A Reductive Amination Using Methyl Esters as Nominal Electrophiles

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Abstract

This report investigates a one-pot catalytic domino reaction for the synthesis of amines from methyl esters. The first step is a 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) catalysed amidation immediately followed by a zinc acetate catalysed reduction using phenyl silane as the terminal reductant. These conditions were then used to successfully synthesis 11 tertiary amines with yields ranging from 40 % to 92 %, and nine secondary amines with yields ranging from 23 % to 81 %. Both primary and secondary amines were investigated along with a range of different methyl esters which allowed us to investigate the versatility of the substrate scope. The reaction is then exemplified through the synthesis of active pharmaceuticals Piribedil and Cinacalcet.

Acknowledgements

I’d like to start by thanking Ross Denton for the opportunity to develop and explore an interesting project along with all the support he has offered throughout. I’d also like to thank James Wilson and Nick Atkinson for their expertise and advice throughout my studies. I’d also like to greatly thank Amelia Stoneley for all the help and support throughout the year especially when writing my thesis. Finally, I’d like to thank the rest of the Denton group for being so welcoming and offering help and guidance throughout a challenging year.

Abbreviations

$CDCl_3$ – Deuterated chloroform

CH_2Cl_2 – Dichloromethane

$Cu(OAc)_2$ – Copper(II) acetate

DIBAL-H – Diisobutylaluminium hydride

DMF – Dimethylformamide

dppe – 1,2-Bis(diphenylphosphino)ethane

Et_3N – Triethylamine

EtOAc – ethyl acetate

HCl – Hydrochloric acid

HRMS – High resolution mass spectrometry

IR – Infrared

K_2CO_3 – potassium carbonate

$KMnO_4$ - Potassium permanganate

LiHMDS – Lithium bis(trimethylsilyl)amide

$MgSO_4$ – magnesium sulfate

MTBE – methyl tert-butyl ether

$NaBH_3CN$ – sodium cyanoborohydride

nBu_2O – Dibutyl ether

NaOtBu – Sodium tert-butoxide

$PhSiH_3$ – Phenyl silane

Ppm – parts per million

ROP – ring opening polymerisation

SNAr – Nucleophilic aromatic substitution

STAB - Sodium Triacetoxyborohydride

TBD – 1,5,7-Triazabicyclo[4.4.0]dec-5-ene

TsOH – *p*-toluenesulfonic acid

UV – Ultraviolet

$Zn(OAc)_2$ – Zinc acetate

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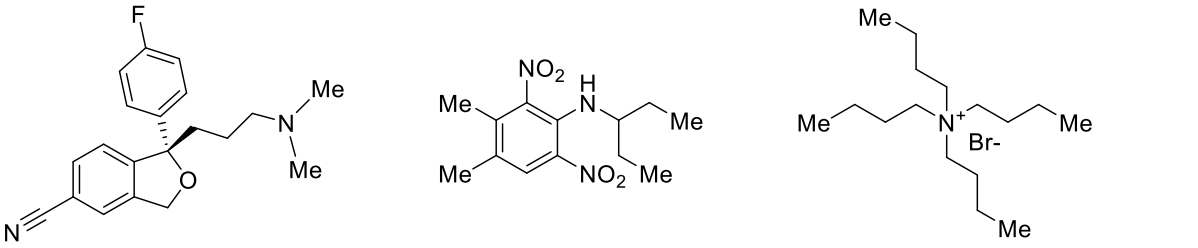
Introduction

Amines

Amines are key compounds in both Chemistry and Biology, and the key reactivity and functionality of amines originates from the lone pair of electrons which allows for good nucleophilic properties. This important characteristic allows primary and secondary amines to hydrogen bond; the nitrogen atom acting as a hydrogen bond acceptor and the N-H as a donor. This is extremely desirable in many areas of chemistry such as drug discovery and multistep synthesis. These important nitrogen containing compounds are found throughout chemistry and everyday life, from antidepressants such as Citalopram in pharmaceuticals, to Pendimethalin in Agrochemistry or form ammonium salts to be used in laboratory synthesis such as tetrabutyammonium bromide (TBAB) a phase transfer catalyst (Figure 1).



citalopram - Antidepressant pendimethalin – Herbicide TBAB - Phase transfer catalyst

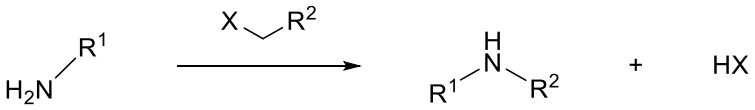
Figure 1 – important C-N bond containing compounds

Synthesis of amines

A review in 2011 highlighted that a large percentage of all reactions used in the pharmaceutical industry are C-N bond forming or nitrogen-based manipulations, [1] therefore the synthesis of amines is vitally important for many areas of chemistry. As such, there is a large variety of amine synthesis method available; here I will discuss the most widespread methods used for synthesis. [2-4]

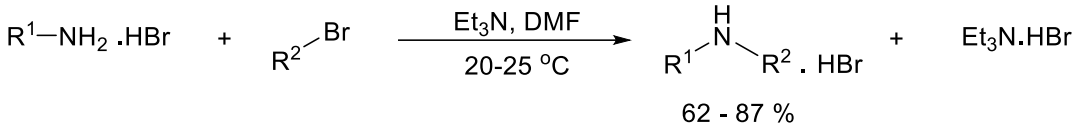
Amine alkylation

Amine alkylation is one of the most researched methods and is widely used in a laboratory setting. The reaction occurs between an alkyl halide with an amine or ammonia (see Scheme 1) to form a higher order amine product.



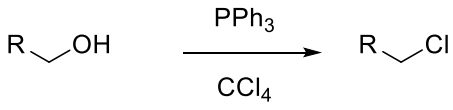
Scheme 1 – general amine alkylation reaction between amine and aryl halide

Although useful for the synthesis of tertiary amines, one of the main issues with this reaction is the over alkylation of the product, caused by sequential reactions which result in a mixture of primary, secondary, tertiary and even quaternary amines.[5] However, in 2014 a method for the selective alkylation of primary amines was published.[6] This method took advantage of a competitive protonation/deprotonation strategy and used a primary amine salt in the presence of an alkyl halide and a base to achieve the monoalkylated product (scheme 2). The difference in basicity of the starting material and alkylated product allows for this method to be successful. High yields and excellent selectivity demonstrate the usefulness of this reaction.



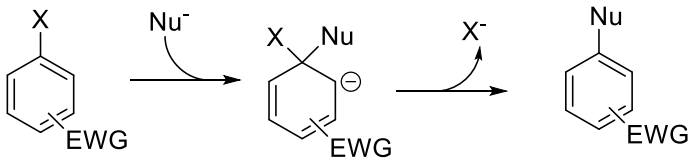
Scheme 2 – monoalkylation of primary amines using amine hydrobromides and alkyl bromides by Bhattacharyya and co-workers.[6]

Despite this method presenting a step forward for selective amine alkylation, the issues with this type of reaction still stand. The use of this method relies on the use of toxic halide reagents which although commercially available, have a limited range of substrates. As such these need to be synthesised from the alcohol in stoichiometric reactions such as the Appell reaction which also uses toxic reagents (Scheme 3). [7]



Scheme 3 – General scheme for the Appell reaction. [7]

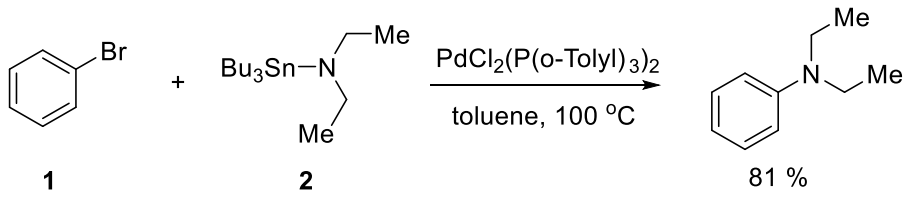
For the synthesis of aryl-N bonds, methods such as SnAr have been developed (Scheme 4). Although this method has more synthetic application, certain conditions must be met for this reaction to be successful. These include the need for electron withdrawing groups (EWG) to stabilise the resulting Meisenheimer intermediate and harsh conditions to cause the destruction of the stable aromatic ring.



Scheme 4 – General SnAr reaction between aryl halide and a nucleophile.[8]

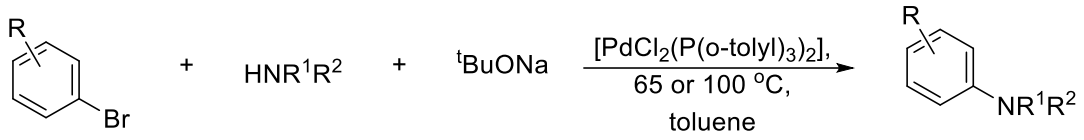
Buchwald-Hartwig amination

A more popular method for the synthesis of aryl amine bonds is through the use of the palladium catalysed Buchwald-Hartwig coupling. This method uses an aryl halides (**1**) and amine in the presence of a base and a palladium catalyst to achieve an arylated product. The development of this method stems from the work published in 1983 by Migita and co-workers who used an amino tin reagent (**2**) (Scheme 5).[9-10]



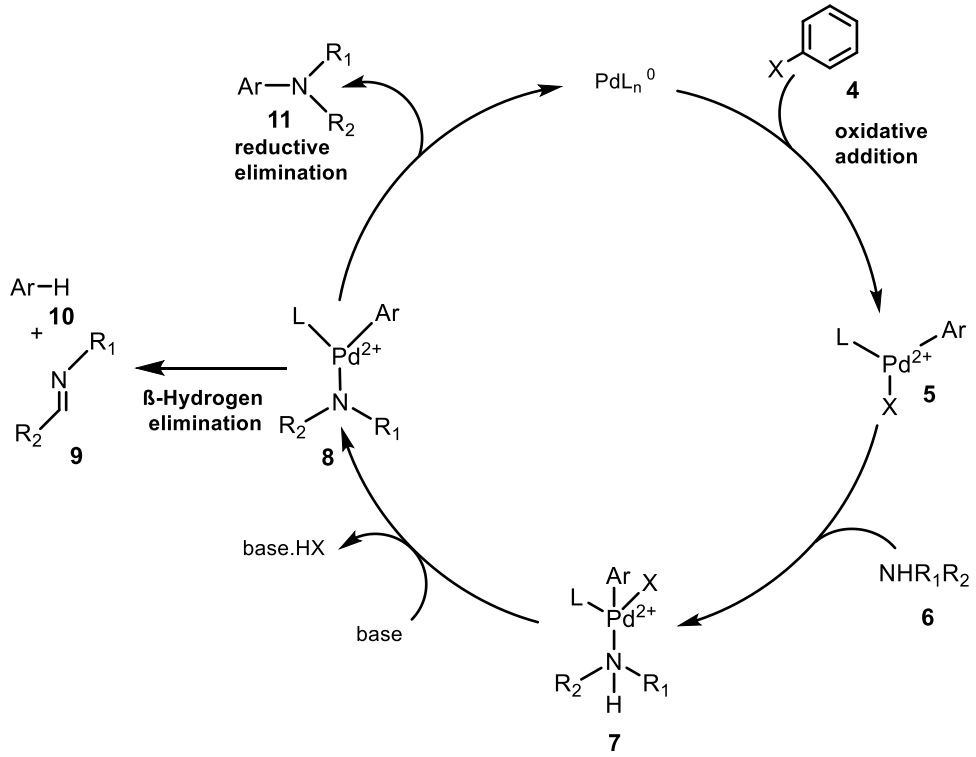
Scheme 5 – Formation of C-N bond by Migita and co-workers.[9-10]

Developments in this area led to the replacement of the toxic tin reagent with the free amine,[11] an improvement in scope(Scheme 6)[12] and more recent work had utilised phosphine bases to prevent decomposition via beta hydride elimination.[13-14]



Scheme 6 – improved methodology for Buchwald and Hartwig allowing extension of substrate scope.[15]

The mechanism for this reaction has been studied extensively (scheme 7). The reaction starts with an initial oxidative addition of the aryl halide (**4**) to the palladium species, followed by the addition of the chosen amine (**5**) to the complex. Finally, there's deprotonation by a base followed by reductive elimination to form the desired product (**11**). However, an unwanted side reaction can occur which results in the formation of the imine (**9**) and hydrodehalogenated arene (**10**) through beta hydride elimination which competes with the desired product. [15]



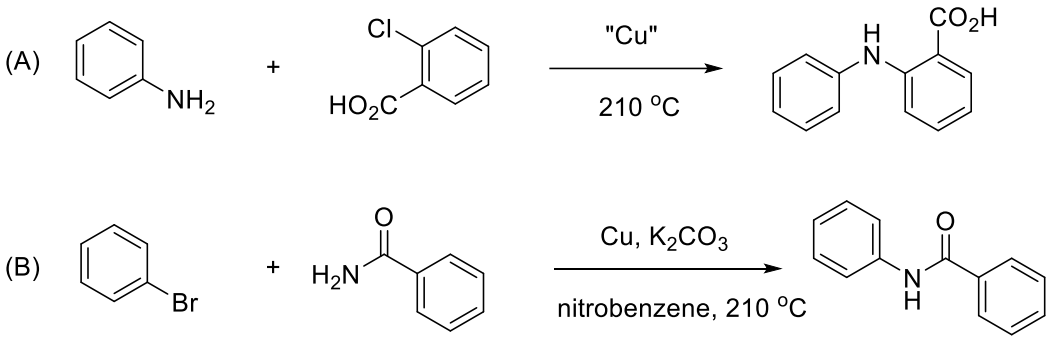
Scheme 7 – Proposed mechanistic cycle for Buchwald-Hartwig reaction. [15]

Despite the unpopularity surrounding the use of palladium in scale up reactions, this method represents an important branch of amine synthesis. As such, there is a drive towards lower catalyst

loadings.[16] cleaner solvents[17] and even through replacing palladium with more abundant metals such as nickel.[18]

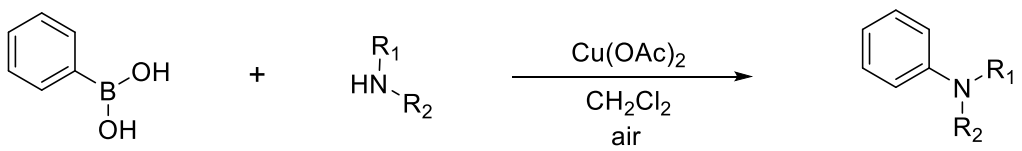
Chan-Lam reaction

An alternative route in amine synthesis is the use of copper-catalysed cross coupling. This has advantages over palladium-catalysed reactions as it avoids the need for expensive and environmentally damaging catalysts. One of the first examples of this was the Ullman condensation. This copper catalysed reaction utilises an aryl halide and an amine to achieve cross coupling (Scheme 8). [19] A related method for the synthesis of amides is the Goldberg reaction, which couples aryl halides with anilines or aryl amides in the presence of a copper catalyst and a strong base [20] (Scheme 8). Though both methods are useful in C-N bond synthesis these reactions are plagued by a poor substrate scope, harsh conditions and use stoichiometric amounts of copper.



