Catalytic Approaches to the Synthesis of Amide Bonds

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CONTENTS

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Abbreviations

Å	Ångstrom
Ac	Acyl
acac	Acetylacetonate
AOP	(7-Azabenzotriazol-1-yl)oxytris(dimethylamino) phosphonium hexafluorophosphate
Ar	Aryl
Asp	Aspartic
atm	Atmospheres
BEMT	2-Bromo-3-ethyl-4-methylthiazolium tetrafluoroborate
BEP	2-Bromo-1-ethylpyridinium tetrafluoroborate
BMTB	2-Bromo-3-methyl-4-methylthiazolium bromide
BOP-Cl	*N*,*N*-Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BMMP	1-(1-(1H-Benzo[d][1,2,3]triazol-1-yloxy)ethylidene) pyrrolidinium hexachloroantimonate
Bn	Benzyl
CDMS	Chlorodimethylsulfonium hexachloroantimonate
CDMT	2-Chloro-4,6-dimethoxy-1,3,5-triazine
cod	Cyclooctadiene
conv.	Conversion
Cp	Cyclopentadienyl
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMEDA	*N*,*N*-Dimethylethylenediamine
DPEPhos	Bis(2-diphenylphosphinophenyl)ether
dppe	1,2-Bis(diphenylphosphino)ethane
ee	enantiomeric excess
EEDQ	2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline
equiv.	Equivalents
Et	Ethyl
g	grams

GC-MS	Gas Chromatography – Mass Spectroscopy
Gly	Glycine
h	Hours
HATeU	*O*-(1H-1,2,3-Triazolo[4,5-b]pyridin-1-yl)-1,1,3,3-tetraethyluronium hexafluorophosphate
HATU	(2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3 tetramethyluronium hexafluorophosphate)
HOAt	1-Hydroxy-7-azabenzotriazole
IIDQ	1-Isobutoxycarbonyl-2-isobutoxy-1,2-dihydroquinoline
^{i}Pr	Isopropyl
M	Molar
Me	Methyl
Mes	Mesitylene
MHz	Megahertz
Min	minutes
mL	Millilitres
mmol	Millimoles
NHC	*N*-Heterocyclic carbene
NMR	Nuclear magnetic resonance
Ph	Phenyl
Phe	Phenylalanine
ppm	Parts Per Million
PTSA	Para-toluene sulphonic acid
PyClopP	Chlorobispyrrolidinophenylphosphonium hexachloroantimonate
r.t.	Room temperature
^{t}Bu	Tertiary butyl
Tf	Triflate
Ts	Tosyl
TFFH	Tetramethylfluoroformamidinium hexafluorophosphate
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
UV	Ultraviolet
Val	Valine

Abstract

This thesis outlines work carried out in the last three years concerning the development of novel, atom-economic, catalytic syntheses of amide bonds, determination of the ranges of these reactions through substrate screenings and investigations into the mechanisms by which the reactions are operating.

In Chapter 1, an introduction to amide bonds is given, after which a discussion on the synthesis of amide bonds is presented, covering direct coupling methods, enzymatic methods and both non-metal catalysts and metal catalysts used for amide bond synthesis.

In the Results and Discussion section, an iron catalysed coupling of nitriles and amines is presented in Chapter 2.

In Chapter 3, firstly the development of an indium and zinc catalysed rearrangement of aldoximes into primary amides is discussed, followed by development of a novel, nickel catalysed coupling of aldehydes and amines. Detailed mechanistic studies using ^{18}O labelled substrates are then presented for both of these reactions.

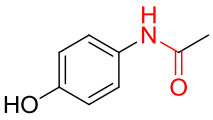
Chapter 4 details work on a novel, hydroxylamine hydrochloride catalysed transamidation of primary amides with amines, including ^{1}H NMR studies to attempt to elucidate the mechanism of the reaction.

Finally, in Chapter 5, work investigating the direct coupling of unactivated carboxylic acids and amines is discussed, followed by an investigation into suitable catalysts to improve the efficiency of the reaction and a comparison of the rates in the catalysed and uncatalysed reactions for a wide range of substrates.

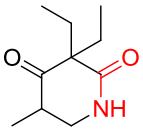
1. Introduction

1.1 Introduction to Amides

The amide bond is arguably one of the most important in chemistry. It is essential to sustain life, making up the peptide bonds in proteins such as enzymes, and it is also one of the most prolific moieties in pharmaceutical molecules, agrochemicals and natural products (Figure 1.1, 1.**1-1.7**).



Paracetamol 1.1



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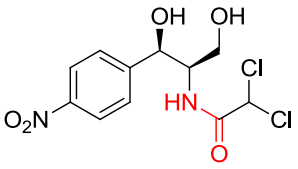
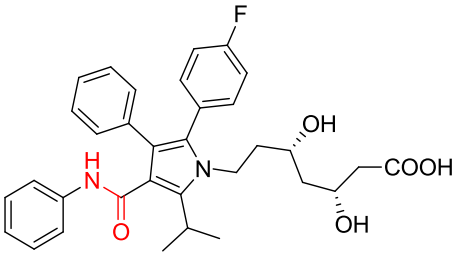
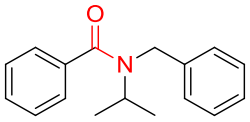


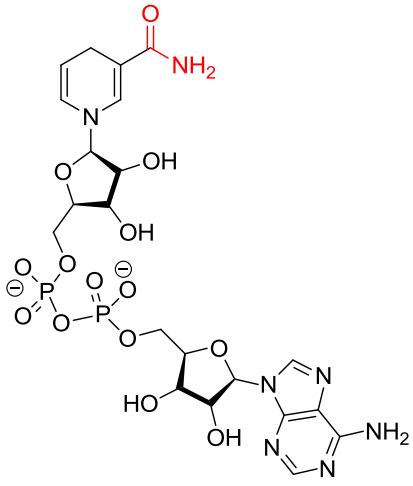
Chloramphenicol 1.3



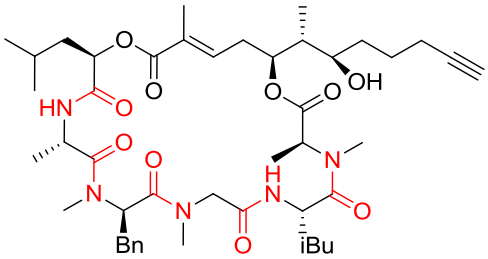
Atorvastatin 1.4



Benzipram 1.5



NADH 1.6



Palau'amide 1.7

Figure 1.1. Amide bonds in drug molecules (1.1-1.4), agrochemicals (1.5), biological molecules (1.6) and natural products (1.7)

The structural characteristics of amide bonds, specifically the partial delocalisation of electrons over the N-C-O bond and their hydrogen bonding abilities, play crucial roles in their behaviour as a functional group within a larger molecule. In proteins, these characteristics allow the peptide bonds to contribute to the secondary structures which are adopted by the chains of amino acids, as well as linking the individual residues together. The partial double bond nature of the peptide bond means it is not completely rigid and therefore its dihedral angle can adopt both *cis* and *trans* values, providing a 'hinge' in the protein backbone. The *cis* configuration, however, is less frequently observed due to the much higher stability of the *trans* isomer (Figure 1.2).[1]

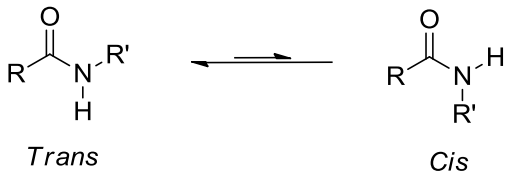


Figure 1.2. *Cis* and *trans* configurations of an amide bond

The repeating pattern of backbone hydrogen bonds along a protein in an α-helix configuration lends stability to this secondary structure. Such bonds occur between a carbonyl group (C=O) and an amide hydrogen (N-H) located four residues apart in the sequence, due to each turn of the helix containing 3.6 amino acids (Figure 1.3).

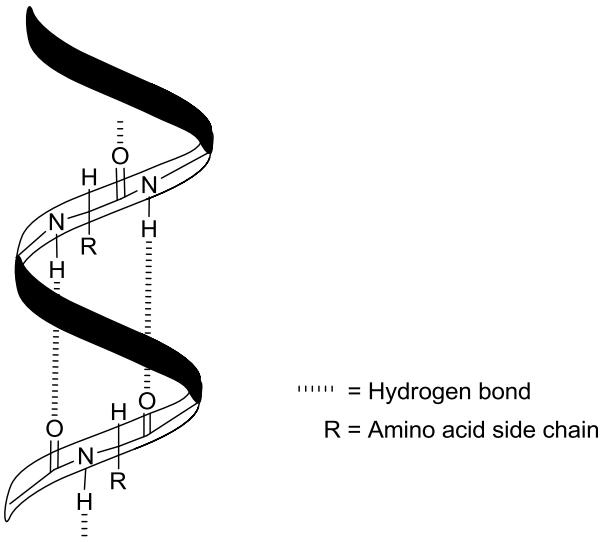


Figure 1.3. Hydrogen bonds in protein backbones lend stability to the α-helix structure

In proteins adopting a β-sheet conformation, hydrogen bonding between the amides also plays an important role in stabilising the secondary structures. The peptide bonds involved in these hydrogen bonds are inherently further apart than those in an α-helix due to the interacting groups originating from different strands of the protein. Overall, there are thousands of these hydrogen bonding interactions between residues in proteins, creating stabilisation of the structures yet still allowing them to be dynamic, which is essential for their function.

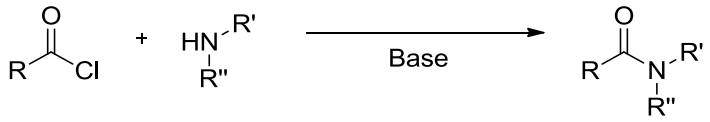
The binding between proteins and ligands (which can be biological molecules as diverse as elemental ions, small organic molecules and macromolecules such as other proteins) also involve electrostatic interactions between the amide bonds. The match between the binding site and ligand is dependent on two main features; geometry and electrostatic complementarity. It is mainly the coordination of favourable electrostatic interactions which provides specificity to protein-ligand bindings as correct binding is designed to optimise the number hydrogen bonds. A survey of protein complexes showed hydrogen bonds to mediate recognition in 67% of protein-small organic molecule complexes.[2]

This prevalence and significance of amide bonds in biological processes has led to them being present in a huge number of drug molecules and also makes them logical targets in *de novo* drug molecule design. In a recent industry-led survey of 128 drug syntheses, acylations accounted for 12% of the reactions involved (second only to heteroatom alkylations/arylations), of which 66% were *N*-acylations to form amides.[3] However, despite accounting for such a large proportion of the transformations, none of the *N*-acylation reactions used were catalytic. In a separate survey concerned with identifying key green chemistry research areas, amide formation avoiding poor atom economy reagents was voted the highest priority reaction which companies would like to see investigated.[4] Both these observations highlight the need for new, atom-efficient, economic and preferably environmentally friendly catalytic processes for synthesising amide bonds to be developed.

1.2 Synthesis of Amides

1.2.1 Direct Coupling Methods

One of the most popular syntheses of amide bonds is the Schotten-Baumann reaction, first described in 1883 by Carl Schotten and Eugen Baumann.[5] This reaction is the coupling of an acid chloride and an amine to produce an amide and hydrochloric acid (Scheme 1.1). Due to the formation of the acid by-product, a base must be present in order for the reaction to proceed. Normally an aqueous solution of a base is slowly added to the reaction mixture in order to neutralise the acid and stop it forming the inactive amine salt. Alternatively, the reaction can be carried out in a two-phase system of water and an immiscible solvent such as dichloromethane. In this case, the acid chloride and amine remain in the organic layer, while the base remains in the aqueous phase. Any HCl produced can dissolve in the aqueous layer and be neutralised by the base.



Scheme 1.1. The Schotten-Baumann reaction

Nonivamide (Figure 1.4), a food additive and active lachrymator ingredient in pepper spray is synthesised using the Schotten-Baumann reaction.

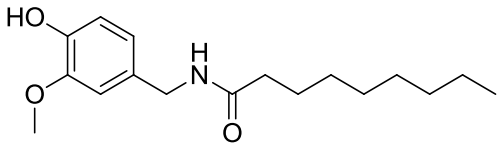
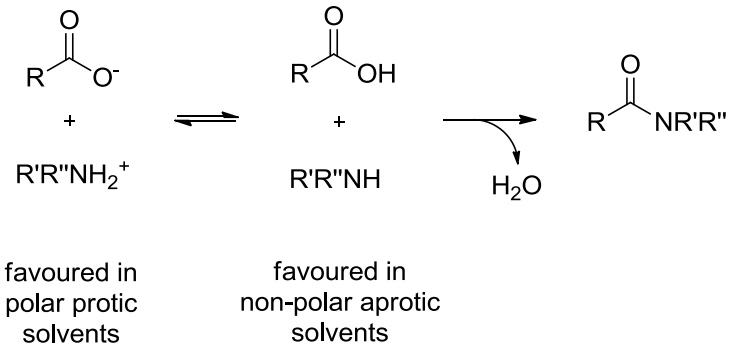


Figure 1.4. Nonivamide

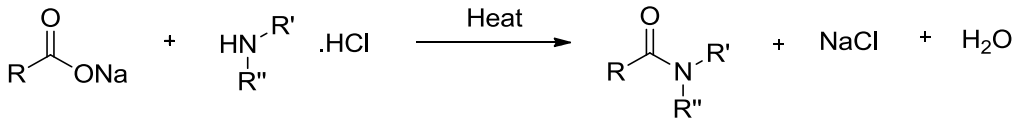
This reaction has been applied to the synthesis of polypeptides in the Fischer peptide synthesis, in which α-chloro or α-bromo acyl chlorides are treated with an amino acid ester.[6] Hydrolysis of the resultant ester into the acid and conversion into a new acid chloride follows; this is condensed with a second amino acid ester, and so on. The terminal chloride is finally converted into an amino group with ammonia.

The direct coupling of a carboxylic acid and an amine to form an amide bond is highly desirable due to the ready availability of these compounds and the relative cleanliness and atom economy of such a process - the only side product being water (Scheme 1.2). This reaction, however, has been largely unoptimised because the reaction is traditionally thought to require very high temperatures (>180 ^{o}C) to overcome the thermodynamic barrier of salt formation.[7] To this end, many coupling reagents and stoichiometric reagents (see Chapter 1.2.2) have been developed to activate the carboxylic acid towards nucleophilic attack; however, these all suffer from the drawback of producing a stoichiometric amount of waste product. Catalytic methods have generally involved the use of arylboronic acids and their derivatives (see Chapter 1.2.4), although other catalysts have also been reported (see Chapter 1.2.5). Typically, water is removed under the reaction conditions in order to drive the equilibrium towards amide formation.



Scheme 1.2. Carboxylic acid and amine coupling

The direct uncatalysed formation of amides was reported as early as 1902.[8] In this early paper by Dunlap, he describes the reaction between the sodium salts of carboxylic acids and amine hydrochloride salts (Scheme 1.3). Various combinations of substrates were heated at very high temperatures (up to 320 ^{o}C) and the yields of isolated amide ranged from 23 – 72%.

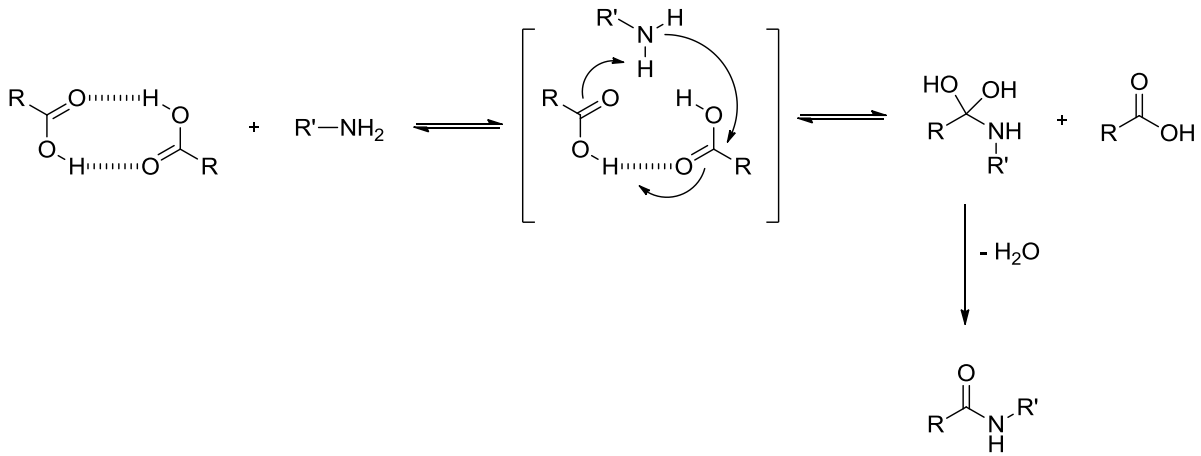


Scheme 1.3. Formation of amides from carboxylic acid sodium salts and amine hydrochloride salts.

In 1989, Cossy reported the synthesis of a small range of amides at 140 ^{o}C under neat conditions in the presence of 4Å molecular sieves.[9] Later, in 2006, Whiting *et al.* observed 60% conversion into *N*-benzyl-4-phenylbutyramide after heating 4-phenylbutyric acid and benzylamine in toluene at reflux for 22 hours in the presence of 3Å molecular sieves.[10] While these results were encouraging, further investigation revealed that this reaction was highly substrate dependant. A later report by Gooßen *et al.* showed a range of amides could be formed under solvent free thermal conditions at a temperature of 160 ^{o}C, again in the presence of 3Å molecular sieves.[11]

Whiting *et al.* published a detailed study into the reaction mechanism by which direct amide bond formation may occur in non-polar, aprotic solvents.[12] They found that carboxylic acids and amines do react to form the ammonium carboxylate salt (even in toluene) and the extent of this reaction is dependent on the p*K*a of the acid and basicity of the amine. When formation of the salt does not go to completion, a number of species can be formed from mixing the two substrates.

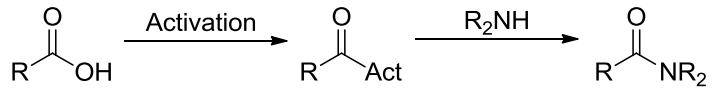
No evidence for acid or base catalysis was observed in their studies. A neutral, hydrogen bonded carboxylic acid dimer was proposed to be the active species in the direct amide bond formation, supported by DFT calculations and experimental evidence (Scheme 1.4).



Scheme 1.4. Mechanism of direct amide formation involving an active hydrogen bonded complex, proposed by Whiting *et al.*

1.2.2 Coupling Reagents

Currently, the most common way to make an amide bond is by using a coupling reagent to activate a carboxylic acid, which in turn reacts with an amine (Scheme 1.5).



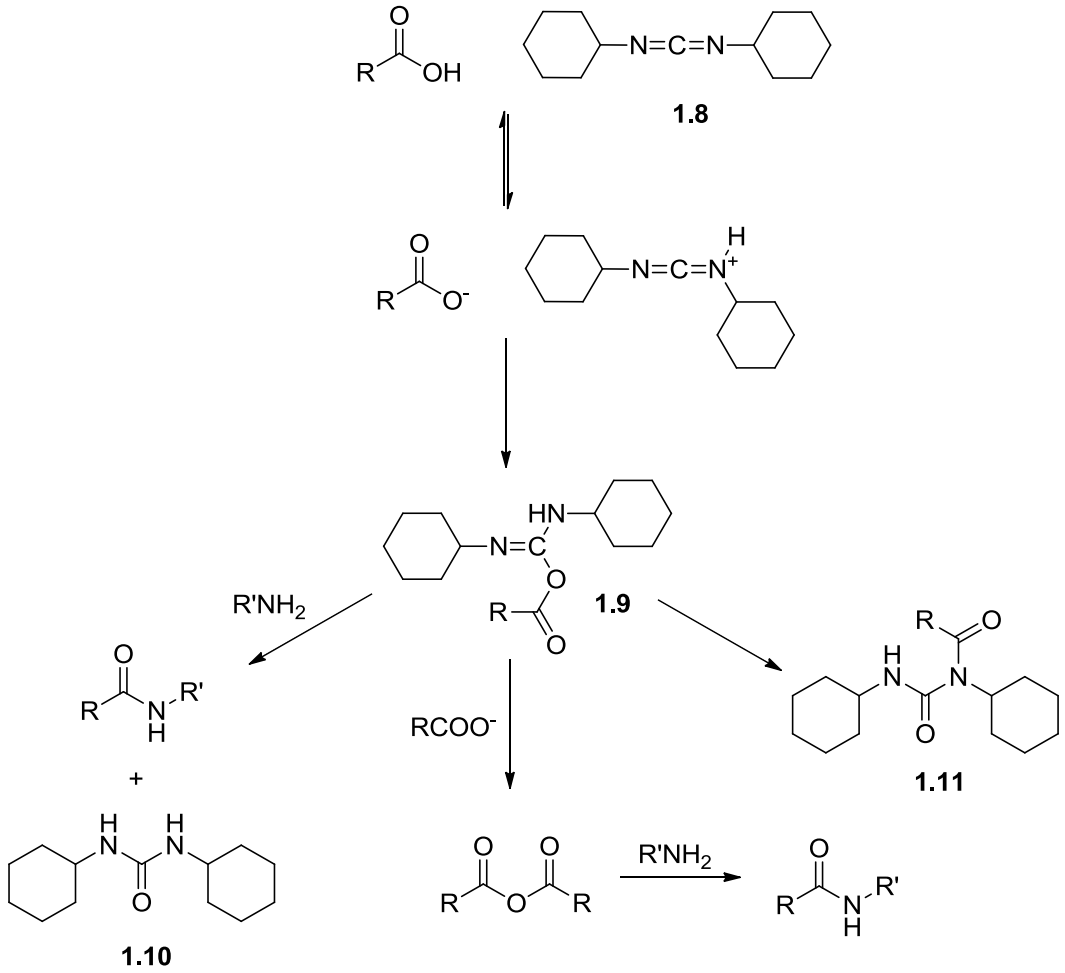
Scheme 1.5. Coupling reagent activation of a carboxylic acid

Carbodiimides were first used for this reaction in 1955,[13] with many modifications being made to the original structure since then.[14] The mechanism of activation of a carboxylic acid by dicyclohexylcarbodiimide (DCC) **1.8** is shown in Scheme 1.6.

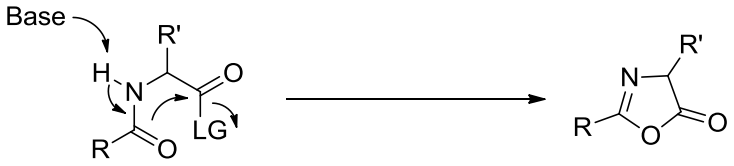
The first step is the reaction of the carboxylic acid with DCC to form *O*-acylurea **1.9**. This can then go on to yield several different products;

1. Direct reaction with the amine will give the amide and by-product DCU **1.10**
2. Reaction with another molecule of carboxylic acid will give a carbonic anhydride, which can then react with the amine, giving the amide product
3. Acyl transfer from O to N will give side product *N*-acylurea **1.11**.

Apart from the production of unwanted side products, epimerisation can be another problem in this reaction if oxazolone formation takes place (Scheme 1.7). This can occur if the carboxylic acid also contains a carbamate or urea group.

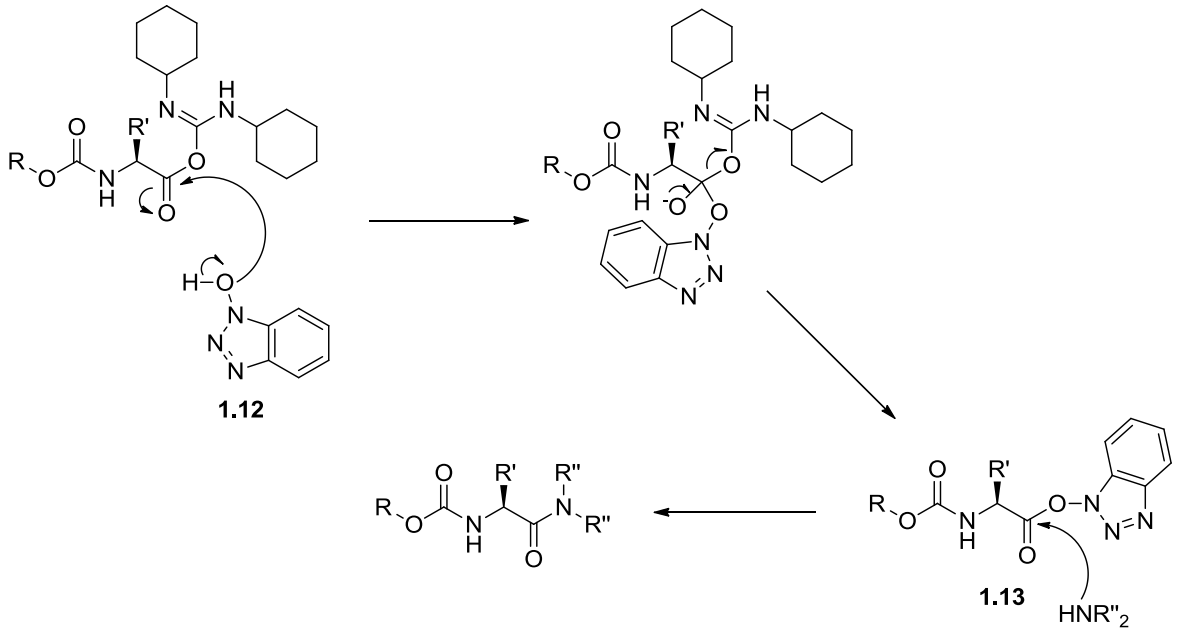


Scheme 1.6. Amide formation using DCC as coupling reagent



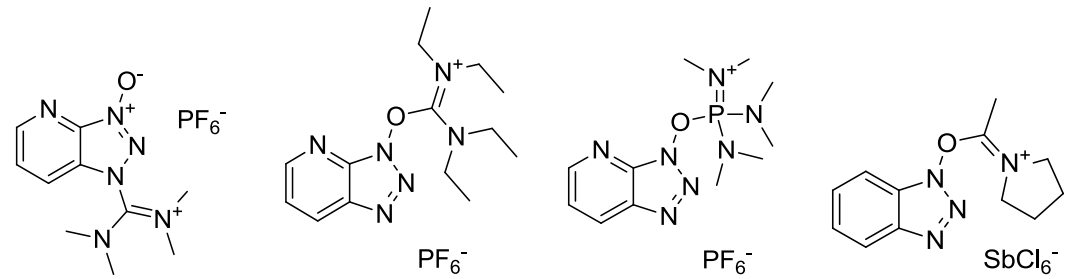
Scheme 1.7. Oxazolone side product formation (R, R' = amino acid side chains)

To reduce the level of epimerisation, several additives to coupling reagents have been developed by various groups, an early example of which is 1-hydroxy-1*H*-benzotriazole, **1.12**, first used by Koenig and Geiger in 1970 (Scheme 1.8).[15] This successfully reduced epimerisation levels from 35% to 1.5% when coupling Z-Gly-Phe-OH to H-Val-OMe. The generally accepted mechanism of this reagent is shown below in Scheme 1.8. The benzotriazole-carboxylic acid complex **1.13** is incapable of cyclising to the oxazolone, thus the stereochemistry in the alpha position remains intact in the product.



Scheme 1.8. Amide formation using 1-hydroxy-1*H*-benzotriazole with DCC

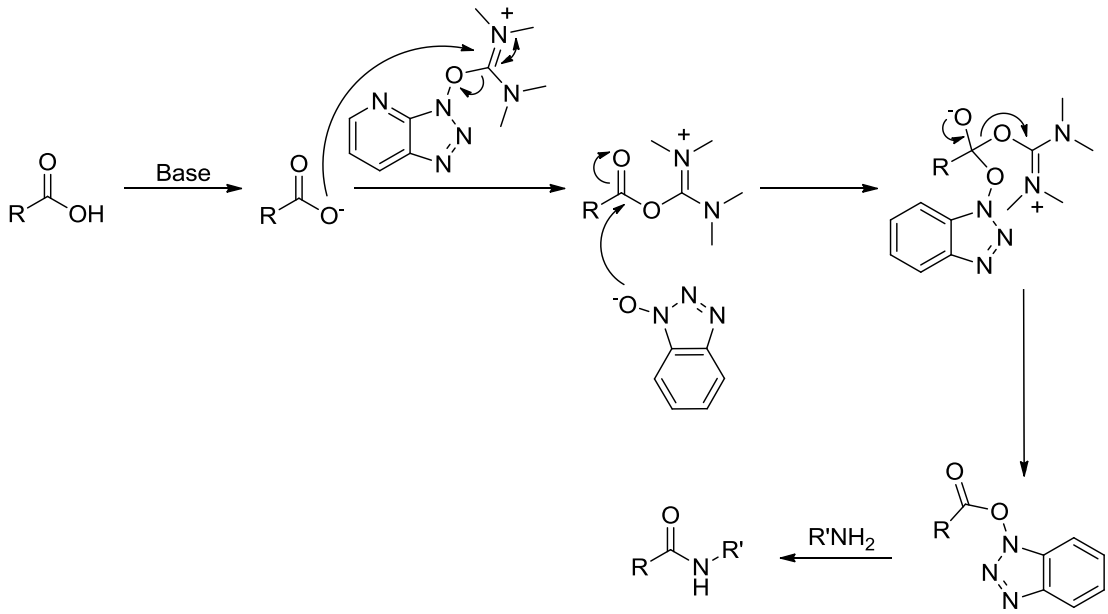
As with carbodiimides, work has been done to improve this activation system, mainly based around using aminium **1.14,** uronium **1.15**, phosphonium **1.16** or immonium **1.17** salts of 1-hydroxy-1*H*-benzotriazole (Figure 1.5, Scheme 1.9).[16]



HATU 1.14 **HATeU 1.15** **AOP 1.16** **BMMP 1.17**

Figure 1.5. Coupling reagents based on salts of 1-hydroxy-1*H*-benzotriazole

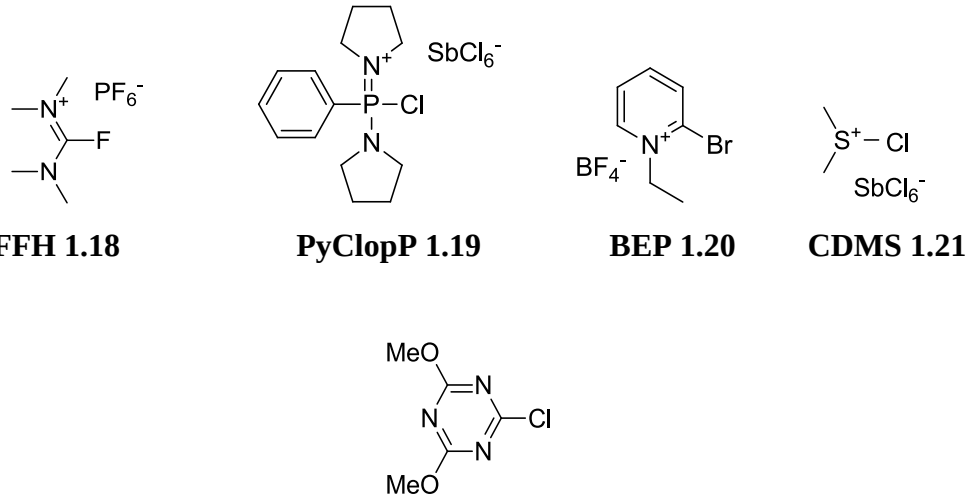
Although many variations of this type of reagent have been developed, they are still far from ideal. Side reactions are also still a problem, with the formation of guanidinium occurring when using aminium or uronium salts if the amine reacts directly with the coupling reagent.[17] Despite many variations of structure and counterion having been investigated, to date, very little improvement in terms of yields and efficiency on the original HATU system has been made.[18]



Scheme 1.9. Amide formation using uronium/aminium salt reagents

Reagents generating acid halides as a means of activation also represent a large class of coupling reagent. It is almost certainly one of the oldest methods, with reports from 1901 detailing a dipeptide (Gly-Gly) synthesis using thionyl chloride to activate the carboxylic acid.[19] Since then many reagents have been developed to avoid the harsh

conditions required when using thionyl chloride, including halo-uronium **1.18**), –phosphonium **1.19**, -pyridinium **1.20** and –sulphonium **1.21**, reagents[20] and triazine type reagents **1.22** (Figure 1.6).[21]



TFFH 1.18 **PyClopP 1.19** **BEP 1.20** **CDMS 1.21**

CDMT 1.22

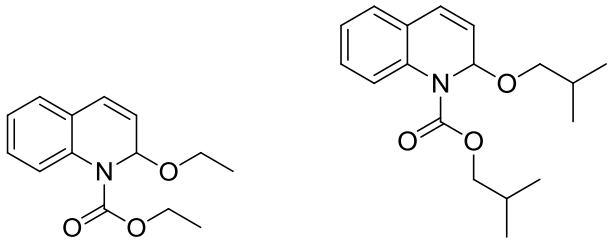
Figure 1.6. Acid halide generating coupling reagents

Reagents of this type currently available are not without their drawbacks. Many uronium salt based reagents (especially chlorine analogues) were found to not only be incompatible with many protecting groups, but also unstable towards hydrolysis in the presence of a base[22] and some sulfonium reagents (including CDMS **1.21**) were simply too reactive and decomposed under the coupling reaction conditions.[23] BOP-Cl, a phosphonium variant, was found to be suitable for coupling hindered substrates but was incompatible with primary amines.[24]

2-Halopyridinium salts, designed by Li, were an attempt to circumvent the problem of carbocation stabilisation *via* lone pairs on the amine groups, which makes it less reactive towards a carboxylic acid *in situ.* Li replaced an amine group with more electronegative groups possessing lone pairs, or with groups without lone pairs. Replacing one nitrogen group with a sulphur yielded the first thioazolium salt reagent, BEMT,[25] a counterion analogue of which, BMTB, was later reported as having better reactivity than HATU (**1.14**) in coupling two protected amino acids.[26] While efficient for amide synthesis under relatively harsh reaction conditions,[27] the poor solubility of the 2-halopyridinium salts was problematic in the milder conditions needed for peptide

synthesis. To try and increase the solubility of these reagents, Li attempted to use different counterions and a fluorine analogue for higher reactivity, but these changes presented the new problem of the reagents being too reactive and the base had to be added slowly to avoid a violent reaction.[28]

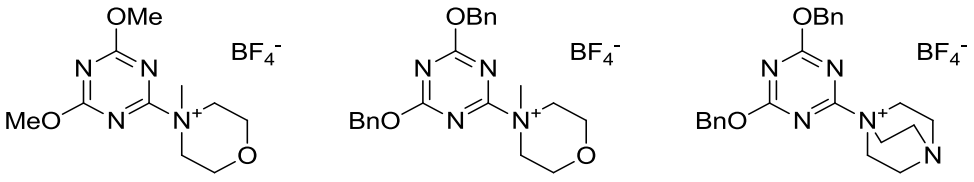
Several other classes of coupling reagents exist, including those generating carbon anhydrides as a means of activation, such as EEDQ **1.23** and IIDQ **1.24** (Figure 1.7). These have the advantage of fewer side reactions over most other coupling reagents as the anhydride is formed slowly but consumed rapidly, avoiding its accumulation and minimising the chances of by-products and also a guanidinium salt cannot be formed through reaction with the amine, a common problem with uronium type reagents.[29]



EEDQ 1.23 **IIDQ 1.24**

Figure 1.7. Carbon anhydride generating coupling reagents

Another group of coupling reagents incorporating the triazine moiety is that based on the 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methyl-morpholinium structure (DMTMM **1.25,** Figure 1.8).



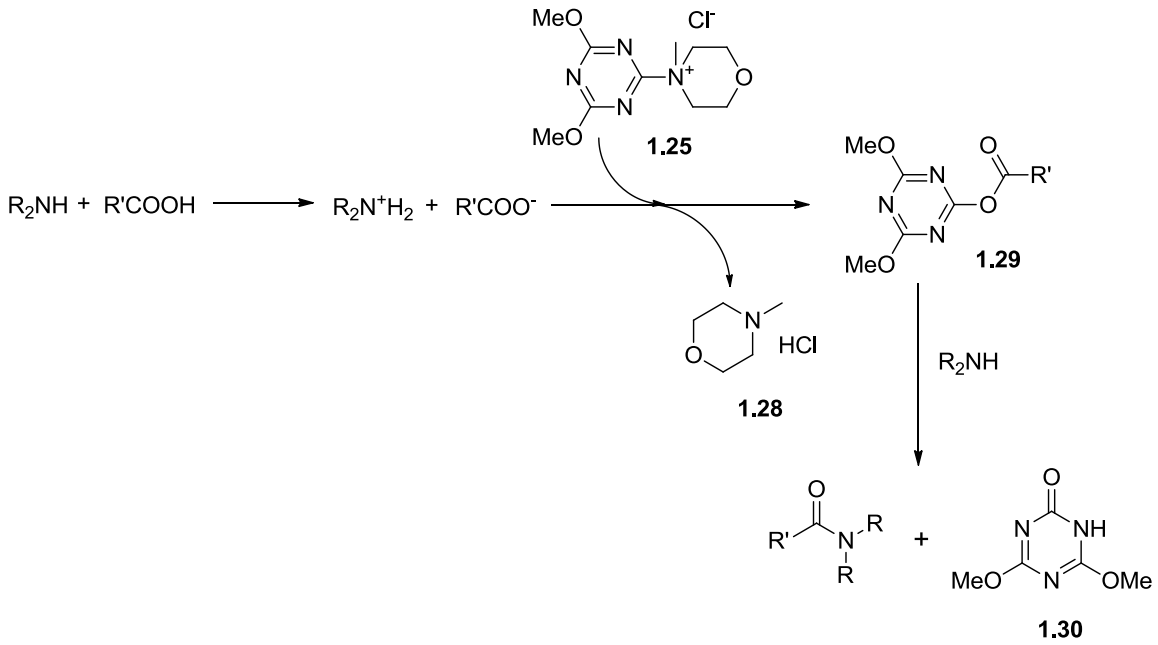
DMTMM 1.25 **DBTMM 1.26** **DBT-DABCO 1.27**

Figure 1.8. Triazine derivative based coupling reagents

These reagents allow for amide formation in aqueous media, with high yields and low epimerisation levels.[30] Structural variations on the original DMTMM compound, including a benzyloxy-, **1.26**,[31] and DABCO-, **1.27**,[32] derivative have been synthesised

and show slightly improved reactivity compared to the parent compound. These reagents also represent a move from a two-step procedure required with older triazine based reagents such as CDMT (where the initial activation of the acid must be confirmed before the amine is added to obtain good results) to a one step approach in which the acid can be activated in the presence of the amine substrate. In addition to this the reaction proceeds at room temperature under atmospheric pressure in hydrous solvents. However, stoichiometric by-products *N*-methylmorpholine HCl salt **1.28**, and (4,6-dimethoxy-1,3,5-triazin-2(1*H*)-one, **1.30**, are produced during the course of the reaction and must be removed *via* extraction to obtain pure amide product.[33]

The mechanism of carboxylic acid activation of these triazine derivatives is shown below in Scheme 1.10. Reaction of the carboxylate anion with DMTMM **1.25** conveniently liberates *N*-methylmorpholine **1.28**, which in turn regenerates the amine from the ammonium, allowing it to react with the 'active ester' complex **1.29**. This forms the amide and the second by-product, **1.30**.



Scheme 1.10. Amide formation using triazine derivative DMTMM 1.25

Despite the extensive work designing and synthesising ever more complex structural variations of known coupling reagents, they are still far from perfect. Unavoidable production of stoichiometric by-products, however easily they may be removed at the

end of the reaction, still adds extra purification steps to any procedure, in addition to making these reactions very atom-inefficient. While some perform better than others in certain areas (reduction of side products, low levels of epimerisation, speed, purity, cost), one coupling reagent which out performs all others in every respect remains elusive.[34]

1.2.3 Enzymatic Methods

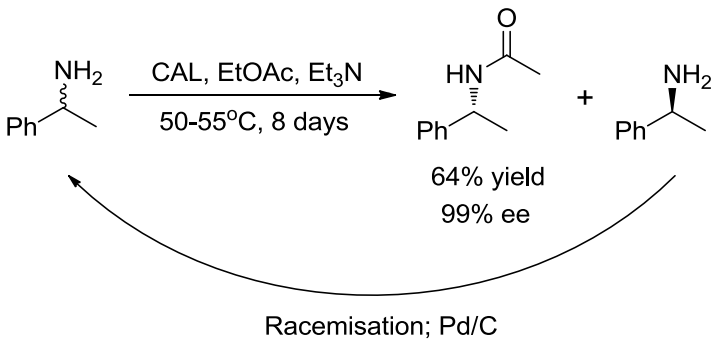
Nature needs to synthesise amide bonds constantly to sustain life as they are present in proteins such as enzymes, haemoglobin, collagen and antibodies. To address this need, there are countless enzymes devoted to making amide bonds, many of which have been exploited by chemists in the synthesis of drug molecules, bioactive peptides and natural products in the laboratory and in industry.[35] Due to their inherent lability (arising from the fact that they are designed to be biological catalysts, working under very specific conditions), enzyme catalysed reactions on an industrial scale need to be designed carefully and every variable, from pH to the presence of an organic solvent, must be investigated.

Protease enzymes are often used in this type of synthesis. Under normal aqueous conditions they catalyse the hydrolysis of peptide bonds, but the reverse reaction will proceed when the presence of water is restricted.[36] The position of the thermodynamic equilibrium between hydrolysis and synthesis can be shifted to complete synthesis in the presence of organic solvents.[37] The metalloprotease PST-01 was recently used by Ogino and co-workers in the peptide synthesis of an aspartame (artificial sweetener) precursor to couple *N*-carbobenzoxy-L-aspartic acid (Cbz-Asp) and L-phenylalanine methyl ester (Phe-OMe). After measuring the reaction rates under many sets of conditions, the best yield was found in 50% (v/v) DMSO at pH 8.0 and 37 ^{o}C.[38]

The formation of primary amides is readily facilitated by nitrile hydratase enzymes. Mukherjee *et al.* converted several β-hydroxynitriles into their corresponding amides in good yields using nitrilase ZmNIT2 (isolated from maize). This procedure was desirable for these substrates as chemical hydrolysis of β-hydroxynitriles usually requires

strongly acidic or basic conditions which can lead to side reactions like elimination of the –OH to yield unsaturated products.[39]

The potential for concurrent kinetic (or dynamic kinetic) resolution of racemic substrates has also been studied and represents an enantioselective route to amides, which would be especially useful in the pharmaceutical industry.[40] An example of this comes from Reetz *et al.* who achieved the enantioselective acylation of a racemic primary amine with CAL (*Candidia Antarctica* Lipase). They also found the lipase-catalysed acylation to be compatible with palladium-catalysed racemisation of the amine, thus an interesting dynamic kinetic resolution of phenethylamine was able to take place, resulting in a good yield of one enantiomer of the corresponding amide (Scheme 1.11).[41]



Scheme 1.11. CAL and palladium catalysed dynamic kinetic resolution of racemic phenethylamine

Despite these (and many other) successful applications, the use of enzymes in peptide synthesis is still limited. New technologies are being explored to overcome the difficulties which often discourage enzyme catalysis. Modification of the enzymes themselves could offer advantages such as increased activity in aqueous solutions,[42] or resistance to thermal deactivation.[43] Obvious advantages over the traditional coupling reagent-mediated synthesis of amide bonds include the relative ease of recycling enzymes (compared with recycling coupling reagents), elimination of racemisation due to their stereoselectivity and compatibility with unprotected amino acid residues. However, there is still much work to be done investigating optimal reaction conditions for each enzyme before they can come into general use for catalysing amide bond formation.

1.2.4 Non-Metal Catalysts

The use of boron reagents in the formation of amide bonds from carboxylic acids and amines has been explored since 1970,[44] however the first procedure that was catalytic in the boron reagent was reported by Yamamoto and co-workers[45] in 1991. At a catalyst loading of just 1 mol%, 3,4,5-trifluoroarylboronic acid **1.31** furnished a range of secondary and tertiary amides in excellent yields, including some intramolecular examples and one amino acid substrate (Figure 1.9). The reactions had to be run in the presence of molecular sieves at temperatures between 110 – 150 ^{o}C for an average of 18 hours to achieve such excellent yields.

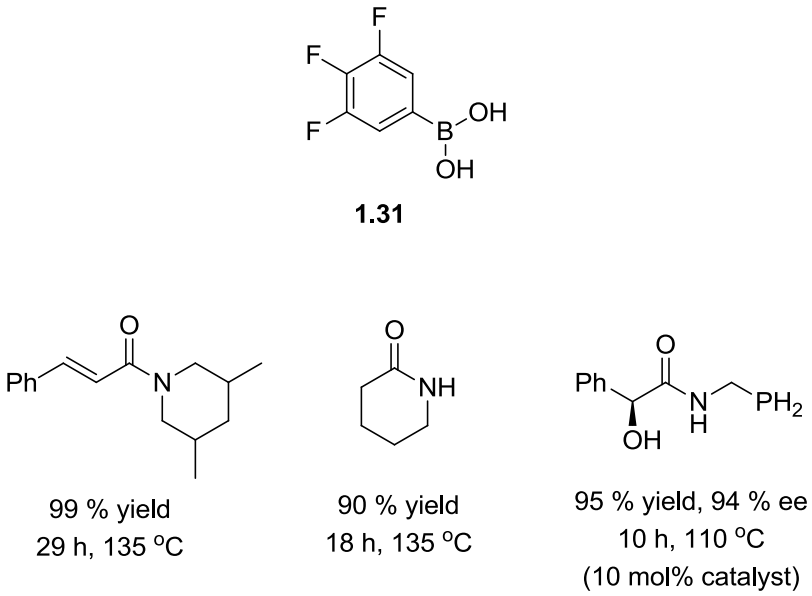
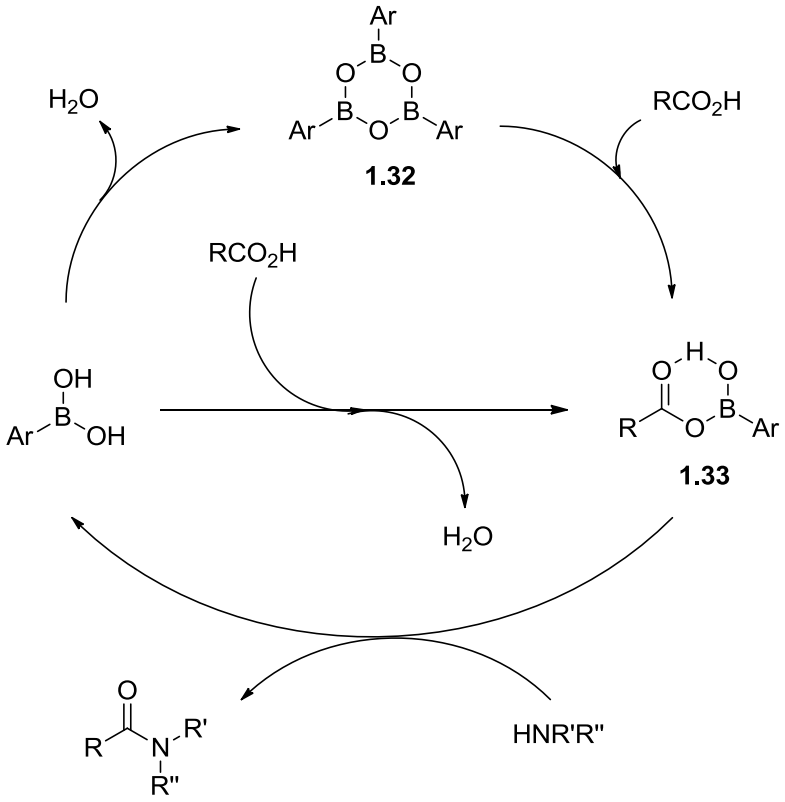


Figure 1.9. 3,4,5-Trifluoroarylboronic acid catalyst and selected examples

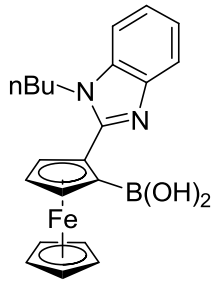
The mechanism proposed to explain the reactivity of boronic acids in this reaction is shown in Scheme 1.12. Arylboronic acids generally contain varying amounts of trimeric anhydrides **1.32**. Reaction of the arylboronic acid or the trimer with the carboxylic acid generates the (acyloxy)boronic acid **1.33**. Reaction of this species with the amine yields the product amides and regenerates the arylboronic acid catalyst. In all cases where arylboronic acids are employed as catalysts, removal of water is still essential to limit hydrolysis of the boronic acid.



Scheme 1.12. Mechanism of boronic acid catalysed amide bond formation

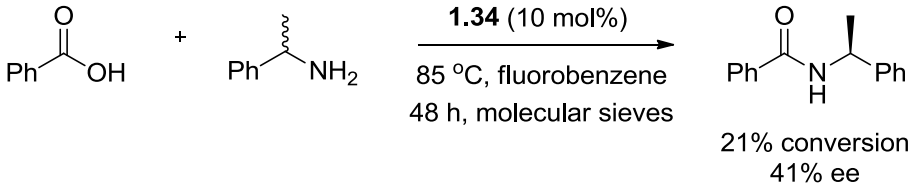
Some notable advances in arylboronic acid catalysed amide bond formation have been reported since,[46] although most modifications to the original boronic acid catalyst have not succeeded in significantly improving the reaction conditions required or expanding the substrate range.

In 2008, Whiting *et al.* reported their initial studies into a boronic acid catalyst for asymmetric amide synthesis between a racemic amine and an achiral carboxylic acid.[47] Boronic acid catalyst **1.34** was prepared from the ferrocene aldehyde in three steps in 60% yield and 99% ee (Figure 1.10). Evaluation of the catalyst with several acids and amines gave low to moderate yields of amide with moderate enantiomeric excesses. The best result in terms of enantioselectivity was obtained with benzoic acid and α-methylbenzylamine, where 41% ee was observed in the amide product (Scheme 1.13). These preliminary studies show potential for an asymmetric amide synthesis using a boronic acid catalyst.



1.34

Figure 1.10. Enantiomerically pure aminoboronic acid catalyst prepared by Whiting *et al.*



Scheme 1.13. Example of asymmetric amide bond formation

The first room temperature boronic acid catalysed activation of carboxylic acids was reported in 2008 by Hall *et al.*.[48] Utilising 10 mol% ortho-haloarylboronic acids **1.35** or **1.36** allowed a range of secondary and tertiary amides to be formed at room temperature in the presence of 4 Å molecular sieves in chloroform after 48 hours (Figure 1.11). Importantly, when enantiomerically pure amines or acids were employed in this reaction, less than 5% racemisation was observed in the amide products. The corresponding *o,o*-disubstituted haloarylboronic acids were found to be much less active as catalysts, displaying the need for an unsubstituted ortho position. X-ray crystallography of the *o*-iodoarylboronic acid showed unusual angular distortion of the B-C-C bonds, suggesting a structural feature may be responsible for the particularly active nature of this catalyst.

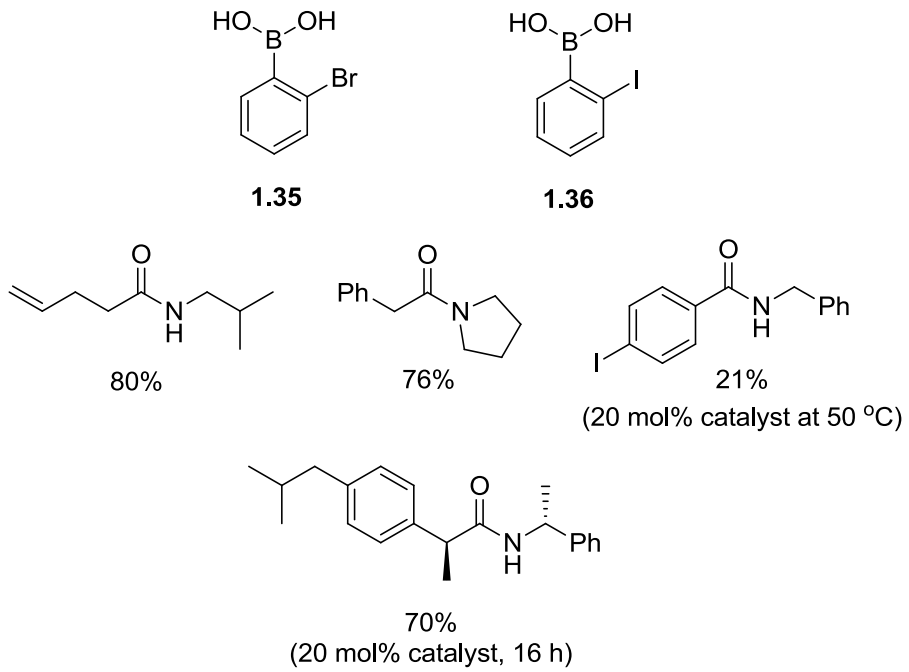
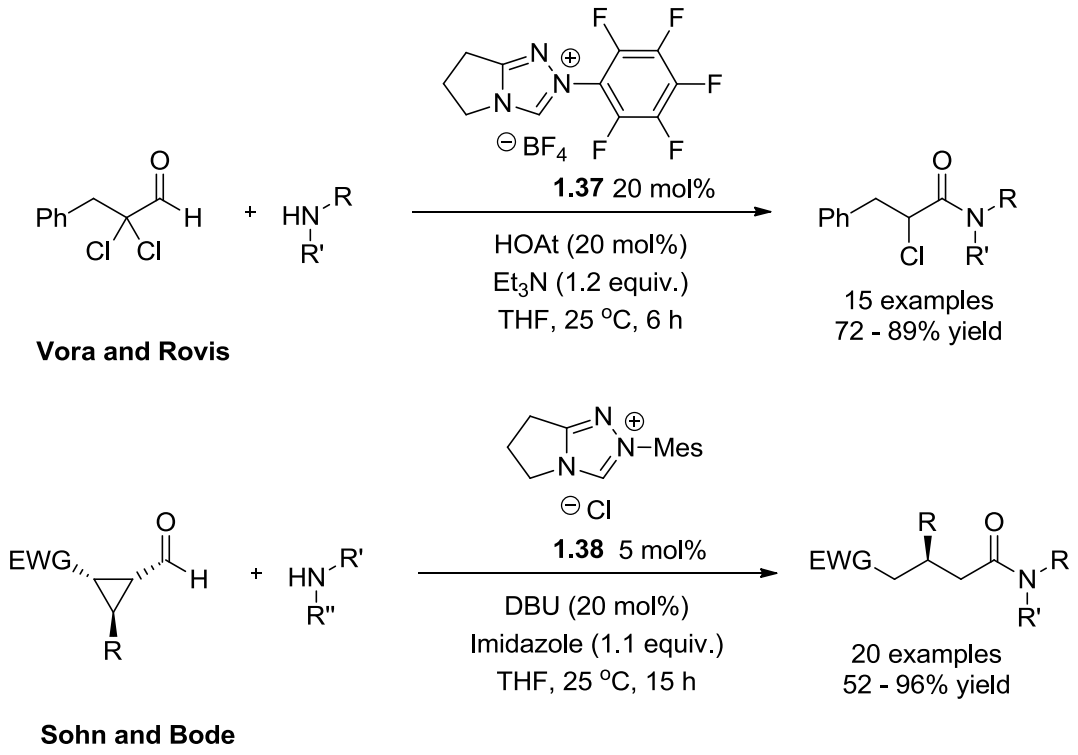
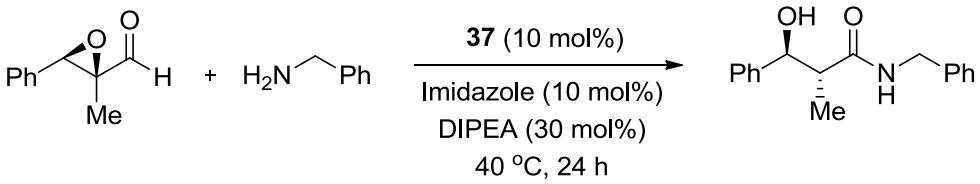


Figure 1.11. *O*-haloboronic acid catalysts prepared by Hall *et al.* and selected examples of amides formed

Nucleophilic carbenes have also been reported as catalysts in amidation reactions. In 2007, Rovis[49] and Bode[50] independently reported the amidation of aldehydes with an α-reducible centre using catalytic amounts of *N*-heterocyclic carbenes **1.37** and **1.38** respectively (Scheme 1.14). Both of these reactions have the advantage of proceeding at room temperature, however, they also both require stoichiometric amounts of an additive and the starting α-functionalised aldehydes are not readily available.[51] In both cases, if the α-reducible functionality is chiral, stereochemistry is preserved in the amide products (Schemes 1.14 and 1.15).



Scheme 1.14. *N*-Heterocyclic carbene catalysed amidation of α-reducible aldehydes



Scheme 1.15. Example bearing α-stereochemistry by Rovis

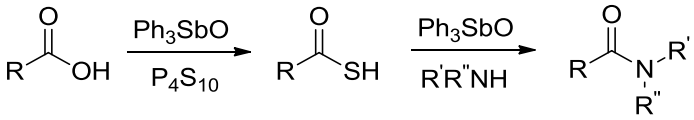
1.2.5 Metal Catalysts

Increasing attention is now being devoted to developing amide bond syntheses which employ metals as catalysts, making the reactions highly atom-economical and less expensive. Employing metal catalysis in amide bond syntheses also creates the possibility to start from substrates other than carboxylic acids, opening up previously unavailable synthetic routes to target molecules.[52]

Amides from carboxylic acids

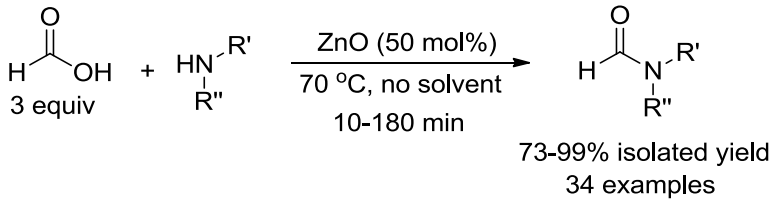
The natural equilibrium between a carboxylic acid and an amine lies heavily towards salt formation (except under specific conditions), making a catalytic coupling reaction between them challenging. This fact, together with the abundance of coupling reagents and non-metal catalysts already reported to facilitate the dehydration reaction, means there are very few reports of metal catalysed acid and amine couplings in the literature. In 1988, Nordahl and Carlson[53] reported a study on the effects of reaction conditions on the direct amide bond formation from carboxylic acids and amines. One part of their study involved addition of Lewis acid catalysts, namely $TiCl_4$, $AlCl_3$, ZnI_2 and $ZnCl_2$. Of these catalysts, they observed that $TiCl_4$ was the most effective, although it consistently failed to out-perform using BF_3 as a catalyst for the four amines they conducted the experiment with (benzoic acid was used as a standard coupling partner).

Another report, appearing in 1991,[54] used 5 mol% of the antimony reagent Ph_3SbO combined with up to 20 mol% of Lawesson's reagent P_4S_{10} to acylate amines using a thiocarboxylic acid intermediate generated *in situ* (Scheme 1.16).



Scheme 1.16. Acylation of amines *via* thiocarboxylic acids

N-Formylation of amines using formic acid as the formylating agent has been reported to proceed under catalytic conditions. Hosseini-Sarvari and Sharghi published the first example of this using ZnO as a catalyst under solvent-free conditions at 70 ^oC, achieving some excellent yields in short reaction times (Scheme 1.17).[55] They also demonstrated the reusability of the ZnO catalyst, incurring only a small decrease in yield of amide after the third use. A large range of amines was shown to react under their conditions, including anilines, highly hindered amines and ester-protected amino acids.



Scheme 1.17. *N*-Formylation of an amine with formic acid

Rao and co-workers later published their studies into a range of Lewis acid catalysts for the same reaction, reporting dichloride complexes of zinc, tin, lanthanum, iron, aluminium and nickel to give yields in the range of 80-100%.[56] They found the best results were obtained when using $ZnCl_2$ as a catalyst under the same solvent-free, 70 ^oC conditions that Hosseini-Sarvari and Sharghi had used. Although the catalyst loading could now be reduced from 50 mol% (ZnO) to just 10 mol% ($ZnCl_2$) and the reaction times were reduced to as short as 10 minutes, there was no report of possible recovery and reuse of Rao's catalyst.

Kim and Jang have reported the use of indium metal as a catalyst for the *N*-formylation of amines with formic acid, again under solvent-free conditions at 70 ^oC.[57] They found the reaction to be efficiently catalysed by 10 mol% of the indium metal, which they presume reacts with the formic acid to form $In(O_2CH)_3$ and acts as a Lewis acid in the reaction. Importantly, chemoselective *N*-formylation of an amine in the presence of a free hydroxyl group could be achieved with this catalyst, something that could not be achieved using a zinc catalyst.

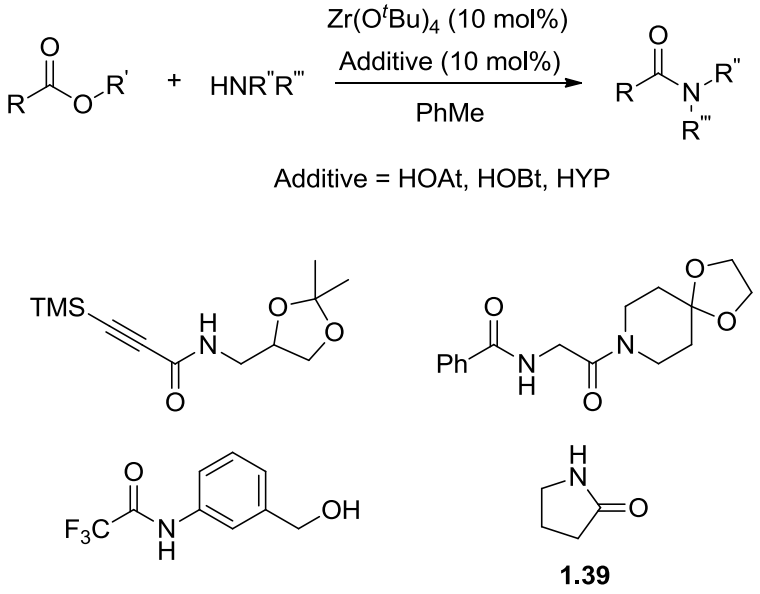
Amides from esters

As the preparation of amides from carboxylic acids is somewhat difficult to achieve in a catalytic manner, their derivatives, particularly esters, have been explored as an alternative in catalytic amide bond forming reactions. A simple procedure was published by Ranu and Dutta in 2003 using a catalytic amount of indium triiodide and an excess of the amine reagent.[58] The operational simplicity made this reaction a good alternative to other methods known at that time. Several excellent yields were reported for a range of amides containing diverse functional groups using their conditions, but

the reaction was not successful with secondary amines, thus making it unsuitable for the synthesis of tertiary amides.

In 2005, the same transformation was reported by Gupta *et al.* using zinc dust as a reusable catalyst under either microwave or conventional heating.[59] A modest range of amides was synthesised, using only aromatic esters and amines and again no demonstration of tertiary amide synthesis. Despite the reported substrate range being limited, their procedure had the advantages of the zinc dust being reusable up to six times (after washing with dilute HCl) with only slight decreases in yield and a very short reaction time (2-8 minutes) if microwave heating was used.

