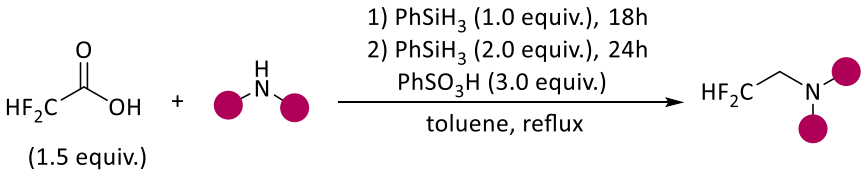
Conclusions and Future Work

Final conclusions to this work and a brief discussion of ongoing projects the Denton group that utilises this chemistry.

Amelia Stoneley

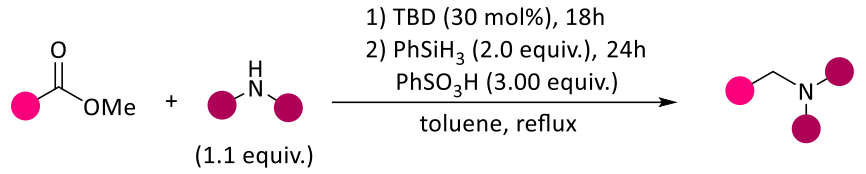
Throughout this thesis, we have demonstrated the mild and selective nature of the phenylsilane and benzenesulfonic acid reducing system; first in the synthesis of amines in a reductive amination process, but also for the reduction of phosphine oxides. In our mechanistic studies, silylsulfonates were shown to be the active reducing species, formed through the initial elimination of benzene, although higher order species were shown to have increased reducing power.

Since the discovery of this powerful reducing system, the Denton group has further investigated the reach of this method and has successfully applied it to other processes. The trifluoroethylation of amines has been demonstrated using trifluoracetic acid in a modified method to the reductive amination described *herein*. This method has been demonstrated in the synthesis of trifluoroethylated amines, bearing a range of functional groups.



Scheme 100: *General scheme for the metal-free trifluoroethylation of amines*

In addition, this chemistry has been applied in the metal-free reductive amination from the methyl ester. This process uses a triazabicyclodecene (TBD) catalysed amidation to construct the amide and is subsequently reduced using the silane/ sulfonic acid system in a one-pot process.



Scheme 101: *General scheme for the metal-free reductive amination from methyl esters*

The future work for the chemistry presented *herein* is described at the end of each chapter, and it is clear that further investigations could be carried out to develop both the understanding and scope of the systems. It has been a pleasure working on this project and I am excited to see its future development.