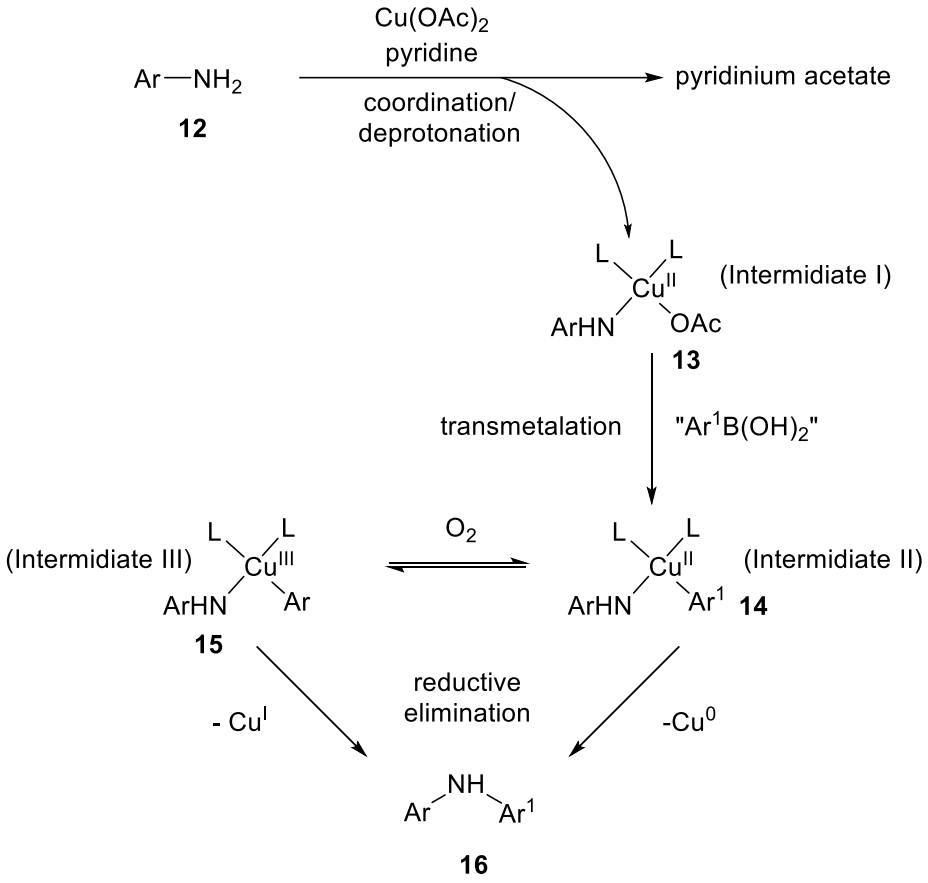
Scheme 8 – Ullman reaction between Aryl halide and amine[19] (A) and Goldberg reaction between aryl halide and aryl amide[20](B).

A variation on this Ullman coupling was developed by Chan and Lam in 1998. This variation uses boronic acids and amines in the presence of stoichiometric amounts of copper to achieve the cross coupled product (Scheme 9). The main advantage of this method over other types of copper coupling is the mild conditions that take place at room temperature and in air.[21-22]



Scheme 9 – Chan-Lam coupling reaction between boronic acid and amine.[21-22]

The proposed mechanism has been shown to proceed through deprotonation and coordination of the aryl amine (**12**) to the Copper catalyst to form intermediate I (**13**). This is followed by tansmetallation of the arylboronic acid to product intermediate II (**14**). The reaction can then proceed through either reductive elimination to form the desired product (**16**), or the copper species is oxidised by ambient oxygen to form intermediate III (**15**) which can then form the product (**16**) via reductive elimination (scheme 10).[23]

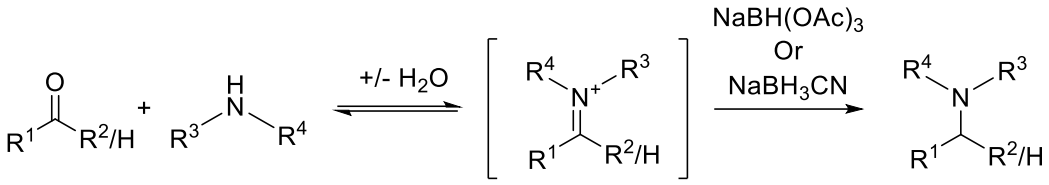


Scheme 10 – proposed mechanism of copper catalysed Chan-Lam coupling[23]

Despite the use of the more available copper and the ability to be carried out in air, the stoichiometric amount of this reagent makes this process less appealing for amine synthesis.

Reductive amination

Reductive amination is a key coupling reaction for the formation of amines and is widely used in the pharmaceutical industry. [2] The reaction involves the conversion of an aldehyde or ketone to an amine via an iminium intermediate (Scheme 11).

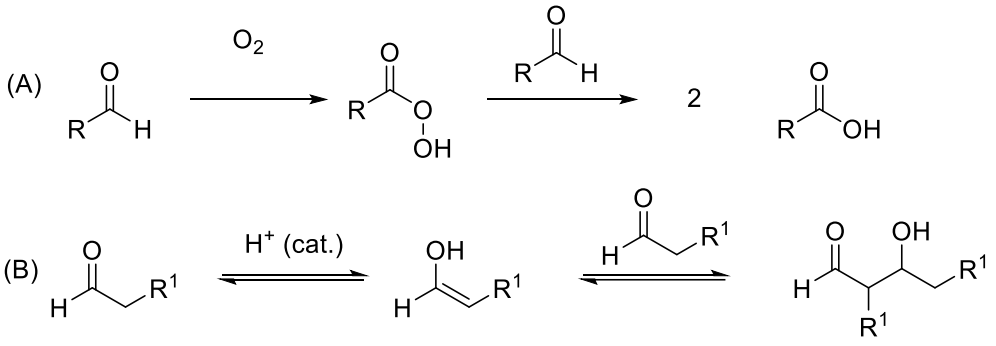


Scheme 11 – Reductive amination of ketones and aldehydes using sodium triacetoxyborohydride [24]or sodium cyanoborohydride.[25]

The first step is the formation of the iminium ion which is subsequently reduced to the amine. The reducing agents for this process are most commonly sodium triacetoxyborohydrife (STAB) or sodium cyanoborohydride, which can reduce the iminium ion selectively in the presence of aldehyde starting material unlike other borane reducing agents. [24-25]

Although this chemistry is exceptionally useful in pharmaceutical synthesis, [2] there are many problems that come from this methodology. The long reaction times of 2-4 days in conjunction with expensive and toxic reducing agents makes this process unattractive.

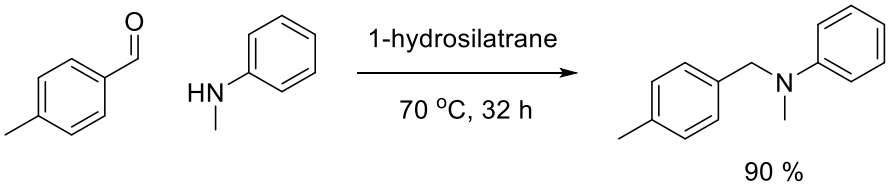
In addition, another problem that plagues reductive amination chemistry is the use and handling of the starting materials. Aldehydes can undergo autooxidation which is the formation of carboxylic acids through reaction with atmospheric oxygen (Scheme 12A). The resulting peracid can further react via a Baeyer-villiger oxidation to form the corresponding carboxylic acid. [26] In addition, some aldehyde can undergo aldol reactions to form the corresponding β-hydroxyketone(Scheme 12B) further degrading the starting material feedstock.



Scheme 12 – (A) autoxidation by atmospheric oxygen followed by Baeyer-villiger oxidation.[26]

(B)Aldol reaction to form β-hydroxyketone

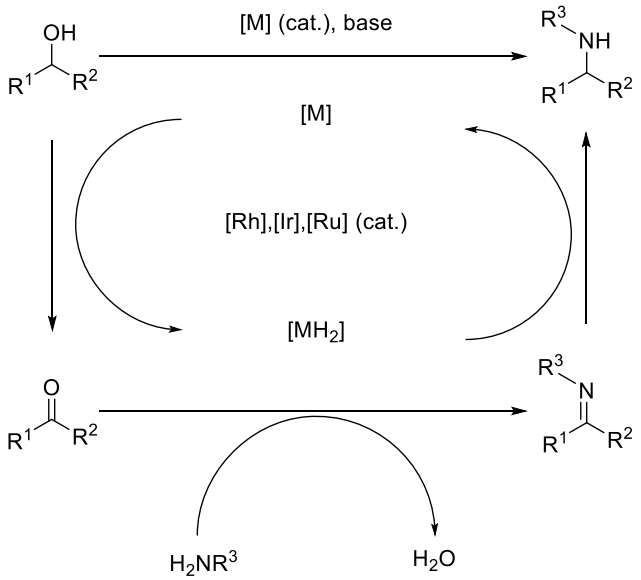
An interesting development in this area is the work done by Varjosaari and co-workers in the development of a new reductive amination reaction utilising hydrosilatrane as the terminal reductant. The advantages of this development are the hydrosilatrane reductant is cheap and readily available, using this readily available reagent makes this method metal free which is an important improvement. Another major improvement is the decrease in reaction time from multiple days to overnight (Scheme 13). [27]



Scheme 13 – Reaction using 1-hydrosilatrane under solvent free conditions. [27]

Developments in reductive amination

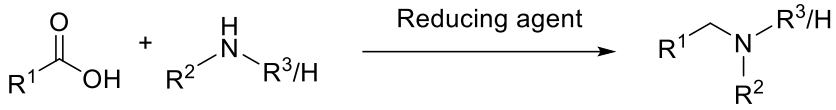
As mentioned previously, there are many issues surrounding the use of aldehydes in a traditional reductive amination. Research moved towards the use of alcohols as a starting material in a 'Hydrogen borrowing' reaction. This process utilises the ability of alcohols to oxide *in situ* to the more reactive aldehyde in the presence of a metal catalyst such as iridium, rhodium or ruthenium. [28-29] This aldehyde can undergo reductive amination to form the amine and the catalyst recycled (Scheme 14).



Scheme 14 – "Borrowing" hydrogen reaction for synthesis of amines from an alcohol.

This reaction (Scheme 14) though novel and producing only water as the by-product. The potential of this reaction was greatly reduced by its need for high catalyst loading of expensive metals and high reaction temperatures. [28-29]

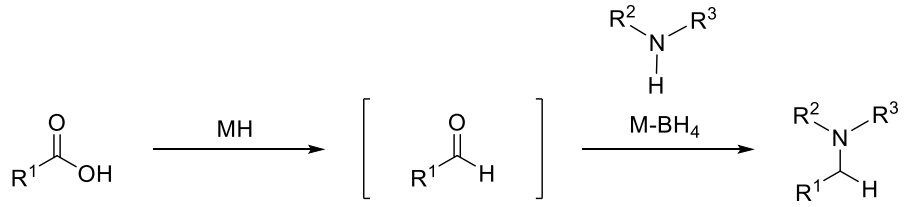
A less developed pathway would be through the direct use of carboxylic acids (scheme 14). This pathway is less prevalent in the literature due to the lesser reactivity of this starting material. However, the use of this starting material presents an easy to handle, stable and widely available starting material so a reductive amination from carboxylic acids would be a powerful method for the synthesis of amines.