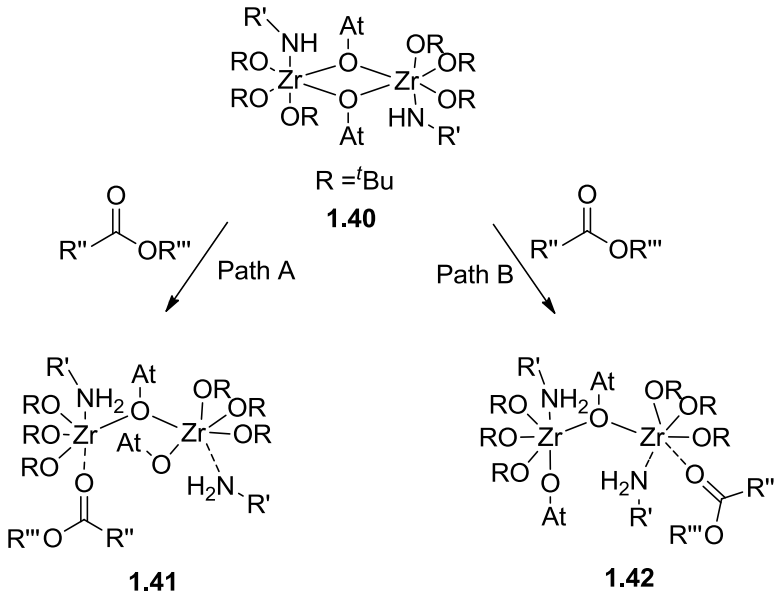
Also in 2005, Porco and co-workers reported their findings of group (IV) metal alkoxide complexes which, in conjunction with an activator, could be used for the formation of amides from esters and amines (Scheme 1.18).[60] They demonstrated a varied substrate range, including intramolecular example **1.39**.



Scheme 1.18. Zirconium catalysed coupling of esters and amines with selected examples

A detailed mechanistic study was also carried out by the group using X-ray crystallography and NMR studies. They were able to determine the structures of key intermediates along the reaction pathway and deduce the active catalyst to be a dimeric

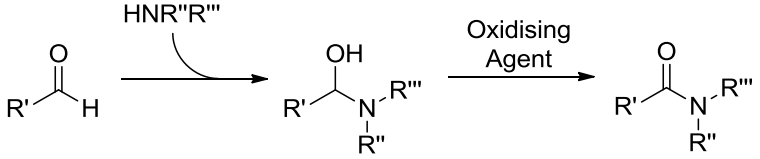
zirconium complex (Scheme 1.19). Dimeric species **1.40** in which both zirconium centres are hexacoordinate, is formed in the presence of amines. Coordination of an ester to one of the zirconium centres results in formation of either **1.41** or **1.42** by breaking of one bridging Zr-O bonds. Nucleophilic attack of the amine onto the ester then proceeds *via* a six-membered (path A) or four-membered (path B) transition state.



Scheme 1.19. Formation of key intermediate dimeric zirconium complexes

Amides from aldehydes

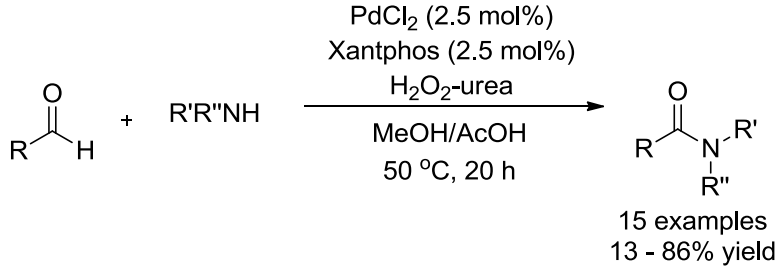
Oxidative amidation of aldehydes into amides has been known since the early 1980s. The general mechanism of this process is based on the reaction of an aldehyde with an amine to form a hemiaminal intermediate and subsequent oxidation of this intermediate to the amide product (Scheme 1.20). Loss of water from the hemiaminal to form the imine, then hydrogenation of the imine to form an amine is a potential side reaction in this process.



Scheme 1.20. General mechanism of amide formation from aldehydes and amines

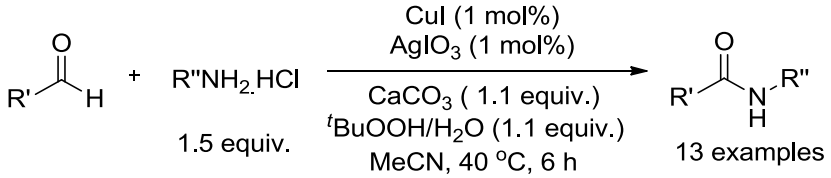
The first catalyst system to be used for this transformation was reported in 1983 by Yoshida, using $Pd(OAc)_2$ (5 mol%), triphenylphosphine (15 mol%), potassium carbonate and an aryl bromide as the oxidant.[61] Several aldehydes were successfully coupled with morpholine to form the corresponding amides under these conditions.

Improved reaction conditions using another palladium catalyst were reported by Torisawa and co-workers in 2008.[62] Their use of H_2O_2 in urea as the oxidant combined with $PdCl_2$ (2.5 mol%) and xantphos (2.5 mol%) allowed the reaction temperature and required time to be reduced, as well as greatly expanding the range of amides that could be synthesised in this reaction (Scheme 1.21).



Scheme 1.21. Palladium catalysed oxidative amidation

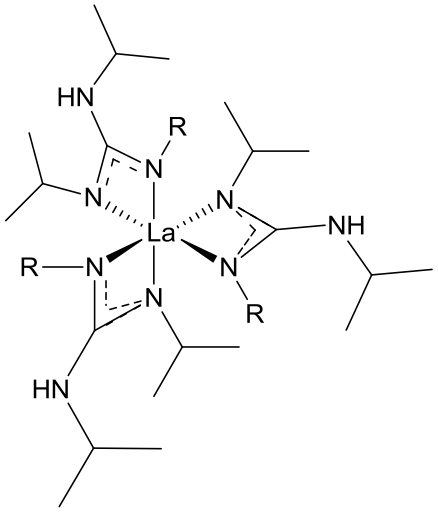
A copper catalysed oxidative amidation has been reported by Yoo and Li (Scheme 1.22).[63] ^{t}Butyl hydroperoxide solution in water serves as the oxidising agent and the use of amine hydrochloride salts minimises the competing reaction, oxidation of the amine. Their yields decreased when an aliphatic or electron-poor arylaldehyde was used, but when the reaction was applied to an enantiomerically pure amine, no racemisation occurred.



Scheme 1.22. Copper catalysed oxidative amidation

Recently, several lanthanide catalysts have been reported to catalyse the oxidative coupling of aldehydes and amines. These catalysts are generally capable of facilitating

the reaction at room temperature, which is a useful advantage. Additionally, no external oxidant is required, as the aldehyde is presumed to act as a hydrogen acceptor in the proposed catalytic cycle. Lanthanide-amido complex $La[N(TMS)_2]_3$, developed by Marks and Seos, achieved varied yields of amides at room temperature in deuterated benzene.[64] Due to the aldehyde substrate also acting as a hydrogen acceptor, a threefold excess was required. Shen *et al.* have reported several bimetallic lanthanide complexes used to catalyse this reaction. Their 2009 paper[65] details the first fully characterised complex of lanthanide and lithium metals with dianionic guanidinate ligands, with the lanthanum complex **1.43** demonstrating its effectivness for amidation of aldehydes with amines at 5 mol% catalyst loading at room temperature (Figure 1.12).

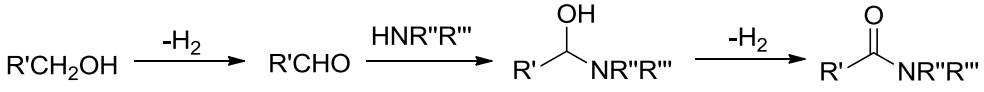


1.43

Figure 1.12. Lanthanum catalyst for the amidation of aldehydes with amines

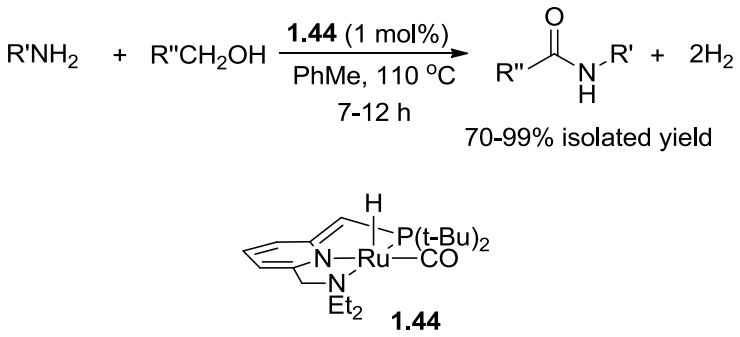
Amides from alcohols

The direct catalytic conversion of alcohols and amines into amides and dihydrogen is a particularly desirable reaction due to its high atom efficiency and widely available starting materials. The general mechanism of this reaction is the same as that of oxidative amidation involving aldehydes and amine, but with an additional oxidation step at the start to convert the alcohol into the aldehyde (Scheme 1.23).



Scheme 1.23. General mechanism of amide formation from alcohols and amines

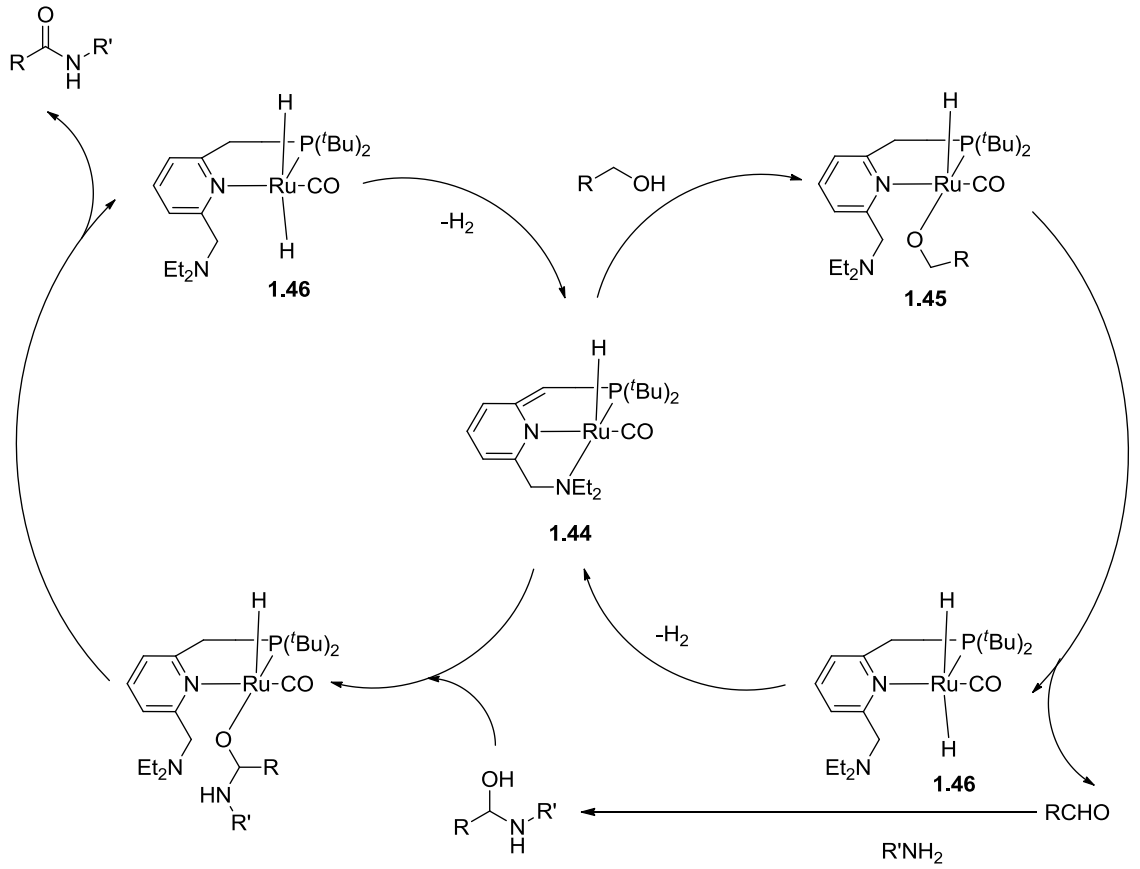
This reaction was first realised by Milstein and co-workers in their breakthrough report from 2007.[66] Catalysed by a ruthenium pincer complex with molecular hydrogen being the only by-product, this exceptionally clean and simple reaction has been emulated by several other groups since Milstein's original publication (Scheme 1.24).



Scheme 1.24. Milstein's catalyst for conversion of alcohols into amides

Milstein's PNN pincer complex **1.44** undergoes an aromatisation/dearomatisation catalytic cycle, where initial addition of the alcohol to complex **1.44** makes the pyridine group in complex **1.45** aromatic. Subsequent loss of an aldehyde generates the known *trans* ruthenium dihydride complex **1.46**. Elimination of dihydrogen regenerates the catalyst **1.44** and enables the catalytic cycle to continue (Scheme 1.25). The aldehyde forms an aminol by reaction with the amine and a similar cycle oxidises this to the amide product.

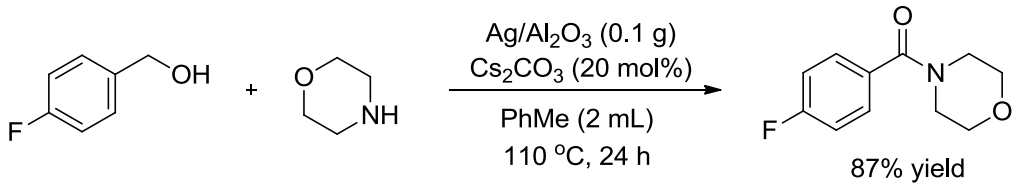
Alternative ruthenium catalyst systems using ruthenium precursors in combination with *N*-heterocyclic carbenes have been reported by the groups of Madsen[67] and Hong.[68] Although this was the first step towards the use of a simple, commercially available catalyst in this reaction, there was no real improvement in terms of yields or scope of reagents on those reported by Milstein. The first commercially available catalyst system for formation of amides from alcohols and amines was reported by the Williams group[69] (although Milstein's catalyst is now commercially available). The use of [Ru(*p*-cymene)Cl_2]$_2$ in combination with dppb, a base and a hydrogen acceptor produced the amide products in reasonable to good yields, however increased reaction times were required.



Scheme 1.25. Catalytic cycle for Milstein's catalyst

An example of primary amide formation in this reaction has been demonstrated by Grützmacher[70] using a rhodium catalyst and ammonia as the nitrogen source. Primary amides were obtained in excellent yields in just four hours at temperatures between -30 ^{o}C and 25 ^{o}C.

These catalysts, though efficient and highly chemoselective in favour of amide formation, can be expensive, difficult to handle and do not tolerate secondary amines well. Some of these issues were addressed by Satsuma and co-workers in their reported γ-alumina supported silver cluster (Scheme 1.26).[71] This re-usable, heterogeneous, easily prepared catalyst is clearly a more economic alternative to the homogeneous ruthenium and rhodium catalysts reported. In addition to this, secondary amines could be used in the reaction, giving tertiary amides in very good yields.

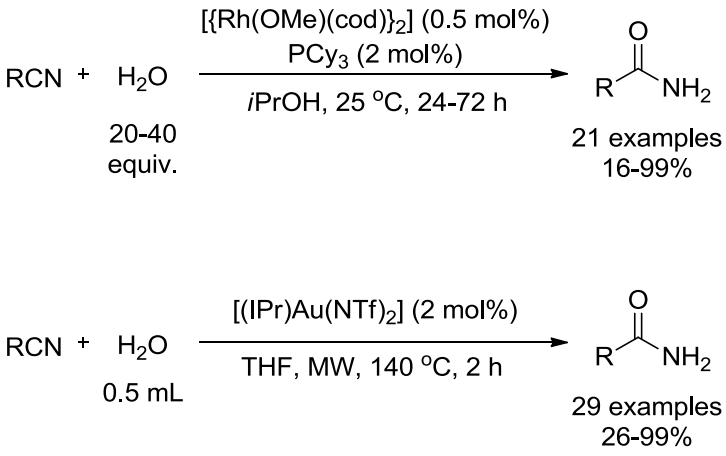


Scheme 1.26. Heterogenous catalysis by Satsuma *et al.*

Amides from nitriles

Despite their importance as substrates in organic chemistry due to their chemical versatility, the use of nitriles in the synthesis of amides has been somewhat limited to the three reactions discussed below.

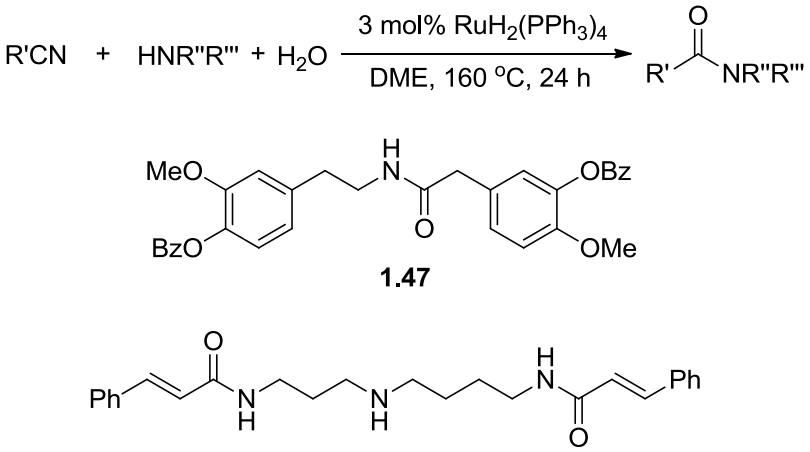
A simple and efficient method of synthesising primary amides is the hydration of nitriles. Many metal catalysts have been reported to efficiently facilitate this transformation.[72] Recently, catalysts which allow the hydration of organonitriles under ambient conditions[73] or in reaction times as short as 2 hours using microwave radiation[74] have been published (Scheme 1.27).



Scheme 1.27. Rhodium and gold catalysed nitrile hydration

A little known reaction to yield amides is the hydrolytic amidation of nitriles with amines. This was first published in 1986 by Murahashi and co-workers using the ruthenium catalyst $RuH_2(PPh_3)_4$ (Scheme 1.28).[75] They demonstrated the wide scope of this reaction with the efficient synthesis of several drug precursors (including **1.47**) as

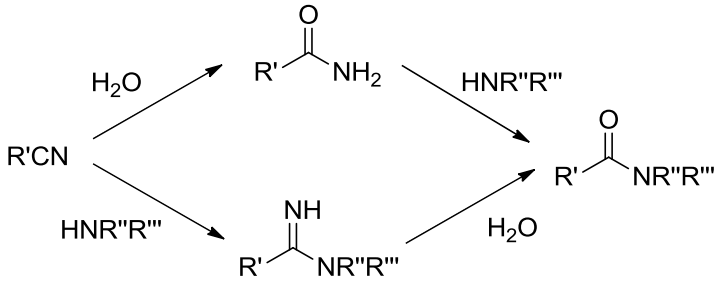
well as lactams from the intramolecular reaction and polyamides from dinitriles and diamines.



Scheme 1.28. Murahashi's ruthenium catalysed hydrolytic coupling of nitriles with amines

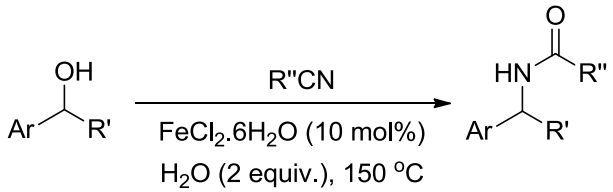
Development of this reaction has been limited to a report in 2000 using a platinum catalyst by de Vries and co-workers.[76] Using their platinum complex they were able to decrease the catalyst loading from 3 mol% (with the ruthenium catalyst) to levels as low as 0.1 mol% with the platinum (II) complex, however the reaction temperature remained at 160 ^{o}C and the yields were moderate.

Mechanistic investigations point to the involvement of an amidine intermediate formed from nucleophilic attack of the amine on the nitrile, as opposed to initial hydration of the nitrile into the primary amide and subsequent *N*-alkylation (Scheme 1.29). De Vries and co-workers found that when the reaction is run in the absence of water, the major product isolated is the amidine.



Scheme 1.29. Proposed mechanism pathways for the addition of amines to nitriles

Nitriles can also be coupled with alcohols to form amides in the Ritter reaction. As an alternative to sulfuric acid, the Ritter reaction can be catalysed by metal complexes. One of the first examples of this was the use of bismuth triflate by Barrett and co-workers who published a wide range of amides synthesised from coupling various nitriles and tertiary alcohols.[77] A later example by Cosey's group described an iron-catalysed Ritter reaction with a wider substrate range than those previously reported, but the reaction conditions are less desirable (Scheme 1.30).[78]



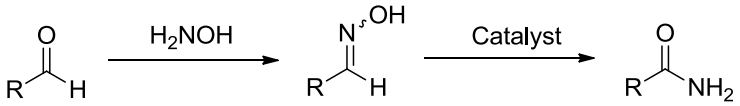
Scheme 1.30. Iron-catalysed Ritter reaction

Amides from oximes

Oximes have been used in organic synthesis since the 19th century in a diverse range of reactions. Their applications in metal catalysed amide bond synthesis have been well documented in the areas of aldoxime rearrangement into primary amides and the Beckmann rearrangement of ketoximes.

Rearrangement of aldoximes into primary amides

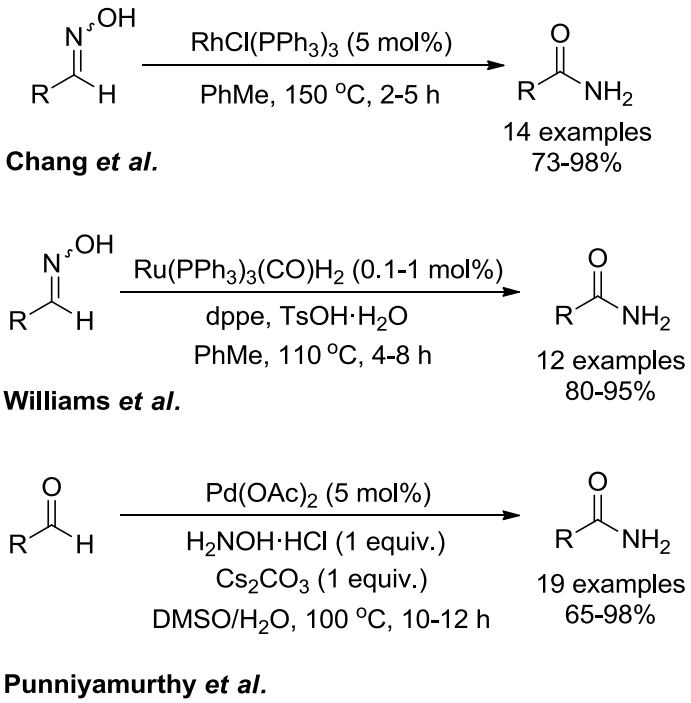
The rearrangement of aldoximes into primary amides has been shown to be catalysed by several metal complexes.[79] This highly atom-efficient reaction can also start from an aldehyde and hydroxylamine (which react to form the aldoxime *in situ*) (Scheme 1.31).



Scheme 1.31. Rearrangement of aldoximes into primary amides starting from an aldehyde

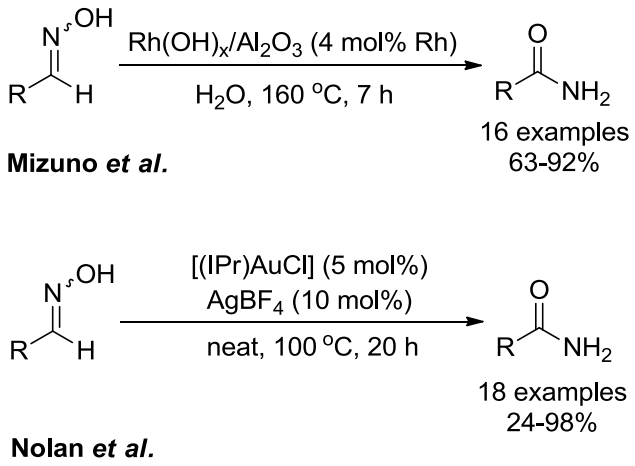
The first catalytic conditions for this rearrangement were reported by Chang and co-workers in 2003[80] using Wilkinson's complex (at a catalyst loading of 5 mol%). They found this catalyst efficiently facilitated the conversion of a range of aldoximes into

their corresponding primary amides at a temperature of 150 °C. Following this initial publication, reports of iridium[81] ruthenium[82] and palladium[83] catalysts performing the rearrangement have appeared in the literature, all describing procedures using lower temperatures (Scheme 1.32).



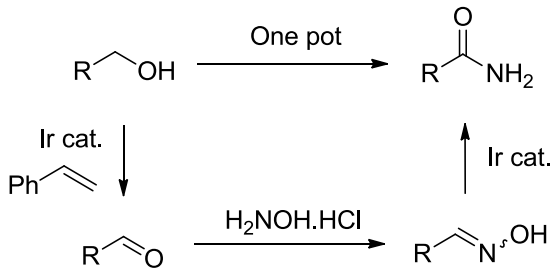
Scheme 1.32. Conditions for aldoxime rearrangement reported by Chang, Williams and Punniyamurthy

Research into this rearrangement has more recently been focussed towards finding lower cost metal catalysts and more desirable reaction conditions such as procedures that can be run in the absence of organic solvents. Mizuno and co-workers have reported a reusable, supported rhodium hydroxide catalyst to be effective in this reaction in aqueous conditions,[84] followed later by Nolan *et al.* reporting a gold/silver co-catalysed reaction proceeding under solvent free conditions (Scheme 1.33).[85]



Scheme 1.33. Milder conditions for aldoxime rearrangement reported by Mizuno and Nolan

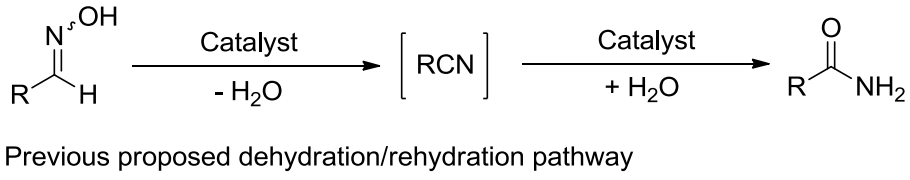
A report by Williams *et al.* demonstrates the potential to start from the alcohol with the first step of the mechanism then being oxidation of the alcohol to the aldehyde, then condensation with hydroxylamine and subsequent rearrangement to the primary amide (Scheme 1.34).[81] The oxidation step was conveniently catalysed by the same iridium catalyst used for the rearrangement and use of styrene as a sacrificial hydrogen acceptor. These current conditions are not desirable, but the novel concept of transformation of an alcohol into a primary amide *via* an oxime is clearly demonstrated.



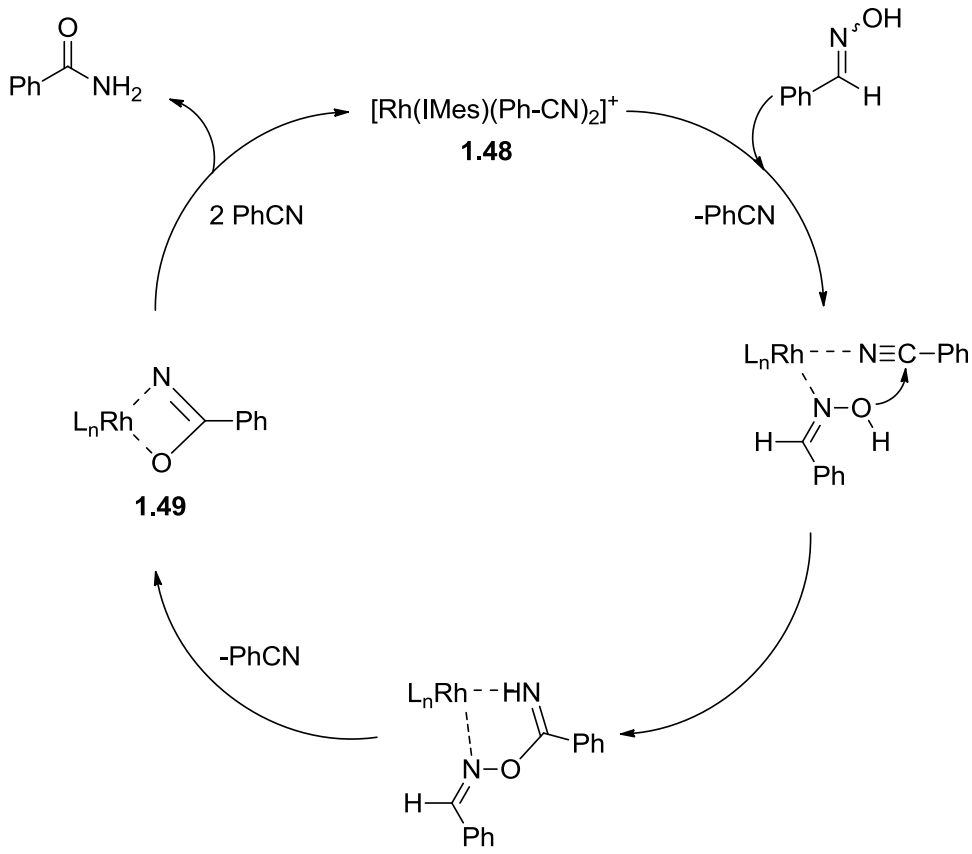
Scheme 1.34. Formation of primary amides from alcohols *via* aldoximes

Chang *et al*. have observed a rate acceleration of the rearrangement reaction when a nitrile additive is present. In their 2009 paper,[86] they describe the reactivity of the rhodium complex Rh(cod)(IMes)Cl together with *p*-toluenesulfonic acid towards a range of aldoximes, with the yields after 6 hours at 80 °C being reported with and without the corresponding nitrile additive. A clear rate enhancement is seen in the

presence of the nitrile, leading them to propose a different mechanism to the generally accepted dehydration/rehydration pathway (Scheme 1.35). This new bimolecular mechanism is further supported by the fact that nitriles were inert towards hydration with some of the metal catalysts reported to facilitate the rearrangement.



Previous proposed dehydration/rehydration pathway



New pathway (using Rh/NHC catalyst and nitrile additive) proposed by Chang *et al.*

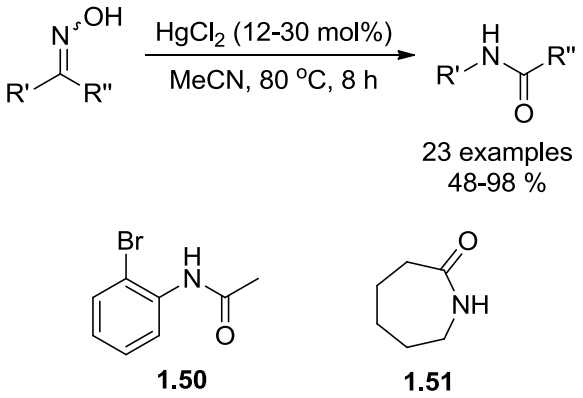
Scheme 1.35. Proposed aldoxime rearrangement mechanisms

Generation of active catalyst **1.48** is facilitated by initial removal of a coordinated chlorine by *p*-toluenesulfonic acid, with subsequent release of the cyclooctadiene ligand and addition of two molecules of nitrile give the cationic rhodium complex. Intramolecular attack on to the coordinated nitrile by a molecule of aldoxime (as

opposed to a molecule of water) leads to cyclic intermediate **1.49,** which delivers the primary amide product and regenerates the catalyst.

Beckmann rearrangement of ketoximes into secondary amides

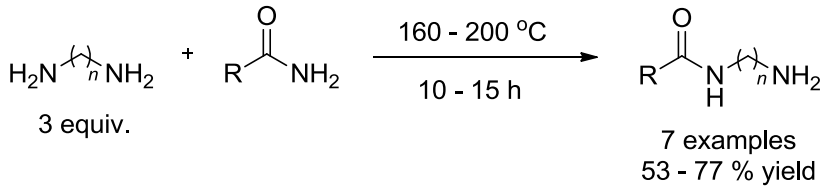
The Beckmann rearrangement of ketoximes into amides is a very well known piece of methodology in organic synthesis. Traditionally this reaction requires harsh conditions such as high temperatures and strong acids,[87] although recently, metal catalysed Beckmann rearrangements have been published, including conditions such as using an ionic liquid medium,[88] and reactions conducted in the vapour phase.[89] A notable metal catalysed variant has been reported by Ramalingan and Park and details a mercury(II) chloride catalysed reaction, run in acetonitrile at 80 ^{o}C (Scheme 1.36).[90] A wide range of ketoximes was transformed into the corresponding secondary amides under their conditions, including halogen substituted amide **1.50** and a cyclic ketoxime yielding caprolactam **1.51** as the product.



Scheme 1.36. Mercury catalysed Beckmann rearrangement of ketoximes

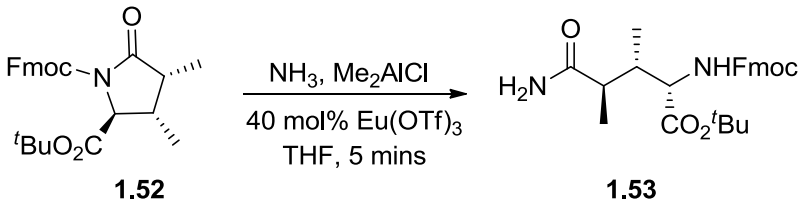
Transamidation

Primary carboxamide groups are exceptionally stable chemical moieties and due to this stability they are rarely used as acylating agents. However, there are several reports of thermal transamidation reactions,[91] requiring very high temperatures and thus having a very limited substrate range. A report of a thermal transamidation procedure from 1988 by von Kierdrowski *et al.* described the mono-acylation of diamines.[92] The reactions took between 10 and 15 hours and required temperatures of between 160 and 200 ^{o}C (Scheme 1.37).



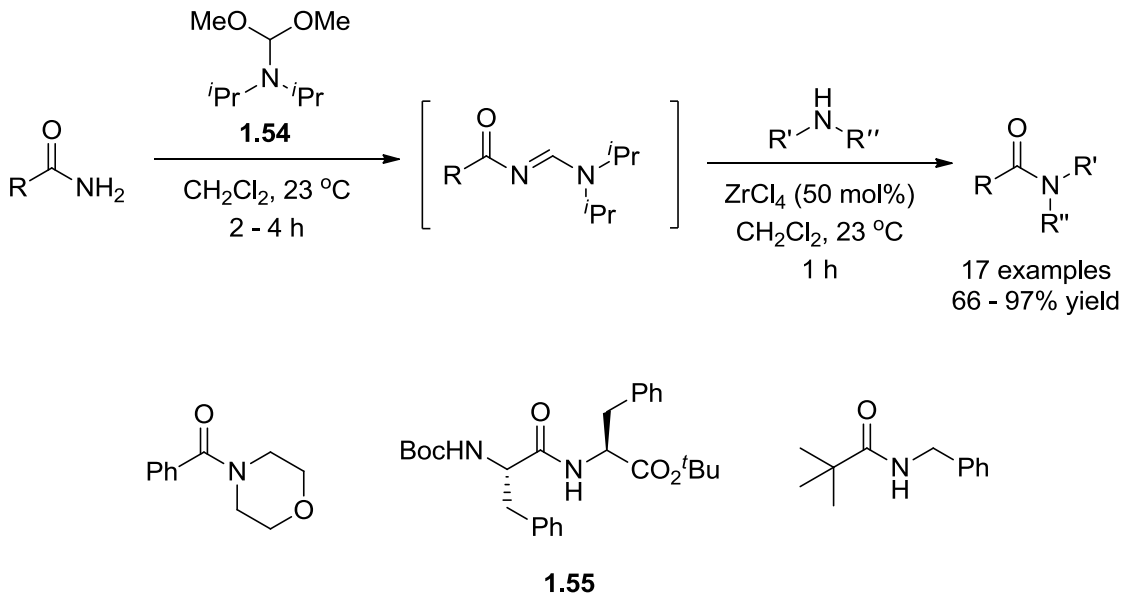
Scheme 1.37. Thermal transamidation between diamines and primary amides

In the last two decades, several metal complexes have been reported to promote transamidation reactions. One of the earliest reports of this nature was by Bertrand *et al.*, using aluminium chloride to catalyse amide exchange between several amines and unactivated amides.[93] In contrast with the known methods at that time, better results were obtained with secondary amides compared with primary amides. $Sc(OTf)_3$,[94] $Ti(NMe_2)_4$[95] and polymer-bound $HfCl_4$[96] have since also been shown to catalyse tranamidation reactions. Lanthanide catalysts (in conjunction with an amine-aluminium complex) have been reported to promote transamidation between Fmoc protected lactams and various amines. One particular reaction was used by Lipton and co-workers in the course of a total synthesis to ring open Fmoc protected lactam **1.52** giving the primary amide **1.53** (Scheme 1.38).[97]



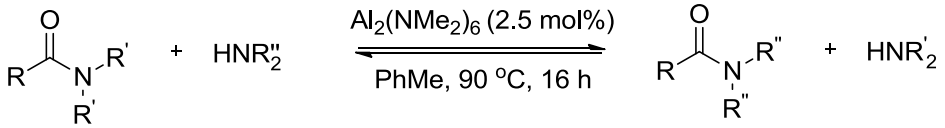
Scheme 1.38. Thermal transamidation between diamines and primary amides

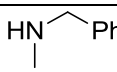
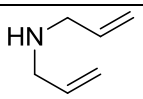
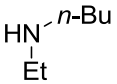
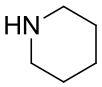
In 2006, Myers *et al*. described the *in situ* activation of primary amides using *N*,*N*,-dialkylformamide dimethyl acetal **1.54**. 1.3 equivalents of the activating reagent were required, along with a metal catalyst to effect the full transformation (Scheme 1.39).[98] This mild procedure progressed at room temperature and the short reaction times made it an attractive reaction despite the super-stoichiometric amounts required of some reagents. In addition to this, any stereochemistry in the α-position was completely preserved during the reaction, such as in amide **1.55**.



Scheme 1.39. Transamidation of primary amides by *in situ* activation and selected examples

Stahl *et al*. have found some metal complexes will facilitate the equilibration between a secondary or tertiary amide and an amine when the reaction is thermoneutral.[99] Their 'dynamic covalent chemistry' approach to amide exchange reactions led to the development of the first catalytic equilibration of tertiary amide – secondary amine mixtures (Scheme 1.40).

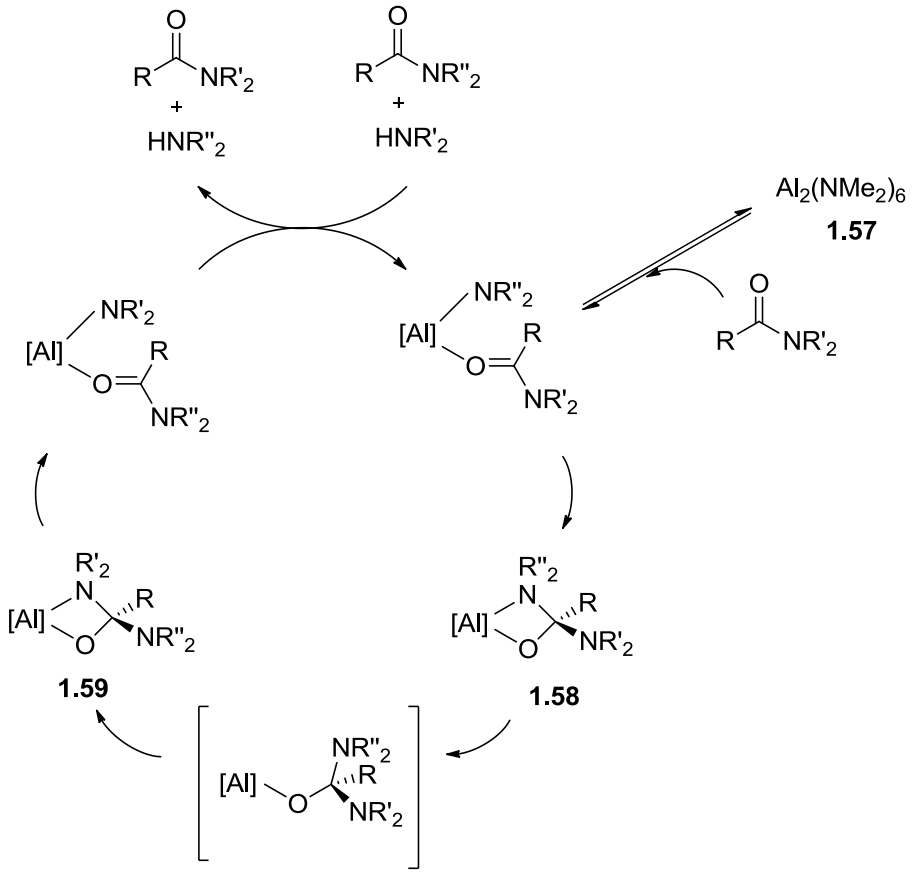


R	NR_2'	NR_2''	% **1.56**
n-C_6H_{13}			58
p-Tol			56

Scheme 1.40. Catalytic equilibration between tertiary amides and secondary amines

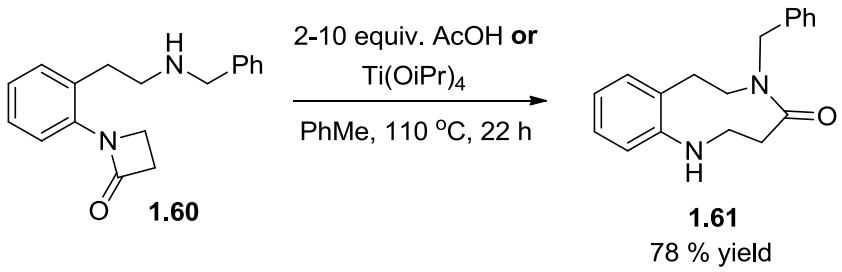
Mechanistic studies into this equilibration reaction revealed the dimeric aluminium complex **1.57** to be the pre-catalyst, which reacts with the tertiary amide to form

tetrahedral intermediate **1.58** (Scheme 1.41). This complex undergoes interchange of the dialkylamino fragments to form complex **1.59** (this is the rate determining step). Each step in the cycle is under thermodynamic control, leading to the observed equilibration between the tertiary amide and the amine.



Scheme 1.41. Proposed catalytic cycle for the equilibration between tertiary amides and secondary amines

Buchwald *et al.* have reported a ring expansion *via* intramolecular transamidation between a lactam and an alkylamine (Scheme 1.42).[100] This elegant methodology allows for the construction of 7-, 8-, 9- and 10-membered nitrogen heterocycles such as **1.61 (**from starting materials such as lactam **1.60**) in good yield.



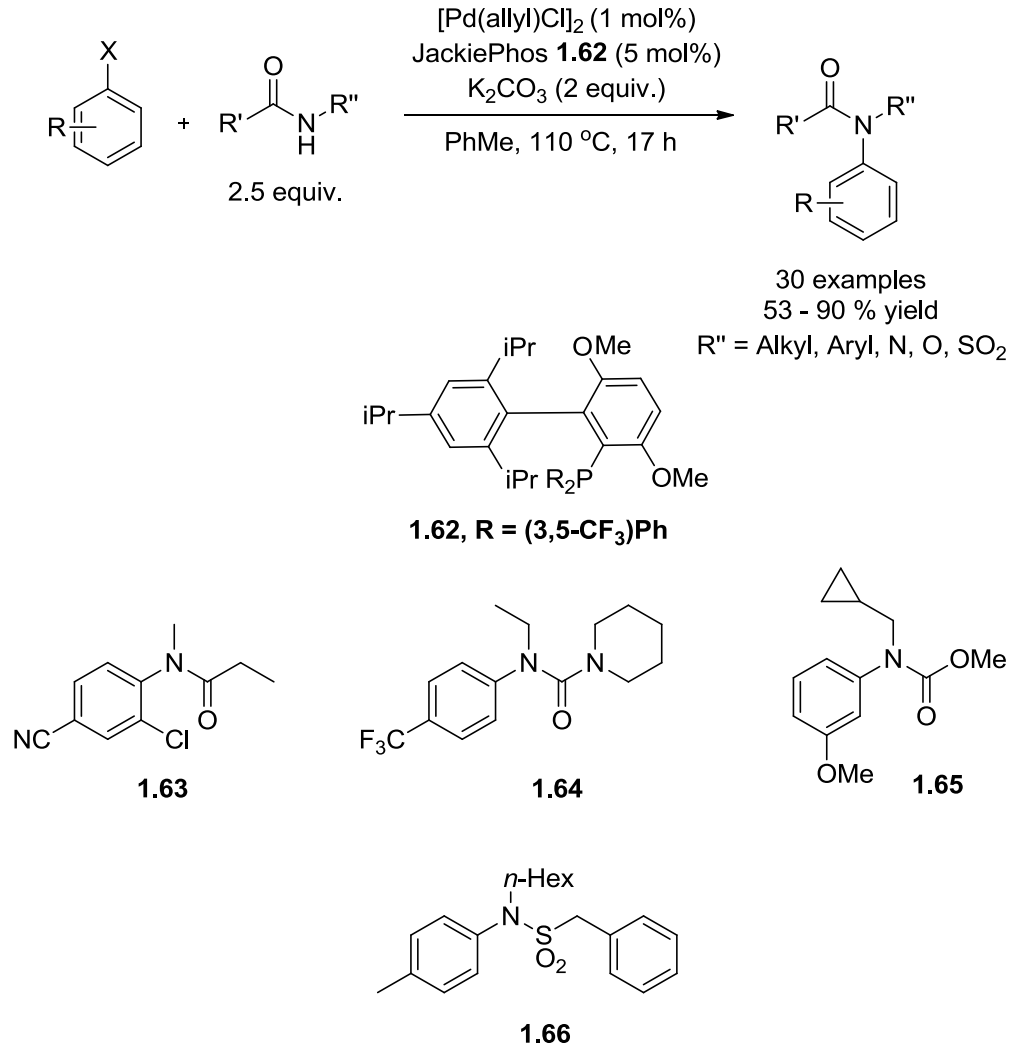
Scheme 1.42. Ring expansion *via* intramolecular transamidation by Buchwald *et al.*

***N*-Arylation and *N*-alkenylation of amides**

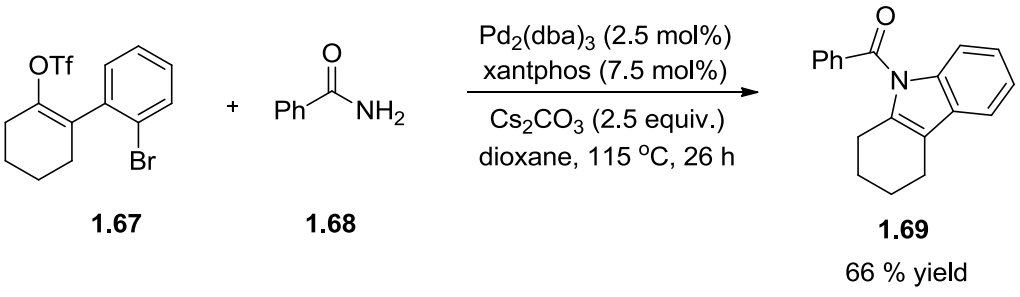
Amides can be used as cross coupling partners with aryl and alkenyl halides to give *N*-aryl or *N*-alkenyl amides. These reactions have predominantly used palladium[101] or copper catalysts,[102] although other metals have been shown to be effective, including simple iron catalysts.[103]

In 2009, Buchwald and co-workers published results using a palladium catalyst and electron deficient ligand JackiePhos **1.62** in the cross coupling of a very broad range of amides (or amide equivalents) with aryl chlorides, triflates or nonaflates (Scheme 1.43).[104] The catalyst and reaction conditions showed excellent tolerance of functionality in both coupling partners, including nitrile groups (**1.63**), trifluoromethyl groups (**1.64**), cyclopropyl and carbamates (**1.65**) and sulfonamide groups (**1.66**).

Application of this type of cross coupling has even extended to substrates such as *N*-acylated indoles. In a double cross coupling reaction developed by Willis *et al.*, aryl bromide **1.67** is reacted with benzamide **1.68** to yield indole product **1.69** (Scheme 1.44).[105]

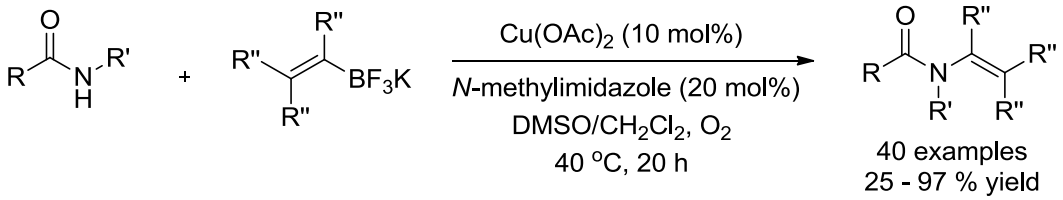


Scheme 1.43. Palladium catalysed *N*-arylation of amides by Buchwald *et al.* with selected examples



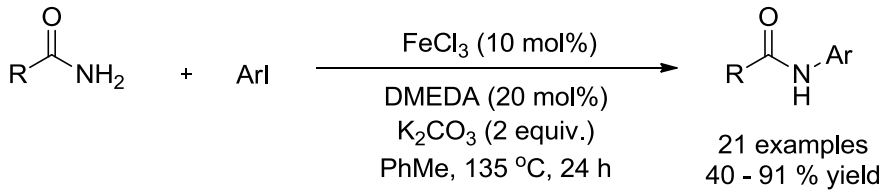
Scheme 1.44. *N*-Acylated indole formation *via* double cross coupling

Copper complexes have also been shown to be a highly effective catalyst in *N*-arylation and *N*-alkylations of amides. Buchwald *et al.* have reported several copper(I)/diamine catalysts which are effective in the coupling of aryl halides and simple primary amides or lactams. [106] Batey and co-workers have used potassium alkenyltrifluoroborate salts of alkenes as coupling partners to give a range of enamides (Scheme 1.45).[107]



Scheme 1.45. Copper catalysed cross coupling of amides with alkenyltrifluoroborate salts by Batey *et al.*

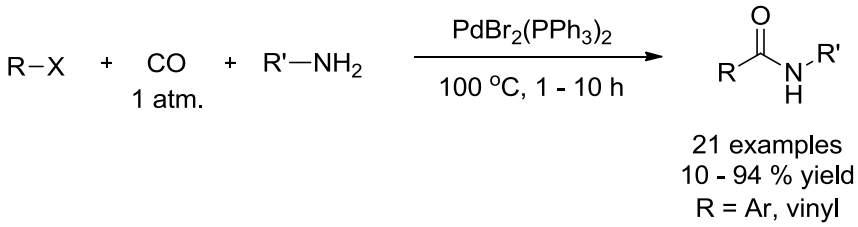
Bolm *et al.* have published a convenient and experimentally simple $FeCl_3$/DMEDA catalysed *N*-arylation of primary amides using aryl iodides (Scheme 1.46).[103] This procedure is particularly attractive due to its low cost, especially when compared with the equivalent palladium-catalysed reaction.



Scheme 1.46. Iron catalysed cross coupling of amides with aryl iodides by Bolm *et al.*

Aminocarbonylation

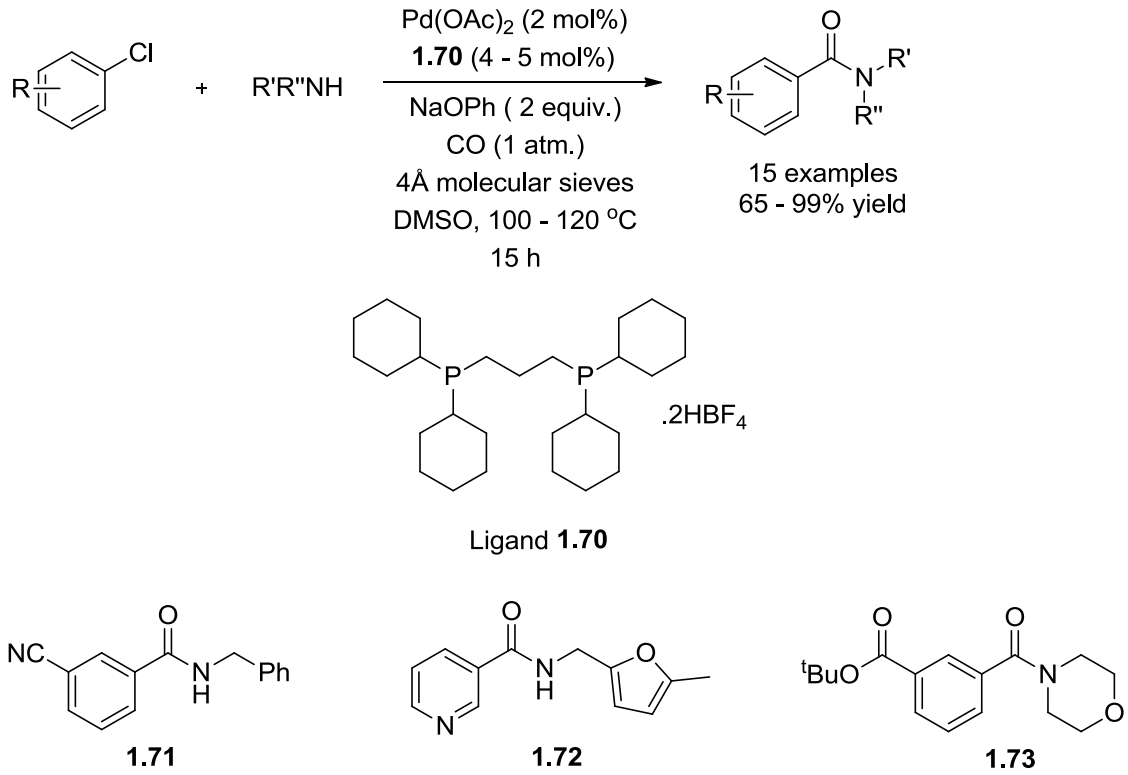
The reaction of various substrates with an amine and carbon monoxide has been used to form amide bonds for almost 40 years.[108] The first example of this reaction was published by Schoenberg and Heck, utilising a palladium catalyst for the aminocarbonylation of aryl and vinyl halides (Scheme 1.47).[109]



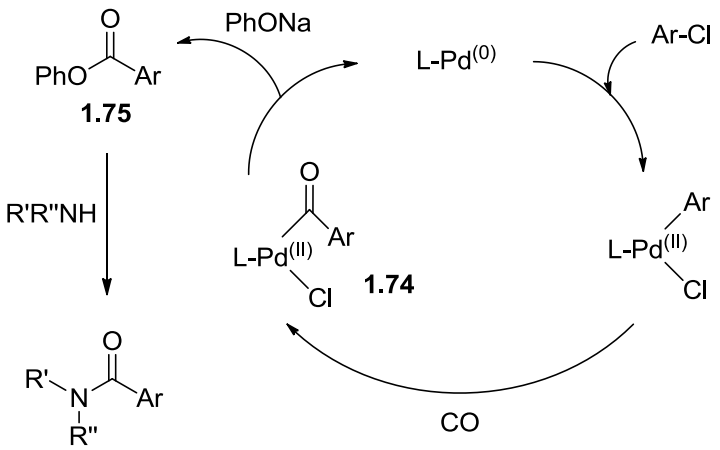
Scheme 1.47. Palladium catalysed aminocarbonylation by Schoenberg and Heck

Since this report there have been many others showing imporvements to the original catalytic system (including a reaction that proceeded using water as the solvent[110] and one using $Mo(CO)_6$ as a solid source of CO),[111] the most notable of which is the work of Buchwald *et al.*, who developed a sodium phenoxide assisted $Pd(OAc)_2$/ligand **1.70** catalysed reaction (Scheme 1.48).[112] A comprehensive range of acyl chlorides and amines was shown to be tolerated by the reaction, giving a number of functionalised amides including nitrile **1.71**, heterocyclic compound **1.72** and tertiary amide **1.73**.

The mechanism of this important transformation involves phenyl ester intermediate **1.74** formed when the intermediate palladium-acyl complex **1.75** reacts with sodium phenoxide (which is a better nucleophile than the amine). This phenyl ester intermediate can then react with the amine in a subsequent uncatalysed step to yield the amide products (Scheme 1.49).



Scheme 1.48. Sodium phenoxide assisted aminocarbonylation by Buchwald *et al.*



Scheme 1.49. Mechanism of aminocarbonylation by Buchwald *et al.*

1.3 Summary

The direct, uncatalysed couplings of acid chlorides or carboxylic acids and amines have been well known reactions for the construction of amide bonds since 1883. Although the most atom-economical of syntheses, limited substrate ranges due to undesirable reaction conditions have rendered it necessary for alternative syntheses to be developed.

Other than direct coupling reactions, the most common method of amide bond synthesis involves the use of coupling reagents to activate a carboxylic acid towards nucleophilic attack by an amine. Enzymatic methods have found limited success in this area but development remains hindered by their intrinsic lability.

Catalytic amide bond syntheses have opened up new routes to amide bonds, allowing substrates such as nitriles, aldehydes and alcohols to be used as starting materials, and eliminating the need for stoichiometric coupling reagents. The remaining challenge now is to find catalysts to perform these reactions which are low cost, recyclable, environmentally friendly and tolerate all substrates for these processes to be useful for industrial applications.

1.4 Project Aims

The research presented in this thesis aims to address some of the problems with current amide bond forming reactions which are outlined above. Specifically, catalyst economy and atom efficiency are addressed by using low cost, commercially available catalysts and avoiding the use of additives to the reaction where possible.

Results and Discussion I

Amides from Nitriles

"An Iron-Catalysed Synthesis of Amides from Nitriles and Amines"

C. L. Allen, A. A. Lapkin, J. M. J. Williams, *Tetrahedron Lett.,* **2009**, 50, 4262.

2. Results and Discussion I – Amides from Nitriles

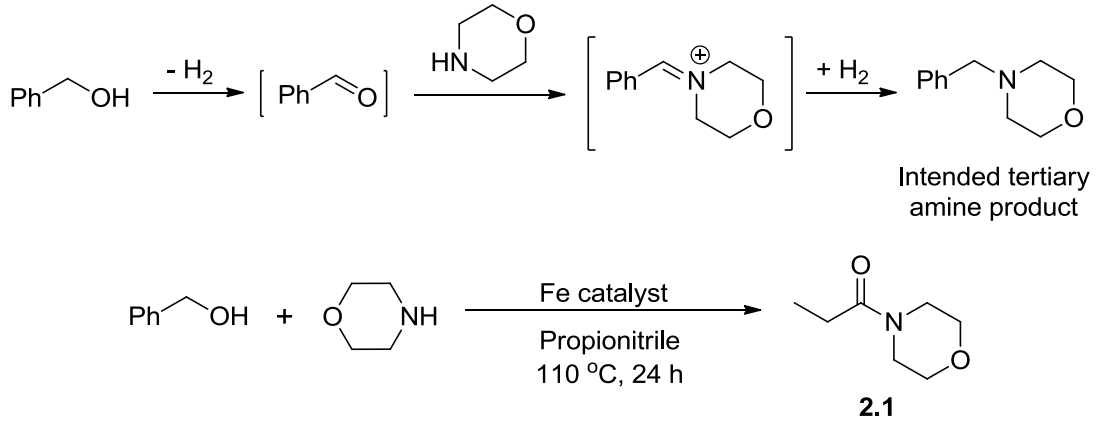
2.1 Introduction

Nitriles are well recognised as important substrates in organic chemistry due to their chemical versatility, allowing addition to the C≡N group by nucleophiles or electrophiles to lead to new C-N, C-C and C-O bonds.

Metal ions are used to activate nitriles towards both nucleophilic and, less often, electrophilic attack. Reactions of coordinated organonitriles at metal centres has allowed for the formation of metallacycles, cycloadditions and coupling with heterocycles, oximes and imines as well as the traditional C-C or C-N bond forming reactions.

2.2 Initial Work

Through previous work attempting to use an iron catalyst in the borrowing hydrogen reaction between benzylalcohol and morpholine, we discovered that, when using propionitrile as a solvent, the major product was in fact amide **2.1** instead of the intended tertiary amine product (Scheme 2.1).



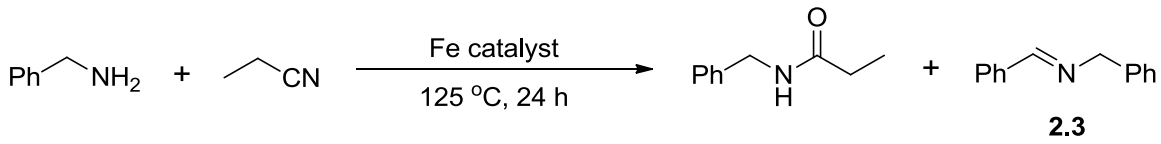
Scheme 2.1. Reaction of morpholine and benzyl alcohol in propionitrile

Although the reaction between a nitrile and an amine to form an amide was already documented in the literature, it appeared to not have received much attention and the only paper published on this transformation since the original report using a ruthenium catalyst in 1986[75] was a paper in 2000 using a platinum catalyst.[76] Thus, we decided to persue optimising this reaction using the much less expensive iron catalysts.

2.3 Optimisation

The reaction of benzylamine and propionitrile was used as a standard in initial studies. Through varying the ratio of amine to nitrile, maximum conversion into amide **2.2** was found with an 8:1 ratio of nitrile to amine (essentially using the nitrile as a solvent as well as a reactant). We then compared the performance of a range of iron complexes. The results of this initial catalyst screening are summarised in Tables 2.1 and 2.2. Conversions were determined by NMR analysis and in the absence of catalyst there was no conversion into amide.

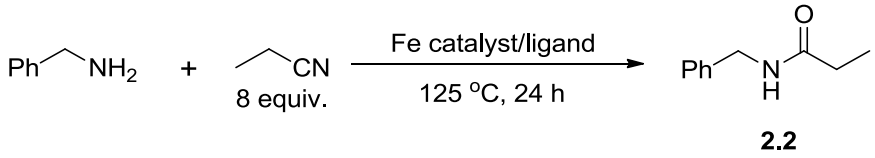
Variation of catalyst loading highlighted an interesting imine side product to this reaction when using an iron based catalyst (Scheme 2.2).



Scheme 2.2. Products found in optimisation studies

This transformation into imine has been reported using photochemical[113] or electrochemical[114] conditions, or iron catalysts (e.g. pentacyanonitrosyl ferrate(II)).[115] In the absence of a nitrile substrate, imine **2.3** was formed in 88% conversion with 10 mol% $FeCl_2 \cdot 4H_2O$ and 90% conversion with 10 mol% $Fe(NO_3)_3 \cdot 9H_2O$ (Scheme 2.3). The oxidising agent here is proposed to be oxygen in the air as these reactions are not run in an inert atmosphere.

Table 2.1. Effect of different iron catalysts and catalyst loading



2.2

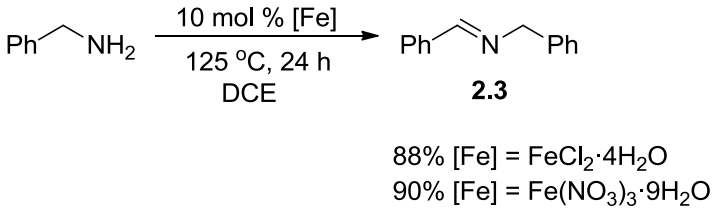
Entry	Catalyst	Catalyst loading (mol%)	Conversion into 2.2 (%)
1	None	-	0
2	$FeCl_2 \cdot 4H_2O$	5	47
3	$FeCl_2 \cdot 4H_2O$	10	55
4	$FeCl_2 \cdot 4H_2O$	20	71
5	$FeCl_2 \cdot 4H_2O$	25	82
6	$FeCl_3 \cdot 6H_2O$	5	30
7	$FeCl_3 \cdot 6H_2O$	15	36
8	$FeBr_2 \cdot xH_2O$	10	50
9	$FeI_2 \cdot xH_2O$	10	60
10	$Fe(NO_3)_3 \cdot 9H_2O$	2.5	42
11	$Fe(NO_3)_3 \cdot 9H_2O$	10	87
12	$Fe(NO_3)_3 \cdot 9H_2O$	20	88
13	$Fe(acac)_3$	25	0

Conditions: Benzylamine (0.11 mL, 1 mmol), propionitrile (0.55 mL, 8 mmol), catalyst, 125 ^{o}C, 24 h.

