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Novel Approaches to Catalytic Acyl Transfer Reactions

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Novel Approaches to Catalytic Acyl Transfer Reactions

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Contents

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Abbreviations

°C	Degrees Centigrade
Å	Angstrom
Act	Activated
BEMP	2-*tert*butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-phosphorine
Bn	Benzyl
***n*Bu**	Butyl
^{13}C NMR	Carbon 13 Nuclear magnetic resonance
cat.	Catalyst
CDCl$_3$	Deuterated chloroform
conv.	Conversion
Cp	Cyclopentadienyl
DABCO	1,4-Diazabicylco[2.2.2]octane
DBN	1,5-Diabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsufoxide
DTBP	Di-*tert*-butyl peroxide
e.e.	Enantiomeric excess
Equiv.	Equivalents
EtOH	Ethanol
G	Gram
^{1}H NMR	Proton Nuclear Magnetic resonance
h	Hour
HOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium hexafluorophosphate
Hz	Hertz
J	Coupling constant

M	Molar
MeCN	Acetonitrile
MeOH	Methanol
MHz	Megahertz
Min	Minute
mg	Milligram
mL	Millilitre
mmol	Millimole
MS	Molecular sieves
Nuc.	Nucleophile
OAc	Acetate
pTSA	*para*-toluene sulfonic acid
PhMe	Toluene
PPh$_3$	Triphenylphosphine
Ppm	Parts per million
R	Unspecified generic group
Rac	Racemic
r.t	Room temperature
s	Seconds
TCT	2,4,6-trichloro[1,3,5]triazine
TBD	1,5,7-Trazabicyclo[4.4.0]dec-5-ene
tert	Tertiary
Tf	Triflate
THF	Tetrahydrofuran
TOTT	*S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium tetrafluoroborate

Abstract

This thesis describes work carried out over the past 3 years towards the development of novel catalytic methods for acyl transfer reactions.

Chapter 1 presents the current industrial and literature methods of forming amide bonds from carboxylic acids and amines. The use of coupling agents and activators is explained in addition to the development of catalytic methods including homogeneous (transition metal, p-block, and non-metals) and heterogeneous methods. Following this, results are presented on improving a previously established catalytic system for the direct coupling of carboxylic acids and amines using zirconocene dichloride. Three methods of achieving this were explored, firstly by addition of a nucleophilic additive, secondly by utilising a more active zirconium catalyst and finally by removing water from the system.

Chapter 2 builds on the material presented in Chapter 1, by exploring the use of alternative acyl donors in the formation of amide bonds. It details the use of esters, carbamates, ureas and amides in amide bond formation and transamidation reactions. The zirconocene dichloride system is then applied to these alternative acyl donors to form amides from esters and substituted ureas from carbamates.

Chapter 3 focusses on the formation of primary amides from carboxylic acids. Recent literature methods towards the synthesis of primary amides are first described, followed by a novel catalytic methodology for the formation of primary amides from carboxylic acids with urea as an ammonia source.

Chapter 4 then provides details of all experimental procedures and characterisation of the compounds that were synthesised.

Chapter 1: Amide Bond Formation from Carboxylic Acids and Amines

B. N. Atkinson, A. R. Chhatwal, D. P. van der Waals, J. W. Walton, J. M. J. Williams

Amide bond formation from carboxylic acids

Amide bonds are one of the most important functionalities in natural and synthetic chemistry. They are crucial components in a number of pharmaceuticals, agrochemicals, natural products and functional materials. Some examples of these include Lipitor (Atorvastatin), Fentanyl anaesthetic, Metolachlor, capsaicin and nylon (Figure 1). They are also found within biological systems as the peptide bonds found in proteins, rendering them essential for life.
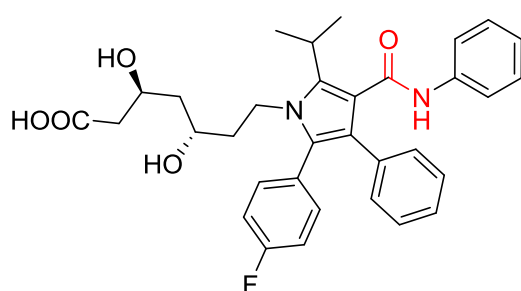
Atorvastatin
Anti-cholesterol treatment
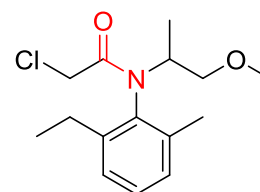
Metolachlor
Herbicide
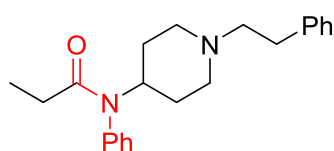
Fentanyl
Anaesthetic
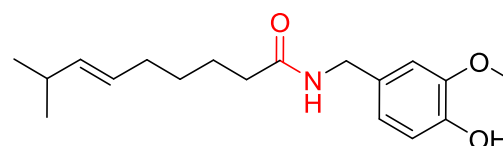
Capsaicin
Active component of chilli peppers
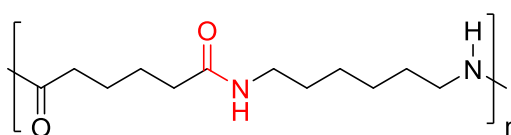
Nylon 6,6
Functional material

Figure 1.01: Examples of amide containing products

The importance of this chemical moiety is further exemplified by a recent survey which found that of all known pharmaceuticals, 25% of them contain at least one amide bond.[1] In 2007, the ACS Green Chemistry Institute

highlighted 'amide formation avoiding poor atom economy reagents' as the top challenge in organic chemistry.[2]

The thermal (uncatalysed) formation of amides

Although amide bonds can be synthesised from a variety of starting compounds, including acid chlorides, aldehydes, nitriles and alcohols, the most direct method of forming these bonds is *via* the condensation of carboxylic acids and amines. The sole by-product of this reaction being water makes this reaction both clean and atom efficient.

The uncatalysed synthesis of amide bonds is most easily accomplished by coupling an acid chloride and an amine together. This reaction is formally known as the Schotten–Baumann reaction after the scientists that discovered it in 1883 (Scheme 1.01).[3],[4]

Scheme 1.01: Schotten–Baumann formation of amide bonds from acid chlorides and amines

The direct coupling of carboxylic acids and amines is somewhat difficult to achieve in the absence of a catalyst or coupling agent. Although the resulting amide bond is thermodynamically stable, a large activation energy is required in order to carry out the thermal dehydration. The formation of ammonium and carboxylate salts prevents this direct coupling from occurring. These salts only collapse to form the amide product at high temperatures (in excess of 160 °C).[5]

An early discovery in 1989 by Cossy and co-workers details the thermal formation of amides in the presence of molecular sieves at high temperatures (140 °C) typically after two hours.[6] Since this discovery, further investigations have suggested that the temperature of this reaction could be decreased if the water is removed from the reaction *via* azeotropic reflux.[7] This work was enhanced by one of the more recent developments in

this area. Investigations by Williams and co-workers in 2012, showed that the use of non-polar, aprotic solvents disfavoured formation of the respective ammonium and carboxylate salts. This enabled a wide range of amides to be synthesised in 22 hours at 110 °C, with the only by-product being water (Scheme 1.02).[8]
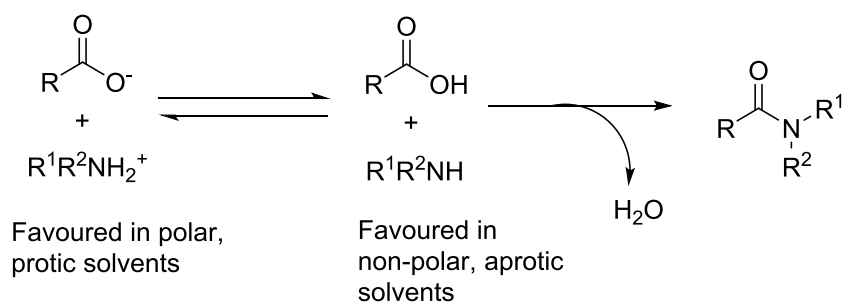
Scheme 1.02: Eliminating salt formation by the use of non-polar solvents

Alternative studies by Whiting *et al.* suggest that the salt is able to form in non-polar, aprotic solvents such as toluene (Scheme 1.03), however these solvents facilitate the formation of a hydrogen bond stabilised carboxylic acid dimer **1.01**. Nucleophilic attack of an amine on this dimer then results in transition state **1.02** whereby the second carboxylic acid acts as a proton acceptor. This concerted step results in the transfer of a proton from the amine to the acid and the release of the second acid molecule. The subsequent formation of species **1.03** allows the loss of water, avoiding the formation of the salts.[9]

1.01 + R^1-NH$_2$ ⇌ 1.02

-H$_2$O

1.03
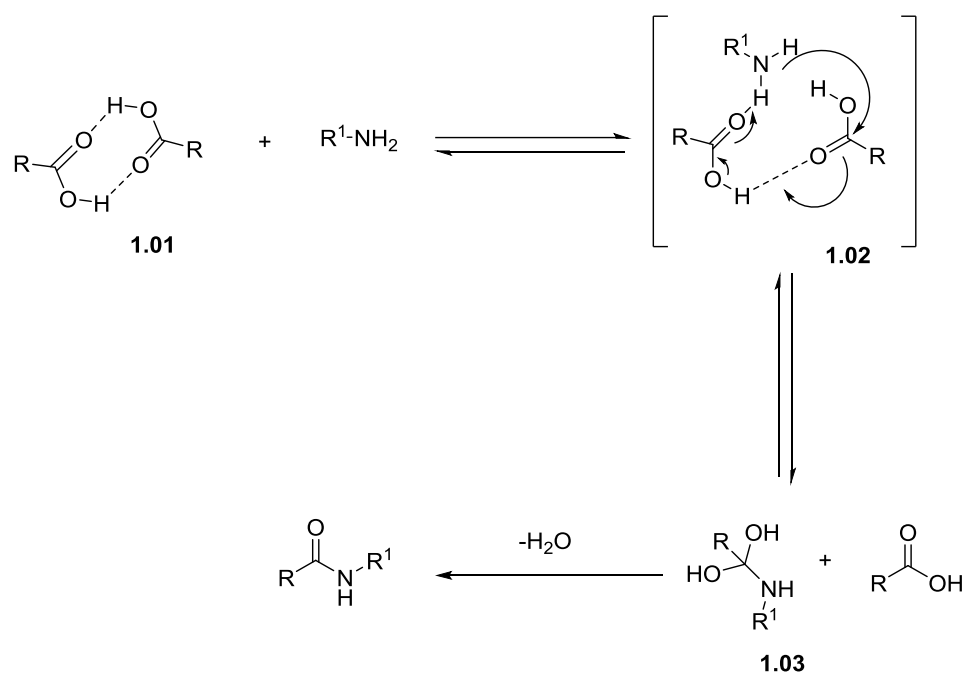
Scheme 1.03: Mechanism of direct amide bond formation from acids and amines via a hydrogen bonded active complex

Amide bond formation from carboxylic acids using activating/coupling agents

This is the method often carried out within industry, due to its reliability and high yielding product. These methods involve the use of an activating agent to form an activated carboxylic acid (1.04). This species is then more susceptible to nucleophilic attack by an amine to form the desired amide (Scheme 1.04).

1.04
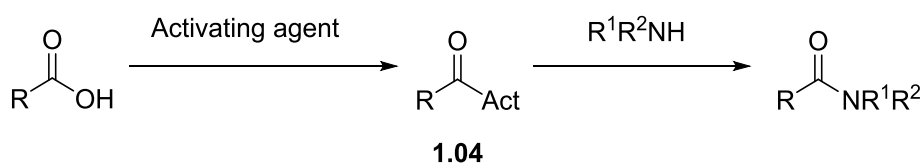
Scheme 1.04: Coupling agent activation of a carboxylic acid

One of the most commonly used coupling agents is DCC (*N,N*-dicyclohexylcarbodiimide). Since its discovery in 1955, the use of DCC has escalated and is now used in numerous industries including the manufacture of polyester and resilient materials. The pathway taken by DCC in amide formation and the side products formed is outlined in Scheme 1.05.
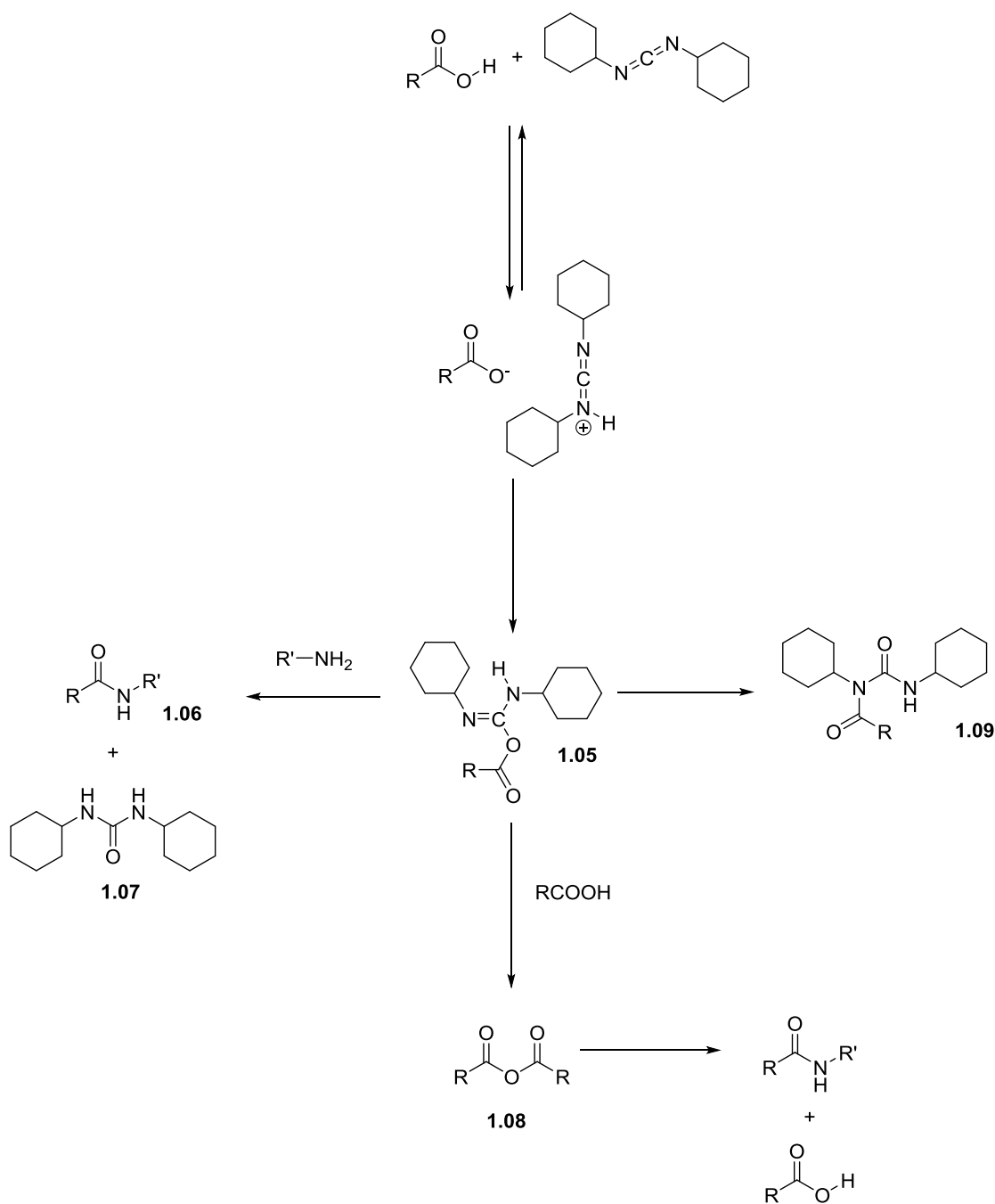
Scheme 1.05: DCC as a coupling agent for amide formation from carboxylic acids

The initial step involves the activation of the carboxylic acid with DCC to form
O-acylisourea (**1.05**). This species can then react in one of three different
pathways. Firstly *O*-acylisourea can react directly with the amine to yield the
desired amide product 1.06 and a symmetrical urea by-product **1.07**.
Alternatively, reaction with a second molecule of carboxylic acid can also
occur, yielding the carbonic anhydride **1.08**. This species is then able to react
with the amine to form the desired amide product. However, the final

pathway is an O to N acyl transfer, forming the *N*-acylurea side product **1.09**. Despite two of the three possible pathways ending in the formation of the required amide, this process is still highly inefficient with a large quantity of waste product being generated. In addition to the mentioned by-products, if the carboxylic acid contains other functionalities such as carbamate or urea groups, more by-products can form, rendering this process substrate dependent.[10]

Additives can be used to limit the formation of the unwanted by-products. The most commonly employed additives are the benzotriazole class of compounds. The two main additives (Figure 1.02) are 1-hydroxy-1-H-benzotriazole (HOBt) and 1-hydroxy-7-azabenzotriazole (HOAt).

1-Hydroxy-1-H benzotriazole   1-Hydroxy-7-azabenzotriazole

Figure 1.02: HOBt and HOAt additives

These additives are believed to reduce the levels of epimerisation in the peptide coupling reactions by preventing formation of the oxazolone by-product. In the absence of an additive oxazolone formation can occur as shown in Scheme 1.06.
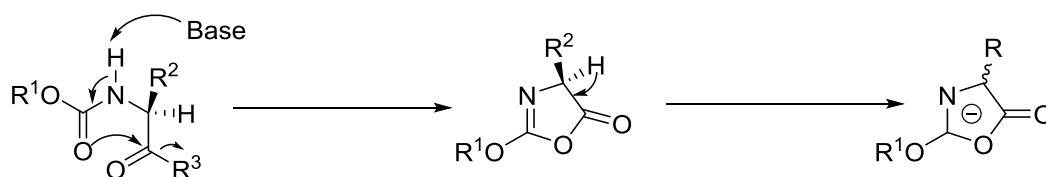
Scheme 1.06: Oxazolone formation leading to epimerisation in peptide synthesis

In the presence of HOBt and HOAt the transformation in Scheme 1.06 cannot occur. The mechanisms of HOBt and HOAt are thought to occur as shown in Scheme 1.07. HOBt firstly reacts with the *O*-acylisourea species to form the OBt active ester (**1.10**). Nucleophilic attack by the amine can then occur (**1.11**).[11]
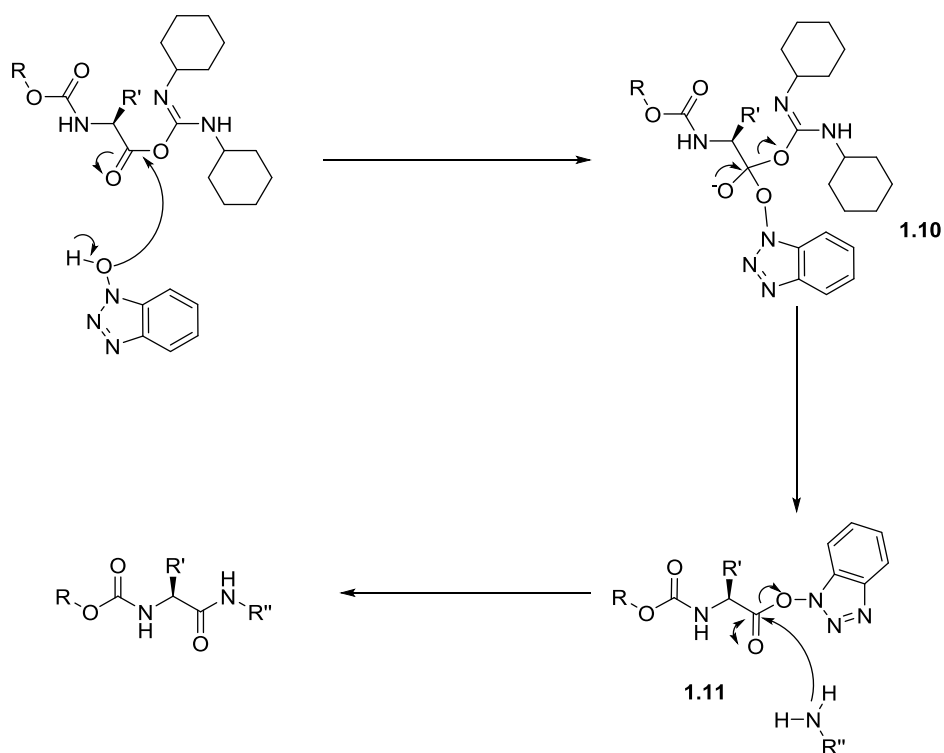
Scheme 1.07: HOBt additive mechanism of amide bond formation when used with DCC

Catalysed amide bond formation from carboxylic acids and amines

As a result of the inefficiency and waste generation produced by the use of coupling agents within industry, many efforts have been focussed on developing catalytic methods of forming amide bonds. These methods aim to be atom efficient, with the generation of minimal waste and the use of cheap and readily available catalysts.

Homogeneous Catalysis

Transition metals

The metal catalysed synthesis of amides from carboxylic acids is largely unexplored where major developments have taken place in non-metal catalysed methods.[12]

The use of transition metal catalysts in the coupling of carboxylic acids and amines has generated great interest in recent years. One of the first examples of transition metals being used in this direct coupling reaction was by Hosseini–Savari and Sharghi in their publication displaying the

N-formylation of amines using formic acid and with zinc oxide as a catalyst (Scheme 1.08). This catalyst was required in a high loading of 50 mol% at 70 °C, under solvent free conditions. The recovery and reusability of the catalyst was also noted, with a decrease in activity being recorded only after the third cycle.[13] Studies building on these discoveries, investigated the use of some metal dichloride complexes. Rao and co-workers demonstrated that zinc dichloride ($ZnCl_2$) was the most active of the salts screened. Under the same conditions that ZnO was most active, the catalyst loading could be reduced to 10 mol% for $ZnCl_2$, although the recovery and reuse of the catalyst was not reported in this case.[14]
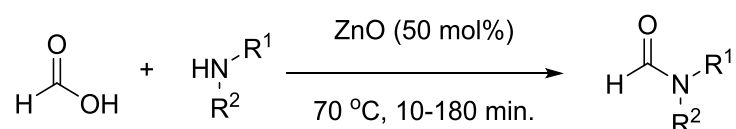
Scheme 1.08: Zinc oxide catalysed formation of formamides from formic acid and amines

Group IV metal catalysts have shown great potential in catalysing this coupling. Titanium(IV) isopropoxide, ($Ti(O^iPr)_4$, [15] zirconium tetrachloride ($ZrCl_4$)[16] and zirconocene dichloride (Cp_2ZrCl_2),[8] have all shown the ability to catalyse the reaction between non-activated carboxylic acids and amines. With the a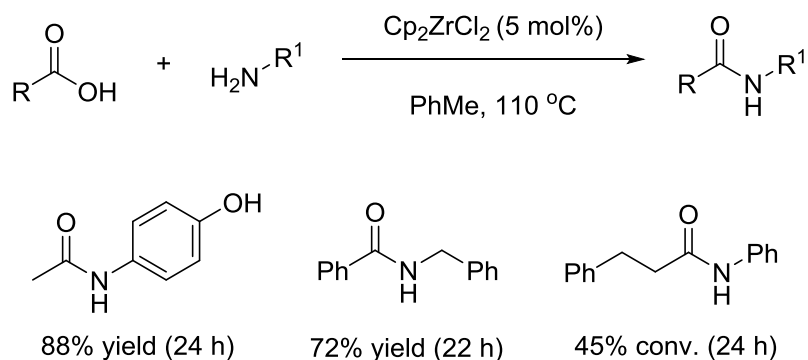ddition of 5 mol% Cp_2ZrCl_2, reaction times could be reduced from 22 hours to only four hours. In the case of more challenging substrates, such as anilinic amines, 45% conversion was seen, where in the absence of the catalyst no reaction occurred (Scheme 1.09).


88% yield (24 h)   72% yield (22 h)   45% conv. (24 h)

Scheme 1.09: Amide bond formation from non-activated carboxylic acids and amines catalysed by Zirconocene dichloride

Despite this catalyst running at reduced times with a cleaner reaction (only water being produced), high reaction temperatures of 110 °C were still needed. In the case of the titanium based catalyst, 10 mol% catalyst loading was needed and 24 hours was required for all investigated substrates. The final example, reported by Adolfsson and co-workers, using $ZrCl_4$, also required up to 10 mol% catalyst loading but lower temperatures of 70 °C in THF were compatible. For these reactions, an excess of amine and molecular sieves were required in order for the reaction to reach completion.[16]

Recent discoveries have included the use of copper triflate ($Cu(OTf)_2$) for coupling carboxylic acids and formamides together. This system also required two equivalents of di-*tert*-butyl peroxide (DTBP) as an oxidant and temperatures of 130 °C. A range of benzoic acid derivatives was successfully coupled to DMF in high yields, however lower yields were obtained on altering the formamide.[17]

p-Block metal catalysts

A report in 1991 highlighted that 5 mol% of the antimony reagent triphenylstibine oxide (Ph_3SbO), when used in conjunction with 20 mol% P_4S_{10}, was able to acylate amines. It was found that the reaction proceeded through a thiocarboxylic acid intermediate that was generated *in situ* (Scheme 1.10).[18]
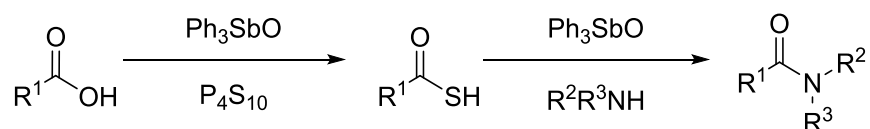
Scheme 1.10: Formation of amides from carboxylic acids via a thiocarboxylic acid intermediate

A method for the *N*-formylation of amines with formic acid has been developed using indium (10 mol%) as a catalyst (Scheme 1.11) Formic acid was coupled with a wide variety of amines under solvent free conditions although three equivalents of formic acid were required. A relatively low

reaction temperature of 70 °C was sufficient for the majority of the substrates and in some cases high yields were obtained in only 1.5 hours.
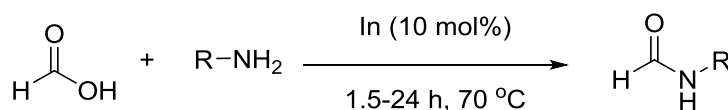
Scheme 1.11: Indium catalysed *N*-formylation of amines with formic acid

Other p-block catalysts include triarylbismuthanes, which can carry out the transformations within 12 hours. However, the reaction conditions are not as mild as some of the more recent studies as the reaction must be heated at reflux in benzene in order to achieve the best conversions. Various carboxylic acids were investigated, it was found that some hindered substrates were not compatible with this methodology.[19]

Non-metal catalysed methods

Initial approaches to coupling carboxylic acids and amines involved the use of boric and boronic acids. These methods are widely documented and are attractive on a large scale as the catalysts are required in low loadings and are cheap and readily available.

Boric acid (Figure 1.03, 1.12) itself was considered as a possible catalyst for amide coupling by Tang and co-workers in 2005. It was found that 4-phenylbutyric acid and benzylamine could be coupled together on the addition of 5 mol% boric acid in heptane at 100 °C. However, more challenging substrates, including less nucleophilic amines, required higher catalyst loadings of 25 mol%. This protocol was applied to the synthesis of amides on a larger scale where only 1 mol% boric acid was needed and the desired amide was isolated in 91% yield after 16 hours (Scheme 1.12).[20]
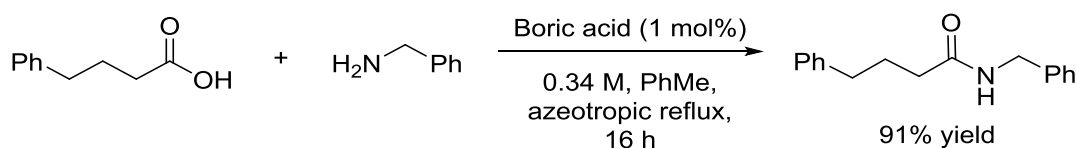
Scheme 1.12: Large scale synthesis of amides using boric acid as a catalyst
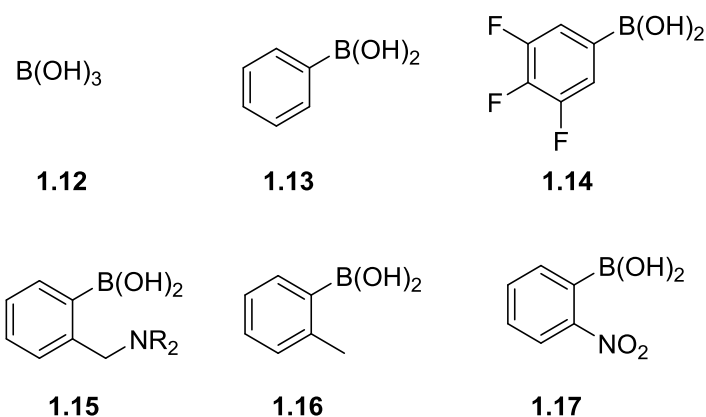
Figure 1.03: Boric and boronic acid catalysts

There have been numerous investigations into the application of boronic acids as catalysts for this transformation. One of the first examples of boronic acids as catalysts for this direct coupling reaction was in 1991 carried out by Yamamoto and co-workers. This particular system used 3,4,5-trifluoroarylboronic acid (Figure 1.03, **1.14**) to synthesise a range of secondary and tertiary amides in high yields. Temperatures between 110-150 °C were necessary in addition to the presence of molecular sieves. These reactions were carried out for 18 hours in the presence of 1 mol% catalyst. The authors outlined a possible reaction mechanism (Scheme 1.13). In many cases arylboronic acids contain varying amounts of boroxines (**1.18**). Either reaction of the boronic acid or boroxine with the carboxylic acid leads to formation of (acyloxy)boronic acid **1.19**. Subsequent reaction of species 1.19 with an amine leads to the formation of the amide product **1.20** and reformation of the boronic acid catalyst **1.21**.[21]
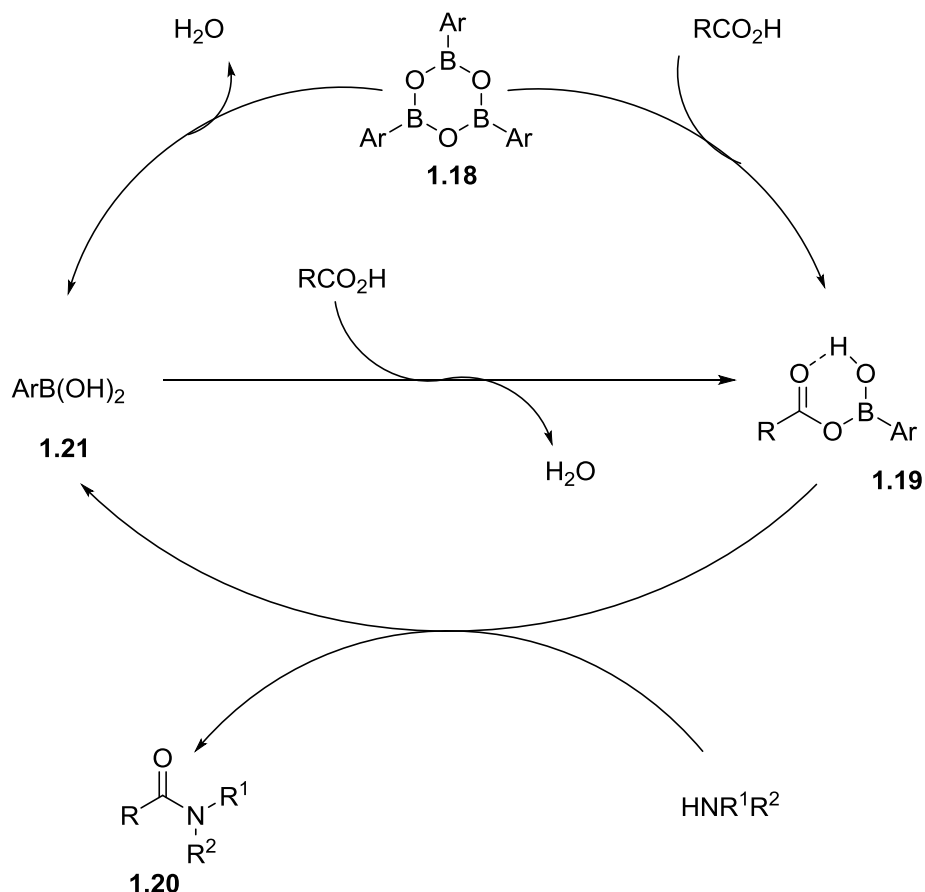
Scheme 1.13: Mechanism of boronic acid catalysed amide formation

Several developments have been reported with different boronic acid derivatives and milder reaction conditions.[22] *ortho* Functionalised boronic acids were investigated by Hall and co-workers. A system employing *ortho*-bromo or *ortho*-iodo phenylboronic acids as catalysts was developed, where only 10 mol% catalyst was needed and mild temperatures of 25 °C could be used to synthesise a range of amide products.[5] Other significant studies were carried out by Whiting and co-workers. Numerous boronic acid catalysts were developed, including *N,N*-di*iso*propylbenzylamineboronic acid.[23] Further to this, the synthesis of dipeptides was also investigated using the catalysts shown in Figure 1.03. This was achieved with limited success, with low conversions being obtained when 25 mol% catalyst was used. On using one equivalent of the catalyst conversions ranging between 50% and 60% could be achieved.[24]

Bifunctional boronic acids, developed by Whiting and co-workers, have shown potential in the kinetic resolution of amines to produce chiral amides. (pS)-2-(2-Boronoferrocenyl)-N-n-butylbenzimidazole (Scheme 1.14) was identified as a suitable catalyst. 10 mol% catalyst in addition to long reaction times of 48 hours were required in order to achieve reasonable conversions, however even then low enantiomeric excesses of 41% were obtained.[25]
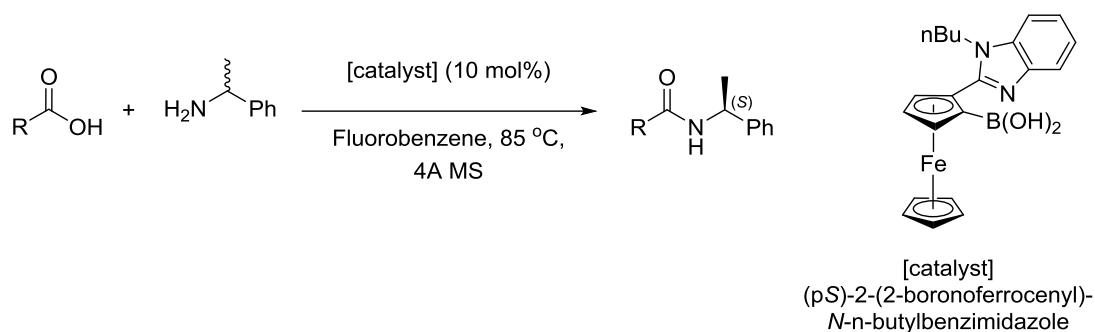
Scheme 1.14: The use of birfunctional boronic acid catalysts in the kinetic resolution of amines for chiral amide bond formation

More recently the use of borate esters has been documented in carboxylic acid and amine coupling reactions. These studies required the preparation of the tris-(2,2,2-trifluoroethyl)borate $(B(OCH_2CF_3)_3)$[26] activator from 2,2,2 trifluoroethanol and B_2O_3. Mild reaction conditions of 80 °C and 5 hours were required for effective coupling, however this was not a catalytic system as the borate ester was required in 2 equivalents. Nevertheless, an extensive reaction scope was studied with a wide variety of phenylacetamides being synthesised in high yields, including those made from primary and secondary amines containing varying functionalities. Anilinic amines however required slightly harsher reaction conditions due to the lower nucleophilicity. Limitations included lower yields when *tert*-butylamine was used and no coupling when adamantylamine was coupled to phenylacetic acid. However, *N*-benzylamides were produced in high yields from a variety of different carboxylic acids, although benzoic acids required more forcing reaction conditions. Gram scale syntheses were also possible obtaining moderate yields after purification (Scheme 1.15). This system produced amides in high yields after purification by solid phase work ups. Firstly Amberlyst acidic

and basic resins were required, followed by an Amberlite boron scavenger. Finally the crude reaction mixture was dried over magnesium sulfate to yield the desired amides.[27]
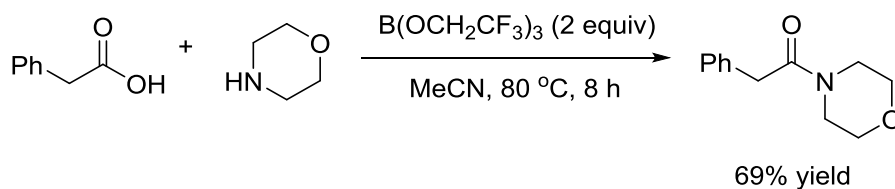
Scheme 1.15: Gram scale borate ester mediated direct amide bond formation

This methodology was also applied to transamidation reactions, although longer reaction times and higher reaction temperatures were necessary for this coupling (Scheme 1.16).
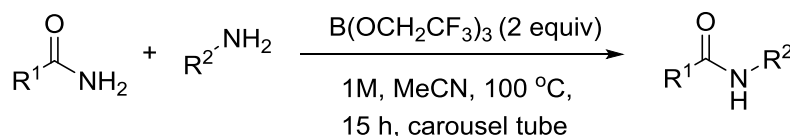
Scheme 1.16: Borate ester mediated transamidation

Other recent reports have proposed a PPh_3/CCl_4 mediated system for the direct formation of amides. Diethoxymethylsilane and bis(4-nitrophenyl)phosphate were also required for the *in situ* reduction of the triphenylphosphine oxide to triphenylphosphine. This system was applied to the coupling of challenging aromatic carboxylic acids to a variety of amines (Scheme 1.17). Under these conditions the more electrophilic carboxylic acids would undergo amide bond formation without the presence of a catalyst. These were isolated in moderate yields, although long reaction times of 20 hours were needed in addition to the relatively high triphenylphosphine catalyst loading of 25 mol% and two equivalents of carbon tetrachloride (Scheme 1.18).[28]
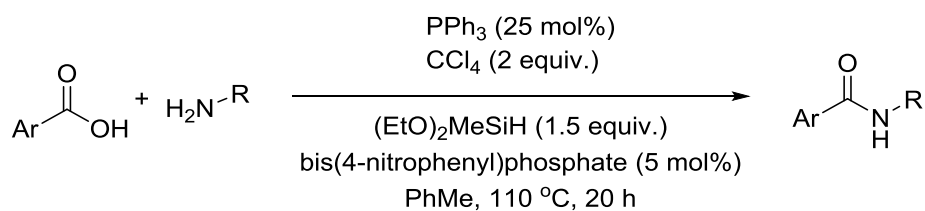
Scheme 1.17: PPh₃/CCl₄ mediated amide bond formation from aromatic carboxylic acids and amines
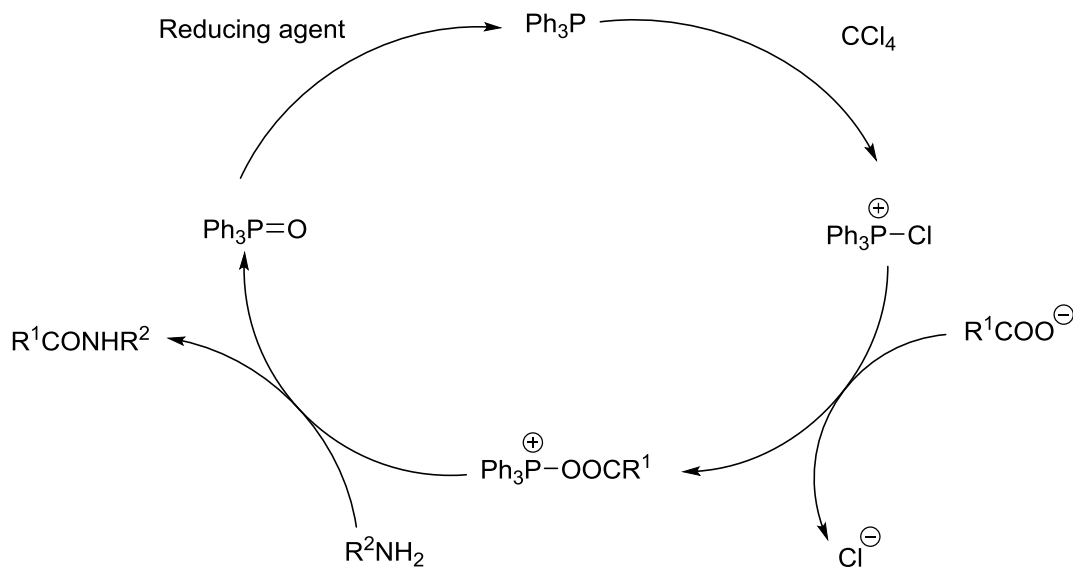
Scheme 1.18: Catalytic cycle of triphenylphosphine catalysed amidation of carboxylic acids

Heterogeneous catalysts

The use of heterogeneous catalysts has been an area of growing interest in recent years. They have become attractive alternatives for larger scale syntheses of amides as the catalyst can be easily recovered and reused. Some methods that have been developed involve the use of radiofrequency, sulfated tungstate, silica and activated alumina balls.