Scheme 14 – General scheme for reductive amination of carboxylic acids

Reductive amination using carboxylic acids

Another method which is less explored and shows great potential for amine synthesis is through the use of carboxylic acids. These compounds are benchtop stable, easy to handle, widely abundant and inexpensive. The first reported used of carboxylic acids for this purpose was in the 1970's, whereby the carboxylic acid starting material was reduced to the aldehyde using stoichiometric amounts of metal hydride. This intermediate reacts with the amine to form an imine intermediate and finally reduced using the same metal borohydride (scheme 15).[30-32]

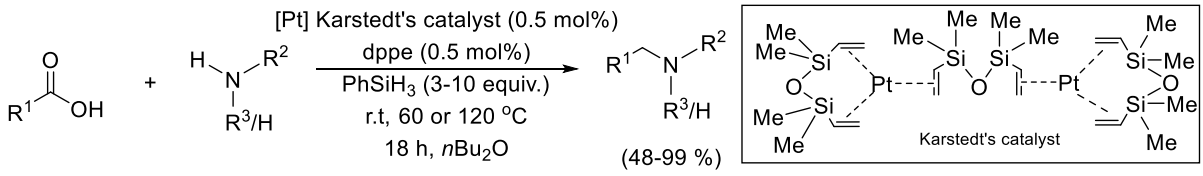


Scheme 15 – general reductive amination of carboxylic acids using metal borohydrides[30-32]

Although this method is the first reductive amination from carboxylic acids, this reaction is hindered by a limited scope and reduced functional group tolerance, mainly due to the use of the carboxylic

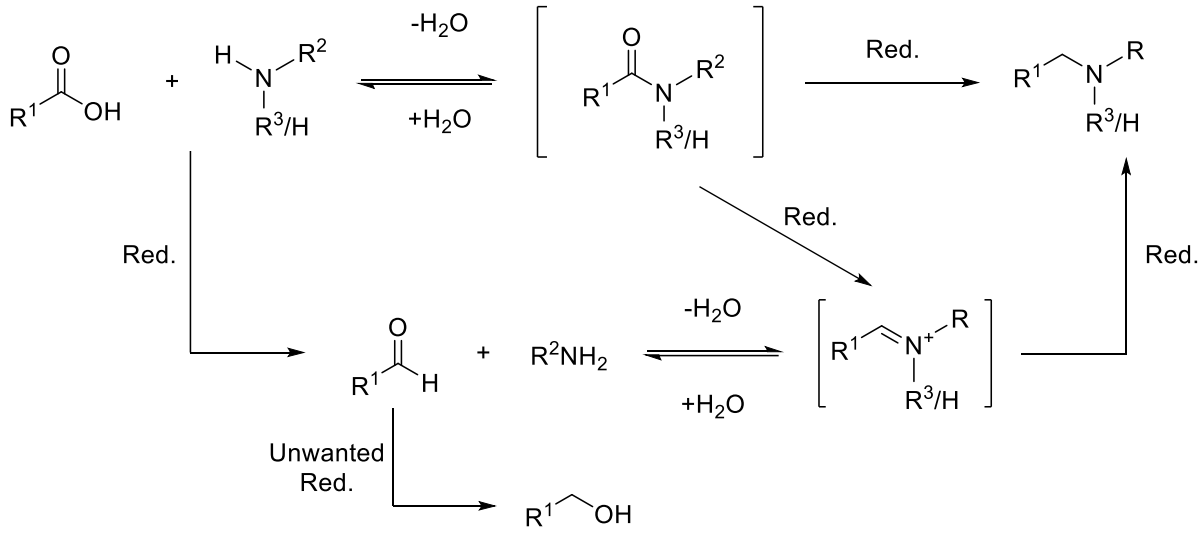
acid starting material as the solvent. Finally, the use of stoichiometric amounts of metal hydride and the reducing agents renders this method unattractive.

A breakthrough in this area was the more recent publication from Beller and co-workers, who developed a catalytic reductive amination from carboxylic acids amines using Karstedt's catalyst and phenyl silane (Scheme 16). This further developed this chemistry into a range of alkylated secondary and tertiary amine products under mild conditions with some functional group tolerance. [33]



Scheme 16 – Reductive amination of carboxylic acids using Karstedt's catalyst and phenyl silane by Beller and co-workers.[33]

After investigation of the scope of the reaction, mechanistic details were then probed. Two interlinked mechanisms were proposed. The first was the direct coupling of the acid and amine to form the amide intermediate and the second was reduction of the acid *in situ* to form the aldehyde. The first route proceeds through the amide intermediate which can be reduced directly to the amine or via the iminium ion. The second proposed route is a more traditional reductive amination through the iminium intermediate (scheme 17).[33]

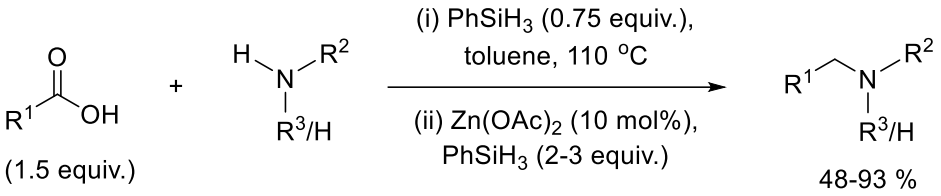


Scheme 17 – Proposed mechanism for Pt catalysed reductive amidation using carboxylic acids by Beller and co workers[33]

Despite this reaction being a good example for the potentials for carboxylic acids in amine synthesis, the expensive and low availability catalyst, coupled with the large excesses of phenylsilane (up to 10 equiv.) and carboxylic acid (up to 5.5 equiv.) lowers the attractiveness of this method. In addition, as the reducing agent was added at the start of the reaction there is some reduction of the starting material to the alcohol, resulting in the need for the large excesses of reagents.

Despite this reaction being the first breakthrough in this area, there is still a long way to achieve a practical method using carboxylic acids. Since this publication, there have been more useful methods using, ruthenium,[34] rhodium,[35] iridium,[36] copper[37] catalysts in addition to metal-free processes.[38]

A recent publication from the Denton group describes a two-step reaction which exploits the dual reactivity of phenyl silane, through an initial silane-mediated amidation followed by a zinc acetate catalysed reduction (Scheme 18). This work uses the findings from Beller and co-workers to develop a method in which the amidation takes places before the reduction. This reduces the risk of reduction of the starting material to the alcohol. As a result, lower equivalents of carboxylic acid and silane starting materials were required. After researching possible catalysts, the group were finally drawn to zinc acetate due to its low cost and previously reported activity for tertiary amide reduction with triethoxysilane.[39] During optimisation the addition of 50 mol% (1.5 equiv. total) of the carboxylic was added in order to aid in the formation of the modified silane with increased reducing properties. [40-41]

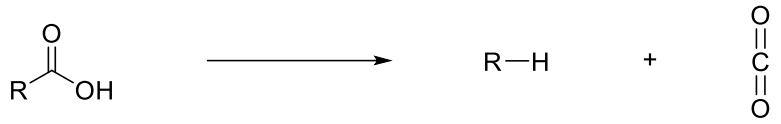


Scheme 18 – Reductive amination of carboxylic acid using silane-mediated amidation followed by a zinc acetate catalysed reduction. *[41]*

As the amidation is a known procedure, [40-41] investigations turned to the mechanistic details. As the yield increased with a slight excess of carboxylic acid, it was postulated that sily esters were being formed and were participating in the reaction. NMR studies allowed observation of further silane mediation upon addition of the zinc acetate to higher order silyl esters and a zinc hydride species which are postulated to be active reducing species.

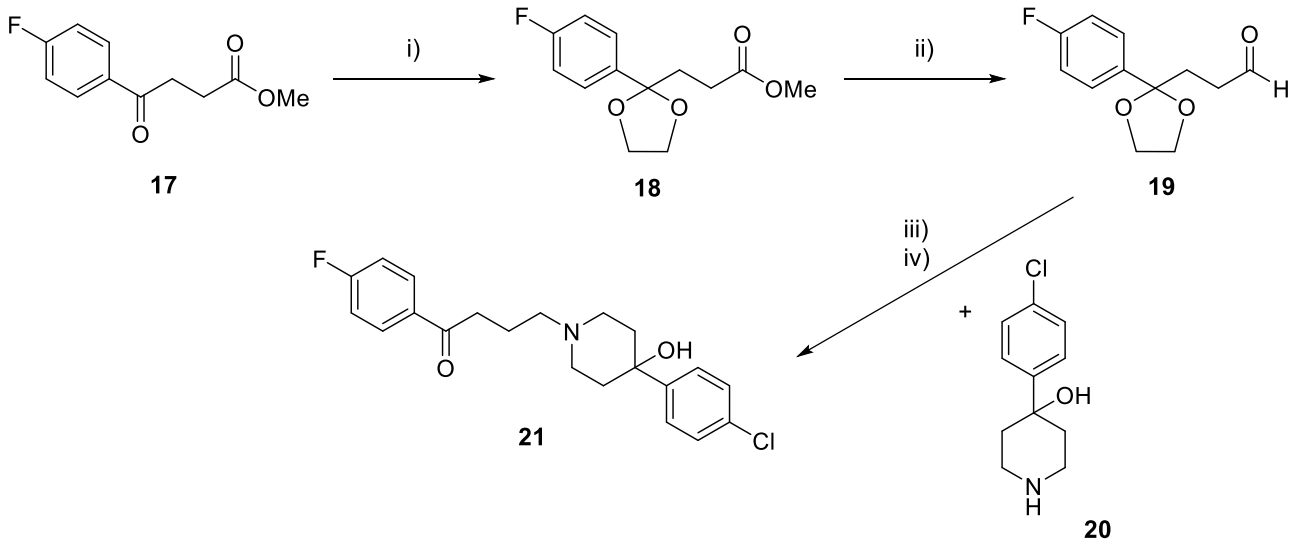
Problems with the use of carboxylic acids

Despite there being great progression in this area of chemistry, there are some issues surrounding the use of carboxylic acids. Some substrates readily decarboxylate (Scheme 19), either in air or when heated, making products containing these motifs hard to obtain.



Scheme 19 – General decarboxylation of carboxylic acids

During synthesis pathways, there are often functional groups that require modification to prevent breakdown in the reductive amination process. If there are any other carbonyl groups such as aldehydes or ketones in the target molecule, there will be competition for these sites over the intended carboxylic acid site. As a result, these interfering groups will cause a reduction in the yield therefore, protecting groups are often used to circumvent this issue. An example of this is the synthesis of Haloperidol (scheme 20). [42]



Scheme 20 – Synthesis of Haloperidol. Reagents and conditions: i) ethyl glycol, *p*-TsOH, benzene, reflux, 18 h, 83%; ii) Dibal-H, -78 °C, 1 h, 93%; iii) $NaBH_3CN$, AcOH, MeOH, rt, 36 h; iv) Conc. HCl, MeOH, reflux, 2 h, 70% (two steps).[42]

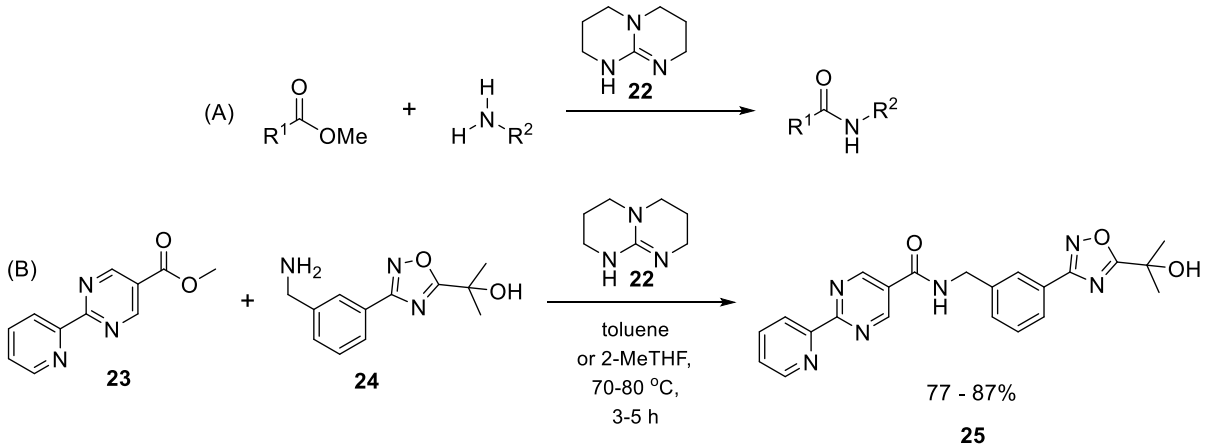
The carboxylic acid starting material is first protected as the methyl ester and the ketone is subsequently protected as the acetal. This method then uses DIBALH to reduce the ester to the aldehyde to carry out the reductive amination process. However, even if the method used the carboxylic acid as the electrophile, a hydrolysis would have to occur, extending this synthesis and causing further loss in yield.

If a method could be developed that carries out a reductive amination from the ester over the carbonyl compound without the need for protection immediately followed by the formation of the aldehyde, then many other synthetic routes would be simplified and improved upon.

This Chemistry

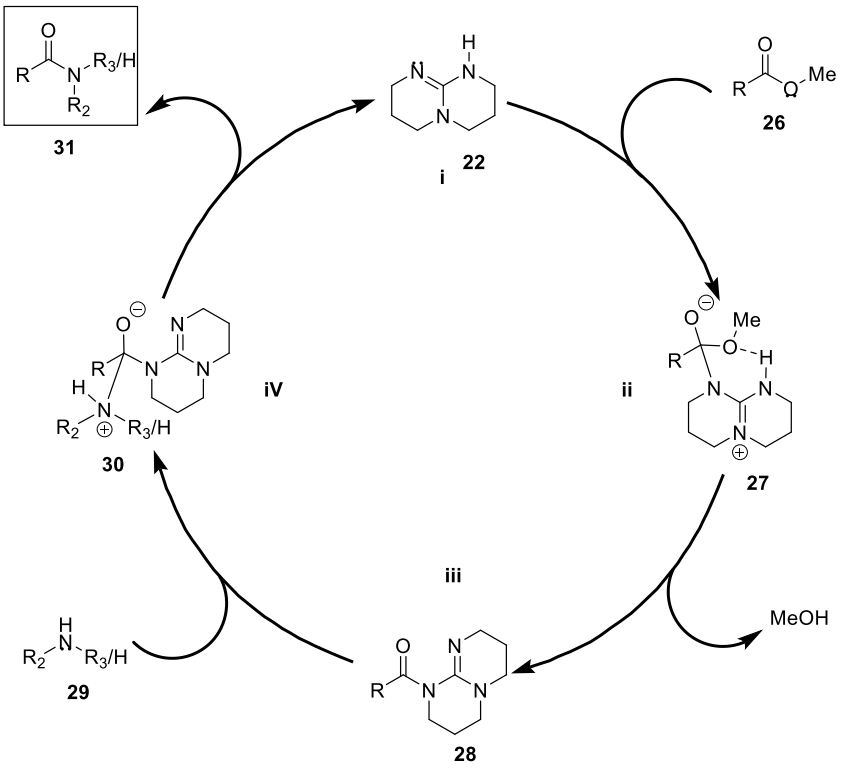
TBD mediated amidation from methyl esters

Originally TBD (***22***) and other strong amidine bases had shown promise in promoting many reactions such as elimination reaction and Wittig reactions. More recent work from Waymouth, Hedrick and co-workers has shown TBDs ability to promote acyl transfer and ring opening polymerisation (ROP) of cyclic ester such as δ-valerolactone, ε-caprolactone, and L-lactide.[46] This chemistry has also shown promise for amide formation from methyl esters (scheme 21A) and has been shown to synthesise important drug compound such as 2-(Pyridin-2-yl)pyrimidine-5-carboxylic Acid 3-[5-(1-Hydroxy-1-methylethyl)-1,2,4]oxadiazol-3-yl]benzylamide (**25**). a known H-PGDS inhibitor (scheme 21B). [43-44]



Scheme 21 – amidation of methyl esters (A). Synthesis of the H-PGDS inhibitor using TBD catalysed amidation[44] (B).