Table 2.2. Addition of ligands

Entry	Catalyst	Ligand	Conversion into 2.2 (%)
1	$FeCl_2 \cdot 4H_2O$	2,2-Bipyridyl	30
2	$FeCl_2 \cdot 4H_2O$	DPEPhos	0
3	$FeCl_2 \cdot 4H_2O$	Ethylenediamine	0
4	$FeCl_2 \cdot 4H_2O$	1,2-Diaminocyclohexane	35
5	$Fe(NO_3)_3 \cdot 9H_2O$	2,2-Bipyridyl	67

Conditions: Benzylamine (0.11 mL, 1 mmol), propionitrile (0.55 mL, 8 mmol), catalyst (5 mol%), ligand (5 mol%), 125 ^{o}C, 24 h.



Scheme 2.3. Reaction of benzylamine in the absence of nitrile

Fortunately, very little imine side product was observed when using $Fe(NO_3)_3 \cdot 9H_2O$ as the catalyst in the presence of a nitrile. From the results in Tables 2.1 and 2.2, we decided to use the catalyst $Fe(NO_3)_3 \cdot 9H_2O$ (with no ligand) and the same reaction of benzylamine and propionitrile for further optimisation studies, which are summarised in Table 2.3. We found that addition of excess water when using a lower catalyst loading (additional to the water of crystallisation already in the catalyst) or use of a solvent had negative effects on the conversion into amide (Table 2.3).

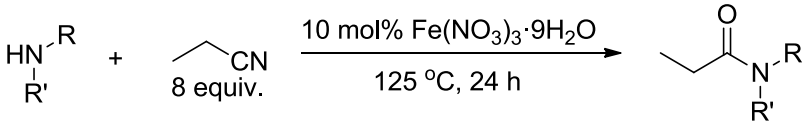
Table 2.3. Variation of additives and solvent

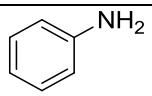
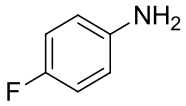
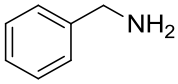
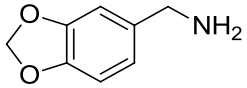
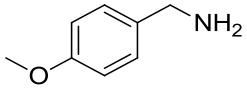
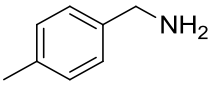
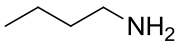
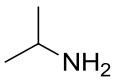
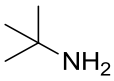
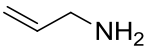
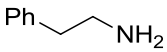
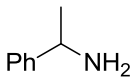
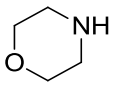
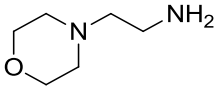
Entry	Catalyst	Mol% (Catalyst)	Additive	Amount (Additive)	Conversion into 2.2 (%)
1	$Fe(NO_3)_3 \cdot 9H_2O$	2.5	H_2O	80 mol%	13
2	$Fe(NO_3)_3 \cdot 9H_2O$	10	PhMe	1 mL	18
3	$Fe(NO_3)_3 \cdot 9H_2O$	10	DCE	1 mL	77
4	$Fe(NO_3)_3 \cdot 9H_2O$	10	THF	1 mL	60
5	$Fe(NO_3)_3 \cdot 9H_2O$	10	-	-	87

Conditions: Benzylamine (0.11 mL, 1 mmol), propionitrile (0.27 mL, 4 mmol), catalyst, additive, 125 ^oC, 24 h.

Having concluded from the results above that the optimal catalyst system was 10 mol% $Fe(NO_3)_3 \cdot 9H_2O$ (Table 2.3, entry 5), we then turned our attention to expanding the scope of this reaction, the results of which are summarised in Tables 2.4 and 2.5.

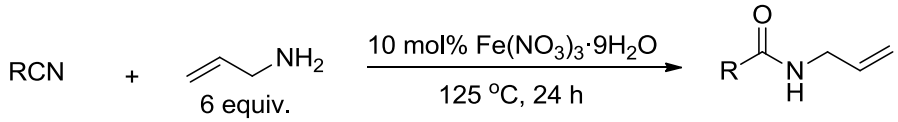
Table 2.4. Range of amines

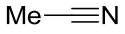
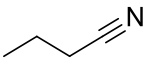
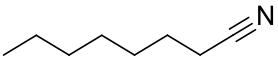
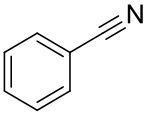
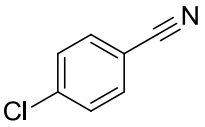
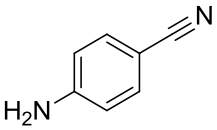
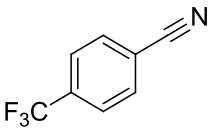
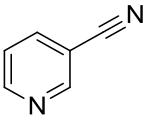


Entry	Amine	Product	Conversion into amide (%)	Isolated yield (%)
1		**2.4**	~8	-
2		**2.5**	15	-
3		**2.6**	87	65
4		**2.7**	43	-
5		**2.8**	88	79
6		**2.9**	90	82
7		**2.10**	100	87
8		**2.11**	86	-
9		**2.12**	0[a]	-
10		**2.13**	100	91
11		**2.14**	89	78
12		**2.15**	31	-
13		**2.16**	88	79
14		**2.17**	78	-

Conditions: Amine (1 mmol), propionitrile (0.55 mL, 8 mmol), $Fe(NO_3)_3 \cdot 9H_2O$, (0.04 g, 10 mol%), 125 °C, 24 h; [a] 80% conversion into propionamide observed.

Table 2.5. Range of nitriles



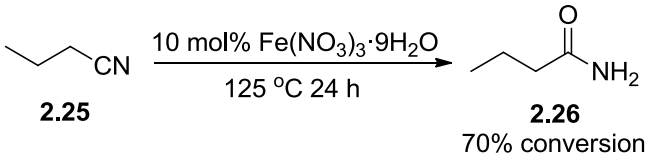
Entry	Nitrile		Conversion into amide (%)	Isolated yield[a] (%)
1		**2.18**	100	89
2		**2.19**	100	-
3		**2.20**	87	-
4		**2.21**	50	-
5[b]		**2.22**	100	69
6		**2.23**	0	-
7		**2.24**	100	72
8		**2.25**	100	94

Conditions: Allylamine (0.45 mL, 6 mmol), nitrile (1 mmol), $Fe(NO_3)_3 \cdot 9H_2O$, (0.04g, 10 mol%), 125 ^oC, 24 h.

From this substrate screening we can see that the reaction is tolerant to many common functional groups such as halogen and methoxy-substitutions on the benzene ring (Table 2.4, entry 2, Table 2.5, entries 5 and 7), alkenes (Table 2.4, entry 10) and pyridines (Table 2.5, entry 8), with several reactions giving 100% conversion. Noteworthy is entry 7 of Table 2.5, as the amide product is a precursor to a drug molecule which has diuretic and anti-inflammatory properties.[116]

From the conversions observed for the above substrates, it also appears the reaction is sensitive to branching at the α-position of the amine. 1-Phenylethylamine (Table 2.4, entry 12) exemplifies this observation, giving only 31% conversion into amide. Substrates where the imine side product is thermodynamically favoured also show relatively low conversions, such as piperonylamine (Table 2.4, entry 4) where the major product (53%) is the imine. When aniline or *p*-fluoroaniline were used as substrates (Table 2.4, entries 1 and 2), only trace amounts of amide were seen, most likely due to their poor nucleophilicity.

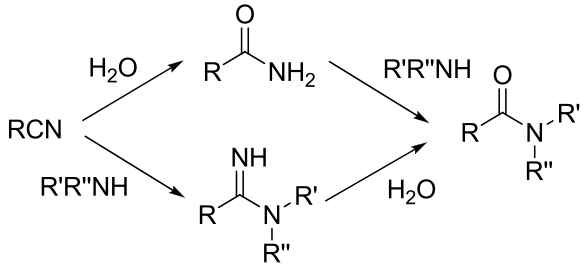
In the absence of an amine, the nitrile will react with water to form the primary amide. Butyronitrile **2.25** was hydrolysed to butyramide **2.26** in 70% conversion (Scheme 2.4). Although many reactions in which a nitrile is hydrolysed to a primary amide already exist, to our knowledge, this is the first example of an iron catalysed synthesis of a primary amide *via* hydrolysis of a nitrile.



Scheme 2.4. Hydrolysis of butyronitrile into butyramide

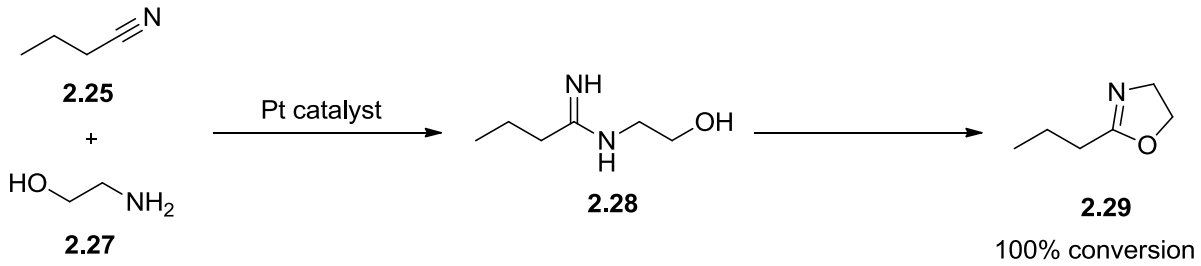
2.4 Mechanism Studies

Two possible routes to the amide from the coupling of a nitrile and amine have been proposed, the first proceeding *via* the primary amide which then reacts with the amine, the second going *via* an amidine intermediate which is then hydrolysed to the amide (Scheme 2.5).



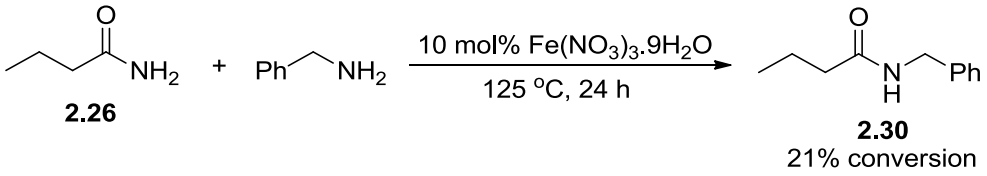
Scheme 2.5. Proposed mechanisms of amide formation

The metal catalysed formation of amidines from nitriles and amines has previously been reported. Evidence specifically supporting the amidine mechanism has been put forward by de Vries *et al*.,[76] who found firstly when *n*-propylamine is reacted with acetonitrile in the absence of water, the major products formed are mono- and bisamidines and secondly, in the reaction between butyronitrile **2.25** and 2-aminoethanol **2.27**, the first product formed is the amidine **2.28**, which then goes on to ring-close forming the final product, 2-ethyl-1,3-oxazoline **2.29** (Scheme 2.6).



Scheme 2.6. Oxazoline formation from nitrile and amino alcohol

In our own attempt to confirm the mechanism of the reaction, we treated primary amide **2.26** with benzylamine (Scheme 2.7).



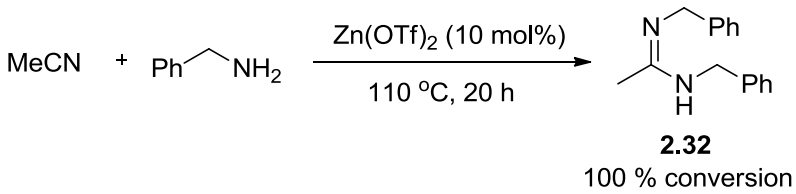
Scheme 2.7. Mechanistic investigation

The low conversion into secondary amide **2.30** after 24 hours when exposed to the iron catalyst under the same reaction conditions as used in our study above suggests that this pathway is not predominant and supports the initial formation of an amidine intermediate, which is then hydrolysed to give the amide product.

2.5 Further Work

In an attempt to improve the efficiency of this reaction, we screened a number of alternative metal catalysts known to show Lewis acidic behaviour (Table 2.6). We were aiming to find a catalyst that would match or better the conversions seen with our iron catalyst but at a lower catalyst loading, lower temperature, shorter reaction time or solvent free.

The two side products observed in these reactions were the amidine and the imine. Under anhydrous, inert conditions, zinc catalyst $Zn(OTf)_2$ gave 100% conversion (with respect to amine) into bisamidine **2.32** (Scheme 2.8). When one equivalent of water was added to the reactions previously seen to produce the most amidine product, the overall conversion dropped (into amide or amidine), but the only product seen was the desired secondary amide (Table 2.6, entries 20-22).

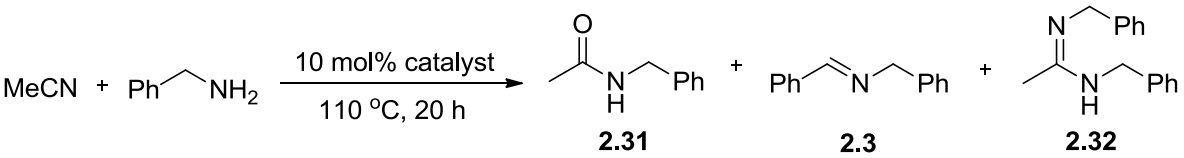


2.32
100 % conversion

Scheme 2.8. Formation of amidine

From this catalyst screen it is clear there is potential to find more efficient metal complexes to catalyse the coupling of amines and nitriles to form amides. Under specific conditions (such as shown in Scheme 2.8), the major product seen is the amidine.

Table 2.6. Screen of alternative catalysts



Entry	Catalyst	Conversion into amide 2.31 (%)	Conversion into imine 2.3 (%)	Conversion into amidine 2.32 (%)
1	MgBr	0	0	0
2	$Ti(O^iPr)_4$	0	0	0
3	$Al(O^iPr)_3$	0	0	79
4	$NiCl_2$	9	0	0
5	$Co(OAc)_2$	50	50	0
6	CuCl	51	49	0
7	$Cu(NO_3)_2$	40	24	36
8	$Cu(OTf)_2$	66	34	0
9	CuI	67	33	0
10	$Zn(NO_3)_2$	53	0	37
11	ZnI_2	0	0	100
12	$Zn(OTf)_2$	0	0	100
13	AgCl	0	0	0
14	$AgNO_3$	0	0	0
15	AgOAc	0	0	0
16	$In(NO_3)_3$	36	0	34
17	$In(OTf)_3$	36	0	60
18	$AuCl_3$	0	0	0
19	$Au(PPh_3)_3Cl$	0	0	0
20	$Zn(NO_3)_2$ / H_2O	74	4	3
21	ZnI_2 / H_2O	51	0	0
22	$Zn(OTf)_2$ / H_2O	69	0	0

Conditions: Acetonitrile (0.21 mL, 4 mmol), benzylamine (0.22 mL, 2 mmol), catalyst (10 mol%), 110 ^oC, 20 h.

2.6 Conclusions

The coupling of amines and nitriles to form amides is a useful synthetic transformation as both the starting materials are readily available. $Fe(NO_3)_3 \cdot 9H_2O$ as a catalyst is relatively inexpensive and has been proven to be efficient in coupling a range of amines and nitriles under neutral conditions. The same catalyst has also been shown to catalyse the formation of imines from the coupling of two amines as well as hydrolysis of nitriles into primary amides. Experimental evidence to support the mechanism proceeding *via* an amidine intermediate has been demonstrated.

Initial studies into a more efficient catalyst have been performed, the results of which firstly indicate that with further investigation a better catalyst could be found, and secondly that an efficient method of making amidines from the coupling of an amine and a nitrile could be developed by careful alteration of the reaction conditions.

Results and Discussion II

Amides from Oximes

"Mechanistic Studies into Metal Catalysed Aldoxime to Amide Rearragments"
C. L. Allen, R. Lawrence, L. Emmett, J. M. J. Williams *Adv. Synth. Catal.*, **2011,** 353, 3262.

"Copper Catalyzed Rearrangement of Oximes into Primary Amides"
S. K. Sharma, S. D. Bishopp, C. L. Allen, R. Lawrence, M. J. Bamford, A. A. Lapkin, P. Plucinski, R. J. Watson, J. M.J. Williams *Tetrahedron Lett.,* **2011,** 52, 4252.

"Catalytic Acylation of Amines with Aldehydes or Aldoximes"
C. L. Allen, S. Davulcu, J. M. J. Williams, *Org. Lett.*, **2010**, 12, 5096.

"Cost Efficient Synthesis of Amides from Oximes with Indium or Zinc Catalysts"
C. L. Allen, C. Burel, J. M. J. Williams, *Tetrahedron Lett.,* **2010**, 51, 2724.

3. Results and Discussion II – Amides from Oximes

3.1 Introduction

Oximes are employed in a diverse range of reactions and as a result have found extensive application within organic synthesis.[117] Of these transformations, hydrolysis into ketones and aldehydes, dehydration to nitriles, reduction to amines and hydroxylamines, oxidation to nitro compounds and *O*-substitution to form oxime ethers have been well known for many years.[118] Additionally, oximes may be used as protecting groups in carbonyl chemistry and due to their crystalline nature, can also be used to purify and characterise carbonyl compounds, specifically aldehydes and ketones.[119]

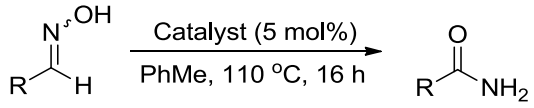
Aldoximes can be synthesised in a number of ways (e.g. reduction of a nitro group[120] or oxidation of an amine)[121] but the most common method by far is the condensation of an aldehyde and hydroxylamine hydrochloride, a reaction typically run at room temperature in an alcoholic solvent in the presence of a base.[122]

3.2 Initial Work

The rearrangement of an aldoxime into a primary amide is an attractive procedure due to its 100% atom efficiency. However, the catalysts reported for this transformation are all expensive, precious metal based complexes, making the reaction cost inefficient despite its atom efficiency.[80-86] We decided to screen a number of cheaper catalysts to compare their reactivity with the ruthenium, iridium and rhodium catalysts already reported to catalyse this rearrangement (Table 3.1).

This initial catalyst screen gave mixed results, but indium triflate stood out as the best potential lead, giving over 90% conversion into both aromatic and alkyl primary amides in 16 hours.

Table 3.1. Catalyst screen



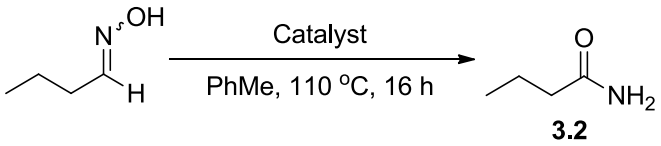
Entry	Catalyst	Conversion (%) R = phenyl (3.1)	Conversion (%) R = *n*-butyl (3.2)
1	$Al(O^iPr)_3$	0	0
2	$Ca(OH)_2$	41	60
3	$Sc(OTf)_3$	0	0
4	$Ti(O^iPr)_4$	0	0
5	$FeCl_3$	0	0
6	$Fe(NO_3)_3$	15	12
7	FeI_2	0	0
8	$Co(OAc)_2$	0	0
9	CuBr	60	84
10	ZnI_2	55	80
11	$ZrCl_4$	0	0
12	AgCl	0	0
13	$In(OTf)_3$	91	98
14	$Ce(SO_4)_2$	0	0
15	$EuCl_3$	0	0
16	No catalyst	0	0

Conditions: Benzaldoxime (0.121 g, 1 mmol) or butyraldoxime (0.9 mL, 1 mmol), catalyst (5 mol%), PhMe (1 mL), 110 °C, 16 h.

3.3 Primary Amides

Intrigued by how efficient we could make the rearrangement with indium salts, we undertook several optimisation steps, summarised below in Tables 3.2 and 3.3. The first set of results details attempts to find the lowest catalyst loading to still give very high conversion into butyramide (Table 3.2).

Table 3.2. Indium catalysts screen



3.2

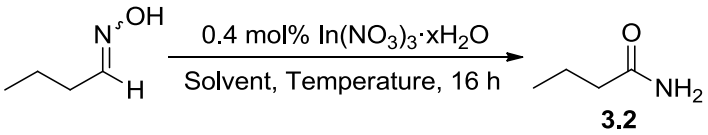
Entry	Catalyst	Catalyst loading (mol%)	Conversion into amide 3.2 (%)
1	$In(OTf)_3$	1	99
2	$In(OTf)_3$	0.5	90
3	$In(OTf)_3$	0.1	67
4	$InCl_3$	2.5	98
5	$InCl_3$	1	95
6	$InCl_3$	0.5	90
7	$InCl_3$	0.1	65
8	$In(NO_3)_3 \cdot xH_2O$	2.5	96
9	$In(NO_3)_3 \cdot xH_2O$	1	97
10	$In(NO_3)_3 \cdot xH_2O$	0.5	96
11	$In(NO_3)_3 \cdot xH_2O$	0.1	88

Conditions: Butyraldoxime (0.9 mL, 1 mmol), catalyst, PhMe (1 mL), 110 °C, 16 h.

Taking into account the higher cost of indium triflate (as compared with the other indium catalysts screened), we chose indium nitrate as our catalyst to continue optimisation studies (Table 3.3).

The solvent screen showed toluene at reflux gave the best conversion into primary amide **3.2** (Table 3.3, entry 1). Adding water to the reaction gave no conversion, presumably due to an inhibitory effect on the catalyst (Table 3.3, entries 7, 10, 12, 14). When using acetonitrile as a solvent, the major product observed was acetamide, suggesting that the water removed from butyraldoxime was then used to hydrolyse acetonitrile into the amide.

Table 3.3. Solvent and temperature screen



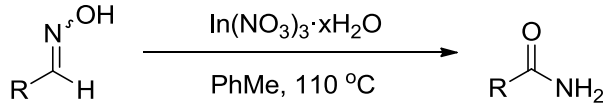
3.2

Entry	Solvent	Temperature (^{o}C)	Conversion into 3.2 (%)
1	Toluene	110	98
2	1,4-Dioxane	105	16
3	1-Propanol	100	41
4	1-Propanol	90	11
5	Acetonitrile	90	0
6	DME	90	8
7[a]	Ethanol/H_2O	90	0
8	Ethanol	80	78
9	Ethyl Acetate	100	60
10[a]	Ethyl Acetate/H_2O	90	0
11	Ethyl Acetate	80	49
12[a]	Petrol Ether (60-80)/H_2O	90	0
13	Hexane	90	58
14[a]	Hexane/H_2O	90	0
15	Methanol	65	6
16	2-MethylTHF	65	0

Conditions: Butyraldoxime (0.9 mL, 1 mmol), $In(NO_3)_3 \cdot xH_2O$ (0.001 g, 0.4 mol%), solvent (1 mL), 16 h; [a] 9:1 Organic:H_2O mixtures.

We then turned our attention to the scope of this reaction. Several oximes were converted into the corresponding primary amides in good to excellent yields, although some were found to require higher catalyst loading and longer reaction time to reach conversions over 90%. Specifically, steric hinderance around the reaction site (Table 3.4, entry 5) led to no conversion into amide being observed, as did the presence of a pyridine ring (Table 3.4, entry 6).

Table 3.4. Oximes screen with indium catalyst



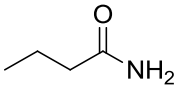
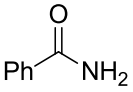
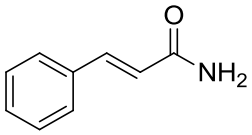
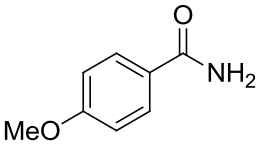
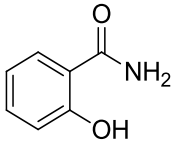
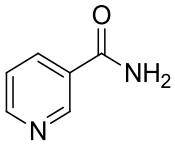
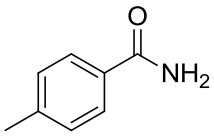
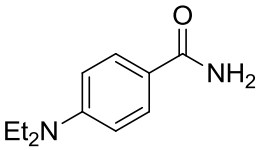
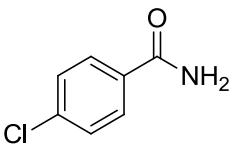
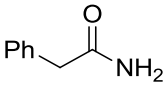
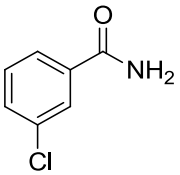
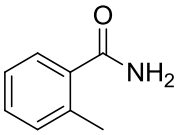
Entry	Amide product		Catalyst loading (mol%) / time (h)	Conversion into amide (%)	Isolated Yield (%)
1		**3.2**	0.4 / 16	98	87
2		**3.1**	1.0 / 18	85	79
3		**3.3**	0.4 / 16	100	90
4		**3.4**	1.0 / 18	30	-
5		**3.5**	2.0 / 18	0	-
6		**3.6**	2.0 / 18	0	-
7		**3.7**	0.8 / 18	97	88
8		**3.8**	0.8 / 18	98	95
9		**3.9**	1.0 / 18	96	88
10		**3.10**	0.8 / 16	97	86

Table cont.

11		**3.11**	1.0 / 18	96	87
12		**3.12**	1.0 / 18	14	-

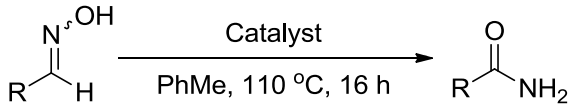
Conditions: Aldoxime (2 mmol), $In(NO_3)_3 \cdot xH_2O$, PhMe (2 mL), 110 ^oC.

Despite having this optimised reaction in hand, we were aware that indium catalysts are still relatively expensive and also reserves of indium have been reported to be very low. With this in mind, we reconsidered our results shown in Table 3.1 and chose to try and optimise the reaction using a zinc catalyst as a cheaper alternative, even if this meant the catalyst loading had to increase to give comparable conversions as obtained with indium (Scheme 29, Table 14).

Excellent conversions were seen at 10 mol% catalyst loading, with $ZnCl_2$ giving the best conversion into benzamide (Table 3.5, entry 7) and $Zn(NO_3)_3$ the best conversion into butyramide (Table 3.5, entry 8). Pleasingly, attempts to lower the reaction temperature were successful, with the highest conversions seen in heptane at 100 ^oC.

These conditions were then applied to the same range of oximes in order to offer a comparison between the two metals as catalysts (Table 3.6).

Table 3.5. Zinc catalysts screen



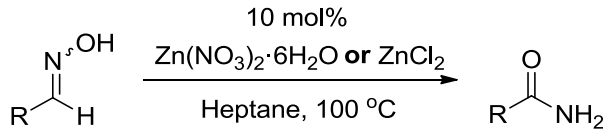
Entry	Catalyst	Mol%	Solvent/ Temp. (^{o}C)	Time (h)	Conversion into amide (%) R = phenyl (3.1)	Conversion into amide (%) R = *n*-butyl (3.2)
1	$ZnCl_2$	8	PhMe / 110	18	92	68
2	ZnI_2	8	PhMe / 110	18	58	66
3	$Zn(NO_3)_2{\cdot}6H_2O$	8	PhMe / 110	18	75	95
4	$Zn(OTf)_2$	8	PhMe / 110	18	90	80
5	$ZnCl_2$	10	PhMe / 110	18	93	-
6	$Zn(NO_3)_2{\cdot}6H_2O$	10	PhMe / 110	18	-	100
7	$ZnCl_2$	10	Heptane / 100	18	97	-
8	$Zn(NO_3)_2{\cdot}6H_2O$	10	Heptane / 100	18	-	100
9	$ZnCl_2$	10	EtOH / 90	18	0	-
10	$Zn(NO_3)_2{\cdot}6H_2O$	10	EtOH / 90	18	-	42

Conditions: Butyraldoxime (0.9 mL, 1 mmol) or benzaldoxime (0.121 g, 1 mmol), catalyst, PhMe (1 mL), 110 ^{o}C, 16 h.

From the results in Tables 3.4 and 3.6 it is clear that there are some limitations to the scope of this reaction using these catalysts. 4-Methoxybenzaldoxime only gave 30% conversion into the amide with $In(NO_3)_3{\cdot}xH_2O$ (Table 3.4, entry 4), the remaining material being a mixture of the corresponding aldehyde (35%) and starting aldoxime (35%). Pleasingly, the same substrate gave 96% conversion into amide with $ZnCl_2$ in heptane (Table 3.6, entry 4). A similar problem was experienced with salicylaldoxime (Table 3.4, entry 5 and Table 3.6, entry 5). While the reaction with the indium catalyst returned 100% starting material, a 50% conversion into salicyaldehyde was seen with $ZnCl_2$. 3-Pyridinealdoxime showed no conversion into primary amide in either case (Table 3.4, entry 7 and Table 3.6, entry 7). The presence of the basic pyridine nitrogen

may have a deactivating effect on the catalysts, although no problems were encountered when using 4-(*N*,*N*-diethylamino)benzaldoxime.

Table 3.6. Oximes screen with zinc catalysts



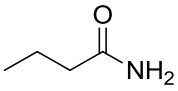
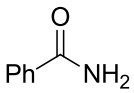
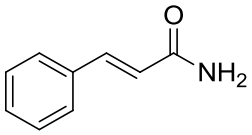
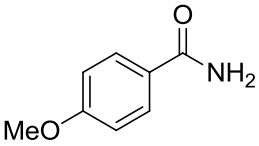
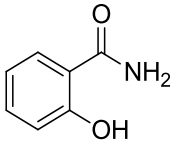
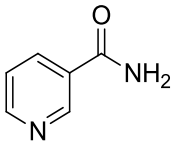
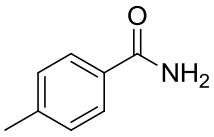
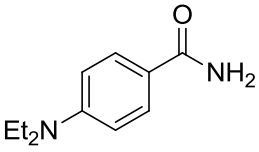
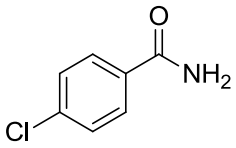
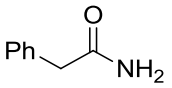
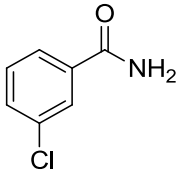
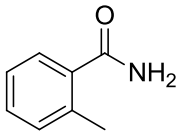
Entry	Amide product		Catalyst	Time (h)	Conversion into amide (%)	Isolated Yield (%)
1		**3.2**	$Zn(NO_3)_2 \cdot 6H_2O$	16	96	91
2		**3.1**	$ZnCl_2$	18	97	88
3		**3.3**	$Zn(NO_3)_2 \cdot 6H_2O$	16	100	93
4		**3.4**	$ZnCl_2$	18	96	89
5		**3.5**	$ZnCl_2$	18	0	-
6		**3.6**	$ZnCl_2$	18	0	-
7		**3.7**	$ZnCl_2$	18	96	84
8		**3.8**	$ZnCl_2$	16	98	91

Table cont.

9		**3.9**	$ZnCl_2$	18	95	90
10		**3.10**	$Zn(NO_3)_2 \cdot 6H_2O$	18	98	94
11		**3.11**	$ZnCl_2$	18	97	91
12		**3.12**	$ZnCl_2$	18	31	-

Conditions: Aldoxime (2 mmol), $Zn(NO_3)_2 \cdot 6H_2O$, (0.06 g, 10 mol%) or $ZnCl_2$ (0.02 g, 10 mol%), PhMe (2 mL), 110 ^oC.

Comparing these catalysts with those already reported to rearrange aldoximes to primary amides (see Chapter 1.2.5), there is a clear cost advantage (Table 3.7). Based on a one mole reaction of benzaldoxime, the prices of the amount required of each catalyst are calculated. Despite the higher catalyst loading, the significantly lower price of using 10 mol% of $ZnCl_2$, especially when compared to the iridium catalyst, outweighs any extra work up costs.

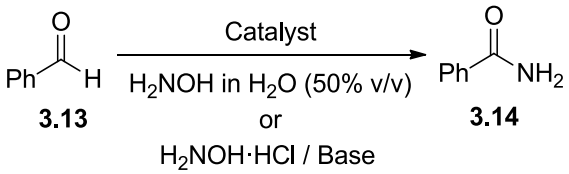
Table 3.7. Comparison of catalyst prices

Entry	Catalyst	Mol%	Price (£)
1	$Ru(PPh_3)_3(CO)H_2$	0.1	62.75
2	$[Ir(Cp^*)Cl_2]_2$	2.5	4123.51
3	$Pd(OAc)_2$	5.0	913.25
4	$Rh(PPh_3)_3Cl$	5.0	3629.63
5	$In(NO_3)_3 \cdot xH_2O$	1.0	14.44
6	$ZnCl_2$	10	2.86

Catalyst prices from Strem 2010 catalog, cheapest catalyst price.

A natural expansion of this reaction would be to start from the aldehyde and make the oxime *in situ* with hydroxylamine. Attempts at this reaction were made using benzaldehyde **3.13,** with hydroxylamine in water and also with the hydroxylamine hydrochloride salt and an additional base. Only the latter proved successful in giving the primary amide, presumably due to the same catalyst deactivation with water as seen when screening solvents for this reaction (Table 3.8).

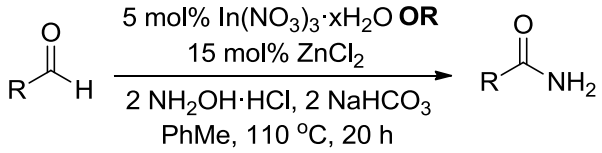
Table 3.8. Aldehyde to amide reaction conditions screen

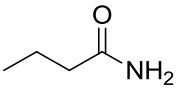
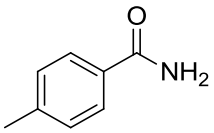
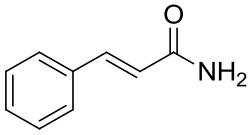
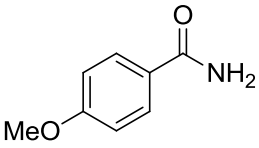
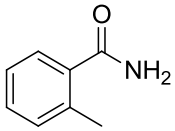
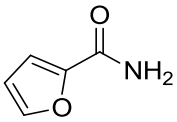
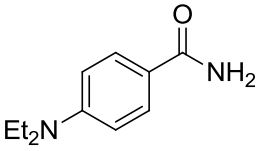
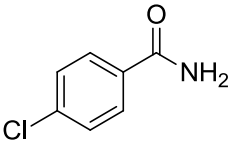


Entry	Catalyst	Mol %	Solvent / Temp. (^{o}C)	Time (h)	Reaction conditions	Conversion into 3.14 (%)
1	$In(NO_3)_3$	2	PhMe / 110	20	A	0
2	$In(NO_3)_3$	2	EtOH / 110	20	B	0
3	$In(NO_3)_3$	2	PhMe / 110	20	C	0
4	$Zn(OTf)_2$	5	PhMe/110	20	C	26
4	$In(OTf)_3$	5	- / 100	20	D	0
5	$In(OTf)_3$	5	EtOH / 100	20	E	0
6	$InCl_3$	5	PhMe / 110	24	A	63
7	$Zn(OTf)_2$	10	PhMe / 110	24	A	49
8	$InCl_3$	5	PhMe / 110	24	F	77
9	$Zn(OTf)_2$	10	PhMe / 110	24	F	48
10	$ZnCl_2$	10	Heptane / 100	20	G	0
11	$Zn(NO_3)_2{\cdot}6H_2O$	10	Heptane / 100	20	G	0
12	$Zn(OTf)_2$	10	Heptane / 100	20	G	0
13	$In(NO_3)_3$	5	PhMe / 110	20	G	93
14	$ZnCl_2$	15	PhMe / 100	20	G	100

Conditions; A) 1 equiv. $H_2NOH{\cdot}HCl$, 1 equiv. Na_2CO_3; B) 1 equiv. H_2NOH in H_2O; C) 1 equiv. $H_2NOH{\cdot}HCl$, no base; D) 4 equiv H_2NOH in H_2O; E) 2 equiv. H_2NOH in H_2O; F) 1 equiv. $H_2NOH{\cdot}HCl$, 1 equiv. $NaHCO_3$, N_2 atmosphere; G) 2 equiv. $H_2NOH{\cdot}HCl$, 2 equiv. $NaHCO_3$, N_2 atmosphere.

Table 3.9. Aldehydes Screen

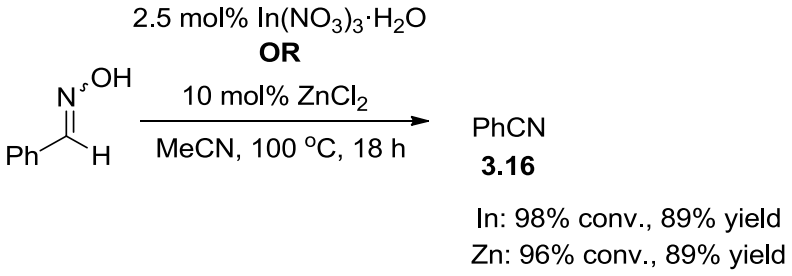


Entry	Amide product		Catalyst	Conversion (%)	Yield (%)
1		**3.2**	$In(NO_3)_3 \cdot xH_2O$	0	-
			$ZnCl_2$	100	91
2		**3.7**	$In(NO_3)_3 \cdot xH_2O$	95	89
			$ZnCl_2$	100	89
3		**3.3**	$In(NO_3)_3 \cdot xH_2O$	100	94
			$ZnCl_2$	96	86
4		**3.4**	$In(NO_3)_3 \cdot xH_2O$	100	87
			$ZnCl_2$	12	-
5		**3.12**	$In(NO_3)_3 \cdot xH_2O$	37	-
			$ZnCl_2$	0	-
6		**3.15**	$In(NO_3)_3 \cdot xH_2O$	94	83
			$ZnCl_2$	86	-
7		**3.8**	$In(NO_3)_3 \cdot xH_2O$	100	80
			$ZnCl_2$	46	-
8		**3.9**	$In(NO_3)_3 \cdot xH_2O$	68	-
			$ZnCl_2$	34	-

Conditions: Aldehyde (2 mmol), $In(NO_3)_3 \cdot H_2O$ (0.03 g, 5 mol%) or $ZnCl_2$ (0.02 g, 15 mol%), $NH_2OH \cdot HCl$ (0.14 g), $NaHCO_3$ (0.16 g), PhMe (2 mL), 110 °C, 20 h.

The conversions into primary amide seen when starting from the aldehyde and generating the oxime *in situ* reflects those seen when starting with the oxime. Groups in the ortho position to the aldoxime again hindered the reaction (Table 3.9, entry 5). Interestingly, the zinc catalysed rearrangement appears to be slower in the presence of hydroxylamine hydrochloride and the base, with conversions into primary amide dropping for several substrates (Table 3.9, entries 4 – 8). This could possibly be due to the hydroxylamine deactivating the zinc catalyst in some way.

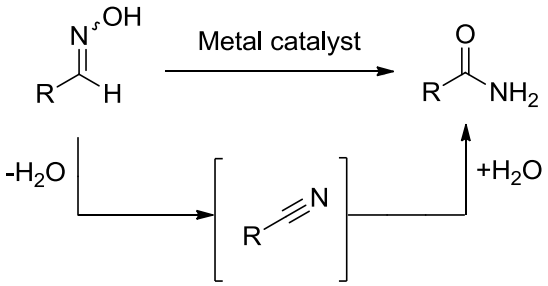
While oxime ethers and ketoximes were found to be unreactive in the presence of the chosen zinc and indium catalysts, an interesting result was observed when the reaction was carried out using acetonitrile as solvent. Almost 100% conversion of benzaldoxime into benzonitrile **3.16**, as well as an equal amount of acetamide was observed, suggesting that in the presence of another water acceptor, the dehydration as opposed to the rearrangement product will be given.[123]



Scheme 3.1. Conversion of benzaldoxime into benzonitrile

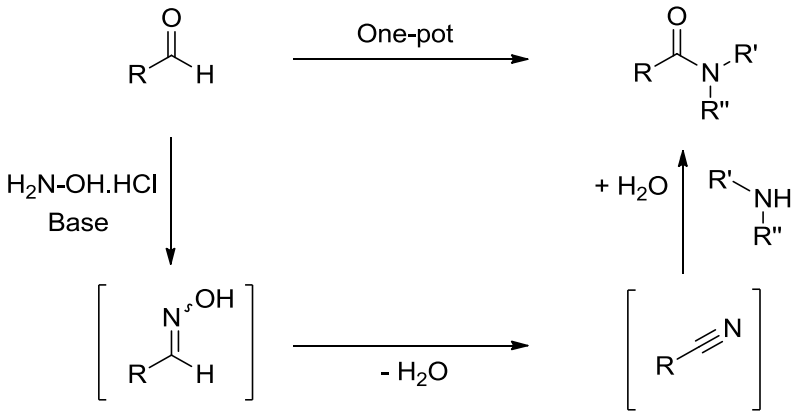
3.4 Secondary Amides

In the rearrangement of an aldoxime into a primary amide, the involvement of a nitrile intermediate seems likely (Scheme 3.2), as it has been shown that when reactions are run in the presence of acetonitrile, acetamide is formed and the oxime is converted into a nitrile (Scheme 3.1)



Scheme 3.2. Metal-catalysed rearrangement of aldoximes into primary amides

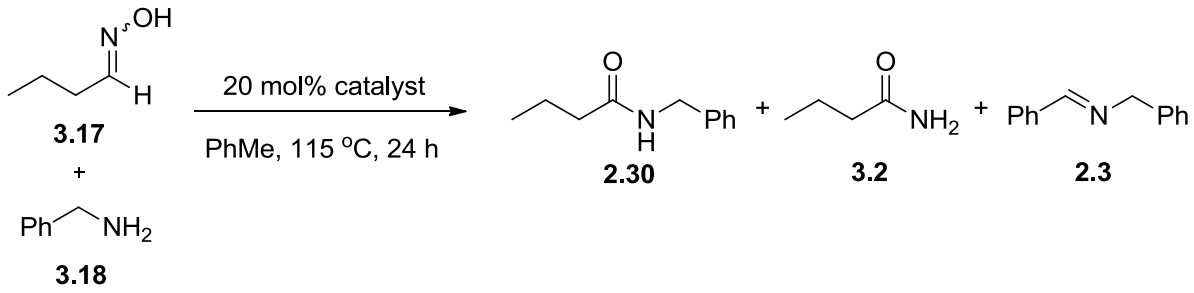
The conversion of nitriles into primary amides by metal-catalysed hydration is a known reaction, but more significantly, there are also reports of the metal-catalysed coupling of nitriles with amines leading to the formation of secondary and tertiary amines (including our own work – see Chapter 2). We therefore reasoned that by performing the oxime to amide rearrangement in the presence of an amine, it may be possible to divert the reaction pathway to allow for the formation of secondary and tertiary amides. By generating the oxime *in situ* from the parent aldehyde, this would lead to a one pot conversion of aldehydes into secondary or tertiary amides as outlined in Scheme 3.3.



Scheme 3.3. Proposed scheme for amide formation from amines and aldehydes

Initially, we chose to focus on identifying a suitable catalyst for the conversion of an oxime into a secondary amide and we selected the reaction of butyraldehyde oxime **3.17** with benzylamine **3.18** as a model reaction. The catalysts screened were those known to catalyse the rearrangement of an aldoxime into a primary amide. The use of indium nitrate (Table 3.10, entry 1) and a ruthenium complex (Table 3.10, entry 3) led mainly to the formation of undesired primary amide **3.2**. Zinc triflate (Table 3.10, entry 2) was more successful, giving the secondary amide **2.30** as the major product, although further reactions to improve the selectivity were unsuccessful. However, we were pleased to find that $NiCl_2$ gave a very high conversion into the secondary amide and further optimisation studies allowed us to reduce the catalyst loading and reaction time to 5 mol% and 18 hours when the reaction was run at a temperature of 155 ^{o}C (Table 3.11).

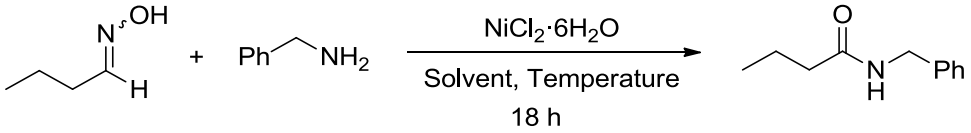
Table 3.10. Initial catalyst screen



Entry	Catalyst	Conversion into 2.30 (%)	Conversion into 3.2 (%)	Conversion into 2.3 (%)
1	$In(NO_3)_3 \cdot xH_2O$	11	84	5
2	$Zn(OTf)_2$	59	33	0
3	$Ru(PPh_3)_4H_2$	6	94	0
4	$NiCl_2 \cdot 6H_2O$	98	0	2
5	$NiBr_2$	88	12	0
6	$NiSO_4$	14	86	0
7	$Ni(NO_3)_2$	0	76	14
8	NiO	0	0	0

Conditions: Butyraldoxime (2 mmol), benzylamine (2 mmol), toluene (2 mL), catalyst (20 mol%), atmosphere of nitrogen.

Table 3.11. Temperature and catalyst amount screen



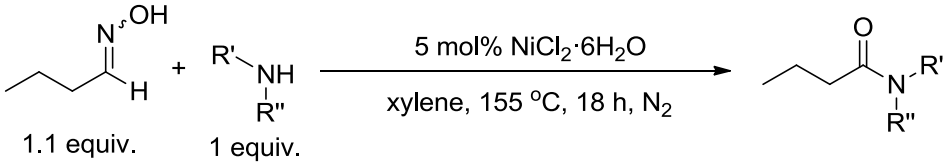
Entry	Mol % catalyst	Solvent	Temperature (^{o}C)	Conversion into 2.30 (%)
1	20	PhMe	115	99
2	15	PhMe	115	51
3	10	PhMe	115	41
4	5	PhMe	115	0
5	20	*p*-xylene	155	100
6	10	*p*-xylene	155	98
7	5	*p*-xylene	155	98

Conditions: Butyraldoxime (1.1 mmol), benzylamine (1 mmol), solvent (1 mL), atmosphere of nitrogen.

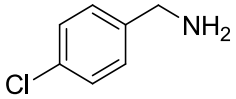
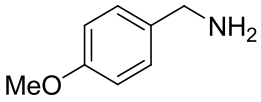
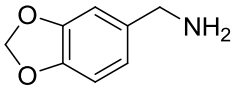
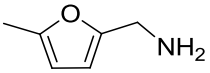
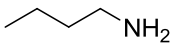
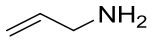
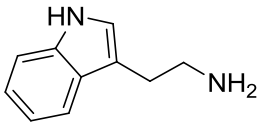
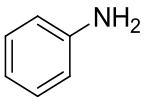
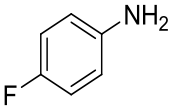
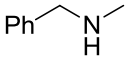
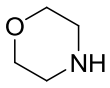
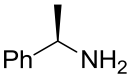
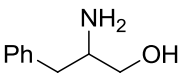
The results in Table 3.11 show that the reaction proceeds to 99% conversion at the lower temperature of 115 ^{o}C, but a catalyst loading of 20 mol% is required. In the same time, an equal conversion can be achieved using only 5 mol% catalyst, but at the higher temperature of 155 ^{o}C. For the purpose of this study, the higher temperature conditions were used, but if a temperature sensitive reactant was being used, there would be the option of using a higher catalyst loading at 115 ^{o}C instead.

Having established conditions for the catalytic conversion of oxime **3.17** into the secondary amide **2.30**, we turned our attention to exploring the range of secondary and tertiary amides that can be synthesised using this new reaction. The results from the reaction of a range of amines with butyraldehyde oxime **3.17** are presented in Table 3.12. We also examined the range of aldoximes which could be employed as substrates for the formation of secondary *N*-benzyl amides, and the results are presented in Table 3.13.

Table 3.12. Range of amine substrates in catalytic amide formation

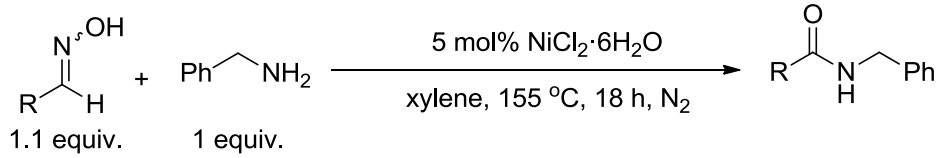


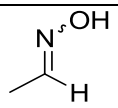
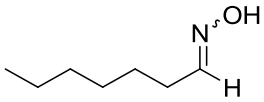
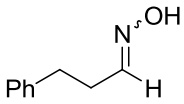
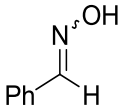
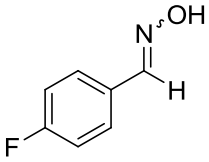
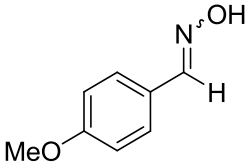
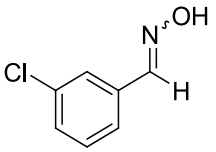
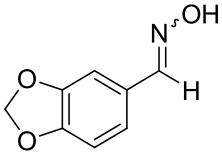
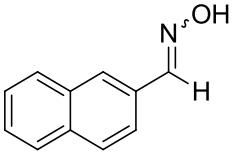
1.1 equiv. **3.17** 1 equiv.

Entry	Amine	Product	Conversion into amide (%)	Isolated yield (%)
1		**3.19**	100	83
2		**3.20**	100	88
3		**3.21**	100	89
4		**3.22**	100	90
5		**3.23**	100	96
6		**3.24**	100	79
7		**3.25**	67	-
8[a]		**3.26**	100	91
9[a]		**3.27**	68	-
10		**3.28**	100	89
11		**3.29**	100	83
12		**3.30**	100	91 (>95% ee)
13		**3.31**	60[b]	-

Conditions: Butyraldoxime (0.2 mL, 2.2 mmol), amine (2 mmol), $NiCl_2 \cdot 6H_2O$ (5 mol%), *p*-xylene (2 mL), 155 °C, 18 h, atmosphere of nitrogen. [a] 1.2 equivalents oxime to amine; [b] Remaining 40% was oxazoline side-product.

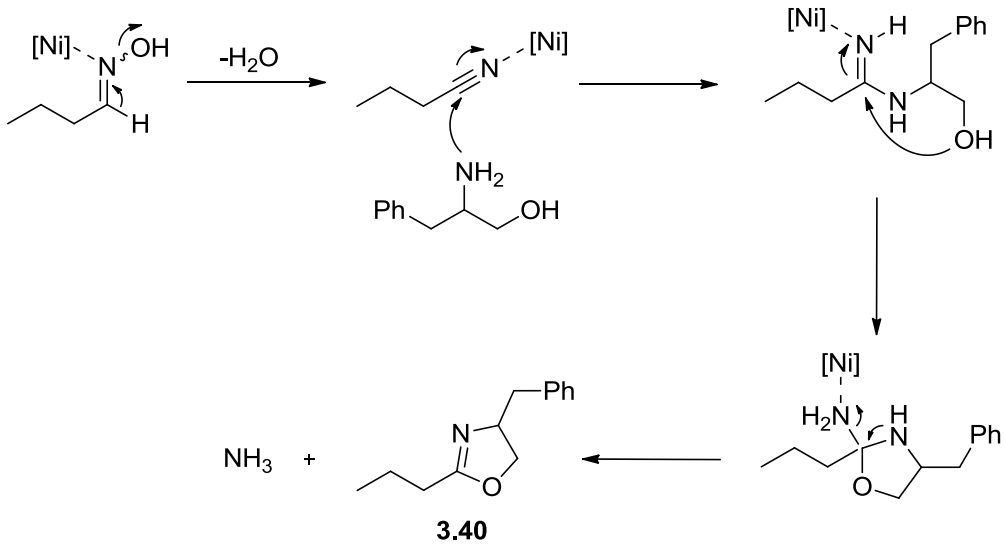
Table 3.13. Oxime substrates converted into *N*-benzylamides



Entry	Aldoxime	Product	Conversion into amide (%)	Isolated yield (%)
1		**2.31**	100	88
2		**3.32**	100	89
3		**3.33**	100	90
4		**3.34**	70	62
5		**3.35**	100	83
6		**3.36**	36	-
7		**3.37**	71	66
8		**3.38**	100	76
9		**3.39**	92	76

Conditions: Aldoxime (2.2 mmol), benzylamine (0.22 mL, 2 mmol), $NiCl_2 \cdot 6H_2O$ (5 mol%), *p*-xylene (2 mL), 155 ^oC, 18 h, atmosphere of nitrogen.

Most substrates gave a very high conversion into secondary amide, demonstrating that the reaction tolerates a wide range of functional groups including halogens (Table 3.12, entries 1 and 9, Table 3.13, entries 5 and 7), alkenes (Table 3.12, entry 6) and heterocycles (Table 3.12, entries 3, 4, 7 and 11, Table 3.13, entry 8), as well as some secondary (Table 3.12, entries 10 and 11) and α-branched amines (Table 3.12, entries 12 and 13). Enantiopurity was completely preserved when an amine containing a chiral centre was used the reaction (Table 3.12, Entry 12). Using particularly sterically hindered amines resulted in lowered conversions into the secondary amide, as did using less nucleophilic amines. The presence of a second nucleophilic nitrogen atom in the molecule also lowered conversions, possibly due to co-ordination of this nitrogen to the catalyst (Table 3.12, entry 7). As has been found with other metal-catalysed rearrangements of oximes, ketoximes and oxime ethers were unreactive in our reaction conditions. An interesting result was observed when an amino alcohol was used in the reaction (Table 3.12, entry 13). As well as the secondary amide, oxazoline by-product **3.40** was formed in 40% conversion, presumably by intramolecular cyclisation of the hydroxyl group.

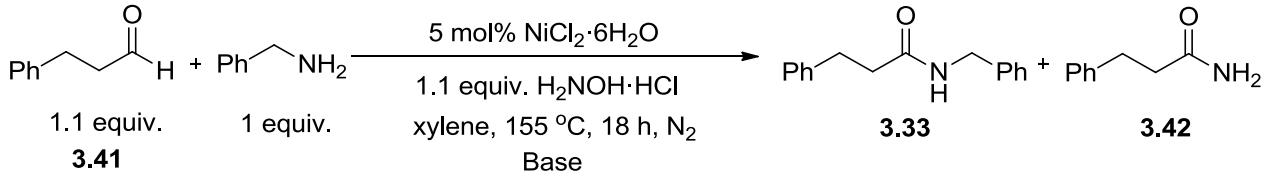


3.40

Scheme 3.4. Proposed mechanism for the formation of oxazoline side product

To make this reaction applicable to a wider range of substrates, we wanted to allow direct transformation of aldehydes into secondary and tertiary amides by generating the aldoxime *in situ*. This required the addition of hydroxylamine hydrochloride and a suitable base to the reaction mixture of an aldehyde, an amine and the nickel catalyst.

Table 3.14. Screen of bases



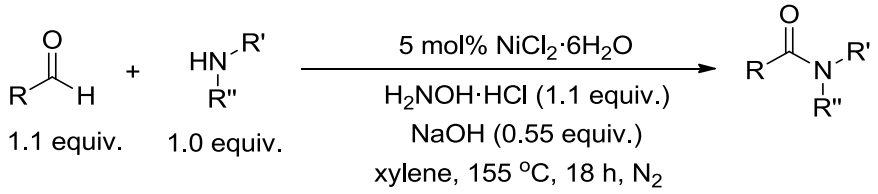
Entry	Base	Equivalents base	Conversion into 3.33 (%)	Conversion into 3.42 (%)
1	Na_2CO_3	1.1	0	99
2	KOH	1.1	0	97
3	KO^tBu	1.1	65	0
4	Cs_2CO_3	1.1	0	0
5	Et_3N	1.1	88	0
6	$Ca(OH)_2$	1.1	0	81
7	NaOH	1.1	100	0
8	NaOH	0.55	100	0

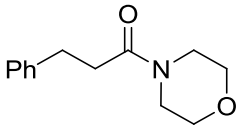
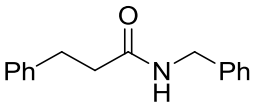
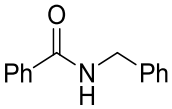
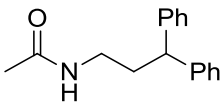
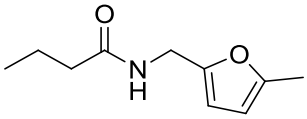
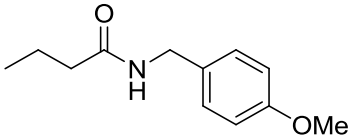
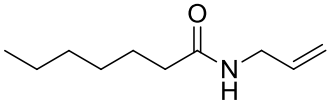
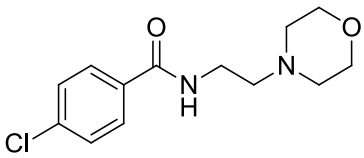
Conditions: 3-Phenylpropaldehyde (0.165 g, 1.1 mmol), benzylamine (0.11 mL, 1 mmol), $NiCl_2·6H_2O$ (5 mol%), $NH_2OH·HCl$ (0.077 g, 1.1 mmol), *p*-xylene (1.5 mL), 18 hours, atmosphere of nitrogen, base.

With some of the bases tested, the major product observed was the primary amide (Table 3.14, entries 1, 2 and 6). Another notable by-product was the imine formed from condensation between the aldehyde **3.41** and benzylamine, observed in 12% conversion when triethylamine was the base present. Sodium hydroxide clearly gave the best results (Table 3.14, entries 7 and 8), with 100% conversion into secondary amide achieved with just 0.5 equivalents.

A range of different aldehydes and amines was coupled to form the respective amides using these new reaction conditions (Table 3.15). A broad range of amides was successfully synthesised with good isolated yields using this new methodology. As with the reaction using the pre-made aldoxime, several functional groups commonly found in industrial syntheses were shown to be tolerated in the reaction conditions, irrespective of whether these groups are placed on the aldehyde or amine substrate.

Table 3.15. Use of aldehydes as substrates for amide formation

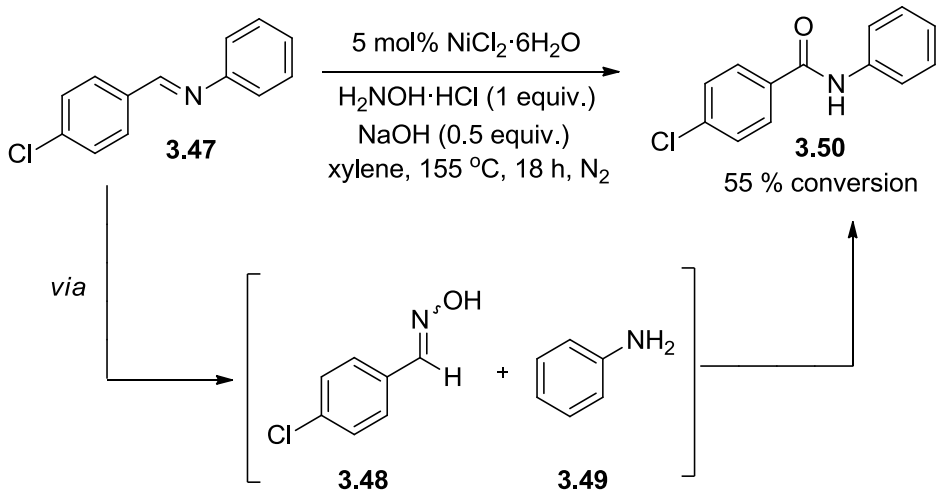


Entry	Amide product		Conversion into amide (%)	Isolated yield (%)
1		**3.43**	92	80
2		**3.33**	100	81
3		**3.34**	100	91
4		**3.44**	100	81
5		**3.22**	100	83
6		**3.20**	95	78
7		**3.45**	100	92
8		**3.46**	86	73

Conditions: Aldehyde (1.1 mmol), amine (1 mmol), $NiCl_2 \cdot 6H_2O$ (5 mol%), $NH_2OH \cdot HCl$ (0.077 g, 1.1 mmol), NaOH (0.22 g, 0.55 mmol), *p*-xylene (1.5 mL), 18 h, atmosphere of nitrogen.

The drug molecule Moclobemide (Manerix®)[124] was synthesised in 73% isolated yield from 4-chlorobenzaldehyde and (1-ethylamino)morpholine (Table 3.15, entry 8).

Unlike other amide syntheses starting from an aldehyde and amine, this reaction offers the opportunity to start from the imine. The imine **3.47** can be attacked by hydroxylamine, generating the oxime **3.48** and an amine fragment **3.49**. These two substrates can then undergo the amide forming reaction as seen previously to give secondary amide **3.50**.



Scheme 3.5. Synthesis of a secondary amide from an imine

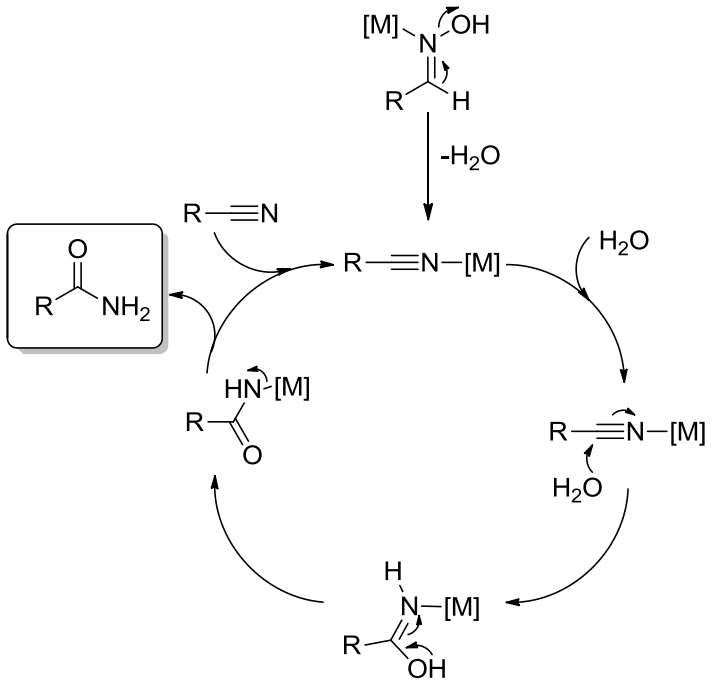
3.5 Mechanism Studies

3.5.1 Primary Amide Formation

In order to further optimise the conditions of the two reactions discussed above, it was necessary to investigate their mechanisms in more detail. The following studies were carried out in conjunction with two project students in the Williams group, Ruth Lawrence and Liam Emmett.

It has been proposed that the mechanism for the metal catalysed rearrangement proceeds *via* a discrete nitrile intermediate which is formed through dehydration of a coordinated oxime species.[80-86] This is supported by the frequent detection of a small quantity of nitrile by-product on analysis of the crude reaction mixture and an observed increase in rate of reaction when a catalytic amount of nitrile is added to the reaction. Specifically, in the rearrangement of benzaldoxime into benzamide using a supported rhodium catalyst, the reaction profile showed initial formation of benzonitrile before subsequent formation of benzamide. Additionally, the universal inertness of *O*-alkylated aldoximes and ketoximes towards rearrangement suggests that the transformation requires the presence of both an imine hydrogen and a hydroxyl group.