Radiofrequency was investigated for use in direct amide bond formation in 2013. This method involved the coupling of AC magnetic fields to radio frequency absorbing magnetic materials, in this case nickel ferrite nanoparticles. This coupling generated a large amount of heat locally (150-220 °C) within the chemical reactor resulting in a fast controllable chemical reaction. Multiple substrates were converted in fast reaction times

of 10 minutes with more robust substrates requiring slightly longer times of 20 minutes. This method was also applied to a larger 5 mmol scale synthesis yielding 90% product.[29]

Nano-catalysts have also been reported for use in this transformation. Magnesium oxide (MgO), as a Lewis base, has shown catalytic properties under solvent free conditions. With only 5 mol% catalyst for times as short as 10 minutes, high yields were obtained after purification by centrifugation. The catalyst was also recovered and reused up to 5 times.[30] A possible reaction pathway was suggested involving attack of the amine on the carbonyl, facilitated by the coordination of both species to the magnesium. Other studies, demonstrated the use of this catalyst in the synthesis of formamides from formic acid and amines which proceeded to completion in 1-2 minutes.[31]

Chaudhari *et al.* developed a method using sulfated tungstate as a reusable solid inorganic acid catalyst. This protocol used 7-18 wt% sulfated tungstate for 12-18 hours, with the reactions being carried out at azeotropic reflux in toluene, for the removal of the water. The catalyst was recovered up to 4 times without reducing the catalytic ability.[32] In addition to its application in this reaction, further reports were made demonstrating its potential as a transamidation catalyst.[33]

Silica and activated alumina balls have been reported as catalysts for the synthesis of amides. Initial investigations focused on the development of a silica (K60) catalysed system. This process required high temperatures of 700 °C to activate the K60 which was then needed in 10-20 wt% loadings for 24 hours. The catalyst was recovered and reused up to four times without reduction in turnover. It was suggested that the weak acidity and hydrophobicity of the silica presented an ideal environment for amide formation without forming the inactive ammonium salt of the amine.[34] Subsequent studies in 2012 revealed the catalytic activity of alumina balls in a similar system. These again required a high calcination temperature of 700 °C in order to be activated. However shorter reaction times of 3 hours under solvent free conditions with a reaction temperature of 140 °C were

sufficient for the synthesis of amides containing aliphatic and aromatic functionalities. In addition to the coupling of robust anilinic amines.[35]

Summary

The synthesis of amide bonds from unactivated carboxylic acids and amines has been an area of great interest to synthetic chemists. Numerous methods have been developed in order to combat some of the issues presented by the current industrial techniques which can be hazardous, expensive and wasteful. Both homogeneous and heterogeneous methods have been explored, with significant progress being made towards a hazard free and atom efficient method. However, several challenges still remain including developing systems that are high yielding at low temperatures, those with an extensive substrate scope including hindered substrates, those with mild reaction conditions to allow for chiral substrates and for the system to be efficient without the removal of the water by-product.[36]

Chapter 1: Results and Discussion 1

Amide Bond Formation From Carboxylic Acids and Amines

Previous work

Initial studies conducted within the Williams group focused on the thermal coupling of unactivated carboxylic acids and amines to form amides.[8] It was found that this reaction would proceed to completion at 110 °C in 24 hours, when run in a non-polar solvent such as toluene. Polar solvents proved to be unsuccessful as they are able to stabilise the ammonium and carboxylate salts that form. Toluene however is less able to stabilise these salts; therefore a coupling reaction takes place instead of an acid-base reaction (Scheme 1.19).
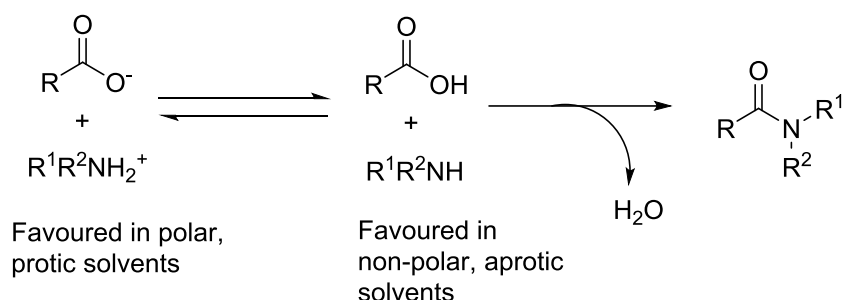
Scheme 1.19: Preventing the formation of salt by using non-polar solvents

Subsequent studies were focused on finding a catalytic method for carrying out this direct coupling reaction. A system employing zirconocene dichloride as a catalyst was developed and a variety of amides was synthesised using this method, however high temperatures of 110 °C or 150 °C were still required in addition to long reaction times for more challenging substrates (Scheme 1.20).[8]
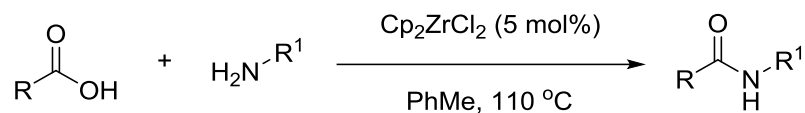
Scheme 1.20: Zirconocene dichloride catalysed amide bond formation

In conjunction with the work presented in this chapter, mechanistic studies were carried out on the acid and amine coupling reaction catalysed by zirconocene dichloride. These studies were conducted by Dr James Walton and they provide insight into how this catalyst functions and how the system could be improved. These studies were carried out using benzoic acid as the acid species and benzylamine as the amine species.
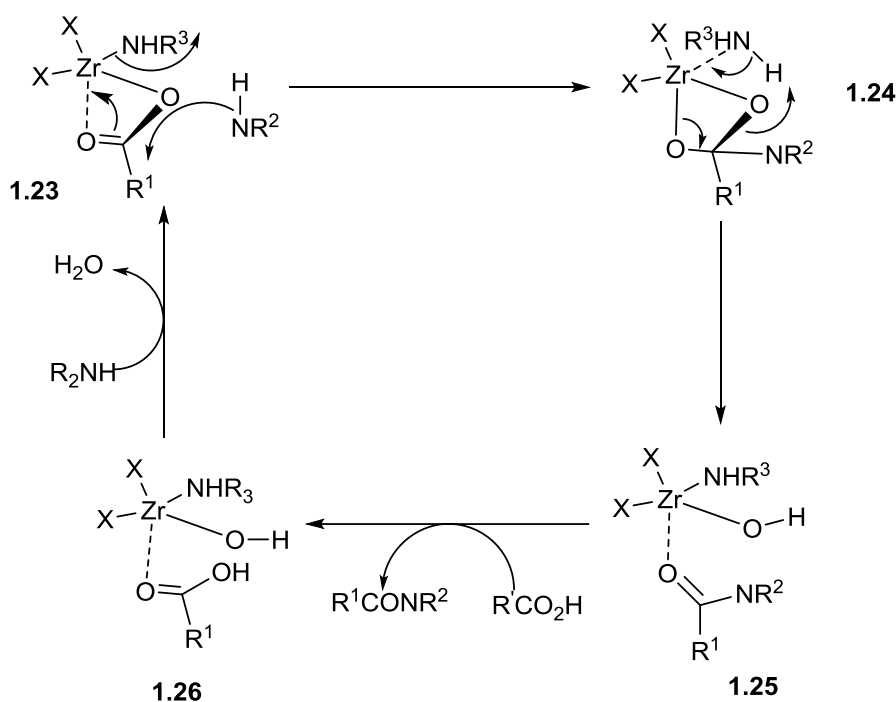
Figure 1.04: Proposed mechanism for the zirconocene dichloride catalysed coupling of carboxylic acids and amines.

It is proposed that the acid species binds to the zirconium catalyst with loss of chloride (Cl⁻). This was determined by analysis of the benzylammonium chloride (PhCH₂NH₃Cl) salt that is produced during the reaction. There is also ¹H NMR evidence of two different cyclopentadienyl (Cp) species being present. With one of these signals corresponding to an alternative Cp

species and the other to a possible Cp-Zr bound species. The active species is then able to deprotonate a non-bound amine molecule; this facilitates nucleophilic attack on the acid carbonyl. This is likely to be a concerted reaction and proceeds through a six-membered intermediate **1.24**. Consequently, proton transfer and elimination lead to the formation of intermediate **1.25**. This is then followed by exchange of the desired amide with another acid molecule. This step generates one equivalent of H_2O as a by-product, reforming the active catalytic species **1.26** (Figure 1.04).

Aims

The aim of this investigation was to develop an enhanced catalytic system for the formation of amides from non-activated carboxylic acids and amines. This enhanced system would allow for lower reaction temperatures, faster reaction times and the use of more unreactive substrates.
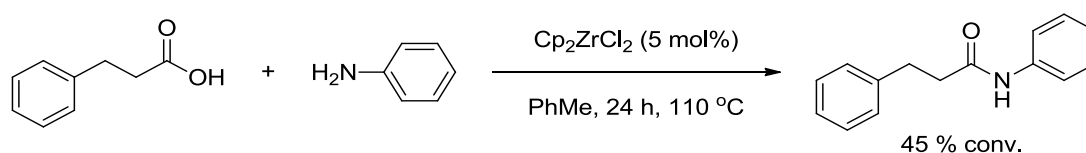
Previous studies of the zirconocene dichloride system highlighted limitations when using particularly robust substrates. These included benzoic acids and anilinic amines, which required long reaction times of 24 hours and high temperatures of 110 °C; even under these conditions low conversions were obtained (Scheme 1.21).[8]

**Scheme 1.21: Low conversions obtained with anilinic amines in the zirconium catalysed system**

Taking the mechanistic studies and these previous reaction limitations into account, three approaches were adopted in order to develop an enhanced and milder system.

1) Addition of nucleophilic catalysts and additives
2) More active zirconium complexes (commercially available and generated *in situ*)
3) Removal of water from the system

Nucleophilic additives

Our initial studies were focused on employing cheap, readily available and environmentally benign organocatalysts as additives to activate further the carbonyl oxygen to nucleophilic attack. It was envisaged that the nucleophile would attack the carbonyl, providing a stable leaving group, resulting in a fast second substitution on addition of an amine. It was also possible that these nucleophilic organocatalysts could catalyse this reaction without the need for a metal (Scheme 1.20). Thus, the possibility for a solely organocatalytic system was explored.
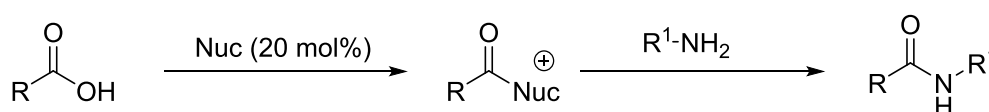
Scheme 1.20: Organocatalytic amide bond formation from carboxylic acids and amines

Preliminary investigations were carried out using 3-phenylpropionic acid and benzylamine, as they are cheap, commercially available and the products and reactants are easily identifiable by ^{1}H NMR. Initial screens were conducted with 20 mol% catalyst and the results are illustrated in Table 1.

Table 1: Nucleophilic catalyst screen
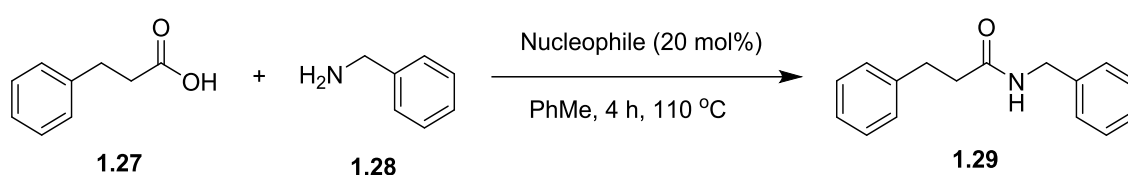
Entry	Nucleophilic catalyst	Conversion into 1.29 (%)
1	DMAP	29
2	4-Pyrrolidinopyridine	43
3	Pyridine	17
4	DBN	15
5	Imidazole	29

6	1-Methylimidazole	33
7	2-Methylimidazole	32
8	DABCO	30
9	Pyridine *N*-oxide	22
10	Picoline *N*-oxide	38
11	-	23

Conditions: 3-Phenylpropionic acid (1 mmol), benzylamine (1 mmol), nucleophilic catalyst (20 mol%), PhMe (1 mL), 110 °C, 4 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

The catalyst screen (Table 1) suggests that when using 20 mol% catalyst loading, in the specified time and at reflux, only moderate conversions can be obtained; DMAP, imidazole and DABCO (Table 1, entries 1, 5 and 8) resulted in only a marginal increase from the background conversion. The highest conversion achieved was 43% with 4-pyrrolidinopyridine as a catalyst (Table 1, entry 2).

These conversions were significantly lower than anticipated, as with only 5 mol% of the metal catalyst, this transformation proceeded to completion under these same conditions. With a background conversion of 23% (Table 1, entry 11), there was not a particular catalyst that appeared to increase the conversion significantly.

The stoichiometry of the system was then considered and the acid to amine ratio was altered to determine if this could increase the conversion. The reaction was run with DMAP and 4-pyrrolidinopyridine initially with excess amine and then with excess acid (Table 2).

Table 2: Determining the stoichiometry for the reaction

Entry	Catalyst	Conversion (%) 2 equiv. amine	Conversion (%) 2 equiv. acid
1	DMAP	46	45
2	4-Pyrrolidinopyridine	49	49
3	No catalyst	47	51

Based on these results it was decided that within this system the stoichiometry had no particular significance, except resulting in an increased background rate (Table 2, entry 3). Under these conditions, the background rate was too competitive, indicating that the presence of the catalyst was having little effect.

Our efforts were then turned to using these organocatalysts as additives in the already established zirconocene dichloride catalysed system.

Table 3: Nucleophilic additive screen
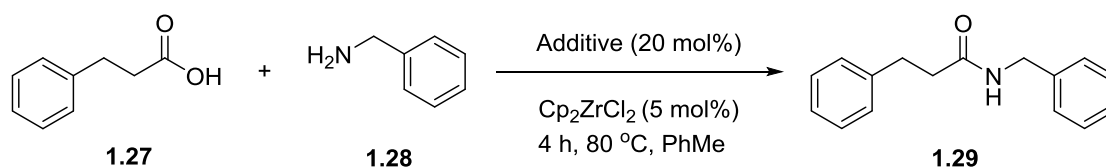
Entry	Additive	Conversion (%)
1	No catalyst	10
2	Just Cp$_2$ZrCl$_2$	30
3	DMAP	28
4	4-Pyrrolidinopyridine	10
5	Imidazole	31
6	DBU	8
7	DABCO	27
8	Phenylhydrazine	27

Conditions: 3-phenylpropionic acid (1 mmol), benzylamine (1 mmol), Cp$_2$ZrCl$_2$ (5 mol%), Additive (20 mol%), PhMe (1 mL), 80 °C, 4 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

The nucleophile screen (Table 3) was conducted at a lower temperature of 80 °C, reduced from the previously published temperature of 110 °C so that any positive effects of the additive could be observed. It is clear that none of these additives had a positive catalytic effect, with the majority of them reducing the conversion. This suggested that the nucleophilic additive was

retarding the reaction, possibly by binding to the catalyst in place of the acid or amine, preventing the reaction from occurring efficiently. It is also possible that these nucleophilic additives bound to the carboxylic acid preventing it from binding to the catalyst, as we have already seen that these additives have slight catalytic activity on their own.

At this point it was decided that as the additives were not effective at these reduced temperatures, a system using a higher temperature with an additive would not be significantly better than the metal catalysed system. Therefore other methods of improving this system were considered.

More active zirconium complexes

There are several zirconium based analogues that are available commercially, although these are considerably more expensive, they were screened in a shorter time frame to show any enhanced reactivity (Figure 1.05).
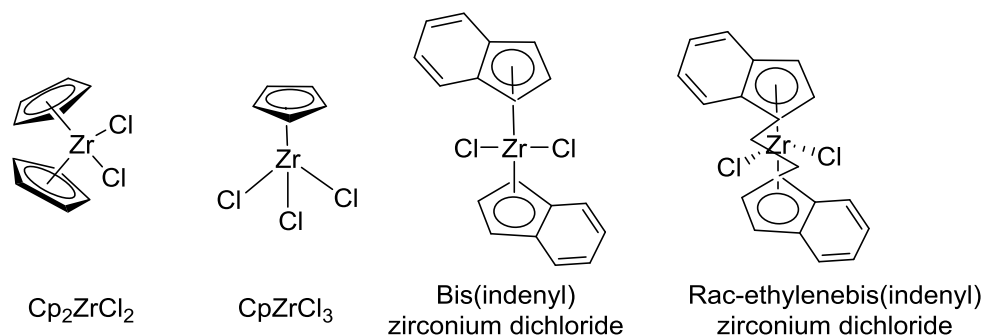
Figure 1.05: Alternative zirconium catalysts

Table 4: Alternative zirconium catalysts
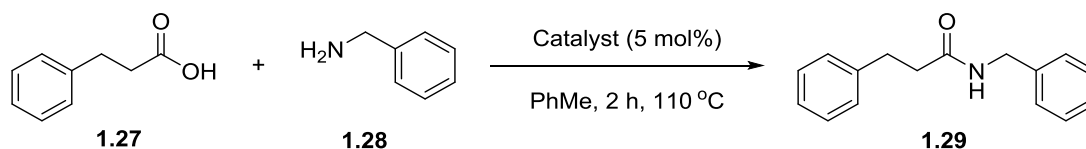
Entry	Catalyst	Conversion (%)
1[a]	Cp_2ZrCl_2	59
2	$CpZrCl_3$	27
3	Bis(indenyl) zirconium dichloride	58
4	*Rac*-ethylenebis(indenyl) zirconium dichloride	63

Conditions: 3-Phenylpropionic acid (1 mmol), benzylamine (1 mmol), catalyst (5 mol%), PhMe (1 mL), 110 °C, 2 h, (a) 1.5 h. Conversions were determined by analysis of the ^{1}H NMR spectra.

Despite the alternative electronic systems presented by these catalysts, little or no enhanced activity was seen. When CpZrCl$_3$ (Table 4, entry 2) was used, a significant decrease in the conversion was seen; thus suggesting that the presence of the second Cp ring is important. Bis(indenyl) zirconium dichloride and Rac-ethylenebis(indenyl) zirconium dichloride (Table 4, entries 3 and 4), both showed comparable conversions to zirconocene dichloride (Table 4, entry 1) under these conditions. However, these other catalysts are significantly more expensive and showed no increase in reactivity. Therefore no further investigations were carried out regarding these catalysts.

Further efforts were then focused on generating a more active zirconium species *in situ*. From postulated mechanistic studies it was suggested that dissociation of chloride ions was a key step, followed by chelation of the amine to the metal centre. In order to increase the rate of this step, several other ligands were investigated, in the hope that these may be able to dissociate at a faster rate.
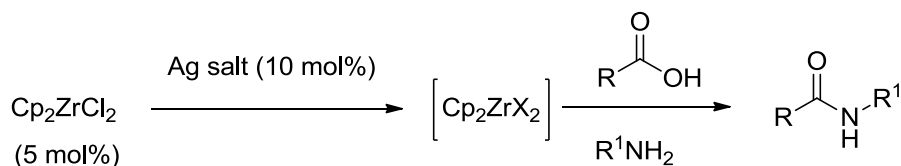
Scheme 1.21: The use of silver salts to generate a more active zirconium catalyst *in situ*

Previously published methodologies have suggested that silver salts are ideal candidates for carrying out halide abstraction as they form the very stable silver chloride precipitate which is a driving force for the reaction (Scheme 1.21).[37] In addition to this, silver salts have resulted in an improved reaction for some transamidation studies carried out within the group by Dr Ben Atkinson while using this same catalyst. Consequently, these were explored first.

Table 5: Silver salt additive screen
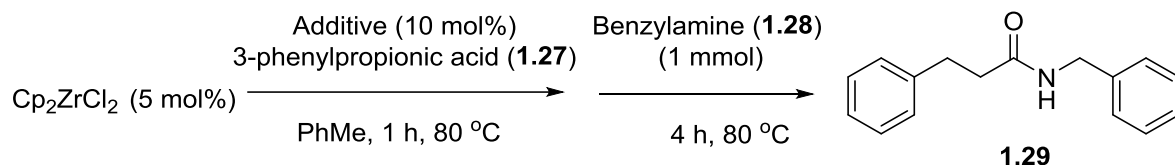
Entry	Silver Additive	Conversion (%)
1	AgI	27
2	AgSCN	20
3	AgClO$_4$	24
4	AgNO$_3$	20
5	AgBPh$_4$	14
6	AgSO$_3$CH$_3$	20
7	No additive	22
8	No catalyst	10

Conditions: 3-Phenylpropionic acid (1 mmol), benzylamine (1 mmol), Cp$_2$ZrCl$_2$ (5 mol%), silver salt (10 mol%), Anhydrous PhMe (1 mL), 80 °C, 4 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

The screen indicated that the presence of the silver additive was having little or no effect on the rate of the reaction; with the catalyst alone (Table 5, entry 7) producing 22% of the desired product and only a 5% increase in conversion being observed in the presence of an additive (Table 5, entry 1).

As a result, other additives were considered for use in this system. Transamidation studies carried out by Dr Ben Atkinson, had also revealed that trimethylsilyl isothiocyanate (Me$_3$SiNCS) was a promising additive when used in conjunction with zirconocene dichloride as a catalyst. It was hoped that the use of this additive in the carboxylic acid system would result in an enhanced method of forming amide bonds.

Table 6: The effect of Me$_3$SiNCS as an additive

Entry	Cp$_2$ZrCl$_2$ (mol%)	Me$_3$SiNCS (mol%)	Conversion (%)
1	-	-	0
2	5	-	37
3	5	10	35

Conditions: 3-Phenylpropionic acid (1 mmol), benzylamine (1.2 mmol), Cp$_2$ZrCl$_2$ (5 mol%), Me$_3$SiNCS (10 mol%), PhMe (1 mL), 4 h, 80 °C. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

With little or no catalytic effect being observed in the presence of the Me$_3$SiNCS additive (Table 6, entry 3) it was concluded that activation of the zirconium catalyst in this manner is ineffective for this system, despite its success in related reactions involving this catalyst.

The removal of water

As water is the sole by-product of this reaction and zirconium complexes of this type are oxophilic in nature,[38] it is possible that the water can bind to the metal centre, in place of the acid or the amine and hinder the catalytic cylce. This would result in a slower rate of reaction. Therefore, by removing the water in the reaction, the catalyst should be able to function more efficiently and proceed under milder conditions or at a faster rate.

In order to determine the most ideal method for removing the water from the system, a range of drying agents was screened.

Table 7: Drying agent screen
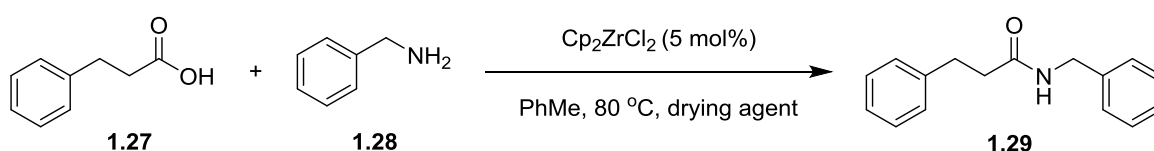
Entry	Drying agent	Conversion[a] (%) after 4 h	Conversion[a] (%) after 10 h	Conversion[b] (%) after 1 h
1	Molecular sieves (4Å) beaded	49	84	84
2	Powdered molecular sieves (4Å)	56	100	100
3	Calcium chloride	12	-	-
4	Magnesium sulphate	0	-	-
5	Potassium carbonate	29	-	-
6	No drying agent	31	58	65
7	Only powdered sieves	-	17	10

Conditions: 3-Phenylpropionic acid (1 mmol), Benzylamine (1.2 mmol), Cp$_2$ZrCl$_2$ (5 mol%), anhydrous PhMe (1 mL) 4 h, (a) 80 °C, (b) 110 °C. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

The effect of the drying agents can be seen by the conversions in Table 7. In the absence of the drying agent (Table 7, entry 6), when only the catalyst

was present, a background conversion of 31% was seen. This screen was conducted at 80 °C, as at the reflux temperature of toluene (110 °C), this particular reaction proceeds to 100% conversion in just the presence of the zirconium catalyst. On the addition of calcium chloride, magnesium sulphate and potassium carbonate (Table 7, entries 3, 4 and 5), a decrease in the formation of product 1.29 was observed. This could be a result of interaction between the drying agent and either of the reagents or the amide product. As these drying agents must be removed from the reaction by filtration before analysis, it is possible that some of the reagents or products could remain bound to these and are consequently lost. Conversely, in the presence of molecular sieves, an increase in conversion was observed (Table 7, entries 1 and 2). The addition of powdered molecular sieves resulted in a higher production of the desired amide product than beaded molecular sieves as a result of the larger surface area available to remove the water.

This encouraging result led to further optimisation of this system. The reaction time was extended to 10 hours in order to obtain higher conversions. It was seen that under these extended reaction times, powdered molecular sieves yielded quantitative conversion, whereas the catalyst alone under the same conditions showed only 58% conversion of the desired amide.

Reducing the reaction time at higher temperatures was also considered and a similar catalytic trend was seen. The presence of the powdered MS and the catalyst at these higher temperatures resulted in a reduction of reaction time from four hours to only one hour.

To ensure that both the removal of the water and the increase in amine concentration were both required, a series of reactions was carried out to demonstrate the effect of each change.
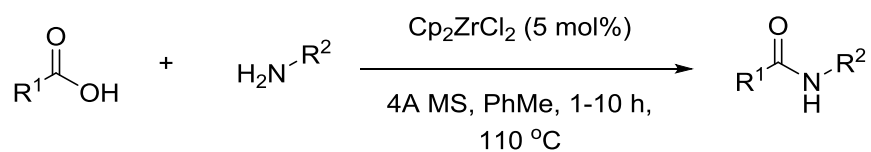
Table 8: Demonstrating the effect of the molecular sieves in the presence of the catalyst
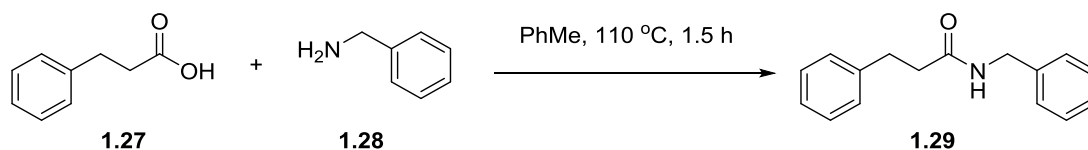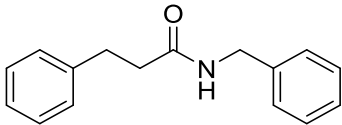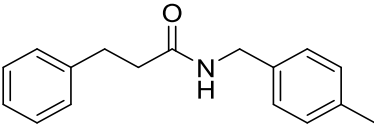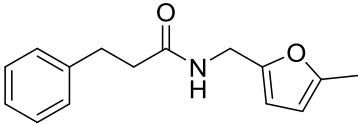

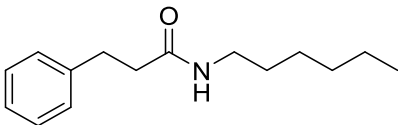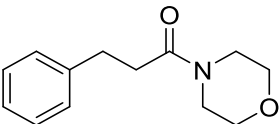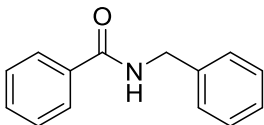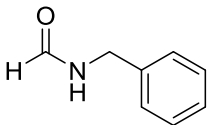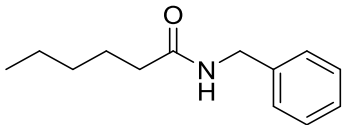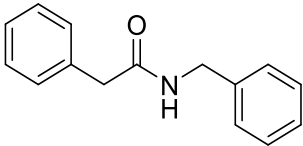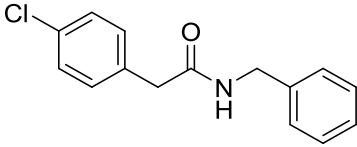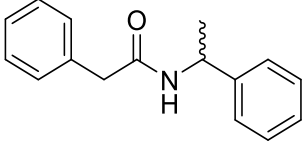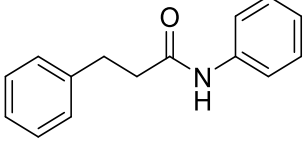| Entry	Equivalents of amine	Cp$_2$ZrCl$_2$ (mol%)	MS	Conversion (%)
1	1	-	-	11
2	1.2	-	-	11
3	1	5	-	59
4	1.2	5	-	75
5	1	-	✓	12
6	1.2	-	✓	10
7	1	5	✓	66
8	1.2	5	✓	100

Conditions: 3-Phenylpropionic acid (1 mmol), benzylamine (as indicated), Cp$_2$ZrCl$_2$ (5 mol%), PhMe (1 mL), activated powdered 4Å MS (200 mg), 110 °C, 1.5 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

The results in Table 8 indicate that in the absence of catalyst, the addition of excess amine has no effect on the low conversion of 11% (Table 8, entry 2). However, in the catalysed system this excess amine results in an increase in conversion from 59% to 75% (Table 8, entries 3 and 4). It is also clear that the molecular sieves alone do not facilitate the reaction in any way, with conversions of 12% and 10% being achieved in the absence of the catalyst (Table 8, entries 5 and 6). On the addition of both the excess of amine and the molecular sieves, a considerable increase in product is seen, with 100% conversion being reached after 1.5 hours (Table 8, entry 8). This increase indicates that the molecular sieves enable the catalyst to function more efficiently and therefore that the presence of water in the system can slow the progression of the reaction. Following this a study of the substrate scope was carried out in order to determine the limitations of the methodology.

Table 9: Substrate scope at reduced reaction times

$$R^1\text{-COOH} + H_2N\text{-}R^2 \xrightarrow[\substack{\text{4A MS, PhMe, 1-10 h,} \\ 110\ ^{\circ}C}]{\text{Cp}_2\text{ZrCl}_2\ (5\ \text{mol\%})} R^1\text{-CO-NH-}R^2$$

Entry	Compound number of product	Amide product	Time (h)	Conversion (%)
1	**1.29**		1	100
2	**1.30**		1	79
3	**1.31**		1	100 (92)
4	**1.32**		3	86 (70)
5	**1.33**		6	66
6	**1.34**		18	90 (87)
7[a]	**1.35**		4	100
8	**1.36**		4	100

9	**1.37**		1	100 (78)
10	**1.38**		1	100
11	**1.39**		4	76 (72)
12	**1.40**		24	60

Conditions: Acid species (2 mmol), amine species (2.4 mmol), Cp$_2$ZrCl$_2$ (5 mol%), 110 °C, PhMe (2 mL), time (as stated (h)), 4Å MS. (a) reaction run at 60 °C. Conversions were determined by ^{1}H NMR. Isolated yields in parentheses.

The reaction times were reduced from the previously published methodology as a result of the water removal and increase in amine concentration. This enabled a variety of aliphatic and benzylic amines to be coupled to 3-phenylpropionic acid within one hour at 110 °C in high conversions (Table 9, entries 1-3). Aliphatic amines (Table 9, entry 4) required a slightly longer reaction time of three hours, however this is a reduction from the eight hours that were previously needed. In addition, secondary amines such as morpholine (Table 9, entry 5), reached moderate conversions of 66% in just six hours, when they previously required 24 hours to reach completion. Branched primary amines were tolerated and isolated in moderate yields (Table 9, entry 11).

This methodology also enabled a range of acids to be coupled to benzylamine. Including aliphatic acids such as hexanoic acid (Table 9, entry 8) and benzylic acids (Table 9, entries 9-11) reaching full conversion in one hour. *N*-Benzylformamide (Table 9, entry 7) was synthesised with complete conversion from formic acid, at a reduced temperature and time of four hours at 60 ˚C.

This system was, however, less successful with benzoic and anilinic substrates due to their reduced reactivities. A high yield was obtained on forming *N*-benzylbenzamide from benzoic acid (Table 9, entry 6), however a long reaction time of 17 hours was still required. The lower conversion of compound **1.40**, suggests that the slow reactivity of aniline could not be overcome by the enhanced conditions. Despite this, 60% conversion was achieved where 45% was reached in the absence of the molecular sieves.

Following this, studies were conducted in order to reduce the reaction temperature.

Table 10: Substrate scope at reduced temperature

$$R^1 \overset{O}{\underset{OH}{\parallel}} \quad + \quad H_2N{-}R^2 \quad \xrightarrow[\substack{4A\ MS,\ PhMe,\ 24\ h,\\40\text{-}80\ ^\circ C}]{Cp_2ZrCl_2\ (5\ mol\%)} \quad R^1 \overset{O}{\underset{\underset{H}{N}}{\parallel}} R^2$$
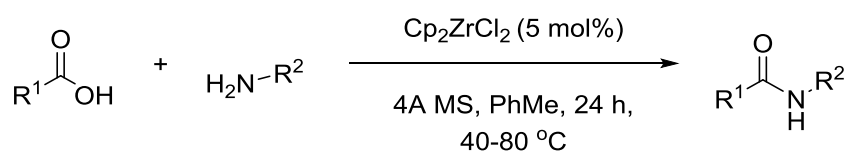
Entry	Compound number	Temperature (°C)	Conversion (%)
1	**1.29**	70	100 (75)
2	**1.30**	70	83 (64)
3	**1.31**	70	100
4	**1.32**	90	90
5	**1.33**	80	96 (53)
6	**1.34**	90	45
7	**1.35**	40	100 (76)
8	**1.36**	80	73
9	**1.37**	60	100
10	**1.38**	80	100 (81)
11	**1.39**	90	56
12	**1.40**	-	-

Conditions: Acid species (2 mmol), Amine species (2.4 mmol), Cp_2ZrCl_2 (5 mol%), PhMe (2 mL), 4Å MS, 24 h, Temperature (as indicated (°C)). Conversions were determined by analysis of the crude ^1H NMR spectra. Isolated yields are in parentheses.

The removal of the water by-product has resulted in this coupling being conducted at lower reaction temperatures of 40-80 °C. As with the reduced

reaction time, several substrates were tolerated under these conditions, including aliphatic and benzylic substrates. These required slightly milder temperatures of 70 °C to achieve high conversions in 24 hours (Table 10, entries 1-4). Notably *N*-benzylformamide was synthesised in 76% yield at only 40 °C (Table 10, entry 7).

The limitations of this methodology were very similar to those presented previously, with the milder conditions being unable to overcome the less reactive substrates with lower electro- and nucleophilicities. Benzoic acid was very slow to react with benzylamine, producing only 45% of the corresponding benzamide when the temperature was lowered by 20 °C (Table 10, entry 6). In addition, bulkier amines such as *α*-methylbenzylamine only produced 56% of the amide product at 90 °C (Table 10, entry 11).

Conclusions

Initial attempts to develop an organocatalytic method of synthesising amides from non-/unactivated carboxylic acids and amines were unsuccessful. The subsequent use of these organocatalysts in an already established metal catalysed system also proved ineffective. The use of alternative commercially available zirconium complexes was ineffective, in addition to efforts to enhance the existing system by forming more active catalysts *in situ.*

The removal of the water by-product from the system proved to be the most effective method of improving this system. This allowed for a reduction in both reaction time and temperature with more reactive substrates. However this methodology was could not be extended for the coupling of anilinic amines, which showed little increase in conversion under these new conditions and benzoic substrates where it was only possible to reduce the reaction times marginally.

Chapter 2: Alternative Acyl Donors- Esters, Ureas and Carbamates

Alternative acyl donors

Although there are numerous methods of forming amide bonds from a variety of acyl donors including aldehydes,[39],[40] alcohols,[41] oximes and via carbonylation reactions,[42] discussion will be limited to esters, carbamates, ureas and amides for the purposes of this thesis.

Esters in amide bond formation

The amidation of esters is also a highly useful process and within industry esters are preferred over other carboxylic acid derivatives such as acid chlorides and acid anhydrides, due to waste disposal and atom economy issues. However when using an ester, an equivalent of alcohol is still produced; thus rendering this process less efficient than the direct coupling between a carboxylic acid and an amine. Despite this, the aminolysis of esters is still considered a model reaction for use within industry.[43],[44]

Uncatalysed aminolysis of esters

The aminolysis of esters in the absence of a catalyst is once again a problematic process with high temperatures and long reaction times being needed.[45]

The catalysed synthesis of amides from esters is widely documented in the literature. Several metal and non-metal catalysts have proven to be effective in catalysing this transformation.

Metal catalysts for the aminolysis of esters

A simple procedure was documented by Ranu and Dutta in 2003. A catalytic amount of indium triiodide was required in addition to an excess of the amine. The amides were obtained in high yields, however this system could not be applied to the coupling of esters with secondary amines, thus the tertiary amides could not be formed.[46]

One of the most significant discoveries concerning this transformation was that made by Han *et al.* in 2005 where metal alkoxides showed substantial catalytic activity.[47] The most noteworthy of these was zirconium *tert*-butoxide (Zr(O^{t}Bu)$_4$) required in 10 mol% loading. In addition to the metal, 10 mol% HOBt/HOAt was also required as an additive. A large substrate

scope was investigated and some limitations were reported mainly due to adverse side reactions with the zirconium catalyst. Functional groups that were not compatible included acidic phenols and esters containing terminal epoxides. In depth mechanistic studies revealed that possible formation of a dimeric zirconium complex acted as the active catalyst (Figure 2.01). The dimeric zirconium complex forms in the presence of amines, in this complex both zirconium centres are hexacoordinate. Coordination of the ester breaks one of the bridging Zr-O bonds resulting in pathway A or B. Attack by the amine species then either leads to intermediate **2.01** which can then react via a six membered transition state, in the case of path A. Or in the case of path B aintermediate **2.02** can be formed which then reacts via a four membered transition state.
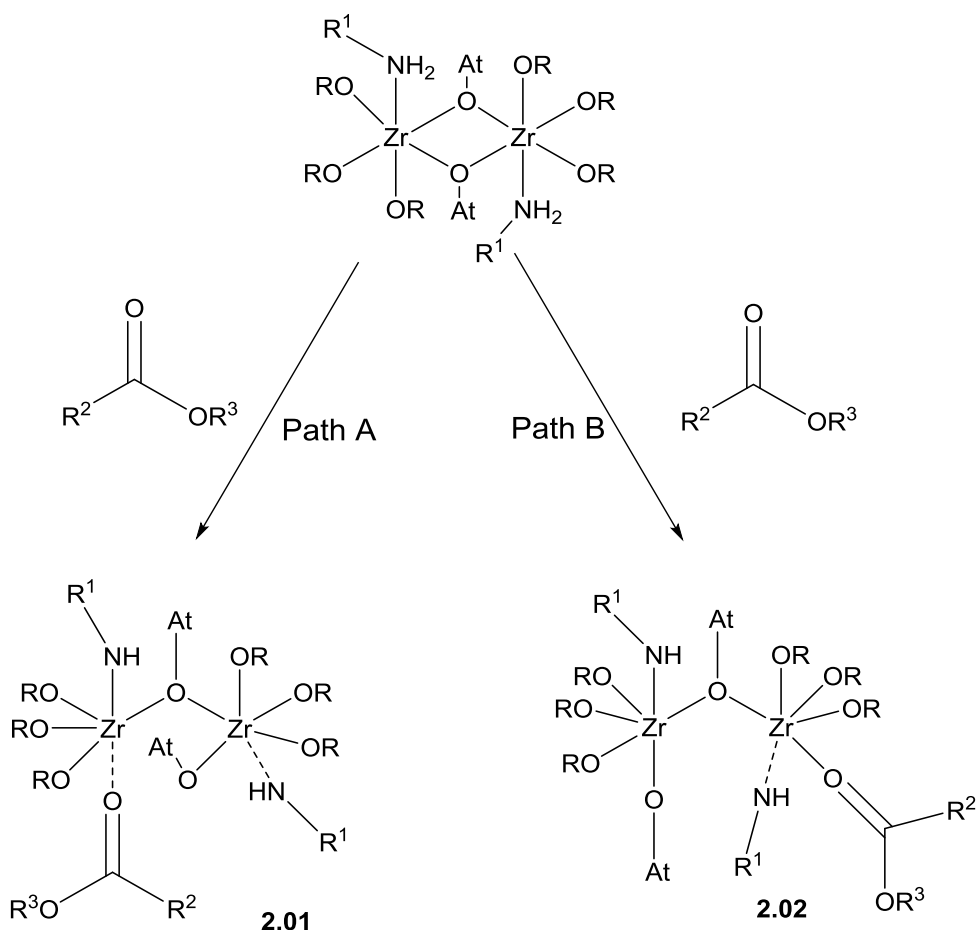

Figure 2.01: Mechanistic pathway of the dimeric zirconium species

Furthermore, significant findings by Milstein and co-workers involve the application of a ruthenium based pincer catalyst (Ru-PNN where PNN is 2-(di-*tert*-butylphosphinomethyl)-6-(diethylaminomethyl)pyridine)) (Scheme 2.01).[48] This discovery was made after the application of a similar catalyst to an alcohol and amine coupling reaction.[49] This transformation is unique as it produces dihydrogen as its sole by-product, as opposed to an alcohol. This catalyst was required in low catalyst loadings of 0.1 mol% when heated at reflux in toluene, making it an attractive method of forming amides from esters. In addition to these characteristics, this process is compatible with an extensive range of substrates. However long reaction times of up to 36 hours were required as well as a high reaction temperature and inert conditions. Another limitation posed by this methodology is that only symmetrical esters could be used, as both moieties are transferred to the product.