The proposed mechanism formed from analysis of Waymouth, Hedrick and co workers previous work highlights TBDs ability as a bifunctional nucleophilic organocatalyst (scheme 22)[45]



Scheme 22 – proposed TBD catalytic cycle from analysis of Waymouth,Hedrick and co-workers.[45]

The first step is the reaction of TBD (**22**) with the methyl ester (**26**) starting material to form intermediate ii (**27**). After which proton transfer affords intermediate iii (**28**) and elimination of methanol. Finally, the amine (**29**) through hydrogen bond activation attacks in to form the amide (**31**) and reform the TBD catalyst.[45]

This new route for the formation of amides using a nontoxic inexpensive TBD catalyst [45] shows great promise to help remove a lot of the issues surrounding more classic reductive amination chemistry. The advantages of using methyl esters as starting materials is they are readily available, easy to store and help avoid a lot of unwanted side reactions which are associated with aldehyde use and unwanted decarboxylation of carboxylic acids in addition to potentially shortening long synthesis routes.

Project aims

The aim of this project was to develop and optimise a simple one pot reductive amination reaction for methyl esters. The aim was to couple together two known reactions, the first being TBD catalysed

amide formation (scheme 21 (A))[45-46] and immediately after using a preoptimised zinc acetate/phenyl silane reductive method developed by the Denton group (scheme 18).[41] The reaction would be optimised for use with both primary and secondary amines and a range of different methyl esters which would help explore the tolerance of the reaction. As the mechanism for both steps have already been researched extensively, this project aimed to focus on optimisation and developing the scope of the reaction.

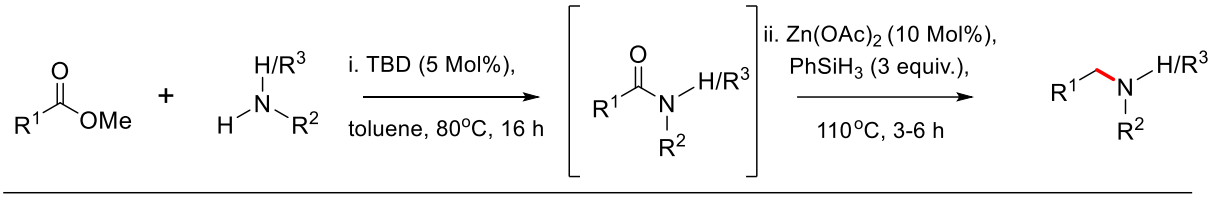
To the best of our knowledge this is the first method detailing direct reductive amination from methyl esters and represent a major breakthrough in this area.

Results and discussion

Initial reactions

Previous work from the Denton group highlighted and utilised the duel reactivity of phenylsilane to mediate amide coupling alongside amide reduction in the presence of a metal catalyst.[41] I aimed to couple this established Phenylsilane/zinc acetate reductive process with a known TBD mediated amidation, to achieve reductive amination from a methyl ester starting material. The initial TBD amidation conditions were developed from the previous work done by Waymouth, Hedrick and co-workers on TBDs role as a simple bifunctional organocatalyst[46] and the reduction conditions from previous work from the Denton group.[41] These initial conditions were used to couple three different esters with both benzylamine and pyrrolidine (Scheme 23). Although these products were all successfully formed using these conditions, the yields (starting material converted to desired product) and purity of these compounds highlighted the need for reaction monitoring and optimisation.

These starting materials were selected as they offered a simple and diverse range of ester and amine combinations. Pyrrolidine and benzylamine offers one of the simplest examples of both secondary and tertiary amine formation.

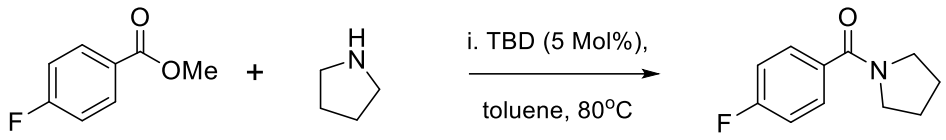


Scheme 23 – initial reaction conditions used for amine synthesis

Reaction monitoring of tertiary products

When reviewing the conditions of the initial reactions I knew that the zinc acetate/phenylsilane reduction method had previously been optimised for reduction of amides and would be successful, therefore the issue with the low yields had to be with the amidation step. To fully investigate this, I performed reaction monitoring for the amidation over 24 hours (Figure 24).

To begin reaction monitoring and optimisation methyl 4-fluorobenzoate was selected as a model substrate as ^{19}F NMR spectroscopy could be used to quickly identify if the conversion was successful. 1,3-benzodioxole was later added as an internal standard and ^{1}H NMR used to accurately determine the amount of conversion of starting material to desired product.



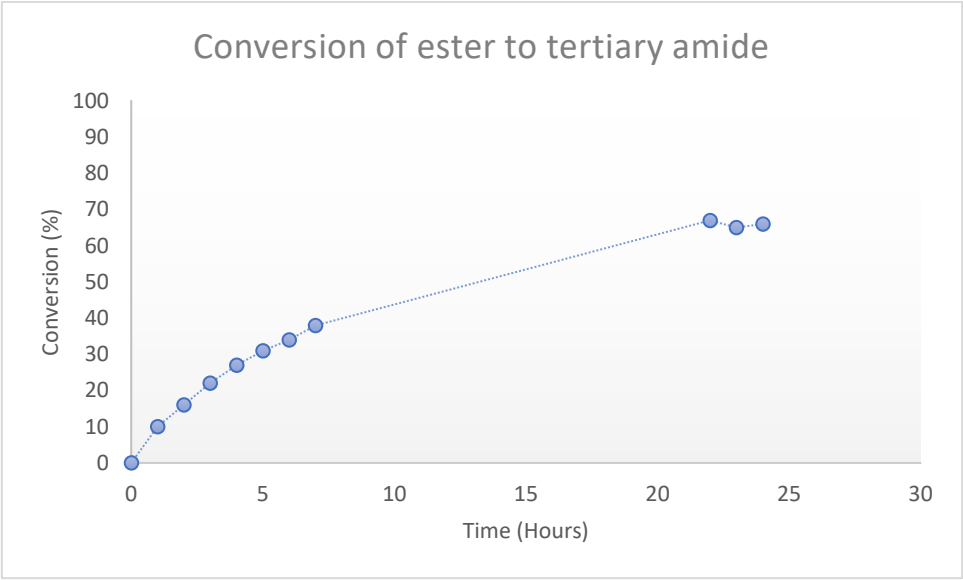
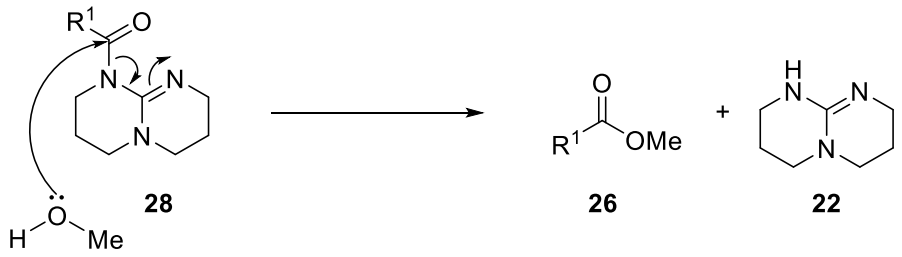


Figure 24 – Conversion from ester to tertiary amide over time. Conversion of starting material to desire product determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

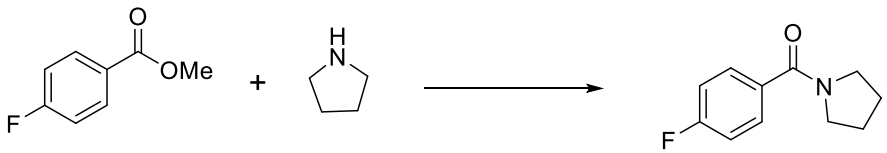
Unsurprisingly, conversion to the amide product increased steadily over time. However, after 22 hours the conversion reached 66 % after which it plateaued. Upon reviewing the NMR data, it was clear that both starting materials were still present and therefore the stall in reactivity could not be due to side reactions or starting material decomposition. Following this observation, investigation then focused on the possibility of unwanted interactions with the TBD. This was postulated to be through the methanol by-product quenching the activated acid intermediate during amidation (Scheme 25). Optimisation was then designed to look into testing this hypothesis and checking for other limiting factors.



Scheme 25 – Postulated quenching of activated acid by methanol by-product

Reaction optimisation of Tertiary amides

Methyl 4-fluorobenzoate (**32**) was selected along with pyrrolidine (**33**) for the optimisation, and 1,3-benzodioxole was added in order to monitor conversion through ^{1}H NMR. The reaction was then subjected to a range of different conditions.

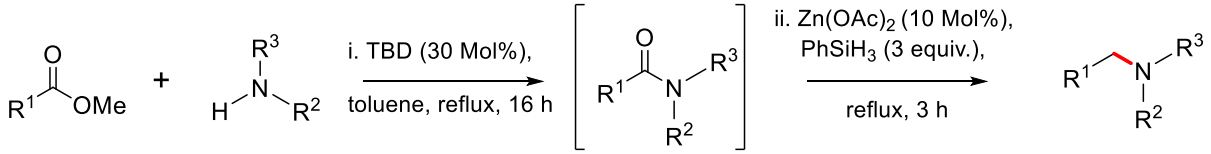


Entry	Catalyst loading (mol%)	Temperature (°C)	Additive	Yield (%)[a]
1	5	80	N/A	62
2	5	110	N/A	72
3	10	110	N/A	96
4	5	110	0.75 equiv. $PhSiH_3$	0
5	5	110	1.5 equiv. $PhSiH_3$	0
6	5	110	1 equiv. methanol	67
7	30	110	N/A	99

Table 1 – Optimisation of conversion from methyl ester to tertiary amide in toluene for 18 hours. [a] Conversion of starting material to desire product determined by ^{1}H NMR analysis of reactions mixtures using 1,3-benzodioxole as an internal standard.

Entry 1 was under the standard conditions procured from the TBD paper.[46] It was speculated that an increase in temperature would have an increase in the conversion and, this was evident from entry 2 as a 10% increase in conversion was observed. Therefore, all further entries were performed at 110 ^{o}C. As previously stated, it was postulated above that methanol was having an adverse effect on the TBD catalyst (Scheme 25), therefore, phenyl silane was added to react with any methanol formed and stop unfavourable interactions with the catalyst. However, as can be seen in entries 4 and 5, this completely stopped any conversion to the amide leaving only starting material. I then tried adding one equivalent of methanol, to see how an increase in the perceived interfering compound would affect the yield. However, this was found to have no effect on the overall conversion and therefore the plateau in reaction progression was not due to interactions of methanol with the catalyst. Although I was not able to confirm what this interaction was, a final attempt to optimise the reaction was through changes to the catalyst loading. Entry 3 was doubling the loading from 5 mol% to 10 mol%, this resulted in a very significant increase to 96 %. Although this entry appears to be fully optimised, I am aware that this is a very simple substrate and as such more complex molecules may require more optimised conditions. In addition to this, Sabot and co-workers paper on TBD mediated amidation[44] required 35 mol% of the catalyst to reach full conversion to the amide product using a primary amine, therefore, we decided to attempt a final increase to 30 mol% of catalyst loading for the tertiary scope. This further increased yield to be almost quantitative confirming that these conditions are the most viable for a wide range of substrates. Although 30 mol% is a high loading for a catalyst, TBD is both organic and inexpensive, making this loading suitable for this transformation.

Throughout the optimisation process, the Denton phenylsilane/zinc acetate reduction conditions (Scheme 18) successfully reduced any amide formed from the amidation step. These newly optimised amidation conditions could then be used in a one-pot two step reaction from methyl esters to amines via amide intermediate (Scheme 26). The coupling of these two processes demonstrated a high yielding simple one-pot reductive amination.

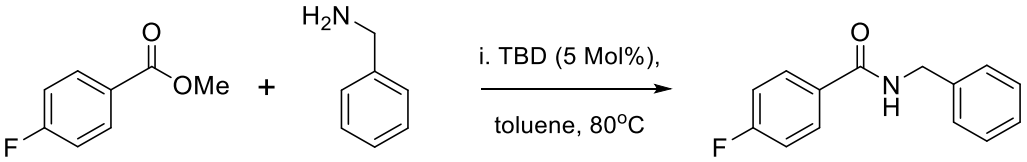


Scheme 26 – optimised secondary amine reaction conditions

Reaction monitoring for secondary amides

It is known that primary amines are less nucleophilic and thus less reactive than secondary amines and as such I expected them to require further optimisation. From observations made during the initial reactions phase of the project and previous work from the Denton group, it was clear that this was the case. Much like the previously discussed tertiary products, the problem was with the amidation step as the reduction used has been demonstrated to be effective on secondary amides. I decided to carry out reaction monitoring for the standard secondary conditions.

Methyl 4-fluorobenzoate (**32**) and 1,3-benzodioxole were once again selected along with benzylamine (**35**) for monitoring the amidation for secondary products.