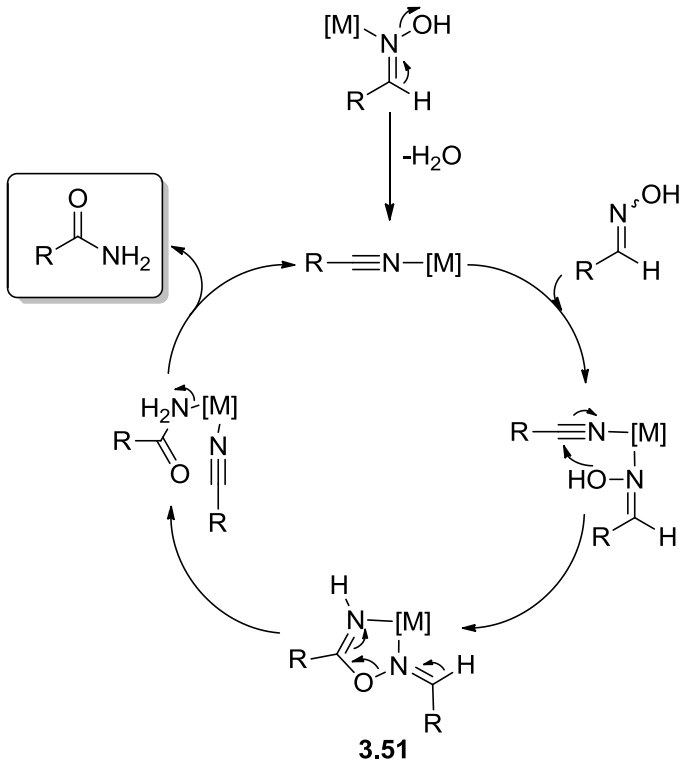
The corresponding primary amide is thought to then be generated through hydration of this nitrile intermediate. The most commonly proposed mechanism involves nucleophilic attack by water (Scheme 3.6). Both individual metal mediated steps for this dehydration/hydration process are independently reported within the literature to occur in the presence of a range of metal complexes. Whilst this dehydration/rehydration process has become the generally accepted mechanism for an oxime into amide rearrangement, inconsistencies have been reported which suggest that water may not be acting as the nucleophile in the hydration step. In completely anhydrous conditions, rearrangement into the amide was still observed. Additionally, some of the catalysts used to promote the oxime rearrangement were shown not to be active in the hydration of a nitrile with water.



Scheme 3.6. Proposed mechanism A

A second proposed mechanism involves another molecule of aldoxime acting as the nucleophile to attack the metal bound nitrile species instead of water (Scheme 3.7, see Chapter 1.2.5). This would generate 5-membered cyclic intermediate **3.51**, decomposition of which would yield the primary amide product and another metal bound nitrile to continue the catalytic cycle.

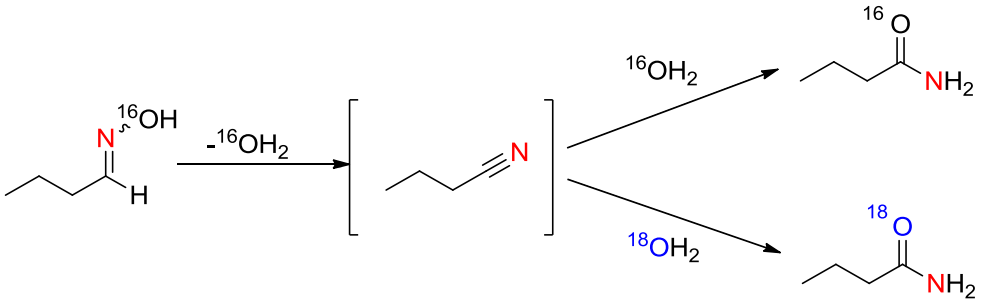
In order to understand the rearrangement reaction further, we were interested in examining these proposed mechanisms in more detail. We planned to do this not just with our own catalysts but with all catalysts that had been reported to facilitate the rearrangement with the intention of deducing if one mechanism was universal to all catalysts or if the reaction pathway was metal-dependant.



Scheme 3.7. Proposed mechanism B

Experiments using ^{18}O labelled water

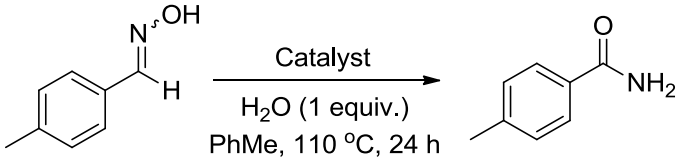
Performing the rearrangement in the presence of 1 equivalent of $^{18}OH_2$ would determine whether water was acting as a nucleophile in the hydration of the nitrile intermediate. If water did indeed attack the nitrile intermediate, there would be ^{18}O incorporation into the amide product (Scheme 3.8).



Scheme 3.8. Possible products when performing the reaction in the presence of $^{18}OH_2$

As most of the catalysts reported had been used under anhydrous conditions, it was first determined which of these catalysts were still active in the presence of water (Table 3.16). Table 3.16 entries 3, 5 and 7 show the catalysts $[IrCp^*I_2]_2$, $In(NO_3)_3$ and $ZnCl_2$ to be inhibited by the presence of water, hence they were not used in the $^{18}OH_2$ study. The other six catalysts were then used in the rearrangement of 4-methylbenzaldoxime **3.52** in the presence of one equivalent $^{18}OH_2$ (Table 3.17).

Table 3.16. Catalyst screen in the presence of water

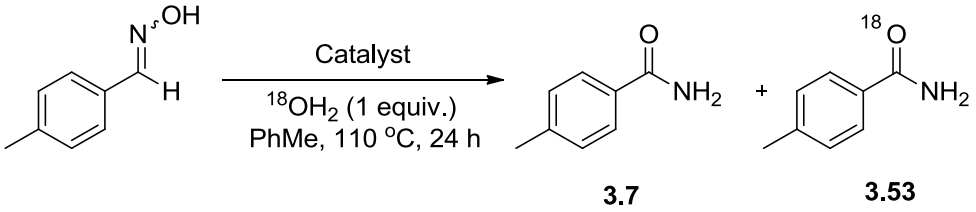


3.52 **3.7**

Entry	Catalyst	Loading (mol %)	Conversion into 3.7 (%)
1	$RhCl(PPh_3)_3$	5	100
2[a]	$Ru(PPh_3)_3(CO)H_2$	0.1	48
3	$[IrCp^*I_2]_2$	2.5	9
4[b]	$Pd(OAc)_2$	5	100
5[b]	$In(NO_3)_3$	1	18
6[b]	$In(OTf)_3$	3	100
7[b]	$ZnCl_2$	10	3
8	$NiCl_2{\cdot}6H_2O$	10	61
9[b]	$Cu(OAc)_2$	2	100

Conditions: 4-Methylbenzyaldoxime (0.14 g, 1 mmol), H_2O (0.018 g, 1 mmol), catalyst, PhMe (1 mL), 110 °C, 24 h; [a] Run with dppe (0.1 mol %) and PTSA (0.4 mol %); [b] Experiments performed by project student.

Table 3.17. Catalyst screen in the presence of ^{18}O labelled water



3.7 **3.53**

Entry	Catalyst	Loading (mol %)	Conversion into 3.7 (%)	Conversion into 3.53 (%)
1	$RhCl(PPh_3)_3$	5	100	0
2[a]	$Ru(PPh_3)_3(CO)H_2$	0.1	54	0
3[b]	$Pd(OAc)_2$	5	100	0
4[b]	$In(OTf)_3$	3	100	0
5	$NiCl_2 \cdot 6H_2O$	10	68	0
6[b]	$Cu(OAc)_2$	2	100	0

Conditions: 4-Methylbenzyaldoxime (0.14 g, 1 mmol), $H_2{}^{18}O$ (0.018 g, 1 mmol), catalyst, PhMe (1 mL), 110 ^oC, 24 hours; [a)] Run with dppe (0.1 mol %) and PTSA (0.4 mol %); [b)] Experiments performed by project student.

Analysis of the mass spectra data for the crude reaction mixtures showed the presence of a peak with *m/z* of 136.08, corresponding to the unlabelled 4-methylbenzamide **3.7** (conversion into amide was confirmed by ^1H NMR spectroscopy). However, a peak with an *m/z* of 138.08 was not observed for any of the catalytic systems (Figure 3.1), indicating that incorporation of ^{18}O into the amide product had not occurred, supporting an alternative hydration pathway where water is not acting as the nucleophile.

Experiments using ^{18}O labelled aldoximes

In order to ascertain whether the aldoxime is acting as a nucleophile to attack the coordinated nitrile species, a second ^{18}O labelling study was carried out using ^{18}O labelled 3-phenylpropanaldoxime.

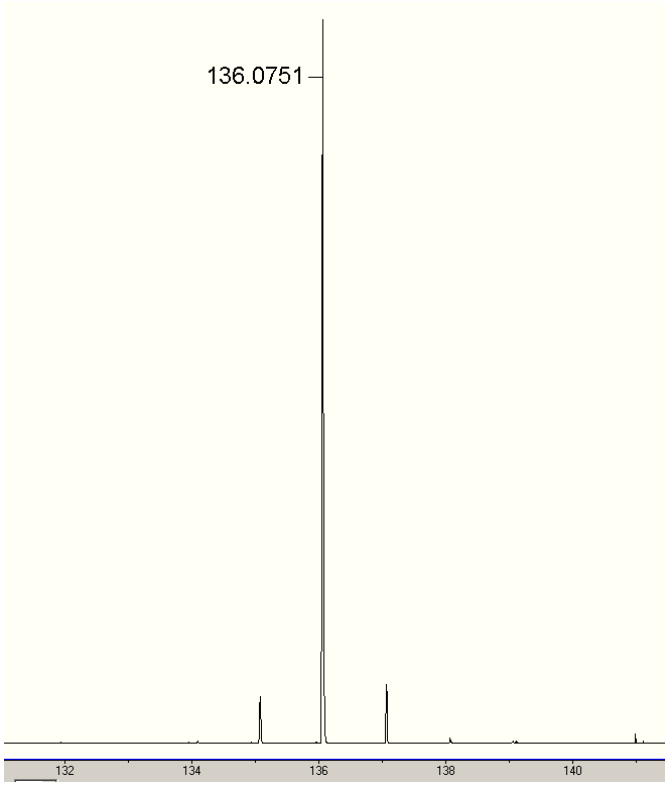
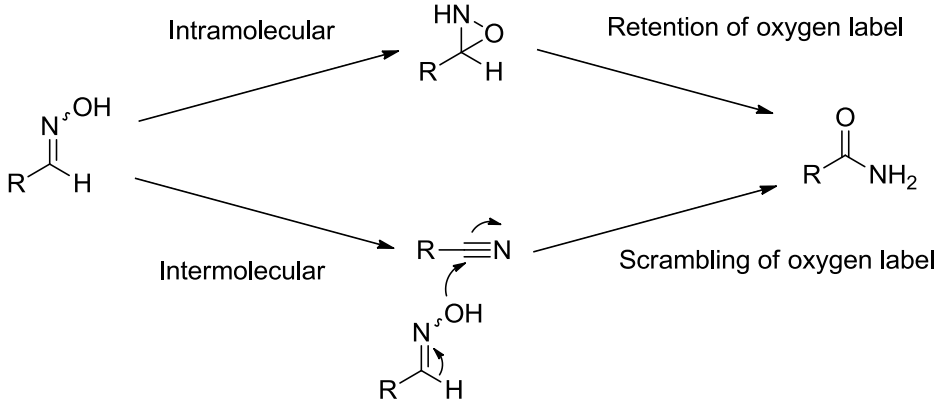


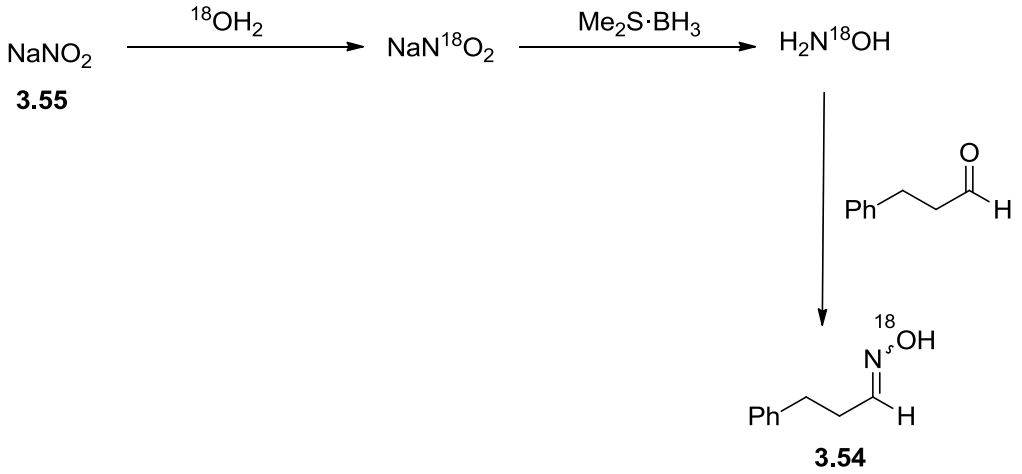
Figure 3.1. Mass spectrum for the amide product from rearrangement of 4-methylbenzaldoxime, showing no ^{18}O incorporation (peak at *m/z* of 136.08 corresponds to the unlabelled 4-methylbenzamide).



Scheme 3.9. Crossover reaction between labelled and unlabelled aldoximes

Scrambling of the ^{18}O label between the two primary amide products would be expected for a mechanism involving attack of the coordinated nitrile by an oxime. Following this mechanism (Scheme 3.9), there is the potential for nucleophilic attack of a nitrile derived from unlabelled butyraldoxime by ^{18}O labelled 3-phenylpropanaldoxime to afford ^{18}O labelled butyramide and *vice versa* to afford ^{16}O 3-phenylpropanamide. If an alternative, intramolecular mechanism were operating, no crossover of the ^{18}O label should be observed in the primary amide products.

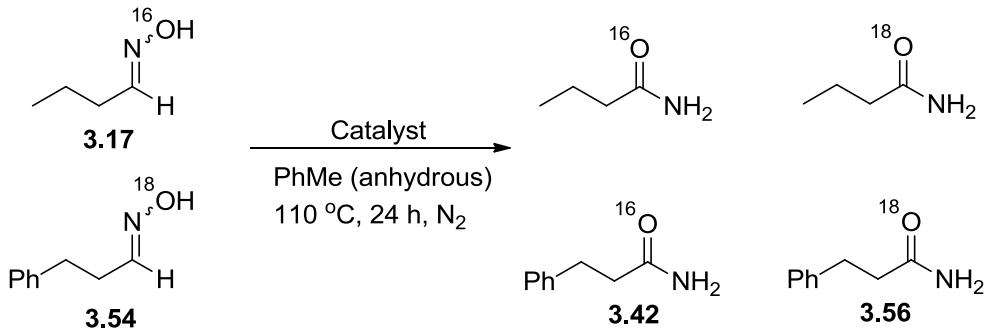
Two batches of ^{18}O labelled 3-phenylpropanaldoxime **3.54** were synthesised from sodium nitrite **3.55** following a literature procedure,[125] with comparable levels of ^{18}O incorporation achieved within both: 67 and 63 atom% (Scheme 3.10). The level of ^{18}O incorporation was determined by comparison of the intensity of the parent ions for ^{16}O and ^{18}O aldoxime in the mass spectra.



Scheme 3.10. Synthesis of ^{18}O-labelled aldoxime

The rearrangement of the synthesised ^{18}O labelled 3-phenylpropanaldoxime **3.54** was performed in the presence of an equimolar quantity of unlabelled butyraldoxime **3.17**. In all cases, conversion into amide was determined by ^{1}H and ^{13}C NMR spectroscopy. In the absence of any catalyst, no conversion into amide was seen and the level of ^{18}O label incorporation in 3-phenylpropanaldoxime remained the same.

Table 3.18. Change in levels of ^{18}O incorporation upon rearrangement of ^{18}O labelled 3-phenylpropanaldoxime



Entry	Catalyst	Loading (mol%)	Oxime 3.54 atom% ^{18}O	Amide 3.56 atom% ^{18}O
1	$RhCl(PPh_3)_3$	5	63	37
2[a]	$Ru(PPh_3)_3(CO)H_2$	1	63	22
3[b]	$Pd(OAc)_2$	5	67	39
4[b]	$In(NO_3)_3$	1	63	30
5[b]	$ZnCl_2$	10	63	28
6[b]	$Cu(OAc)_2$	2	67	33
7	$NiCl_2{\cdot}6H_2O$	10	64	36

Conditions: Butyraldoxime (0.009 g, 0.1 mmol), O^{18} 3-phenylpropanaldoxime (0.015 g, 0.1 mmol), catalyst, PhMe (0.2 mL), atmosphere of nitrogen, 110 °C, 24 hours; [a)] Run with dppe (0.1 mol%) and PTSA (0.4 mol%); [b)] Experiments performed by project student.

As shown in Table 3.18, significantly lower ^{18}O label incorporation was observed for 3-phenylpropanamide relative to the starting oxime, indicating scrambling of this label had occurred (Figure 3.2). Although butyramide did not ionise under the mass spectrometry conditions, it was possible to determine by ^{13}C NMR spectroscopy that partial incorporation of the ^{18}O label into this amide had occurred. Analysis of the peak attributed to the carbonyl carbon showed two peaks due to the presence of both isotopic forms.

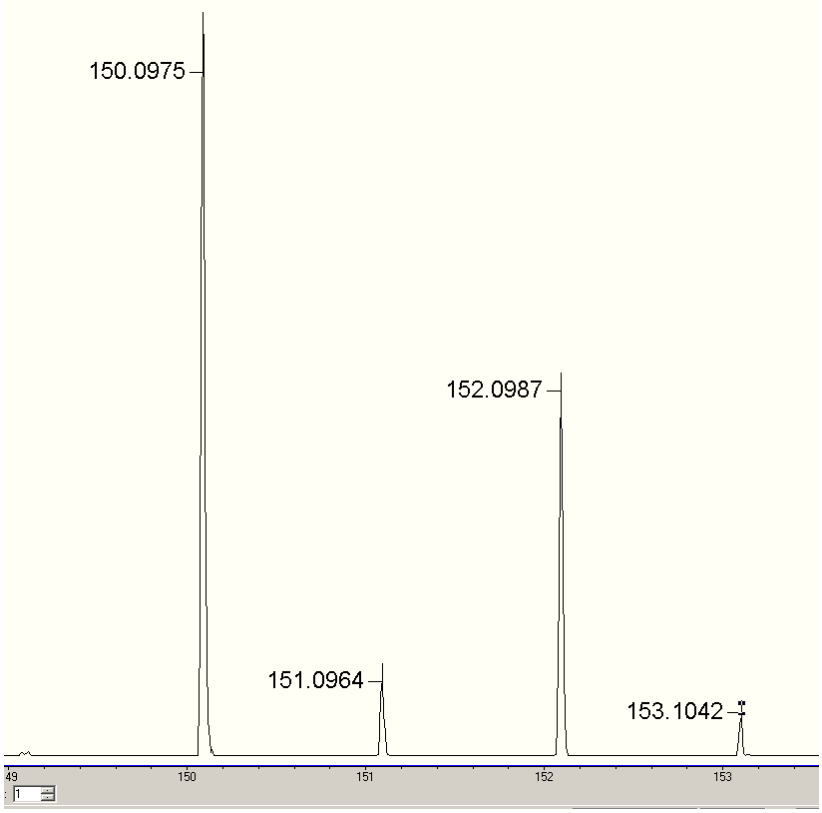
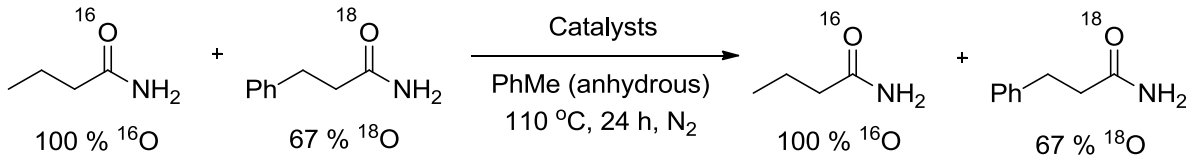


Figure 3.2. Mass spectrum demonstrating the ratio of ^{16}O to ^{18}O within 3-phenylpropanamide

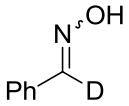
The two amide products were also subjected to the same reaction conditions to ensure that scrambling of the label was not occurring after the rearrangement, however no transfer of the label was observed in the presence of any of the catalysts (Scheme 3.11).



Scheme 3.11. Crossover reaction between ^{18}O labelled and unlabelled primary amides

These results support proposed mechanism B, attack of another molecule of aldoxime on the coordinated nitrile species. The results also show that this bimolecular mechanism is universal to all the catalysts studied. Evidence of a bimolecular mechanism operating in the nickel catalysed rearrangement of aldoximes into primary

amides has been reported by Johnson and Miller[126] who found that the reaction can be described by two consecutive pseudo-first order rate constants. They report the first step to be cleavage of the C-H bond, which is seen to be dependent on the concentration of nickel catalyst. This step is also assumed to be the rate limiting step, as evidenced by the strong kinetic isotope effect seen when deuterated oxime **3.56** is used as a substrate (Figure 3.3). The second step they propose to be the bimolecular process of attack of a solvent molecule on the coordinated oxime, yielding an imidate, which can then undergo thermal rearrangement to the amide.



3.56

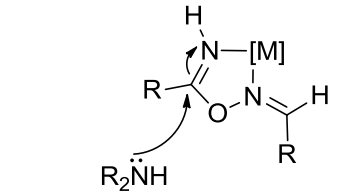
Figure 3.3. Deuterated aldoxime used in kinetic isotope studies

Chang *et al.* have reported their investigation into the mechanism of rearrangement of an aldoxime into a primary amide using a rhodium catalyst. They also suggest a bimolecular process, whereby a coordinated nitrile is attacked by the hydroxy group of a molecule of oxime, which itself is associated with the metal centre through the nitrogen atom (Scheme 1.35). Their mechanism is supported by the significant rate increase seen when a catalytic amount of nitrile is added to the reaction.[86]

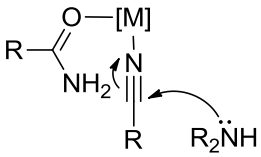
Although we have seen evidence to support our proposed mechanism, other possible pathways cannot be completely excluded at this stage. In the course of their work on novel ligand syntheses, Kukushkin *et al.* have shown when platinum-nitrile complexes are treated with nitrile oxides,[127] addition of the nitrogen-oxygen bond across the carbon nitrogen triple bond proceeds with the nitrile remaining coordinated to the metal and the nitrile oxide remaining uncoordinated. It should be noted however that the platinum - nitrile complexes were preformed before addition of the nitrile oxide. Nonetheless, this observation indicates the possibility of another reaction pathway in which a coordinated nitrile is attacked by a free oxime in the reaction.

3.5.2 Secondary Amide Formation

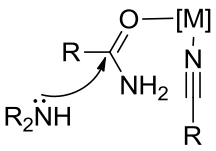
We then turned our attention to probing the mechanism of the nickel catalysed acylation of amines using aldoximes. Several possible mechanisms where the amine attacks at a different stage of the catalytic cycle are plausible (Scheme 3.12).



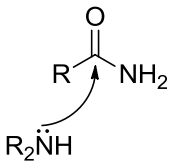
1. Attack of the cyclic intermediate



2. Attack of a coordinated nitrile



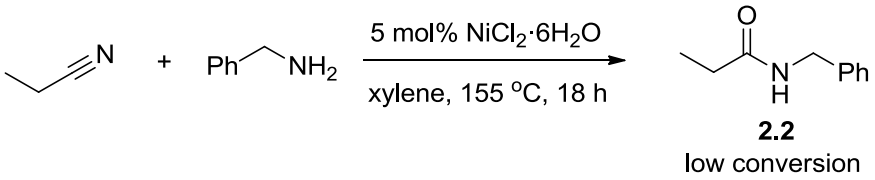
3. Attack of a coordinated primary amide



4. Attack of a free primary amide

Scheme 3.12. Proposed mechanisms of secondary amide formation in the nickel catalysed acylation of amines with aldoximes

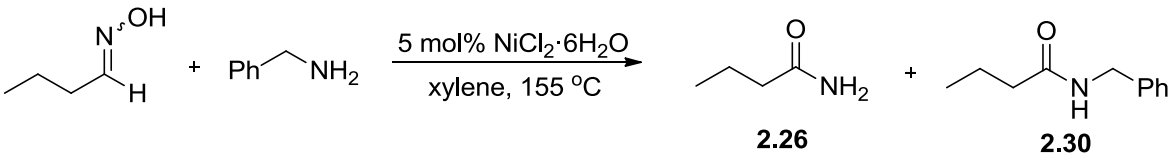
The coupling of nitriles and amines is known to be promoted by some metal complexes. Taking propionitrile and benzylamine under the standard reaction conditions revealed a very low conversion into the secondary amide product **2.2**, confirming that this cannot be a major reaction pathway (Scheme 3.13).



Scheme 3.13. Reaction of propionitrile and benzylamine

The reaction of benzylamine with butyraldoxime in the presence of 5 mol% $NiCl_2 \cdot 6H_2O$ was then followed over time to see if any significant reaction intermediates could be observed (Table 3.19). The results clearly show a build-up of the primary amide (rearrangement product of butyraldoxime) before the secondary amide is seen in the reaction mixture. Based on this observation it is apparent that the aldoxime is completely undergoing the rearrangement into the primary amide and it is this species that is coupling to the amine. Whether it is the free primary amide or the metal-bound primary amide that is attacked was unclear at this stage.

Table 3.19. Reaction of benzylamine and butyraldoxime followed over time[a]



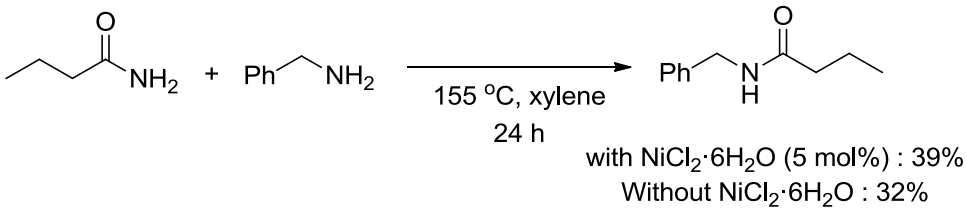
2.26 **2.30**

Entry	Reaction time (h)	Conversion into 1° amide 2.26 (%)	Conversion into 2° amide 2.30 (%)
1	2	35	18
2	3	50	50
3	4	48	52
4	6	26	74
5	16	2	98
6	24	4	96

Conditions: Butyraldoxime (0.087 g, 1 mmol), benzylamine (0.11 mL, 1 mmol), $NiCl_2 \cdot 6H_20$ (5 mol%), *p*-xylene (1 mL), 155 °C; [a)] Experiments performed by project student.

The reaction of butyramide with benzylamine was run with and without the $NiCl_2$ catalyst present to see if the metal was involved in the primary amide and amine coupling. In both reactions, a similar conversion into the secondary amide was seen;

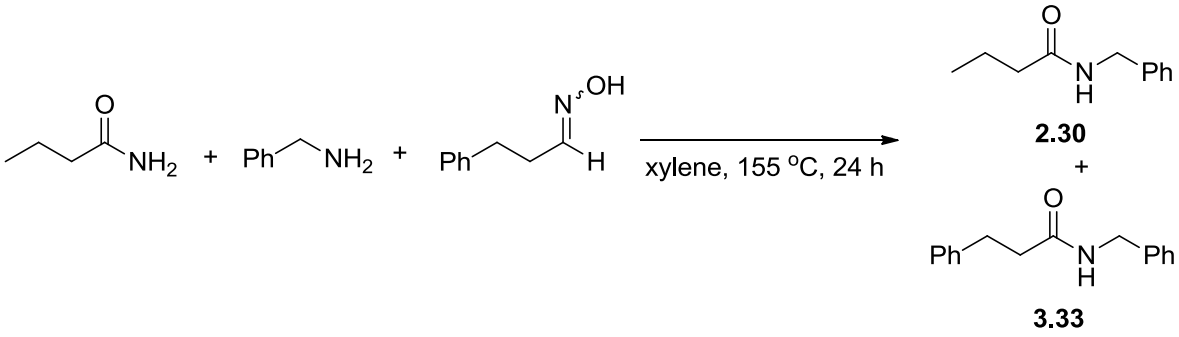
39% with the nickel catalyst and 32% without (Scheme 3.14). This suggests not only that the nickel is not involved in this step of the mechanism but also that direct attack of the amine on the unactivated, free primary amide is not the major reaction pathway in operation.



Scheme 3.14. Reaction of butyramide and benzylamine

The same reaction between butyramide and benzylamine was run in the presence of an equivalent of 3-phenylpropionaldoxime to see if the coupling of the primary amide and amine involved the oxime in any way (Table 3.20).

Table 3.20. Competition reaction between butyramide and 3-phenylpropaldoxime



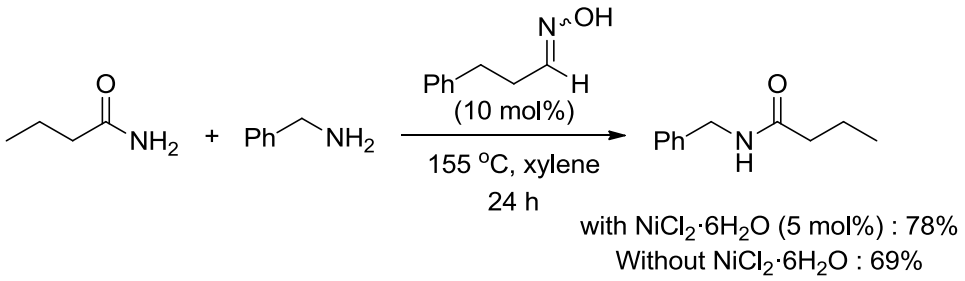
Entry	Catalyst (5 mol%)	Conversion into amide 2.30 (%)	Conversion into amide 3.33 (%)
1	$NiCl_2·6H_2O$	56	44
2	-	78	22

Conditions: Butyramide (0.087 g, 1 mmol), benzylamine (0.11 mL, 1 mmol), 3-phenylpropanaldoxime (0.150 g, 1 mmol), *p*-xylene (1 mL), 155 °C, 24 h.

These reactions showed that the aldoxime itself is involved in the coupling of the primary amide and amine. 100% conversion of the amine was observed in each case, indicating again that the nickel catalyst is not involved in this step. In the reaction run

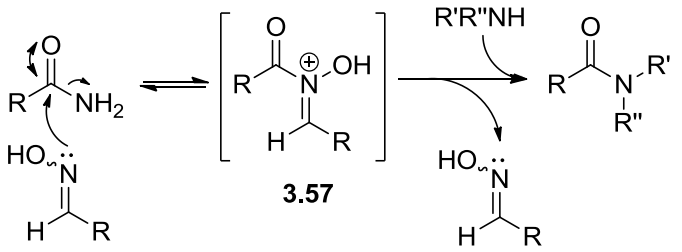
with the catalyst, increased conversion into amide **3.33** was seen due to the rearrangement of the aldoxime into the corresponding primary amide also occurring in the reaction.

When the same reaction was run with a catalytic amount of 3-phenylpropaldoxime, a significant increase in conversion into the secondary amide was observed (Scheme 3.21).

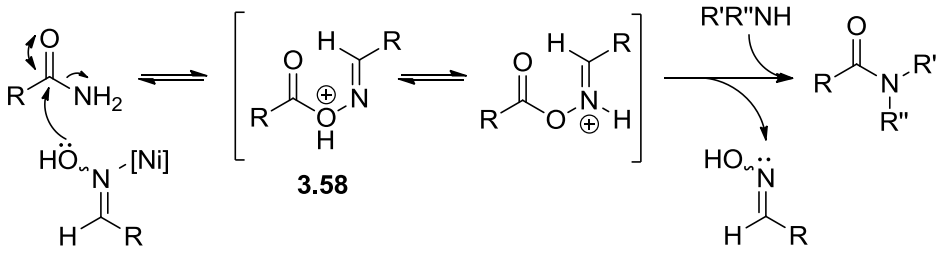


Scheme 3.21. Coupling of butyramide and benzylamine catalysed by 3-phenylpropaldoxime.

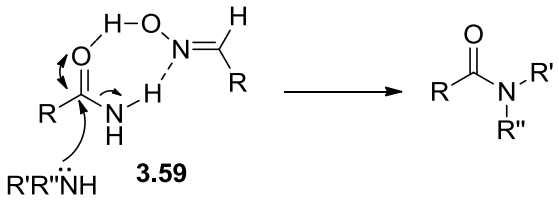
These results clearly indicate that the oxime is in some way acting catalytically in the reaction between the primary amide and the amine. An increased rate of reaction is seen when the aldoxime species is used in slight excess (compared with the amine), a result which can be justified by the oxime acting catalytically to couple the primary amide and amine, either by forming a charged intermediate (**3.57** and **3.58**, Scheme 3.22), which is then attacked by the amine, or by activation of the primary amide through hydrogen bonding (**3.59**, Scheme 3.22). It is possible that the primary amide or the aldoxime are coordinated to the nickel catalyst during this second step of the mechanism.



1. Attack of aldoxime nitrogen forms charged intermediate **3.57**



2. Attack of aldoxime oxygen forms charged intermediate **3.58**



3. Hydrogen bonding activates the primary amide

Scheme 3.22. Proposed pathways of aldoxime catalysed primary amide and amine coupling

The mechanism of the nickel catalysed acylation of amines with aldoximes proceeds *via* the primary amide (formed by the rearrangement of the aldoxime). The subsequent coupling of the primary amide and amine has been shown to be catalysed by the aldoxime itself.

3.6 Conclusions

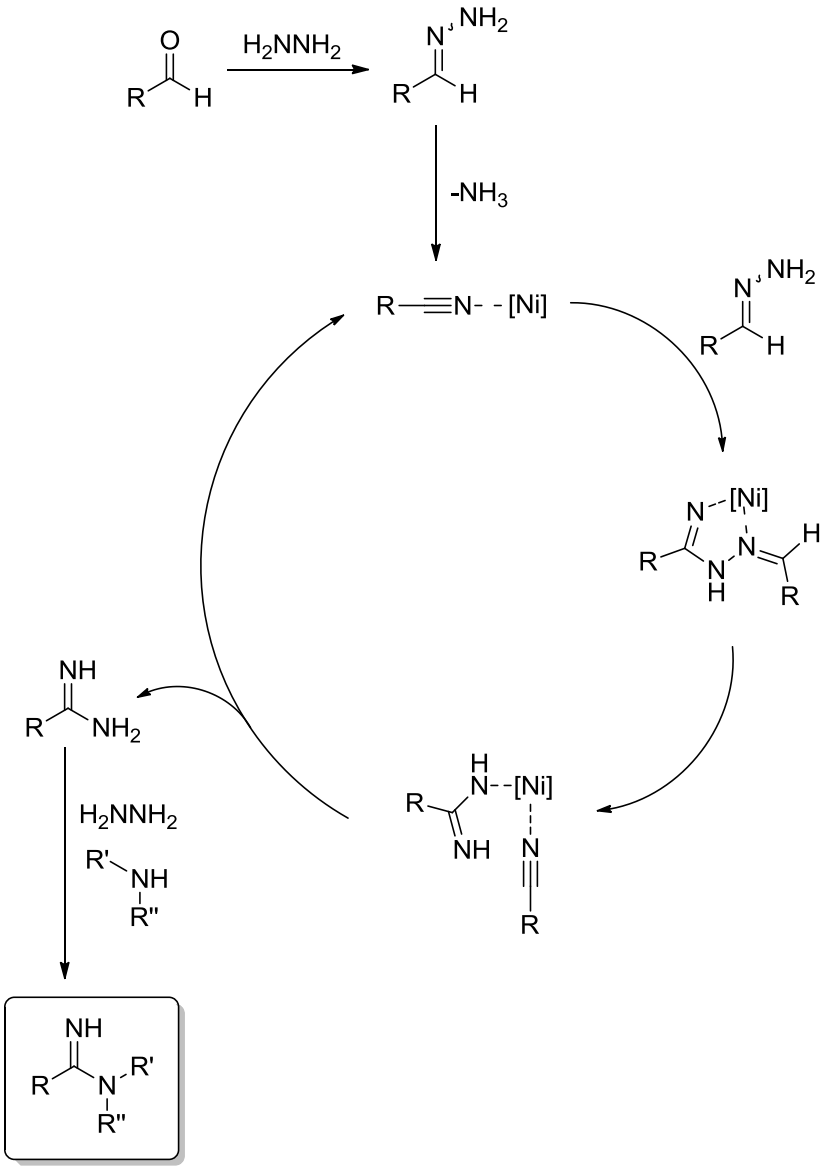
The rearrangement of aldoximes into primary amides has been shown to be catalysed by cheap, simple metal salts indium nitrate, zinc chloride and zinc nitrate. When the rearrangement is run in the presence of an amine, the reaction products are secondary or tertiary amides. Both of these reactions can be run from the aldehyde if hydroxylamine hydrochloride (and a suitable base) is added.

The mechanisms of both the rearrangement and the coupling to make secondary and tertiary amides have been investigated, mainly by using ^{18}O labelled substrates. The rearrangement was found to proceed *via* a nitrile intermediate (formed by dehydration of the aldoxime) and subsequent attack of this intermediate by a second molecule of aldoxime. This differs from the generally proposed mechanism in that the intermediate nitrile is not hydrated by a molecule of water to form the primary amide product.

The formation of secondary and tertiary amides was found to proceed *via* the primary amide and a subsequent transamidation reaction with the amine present. This transamidation is catalysed by the aldoxime itself. This insight into the mechanism suggests that the rate of reaction may be able to be increased significantly with further optimisation of the catalytic system used. In this study, nickel was found to be the ideal metal catalyst as it performed the rearrangement of the aldoxime sufficiently slowly that there was always enough present in the reaction to catalyse the transamidation step. This is why some metal catalysts tested showed high levels of primary amide formation and the selectivity could not be improved. If a different transamidation catalyst (i.e. one that would not be affected by the metal catalyst like an aldoxime) could be combined with a highly efficient rearrangement catalyst, this would make both steps of the mechanism faster and thus improve the overall rate.

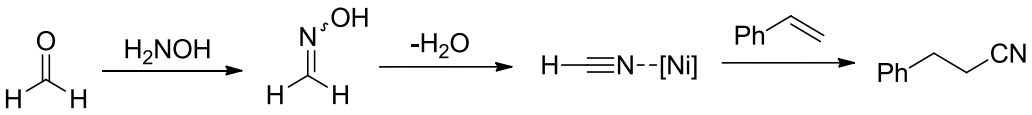
3.7 Future Work

Understanding the mechanism of this reaction has led to the possibility of further novel reactions being developed. Firstly, replacing hydroxylamine hydrochloride with a hydrazine salt in the reaction could potentially lead to a synthesis of amidines (Scheme 3.23).



Scheme 3.23. Amidine formation from aldehydes

Secondly, if the aldoxime used is that derived from formaldehyde, the nitrile produced upon dehydration will be hydrogen cyanide. This reaction could therefore be used as a potential method of *in situ* HCN generation in hydrocyanation reactions (Scheme 3.24).



Scheme 3.24. Hydrogen cyanide generation *in situ*

Results and Discussion III

Catalytic Transamidation

"Catalytic Transamidation of Primary Amides with Amines Using Hydroxylamine Hydrochloride as an Inorganic Catalyst"

C. L. Allen*, Benjamin N. Atkinson, J. M. J. Williams, *Angew. Chem., Int. Ed.,* **2012**, *51,* 1383.

4. Results and Discussion III – Catalytic Transamidation

4.1 Introduction

Transamidation is a synthetically useful reaction normally hindered by the very high stability of carboxamide groups. There are reports of thermal transamidation reactions, typically requiring very high temperatures (>180 ^{o}C), thus having a very limited substrate range. Several metal complexes have been reported to promote transamidation reactions in the last two decades, including $AlCl_3$, $Sc(OTf)_3$, $Ti(NMe_2)_4$ and polymer-bound $HfCl_4$. Borate esters have also been reported to be effective reagents for transamidation reactions between primary amides and amines, however two equivalents of the boron reagent are required for the reaction.[128] Stahl *et al.* have found some metal complexes will facilitate the equilibration between a secondary amide and an amine when the reaction is thermoneutral.[99]

4.2 Initial Work

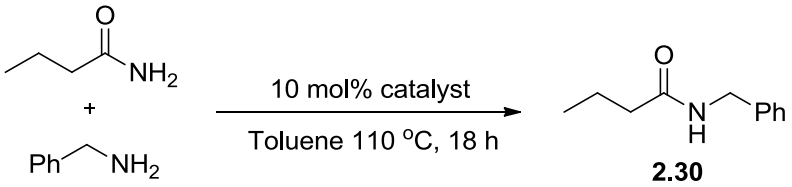
During studies of the mechanism of the aldoxime and amine coupling, we discovered that the reaction proceeds *via* a build-up of primary amide (the rearrangement product of the aldoxime) before the secondary amide starts to be formed. We therefore reasoned that either the nickel catalyst or the aldoxime itself must be catalysing the reaction between the primary amide and the amine.

Heating butyramide with benzylamine showed a 32% conversion into secondary amide, which only increased to 39% when 5 mol% $NiCl_2{\cdot}H_2O$ was included in the reaction. Using a catalytic amount of aldoxime in the absence of nickel catalyst showed a 69% conversion into secondary amide, with only a marginal increase in conversion seen when the nickel catalyst was added. From this evidence, it was concluded that this reaction was being catalysed by the aldoxime itself, which suggested that this transamidation could be optimised as a separate reaction.

4.3 Optimisation

Initially, we screened several catalysts (that we reasoned may act in the same catalytic manner as the aldoxime) at a reduced temperature of 110 ^{o}C to find the most effective transamidation catalyst (Table 4.1).

Table 4.1. Screen of catalysts

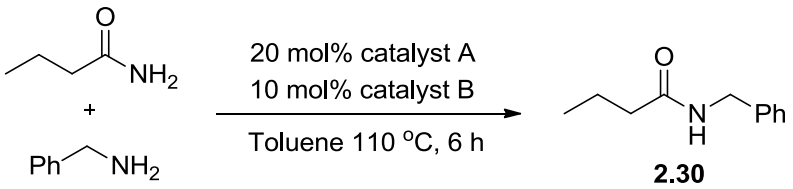


2.30

Entry	Catalyst	Conversion into 2.30 (%)
1	*n*-Butyraldoxime	36
2	Benzaldoxime	30
3	4-Diethylaminobenzaldoxime	25
4	4-Fluorobenzaldoxime	25
5	Hydroxylamine sulfate	100
6	Hydroxylamine hydrochloride	100
7	*N*-Methylhydroxylamine hydrochloride	96
8	*O*-Methylhydroxylamine hydrochloride	91
9	*N,N*-Diethylhydroxylamine hydrochloride	71
10	*O*-Benzylhydroxylamine	13
11	*O*-Benzylhydroxylamine hydrochloride	73
12	Hydrazine monohydrate	23
13	*N,N'*-Diphenylthiourea	13
14	Hydrochloric acid	51
15	No catalyst	10

Conditions: Butyramide (0.087 g, 1 mmol), benzylamine (0.11 mL, 1 mmol), catalyst (10 mol%), PhMe (1 mL), 110 ^{o}C, 18 h.

Table 4.2. Addition of metal salts



2.30

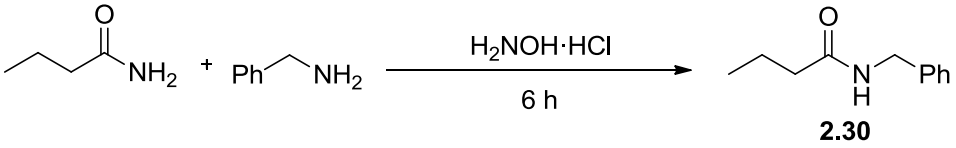
Entry	Catalyst A	Catalyst B	Conversion into 2.30 (%)
1	$H_2NOH{\cdot}HCl$	-	53
2	Me(H)NOH·HCl	-	36
3	$H_2NOMe{\cdot}HCl$	-	37
4	$H_2NOH{\cdot}HCl$	$NiCl_2{\cdot}6H_2O$	15
5	Me(H)NOH·HCl	„	22
6	$H_2NOMe{\cdot}HCl$	„	18
7	$H_2NOH{\cdot}HCl$	$In(NO_3)_3$	45
8	Me(H)NOH·HCl	„	49
9	$H_2NOMe{\cdot}HCl$	„	35
10	$H_2NOH{\cdot}HCl$	$Zn(NO_3)_2$	22
11	Me(H)NOH·HCl	„	27
12	$H_2NOMe{\cdot}HCl$	„	28
13	$H_2NOH{\cdot}HCl$	$Cu(OAc)_2$	34
14	Me(H)NOH·HCl	„	48
15	$H_2NOMe{\cdot}HCl$	„	47

Conditions: Butyramide (0.087 g, 1 mmol), benzylamine (0.11 mL, 1 mmol), catalyst A (20 mol%), catalyst B (10 mol%), PhMe (1 mL), 110 ^{o}C, 6 h.

From the catalyst screens shown above it was clear that hydroxylamine salts were the most efficient species for catalyzing the transamidation reaction, with hydroxylamine hydrochloride giving 100% conversion into the secondary amide after 18 hours at 110 ^{o}C. This result demonstrates a remarkable increase in reaction rate when compared to butyraldoxime under the same reaction conditions, which gave only 36% conversion. In the absence of catalyst, only 10% conversion was observed. Addition of any metal salts did not improve the conversion over using just hydroxylamine hydrochloride (Table 4.2).

Using hydroxylamine hydrochloride as the catalyst, the reaction conditions were varied to elucidate the mildest conditions the transamidation could occur under (whilst the amount of hydroxylamine remained catalytic).

Table 4.3. Variation of reaction conditions

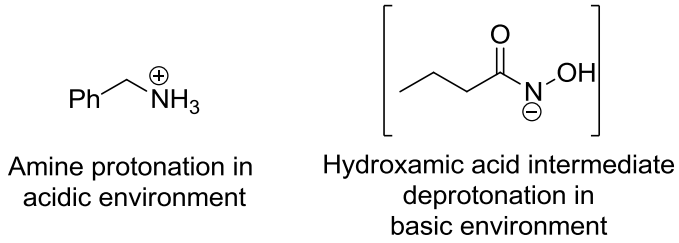


2.30

Entry	$H_2NOH.HCl$ (mol%)	Solvent	Temperature	Conversion into 2.30 (%)
1	20	PhMe	110	48
2	50	PhMe	110	68
3	100	PhMe	110	100
4	20	H_2O	100	0
5	20	MeCN	100	21
6	20	IPA	100	0
7	20	Hexane	100	28
8	20	EtOAc	100	16
9	20	PhMe	100	39
10	10	PhMe	100	31
11	5	PhMe	100	12
12[a]	10	PhMe	105	100

Conditions: Butyramide (0.087g, 1 mmol), benzylamine (0.11 mL, 1 mmol), $H_2NOH{\cdot}HCl$; [a)] Run for 16 h.

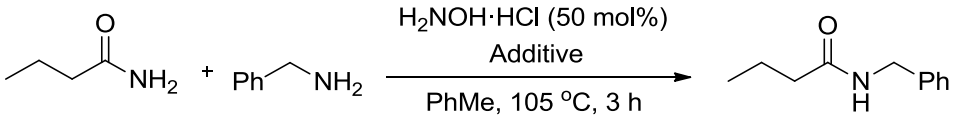
The pH of the reaction mixture may have an effect on the rate at which secondary amide is formed. If the solution is too acidic, some of the amine may be protonated, which could explain why only a 20% increase in conversion was seen when the amount of hydroxylamine catalyst was increased by 150% (Table 4.3, entries 1 and 2). However, making the solution too basic may lead to deprotonation of the proposed hydroxamic acid intermediate (Scheme 4.1).



Scheme 4.1. Possible protonation or deprotonation of reactants

The use of hydroxylamine free base in water or ethanol gave no reaction, but these two solvents have both been shown to stop the reaction even when hydroxylamine hydrochloride is used (Table 4.3, entries 4 and 8). Unfortunately, hydroxylamine could not be extracted into any other solvents as the free base, so a screen of acids and bases added to the reaction was run to see if the conversion into amide could be increased (Table 4.4).

Table 4.4. Addition of acid or base

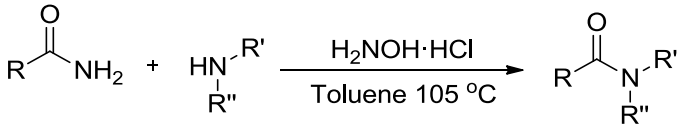


Entry	Additive	Additive (mol%)	Conversion into 1 (%)
1	-	-	43
2	Et_3N	50	43
3	Et_3N	100	37
4	KOH	50	47
5	KOH	100	37
6	HCl (36%)	50	28
7	HCl (36%)	100	30
8	DBU	50	0

Conditions: Butyramide (0.087g, 1 mmol), benzylamine (0.11 mL, 1 mmol), $H_2NOH{\cdot}HCl$ (0.035 g, 0.5 mmol, 50 mol%), PhMe (1 mL), 105 ^oC, 3 h.

For the substrates used in this optimization study, the optimal conditions were found to be using toluene as a solvent at 105 ^{o}C with 10 mol% of $H_2NOH{\cdot}HCl$, with 100% conversion being achieved after 16 hours. Inclusion of additional acid or base was not found to increase the conversion. We next undertook a screen of various primary amide and amine substrates to assess the range of this reaction (Table 4.5). When the primary amide was changed to a less reactive substrate, the conversion (under the same conditions used for the coupling of butyramide and benzylamine) was found to be considerably lower. Thus the amount of hydroxylamine hydrochloride was increased (and in some cases the length of reaction was also increased) for some substrates.

Table 4.5. Range of primary amides and amines



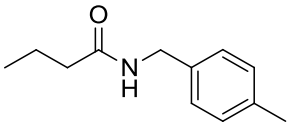
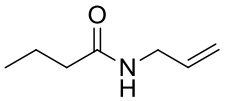
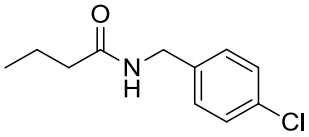
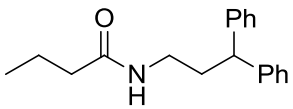
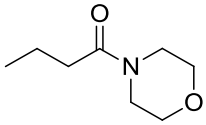
Entry	Product		$H_2NOH{\cdot}HCl$ (mol%)	Time (h)	Conversion (%)	Yield (%)
1		**4.1**	10	16	100	81
2		**3.24**	10	16	100	86
3		**3.19**	10	20	100	91
4		**4.2**	20	20	100	83
5		**3.29**	20	20	95	90

Table cont.

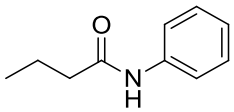
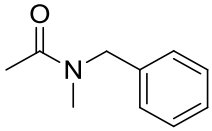
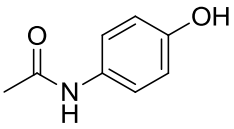
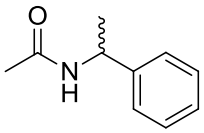
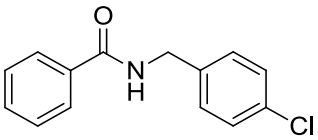
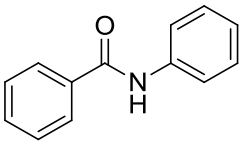
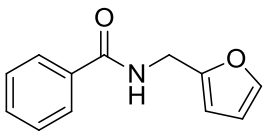
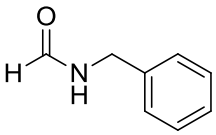
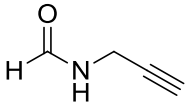
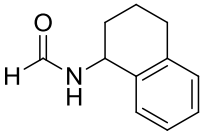
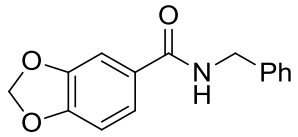
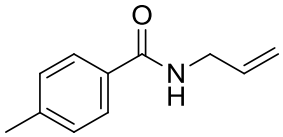
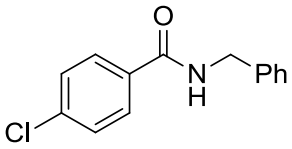
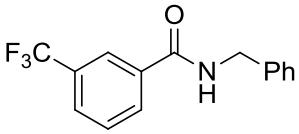
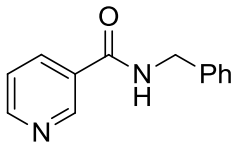
6		**3.26**	50	20	63	-
7		**4.3**	50	24	62	-
8		**4.4**	50	24	83	76
9		**4.5**	50	24	90	81
10		**4.6**	50	24	88	71
11		**4.7**	50	24	70	59
12		**4.8**	50	24	63	-
13		**4.9**	10	16	100	86
14		**4.10**	10	20	98	87
15		**4.11**	10	20	100	82

Table cont.

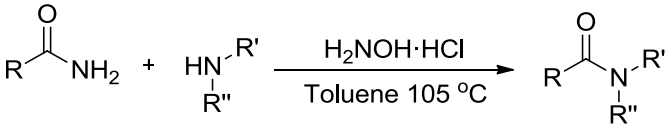
16		**3.38**	50	24	86	74
17		**4.12**	50	22	68	-
18		**4.13**	50	24	79	70
19		**4.14**	50	24	52	-
20		**4.15**	50	24	47	-

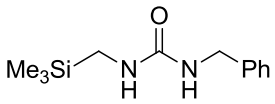
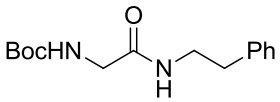
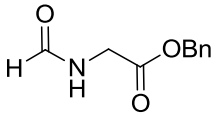
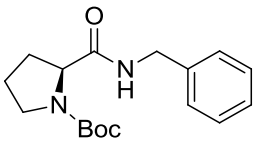
Conditions: Primary amide (1 mmol), amine (1 mmol), $H_2NOH{\cdot}HCl$, PhMe (1 mL), 105 ^{o}C.

A wide range of functional groups was shown to be tolerated by the reaction conditions, including halogens (Table 4.5, entries 3 and 10), free phenolic hydroxy groups (Table 4.5, entry 8), heterocycles (Table 4.5, entries 5, 12 and 20), alkenes (Table 4.5, entries 2 and 17) and alkynes (Table 4.5, entry 14). Aliphatic amides generally gave the highest conversions, with some substrates requiring only 10 mol% hydroxylamine hydrochloride to reach complete conversion in 16 hours (Table 4.5, entries 1 and 2). Formamide can be used as a formylating agent in this reaction, giving *N*-formyl products, (Table 4.5, entries 13-15).

A smaller range of more challenging substrates was run to see if protected amino amides could be amidated in this way, the results of which are shown in Table 4.6.

Table 4.6. Range of primary amide equivalents or protected amino acids and amines



Entry	Product		Mol % $H_2NOH.HCl$	Time (h)	Conversion (%)	Yield (%)
1		**4.16**	50	22	69	-[a]
2		**4.17**	50	22	79	71
3		**4.18**	10	22	100	91
4		**4.19**	20	24	64	56

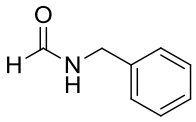
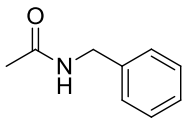
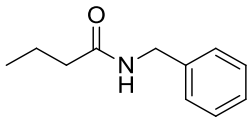
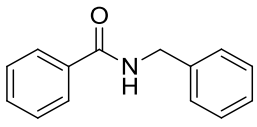
Conditions: Primary amide (1 mmol), amine (1 mmol), $H_2NOH·HCl$, PhMe (1 mL), 105 ^oC; [a]Attempts to isolate the product resulted in loss of $SiMe_3$ group.

Notable observations from this additional substrate screening are that Boc protecting groups are unaffected in the reaction (Table 4.6, entries 2 and 4), allowing for selective acylation of one nitrogen atom in a mono-protected diamine, or selective coupling of a Boc-protected amino amide to an amine. Ester protected amino acids can also be *N*-acylated without any loss of the ester functionality (Table 4.6, entry 3). Mono-substituted ureas can be selectively acylated, yielding unsymmetrical ureas (Table 4.6, entry 1).

An enantiomerically pure substrate, *N*-boc-L-prolinamide was run and only slight racemisation was detected by HPLC in the *N*-acylated product which was determined to have 88% ee (Table 4.6, entry 4).

In the interest of atom efficiency, we have run these reactions at a temperature of 105 ^{o}C, allowing for the use of a *catalytic* amount of hydroxylamine hydrochloride to activate the primary amide group. However, several aliphatic amide substrates gave good conversions into secondary amide at lower temperatures when an increased amount of hydroxylamine hydrochloride was used (Table 4.7). The benzoic primary amide, however, was very slow to react at 80 ^{o}C, even with 1 equivalent of hydroxylamine hydrochloride present (Table 4.7, entry 8).

Table 4.7. Examples of primary amides and amines used in the transamidation reaction at lower temperatures.

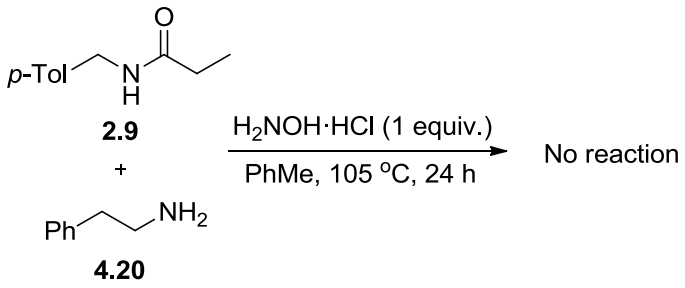
Entry	Product		Temp. (^{o}C)	Mol% $H_2NOH{\cdot}HCl$	Conversion (%)[a]
1		**4.9**	50	10	94
2			20	30	100
3			20	0	<1%
4		**2.31**	80	50	100
5			50	100	78
6		**2.30**	80	50	80
7			50	100	64
8		**3.34**	80	100	25

Conditions: Primary amide (1 mmol), benzylamine (0.11 mL, 1 mmol), $H_2NOH{\cdot}HCl$, PhMe (1 mL), 16 h.

Most notable in Table 4.7 are the examples using formamide. At room temperature (20 ^{o}C), the uncatalysed reaction gave < 1% conversion. Addition of just 30 mol% hydroxylamine hydrochloride increased this to 100% (Table 4.7, entries 2 and 3). This is a remarkable result when compared with other catalytic formylation reactions which generally use much more active formylating agents (formic acid, formaldehyde) and are run at higher temperatures.

4.4 Mechanism Studies

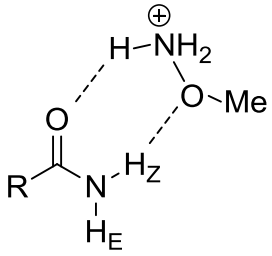
To understand this chemistry further, we conducted a series of experiments to gain an insight into possible mechanisms by which this reaction may be operating. It was clear that once the reaction reaches the secondary or tertiary amide product, it is irreversible. Running secondary amide **2.9** in the presence of amine **4.20** under the same reaction conditions did not lead to a crossover (Scheme 4.2). Even increasing the ratio of amine to five equivalents (compared with the secondary amide) did not result in a crossover reaction.



Scheme 4.2. Crossover with a secondary amide not observed under the reaction conditions.

In the absence of catalyst, only 10% conversion into secondary amide was observed after 18 hours (Table 4.1, entry 15), therefore the primary amide must be activated in some way by the hydroxylamine hydrochloride. In the absence of acid, a marked decrease in conversion is seen (Table 4.1, entries 10 and 11), suggesting the acid is participating in the reaction mechanism in some way. Using just hydrochloric acid (36% w/v) as the catalyst, however, gave only 51% conversion into secondary amide (Table 4.1, entry 14).

A series of ^{1}H NMR experiments was run in an attempt to detect any reaction intermediates. ^{1}H NMR experiments run in d_8-toluene at 80 ^{o}C (to mimic actual reaction conditions as closely as possible) showed a clear interaction between the NH amide protons and *O*-methylhydroxylamine hydrochloride, (Table 4.8), suggesting a hydrogen bonding interaction between the two species in the reaction solvent (Figure 4.1), such as the complex **4.21**. In random conformations, NOE data has shown the *Z*-NH proton (relative to the carbonyl oxygen) to appear upfield from the *E*-NH proton, however in hydrogen bonded conformation this order is reversed, so the NH signal seen to shift downfield in our ^{1}H NMR spectra can be attributed to the hydrogen bonded *Z*-NH proton.



4.21

Figure 4.1. Proposed method of primary amide activation *via* hydrogen bonding

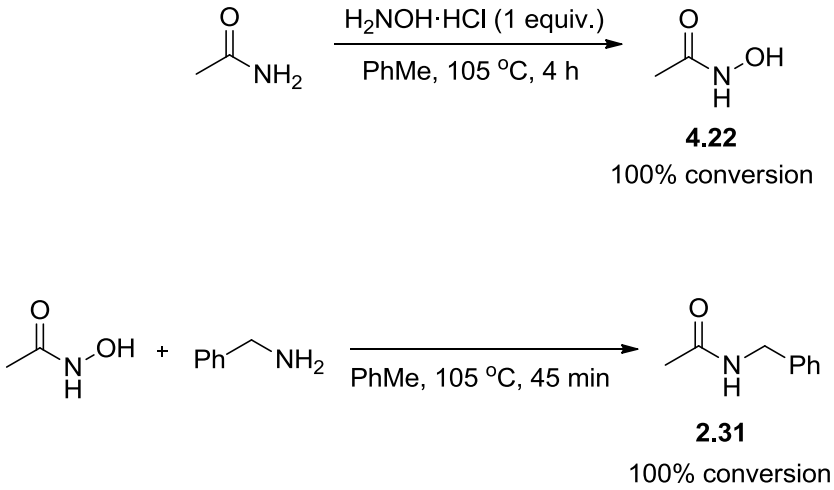
Table 4.8. NMR experiments run in d_8-toluene

Entry	Conditions	NH shifts (ppm)
1	0.05M butyramide	4.37, 4.70
2	0.1M butyramide	4.40, 5.25
3	0.2M butyramide	4.37, 5.23
4	0.05M butyramide-$MeONH_2$·HCl	4.40, 4.68
5	0.1M butyramide-$MeONH_2$·HCl	4.37, 5.53
6	0.2M butyramide-$MeONH_2$·HCl	4.53, 5.86

Conditions: d_8-toluene, 55^{o}C, NMRs run at 500 MHz.

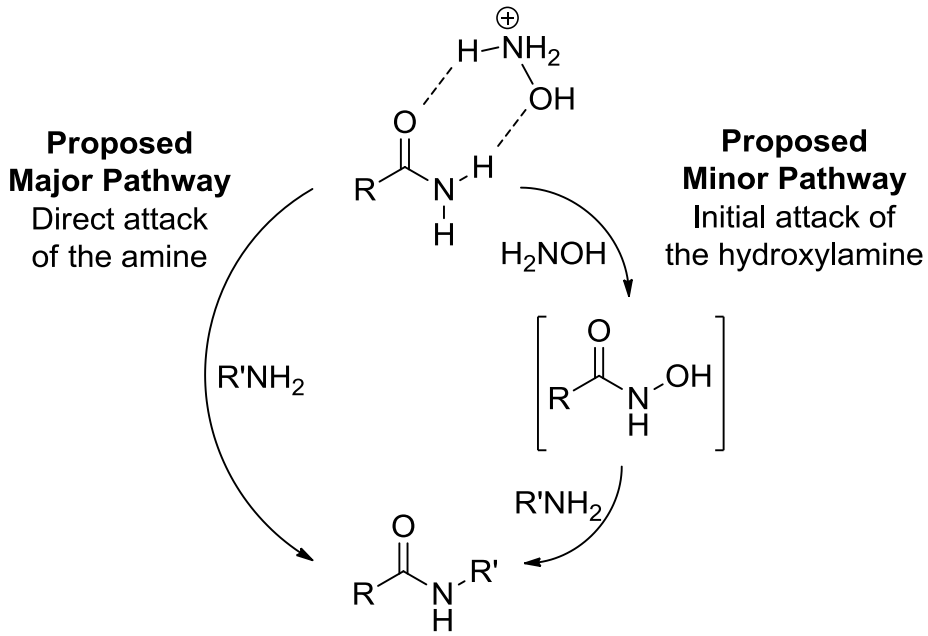
It is possible that the hydroxylamine attacks the 'activated' hydrogen-bonded primary amide, generating an intermediate hydroxamic acid. When the reaction between *n*-butyramide and benzylamine was followed over time by ^{1}H NMR, no evidence of the hydroxamic acid could be seen in the spectra. However, it is possible that the hydroxamic acid is simply not observable on the NMR timescale.