A mechanistic cycle was proposed, although it was noted that further mechanistic studies would need to be carried out before the cycle is completely plausible. The suggested cycle (Scheme 2.02) indicates that the aromatised and coordinatively saturated species **2.04** is formed from the N-H activation of dearomatised complex **2.03**. Dissociation of the hemi-labile amine arm allows coordination of the ester to species **2.04**. This can then lead to the formation of species **2.05**. Intramolecular nucleophilic attack on the coordinated ester species by the amido ligands generate the amide product and an alkoxy intermediate **2.06**. β-Hydride elimination forms the Ru dihydride species with coordinated aldehyde. Further, nucleophilic attack of the amine on the aldehyde generates dihydrogen and species **2.08**. Consequent β-hydride elimination forms the *trans* dihydride intermediate **2.09** with liberation of the second amide product. The release of dihydrogen from species **2.09** reforms the active catalyst to restart the cycle. [48]
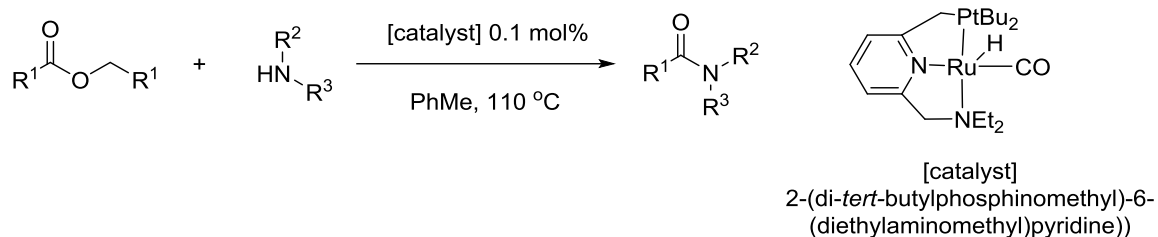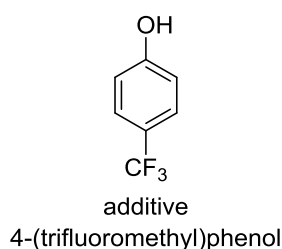
Scheme 2.01: Ru-PNN catalysed amide formation from esters and amines
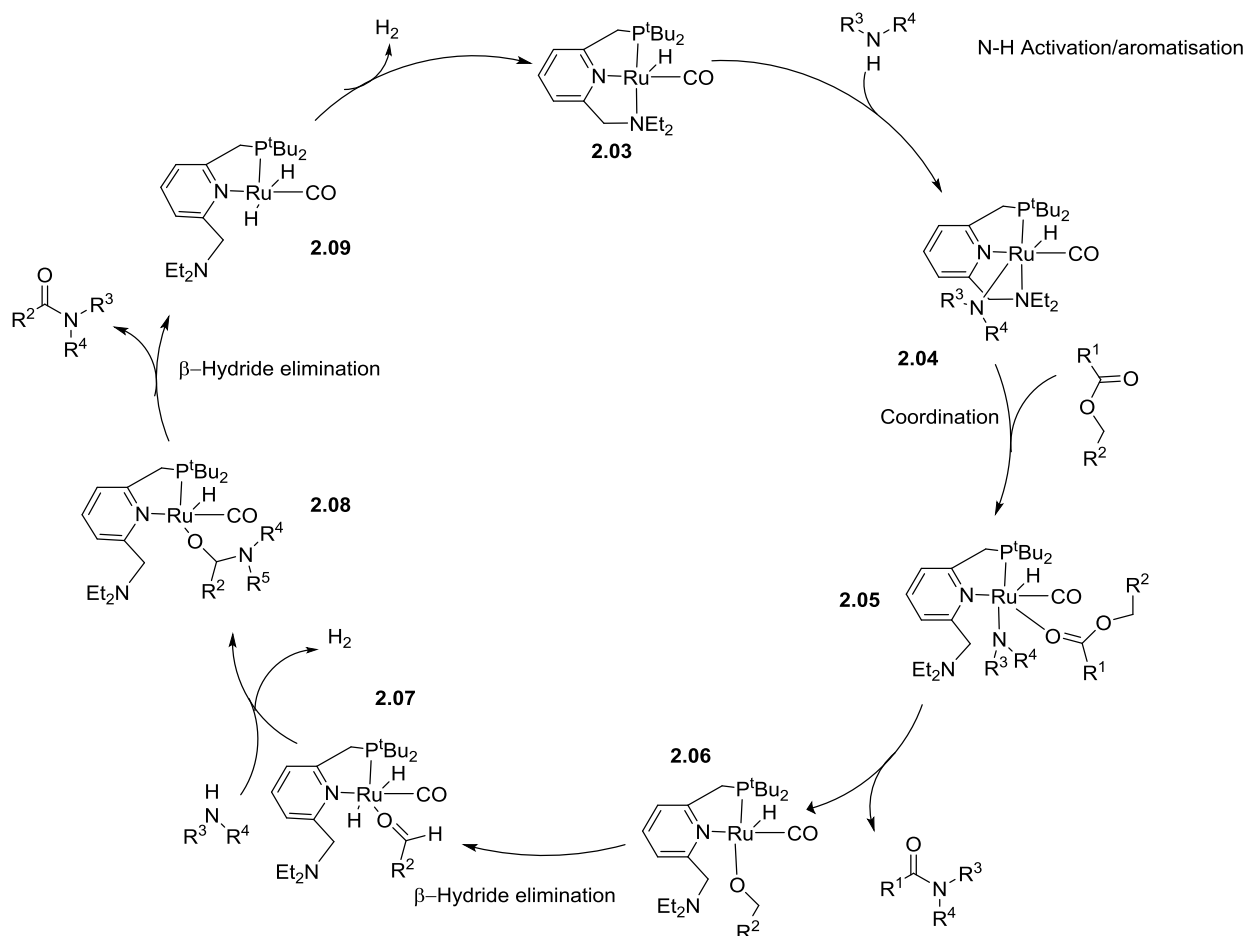
Scheme 2.02: Proposed mechanism of amide formation from esters with Ru-PNN catalyst

Sodium methoxide (NaOMe) was proven as an ideal catalyst for this transformation by Ohshima *et al.* in 2012 (Scheme 2.03). This protocol was designed to overcome some of the problems posed by previous attempts at this reaction as it only requires temperatures of 50 °C with 5 mol% NaOMe. Further studies indicated that in the presence of a dessicant, the catalyst loading could be reduced to just 1 mol%. With alterations to the conditions,

48

this methodology was extended to the synthesis of dipeptides, producing the amides in high enantiomeric excesses without racemisation.[50]
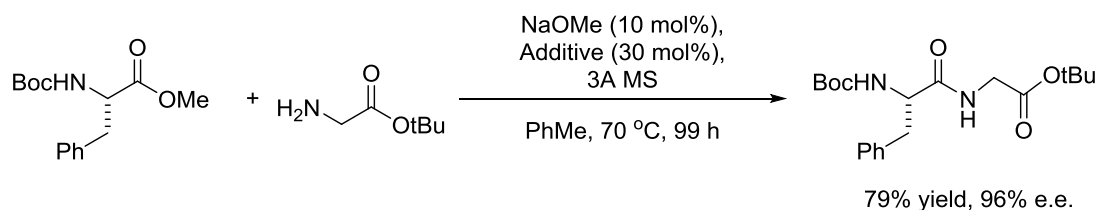
Scheme 2.03: Sodium methoxide catalysed dipeptide formation between amino acid esters and amines

More recently in 2014, lanthanum triflate ($La(OTf)_3$) was reported for the formation of amides from esters and amines (Scheme 2.04). This protocol was developed to run at milder conditions than with some of the previously developed methods, with the activated substrates being coupled at room temperature and in some cases only requiring 2 mol% catalyst. This system was also extended to challenging esters such as ethyl 2-pyridine-carboxylate which could be coupled to a range of amines with only 1 mol% $La(OTf)_3$.[51]
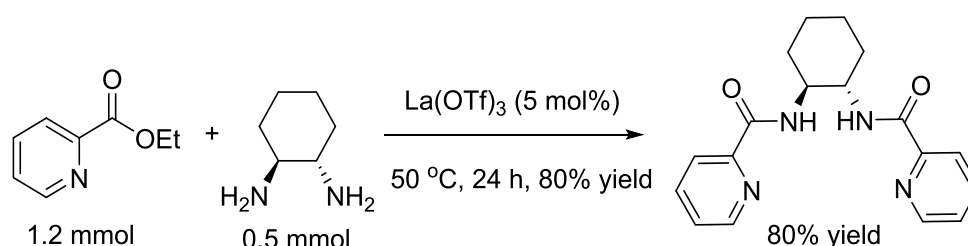
Scheme 2.04: Formation of diamide ligands from the aminolysis of esters with lanthanum triflate

The formation of primary amides from esters is largely unexplored. However in 2008 Ley and co-workers developed a protocol using magnesium nitride (Mg_2N_3) as an *in situ* source of ammonia (Scheme 2.05). The magnesium salt was required in five equivalents in order to produce the primary amides

in high conversions. Protic solvents were the most successful, thus optimisation was carried out with methanol as the solvent of choice in sealed microwave vials. Esters with a wide range of functionalities were tolerated producing the desired primary amides in high yields of 75-99%. Limitations included the incompatibility of β-ketoesters. These, unsurprisingly, cleanly yielded the acetamide and corresponding primary amide *via* a retro-Claisen condensation.[52]


90% yield

99% yield

82% yield (synthesised from the lactone)
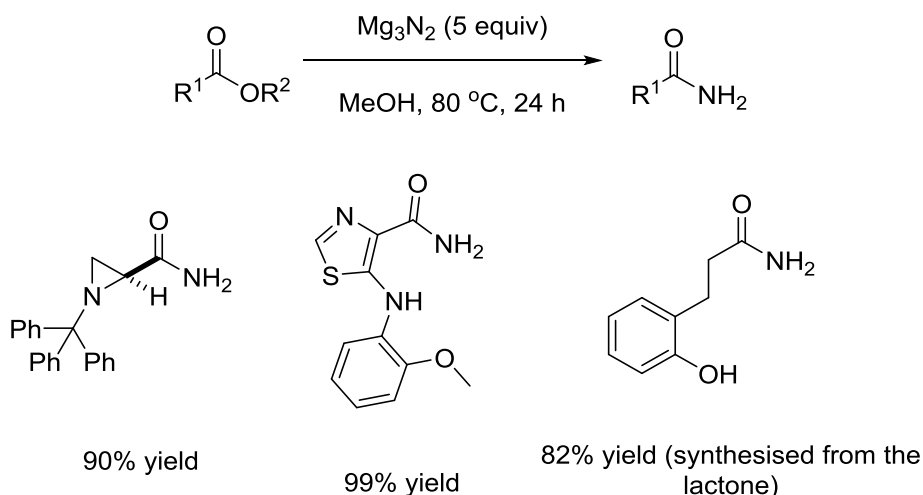
Scheme 2.05: Magnesium nitride as an ammonia source in primary amide synthesis from esters

Non-metal catalysts for the amidation of esters

Several organocatalysts have shown significant catalytic activity in this transformation. 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)[53] and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) have been studied as organocatalysts in ester-amine coupling reactions. Typically, these catalysts are needed in higher catalytic loadings than metal catalysts and in these cases 30 mol% catalyst was required.

DBU has been shown to convert methyl esters into amides however this method is limited to benzylamine, aniline and pyrrolidine. These reactions still required long reaction times of up to 48 hours and in some cases the conversions were lower than 90%.[43] Other examples of DBU catalysed aminolysis of esters involve the use of additives such as 1,2,4-triazole (Scheme 2.06). The temperature of these reactions varied depending on the

substrate with some reacting at temperatures as low as 45 °C, other more challenging substrates required harsher conditions of 95 °C.[54]
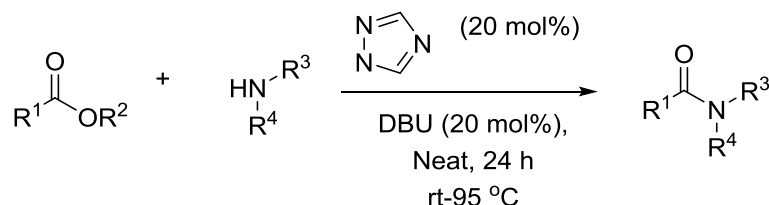
Scheme 2.06: DBU and 1,2,4-triazole catalysed aminolysis of esters

One area of ester amidation that is particularly unexplored is the coupling of esters and aminoalcohols. In 2005 the use of nitrogen heterocyclic carbenes (NHC) was investigated for this application. It was found that 1,3-bis(2,4,6-trimethylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene (IMes) was a suitable catalyst for this transformation. Low catalyst loadings of only 5 mol% were needed with mild reaction temperatures of 23 °C, making this a favourable method for carrying out enantioselective reactions. The reaction time varied depending on the steric bulk and electrophilicity of the ester. Mechanistic studies revealed initial transesterification activated by a carbon centred Brønsted base allowing for a rapid N→O acyl transfer reaction to occur. [55]

BEMP (Scheme 2.07) has also shown catalytic abilities in catalysing the coupling of aminoalcohols and esters to form amides. 10 mol% catalyst loadings were required, with the reactions being conducted at room temperature for 15 hours. This method was compatible with aliphatic, aromatic and heteroaromatic functionalities.[56]
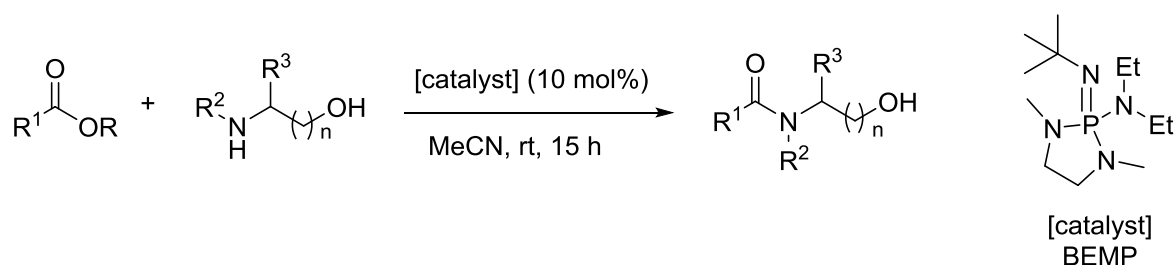
**Scheme 2.07: BEMP catalysed amidation of esters with aminoalcohols**

Carbamates as Acyl Donors

Carbamates are very useful compounds in natural and synthetic chemistry. The synthesis of *N*-substituted carbamates is of particular interest due to their importance in a range of pharmaceuticals, agrochemicals and the protection of amino groups in peptide chemistry.[57] The functionalisation of carbamates is achieved by alkylation on the nitrogen or by substitution of the nitrogen with an amine. It has been found that these transformations often require the use of hazardous reagents or that multi-step procedures are required.[58]
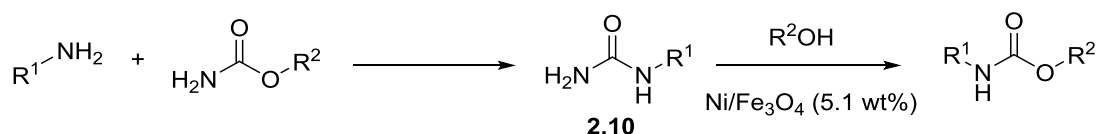
N-Substituted carbamates

Traditionally these types of carbamates are synthesised from isocyanates which in turn are derived from phosgene gas. As a result numerous efforts have been placed on finding an alternative route for their formation. Typically these routes involve the use of alternative carbonyl sources that are environmentally benign such as urea, dimethyl carbonate and CO_2. Alkyl carbamates can also be used to form *N*-substituted carbamates, they themselves can be formed from the alcoholysis of urea and present an abundant, cheap, and non-toxic carbonyl source.[57]

Several methodologies have been documented involving the use of metal catalysts to form *N*-substituted carbamates from alkyl carbamates. In 2011, Shang *et al.* identified Ni/Fe_3O_4 as a suitable catalyst for this transformation. The magnetic catalyst was required in 5.1 wt% loading, with high temperatures of 190 °C (Scheme 2.08). A wide range of amines was tolerated, including diamines, aliphatic and aromatic substrates, although this method was not extended to the use of secondary amines. High yields of 91-98% were obtained in 5-12 hours.[57]
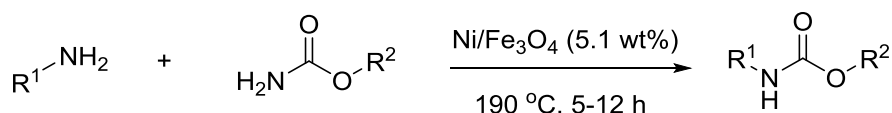
Scheme 2.08: *N*-Alkylation of carbamates with amines

The proposed mechanism for this transformation involved the presence of a monosubstituted urea intermediate (**2.10**) (Scheme 2.09). This was formed by initial attack of the amine on the carbamate, with substitution of the oxygen. Subsequent attack of the alcohol on the urea species, mediated by the catalyst, resulted in liberation of ammonia, forming an *N*-substituted carbamate. The formation of this intermediate species was confirmed by several mechanistic labelling studies.
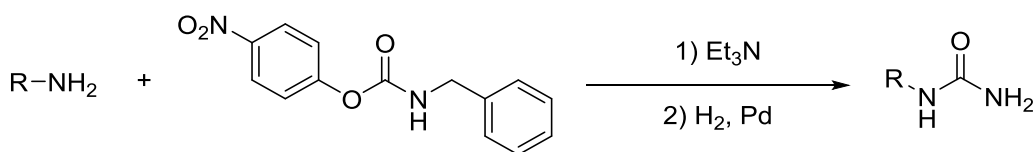

Scheme 2.09: Formation of *N*-substituted carbamates via a monosubstituted urea intermediate

In addition to these studies methyl carbamate has been used as a carbonyl source for the formation of methyl-phenyl carbamate. This compound is a crucial starting material for the formation of isocyanates. A $ZnCl_2$ catalysed system was documented for this reaction at 160 °C for 4 hours.[59]

O-Substituted carbamates

Other examples of carbamate based reactions involve substitution of the oxygen rather than the nitrogen, forming a monosubstituted urea; these are also highly useful and interesting compounds, found in numerous natural products, pharmaceuticals [60] and agrochemicals.[61] Monosubstituted ureas have been synthesised from *N*-substituted carbamates in a two-step method. Initial reaction of an amine with 4-nitrophenyl-*N*-benzylcarbamate in the presence of triethylamine produced the disubstituted urea product. The pure monosubstituted product is formed after hydrogenolysis, requiring no further purification (Scheme 2.10).[61]

Scheme 2.10: Two-step formation of monosubstituted ureas from *N*-substituted carbamates and amines

Other methods of forming monosubstituted ureas include using carbamate protected primary or secondary amines with stoichiometric quantities of trimethylaluminium. This methodology was compatible with a variety of substrates, with more challenging substrates requiring slightly longer reaction times of 5 hours and increased temperatures of 50 or 80 °C.[62]

One of the more significant contributions to this area was carried out by Han *et al.* further to their ester based work previously discussed. The same Zr(O^{t}Bu)$_4$ catalyst was used in coupling carbamates and amines to form both mono and disubstituted ureas. The use of a coupling agent 4-methyl-2-hydroxyquinoline (MeHYQ) was also required in 20 mol% loading in addition to the 10 mol% Zr *tert*-butoxide catalyst (Scheme 2.11). In the presence of these reagents, high temperatures of up to 140 °C were needed, though short reaction times of 15 minutes were sufficient when conducted in a microwave. The initial studies of this reaction involved the formation of carbamates from carbonates and amines using a similar catalytic system. After forming the carbamate this could then be reacted with an amine to form a range of urea products, with substitution occurring on the oxygen moiety. This could be extended to reactions with *N*-substituted carbamates, forming the *N,N'*-disubstituted urea products.[63]
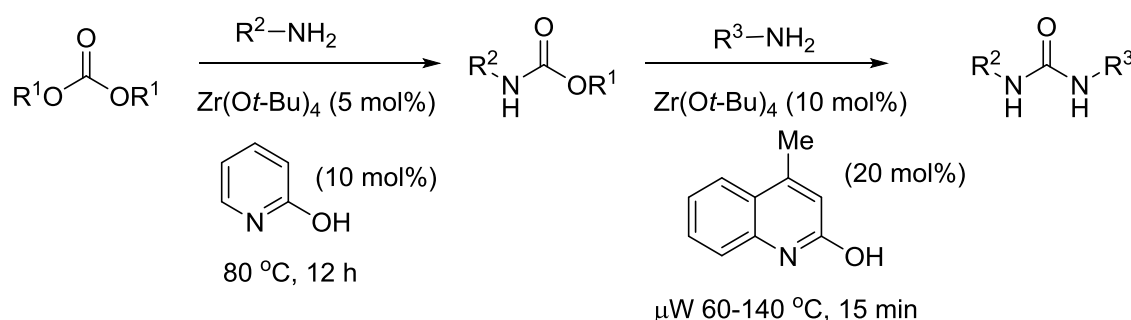

Scheme 2.11: Zirconium *tert*-butoxide catalysed carbamate and urea fromation

The authors do not give a catalytic mechanism for this transformation, however it is postulated that the carbamate decomposes *via* an isocyanate intermediate.

Early methods of forming *N,N'*-disubstituted ureas from *N*-substituted carbamates involved the use of Grignard reagents with reaction times

ranging from 24-48 hours.[64] Since then, further studies have been conducted to reveal the use of *N*-methylpyrrolidine as a catalyst when reacting isopropenylcarbamates and amines.[65] A range of unsymmetric disubstituted ureas was synthesised in this way, by displacement of the alkoxide with some substrates reaching full conversion in just 30 minutes whereas others required 45 hours. The driving force for this reaction was the formation as acetone as a by-product.
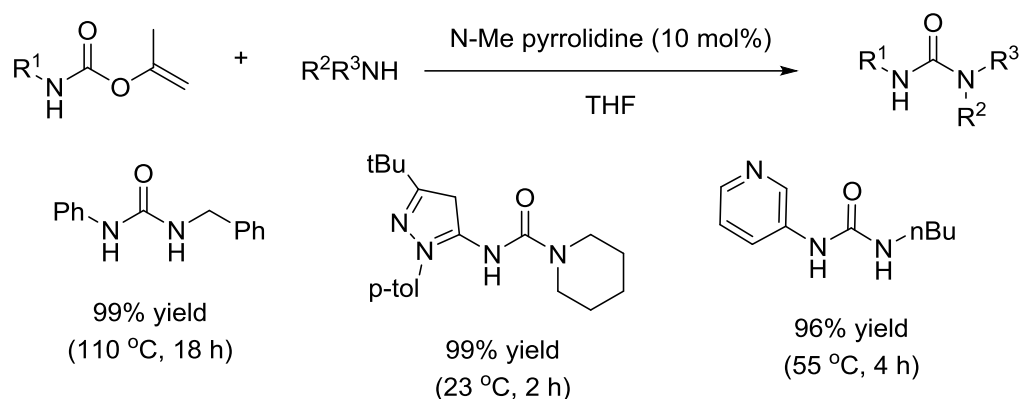
Scheme 2.12: Synthesis of disubstituted ureas from isoproprenylcarbamates

Other heterogeneous methods include the use of activated alumina to form *N,N'*-substituted ureas from *N*-substituted carbamates. This method required long reaction times of 48 hours when heated in toluene at 110 °C, with an excess of the reacting amine.[66]
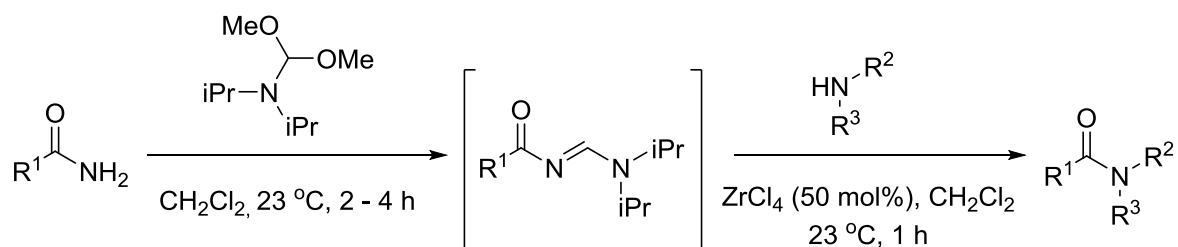
Amides and ureas as acyl donors

The use of amides and ureas as acyl donors is a somewhat less conventional route to synthesising other amides. Despite the synthetic advantages of transamidation, these reactions often require harsh and forcing conditions. This is due to the high stability of the strong C-N bond and the acidic N-H bond.[67],[68]

In the absence of a catalyst, this reaction requires temperatures in excess of 180 °C, with secondary and tertiary amides being especially inert.[69] Examples of these thermal transamidations have included studies by Kierdrowski *et al.* where the mono-acylation of diamines required temperatures between 160 °C and 200 °C, in addition to reaction times of 10-15 hours.[70]

Metal catalysed transamidation reactions of amides and ureas

Significant efforts in transamidation reactions have been conducted by Stahl *et al*. Metal amido complexes were screened and revealed titanium, scandium and aluminium complexes as potential catalysts for the transamidation of carboxamides.[67] Since the initial report, several other studies have been undertaken including mechanistic studies,[71] the investigation of side reactions[72] and the extension of this methodology to more challenging substrates.

In depth investigations were conducted to elucidate the mechanistic pathway of the transamidation reaction. This catalytic cycle was investigated using a trisamidoaluminium(III) dimer. However this particular catalyst was only beneficial in the transamidation of secondary amides, thus alternative catalysts were investigated for the reactions of tertiary amides.[71] Zirconium amido complexes were identified as suitable catalysts for this purpose, the mechanism was found to be the same as the aluminium based cycle (Scheme 2.13).[73] It was proposed that coordination to the zirconium results in simultaneous activation of the carboxamide and the amido species. This was followed by intramolecular attack of the amido species on the coordinated amide **2.11**, leading to the formation of the zirconium stabilised tetrahedral intermediate **2.12**. This is then able to interconvert with the isomeric intermediate, eventually leading to the formation of a new amide/amido species coordinated to the zirconium.

Scheme 2.13: Mechanistic pathway of zirconium catalysed transamidation

Myers and co-workers reported the use of *N,N*-dialkylformamide dimethyl acetals in conjunction with a zirconium metal catalyst for transamidation reactions (Scheme 2.14). This transformation proceeded via an *N,N*-dialkylformamidine intermediate, a well-documented pathway in amide formation. In addition this process required low temperatures and short reaction times; conversely a high catalyst loading of 50 mol% was also needed.[74]

Scheme 2.14: Transamidation of primary amides catalysed by zirconium tetrachloride, proceeding *via* an *N,N*-dialkylformamidine intermediate

More recent examples of efficient transamidation procedures, include that published by Beller and co-workers. This protocol used 10 mol% copper(II) acetate (Cu(OAc)$_2$) to transamidate a large range of amides. High temperatures of 140 °C were still required in *tert*-amyl alcohol as the solvent. This methodology was extended to the synthesis of substituted ureas by the transamidation of urea. The synthesis of asymmetric and cyclic ureas is of particular interest to the pharmaceutical industry.[75]

Another interesting account details an iron(III) and water catalysed method of transamidation. In this case 5 mol% hydrated iron nitrate (Fe(NO$_3$)$_3$·9H$_2$O) was used as the catalyst when heated at reflux in toluene. This methodology was applied to the synthesis of secondary amides, formamides, phthalimides and substituted ureas. With reaction times ranging from 7-96 hours for some bulky phthalimides (Scheme 2.15).[76]
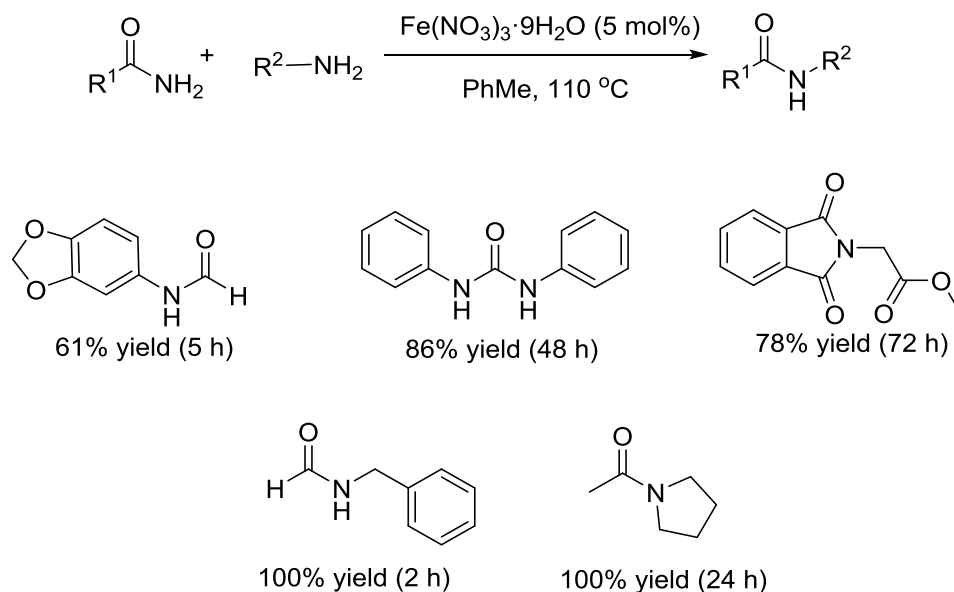
Scheme 2.15: Iron (III) and water catalysed transamidation of amides, ureas and phthalimides with primary and secondary amines

Non-metal catalysed transamidation of amides and ureas

More traditional non-metal catalysed methods of transamidation, as with amide bond formation, often involve boron based derivatives. As previously discussed, boric acid was investigated as a catalyst for the direct coupling of carboxylic acids and amines, however it also has been successfully applied to transamidation reactions. Primary, secondary and tertiary amides were transamidated on the addition of 10 mol% boric acid under solvent free conditions. This method was reliant on the presence of 1-2 equivalents of water allowing for bench top conditions to be used.[77]

A report by Allen *et al.* indicated that the use of hydroxylamine hydrochloride is highly effective (Scheme 2.16).[68] There was substantial investigation of the reaction scope, with a variety of functional groups being tolerated within the reaction. Secondary amides were easily formed with 10 mol% catalyst, however more robust substrates required higher catalytic loadings of up to 50 mol%, these included heteroaromatic, protected amides and benzamides. A mechanistic pathway was also proposed based on ^{1}H NMR and kinetic studies (Scheme 2.17).
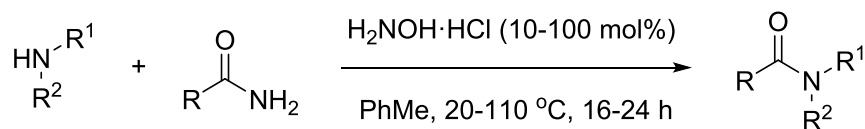
Scheme 2.16: Hydroxylamine hydrochloride as an inorganic catalyst for the transamidation of primary amides with amines
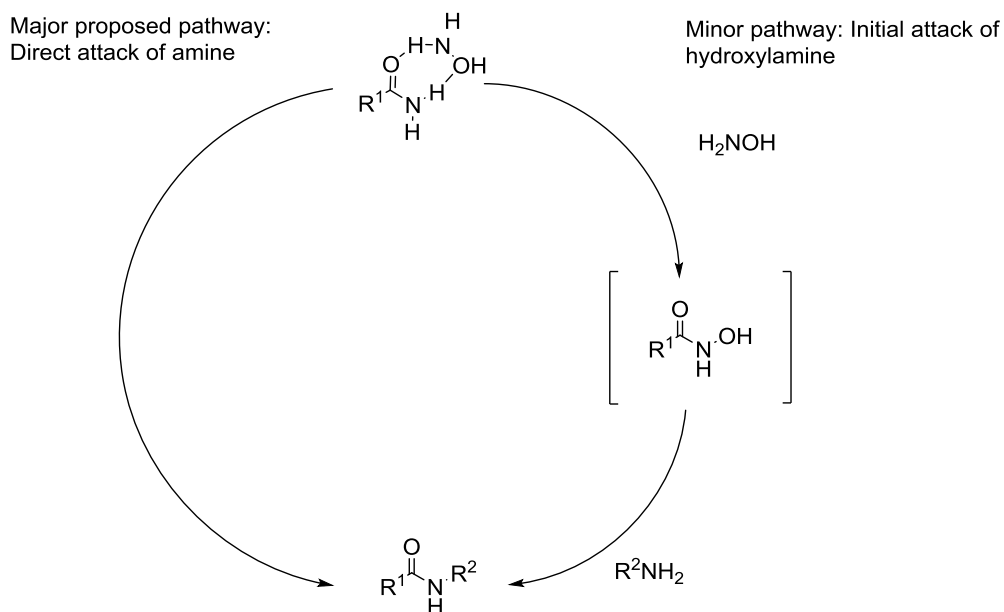

Scheme 5.17: Proposed pathways of hydroxylamine hydrochloride catalysed transamidation

A recent report demonstrates the use of L-proline as an organocatalyst for transamidation reactions (Scheme 2.18).[78] The cheap and readily available catalyst was required in 10 mol% loading, which is low in comparison with other organocatalysts, with reactions being conducted at 100 °C, under solvent free conditions. Despite the low catalyst loadings, long reaction times of 36 hours were still required. For the more challenging secondary amines, the reaction temperature was increased to 150 °C in order to achieve reasonable conversions. In addition, this protocol was also extended to the transamidation of phthalimides. The mechanistic investigations along with kinetic reactions revealed a possible, although unlikely, reaction pathway (Scheme 2.19).
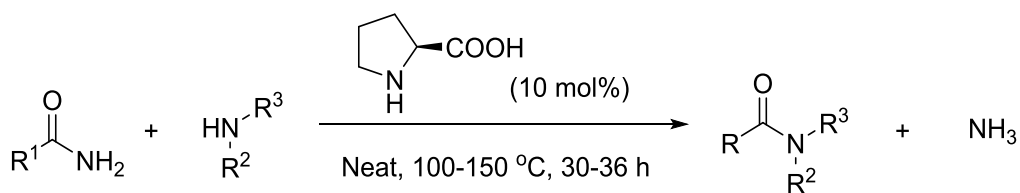
Scheme 2.18: L-Proline as a catalyst for transamidation
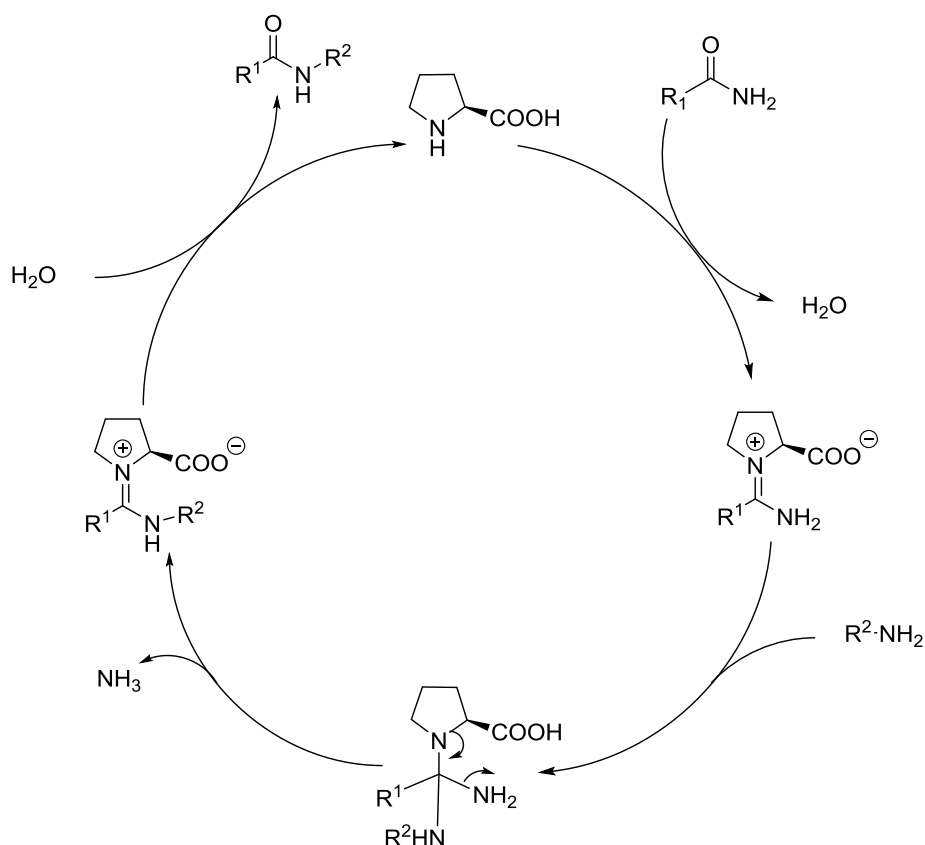
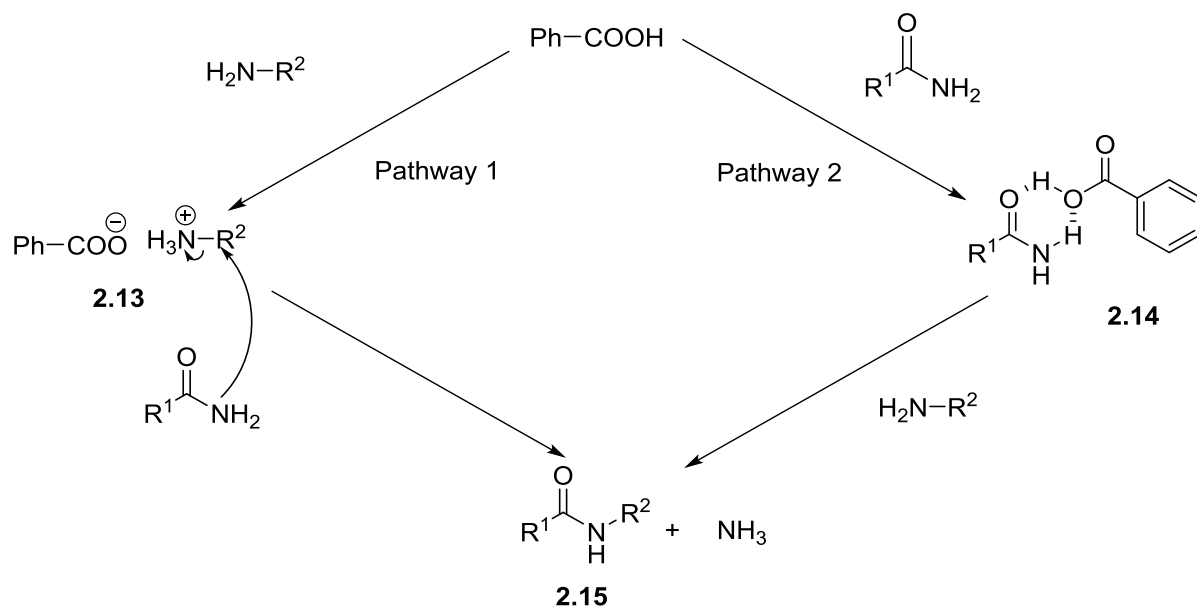**Scheme 2.19: L-Proline catalysed transamidation mechanism**

More recently in 2014, Wu *et al.* reported the use of benzoic acid as a catalyst for the transamidation of amides, ureas, phthalimides and thioamides.[79] This highly interesting discovery utilised 15 mol% benzoic acid at 130 °C for 8 hours to transamidate amides with amines. This protocol was carried out under inert conditions with an argon atmosphere being required. Numerous amides and amines were tolerated under the optimised conditions, although lower yields were obtained with anilinic amines and formamides were synthesised easily at lower temperatures of 80 °C in just one hour. Furthermore, this system was also compatible with ureas, forming

disubstituted products. *N,N'*-Disubstituted ureas were formed when transamidating a monosubstituted urea, with the loss of ammonia rather than the amine (Scheme 2.20).
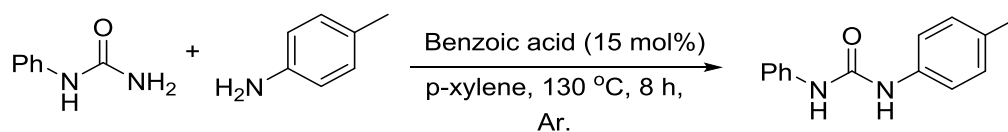
Scheme 2.20: Benzoic acid catalysed formation of *N,N'*-disubstituted ureas from monosubstituted ureas and amines

Mechanistic studies on this transamidation system revealed the formation of either an ammonium salt **2.13** or a hydrogen bonded acid/amide species **2.14** (Scheme 2.21). Pathway 1 shows initial formation of ammonium salt **2.13** by proton transfer from benzoic acid to the amine species. This is then attacked by the amide species to give to desired amide product, liberating ammonia and regenerating the benzoic acid catalyst. Pathway 2 suggests the formation of an acid/amide hydrogen bonded species **2.14**. The amine then is able to attack this species, forming the desired amide product **2.15** and ammonia. In order to determine the correct pathway a labelling study could be conducted. By using ^{15}N labelled amide, if the product contained the labelled species, then pathway 1 is likely whereas pathway 2 is probably in the event that the product does not contain the labelled species.