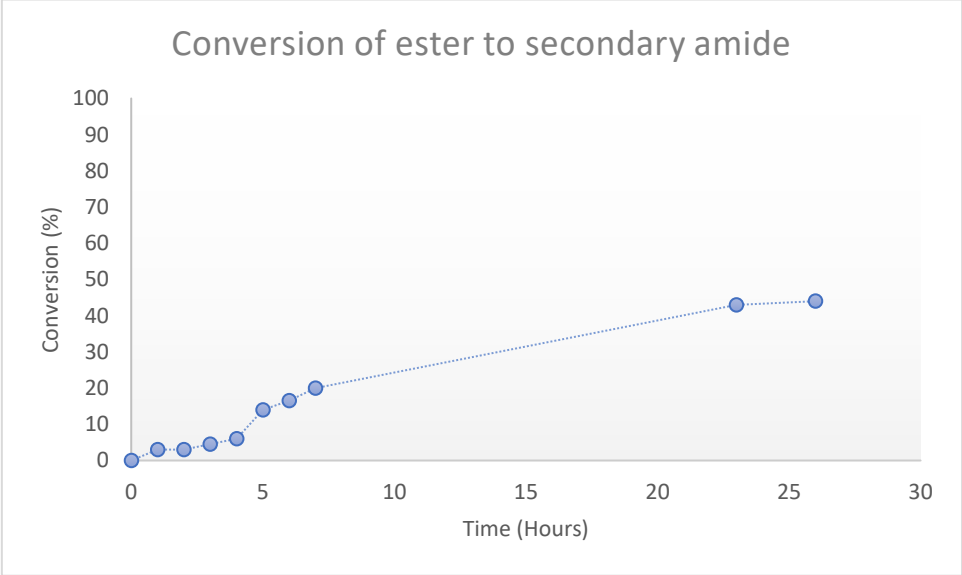
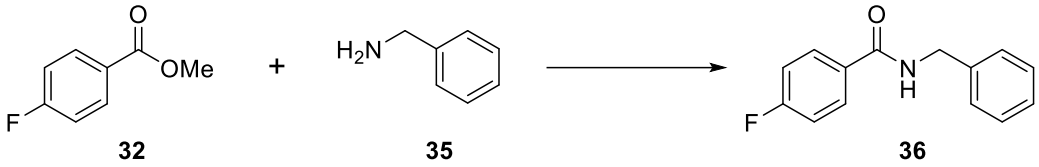


Figure 27 – Conversion from ester to secondary amide over time. Conversion of starting material to desire product determined by ^{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard.

Similar to the tertiary amide formation, the conversion increased steadily with time and eventually plateaued off. However, for secondary amide formation the data showed that conversion occurred to a total conversion of 44 % after around 23 hours, which was 10% less than for the tertiary amides before optimisation. From the ^{1}H NMR data there was clearly both starting materials present, which

brought to the assumption that again it must be a problem with catalyst side reactions. At this point, the optimised conditions for the tertiary products were applied to secondary amide formation and the focus shifted to optimisation.



32 **35** **36**

Entry	Catalyst loading (mol%)	Temperature (°C)	Solvent	Yield (%)[a]
1	5	80	Toluene	43
2	5	110	Toluene	46
3	10	110	Toluene	53
4	10	139	Xylenes	62
5	20	139	Xylenes	69
6	30	139	Xylenes	71

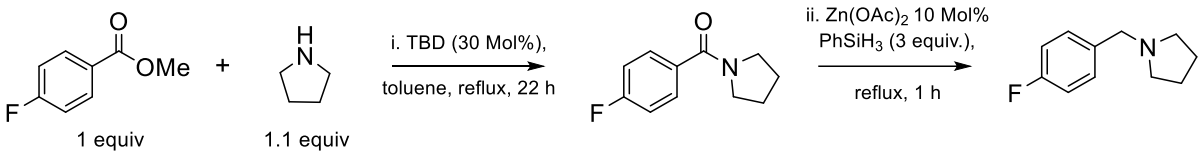
Table 2 – Optimisation of conversion from methyl ester to tertiary amide over 18 hours. [a] Conversion of starting material to desire product determined by ^{1}H NMR analysis of reactions mixtures using 1,3-benzodioxole as an internal standard.

Entry 1 shows the original conditions from the Waymouth paper[46] which resulted in a reasonable conversion of 43 %. Entry 2 shows the effect of increasing the temperature to 110 °C which caused a very slight increase in conversion at 46 %. After this I used the findings from the tertiary amide optimisation to both increase the temperature to 110 °C and double the catalyst loading to 10 mol% for entry 3 which resulted in an increase of 10 % to 53%. As an increase in temperature from 80 °C to 110 °C caused the yield to improve by 10 %, I thought that a further increase in temperature would offer higher yields. This required me to search for a more suitable solvent, and after a couple of attempts, xylenes offered the increase in temperature required, whilst having no adverse side effects

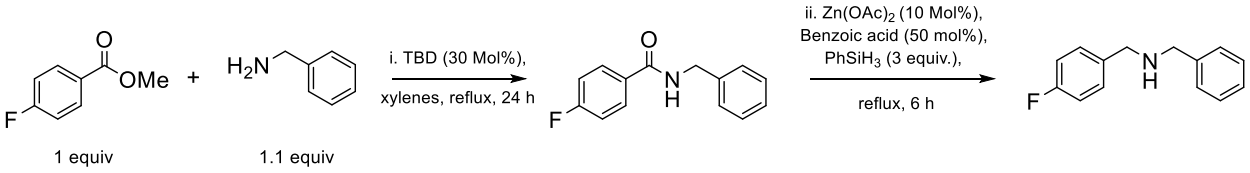
on the conversion. Further optimisation included an increase in catalyst loading for entries 5 and 6, which finally achieved the desired conversion with a 71 % yield resulting from 30 mol% catalyst loading. This finally resulted in a compromise of 30 mol% catalyst loading and 139°C in xylenes.

Development of a one-pot process

Having optimised the amidation steps for both secondary and tertiary products I began development of the simple one-pot reductive amination reaction. Having completed the full process I found that an increase in time for both secondary and tertiary amidation steps was required: Tertiary amides to 22 hours and secondary amides to 24 hours to allow for maximum conversion before reduction. The same reduction conditions were applied from Dentons original work of 10 mol% of zinc acetate and three equivalents of phenyl silane (Scheme 28). These conditions successfully reduced all amide formed in the previous step. The Schemes below demonstrate optimised conditions for the full one-pot reactions used for the substrate scope.



Scheme 28 – Optimised one pot reductive amination for tertiary amine formation

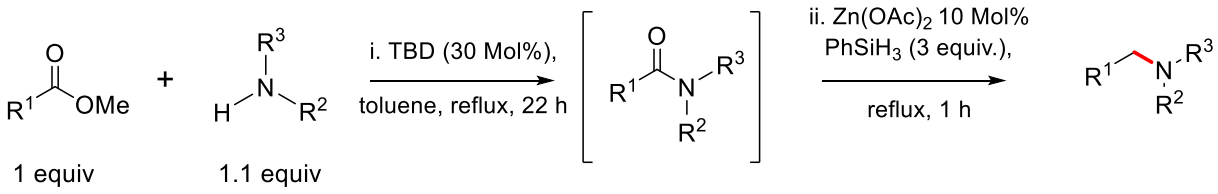


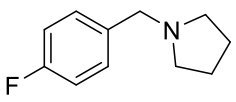
Scheme 29 - Optimised one pot reductive amination for secondary amine formation

Substrate scope

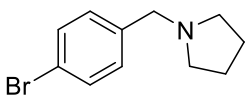
With the synthesis of tertiary and secondary amines optimised, (Scheme 28 and 29). I then began to explore the substrate scope for the reactions, investigating tolerance, general applicability and access to novel compounds.

During the initial stages of the substrate scope it became clear that the reduction time was clearly reduced for certain compounds, 15 minutes for compounds 34, 37 and 38 and an hour for others. Therefore, to cover all substrates, I set the reduction time for the tertiary products to one hour. As in Dentons paper, the reduction time for secondary amine products was longer, therefore the full six hours was required to achieve full conversion.

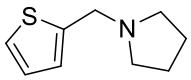




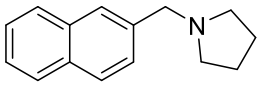
34 - 76 %*



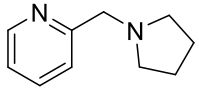
37 - 92 %*



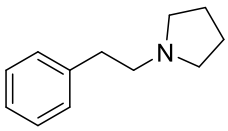
38 - 60 %*



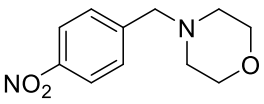
39 - 72 %*



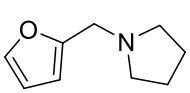
40 - 78 %



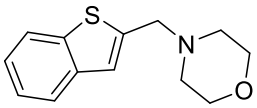
41 - 40 %*



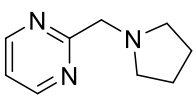
42 - 56 %



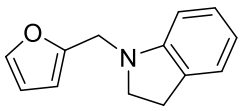
43 - 59 %*



44 - 58 %



45 - 7 %



46 - 4 %

*No chromatographic purification needed

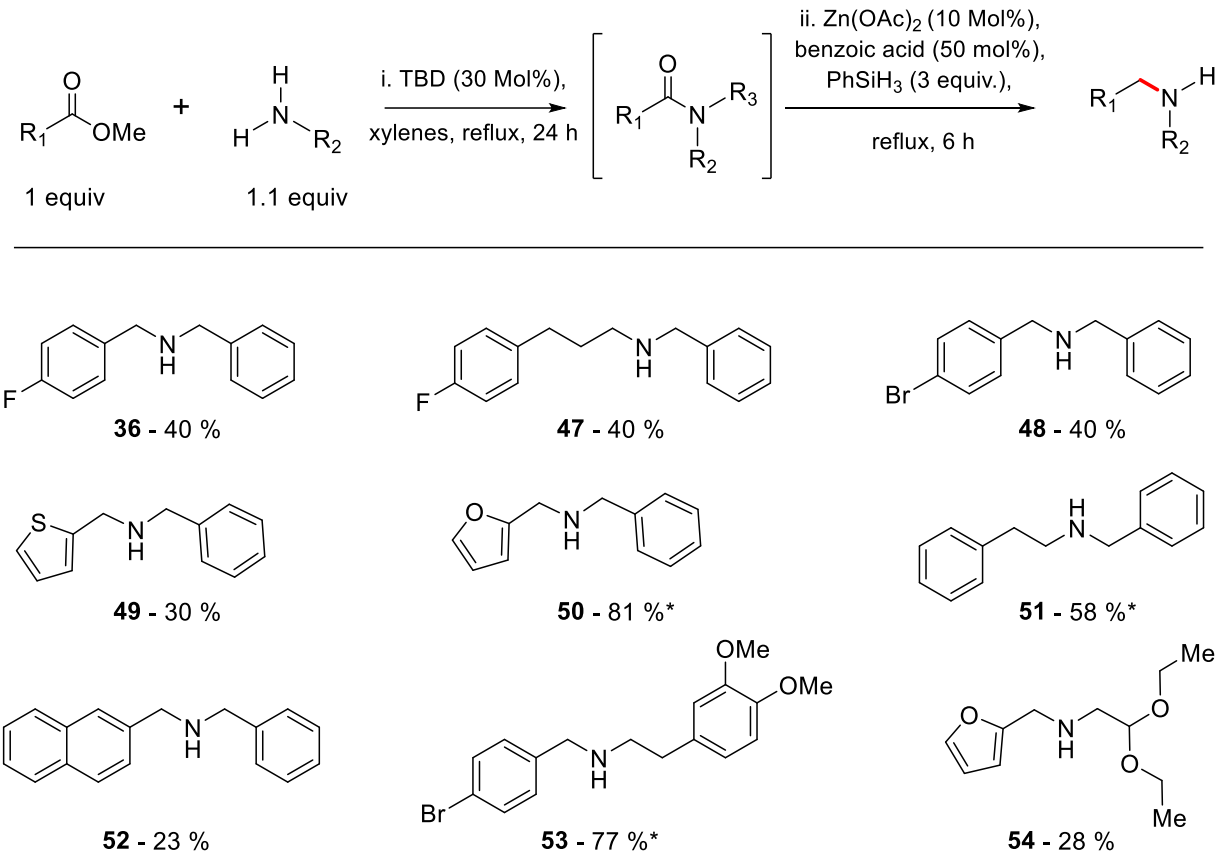
Table 3 – Tertiary substrates for reductive amination reaction – conditions: TBD (30 mol%), Toluene, reflux, 22 hours. $PhSiH_3$ (3 equivs), $Zn(OAc)_2$ (10 mol%),1 hour.

Investigating tertiary substrates, I was able to achieve eight examples in excellent to moderate yields (Table 3). Using pyrrolidine and a range of different methyl esters we attempted to demonstrate functional group tolerance. Aryl halides (**34** and **37**) and electron rich aromatics (**38**, **39** and **43**) all resulted in good to excellent yields with most not needing any further purification. These products are key examples as they contain potentially reducible functional groups which can be used in further synthesis such as cross coupling or electrophilic aromatic substitution reactions. Compound **44** is another electron rich aromatic and is an example of a potentially important pharmacophore. Benzothiophene is currently being researched due to its privileged structure and activity towards a range of different diseases. [47] An example of an electron withdrawing group (**42**) was also included as a key functional group as this allows for further reduction and additional reactions. The inclusion of the nitro group demonstrates a further example of potentially reducible functional groups, again demonstrating the tolerance of this reaction. As mentioned previously, one of the main benefits of using methyl esters over carboxylic acids was the possibility for decarboxylation of starting materials for some substrates. Here, I have demonstrated reductive amination using these starting materials (**40**, **41** and **45**) that other chemistry using acid starting materials could not access easily. This gives access to more interesting and novel substrates that could be of interest in pharmaceuticals and other key areas in chemistry. Compound **40** highlights that pyridines are also very tolerant of this chemistry offering good, isolated yields.