When hydroxylamine hydrochloride and acetamide (in a 1:1 ratio) were subjected to the reaction conditions, complete conversion into the hydroxamic acid **4.22** was observed within four hours. Furthermore, when acetohydroxamic acid **4.22** and benzylamine were subjected to the reaction conditions, complete conversion into the secondary amide **2.31** was observed within 45 minutes, suggesting that, if the hydroxamic acid is formed, transformation into the product (and thus regeneration of the catalyst) is very rapid (Scheme 4.3).



Scheme 4.3. Hydroxamic acid synthesis and reaction

The relative *p*Ka of the amine and hydroxylamine dictate that the amine is more basic and thus more nucleophilic towards the carbonyl – the opposite order of reactivity seen in S_N2 reactions at saturated centres. It can therefore be proposed that the major pathway in this reaction is attack of the amine onto the hydrogen bonded primary amide-hydroxylamine complex (Scheme 4.4).



Scheme 4.4. Proposed reaction pathways

4.5 Conclusions

In conclusion, we have reported a novel method for the transamidation between primary carboxamides and primary or secondary amines to give secondary or tertiary amides, utilizing catalytic quantities of hydroxylamine hydrochloride to activate the usually chemically robust primary amide group. This metal-free, simple process represents a significant step towards the goal of atom economical and cost efficient syntheses of amide bonds. A proposed mechanism of primary amide activation *via* a hydrogen bonding complex is also presented with ^{1}H NMR studies.

Results and Discussion IV

Amides from Carboxylic Acids

"Catalyzed and Uncatalyzed Direct Amide Formation from Unactivated Carboxylic Acids and Amines"

C. L. Allen, R. Chhatwal, J. M. J. Williams, *Chem. Commun.,* **2012**, *48,* 666

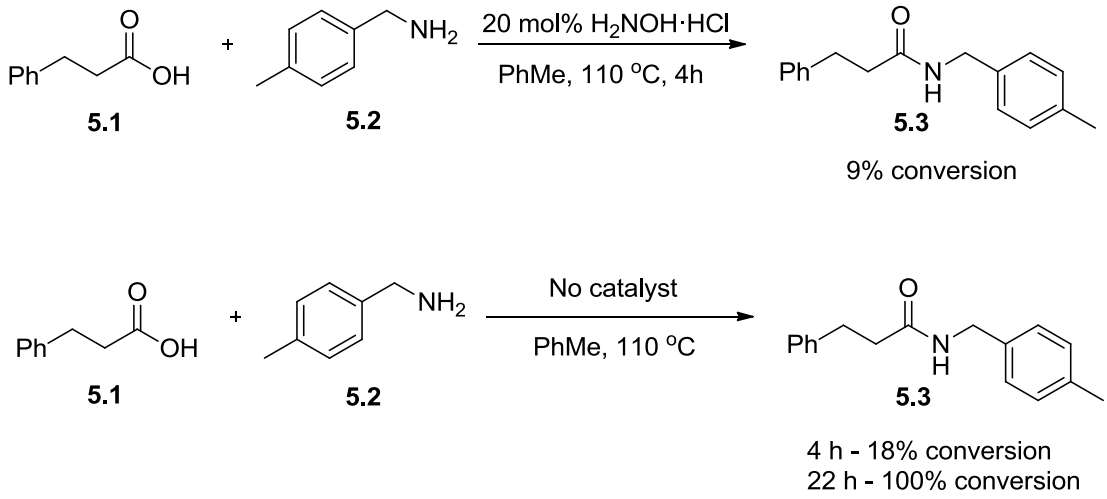
5. Results and Discussion IV - Amides from Carboxylic Acids

5.1 Introduction

With the abundance of coupling reagents available for the formation of amide bonds from carboxylic acids and amines, there has been little development in the area of metal catalysts for this reaction. The natural equilibrium of a neat mixture of a carboxylic acid and an amine is heavily towards the salt formation (except at high temperatures), making a catalytic reaction between them challenging. Despite sporadic literature evidence that this equilibrium might be reversed in certain reaction conditions, little work has been done towards exploring the range and limitations of such a reaction (see Chapter 1.2.1 and Chapter 1.2.5).

5.2 Initial Work

In the course of our studies into developing an atom-efficient reaction coupling carboxylic acids and amines, we observed a larger than expected background rate in the reaction between 3-phenylpropionic acid **5.1** and 4-methylbenzylamine **5.2** to form secondary amide **5.3** when the reaction was run in certain solvents (Scheme 5.1). In 4 hours, with no catalyst or additives, conversion into **5.3** was 18%. When the reaction time was increased to 22 hours, complete conversion into **5.3** was observed.



Scheme 5.1. Coupling reaction between 3-phenylpropionic acid and 4-methylbenzylamine

This observation can be explained as the formation of charged species is disfavoured in non-polar solvents, the equilibrium towards ammonium carboxylate salt formation is disfavoured (Figure 5.1). The position of equilibrium is therefore reversed from that observed in water and the free amine and free carboxylic acid are favoured. We therefore reasoned that direct amide formation would be more facile in non-polar solvents and attempted the coupling of 3-phenylpropanoic acid with 4-methylbenzylamine in a variety of solvents (Table 5.1).

In particular, toluene stood out as an excellent solvent for the uncatalysed direct formation of amides (Table 5.1, entry 1), while no reaction was observed when the reaction was performed in water. Increasing the concentration of the reaction run in toluene to 2.0 M allowed complete conversion into product after 22 hours at reflux (Table 5.1, entry 10).

The reaction was performed in a sealed vessel, demonstrating that the equilibrium is favourable without the need to remove water. Significant amide formation was also observed when the reaction was run in the absence of solvent despite the relatively mild reaction conditions.

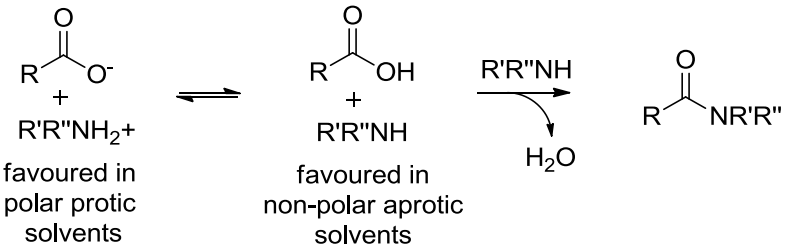
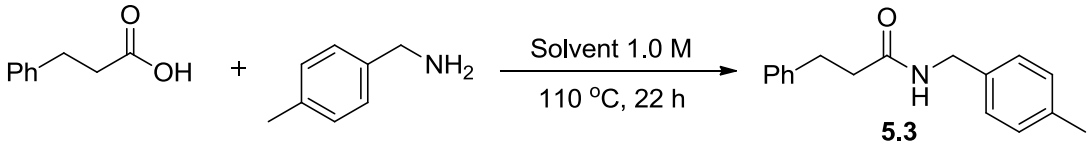


Figure 5.1. Overcoming salt formation by the use on a non-polar solvent

Table 5.1. Direct amide bond formation in a range of solvents after 20 hours



5.3

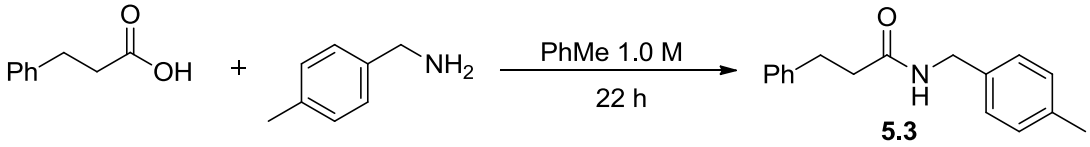
Entry	Solvent	Conversion into 5.3 (%)
1	Toluene	92
2	Cyclohexane	4
3	Isopropanol	3
4	Dimethylsulfoxide	0
5	Water	0
6	1,2-Dichloroethane	12
7	1,4-Dioxane	66
8	Acetonitrile	50
9	No solvent	58
10	Toluene	100[a]

Conditions: 3-Phenylpropionic acid (0.150 g, 1 mmol), 4-methylbenzylamine (0.13 mL, 1 mmol), solvent (1 mL), 110 °C, 22 h; [a] 2.0 M in toluene.

5.3 Catalyst free coupling

Having established that using toluene as a non-polar solvent leads to significant amide formation between carboxylic acids and amines at 110 ^{o}C, we then explored optimising these conditions (Tables 5.2 and 5.3).

Table 5.2 Variation of reaction temperature



5.3

Entry	Temperature (^{o}C)	Conversion into 5.3 (%)
1	110	100
2	100	64
3	90	42
4	80	0

Conditions: 3-Phenylpropionic acid (0.150 g, 1 mmol), 4-methylbenzylamine (0.13 mL, 1 mmol), toluene (1 mL), 22 h.

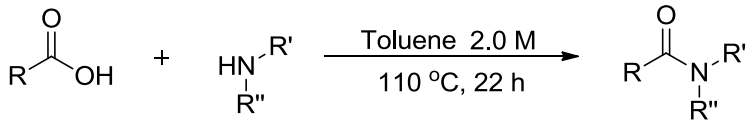
Table 5.3 Variation of reactant concentration

Entry	Concentration (M)	Conversion into 5.3 (%)
1	0.5	87
2	1.0	69
3	2.0	71
4	4.0	64

Conditions: 3-Phenylpropionic acid (0.150 g, 1 mmol), 4-methylbenzylamine (0.13 mL, 1 mmol), toluene, 110 ^{o}C, 16 h.

From the results in Tables 5.2 and 5.3, the optimal reaction conditions were determined to be 110 ^{o}C with a reactant concentration of 0.5 M in toluene. Next, the range of substrates that could be used in these conditions was thoroughly explored, as previous reports of catalyst free direct coupling had all been highly substrate dependant (Table 5.4).

Table 5.4 Direct uncatalysed formation of a range of amides



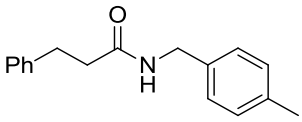
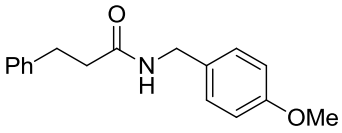
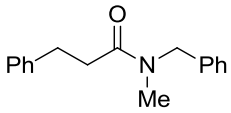
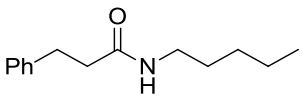
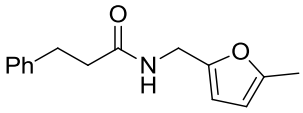
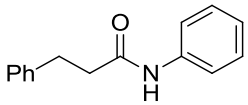
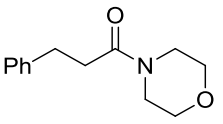
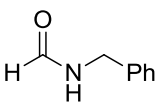
Entry	Amide		Temp. (^{o}C)	Conversion (%), no solvent	Conversion (%), in PhMe[a]
1		**5.3**	110	58	100 (81)
2		**5.4**	110	49	84 (72)
3		**5.5**	110	18	100 (95)
4		**5.6**	110	51	100 (94)
5		**5.7**	110	18	100 (92)
6		**5.8**	110 150[b]	9 48	30 73
7		**3.43**	110 150[b]	39 51	67 100 (94)
8		**4.9**	110	100	100 (89)

Table cont.

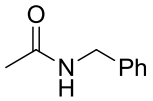
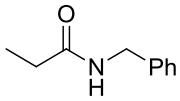
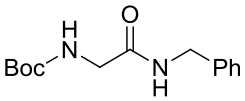
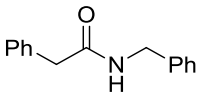
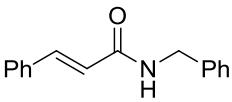
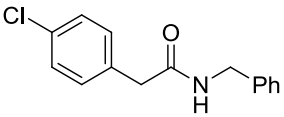
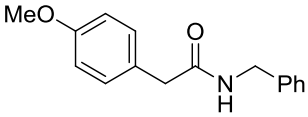
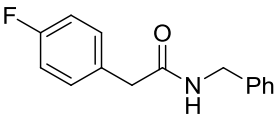
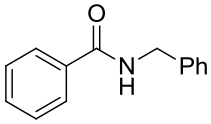
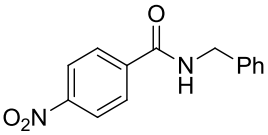
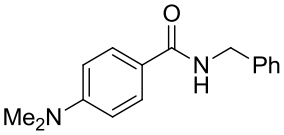
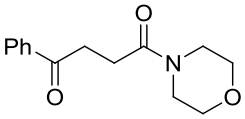
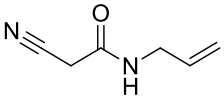
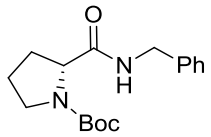
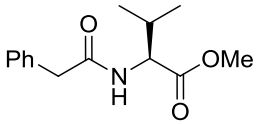
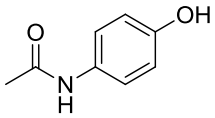
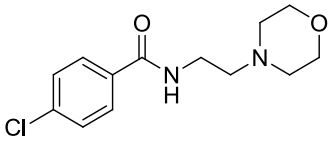
9		**2.31**	110	100	100 (83)
10		**2.6**	110	79	100 (90)
11		**5.9**	110	27	71
12		**5.10**	110	48	100 (91)
13		**5.11**	110	<1	32
			150[b]	56	100 (91)
14		**5.12**	110	53	100 (92)
15		**5.13**	110	61	100 (92)
16		**5.14**	110	56	100 (90)
17		**3.34**	110	<1	6
			150[b]	28	44
18		**5.15**	110	0	0
			150[b]	0	0
19		**5.16**	110	0	0
			150[b]	0	0
20		**5.17**	110	58	82 (78)
21		**5.18**	110	0	84 (76)

Table cont.

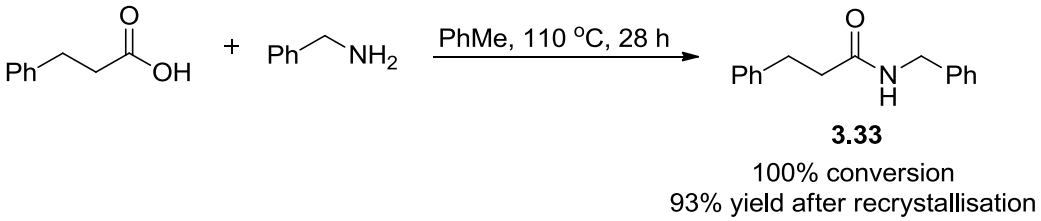
22		**4.19**	110	0	0
			150[b]	0	79
23		**5.19**	110	81	92 (88)
24		**4.4**	110	0	37
			150[b]	0	69
25		**3.46**	110	0	14
			150[b]	49	66

Conditions: Carboxylic acid (2 mmol), amine (2 mmol), PhMe (1 mL); [a]Figures in brackets are isolated yields (%); [b]Reactions run at 150 ^{o}C were performed in xylenes.

Many substrates gave good to excellent yields of the corresponding secondary amides and all showed increased (or equivalent) conversions when compared with the same reaction run under neat conditions. 3-Phenylpropionic acid reacted well with a range of amines to give the corresponding amides (Table 5.4, entries 1-7). Benzylamine was converted into a range of amides by coupling with carboxylic acids (Table 5.4, entries 8-19). A wide variety of functional groups was shown to be tolerated by the reaction conditions, including halogens (Table 5.4, entries 14, 16 and 25), heterocycles (Table 5.4, entries 5, 7, 20, 22 and 25) and unsaturated bonds (Table 5.4, entries 13 and 21). Common protecting groups were also unaffected under the relatively mild reaction conditions, including Boc and methyl ester groups (Table 5.4, entries 11, 22 and 23), allowing protected amino acids to be used as substrates.

The reaction was applied to the synthesis of two simple amide-containing pharmaceutical drugs; the analgesic agent paracetamol and the anti-depressant Moclobemide (Manerix ®) (Table 5.4, entries 24 and 25), but even at 150 ^{o}C, these reactions did not reach above 70% conversion.

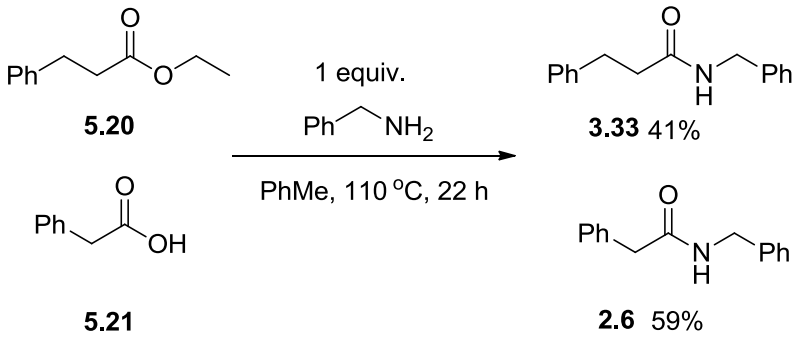
We wanted to see if this procedure could be successfully scaled up to produce a larger amount of amide (all other reactions were run on a 1-2 mmol scale). After 28 hours, 100% conversion into the amide **3.33** was achieved and after recrystallisation from dichloromethane the isolated yield was found to be 93% (93 g), as seen in Scheme 5.2.



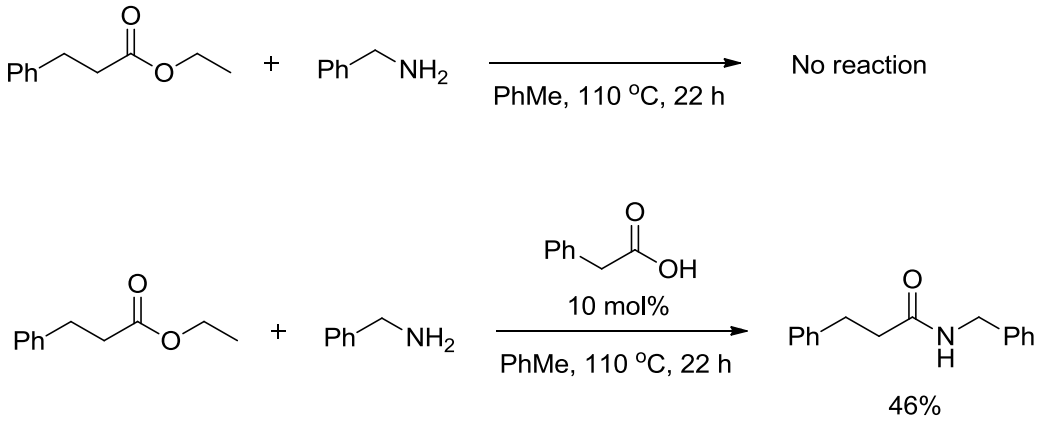
Scheme 5.2. Large scale uncatalysed amide formation

Interestingly, the reactivity of a carboxylic acid towards direct coupling with an amine appears to be greater than for the corresponding ester under our reaction conditions (Scheme 5.3). In a direct competition reaction between ethyl 3-phenylpropanoate **5.20** and phenylacetic acid **5.21** with just one equivalent of benzylamine available, the acid proved to be more active, giving 59% conversion into the corresponding secondary amide.

Additionally, there was no conversion into secondary amide when ethyl-3-phenylpropionate was heated with benzylamine in toluene at reflux for 22 hours, yet when a catalytic amount of phenylacetic acid was added to the reaction, 46% coupling of the ester and amine was observed (Scheme 5.4).



Scheme 5.3. Competition reaction with an ester



Scheme 5.4. Ester reactivity

5.4 Catalyst Studies

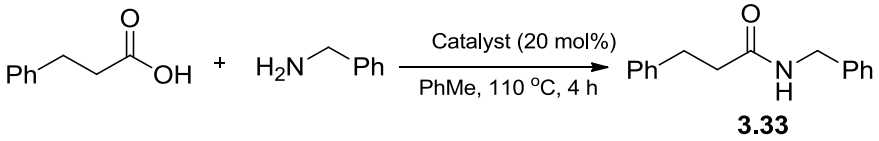
Having established that direct amide formation was favoured using toluene as solvent, we wished to identify catalysts which would further improve the rate of reaction in order to minimise the time taken for complete conversion. This work was carried out in conjunction with a project student in the Williams group, Rosie Chhatwal.

We performed a coupling of 3-phenylpropionic acid with benzylamine in toluene at reflux for just 4 hours in the presence of a series of potential catalysts (Table 5.5). Under these conditions, the uncatalysed reaction proceeded to 20% conversion (Table 5.5, entry 1). We were pleased to find that $FeCl_2$, $ZrCl_4$, CuBr, $Ni(NO_3)_2$ and $TiCl_4$ all led to full conversion in this time (Table 5.5, entries 2, 4, 5, 6 and 9). When the catalyst loading was reduced to 5 mol%, the best result was achieved using $ZrCl_4$, which gave 83% conversion after 4 hours (Table 5.5, entry 16). Examination of alternative zirconium catalysts did not lead to improvement of this result, except in the case of Cp_2ZrCl_2, which gave full conversion to product after 4 hours (Table 5.5, entry 19). Cp_2ZrCl_2 is therefore a more reactive catalyst, but is significantly more expensive than $ZrCl_4$.

Hydrochloric acid (Table 5.5, entry 14) only had a weak catalytic effect, indicating that it is not degradation of the catalyst to HCl which provides catalytic activity.

Interestingly, *N*,*N*-diphenylurea (Table 5.5, entry 15) had some catalytic effect, presumably by acting as a hydrogen bond donor.

Table 5.5 Identification of catalysts for direct amide formation[a]



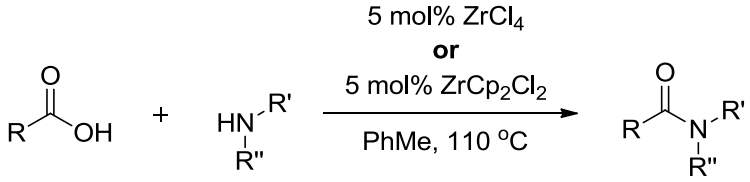
3.33

Entry	Catalyst	Conversion into 3.33 (%)
1	No catalyst	20
2	$FeCl_2$	100
3	$ZnCl_2$	18
4	$ZrCl_4$	100
5	CuBr	100
6	$Ni(NO_3)_2$	100
7	$Al(O^iPr)_3$	30
8	$Ti(O^iPr)_4$	63
9	$TiCl_4$	100
10	LiBr	18
11	NaCl	19
12	$Sc(OTf)_3$	14
13	$La(O^iPr)_3$	17
14	HCl	30
15	*N*,*N*-Diphenylurea	51
16	$ZrCl_4$ (5 mol%)	83
17	$FeCl_2$ (5 mol%)	35
18	$TiCl_4$ (5 mol%)	26
19	$ZrCp_2Cl_2$ (5 mol%)	100
20	$Zr(acac)_4$ (5 mol%)	77

Conditions: 3-Phenylpropionic acid (0.150 g, 1 mmol), benzylamine (0.11 mL, 1 mmol), solvent (1 mL), catalyst (20 mol% unless otherwise stated), 110 °C, 4 h; [a)] Experiments performed by project student.

We chose to investigate the use of Cp_2ZrCl_2 and $ZrCl_4$ as catalysts for a range of substrates as these proved to be the most efficient at the lower catalyst loading as well as being the most selective for secondary amide formation (CuBr and $Ni(NO_3)_2$ gave significant amounts of the side-products imine and aldehyde at lower catalyst loadings). Appyling the catalytic conditions to the same range of amides tested in the uncatalysed reaction showed a rate increase over the background rate in all cases when using a zirconium catalyst (Table 5.6).

Table 5.6. Direct catalyzed formation of a range of amides



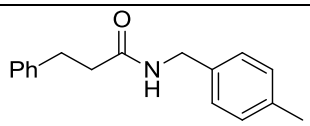
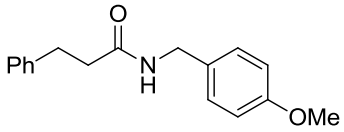
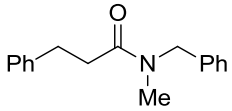
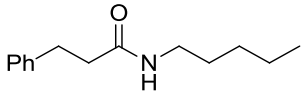
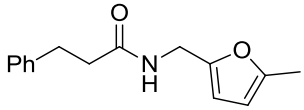
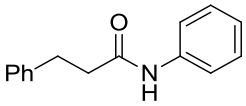
Entry	Amide	Conversion(%) Uncatalysed in PhMe, 110 °C[a]	Catalyst (Time, h)	Conversion into amide (%)[a]
1		100 (81)	$ZrCl_4$ (5) $ZrCp_2Cl_2$ (4)	100 (92) 100 (94)
2		84 (72)	$ZrCl_4$ (10) $ZrCp_2Cl_2$ (4)	100 (89) 86 (60)
3		100 (95)	$ZrCl_4$ (18)	96 (81)
4		100 (94)	$ZrCl_4$ (10)	81 (71)
5		100 (92)	$ZrCl_4$ (10)	100 (91)
6		30	$ZrCl_4$ (24) $ZrCp_2Cl_2$ (24)	37 45

Table cont.

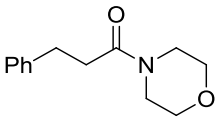
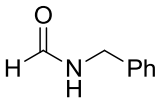
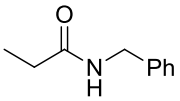
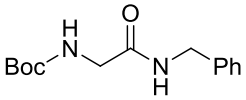
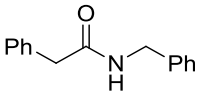
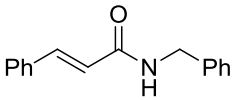
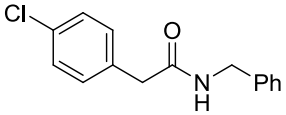
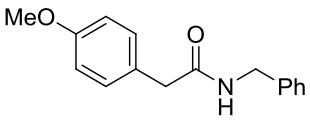
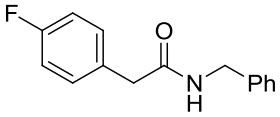
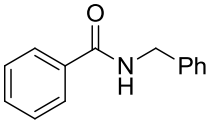
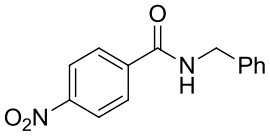
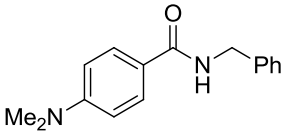
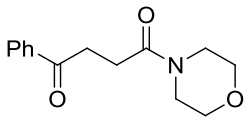
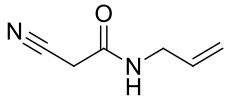
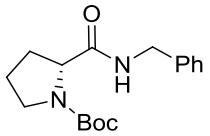
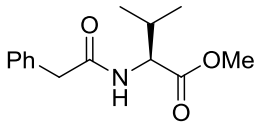
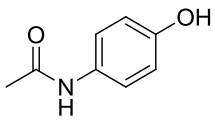
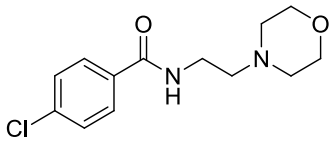
7		67	$ZrCl_4$ (18) $ZrCp_2Cl_2$ (24)	72 100 (88)
8		100 (89)	$ZrCl_4$ (5)	100 (93)
9		100 (90)	$ZrCl_4$ (5)	100 (81)
10		71	$ZrCl_4$ (22)	91 (80)
11		100 (91)	$ZrCl_4$ (5)	100 (88)
12		32	$ZrCl_4$ (18)	57
13		100 (92)	$ZrCl_4$ (10)	100 (89)
14		100 (92)	$ZrCl_4$ (5)	100 (91)
15		100 (90)	$ZrCl_4$ (5)	100 (91)
16		6	$ZrCl_4$ (24) $ZrCp_2Cl_2$ (22)	55 83 (72)
17		0	$ZrCl_4$ (24) $ZrCp_2Cl_2$ (24)	0 3
18		0	$ZrCl_4$ (24) $ZrCp_2Cl_2$ (24)	0 1

Table cont.

19		82 (78)	$ZrCl_4$ (10)	89 (78)
20		84 (76)	$ZrCl_4$ (16)	93 (84)
21		0	$ZrCl_4$ (22)	64 (56) > 99% ee
22		92 (88)	$ZrCl_4$ (12)	100 (81)
23		37	$ZrCp_2Cl_2$ (24)	100 (88)
24		14	$ZrCp_2Cl_2$ (24)	100 (85)

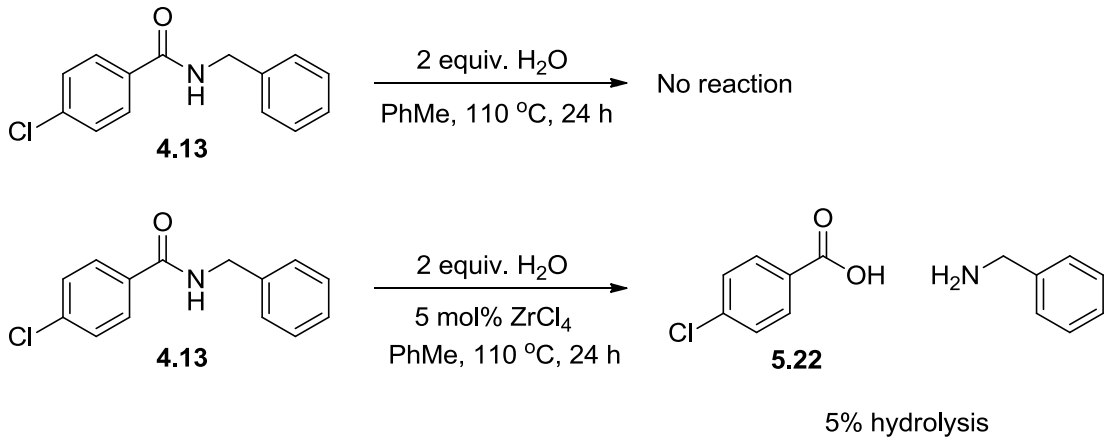
Conditions: Carboxylic acid (2 mmol), amine (2 mmol), catalyst, PhMe (2 mL); [a] Figures in brackets are isolated yields (%).

3-Phenylpropionic acid reacted well with a range of amines to give the corresponding amides (Table 5.6, entries 1-7). Benzylamine was again converted into a range of amides by coupling with carboxylic acids (Table 5.6, entries 8-18). A wide variety of functional groups was shown to be tolerated by the reaction conditions (even when the zirconium catalyst was used) including heterocycles (Table 5.6, entries 5, 7, 19, 21 and 24), halogens (Table 5.6, entries 13, 15 and 24) and unsaturated groups (Table 5.6, entries 12 and 20). The relatively mild conditions allowed ketone (Table 5.6, entry 19), nitrile (Table 5.4, entry 20) and even ester groups (Table 5.6, entry 22) to remain unaffected in the reaction. Amino acids *N*-Boc glycine, *N*-Boc proline and valine methyl ester were successfully converted into secondary amides without loss of the protecting groups (Table 5.6, entries 10, 21 and 22). Pleasingly, there was no racemisation of the stereocentre in the prolinamide product.

Aniline was found to be the least reactive amine substrate tested (presumably due to its relatively lower nucleophilicity), with only 45% conversion seen even when using the more active $ZrCp_2Cl_2$ catalyst (Table 5.6, entry 6). The benzoic acid derivatives were also found to be very unreactive (Table 5.6, entries 17 and 18). The rate of reaction of benzoic acid itself, however, was found to be greatly accelerated using $ZrCp_2Cl_2$ as the catalyst, as after 22 hours, 83% conversion into secondary amide was observed, compared with only 6% background rate (Table 5.6, entry 16).

The catalysed reaction was applied to the synthesis of the same two amide-containing pharmaceutical drugs; the analgesic agent paracetamol and the anti-depressant Moclobemide (Manerix ®) (Table 5.6, entries 23 and 24). As the paracetamol synthesis required the use of an aniline as a reacting partner and the moclobemide synthesis required the use of a benzoic acid, the reactions were run for 24 hours and were pleased to find that 100% conversion was achieved in both cases, compared with the uncatalyzed rates which gave 37% conversion for paracetamol and only 14% conversion for moclobemide (at 110 ^{o}C).

The reversibility of this reaction was tested by taking a secondary amide (*N*-benzyl-4-chlorobenzamide, **4.13**) and water under the standard reaction conditions. In the absence of zirconium catalyst, no hydrolysis into 4-chlorobenzoic acid **5.22** and benzylamine was observed and with 5 mol% $ZrCl_4$ only 5% hydrolysis was seen (Scheme 5.5).



Scheme 5.5. Reversibility of the reaction

5.6 Conclusions

The direct thermal amidation of carboxylic acids with amines is possible at 110 ^{o}C when using toluene as a solvent for a range of substrates. For less reactive substrates, sometimes increasing the temperature to 150 ^{o}C and running the reactions in *p*-xylenes allows higher conversions to be achieved.

Several simple catalysts allowed the reaction to be performed in less time and two zirconium catalysts were shown to be particularly effective for the synthesis of a range of amides. A comprehensive study of substrates in this reaction has been undertaken.

From the mechanism studies published by Whiting *et al.* and our own observations, it can be concluded that the extent of conversion into secondary amide seen in the uncatalysed reaction is heavily dependant upon the nature of the carboxylic acid, with less dependence on the nucleophilicity of the amine coupling partner. This is due to the active species being the hydrogen bonded carboxylic dimer. As this hydrogen bonding interaction ‘activates’ the carboxylic acid towards nucleophilic attack, any catalyst used in this reaction (which ever mode of catalysis it is employing) must be a better ‘activator’ than the carboxylic acid itself, otherwise an increase over the background rate will not be observed.

Experimental

6. Experimental

6.1 General Experimental Methods

All reactions requiring an anhydrous, inert atmosphere were carried out under a nitrogen atmosphere using evacuated carousel or ampules. Unless preparative details are provided, all reagents were purchased from commercial suppliers Aldrich, Fluka, Lancaster, TCI and Acros Organics and used without further purification. All solvents were distilled and degassed and stored in the presence of 3Å molecular sieves prior to use. Thin layer chromatography was carried out on aluminium or glass backed silica plates, purchased from Aldrich. The plates were visualised under UV (254 nm) light, sometimes followed by staining with potassium permanganate or ninhydrin dip 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 $CDCl_3$, unless stated otherwise, on either a Bruker Avance 250 (250 MHz) or a Bruker Avance 300 (300 MHz). Any chemical shifts (δ) are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) (δ_H = 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), doublet of triplets (dt), triplet of triplets (tt), multiplet (m), or broad (br. s).

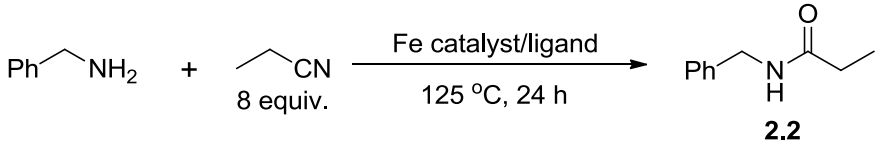
For mass spectrometry data aquisition a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10 µL of 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 ATR accessory for sampling, with relevant absorbances quoted as *v* in cm^{-1}. Optical rotations were measured on an AA-10 Automatic Polarimeter.

Enantiomeric excess was measured using a Perkin Elmer 200 Series HPLC machine fitted with a Chiralcel OJ column (25 cm, 0.8 cm diameter), eluting with HPLC grade hexane and isopropylalcohol.

6.2 Chapter 2 Experimental Procedures

Representative Procedure I



2.2

The chosen iron catalyst was added to an oven dried Schlenk tube, followed by the appropriate nitrile and amine species (and solvent where required) being added dropwise to the tube, which was then sealed and the reaction mixture allowed to stir at room temperature for 10 minutes before being heated (125 ^{o}C) for 24 hours. The resulting reaction mixture was filtered through a short plug of silica, eluting with 92:8 DCM:methanol, then concentrated *in vacuo*. Where appropriate, the product was recrystallised from DCM/hexane and allowed to stand in a freezer overnight before being filtered. The resulting amides were analysed by their ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data.

Variation of iron catalyst, ligand and catalyst loading

(Tables 2.1 – 2.2, Results and Discussion I)

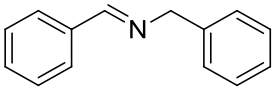
Following representative procedure I, the appropriate iron catalyst and ligand were used according to Tables 2.1 – 2.2. Benzylamine (0.21 mL, 2 mmol) and propionitrile (1.14 mL, 16 mmol) were used as the amine and nitrile species.

Imine formation

(Scheme 2.3, Results and Discussion I)

Following representative procedure I, either $FeCl_2 \cdot 4H_2O$ (0.025 g, 0.20 mmol, 10 mol%) or $Fe(NO_3)_3 \cdot 9H_2O$ (0.080 g, 0.20 mmol, 10 mol%) were used as iron catalyst. Benzylamine (0.21 mL, 2.00 mmol) was added to the catalyst, followed by 1.0 mL dichloroethane as solvent. No nitrile species was added.

2.3 *N*-Benzylidenebenzylamine[129]



2.3

Following the procedure outlined in 5.2.3, *N*-benzylidenebenzylamine **2.3** was synthesised from benzylamine. ^{1}H NMR of the crude reaction mixture showed 70% conversion. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 4.75 (2H, s, CHNC$\underline{H_2}$Ph), 7.12 – 7.34 (8H, m, aromatic), 7.72 (2H, m, aromatic), 8.30 (1H, s, PhC$\underline{H}$NCH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 65.5, 127.4, 128.4, 128.7, 128.9, 129.0, 131.2, 136.6, 139.7, 162.4; ESI-MS of $[C_{14}H_{14}N]^+$; theoretical m/z of $[M+H]^+$ = 196.108, measured m/z of $[M+H]^+$ = 196.108.

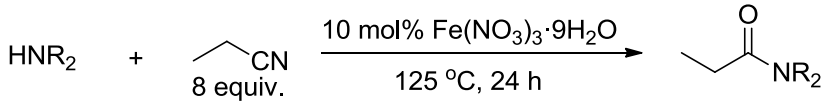
Addition of solvents

(Table 2.3, Results and Discussion I)

Following representative procedure I, $Fe(NO_3)_3 \cdot 9H_2O$ (0.080 g, 0.20 mmol, 10 mol%) was used as iron catalyst. Benzylamine (0.21 mL, 2.0 mmol) and propionitrile (1.14 mL, 16 mmol) were used as the amine and nitrile species. Water, toluene, dichloroethane or tetrahydrofuran were added according to Table 2.3.

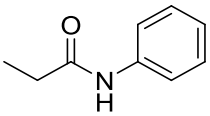
Representative Procedure II

(Table 2.4, Results and Discussion I)



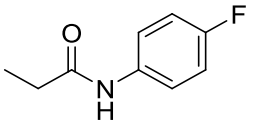
$Fe(NO_3)_3 \cdot 9H_2O$ (0.080 g, 0.20 mmol, 10 mol%) was added to an oven dried Schlenk tube, followed by propionitrile **42** (1.14 mL, 16 mmol) and the appropriate amine species (2 mmol) according to Table 7. The tube was then sealed and the reaction mixture allowed to stir at room temperature for 10 minutes before being heated (125 ^{o}C) for 24 hours. The resulting reaction mixture was filtered through a short plug of silica, eluting with 92:8 DCM:methanol, then concentrated *in vacuo*. Where required, the product was recrystallised from DCM/hexane and allowed to stand in a freezer overnight before being filtered. The resulting amides were analysed by their ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data.

2.4 *N*-Phenylpropionamide[130]



Following representative procedure II, aniline (0.18 mL, 2.0 mmol) was used as amine species. An ^{1}H NMR of the crude reaction mixture showed 8% conversion into **2.4** by comparison of peaks at 7.10 ppm (2H, aniline) and 7.81 ppm (2H, **2.4**). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.20 (3H, t, *J* = 5.9 Hz, $CH_2C\underline{H}_3$), 2.10 – 2.20 (2H, q, *J* = 5.9 Hz, $C(O)C\underline{H}_2CH_3$), 4.06 (1H, br. s, NH), 7.15 – 7.25 (1H, m, aromatic), 7.40 – 7.50 (3H, m, aromatic), 7.71 – 7.80 (2H, m, aromatic).

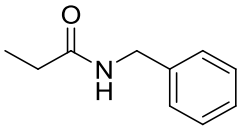
2.5 *N*-(*p*-Fluoro)phenylpropionamide[90]



Following representative procedure II, *p*-fluoroaniline (0.21 mL, 2.0 mmol) was used as amine species. An ^{1}H NMR of the crude reaction mixture showed 15% conversion into **2.5** by comparison of peaks at 6.65 (2H, *p*-fluoroaniline) and 7.51 (2H, **2.5**). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.00 (3H, t, *J* = 6.0, $CH_2C\underline{H}_3$), 2.21 – 2.30 (2H, q, *J* =

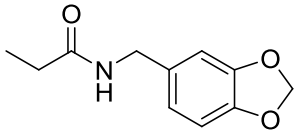
6.0 Hz, C(O)C$\underline{H}_2$CH$_3$), 4.22 (1H, br. s, NH), 7.19 – 7.24 (2H, m, aromatic), 7.55 – 7.65 (2H, m, aromatic).

2.6 *N*-BenzylpropionamideError! Bookmark not defined.



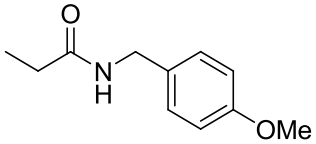
Following representative procedure II using benzylamine (0.24 mL, 2.0 mmol) as amine species, compound **2.6** was recovered as yellow crystals (0.213 g, 65%). ^{1}H NMR (250 MHz, CDCl$_3$, 25 °C): δ = 1.05 (3H, t, *J* = 6.0 Hz, C$\underline{H}_3$CH$_2$), 2.08 – 2.14 (2H, q, *J* = 6.0 Hz, CH$_3$C$\underline{H}_2$C(O)), 4.31 (2H, d, *J* = 9.0 Hz, PhC$\underline{H}_2$NH), 7.08 – 7.22 (5H, m, aromatic); ^{13}C NMR (75.5 MHz, CDCl$_3$, 25 °C): δ = 10.2, 30.1, 40.0, 127.9, 128.2, 129.1, 138.8, 173.9; ESI-MS of [C$_{10}$H$_{13}$NO]$^+$; theoretical m/z of [M+H]$^+$ = 164.11, measured m/z of [M+H]$^+$ = 164.11; IR: ν (cm^{-1}) = 1642.09 (C=O stretch).

2.7 *N*-Piperonylpropionamide[131]



Following representative procedure II, piperonylamine (0.25 mL, 2.0 mmol) was used as amine species. An ^{1}H NMR of the crude reaction mixture showed a 43% conversion into **2.7** by comparison of peaks at 3.82 (2H, piperonylamine) and 4.36 (2H, **2.7**). ^{1}H NMR (250 MHz, CDCl$_3$, 25 °C): δ = 1.20 (3H, t, *J* = 7.5 Hz, CH$_2$C$\underline{H}_3$), 2.22 – 2.31 (2H, q, *J* = 7.5 Hz, C(O)C$\underline{H}_2$CH$_3$), 4.36 (2H, d, *J* = 5.7 Hz, NHC$\underline{H}_2$Ph) 5.88 (1H, br. s, NH), 6.11 (2H, s, OC$\underline{H}_2$O), 6.88 (1H, d, *J* = 6.8 Hz, aromatic), 6.93 (1H, d, *J* = 6.8 Hz, aromatic), 7.12 (1H, s, aromatic); ESI-MS of [C$_{11}$H$_{14}$NO$_3$]$^+$; theoretical m/z of [M+H]$^+$ = 208.093, measured m/z of [M+H]$^+$ = 208.093; IR: ν (cm^{-1}) = 1632.29 (C=O stretch).

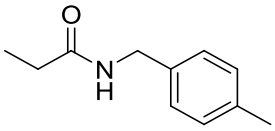
2.8 *N*-(*p*-Methoxy)benzylpropionamide[132]



Following representative procedure II using *p*-methoxybenzylamine (0.25 g, 2.0 mmol) as amine species, compound **2.8** was recovered as a yellow solid (0.307 g, 79%). ^{1}H

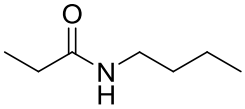
NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.17 (3H, t, *J* = 6.0 Hz, $C\underline{H}_3CH_2$), 2.20 – 2.27 (2H, q, *J* = 6.0 Hz, $CH_3C\underline{H}_2C(O)$), 3.81 (3H, s, $OC\underline{H}_3$), 4.38 (2H, d, *J* = 10.0 Hz, $NHC\underline{H}_2Ph$), 5.70 (1H, br. s, NH), 6.87 (2H, d, *J* = 9.1 Hz, aromatic), 7.22 (2H, d, *J* = 9.1 Hz, aromatic); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 10.0, 29.2, 43.4, 55.7, 114.4, 114.7, 129.5, 129.6, 130.8, 159.4, 174.0; ESI-MS of $[C_{11}H_{15}NO_2]^+$; theoretical m/z of $[M+Na]^+$ = 216.10, measured m/z of $[M+Na]^+$ = 216.10; IR: ν (cm^{-1}) = 1633.09 (C=O stretch).

2.9 *N*-(*p*-Methyl)benzylpropionamide[133]



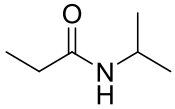
Following representative procedure II using *p*-methylbenzylamine (0.28 mL, 2.0 mmol) as amine species, compound **2.9** was recovered as a white solid (0.291 g, 82%). ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.20 (3H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 2.22 – 2.31 (2H, q, *J* = 7.6 Hz, $C(O)C\underline{H}_2CH_3$), 2.37 (3H, s, $C\underline{H}_3$), 4.43 (2H, d, *J* = 5.6 Hz, $NHC\underline{H}_2Ph$), 5.71 (1H, br. s, NH), 7.12 – 7.22 (4H, m, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 10.2, 21.5, 30.6, 43.7, 128.2, 129.8, 135.7, 137.6, 173.9; ESI-MS of $[C_{11}H_{15}NO]^+$; theoretical m/z of $[M+H]^+$ = 178.12, measured m/z of $[M+H]^+$ = 178.12; IR: ν (cm^{-1}) = 1640.01 (C=O stretch).

2.10 *N*-Butylpropionamide[134]



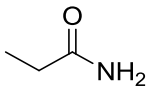
Following representative procedure II, *n*-butylamine (0.21 mL, 2.0 mmol) as amine species, compound **2.10** was recovered as a light brown oil (0.224 g, 87%). ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.93 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2CH_2$), 1.17 (3H, t, *J* = 7.6 Hz, $C\underline{H}_3CH_2C(O)$), 1.27 - 1.53 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2CH_2$), 2.17 - 2.23 (2H, q, *J* = 7.6 Hz, $CH_3C\underline{H}_2C(O)$), 3.22 - 3.27 (2H, q, *J* = 5.9 Hz, $CH_2C\underline{H}_2NH$), 5.60 (1H, br. s, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 10.1, 14.0, 19.8, 29.6, 32.7, 39.2, 174.7; ESI-MS of $[C_7H_{16}NO]^+$; theoretical m/z of $[M+H]^+$ = 130.118, measured m/z of $[M+H]^+$ = 130.118; IR: ν (cm^{-1}) = 1655.05 (C=O stretch).

2.11 *N*-Isopropylpropionamide[135]



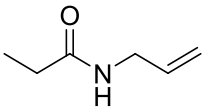
Following representative procedure II, isopropylamine (0.32 mL, 2.0 mmol) was used as amine species. Durene (0.324 g, 1.0 mmol) was also added as an internal standard to assess conversion. An ^{1}H NMR of the crude reaction mixture showed an 86% conversion into **2.11** by comparison of peaks at 6.95 (2H, 1 mmol durene) and 4.14 (1H, **2.11**). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.33 (3H, t, *J* = 7.5 Hz, $C\underline{H}_3CH_2$), 2.22 – 2.43 (2H, q, *J* = 7.6 Hz, $C(O)C\underline{H}_2CH_3$), 4.11 – 4.19 (1H, q, *J* = 7.2 Hz, $NHC(CH_3)_2\underline{H}$), 5.49 (1H, br. s, NH); ESI-MS of $[C_6H_{14}NO]^+$; theoretical m/z of $[M+H]^+$ = 116.102, measured m/z of $[M+H]^+$ = 116.102; IR: ν (cm^{-1}) = 1649.18 (C=O stretch).

2.12 Propionamide[136]



Following representative procedure II, *n*-butylamine (0.28 mL, 2.0 mmol) was used as amine species. An ^{1}H NMR of the crude reaction mixture showed 56% conversion into **2.12** by comparison of the peaks at 1.15 ppm (3H, propionitrile) and 7.33 ppm (3H, **2.12**). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.20 (3H, t, *J* = 6.0 Hz, $CH_2C\underline{H}_3$), 2.21 – 2.30 (2H, q, *J* = 6.0 Hz, $C(O)C\underline{H}_2CH_3$), 5.75 (2H, br. s, $N\underline{H}_2$); ESI-MS of $[C_3H_8NO]^+$; theoretical m/z of $[M+H]^+$ = 74.056, measured m/z of $[M+H]^+$ = 74.057; IR: ν (cm^{-1}) = 1630.63 (C=O stretch).

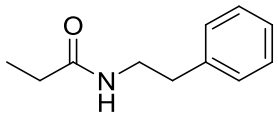
2.13 *N*-Allylpropionamide[137]



Following representative procedure II using allylamine (0.30 mL, 2.0 mmol) as amine species, compound **2.13** was recovered as a dark brown oil (0.205 g, 91%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.19 (3H, t, *J* = 7.5 Hz, $C\underline{H}_3CH_2$), 2.21 – 2.30 (2H, q, *J* = 7.5 Hz, $C(O)C\underline{H}_2CH_3$), 3.88 – 3.94 (2H, tt, *J* = 1.5 Hz, 5.6 Hz, $NHC\underline{H}_2CH$), 5.13 – 5.24 (2H, m, $NHC\underline{H}_2CH$), 5.59 (1H, br. s, NH), 5.79 – 5.94 (1H, m, $CH_2C\underline{H}CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 14.2, 19.6, 39.1, 42.3, 51.2, 116.71, 134.8, 173.2; ESI-

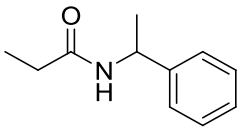
MS of $[C_6H_{12}NO]^+$; theoretical m/z of $[M+H]^+$ = 114.088, measured m/z of $[M+H]^+$ = 114.088; IR: ν (cm^{-1}) = 1629.65 (C=O stretch).

2.14 *N*-(2-Phenethyl)-propionamide[138]



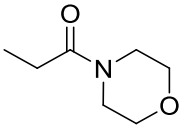
Following representative procedure II using phenethylamine (0.25 mL, 2.0 mmol) as amine species, compound **2.14** was recovered as a thick brown oil (0.276 g, 78%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.06 (3H, t, *J* = 7.6 Hz, $C\underline{H}_3CH_2$), 2.04 – 2.13 (2H, q, *J* = 7.6 Hz, $C(O)C\underline{H}_2CH_3$), 2.75 (2H, t, *J* = 6.9 Hz, $PhC\underline{H}_2CH_2$), 3.41 – 3.49 (2H, q, *J* = 6.9 Hz, $CH_2C\underline{H}_2NH$), 5.39 (1H, br. s, NH), 7.11 – 7. 26 (5H, m, aromatic); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 10.3, 30.1, 36.1, 40.9, 126.9, 129.0, 129.2, 139.3, 174.2; ESI-MS of $[C_{11}H_{15}NO]^+$; theoretical m/z of $[M+H]^+$ = 178.12, measured m/z of $[M+H]^+$ = 178.12; IR: ν (cm^{-1}) = 1632.08 (C=O stretch).

2.15 *N*-(1-Phenethyl)-propionamide[139]



Following representative procedure II, 1-methylbenzylamine (0.28 mL, 2.0 mmol) was used as amine species. An ^{1}H NMR of the crude reaction mixture showed a 31% conversion into **2.15** by comparison of the peaks at 4.21 ppm (1H, 1-methylbenzylamine) and 5.10 ppm (1H, **2.15**). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.15 (3H, t, *J* = 7.5 Hz, $CH_2C\underline{H}_3$), 2.18 – 2.23 (2H, q, *J* = 5.0 Hz, $C(O)C\underline{H}_2CH_3$), 3.48 (3H, s, $PhCH(C\underline{H}_3)NH$), 5.1 (1H, m, $PhC\underline{H}(CH_3)NH$), 5.85 (1H, br. s, $PhCH(CH_3)N\underline{H}$), 7.34 – 7.39 (5H, m, aromatic); ESI-MS of $[C_{11}H_{16}NO]^+$; theoretical m/z of $[M+H]^+$ = 178.119, measured m/z of $[M+H]^+$ = 178.119; IR: ν (cm^{-1}) = 1650.51 (C=O stretch).

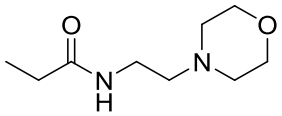
2.16 4-Propionylmorpholine[140]



Following representative procedure II using morpholine (0.22 mL, 2.0 mmol) as amine species, compound **2.16** was recovered as a yellow oil (0.226 g, 79%). ^{1}H NMR (250

MHz, $CDCl_3$, 25 °C): δ = 1.09 (3H, t, *J* = 7.4 Hz, CH_3CH_2), 2.23 – 2.32 (2H, q, *J* = 7.5 Hz, $C(O)C\underline{H}_2CH_3$), 3.32 – 3.41 (2H, m, $C\underline{H}_2NCH_2$), 3.51 – 3.66 (6H, m, $C\underline{H}_2OC\underline{H}_2C\underline{H}_2N$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 9.7, 26.7, 46.2, 67.0, 172.9; ESI-MS of $[C_7H_{13}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 144.10, measured m/z of $[M+H]^+$ = 144.10; IR: ν (cm^{-1}) = 1635.34 (C=O stretch).

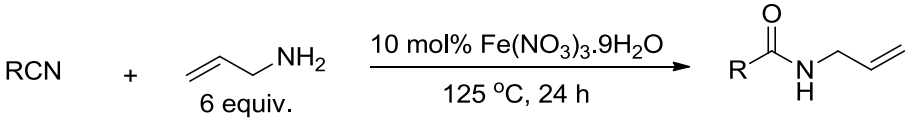
2.17 *N*-(2-Morpholinoethyl)propionamide[141]



Following representative procedure II, (*N*-ethylamine)morpholine (0.26 mL, 2.0 mmol) was used as amine species. An ^1H NMR of the crude reaction mixture showed a 78% conversion into **2.17** by comparison of the peaks at 2.82 ppm (2H, *N*-(ethylamino)morpholine) and 3.33 ppm (2H, **2.17**). ^1H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.09 (3H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_3$), 2.11 – 2.21 (2H, q, *J* = 9.9 Hz, $C(O)C\underline{H}_2CH_3$), 2.37 – 2.45 (6H, m, $C\underline{H}_2N(C\underline{H}_2CH_2)C\underline{H}_2$), 3.25 – 3.32 (2H, m, $CH_2C\underline{H}_2NH$), 3.62 – 3.66 (4H, m, $C\underline{H}_2OC\underline{H}_2$), 6.0 (1H, br. s, NH); ESI-MS of $[C_9H_{19}N_2O_2]^+$; theoretical m/z of $[M+H]^+$ = 187.140, measured m/z of $[M+H]^+$ = 187.140; IR: ν (cm^{-1}) = 1640.30 (C=O stretch).

Representative Procedure III

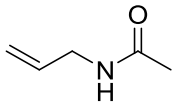
(Table 2.5, Results and Discussion I)



$Fe(NO_3)_3{\cdot}9H_2O$ (0.080 g, 0.20 mmol, 10 mol%) was added to an oven dried Schlenk tube, followed by allylamine (0.91 mL, 12 mmol) and the appropriate nitrile species (2 mmol) according to Table 2.5. The tube was then sealed and the reaction mixture allowed to stir at room temperature for 10 minutes before being heated (125 ^oC) for 24 hours. The resulting reaction mixture was filtered through a short plug of silica, eluting with 92:8 DCM:methanol, then concentrated *in vacuo*. Where required, the product was recrystallised from DCM/hexane and allowed to stand in a freezer overnight before

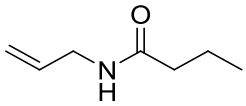
being filtered. The resulting amides were analysed by their ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data.

2.18 *N*-Allylacetamide[142]



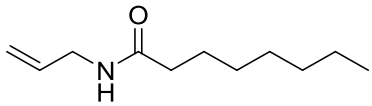
Following representative procedure III using acetonitrile (0.10 mL, 2.0 mmol) as nitrile species, compound **2.18** was recovered as a yellow oil (0.176 g, 89%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 2.01 (3H, s, C(O)C<u>H</u>$_3$), 3.85 - 3.90 (2H, tt, *J* = 1.3 Hz, 4.9 Hz, CHC<u>H</u>$_2$NH), 5.09 - 5.23 (2H, m, C<u>H</u>$_2$CHCH$_2$), 5.63 (1H, br. s, NH), 5.76 – 5.91 (1H, m, CH$_2$C<u>H</u>CH$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 23.6, 42.4, 117.9, 135.7, 170.2; $[C_5H_{10}NO]^+$; theoretical m/z of $[M+H]^+$ = 100.072, measured m/z of $[M+H]^+$ = 100.073; IR: ν (cm^{-1}) = 1644.30 (C=O stretch).

2.19 *N*-Allylbutyramide[143]



Following representative procedure III, butyronitrile (0.17 mL, 2.0 mmol) was used as nitrile species. An ^{1}H NMR of the crude reaction mixture showed a 100% conversion into **2.19.** ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.80 (3H, t, *J* = 7.4 Hz, C<u>H</u>$_3$CH$_2$), 1.44 - 1.58 (2H, sextet, *J* = 7.3 Hz, CH$_3$C<u>H</u>$_2$CH$_2$), 2.06 (2H, t, *J* = 7.2 Hz, CH$_2$C<u>H</u>$_2$C(O)), 4.34 - 4.37 (2H, dt, *J* = 1.4 Hz, 5.7 Hz, CHC<u>H</u>$_2$NH), 5.19 – 5.63 (2H, m, C<u>H</u>$_2$CHCH$_2$), 5.78 – 5.97 (1H, m, CH$_2$C<u>H</u>CH$_2$), 6.03 (1H, br. s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.78, 19.18, 38.69, 41.86, 116.29, 134.40, 172.84; ESI-MS of $[C_7H_{13}NO]^+$; theoretical m/z of $[M+H]^+$ = 128.108, measured m/z of $[M+H]^+$ = 128.106; IR: ν (cm^{-1}) = 1640.08 (C=O stretch).

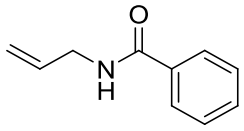
2.20 *N*-Allyloctanamide[144]



Following representative procedure III, octonitrile (0.31 mL, 2.0 mmol) was used as nitrile species. An ^{1}H NMR of the crude reaction mixture showed an 87% conversion into **2.20** by comparison of the peaks at 2.00 ppm (2H, octonitrile) and 2.28 ppm (2H,

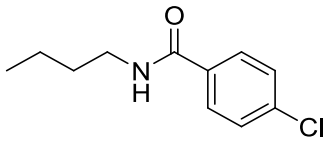
2.20). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.72 (3H, t, *J* = 7.5 Hz, $C\underline{H}_3CH_2$), 1.12 – 1.24 (8H, m, $CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.40 – 1.49 (2H, m, $C(O)CH_2C\underline{H}_2$), 2.28 (2H, t, *J* = 7.2 Hz, $C(O)C\underline{H}_2CH_2$), 4.26 – 4.28 (2H, tt, *J* = 2.5 Hz, 5.0 Hz, $CHC\underline{H}_2NH$), 5.17 – 5.25 (2H, m, $C\underline{H}_2CHCH_2$), 5.78 – 5.87 (1H, m, $CH_2C\underline{H}CH_2$), 6.21 (1H, br. s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.03, 22.51, 25.79, 28.99, 31.56, 36.70, 41.83, 116.06, 134.46, 173.22; ESI-MS of $[C_{10}H_{19}NO]^+$; theoretical m/z of $[M+H]^+$ = 170.154, measured m/z of $[M+H]^+$ = 170.153; IR: ν (cm^{-1}) = 1642.53 (C=O stretch).

2.21 *N*-Allylbenzamide[145]



Following representative procedure III, benzonitrile (0.21 mL, 2.0 mmol) was used as nitrile species. An ^{1}H NMR of the crude reaction mixture showed a 50% conversion into **2.21** by comparison of the peaks at 7.68 ppm (2H, benzonitrile) and 7.92 ppm (2H, **2.21**). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 4.09 – 4.15 (2H, tt, *J* = 2.5 Hz, 5.0 Hz, $NHC\underline{H}_2CH$), 5.18 – 5.26 (2H, m, $CHC\underline{H}_2$), 5.92 – 6.03 (1H, m, $CH_2C\underline{H}CH_2$), 6.29 (1H, br. s, NH), 7.62 – 7.71 (3H, m, aromatic), 7.92 – 8.0 (2H, m, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.6, 116.7, 127.2, 128.8, 131.6, 134.4, 134.7, 167.6; IR: ν (cm^{-1}) = 1634.42 (C=O stretch).

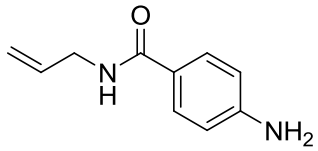
2.22 *N*-Butyl-4-chlorobenzamide[146]



Following representative procedure III using *p*-chlorobenzonitrile (0.28 g, 2.0 mmol) as nitrile species and *n*-butylamine (0.61 mL, 6.0 mmol) as amine species, compound **2.22** was recovered as an off-white solid (0.269 g, 69%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.97 (3H, t, *J* = 5.6 Hz, $C\underline{H}_3CH_2$), 1.56 – 1.68 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2CH_2$), 3.42 – 3.49 (2H, q, *J* = 5.4 Hz, $CH_2C\underline{H}_2NH$), 6.12 (1H, br. s, NH), 7.40 (2H, d, *J* = 7.2 Hz, aromatic), 7.70 (2H, d, *J* = 7.2 Hz, aromatic); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 14.2, 20.6, 32.1, 40.3, 128.7, 129.2, 132.3, 138.1, 168.4; ESI-MS of $[C_{11}H_{14}NOCl]^+$;

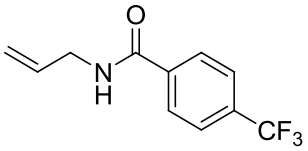
theoretical m/z of $[M+Na]^+$ = 246.74, measured m/z of $[M+Na]^+$ = 246.74; IR: ν (cm^{-1}) = 1632.31 (C=O stretch).

2.23 *N*-Allyl-4-aminobenzamide



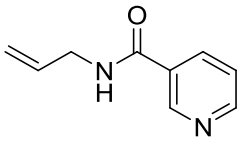
Following representative procedure III, *p*-aminobenzonitrile (0.212 g, 2.0 mmol) was used as nitrile species. An ^{1}H NMR of the crude reaction mixture showed no conversion into **2.23**.