Scheme 2.21: Mechanism of benzoic acid catalysed transamidation

Heterogeneous transamidation

As previously discussed, heterogeneous catalysts provide an attractive alternative to homogeneous methods, as they are easily recyclable, are often required in low loadings and are usually cheap and readily available. They do however often require harsh conditions including elevated temperatures and long reaction times.

Cerium dioxide (CeO_2) was reported as a heterogeneous catalyst for the transamidation of amides with amines. Octylamine was coupled with a variety of amides in high conversion, including aliphatic, aromatic and heteroaromatic amides all within 24 hours with only 5.8 mol% CeO_2. High temperatures of 160 °C were required, rendering this system limited when applied to chiral or heat sensitive functionalities.[80]

Mesoporous niobium oxide spheres (MNOS) (Figure 2.02) have also been investigated for the transamidation of amides and urea.[81] The optimised system was solvent free, with only 5 mol% Nb_2O_5 required. Numerous substrates, including benzamides and heterocyclic amides, were transamidated within 16 hours at 160 °C. An *N,N*-disubstituted urea was also

synthesised under the optimised system. The possibility of reusing the catalyst was also investigated, revealing that after 5 cycles, there was no decrease in catalytic activity. In addition, a dual Brønsted and Lewis acid mechanism was proposed. This mechanism utilises both the Brønsted and Lewis acid moieties on the MNOS for coordination to the amide. This interaction facilitates the attack of the amine on the amide carbonyl leading to the formation of intermediate **2.16**. This can undergo reversible proton exchange forming species **2.17**. Ammonia gas and the amide product are then liberated, restarting the cycle (Scheme 2.22).
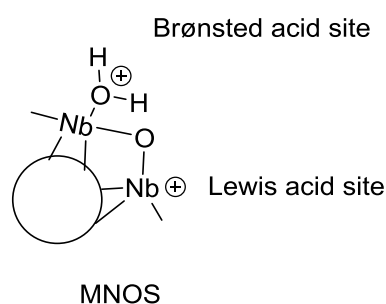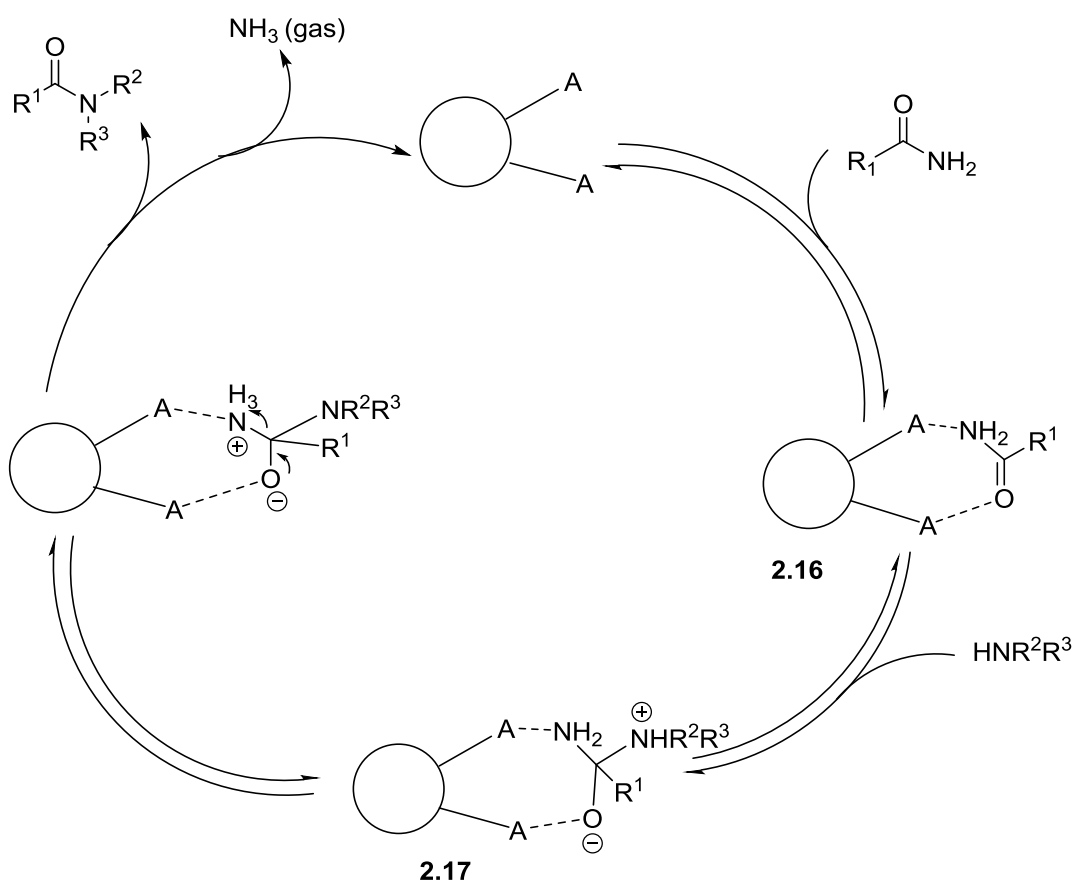

Figure 2.02: MNOS structure

Scheme 2.22: MNOS catalysed transamidation

In other sections, the use of urea as an ammonia source has been mentioned, however, urea has great potential as a cheap, abundant and bench stable acyl donor by substitution of either one or both of the nitrogens moieties. As urea contains, in effect two amide like moieties, it is incredibly stable. The formation of mono and disubstituted products of urea is an area of great interest due to their pharmaceutical and agrochemical relevance as previously mentioned.[82] As traditional methods for the formation of substituted ureas involve phosgene gas or the substitution of carbamates, new investigations have focussed on catalytically transamidating urea.

The reaction of amines with urea upon heating is known and well documented. It was found that the urea decomposes to form isocyanic acid, which then reacts with an amine to form a mono-substituted urea. This can then form an isocyanate, which can then again further react with an amine to form a disubstiuted urea.[83] Other systems have required the addition of strong acids and high temperatures in order for reaction to occur.[84]

Although several systems for the transamidation of amides have been applied to the similar reactions involving ureas, there are few protocols designed specifically for ureas. One of these methods utilises transition metals. Zinc dichloride was particularly effective at synthesising *N,N'*-disubstituted ureas from urea and thiourea. Low catalyst loadings of 5 mol% were sufficient with mild temperatures of 80-85 °C. This was a solvent free procedure, carried out for short times ranging between 5 to 10 minutes. High yields of the symmetric disubstituted products were obtained after isolation, in these cases the mono-substituted product was not isolated.[85]

Summary

The formation of amides from a range of acyl donors has been discussed with literature methods presented for esters, carbamates, ureas and amides. However, despite the numerous methodologies that have been developed for these transformations, there is still scope for further improvements, with several protocols still needing high temperatures or long reaction times, in

addition to the use of expensive catalysts. Therefore, additional endeavours must be made to find alternative methodologies.

Chapter 2: Results and Discussion 2
## Esters, Ureas and Carbamates as Acyl Donors

Introduction and Initial Work

Amide bond forming reactions and transamidation reactions have been widely documented in the literature.[8],[75] Examples presented by previous members of this group are where investigations for this study began. Zirconocene dichloride was found to be a suitable catalyst for the coupling of carboxylic acids and amines and improved systems for this were investigated in Chapter 1 (Scheme 2.23).
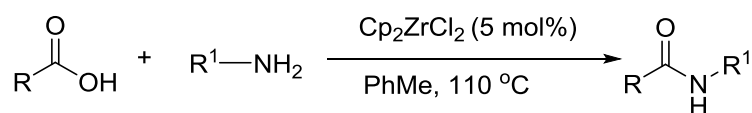
Scheme 2.23: Zirconocene dichloride catalysed amide bond formation[8]

Transamidation studies, carried out by Dr Ben Atkinson, also demonstrates the use of zirconocene dichloride in a similar catalytic system. This work focusses on the use of amides as acyl for transamidation reactions. It was found that this reaction could proceed to completion in the presence of zirconocene dichloride in mild conditions (Scheme 2.24).[86]
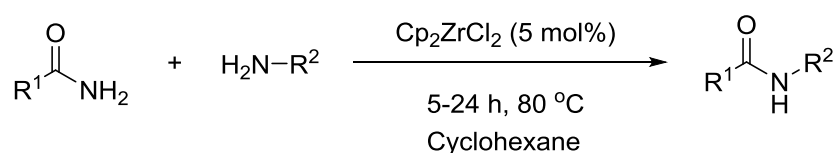
Scheme 2.24: Transamidation of primary amides with amines catalysed by zirconocene dichloride

Aim

Having only focussed on the direct coupling of carboxylic acids and amines to form amides, our efforts were then turned to applying the catalytic system to other carbonyl containing compounds, esters, carbamates and ureas. The aim of these investigations was to determine the suitability of zirconocene dichloride as a catalyst in the nucleophilic substitution reactions of these types of substrates to form a number of amide derivatives.

Esters as acyl donors

General carbonyl reactivity suggests that esters are more reactive than both acids and amides. On this basis, our attention was turned to the aminolysis of esters using zirconocene dichloride. Using 3-phenylpropionic acid ethyl ester as a parent substrate, investigations commenced with screening a range of solvents.

Table 1: Solvent screen for ester-amine coupling in the presence and absence of the catalyst
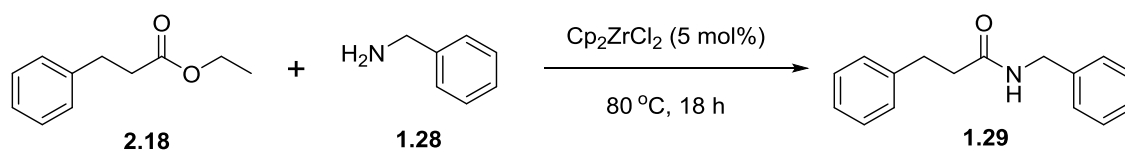
Entry	Solvent	Conversion with catalyst (%)	Background conversion (%)
1	H_2O	7	7
2	Acetonitrile	15	0
3	DCE	6	0
4	THF	23	0
5	1,4-Dioxane	4	0
6	Toluene	8	0
7	Hexane	32	5
8	Cyclohexane	17	0
9	Ethanol	6	0
10[a]	Toluene	42	0
11[b]	Heptane	88	5

Conditions: 3-Phenylpropionic acid ethyl ester (1 mmol), benzylamine (1.2 mmol), solvent (1 mL), Cp₂ZrCl₂ (5 mol%), 18 h, 80 °C. (a) 110 °C, 24 h (b) 100 °C, 24 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

From the results of the background reaction, it is clear that this reaction will not proceed in the majority of solvents. However, in water a conversion of 7% was obtained (Table 1, entry 1); this is unsurprising as the transition state

is stabilised in the polar solvent due to solvation. The only other solvent to show any formation of **1.29** was hexane with 5% conversion (Table 1, entry 7).

Under the tested conditions of 80 °C and 18 hours the conversions were very low; indicating that this is a robust reaction requiring either longer reaction times or higher reaction temperatures. The highest conversion obtained in the presence of the catalyst was 32% when hexane was employed as the reaction solvent (Table 1, entry 7). Interestingly the reaction proceeded to 7% conversion in water, both in the presence and absence of the catalyst. This implies that the catalyst, in this case, was having no effect on the reaction. This is potentially due to the poor solubility of the catalyst in water, therefore preventing sufficient interaction with the substrates. It is also possible that the catalyst decomposed in water due to its high oxophilicity.

As a result of the low conversion obtained at 80 °C, an increase in temperature was explored. Consequently, the solvent was changed to heptane, allowing for an increase in temperature to 100 °C at ambient pressure. Despite a longer reaction time of 24 hours in addition to the increased temperature, only 88% conversion was reached (Table 1**,** entry 11). This was a disappointing result for this reaction, as literature has shown that it is able to proceed at lower temperatures and shorter times. Thus, ester-amine coupling reactions were not investigated any further and attention was turned to the use of alternative acyl donors.

The effect of additives on this transformation was investigated by Dr Dominic van der Waals as a continuation of the work presented in this section. This recent yet unpublished work details that this system could benefit from the addition of 10 mol% ammonium thiocyanate (NH_4SCN). This additive allows the reaction to reach quantitative conversions at a reduced temperature of 80 °C with a range of ester leaving groups (Scheme 2.25). These included methyl, ethyl and benzyl esters. Formyl esters tolerated substitution from secondary amines in high conversion and yield. Amides were synthesised in high yield from a variety of primary amines including primary aliphatic and

benzylic functionalities. This methodology could not be extended to the acylation of sulfonamides.
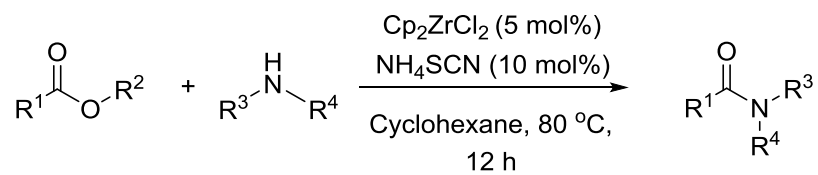

Scheme 2.25: Zirconocene dichloride catalysed synthesis of amides from esters

Ureas

As previously mentioned, zirconocene dichloride has been shown to catalyse transamidation reactions between primary amides and amines.[86] In the hope of applying this methodology to related compounds, urea was considered as a possible carbonyl source.

**Table 2: Solvent screen for urea-amine coupling reaction**
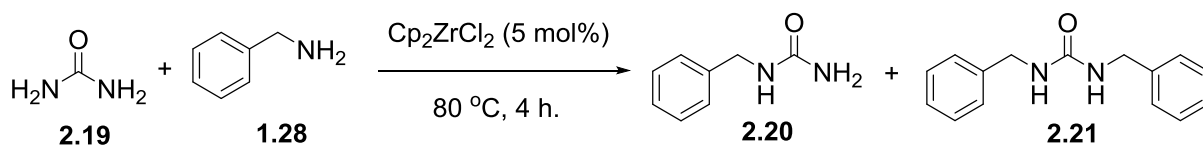
Entry	Solvent	Conversion into 2.20 (%)
1	Toluene	10
2	DCE	0
3	Cyclohexane	0
4	THF	0
5	H_2O	0
6	Ethyl acetate	0
7	Hexane	0

Conditions: Urea (1 mmol), benzylamine (1 mmol), Cp_2ZrCl_2 (5 mol%), solvent (1 mL), 80 °C, 4 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

Urea (**2.19**) was reacted with benzylamine (**1.28**) in the presence of zirconocene dichloride in a range of solvents and the observed conversions are given in Table 2. Interestingly, of the solvents investigated, this transformation seems to occur only in toluene. This is contrary to the transamidation reaction, which is most active in cyclohexane and has reduced activity in toluene, the reason for this remains unclear. However, for these studies all further investigations were carried out in toluene. Furthermore, only the formation of product **2.20** was observed and none of the disubstituted product **2.21** was seen under these conditions.

Further investigations were conducted under more forcing conditions, to determine if the disubstituted product **2.21** could be formed.

Table 3: **Amine concentration screen**
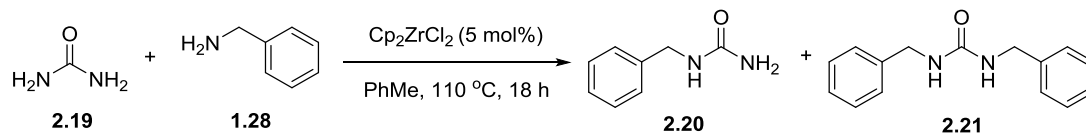
Entry	Catalyst (mol%)	Equivalents of amine	Conversion into 2.20 (%)	Conversion into 2.21 (%)
1	-	1	0	0
2	-	2	0	0
3	5	1	66	12
4	5	2	54	7

Conditions: Urea (1 mmol), benzylamine (as indicated), Cp$_2$ZrCl$_2$ (5 mol%), 18 h, 110 °C, PhMe (1 mL). Conversions were determined by analysis of the crude ^{1}H NMR spectra.

On altering the reaction conditions and the equivalents of amine, it can be seen that the major product is still the monosubstituted urea (**2.20**). It can also be seen that in the absence of the catalyst no reaction occurs (Table 3, entries 1 and 2), even on increasing the amount of amine no product is observed. However, in the presence of the catalyst 66% conversion into product **2.20** and 12% into product **2.21** was seen (Table 3, entry 3). In an attempt to reach full conversion, the number of equivalents of amine were increased. This resulted in a decrease in conversion, where only 54% conversion was observed.

In order to determine if the disubstituted urea product **2.21** could be formed from the monosubstituted urea, the reaction was performed under harsher conditions. The temperature was increased to 130 °C and a subsequent change of solvent to *p*-xylene was made to allow for this change (Table 4).

Table 4: The effect of a higher temperature
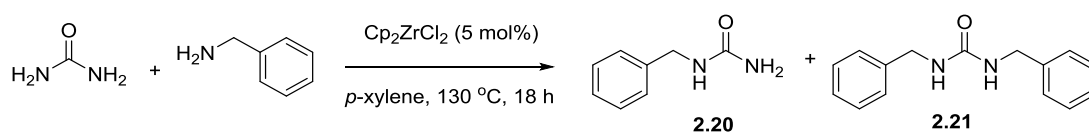
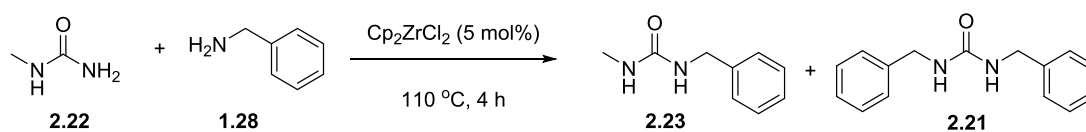| Entry	Cp$_2$ZrCl$_2$ (mol%)	Conversion into 2.20 (%)	Conversion into 2.21 (%)
1	-	40	38
2	5	27	35

Conditions: Urea (1 mmol), benzylamine (2 mmol), Cp$_2$ZrCl$_2$ (5 mol%), *p*-xylene (1 mL),130 °C, 18 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

It can be seen that the increase in temperature to 130 °C did not result in a significant increase in conversion. There was however a change in the product distribution; under the higher temperatures **2.21** was the major product, formed in 35% conversion (Table 4, entry 2), where previously only 7% (Table 3, entry 4) had been observed.

In the absence of the catalyst (Table 4, entry 1) a higher overall conversion of 78% was seen. This result implies that at these higher temperatures, the thermal reaction is too competitive for the catalyst. In addition to this, even under forcing conditions it was not possible to form one product in high conversion.

Transamidation of monosubstituted ureas

Additional studies were undertaken in order to determine if the monosubstituted urea can undergo further transamidation to form the disubstituted urea product.

Table 5: Transamidation of *N*-methylurea with benzylamine

Entry	Cp$_2$ZrCl$_2$ (mol%)	Equivalents of amine	Conversion into 2.23 (%)
1	-	1	22
2	-	2	50
3	5	1	42
4	5	2	58

Conditions: *N*-methylurea (1 mmol), benzylamine (as indicated), Cp$_2$ZrCl$_2$ (5 mol%), PhMe (1 mL), 4 h, 110 °C. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

Transamidation reactions carried out using *N*-methylurea (**2.22**) showed the formation of only one product (product **2.23**) in all cases. Interestingly, these conversions were obtained in short reaction times of only four hours, when the transamidation of urea required much more forcing conditions. Although the catalyst appears to have a positive effect on the progression of the reaction, there is only a marginal increase in conversion from 50% (Table 5, entry 2), to 58% (Table 5, entry 4)

These results suggest that the loss of ammonia is favoured over the loss of methylamine. Furthermore, substitution of a secondary amide, would be expected to be slower due to the increased steric hindrance of the R groups. However this trend was not observed in the previous section where monosubstituted ureas were slow to form the disubstituted product.

Although it was promising that product **2.23** was formed, the catalyst proved to have a limited effect. In order to investigate further the potential of the catalyst for these reactions, an alternative starting monosubstituted urea,

N-phenylurea, was selected. It was hoped that as aniline is a good leaving group, that formation of the symmetrical product would be more favoured.

Table 6: Formation of disubstituted ureas from *N*-phenylurea
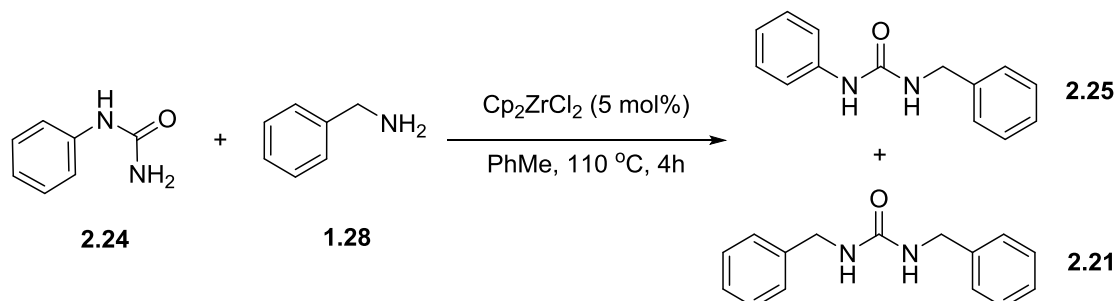
Entry	Cp$_2$ZrCl$_2$ (mol%)	Equivalents of amine	Conversion into 2.25 (%)	Conversion into 2.21 (%)
1	-	1	19	38
2	-	2	24	18
3	5	1	19	29
4	5	2	-	50

Conditions: *N*-Phenylurea (1 mmol), benzylamine (as indicated), Cp$_2$ZrCl$_2$ (5 mol%), PhMe (1 mL), 110 °C, 4 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

The same experiments were carried out with *N*-phenylurea (**2.24**) and these exhibited different results; the main difference being that in this case, two products were observed, product **2.25** and product **2.21**. In the absence of the catalyst high total conversions into product were seen with 57% and 42% for one and two equivalents of amine respectively. However, these conversions did not increase on addition of the catalyst. Suggesting that due to the favourable leaving group ability of aniline, the thermal reaction was incredibly competitive. Conversely to previous studies, the symmetrical product **2.21** was formed as the only product in 50% conversion under certain reaction conditions (Table 6, entry 4) and in this case 1-benzyl-3-phenylurea (**2.25**) was not observed.

Based on these observations, it can be concluded that monosubstituted ureas can undergo substitution at either side of the carbonyl, depending on the leaving group ability. Those with a better leaving group, such as

phenylureas, are able to form the symmetrical urea, by substitution on both sides. Those with less stable leaving groups only favour substitution on one side, with liberation of ammonia being preferred.

Carbamates as acyl donors

With limited success in forming amides from esters and ureas, carbamates were then considered for use with this catalyst. Three possible products could have been formed in this reaction either the monosubstituted urea (**2.20**), formed by liberation of the alcohol from the carbamate, or the *N*-substituted carbamate (**2.27**) formed by liberation of ammonia. It is also possible for the disubstituted urea (**2.21**) to form, by reaction on both sides of the carbonyl. With transamidation reactions proving to occur more readily than aminolysis of esters in the presence of this catalyst, it was hoped that substitution of the nitrogen would occur, rather than of the oxygen of the carbamate. Not only this but the release of ammonia gas would be more entropically favourable over the liberation of ethanol, however as the alkoxide is a better leaving group, loss of this was also probable.

Table 7: Solvent screen for carbamate-amine reaction
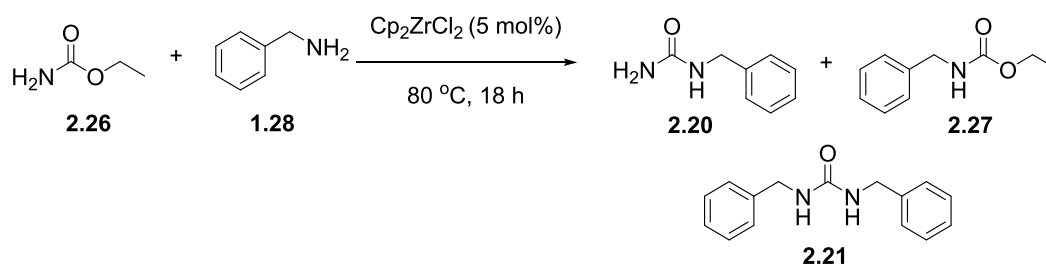
Entry	Solvent	Conversion into 2.20 (%)
1	Anhydrous Cyclohexane	42
2	DMSO	24
3	Acetonitrile	27
4	THF	16
5	Toluene	31
6	DCE	28
7	Heptane	30

Conditions: Ethyl carbamate (1 mmol), benzylamine (1.2 mmol), Cp$_2$ZrCl$_2$ (5 mol%), solvent (1 mL), 80 °C, 18 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

In all cases only the monosubstituted urea, product **2.20**, was observed. This involved nucleophilic substitution at the ester moiety of the carbamate to liberate the alcohol. Under the stated conditions and with the solvents screened products **2.27** and **2.21** were not observed.

Transamidation studies suggested that amides are more reactive than esters in substitution reactions of this type with Cp_2ZrCl_2. Bearing this in mind, it was perhaps surprising for nucleophilic substitution to occur at the O-terminus of the carbamate. It can be suggested that substitution of the alkoxide is favoured over the loss of ammonia due to the stability of this leaving group and its ability to be solvated by the reaction solvent.

The results presented in the solvent screen (Table 7) suggest that anhydrous cyclohexane was the best solvent for the reaction of ethyl carbamate and benzylamine to form monosubstituted urea **2.20**. The product was formed in 42% conversion (Table 7, entry 1). In order to achieve a higher conversion the reaction was carried out for 24 hours, however this only achieved the desired product in 62% conversion. In an attempt to drive the reaction further the solvent was changed to toluene, which gave the desired product in 31% conversion (Table 7, entry 5); in this solvent the temperature could be increased to 110 °C due to its higher boiling point.

Table 8: **Amine concentration screen**
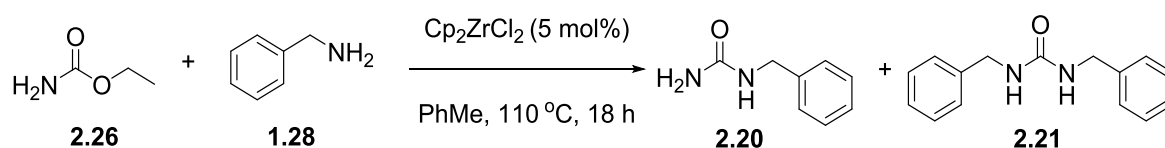
| Entry	Catalyst (mol%)	Amine equivalents	Conversion (%) into 2.20	Conversion (%) into 2.21
1	-	1.2	0	0
2	-	2.4	4	2
3	5	1.2	73	27
4	5	2.4	63	26

Altering the quantity proportion of amine (Table 8) resulted in the formation of two products, with **2.20** being the major product and **2.21** being the minor product. As this mixture was not observed when the reaction was conducted at a lower temperature of 80 °C, it is probable that the increase in temperature caused the formation of the disubstituted product **2.21**.

A significant increase in the formation of product **2.20** was seen on increasing the temperature to 110 °C, from 31% (Table 7, entry 5) to 73% (Table 8, entry 3).

It is clear that the catalyst had a positive effect on this reaction, with a negligible background rate when both 1.2 and 2.4 equivalents of amine **1.28** were present (Table 8, entries 1 and 2); the catalysed conversions were considerably higher.

A decrease in the total conversion from 100% to 89% was seen when 2.4 equivalents of amine **1.28** were added. Indicating that excess amine could be detrimental to the progression of the reaction (Table 8, entries 3 and 4). As a result, further studies were conducted with only 1.2 equivalents of the amine.

Being unable to obtain only one product by running the reaction in toluene; heptane was selected as another, non-polar, aprotic, high boiling solvent. On increasing the reaction time to 24 hours and the reaction temperature to 100 °C, 100% conversion into monosubstituted urea **2.20** was observed. Consequently further optimisation studies were carried out in heptane at 100 °C.

Table 9: Temperature Screen
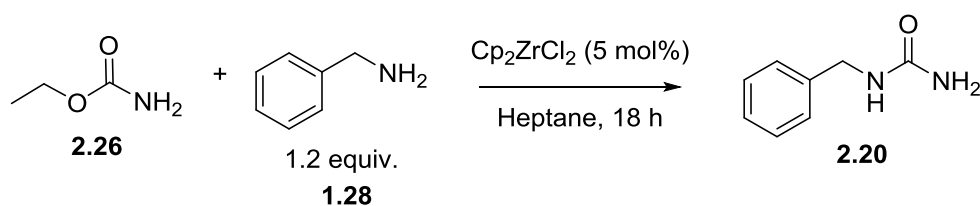
Entry	Temperature (°C)	Conversion into 2.20 (%)
1	80	10
2	90	38
3	100	100

Conditions: Ethyl carbamate (1 mmol), benzylamine (1.2 mmol), PhMe (1 mL), Cp_2ZrCl_2 (5 mol%), 18 h. Conversions were determined by analysis of the crude ^1H NMR spectra.

A brief temperature screen was conducted in heptane (Table 9). This indicated that lower temperatures of 80 and 90 °C yielded significantly lower conversions of 10% and 38% (Table 9, entries 1 and 2) than that observed at 100 °C. These results suggest that 18 hours and 100 °C were required for this substrate to form the desired product in quantitative conversion (**2.20**). Pleasingly, only one product was formed under these conditions.

Table 10: Catalyst loading optimisation
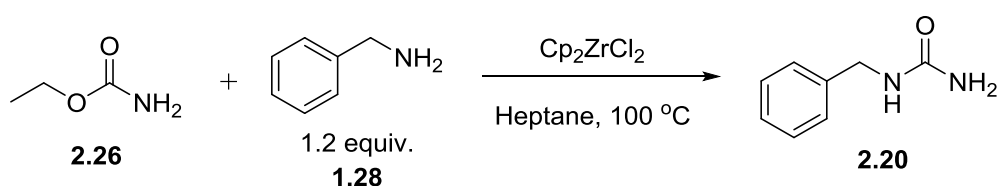
Entry	Catalyst loading (mol%)	Time (h)	Conversion into 2.20 (%)
1	5	18	100
2	2.5	18	76
3	2.5	24	91
4	0	24	0

The catalyst loading was then investigated (Table 10). It was found that reducing the catalyst loading to 2.5 mol% resulted in a decrease in conversion from 100% to 76% (Table 10, entry 2). On increasing the reaction time with this lower catalytic loading, the conversion only increased by 15% in the extra six hours. Despite showing 91% conversion with 2.5 mol% catalyst (Table 10, entry 3), with more robust substrates or less nucleophilic amines, these conversions may have been considerably lower; therefore the remainder of the investigation was conducted with 5 mol% catalyst.

Substrate Scope

To ensure that the system was not simply optimised for a specific carbamate and amine, several carbamates were subjected to this coupling reaction.

Table 11: Scope of carbamates
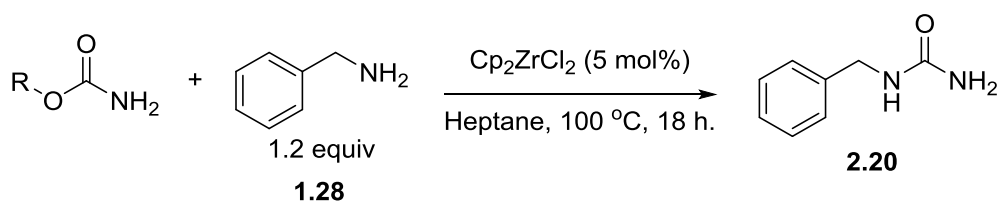
Entry	Carbamate	Conversion (%)
1		100
2		96 (mixture of products observed)
3		83
4		95

Conditions: Carbamate (1 mmol), benzylamine (1.2 mmol), Cp$_2$ZrCl$_2$ (5 mol%), heptane (1 mL), 100 °C, 18 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.
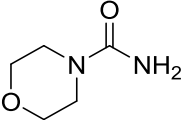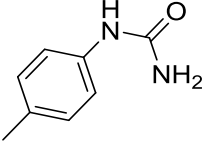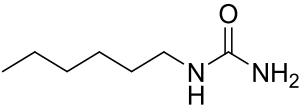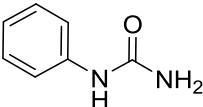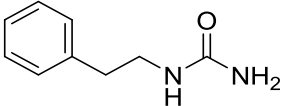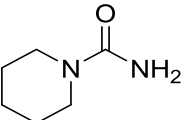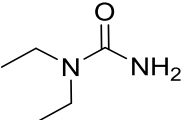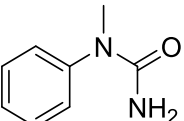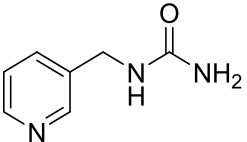
The range of tested carbamates (Table 11) showed that ethyl carbamate (Table 11, entry 1) was the most suitable carbamate for this reaction proceeding to full conversion in the presence of the catalyst. It is also cheap and commercially available, in addition to being easily identifiable by ^{1}H NMR analysis. n-Butyl carbamate, reacted at a slightly slower rate, reaching 83% conversion (Table 11, entry 3). Even bulky *tert*-butylcarbamate (Table 11, entry 4) could be used as a carbonyl source in this coupling. Benzyl carbamate (Table 11, entry 2) however resulted in a mixture of products, 92% of the desired monosubstituted urea (**2.20**) and 4% disubstituted urea (**2.21**). This trend was seen when the reaction solvent was toluene and higher temperatures were employed.

To make this process as atom economic as possible, the smallest leaving group is most favoured, not only this but this substrate reacts at a faster rate and the by-product (ethanol) can be removed under reduced pressure. Therefore ethyl carbamate (**2.26**) was the carbamate of choice for the remainder of the project.
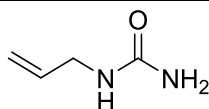
Table 12: Amine-carbamate substrate scope
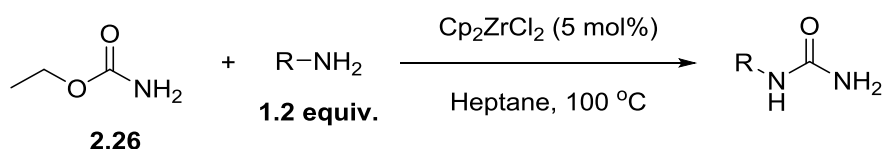
Entry	Compound number of product	Urea product	Conversion (%)	Yield (%)
1[a]	**2.20**		100	87
2	**2.28**		100	61

3	**2.29**		100	84
4[b]	**2.30**		100	89
5	**2.31**		100	80
6[b]	**2.32**		100	92
7	**2.33**		100	69
8[b]	**2.34**		100	60
9	**2.35**		80	49
10	**2.36**		64	-
11	**2.37**		13	-

| 12 | **2.38** | | 0 | - |

Conditions: Ethyl carbamate (1 mmol), amine (1.2 mmol), Cp$_2$ZrCl$_2$ (5 mol%), heptane (1 mL), 100 °C, 24 h. (a) 18 h. (b) Experiments and isolations were conducted by Dr James Walton. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

A variety of substrates was investigated including primary, secondary, aliphatic and aromatic amines. Primary amines such as benzylamine (Table 12, entry 1) and hexylamine (Table 12, entry 5) produced the monosubstituted urea in quantitative conversion and high yield. Secondary amines such as morpholine (Table 12, entry 3) and piperidine (Table 12, entry 8) also proceeded to quantitative conversions and yielded 84% and 60% respectively. Anilinic amines (Table 12, entries 4 and 6), with low nucleophilicity, were also compatible with this system under the optimised conditions.

Limitations of this methodology included the lower conversions obtained when diethylamine (Table 12, entry 9) and N-methylaniline (Table 12, entry 10) were used. These lower conversions are as a result of the increased steric hindrance around the nitrogen of these amines. In addition, this method is incompatible with pyridine containing amines, as only 13% conversion was observed when 3-pyridinylmethylamine (Table 12, entry 11) was used. This is surprising as similar amines such as benzylamine achieved such high conversions. This additional pyridine nitrogen may have resulted in binding to the catalyst, therefore preventing reaction from occurring. In addition, allylamine (Table 12, entry 12) resulted in 0% conversion to the desired urea product, potentially due to the presence of the terminal double bond causing chelation to the catalyst or more likely due to the lower boiling point of the amine and high reaction temperature.

Alternative carbamate reactions

Alternative reactions were investigated in order to apply the methodology to other carbamate based reactions. The possibility of forming cyclic ureas was

explored by using diamines. These are known to be formed when diamines are reacted with urea in the absence of a catalyst. However this process does require high temperatures of 150 °C and high pressures.[87]
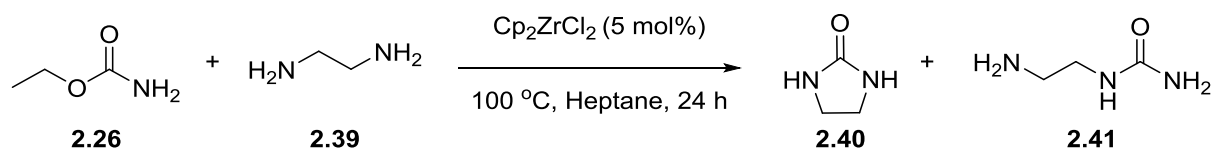
Scheme 2.26: Formation of cyclic ureas from carbamates and diamines

The potential to form cyclic ureas was studied using the developed methodology, by coupling ethylenediamine (**2.39**) and ethyl carbamate (**2.26**) together (Scheme 2.26). Two possible products were likely to form, the cyclic urea, imidazolidin-2-one (**2.40**) and (2-amino-ethyl) urea (**2.41**). It was expected that the monosubstituted urea 2.41 may be observed, however neither product was seen by analysis of the crude ^{1}H NMR spectrum and only starting materials were returned. This low reactivity is possibly as a result of chelation of the amine to the zirconium metal centre, therefore inhibiting the catalyst from functioning.

Other possible substrates were studied such as *N*-substituted carbamates. Substitution on the oxygen side of the carbonyl would result in the formation of *N,N'*-disubstituted ureas (Scheme 2.27).
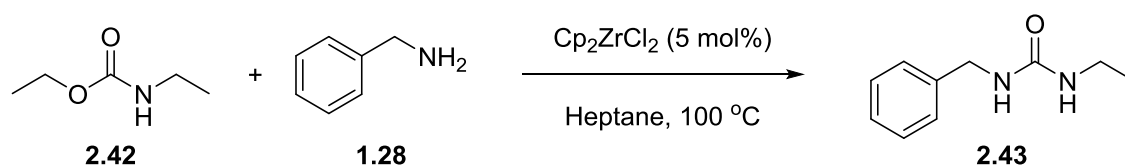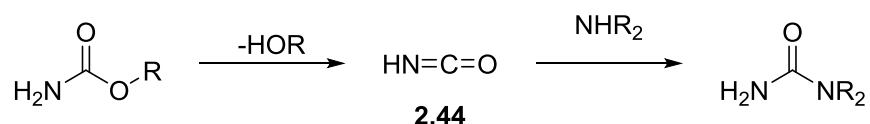

Scheme 2.27: Formation of *N-N'*disubstituted ureas from *N*-substituted carbamates and amines

It was anticipated that *N-N'* disubstituted urea **2.43** would be formed with substitution of the alcohol with the amine and that the amide moiety would be left unreacted. However, disappointingly no reaction was observed at all. This means that this system could be compatible with Boc protected

substrates, where the Boc group is attached to a free nitrogen. In this case the Boc group would remain unreacted.