During the tertiary substrate scope I began looking for esters and amines which would result in the formation of novel compounds of interest. Compounds **45** and **46** are good examples of novel compounds this chemistry allows access to. Compound **45** and similar nitrogen containing hetero cycles in the tertiary substrate scope highlight the advantageous abilities of this chemistry as the carboxylic alternative would readily decarboxylate under these conditions. Though the yields for these compounds are poor, with additional optimisation and looking into an alternative work up, the yields and purity of these compounds would improve greatly.

The yields of these examples are hypothesised to be low due to difficulties in work up and purification. An observation made during the scopes for all compounds was that if the amidation step was slow for any reaction then any remaining methyl ester would quickly and readily be reduced to the alcohol upon addition of zinc acetate and phenylsilane. This would then have a detrimental effect on the final yield and purity. This is because some of the reduced alcohol would be carried through the acid base

workup and further purification by column chromatography would have to be carried out. It was found during this process that the Rf for the amine was very similar to that of the reduced alcohol. As such column chromatography was very difficult and mixed fractions resulted in much depressed yields. Further reductions to yields occurred in the acid bas workup. It was found that a thick emulsion would form during this process and as such some product would be lost during this process. The combination of these two issues seen throughout the scope are responsible for the lower yields seen for some substrates. With further optimisation of both the amidation and work up procedures, this chemistry could be a powerful tool in amine synthesis.



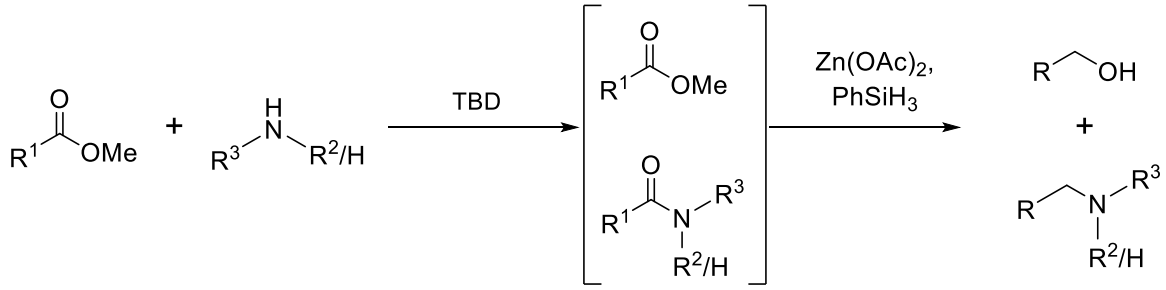
*No chromatographic purification needed

Table 4 - secondary substrates for reductive amination reaction – conditions: TBD 30 mol%, xylenes, reflux, 24 hours. $PhSiH_3$ 3 equivs, benzoic acid (50 mol%), $Zn(OAc)_2$ 10 mol%,6 hour.

The yields of secondary amine products were slightly lower than that of the tertiary products, similar to what was found previously observed in the Denton group for this type of chemistry. This is theorised to be caused by reduced nucleophilicity of the primary amines when compared to the secondary

amines. However, all attempted successfully produced the desired products in high conversion. Similar to the tertiary substrate scope, I started by using simple benzylamine and reacting it with a range of different methyl esters, starting with heterocyclic esters, including electron rich aromatic methyl esters (**49**, **50** and **52**) and a range of different amines. A number of reducible functional groups were also tolerated, aryl halides (**36**, **47** and **48**) and an example of a methyl ester alternative to a carboxylic acid that would readily decarboxylate (**51**). As displayed by compounds **53** and **54** methoxy and acetal groups are also tolerated under this type of chemistry, this is an advantageous over previous work in this area [48] as acetal groups could not be tolerated under acidic conditions. Compounds **53** and **54** also highlight the potential of this methodology as it gives access to novel compounds which provide further reactions sites for important reactions such as for cross coupling and aromatic substitutions.

A persistent problem for all reactions was if full conversion didn't occur, any remaining ester would be readily reduced to the alcohol (Scheme 30) which was difficult to remove in the acid base work up. Therefore, column chromatography was required which would further reduce the yield of this reaction.



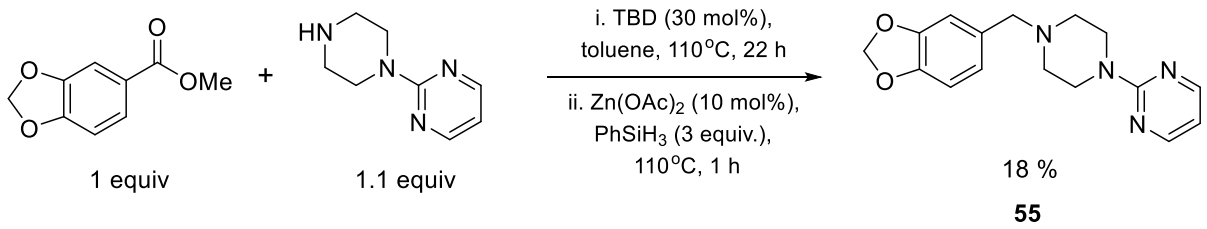
Scheme 30 – Reduction of methyl ester to alcohol

An interesting observation made was that it appeared that when full conversion from the ester to the amide occurred and the reduction was carried out the solution would no longer turn black/grey it would appear pale yellow. This seemed to indicate almost full conversion to the amide and therefore much better final yields as no purification was needed after the acid base work up.

Active pharmaceutical ingredient synthesis

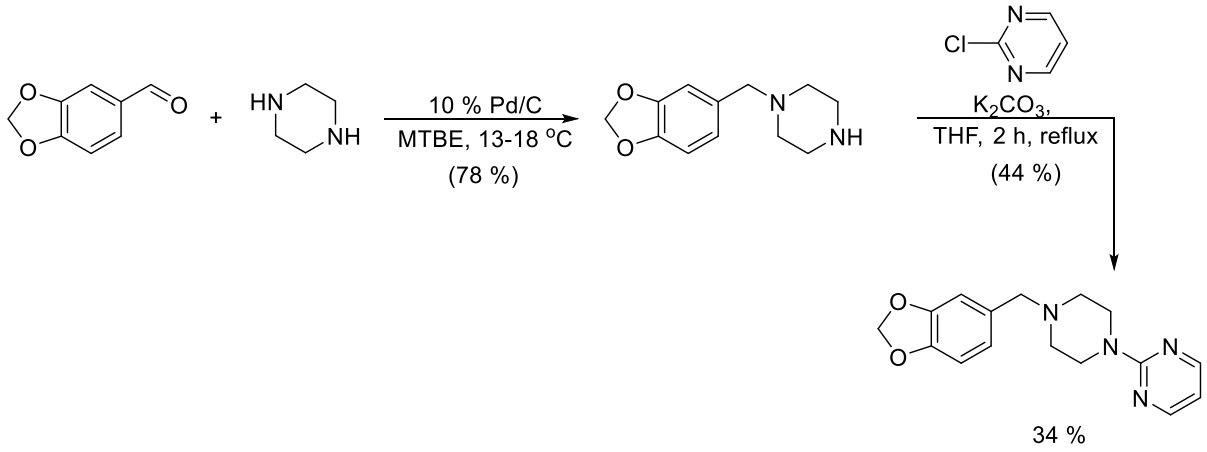
It is important for all chemistry to demonstrate applicability to everyday life, a key area in which this project shows potential is through the synthesis of pharmaceuticals. Towards the end of the project, I attempted to produce two pharmaceutical targets using this chemistry. The first reaction attempted

was the synthesis of Piribedil (55) (Scheme 31), which is a treatment for Parkinson's (D2 and D3 receptor agonist).



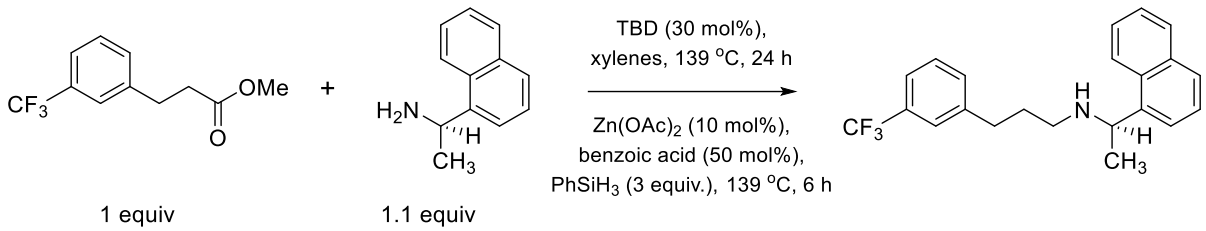
Scheme 31 – Reaction scheme for the synthesis of piribedil

Current industrial methods for the synthesis of Piribedil is through a reductive amination of piperonly aldehyde and piperazine, and a subsequent SNAr with the heterocycle (scheme 32). This is a two-step process which achieves a 34 % yield over two step and requires purification by column chromatography. [49] Although this chemistry so far has a lower yield to that currently being used in industry, additional optimisation and improved purification would radically improve this synthesis.



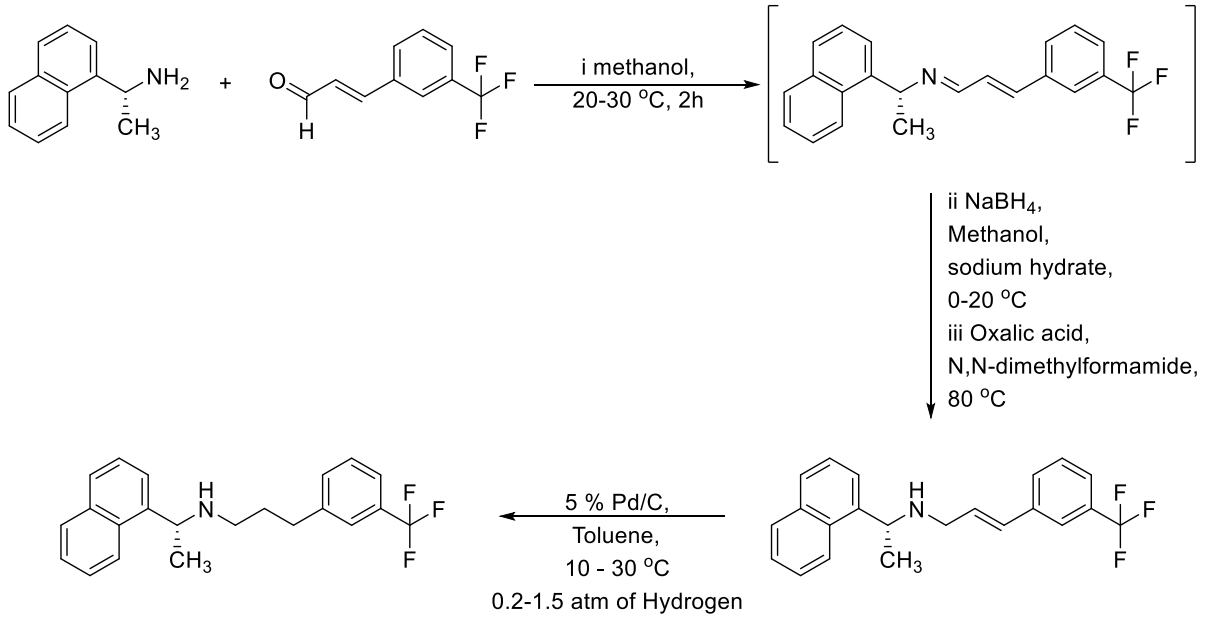
Scheme 32 – Current industrial method for synthesis of Piribedil

I also attempted a secondary pharmaceutical target Cinacalcet (Scheme 33), a drug used for the treatment of thyroid conditions Although the product was detected using HRMS the work up and purification was challenging and unfortunately full analysis couldn't be achieved. This low yield is hardly surprising it is known that an increase in sterics around either of the starting materials has a detrimental impact on the yield, therefore it is suspected that this yield is down to issues with the amidation step.



Scheme 33 - Reaction scheme for the synthesis of Cinacalcet

Current industrial methods use 3-[3-(trifluoromethyl)phenyl]propenaldehyde and the corresponding amine and is achieved through reductive amination using $NaBH_4$. A further reduction of the remaining double bond achieves Cinacalcet in a 66 % yield over the two steps[50] (Scheme 34). Again, these yields are higher than those reported here, however with further optimisation I believe this chemistry could compete with these existing methods.



Scheme 34 - Current industrial method for synthesis of Cinacalcet

The results from the pharmaceutical targets of this research project, though resulting in poor yields highlights the potential of this one pot two step reaction. Both reactions were successful in producing the desired product and could then be isolated, therefore with more focused optimisation this chemistry could provide a new simple non harmful route to these types of important pharmaceutical compounds.

Conclusion

I have coupled together a known TBD mediated amidation of methyl esters and a phenylsilane and zinc acetate reductive process of the resulting amide, to achieve a full reductive amination process of methyl esters in conventional glassware.

I monitored the reaction of both tertiary and secondary amide formation and then proceeded to optimise both reactions to 99 % and 71 % respectively. This was achieved through raising the temperature of the reaction while also increasing the catalyst loading to 30 mol%. As the reductive process is already known, conditions were taken from Denton's paper and this was successful in reducing any amide formed.

A scope was also demonstrated for both tertiary and secondary amine products, including potentially reduceable functional groups, electron rich and poor aromatics and products containing groups for further reaction sites, most with high to moderate yields and some with excellent yields. In addition, I was able to demonstrate novel compounds and use starting materials that would otherwise be unstable for current reductive amination processes.

I have also highlighted real world application of this chemistry in the synthesis of Piribedil and Cinacalet under standard conditions. Although these yields were not as high as those currently being used in industry, I am aware that this chemistry has this potential with further optimisation.

This chemistry while offering an inexpensive and non-toxic route to amines, also allows for synthesis and isolation of important novel compounds.