2.24 *N*-Allyl-4-trifluoromethanebenzamide[116]



Following representative procedure III using *p*-trifluoromethylbenzonitrile (0.34 g, 2.0 mmol) as nitrile species, compound **2.24** was recovered as a beige solid (0.252 g, 72%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 4.11 – 4.17 (2H, tt, *J* = 1.4 Hz, 5.6 Hz, $CHC\underline{H}_2NH$), 5.22 – 5.28 (2H, m, $C\underline{H}_2CHCH_2$), 5.89 – 6.04 (1H, $CH_2C\underline{H}CH_2$), 6.29 (1H, br. s, NH), 7.73 (2H, d, *J* = 8.3 Hz, aromatic), 7.92 (2H, d, *J* = 8.3 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 43.0, 117.5, 122.2, 125.8, 126.0, 126.0, 126.1, 126.1, 127.8, 133.4, 133.8, 134.1, 138.1, 166.4; ESI-MS of $[C_{11}H_{10}NOF_3]^+$; theoretical m/z of $[M+H]^+$ = 230.08, measured m/z of $[M+H]^+$ = 230.08; IR: ν (cm^{-1}) = 1638.40, 1651.73.

2.25 *N*-Allylnicotinamide[147]

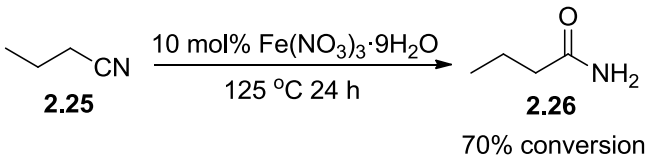


Following representative procedure III using 3-cyanopyridine (0.21 g, 2.0 mmol) as nitrile species, compound **2.25** was recovered as a thick brown oil (0.305 g, 94%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 4.10 – 4.16 (2H, tt, *J* = 1.5 Hz, 5.6 Hz, $NHC\underline{H}_2CH$), 5.21 – 5.34 (2H, m, $C\underline{H}_2CHCH_2$), 5.92 (1H, $CH_2C\underline{H}CH_2$), 6.53 (1H,

br. s, NH), 7.40 – 7.45 (1H, m, aromatic), 8.15 – 8.19 (1H, dt, *J* – 1.9 Hz, 7.9 Hz, aromatic), 8.73 – 8.75 (1H, dd, *J* = 1.6 Hz, 4.8 Hz, aromatic), 9.01 (1H, d, *J* = 1.9, aromatic); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 43.3, 117.5, 127.1, 133.6, 134.9, 141.3, 141.9, 146.9, 161.2; ESI-MS of $[C_9H_{10}N_2O]^+$; theoretical m/z of $[M+H]^+$ = 163.09, measured m/z of $[M+H]^+$ = 163.09; IR: ν (cm^{-1}) = 1642.82, 1662.63.

Primary amide formation

(Scheme 2.4, Results and Discussion I)

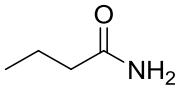


2.25 **2.26**

70% conversion

Following representative procedure I, $Fe(NO_3)_3{\cdot}9H_2O$ (0.080 g, 0.20 mmol, 10 mol%) was used as iron catalyst and butyronitrile **2.25** (0.27 mL, 5.0 mmol) was used as the nitrile species. No amine species was added.

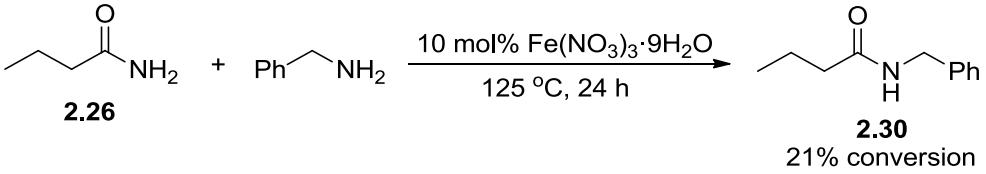
2.26 Butyramide[81]



Following the procedure outlined above, butyronitrile was hydrolysed into butyramide. ^{1}H NMR of the crude reaction mixture showed 70% conversion into **2.26**. ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.90 (3H, t, *J* = 7.4 Hz, $C\underline{H_3}CH_2$), 1.59 (2H, sextet, *J* = 7.4 Hz, $CH_3C\underline{H_2}CH_2$), 2.13 (2H, t, *J* = 7.4 Hz, $CH_2C\underline{H_2}C(O)$) 5.61 (1H, br. s, N<u>H</u>), 5.99 (1H, br. s, N<u>H</u>). ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 14.1, 19.3, 38.2, 175.8; ESI-MS of $[C_4H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 110.06, measured m/z of $[M+H]^+$ = 110.06; IR: ν (cm^{-1}) = 1630.43 (C=O stretch).

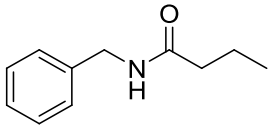
Mechanistic study

(Scheme 2.7, Results and Discussion I)



Following representative procedure I, $Fe(NO_3)_3 \cdot 9H_2O$ (0.080 g, 0.20 mmol, 10 mol%) was used as iron catalyst. Benzylamine (0.64 mL, 6.0 mmol) and butyramide **2.26** (0.26 g, 3.0 mmol) were used as substrates.

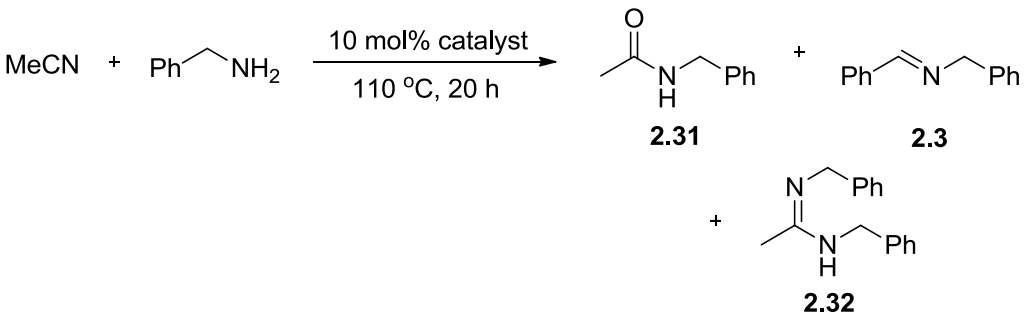
2.30 *N*-Benzylbutyramide[148]



An ^1H NMR of the crude reaction mixture showed a 21% conversion into **2.30** by comparison of the peaks at 3.89 ppm (2H, benzylamine) and 4.65 ppm (2H, **2.30**). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3H, *J* = 7.5 Hz, $CH_2CH_2C\underline{H}_3$), 1.56 - 1.69 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.13 (t, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_2CH_3$), 4.37 (d, 2H, *J* = 5.7 Hz, $PhC\underline{H}_2NH$), 5.66, (br. s, 1H, N<u>H</u>), 7.18 - 7.29 (m, 5H, Ph); ESI-MS of $[C_{11}H_{15}NO]^+$; theoretical m/z of $[M+H]^+$ = 178.123, measured m/z of $[M+H]^+$ = 178.125; IR: ν (cm^{-1}) = 1632.04 (C=O stretch).

Representative Procedure IV

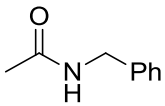
(Table 2.6, Results and Discussion I)



The chosen catalyst (10 mol%) was added to an oven dried Schlenk tube, followed by acetonitrile (0.21 mL, 1.0 mmol) and benzylamine (0.22 mL, 2.0 mmol) being added to

the tube, which was then sealed and the reaction mixture heated (110 ^{o}C) for 20 hours. The resulting reaction mixture was concentrated *in vacuo* and the products analysed by ^{1}H NMR and ^{13}C NMR spectroscopy.

2.31 *N*-Benzylacetamide[149]

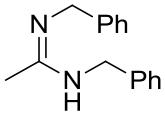


When following representative procedure IV, **2.31** was observed in the crude NMRs. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 2.14 (3H, s, C$\underline{H}_3$C(O)NH), 4.23 (2H, d, *J* = 6.0 Hz, NHC$\underline{H}_2$Ph), 7.21 – 7.33 (5H, m, Ph), 8.29 (1H, br. s., N$\underline{H}$); ^{13}C NMR (75.5 MHz, DMSO-d_6, 25 °C): δ = 22.9, 48.9, 127.1, 127.6, 128.5, 128.6, 128.8, 129.1, 169.5; ESI-MS of $[C_9H_{12}NO]^+$; theoretical m/z of $[M+H]^+$ = 150.088, measured m/z of $[M+H]^+$ = 150.089.

2.3 *N*-Benzylidenebenzylamine

When following representative procedure IV, **2.3** was observed in the crude NMRs. Analytical data matched that previously reported.

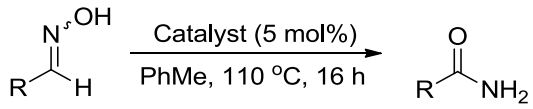
2.32 *N,N'*-Dibenzylacetimidamide[150]



When following representative procedure IV, **2.32** was observed in the crude NMRs. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C): δ = 1.92 (3H, s, C$\underline{H}_3$C(N)NH), 4.35 (4H, s, NC$\underline{H}_2$Ph and NHC$\underline{H}_2$Ph), 7.18 – 7.34 (10H, m, 2xPh); ^{13}C NMR (75.5 MHz, DMSO-d_6, 25 °C): δ = 16.7, 40.7, 42.5, 127.1, 127.6, 128.0, 128.4, 128.6, 128.9, 158.1.

6.3 Chapter 3 Experimental

Representative Procedure V



The chosen catalyst (5 mol%) was added to an oven dried Schlenk tube, followed by the appropriate oxime species (benzaldoxime, 0.121 g, 1.00 mmol; butyraldoxime, 0.09 mL, 1.00 mmol). Solvent (1.0 mL) was added to the tube, which was then sealed and the reaction mixture was allowed to stir at room temperature for 10 minutes before being heated at reflux. The resulting reaction mixture was allowed to cool before being concentrated *in vacuo*. Where appropriate, the product was purified by column chromatography on silica gel (dichloromethane/methanol as eluent) or simply filtered through a short plug of silica (eluting with 95:5 dichloromethane/methanol unless otherwise stated) and then recrystallised from suitable solvent(s). The resulting primary amides were anaylsed by their NMR spectroscopy and mass spectrometry data.

Variation of catalyst and solvent

(Tables 3.1 – 3.3 and Table 3.5, Results and Discussion II)

Following representative procedure V, the appropriate catalysts and solvents were used according to Tables 3.1 – 3.5. Benzaldoxime (0.121 g, 1.00 mmol) and butyraldoxime, (0.09 mL, 1.00 mmol) were used as the aldoxime species.

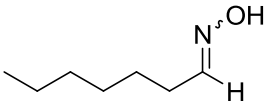
Representative Procedure VI

Synthesis of Aldoximes[151]

To a stirred solution of hydroxylamine hydrochloride (2.78 g, 40.0 mmol) in ethanol/water (5:1) (60 mL) was added the appropriate aldehyde (20 mmol) at 0 ^{o}C. Sodium acetate (4.92 g, 60.0 mmol) was added slowly and the reaction mixture was allowed to warm to room temperature and left stirring for 2 - 3 hours. Ethanol was removed from the solution, then 30 mL water was added and the product was extracted into dichloromethane (2 x 60 mL). The combined organic extracts were dried over magnesium sulphate and the solvent removed *in vacuo*. The resulting aldoximes were

analysed by their ^{1}H and ^{13}C NMR spectra and mass spectrometry data and used without further purification.

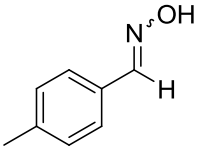
Heptaldoxime[148]



Following representative procedure VI, heptaldehyde (2.69 mL, 20.0 mmol) was used and the resulting aldoxime isolated in 76% yield (1.96 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82 (t, 3H, *J* = 6.8 Hz, $C\underline{H}_3CH_2CH_2$), 1.22 - 1.44 (m, 8H, $CH_3C\underline{H}_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_2$), 2.09 - 2.35 (m, 2H, $CH_3CH_2CH_2CH_2CH_2C\underline{H}_2$), 6.65 (t, 1/2H, *J* = 5.4 Hz, C(=NOH)H), 7.36 (t, 1/2H, *J* = 5.4 Hz, C(=NOH)H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.02, 14.06, 22.51, 22.52, 24.83, 25.03, 28.75, 29.04, 29.24, 29.83, 31.50, 31.79, 152.23, 152.83; ESI-MS of $[C_7H_{15}NO]^+$; theoretical m/z of $[M+H]^+$ = 130.126, measured m/z of $[M+H]^+$ = 130.125.

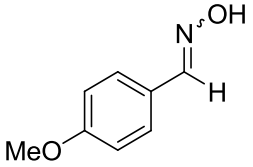
4-Methylbenzaldoxime[148]



Following representative procedure VI, 4-methylbenzaldehyde (2.36 mL, 20.0 mmol) was used and the resulting aldoxime isolated in 89% yield (2.40 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H, $C\underline{H}_3$), 7.11 (d, 2H, *J* = 7.8 Hz, Ph), 7.38 (d, 2H, *J* = 7.8 Hz, Ph), 8.05 (s, 1H, C(=NOH)H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.46, 127.01, 129.07, 129.56, 140.41, 150.13; ESI-MS of $[c_8H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 136.076, measured m/z of $[M+H]^+$ = 136.076.

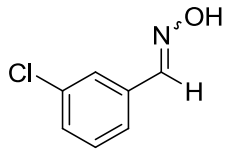
4-Methoxybenzaldoxime[148]



Following representative procedure VI, 4-methoxybenzaldehyde (2.43 mL, 20.0 mmol) was used and the resulting aldoxime isolated in 79% yield (2.39 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 3H, OC<u>H</u>$_3$), 6.90 (d, 2H, *J* = 8.7 Hz, Ph), 7.51 (d, 2H, *J* = 8.7 Hz, Ph), 8.12 (s, 1H, C(=NOH)<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.36, 113.83, 114.31, 128.57, 133.02, 149.86, 161.10; ESI-MS of $[C_8H_9NO_2]^+$; theoretical m/z of $[M+H]^+$ = 152.071, measured m/z of $[M+H]^+$ = 152.071.

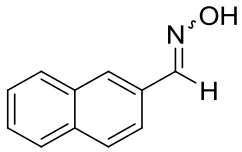
3-Chlorobenzaldoxime[148]



Following representative procedure VI, 3-chlorobenzaldehyde (2.26 mL, 20.0 mmol) was used and the resulting aldoxime isolated in 83% yield (2.57 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 - 7.46 (m, 3H, Ph), 7.58 (s, 1H, Ph), 8.10 (s, 1H, C(=NOH)<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 125.28, 126.85, 130.07, 133.73, 134.87, 149.14; ESI-MS of $[C_7H_6NOCl]^+$; theoretical m/z of $[M+H]^+$ = 156.015, measured m/z of $[M+H]^+$ = 156.015.

2-Naphthaldoxime[148]

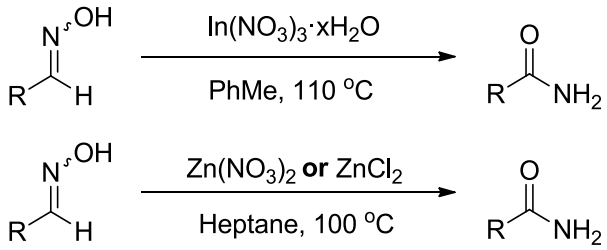


Following representative procedure VI, 2-naphthaldehyde (3.12 g, 20.0 mmol) was used and the resulting aldoxime isolated in 91% yield (3.11 g).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 - 7.46 (m, 2H, naphthyl), 7.70 - 7.81 (m, 5H, naphthyl), 8.23 (s, 1H, C(=NOH)<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 122.65, 126.70, 127.09, 127.89, 128.36, 128.69, 128.76, 129.54, 133.16, 134.18, 150.40; ESI-MS of $[C_{11}H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 172.076, measured m/z of $[M+H]^+$ = 172.076.

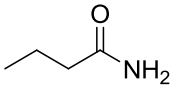
Representative Procedure VII

(Tables 3.4 and 3.6, Results and Discussion II)



$In(NO_3)_3 \cdot xH_2O$, $ZnCl_2$ or $Zn(NO_3)_3$ was added to an oven dried Schlenk tube, followed by the appropriate oxime species (2.0 mmol). Toluene or heptanes (1.5 mL) was added to the tube, which was then sealed and the reaction mixture was allowed to stir at room temperature for 10 minutes before being heated at reflux. The resulting reaction mixture was allowed to cool before being concentrated *in vacuo*. Where appropriate, the product was purified by column chromatography on silica gel (dichloromethane/methanol as eluent) or simply filtered through a short plug of silica (eluting with 95:5 dichloromethane/methanol unless otherwise stated) and then recrystallised from suitable solvent(s). The resulting amides were anaylsed by their NMR and IR spectroscopy and mass spectrometry data.

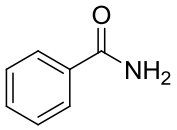
3.2 Butyramide[82]



Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (2.4 mg, 0.008 mmol, 0.4 mol%) was used with butyraldoxime (0.20 mL, 2.0 mmol). The reaction mixture was heated at reflux for 16 hours. After purification, **3.2** was recovered as a white solid (0.157 g, 87%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 0.90 (3H, t, *J* = 7.4 Hz, $C\underline{H}_3CH_2$), 1.59 (2H, sextet, *J* = 7.4 Hz, $CH_3C\underline{H}_2CH_2$), 2.13 (2H, t, *J* = 7.4 Hz, $CH_2C\underline{H}_2C(O)$) 5.61 (1H, br. s, N<u>H</u>), 5.99 (1H, br. s, N<u>H</u>). ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 14.1, 19.3, 38.2, 175.8; ESI-MS of $[C_4H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 110.06, measured m/z of $[M+H]^+$ = 110.06; IR: ν (cm^{-1}) = 1630.43 (C=O stretch).

Following representative procedure VII, $Zn(NO_3)_2$ (0.059 g, 0.20 mmol, 10 mol%) was used with butyraldoxime (0.20 mL, 2.0 mmol). The reaction mixture was heated at reflux for 16 hours. After purification, **3.2** was recovered as a white solid (0.168 g, 93%). Analytical data was consistent with that reported above.

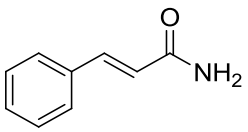
3.1 Benzamide[82]



Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (6.0 mg, 0.02 mmol, 1.0 mol%) was used with benzaldoxime (0.242 g, 2.0 mmol). The reaction mixture was heated at reflux for 18 hours. After purification, **3.1** was recovered as a white solid (01912 g, 79%). ^{1}H NMR (300MHz, $CDCl_3$, 25 °C): δ = 6.20 (2H, br. s, N$\underline{H}_2$), 7.42-7.56 (3H, m, aromatic), 7.81-7.84 (2H, m, aromatic). ^{13}C NMR (75MHz, $CDCl_3$, 25 °C): δ = 127.7, 129.0, 132.5, 133.8, 169.8; ESI-MS of $[C_7H_7NO]^+$; theoretical m/z of $[M+H]^+$ = 144.04, measured m/z of $[M+H]^+$ = 144.04; IR: ν (cm^{-1}) = 1655.22 (C=O stretch).

Following representative procedure VII, $ZnCl_2$ (0.031 g, 0.1 mmol, 10 mol%) was used with benzaldoxime (0.242 g, 2 mmol). The reaction mixture was heated at reflux for 18 hours. After purification, **3.1** was recovered as a white solid (0.213 g, 88%). Analytical data was consistent with that reported above.

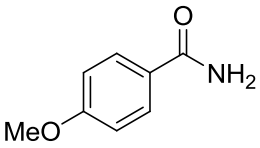
3.3 Cinnamamide[82]



Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (2.4 mg, 0.008 mmol, 0.4 mol%) was used with cinnamaldoxime (0.294 g, 2.0 mmol). The reaction mixture was heated at reflux for 16 hours. After purification, **3.3** was recovered as an off-white solid (0.265 g, 90%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 ^{o}C): δ = 5.61 (2H,br. s, N$\underline{H}_2$), 6.42 (1H, d, *J* = 15.6 Hz, CHC$\underline{H}$C(O)NH_2), 7.34 – 7.46 (3H, m, aromatic), 7.45 – 7.55 (2H, m, aromatic), 7.73 (1H, d, C$\underline{H}$CHC(O)NH_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 119.7, 128.3, 129.2, 130.4, 134.8, 143.0, 168.1; ESI-MS of $[C_9H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 148.07, measured m/z of $[M+H]^+$ = 148.07; IR: ν (cm^{-1}) = 1631.03, 1659.78.

Following representative procedure VII, $Zn(NO_3)_2$ (0.059 g, 0.20 mmol, 10 mol%) was used with cinnamaldoxime (0.294 g, 2 mmol). The reaction mixture was heated at reflux for 16 hours. After purification, **3.3** was recovered as an off-white solid (0.272 g, 93%). Analytical data was consistent with that reported above.

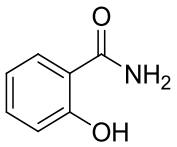
3.4 4-Methoxybenzamide[82]



Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (6.0 mg, 0.02 mmol, 1.0 mol%) was used with 4-methoxybenzaldoxime (0.294 g, 2.0 mmol). The reaction mixture was heated at reflux for 18 hours. An ^1H NMR of the crude reaction mixture showed a 30% conversion to the title compound by comparison of the peaks at 7.08 (2H, 4-methoxybenzaldoxime) and 6.87 (2H, 4-methoxybenzamide). ^1H NMR (250 MHz, $CDCl_3$, 25 ^oC): δ = 3.79 (3H, s, CH_3), 5.95 (2H, br. s, NH_2), 6.84 (2H, d, *J* = 10.0 Hz, aromatic), 7.72 (2H, d, *J* = 10.0 Hz, aromatic).

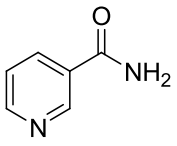
Following representative procedure VII, $ZnCl_2$ (0.031 g, 0.10 mmol, 10 mol%) was used with 4-methoxybenzaldoxime (0.302 g, 2.0 mmol). The reaction mixture was heated at reflux for 18 hours. After purification, **3.4** was recovered as a white solid (0.266 g, 88%). Analytical data was consistent with that reported above. ^{13}C NMR (75.5 MHz, $CD_3C(O)CD_3$): δ = 55.9, 114.25, 129.5, 129.8, 163.2, 169.7; ESI-MS of $[C_8H_9NO_2]^+$; theoretical m/z of $[M+H]^+$ = 152.07, measured m/z of $[M+H]^+$ = 152.07; IR: ν (cm^{-1}) = 1642.17 (C=O stretch).

3.5 Salicylamide



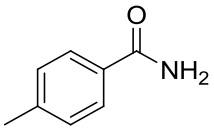
Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (0.012 g, 0.04 mmol, 2.0 mol%) was used with salicylaldoxime (0.274 g, 2.0 mmol). An ^1H NMR of the crude reaction mixture showed no reaction to have taken place.

3.6 Nicotinamide



Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (0.012 g, 0.04 mmol, 2.0 mol%) was used with 3-pyridinealdoxime (0.244 g, 2.0 mmol). An ^1H NMR of the crude reaction mixture showed no reaction to have taken place.

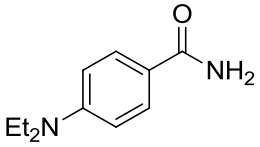
3.7 4-Methylbenzamide[82]



Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (6.0 mg, 0.02 mmol, 1.0 mol%) was used with 4-methylbenzaldoxime (0.324 g, 2.0 mmol). The reaction mixture was heated at reflux for 16 hours. After purification, **3.7** was recovered as a pale yellow solid (0.234 g, 88%). ^{1}H NMR (250 MHz, $CDCl_3$, 25 ^{o}C): δ = 2.42 (3H, s, C$\underline{H}_3$), 5.90 (2H, br. s, N$\underline{H}_2$), 7.29 (2H, d, *J* = 7.8 Hz, aromatic), 7.76 (2H, d, *J* = 7.8 Hz, aromatic); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.4, 127.2, 129.2, 131.5, 142.0, 168.0; ESI-MS of $[C_8H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 136.08, measured m/z of $[M+H]^+$ = 136.08; IR: ν (cm^{-1}) = 1666.77 (C=O stretch).

Following representative procedure VII, $ZnCl_2$ (0.031 g, 0.10 mmol, 10 mol%) was used with 4-methylbenzaldoxime (0.324 g, 2.0 mmol). After purification, **3.7** was recovered as an off-white solid (0.209 g, 83%). Analytical data was consistent with that reported above.

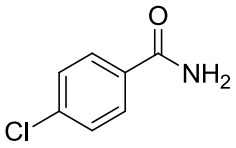
3.8 4-(*N*,*N*-Diethylamino)benzamide[82]



Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (4.8 mg, 0.016 mmol, 0.8 mol%) was used with *N*,*N*-dimethylaminobenzaldoxime (0.384 g, 2.0 mmol). The reaction mixture was heated at reflux for 16 hours. After purification, **3.8** was recovered as a brown solid (0.369 g, 96%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 ^{o}C): δ = 1.20 (6H, t, *J* = 7.5 Hz, 2 C$\underline{H}_3$CH$_2$), 3.37 – 3.44 (4H, q, *J* = 7.1 Hz, 2 CH$_3$C$\underline{H}_2$), 5.63 (2H, br. s, NH_2), 6.64 (2H, d, *J* = 9.0 Hz, aromatic), 7.69 (2H, d, *J* = 9.0 Hz, aromatic); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.8, 44.8, 110.7, 119.3, 129.7, 150.7, 169.7; ESI-MS of $[C_{11}H_{16}N_2O]^+$; theoretical m/z of $[M+H]^+$ = 193.13, measured m/z of $[M+H]^+$ = 193.13; IR: ν (cm^{-1}) = 1644.62 (C=O stretch).

Following representative procedure VII, $ZnCl_2$ (0.031 g, 0.10 mmol, 10 mol%) was used with 4-(*N*,*N*-diethylamino)-benzaldoxime (0.384 g, 2.0 mmol). After purification, **3.8** was recovered as a white solid (0.319 g, 91%). Analytical data was consistent with that reported above.

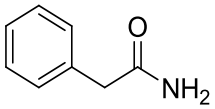
3.9 4-Chlorobenzamide[82]



Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (6.0 mg, 0.02 mmol, 1.0 mol%) was used with 4-chlorobenzaldoxime (0.310 g, 2.0 mmol). The reaction mixture was heated at reflux for 18 hours. After purification, **3.9** was recovered as an off-white solid (0.274 g, 88%). ^{1}H NMR (250 MHz, $CD_3C(O)CD_3$, 25 ^oC): δ = 6.80 (2H, br. s, $N\underline{H}_2$), 7.42 (2H, d, *J* = 8.6 Hz, aromatic), 7.88 (2H, d, *J* = 8.6 Hz, aromatic); ^{13}C NMR (75.5 MHz, $CD_3C(O)CD_3$): δ = 129.2, 129.4, 131.9, 138.4, 168.8; ESI-MS of $[C_7H_6NOCl]^+$; theoretical m/z of $[M+Na]^+$ = 178.00, measured m/z of $[M+Na]^+$ = 178.00; IR: ν (cm^{-1}) = 1662.13 (C=O stretch).

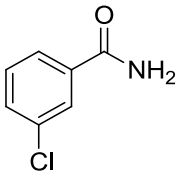
Following representative procedure VII, $ZnCl_2$ (0.031 g, 0.10 mmol, 10 mol%) was used with 4-chlorobenzaldoxime (0.310 g, 2.0 mmol). The reaction mixture was heated at reflux for 16 hours. After purification, **3.9** was recovered as a white solid (0.281 g, 90%). Analytical data was consistent with that reported above.

3.10 2-Phenylacetamide[152]



Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (4.8 mg, 0.016 mmol, 0.8 mol%) was used with 2-phenylacetaldoxime (0.312 g, 2.0 mmol). The reaction mixture was heated at reflux for 16 hours. After purification, **3.10** was recovered as a brown solid (0.229 g, 86%). ^{1}H NMR (250 MHz, $CD_3C(O)CD_3$, 25 ^oC): δ = 3.51 (2H, s, $PhCH_2C(O)$), 5.54 (2H, br. s, NH_2), 7.32 – 7.46 (5H, m, aromatic); ^{13}C NMR (75.5 MHz, $CD_3C(O)CD_3$): δ = 43.7, 127.9, 129.5, 129.8, 135.2, 173.5; ESI-MS of $[C_8H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 136.08, measured m/z of $[M+H]^+$ = 136.08. Following representative procedure VII, $Zn(NO_3)_2$ (0.059 g, 0.20 mmol, 10 mol%) was used with 2-phenylacetaldoxime (0.294 g, 2.0 mmol). The reaction mixture was heated at reflux for 16 hours. After purification, **3.10** was recovered as a brown solid (0.256 g, 94%). Analytical data was consistent with that reported above.

3.11 3-Chlrorbenzamide[153]

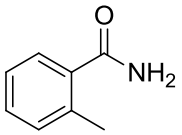


Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (6.0 mg, 0.02 mmol, 1.0 mol%) was used with 3-chlorobenzaldoxime (0.310 g, 2.0 mmol). The reaction mixture was heated at reflux for 18 hours. After purification, **3.11** was recovered as a white solid (0.269 g, 87%).

^{1}H NMR (250 MHz, $CDCl_3$, 25 ^{o}C): δ = 6.04 (2H, br. s, N<u>H</u>$_2$), 7.44 – 7.76 (4H, m, aromatic); ^{13}C NMR (75.5 MHz, $CD_3C(O)CD_3$): δ = 124.9, 127.8, 129.2, 129.4, 131.9, 136.4, 168.0; ESI-MS of $[C_7H_7NOCl]^+$; theoretical m/z of $[M+H]^+$ = 155.015, measured m/z of $[M+H]^+$ = 155.017; IR: ν (cm^{-1}) = 1665.23 (C=O stretch).

Following representative procedure VII, $Zn(NO_3)_2$ (0.059 g, 0.20 mmol, 10 mol%) was used with 3-chlorobenzaldoxime (0.310 g, 2.0 mmol).. The reaction mixture was heated at reflux for 16 hours. After purification, **3.11** was recovered as a white solid (0.282 g, 91%). Analytical data was consistent with that reported above.

3.12 2-Methylbenzamide[85]



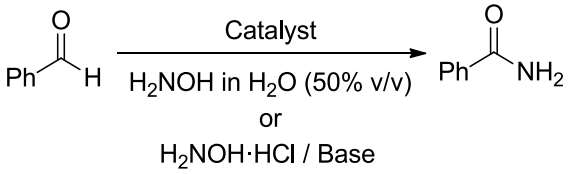
Following representative procedure VII, $In(NO_3)_3 \cdot xH_2O$ (6.0 mg, 0.02 mmol, 1.0 mol%) was used with 2-methylbenzaldoxime (0.270 g, 2.0 mmol). The reaction mixture was heated at reflux for 18 hours. An ^{1}H NMR of the crude reaction mixture showed a 14% conversion into **3.12**.

^{1}H NMR (250 MHz, $CDCl_3$, 25 ^{o}C): δ = 2.61 (3H, s, C<u>H</u>$_3$), 6.34 (2H, br. s, N<u>H</u>$_2$), 7.32 – 7.46 (4H, m, aromatic); ESI-MS of $[C_8H_{10}NO]^+$; theoretical m/z of $[M+H]^+$ = 135.068, measured m/z of $[M+H]^+$ = 135.068.

Following representative procedure VII, $Zn(NO_3)_2$ (0.059 g, 0.20 mmol, 10 mol%) was used with 2-methylbenzaldoxime (0.270 g, 2.0 mmol). The reaction mixture was heated at reflux for 16 hours An ^{1}H NMR of the crude reaction mixture showed a 31% conversion into **3.12**. Analytical data was consistent with that reported above.

Representative Procedure VIII

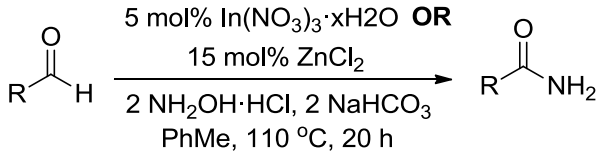
(Table 3.8, Results and Discussion II)



To an oven dried Schlenk tube was added the appropriate catalyst followed by hydroxylamine hydrochloride or hydroxylamine solution in water (50% w/w) and sodium hydrogen carbonate, then benzaldehyde (2.0 mmol), all according to the reaction conditions in Table 3.9. Solvent (1.5 mL) was added to the tube, which was then sealed and the reaction mixture allowed to stir at room temperature for 10 minutes before being heated at reflux. The resulting reaction mixture was allowed to cool and then methanol (3.0 mL) was added. The crude reaction mixture was filtered through a short plug of celite (eluting with dichloromethane) and concentrated *in vacuo*. The resulting amides were analysed by their ^{1}H NMR, ^{13}C NMR and mass spectrometry data.

Representative Procedure IX

(Table 3.9, Results and Discussion II)



To an oven dried Schlenk tube was added the appropriate catalyst ($In(NO_3)_3 \cdot xH_2O$ or $ZnCl_2$) followed by hydroxylamine hydrochloride (0.14g, 4.0 mmol) and sodium hydrogen carbonate (0.16g, 4.0 mmol), then the appropriate aldehyde (2.0 mmol). Toluene (2.0 mL) was added to the tube, which was then sealed and the reaction mixture allowed to stir at room temperature for 10 minutes before being heated at reflux for 20 hours. The resulting reaction mixture was allowed to cool and then methanol (3.0 mL) was added. Where appropriate, the product was purified by column chromatography on silica gel (dichloromethane/methanol as eluent) or simply filtered through a short plug of silica (eluting with 95:5 dichloromethane/methanol unless otherwise stated) and then recrystallised from suitable solvent(s). The resulting amides were analysed by their ^{1}H NMR, ^{13}C NMR and mass spectrometry data.

3.2 Butyramide

Following representative procedure IX, butyraldehyde (0.09 mL, 1.0 mmol) was used as the aldehyde species. After purification, **3.2** was recovered as a white solid ($ZnCl_2$: 0.079 g, 91%). Analytical data was consistent with that reported above.

3.7 4-Methylbenzamide

Following representative procedure IX, 4-methylbenzaldehyde (0.13 mL, 1.0 mmol) was used as the aldehyde species. After purification, **3.7** was recovered as a pale yellow solid ($In(NO_3)_3 \cdot xH_2O$: 0.120 g, 89%; $ZnCl_2$: 0.120 g, 89%). Analytical data was consistent with that reported above.

3.3 Cinnamamide

Following representative procedure IX, cinnamaldehyde (0.13 mL, 1.0 mmol) was used as the aldehyde species. After purification, **3.3** was recovered as a light brown solid ($In(NO_3)_3 \cdot xH_2O$: 0.138 g, 94%; $ZnCl_2$: 0.127 g, 86%). Analytical data was consistent with that reported above.

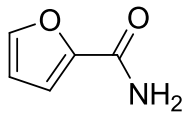
3.4 4-Methoxybenzamide

Following representative procedure IX, 4-methoxybenzaldehyde (0.12 mL, 1.0 mmol) was used as the aldehyde species. After purification, **3.4** was recovered as a yellow solid ($In(NO_3)_3 \cdot xH_2O$: 0.131 g, 87%). Analytical data was consistent with that reported above.

3.12 2-Methylbenzamide

Following representative procedure IX, 2-methylbenzaldehyde (0.12 mL, 1.0 mmol) was used as the aldehyde species. An ^1H NMR of the crude reaction mixture showed a 37% conversion into **3.12** when $In(NO_3)_3 \cdot xH_2O$ was used as catalyst and no reaction to have taken place when $ZnCl_2$ was used as catalyst. Analytical data was consistent with that reported above.

3.15 2-Furamide[85]



Following representative procedure IX, furaldehyde (0.08 mL, 1.0 mmol) was used as the aldehyde species. After purification, **3.15** was recovered as a dark brown solid ($In(NO_3)_3 \cdot xH_2O$: 0.093 g, 83%).

^{1}H NMR (300 MHz, $CDCl_3$, 25 ^oC): δ = 6.10 (2H, br. s, NH_2), 6.52 (1H, dd, *J* = 3.6 Hz, 1.8 Hz), 7.17 (1H, dd, *J* = 3.6 Hz, 0.6 Hz) 7.48 (1H, d, *J* = 0.6 Hz); ^{13}C NMR (75MHz, $CDCl_3$, 25 °C): δ = 112.7, 115.6, 144.8, 147.8, 160.5; ESI-MS of $[C_5H_6NO_2]^+$; theoretical m/z of $[M+H]^+$ = 112.038, measured m/z of $[M+H]^+$ = 112.038; IR: ν (cm^{-1}) = 1675.23 (C=O stretch).

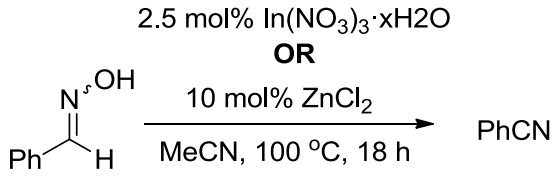
3.8 4-(*N,N*-Diethylamino)benzamide

Following representative procedure IX, *N,N*-diethylbenzaldehyde (0.18 g, 1.0 mmol) was used as the aldehyde species. After purification, **3.8** was recovered as a brown solid ($In(NO_3)_3 \cdot xH_2O$: 0.154 g, 80%). Analytical data was consistent with that reported above.

3.9 4-Chlorobenzamide

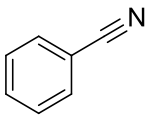
Following representative procedure IX, 4-chlorobenzaldehyde (0.14 g, 1.0 mmol) was used as the aldehyde species. An ^{1}H NMR of the crude reaction mixture showed a 68% conversion into **3.9** when $In(NO_3)_3 \cdot xH_2O$ was used as catalyst and a 34% conversion into **3.9** when $ZnCl_2$ was used as catalyst. Analytical data was consistent with that reported above.

Representative Procedure X



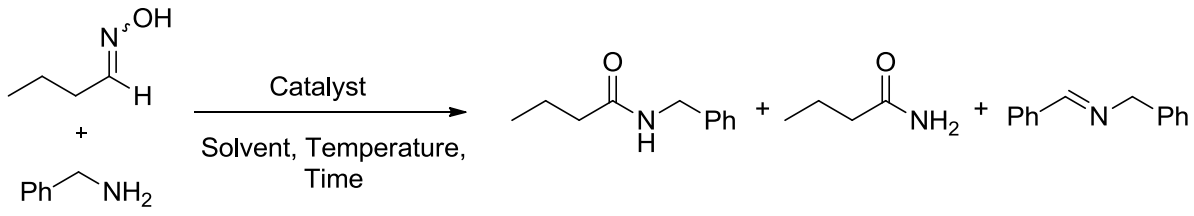
Benzaldoxime (0.242g, 2.00 mmol) and the appropriate catalyst were added to an oven dried Radleys carousel tube, followed by acetonitrile (2.0 mL). The tube was then sealed and heated at 100 ^{o}C for 18 hours. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* and the products analysed by their ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. Purification by column chromatography (eluting with 98:2 dichloromethane:methanol) was carried out.

3.16 Benzonitrile



Following representative procedure X, **3.16** was recovered as a white solid ($In(NO_3)_3 \cdot xH_2O$: 0.184 g, 89%; $ZnCl_2$: 0.184 g, 89%).
^{1}H NMR (250 MHz, $CDCl_3$, 25 ^{o}C): δ = 7.47 – 7.53 (3H, m, Ph) 7.61 – 7.71 (2H, m, Ph); ^{13}C NMR (75MHz, $CDCl_3$, 25 °C): δ = 112.7, 117.6, 127.6, 127.8, 130.5, 133.3; ESI-MS of $[C_7H_6N]^+$; theoretical m/z of $[M+H]^+$ = 103.041, measured m/z of $[M+H]^+$ = 103.043. Analtyical data was compared to that of an authentic sample.

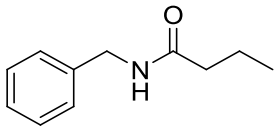
Representative Procedure XI



The chosen catalyst was added to an oven dried carousel tube, followed by butyraldoxime (0.20 g, 2.2 mmol), benzylamine (0.22 mL, 2.0 mmol) and the chosen solvent (2.0 mL). The tube was then sealed and the reaction mixture placed under an atmosphere of nitrogen before the reaction mixture was heated at the chosen

temperature for the chosen length of time. The resulting mixture was allowed to cool to room temperature before being filtered through a short plug of celite if necessary. The resulting amides were anaylsed by their NMR and IR spectroscopy and mass spectrometry data.

2.30 *N*-Benzylbutyramide[148]



Following representative procedure II, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-Benzylbutyramide was recovered as an off-white solid (0.299 g, 84%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (ethanol/water).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3H, *J* = 7.5 Hz, $CH_2CH_2C\underline{H}_3$), 1.56 - 1.69 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.12 (t, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_2CH_3$), 4.37 (d, 2H, *J* = 5.7 Hz, $PhC\underline{H}_2NH$), 5.66, (br. s, 1H, N<u>H</u>), 7.18 - 7.29 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.81, 19.19, 38.73, 43.59, 127.51, 127.84, 128.73, 138.46, 172.78; ESI-MS of $[C_{11}H_{15}NO]^+$; theoretical m/z of $[M+H]^+$ = 178.123, measured m/z of $[M+H]^+$ = 178.125; IR: ν (cm^{-1}) = 1632.04 (C=O stretch).

Variation of catalyst

(Table 3.10, Results and Discussion II)

Following representative procedure XI, the appropriate catalyst (20 mol%) was used according to Table 3.10. Toluene (2.0 mL) was used as solvent and the reaction mixture heated at 115 ^{o}C for 24 hours.

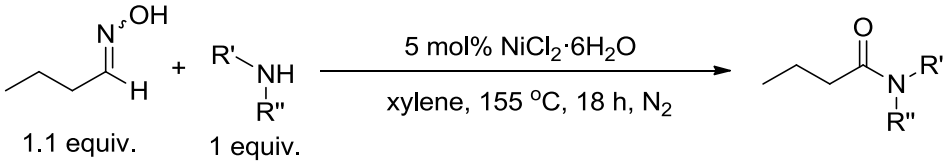
Variation of catalyst loading, solvent and temperature

(Table 3.11, Results and Discussion II)

Following representative procedure XI, $NiCl_2{\cdot}6H_2O$ was used as catalyst with the loading, solvent and temperature varied according to Table 3.11. The reaction mixture was heated for 18 hours.

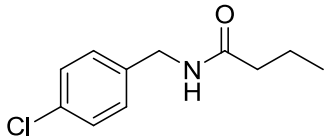
Representative Procedure XII

(Table 3.12, Results and Discussion II)



$NiCl_2 \cdot 6H_2O$ (5 mol%) was added to an oven dried carousel tube, followed by butyraldoxime (0.2 mL, 2.2 mmol) and *p*-xylene (2.0 mL). The tube was then sealed and the reaction mixture placed under an atmosphere of nitrogen before the appropriate amine species was added and the reaction mixture heated at 155 ^{o}C for 18 hours. The resulting mixture was allowed to cool to room temperature before being filtered through a short plug of celite. Where appropriate, the product was purified by column chromatography on silica gel (dichloromethane/methanol or diethyl ether/heptanes as eluent), then recrystallised from suitable solvent(s). The resulting amides were anaylsed by their NMR and IR spectroscopy and mass spectrometry data.

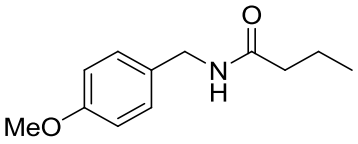
3.19 *N*-(4-Chlorobenzyl)butyramide[148]



Following representative procedure XII, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and 4-chlorobenzylamine (0.24 mL, 2.0 mmol) was used as the amine species. *N*-(4-Chlorobenzyl)butyramide was recovered as a white solid (0.351 g, 83%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (ethanol/water).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 7.5 Hz, $CH_2CH_2C\underline{H}_3$), 1.56 - 1.68 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.13 (t, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_2CH_3$), 4.44 (d, 2H, *J* = 6. 0 Hz, (4-Cl)Ph$C\underline{H}_2$NH), 5.70, (br. s, 1H, N$\underline{H}$), 7.12 - 7.24 (m, 4H, (4-Cl)Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.79, 19.15, 38.65, 42.83, 128.82, 129.13, 133.27, 137.07, 172.89; ESI-MS of $[C_{11}H_{14}NOCl]^{+}$; theoretical m/z of $[M+H]^{+}$ = 212.083, measured m/z of $[M+H]^{+}$ = 212.083; IR: ν (cm^{-1}) = 1632.62 (C=O stretch).

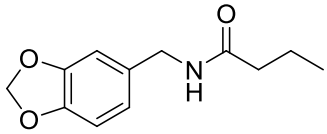
3.20 *N*-(4-Methoxybenzyl)butyramide[148]



Following representative procedure XII, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and 4-methoxybenzylamine (0.26 mL, 2.0 mmol) was used as the amine species. *N*-(4-Methoxybenzyl)butyramide was recovered as a white solid (0.364 g, 88%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 - 0.93 (2t, 6H, *J* = 7.2 Hz, $CH_2CH_2C\underline{H}_3$), 1.41 - 1.53 (m, 2H, $CH_2C\underline{H}_2CH_3$), 1.95 (t, 2H, *J* = 7.2 Hz, $C\underline{H}_2CH_2CH_3$), 3.58 (s, 3H, $OC\underline{H}_3$), 4.16 (d, 2H, *J* = 5.7 Hz, (4-OMe)Ph$C\underline{H}_2$NH), 5.42, (br. s, 1H, N$\underline{H}$), 6.64 (d, 2H, *J* = 8.7 Hz, (4-OMe)Ph); 6.99 (d, 2H, *J* = 8.7 Hz, (4-OMe)Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.83, 19.21, 38.77, 43.08, 53.47, 55.34, 114.10, 129.23, 130.51, 159.04, 172.72; ESI-MS of $[C_{12}H_{17}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 208.134, measured m/z of $[M+H]^+$ = 208.134; IR: ν (cm^{-1}) = 1631.01 (C=O stretch).

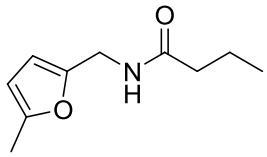
3.21 *N*-Piperonylbutyramide[148]



Following representative procedure XII, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and piperonylamine (0.25 mL, 2.0 mmol) was used as the amine species. *N*-Piperonylbutyramide was recovered as an off-white solid (0.393 g, 89%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3H, *J* = 7.5 Hz, $CH_2CH_2C\underline{H}_3$), 1.55 - 1.68 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.12 (t, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_2CH_3$), 4.27 (d, 2H, *J* = 6.0 Hz, ((CH_2O_2)Ph$C\underline{H}_2$NH), 5.61, (br. s, 1H, N$\underline{H}$), 5.88 (s, 2H, ($C\underline{H}_2O_2$)Ph), 6.67 - 6.70 (m, 3H, (CH_2O_2)$\underline{Ph}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.84, 19.19, 38.73, 43.41, 53.47, 101.10, 108.32, 108.44, 121.12, 132.31, 146.97, 147.93, 172.76; ESI-MS of $[C_{12}H_{15}NO_3]^+$; theoretical m/z of $[M+H]^+$ = 222.113, measured m/z of $[M+H]^+$ = 222.111; IR: ν (cm^{-1}) = 1625.46 (C=O stretch).

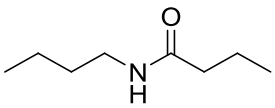
3.22 *N*-(5-Methylfurfuryl)butyramide[148]



Following representative procedure XII, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and (5-methyl)furfurylamine (0.21 mL, 2.0 mmol) was used as the amine species. *N*-(5-Methylfurfuryl)butyramide was recovered as a dark brown oil (0.327 g, 90%) after column chromatography (eluting with dichloromethane/methanol 97:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 7.5 Hz, $CH_2CH_2C\underline{H}_3$), 1.54 - 1.66 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.10 (t, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_2CH_3$), 2.19 (s, 3H, $C\underline{H}_3$), 4.30 (d, 2H, *J* = 5.4 Hz, $C\underline{H}_2NHC(O)$), 5.72 (br. s, 1H, N<u>H</u>), 5.81 (d, 1H, *J* = 2.1 Hz, furyl), 6.01 (d, 1H, *J* = 2.1 Hz, furyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.51, 13.74, 19.09, 36.61, 38.59, 106.27, 108.23, 149.50, 151.88, 172.75; ESI-MS of $[C_{10}H_{15}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 182.118, measured m/z of $[M+H]^+$ = 182.118; IR: ν (cm^{-1}) = 1643.48 (C=O stretch).

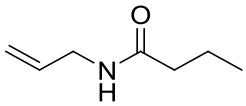
3.23 *N*-Butylbutyramide[148]



Following representative procedure XII, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and *n*-butylamine (0.20 mL, 2.0 mmol) was used as the amine species. *N*-Butylbutyramide was recovered as an off-white solid (0.276 g, 96%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 - 0.93 (m, 6H, $CH_2CH_2C\underline{H}_3$ and $C\underline{H}_3CH_2CH_2CH_2$), 1.22 - 1.34 (m, 2H, $CH_3C\underline{H}_2CH_2CH_2$), 1.36 - 1.46 (q, 2H, *J* =7.2 Hz, $CH_3CH_2C\underline{H}_2CH_2$), 1.53 - 1.65 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.06 (t, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_2CH_3$), 3.15 - 3.22 (q, 2H, *J* = 6..9 Hz, $CH_3CH_2CH_2C\underline{H}_2$), 5.36, (br. s, 1H, N<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.74, 19.23, 20.06, 38.78, 39.18, 173.03; ESI-MS of $[C_8H_{17}NO]^+$; theoretical m/z of $[M+H]^+$ = 144.139, measured m/z of $[M+H]^+$ = 144.139; IR: ν (cm^{-1}) = 1643.11 (C=O stretch).

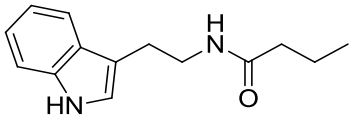
3.24 *N*-Allylbutyramide[148]



Following representative procedure XII, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and allylamine (0.15 mL, 2.0 mmol) was used as the amine species. *N*-Allylbutyramide was recovered as a brown oil (0.198 g, 79%) after column chromatography (eluting with dichloromethane/methanol 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 7.2 Hz, $CH_2CH_2C\underline{H}_3$), 1.55 - 1.67 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.12 (t, 2H, *J* = 7.2 Hz, $C\underline{H}_2CH_2CH_3$), 3.79 - 3.84 (tt, 2H, *J* = 5.7 Hz, 1.5 Hz, $CH_2CHC\underline{H}_2NH$), 5.03 - 5.15 (m, 2H, $C\underline{H}_2CHCH_2NH$), 5.54 (br. s, 1H, N<u>H</u>), 5.71 - 5.84 (m, 1H, $CH_2C\underline{H}CH_2NH$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.78, 19.18, 38.69, 41.86, 116.29, 134.40, 172.84; ESI-MS of $[C_7H_{13}NO]^+$; theoretical m/z of $[M+H]^+$ = 128.108, measured m/z of $[M+H]^+$ = 128.106; IR: ν (cm^{-1}) = 1640.08 (C=O stretch).

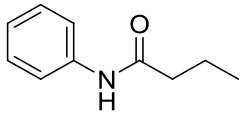
3.25 *N*-Butanoyltryptamine[148]



Following representative procedure II, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and tryptamine (0.32 g, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 67% conversion into *N*-butanoyltryptamine.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.94 (t, 3H, *J* = 7.2 Hz, $CH_2CH_2C\underline{H}_3$), 1.59 - 1.67 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.10 (t, 2H, *J* = 7.2 Hz, $C\underline{H}_2CH_2CH_3$), 2.98 (t, 2H, *J* = 6.75 Hz, $C\underline{H}_2CH_2NH$), 3.57 - 3.65 (q, 2H, *J* = 6.75 Hz, $CH_2C\underline{H}_2NH$), 5.85 (br. s, 1H, N<u>H</u>), 7.01 (1H, d, *J* = 2.25 Hz, indole), 7.13 - 7.24 (m, 2H, indole), 7.39 (d, 1H, *J* = 7.75 Hz, indole), 7.62 (d, 1H *J* = 7.75 Hz, indole), 8.86 (br. s, 1H, N<u>H</u> indole); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.73, 19.17, 37.18, 38.72, 39.78, 111.44, 112.67, 118.62, 119.27, 121.99, 122.28, 127.36, 136.55, 173.28; ESI-MS of $[C_{14}H_{17}N_2O]^+$; theoretical m/z of $[M+H]^+$ = 231.148, measured m/z of $[M+H]^+$ = 231.149; IR: ν (cm^{-1}) = 1633.41 (C=O stretch).

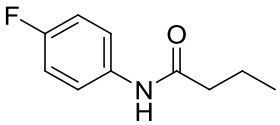
3.26 *N*-Phenylbutyramide[148]



Following representative procedure XII, butyraldoxime (0.22 mL, 2.4 mmol) was used as the oxime species and aniline (0.18 mL, 2.0 mmol) was used as the amine species. *N*-Phenylbutyramide was recovered as an off-white solid (0.293 g, 91%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11 (t, 3H, *J* = 7.5 Hz, $CH_2CH_2C\underline{H}_3$), 1.80 - 1.90 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.43 (t, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_2CH_3$), 7.19 (t, 1H, *J* = 7.5 Hz, Ph), 7.25 (br. s, 1H, N<u>H</u>), 7.42 (t, 2H, *J* = 7.5 Hz, Ph), 7.61 (d, 2H, *J* = 7.8 Hz, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.76, 19.09, 39.70, 119.85, 124.18, 128.98, 138.00, 171.35; ESI-MS of $[C_{10}H_{13}NO]^+$; theoretical m/z of $[M+H]^+$ = 164.108, measured m/z of $[M+H]^+$ = 164.107; IR: ν (cm^{-1}) = 1655.36 (C=O stretch).

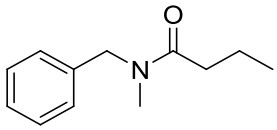
3.27 *N*-(4-Fluorophenyl)butyramide[148]



Following representative procedure XII, butyraldoxime (0.22 mL, 2.4 mmol) was used as the oxime species and 4-fluoroaniline (0.19 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 68% conversion into *N*-(4-fluorophenyl)butyramide.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.02 (t, 3H, *J* = 7.25 Hz, $CH_2CH_2C\underline{H}_3$), 1.63 - 1.80 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.36 (t, 2H, *J* = 7.25 Hz, $C\underline{H}_2CH_2CH_3$), 5.53, (br. s, 1H, N<u>H</u>), 7.03 (t, 2H, (4-F)Ph), 7.47 - 7.53 (m, 2H, (4-F)Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.68, 19.13, 39.55, 115.22, 120.05, 138.13, 146.34, 176.81; ESI-MS of $[C_{10}H_{12}NOF]^+$; theoretical m/z of $[M+H]^+$ = 182.098, measured m/z of $[M+H]^+$ = 182.098; IR: ν (cm^{-1}) = 1659.86 (C=O stretch).

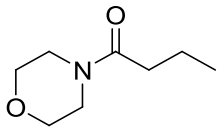
3.28 *N*-Benzyl-*N*-methylbutyramide[148]



Following representative procedure XII, butyraldoxime (0.22 mL, 2.4 mmol) was used as the oxime species and *N*-methylbenzylamine (0.25 mL, 2.0 mmol) was used as the amine species. *N*-Benyl-*N*-methylbutyramide was recovered as a white solid (0.340 g, 89%) after column chromatography (eluting with dichloromethane/methanol 98:2) and recrystallisation (dichloromethane/hexane). Both rotamers are visible by ^{1}H and ^{13}C NMR.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89 (0.92) (2t, 3H, *J* = 7.25 Hz, $CH_2CH_2C\underline{H}_3$), 1.59 - 1.70 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.29 (t, 2H, *J* = 7.25 Hz, $C\underline{H}_2CH_2CH_3$), 2.85 (2.87) (2s, 3H, $C\underline{H}_3$), 4.47 (4.53) (2s, 2H, $PhC\underline{H}_2N(CH_3)$), 7.08 - 7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.71, (13.98), 18.58, (18.80), 33.79, (34.81), 35.04, (35.45), 50.70, (53.32), 126.27, (127.25), 127.54, (127.93), 128.54, (128.88), 136.77, (137.56), 173.13, (173.47); ESI-MS of $[C_{12}H_{17}NO]^+$; theoretical m/z of $[M+H]^+$ = 192.139, measured m/z of $[M+H]^+$ = 192.137; IR: ν (cm^{-1}) = 1630.82 (C=O stretch).

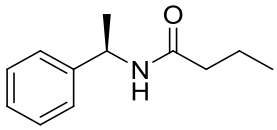
3.29 1-Morpholinobutan-1-one[148]



Following representative procedure XII, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and morpholine (0.17 mL, 2.0 mmol) was used as the amine species. 1-Morpholinobutan-1-one was recovered as a yellow oil (0.261 g, 83%) after column chromatography (eluting with dichloromethane/methanol 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, 3H, *J* = 7.2 Hz, $CH_2CH_2C\underline{H}_3$), 1.53 - 1.66 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.23 (t, 2H, *J* = 7.2 Hz, $C\underline{H}_2CH_2CH_3$), 3.39 (t, 2H *J* = 4.8 Hz, $NC\underline{H}_2CH_2O$), 3.49 - 3.64 (m, 6H, $NCH_2C\underline{H}_2OC\underline{H}_2C\underline{H}_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.98, 18.67, 35.03, 41.87, 46.06, 66.70, 66.98, 171.74; ESI-MS of $[C_8H_{15}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 158.118, measured m/z of $[M+H]^+$ = 158.118; IR: ν (cm^{-1}) = 1636.91 (C=O stretch).

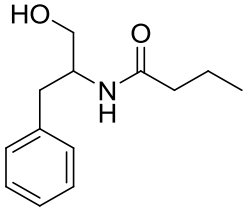
3.30 (*R*)-*N*-(1-phenylethyl)butyramide[148]



Following representative procedure XII, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and (*R*)-1-methylbenzylamine (0.25 mL, 2.0 mmol) was used as the amine species. (*R*)-*N*-(1-phenylethyl)butyramide was recovered as an off-white solid (0.348 g, 91%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 7.2 Hz, $CH_2CH_2C\underline{H}_3$), 1.42 (d, 3H, *J* = 6.9 Hz, $PhC(H)C\underline{H}_3$), 1.53 - 1.65 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.07 (t, 2H, *J* = 7.2 Hz, $C\underline{H}_2CH_2CH_3$), 5.03 - 5.13 (qu, 1H, *J* = 6.9 Hz, $PhC(\underline{H})CH_3$), 5.61 (br. s, 1H, N<u>H</u>), 7.18 - 7.27 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.75, 19.18, 21.73, 38.83, 48.56, 126.20, 127.34, 128.67, 143.32, 171.99; ESI-MS of $[C_{12}H_{17}NO]^+$; theoretical m/z of $[M+H]^+$ = 192.139, measured m/z of $[M+H]^+$ = 192.138; IR: ν (cm^{-1}) = 1636.30 (C=O stretch); ee > 99%, Chiracel OD column, 97:3 hexane: isopropylalcohol, 1.0 mL min^{-1}, retention time (*R*) = 18.5 mins (retention time (*S*) = 21.48 mins); $[\alpha]_D^{20}$ = +107.0.

3.31 *N*-(1-hydroxy-3-phenylpropan-2-yl)butyramide[148]

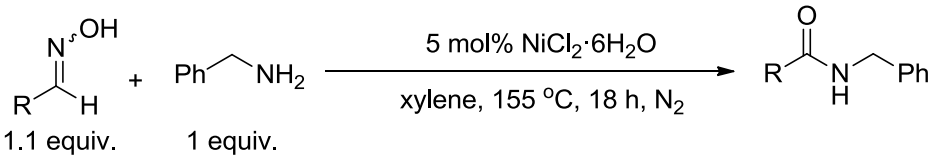


Following representative procedure XII, butyraldoxime (0.21 mL, 2.2 mmol) was used as the oxime species and 2-amino-3-phenyl-propan-1-ol (0.30 g, 2.0 mmol) was used as the amine species. A ^{1}H NMR of the crude reaction mixture showed a 60% conversion into *N*-(1-hydroxy-3-phenylpropan-2-yl)butyramide.

^{1}H NMR (300 MHz, $CDCl_3$): δ = (300 MHz, $CDCl_3$): δ = 0.80 (t, 3H, *J* = 7.5 Hz, $CH_2CH_2C\underline{H}_3$), 1.47 - 1.55 (m, 2H, $CH_2C\underline{H}_2CH_3$), 2.05 (t, 2H, *J* = 7.5 Hz, $C\underline{H}_2CH_2CH_3$), 2.73 - 2.86 (m, 2H, $C\underline{H}_2Ph$), 3.47 - 3.61 (m, 2H, $C\underline{H}_2OH$), 4.08 - 4.13 (qu, 1H, *J* = 4.5 Hz, $NHC\underline{H}(CH_2)_2$), 5.94 (d, 1H, *J* = 7.5 Hz, N<u>H</u>), 7.13 - 7.22 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.64, 19.14, 37.00, 38.70, 52.75, 64.04, 126.64, 128.61, 129.24, 137.77, 173.87; ESI-MS of $[C_{13}H_{18}NO]^+$; theoretical m/z of $[M+H]^+$ = 222.147, measured m/z of $[M+H]^+$ = 222.148; IR: ν (cm^{-1}) = 1638.02 (C=O stretch).

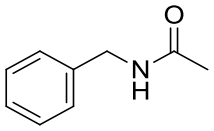
Representative Procedure XIII

(Table 3.13, Results and Discussion II)



$NiCl_2 \cdot 6H_2O$ (5 mol%) was added to an oven dried carousel tube, followed by the appropriate aldoxime species (2.2 mmol) and *p*-xylene (2.0 mL). The tube was then sealed and the reaction mixture placed under an atmosphere of nitrogen before benzylamine (0.22 mL, 2.0 mmol) was added and the reaction mixture heated at 155 ^{o}C for 18 hours. The resulting mixture was allowed to cool to room temperature before being filtered through a short plug of celite. Where appropriate, the product was purified by column chromatography on silica gel (dichloromethane/methanol or diethyl ether/heptanes as eluent), then recrystallised from suitable solvent(s). The resulting amides were anaylsed by their NMR and IR spectroscopy and mass spectrometry data.

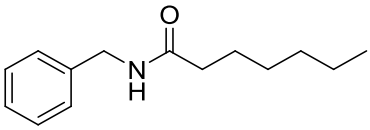
2.31 *N*-Benzylacetamide[148]



Following representative procedure XIII, acetaldoxime (0.26 g, 2.2 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-Benzylacetamide was recovered as a brown oil (0.251 g, 84%) after column chromatography (eluting with dichloromethane/methanol 92:8).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.06 (s, 3H, C$\underline{H}_3$), 4.47 (d, 2H, J = 5.5 Hz, PhC$\underline{H}_2$NH), 5.79 (br. s, 1H, N$\underline{H}$), 7.29 - 7.37 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.26, 43.79, 127.56, 127.87, 128.73, 138.25, 169.96; ESI-MS of $[C_9H_{11}NO]^+$; theoretical m/z of $[M+H]^+$ = 150.092, measured m/z of $[M+H]^+$ = 150.093; IR: ν (cm^{-1}) = 1643.07 (C=O stretch).