Possible reaction pathway

Carbamates are known to decompose thermally to give isocyanates.[88] In this case, isocyanic acid (**2.44**) would be formed and ethanol would be liberated. This isocyanic acid intermediate **2.44** can then be attacked by the amine, in a zirconium mediated step, to form the monosubsituted urea product (Scheme 2.28). An alternative pathway involves the direct attack of the amine on the carbamate, also liberating the corresponding alcohol.

Scheme 2.28: Formation of monosubstituted ureas from carbamates via an isocyanic acid intermediate

In order to determine a potential reaction pathway, further studies were conducted. The reaction of benzyl carbamate **2.45** was investigated due to the higher boiling point of the corresponding alcohol. This study was carried out in the absence of amine (Scheme 2.29). Under these conditions, production of benzyl alcohol (**2.46**) was seen by analysis of the ^{1}H NMR spectrum.
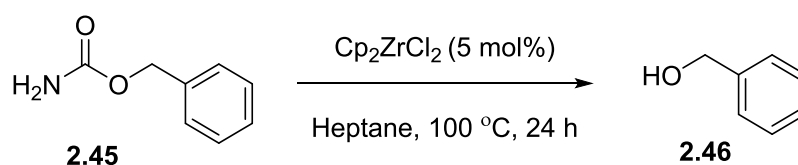
Scheme 2.29: Liberation of benzyl alcohol from benzylcarbamate in the absence of amine

This indicates that formation of the isocyanic acid, is a possible pathway, as in the absence of the amine the carbamate still decomposed. However, as there was still evidence of the starting carbamate being present, it suggests that this decomposition pathway is not the only functioning mechanism in this transformation. On this basis the direct attack of the amine on the carbamate cannot be dismissed. In order to gain an improved understanding of the

mechanism for this transformation further studies would have to be conducted.

Discussion

The reactivities of esters, ureas and carbamates have been investigated in relation to other carbonyl containing compounds.
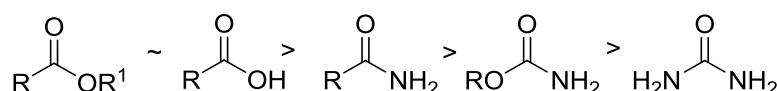

Figure 2.03: General reactivity series of the carbonyls

It is generally accepted that ureas are the least reactive of the carbonyl species. The unreactive nature of ureas can be attributed to the electron donating ability of the nitrogens. The lone pair is able to donate into the π^* orbital of the carbonyl, resulting in a strong C-N bond. In carboxylic acids and esters, the oxygen is less able to donate into this orbital due to the increased electronegativity of oxygen in comparison with nitrogen. This means that it does not donate as strongly. In addition, when the π^* orbital is being populated by a strong donor (such as nitrogen) it is less susceptible to nucleophilic attack, which usually occurs by donating into this orbital. This means that the carbonyl carbon in esters and carboxylic acids is more susceptible to nucleophilic attack than in amides and ureas.[89]

Carbamates are considered less reactive than both esters and amides as a result of both the oxygen and the nitrogen donating into the π^* orbital of the carbonyl. Consequently, the carbonyl carbon is even less susceptible to nucleophilic attack than in amides.[90]

The results presented in this Chapter and Chapter 1, show a different trend in reactivity. In conjunction with transamidation studies conducted within the group, it can be concluded that with the given catalyst, amides are more reactive than carbamates, carboxylic acids and esters in this system.
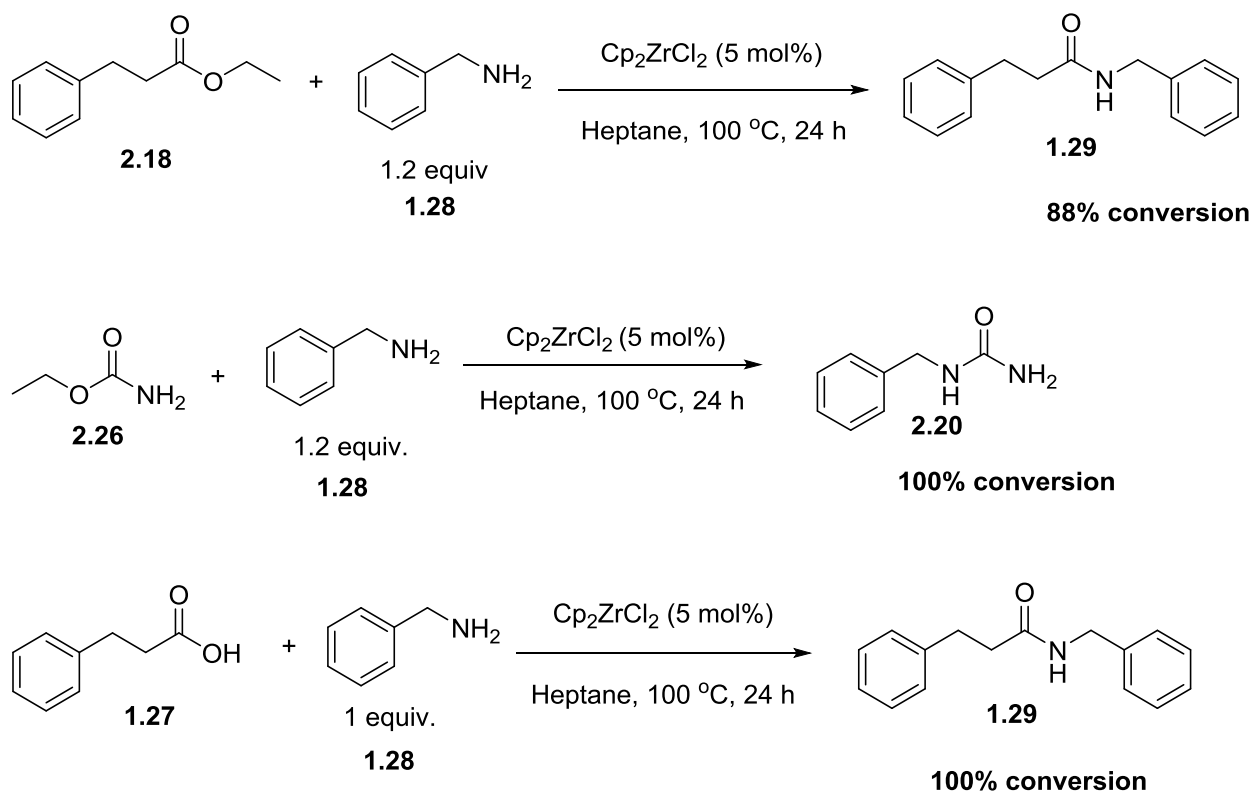
Scheme 2.30: Ester and carbamate reaction schemes with amines

The results presented in this Chapter are inconsistent with the accepted trend in reactivity. It is suggested that in the presence of Cp_2ZrCl_2, amides are more reactive than other carbonyl containing compounds, as they will undergo transamidation reactions at milder conditions than substitution reactions of other carboxylic acid derivatives. In this case the production of ammonia drives the reaction and its insolubility in the reaction solvent pushes the reaction further. This deviation from the accepted trend suggests that the presented results are a reflection of the ability of the catalyst to interact with the substrate, rather than the stability of the leaving groups and products.

Carboxylic acids are surprisingly less reactive than amides in the given catalytic system. During this condensation reaction, water is produced as a by-product and due to the oxophilic nature of zirconium, this can cause obstruction of the catalytic cycle. Consequently, carboxylic acids require higher reaction temperatures and in some cases longer reaction times. Even on removal of this by-product they are not as reactive as amides (Chapter 2),

perhaps as a result of the more favourable interaction between the Lewis basic amide and the Lewis acid catalyst.

This Chapter has demonstrated that esters are less reactive than both of these species, as quantitative conversions could not be obtained with this catalyst, even under forcing conditions. Where esters achieved 88% conversion under the specified conditions, carboxylic acids, amides and carbamates achieve quantitative conversions (Scheme 2.30). Although it is unclear as to why this low reactivity is observed with esters, it is possibly as a consequence of the alcohol by-product that is formed. Due to the oxophilic nature of zirconium, binding to the oxygen of the alcohol would be favourable, thus blocking a coordination site on the metal for further reaction to occur. This alkoxide would also result in a greater degree of steric hindrance in comparison with water, resulting in further obstruction of the catalyst, causing a lower reactivity than carboxylic acids.

Carbamates also generate an alcohol when substitution occurs on the oxygen. However, quantitative conversions are possible to achieve in this case (Scheme 7). As a result of the amide moiety on the other side of the carbonyl, carbamates are more Lewis basic in nature, resulting in a more favourable interaction with the Lewis acid catalyst. Thus improving the catalytic ability of zirconocene dichloride. In the same way, carbamates show a decreased reactivity when compared with amides. As expected they require higher temperatures and longer reaction times, as a consequence of the ester character. Thus resulting in a less Lewis basic nature than amides and therefore a less favourable interaction with the catalyst.

Conclusions

Zirconocene dichloride has been applied as a catalyst to a variety of carbonyl containing compounds to carry out both amidation and transamidation reactions. In the case of esters these investigations demonstrated that Cp_2ZrCl_2 was not a suitable catalyst for the desired transformations. Although ureas proved to be relatively inert, with high temperatures and long reaction times, Cp_2ZrCl_2 catalysed their reaction with amines obtaining a mixture of mono and disubstituted products in varying conversions.

A novel method for the formation of monosubsituted ureas from carbamates and amines was developed using zirconocene dichloride catalytically. This method was compatible with a range of amines including less nucleophilic anilines and primary and cyclic secondary amines. Lower conversions were obtained with aliphatic secondary amines. This methodology was however limited to carbamates substituted at the *O*-terminus as *N*-substituted carbamates remained unreactive.

Future Work

As zirconocene dichloride was the primary candidate for catalysing these reactions, no other catalysts were investigated. There could be more suitable metals for carrying out the investigated transformations. This would also open up investigation for other nucleophiles in these reactions such as oxygen based nucleophiles. As zirconium is very oxophilic, it is incompatible with these types of compounds. They would bind to the catalyst in preference over the amine and this would hinder the reaction. This would then allow alcohols to be used and open up the possibility of performing transesterification reactions.

Further investigations on the urea system would enable the formation of mono and disubstituted ureas using this simple catalyst, although the formation of these would be leaving group dependent. Supplementary studies on this area could allow for the formation of *N,N'*-disubstituted ureas, an area of great industrial interest.

Chapter 3: Synthesis of Primary Amides from Carboxylic Acids

"Magnesium Nitrate Catalysed Primary Amide Bond Formation
from Carboxylic Acids and Urea"

A. R. Chhatwal and J. M. J. Williams
Manuscript in preparation

Synthesis of primary amides from carboxylic acids

Primary amides are also highly useful in natural and synthetic chemistry. They are found in numerous pharmaceuticals (Figure 3.01) and natural products.[52] They are also highly versatile and can be easily converted into other functional groups and they are therefore very valuable in synthetic chemistry.[91]

Oleamide

Nepfenac

Atenolol
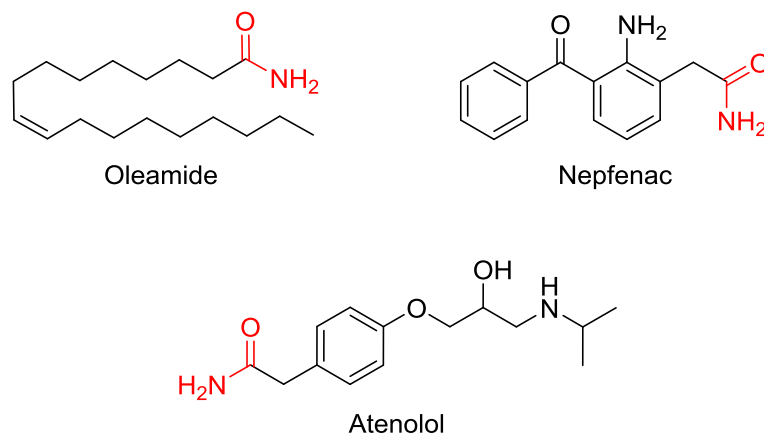
Figure 3.06: Primary amide containing products

Traditional methods of synthesising primary amides from carboxylic acids, as with secondary and tertiary amides, utilise the reactivity of acid chlorides with ammonia to form the corresponding primary amide. In many cases ammonia must be bubbled through the reaction solvent or aqueous solution (Scheme 3.01). The use of ammonia in these reactions can be troublesome, due to the low nucleophilicity and toxic nature of this reactant.[92] Numerous reports still utilise this two-step reaction although employing a simple one-pot procedure would be beneficial.
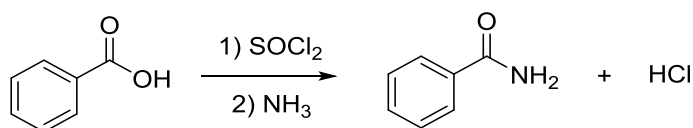
Scheme 3.01: Classical method of primary amide formation from carboxylic acids

Activating agents have been developed to facilitate the synthesis of primary amides from carboxylic acids. However they do not completely address all of the issues associated with this transformation as they are still highly atom inefficient. As with the formation of secondary and tertiary amides from

carboxylic acids, coupling agents derived from DCC and HOBt additves have been highly useful.[93] Similar activators have included *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HOTT) and tetrafluoroborate (TOTT). These were used in the presence of a base to form primary amides from carboxylic acids and ammonium chloride.[94]

In 2003 stoichiometric imidazole was utilised as an activator in coupling carboxylic acids with urea as an ammonia source to form primary amides. This investigation was carried out under microwave conditions for 90-360 s to produce the primary amides in 41-88% yield. The methodology tolerated a wide range of substrates including aliphatic, aromatic and heteroaromatic carboxylic acids. Even the more challenging, less electrophilic benzoic acids were compatible (Scheme 3.02).[95]
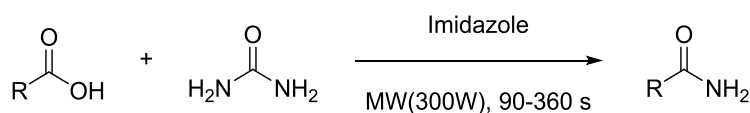
Scheme 3.02: Imidazole as an activator for the synthesis of primary amides from carboxylic acids and urea

Catalytic methods

In order to tackle the problems posed by this transformation, catalytic methods were investigated. It was hoped that these methods would be atom efficient, easy to carry out and require mild conditions.

One of the first metal catalysed methods of coupling carboxylic acids and ammonia was proposed in 2002 by Shteinberg *et al.* It was found that 2 mol% titanium *tert*-butoxide (Ti(OBu)$_4$) when used in conjunction with PEG-400 was able to couple 4-nitrobenzoic acid and ammonia to form 4-nitrobenzamide.[96] Other group IV metal catalysts were investigated by Adolfsson and co-workers, when using cheap and abundant ammonium salts. Titanium tetrachloride (TiCl$_4$) and zirconium tetrachloride (ZrCl$_4$) were explored as catalysts for primary amide formation from carboxylic acids. Temperatures up to 120 °C and three equivalents of the carbamate were required with 24 hours for the reaction to occur (Scheme 3.03). It was noted that this system was not compatible with electron rich systems such as

benzoic acids and alkenes where the double bond was conjugated with the carbonyl.[97]
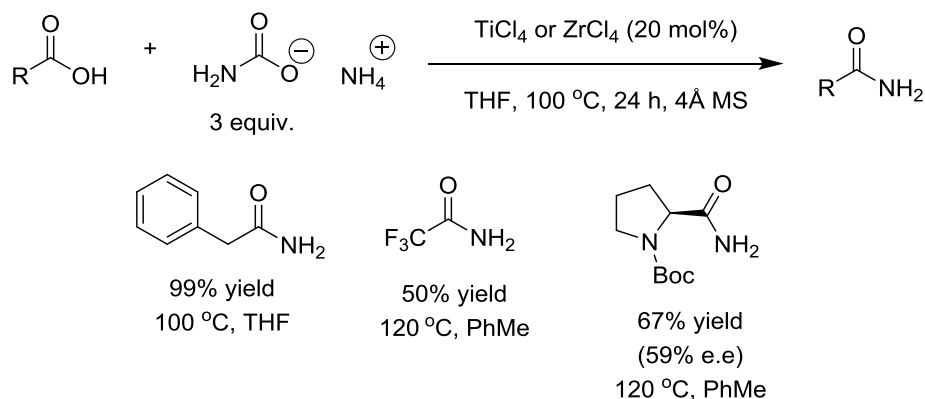
Scheme 3.03: Primary amide synthesis from carboxylic acids and ammonium carbamate

The catalytic system was also applied to the synthesis of dimethylamides by using dimethyl ammonium carbamate. This provided a catalytic method of producing tertiary amides from carboxylic acids, where otherwise the sterically hindered and bulky secondary amines would have to be used.

More recently, in 2014, a copper catalysed method was reported by Song *et al.*[98] This method was specifically for the decarboxylative ammoxidation of phenylacetic acids to benzamides. This protocol employed the cheap copper(I) oxide (Cu_2O) salt as a catalyst (Scheme 3.04). Where 20 mol% was required with molecular oxygen as an oxidant and aqueous ammonia was needed. In addition to this, high temperatures of up to 130 °C and long reaction times of up to 40 hours were necessary. For the more robust substrates, such as those with electron donating groups, an increase in temperature to 150 °C was needed in order to reach a high conversion. Nevertheless, a wide range of benzamides was produced from their corresponding phenylacetic acids and extension of this methodology to α-hydroxyphenylacetic acids was successful.
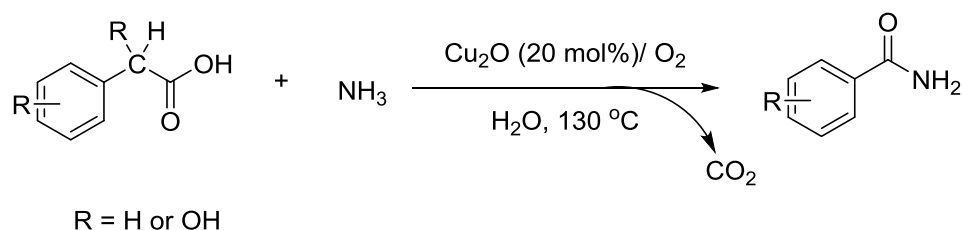
Scheme 3.04: Copper catalysed decarboxylative ammoxidation of phenyl and α-hydroxyphenylacetic acids to benzamides

A possible mechanism was proposed for this transformation (Scheme 3.05), although it was also noted that the reaction could also proceed via a radical based mechanism. The authors suggested initial oxidation of the phenylacetic acid to 2-oxo-2-phenylacetic acid **3.01**, followed by decarboxylation to yield the organocopper species **3.02**. Due to the azaphilicity of copper, coordination of the ammonia to the copper could lead to reductive elimination of the copper, regenerating the catalyst and forming benzonitrile (**3.03**). Subsequent ammonolysis gave amidine **3.04**. Finally, hydrolysis of the amidine produced the desired benzamide **3.05**.
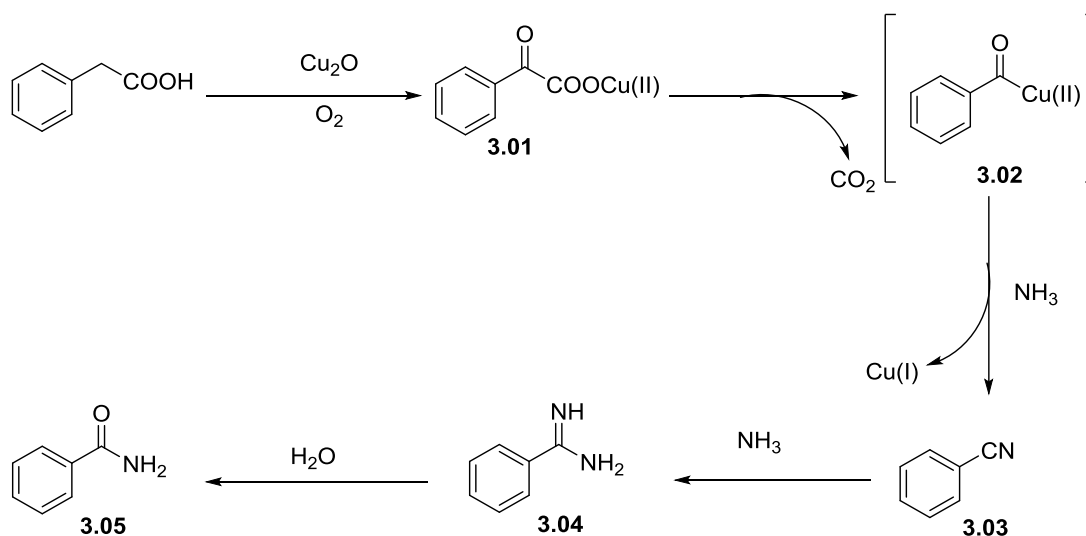
Scheme 3.05: Proposed mechanism for the copper catalysed decarboxylative ammoxidation of phenylacetic acid into benzamide

Non-metal catalysed methods

There are very few non-metal catalysed systems for this transformation. One of these was presented by Shteinberg *et al.* in association with the titanium

catalysed process. It was found that boric acid (2 mol%) when used in addition to PEG-400 (1 mol%) was able to form primary amides from 4-nitrobenzoic acid and ammonia (Scheme 3.06). This system, as before, required the ammonia to be bubbled through the solvent of 1,2,4-trichlorobenzene. High temperatures of 170-175 °C were needed for 10 hours for moderate conversions.[96]
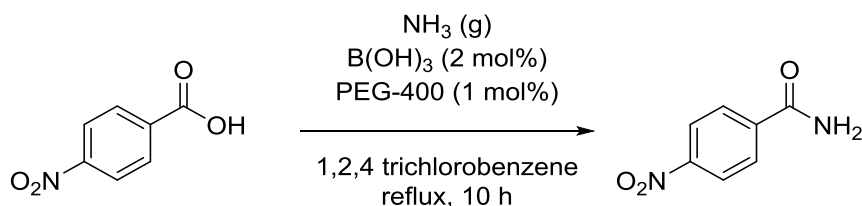
**Scheme 3.06: Boric acid and PEG-400 catalysed primary amide formation**

Heterogeneous methods

Ceric ammonium nitrate (CAN) has been demonstrated as an active solid phase catalyst for forming primary amides from carboxylic acids and urea. Only 2 mol% CAN was needed for high yields to be achieved, under microwave conditions ranging from 1 to 3 minutes depending on the substrate. An extensive substrate scope was studied, showing the tolerance of this system. Aliphatic, benzoic and conjugated acids were all compatible, producing the primary amide in high yield (Scheme 3.07).[99]

82% yield (180 s)   86% yield (60 s)   90% yield (60 s)
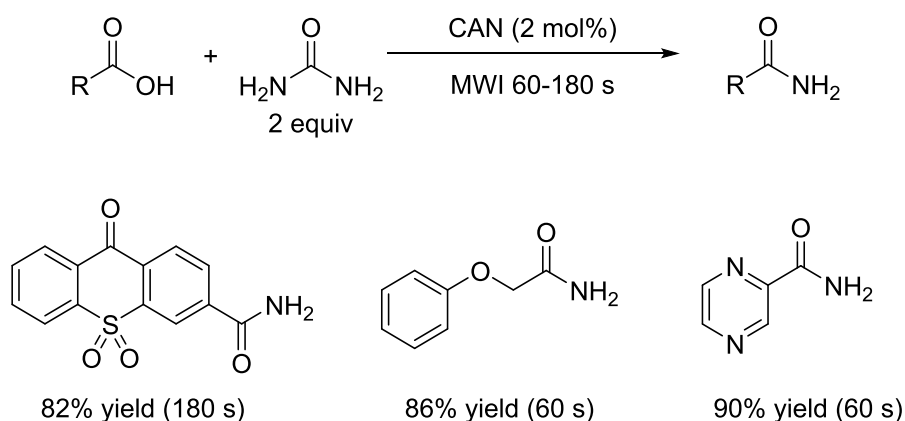
Scheme 3.07: CAN catalysed primary amide formation from carboxylic acids and urea under microwave conditions

Reddy and co-workers documented the use of zirconyl chloride ($ZrOCl_2 \cdot 8H_2O$) as a solid phase, heterogeneous catalyst for this same transformation. The amides were synthesised in a microwave and short times between 30-60 s were needed.[100] Further developing this work, in 2011 the same catalyst was reported by a different group in the synthesis of *N*-methyl amides from carboxylic acids and *N,N*-dimethylurea (Scheme 3.08).[101] In this case methylamine and carbon dioxide were produced as by-products of the reaction, perhaps acting as a driving force. This protocol could be applied to numerous substrates, including benzoic and conjugated amides.

50% yield
(15 min)

50% yield
(9 min)

90% yield
(10 min)

65% yield
(30 min)
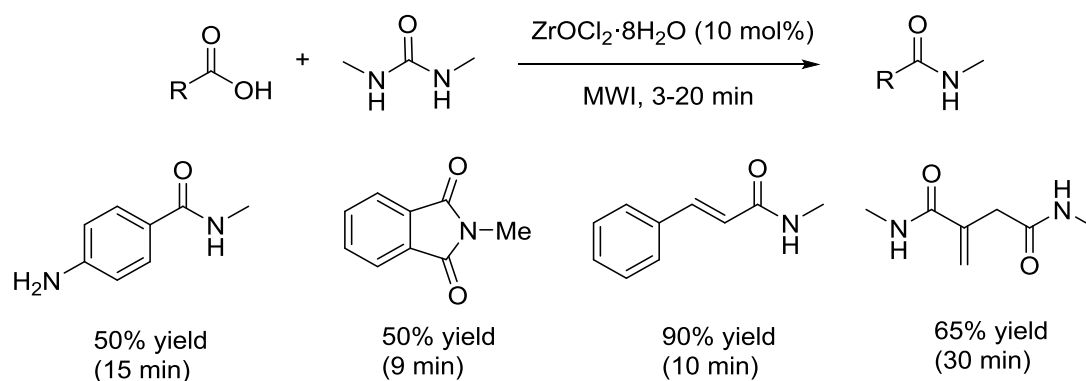
Scheme 3.08: Zirconyl chloride catalysed methyl amide formation from carboxylic acids and dimethylurea

Chapter 3: Results and Discussion

Aim

The main focus of this investigation was to develop a catalytic methodology for the synthesis of primary amides from non-activated carboxylic acids and a cheap, abundant and bench stable ammonia source.

Initial work

Ammonia source identification

Our initial investigations began with identifying an ammonia source for the reaction. For these studies, phenylacetic acid (**3.06**) was selected as the model substrate, with toluene being the test solvent as a result of its ability to prevent salt formation, as noted in Chapter 1.[8]

Table 1: Ammonia source screen
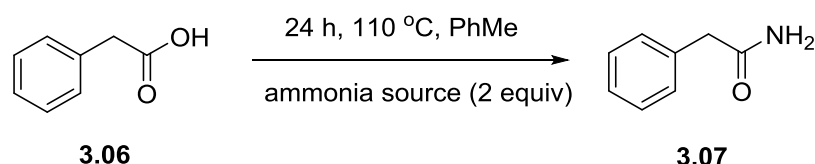
Entry	Ammonia source	Conversion (%)
1	Ammonium carbamate	12
2	Ammonium formate	12
3	Ammonium acetate	0
4	Ammonium iodide	0
5	Ammonium chloride	0
6	Formamide	3
7	Urea	17
8	Malonamide	0
9	NH_3 in Dioxane	0

Conditions: Ammonia source (2 mmol), phenylacetic acid (1 mmol), PhMe (1 mL), 110 °C, 24 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

It can be concluded that under the chosen conditions, very few ammonia sources reacted to form 2-phenylacetamide (**3.07**) despite the long reaction

time and high temperature (Table 1). Possibly as a result of low solubility of the ammonium salts in polar, aprotic solvents.

Using urea as the ammonia source resulted in the highest conversion of 17% (Table 1, entry 7). In this case a possible four equivalents of ammonia would have been released. Whereas in the case of the other ammonia sources not including malonamide, only two equivalents of ammonia would be generated.

Catalyst identification

In light of these results and taking in to account that urea is cheap, readily available and bench stable, further investigations were conducted employing urea as an ammonium source. Our aim was to identify a cheap, non-toxic and readily available catalyst for this transformation, hence the catalysts listed in Table 2 were screened.

Table 2: Catalyst screen
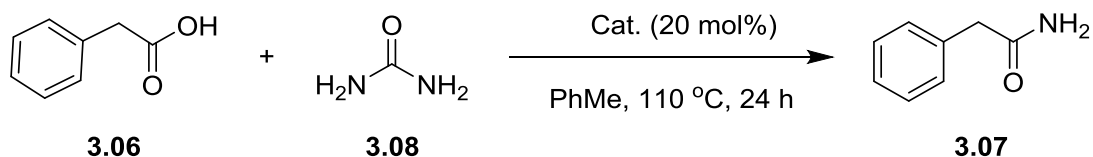
Entry	Catalyst	Conversion (%)
1	Cp$_2$ZrCl$_2$	57
2	Ti(O^{i}Pr)$_4$	57
3	Ni(NO$_3$)$_2$·6H$_2$O	32
4	ZnCl$_2$	10
5	LiBr	17
6	Sc(OTf)$_3$	20
7	Mg(OAc)$_2$·4H$_2$O	54
8	AgI	8
9	KI	15
10	pTSA	8
11	Zn(OAc)$_2$·2H$_2$O	18
12	InCl$_3$	7
13	NaI	11
14	Acetic acid	12
15	Nitric acid	9
16	CaI$_2$	10
17	-	12

*Conditions:* Phenylacetic acid (1 mmol), urea (1 mmol), catalyst (20 mol%), PhMe (1 mL), 110 °C, 24 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

Group IV metals such as titanium and zirconium (Table 2, entries 1 and 2) have been reported to show significant activity in similar systems.[97] From these previous studies, it was expected that these catalysts would yield a higher conversion and 57% was slightly disappointing.

Other cheap and abundant transition metal catalysts, such as zinc dichloride (ZnCl$_2$) and nickel nitrate (Ni(NO$_3$)$_2$·6H$_2$O) were also screened. Zinc acetate

(Zn(OAc)$_2$·2H$_2$O) (Table 2, entry 11) only resulted in 18% conversion into the desired primary amide and ZnCl$_2$ showed a comparable conversion to the background.

Interestingly, magnesium acetate (Mg(OAc)$_2$·4H$_2$O) showed 54% conversion into primary amide 3.07, (Table 2, entry 7). During this reaction, it is probable that the dissociation of the acetate ligands, could produce acetic acid. To ensure that this conversion was not as a result of acetic acid acting as a catalyst, the reaction was conducted in the presence of only acetic acid (Table 2, entry 11) and 12% conversion was observed; suggesting that the acetic acid was not acting as a catalyst in this transformation.

Although titanium(IV) isopropoxide (Ti(O^{i}Pr)$_4$) and zirconocene dichloride (Cp$_2$ZrCl$_2$) both showed comparable conversions to Mg(OAc)$_2$·4H$_2$O, they are less abundant and more expensive than magnesium salts. These metals have also previously shown activity within similar systems.[97] With the aim of developing a novel method with a cheap and abundant catalyst, further studies were performed with Mg(OAc)$_2$·4H$_2$O.

Following this, optimisation steps were carried out in order to determine the best conditions for this reaction using Mg(OAc)$_2$·4H$_2$O as the catalyst.

An initial solvent screen was conducted at 80 °C, however the conversions indicated that at this temperature, minimal product was formed. Consequently, other solvents were screened at a higher temperature of 110 °C (Table 3).

Table 3: Screen of Solvents
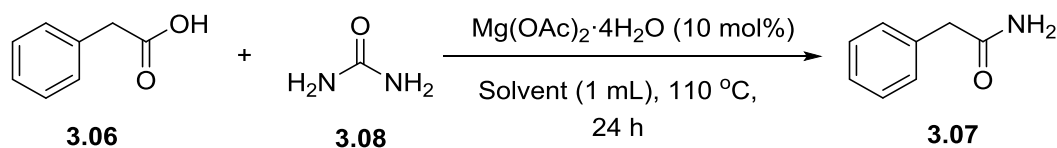
Entry	Solvent	Conversion (%)
1	Cyclopentyl Methyl ether	43
2	2-Methyl-2-butanol	43
3	Octane	68
4	DMF	4
5	Toluene	52
6	*p*-Xylene	42
7	Butyronitrile	45
8	DMSO	3

Conditions: Phenylacetic acid (1 mmol), urea (1 mmol), Mg(OAc)$_2$·4H$_2$O (10 mol%), solvent (1 mL), 110 °C, 18 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

These high boiling solvents were screened to allow for the reaction to be run at higher temperatures. At this temperature most solvents exhibited some activity and product was observed in the presence of the catalyst. Polar solvents such as DMF and DMSO (Table 3, entries 4 and 8), demonstrated particularly low conversions to the desired amide product **3.07**. Possibly as a result of carboxylate and ammonium salt formation, preventing amide bond formation taking place. Ethereal, alcohol and nitrile containing solvents also exhibited reasonable conversions, however toluene (Table 3, entry 5) and octane (Table 3, entry 3) showed the highest conversions into the primary amide.

Reaction optimisation

A variety of magnesium salts was then screened in both toluene and octane in order to achieve the highest conversion.

Table 4: Screen of magnesium salts
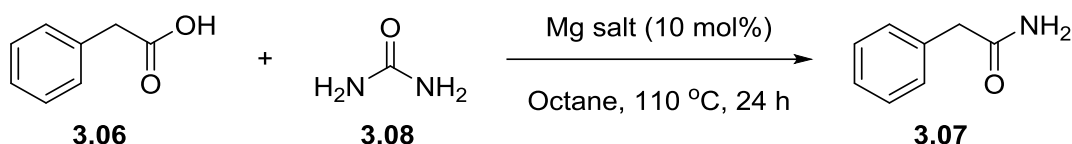
Entry	Mg catalyst	Conversion (%)
1	$Mg(OAc)_2 \cdot 4H_2O$	68
2	Mg turnings	51
3	$Mg(NO_3)_2 \cdot 6H_2O$	64
4	MgO	54
5	$Mg(OTf)_3$	61
6	$MgCl_2 \cdot 6H_2O$	65
7	$MgSO_4$	50
8	-	26

Conditions: Phenylacetic acid (1 mmol), urea (1 mmol), Mg catalyst (10 mol%), octane (1 mL), 110 °C, 24 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

The reaction of phenylacetic acid and urea was carried out in octane with a range of magnesium based catalysts (Table 4). All the catalysts that were screened showed a positive catalytic ability in this transformation. Even magnesium sulphate ($MgSO_4$) increased the conversion from the background conversion of 26% to 50% (Table 4, entries 8 and 7).

$Mg(OAc)_2 \cdot 4H_2O$, showed the greatest catalytic activity, increasing the conversion to 68% (Table 4, entry 1). This was closely followed by magnesium chloride ($MgCl_2 \cdot 6H_2O$) (Table 4, entry 6) and magnesium nitrate ($Mg(NO_3)_2 \cdot 6H_2O$) (Table 4, entry 3) reaching 65% and 64% conversion. As these salts achieved similar conversions, but $MgCl_2 \cdot 6H_2O$ was £20.70/mole

in comparison with $Mg(NO_3)_2 \cdot 6H_2O$ at £14.51/mole, $MgCl_2 \cdot 6H_2O$ was not used in further investigations.

In order to improve the reaction further, the optimal amount of urea was subjected to study.

Table 5: Urea stoichiometry
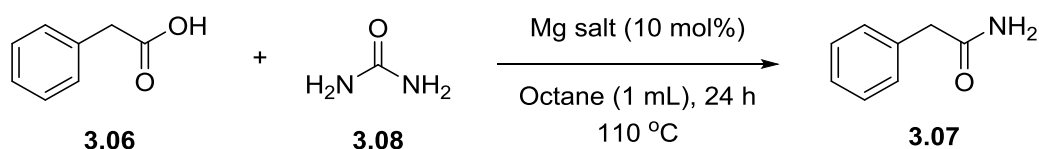
Entry	Equivalents of urea	Conversion (%) $Mg(OAc)_2 \cdot 4H_2O$	Conversion (%) $Mg(NO_3)_2 \cdot 6H_2O$	No catalyst
1	0.5	50	52	-
2	1	57	64	26
3	2	67	60	-
4	3	30	55	34

Conditions: Phenylacetic acid (1 mmol), $Mg(OAc)_2 \cdot 4H_2O$ (10 mol%), $Mg(NO_3)_2 \cdot 6H_2O$ (10 mol%), octane (1 mL), 110 °C, 24 h. Conversions were determined by analysis of the crude ^1H NMR spectra.

Increasing the equivalents of urea from 0.5 to 1, an increase in conversion was observed with both catalysts (Table 5, entries 1 and 2). However on increasing it from 1 to 2 equivalents, a slight decrease was seen when $Mg(NO_3)_2 \cdot 6H_2O$ was employed (Table 5, entry 3). This decrease continued on the addition of three equivalents of urea to 55% conversion (Table 5, entry 4). In the case of $Mg(OAc)_2 \cdot 4H_2O$, an increase in conversion was seen with two equivalents of urea and a dramatic decrease in product formation was seen with three equivalents of urea (Table 5, entry 4). This drop in conversion, in the presence of excess urea indicates that the additional urea or ammonia inhibits the progress of the reaction.

At this point it was noted that acetamide was produced in the $Mg(OAc)_2 \cdot 4H_2O$ reactions. This was formed by reaction of the acetate ligands with the ammonia in solution (Scheme 3.09).
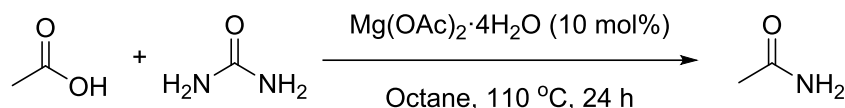
Scheme 3.09: Production of acetamide as a by-product

This may have resulted in competition for the ammonia source. In addition to this, it was not possible to separate the acetamide easily from the desired amide product. The use of $Mg(NO_3)_2 \cdot 6H_2O$ did not result in any unwanted by-products, thus only this catalyst was used in the remainder of the investigation.

At this point, the temperature was increased to 120 °C, in order to drive the reaction to reach quantitative conversion.

Table 6: Finding the optimum urea concentration
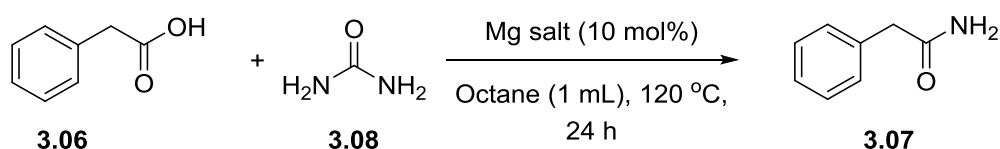
Entry	Urea (mmol)	Conversion (%) $Mg(NO_3)_2 \cdot 6H_2O$	Conversion (%) $Mg(OAc)_2 \cdot 4H_2O$
1	0.5	51	-
2	1	69	-
3	1.5	78	-
4	2	93	96
5	3	85	-

Conditions: Phenylacetic acid (1 mmol), $Mg(NO_3)_2 \cdot 6H_2O$ (10 mol%), $Mg(OAc)_2 \cdot 4H_2O$ (10 mol%), octane (1 mL), 24 h, 120 °C. Conversions were determined by analysis of the crude ^1H NMR spectra.

The equivalents of urea were then considered again at 120 °C (Table 6). Using $Mg(NO_3)_2 \cdot 6H_2O$ as the catalyst it was found that with only half an equivalent of urea, it was possible to obtain 51% of amide 3.07 (Table 6, entry 1). It can also be seen that increasing the urea equivalents, an increase in conversion was observed. However, when 3 equivalents of urea were added, a drop in conversion was observed, being consistent with the trend

observed at the lower temperature of 110 °C (Table 5). It was clear that on the addition of 2 equivalents of urea, the highest conversion, of 93%, could be achieved (Table 6, entry 4). This was comparable with the 96% conversion obtained with Mg(OAc)$_2$·4H$_2$O (Table 6, entry 4).