Future work

To continue the work from this project it, would be of interest to further develop the substate scope, looking into sterics and functional group tolerance. To successfully expand upon the substrate scope further optimisation would be needed on both types of reactions, initially into catalyst loading and then into the time required for each reaction, in addition to the work up procedure. From the positive results in this report, it would also be of interest to attempt the use of other esters rather than only methyl esters. Another potential area to investigate would be an intermolecular cyclisation reaction.

As seen above this chemistry shows a lot of promise in the area of pharmaceuticals. With additional optimisation this one-pot reaction could open up a new and powerful route to these important everyday compounds.

Another area that was investigated initially, was to achieve reductive amination using sulfonamides and methyl esters. I attempted a number of different pathways and were unsuccessful at this time, however, work is ongoing in the Denton group to achieve this goal.

Experimental

General details

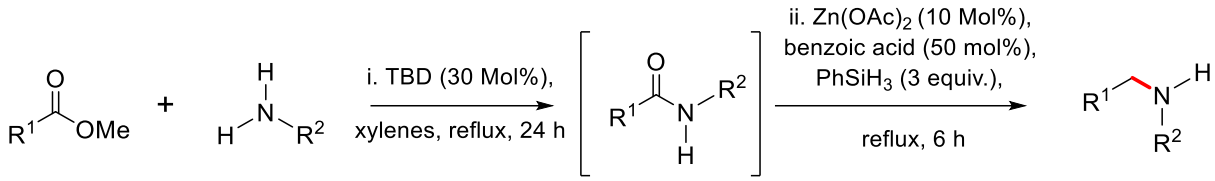
Unless stated, all reactions were carried out in standard glassware which was oven dried at 125 ^{o}C and placed under an argon balloon atmosphere. All reagents were purchased from reputable suppliers and used without any further purification, with the exception of toluene and xylenes which were collected from solvent towers and stored with sodium wire and molecular sieves respectively. All water used was deionised before use.

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

^{1}H, ^{13}C and ^{19}F NMR were recorded on either Bruker AV(III)400HD or Bruker AV(III)500HD in the deuterated solvent $CDCl_3$ and their chemical shifts (δ) given in parts per milliom (ppm) relative to residual solvent peaks. All coupling constants (*J*) are given in Hz. ^{1}H NMR signals are described using the abbreviations: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, p = pentet, m = multiplet.

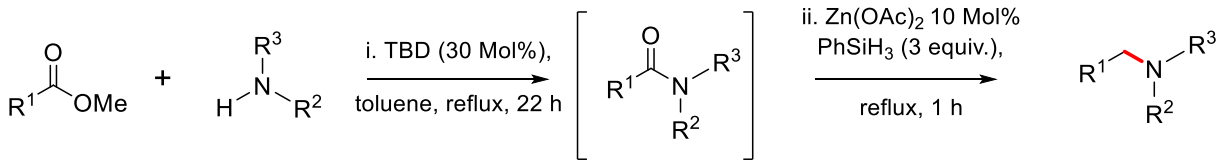
General procedures

General Procedure 1 – Secondary amine synthesis



To a solution of ester (1.00 mmol) and amine (1.10 mmol) in xylenes (5.00 mL) was added TBD (41.7 mg, 30 mol%) and the reaction mixture was heated at 139°C. After 24 hours, $Zn(OAc)_2$ (18.3 mg, 10 mol%) and benzoic acid (61.0 mg, 50 mol%) was added followed by dropwise addition of phenylsilane (370 µL, 3.00 mmol). Following a further 6 hours at 139°C, the reaction mixture was cooled to room temperature and quenched with acetic acid (1.00 mL of 3.00 M aqueous solution), added dropwise. The solution was then diluted using EtOAc (10 0 mL). The product was then extracted using acetic acid (3 x 10.0 mL of 3 M of aqueous solution). The aqueous washings were combined and adjusted to a pH of 12 using NaOH (6.00 M aqueous solution), and the product reextracted using CH_2Cl_2 (3 x 10.0 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The product was then purified using column chromatography as necessary.

General procedure 2 - Tertiary amine synthesis

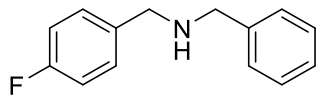


To a solution of ester (1.00 mmol) and amine (1.10 mmol) in toluene (5.00 mL) was added TBD (41.7 mg, 30 mol%) and the reaction mixture was heated at 110°C. After 22 hours, $Zn(OAc)_2$ (18.3 mg, 10 mol%) was added followed by dropwise addition of phenylsilane (370 µL, 3.00 mmol). Following a further 1 hours at 110°C, the reaction mixture was cooled to room temperature and quenched with

HCl (1.00 mL of 3.00 M aqueous solution), added dropwise. The solution was then diluted using EtOAc (10.0 mL). The product was then extracted using HCl (3 x 10.0 mL of 3.00 M of aqueous solution). The aqueous washings were combined and adjusted to a pH of 12 using NaOH (6.00 M aqueous solution), and the product reextracted using CH_2Cl_2 (3 x 10.0 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The product was then purified using column chromatography as necessary.

Substrate scope

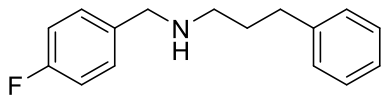
N-benzyl-1-(4-fluorophenyl)methanamine (36)



Prepared using general procedure 1 – Using methyl 4-fluorobenzoate (129 µL, 1.00 mmol) and benzylamine (120 µL, 1.10 mmol). The crude product was then purified using flash column chromatography (3:7 EtOAc:Pentane, R_f 0.20) to generate a pale yellow oil of the above compound (85 mg,0.39 mmol, 40%)

IR (ATR) vmax/cm^{-1} 3063, 3028, 2919, 1818, 1601, 1507, 1453, 1218, 1154; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 4.4 Hz, 4H), 7.35 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.32 – 7.28 (m, 1H), 7.04 (t, *J* = 8.5 Hz, 2H), 3.83 (s, 2H), 3.81 (s, 2H), 1.65 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1(d, *J* = 244.0 Hz), 140.2 (s), 136.0(d, *J* = 3.0 Hz), 129.6(d, *J* = 7.7 Hz), 128.4, 128.1, 127.0, 115.2, 53.1, 52.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.08; **MS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{15}NF^+$ 216.1183 found at 216.1180.[59]

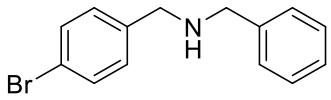
N-(4-fluorobenzyl)-3-phenylpropan-1-amine (47)



Prepared using general procedure 1 – Using methyl 4-fluorobenzoate (129 µL, 1.00 mmol) and 3-phenylpropan-1-amine (156 µL, 1.10 mmol) The crude product was then purified using flash column chromatography (1:9 ammonium hydroxide:methanol): 95 % DCM, R_f 0.20) to generate a pale yellow oil of the above compound (96 mg, 0.40 mmol, 40 %).

IR (ATR) vmax/cm^{-1} 2929, 2856,1602,1508, 1453, 1219; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.18 (m, 7H), 7.11 – 6.97 (m, 2H), 3.76 (s, 2H), 2.72 – 2.64 (m, 4H), 1.86 (p, *J* = 7.6 Hz, 2H), 1.79 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.1, 160.7, 142.1, 136.1, 129.6, 128.3, 125.1, 115.2, 53.2, 48.8, 33.6, 31.6; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.08; **MS** [ESI (M + H^+)] m/z calculated for $C_{16}H_{19}NF^+$ 244.1496 found at 244.1495.[61]

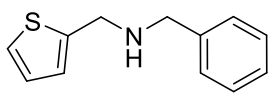
N-benzyl-1-(4-bromophenyl)methanamine (48)



Prepared using general procedure 1 – Using methyl 4-bromobenzoate (215 mg, 1.00 mmol) and benzylamine (120 µL, 1.10 mmol). The crude product was then purified using flash column chromatography (3:7 EtOAc:Pentane, R_f 0.20) to generate a pale yellow oil of the above compound (118 mg, 0.43 mmol 40 %).

IR (ATR) vmax/cm^{-1} 3027, 2823, 1486, 1452, 1264; 1103 1069, 1027; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.34 (m, 4H), 7.33 – 7.28 (m, 1H), 7.24 (d, *J* = 8.3 Hz, 2H), 3.82 (s, 2H), 3.78 (s, 2H), 1.72 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.1, 139.3, 131.4, 129.8, 128.4, 128.1, 127.0, 120.7, 53.1, 52.4; **MS** [ESI (M + H^+)] m/z calculated for $C_{14}H_{15}NBr^+$ 276.0382 found at 276.0374. [41]

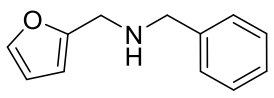
N-benzyl-1-(thiophen-2-yl)methanamine (49)



Prepared using general procedure 1 – Using methyl thiophene-2-carboxylate (117 mg, 1.00 mmol) and benzylamine (120 µL, 1.10 mmol). The crude product was then purified using flash column chromatography (3:7 EtOAc:Pentane, R_f 0.20) to generate a yellow oil of the above compound (60 mg, 0.29 mmol 30 %).

IR (ATR) vmax/cm^{-1} 3062, 3025, 2916, 2825, 1494, 1452, 1359, 1330, 1075; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 4H), 7.26 (d, *J* = 1.3 Hz, 1H), 7.25 (d, *J* = 1.3 Hz, 1H), 7.01 – 6.97 (m, 1H), 6.97 – 6.95 (m, 1H), 4.03 (s, 2H), 3.87 (s, 2H), 1.72 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.2, 140.0, 128.4, 128.2, 127.0, 126.6, 124.9, 124.4, 52.8, 47.6; **MS** [ESI (M + H^+)] m/z calculated for $C_{12}H_{14}NS^+$ 204.0841, found at 204.0838. [59]

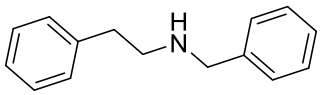
N-benzyl-1-(furan-2-yl)methanamine (50)



Prepared using general procedure 1 – Using methyl furan-2-carboxylate (107 µL, 1.00 mmol) and benzylamine (120 µL, 1.10 mmol). to generate a yellow oil of the above compound (0.151 mg, 0.80 mmol 81 %).

IR (ATR) vmax/cm^{-1} 2921, 2829, 1495, 1453, 1145; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.35 (d, *J* = 4.4 Hz, 4H), 7.30 – 7.26 (m, 1H), 6.35 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.21 (d, *J* = 3.3 Hz, 1H), 3.82 (s, 4H), 1.64 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.8, 142.7, 139.9, 129.2, 128.2, 127.0, 110.5, 107.7, 52.8, 45.4; **MS** [ESI (M + H^+)] m/z calculated for $C_{12}H_{14}NO^+$ 188.1070 found at 188.1071.[60]

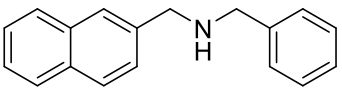
N-benzyl-2-phenylethan-1-amine (51)



Prepared using general procedure 1 – Using methyl 2-phenylacetate (141 µL, 1.00 mmol) and benzylamine (120 µL, 1.10 mmol) to generate a yellow oil of the above compound (0.123 mg, 0.58 mmol 58 %).

IR (ATR) vmax/cm^{-1} 2925, 2817, 1602, 1494, 1452; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.20 (m, 10H), 3.83 (s, 2H), 2.97 – 2.91 (m, 2H), 2.89 – 2.82 (m, 2H), 1.61 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.0, 128.7,128.4, 128.4, 128.1, 126.9, 126.1, 53.8, 50.5, 35.7; **MS** [ESI (M + H^+)] m/z calculated for $C_{15}H_{18}N^+$ 212.1434 found at 212.1436.[62]

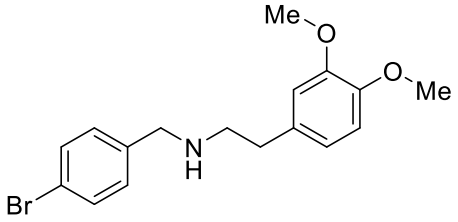
N-benzyl-1-(naphthalen-2-yl)methanamine (52)



Prepared using general procedure 1 – Using methyl naphthoate (186 mg, 1.00 mmol) and benzylamine (120 µL, 1.10 mmol). The crude product was then purified using flash column chromatography (3:7 EtOAc:Pentane, R_f 0.20) to generate a colourless oil of the above compound (57 mg, 0.23 mmol 23 %).

IR (ATR) vmax/cm^{-1} 3054, 3024, 2816, 1600, 1507, 1494, 1452, 1329, 1124, 1103, 1027; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 3H), 7.81 (s, 1H), 7.53 – 7.47 (m, 3H), 7.41 – 7.36 (m, 4H), 7.32 – 7.26 (m, 1H), 4.01 (s, 2H), 3.88 (s, 2H), 1.67 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.3, 137.8, 133.4, 132.7, 128.4, 128.2, 128.1, 127.7, 127.6, 127.0, 126.6, 126.5, 126.0, 125.5, 53.2, 53.2; **MS** [ESI (M + H^+)] m/z calculated for $C_{18}H_{18}N^+$ 248.1434, found at 248.1438.[63]

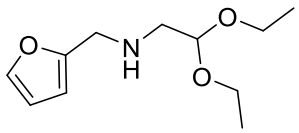
N-(4-bromobenzyl)-2-(3,4-dimethoxyphenyl)ethan-1-amine (53)



Prepared using general procedure 1 – Using methyl 4-bromobenzoate (215 mg, 1.00 mmol) and 2-(3,4-dimethoxyphenyl)ethan-1-amine (186 µL, 1.10 mmol) to generate a yellow oil of the above compound (270 mg, 0.77 mmol, 77 %).