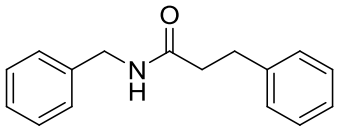
3.32 *N*-Benzylheptanamide[148]



Following representative procedure XIII, heptaldoxime (0.271 g, 2.2 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-Benzylheptanamide was recovered as a yellow oil (0.391 g, 89%) after column chromatography (eluting with dichloromethane/methanol 95:5).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 6.6 Hz, $CH_2CH_2C\underline{H}_3$), 1.26 - 1.36 (m, 6H, $CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.61 - 1.71 (qu, 2H, *J* = 7.8 Hz, $C(O)CH_2C\underline{H}_2CH_2$), 2.21 (t, 2H, *J* = Hz, $C(O)C\underline{H}_2CH_2$), 4.45 (d, 2H, *J* = 5.7 Hz, $PhC\underline{H}_2NH$), 5.68 (br. s, 1H, N<u>H</u>), 7.26 - 7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.03, 22.52, 25.75, 29.00, 31.54, 36.85, 43.61, 127.51, 127.85, 128.72, 138.46, 173.00; ESI-MS of $[C_{14}H_{21}NO]^+$; theoretical m/z of $[M+H]^+$ = 220.170, measured m/z of $[M+H]^+$ = 220.169; IR: ν (cm^{-1}) = 1635.83 (C=O stretch).

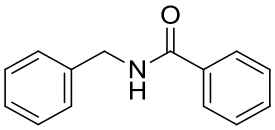
3.33 *N*-Benzyl-3-phenylpropanamide[148]



Following representative procedure XIII, 3-phenylpropaldoxime (0.300 g, 2.2 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-Benzyl-3-phenylpropanamide was recovered as a yellow solid (0.268 g, 90%) after column chromatography (eluting with diethyl ether/hexane 3:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.55 (t, 2H, *J* = 7.8 Hz, $CH_2C\underline{H}_2Ph$), 3.03 (t, 2H, *J* = 7.8 Hz, $C\underline{H}_2CH_2Ph$), 4.43 (d, 2H, *J* = 5.8 Hz, $PhC\underline{H}_2NH$), 5.68 (br. s, 1H, N<u>H</u>), 7.16 - 7.35 (m, 10H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.74, 38.54, 43.61, 126.28, 127.48, 127.77, 128.42, 128.58, 128.68, 138.17, 140.79, 171.89; ESI-MS of $[C_{16}H_{17}NO]^+$; theoretical m/z of $[M+H]^+$ = 240.139, measured m/z of $[M+H]^+$ = 240.139; IR: ν (cm^{-1}) = 1637.28 (C=O stretch).

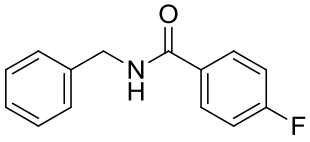
3.34 *N*-Benzylbenzamide[148]



Following representative procedure XIII, benzaldoxime (0.284 g, 2.4 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-Benzylbenzamide was recovered as a white solid (0.262 g, 62%) after column chromatography (eluting with dichloromethane/methanol 98:2) and recrystallisation (dichloromethane/hexanes).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.58 (d, 2H, *J* = 5.7 Hz, PhC$\underline{H}_2$NH), 6.36 (br. s, 1H, N$\underline{H}$), 7.18 - 7.43 (m, 8H, 2Ph), 7.70 - 7.73 (m, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.17, 126.97, 127.66, 127.95, 128.62, 128.82, 131.56, 134.43, 138.21, 167.35; ESI-MS of $[C_{14}H_{13}NO]^+$; theoretical m/z of $[M+H]^+$ = 212.107, measured m/z of $[M+H]^+$ = 212.106; IR: ν (cm^{-1}) = 1635.55 (C=O stretch).

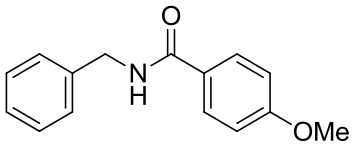
3.35 *N*-Benzyl-(4-fluoro)benzamide[148]



Following representative procedure XIII, 4-fluorobenzaldoxime (0.306 g, 2.2 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-Benzyl-(4-fluoro)benzamide was recovered as an off white solid (0.380 g, 83%) after column chromatography (eluting with dichloromethane/methanol 95:5).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.68 (d, 2H, *J* = 5.8 Hz, PhC$\underline{H}_2$NH), 6.34 (br. s, 1H, N$\underline{H}$), 7.11 - 7.18 (m, 2H, C(O)(4-F)$\underline{Ph}$), 7.37 - 7.41 (m, 5H, $\underline{Ph}CH_2NH$), 7.81 - 7.86 (m, 2H, C(O)(4-F)$\underline{Ph}$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.24, 155.50, 155.79, 127.73, 127.96, 128.85, 129.25, 129.36, 130.60, 138.07, 163.11, 166.30; ESI-MS of $[C_{14}H_{12}NOF]^+$; theoretical m/z of $[M+H]^+$ = 230.098, measured m/z of $[M+H]^+$ = 230.097; IR: ν (cm^{-1}) = 1638.96 (C=O stretch).

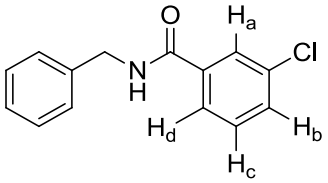
3.36 *N*-Benzyl-(4-methoxy)benzamide[148]



Following representative procedure XIII, 4-methoxybenzaldoxime (0.31 g, 2.2 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 36% conversion into *N*-benzyl-(4-methoxy)benzamide.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.78 (s, 3H, OC<u>H</u>$_3$), 4.57 (d, 2H, *J* = 5.5 Hz, PhC<u>H</u>$_2$NH), 6.88 (d, 2H, *J* = 7.5 Hz, C(O)(4-OMe)<u>Ph</u>), 7.26 - 7.30 (m, 5H, <u>Ph</u>CH$_2$NH), 7.70 (d, 2H, *J* = 7.5 Hz, C(O)(4-OMe)<u>Ph</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.09, 55.44, 113.93, 114.02, 126.93, 127.01, 127.55, 128.51, 128.62, 129.86, 130.79, 138.47, 162.25, 162.61; ESI-MS of $[C_{15}H_{15}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 242.118, measured m/z of $[M+H]^+$ = 242.117.

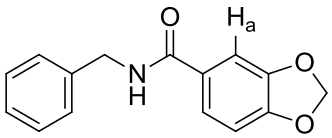
3.37 *N*-Benzyl-(3-chloro)benzamide[148]



Following representative procedure XIII, 3-chlorobenzaldoxime (0.31 g, 2.2 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-Benzyl-3-chlorobenzamide was recovered as a white solid (0.242 g, 66%) after column chromatography (eluting with diethyl ether/hexane 3:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.57 (d, 2H, *J* = 5.5 Hz, PhC<u>H</u>$_2$NH), 6.31 (br. s, 1H, NH), 7.27 - 7.33 (m, 6H, <u>Ph</u>CH$_2$NH and H_c), 7.38 - 7.43 (m, 1H, H_b), 7.56 - 7.61 (dt, 1H, *J* = 1.25 Hz, 7.5 Hz, H_d), 7.71 (t, 1H, *J* = 1.75 Hz, H_a); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.29, 125.08, 127.36, 127.78, 127.97, 128.87, 129.93, 131.60, 134.81, 136.20, 137.86, 166.03; ESI-MS of $[C_{14}H_{12}NOCl]^+$; theoretical m/z of $[M+H]^+$ = 246.069, measured m/z of $[M+H]^+$ = 246.067; IR: ν (cm^{-1}) = 1632.83 (C=O stretch).

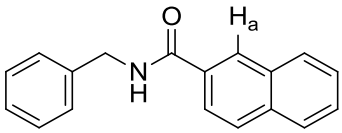
3.38 *N*-Benzylbenzo(1,3)dioxole-5-carboxamide[148]



Following representative procedure XIII, piperonaldoxime (0.363 g, 2.2 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-Benzylbenzo(1,3)dioxole-5-carboxamide was recovered as a yellow solid (0.387 g, 76%) after column chromatography (eluting with dichloromethane/methanol 92:8) and recrystallisation from ethanol.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.54 (d, 2H, *J* = 5.7 Hz, PhC$\underline{H}_2$NH), 5.94 (s, 2H, OC$\underline{H}_2$O), 6.23 (br. s, 1H, N$\underline{H}$), 6.74 (d, 1H, *J* = Hz, H_a), 7.19 - 7.29 (m, 7H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.17, 101.69, 107.71, 107.99, 121.58, 127.90, 128.64, 128.77, 138.31, 148.00, 150.38, 166.66; ESI-MS of $[C_{15}H_{13}NO_3]^+$; theoretical m/z of $[M+H]^+$ = 256.097, measured m/z of $[M+H]^+$ = 256.097; IR: ν (cm^{-1}) = 1637.17 (C=O stretch).

3.39 *N*-Benzyl-2-naphthamide[148]



Following representative procedure XIII, naphthaldoxime (0.345 g, 2.2 mmol) was used as the oxime species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. *N*-Benzyl-2-naphthamide was recovered as a pale brown solid (0.399 g, 76%) after column chromatography (eluting with dichloromethane/methanol 92:8) and recrystallisation from chloroform/hexane.

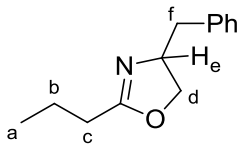
^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.74 (d, 2H, *J* = 5.8 Hz, PhC$\underline{H}_2$NH), 6.63 (br. s, 1H, N$\underline{H}$), 7.29 - 7.45 (m, 5H, aromatic), 7.55 - 7.61 (m, 2H, aromatic), 7.88 - 7.94 (m, 4H, aromatic), 8.34 (s, 1H, H_a); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.32, 123.60, 126.80, 126.88, 127.45, 127.70, 127.77, 128.03, 128.53, 128.86, 128.93, 129.06, 134.78, 135.02, 135.17, 138.23; ESI-MS of $[C_{18}H_{15}NO]^+$; theoretical m/z of $[M+H]^+$ = 262.123, measured m/z of $[M+H]^+$ = 262.124; IR: ν (cm^{-1}) = 1640.03 (C=O stretch).

Representative Procedure XIV

Formation of oxazoline side product

(Scheme 3.4, Results and Discussion II)

3.40 4-Benzyl-2-propyl-4,5-dihydrooxazole[154]



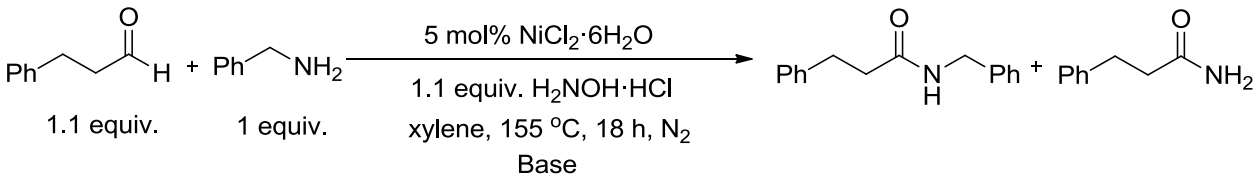
3.40

Butyraldoxime (0.21 mL, 2.2 mmol) and $NiCl_2 \cdot 6H_2O$ (5 mol%) were added to an oven dried carousel tube, followed by *p*-xylene (2.0 mL). The tube was then sealed and the reaction mixture placed under an atmosphere of nitrogen before 2-amino-3-phenyl-propan-1-ol (0.30 g, 2.0 mmol) was added and the reaction mixture heated at 155 ^oC for 18 hours. The resulting mixture was allowed to cool to room temperature before being filtered through a short plug of celite. The products were anaylsed by their NMR and IR spectroscopy and mass spectrometry data. An ^1H NMR of the crude reaction mixture showed a 40% conversion into **3.40**.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (3H, t, J = 7.5 Hz, H_a), 1.50 – 1.64 (4H, m, H_b + H_c), 2.53 – 2.61 (1H, dd, J = 13.8 Hz, 8.7 Hz, H_f), 3.07 – 3.01 (1H, dd, J = 13.8 Hz, 8.7 Hz, H_f), 3.88 (1H, t, J = 7.2 Hz, H_d), 4.09 (1H, t, J = 7.2 Hz, H_d), 7.12 - 7.23 (m, 5H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 18.9, 36.1, 41.7, 66.8, 71.5, 126.5, 128.2, 129.3, 137.9, 173.7; ESI-MS of $[C_{13}H_{18}NO]^+$; theoretical m/z of $[M+H]^+$ = 204.134, measured m/z of $[M+H]^+$ = 204.134.

Representative Procedure XV

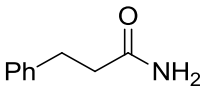
(Table 3.14, Results and Discussion II)



$NiCl_2 \cdot 6H_2O$ (5 mol%) was added to an oven dried carousel tube, followed by hydroxylamine hydrochloride (2.2 mmol), 3-phenylpropaldehyde (0.333 g, 2.2 mmol),

p-xylene (2.5 mL) and the chosen base according to Table 3.14. The tube was then sealed and the reaction mixture placed under an atmosphere of nitrogen before benzylamine (0.22 mL, 2.0 mmol) was added and the reaction mixture heated at 155 ^{o}C for 18 hours. The resulting mixture was allowed to cool to room temperature before being filtered through a short plug of silica. The resulting amides were anaylsed by their NMR and IR spectroscopy and mass spectrometry data.

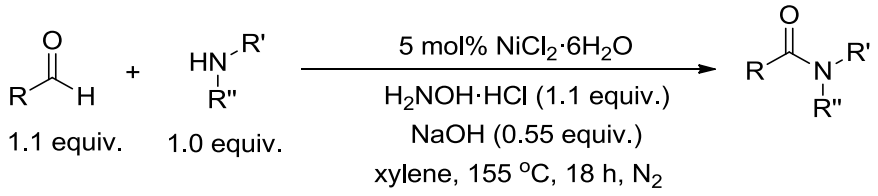
3.42 3-Phenylpropionamide[85]



Following representative procedure XV, **3.42** was observed in the crude NMR spectra. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.58 (t, 2H, *J* = 6.0 Hz, PhC$\underline{H}_2$CH$_2$), 3.01 (t, 2H, *J* = 6.0 Hz, PhCH$_2$C$\underline{H}_2$), 5.39 (br. s, 2H, N$\underline{H}_2$), 7.22 - 7.36 (m, 5H, aromatic); ESI-MS of $[C_9H_{12}NO]^+$; theoretical m/z of $[M+H]^+$ = 150.099, measured m/z of $[M+H]^+$ = 150.100.

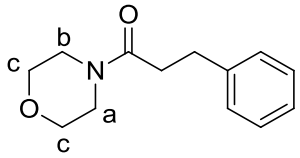
Representative Procedure XVI

(Table 3.15, Results and Discussion II)



$NiCl_2{\cdot}6H_2O$ (5 mol%) was added to an oven dried carousel tube, followed by hydroxylamine hydrochloride (2.2 mmol), sodium hydroxide (1.1 mmol), the appropriate aldehyde species (2.0 mmol) and *p*-xylene (2.5 mL). The tube was then sealed and the reaction mixture placed under an atmosphere of nitrogen before the appropriate amine species was added and the reaction mixture heated at 155 ^{o}C for 18 hours. The resulting mixture was allowed to cool to room temperature before being filtered through a short plug of silica. Where appropriate, the product was purified by column chromatography on silica gel (dichloromethane/methanol or diethyl ether/heptanes as eluent), then recrystallised from suitable solvent(s). The resulting amides were anaylsed by their NMR and IR spectroscopy and mass spectrometry data.

3.43 1-Morpholino-3-phenyl-propan-1-one[148]



Following representative procedure XVI, 3-phenylpropaldehyde (0.30 mL, 2 mmol) was used as the aldehyde species and morpholine (0.17 mL, 1.8 mmol) was used as the amine species. 1-Morpholino-3-phenyl-propan-1-one was recovered as a light brown oil (0.351 g, 80%) after column chromatography (eluting with dichloromethane/methanol 92:8).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.54 (t, 2H, *J* = 8.3 Hz, $PhC\underline{H}_2CH_2$), 2.91 (t, 2H, *J* = 8.3 Hz, $PhCH_2C\underline{H}_2$), 3.28 (t, 2H, *J* = 6.3 Hz, a), 3.44 (t, 2H, *J* = 6.3 Hz, b), 3.55 (s, 4H, c), 7.13 - 7.22 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.49, 34.76, 41.94, 45.95, 66.44, 66.80, 126.29, 128.49, 128.56, 141.06, 170.89; ESI-MS of $[C_{13}H_{17}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 220.134, measured m/z of $[M+H]^+$ = 220.132; IR: ν (cm^{-1}) = 1635.83 (C=O stretch).

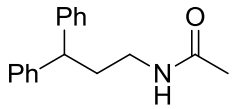
3.33 *N*-Benzyl-3-phenylpropanamide

Following representative procedure XVI, 3-phenylpropaldehyde (0.30 mL, 2.0 mmol) was used as the aldehyde species and benzylamine (0.20 mL, 1.8 mmol) was used as the amine species. *N*-Benzyl-3-phenylpropanamide was recovered as white crystals (0.387 g, 81%) after column chromatography (eluting with dichloromethane/methanol 92:8) and recrystallisation (dichloromethane/hexane). Analytical data was consistent with that above.

3.34 *N*-Benzylbenzamide

Following representative procedure XVI, benzaldehyde (0.20 mL, 2.0 mmol) was used as the aldehyde species and benzylamine (0.20 mL, 1.8 mmol) was used as the amine species. *N*-Benzyl-3-phenylpropanamide was recovered as a white solid (0.383 g, 91%) after column chromatography (eluting with dichloromethane/methanol 92:8). Analytical data was consistent with that above.

3.44 *N*-(3,3-Diphenylpropyl)acetamide[148]



Following representative procedure XVI, acetaldehyde (0.11 mL, 2.0 mmol) was used as the aldehyde species and 3,3-diphenylpropylamine (0.38 g, 1.8 mmol) was used as the amine species. *N*-(3,3-diphenylpropyl)acetamide was recovered as a pale brown solid (0.410 g, 81%) after column chromatography (eluting with dichloromethane/methanol 92:8).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.87 (s, 3H, C(O)C$\underline{H}_3$), 2.25 - 2.32 (q, 2H, *J* = 6.6 Hz, C(Ph_2)HC$\underline{H}_2$$CH_2$NH), 3.20 - 3.27 (q, 2H, *J* = 6.6 Hz, C(Ph_2)HCH_2C$\underline{H}_2$NH), 3.95 (t, 1H, *J* = 7.8 Hz, C(Ph_2)$\underline{H}$$CH_2CH_2$NH), 5.37 (br. s, 1H, N$\underline{H}$), 7.18 - 7.31 (m, 10H, 2 Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.31, 35.23, 38.69, 49.29, 126.46, 127.74, 128.65, 144.26, 169.99; ESI-MS of $[C_{17}H_{19}NO]^+$; theoretical m/z of $[M+H]^+$ = 254.154, measured m/z of $[M+H]^+$ = 254.154; IR: ν (cm^{-1}) = 1632.82 (C=O stretch).

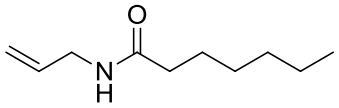
3.22 *N*-(5-Methylfurfuryl)butyramide

Following representative procedure XVI, butyraldehyde (0.18 mL, 2.0 mmol) was used as the aldehyde species and (5-methyl)furfurylamine (0.20 mL, 1.8 mmol) was used as the amine species. *N*-(5-Methylfurfuryl)butyramide was recovered as a dark brown oil (0.271 g, 83%) after column chromatography (eluting with dichloromethane/methanol 92:8). Analytical data was consistent with that above.

3.20 *N*-(4-Methoxybenzyl)butyramide

Following representative procedure XVI, butyraldehyde (0.18 mL, 2.0 mmol) was used as the aldehyde species and 4-methoxybenzylamine (0.20 mL, 1.8 mmol) was used as the amine species. *N*-(4-methoxybenzyl)butyramide was recovered as an off white solid (0.323 g, 78%) after column chromatography (eluting with dichloromethane/methanol 92:8). Analytical data was consistent with that above.

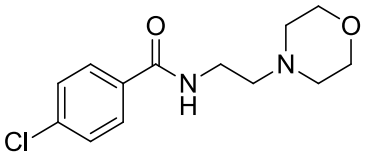
3.45 *N*-Allylheptanamide[148]



Following representative procedure XVI, heptaldehyde (0.28 mL, 2.0 mmol) was used as the aldehyde species and allylamine (0.16 mL, 1.8 mmol) was used as the amine species. *N*-Allylheptanamide was recovered as a brown oil (0.311 g, 92%) after column chromatography (eluting with dichloromethane/methanol 92:8).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.91 - 0.93 (m, 3H, $CH_2C\underline{H}_3$), 1.32 - 1.37 (m, 6H, $CH_2(C\underline{H}_2)_3CH_3$), 1.64 - 1.69 (m, 3H, $C(O)CH_2C\underline{H}_2CH_2$), 2.22 (t, 2H, *J* = 7.3 Hz, $C(O)C\underline{H}_2CH_2$), 3.89 - 3.95 (tt, 2H, *J* = 1.5 Hz, 5.8 Hz, $CH_2CHC\underline{H}_2NH$), 5.14 - 5.24 (m, 2H, $C\underline{H}_2CHCH_2NH$), 5.53 (br. s, 1H, N<u>H</u>), 5.79 - 5.95 (m, 1H, $CH_2C\underline{H}CH_2NH$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.03, 22.51, 25.79, 28.99, 31.56, 36.70, 41.83, 116.06, 134.46, 173.22; ESI-MS of $[C_{10}H_{19}NO]^+$; theoretical m/z of $[M+H]^+$ = 170.154, measured m/z of $[M+H]^+$ = 170.153; IR: ν (cm^{-1}) = 1642.53 (C=O stretch).

3.46 4-Chloro-*N*-(2-morpholinoethyl)benzamide[148]



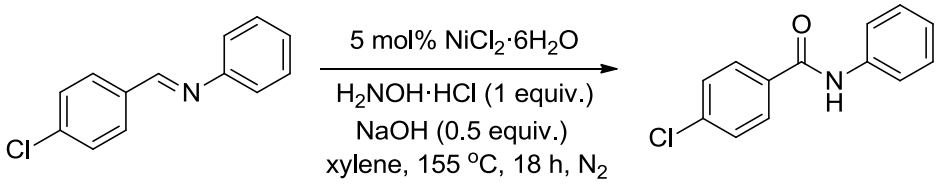
Following representative procedure XVI, 4-chlorobenzaldehyde (0.281 g, 2.0 mmol) was used as the aldehyde species and 2-(morpholine)ethylamine (0.24 mL, 1.8 mmol) was used as the amine species. 4-Chloro-*N*-(2-morpholinoethyl)benzamide was recovered as an off white powder (0.392 g, 73%) after column chromatography (eluting with diethyl ether/hexane 3:1).

^{1}H NMR (250 MHz, Acetone-D_6): δ = 2.36 (t, 4H, *J* = 4.5 Hz, $C\underline{H}_2NC\underline{H}_2$), 2.46 (t, 2H, *J* = 6.6 Hz, $CH_2C\underline{H}_2N(CH_2)_2$), 2.71 (br. s, 1H, N<u>H</u>), 3.39 - 3.45 (q, 2H, *J* = 6.6 Hz, $NHC\underline{H}_2CH_2$), 3.51 (t, 4H, *J* = 4.5 Hz, $C\underline{H}_2OC\underline{H}_2$), 7.39 (d, 2H, *J* = 8.7 Hz, (4-Cl)Ph), 7.76 (d, 2H, *J* = 8.7 Hz, (4-Cl)Ph); ESI-MS of $[C_{13}H_{17}N_2O_2Cl]^+$; theoretical m/z of $[M+H]^+$ = 269.105, measured m/z of $[M+H]^+$ = 269.104; IR: ν (cm^{-1}) = 1634.53 (C=O stretch).

Representative Procedure XVII

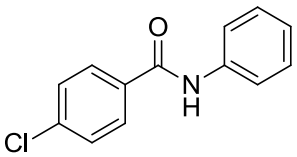
Synthesis of a secondary amide from an imine

(Scheme 3.5, Results and Discussion II)



N-(4-Chlorobenzylidene)aniline (0.215 g, 1.0 mmol) and $NiCl_2 \cdot 6H_2O$ (5 mol%) were added to an oven dried carousel tube, followed by hydroxylamine hydrochloride (0.069 g, 1 mmol), sodium hydroxide (0.022 g, 0.55 mmol) and *p*-xylene (2.0 mL). The tube was then sealed and the reaction mixture placed under an atmosphere of nitrogen before the reaction mixture was heated at 155 ^{o}C for 18 hours. The resulting mixture was allowed to cool to room temperature before being filtered through a short plug of silica. The resulting products were anaylsed by their NMR and IR spectroscopy and mass spectrometry data.

3.50 *N*-(Phenyl)-4-chlorobenzamide[145]



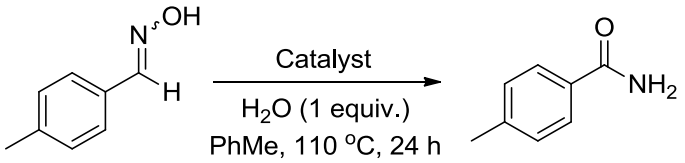
Following representative procedure XVII, an NMR of the crude reaction mixture showed a 55% conversion into **3.50.**

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.83 (br. s, 1H, N<u>H</u>), 7.41 - 7.45 (m, 2H, aromatic), 7.48 - 7.62 (m, 4H, aromatic), 8.05 - 8.08 (m, 2H, aromatic); ESI-MS of $[C_{13}H_{11}NOCl]^{+}$; theoretical m/z of $[M+H]^{+}$ = 232.123, measured m/z of $[M+H]^{+}$ = 232.124; IR: ν (cm^{-1}) = 1649.93 (C=O stretch).

Representative Procedure XVIII

Oxime rearrangement in the presence of water

(Table 3.16, Results and Discussion II)



To an oven dried carousel tube was added the chosen catalyst according to Table 3.16, 4-methylbenzaldoxime (0.14 mL, 1.0 mmol), and water (0.018 mL, 1.0 mmol). The carousel tube was then flushed with nitrogen, sealed and heated at 110 ^{o}C for 24 hours. The resulting mixture was passed through a short plug of celite (eluting with dichloromethane) if necessary and the solvent removed *in vacuo*. An ^{1}H NMR confirmed 100% conversion into 4-methylbenzamide (when compared to an authentic sample of 4-methylbenzamide). Analytical data was consistent with that reported above.

Use of $^{18}OH_2$

(Table 3.17, Results and Discussion II)

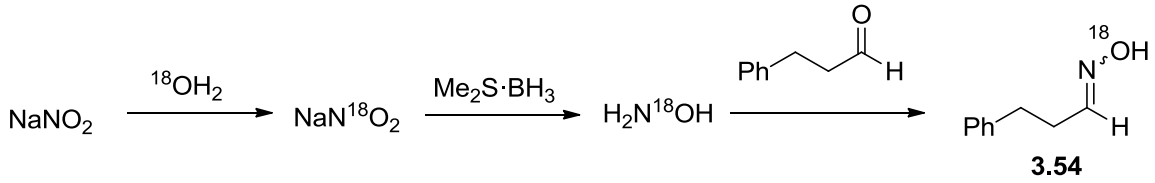
Following representative procedure XVIII, $^{18}OH_2$ (0.018 mL, 1.00 mmol) was used inm place of unlabelled water. An ^{1}H NMR confirmed 100% conversion into 4-methylbenzamide (when compared to an authentic sample of 4-methylbenzamide). Analytical data was consistent with that reported above.

ESI-MS of $[C_8H_9NO]^+$; theoretical m/z of $[M+H]^+$ = 136.072, measured m/z of $[M+H]^+$ = 136.072. No peak was seen for $[C_4H_9N^{18}O]$.

Representative Procedure XIX

Synthesis of ^{18}O labelled 3-phenylpropanal oxime 3.54[125]

(Scheme 3.10, Results and Discussion II)



3.54

^{18}O labelled water (1.00 mL, 55.00 mmol, 97 atom% ^{18}O) was added to a flask containing sodium nitrite (0.800 g, 12.00 mmol). The resulting suspension was cooled in an ice-salt mixture before being acidified by the slow addition of concentrated HCl (0.04 mL). After the addition was complete, the mixture was allowed to gradually warm to room temperature and was then stirred for a further 24 h. Neutralisation of the mixture was performed at -5 ^{o}C using solid NaOH and the residual water was removed *in vacuo* to afford a dry solid. A reflux condenser was attached to the flask, which was then purged with nitrogen and dry tetrahydrofuran (17.0 mL) was added. Borane dimethyl sulfide (2.36 mL, 24.0 mmol) was introduced dropwise at rt to avoid frothing and the reaction mixture was stirred for 24 h under a nitrogen atmosphere. After cooling in an ice-salt bath, the reaction mixture was hydrolysed with water (4.60 mL) and whilst maintaining the temperature below 5 ^{o}C, 6 N HCl (4.60 mL) was added to decompose the borohydride. The mixture was stirred for 20 min before 3-phenylpropanaldehyde (2.08 mL, 16.0 mmol) was added. The reaction mixture was then held at room temperature for 24 hours. NaOH solution was then carefully added to adjust the reaction mixture to pH 8-9 and the solution was then saturated with NaCl. The organic phase was separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). Combined organic phases were then dried with $MgSO_4$ and concentrated *in vacuo*. The crude material was analysed by ^{1}H NMR spectrum and purified by column chromatography, eluting with a 4:1 mixture of petroleum ether : diethyl ether. Purification by recrystallisation (dichloromethane and hexane) was then performed affording ^{18}O labelled 3-phenylpropanal oxime **3.54** as a white, crystalline solid.

i) Batch 1: 3-phenylpropanaloxime **3.54** was afforded as a white, crystalline solid (0.122 g, 7%), with 67% incorporation of ^{18}O observed

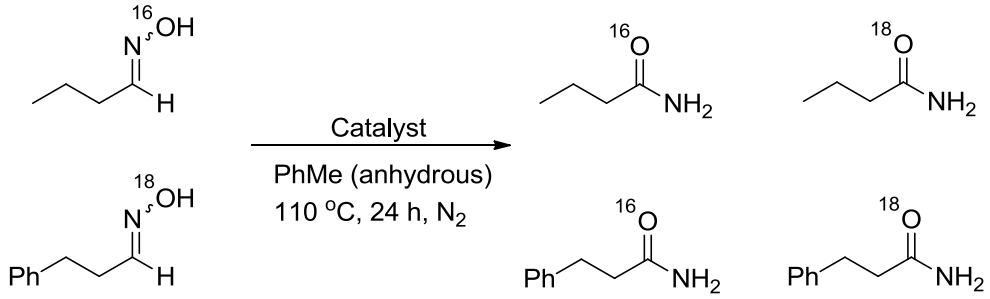
Z isomer; δ_H (250 MHz, $CDCl_3$) 2.39-2.48 (2H, m, NCHC<u>H</u>$_2$), 2.74 (2H, t, *J* = 8.1 Hz, PhC<u>H</u>$_2$), 7.08-7.25 (5H, m, Ar), 7.37 (1H, t, *J* = 5.7 Hz, NCH); *E* isomer; δ_H (250 MHz, $CDCl_3$) 2.57-2.66 (2H, m, NCHC<u>H</u>$_2$), 2.74 (2H, t, *J* = 8.1 Hz, PhC<u>H</u>$_2$), 6.67 (1H, t, *J* = 5.3 Hz, NCH), 7.08-7.25 (5H, m, Ar); δ_C (75.5 MHz, $CDCl_3$) mixture of *E* and *Z* isomers: 31.0, 31.2, 32.0, 32.8, 126.3, 128.3, 128.6, 140.5, 140.7, 151.4, 151.8; *m/z* $[M+H]^+$ 150.09, 152.10.

ii) Batch 2: 3-phenylpropanaldoxime **3.54** was afforded as a white, crystalline solid (0.577 g, 17%), with 63% incorporation of ^{18}O. Analytical data was consistent with that previously reported.

Representative Procedure XX

Label crossover experiment

(Table 3.18, Results and Discussion II)



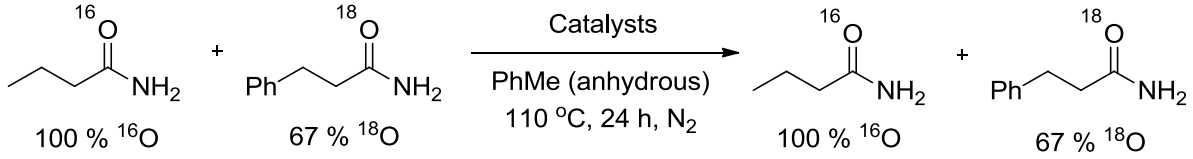
To an oven dried carousel tube was added the chosen catalyst according to Table 3.18, anhydrous toluene (0.20 mL), ^{18}O-3-phenylpropanaldoxime (0.015 mL, 0.10 mmol) and butyraldoxime (0.009 g, 0.10 mmol). The carousel tube was then flushed with nitrogen, sealed and heated at 110 ^oC for 24 hours. The resulting mixture was passed through a short plug of celite (eluting with dichloromethane) and the solvent removed *in vacuo*. An ^1H NMR confirmed 100% conversion into butyramide and 3-phenylpropamide with respect to the starting oximes (when compared to authentic samples). ^{18}O incorporation was measured by mass spectrometry.

ESI-MS of $[C_9H_{11}NO]^+$; theoretical m/z of $[M+H]^+$ = 150.094, measured m/z of $[M+H]^+$ = 150.094. Additional peak for $[C_9H_{11}N^{18}O]^+$; theoretical m/z of $[M+H]^+$ = 152.097, measured m/z of $[M+H]^+$ = 152.097.

Representative Procedure XXI

Label crossover experiment with primary amide products

(Scheme 3.11, Results and Discussion II)



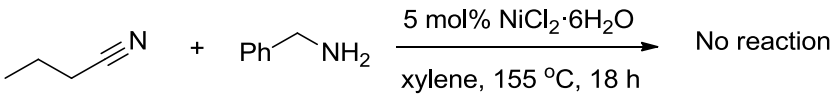
To an oven dried carousel tube was added ^{18}O-3-phenylpropanamide (0.015 mL, 0.10 mmol, 67 atom% ^{18}O), butyramide (0.009 g, 0.10 mmol) and anhydrous toluene (0.20 mL). The carousel tube was then flushed with nitrogen, sealed and heated at 110 ^{o}C for 24 hours. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo*. An ^{1}H NMR confirmed that no reaction had taken place. ^{18}O incorporation was measured by mass spectrometry.

ESI-MS of $[C_9H_{11}NO]^+$; theoretical m/z of $[M+H]^+$ = 150.094, measured m/z of $[M+H]^+$ = 150.094 (33%). Additional peak for $[C_9H_{11}N^{18}O]^+$; theoretical m/z of $[M+H]^+$ = 152.097, measured m/z of $[M+H]^+$ = 152.097 (67%).

Representative Procedure XXII

Reaction of amine with nitrile

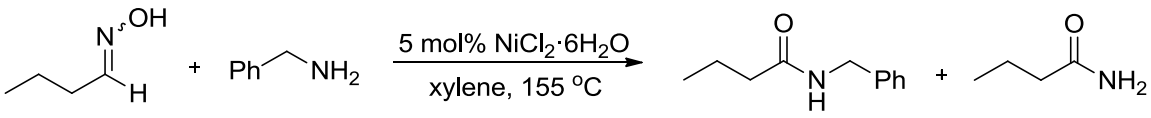
(Scheme 3.13, Results and Discussion II)



To an oven dried carousel tube was added $NiCl_2 \cdot 6H_2O$ (0.024g, 0.0002 mmol, 5 mol%), *p*-xylene (2.0 mL), butyronitrile (0.19 mL, 2.0 mmol), and benzylamine (0.22 mL, 2.0 mmol). The carousel tube was then flushed with nitrogen, sealed and heated at 155 ^{o}C for 18 hours. The resulting mixture was passed through a short plug of celite (eluting with dichloromethane) and the solvent removed *in vacuo*. An ^{1}H NMR showed no reaction to have taken place.

Reaction of benzylamine and butyraldoxime followed over time

(Table 3.19, Results and Discussion II)

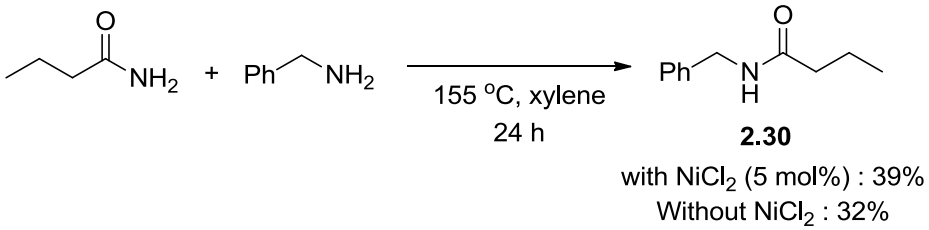


Following representative procedure XII, butyraldoxime (0.087 g, 1.00 mmol) was used as the aldoxime species and benzylamine (0.11 mL, 1.0 mmol) used as the amine species. The reaction mixture was heated at 155 ^{o}C for the appropriate amount of time according to Table 3.19. The resulting mixture was allowed to cool to room temperature before being filtered through a short plug of silica. The resulting amides were anaylsed by their NMR spectroscopy and mass spectrometry data.

Representative Procedure XXIII

Reaction of primary amide with amine

(Scheme 3.14, Results and Discussion II)

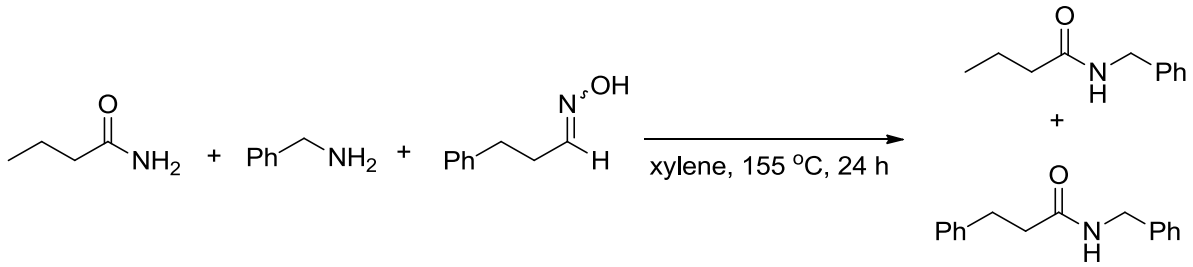


To an oven dried carousel tube was added $NiCl_2 \cdot 6H_2O$ (0.024 g, 0.0002 mmol, 5 mol%), *p*-xylene (2.0 mL), butyramide (0.18 g, 2.0 mmol), and benzylamine (0.22 mL, 2.0 mmol). The carousel tube was then flushed with nitrogen, sealed and heated at 155 ^{o}C for 24 hours. The resulting mixture was passed through a short plug of silica (eluting with dichloromethane) and the solvent removed *in vacuo*. An ^{1}H NMR showed 39% conversion into **2.30** when the reaction was run in the presence of $NiCl_2 \cdot 6H_2O$ and a 32% conversion into **2.30** when the reaction was run in the absence of $NiCl_2 \cdot 6H_2O$.

Representative Procedure XXIV

Competition reaction between butyramide and 3-phenylpropanaldoxime

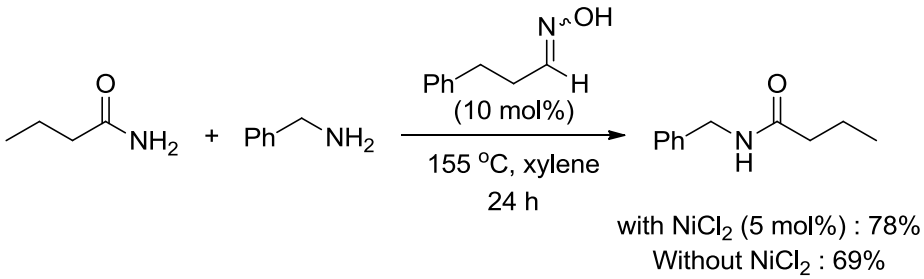
(Table 3.20, Results and Discussion II)



Butyramide (0.087 g, 1.00 mmol), benzylamine (0.11 mL, 1.0 mmol), 3-phenylpropanaldoxime (0.150 g, 1.00 mmol) and the appropriate additive according to Table 3.20 were added to an oven dried carousel tube. *p*-Xylene (1.0 mL) was added to the tube which was then sealed and heated at reflux (155 ^{o}C) for 20 hours. The reaction mixture was then allowed to cool to room temperature before the solvent was removed in vacuo and the crude reaction mixtures were analyzed by ^{1}H NMR and ^{13}C NMR spectroscopy.

Coupling of butyramide and benzylamine catalysed by 3-phenylpropaldoxime.

(Scheme 3.21, Results and Discussion II)



Following representative procedure XXIV, 3-phenylpropanaldoxime was used at 10 mol% loading (0.015 g). An ^{1}H NMR showed 78% conversion into **2.30** when the reaction was run in the presence of $NiCl_2 \cdot 6H_2O$ and a 69% conversion into **2.30** when the reaction was run in the absence of $NiCl_2 \cdot 6H_2O$.

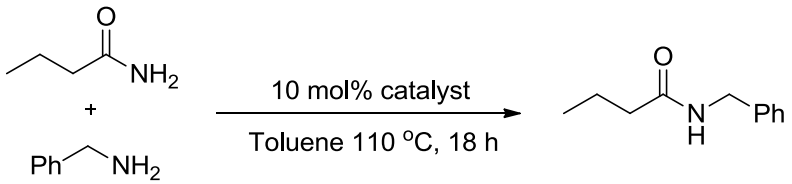
6.4 Chapter 4 Experimental

Representative Procedure XXV

n-Butyramide (0.087 g, 1.00 mmol) was added to an oven dried Radleys carousel tube. Benzylamine (0.11 mL, 1.0 mmol), the appropriate catalyst (10 mol%) or additive and solvent (1.0 mL) were then added, the tube was sealed and heated at reflux for the appropriate length of time. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* on a rotary evaporator and the crude reaction mixtures were analysed by their ^{1}H NMR and ^{13}C NMR spectra.

Screen of catalysts

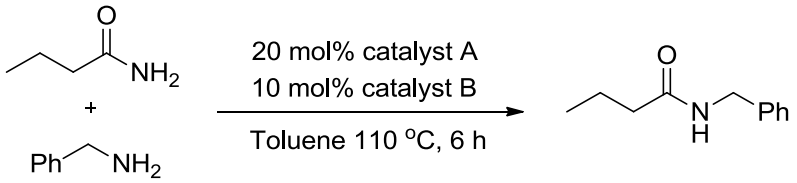
(Table 4.1, Results and Discussion III)



Following representative procedure XXV, the catalysts were varied according to Table 4.1. The reaction mixture was heated at 110 ^{o}C for 18 hours using toluene as solvent.

Addition of metal salts

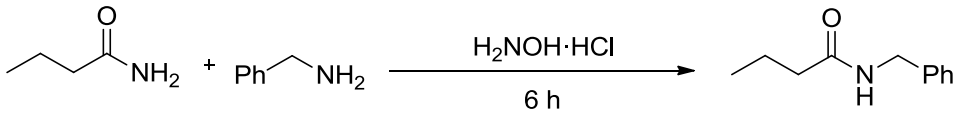
(Table 4.2, Results and Discussion III)



Following representative procedure XXV, the catalysts were varied according to Table 4.2. The reaction mixture was heated at 110 ^{o}C for 6 hours using toluene as solvent.

Variation of reaction conditions

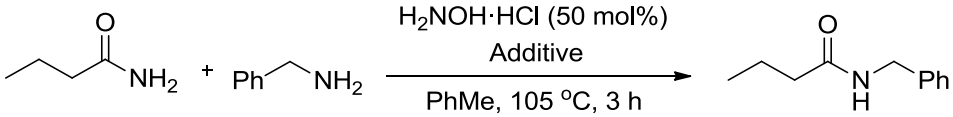
(Table 4.3, Results and Discussion III)



Following representative procedure XXV, the reaction conditions were varied according to Table 4.3. The reaction mixture was heated at reflux for 6 hours.

Addition of acid or base

(Table 4.4, Results and Discussion III)

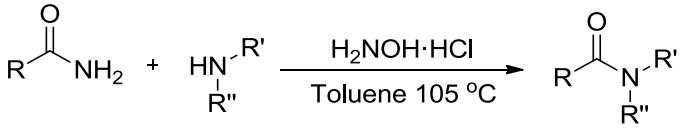


Following representative procedure XXV, the reaction conditions were varied according to Table 4.3. The reaction mixture was heated at 105 ^{o}C for 3 hours using toluene as solvent.

Representative Procedure XXVI

Range of primary amides and amines in the transamidation reaction

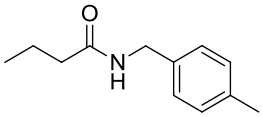
(Table 4.5, Results and Discussion III)



The primary amide species (2.0 mmol) was added to an oven dried Radleys carousel tube, followed by toluene (2.0 mL) and the amine species (2.0 mmol, see Table 2). Hydroxylamine hydrochloride was then added (see Table 4.5 for mol% used) and the carousel tube was sealed before the reaction mixture was heated at reflux (see Table 4.5 for time). After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and 20 mL dichloromethane added. The reaction mixture was then washed with water (2 x 30 mL) to remove the hydroxylamine hydrochloride, and the resulting organic layer was dried over $MgSO_4$. The solution was concentrated *in vacuo* and then analysed by their ^{1}H NMR and ^{13}C NMR spectroscopy and mass

spectrometry data. Purification by column chromatography and recrystallization was carried out as necessary.

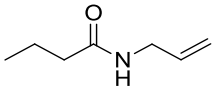
4.1 *N*-(4-Methylbenzyl)butyramide[155]



Following representative procedure XXVI, butyramide (0.17 g, 2.0 mmol) was used as the amide species and 4-methylbenzylamine (0.25 mL, 2.0 mmol) was used as the amine species. **4.1** was recovered as a white solid (0.307 g, 81%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

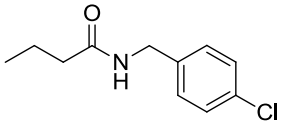
^{1}H NMR (300 MHz, DMSO-d6): δ = 0.92 (3H, t, *J* = 7.2 Hz, C$\underline{H}_3$CH$_2$CH$_2$), 1.59 (2H, q, *J* = 7.2 Hz, CH$_3$C$\underline{H}_2$CH$_2$), 2.15 (2H, t, *J* = 7.2 Hz, CH$_3$CH$_2$C$\underline{H}_2$), 3.39 (3H, s, PhC$\underline{H}_3$), 4.27 (2H, d, *J* = 6.0 Hz, NHC$\underline{H}_2$Ph), 7.18, (4H, s, Ph), 8.29 (1H, br. s, N$\underline{H}$); ^{13}C NMR (75 MHz, DMSO-d6): δ = 14.0, 19.1, 21.0, 37.7, 42.0, 127.5, 129.1, 136.0, 137.1, 172.2; ESI-MS of $[C_{12}H_{18}NO]^+$; theoretical m/z of $[M+H]^+$ = 192.145, measured m/z of $[M+H]^+$ = 192.145; IR: ν (cm^{-1}) = 1635.99 cm^{-1} (C=O stretch).

3.24 *N*-(Allyl)butyramide



Following representative procedure XXVI, butyramide (0.17 g, 2.0 mmol) was used as the amide species and allylamine (0.15 mL, 2.0 mmol) was used as the amine species. **3.24** was recovered as a yellow oil (0.218 g, 86%) after column chromatography (eluting with dichloromethane/methanol 95:5). Analytical data was consistent with that reported above.

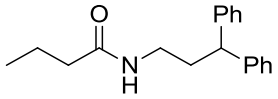
3.19 *N*-(4-Chlorobenzyl)butyramide



Following representative procedure XXVI, butyramide (0.17 g, 2.0 mmol) was used as the amide species and 4-chlorobenzylamine (0.26 mL, 2.0 mmol) was used as the amine species. **3.19** was recovered as a white solid (0.386 g, 91%) after column

chromatography (eluting with dichloromethane/methanol 92:8) and recrystallisation (with dichloromethane/hexane). Analytical data was consistent with that reported above.

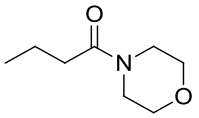
4.2 *N*-(3,3-diphenylpropyl)butyramide[155]



Following representative procedure XXVI, butyramide (0.17 g, 2.0 mmol) was used as the amide species and (3,3-diphenyl)propylamine (0.40 mL, 2.0 mmol) was used as the amine species. **4.2** was recovered as an off-white solid (0.467 g, 83%) after column chromatography (eluting with dichloromethane/methanol 98:2) and recrystallisation (with dichloromethane/hexane).

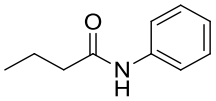
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (3H, t, *J* = 7.2 Hz, $C\underline{H}_3CH_2CH_2$), 1.45 - 1.57 (2H, m, $CH_3C\underline{H}_2CH_2$), 1.95 (2H, t, *J* = 7.2 Hz, $CH_2C\underline{H}_2C(O)$), 2.20 (2H, q, *J* = 7.8 Hz, $CH_2C\underline{H}_2CH$), 3.16 (2H, q, *J* = 6.3 Hz, $NHC\underline{H}_2CH_2$), 3.86 (1H, t, *J* = 7.8 Hz, $CH_2CH_2C\underline{H}$), 5.33 (1H, br. s., N<u>H</u>), 7.10 - 7.20 (10H, m, 2xPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 19.1, 35.4, 38.5, 38.7, 49.3, 126.4, 127.8, 128.6, 144.3, 172.9; ESI-MS of $[C_{19}H_{24}NO]^+$; theoretical m/z of $[M+H]^+$ = 282.186, measured m/z of $[M+H]^+$ = 282.188; IR: ν (cm^{-1}) = 1632.82 cm^{-1} (C=O stretch).

3.29 *N*-(Morpholino)butyramide



Following representative procedure XXVI, butyramide (0.17 g, 2.0 mmol) was used as the amide species and morpholine (0.18 mL, 2.0 mmol) was used as the amine species. **3.29** was recovered as a yellow oil (0.251 g, 90%) after column chromatography (eluting with dichloromethane/methanol 95:5). Analytical data was consistent with that reported above.

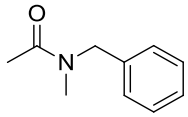
3.26 *N*-(Phenyl)butyramide[155]



Following representative procedure XXVI, butyramide (0.17 g, 2.0 mmol) was used as the amide species and aniline (0.18 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 63% conversion into **3.26**, determined

by comparison of the peaks at 2.32 ppm (2H, butyramide) and 2.39 ppm (2H, *N*-(phenyl)butyramide).

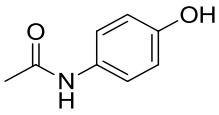
4.3 *N*-Methyl-*N*-benzylacetamide[155]



Following representative procedure XXVI, acetamide (0.12 g, 2.0 mmol) was used as the amide species and *N*-methylbenzylamine (0.25 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 62% conversion into **4.3**, determined by comparison of the peaks at 3.91 ppm (2H, benzylamine) and 4.49 and 4.55 ppm (2H, *N*-methyl-*N*-benzylacetamide, 2 rotamers).

ESI-MS of $[C_{10}H_{14}NO]^{+}$; theoretical m/z of $[M+H]^{+}$ = 163.101, measured m/z of $[M+H]^{+}$ = 163.101.

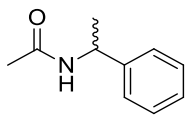
4.4 *N*-(4-Hydroxyphenyl)acetamide[115]



Following representative procedure XXVI, acetamide (0.12 g, 2.0 mmol) was used as the amide species and 4-hydroxyaniline (0.22 g, 2.0 mmol) was used as the amine species. **4.4** was recovered as a white solid (0.230 g, 76%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, DMSO-d6): δ = 1.99 (3H, s, C(O)C$\underline{H}_3$), 6.68 (2H, d, *J* = 8.75 Hz, Ph), 7.35 (2H, d, *J* = 8.75 Hz, Ph), 9.16 (1H, s, N$\underline{H}$), 9.67 (1H, s, O$\underline{H}$); ^{13}C NMR (75 MHz, DMSO-d6): δ = 24.1, 115.3, 121.1, 131.4, 153.5, 167.8; ESI-MS of $[C_8H_9NO_2]^{+}$; theoretical m/z of $[M+H]^{+}$ = 152.071, measured m/z of $[M+H]^{+}$ = 152.072.

4.5 *N*-(α-Methylbenzyl)acetamide[155]

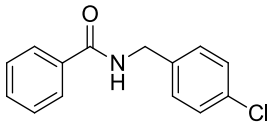


Following representative procedure XXVI, acetamide (0.12 g, 2.0 mmol) was used as the amide species and α-methylbenzylamine (0.25 mL, 2.0 mmol) was used as the amine species. **4.5** was recovered as a white solid (0.264 g, 81%) after column

chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (3H, d, *J* = 6.9 Hz, NHC(H)C<u>H</u>$_3$Ph), 1.96 (3H, s, C<u>H</u>$_3$C(O)), 5.11 (1H, qu., *J* = 6.9 Hz, NHC(<u>H</u>)CH$_3$Ph), 5.96 (1H, br. s., N<u>H</u>), 7.25 - 7.34 (5H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 23.4, 48.8, 126.2, 127.4, 128.7, 143.2, 169.2; ESI-MS of $[C_{10}H_{14}NO]^+$; theoretical m/z of $[M+H]^+$ = 164.115, measured m/z of $[M+H]^+$ = 164.115; IR: ν (cm^{-1}) = 1632.42 cm^{-1} (C=O stretch).

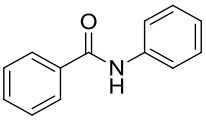
4.6 *N*-(4-Chlorobenzyl)benzamide[155]



Following representative procedure XXVI, benzamide (0.24 g, 2.0 mmol) was used as the amide species and 4-chlorobenzylamine (0.26 mL, 2.0 mmol) was used as the amine species. **4.6** was recovered as a white solid (0.347 g, 71%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.65 (2H, d, *J* = 5.75 Hz, NHC<u>H</u>$_2$Ph), 6.50 (1H, br. s., N<u>H</u>), 7.33 - 7.55 (7H, m, 2xPh), 7.82 (2H, d, *J* = 6.75 Hz, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.3, 127.6, 128.6, 128.7, 129.4, 131.6, 134.5, 139.1, 166.6; ESI-MS of $[C_{14}H_{13}NOCl]^+$; theoretical m/z of $[M+H]^+$ = 246.069, measured m/z of $[M+H]^+$ = 246.068; IR: ν (cm^{-1}) = 1636.19 cm^{-1} (C=O stretch).

4.7 *N*-Phenylbenzamide[155]

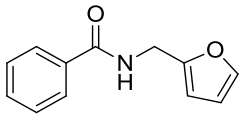


Following representative procedure XXVI, benzamide (0.24 g, 2.0 mmol) was used as the amide species and aniline (0.18 mL, 2.0 mmol) was used as the amine species. **4.7** was recovered as an off-white solid (0.234 g, 59%) after column chromatography (eluting with dichloromethane/methanol 9:1) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09 (1H, t, *J* = 7.5 Hz, Ph), 7.30 (2H, t, *J* = 7.5 Hz, Ph), 7.40 - 7.49 (3H, m, Ph), 7.58 (2H, d, *J* = 7.5 Hz, Ph), 7.74 (1H, br. s., N<u>H</u>), 7.80 (2H, d, *J* = 6.9 Hz, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 120.2, 124.6, 127.0, 128.8,

129.1, 131.9, 135.1, 137.9, 165.7; ESI-MS of $[C_{13}H_{12}NO]^+$; theoretical m/z of $[M+H]^+$ = 198.096, measured m/z of $[M+H]^+$ = 198.096; IR: ν (cm^{-1}) = 1651.56 cm^{-1} (C=O stretch).

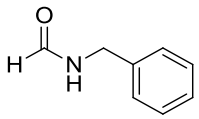
4.8 *N*-Furfurylbenzamide[155]



Following representative procedure XXVI, benzamide (0.24 g, 2.0 mmol) was used as the amide species and furfurylamine (0.19 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 63% conversion into **4.8** determined by comparison of the peaks at 3.98 ppm (2H, furfurylamine) and 4.68 ppm (2H, *N*-furfurylbenzamide).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.68 (2H, d, *J* = 6.75 Hz, NHC$\underline{H}_2$Furyl) 5.78 (1H, br. s., N$\underline{H}$), 6.31 - 6.38 (2H, m, Furyl), 7.22 - 7.56 (4H, m, 1xFuryl + 3xPh), 8.02 - 8.05 (2H, m, Ph); ESI-MS of $[C_{11}H_{14}NOCl]^+$; theoretical m/z of $[M+H]^+$ = 202.092, measured m/z of $[M+H]^+$ = 202.092.

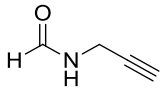
4.9 *N*-(Formyl)benzylamine[155]



Following representative procedure XXVI, formamide (0.09 g, 2.0 mmol) was used as the amide species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **4.9** was recovered as a white solid (0.232 g, 86%) after adding dichloromethane (25 mL) to the reaction mixture and washing with water (2 x 50 mL). The product was observed as 2 rotamers in its NMR spectra.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.30 (2H (minor rotamer), d, *J* = 6.3 Hz, NHC$\underline{H}_2$Ph), 4.37 (2H (major rotamer), d, *J* = 6.3 Hz, NHC$\underline{H}_2$Ph), 6.11 (1H, br. s., N$\underline{H}$), 7.18 - 7.25 (5H, m, Ph), 8.03 (1H (minor rotamer), s, $\underline{H}$C(O)NH), 8.14 (1H (major rotamer), s, $\underline{H}$C(O)NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.2 (major rotamer), 45.7 (minor rotamer), 126.9, 127.7, 127.8, 128.8, 128.9, 137.5 (major rotamer), 137.6 (minor rotamer), 161.1 (major rotamer), 164.7 (minor rotamer); ESI-MS of $[C_8H_{10}NOCl]^+$; theoretical m/z of $[M+H]^+$ = 136.076, measured m/z of $[M+H]^+$ = 136.078; IR: ν (cm^{-1}) = 1649.88 cm^{-1} (C=O stretch).

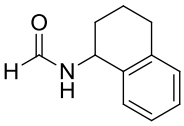
4.10 *N*-(Formyl)propargylamine[155]



Following representative procedure XXVI, formamide (0.09 g, 2.0 mmol) was used as the amide species and propargylamine (0.11 mL, 2.0 mmol) was used as the amine species. **4.10** was recovered as a viscous dark brown oil (0.144 g, 87%) after column chromatography (eluting with dichloromethane/methanol 9:1). The product was observed as 2 rotamers in its NMR spectra.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (1H (major rotamer), t, *J* = 2.4 Hz, CC<u>H</u>), 2.34 (1H (minor rotamer), t, *J* = 2.7 Hz, CC<u>H</u>), 3.99 - 4.02 (2H (minor rotamer), dd, *J* = 5.2 Hz and 2.4 Hz, NHC<u>H</u>$_2$CCH), 4.06 - 4.09 (2H (major rotamer), dd, *J* = 5.2 Hz and 2.4 Hz, NHC<u>H</u>$_2$CCH), 6.33 (1H, br. s., N<u>H</u>), 8.09 (1H (minor rotamer), s, <u>H</u>C(O)NH), 8.16 (1H (major rotamer), s, <u>H</u>C(O)NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.8 (major rotamer), 31.42 (minor rotamer), 71.8 (major rotamer), 73.1 (minor rotamer), 78.9, 160.9 (major rotamer), 164.5 (minor rotamer); ESI-MS of $[C_4H_6NO]^+$; theoretical m/z of $[M+H]^+$ = 106.027, measured m/z of $[M+H]^+$ = 106.028; IR: ν (cm^{-1}) = 1650.75 cm^{-1} (C=O stretch).

4.11 *N*-(1,2,3,4-Tetrahydronaphthalen-1-yl)formamide[155]

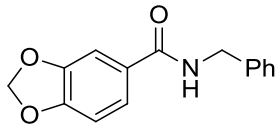


Following representative procedure XXVI, formamide (0.09 g, 2.0 mmol) was used as the amide species and 1,2,3,4-tetrahydro-1-naphthylamine (0.29 mL, 2.0 mmol) was used as the amine species. **4.11** was recovered as a white solid (0.291 g, 82%) after after adding dichloromethane (25 mL) to the reaction mixture and washing with water (2 x 50 mL). The product was observed as 2 rotamers in its NMR spectra.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75 - 1.79 (3H, m, $CH_2HC\underline{H}C\underline{H}_2CH(NH)$), 1.96 - 2.04 (1H, m, $CH_2\underline{H}CHCH_2CH(NH)$), 2.69 - 2.74 (2H, m, $C\underline{H}_2HCHCH_2CH(NH)$), 4.54 (1H (minor rotamer), q, *J* = 7.5 Hz, $CH_2C\underline{H}(NH)$), 5.20 (1H (major rotamer), q, *J* = 7.5 Hz, $CH_2C\underline{H}(NH)$), 5.79 (1H, br. s., N<u>H</u>), 7.00 - 7.21 (4H, m, Ph), 8.13 (1H (minor rotamer), s, NHC(O)<u>H</u>), 8.14 (1H (major rotamer), s, NHC(O)<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9 (major rotamer), 20.2 (minor rotamer), 29.0 (major rotamer), 29.1 (minor rotamer), 30.2 (major rotamer), 32.6 (minor rotamer), 126.3, 127.5, 128.7, 129.3, 136.0, 137.6, 160.4 (major rotamer), 163.8 (minor rotamer); ESI-MS of

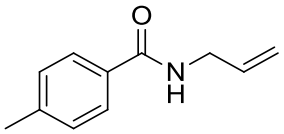
$[C_{11}H_{14}NO]^+$; theoretical m/z of $[M+H]^+$ = 176.107, measured m/z of $[M+H]^+$ = 176.109; IR: ν (cm^{-1}) = 1647.17 cm^{-1} (C=O stretch).

3.38 *N*-Benzylbenzo(1,3)dioxole-5-carboxamide



Following representative procedure XXVI, piperonamide (0.363 g, 2.2 mmol) was used as the amide species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **3.38** was recovered as a yellow solid (0.387 g, 74%) after column chromatography (eluting with dichloromethane/methanol 92:8) and recrystallisation from ethanol. Analytical data was consistent with that reported above.

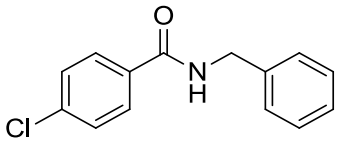
4.12 (*N*-Allyl)-4-methylbenzamide[155]



Following representative procedure XXVI, 4-methylbenzamide (0.27g, 2.0 mmol) was used as the amide species and allylamine (0.14 mL, 2.0 mmol) was used as the amine species. An ^1H NMR of the crude reaction mixture showed a 68% conversion into **4.12**, as determined by comparison of the peaks at 3.55 ppm (2H, allylamine) and 4.12 ppm (2H, (*N*-allyl)-4-methylbenzamide).

ESI-MS of $[C_{11}H_{14}NO]^+$; theoretical m/z of $[M+H]^+$ = 176.107, measured m/z of $[M+H]^+$ =176.107.