Table 7: Temperature screen
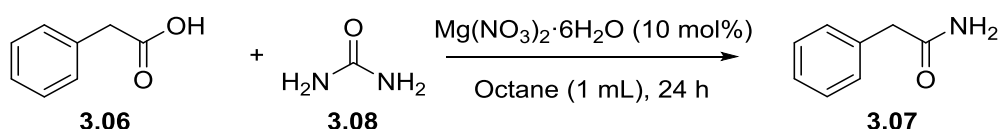
Entry	Temperature (°C)	Catalysed Conversion (%)	Background Conversion (%)
1	70	7	1
2	80	20	2
3	90	33	6
4	100	47	15
5	110	72	25
6	120	93	33

Conditions: Phenylacetic acid (1 mmol), urea (2 mmol), Mg(NO$_3$)$_2$·6H$_2$O (10 mol%), octane (1 mL), 24 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

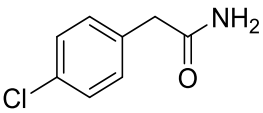In order to determine the ideal temperature for this transformation, a temperature screen was conducted (Table 7). The temperature screen indicated that this reaction proceeded to 33% in 24 hours without the presence of the catalyst (Table 7, entry 6). As expected, a steady increase was observed on increasing the temperature. However, these results clearly suggest that high temperatures of 120 °C are required to achieve the highest conversions within 24 hours (Table 7, entry 6).

Table 8: Catalyst loading optimisation
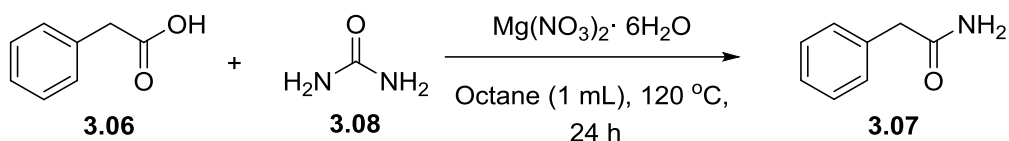
Entry	Urea	Conversion with 5%	Conversion with 10%	Conversion with 15%
1	0.5	-	51	35
2	1	-	68	63
3	1.5	-	78	88
4	2	69	93	94
5	3	68	85	-

Conditions: Phenylacetic acid (1 mmol), urea (as indicated), $Mg(NO_3)_2 \cdot 6H_2O$ (as indicated), octane (1 mL), 120 °C, 24 h. Conversions determined by analysis of the crude ^{1}H NMR spectra.

The catalyst loading screen (Table 8) indicates that decreasing the catalyst loading to 5 mol% causes a significant reduction in conversion from 93% to 69% (Table 8, entry 4). However increasing the loading to 15 mol% does not show any further increase in conversion (Table 8, entry 4).

Reaction concentration screen

The final variable to optimise was the concentration of the reaction (Table 9). The parent reaction was subjected to the optimised conditions under a range of different concentrations.

Table 9: Concentration screen
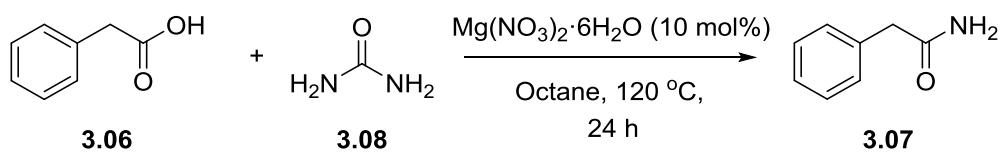
Entry	Concentration (M)	Conversion (%)
1	0.5	55
2	1	78
3	2	76

Conditions: Phenylacetic acid (1 mmol), urea (2 mmol), Mg(NO$_3$)$_2$·6H$_2$O (10 mol%), octane (as indicated), 120 °C, 24 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.
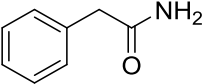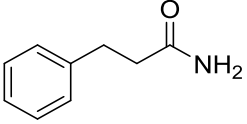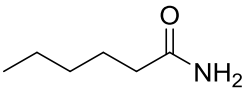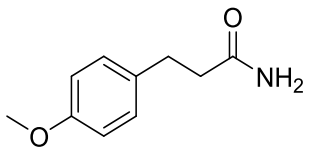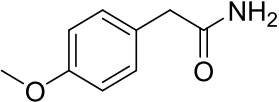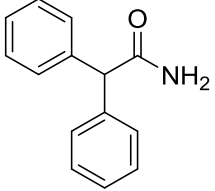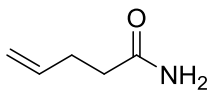
As expected a decrease in conversion was observed in a less concentrated reaction of 0.5 M (Table 9, entry 1). However there was not a significant difference between the reactions at 1 M and 2 M. This was unexpected, however it could be due to a solubility issue, where the urea required more solvent in order to dissolve and achieve higher conversions. Once the optimal conditions were found for this transformation, the substrate scope was subjected to study.
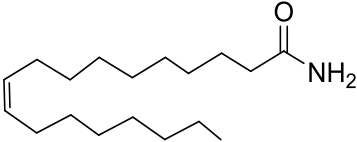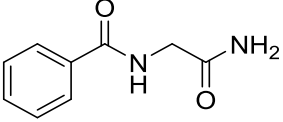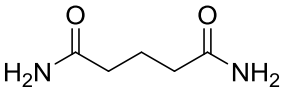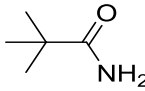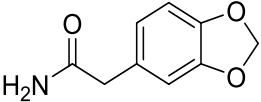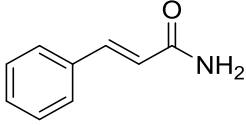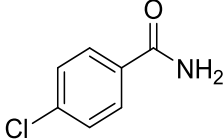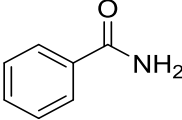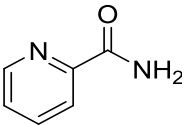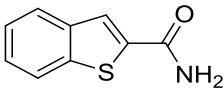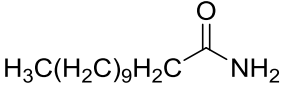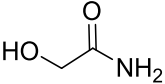
Substrate scope

A variety of carboxylic acids was subjected to this amidation reaction to form the primary amide under the optimised conditions.

Table 10: Substrate scope for the formation of primary amides from carboxylic acids and urea.
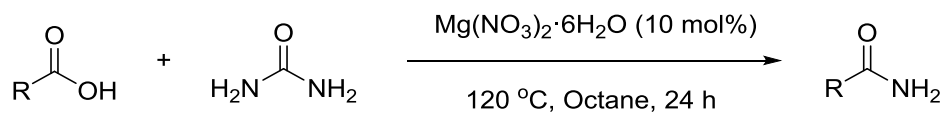
Entry	Compound Number of product	Product	Background conversion (%)	Catalysed conversion (%)
1	**3.07**		33	93 (72)
2	**3.09**		32	100 (75)
3	**3.10**		0	86 (65)
4	**3.11**		49	91 (60)
5	**3.12**		40	100 (72)
6	**3.13**		61	100 (74)
7[a,b]	**3.14**		16	100 (76)
8	**3.15**		50	100 (85)

|				
9[c]	**3.16**		35	50 (38)
10[c]	**3.17**		57	56 (54)
11[c]	**3.18**		0	68 (44)
12	**3.19**		0	58
13	**3.20**		53	67
14[b]	**3.21**		15	50
15[b]	**3.22**		10	25
16	**3.23**		0	0
17	**3.24**		21	38
18	**3.25**		0	0
19	**3.26**		0	78
20[c]	**3.27**		-	-

This methodology was effective for a range of substrates including aliphatic and phenylacetic acids. 3-Phenylpropionic acid formed the corresponding primary amide in 75% yield (Table 10, entry 2). Analogues containing electron donating and withdrawing functionalities were also tolerated well (Table 10, entries 4, 5 and 6). The methodology was compatible with aliphatic acids including shorter chains such as hexanoic acid (Table 10, entry 3), longer chains (Table 10, entry 19) and those containing a terminal double bond (Table 10 entry 8). Aliphatic acids containing conjugated double bonds were more challenging substrates, due to the delocalisation of electrons and subsequent decrease in electrophilicity, lower conversions were achieved (Table 10, entry 14). Even at elevated temperatures of 130 °C only 50% conversion was seen. Diamides were also synthesised in moderate conversions (Table 10, entry 11).

Bulkier and sterically hindered substrates such as diphenylacetic acid (Table 10, entry 7) required higher temperatures of 130 °C, in order to raise the conversion from 50% to 100%. In addition pivalic acid formed the corresponding pivalamide in 58% conversion (Table 10, entry 12).

Limitations of this method included the poor conversions obtained with conjugated acids. This low reactivity was caused by the delocalisation of electrons from the carbonyl around the ring, resulting in the carbonyl carbon being less electrophilic. These substrates included benzoic acid derivatives, where no conversion into the primary amide was seen in either the presence or absence of the catalyst (Table 10, entry 16). This theory was reinforced by the reaction of 2-thianaphthene with urea where 0% conversion was also seen for the same reason (Table 10, entry 18). Other limitations included the incompatibility of free hydroxyl groups (Table 10, entry 20). Possible ester formation was observed from the reaction of glycolic acid with itself.

In some cases an extremely high background rate was seen (Table 10, entries 10). These substrates contain hydrogen bonding groups that are able to bind to the urea or the catalyst. In this way the urea can be more activated in the absence of the catalyst, resulting in a higher conversion. It is also possible for these hydrogen bonding groups to hinder the catalyst, preventing it from working as effectively. This suggests that the catalyst is facilitating the urea breakdown process or stabilising an intermediate rather than carrying out the direct coupling of the carboxylic acid and ammonia. This is reinforced by the low conversion seen when $Mg(NO_3)_2 \cdot 6H_2O$ was used in the coupling reaction between 3-phenylpropionic acid and benzylamine.

It was also noted that the isolated yields are slightly lower than anticipated for such high conversions. A possible explanation is the formation of unsymmetrical imides, from reaction between the primary amide product and the carboxylic acid starting material (Scheme 3.10). Although amides are considered poor nucleophiles, at such forcing conditions it is possible that they could react with the carboxylic acids. Subsequent investigations concerning this side reaction were undertaken.
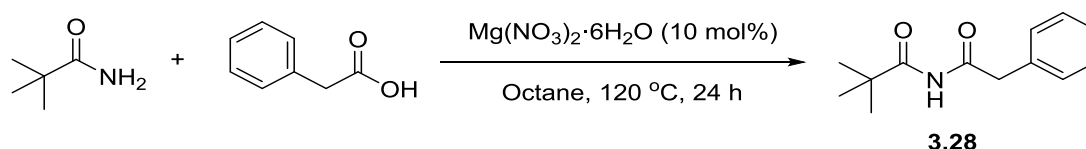

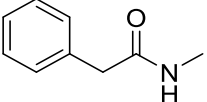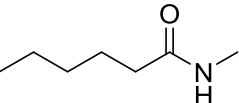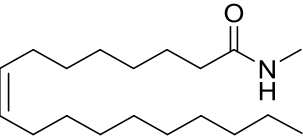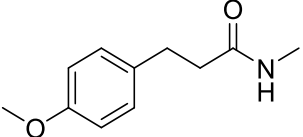**Scheme 3.10: Formation of unsymmetrical imides from primary amides and carboxylic acids**
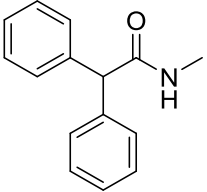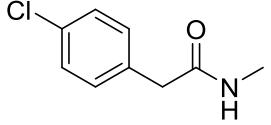
From analysis of the crude ^{1}H NMR spectrum there is evidence to suggest that there was formation of imide **3.28**. If these were present in the reactions presented in Table 10, there is very little difference between the shifts for the primary amide and the imide. Therefore this additional species would be difficult to determine in the reaction mixture. However on isolation of these products, due to the addition of $NaHCO_3$ for removal of the excess acid and urea species, the imide would be removed on work up. Thus suggesting that not all of the carboxylic acid had reacted to form the product, but some with the product to form the imide.
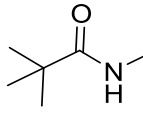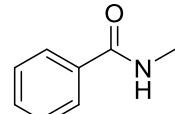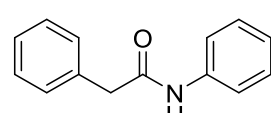
Urea scope

By changing the urea, it was possible to form secondary amides. This is particularly useful in the synthesis of methyl amides, where for a direct coupling, the use of methylamine gas is required. Despite methyl amides being highly useful in drug development, there have been very few methods reported for their synthesis.[99]

Table 11: Amide scope from methyl and phenyl ureas
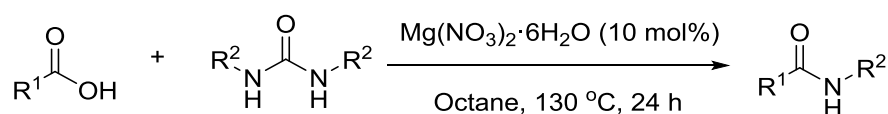
Entry	Compound	Product	Background conversion (%)	Conversion yield (%)
1	**3.29**		34	90 (72)
2	**3.30**		44	76 (70)
3	**3.31**		34	79 (52)
4	**3.32**		51	88
5[a]	**3.33**		42	50
6	**3.34**		32	59

7	**3.35**		24	76
8	**3.36**		0	0
9	**3.37**		10	51

Conditions: Acid species (3 mmol), urea (6 mmol), $Mg(NO_3)_2 \cdot 6H_2O$ (10 mol%), octane (3 mL), 130 °C, 24 h. (a) 1 mmol scale. Conversions were determined by analysis of the crude ^1H NMR spectra. Isolated yields are in parentheses.

It was possible to synthesise a range of methylamides from the corresponding carboxylic acids and dimethylurea. As with the previous method, a wide range of carboxylic acids was well-tolerated, including aliphatic and phenylacetic acids (Table 11, entries 1, 2 and 4). This could be extended to long aliphatic chains bearing a double bond functionality (Table 11, entry 3). Furthermore, bulky acids were also tolerated, achieving 76% conversion into the desired methyl amide product (Table 11, entry 7). Less electrophilic substrates were incompatible with this method, showing no conversion into the methylamide product (Table 11, entry 8).

Higher temperatures of 130 °C were required for this reaction, due to the steric hindrance presented by the methyl group on the urea. As a result of the higher temperature, a higher background rate was also observed. In some cases, this background rate was too competitive for the catalyst and little increase in conversion was observed (Table 11, entry 5).

This methodology is also compatible with other *N,N'*-disubstituted ureas, such as 1,3-diphenylurea to form the corresponding phenylamides proceeding to 51% conversion under the optimised conditions. However, the formation of this amide occurs at a faster rate when aniline is used as the amine. Thus suggesting that the use of the urea as the amine source is inefficient in this instance (Table 11, entry 9).

Amide synthesis from asymmetric ureas

We have shown that symmetrical ureas have great potential in this methodology as the amine/ammonia source, however we decided to turn our attention to the use of non-symmetric, monosubstituted ureas to determine if selectively the primary or secondary amide could be formed from this using $Mg(NO_3)_2 \cdot 6H_2O$ as a catalyst.

Table 12: Product distribution with monosubstituted ureas
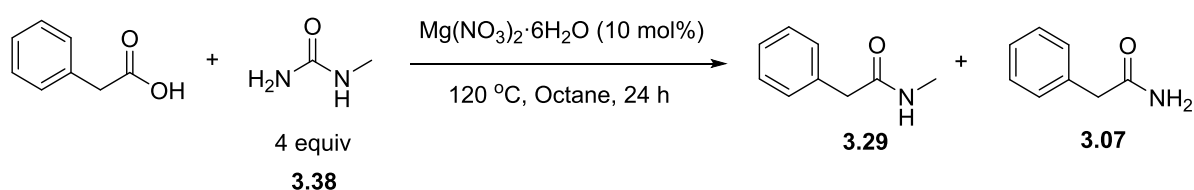
| Entry	Catalyst (mol%)	Urea	Conversion (%) into product 3.29	Conversion (%) into product 3.07
1	10	*N*-methylurea	66	14
2	-	*N*-methylurea	44	14
3	10	dimethyl urea	65	-

Conditions: Phenylacetic acid (1 mmol), *N*-methylurea (4 mmol), dimethylurea (2 mmol) $Mg(NO_3)_2 \cdot 6H_2O$ (10 mol%), octane (1 mL), 120 °C, 24 h. Conversions were determined by analysis of the crude ^1H NMR spectra.

The reaction above can form two possible products, the secondary amide **3.29** and the primary amide **3.07**. The secondary amide appears to form preferentially over the primary amide in 66% conversion in comparison with 14% for product **3.07**. It is interesting to note that the conversion into the primary amide is the same in both the catalysed and uncatalysed reactions (Table 12, entries 1 and 2).

The conversion into the secondary amide when *N*-methylurea and the disubstituted urea are used is the same in the presence of the catalyst. This suggests that the mechanism is not hindered by the presence of the NH_2 on

one side. Perhaps an indication that the secondary amide moiety is more nucleophilic than the primary amide or more likely, that the intermediate formed from this side is less stable and therefore forms the product more readily.

In addition to these studies, the formation of tertiary amides was attempted from tetramethyl urea (**3.39**), however a negligible conversion into **3.40** was obtained (Scheme 3.11).
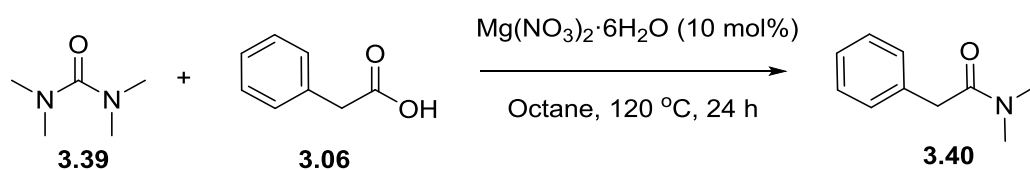
Scheme 3.11: Formation of tertiary amides from tetrasubstituted ureas and carboxylic acids

The possibility of employing ethyl carbamate as an ammonia source was subjected to study (Scheme 3.12). It was found that this reaction formed primary amide **3.07** in 10% conversion with the catalyst, where no conversion at all was seen in the uncatalysed reaction.
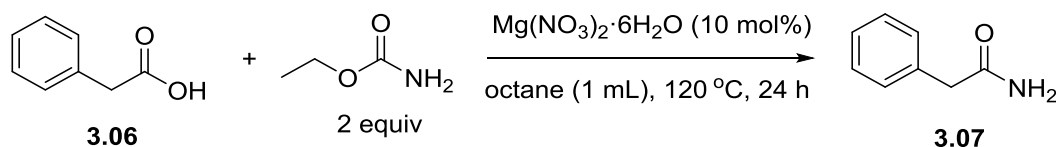
Scheme 3.12: Primary amide formation from carboxylic acids and carbamates

Alternative acyl donors

After investigating alternative ureas, our attention was focused on the use of alternative acyl donors to form primary amides from these. In this first instance esters were employed as an acyl donor (Scheme 3.13).

As previously mentioned the synthesis of primary amides from esters has not been widely investigated, with only a few examples being reported in the literature.[52] In these cases, activators are required in stoichiometric amounts nevertheless they provide an interesting transformation, particularly in the case where magnesium nitride was used as an *in situ* ammonia generator.
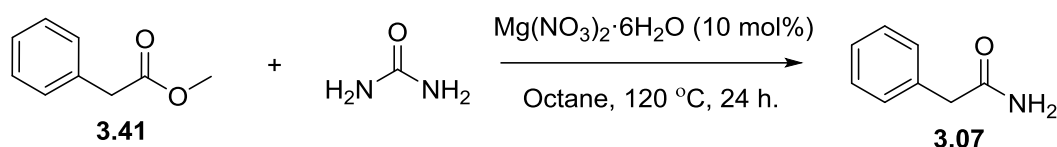
Scheme 3.13: Formation of primary amides from esters and urea

Unfortunately, by ^{1}H NMR analysis the formation of the primary amide could not be seen. Indicating that esters are not compatible as acyl donors in this methodology.

The methodology was also applied to the synthesis of sulfonamides from sulfonic acids. Sulfonamides are found in a large number of pharmaceuticals and agrochemicals making their synthesis of high importance within industries.[102] They are commonly synthesised from sulfonyl chlorides, as there are very few methods for their direct synthesis from sulfonic acids.[103] The existing methods have used stoichiometric activators such as 2,4,6-trichloro[1,3,5]triazine (TCT) or triphenylphosphine ditriflate.[104]

Although this transformation seems synthetically difficult to achieve, our efforts were focussed on extending our existing methodology to alternative substrates. This work was carried out by a Masters student, Lewis Cooper.
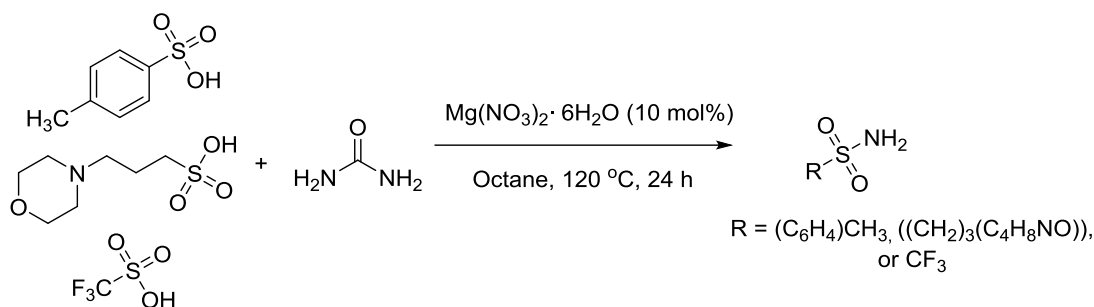
Scheme 3.14: Magnesium catalysed sulfonamide formation from sulfonic acids and urea

Initial attempts were based on *p*-toluenesulfonic acid (p-TSA) (Scheme 3.14), however, due to its inherent low electrophilicity no conversion into the corresponding sulfonamide was observed. Consequently a more reactive sulfonic acid was chosen. As this method could easily be applied to aliphatic carboxylic acids, an aliphatic sulfonic acid was selected. It was expected that the formation of the sulfonamide would be observed on analysis of the crude

^{1}H NMR, however in this case only the starting materials were returned. In a final attempt to synthesise sulfonamides from their corresponding sulfonic acids, a highly reactive sulfonic acid was chosen, in the hope that its increased electrophilicity would encourage attack by the urea. Trifluoromethanesulfonic acid was subjected to the reaction conditions and disappointingly did not yield any of the corresponding sulfonamide. Thus, investigations on the formation of sulfonamides from sulfonic acids were abandoned at this point.

Mechanistic insights

There are two possible mechanisms for the formation of the primary amides from carboxylic acids and urea with $Mg(NO_3)_2 \cdot 6H_2O$ as a catalyst.

The breakdown of urea to form ammonia

It is possible that urea can break down to form ammonia in solution which then nucleophilically attacks the carboxylic acid to form the primary amide (Scheme 3.15).
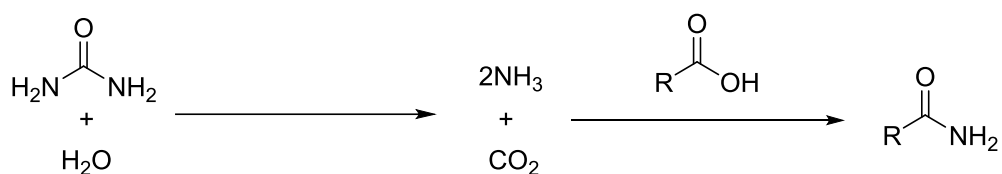
**Scheme 3.15: Direct attack of ammonia on the carboxylic acid**

The Lewis acid can bind to the carbonyl oxygen, withdrawing electrons, causing the carbon to be more electrophilic and therefore favour the reaction with ammonia. If this mechanism occurs, urea would break down to form ammonia on heating. This process is known at high temperatures of 150 °C.[105]

Urea was heated in the presence and absence of the catalyst and in both cases the urea NH_2 peak was still present in the ^{1}H NMR. This suggests that under the reaction conditions, the primary degradation pathway is not by initial loss of ammonia, unless the carboxylic acid is also involved in the breakdown of urea. There were also two other NH peaks, possibly corresponding to the known urea dimer, biuret, which forms on the coupling of two urea molecules at high temperatures.[106] During this process there is also loss of ammonia, which cannot easily be monitored by ^{1}H NMR, which is then able to couple to the carboxylic acid.

When diphenyl urea was used as the amine source 51% conversion into the phenyl amide was observed (Table 11, entry 11). To determine the role of the urea in this instance, the reaction was conducted with aniline. If a similar conversion was observed, the urea is acting purely as a source of the amine

and has no other role in promoting this reaction, however if an increase in conversion was seen by the *in situ* generation of the amine, then the urea could have another activating role in the mechanism.

When aniline was used as the amine to form the phenylamide, the conversion was significantly higher than when diphenylurea was used as the amine source (72% in comparison to 51%) (Scheme 3.16). This implies that the urea is purely acting as the amine source and has no other role in promoting the reaction. Not only this but the background and catalysed conversions for these reactions were similar. Thus implying that the magnesium catalyst does not carry out the acid/amine coupling reaction and that its main role is in the breakdown of the urea or stabilisation of an alternative species.


Catalysed: 77% conv.
Uncatalysed: 75% conv.
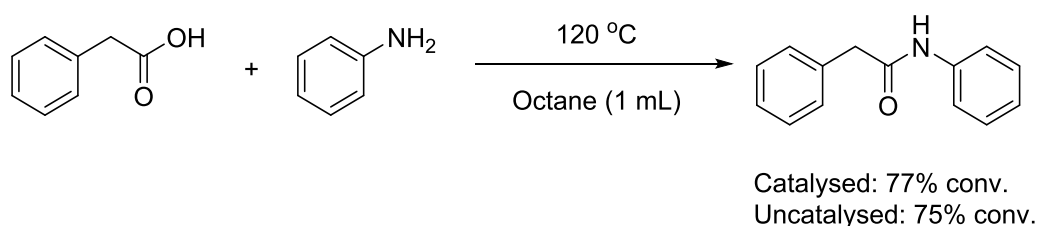
Scheme 3.16: Formation of secondary amides from carboxylic acids and amines

The formation of an *N*-acylurea intermediate

It is possible that this reaction proceeds via formation of an *N*-acylurea intermediate. This intermediate **3.42** is able to form by initial nucleophilic attack of urea on the carboxylic acid, liberating water as a by-product. The water that is produced is then able to hydrolyse the intermediate, releasing the desired primary amide as product and carbamic acid. This is highly unstable and rapidly decomposes to form carbon dioxide and an equivalent of ammonia which possibly acts as a driving force for the reaction.

In order to determine if this mechanism was plausible, studies were carried out on the breakdown of intermediate **3.42**. The *N*-acylurea intermediate was synthesised following literature procedure from an acid chloride and urea (Scheme 3.17).[107]
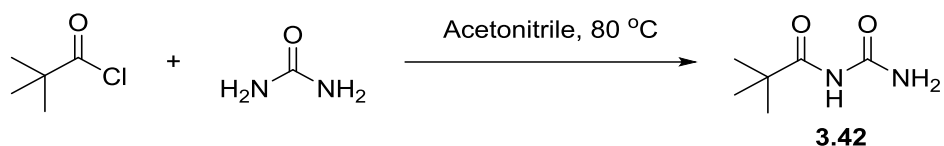
Scheme 3.17: Formation of *N*-acylurea intermediate

The resulting compound was then used in a series of experiments to establish if it could be hydrolysed to form the desired primary amide (Table 13).

Table 13: Breakdown of the *N*-acylurea intermediate
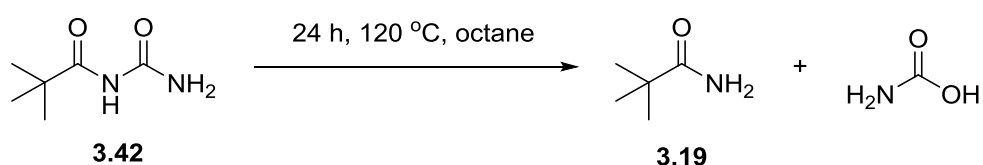
Entry	Catalyst (mol%)	Water (equiv.)	Conversion (%)
1	10	-	6
2	-	-	0
3	-	2	6
4	10	2	25

Conditions: *N*-Acylurea (0.5 mmol), Mg(NO₃)₂·6H₂O (10 mol%), water (1 mmol), octane (0.5 mL), 120 °C, 24 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra

N-Acyl urea **3.42** was subjected to the optimised reaction conditions and 6% conversion into the primary amide **3.19** was seen (Table 13, entry 1). In the absence of the catalyst and additional water, only the starting material was recovered (Table 13, entry 2) and in the presence of two equivalents of water, 6% of the product was identified (Table 13, entry 3). However in the presence of both the catalyst and the addition of two equivalents of water, 25% of the product was identified by ^{1}H NMR spectroscopy (Table 13, entry 4). This suggests that both the catalyst and the water are required for this step to occur. It is possible that the reaction proceeds via a magnesium chelated *N*-acylurea intermediate (**3.43**), which will be highly susceptible to attack by water (Scheme 3.18). Carbamic acid would be formed as a

by-product of this reaction, which then readily decomposes to CO_2 and NH_3. A simple litmus paper test was conducted to test for the presence of NH_3. A positive result for this test confirmed the presence of a basic gas, with a colour change from yellow to blue being observed.
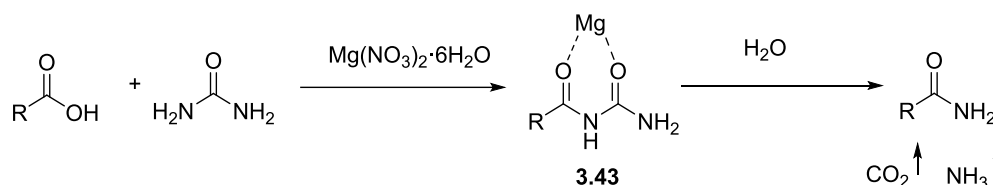
Scheme 3.18: Possible reaction pathway via an *N*-acylurea magnesium chelated intermediate

Additional studies to determine the optimum concentration of water could be conducted in order to optimise this step fully. However due to time constraints this was not possible.

To confirm the presence of species **3.44**, a mass spectrum was carried out on a crude reaction sample (Scheme 3.19). This confirmed the presence of the intermediate as the sodium adduct (m/z of 201.0637).
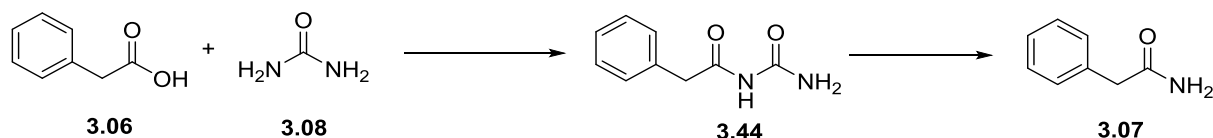
Scheme 3.19: Confirmation of the *N*-acyl urea intermediate

This mechanism is supported by the evidence when methyl ureas were used. In this case (Scheme 3.20), formation of intermediate **3.45** would occur. The nitrogen from the methylurea is more nucleophilic than the nitrogen on the unsubstituted urea, favouring the formation of intermediate **3.45**. This reaction required higher temperatures of 130 °C due to the presence of the methyl group. This steric hindrance can also cause slower attack of water on the intermediate.

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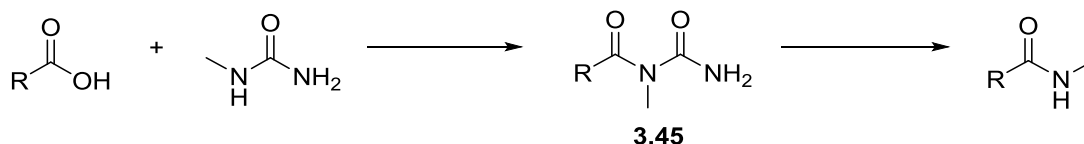
Scheme 3.20: Formation of secondary amides from *N*-methylurea

Furthermore, when tetramethyl urea was employed to form tertiary amides no conversion was observed. This could be due to the poor nucleophilicity of the urea nitrogen. The presence of the extra methyl group could hinder the nitrogen from attacking the carboxylic acid.

Moreover, in the case of the monosubstituted ureas, a mixture of secondary and primary amides were observed. In fact, a higher percentage of the secondary amide was seen in comparison to the primary amide. Perhaps suggesting that the substituted side is more nucleophilic, however this could also imply that the intermediate formed with the substituted side is less stable. Thus water is more able to attack this intermediate, despite the presence of the methyl group on the central nitrogen.

It was then thought that in the case of a 1,1-disbsituted urea (**2.35**, prepared following the methodology developed in Chapter 2), that only the primary amide would be formed (Scheme 3.21). In this instance the disubstituted nitrogen would be unable to form the intermediate with the carboxylic acid. Leaving only the non-substituted side free for reaction and therefore only producing the primary amide.
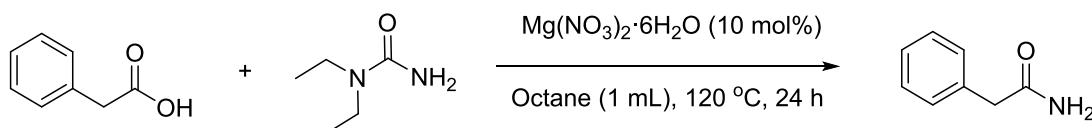
Scheme 3.21: Magnesium nitrate catalysed reaction between carboxylic acids and monosubsituted ureas

On analysis of the crude reaction mixture, the primary amide (**3.07**) and the unexpected tertiary amide (**3.46**) were found by ^{1}H NMR. There was however more of the tertiary amide (**3.46**) than of the expected primary amide. This was unexpected as the intermediate formed in order to make this amide would have been unfavourable. On further inspection of the mass

spectrum, presence of the expected intermediate **3.44** was confirmed (Scheme 3.21)

It is possible to form the tertiary amide from initial formation of *N*-acylurea **3.44**. On hydrolysis of this intermediate the desired primary amide 3.07 and species **3.47** are formed. Species **3.47** rapidly decomposes into diethylamine and CO_2 which acts as the driving force for the reaction (Scheme 3.22). The diethylamine, can compete with the water and nucleophilically attack intermediate **3.44** liberating the starting monosubstituted urea **2.35** and a new tertiary amide **3.46** (Scheme 3.23). It is also possible for this tertiary amide to form via a transamidation reaction between the desired primary amide product (**3.07**) and the diethylamine that is produced. Under these conditions, this reaction cannot be dismissed.
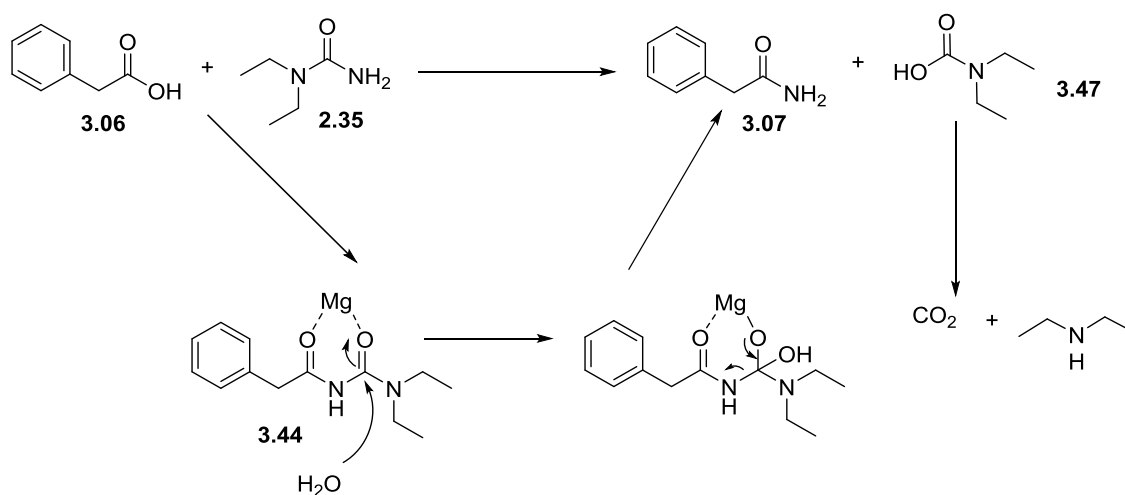
Scheme 3.22: Possible reaction mechanism via a magnesium chelated *N*-acylurea intermediate
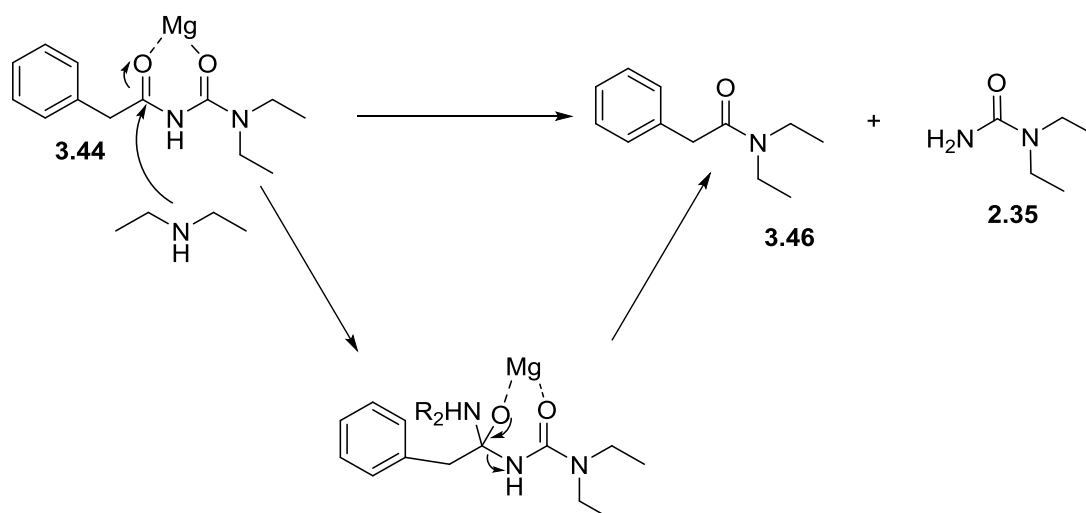
Scheme 3.23: Possible reaction pathway for the formation of tertiary amides from carboxylic acids and monosubstituted ureas

This mechanism can also explain the poor reactivity of ethyl carbamate (**2.26**) as an ammonia source (Scheme 3.24).
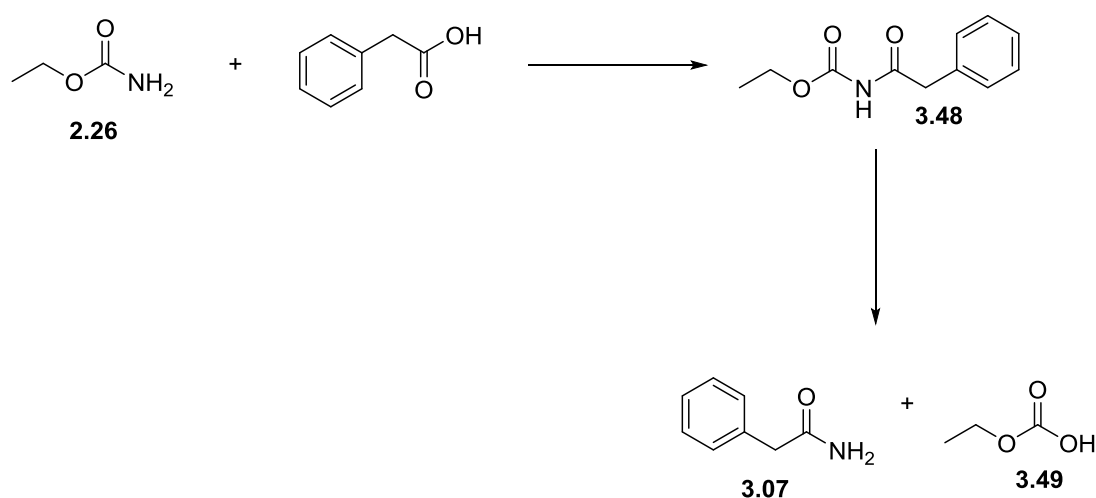
Scheme 3.24: Pathway of primary amide formation from carbamates and carboxylic acids

This poor conversion could be a consequence of the poor nucleophilicity of the carbamate nitrogen, resulting in a slower formation of *N*-acylcarbamate **3.48**. On the other hand, intermediate **3.48** is less Lewis basic than in the previous case, resulting in a weaker interaction with the Lewis acid catalyst.

The lack of reactivity when using esters as the acyl donor for this transformation could be explained by the low nucleophilicity of the alcohol by product. When methyl phenylacetate was employed as the starting material, methanol was produced as a by-product on reaction between the ester and urea. Methanol is then not nucleophilic enough to attack the intermediate and liberate the product. In contrast it has been shown that the production of water was crucial to the decomposition of the intermediate.