IR (ATR) vmax/cm^{-1} 2997,2932, 1513, 1461,1258; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.83 – 6.72 (m, 3H), 3.87 (d, *J* = 1.1 Hz, 6H), 3.76 (s, 2H), 2.87 (t, *J* = 1.2 Hz, 2H), 2.78 (t, *J* = 5.6 Hz, 2H), 1.68 (s, 1H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.9, 147.4, 139.3, 132.4, 131.4, 129.7, 120.6, 120.6, 112.0, 111.9, 111.3, 55.9, 55.8, 53.1, 50.4, 35.9; **MS** [ESI (M + H$^+$)] m/z calculated for $C_{17}H_{21}BrNO_2^+$,350.0750 found at 350.0740

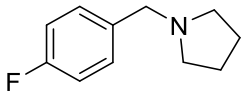
2,2-diethoxy-N-(furan-2-ylmethyl)ethan-1-amine (54)



Prepared using general procedure 1 – Using methyl furan-2-carboxylate (107 mg, 1.00 mmol) and 2,2-diethoxyethan-1-amine (160 µL, 1.10 mmol) to generate a pale yellow oil of the above compound (58 mg,0.27 mmol,28 %)

IR (ATR) vmax/cm^{-1} 2974, 2928, 1651, 1453, 1119, 1057; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.20 (d, *J* = 3.0 Hz, 1H), 4.61 (t, *J* = 5.6 Hz, 1H), 3.82 (s, 2H), 3.71 (dq, *J* = 9.4, 7.1 Hz, 2H), 3.55 (dq, *J* = 9.4, 7.0 Hz, 2H), 2.76 (d, *J* = 5.6 Hz, 2H), 1.61 (s, 1H), 1.23 (t, *J* = 7.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.7, 141.8, 110.0, 106.9 102.2, 62.4, 51.3, 46.1, 15.4; **MS** [ESI (M + H$^+$)] m/z calculated for $C_{11}H_{20}NO_3^+$ 214.1438, found at 214.1444

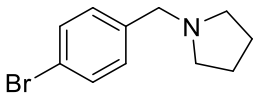
1-(4-fluorobenzyl)pyrrolidine (34)



Prepared using general procedure 2 – Using methyl-4-fluorobenzoate (129µL, 1.00 mmol) and pyrrolidine (92µL, 1.10 mmol) to generate a Pale yellow oil of the above compound (136 mg, 0.76 mmol,76 %).

IR (ATR) vmax/cm^{-1} 2960, 2927, 2779, 1602, 1460, 1153; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.01 (t, *J* = 9.0 Hz, 2H), 3.60 (s, 2H), 2.55 – 2.47 (m, 4H), 1.80 (p, *J* = 3.3 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.9 (d, *J* = 244.7 Hz), 135.0, 130.3 (d, *J* = 7.7 Hz), 114.9 (d, *J* = 21.2 Hz), 59.9, 54.1, 23.4; **^{19}F NMR** (376 MHz, $CDCl_3$) δ -116.27; **MS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{15}NF^+$ 180.1183 found at 180.1184. [51]

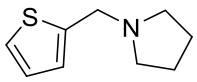
1-(4-bromobenzyl)pyrrolidine (37)



Prepared using general procedure 2 – Using methyl-4-bromobenzoate (0.215 mg, 1.00 mmol) and pyrrolidine (92µL, 1.10 mmol) to generate a colourless oil of the above compound (220 mg, 0.92 mmol,92 %).

IR (ATR) vmax/cm^{-1} 2962, 2784, 1486; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.41 (m, 2H), 7.27 – 7.19 (m, 2H), 3.58 (s, 2H), 2.54 – 2.48 (m, 4H), 1.85 – 1.77 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.5, 131.3, 130.5, 120.6, 60.1, 54.1, 23.4; **MS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{15}NBr^+$ 240.0382 found at 240.0382. [41]

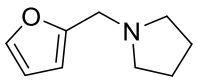
1-(thiophen-2-ylmethyl)pyrrolidine (38)



Prepared using general procedure 2 – Using methyl-thiophene-2-carboxylate (117µL, 1.00 mmol) and pyrrolidine (92µL, 1.10 mmol) to generate a Colourless oil of the above compound (100 mg, 0.60 mmol, 60 %).

IR (ATR) νmax/cm^{-1} 3069,2963, 2780,1375, 1164, 1123, 940; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 4.8, 1.4 Hz, 1H), 6.97 – 6.93 (m, 2H), 3.85 (s, 2H), 2.63 – 2.54 (m, 4H), 1.89 – 1.75 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.7, 126.3, 125.4, 124.6, 54.6, 53.9, 23.5.; **MS** [ESI (M + H$^+$)] m/z calculated for $C_9H_{14}NS^+$ 168.0841, found at 168.0851.[52]

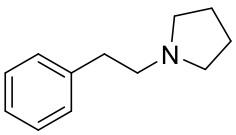
1-(furan-2-ylmethyl)pyrrolidine (43)



Prepared using general procedure 2 – Using methyl-furan-2-carboxylate (107µL, 1.00 mmol) and pyrrolidine (92µL, 1.10 mmol) to generate a Colourless oil of the above compound (89 mg, 0.59 mmol, 59 %)

IR (ATR) νmax/cm^{-1} 2963, 2784, 1648, 1504, 1459, 1131, 1012, 914; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 1.8 Hz, 1H), 6.33 – 6.31 (m, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 3.65 (s, 2H), 2.61 – 2.51 (m, 4H), 1.85 – 1.77 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.0, 141.8, 110.0, 107.5, 53.9, 52.0, 23.4; **MS** [ESI (M + H$^+$)] m/z calculated for $C_9H_{14}NO^+$ 152.1070, found at 152.1073. [51]

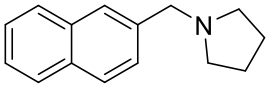
1-phenethylpyrrolidine(41)



Prepared using general procedure 2 – Using methyl 2-phenylacetate (142µL, 1.00 mmol) and pyrrolidine (92µL, 1.10 mmol) to generate a Colourless oil of the above compound (69 mg, 0.39 mmol, 40 %)

IR (ATR) vmax/cm^{-1} 3080, 3026, 2783, 1635, 1453, 1378, 1121, 1079; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 2.92 – 2.83 (m, 2H), 2.78 – 2.67 (m, 2H), 2.65 – 2.56 (m, 4H), 1.83 (p, *J* = 3.1 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.4, 128.6, 128.3, 126.0, 58.3, 54.2, 35.4, 23.4; **MS** [ESI (M + H^+)] m/z calculated for $C_{12}H_{18}N^+$ 176.1434, found at 176.1430.[53]

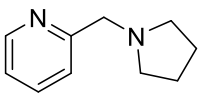
1-(naphthalen-2-ylmethyl)pyrrolidine(39)



Prepared using general procedure 2 – Using methyl 2-naphthoate (186 mg, 1.00 mmol) and pyrrolidine (92µL, 1.10 mmol) to generate a Colourless oil of the above compound (152 mg, 0.72 mmol, 72 %)

IR (ATR) vmax/cm^{-1} 3052, 2961, 2783, 1508, 1346, 1123, 1031; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 – 7.80 (m, 4H), 7.80 – 7.77 (m, 1H), 7.55 – 7.42 (m, 2H), 3.81 (s, 2H), 2.66 – 2.53 (m, 4H), 1.83 (p, *J* = 3.7 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.0, 133.4, 132.6, 127.6, 127.4, 127.2, 125.8, 125.4, 60.9, 54.2, 23.4; **MS** [ESI (M + H^+)] m/z calculated for $C_{15}H_{18}N^+$ 212.1434, found at 212.1436. [54]

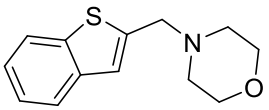
2-(pyrrolidin-1-ylmethyl)pyridine(40)



Prepared using general procedure 2 – Using methyl picolinate (121 µL, 1.00 mmol) and pyrrolidine (92 µL, 1.10 mmol) to generate a yellow oil of the above compound (126 mg, 0.78 mmol, 78%).

IR (ATR) νmax/cm^{-}1 3009,2962, 2790,1587, 1460, 1431, 1326, 1123; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.5 Hz, 1H), 7.64 (td, *J* = 7.7, 1.9 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.17 – 7.10 (m, 1H), 3.77 (s, 2H), 2.62 – 2.52 (m, 4H), 1.85 – 1.75 (m, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.1, 148.9, 135.1, 122.8, 121.2, 62.1, 55.5, 24.4; **MS** [ESI (M + H^+)] m/z calculated for $C_{10}H_{14}N_2$ 163.2360, found at 163.123. [55]

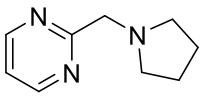
4-(benzo[b]thiophen-2-ylmethyl)morpholine(44)



Prepared using general procedure 2 – Using methyl benzo[*b*]thiophene-2-carboxylate (192 mg, 1.00 mmol) and morpholine (93 µL, 1.10 mmol) The crude product was then purified using flash column chromatography (1:9 EtOAc:Pentane, R_f 0.10) to generate a yellow solid of the above compound (135 mg, 0.58 mmol, 58%) (m.p. 80 ^{o}C).

IR (ATR) νmax/cm^{-1} 2971, 2855, 2799, 1434, 1109, 1005; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 7.0 Hz, 1H), 7.48 – 7.34 (m, 2H), 7.26 (s, 1H), 3.89 (d, *J* = 1.1 Hz, 2H), 3.84 (t, *J* = 4.7 Hz, 4H), 2.65 (t, *J* = 3.7 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.9, 140.1, 139.6, 124.1, 123.9, 123.1, 122.3, 122.3, 67.0, 58.3, 53.5; **MS** [ESI (M + H^+)] m/z calculated for C_{13} H_{16} NOS^+ 234.0947, found at 234.0942. [56]

2-(pyrrolidin-1-ylmethyl)pyrimidine(45)

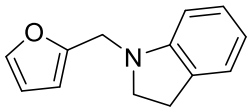


Prepared using general procedure 2 – Using methyl pyrimidine-2-carboxylate (138 mg, 1.00 mmol), and pyrrolidine (92 µL, 1.10 mmol) to generate a yellow oil of the above compound (12 mg, 0.07 mmol, 7 %).

IR (ATR) νmax/cm^{-1} 2958, 2925, 2798, 1658, 1562, 1419, 1123, 1034; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.0 Hz, 2H), 7.19 (t, *J* = 4.9 Hz, 1H), 3.95 (s, 2H), 2.74 – 2.61 (m, 4H), 1.91 – 1.76 (m, 4H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.4, 119.2, 62.8, 54.4, 22.6; **MS** [ESI (M + H^+)] m/z calculated for $C_9H_{13}N_3^+$ 164.1182, found at 164.1184. [55]

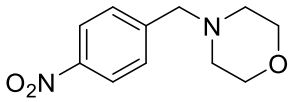
1-(furan-2-ylmethyl)indoline(46)



Prepared using general procedure 2 – Using methyl furan-2-carboxylate (107 µL, 1.00 mmol), and indoline (123 µL, 1.10 mmol) The crude product was then purified using flash column chromatography (1 % EtOAc in Pentane, R_f 0.10) to generate a yellow solid of the above compound (8 mg, 0.04 mmol,4 %).

IR (ATR) vmax/cm^{-1} 2922, 2846, 1606, 1486, 1251, 1145, 1006; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.38 (m, 1H), 7.10 (t, *J* = 7.2 Hz, 2H), 6.71 (t, *J* = 7.0 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.34 (q, *J* = 3.3 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 4.28 (s, 2H), 3.38 (t, *J* = 8.3 Hz, 2H), 2.98 (t, *J* = 8.1 Hz, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.7, 142.0, 130.2, 127.2, 124.5, 118.0, 110.2, 107.9, 107.5, 53.4, 46.0, 28.5; **MS** [ESI (M + H^+)] m/z calculated for $C_{13}H_{13}NO^+$ 200.1072, found at 200.1069.

4-(4-nitrobenzyl)morpholine(42)

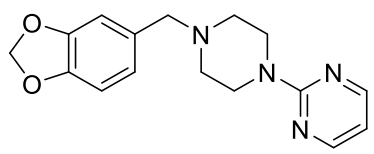


Prepared using general procedure 2 – Using methyl 4-nitrobenzoate (181 mg, 1.00 mmol), and morpholine (93 µL, 1.10 mmol) The crude product was then purified using flash column chromatography (4:6 EtOAc:Pentane, R_f 0.20) to generate a bright yellow oil of the above compound (125 mg, 0.56 mmol,56 %).

IR (ATR) vmax/cm^{-1} 2924, 2853, 2807, 1603, 1517, 1341, 1114, 1008; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 3.75 (t, *J* = 4.7 Hz, 4H), 3.61 (s, 2H), 2.48 (t, *J* = 4.6 Hz, 4H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 129.5, 123.5, 66.5, 62.5, 53.6; **MS** [ESI (M + H^+)] m/z calculated for $C_{11}H_{15}N_2O_3^+$ 223.1077, found at 223.1076. [57]

Piribedil(55)



Prepared using general procedure 2 – Using methyl piperonylate (180 mg, 1.00 mmol), and 1-(2-pyrimidyl)piperazine (156 µL, 1.10 mmol) The crude product was then purified using flash column chromatography (3:7 EtOAc:Pentane, R_f 0.10) to generate an off White solid (54 mg,0.18 mmol,18 %) (m.p. 95 °C).

IR (ATR) νmax/cm^{-1} 2927, 2857, 1579, 1480, 1443; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 4.7 Hz, 2H), 6.91 (t, *J* = 1.0 Hz, 1H), 6.78 (s, 2H), 6.48 (t, *J* = 4.7 Hz, 1H), 5.97 (s, 2H), 3.83 (t, *J* = 5.1 Hz, 4H), 3.47 (s, 2H), 2.50 (t, *J* = 5.2 Hz, 4H); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.6, 157.7, 147.6, 146.6, 131.8, 122.6, 109.7, 109.5, 107.9, 100.9, 62.9, 52.8, 43.7; **MS** [ESI (M + H^+)] m/z calculated for $C_{16}H_{19}N_4O_2^+$ 299.1503, found at 299.1501.[58]

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