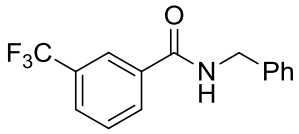
4.13 (*N*-Benzyl)-4-chlorobenzamide[155]



Following representative procedure XXVI, 4-chlorobenzamide (0.310 g, 2.0 mmol) was used as the amide species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **4.13** was recovered as a white solid (0.343 g, 70%) after column chromatography (eluting with dichloromethane/methanol 95:5) and recrystallisation (dichloromethane/hexane).

^{1}H NMR (300 MHz, DMSO-d6): δ = 4.46 (2H, d, *J* = 6.0 Hz, NHC<u>H</u>$_2$Ph), 7.28 - 7.31 (5H, m, NHCH$_2$<u>Ph</u>), 7.54 (2H, d, *J* = 8.0 Hz, (4-Cl)Ph), 7.90 (2H, d, *J* = 8.0 Hz, (4-Cl)Ph), 9.10 (1H, t, *J* = 5.7 Hz, N<u>H</u>); ^{13}C NMR (75 MHz, DMSO-d6): δ = 43.0, 127.1, 127.6, 128.6, 128.8, 129.1, 129.5, 131.5, 139.8, 165.5; ESI-MS of $[C_{11}H_{12}NOClNa]^+$; theoretical m/z of $[M+Na]^+$ = 268.051, measured m/z of $[M+H]^+$ = 268.050; IR: ν (cm^{-1}) = 1656.51 cm^{-1} (C=O stretch).

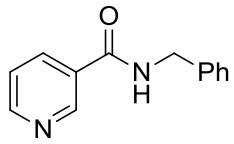
4.14 (*N*-Benzyl)-3-trifluoromethylbenzamide[155]



Following representative procedure XXVI, 3-(trifluoromethyl)benzamide (0.378 g, 2.0 mmol) was used as the amide species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 52% conversion into **4.14**, determined by comparison of the peaks at 4.02 ppm (2H, benzylamine) and 4.51 ppm (2H, (*N*-benzyl)-3-trifluoromethylbenzamide).

^{1}H NMR (250 MHz, DMSO-d$_6$): δ = 4.51 – 4.53 (2H, d, *J* = 5.75 Hz, NHC<u>H</u>$_2$Ph), 7.34 - 7.53 (6H, m, Ph and (3-CF$_3$)Ph), 7.72 (1H, m, (3-CF$_3$)Ph), 8.12 – 8.31 (2H, m, (3-CF$_3$)Ph), 9.44 (1H, br. s., N<u>H</u>).

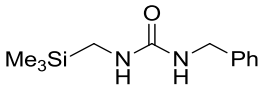
4.15 (*N*-Benzyl)-nicotinamide[155]



Following representative procedure XXVI, nicotinamide (0.245 g, 2.0 mmol) was used as the amide species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 47% conversion into **4.15**, determined by comparison of the peaks at 4.02 ppm (2H, benzylamine) and 4.52 ppm (2H, (*N*-benzyl)-nicotinamide).

^{1}H NMR (250 MHz, DMSO-d$_6$): δ = 4.50 – 4.53 (2H, d, *J* = 6.0 Hz, NHC<u>H</u>$_2$Ph), 7.33 – 7.42 (5H, m, Ph), 7.50 – 7.53 (1H, m, Py), 8.21 – 8.29 (1H, m, Py), 8.69 – 8.74 (1H, m, Py), 9.04 – 9.09 (1H, m, Py), 9.37 (1H, br. s., N<u>H</u>).

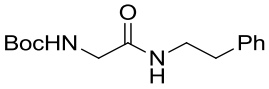
4.16 1-Benzyl-3-((trimethylsilyl)methyl)urea[155]



Following representative procedure XXVI, [*N*-(trimethylsilyl)methyl]urea (0.29 g, 2.0 mmol) was used as the amide species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 69% conversion into **4.16**, determined by comparison of the peaks at 3.89 ppm (2H, benzylamine) and 4.20 ppm (2H, 1-benzyl-3-((trimethylsilyl)methyl)urea).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.00 (9H, s, 3xSiC$\underline{H}_3$), 2.41 (2H, d, *J* = 5.0 Hz, SiC$\underline{H}_2$NH), 4.17 (2H, d, *J* = 6.0 Hz, NHC$\underline{H}_2$Ph), 5.09 (1H, br. s., N$\underline{H}$), 6.14 (1H, br. s., N$\underline{H}$), 7.18 - 7.23 (5H, m, Ph).

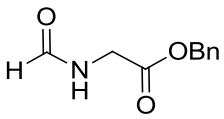
4.17 [*N*-(2-Phenyl)ethyl]*N*-Boc-glycinamide[155]



Following representative procedure XXVI, *N*-(Boc)glycinamide (0.087 g, 0.5 mmol) was used as the amide species and 2-phenylethylamine (0.06 mL, 0.5 mmol) was used as the amine species. **4.17** was recovered as a clear oil (0.101 g, 71%) after addition of hexane to the crude reaction mixture and removal of the resulting solid by filtration.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (9H, s, 3xCH_3), 2.75 (2H, t, *J* = 7.0 Hz, $CH_2C\underline{H}_2$Ph), 3.46 (2H, q, *J* = 7.0 Hz, NHC$\underline{H}_2CH_2$), 3.68 (2H, d, *J* = 5.75 Hz, NHC$\underline{H}_2$C(O)), 5.11 (1H, br. s., N$\underline{H}$), 6.17 (1H, br. s., N$\underline{H}$), 7.10 - 7.24 (5H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3, 35.6, 40.6, 44.5, 126.6, 128.7, 128.7, 138.7, 158.5, 169.4; ESI-MS of $[C_{15}H_{23}N_2O_3]^+$; theoretical m/z of $[M+H]^+$ = 279.167, measured m/z of $[M+H]^+$ = 279.167; IR: ν (cm^{-1}) = 1658.31 cm^{-1} (C=O stretch).

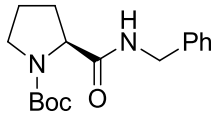
4.18 [*N*-Formyl(O-benzyl)]glycinate[155]



Following representative procedure XXVI, formamide (0.09 g, 2.0 mmol) was used as the amide species and O-benzylglycine (0.33 g, 2.0 mmol) was used as the amine species. **4.18** was recovered as a white solid (0.352 g, 91%) after adding dichloromethane (25 mL) to the reaction mixture and washing with water (2 x 50 mL). The product was observed as 2 rotamers in its NMR spectra.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.94 (2H (minor rotamer), d, *J* = 6.3 Hz, NHC<u>H</u>$_2$C(O)), 4.04 (2H (major rotamer), d, *J* = 5.1 Hz, NHC<u>H</u>$_2$C(O)), 5.12 (2H, s, OC<u>H</u>$_2$Ph), 6.13 (1H, br. s., N<u>H</u>), 7.28 - 7.30 (5H, m, Ph), 7.93 (1H, (minor rotamer), s, NHC(O)<u>H</u>), 8.15 (1H, (major rotamer), s, NHC(O)<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.0, 65.3 (minor rotamer), 67.6 (major rotamer), 127.0, 127.6, 128.6, 128.7, 134.9, 161.1, 169.4; ESI-MS of $[C_{10}H_{12}NO_3]^+$; theoretical m/z of $[M+H]^+$ = 194.077, measured m/z of $[M+H]^+$ = 194.077; IR: ν (cm^{-1}) = 1662.40 cm^{-1} (C=O amide stretch), 1743.33 (C=O ester stretch).

4.19 [*N*-(Benzyl)*N'*-Boc]-L-prolinamide[155]



Following representative procedure XXVI, *N*-Boc-L-prolinamide (0.439 g, 2.0 mmol) was used as the amide species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **4.19** was recovered as a white solid (0.529 g, 87%) after column chromatography eluting with 1:1 hexane : ethyl acetate.

^{1}H NMR (250 MHz, DMSO-d6): δ = 1.30 (5.5H, s, ^{t}Bu), 1.42 (3.5H, s, ^{t}Bu), 1.79 - 1.82 (3H, m, pyrrolidine ring), 2.07 - 2.18 (1H, m, pyrrolidine ring), 3.25 - 3.43 (2H, m, pyrrolidine ring), 4.07 - 4.39 (3H, m, NHC<u>H</u>$_2$Ph and (Boc)NC<u>H</u>C(O)), 7.24 - 7.32 (5H, m, Ph), 8.36 - 8.43 (1H, m, N<u>H</u>); ^{13}C NMR (75 MHz, DMSO-d6): δ = 23.5, 28.3, 31.4, 31.5, 42.4, 46.8, 60.1, 60.3, 78.8, 127.1, 127.6, 128.5, 139.9, 161.7, 172.8; ESI-MS of $[C_{17}H_{23}N_2O_3]^+$; theoretical m/z of $[M+H]^+$ = 305.154, measured m/z of $[M+H]^+$ = 305.148; IR: ν (cm^{-1}) = 1675.75 cm^{-1} (C=O stretch, amide); $[\alpha]_D^{25}$ = - 84.7^o ($CHCl_3$, *c* = 0.118), pure sample $[\alpha]_D^{25}$ = - 80.3^o; HPLC: Chiralcel AD column (25 cm), 0.5 mL min^{-1}, 90:10 hexane:IPA, (*L*) enantiomer retention time 23.87 mins, 88% ee.

Variation of temperature

(Table 4.7, Results and Discussion III)

Following representative procedure XXV, the temperature was varied according to Table 4.7. The reaction mixture was heated for 16 hours using toluene as solvent.

4.9 *N*-(Formyl)benzylamine

Analytical data was consistent with that reported above.

2.31 *N*-Benzylacetamide

Analytical data was consistent with that reported above.

2.30 *N*-Benzylbutyramide

Analytical data was consistent with that reported above.

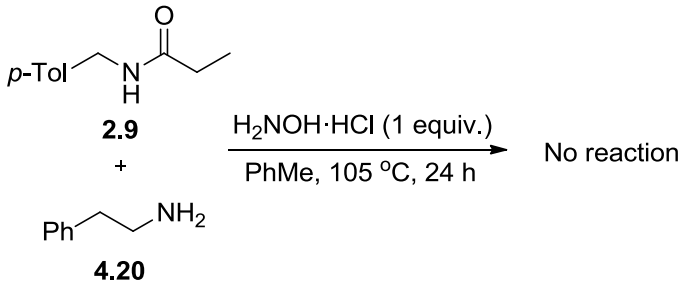
3.34 *N*-Benzylbenzamide

Analytical data was consistent with that reported above.

Representative Procedure XXVII

Crossover Reaction

(Scheme 4.2, Results and Discussion III)



The secondary amide species **2.9** (0.044 g, 0.25 mmol) was added to an oven dried Radleys carousel tube, followed by toluene (0.50 mL) and the amine species **4.20** (0.031 mL, 0.25 mmol). Hydroxylamine hydrochloride was then added (0.017 g, 100 mol%) and the carousel tube was sealed before the reaction mixture was heated at 105 ^{o}C for 24 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and 20 mL dichloromethane added. The reaction mixture was then washed with water (2 x 30 mL) to remove the hydroxylamine hydrochloride, and the resulting organic layer was dried over $MgSO_4$. The solution was concentrated *in vacuo* and then analysed by ^{1}H NMR and ^{13}C NMR spectroscopy. No reaction was observed.

Representative Procedure XXVIII

NMR Experiments

(Table 4.8 and Figure 4.2, Results and Discussion III)

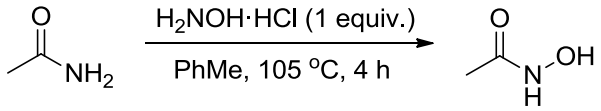
1. Butyramide was added to an oven dried NMR tube, followed by d_8-toluene (1 mL). The tube was sealed and heated to 55 ^{o}C in a Bruker Avance 500 (500 MHz) and an ^{1}H NMR spectrum taken once the solution had reached this temperature. The shifts (in ppm) of the NH protons were recorded.

2. Butyramide was added to an oven dried NMR tube, followed by *O*-methylhydroxylamine hydrochloride and d_8-toluene (1.0 mL). The tube was sealed and heated to 55 ^{o}C in a Bruker Avance 500 (500 MHz) and an 1H NMR spectrum taken once the solution had reached this temperature. The shifts (in ppm) of the NH protons were recorded.

Represntative Procedure XXIX

Hydroxamic Acid Synthesis from a Primary Amide

(Scheme 4.3, Results and Discussion III)

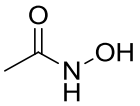


4.22

100% conversion

Acetamide (0.059 g, 1.00 mmol) and hydroxylamine hydrochloride (0.069 g, 1.00 mmol) were added to an oven dried Radleys carousel tube, followed by toluene (1.0 mL). The tube was then sealed and heated to 105 ^{o}C. Small aliquots were removed every hour to monitor the conversion into hydroxamic acid **4.22**. After 4 hours the reaction was complete.

4.22 Acetohydroxamic acid[156]



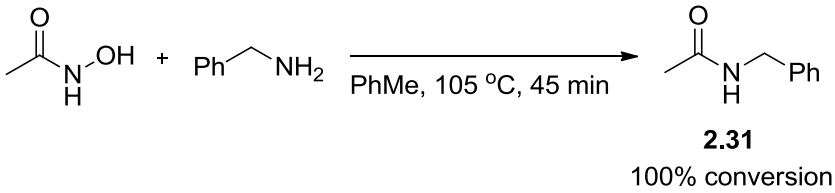
Following representative procedure XXIX, acetohydroxamic acid was observed in the crude NMR spectra.

^{1}H NMR (300 MHz, DMSO-d6): δ = 1.69 (3H, s, C<u>H</u>$_3$), 10.40 (1H, br. s., N<u>H</u>), 10.48 (1H, br. s., O<u>H</u>); ^{13}C NMR (75 MHz, DMSO-d6): δ = 19.8, 166.6.

Representative Procedure XXX

Hydroxamic Acid Coupling

(Scheme 4.3, Results and Discussion III)



2.31

100% conversion

Acetohydroxamic acid **4.22** (0.075 g, 1.00 mmol) and benzylamine (0.11 mL, 1.0 mmol) were added to an oven dried Radleys carousel tube, followed by toluene (1.0 mL). The tube was sealed and heated to 105 °C. Small aliquots were taken every 15 minutes to monitor the conversion into secondary amide **2.31** (analytical data was consistent with that previously reported). After 45 minutes, the reaction was complete.

6.5 Chapter 5 Experimental

Representative Procedure XXXI

5.1 **5.2** **5.3**

3-Phenylpropionic acid **5.1** (0.150 g, 1.00 mmol) and 4-methylbenzylamine **5.2** (0.13 mL, 1.0 mmol) were added to an oven dried carousel tube followed by solvent and catalyst if required. The tube was then sealed and the reaction mixture heated for the appropriate length of time at the appropriate temperature. The reaction mixture was then allowed to cool to room temperature before the solvent was removed *in vacuo* and the resulting amides analysed by their ^{1}H and ^{13}C NMR and IR spectroscopy and mass spectrometry.

Coupling with Hydroxylamine Hydrochloride

(Scheme 5.1, Results and Discussion IV)

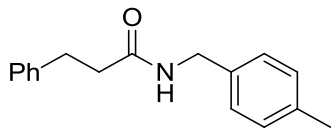
Following representative procedure XXXI, hydroxylamine hydrochloride (20 mol%) was used as catalyst. The reaction mixture was heated for 4 hours. An ^{1}H NMR of the crude reaction mixture showed a 9% conversion into **5.3**.

Direct Coupling

(Scheme 5.1, Results and Discussion IV)

Following representative procedure XXXI, no catalyst was used. The reaction mixture was heated for 4 hours. An ^{1}H NMR of the crude reaction mixture showed an 18% conversion into **5.3**.

5.3 *N*-(4-Methylbenzyl)-3-phenylpropionamide[149]



Following representative procedure XXXI, *N*-(4-Methylbenzyl)-3-phenylpropionamide was observed in the crude NMR spectra.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.36 (3H, s, C$\underline{H}_3$), 2.53 (2H, t, *J* = 7.5 Hz, $PhCH_2C\underline{H}_2$), 3.03 (2H, t, *J* = 7.5 Hz, $PhC\underline{H}_2CH_2$), 4.39 (2H, d, *J* = 5.75 Hz, $NHC\underline{H}_2$(4-Me)Ph), 7.06 – 7.32 (9H, m, 2xPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.1, 31.7, 38.6, 43.4, 126.3, 127.8, 128.4, 128.6, 129.3, 135.1, 137.2, 140.8, 171.8; ESI-MS of $[C_{17}H_{20}NO]^+$; theoretical m/z of $[M+H]^+$ = 254.15, measured m/z of $[M+H]^+$ = 254.14; IR: ν (cm^{-1}) = 1636.58 cm^{-1} (C=O stretch); Elemental analysis: predicted C:80.60, H:7.56, N:5.53; Found C:80.58, H:7.55, N:5.54.

Solvent Screen

(Table 5.1, Results and Discussion IV)

Following representative procedure XXXI, the solvent was varied according to Table 5.1. The reaction mixture was heated for 22 hours.

Variation of reaction temperature

(Table 5.2, Results and Discussion IV)

Following representative procedure XXXI, the reaction temperature was varied according to Table 5.2. The reaction mixture was heated for 22 hours.

Variation of reactant concentration

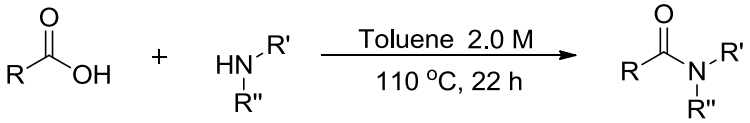
(Table 5.3, Results and Discussion IV)

Following representative procedure XXXI, the reactant concentration in toluene was varied according to Table 5.3. The reaction mixture was heated for 16 hours.

Representative Procedure XXXII

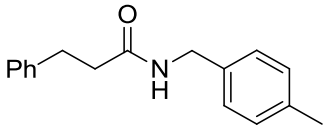
Catalyst free direct coupling of carboxylic acids and amines

(Table 5.2, Results and Discussion IV)



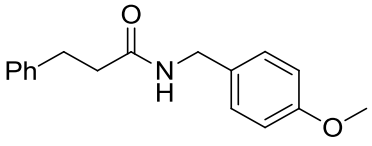
The appropriate carboxylic acid (1.0 mmol) was added to an oven dried Radleys carousel tube, followed by the appropriate amine (1.0 mmol) and 0.5 mL toluene (unless otherwise stated) all according to Table 5.2. The tube was then sealed and the reaction mixture heated at reflux for 22 hours before being allowed to cool to room temperature. The solvent was then removed on a rotary evaporator and the products were isolated by column chromatography and recrystallized where appropriate. The resulting amides were characterised by their IR, ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data.

5.3 *N*-(4-Methylbenzyl)-3-phenylpropionamide



Following representative procedure XXXII, 3-phenylpropionic acid (0.150 g, 1.00 mmol) was used as the acid species and 4-methylbenzylamine (0.13 mL, 1.0 mmol) was used as the amine species.**5.3** was recovered as an off-white solid (0.205 g, 81%) after removal of toluene and recrystallisation (dichloromethane/hexane). Analytical data was consistent with that reported above.

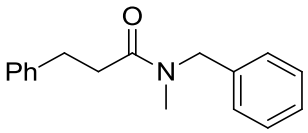
5.4 *N*-(4-Methoxybenzyl)-3-phenylpropionamide[149]



Following representative procedure XXXII, 3-phenylpropionic acid (0.150 g, 1.00 mmol) was used as the acid species and 4-methyoxybenzylamine (0.14 mL, 1.0 mmol) was used as the amine species. **5.4** was recovered as a yellow solid (0.194 g, 72%) after column chromatography (eluting with dichloromethane/methanol 95:5).

^{1}H NMR (250 MHz, $CDCl_3$): 2.53 (2H, t, *J* = 7.75 Hz, $PhCH_2C\underline{H}_2$), 3.02 (2H, t, *J* = 7.75 Hz, $PhC\underline{H}_2CH_2$), 3.82 (3H, s, $OC\underline{H}_3$), 4.36 (2H, d, *J* = 5.75 Hz, $NHC\underline{H}_2Ph$), 5.67 (1H, br. s., N<u>H</u>), 6.85 (2H, d, *J* = 8.75 Hz, (4-OMe)Ph), 7.10 (2H, d, *J* = 8.75 Hz, (4-OMe)Ph), 7.21 - 7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8, 38.5, 43.1, 55.3, 114.1, 126.3, 128.3, 128.4, 128.6, 129.1, 130.2, 140.8, 159.0, 172.0; ESI-MS of $[C_{17}H_{20}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 270.157, measured m/z of $[M+H]^+$ = 270.157; IR: ν (cm^{-1}) = 1637.37 cm^{-1} (C=O stretch).

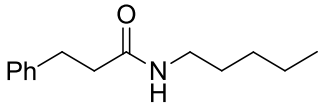
5.5 [*N*-(Benzyl)-*N*-methyl]-3-phenylpropionamide[149]



Following representative procedure XXXII, 3-phenylpropionic acid (0.150 g, 1.00 mmol) was used as the acid species and *N*-methylbenzylamine (0.13 mL, 1.0 mmol) was used as the amine species. **5.5** was recovered as a yellow oil (0.241 g, 95%) after removal of toluene. The product was observed as two rotamers in its ^{1}H and ^{13}C NMR spectra.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.75 (2H, t, *J* = 8.0 Hz, $PhCH_2C\underline{H}_2$), 2.88 (1.8H, s, $C\underline{H}_3$ major rotamer), 2.99 (1.2H, s, $C\underline{H}_3$ minor rotamer), 3.04 (2H, t, *J* = 8.0 Hz, $PhC\underline{H}_2CH_2$), 4.50 (0.8H, s, $N(CH_3)C\underline{H}_2Ph$, minor rotamer), 4.64 (1.2H, s, $N(CH_3)C\underline{H}_2Ph$, major rotamer), 7.23 - 7.36 (10H, m, 2xPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.4, 31.6, 35.4, 50.9, 126.1, 126.3, 127.3, 128.1, 128.5, 128.6, 128.9, 137.4, 141.3, 172.4; ESI-MS of $[C_{17}H_{20}NO]^+$; theoretical m/z of $[M+H]^+$ = 254.154, measured m/z of $[M+H]^+$ =254.155.

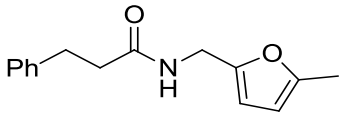
5.6 *N*-(Pentyl)-3-phenylpropionamide[149]



Following representative procedure XXXII, 3-phenylpropionic acid (0.150 g, 1.00 mmol) was used as the acid species and pentylamine (0.13 mL, 1.0 mmol) was used as the amine species. **5.6** was recovered as a dark brown oil (0.199 g, 94%) after removal of toluene.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90 (3H, t, *J* = 6.75 Hz, $CH_2CH_2C\underline{H}_3$), 1.22 - 1.47 (6H, m, $CH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 2.49 (2H, t, *J* = 8.0 Hz, $PhCH_2C\underline{H}_2$), 2.99 (2H, t, *J* = 8.0 Hz, $PhC\underline{H}_2CH_2$), 3.18 - 3.26 (2H, q, *J* = 7.0 Hz, $NHC\underline{H}_2CH_2$), 5.35 (1H, br. s., N<u>H</u>), 7.23 - 7.31 (5H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0, 22.3, 29.0, 29.2, 31.8, 38.6, 39.5, 126.2, 128.3, 128.4, 128.5, 140.9, 172.0; ESI-MS of $[C_{14}H_{22}NO]^+$; theoretical m/z of $[M+H]^+$ = 220.128, measured m/z of $[M+H]^+$ = 220.127.

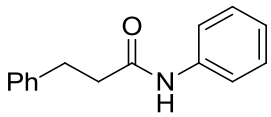
5.7 *N*-(5-Methylfurfuryl)-3-phenylpropionamide[149]



Following representative procedure XXXII, 3-phenylpropionic acid (0.150 g, 1.00 mmol) was used as the acid species and 5-methylfurfurylamine (0.18 mL, 1.0 mmol) was used as the amine species. **5.7** was recovered as a brown oil (0.454 g, 92%) after removal of the solvent.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.17 (3H, s, $C\underline{H}_3$), 2.41 (2H, t, *J* = 8.25 Hz, $PhCH_2C\underline{H}_2$), 2.89 (2H, t, *J* = 8.25 Hz, $PhC\underline{H}_2CH_2$), 4.26 (2H, d, *J* = 5.25 Hz, $NHC\underline{H}_2$Furyl), 5.67 (1H, br. s., N<u>H</u>), 5.79 (1H, d, Furyl), 5.95 (1H, d, Furyl), 7.09 - 7.18 (5H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 31.6, 36.6, 38.4, 106.3, 108.3, 126.2, 128.4, 128.5, 140.8, 149.3, 151.9, 171.8; ESI-MS of $[C_{15}H_{18}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 244.130, measured m/z of $[M+H]^+$ = 244.130; IR: ν (cm^{-1}) = 1647.39 cm^{-1} (C=O stretch); Elemental analysis: predicted C:74.05, H:7.04, N:5.76; Found C:74.05, H:7.05, N:5.74.

5.8 *N*-(Phenyl)-3-phenylpropionamide[149]

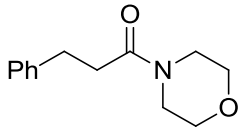


Following representative procedure XXXII, 3-phenylpropionic acid (0.150 g, 1.00 mmol) was used as the acid species and aniline (0.09 mL, 1.00 mmol) was used as the amine species. The reaction mixture was heated at reflux in 0.5 mL *p*-xylene. An ^{1}H NMR of the crude reaction mixture showed a 73% conversion into **5.8**.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.69 (2H, t, *J* = 7.25 Hz, $PhCH_2C\underline{H}_2$), 3.09 (2H, t, *J* = 7.25 Hz, $PhC\underline{H}_2CH_2$), 5.60 (1H, br. S., N<u>H</u>), 7.30 – 7.37 (8H, m, 2xPh), 7.47 (2H, d, *J* =

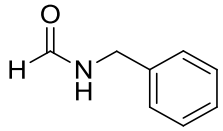
7.5 Hz, Ph); ESI-MS of $[C_{15}H_{16}NO]^+$; theoretical m/z of $[M+H]^+$ = 226.135, measured m/z of $[M+H]^+$ = 226.135; IR: ν (cm^{-1}) = 1649.38 cm^{-1} (C=O stretch).

3.43 *N*-(Morpholino)-3-phenylpropionamide[149]



Following representative procedure XXXII, 3-phenylpropionic acid (0.150 g, 1.00 mmol) was used as the acid species and morpholine (0.08 mL, 1.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 0.5 mL *p*-xylene. **3.43** was recovered as a colourless oil (0.206 g, 94%) after removal of *p*-xylene. Analytical data was consistent with that reported above.

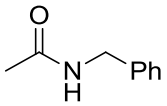
4.9 *N*-(Benzyl)-formamide[149]



Following representative procedure XXXII, formic acid (0.06 mL, 1.0 mmol) was used as the acid species and benzylamine (0.11 mL, 1.0 mmol) was used as the amine species. **4.9** was recovered as a white solid (0.132 g, 89%) after removal of toluene and recrystallisation (dichloromethane/hexane). The product was observed as 2 rotamers in its NMR spectra.

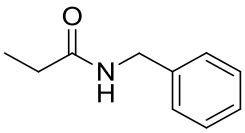
^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.30 (2H (minor rotamer), d, *J* = 6.3 Hz, NHC$\underline{H}_2$Ph), 4.37 (2H (major rotamer), d, *J* = 6.3 Hz, NHC$\underline{H}_2$Ph), 6.11 (1H, br. s., N$\underline{H}$), 7.18 - 7.25 (5H, m, Ph), 8.03 (1H (minor rotamer), s, $\underline{H}$C(O)NH), 8.14 (1H (major rotamer), s, $\underline{H}$C(O)NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.2 (major rotamer), 45.7 (minor rotamer), 126.9, 127.7, 127.8, 128.8, 128.9, 137.5 (major rotamer), 137.6 (minor rotamer), 161.1 (major rotamer), 164.7 (minor rotamer); ESI-MS of $[C_8H_{10}NOCl]^+$; theoretical m/z of $[M+H]^+$ = 136.076, measured m/z of $[M+H]^+$ = 136.078; IR: ν (cm^{-1}) = 1649.88 cm^{-1} (C=O stretch).

2.31 *N*-Benzylacetamide



Following representative procedure XXXII, acetic acid (0.11 mL, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **2.31** was recovered as a white solid (0.249 g, 83%) after removal of toluene and recrystallization (dichloromethane/hexane). Analytical data was consistent with that previously reported.

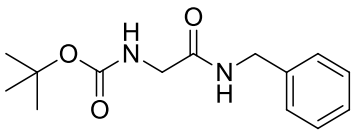
2.6 *N*-(Benzyl)-propionamide[149]



Following representative procedure XXXII, propionic acid (0.15 mL, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **2.6** was recovered as a white solid (0.293 g, 90%) removal of toluene and recrystallisation (dichloromethane/hexane).

^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.04 (3H, t, *J* = 6.0, C<u>H</u>$_3$CH$_2$), 2.08 – 2.14 (2H, q, *J* = 6.0 Hz, CH$_3$C<u>H</u>$_2$C(O)), 4.31 (2H, d, *J* = 9.0 Hz, PhC<u>H</u>$_2$NH), 7.08 – 7.22 (5H, m, aromatic); ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 10.2, 30.1, 40.0, 127.9, 128.2, 129.1, 138.8, 173.9; ESI-MS of $[C_{10}H_{13}NO]^+$; theoretical m/z of $[M+H]^+$ = 164.11, measured m/z of $[M+H]^+$ = 164.11; IR : ν (cm^{-1}) = 1642.09 cm^{-1} (C=O stretch).

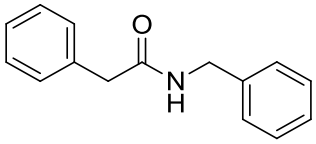
5.9 [*N*-(Benzyl)*N'*-Boc]-glycinamide[149]



Following representative procedure XXXII, *N*-Boc-glycine (0.350 g, 2.00 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 71% conversion into **5.9**.

^{1}H NMR (250 MHz, DMSO-d6): δ = 1.41 (9H, s, 3xC<u>H</u>$_3$), 3.60 (2H, d, *J* = 6.25 Hz, NHC<u>H</u>$_2$C(O)NH), 4.30 (2H, d, *J* = 5.75 Hz, C(O)NHC<u>H</u>$_2$Ph), 7.02 (1H, br. s., N<u>H</u>), 7.24 - 7.32 (5H, m, Ph), 8.32 (1H, br. s., N<u>H</u>).

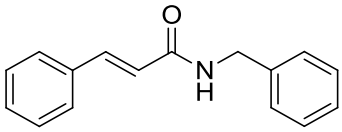
5.10 *N*-(Benzyl)-phenylacetamide[149]



Following representative procedure XXXII, phenylacetic acid (0.272 g, 2.00 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **5.10** was recovered as a white solid (0.410 g, 91%) after removal of toluene and recrystallization (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.56 (2H, s, PhC$\underline{H}_2$C(O)), 4.34 (2H, d, *J* = 5.7 Hz, NHC$\underline{H}_2$Ph), 5.63 (1H, br. s., N$\underline{H}$), 7.09 – 7.28 (10H, m, 2xPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 43.6, 43.9, 127.5, 128.7, 129.1, 129.5, 134.8, 138.1, 170.9; ESI-MS of $[C_{15}H_{16}NO]^+$; theoretical m/z of $[M+H]^+$ = 226.132, measured m/z of $[M+H]^+$ = 226.133; IR: ν (cm^{-1}) = 1636.35 cm^{-1} (C=O stretch).

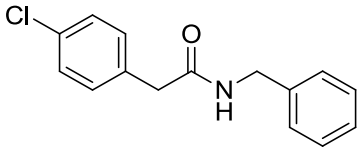
5.11 *N*-(Benzyl)-cinnamamide[149]



Following representative procedure XXXII, cinnamic acid (0.296 g, 2.00 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. The reaction was heated at reflux in 0.5 mL *p*-xylene. **5.11** was recovered as an off-white solid (0.216 g, 91%) after removal of *p*-xylene and recrystallization (dichloromethane/hexane).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.48 (2H, d, *J* = 5.75 Hz, NHC$\underline{H}_2$Ph), 6.05 (1H, br. s., N$\underline{H}$), 6.36 (1H, d, *J* = 15.75 Hz, PhCHC$\underline{H}$C(O)), 7.25 – 7.42 (10H, m, 2xPh), 7.59 (1H, d, *J* = 15.75 Hz, PhC$\underline{H}$CHC(O)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 42.3, 120.5, 127.6, 127.8, 127.9, 128.8, 129.7, 134.8, 138.2, 141.4, 165.8; ESI-MS of $[C_{16}H_{16}NO]^+$; theoretical m/z of $[M+H]^+$ = 238.131, measured m/z of $[M+H]^+$ = 238.132; IR: ν (cm^{-1}) = 1650.39 cm^{-1} (C=O stretch).

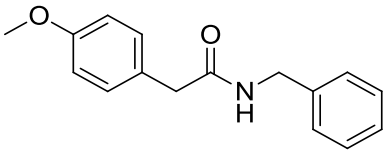
5.12 *N*-(Benzyl)-4-chlorophenylacetamide[149]



Following representative procedure XXXII, 4-chlorophenylacetic acid (0.341 g, 2.00 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **5.12** was recovered as an off-white solid (0.475 g, 92%) after removal of toluene and recrystallization (dichloromethane/hexane).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.57 (2H, s, (4-Cl)PhC$\underline{H}_2$C(O)), 4.45 (2H, d, *J* = 5.75 Hz, NHC$\underline{H}_2$Ph), 5.70 (1H, br. s., N$\underline{H}$), 7.22 – 7.37 (9 H, m, 2xPh); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41.8, 42.5, 127.1, 127.5, 128.3, 128.6, 129.3, 129.8, 130.3, 130.6, 133.2, 133.9, 171.8; ESI-MS of $[C_{15}H_{15}NOCl]^+$; theoretical m/z of $[M+H]^+$ = 260.076, measured m/z of $[M+H]^+$ = 260.075; IR: ν (cm^{-1}) = 1650.39 cm^{-1} (C=O stretch).

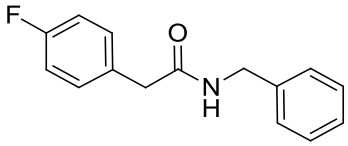
5.13 *N*-(Benzyl)-4-methoxyphenylacetamide[149]



Following representative procedure XXXII, 4-methoxyphenylacetic acid (0.333 g, 2.00 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **5.13** was recovered as a yellow solid (0.469 g, 92%) after removal of toluene and recrystallization (dichloromethane/hexane).

^{1}H NMR (300 MHz, DMSO-d6): δ = 3.38 (2H, s, (4-OMe)PhC$\underline{H}_2$C(O)), 3.70 (3H, s, OC$\underline{H}_3$), 4.23 (2H, d, *J* = 5.7 Hz, NHC$\underline{H}_2$Ph), 6.84 (2H, d, *J* = 8.4 Hz, (4-OMe)Ph), 7.12 – 7.37 (7H, m, 2xPh), 8.47 (1H, br. s., N$\underline{H}$); ^{13}C NMR (75 MHz, DMSO-d6): δ = 41.8, 42.5, 55.4, 114.0, 127.1, 127.5, 128.3, 128.6, 130.3, 130.6, 139.9, 158.3, 170.8; ESI-MS of $[C_{16}H_{18}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 256.135, measured m/z of $[M+H]^+$ = 256.137; IR: ν (cm^{-1}) = 1634.93 cm^{-1} (C=O stretch).

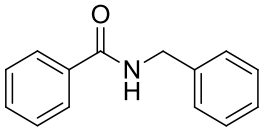
5.14 *N*-(Benzyl)-4-fluorophenylacetamide[149]



Following representative procedure XXXII, 4-fluorophenylacetic acid (0.308 g, 2.00 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **5.14** was recovered as an off white solid (0.435 g, 90%) after removal of toluene.

^{1}H NMR (300 MHz, DMSO-d6): δ = 3.46 (2H, s, C$\underline{H}_2$C(O)), 4.25 (2H, d, *J* = 6.0 Hz, NHC$\underline{H}_2$Ph), 7.08 – 7.32 (9H, m, 2xPh), 8.54 (1H, br. s., N$\underline{H}$); ^{13}C NMR (75 MHz, DMSO-d6): δ = 41.7, 42.5, 114.9, 115.1, 115.2, 115.4, 127.1, 127.6, 127.9, 128.6, 128.7, 131.1, 131.2, 131.5, 131.6, 132.9, 132.9, 139.8, 159.8, 162.9, 170.4; ESI-MS of $[C_{15}H_{15}NOF]^+$; theoretical m/z of $[M+H]^+$ = 244.109, measured m/z of $[M+H]^+$ = 244.109; IR: ν (cm^{-1}) = 1640.13 cm^{-1} (C=O stretch); Elemental analysis: predicted C:74.06, H:5.80, N:5.76; Found C:74.08, H:5.85, N:5.74.

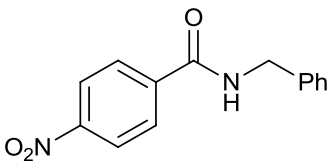
3.34 *N*-(Benzyl)-benzamide[149]



Following representative procedure XXXII, benzoic acid (0.246 g, 2.00 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 0.5 mL *p*-xylene. An ^{1}H NMR of the crude reaction mixture showed a 44% conversion into **3.34**.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.58 (d, 2H, *J* = 5.7 Hz, PhC$\underline{H}_2$NH), 6.36 (br. s, 1H, N$\underline{H}$), 7.18 - 7.43 (m, 8H, 2Ph), 7.70 - 7.73 (m, 2H, Ph).

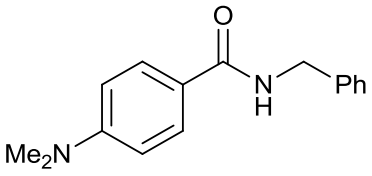
5.15 *N*-(Benzyl)-4-nitrobenzamide[149]



Following representative procedure XXXII, 4-nitrobenzoic acid (0.167 g, 1.00 mmol) was used as the acid species and benzylamine (0.11 mL, 1.0 mmol) was used as the

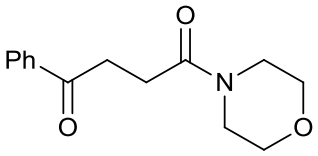
amine species. The reaction mixture was heated at reflux in 0.5 mL *p*-xylene. An ^{1}H NMR of the crude reaction mixture showed no conversion into **5.15**.

5.16 *N*-(Benzyl)-4-dimethylaminobenzamide



Following representative procedure XXXII, benzoic acid (0.165 g, 1.00 mmol) was used as the acid species and benzylamine (0.11 mL, 1.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 0.5 mL *p*-xylene. An ^{1}H NMR of the crude reaction mixture showed no conversion into **5.16**.

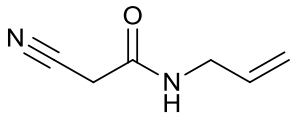
5.17 3-Benzoyl-*N*-morpholinopropionic acid[149]



Following representative procedure XXXII, 3-benzoylpropionic acid (0.178 g, 1.00 mmol) was used as the acid species and morpholine (0.08 mL, 1.0 mmol) was used as the amine species. **5.17** was recovered as a dark yellow oil (0.193 g, 78%) after removal of toluene and recrystallization (dichloromethane/hexane).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.76 (2H, t, *J* = 6.6 Hz, PhC(O)C$\underline{H}_2$), 3.35 (2H, t, *J* = 6.6 Hz, PhC(O)CH$_2$C$\underline{H}_2$), 3.55 – 3.73 (8H, m, morpholine ring), 7.42 – 7.57 (3H, m, $\underline{Ph}$C(O)), 8.00 (2H, d, *J* = 6.9 Hz, $\underline{Ph}$C(O)); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9, 33.5, 42.1, 45.9, 128.0, 128.1, 128.5, 128.6, 133.2, 136.7, 170.5, 199.1; ESI-MS of $[C_{16}H_{18}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 248.124, measured m/z of $[M+H]^+$ = 248.122; IR: ν (cm^{-1}) = 1682.76 cm^{-1} (C=O stretch, amide).

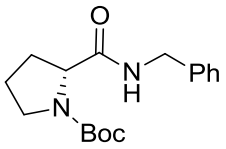
5.18 *N*-(Allyl)-cyanoacetamide[149]



Following representative procedure XXXII, cyanoacetic acid (0.085 g, 1.00 mmol) was used as the acid species and allylamine (0.08 mL, 1.0 mmol) was used as the amine species. **5.18** was recovered as a light brown solid (0.095 g, 76%) after removal of toluene.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.34 (2H, s, NCC<u>H</u>$_2$C(O)), 3.84 – 3.88 (2H, m, NHC<u>H</u>$_2$CH), 5.09 – 5.21 (2H, m, NHCH$_2$CHC<u>H</u>$_2$), 5.71 – 5.84 (1H, m, NHCH$_2$C<u>H</u>CH$_2$), 6.29 (1H, br. s., N<u>H</u>); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 42.7, 117.6, 132.8, 133.5, 160.8; ESI-MS of $[C_6H_9N_2O]^+$; theoretical m/z of $[M+H]^+$ = 125.069 measured m/z of $[M+H]^+$ = 125.068; IR: ν (cm^{-1}) = 1657.64 cm^{-1} (C=O stretch).

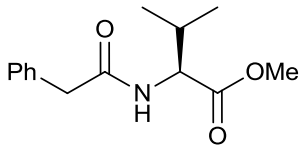
4.19 [*N*-(Benzyl)*N'*-Boc]-D-prolinamide[149]



Following representative procedure XXXII, *N*-Boc-D-proline (0.431 g, 2.00 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. The reaction was heated at reflux in 0.5 mL *p*-xylene. An ^{1}H NMR of the crude reaction mixture showed 79% conversion into **4.19**.

^{1}H NMR (250 MHz, DMSO-d6): δ = 1.30 (5.5H, s, ^{t}Bu), 1.42 (3.5H, s, ^{t}Bu), 1.79 - 1.82 (3H, m, pyrrolidine ring), 2.07 - 2.18 (1H, m, pyrrolidine ring), 3.25 - 3.43 (2H, m, pyrrolidine ring), 4.07 - 4.39 (3H, m, NHC<u>H</u>$_2$Ph and (Boc)NC<u>H</u>C(O)), 7.24 - 7.32 (5H, m, Ph), 8.36 - 8.43 (1H, m, N<u>H</u>); ^{13}C NMR (75 MHz, DMSO-d6): δ = 23.5, 28.3, 31.4, 31.5, 42.4, 46.8, 60.1, 60.3, 78.8, 127.1, 127.6, 128.5, 139.9, 161.7, 172.8; ESI-MS of $[C_{17}H_{23}N_2O_3]^+$; theoretical m/z of $[M+H]^+$ = 305.154, measured m/z of $[M+H]^+$ = 305.148; IR: ν (cm^{-1}) = 1675.75 cm^{-1} (C=O stretch, amide).

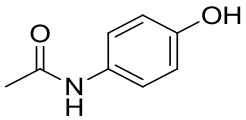
5.19 *N*-(Phenylacetyl)-valine methyl ester[149]



Following representative procedure XXXII, phenylacetic acid (0.135 g, 1.00 mmol) was used as the acid species and valine methyl ester hydrochloride (0.167 g, 1.00 mmol) was used as the amine species. One equivalent of *N*,*N*-diisopropylethylamine (0.17 mL, 1 mmol) was included in the reaction. **5.19** was recovered as a yellow oil (0.218 g, 88%) after removal of toluene and washing with water to remove the base.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (3H, d, *J* = 6.0 Hz, (C$\underline{H}_3$)CH(CH$_3$)CH), 0.78 (3H, d, *J* = 6.0 Hz, (CH$_3$)CH(C$\underline{H}_3$)CH), 1.97 – 2.08 (1H, m, (CH$_3$)C$\underline{H}$(CH$_3$)CH), 3.55 (2H, d, *J* = 3.0 Hz, PhC$\underline{H}_2$C(O)), 3.63 (3H, s, OC$\underline{H}_3$), 4.45 – 4.49 (1H, dd, *J* = 4.8 Hz, 8.7 Hz, (CH$_3$)CH(CH$_3$)C$\underline{H}$NH), 5.83 (1H, br. s, N$\underline{H}$), 7.19 – 7.28 (5H, m, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 18.9, 31.2, 43.7, 52.2, 57.0, 127.5, 128.6, 129.0, 129.4, 134.6, 171.0, 172.4; ESI-MS of $[C_{14}H_{20}NO_3]^+$; theoretical m/z of $[M+H]^+$ = 249.136, measured m/z of $[M+H]^+$ = 249.136.

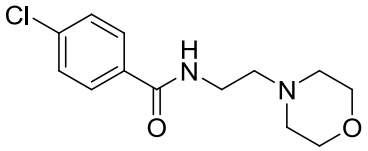
4.4 *N*-(Acetyl)-4-hydroxyaniline (Paracetamol)[149]



Following representative procedure XXXII, acetic acid (0.12 mL, 2.0 mmol) was used as the acid species and 4-aminophenol (0.218 g, 2.00 mmol) was used as the amine species. The reaction mixture was heated at reflux in 1.0 mL *p*-xylene. An ^{1}H NMR of the crude reaction mixture showed 69% conversion into **4.4**.

^{1}H NMR (300 MHz, DMSO-d6): δ = 1.99 (3H, s, C(O)C$\underline{H}_3$), 6.68 (2H, d, *J* = 8.75 Hz, Ph), 7.35 (2H, d, *J* = 8.75 Hz, Ph), 9.16 (1H, s, N$\underline{H}$), 9.67 (1H, s, O$\underline{H}$); ^{13}C NMR (75 MHz, DMSO-d6): δ = 24.1, 115.3, 121.1, 131.4, 153.5, 167.8; ESI-MS of $[C_8H_9NO_2]^+$; theoretical m/z of $[M+H]^+$ = 152.071, measured m/z of $[M+H]^+$ = 152.072.

3.46 *N*-(2-Morpholinoethyl)-4-chlorobenzamide (Moclobemide)[149]



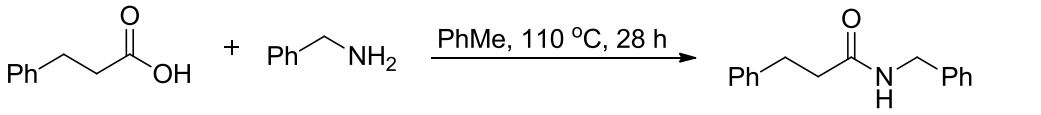
Following representative procedure XXXII, 4-chlorobenzoic acid (0.312 g, 2.00 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. The reaction mixture was heated at reflux in 1.0 mL *p*-xylene. An ^{1}H NMR of the crude reaction mixture showed 66% conversion into **3.46**.

^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.56 (4H, t, *J* = 4.3 Hz, $C\underline{H}_2NC\underline{H}_2$), 2.65 (2H, t, *J* = 6.0 Hz, $NC\underline{H}_2CH_2$), 3.56 – 3.62 (2H, q, *J* = 5.6 Hz, $NHC\underline{H}_2CH_2$), 3.78 (4H, t, *J* = 4.6 Hz, CH_2OCH_2), 6.83 (1H, br. s, NH), 7.45 (2H, d, *J* = 8.6 Hz, aromatic), 7.75 (2H, d, *J* = 8.6 Hz, aromatic). ^{13}C NMR (75.5 MHz, $CDCl_3$, 25 °C): δ = 36.5, 53.6, 57.5, 67.1, 128.8, 129.2, 129.3, 133.4, 138.2, 166.7. IR: 1117.04, 1486.97, 1540.68, 1594.76, 1634.53, 2968.43, 3285.8 cm^{-1}.

Representative Procedure XXXIII

Large Scale Uncatalysed Amide Formation

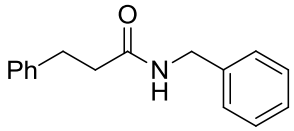
(Scheme 5.2, Results and Discussion IV)



100 % conversion
93 % yield after recrystallisation

3-Phenylpropionamide (62.74 g, 418 mmol) was added to an oven dried single neck 500 mL round bottom flask. Benzylamine (45.6 mL, 418 mmol) and toluene (210 mL) were added and the flask was fitted with a reflux condenser (and left open to the air) before being heated at reflux for 28 hours. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* on a rotary evaporator and the resulting amide was recrystallized from dichloromethane.

3.33 *N*-(Benzyl)-3-phenylpropionamide



Following representative procedure XXXIII, **3.33** was recovered as a pale yellow solid (0.439 g, 92%) after removal of toluene *in vacuo.* Analytical data was consistent with that reported above.

Representative Procedure XXXIV

Reactivity Comparison with an Ester

Ethyl-3-phenylpropanoate (0.18 mL, 1.0 mmol), benzylamine (0.11 mL, 1.0 mmol) and toluene (1.0 mL) were added to an oven dried Radleys carousel tube, followed by an additive if required. The tube was then sealed and the reaction mixture heated at reflux for 22 hours. The reaction mixture was then allowed to cool to room temperature before the solvent was removed *in vacuo* and the products analysed by their ^{1}1 H and ^{13}C NMR spectra.

Direct Reactivity Comparison

(Scheme 5.3, Results and Discussion IV)

Following representative procedure XXXIV, 1 equivalent phenylacetic acid (0.136 g, 1.00 mmol) was added. An NMR of the crude reaction mixture showed a 41% conversion into **3.33** and a 59% conversion into **2.6** (both with respect to benzylamine). Analytical data was consistent with that reported above.

Acid Catalysed Ester and Amine Coupling

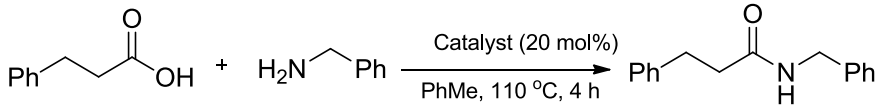
(Scheme 5.4, Results and Discussion IV)

1. Representative procedure XXXIV was followed. An NMR of the crude reaction mixture showed no reaction to have taken place.
2. Following represrntative procedure XXXIV, phenylacetic acid (0.014 g, 0.1 mmol, 10 mol%) was added as catalyst. An NMR of the crude reaction mixture showed a 46% conversion into **3.33**. Analytical data was consistent with that reported above.

Representative Procedure XXXV

Catalyst Screening

(Table 5.3, Results and Discussion IV)

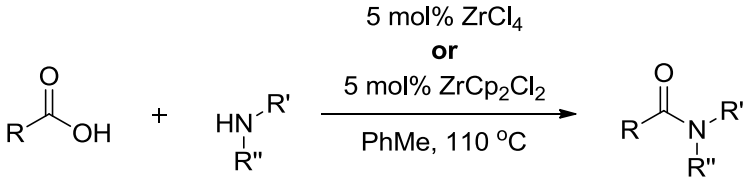


3-Phenylpropionamide (0.150 g, 1.00 mmol) was added to an oven dried Radleys carousel tube. Benzylamine (0.11 mL, 1.0 mmol), the appropriate catalyst (20 mol%, see Table 5.3) and toluene (1.0 mL) was added then the tube was sealed and heated at reflux for 4 hours. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* on a rotary evaporator and the crude reaction mixtures were analysed by their ^{1}H NMR and ^{13}C NMR spectra.

Representative Procedure XXXVI

Direct Catalyzed Amide Formation

(Table 5.4, Results and Discussion IV)



The carboxylic acid species (2.0 mmol) was added to an oven dried Radleys carousel tube, followed by the zirconium catalyst ($ZrCl_4$: 0.023 g, 5 mol% unless otherwise stated; $ZrCp_2Cl_2$: 0.029 g, 5 mol%; see Table 5.4), toluene (2.0 mL) and the amine species (2.0 mmol). The carousel tube was then sealed before the reaction mixture was heated at reflux for the appropriate time (see Table 5.4). 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 their ^{1}H NMR and ^{13}C NMR spectroscopy and mass spectrometry data. Where the reaction had gone to 100% conversion, the reaction mixture was passed through a short plug of silica to remove the catalyst; otherwise the amides were purified by column chromatography where appropriate.

5.3 *N*-(4-Methylbenzyl)-3-phenylpropionamide

Following representative procedure XXXVI, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and 4-methylbenzylamine (0.26 mL, 2.0 mmol) was used as the amine species. **5.3** was recovered as an off-white solid (0.476 g, 94%, $ZrCp_2Cl_2$; 0.466 g, 92%, $ZrCl_4$) after filtration through a pad of silica (eluting with dichloromethane) and recrystallisation (dichloromethane/hexane).

5.4 *N*-(4-Methoxybenzyl)-3-phenylpropionamide

Following representative procedure XXXVI, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and 4-methyoxybenzylamine (0.27 mL, 2.0 mmol) was used as the amine species. **5.4** was recovered as a pale yellow solid (0.323 g, 60% $ZrCp_2Cl_2$; 0.479 g, 89%, $ZrCl_4$) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

5.5 [*N*-(Benzyl)-*N*-methyl]-3-phenylpropionamide

Following representative procedure XXXVI, 3-phenylpropionic acid (0.150 g, 1.0 mmol) was used as the acid species and *N*-methylbenzylamine (0.13 mL, 1.0 mmol) was used as the amine species. **5.5** was recovered as a yellow oil (0.206 g, 81%) after column chromatography (eluting with 98:2 dichloromethane:methanol). Analytical data was consistent with that above.

5.6 *N*-(Pentyl)-3-phenylpropionamide

Following representative procedure XXXVI, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and pentylamine (0.26 mL, 2.0 mmol) was used as the amine species. **5.6** was isolated as a brown oil (0.301 g, 71%) after column chromatography (eluting with 95:5 dichloromethane:methanol). Analytical data was consistent with that above.

5.7 *N*-(5-Methylfurfuryl)-3-phenylpropionamide

Following representative procedure XXXVI, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and 5-methylfurfurylamine (0.36 mL, 2.0 mmol) was used as the amine species. **5.7** was recovered as a brown oil (0.442 g, 91%) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

5.8 *N*-(Phenyl)-3-phenylpropionamide

Following representative procedure XXXVI, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and aniline (0.17 mL, 2.0 mmol) was used as the amine species. 10 mol% $ZrCl_4$ (0.046 g) was used. An ^{1}H NMR of the crude reaction mixture showed a 45% conversion into **5.8** when $ZrCp_2Cl_2$ was used as catalyst and a 41% conversion when $ZrCl_2$ was used as catalyst. Analytical data was consistent with that above.

3.43 *N*-(Morpholino)-3-phenylpropionamide

Following representative procedure XXXVI, 3-phenylpropionic acid (0.300 g, 2.0 mmol) was used as the acid species and morpholine (0.17 mL, 2.0 mmol) was used as the amine species. **3.43** was recovered as a colourless oil (0.386 g, 88%) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

4.9 *N*-(Benzyl)-formamide

Following representative procedure XXXVI, formic acid (0.11 mL, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **4.9** was recovered as a white solid (0.251 g, 93%) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

2.6 *N*-(Benzyl)-propionamide

Following representative procedure XXXVI, propionic acid (0.15 mL, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **2.6** was recovered as a white solid (0.264 g, 81%) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

5.9 [*N*-(Benzyl)*N'*-Boc]-glycinamide

Following representative procedure XXXVI, *N*-Boc-glycine (0.350 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **5.9** was recovered as a pale yellow viscous oil (0.423 g, 80%) after column chromatography (eluting with 97:3 dichloromethane: methanol) and washing with hexanes. ^{1}H NMR data was consistent with that reported above.

^{13}C NMR (75 MHz, DMSO-d6): δ = 28.2, 42.0, 43.4, 78.0, 126.7, 127.1, 128.1, 139.4, 155.8, 169.4; ESI-MS of $[C_{14}H_{21}N_2O_3]^+$; theoretical m/z of $[M+H]^+$ = 265.153, measured m/z of $[M+H]^+$ = 265.153.

5.10 *N*-(Benzyl)-phenylacetamide

Following representative procedure XXXVI, phenylacetic acid (0.272 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **5.10** was recovered as a white solid (0.396 g, 88%) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

5.11 *N*-(Benzyl)-cinnamamide

Following representative procedure XXXVI, cinnamic acid (0.296 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. An ^{1}H NMR of the crude reaction mixture showed a 57% conversion into **5.11** when $ZrCl_4$ was used as catalyst and 72% conversion when $ZrCp_2Cl_2$ was used as catalyst. Analytical data was consistent with that above.

5.12 *N*-(Benzyl)-4-chlorophenylacetamide

Following representative procedure XXXVI, 4-chlorophenylacetic acid (0.341 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **5.12** was recovered as a white solid (0.461 g, 89%) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

5.13 *N*-(Benzyl)-4-methoxyphenylacetamide

Following representative procedure XXXVI, 4-methoxyphenylacetic acid (0.333 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **5.13** was recovered as a yellow solid (0.455 g, 91%) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

5.14 *N*-(Benzyl)-4-fluorophenylacetamide

Following representative procedure XXXVI, 4-fluorophenylacetic acid (0.308 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as

the amine species. **5.14** was recovered as an off white solid (0.442 g, 91%) after filtration through a pad of silica, eluting with dichloromethane and methanol. Analytical data was consistent with that above.

3.34 *N*-(Benzyl)-benzamide

Following representative procedure XXXVI, benzoic acid (0.241 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. 10 mol% $ZrCl_4$ (0.046 g) was used. An ^1H NMR of the crude reaction mixture showed 55% conversion into **3.34** when $ZrCl_4$ was used as catalyst.

N-(Benzyl)-benzamide was recovered as a white solid (0.304g, 72%, $ZrCp_2Cl_2$) after column chromatography (eluting with 92:8 dichloromethane:methanol). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.17, 126.97, 127.66, 127.95, 128.62, 128.82, 131.56, 134.43, 138.21, 167.35; ESI-MS of $[C_{14}H_{13}NO]^+$; theoretical m/z of $[M+H]^+$ = 212.107, measured m/z of $[M+H]^+$ = 212.106.

5.15 *N*-(Benzyl)-4-nitrobenzamide

Following representative procedure XXXVI, 4-nitrobenzoic acid (0.334 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. 10 mol% $ZrCl_4$ (0.046 g) was used. An ^1H NMR of the crude reaction mixture showed 3% conversion into **5.15** when $ZrCp_2Cl_2$ was used as catalyst and no conversion when $ZrCl_4$ was used as catalyst.

5.16 *N*-(Benzyl)-4-dimethylaminobenzamide

Following representative procedure XXXVI, 4-dimethylaminobenzoic acid (0.330 g, 2.0 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. 10 mol% $ZrCl_4$ (0.046 g) was used. An ^1H NMR of the crude reaction mixture showed a 1% conversion into **5.16** when $ZrCp_2Cl_2$ was used as catalyst and no conversion when $ZrCl_4$ was used as catalyst.

5.17 3-Benzoyl-*N*-morpholinopropionamide

Following representative procedure XXXVI, 3-benzoylpropionic acid (0.356 g, 2.0 mmol) was used as the acid species and morpholine (0.16 mL, 2.0 mmol) was used as the amine species. **5.17** was recovered as a dark yellow oil (0.386 g, 78%) after

filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above.

5.18 *N*-(Allyl)-cyanoacetamide

Following representative procedure XXXVI, cyanoacetic acid (0.085 g, 1.0 mmol) was used as the acid species and allylamine (0.08 mL, 1.0 mmol) was used as the amine species. **5.18** was recovered as a light brown solid (0.104 g, 84%) after filtration through a short pad of silica (eluting with 97:3 dichloromethane : methanol). Analytical data was consistent with that above.

4.19 [*N*-(Benzyl)*N'*-Boc]-D-prolinamide

Following representative procedure XXXVI, *N*-Boc-D-proline (0.323 g, 1.5 mmol) was used as the acid species and benzylamine (0.22 mL, 2.0 mmol) was used as the amine species. **4.19** was recovered as a white solid (0.256 g, 56%) after column chromatography eluting with 1:1 hexane : ethyl acetate. Analytical data was consistent with that above.

$[\alpha]_D^{25} = 80.3^o$ ($CHCl_3$, $c = 0.09$); HPLC: Chiralcel AD column (25 cm), 90:10 hexane : isopropylalcohol, 0.5 mL min^{-1} flow rate, 16.39 min (D-enantiomer). No peak observed for L-enantiomer @ 22.94 min.

5.19 *N*-(Phenylacetyl)-valine methyl ester

Following representative procedure XXXVI, phenylacetic acid (0.135 g, 1.0 mmol) was used as the acid species and valine methyl ester hydrochloride (0.167 g, 1.0 mmol) was used as the amine species. One equivalent of *N*,*N*-diisopropylethylamine (0.17 mL, 1 mmol) was included in the reaction. **5.19** was recovered as a yellow oil (0.202 g, 81%) after filtration through a short pad of silica and washing with water to remove the base. Analytical data was consistent with that above.

4.4 *N*-(Acetyl)-4-hydroxyaniline

Following representative procedure XXXVI, acetic acid (0.12 mL, 2.0 mmol) was used as the acid species and 4-aminophenol (0.218 g, 2.0 mmol) was used as the amine species. **4.4** was recovered as a dark brown solid (0.266 g, 88%) after filtration through a pad of celite, eluting with dichloromethane. Analytical data was consistent with that above.

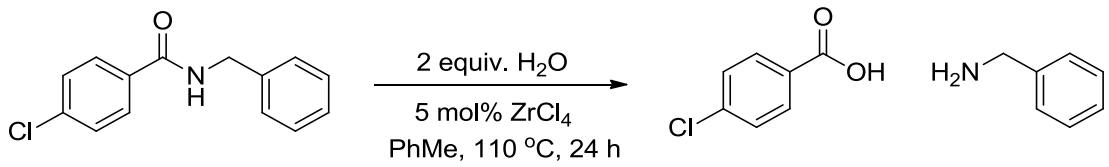
3.46 *N*-(2-Morpholinoethyl)-4-chlorobenzamide

Following representative procedure XXXVI, 4-chlorobenzoic acid (0.313 g, 2.0 mmol) was used as the acid species and 2-(morpholino)ethylamine (0.26 mL, 2.0 mmol) was used as the amine species. **3.46** was recovered as an off white solid (0.462 g, 86%) after filtration through a pad of silica, eluting with dichloromethane. Analytical data was consistent with that above. ESI-MS of $[C_{13}H_{18}N_2O_2Cl]^+$; theoretical m/z of $[M+H]^+$ = 269.105, measured m/z of $[M+H]^+$ = 269.104; IR: ν (cm^{-1}) = 1634.53 (C=O stretch).

Representative Procedure XXXVII

Reversibility Study

(Scheme 5.5, Results and Discussion IV)



N-benzyl-4-chlorobenzamide (0.035 g, 0.15 mmol) and water (0.004 mL, 0.200 mmol) were added to an oven dried Radleys carousel tube. Toluene (0.2 mL) and, if required, $ZrCl_4$ (0.0012 g, 5 mol%) were added and the tube was sealed and heated at reflux for 22 hours. The reaction mixture was allowed to cool to room temperature before the solvent was removed on a rotary evaporator and the products analysed by their ^1H NMR and ^{13}C NMR spectra. With no catalyst, no reaction was observed. With $ZrCl_4$ (0.0012 g, 5 mol%), 5% hydrolysis into 4-chlorobenzoic acid and benzylamine was observed.

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Publications

1. **"**Transamidation of Primary Amides with Amines Using Hydroxylamine Hydrochloride as an Inorganic Catalyst" *Angew. Chem. Int. Ed.*, **2012**, 51, 1383.

2. "Catalyzed and Uncatalyzed Direct Amide Formation from Unactivated Carboxylic Acids and Amines", *Chem. Commun.*, **2012**, 48, 666.

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4. "Catalytic Coupling of Aldoximes and Amines to form Secondary or Tertiary Amides" *Org. Synth. (invited paper), manuscript accepted.*

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