Thus a final mechanism can be proposed based on the findings that have been outlined. A proposed pathway via an *N*-acylurea intermediate, with nucleophilic attack of water, to produce the desired primary amide and carbamic acid as a by-product can be suggested.

Conclusions

A novel, catalytic one pot method for the formation of primary amides from carboxylic acids has been presented using urea as a cheap, abundant and non-toxic ammonia source. This method utilises magnesium nitrate hexahydrate catalytically to synthesise a wide range of primary amides in moderate to high yields. This methodology was not able to be applied to the synthesis of benzamides and other conjugated amides due to the poor electrophilicity of the corresponding carboxylic aicds.

Furthermore, studies were conducted on alternative of ureas to form methylamides and phenylamides from methyl and phenyl ureas respectively. Alternative acyl donors were explored, carbamates showed limited activity whereas esters and sulfonic acids both proved unsuccessful.

Mechanistic investigations were carried out suggesting the major reaction pathway proceeds via an *N*-acylurea intermediate. This was supported by ^{1}H NMR and mass spectrometry techniques in addition to reactivity experiments with substituted ureas. Despite this, it is possible that a minor reaction pathway proceeds via direct coupling of ammonia in solution and the carboxylic acid.

Future work

The developed reaction has shown great potential in catalysing the formation of primary amides from unactivated carboxylic acids and urea. Mechanistic studies were carried out and a potential mechanism was identified. Based on these findings, several improvements could be made to this system.

Finding the optimum concentration of water in the reaction could improve the breakdown of the intermediate. In addition to kinetic investigations to determine the exact mechanism could enable a milder system to be developed.

Organocatalysed primary amide formation from carboxylic acids and urea

This reaction also has the potential to be accelerated by an organocatalyst. Where similar systems are known for the direct amidation of acid chlorides,[108] there have been few reported organocatalytic systems for the formation of primary amides from carboxylic acids. Preliminary investigations indicated that DMAP and imidazole are both good catalysts for this transformation.

Table 14: **Organocatalyst screen**
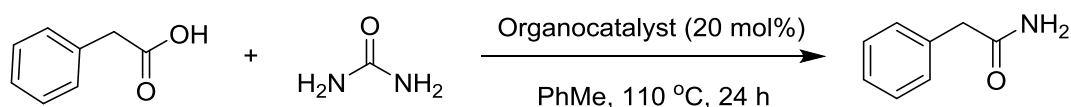
Entry	Organocatalyst	Conversion (%)
1	DBN	8
2	DBU	10
3	Proline	11
4	DABCO	18
5	Imidazole	81
6	1-methylimidazole	33
7	DMAP	81

Conditions: Phenylacetic acid (1 mmol), urea (1 mmol), catalyst (20 mol%), PhMe (1 mL), 110 °C, 24 h. Conversions were determined by analysis of the crude ^{1}H NMR spectra.

As the metal catalysed system showed that this reaction proceeded well in octane as a solvent, this was tested for this system and the concentration of the ammonia source was also screened.

Table 15: **Demonstrating the effect of catalyst loading and the concentration of urea**

Entry	Catalyst loading (mol%)	Urea (equiv)	Conversion (%) DMAP	Conversion (%) imidazole
1	20	1	81	81
2	20	1.5	94	88
3	20	2	90	88
4	10	1	76	64

Conditions: Phenylacetic acid (1 mmol), urea (as indicated), DMAP (10 mol%), imidazole (10 mol%), 110 °C, 24 h, octane (1 mL). Conversions were determined by analysis of the crude ^{1}H NMR spectra.

The results of this screen indicated that DMAP was the more suitable catalyst for this reaction catalysing the reaction to 94% conversion (Table 15, entry 2), in the presence of 1.5 equivalents of urea. Surprisingly the conversion only decreased by 5% when the catalyst loading was decreased from 20 mol% to 10 mol%. This suggests that with further optimisation and increase of urea, this reaction could reach quantitative conversion with only 10 mol% DMAP under these conditions. However due to time restrictions this work could not be completed and is ongoing within the Williams group.

The possibility of using these as additives may also be considered within the metal catalysed system. The use of DMAP could enable a reduction of reaction temperature when used in conjunction with the magnesium nitrate.

Chapter 4: Experimental data

General Experimental Methods

All reactions requiring an anhydrous, inert atmosphere were carried out under a nitrogen atmosphere using evacuated carousel ampules. Unless preparative details are provided, all reagents were purchased from commercial suppliers Acros Organics, Aldrich, Alfa Aesar, Fluka, Lancaster, Maybridge, Strem or TCI UK and used without further purification. Thin layer chromatography was carried out on aluminium or plastic backed silica plates purchased from Aldrich. The plates were visualised under UV (254 nm) light, followed by staining with phosphomolybdic acid dip or potassium permanganate and gentle heating. During compound separations, column chromatography was carried out using 60 micron dry silica purchased from Aldrich. Organic layers were routinely dried with anhydrous $MgSO_4$ and concentrated using a Büchi rotary evaporator.

^{1}H NMR/^{13}C NMR spectra were run in deuterated (≥99.5%) solvents purchased from Fluorochem unless stated otherwise, on either a Bruker Avance 250 (250 MHz), Bruker Avance 300 (300 MHz) or Agilent 500 (500 MHz). Any chemical shifts (δ) are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) (δH = 0.00 ppm) unless otherwise stated. The coupling constants (J) are reported in Hz and signal multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), doublet of doublets (dd), doublets of triplets (dt), triplet or triplets (tt), multiplet (m), or broad singlet (br. s).

For mass spectrometry data acquisition on a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik, GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10 µL of sample was injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10 µL of a calibrant of 5 mM sodium formate was injected after the sample. The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal STR accessory for sampling, with relevant absorbances quoted as υ in cm^{-1}. Melting points were determined using Stuart SMP10 melting point equipment using closed end glass capillary tubes and are uncorrected.
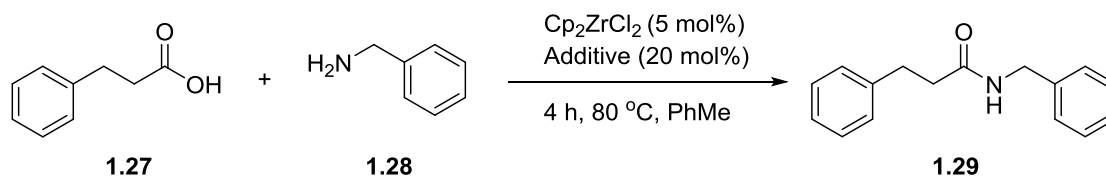
Experimental Procedures Chapter 1
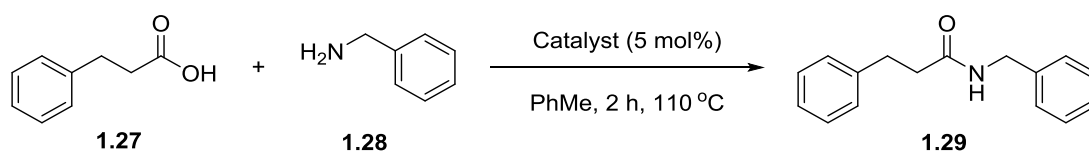
General procedure 1.1: Nucleophile screen
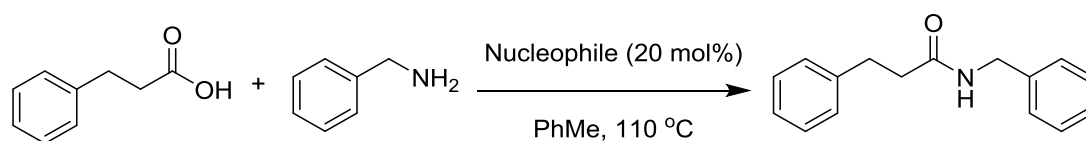
An oven dried Radleys tube was charged with 3-phenylpropionic acid (1 mmol), benzylamine (1 mmol) and the catalyst species (20 mol%) according to Chapter 1, Table 1. Toluene (1 mL) was then added to the tube and the reaction was heated at reflux for 4 hours. The resulting reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*. The ^{1}H NMR of the crude reaction mixtures showed

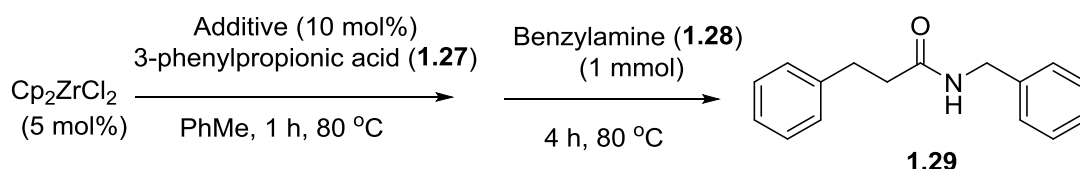General Procedure 1.2: Nucleophilic additive screen

An oven dried Radleys tube was charged with 3-phenylpropionic acid (1 mmol), benzylamine (1 mmol), Cp$_2$ZrCl$_2$ (5 mol%) and the additive (10 mol%) according to Chapter 1, Table 3. Toluene (1 mL) was then added and to the tube and the reaction was heated at 80 °C for 4 hours. The resulting reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*.

General Procedure 1.3

An oven dried Radleys tube was charged with the 3-phenylpropionic acid (1 mmol), benzylamine (1 mmol) and the catalyst species (5 mol%) according to Chapter 1, Table 4. Toluene (1 mL) was then added and the reaction was heated to 110 °C for 2 hours. The resulting reaction mixture was allowed to cool to room temperature and concentrated *in vacuo*.

General Procedure 1.4

An oven dried Radleys tube was charged with 3-phenylpropionic acid (1 mmol), Cp_2ZrCl_2 (5 mol%) and the additive species (10 mol%) in accordance with Chapter 1, Table 5. Toluene (1 mL) was then added and the reaction was heated to 80 °C for 1 hour. After this time, benzylamine (1 mmol) was added and the reaction was heated at 80 °C for an additional 4 hours. The resulting reaction mixture was allowed to cool to room temperature. The additive was then filtered and the mixture was concentrated *in vacuo*.

General Procedure 1.5
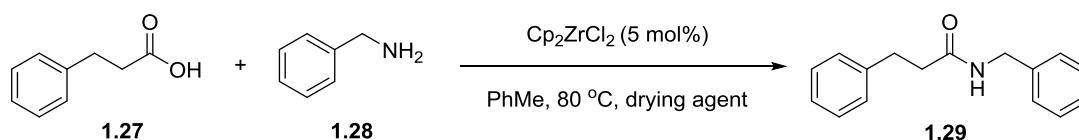
An oven dried Radleys tube was charged with 3-phenylpropionic acid (1 mmol), Cp_2ZrCl_2 (5 mol%) and the drying agent in accordance with

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Chapter 1, Table 7. The tube was then sealed and purged with N_2. After which dry toluene (1 mL) and benzylamine (1.2 mmol) were then added. The reaction was then heated at the appropriate temperature for the appropriate length of time. The reaction was allowed to cool to room temperature and the drying agent was removed via filtration. The crude reaction mixture was then concentrated *in vacuo*.

General procedure 1.6
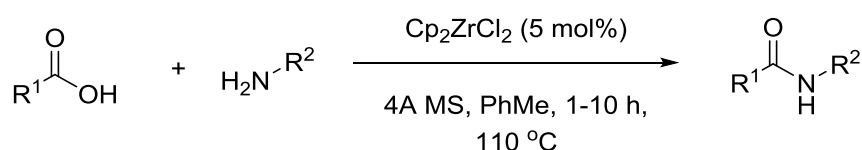
An oven dried Radleys tube was charged with the acid species (2 mmol), zirconocene dichloride (5 mol%) and powdered molecular sieves (4Å). The tube was then sealed and purged with N_2. After which dry toluene (volume as appropriate) and the amine species (1.2 equivalents) were added. The reaction was then heated at the appropriate temperature for the appropriate time (see Chapter 1, Tables 9 and 10). After being allowed to cool to room temperature the crude reaction mixture was then purified by column chromatography (unless otherwise stated). The purified compounds were then analysed by their ^{1}H NMR and ^{13}C NMR spectra.

1.29. N-Benzyl 3-phenylpropionamide[51]
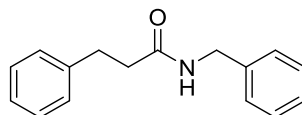
Following general procedure 1.6, 3-phenylpropionic acid (300 mg, 2 mmol) was used as the acid species and benzylamine (260 µL, 2.4 mmol) as the amine species. The *title compound* was recovered as a white solid (358 mg, 75% yield) after column chromatography (eluting with hexane/EtOAc, 70:30). Data in accordance with those previously reported.[51]

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.34-7.19 (m, 10H, aromatic), 5.61 (br. s, 1H, C(O)-N<u>H</u>-CH$_2$), 4.40 (d, 2H, J = 5.7 Hz, C(O)-NH-<u>CH$_2$</u>-Ph), 3.00 (t, 2H, J = 7.6 Hz, Ph-<u>CH$_2$</u>-CH$_2$), 2.52 (t, 2H, J = 7.6 Hz, Ph-CH$_2$-<u>CH$_2$</u>-C(O)). ^{13}C NMR (75 MHz, CDCl$_3$): δ 171.8, 140.8, 138.1, 128.7, 128.6, 128.4, 127.8, 127.5, 126.3, 43.6, 38.6, 31.7.

ESI-MS of [C$_{16}$H$_{17}$NO]; theoretical m/z of [M+H]$^+$ = 240.1388, measured m/z of [M+H]$^+$ = 240.1384.

IR: υ(cm^{-1}) = 1636 (C=O stretch).

Melting point = 81-83 °C (Lit: 84-89 °C)

1.30. *N*-(4-Methylbenzyl)-3-phenylpropionamide[109]
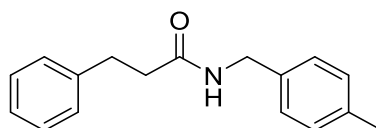
Following general procedure 1.6, 3-phenylpropionic acid (300 mg, 2 mmol) was used as the acid species and 4-methylbenzylamine (280 µL, 2.4 mmol) as the amine species. The *title* compound was isolated as a white solid (336 mg, 64% yield) after purification by column chromatography (eluting with pentane/EtOAc, 80:20). Data in accordance with those previously reported. [109]

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.38-7.04 (m, 9H, aromatic), 5.38 (br.s, 1H, NH), 4.36 (d, 2H, J = 5.0 Hz, Ph-<u>CH$_2$</u>-C(O)), 3.00 (t, 2H, J = 5.0 Hz, Ph-CH$_2$-<u>CH$_2$</u>-C(O)), 2.50 (t, 2H, J = 5.0 Hz, Ph-CH$_2$-CH$_2$), 2.33 (s, 3H, CH$_3$). ^{13}C NMR (125 MHz, CDCl$_3$): δ 172.2, 141.2, 137.6, 135.5, 129.7, 128.9, 128.8, 128.2, 126.6, 43.7, 38.9, 32.1, 21.5.

ESI-MS of [C$_{17}$H$_{19}$NO]; theoretical m/z of [M+H]$^+$ = 254.15, measured m/z of [M+H]$^+$ = 254.1486.

IR: υ(cm^{-1}) = 1643 (C=O stretch).

Melting point = 115 °C (Lit: 117-119 °C)

1.31. *N*-(5-methylfurfuryl)-3-phenylpropanamide[8]
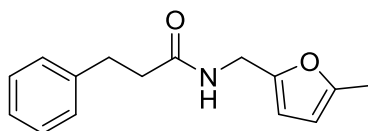
Following general procedure 1.6, 3-phenylpropionic acid (300 mg, 2 mmol) was used as the acid species and 5-methylfurfurylamine (245 μL, 2.4 mmol) was used as the amine species. The *title compound* was recovered as an orange/brown solid (437 mg, 90% yield) after purification through a pad of silica (eluting with EtOAc). Data in accordance with those previously reported.[8]

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.28-7.17 (m, 5H, aromatic), 6.03 (d, 1H, *J* = 5.0 Hz, furyl), 5.87 (d, 1H, *J* = 5.0 Hz, furyl), 5.64 (s, 1H, C(O)-N<u>H</u>-CH$_2$), 4.34 (d, 2H, *J* = 5.0 Hz, C(O)-NH-<u>CH$_2$</u>-), 2.97 (t, 2H, *J* = 10.0 Hz, Ph-<u>CH$_2$</u>-CH$_2$), 2.48 (t, 2H, *J* = 10.0 Hz, Ph-CH$_2$-<u>CH$_2$</u>), 2.24 (s, 3H, <u>CH$_3$</u>). ^{13}C NMR (125 MHz, CDCl$_3$): δ 171.9, 152.2, 149.7, 141.2, 128.9, 128.7, 126.6, 108.7, 106.6, 38.8, 37.0, 32.00, 13.9.

ESI-MS of [C$_{15}$H$_{17}$NO$_2$]; theoretical m/z of [M+H]$^+$ = 244.1337, measured m/z of [M+H]$^+$ = 244.1334.

IR: υ(cm^{-1}) = 1643 (C=O stretch)

Melting point = 65 °C

1.32. *N*-hexyl-3-phenylpropanamide[109]
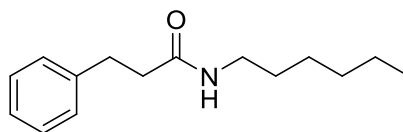
Following general procedure 1.6, 3-phenylpropionic acid (300 mg, 2 mmol) was used as the acid species and hexylamine (317 μL, 2.4 mmol) was used as the amine species. The *title compound* was recovered as an off white solid (324 mg, 70% yield) after column chromatography (pentane/EtOAc, 80:20). Data in accordance with those previously reported. [109]

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.38 - 7.03 (m, 5H, aromatic), 5.56 (s, 1H, <u>NH</u>), 3.17 (m, 2H, C(O)-NH-<u>CH$_2$</u>), 2.94 (t, 2H, *J* = 6.0 Hz, Ph-<u>CH$_2$</u>-CH$_2$), 2.45 (t,
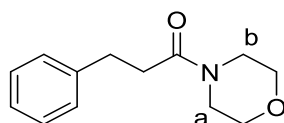
J = 9.0 Hz, 2H, Ph-CH$_2$-C$\underline{H_2}$), 1.52-1.12 (m, 8H, CH$_3$-(C$\underline{H_2}$)$_4$-CH$_2$), 0.87 (t, J = 9.0 Hz, 3H, C$\underline{H_3}$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 172.2, 141.0, 128.5, 128.4, 126.2, 39.6, 38.5, 31.9, 31.5, 29.5, 26.6, 26.3, 22.6, 14.1.

ESI-MS of [C$_{15}$H$_{23}$NO]; theoretical m/z of [M+H]$^+$ = 234.1857, measured m/z of [M+H]$^+$ = 234.1860.

IR: υ(cm^{-1})= 1643 (C=O stretch)

Melting point = 28-30 °C (Lit: 29-30 °C) j Fluroine chem –insert ref.

1.33. *N*-(Morpholino)-3-phenylpropionamide[8]

Following general procedure 1.6, 3-phenylpropionic acid (150 mg, 1 mmol) was used as the acid species and morpholine (100 µL, 1.2 mmol) as the amine species. The *title* compound was recovered as a colourless oil (231 mg, 53% yield,) after column chromatography (eluting with pentane/EtOAc 70:30). Data in accordance with those previously reported. [8]
^{1}H NMR (300 MHz, CDCl$_3$): δ 7.29-7.17 (m, 5H, aromatic), 3.57 (s, 4H, morpholine ring, C$\underline{H_2}$-O-C$\underline{H_2}$), 3.46 (t, 2H, J = 6.0 Hz, b), 3.31 (t, 2H, J = 6.0 Hz, a), 2.95 (t, 2H, J = 9.0 Hz, Ph-CH$_2$-C$\underline{H_2}$), 2.58 (t, 2H, J = 9.0 Hz, Ph-C$\underline{H_2}$-CH$_2$). ^{13}C NMR (125 MHz, CDCl$_3$): δ 171.1, 141.3, 128.8, 128.7, 126.5, 67.1, 66.7, 46.2, 42.1, 35.0, 31.7.

ESI-MS of [C$_{13}$H$_{17}$NO$_2$]; theoretical m/z of [M+H]$^+$ = 220.1338, measured m/z of [M+H]$^+$ = 220.1331.

IR: υ(cm^{-1}) = 1646 (C=O stretch)

1.34. *N*-Benzylbenzamide[51]
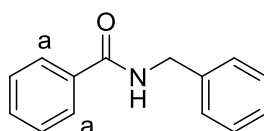
Following general procedure 1.6, benzoic acid (122 mg, 1 mmol) was used as the acid species and benzylamine (131 µL, 1.2 mmol) as the amine species. The *title* compound was recovered as a white solid (184 mg, 87%
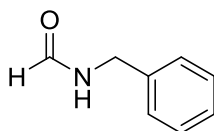
yield) after column chromatography (eluting with pentane/EtOAc, 80:20). Data in accordance with those previously reported.[51] ^{1}H NMR (300 MHz, CDCl$_3$): δ 7.81 (d, 2H, J = 6.0 Hz, a), 7.30-7.53 (m, 8H, aromatic protons), 6.45 (br. s, 1H, <u>NH</u>), 4.65 (d, 2H, J = 6.0 Hz, NH-<u>CH$_2$</u>). ^{13}C NMR (75 MHz, CDCl$_3$): δ 167.9, 138.7, 134.9, 132.1, 129.4, 129.1, 128.5, 128.2, 127.5, 44.7.

ESI-MS of [C$_{14}$H$_{13}$NO]; theoretical m/z of [M+H]$^+$ = 212.0175, measured m/z of [M+H]$^+$ = 212.0184.

IR: υ(cm^{-1}) = 1643 (C=O stretch)

Melting point = 107 °C (Lit: 109-111 °C)

1.35. Phenylmethylformamide[110]

Following general procedure 1.6, formic acid (60 μL, 2 mmol) was used as the acid species and benzylamine (260 μL, 2.4 mmol) was used as the amine species. The *title* compound was recovered as a white solid (205 mg, 76% yield) after column chromatography (eluting with pentane/EtOAc, 60:40). Data in accordance with those previously reported. [110]

^{1}H NMR (300 MHz, CDCl$_3$): Observed as two rotamers in a 5:1 ratio (major: minor) δ 8.24 (s, 1H, major rotamer, NH-C(O)-<u>H</u>), 8.16 (d, 1H, J = 12.0 Hz, NH-C(O)-<u>H</u>), 7.42-7.19 (m, 5H, aromatic), 6.05 (br.s, 1H, <u>NH</u>), 4.47 (d, 2H, J = 6.0 Hz, major rotamer, NH-<u>CH$_2$</u>-Ph), 4.40 (d, 2H, J = 6.0 Hz, minor rotamer, NH-<u>CH$_2$</u>-Ph).

^{13}C NMR (75 MHz, CDCl$_3$): δ 164.6 (minor rotamer), 161.1 (major rotamer), 137.5, 129.0, 128.8, 127.8, 127.7, 127.0, 45.6 (minor rotamer), 42.2 (major rotamer).

ESI-MS of [C$_8$H$_9$NO]; theoretical m/z of [M+H]$^+$ = 136.0762, measured m/z of [M+H]$^+$ = 136.0765.

Melting point = 60-62 °C (Lit: 60 °C)

1.36. *N*-Benzylhexanamide[111]
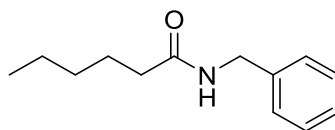
Following general procedure 1.6, hexanoic acid (125 µL, 1 mmol) was used as the acid species and benzylamine (131 µL, 1.2 mmol) as the amine species. The *title* compound was recovered as a white solid (147 mg, 72% yield) after column chromatography (eluting with hexane/EtOAc, 80:20). Data in accordance with those previously reported. [111]

^{1}H NMR (300 MHz, d^6-DMSO): δ 8.29 (t, 1H, J = 5.4 Hz, C(O)-N<u>H</u>-CH$_2$-Ph), 7.38-7.09 (m, 5H, aromatic), 4.23 (d, 2H, J = 6.0 Hz, C(O)-NH-C<u>H$_2$</u>-Ph), 2.10 (t, 2H, J = 7.4 Hz, C<u>H$_2$</u>-C(O)-NH), 1.61-1.37 (m, 2H, CH$_3$-CH$_2$-CH$_2$-C<u>H$_2$</u>-CH$_2$), 1.37-1.04 (m, 4H, CH$_3$-C<u>H$_2$</u>-C<u>H$_2$</u>-CH$_2$), 0.83 (t, 3H, J = 6.9 Hz, C<u>H$_3$</u>).

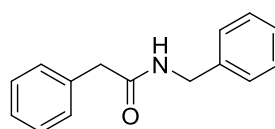^{13}C NMR (75 MHz, d^6-DMSO): δ 172.4, 140.1, 128.6, 127.5, 127.0, 42.3, 35.6, 31.3, 35.6, 25.4, 22.2, 14.3.

ESI-MS of [C$_{13}$H$_{19}$NO]; theoretical m/z of [M+H]$^+$ = 206.1544, measured m/z of [M+H]$^+$ = 206.1549.

IR: υ(cm^{-1}) = 1633 (C=O stretch).

Melting point = 53-55 °C (Lit: 53-55 °C)

1.37. 2-Phenyl-1-(phenylmethyl)acetamide[51]

Following general procedure 1.6, phenylacetic acid (272 mg, 2 mmol) was used as the acid species and benzylamine (260 µL, 2.4 mmol) as the amine species. The *title compound* was recovered as a white solid (353 mg, 78% yield), after column chromatography (eluting with hexane:EtOAc 60:40). Data in accordance with those previously reported.[51]

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.53-6.97 (m, 10H, aromatic), 5.68 (s, 1H, C(O)-N<u>H</u>-CH$_2$), 4.41 (d, J = 5.8 Hz, 2H, C(O)-NH-C<u>H$_2$</u>-Ph), 3.63 (s, 2H, Ph-C<u>H$_2$</u>-C(O)).^{13}C NMR (75 MHz, CDCl$_3$): δ 171.4, 138.4, 135.1, 129.9, 129.5, 129.1, 127.9, 127.9, 44.2, 44.0.

ESI-MS of [C$_{15}$H$_{15}$NO]; theoretical m/z of [M+H]$^+$ = 226.1231, measured m/z of [M+H]$^+$ = 226.1234.

IR: υ(cm^{-1})= 1636 (C=O stretch).

Melting point = 122 °C (Lit: 124-125 °C)

1.38. N-Benzyl-2-(4-chlorophenyl)acetamide[112]

Following general procedure 1.6, 4-chlorophenylacetic acid (340 mg, 2 mmol) was used as the acid species and benzylamine (260 µL, 2.4 mmol) as the amine species. The title compound was recovered as a white solid (422 mg, 81% yield) after column chromatography (eluting with hexane/EtOAc, 60:40). Data in accordance with those previously reported.[112]
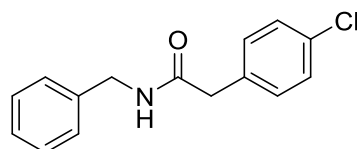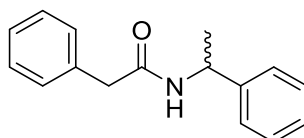
^{1}H NMR (300 MHz, d^6-DMSO): δ 8.59 (t, 1H, J = 5.0 Hz, C(O)-NH-CH$_2$), 7.42-7.19 (m, 9H, aromatic), 4.28 (d, 2H, J = 5.9 Hz, C(O)-NH-CH$_2$-), 3.50 (s, 2H, C(O)-CH$_2$-PhCl).^{13}C NMR (125 MHz, d^6-DMSO): δ 170.2, 139.8, 135.8, 131.3, 128.7, 128.6, 127.7, 127.2, 42.3, 41.7.

ESI-MS of [C$_{15}$H$_{14}$NOCl]; theoretical m/z of [M+H]$^+$ = 260.0842, measured m/z of [M+H]$^+$ = 260.0827.

IR: υ(cm^{-1})= 1652 (C=O stretch).

Melting point = 148-150 °C (Lit: 151-153 °C)

1.39. 2-Phenyl-N-(1-phenylethyl)acetamide[113]

Following general procedure 1.6, phenylacetic acid (270 mg, 2 mmol) was used as the acid species and α-methylbenzylamine (300 µL, 2.4 mmol) as the amine species. The title compound was recovered as a white solid

(170 mg, 71% yield) after column chromatography (eluting with pentane/EtOAc 70:30). Data in accordance with those previously reported.[113]

^{1}H NMR (500 MHz, CDCl$_3$): δ 7.18-7.37 (m, 10H, aromatic), 5.60 (s, 1H, NH), 5.12 (quin., 1H, J = 5.0 Hz, Ph-C<u>H</u>(CH$_3$)-NH), 3.58 (s, 2H, Ph-<u>CH$_2$</u>-C(O)), 1.40 (d, 3H, J = 5.0 Hz, C<u>H$_3$</u>). ^{13}C NMR (125 MHz, CDCl$_3$): δ 170.0, 143.0, 134.9, 129.4, 129.0, 128.6, 127.4, 127.3, 125.9, 48.7, 43.9, 21.8.
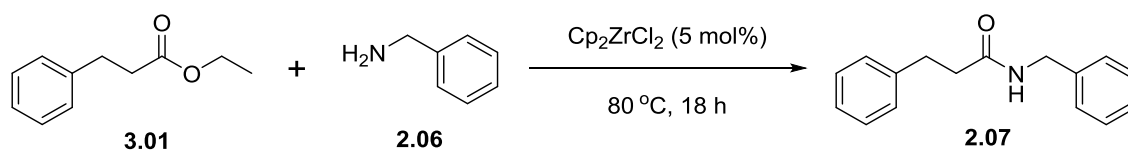
ESI-MS of [C$_{16}$H$_{17}$NO]; theoretical m/z of [M+Na]$^+$ = 262.1208, measured m/z of [M+Na]$^+$ = 262.1182.

IR: υ(cm^{-1})= 1638 (C=O stretch)

Melting point = 118-119 °C (Lit: 111 °C)

Experimental Procedures Chapter 2

General Procedure 2.1

An oven dried Radleys tube was charged with 3-phenylpropionic acid ethyl ester (1 mmol), benzylamine (1.2 mmol) and Cp$_2$ZrCl$_2$ (5 mol%) (catalysed reactions only). The appropriate solvent (1 mL) was then added and heated to 80 °C or 100 °C for 18 or 24 hours in accordance with Chapter 2, Table 1. The reaction mixture was then allowed to cool to room temperature and the solvent was removed *in vacuo* on a rotary evaporator.
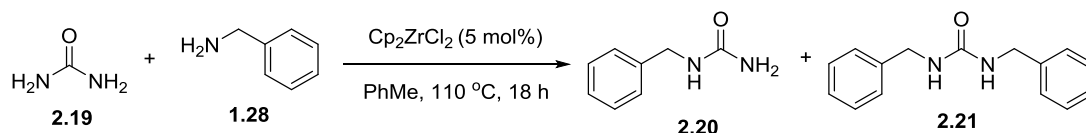
General Procedure 2.2
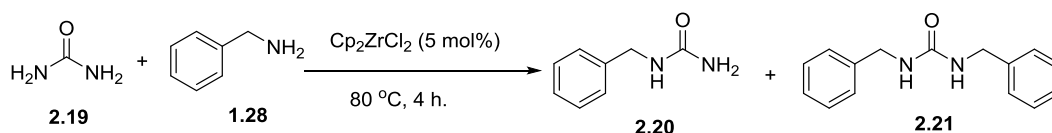
An oven dried Radleys tube was charged with urea (1 mmol), benzylamine (1 mmol) and Cp$_2$ZrCl$_2$ (5 mol%). The appropriate solvent (1 mL) was then added in accordance with Chapter 2, Table 2 and heated at 80 °C for

4 hours. The reaction was then allowed to cool to room temperature and the solvent was removed *in vacuo* on a rotary evaporator.

General Procedure 2.3

An oven dried Radleys tube was charged with urea (1 mmol), benzylamine (in accordance with Chapter 2, Table 3), and Cp$_2$ZrCl$_2$ (5 mol% as appropriate). Toluene (1 mL) was then added and t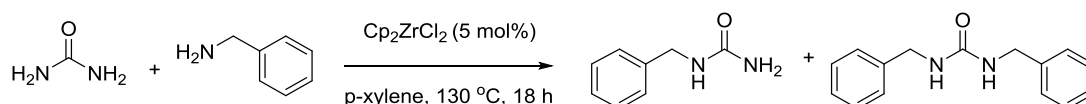he reaction was heated at 110 °C for 18 hours. The reaction was then allowed to cool to room temperature and the solvent was removed *in vacuo* on a rotary evaporator.
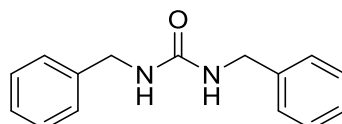
General Procedure 2.4

An oven dried Radleys tube was charged with urea (1 mmol) and benzylamine (2 mmol) in the presence and the absence of the catalyst (Cp$_2$ZrCl$_2$ (5 mol%). Para-xylene (1 mL) was then added and the reaction was heated to 130 °C for 18 hours. The reaction was then allowed to cool to room temperature and the solvent was removed *in vacuo* on a rotary evaporator.
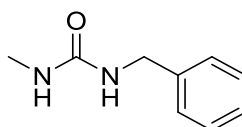
2.21. Dibenzylurea [76]

Following general procedure 2.4, the *title* compound was synthesised in 35% conversion by comparison at the peaks at 4.24 (d, 4H, *J* = 5 Hz, CH$_2$ product) and 3.70 (s, 2H, CH$_2$ starting material).
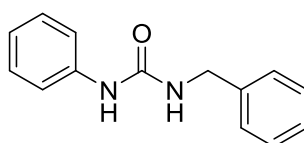
<u>General procedure 2.5</u>

An oven dried Radleys tube was charged with *N*-methylurea or *N*-Phenylurea (1 mmol) and benzylamine (in accordance with Chapter 2, Tables 6 + 7 respectively), in the presence and the absence of the catalyst (Cp_2ZrCl_2 (5 mol%)). Toluene (1 mL) was then added and the reaction was heated at 110 °C for 4 hours. The reaction was then allowed to cool to room temperature and the solvent was removed *in vacuo* on a rotary evaporator.

2.23. 1-Benzyl-3-methylurea [114]

Following general procedure 2.5, *N*-methylurea was used as the urea species and benzylamine (212 µL, 2 mmol) as the amine species. The *title* compound was synthesised in 58% conversion by comparison of the peaks at 4.18 (d, 2H, *J* = 7.5 Hz, CH_2 product) and 3.72 (s, 2H, CH_2 starting material).

2.25. 1-Benzyl-3-phenylurea [115]

Following general procedure 2.5, *N*-phenylurea was used as the urea species and benzylamime (212 µL, 2 mmol) as the amine species. The *title* compound was synthesised in 50% conversion by comparison of the peaks at 4.23 (d, 2H, J = 5 Hz, CH_2 product) and 3.78 (s, CH_2, starting material).

Zirconium Catalysed Coupling of Carbamates and Amines:

General Procedure 2.6
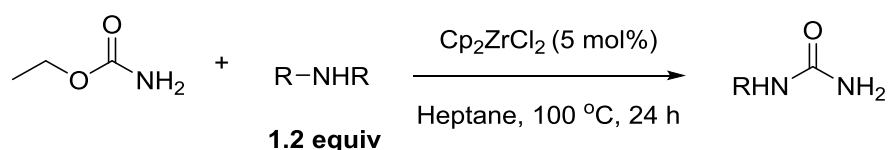
Ethyl carbamate (89 mg, 1 mmol) was added to an oven dried Radleys carousel tube, followed by the Cp$_2$ZrCl$_2$ (0.014 g, 5 mol%). The tube was then sealed and purged with nitrogen. Heptane (1 mL) and the amine species (1.2 mmol) were then added. The carousel tube was then heated at 100 ^{0}C for the appropriate time. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixtures were analysed by ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data. The monosubstituted ureas were then purified by column chromatography.

2.20. 1-Benzylurea[116]
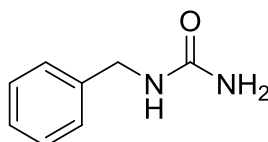
Following general procedure 2.6, ethyl carbamate (1 mmol, 89 mg) was used as the carbamate species and benzylamine (131 μL, 1.2 mmol) as the amine species. The *title compound* was recovered as a white solid (130 mg, 87% yield) after column chromatography (eluting with DCM/MeOH, 95:5). Data in accordance with those previously reported. [116]

^{1}H NMR (250 MHz, d^6-DMSO): δ. 7.27-7.33 (m, 5H, aromatic), 6.40 (t, 1H, *J* = 5.0 Hz, NH), 5.54 (2H, br. s, NH$_2$), 4.17 (d, 2H, *J* = 7.5 Hz, Ph-CH$_2$-NH).

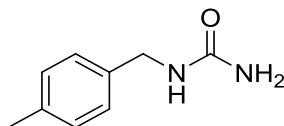^{13}C NMR (63 MHz, d^6-DMSO): δ 158.4, 140.9, 128.2, 127.0, 126.5, 42.8

ESI-MS of [C$_8$H$_{10}$N$_2$O]; theoretical m/z of [M+Na]$^+$ = 173.0691, measured m/z of [M+Na]$^+$ = 173.0704.

IR: υ(cm^{-1}) = 1647 (C=O stretch).

Melting point = 149-150 °C (Lit: 151 °C)

2.28. 1-(4-Methylbenzyl)urea[117]

Following general procedure 2.6, ethyl carbamate (89 mg, 1 mmol) was used as the carbamate species and 4-methylbenzylamine (152 µL, 1.2 mmol) as the amine species. The *title compound* was recovered as a white solid (100 mg, 61% yield) after column chromatography (eluting with DCM/MeOH, 9:1). Data in accordance with those previously reported. [117]
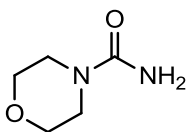
^{1}H NMR (500 MHz, d6-DMSO): δ 7.13 (4H, m, aromatic), 6.34 (t, 1H, J = 4.0 Hz, NH), 5.49 (br. s, 2H, NH$_2$), 4.13 (d, 2H, J = 6.0 Hz, Ph-CH$_2$-NH), 2.28 (s, 3H, CH$_3$).^{13}C NMR (500 MHz, d6-DMSO): δ 159.1, 138.3, 136.0, 129.2, 127.5, 43.0, 21.1.

ESI-MS of [C$_9$H$_{12}$N$_2$O]$^+$; theoretical m/z of [M+H]$^+$ = 165.1023, measured m/z of [M+H]$^+$ = 165.1084.

IR: υ(cm^{-1}) = 1637 (C=O stretch)

Melting point = 171-173 °C (Lit: 94-96 °C)

2.29. Morpholine-4-carboxamide [118]

Following general procedure 2.6, ethyl carbamate (89 mg, 1 mmol) was used as the carbamate species and morpholine (105 mg, 104 µL, 1.2 mmol) as the amine species. The *title* compound was recovered as a white solid (109 mg, 84% yield) after purification by column chromatography (eluting with DCM/MeOH, 95:5). Data in accordance with those previously reported. [118]

^{1}H NMR (250 MHz, CDCl$_3$): δ 5.20 (br s, 2H, NH$_2$), 3.61 (t, 4H, J = 5.0 Hz, CH$_2$-O-CH$_2$), 3.30 (t, 4H, J = 5.0 Hz, CH$_2$-N-CH$_2$). ^{13}C NMR (63 MHz, CDCl$_3$): δ 158.8, 66.4, 44.1

ESI-MS of [$C_5H_{10}N_2O$]; theoretical m/z of [M+Na]$^+$ = 153.0640, measured m/z of [M+Na]$^+$ = 153.0662.

IR: υ(cm^{-1}) = 1652 (C=O stretch)

Melting point = 100 °C (Lit: 107-109 °C)

2.30. (4-Methylphenyl)urea [119]

Following general procedure 2.6, ethyl carbamate (89 mg, 1 mmol) was used as the carbamate species and 4-methylaniline (128 mg, 1.2 mmol) as the amine species. The *title* compound was recovered as an off-white solid (133 mg, 89% yield) after purification by column chromatography (eluting with DCM/MeOH, 95:5). Data in accordance with those previously reported.[119]
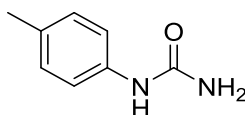
^{1}H NMR (250 MHz, d6-DMSO): δ 8.41 (br s, 1H, NH), 7.28 (d, 2H, *J* = 8.3 Hz), 7.03 (d, 2H, *J* = 8.3 Hz), 5.78 (2H, br s, NH$_2$), 2.22 (s, 3H, CH$_3$).

^{13}C NMR (63 MHz, d6-DMSO): δ 156.1, 137.9, 129.8, 129.0, 117.8, 20.2.

ESI-MS of [$C_8H_{10}N_2O$]; theoretical m/z of [M+H]$^+$ = 151.0866, measured m/z of [M+H]$^+$ = 151.0959.

IR: υ(cm^{-1}) = 1652 (C=O stretch)

Melting point = 181-182 °C (Lit: 181-182 °C)[120]

2.31. Hexylurea[121]
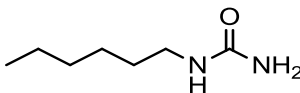
Following general procedure 2.6, ethyl carbamate (89 mg, 1 mmol) was used as the carbamate species and hexylamine (121 mg, 1.2 mmol) as the amine species. The *title* compound was recovered as a colourless solid (115 mg, 80% yield) after purification by column chromatography (eluting with DCM/MeOH, 95:5). Data in accordance with those previously reported.[121]

^{1}H NMR (250 MHz, d6-DMSO): δ 5.91 (t, 1H, *J* = 6.3 Hz, CH$_2$-NH-C(O)), 5.37 (br s, 2H, C(O)-NH$_2$), 2.94 (q, 2H, *J* = 6.3 Hz, C(O)-NH-CH$_2$-CH$_2$), 1.14

– 1.46 (m, 8H, CH_3-($\underline{CH_2}$)$_4$-CH_2). 0.87 (t, 3H, J = 6.6 Hz, $\underline{CH_3}$), ^{13}C NMR (63 MHz, d6-DMSO) δ 159.2, 31.5, 30.4, 26.5, 22.6, 14.4. no additional peaks observed.

ESI-MS of [$C_7H_{16}N_2O$]; theoretical m/z of [M+H]$^+$ = 145.1336, measured m/z of [M+H]$^+$ = 145.1458.

IR: υ(cm^{-1})= 1648.74 (C=O stretch)

M.p = 108-111 °C (Lit: 106-107 °C)

2.32. 1-Phenylurea[122]

Following general procedure 2.6, ethyl carbamate (89 mg, 1 mmol) was used as the carbamate species and aniline (109 μL, 1.2 mmol), as the amine species. The *title compound* was recovered as an off-white solid (125 mg, 92% yield), after column chromatography (eluting with DCM/MeOH, 95:5).

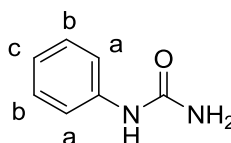^{1}H NMR (250 MHz, d^6-DMSO): δ 8.68 (s, 1H, $\underline{NH}$), 7.46 (d, 2H, J = 7.5 Hz, a), 7.32 (t, 2H, J = 7.5 Hz, b), 6.98 (t, 1H, J = 7.5 Hz, c). ^{13}C NMR (63 MHz, d^6-DMSO): δ 152.4, 139.7, 128.8, 121.8, 118.2.

ESI-MS of [$C_7H_8N_2O$]; theoretical m/z of [M+H]$^+$ = 137.0714, measured [M+H]$^+$ = 137.0716.

IR: υ(cm^{-1}) = 1636 (C=O stretch)

Melting point = 180-183 °C (Lit: 143-145 °C)[120]

2.33. 2-Phenethylurea[116]

Following general procedure 2.6, ethyl carbamate (89 mg, 1 mmol) was used as the carbamate species and 2-phenethylamine (0.152 mL, 1.2 mmol) as the amine species. The *title compound* was recovered as a white solid

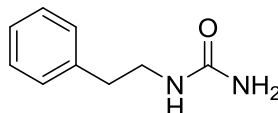(115 mg, 70% yield) after column chromatography (eluting with DCM/MeOH, 95:5). Data in accordance with those previously reported.[116]
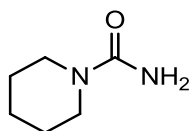
^{1}H NMR (500 MHz, d6-DMSO): δ 7.30 (d, 2H, J = 8.0 Hz, aromatic), 7.20 (m, 3H, aromatic), 5.91 (t, 1H, J = 5.0 Hz, NH), 5.42 (2H, br s, NH$_2$), 3.20 (2H, q, J = 7.3 Hz, NH-CH$_2$-CH$_2$), 2.67 (t, 2H, J = 7.3 Hz, NH-CH$_2$-CH$_2$-Ph). ^{13}C NMR (125 MHz, d6-DMSO): δ 159.1, 140.3, 129.1, 128.8, 126.4, 41.3, 39.1, 36.6.

ESI-MS of [C$_9$H$_{12}$N$_2$O]; theoretical m/z of [M+H]$^+$ = 165.1023, measured m/z of [M+H]$^+$ = 165.1107.

IR: υ(cm^{-1}) = 1653 (C=O stretch).

Melting point = 109-112 °C (Lit: 112-114 °C)

2.34. Piperidine-1-carboxamide[76]

Following general procedure 2.6, ethyl carbamate (89 mg, 1 mmol) was used as the carbamate species and piperidine (102 mg, 118 μL, 1.2 mmol) as the amine species. The *title* compound was recovered as an off white solid (77 mg, 60% yield) after purification by column chromatography (eluting with DCM/MeOH, 95:5). Data in accordance with those previously reported.[76]

^{1}H NMR (250 MHz, CDCl$_3$): δ 4.72 (br s, 2H, NH$_2$). 3.33 (4H, m, CH$_2$-NH-CH$_2$), 1.57 (6H, m, piperidine). ^{13}C NMR (63 MHz, CDCl$_3$): δ 158.4, 45.1, 25.6, 24.2.

ESI-MS of [C$_6$H$_{12}$N$_2$O]; theoretical m/z of [M+H]$^+$ = 129.1023, measured m/z of [M+H]$^+$ = 129.1028.

IR: υ(cm^{-1}) = 1661 (C=O stretch).

Melting point = 100 °C (Lit: 97-98 °C)

2.35. 1,1-Diethylurea
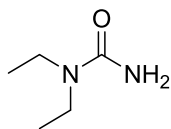
Following general procedure 2.6, ethyl carbamate (267 mg, 3 mmol) was used as the carbamate species and diethylamine (372 µL, 3.6 mmol) as the amine species. The *title* compound was recovered as a white solid, (170 mg, 49% yield) after purification by column chromatography (eluting with DCM/MeOH, 98:2).

^{1}H NMR (300 MHz, CDCl$_3$): δ 4.44 (br. s, 2H, N-C(O)-<u>NH$_2$</u>), 3.27 (q, 4H, *J* = 6.0 Hz, <u>CH$_2$</u>-N-C(O)), 1.16 (t, 6H, *J* = 6.0 Hz, <u>CH$_3$</u>). ^{13}C NMR (125 MHz, CDCl$_3$): δ 158.1, 41.6, 13.7.

ESI-MS of [C$_5$H$_{12}$N$_2$O]; theoretical m/z of [M+H]$^+$ = 117.10, measured m/z of [M+H]$^+$ = 117.1060.

IR: υ(cm^{-1}) = 1640 (C=O stretch).

Melting point = 67-69 °C (Lit: 75 °C)[123]

2.36. *N*-methylaniline urea[124]
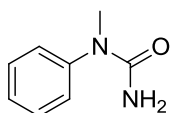
Following general procedure 2.6, ethyl carbamate (89 mg, 1 mmol) was used as the carbamate species and *N*-methylaniline (130 µL, 1.2 mmol) as the amine species. The *title* compound was synthesised in 64% conversion by comparison of the peaks at 3.15 (s, 3H, <u>CH$_3$</u>, product) and 3.99 (q, 2H, <u>CH$_2$</u>, carbamate).

Mechanistic experiments

Determination of reaction pathway

3.28 → **3.29**

Cp$_2$ZrCl$_2$ (5 mol%)

heptane, 100 °C, 24 h

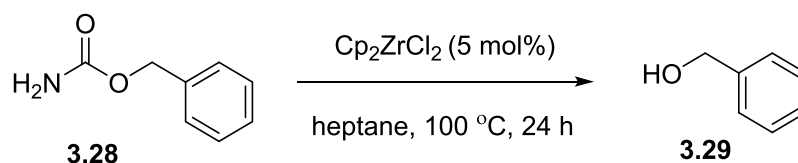An oven dried Radleys tube was charged with benzyl carbamate (1 mmol) and Cp$_2$ZrCl$_2$ (5 mol%). Heptane (1 mL) was then added and the reaction was heated to 100 °C for 24 hours. The reaction mixture was then allowed to cool to room temperature and the solvent was removed *in vacuo* on a rotary evaporator.

Experimental Procedures Chapter 3

General procedure 3.1

Ammonia source screen

3.06 + NH$_3$ → **3.07**

24 h, 110 °C, PhMe

ammonia source (2 equiv)
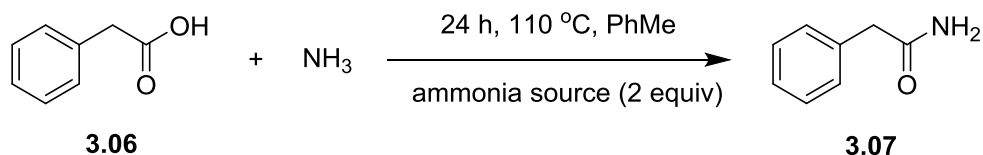
An oven dried Radleys tube was charged with phenylacetic acid (136 mg, 1 mmol) and the ammonia source (in accordance with Chapter 3, Table 1) (2 mmol). Toluene (1 mL) was then added and the reaction was heated at 110 °C for 24 hours. The reaction was allowed to cool to room temperature and the solvent was removed *in vacuo* on a rotary evaporator.

General Procedure 3.2

Variation of the catalyst

An oven dried Radleys tube was charged with phenylacetic acid (1 mmol), Urea (1 mmol) and the appropriate catalyst (20 mol%) was added in accordance with Chapter 3, Table 2. Toluene (1 mL) was used as the solvent and the reaction was heate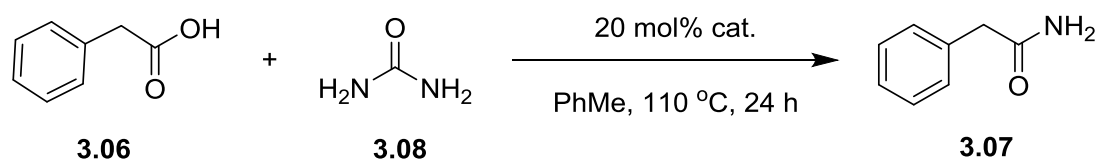d at 110 °C for 24 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* and the resulting crude reaction mixtures were analysed by their ^{1}H NMR spectra.

Variation of the Solvent

Following general procedure 3.2, Mg(OAc)$_2$·4H$_2$O (10 mol%) was used as the catalyst species and the solvent (1 mL) was added in accordance with Chapter 3, Table 3.

Variation of the Magnesium Salt

Following general procedure 3.2, the catalyst species (10 mol%) was added in accordance with Chapter 3, Table 4. Octane (1 mL) was used as the solvent.
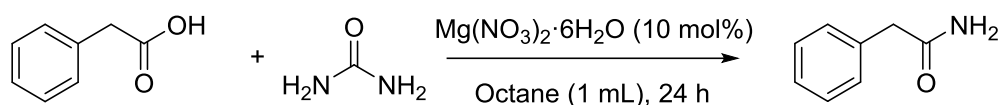
Variation of urea concentration with Mg salt

Following general procedure 3.2, urea was added in accordance with Chapter 3, Table 4. Mg(OAc)$_2$·4H$_2$O (10 mol%) or Mg(NO$_3$)$_2$·6H$_2$O (10 mol%) were added in accordance with. Octane (1 mL) was used as the solvent.

Table 5: as for Table 4, the reaction was heated at 120 °C for 24 hours.

General Procedure 3.3

Temperature Screen

An oven dried Radleys tube was charged with phenylacetic acid (1 mmol), urea (2 mmol) and Mg(NO$_3$)$_2$·6H$_2$O (10 mol%). Octane (1 mL) was then added and the reaction was heated at 120 °C for 24 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* and the resulting crude reaction mixtures were analysed by their ^{1}H NMR spectra.

Variation of Urea concentration with Catalyst loading

Following general procedure 3.3, urea and Mg(NO$_3$)$_2$·6H$_2$O were added in accordance with Chapter 3, Table 8.

Reaction concentration screen

Following general procedure 3.3, octane was added in accordance with Chapter 3, Table 9.

General Procedure 3.4

An oven dried Radleys carousel tube was charged with the acid species (3 mmol) and urea (6 mmol). Mg(NO$_3$)$_2$·6H$_2$O (10 mol%) was then added with octane (3 mL). The reaction mixture was then heated for 24 hours at 120 °C. After being allowed to cool to room temperature, the solvent was removed *in vacuo* and the resulting crude reaction mixtures we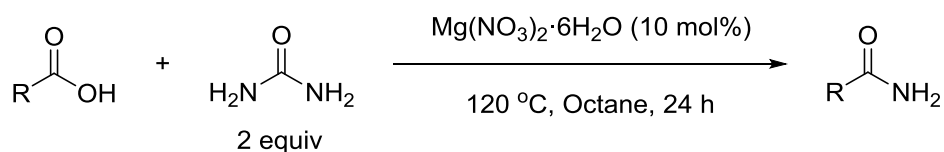re analysed by their ^{1}H NMR spectra. Where high conversions were reached, the crude products were dissolved in EtOAc and washed with NaHCO$_3$ (3 x 10 mL).

The organic layers were then combined and dried over MgSO₄. The solvent was removed *in vacuo* on a rotary evaporator to yield the pure primary amides.

3.07. 2-Phenylacetamide[125]
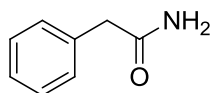
Following general procedure 3.4, phenylacetic acid (408 mg, 3 mmol) was used as the acid species. The *title* compound was recovered as an off white solid (292 mg, 72% yield) after purification. Data in accordance with those previously reported.[125]

^{1}H NMR (300 MHz, CDCl₃): δ 7.27-7.40 (m, 5H, aromatic), 5.65 (br. s, 1H, <u>NH</u>), 5.39 (br. s, 1H, <u>NH</u>), 3.59 (s, 2H, Ph-<u>CH₂</u>-C(O)NH₂). ^{13}C NMR (75 MHz, CDCl₃): δ 173.7, 134.9, 129.8, 129.0, 127.7, 43.4.

ESI-MS of [C₈H₉NO]; theoretical m/z of [M+Na]⁺ = 158.0581, measured m/z of [M+Na]⁺ = 158.0591.

IR: υ(cm⁻¹) = 1627 (C=O stretch)

Melting point = 152-155 °C (Lit: 155-158 °C)

3.09. 3-Phenylpropionamide[51]
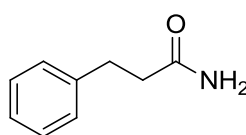
Following general procedure 3.4, 3-phenylpropionic acid (450 mg, 3 mmol) was used as the acid species. The *title* compound was recovered as an off white solid (351 mg, 78% yield) after purification.

^{1}H NMR (300 MHz, CDCl₃): δ 7.22-7.36 (m, 5H, aromatic), 5.51 (br. s, 1H, C(O)-<u>NH₂</u>), 5.39 (br. s, 1H, C(O)-<u>NH₂</u>), 3.01 (t, 2H, *J* = 6.0 Hz, Ph-<u>CH₂</u>-CH₂), 2.56 (t, 2H, *J* = 6.0 Hz, Ph-CH₂-<u>CH₂</u>). ^{13}C NMR (75 MHz, CDCl₃): δ 174.8, 141.0, 129.0, 128.7, 126.7, 37.9, 31.8.

ESI-MS of [C₉H₁₁NO]; theoretical m/z of [M+H]⁺ = 150.0919, measured m/z of [M+H]⁺ = 150.0933.

IR: υ(cm⁻¹) = 1626 (C=O stretch)

Melting point = 98-100 °C (Lit: 102-104 °C)

3.10. Hexanamide[126]

Following general procedure 3.4, hexanoic acid (0.375 mL, 3 mmol) was used as the acid species. The *title* compound was recovered as a white solid (224 mg, 65% yield) after purification. Data in accordance with those previously reported.[126]
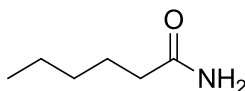
^{1}H NMR (300 MHz, CDCl₃): δ 5.41 (br. s, 2H, C(O)-NH₂), 2.22 (t, 2H, J = 6.0 Hz, CH₂-C(O)-NH₂), 1.59-1.69 (m, 2H, CH₂-CH₂-CH₂-C(O)-NH₂), 1.27-1.37 (m, 4H, CH₃-CH₂-CH₂-CH₂-CH₂-C(O)), 0.9 (t, 3H, J = 6.0 Hz, CH₃). ^{13}C NMR (125 MHz, CDCl₃): δ 176.4, 36.2, 31.7, 25.5, 22.7, 14.2.

ESI-MS of [C₆H₁₃NO]; theoretical m/z of [M+H]⁺ = 116.1075, measured m/z of [M+H]⁺ = 116.1092.

IR: υ(cm⁻¹) = 1631 (C=O stretch)

Melting point = 98 °C (Lit: 101-102 °C)

3.11. 4-Chlorophenylacetamide[127]
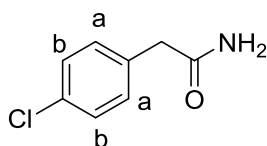
Following general procedure 3.4, 4-chlorophenylacetic acid (510 mg, 3 mmol) was used as the acid species. The *title* compound was recovered as a white solid (305 mg, 60% yield) after purification. Data in accordance with those previously reported.[127]

^{1}H NMR (300 MHz, d6-DMSO): δ 7.52 (br. s, 1H, NH), 7.37 (d, 2H, J = 9.0 Hz, a), 7.28 (d, 2H, J = 9.0 Hz, b), 6.95 (br. s, 1H, NH), 3.36 (s, 2H, Ph-CH₂-C(O)-NH₂), ^{13}C NMR (125 MHz, d6-DMSO): δ 172.1, 135.3, 131.3, 128.4, 41.7.

ESI-MS of [C_8H_8ClNO]; theoretical m/z of [M+H]$^+$ = 170.0373, measured m/z of [M+H]$^+$ = 170.0380.

IR: υ(cm^{-1}) = 1627 (C=O stretch).

Melting point = 178-180 °C (Lit: 179-182) [128]

3.12. 3-(4'-methoxyphenyl)propionamide[129]

Following general procedure 3.4, 4-methoxyphenylpropionic acid (540 mg, 3 mmol) was used the acid species. The *title* compound was recovered as a white solid (382 mg, 72% yield) after purification. Data in accordance with those previously reported. [129]
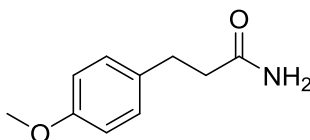
^{1}H NMR (300 MHz, CDCl$_3$): δ 2.50 (t, 2H, *J* = 6.0 Hz, C(O)-C<u>H</u>$_2$-CH$_2$), 2.92 (t, 2H, *J* = 6.0 Hz, Ph-C<u>H</u>$_2$-CH$_2$), 3.79 (s, 3H, Ph-O-C<u>H</u>$_3$), 5.37 (br. s, 1H, C(O)-NH$_2$), 5.52 (br. s, 1H, C(O)-N<u>H</u>$_2$), 6.84 (d, 2H, *J* = 6.0 Hz, C<u>H</u>-C-C<u>H</u>), 7.15 (d, 2H, *J* = 6.0 Hz, C<u>H</u>-C(O)-C<u>H</u>) ^{13}C NMR (125 MHz, CDCl$_3$): δ 174.6, 158.2, 132.9, 129.4, 113.9, 55.5, 37.8, 30.6.

ESI-MS of [$C_{10}H_{13}NO_2$]; theoretical m/z of [M+Na]$^+$ = 202.0844, measured m/z of [M+Na]$^+$ = 202.0840.

IR: υ(cm^{-1}) = 1643 (C=O stretch).

Melting point = 123 °C (Lit: 123-124 °C)[130]

3.13. 4-Methoxyphenylacetamide[127]
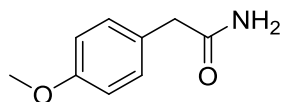
Following general procedure 3.4, 4-methoxyphenylacetic acid (498 mg, 3 mmol) was used as the acid species. The *title* compound was recovered as a yellow solid (340 mg, 74% yield) after purification. Data in accordance with those previously reported.[127]

^{1}H NMR (500 MHz, d6-DMSO): δ 7.37 (br. s, 1H, NH$_2$), 7.16 (d, 2H, J = 10.0 Hz, a), 6.85 (d, 2H, J = 10.0 Hz, b), 6.80 (br. s, 1H, NH$_2$), 3.72 (s, 3H, Ph-O-C$\underline{H}_3$), 3.26 (s, 2H, Ph-C$\underline{H}_2$-C(O)). ^{13}C NMR (125 MHz, d6-DMSO): δ 172.9, 158.2, 130.4, 128.8, 114.0, 55.4, 41.4.

ESI-MS of [C$_9$H$_{11}$NO$_2$]; theoretical m/z of [M+H]$^+$ = 166.0868, measured m/z of [M+H]$^+$ = 166.0873.

IR: υ(cm^{-1}) = 1627 (C=O stretch)

Melting point = 158-160 °C (Lit: 164-166 °C)[131]

3.14. Diphenylacetamide[132]

Following general procedure 3.4, diphenylacetic acid (633 mg, 3 mmol) was used as the acid species. The title compound was recovered as a white solid (478 mg, 76% yield) after purification. Data in accordance with those previously reported.[132]

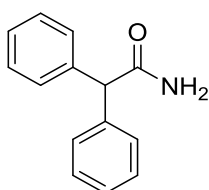^{1}H NMR (300 MHz, CDCl$_3$): δ 7.24-7.37 (m, 10H, aromatic), 5.75 (br. s, 1H, C(O)-N$\underline{H}_2$), 5.58 (br. s, 1H, C(O)-N$\underline{H}_2$), 4.97 (s, 1H, (Ph-(Ph)-C$\underline{H}$-C(O)), ^{13}C NMR (75 MHz, CDCl$_3$): δ 174.9, 139.5, 129.3, 127.8, 59.1.

ESI-MS of [C$_{14}$H$_{13}$NO]; theoretical m/z of [M+H]$^+$ = 212.1075, measured m/z of [M+H]$^+$ = 212.1081.

IR: υ(cm^{-1}) = 1646 (C=O stretch).

Melting point = 166-168 °C (Lit: 169 °C) [133]

3.15. 4-Pentenamide[134]

Following general procedure 3.4, 4-pentenoic acid (307 µL, 3 mmol) was used as the acid species. The *title* compound was recovered as a white solid

(251 mg, 85% yield), after purification. Data in accordance with those previously reported.[134]
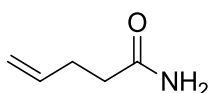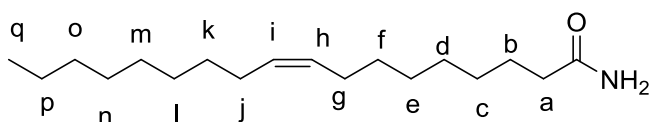
^{1}H NMR (500 MHz, CDCl$_3$): δ 5.85 (ddt, J = 5 Hz, J = 5 Hz, J = 10 Hz, CH$_2$=C<u>H</u>-CH$_2$), 5.48 (br. s, 2H, NH$_2$), 5.02-5.12 (m, 2H, C<u>H$_2$</u>=CH), 2.38-2.43 (m, 2H, C(O)-C<u>H$_2$</u>-CH$_2$), 2.31-2.34 (m, 2H, C(O)-CH$_2$-C<u>H$_2$</u>). ^{13}C NMR (125 MHz, CDCl$_3$) δ 175.2, 137.2, 116.2, 35.5, 29.6.

ESI-MS of [C$_5$H$_9$NO]; theoretical m/z of [M+H]$^+$ = 100.0762, measured m/z of [M+H]$^+$ = 100.0762.

IR: υ(cm^{-1}) = 1663 (C=O stretch), 1629 (C=C stretch).

Melting point = 100-101 °C (Lit: 105-106 °C)

3.16. Oleamide [135]

Following general procedure 3.4, oleic acid (634 μL, 2 mmol) was used as the acid species. The *title* compound was recovered as an off-white solid (214 mg, 38% yield) after aqueous work up. The crude reaction mixture was dissolved in DCM and washed with NaOH (3 x 15 mL). The organic layers were then combined and dried over MgSO$_4$. The solvent was then removed *in vacuo* to yield the pure product. Data in accordance with those previously reported.[135]

^{1}H NMR (500 MHz, d6-DMSO): δ 7.21 (s, 1H, NH), 6.67 (s, 1H, NH), 5.35-5.28 (m, 2H, h + i), 2.02-1.96 (m, 6H, a, g, j), 1.48-1.42 (m, 2H, b), 1.29-1.24 (m, 20H, c-f, k-p), 0.85 (t, 3H, J = 5 Hz, C<u>H$_3$</u>). ^{13}C NMR (125 MHz, d6-DMSO): δ 174.7, 130.0, 128.1, 35.6, 31.8, 29.6, 29.6, 29.3, 29.2, 29.2, 29.2, 29.1, 29.0, 27.1, 27.0, 25.6, 22.6, 14.4.

ESI-MS of [C$_{18}$H$_{35}$NO]; theoretical m/z of [M+H]$^+$ = 282.2791, measured m/z of [M+H]$^+$ = 282.2715

IR: υ(cm^{-1}) = 1631 (C=O stretch)

Melting point = 72-75 °C (Lit: 71-73 °C)

3.17. Benzoylamidoacetamide [136]
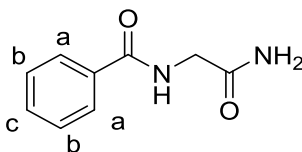
Following general procedure 3.4, Benzoylaminoacetic acid (358 mg, 2 mmol) was used as the acid species. The *title* compound was recovered as an off white solid (192 mg, 54 % yield) after purification by column chromatography (eluting with EtOAc/DCM : MeOH/EtOAc, 70:30). Data in accordance with those previously reported.[136]

^{1}H NMR (500 MHz, d6-DMSO): δ 8.65 (t, 1H, J = 5 Hz, <u>NH</u>), 7.88 (d, 2H, J = 10.0 Hz, aromatic ring a), 7.53 (t, 1H, J = 10.0 Hz, aromatic ring c), 7.47 (t, 2H, J = 5.0 Hz, aromatic ring b), 7.36 (br. s, 1H, <u>NH$_2$</u>), 7.03 (br. s, 1H, <u>NH$_2$</u>), 3.82 (d, 2H, J = 5.0 Hz, C(O)-NH-<u>CH$_2$</u>-C(O)). ^{13}C NMR (125 MHz, d6-DMSO): δ 171.3, 166.6, 131.4, 128.5, 127.6, 42.7.

ESI-MS of [C$_9$H$_{10}$N$_2$O$_2$]; theoretical m/z of [M+Na]$^+$ = 201.0639, measured m/z of [M+Na]$^+$ = 201.0614

IR: υ(cm^{-1}) = 1626 (C=O stretch)

Melting point = 140-143 °C (Lit: 185 °C)

3.18. Pentanediamide [137]

Following general procedure 3.4, glutaric acid was used as the acid species (264 mg, 2 mmol). The *title* compound was recovered as an off white solid (114 mg, 44% yield) after purification by column chromatography (eluting with EtOAc/MeOH, 70-80:30-20). Data in accordance with those previously reported.[137]

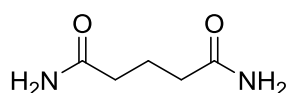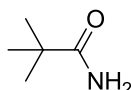^{1}H NMR (500 MHz, d6-DMSO): δ 7.23 (s, 2H, NH$_2$), 6.69 (s, 2H, NH$_2$), 2.03 (t, 4H, J = 5 Hz, C(O)-<u>CH$_2$</u>-CH$_2$-<u>CH$_2$</u>-C(O)), 1.67 (quin., 2H, J = 5 Hz, CH$_2$-<u>CH$_2$</u>-CH$_2$). ^{13}C NMR (125 MHz, d6-DMSO): δ 173.9, 34.5, 21.0.

ESI-MS of [$C_5H_{10}N_2O_2$]; theoretical m/z of [M+Na]$^+$ = 153.0639, measured m/z of [M+Na]$^+$ = 153.0634.

IR: υ(cm^{-1}) = 1624 (C=O stretch)

Melting point = 182-183 °C (Lit: 181 °C)

3.19. Trimethylacetamide[138]

Following general procedure 3.4, trimethylacetic acid (102 mg, 1 mmol) was used as the acid species. The *title* compound was synthesised in 58% conversion by comparison of the peaks at 1.07 (s, 9H, (CH$_3$)$_3$, product) and 1.10 (s, 9H, (CH$_3$)$_3$, starting material).

3.20. (1,3-benzodioxyl-5-ylmethyl)-amide
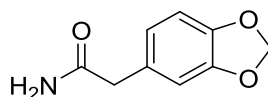
Following general procedure 3.4, 2-(1,3-benzodioxyl-5-yl)-acetic acid (180 mg, 1 mmol) was used as the acid species. The title compound was synthesised in 67% conversion by comparison of the peaks at 3.26 (s, 2H, CH$_2$, product) and 3.35 (s, 2H, CH$_2$ starting material).

3.26. Dodecanamide[139]
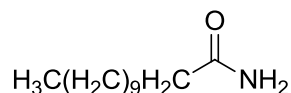
Following general procedure 3.4, lauric acid (600 mg, 3 mmol) was used as the acid species. The *title* compound was synthesised in 78% conversion by comparison of the peaks at 2.01 (t, 2H, CH$_2$, product) and 2.12 (t, 2H, CH$_2$, starting material).

General Procedure 3.5

Synthesis of *N*-methylamides from carboxylic acids and 1,3 dimethyl urea
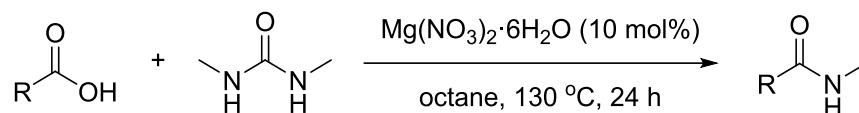
An oven dried Radleys carousel tube was charged with the acid species (3 mmol) and 1,3-dimethylurea (6 mmol). $Mg(NO_3)_2 \cdot 6H_2O$ (10 mol%) was then added with octane (3 mL). The reaction mixture was then heated for 24 hours at 130 °C. After being allowed to cool to room temperature, the solvent was removed *in vacuo* and the resulting crude reaction mixtures were analysed by their ^{1}H NMR spectra. The methylamides were then purified by column chromatography.

3.29. *N*-Methyl phenylacetamide[140]
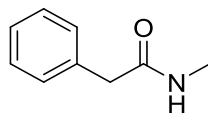
Following general procedure 3.5, phenylacetic acid (408 mg, 3 mmol), was used as the acid species. The *title* compound was recovered as a white solid (322 mg, 72% yield) after purification by column chromatography (eluting with EtOAc/DCM, 1:1). Data in accordance with those previously reported.[140]

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.11-7.22 (m, 5H, aromatic), 6.54 (br. s, 1H, C(O)-NH-CH$_3$), 3.39 (s, 2H, Ph-CH$_2$-C(O)), 2.58 (d, 3H, *J* = 3 Hz, C(O)-NH-CH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 180.0, 135.1, 129.1, 128.6, 126.9, 43.1, 26.2.

ESI-MS of [C$_9$H$_{11}$NO]; theoretical m/z of [M+H]$^+$ = 150.0919, measured m/z of [M+H]$^+$ = 150.0933.

IR: υ(cm^{-1}) = 1627 (C=O stretch)

Melting point = 56 °C (Lit: 51 °C)

3.30. *N*-Methyl hexanamide[141]
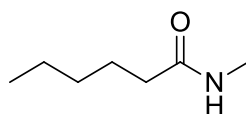
Following general procedure 3.5, hexanoic acid (375 µL, 3 mmol) was used as the acid species. The title compound was recovered as a colourless liquid (281 mg, 70% yield) after purification by column chromatography (eluting with EtOAc/DCM, 1:1). Data in accordance with those previously reported.[141]

^{1}H NMR (300 MHz, CDCl$_3$): δ 7.07 (br. s, 1H, C(O)-NH-CH$_3$), 2.59 (d, 3H, J = 3.0 Hz, C(O)-NH-CH$_3$), 2.02 (t, 2H, J = 9.0 Hz, CH$_2$-CH$_2$-C(O)-NH-CH$_3$), 1.44 (quin., 2H, J = 9.0 Hz, CH$_2$-CH$_2$-C(O)-NH), 1.16-1.05 (m, 4H, CH$_3$-CH$_2$-CH$_2$-CH$_2$), 0.69 (t, 3H, J = 9.0 Hz, CH$_3$-CH$_2$-CH$_2$-). ^{13}C NMR (75 MHz, CDCl$_3$): δ 174.6, 36.5, 31.5, 26.2, 25.2, 22.5, 14.0.

ESI-MS of [C$_7$H$_{15}$NO]; theoretical m/z of [M+H]$^+$ = 130.1232, measured m/z of [M+H]$^+$ = 130.1291.

IR: υ(cm^{-1}) = 1646 (C=O stretch).

3.31. *N*-Methyl Oleamide
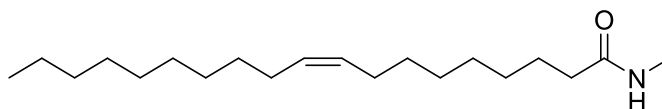
Following general procedure 3.5, oleic acid (326 µL, 1 mmol) was used as the acid species. The title compound was recovered as an off white solid (159 mg, 52% yield) after purification by column chromatography (eluting with EtOAc/Pentane, 1:2).

^{1}H NMR (300 MHz, CDCl$_3$): δ 5.78 (br.s, 1H, NH), 5.37-5.26 (m, 2H, CH$_2$-CH-CH-CH$_2$), 2.77 (d, 3H, J = 6.0 Hz, C(O)-NH-CH$_3$), 2.14 (t, 2H, J = 9.0 Hz, C(O)-CH$_2$-CH$_2$), 2.02-1.97 (m, 4H, CH$_2$-CH-CH-CH$_2$), 1.62-1.57 (m, 2H, C(O)-CH$_2$-CH$_2$-CH$_2$), 1.26 (d, 20H, J = 9.0 Hz, CH$_2$), 0.85 (t, 3H, J = 6.0 Hz, CH$_3$-CH$_2$-CH$_2$-CH$_2$). ^{13}C NMR (125 MHz, CDCl$_3$): δ 174.3, 130.3, 130.0, 36.9, 32.2, 30.7, 30.0, 29.8, 29.6, 29.6, 29.6, 29.5, 27.5, 27.5, 26.5, 26.1, 25.9, 23.0, 14.9.

ESI-MS of [$C_{19}H_{37}NO$]; theoretical m/z of [M+H]$^+$ = 296.2953, measured m/z of [M+H]$^+$ = 296.2936.

IR: υ(cm^{-1}) = 1638 (C=O stretch).

Melting point = 37 °C (Lit: 34-35 °C) [140]

3.32. 3-(4-methoxyphenyl)-N-methylpropanamide[129]
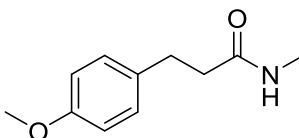
Following general procedure 3.5, 3-(4-methoxyphenyl)-3-phenylpropionic acid (3 mmol, 540 mg) was used as the acid species. The *title* compound was synthesised in 88% conversion by comparison of the peaks at 2.64 (t, 2H, CH_2, starting material), and 2.69 (t, 2H, CH_2 product).

3.34. 2-(4-Chlorophenyl)-*N*-methylacetamide[142]
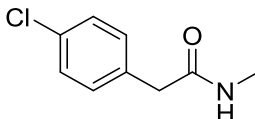
Following general procedure 3.5, 4-chlorophenylacetic acid (3 mmol, 510 mg) was used as the acid species. The *title* compound was synthesised in 58% conversion by comparison of the peaks at 3.23 (s, 2H, CH_2, starting material) and 3.35 (s, 2H, CH_2, product).

3.35. *N*-methyltrimethylacetamide[143]
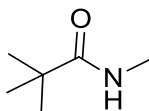
Following general procedure 3.5, trimethylacetic acid (102 mg, 1 mmol) was used as the acid species. The *title* compound was synthesised in 78%

conversion by comparison of the peaks at 1.09 (s, 9H, (CH$_3$)$_3$, starting material) and 1.16 (s, 9H, (CH$_3$)$_3$, product).

Alternative Acyl donors

Ester coupling

Following general procedure 3.4, methyl phenylacetate (1 mmol) was used as the acyl donor.

Sulfonic acid coupling
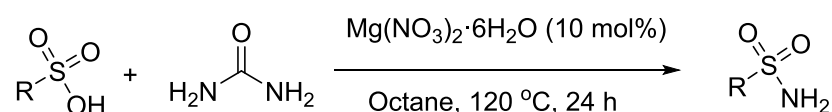
Following general procedure 3.4, p-toluenesulfonic acid (1 mmol), MOPS (1 mmol) or trifluoromethanesulfonic acid (1 mmol) was used as the acyl donor.

Synthesis of *N*-Acyl urea intermediate

Following literature procedure,[107] trimethylacetyl chloride (615 µL, 5 mmol) was dissolved in dry acetonitrile (10 mL). This was slowly added to a boiling solution of urea (1.2 g, 20 mmol) in dry acetonitrile and heated under reflux for two hours. The organic solvent was then removed under reduced pressure. The product was dissolved in ethylacetate (50 mL) and washed with H$_2$O (3 x 20 mL). The organic fraction was dried over MgSO$_4$ and evaporated. The title compound was recovered as a white solid (220 mg, 31% yield).

3.42. 1-(pivaloyl)urea[107]
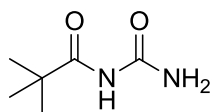
^{1}H NMR (300 MHz, CDCl$_3$): δ 8.30 (d, 2H, J = 15 Hz, <u>NH$_2$</u>), 5.52 (br. s, 1H, C(O)-<u>NH</u>-C(O)), 1.26 (s, 9H, (<u>CH$_3$</u>)$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 179.8, 154.7, 39.8, 26.8.

ESI-MS of [C$_6$H$_{12}$N$_2$O$_2$]; theoretical m/z of [M+Na]$^+$ = 167.0796, measured m/z of [M+Na]$^+$ = 167.0787.

IR: υ(cm^{-1}) = 1706, 1666 (C=O stretches)

Melting point = 144-146 °C (Lit: 151-153 °C)

Data in accordance with those previously reported.

<u>General Procedure 3.6</u>

<u>*N*-acylurea breakdown reactions</u>
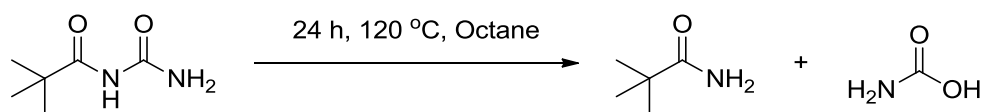
An oven dried Radleys tube was charged with *N*-acylurea (0.5 mmol), Mg(NO$_3$)$_2$·6H$_2$O and H$_2$O in accordance with Chapter 3, Table 13. Octane (0.5 mL) was then added and the reaction was heated at 120 °C for 24 hours. The conversion was then determined by comparison of the peaks at 1.26 (s, 9H, (CH$_3$)$_3$, starting *N*-acylurea) and 1.07 (s, 9H, (CH$_3$)$_3$, primary amide).

General procedure 3.7

Organocatalysed primary amide bond formation from carboxylic acids and urea
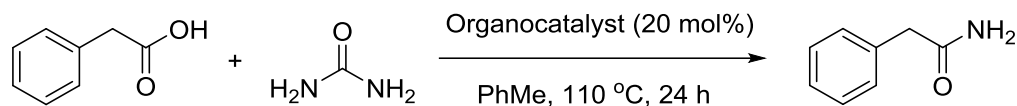
An oven dried Radleys tube was charged with phenylacetic acid (1 mmol), urea (1 mmol) and the catalyst species (20 mol%). Toluene (1 mL) was then added and the tube was heated to 110 °C for 24 hours. After being allowed to cool to room temperature, the crude reaction mixtures were then analysed by their ^{1}H NMR spectra.

General procedure 3.8

An oven dried Radleys tube was charged with phenylacetic acid (1 mmol), urea (in accordance with chapter 3, Table 15) and the catalyst species (in accordance with Chapter 3, Table 15). Octane (1 mL) was then added and the reaction was heated at 110 °C for 24 hours. After being allowed to cool to room temperature, the solvent was removed in vacuo on a rotary evaporator and the crude reaction mixtures were analysed by their ^{1}H NMR spectra.

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